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Dr. Mina Bissell

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Thinking outside the cell

For decades, the scientific world ignored Mina Bissell. Now her insights could revolutionize how cancer is understood and treated.

By [Kara Platoni](#)



FAITHFUL FOLLOWING

Dr. Mina Bissell has always preached an outsider gospel, yet she's won many converts. Lawrence Berkeley National Laboratory made her director of its Cell and Molecular Biology division in 1988, and of its entire Life Sciences Division in 1992.

Courtesy Of Lawrence Berkeley National Laboratory

About the author:

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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 30 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 were 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 how cancer is understood and treated, 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 30 years.

For much of that time, people ignored her. Hers are radical propositions: not only that tumor cells can be normalized, but also 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.

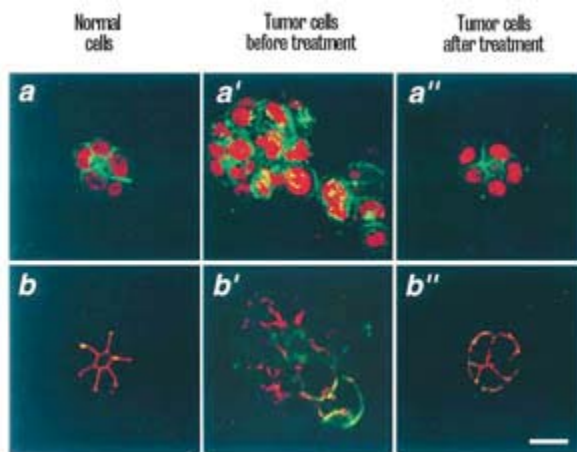
Yet Bissell has always maintained that cancer is not a disease of single cells—"cancer is a problem of the organs."

Over the past few years, though, 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 globetrotts, 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 No. 1 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.



COMPARE AND CONTRAST

In a study on breast cancer co-authored by Bissell, tumorous cells treated by an antibody closely mirrored normal cells. This diagram shows cells dyed to show what's outside (a, a', a'') and the cellular architecture (b, b', b''). Courtesy Of Lawrence Berkeley National Laboratory

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, 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,” she recalls, “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.

“I debated very much between English literature and chemistry. I loved literature. 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.

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 says: “Mina has told me that she was electrified at hearing about this work.”

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.



A TRUE RENAISSANCE WOMAN

Iranian-born Mina Bissell earned a free college education in the United States, though scientific study wasn't a given. "I debated very much between English literature and chemistry. I loved literature. But I then finally decided, 'Oh, literature, I can read that on my own, but I won't learn chemistry on my own.' "

Courtesy Of Lawrence Berkeley National Laboratory

"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's 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. Bissell 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.' "

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 who 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 chairwoman 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?

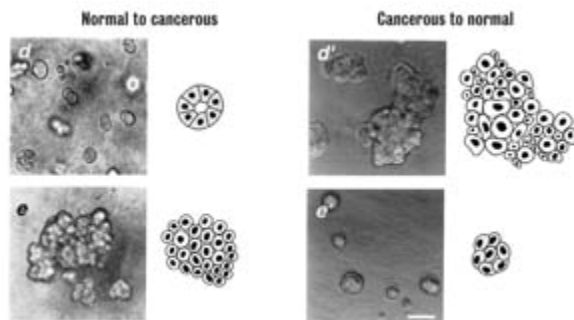
“That’s one of the major observations that Dr. Bissell has made,” Werb says. “If you can change the cells so that they perceive that they have a normal environment, then they’re going to behave normally enough.”

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.

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.



CAUSE AND EFFECT

Bissell’s theory about the importance of a cell’s microenvironment is shown dramatically above in a test she and her colleagues developed. As shown in the diagram, normal breast cells can eventually become malignant if they are made to be continuously disorganized. In her 3-dimensional experiments normal cells form

organized structures and cancer cells don't. When breast cancer cells are treated with a specific antibody to lower their metabolism, they stop growing and behave like a normal cell demonstrating how an external element triggered internal changes even in cancer cells.

Courtesy Of Lawrence Berkeley National Laboratory

“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 outside 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 10 or 20 years ahead of her time, she is 30 or 40.”

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. 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.”

It didn't help that Bissell 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.”

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 15 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. 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.”