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Testing the boundaries

Mina J. Bissell, Ph.D.

Director, Life Sciences Division
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Mina J. Bissell, Ph.D., likes taking risks. Whether moving to the United States from Iran when she was barely 18 or broadening scientists' conceptions of cell behavior and gene regulation, she has consistently tested the boundaries of science—and of life. Driven by her exceptional intellect, energy, and compassion, Bissell is a progressive and outspoken thinker whose ideas have had a significant impact on cellular research. Bissell currently serves as director of the Life Sciences Division at Lawrence Berkeley National Laboratory, where she has been working since 1976.

Bissell has always been interested in understanding the essence and impact of the environment around her. As a young girl, Bissell was encouraged, and inclined, to ask questions and pursue their answers. As an adult, intellectual curiosity directed her first toward literature and then chemistry as an undergraduate at Bryn Mawr College (where she studied for two years) and Radcliffe College, from which she graduated cum laude. Bissell went on to study bacterial genetics at Harvard University for her Ph.D., but began focusing on the cells—and their surroundings—of higher organisms during her postdoctoral work at the University of California at Berkeley.

Bissell's willingness to think outside the box—or, in this case, the cell—prompted her to ask questions about cell morphology and behavior. Her research led to her hypothesis that the extracellular matrix (ECM) was much more than simply cellular scaffolding. Bissell, her research group, and other collaborators began working with breast cells, demonstrating that when normal and cancerous breast cells are grown in culture (in the absence of the ECM), each type grows at the same rate and looks like the other. When the ECM is added to the culture, however, both kinds of cells change behavior: The normal cells organize themselves, stop growing, and become differentiated, while the cancerous cells grow rapidly in a tumorous mass. Bissell's group later showed that by manipulating signals from the ECM, they could get cancer cells to behave normally.

Bissell's three-dimensional approach revealed a crucial social interaction—or "dynamic reciprocity"—between ECM molecules and the nucleus: The ECM affects the

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MEET MINA BISSELL

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"I'm all for finding out what kind of genes people have but at the same time educating them about what this information means."

"People don't realize how much our background shapes us."

"I'm pleased to see how many gains women have made in science, but I still see the difference between being a man and being a woman in the field."

See all topics and questions

pattern of gene expression, and the nucleus affects the makeup of the ECM. Thus, Bissell found that the nature of tissue and organ specificity cannot be known unless the microenvironments of the proteins within the tissues are understood.

Grateful for her upbringing; the support of local, national, and international colleagues; and the role of national labs in fostering scientific and technological advances, Bissell's integrity and scientific insight have earned her many honors and awards, including the U.S. Department of Energy's Ernest Orlando Lawrence Memorial Award and election to the Institute of Medicine of the National Academy of Sciences. Bissell is a past president of the American Society of Cell Biology and the recipient of an honorary doctorate from Pierre & Marie Curie University, Paris (2001).

Incyte Genomics is proud to present an in-depth conversation with Mina Bissell as part of an ongoing series of discussions with the dedicated, passionate scientists who are shaping the world of genomics and the life sciences.

Next: What controls cell behavior?

Mina Bissell was interviewed by Christopher Vaughan, a writer who lives in Menlo Park, California. Vaughan is the author or coauthor of three popular books on science: *How Life Begins* (Dell Publishing 1997); *The Promise of Sleep* (with William C. Dement, Delacorte Press 1999); and *The Prenatal Prescription* (with Peter Nathanielsz, July 2001).

Mina Bissell was photographed by Kristof.

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Q: Twenty years ago everyone was looking inside the cell at genes as the cause of cancer. What led you to look outside the cell instead?

DR. BISSELL: It had a lot to do with my background in chemistry and bacterial genetics. Not having studied biology, I really didn't know any better. When I finished my Ph.D. and came to Berkeley in 1970 to work in cellular and molecular biology, it was my introduction to looking at cells of higher organisms. At that time the most exciting part of biology had to do with viruses that cause cancer. I would look at the virus-infected cells under the microscope and somebody would say, "This is malignant, and this is normal." I had no idea what they were talking about—it was hard for me to distinguish between the two.

