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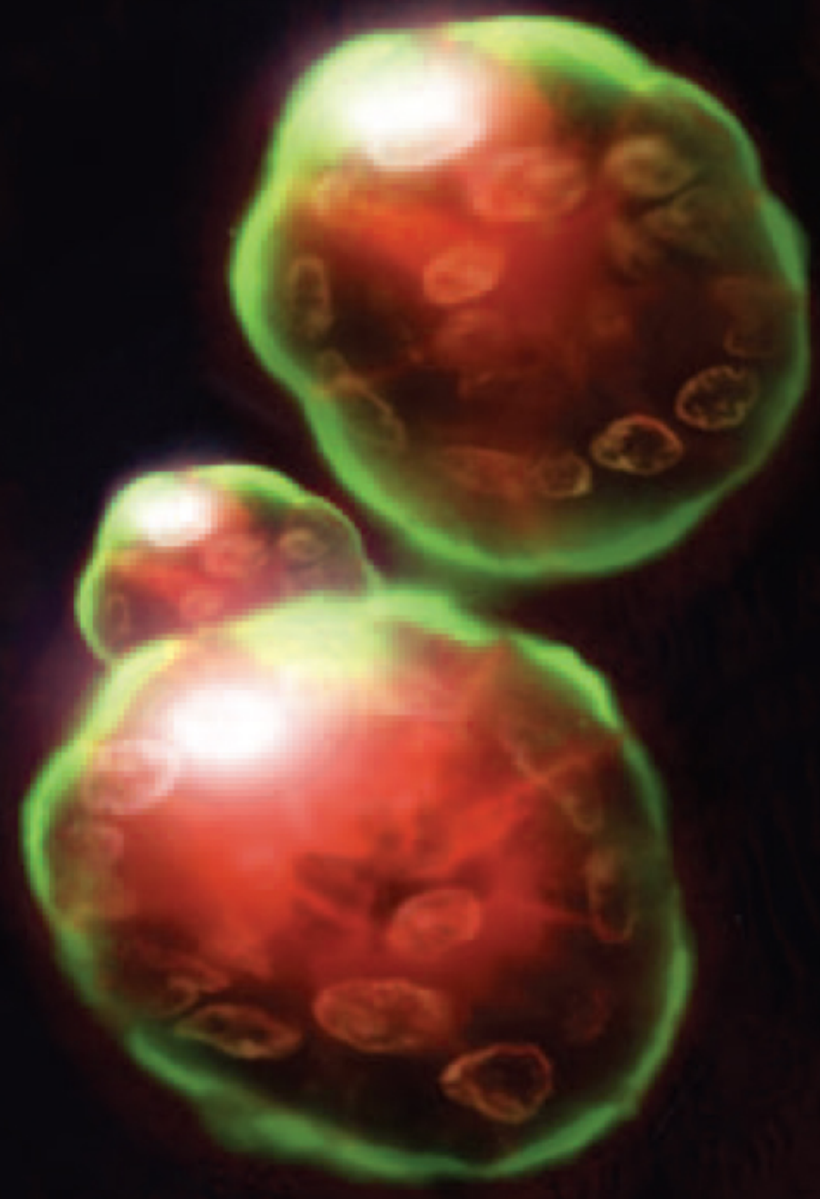

{managing the microenvironment}

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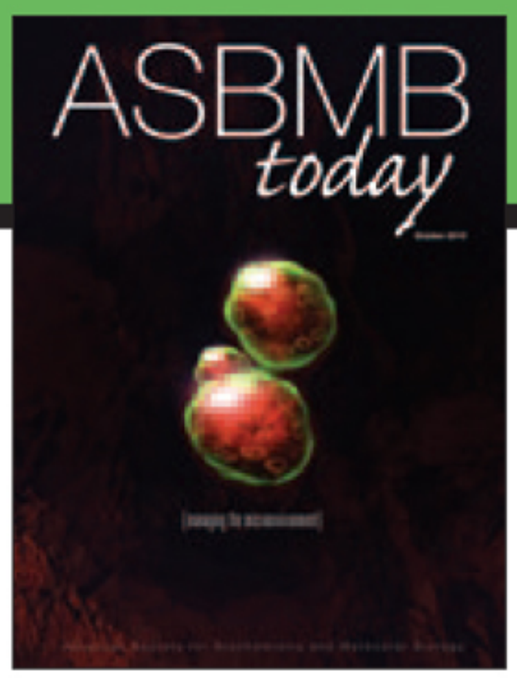

