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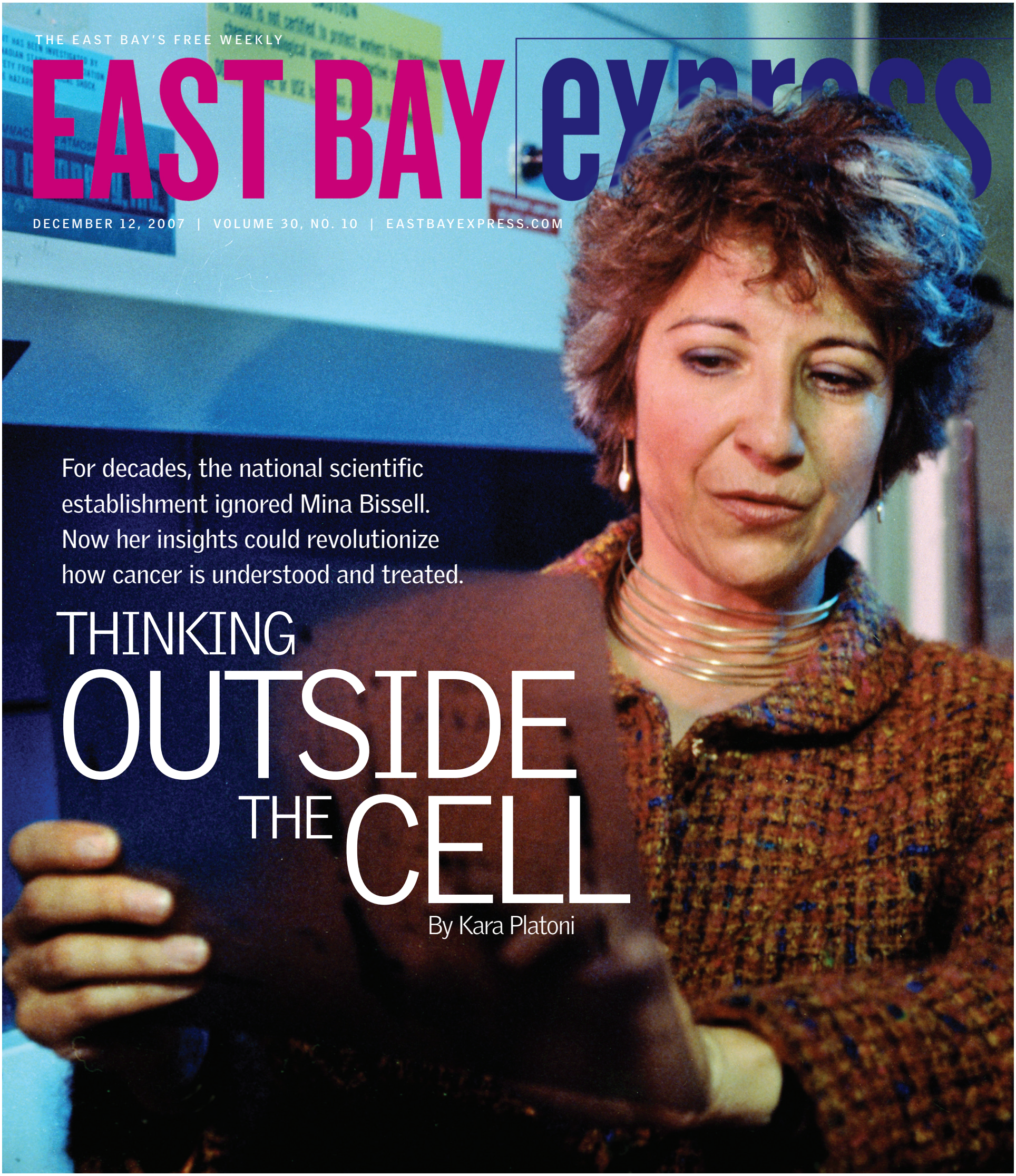