I began to ask, "How do you define 'normal'? How do you define 'malignant'? What is the relationship between normalcy and malignancy?" These kinds of questions led me to doubt that a change in a single gene could cause cancer. It didn't make sense to me.

We know that all the cells in the body have the same genetic information. Yet we were taking cells out of the chicken and putting them in a dish, and they all looked the same. I kept saying, "But *in vivo* they look very different. What makes them look the same in the dish?" If it's all in the gene, why do cells change so rapidly and so completely when their environment changes?

Then we did what I consider some of the best experiments to come out of my lab. We injected *Rous sarcoma* virus into the chicken embryo, and we showed that in the early embryo the virus doesn't cause tumors. The same virus that causes a tumor on the wing of the chicken does not cause a tumor in the embryos. People said that it was because the virus didn't get integrated; we showed them that it was integrated. They said that it was because the virus didn't express the genes; we showed them that it expressed the genes.

This experience began to shape my concept of microenvironment, that the same gene in a different microenvironment behaves differently. I don't know why it's taking people so long to appreciate this. Look at my finger, my nose, my eyes, my mouth—all the cells in

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these places have the same genes. How can they behave so very differently?

I thought, "Probably what is *outside* is actually telling the nucleus what to do." The unit of function in higher organisms is not just the cell, but the cell and what's around it. I came to this idea partly through ignorance and the fact that I was not prejudiced by information. Nobody had told me, "This is the way you should think." At the same time, my own postdoctoral fellows were teaching me what the extracellular matrix consisted of. I have learned and continue to learn from my fellows.

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Q: Many of your concepts were at first considered radical. Do you think you're naturally inclined toward bold ideas?

DR. BISSELL: Yes, and I think that it comes from the way I was raised. Trust me—I'm a great believer in genetics. I, like others, am a creature both of my genes and of how I was born and raised. I come from a very educated family and was encouraged to express myself from an early age. I don't have any brothers, and I was kind of like the son in the family. I am also the youngest. Whether I would have been the same person had I not had the same genetic material, I don't know. I do have a sister and cousins; half of them are as outspoken as I am, and half are not.

I grew up having political debates with my father, and I performed on stage early on. I was raised to question things, and it always fascinated me to ask, "Why?" When I look back on my career, I realize that I have always gotten myself into a bit of trouble by doing things that aren't quite predictable. It's not because I go looking for those things. I honestly don't. I'm given a problem and I start asking questions, like the kid asking about the emperor's clothes. The question is, Why do I do this more than most? It could be partly cultural, partly genetic, and partly the way I was raised.

But believe me, I get myself into more trouble than I need! [*Laughs.*] People say to me, "Mina, you are so direct. How did you ever get to be a division director?" Sometimes I wonder. I think that it takes other people around me who appreciate directness, are not afraid of challenges, and allow me to lead. In that respect, I give a lot of credit to some of the men and women with whom I have worked—people who are able to tolerate this kind of boldness. But I'm afraid I take the same kind of position in many other aspects of my life. I am very interested in human rights, and I'm one of these people who get very upset about injustice in science and in society. I have always had very strong opinions. At times, therefore, I can come across as being self-righteous, which is not a good thing!

The success I've had in saying unconventional things and moving those ideas forward has to do with the context I was in. Initially, being in a national lab was a

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necessity because I was not doing mainstream science and had to stay in the [San Francisco] Bay Area. In the beginning, it wasn't as if I had ten job offers at universities. But it allowed me to be bold and to survive.

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Q: Describe the process of your early breast cancer and cell work.

DR. BISSELL: I used breast cells as a model for how normal behavior of a tissue comes to pass. Breast is one of the few tissues in the body that changes during adult life. After women go through puberty, the breast develops. When an animal becomes pregnant, the breast develops further and produces milk. When you take the babies away, the breast involutes. It changes constantly as a function of the hormones and the microenvironment, so it appeared to be a good model.