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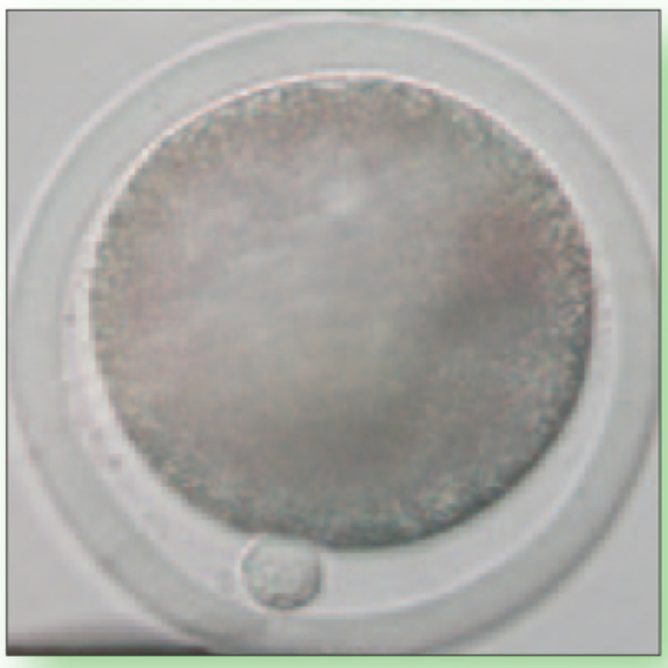

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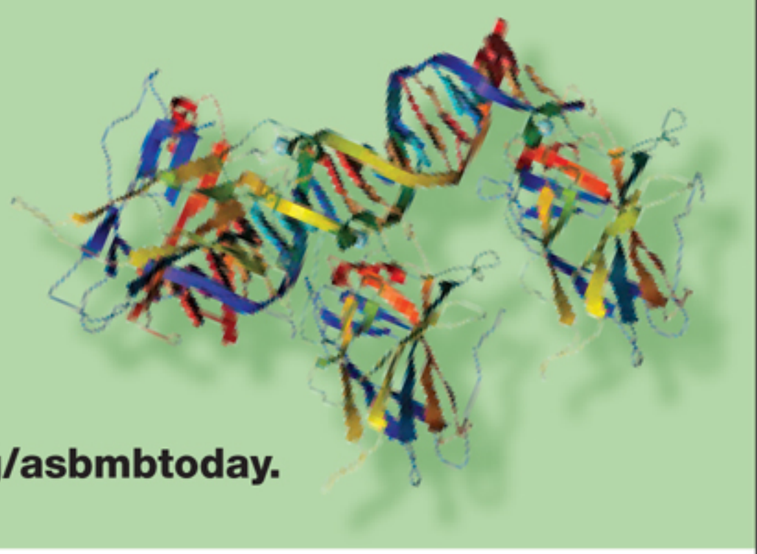
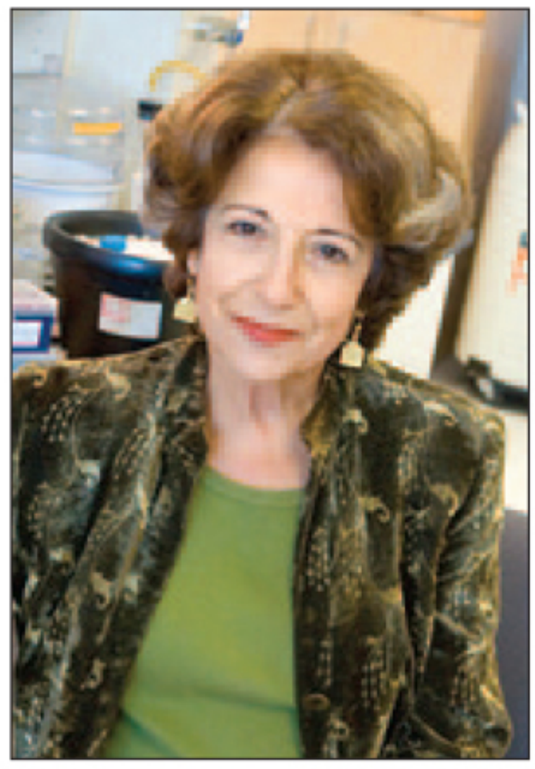