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THINKING OUTSIDE THE CELL

By Kara Platoni

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Thinking Outside the Cell

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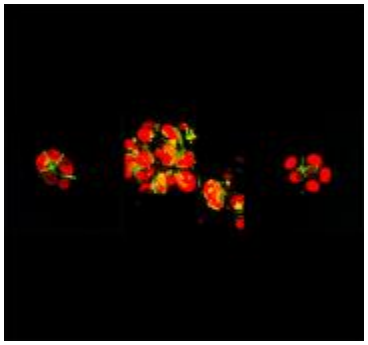
Mina Bissell



Why do we get cancer? For years, conventional wisdom held that cancer begins solely with a DNA mutation that causes cells to run amok and reproduce uncontrollably. Dr. Mina Bissell, who holds the title of Distinguished Scientist at Lawrence Berkeley National Laboratory, is not big on conventional wisdom. For thirty years, she has preached a heretical gospel: half the key to cancer lies outside the cell.

Take, for example, people born with a mutation linked to breast cancer, Bissell's special area of study. If cancer was the inevitable result for any cell with that mutation, shouldn't these people have cancer in every part of their bodies, not just the breast? And why is it that breast cancer develops in adulthood if the gene mutation has been there all along?

Bissell notes that while bodies are made of many different organs, every single cell shares the same DNA. "This has the same gene," she says, pointing to her nose. "This has the same gene," she says again, pointing at her elbow. "This has the same gene," she adds, indicating her eye. If inheriting a single DNA mutation was enough to cause cancer, your entire body should be cancerous. "You would be a lump!" she exclaims — a gigantic tumor.

A crucial part of cancer formation, Bissell believes, is not just what goes wrong inside the cell, but what goes wrong in the way it interacts with its extracellular matrix, the 3-D architecture that surrounds and supports the cell. If Bissell is right, her insight will revolutionize not only how cancer is understood and treated, but perhaps even what it means to have the disease. She champions a startling idea: that cancers can be reversed.

"Until very recently, people thought that once you became a mutated cancer cell you always behaved as a mutated cancer cell," she says.

Instead, Bissell and her group have shown, in lab cultures and in animals, that tumor cells with DNA mutations and active cancer genes could be induced to behave normally again by restoring their cellular architecture. "That reversibility gives this hopeful view of cancer," Bissell says, although no one yet knows how to reformat solid tumor cells in a human patient. Still, she speaks of a day in which cancer is a nonlethal, chronic condition that can be kept in check with drugs.

Bissell was not the first to claim that a cell's microenvironment plays a role in the formation of tumors. But she showed how this happens, by proving that disturbances in the cell's environment can cause mutations. She has produced spectacular lab results to support her claim. Still, she modestly maintains that her most important contribution is that she hammered away at her point for thirty years.

For much of that time, people ignored her. Hers are radical propositions: not only that tumor cells can be normalized, but that organ structure dictates function. She made these claims throughout the '80s and '90s, a time when DNA was king and molecular biology's hot topic was the single oncogene, or cancer-producing gene. It was a much more atomistic approach to understanding cancer: unpacking one molecule at a time, rather than trying to see it in the broader context of tissue function. Yet Bissell has always maintained that cancer is not a disease of single cells. "Cancer is a problem of the organs," she says.

Over the past few years, however, Bissell's work has itself become a hot topic. Academic honors and research money have begun to pour in. The National Cancer Institute started a program to study the tumor microenvironment. Bissell busily globetrots, talking to students, scientists, and pharmaceutical companies interested in her work. *Nature* ran an article hyping the 3-D matrix as "biology's new dimension," and heralding Bissell as its pioneer. The number one champion of the importance of the outside has become, suddenly, very in.

A radical message requires a radical messenger, and Bissell has happily worn her badge as a rebel. She is tiny, animated, forceful. She radiates an extraordinarily high wattage, a combination of sternness and motherly warmth that she uses to alternately chastise, then buck up, the postdoctoral fellows in her lab group. She calls everybody "honey" and gives everyone hugs. She thinks of all of her postdocs, even the ones who've left the lab, as her "kids."

Bissell is convinced of the artistry of science. Over and over in lectures she uses the word "beautiful" to describe a data set, a tissue slide, an illustration of how breast cells organize themselves. Bissell will stop an academic lecture to run out into the hall and invite inside a woman trying to sign people up for a breast cancer walkathon, because she wants that woman to understand the science, too. At the same time, she is unabashedly political, an ardent supporter of Amnesty International, a sharp critic of the president (both the American one and the one in her home country, Iran). "You have to go against the establishment if it is suppressive," she says. "You owe it to your intelligence.