One of my earliest fellows, Joanne Emerman, brought the technique of culturing mouse breast cells to my laboratory. Interestingly, when you put breast cells in tissue-culture plastic, they change shape, won't make milk, and completely forget where they came from. We realized that something had to be missing. We gave the cells hormones; we gave them all the nutrients they need. They grew but did not differentiate. What could be missing? It appeared to be the material of the extracellular matrix. Up to that point, people had thought that the ECM was just like scaffolding, but I thought that maybe this material actually contained the important information. When we isolated the right kind of ECM for breast cell—called basement membrane—put it in a dish, and put the cells on the top, it was miraculous: The cells came together and reorganized. Now we know that ECM molecules and this gelatinous basement membrane have information. The ECM is involved in signaling in the liver, prostate, breast—you name it. The ECM is involved in every single tissue of the body, including the lymphatic and blood tissues as well as the cells in the brain.

In 1980 I wrote a theoretical article with two of the fellows in my laboratory, Glenn Hall and Gordon Parry, posing the question, "How does the extracellular matrix direct gene expression?" I took the concept of "dynamic reciprocity" (a term that one of my colleagues had used to address how a receptor may interact with the interior of the cell), and I applied it to this broader concept. I theorized that the ECM—which of course is the product of the genes—can itself influence the genes, once it gets out and reorganizes. Cells make three-dimensional organizations that are not necessarily specified by the

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genome but by what is surrounding them.

Next I said, "These things have information. They must have receptors so that they can send the information." At the time, the receptors for the ECM molecules had not really been discovered or at least appreciated. I thought, "How would this receptor work? It would have to be attached to the scaffolding cytoskeleton inside the cell." I theorized that it is then attached indirectly to the nuclear matrix, which at that time people didn't even believe existed. Then I postulated—again, by reading some literature and thinking in 3-D—that the chromatin, the structures into which DNA is packed, is probably attached to the nuclear matrix. If something from the outside behaves like a pulley and it is pushed and pulled, it sends information all the way to the nucleus. Some people think that it is either all biochemical or all mechanical, but I suggested that the control is both mechanical and biochemical. If you destroy this unit of control at any given point, then dynamic reciprocity is lost and the cells could go awry.

This made a lot of sense to me and to some of my colleagues. So we set out to show, step by step, how it happens and where the process can go wrong in disease and, specifically, in cancer.

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Q: How did the broader scientific world respond to your theory about the extracellular matrix?

DR. BISSELL: The theory was supported by a small minority in the United States who were thinking along the same lines. But it had enthusiastic support from a few prominent scientists in Russia and Eastern European countries. I think that's partly because back then those people had very few technological gadgets but a good deal of intelligence and time to think. I used to get wonderful letters from people in the Soviet Union and a few other countries saying, "Wow, this is so exciting. We believe that this is true." But in the United States, scientists basically didn't take the idea seriously. Molecular biology and gene-cloning were very exciting—there was not much enthusiasm for complexity!

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Q: What might be the advantages of having cell behavior regulated partly by something outside the cell?

DR. BISSELL: Once again it relates to the fact that the information inside every cell's genome is the same. If you have everything regulated from the inside, how do you bring about local and rapid regulation of gene expression in a way that is tissue specific? It's a very difficult thing to do. On the other hand, if you have a marriage, if you will, between the outside and the inside, the outside factors could very quickly and locally change the regulation of the gene inside, and vice versa. They could create a microenvironment that would allow tissue specificity of cell behavior. It's difficult to think that you could always start with a fixed genome and have each cell respond from within in so many different ways—imagine all these organs, let alone memory, vision, and smell. Over the years, we as well as others have shown that the extracellular matrix is an important player in regulating tissue or organ specificity. It seems to be one of the central regulators.

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Q: What constitutes the designer microenvironments that you talk about in your research? Has that idea changed over the years?

DR. BISSELL: When you put the cells in a microenvironment that is malleable and permissive to a certain tissue, the cells have a memory of organization and three-dimensionality. They recognize it, and they start behaving the way they're supposed to behave. They begin laying down their own ECM—basement membrane—which is now tissue-specific. In a sense, cells make their own designer microenvironments if you allow them to.

In the case of the breast, we use materials such as basement membrane isolated from an interesting mouse tumor or gels made of rat-tail collagen. We have defined what is around the breast cells *in vivo*, but this material is hard to isolate and gets denatured during the process of isolation. When we put cells together with these gelatinous substrata in three dimensions, the cells remember what they are supposed to do and they now make their correct ECM.