Mina J. Bissell: *Going the Extra Mile… and Dimension*

BY NICK ZAGORSKI



In 1992, Mina J. Bissell found herself in an unusual position. She had just been appointed director of all the life sciences at the Lawrence Berkeley National Lab in California and thus also had been placed in charge of LBNL's genome center, which recently had begun sequencing portions of human DNA for the Human Genome Project.

Having LBNL play a central role in such an ambitious endeavor could be considered an honor, but Bissell was troubled: "I remember even before the genome was completed, almost everyone who was talking about the project was promising that it would simplify science and medicine, cure all diseases and answer all our questions."

"And, I remember telling them over and over again that it was not so simple," she adds.

For one thing, why would her colleagues want to make science simple? "For me, at least, the beauty of science has always been its complexity," she says. "Every question you answer opens up more exciting questions, more riddles to solve. The sequence of the genome has opened up a whole host of other questions."

"And, besides, how would the complete genome solve developmental and cell biology questions? An eye and a nose have the exact same genome in an individual, so, why are they so different? The sequence alone won't answer that."

Fiery, passionate and certainly not afraid to upset the scientific apple cart is a brief, but apt, description of Mina Bissell.

In fact, Bissell, a distinguished scientist at LBNL, where she has been since 1972, has spent her entire career challenging traditional views. Fortunately, another of her qualities is doggedness, which is vital, for the scientific establishment puts a heavy burden of proof on those who wish to challenge tradition. And, in Bissell's arena of cancer research, the prevailing view for more than 30 years has been that the "gene is king," and even single mutations dictate cancer incidence and progression.

Bissell, though, has been working tirelessly to prove that the king needs to share his throne. Using an integrative approach that combines an ingenious 3-D cell-culture system with other molecular biology, imaging and high-throughput methodologies, she has demonstrated that a tissue's architecture and its surrounding microenvironment — such as cell-cell interactions and the extracellular matrix — are just as important in cancer progression as the genetic alterations within.

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Berkeley, Calif., in the 1970s was abuzz with oncogenes. Numerous discoveries during that time, including important work done by Peter Deusberg and G. Steve Martin at Berkeley and Peter Vogt at the University of California, Los Angeles had demonstrated how viruses (Rous sarcoma virus) could use their genetic material to turn normal cells into tumor cells, and Michael Bishop, Harold Varmus and colleagues had shown that even some host genes had inherent potential to promote cancer if mutated. Many scientists believed these discoveries would win Richard Nixon's recently declared war on cancer.

Bissell, however, was a bit more skeptical about the oncogene revolution at that time. In reading some literature about cancer, Bissell had been more intrigued by another, older concept: the Warburg hypothesis, which suggested that altered metabolism could induce cancer.

"Of course, by then, most scientists had discredited the Warburg theory, so no one was really pursuing it," she says, then, adding adamantly, "but I was interested in it."

Bissell notes that the main issue she discovered was that researchers who had measured metabolism and cancer cells often did not regulate various external factors like temperature, cell density and pH, which led to inconsistent results in the literature.