Despite her prodigious gift for science, Mina Bissell very nearly was an English major. She was born in Tehran, Iran, into a highly-educated, well-off family. After becoming the top high school student in her country, she was offered a college education in the United States. She enrolled at Bryn Mawr, and struggled to choose a major. "Biology interested

me, but I didn't want to be a medical doctor because everybody had said if you are a medical doctor it is harder to have children, and I had thought I wanted to have children," she recalls.

"I debated very much between English literature and chemistry. I loved literature," she says. "But I then finally decided, 'Oh, literature, I can read that on my own, but I won't learn chemistry on my own."

After two years she transferred to Radcliffe, where she finished her degree in chemistry and married her first husband, another student from Iran. She enrolled at Harvard Medical School to study bacteriology.

During her first year of her Ph.D program, Bissell became pregnant with her daughter Yalda. People assumed she would drop out — it was the '60s, she was a young woman, and her family was on the other side of the globe. But Bissell ardently believes that women can simultaneously pursue career and motherhood, and often cites her own biography as proof for her young female colleagues. She has no patience for women who feel guilty over wanting to work instead of staying home with the kids because, as she says, "Everybody owes themselves the dignity of work."

At a recent meeting of the East Bay Association for Women in Science, Bissell recalled the consternation inspired by her pregnancy. "I walked into my professor's office and he said, 'Of course you are quitting! What is your mother going to say?'" she recalled. "And my mom called from Iran and said, "You are *not* quitting!" Instead, her mother came to help out for several months. Bissell shot her audience a knowing look.

"Microenvironment," she said slyly, to roars of laughter.

Bissell completed her Harvard program in six years — during that time, her first marriage ended, and she met Dr. Montgomery Bissell over a centrifuge. The couple married in Boston, then moved to Berkeley in 1970, when Mina Bissell was awarded an American Cancer Society postdoctoral fellowship at UC Berkeley in the Molecular Biology Department, and her husband began a distinguished career at UC San Francisco, where he is now Chief of Gastroenterology in the Department of Medicine. Their son, Ahrash, was born a few years later.

In the late '70s, Bissell happened to attend a talk given by Dr. Beatrice Mintz of the Fox Chase Cancer Center, who had done an extraordinary experiment, transplanting stem cells from a tumor into an embryonic mouse. Mintz was able to show that even though the tumor cells' genetic code integrated into the mouse's genes, the resulting baby mouse was normal with no tumors. "The tumor stem cell had become stably normalized by integration into the normal microenvironment of the developing embryo," Mintz wrote. In other words, even stem cells from a tumor could give rise to normal tissue, if kept in check by the environment.

The lecture changed Bissell's outlook. "I just was floored with how exciting this was," Bissell remembers. Mintz herself recalls: "Mina has told me that she was electrified at hearing about this work."

But Mintz and others had concluded that the tumor-derived mouse had to have no mutations, because it appeared normal. "At that time, everybody was discovering exciting oncogenic mutations, and they assumed that once genes get mutated they have to give rise to cancer," Bissell recalls. But she set out to prove an entirely different hypothesis: that normal-looking tissues could indeed have tumorous mutations that are suppressed by the cell's environment.