But my real ambition in the next five years or so—in collaboration with my colleague in Denmark, Olé Petersen—is to make an honest-to-goodness model of the breast in 3-D. That would require not only breast epithelial cells but also the other cell types that are around the breast *in vivo*. These cell types all talk to one another, and they each do different things. We have already nearly succeeded in making a replica of breast tumors in 3-D and have made recent advances with putting epithelial and myoepithelial cells of the breast together in 3-D.

We have limited ourselves to the study of the breast because we don't have the time to develop yet another designer model. But more and more, researchers are creating different models. I think that each tissue or organ will require a specific designer microenvironment, probably developed from different materials than we have used.

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Q: You're suggesting that the extracellular matrix tells the cell that it exists in a social environment with other cells?

DR. BISSELL: Correct. There is a social interaction between the cells and also in relation to the nucleus. The outside tells the nucleus what to do, and the nucleus tells the outside what to do. The signals go back and forth and change very rapidly and dynamically. That's why I refer to the concept as "dynamic reciprocity."

We need to understand this interaction in relation to every organ and tissue in the body. My colleagues and I know just a little about that interaction in the breast. Some people know a bit about skin, and others know a bit about brain, but really we all know very little. There is so much to learn, and the sequencing of the genome is just the very beginning.

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Q: What other disorders may be tied to change in the extracellular matrix?

DR. BISSELL: Generally, people think about the ECM in relation to cancer because it's easier to see how disorganization leads to cancer. But I believe that many kinds of disorders and diseases may be tied to misregulation of the ECM. There is, for example, a skin problem called epidermolysis bullosa. One type of this disease results from a mutation in one of the three genes for laminin, which is an important basement membrane component in various tissues. Mutation in these ECM genes can wreak havoc in different kinds of tissues and cause a variety of diseases.

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Q: Might that make the extracellular matrix a more advantageous target for cancer therapies?

DR. BISSELL: I wouldn't say that it makes it a more advantageous target, but I think that it is a very good additional way to attack cancer.

The ECM is not just one molecule; it is a collection of molecules that talk to their receptors, and the receptors in turn talk to the cytoskeleton and the nucleus to change the cell. Any of those molecules involved in signal transduction by the ECM are every bit as good a target for a therapy. In the past we have paid tremendous attention to growth factors and growth regulation, but we need to pay equal attention to those genes that determine organ specificity and structural specificity. The ECM is one part of cell regulation, and thinking about how the ECM can be part of therapy is very good. We now know that many growth factors need ECM signaling to function, so we must understand both kinds of signaling.

Let me make an additional point: We concentrate too much on the cancer cell itself. Often it's what is outside these cells that leads to genomic instability and mutation. For example, when your cells have the BRCA 1 and BRCA 2 mutations, why do you get only breast cancer and ovarian cancer? Why don't you get cancer of the skin? Why don't you get cancer of the gut? These mutations are in every one of your cells but cause only very specific types of cancer. Even with the breast cancer genes, not everybody who has a BRCA 1 or 2 mutation gets breast cancer. And even if you do get breast cancer, you get it in only a few cells.

What happens to the rest of the breast cells that are just sitting there? The breast cells, I think, are all poised to become cancerous sooner or later. Even if you don't have a primary mutation like BRCA 1 or 2, a drastic change in microenvironment can lead to mutation in the epithelial cells. In collaboration with Zena Werb at the University of California at San Francisco, we made transgenic mice that overexpress metalloproteinases in the breast to destroy the ECM. Those mice eventually got breast cancer.

Remember that there is a significant correlation

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between cancer and aging. Aging is an organismic-level phenomenon. As you get older, one of the most important things in your body that changes is the ECM's and cells' microenvironment. We get wrinkles because the ECM that is normally supple and allows correct signaling starts to dissolve. Matrix metalloproteinases, which dissolve the ECM, get up-regulated as you age. They disrupt dynamic reciprocity and create a situation in which the epithelial cells are poised to become unstable.

I argue that we should also be directing cancer therapy toward the field outside the cell. Is there a way to change the whole-field-effect of a tissue? Could we change the microenvironment so that another tumor doesn't develop? In terms of gene therapy, I think these are additional challenges. We have shown that we can revert malignant breast cells by manipulating ECM receptors on the surface of the cells.