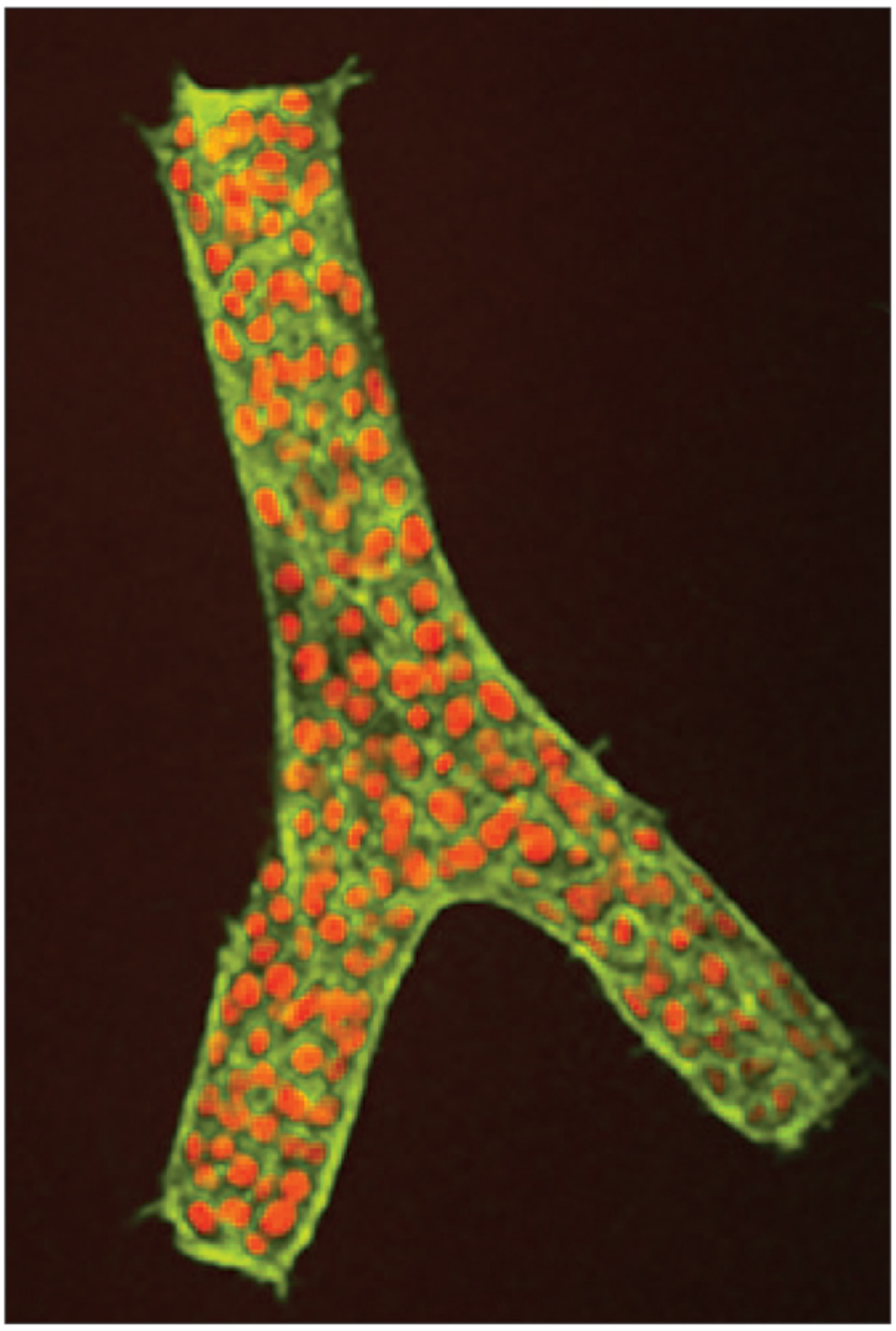
So, together with Al Bassham, a protégé of legendary chemist Melvin Calvin (of Calvin cycle fame), she devised a unique steady-state machine that could keep the environment of cultured cells constant. Then, they adapted some kinetic techniques Calvin and Bassham had employed in studying photosynthesis to animal cells and tracked glucose metabolism in various cell types.

"Everyone thought glucose metabolism was a housekeeping function that should be the same in all cells, but we

found that glucose metabolites had tissue-specific expression patterns," she says proudly. "Furthermore, we found that glycolysis was always higher in cells infected and transformed by RSV once all factors were properly controlled, but the increases were not necessarily due to defects in cellular respiration, which Warburg had believed."

The real intrigue came in further studies in which Bissell manipulated the glucose levels in normal and transformed cells; when she lowered the glucose concentration in RSV-infected cells, they began to appear more normal, whereas increasing the glucose concentration in normal cells could induce them to begin looking transformed.

"These findings were quite exciting to me," she says. "Unfortunately, no one else was particularly interested, because metabolism was the last thing people wanted to hear about at that time; it was old and boring."