Once Bissell had her own lab, she explored this idea with her postdoctoral fellow, David Dolberg. They used the Rous sarcoma virus, which contains a cancer gene, to infect chicken cells in a Petri dish. When the virus was injected into a chicken's wing, it would cause a tumor. Yet if the virus was injected into chicken embryos, no tumors. If the embryo was disassociated and put into a dish, the cells became cancerous again.
"The virus causes that ugly tumor in the chicken; in the embryo it doesn't," says Bissell. "So this meant that context — the microenvironment, which is what is outside the cell — determines even when a potent oncogene can cause cancer."
Becoming increasingly interested in how tissue architecture might influence the genesis of cancer, Bissell chose to study the mammary gland, one of the few tissues that completely remodels itself over a woman's lifetime. In studies of both mouse and human mammary cells, Bissell saw something extraordinary: If the cells were placed on the flat surface of a tissue culture dish, they would lose their polarity, stop producing milk, and "forget" the form and function they had when they were in an animal. Yet if the cells were put in material that simulated the 3-D environment of real tissue, they would reorganize and look normal again.
Dr. Nancy Boudreau, who was one of Bissell's postdoctoral fellows in the early '90s and who now directs the surgical research laboratory at UC San Francisco, recalls how different Bissell's approach to studying this extracellular matrix was. She explored its overall function at a time when other researchers were individually scrutinizing its proteins. "The way scientists do things is they go, 'What's in the matrix?' and take one thing out at a time," recalls Boudreau. "But Mina's whole thing was, 'Let's take the whole thing together.'"
For example, Boudreau recalls an experiment she performed in Bissell's lab that dramatically illustrated how crucial the extracellular matrix is to the cells' well-being: when she destroyed the matrix around mammary cells, the cells essentially committed suicide.
One way to think of this relationship between cells and their surroundings, says Boudreau, is that the cells fit into a communication "network" provided by the matrix. When the cell and the matrix are both communicating with each other correctly, Bissell believes, each cell knows where it is in the system and what it is supposed to do, and malignancies can be kept in check.
But this balance can falter, she believes. Normal wear and tear caused by aging, the sun's radiation, oxidation, and inflammation change the microenvironment. If the cell and its surroundings stop being able to signal each other, Boudreau says, the cell has no social context. "It's kind of like mental illness," she says. "People know where they are in society and within groups, but crazy people are not aware of social boundaries. The tumor cell is like the nutjob on the street that says, 'I don't care.'"
Can these prodigal cells be brought back into the fold? Bissell and her collaborators think so, and their argument reads almost like a "nature vs. nurture" debate for the cell. Zena Werb, vice-chair of the anatomy department at UCSF, and one of Bissell's longtime friends, compares the cell's relationship to its microenvironment to the way a kid relates to his neighborhood. Take a smart kid and raise him on a crummy block where drug-dealing is the only way to get ahead, and he'll excel at criminality. Change that kid's environment to one that rewards scholarship, she says, and maybe he'll grow up to be a concert pianist. And if you drop a cell gone bad back into a healthy environment? "That's

one of the major observations that Dr. Bissell has made," Werb says. "If you can change the cells so that they perceive that they have a normal environment, then they're going to behave normally enough."

Indeed, perhaps one of Bissell's most spectacular results was described in a 1997 paper in the *Journal of Cell Biology*. When dosed with a certain antibody, breast tumor cells suspended in a 3-D culture reverted to their normal state, even though they still had gene mutations. In a 1999 paper she explored the opposite approach, creating spontaneous malignant and premalignant gene changes in previously normal mouse mammary cells by degrading the extracellular matrix, disrupting the interaction between the cells and their microenvironment.

The possibility that "disoriented" tumor cells can be made to behave normally suggests a revolutionary approach to treating cancer, one that starkly contrasts with current treatments that try to eradicate cancer cells with chemotherapy or surgery. Theoretically, Bissell says, one could develop drugs to restore the correct signaling between cells and the extracellular matrix — an analogous process sometimes naturally occurs in cancers that go dormant. "That dormant tumor cell finds a microenvironment that lets it just sit there and get the signal that you're not supposed to grow," she says. "And then ten years later or fifteen years later, sometime something happens and the signal in the microenvironment changes, now it is time to grow again."

If a chemically induced dormancy could make tumor cells quiet down, Werb says, it could be the key to solving breast cancer and possibly other cancers. "You don't have to cure the cancer, you don't have to kill every tumor cell, you just have to stop it from misbehaving," Werb says. "If you can turn it into a more or less normal cell, then you can live with that. It'll be like any other chronic disease."

And if that idea isn't big enough, consider that Bissell's main theory — that what's ouside the cell trumps what's inside — isn't really just about the breast, or even just about cancer. "The concept was that the three-dimensional organization of the organ or a tissue influences the way the genes behave," says Bissell firmly. "So that then is applicable to *all* cancers. That's applicable to *all* diseases."

Bissell became the director of Lawrence Berkeley National Laboratory's Cell and Molecular Biology division in 1988, and of its entire Life Sciences Division in 1992. And although she has always preached an outsider gospel, she won many converts who were awed by the scope of her vision.