In addition to her work uncovering the role of the microenvironment in cancer, Mina J. Bissell has been examining other aspects of its regulation, such as how the ECM, ECM regulatory proteins and tissue geometry influence mammary gland branching and morphogenesis.

Then, one day, near the end of the decade, Bissell happened to attend a most interesting lecture given by Beatrice Mintz of Philadelphia's Fox Chase Cancer Center. In her talk, Mintz discussed studies in which she had integrated mouse cancer cells into developing mouse embryos and shown that, even though the embryos incorporated genetic material from these cancerous cells — which would readily form tumors if injected into adult animals — the mice were born healthy and happy.

The cancer signals had somehow been repressed, which Bissell believed indicated that, much like the metabolic environment, the physical environment of a cell could dictate its predilection for disease.

It was a radical concept — most scientists believed extracellular molecules like collagen merely were inert structural components — and one Bissell could not resist trying to pursue further.

• • •

It might have seemed unusual for a young, still somewhat-unproven researcher to take on such a hefty challenge, but family and friends who knew her during her youth in Iran, before she arrived in the U.S. in 1959 to begin her college studies at Bryn Mawr (having won a prestigious scholarship as Iran's top high school student), probably were not surprised.

Bissell, after all, grew up in a well-to-do academic family in Tehran that had a history of going against the grain. Her father, who came from a long family line of ayatollahs, bucked the tradition of first-born sons attending divinity school and instead became a lawyer, and an agnostic to boot. Yet, this didn't offend her grandfather, who, contrary to the image most Westerners have of these Islamic religious figures, was the most enlightened man Bissell knew.

"I mean, my grandfather's best friend was Tehran synagogue's head rabbi," she says, mentioning a fact that highlights some of the misconceptions Bissell has had to deal with on occasion.

"I've had people comment that they're impressed I've managed to succeed in my career considering I grew up a woman in the Middle East," she says.

"And, I always correct them and say I succeeded precisely because I grew up in the environment I did."

She points out that, prior to the Islamic revolution, Iran featured Muslims, Christians, Jews, Armenians — you name it — all co-existing with very little bias. Likewise, gender discrimination was not a serious issue, at least in large cities. (Even today, despite the changes in government, Bissell notes

Iran is a highly educated country and that women make up an equal percentage of the students in hard sciences, and, at Tehran University, 50 percent of faculty are women.)

"My family always told me that I could become whatever I dreamed of," she says, adding that her father did advise her to stay away from law, because "he knew that fundamental religion was penetrating the legal system, and I might encounter some prejudice against me, which, given my nature, I would fight vigorously and get into more trouble."

Years later, that desire to stand up for her beliefs would be tested in the scientific arena.

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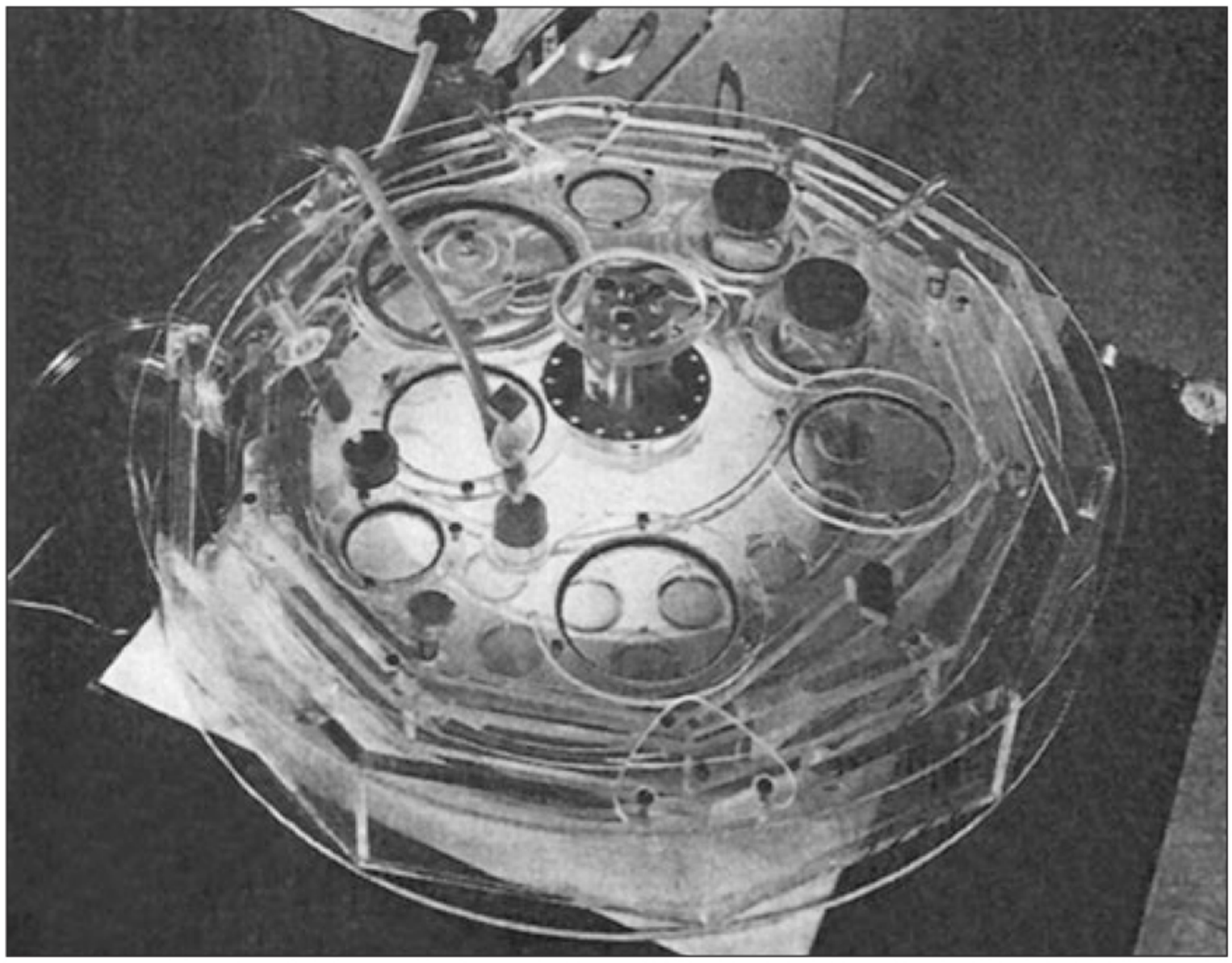

A steady-state apparatus developed by Mina J. Bissell and Al Bassham used to more accurately quantify metabolism in a variety of cell types.

Together with postdoctoral fellow David Dolberg, Bissell continued her studies with oncogenes and changes in the microenvironment by testing whether RSV could transform chicken embryos. It was well-known that if RSV was injected into an adult chicken wing, it formed a tumor; however, when they injected the virus into developing chicken embryos, no tumors formed. But, more intriguingly, if those injected embryo wings were separated into individual cells and put in a dish, they would become cancerous again.

The team looked at another RSV-related fact — that viral administration typically only produced tumors near the site of injection, even though the chickens had viral particles circulating in their blood. However, if they wounded infected chickens at other locations, those sites also could develop tumors, which they determined were not due to metastasis. Subsequently, with another student, Michael Siewke, she demonstrated that a wound-response protein, TGF-β, mediated this postinjury tumor formation.

Now, quite fascinated with how the surrounding tissue architecture might influence these events, Bissell decided to switch to a model more relevant to the human condition. "Fortunately, I had a wonderful postdoc, Joanne Emerman, who had done her thesis on mammary glands, so we decided to focus on that, since the mammary gland undergoes a lot of developmental changes and is frequently associated with cancer. And her help in getting our work underway was quite invaluable."

(Because her own background was primarily bacterial genetics, enzymology and metabolism, Bissell also recognizes two other great postdocs, Rick Schwarz and Glenn Hall, who used their graduate student expertise in collagen and basement membranes, respectively, to mentor her in those areas.)

The key to success, though, would be finding a suitable method to study microenvironment interactions in detail. "Obviously, two-dimensional studies in petri dishes would be limited, but some experiments would be impractical in mouse models as well," she says.