Dr. Derek Radisky, now a research scientist at the Mayo Clinic and one of Bissell's postdoctoral fellows from 1998 to 2005, recalls that it took about nine months of working with Bissell before the implications of her theories really hit him. "I remember I had to sit down on my couch and think about it for about an hour, it's so different," he recalls. "She wasn't ten or twenty years ahead of her time, she is thirty or forty."

Boudreau puts it this way: "I went to Berkeley and had my mind blown, but it was in science and not drugs."

Yet Bissell's revolutionary ideas were not necessarily blowing minds outside of her own lab. "People who work in cancer therapy initially thought this was heresy, this was stupid," says Bissell.

Her frequent collaborator Zena Werb recalls that although they both started exploring similar ideas decades ago, Bissell's work received a much colder reception than her own. Werb's speciality is arthritis, a disease that doesn't involve malignancies. Bissell, on the

other hand, "started to think about these things with respect to cancer, and that was like putting a red flag in front of a bull," says Werb. "Cancer became Mutation Central, and anyone who said, 'Wait, that's not all there is!' was really a wolf crying in the wilderness."
Indeed, Bissell felt that her ideas were often ignored. "It is worse than criticizing, they simply neglected and dismissed without even referring to the work," she recalls.
"For the longest time, nobody could figure out what she meant," Werb agrees. "We ignore things we don't understand, even if they're staring us in the face. We need context, too, just like the cells do."
When journals accepted Bissell's papers, Boudreau recalls, "Sometimes they would sort of keep raising the bar really high and asking for additional experiments."
At scientific conferences, Bissell was known for spiritedly questioning cancer experts, telling them that their ideas were too simple and didn't explain everything. "She could blow holes in people's story for being incomplete, but do it in a very pleasant way," recalls Boudreau. But even then, Boudreau felt Bissell was often disregarded. "In some ways it was like, 'Oh, it's cute, there is this little excitable Persian woman over there screaming about whatever,'" Boudreau says.
To a certain extent, Bissell says, this skepticism is healthy. Scientists are supposed to be a tough crowd. "If you are daring and you make a hypothesis that is very different, you get rejected for good reason. You *should* get rejected because, after all, people have spent years and years proving something, and if you are going to be saying, 'Here I am, I'd like to add something on the top of it,' you have to go and prove it," says Bissell. "That is why it takes a lot of perseverance, it takes a lot of self-confidence, it takes a lot of tenaciousness, and it takes a lot of optimism."
It didn't help that she was out of step with the hot molecular biology topics of the '80s and '90s: mutations, oncogenes, and the Human Genome Project, which it was hoped would shed light on how medicine could target these cancer-causing genes. "When people were sequencing the human genome, everybody was promising, 'Oh, we'll know *everything*,' she recalls. "Here I was at a national lab and I was a director and the genome center was under me and I used to say, 'This is nonsense!' We will know the sequence of all the genes, but we still have to understand *why is the nose a nose*?"
While Bissell and her collaborators agree that cancer wouldn't happen without mutation, they felt mutation was only half the story. To understand cancer, you needed to see the tumor cell within the broader context of tissue organization, not just this or that bit of DNA. "The sum is not simply the addition of the parts," Bissell says. "There is something bigger, larger, more integrated."
Radisky recalls that Bissell would often quote Jules Henri Poincare to drive this point home to her postdocs: "Science is built up of facts, as a house is with stones. But a collection of facts is no more a science than a heap of stones is a house."
However, Radisky notes that it isn't easy for scientists to chase a broader vision. "The way that virtually all biological science is done is that everyone decides they're going to study one molecule and all the things that are touching it and that it touches, and the philosophy is that when I know everything about my molecule, and some guy in Utah knows about all his molecule, and some woman somewhere else knows all about hers, we're all going to get together in one room and we'll know everything," Radisky says.
"It's imposed on us by the way articles are structured, because they have to be about one thing, and the way grants are given, because there has to be a consistent body of research.

But the truth is, part of a toilet or a pipe or a stove can't be studied in isolation. A brick outside of the house doesn't work the same way as a brick inside a house."

Bissell's early supporters knew it would take years of buttressing her theories with scientific papers before her ideas would win any mainstream acceptance. "Conceptually, it was something that was going to take ten or fifteen years' worth of putting little pieces together for it to make sense for most people," says Boudreau. But by now, many of those pieces are in place. Bissell herself has published nearly 300 scientific papers on the microenvironment, and her former postdocs and colleagues have expanded her ideas to new areas outside of breast cancer.

Boudreau, for example, studies angiogenesis, or the creation of blood vessels — a process tumors manipulate to grow blood vessels to feed themselves. Her work is aimed at finding ways to control the vessel-forming factors that tumors produce, so that the malignancies will essentially starve and not be able to grow.

Radisky specializes in matrix metalloproteinases, which are responsible for normal breakdown, repair, and growth functions within the extracellular matrix, but are also thought to play a role in allowing cancers to invade neighboring cells and metastasize. Since they're necessary for normal body function, you can't just wipe them out to treat cancer, but it would be beneficial to know more about which of their processes are tumor-related. Radisky's work focuses on both breast and lung cancers. Other former postdocs, Bissell says, are working on ovarian cancer and viral oncogenes.

Perhaps one of the more surprising connections to Bissell's work is being made by one of her Lawrence Berkeley colleagues, Dr. Judith Campisi. Bissell recruited Campisi to the lab in 1991, where the two worked on breast and prostate cancer, but Campisi began to make some links between cancer — a disease of too much cell proliferation — and aging, a problem of not enough proliferation.

"Normal human cells have intricate mechanisms that stop them from growing very effectively when they are faced with potentially cancer-causing stimuli, for example radiation, chemicals, or mistakes in DNA or even certain oncogenes," Campisi explains. "Cells are hardwired to protect themselves from cancer — they will shut themselves down and not proliferate. If a cell doesn't divide, it will never form a tumor."

However, she says, "You can clearly see how a long time of calling on this mechanism will also cause symptoms that we recognize as aging, a slowdown of repair" — and essentially a pileup of nondividing, senescent cells. So, the cost of not getting cancer all the time is that we get old. "Evolution has had to make some bargains with the devil," Campisi says.

Like cancer cells, these senescent cells interact with their microenvironment — and in this case, Campisi found, they actually secrete chemicals into it. "When the cells stop dividing they act as though they're responding to a wound," she says. "We began to look at what cells were pouring outside and showed that they are changing the tissue microenvironment, and it's causing normal cells to not function properly because of all these secretions. It also stimulates any nearby precancerous cells to become more aggressive.

"The tissue is changing and becoming more permissive," Campisi says, "and one thing Mina has said for a long time is you need a permissive tissue for cancer to grow."

It's a fascinating example of how Bissell's work sheds light on other health questions, and there are likely to be many more as Bissell's theories gain attention. As Campisi puts it,

"Right now, the microenvironment is hot." In 2004, the National Cancer Institute earmarked $40 million annually to study the cancer cell microenvironment. Pharmaceutical companies like Merck, GlaxoSmithKline, and Genentech have asked Bissell to lecture to their scientists. She has won a host of honors and prizes, including election to the Institute of Medicine of the National Academies and the American Academy of Arts and Sciences, becoming president of the American Society of Cell Biology, and most recently receiving the Pezcoller-AACR International Award for cancer research. "I couldn't get any money for fifteen years," Bissell says. "Now, they're all funding me."

Still, there are reminders that hers has long been an outsider point of view. A sore point with Bissell is that, to this day, her ideas are mentioned in only one med school textbook. But as someone who has embraced her role as a rabble-rouser, Bissell has tried to pass on that spirit to the young researchers on her lab team. "I try to teach them to have courage," she says. "I try to teach them also how to work hard and yet think of research as a pleasure, even though it can be very, very frustrating." She encourages them to take on big, difficult questions, and to challenge the wisdom of the establishment — which, she'll admit wryly, she is perhaps becoming. "There is a lot to learn, and there is a lot to do, and the big message that I like to give is that scientists should not be arrogant," she says.

The microenvironment landscape that she helped pioneer is still wide open. "We know a lot about the language and the alphabet of the genome," she says, "but we know very little about the language and alphabet of form."