Her solution was to develop an ingenious three-dimensional culture matrix that resembled a natural extracellular matrix and enabled mammary cells to form spatially relevant structures like a real mammary gland, initially in mice (with postdoc Mary Helen Barcellos-Hoff) and then in human breast (with Ole Petersen, a young professor in Denmark). She states that this is, by no means, a perfect system, but Bissell and her lab continually are working on improving their three-dimensional matrices.

Since then, Bissell and her group have been using these three-dimensional models to explore how cells and the surrounding extracellular matrix interact to shape cell behaviors such as polarity, migration and proliferation; it's a concept she has termed a "dynamic reciprocity" in signaling between the extracellular matrix, transmembrane receptors,

the cytoskeleton, the nucleus and the chromatin.

This has led to some real eye-opening discoveries, perhaps best highlighted by a series of studies in the late 1990s, in which Bissell's group demonstrated that antibodies against the β1-integrin receptor lowered EGF signaling and altered the behavior of cancerous breast cells to a more normal phenotype; conversely, adding matrix metalloproteinases to degrade the three-dimensional matrix could induce invasive phenotypes in otherwise nonmalignant breast cells.

And, these eye-opening results would not have been evident in any two-dimensional system.

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One would imagine that, given the remarkable nature of Bissell's early findings, her pioneering studies with three-dimensional mammary models would establish quickly the importance of the ECM in cell physiology.

However, although scientists often like to think of themselves as a progressive lot, in many ways, science — notably basic academic science — is a conservative field. Discoveries are made in steady, incremental steps, whereas funding agencies tend to favor established scientists providing safe, tractable projects.

So, for many years, Bissell struggled with National Institutes of Health funding, picking up grants from other agencies (especially the Office of Biological and Environmental Research at the U.S. Department of Energy) willing to take a risk on an innovative idea, while also failing to get a significant foothold in the cancer community at large. Even now, she notes, most textbooks still mention the ECM purely as a structural component.

"People can be set in their ways sometimes, and science is no different," she notes. "I think this might have been especially true in the early days of the molecular biology era, with the new techniques that broke research down into simple pieces. Either your gel had a band, or it didn't; a cell had a functional copy of a gene, or it didn't. People didn't step back and consider broader possibilities."

Another influencing factor, Bissell believes, was the growing commercialization of science in the 1980s and beyond. "Now, all of a sudden, a lot of good scientists were spinning their discoveries into businesses and had tangible investments in their products. And, if you have a gene that may be crucial in cancer development, you don't want to hear someone else saying all this stuff outside the cell is important."

Particularly because Bissell believed — and showed — that changing the extracellular environment could help prevent the spread of cancer, even by genetically defective cells.

These were frustrating times, but, Bissell states definitively, "I was not raised to be a quitter."

She certainly did not quit when she became pregnant during her first year of graduate studies at Harvard in 1963 — the medical school had only three female students and 200 males, and most everyone assumed she would drop out. And, she wouldn't quit now.

Slowly, with continued determination and persistence, aided by former lab members who helped spread her ideas to other institutes and "a few wonderful colleagues," Bissell's ideas became more accepted.

Indeed, the past few years have seen her receive many honors as a testament to this, such as election to the Institute of Medicine, American Academy of Arts and Sciences and, more recently, both the American Philosophical Society (2007) and National Academy of Sciences (2010). She also has received the Pezcoller Foundation-American Association for Cancer Research International Award for Cancer Research (2007); the Federation of American Societies for Experimental Biology Excellence in Science Award (2008), the American Cancer Society Medal of Honor (2008) and, recently, her own "Mina J. Bissell" Award, which will be presented every two years by the University of Porto in Portugal.

With her newfound recognition, Bissell has been quite busy on the lecture circuit; even though she says she only can accept about one of every four speaking invitations, she still feels like she's continually on the go. Still, she uses that time to relate her story and encourage others, especially young scientists, to follow their own scientific ideas and not get discouraged by setbacks.

"Innovative people always have to prove themselves, so stay with it and don't let the establishment tell you what to do," is one of her mantras, usually followed by a wink and nod to her own recent success.

"Of course, now that my work has been accepted, I guess I'm part of the establishment too, so I guess you shouldn't listen to me either."

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