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Q: Is there something fundamental about the role of the ECM, like the p53 gene, in causing cancer?

DR. BISSELL: I would say that the extracellular matrix and its interaction with its receptor could regulate genes like p53; in fact, there is some evidence for this from other labs. I think that everything is absolutely interconnected. When we do 2-D studies (on plastic) as opposed to 3-D, we find that a lot of genes get changed. The cells in 2-D express some genes that are not expressed in 3-D, and vice versa. We also find that many genes are modified when cells are grown in 3-D as opposed to 2-D. We have data to show that the ECM and its receptor affect cell-cell interaction—which in turn impacts the ECM and its receptor. Both of these things affect important genes within the nucleus, such as p53. They all work in concert.

I believe that cancer may be caused by a mutation of classical tumor suppressors, by a disorganization of the cytoskeleton, and/or by messing up the extracellular matrix. The result is similar, but the pathways by which someone gets cancer are different.

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Q: In other words, once a person gets cancer, the extracellular matrix may be tied to metastasis by allowing cancer cells to exist in microenvironments that differ from those in which they originated?

DR. BISSELL: Exactly. But I am saying more than that. Cancer can start by messing up the ECM and structure, but loss or change of the ECM is also involved in metastasis. For these cells to get out of their tissue, they have to travel out of their ECM, so extracellular matrix-degrading enzymes get produced. They eat up the ECM, and then the cells are able to move. This doesn't mean that tumor cells can't make extracellular matrix. Sometimes they make gobs of it, but they don't assemble it correctly. They make piles of it, but it doesn't know how to get organized. The process messes up the balance that determines tissue and organ specificity.

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Q: How does genomic science affect the work that you do?

DR. BISSELL: I use all the tools that genomic researchers are developing. All of the genes that are expressed by the mammary gland need to be cloned, need to be known. I didn't discover the metalloproteinases—other people discovered (and continue to discover) them and have cloned and sequenced them—but I use them as markers and tools.

As far as the study of the genome goes, I think of a lovely slide that I usually show at the end of my talks. It says, "Science is built of facts, as a house is built with stones. But a collection of facts is no more science than a heap of stones is a house." I say that a collection of genes doesn't define a particular tissue or organ, in the same way that a lot of bricks do not define a house.

Clearly, we need those collections of genes; we need to understand the proteins that are being expressed and the regulatory sequences that make those proteins carry out their function. My work is just another facet of the biology we need to do. The reason I've been perhaps a little too loud in the last 15 years is that 98 percent of the researchers are working to understand genes, and maybe 2 percent are trying to understand the extracellular regulation of cells. It needs to be 50-50 because both sides are important. We ought to be working together to understand the whole complexity of tissue specificity.

The imbalance is somewhat understandable because science, by its nature, needs to simplify. I do argue, though, that some of the ideas my laboratory is putting forward are not as complicated as they sound. If you isolate genes and then study them in isolation or under unnatural conditions, you make life a lot more complicated because isolated cells can give you misleading information. But if you put them in the right context, they give you the information that you want to know: how those genes and cells may behave when they are in your body. But, of course, in the final analysis you also want to study these regulations *in vivo*.

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Q: Are you worried about the ethical implications of human genome research? For example, once we have the power to test for the presence of genes like BRCA 1 and BRCA 2, how do you advise whether or not to be tested?

DR. BISSELL: At the same time that I'm a great advocate for human rights, I'm also a great advocate for freedom to seek information. No one should muzzle science. Knowledge is a one-way process, and you can't stop it. If people do decide they want genetic tests, then they should have genetic tests. If they don't want to have them, they shouldn't. As scientists, we need to educate as we discover. It's the same way I feel about abortion issues or fetal research. If we're not doing anything that infringes on the basic rights of another human being, we ought to be able to do it.

On the other hand, I do think that we need certain laws and regulations to prevent powerful people from taking advantage of this information. We also need to educate people about the pros and cons of genetic testing. Do you want to know whether you have a BRCA 1 or 2 mutation? If I had a mother and a grandmother and/or a sister who had breast cancer, I would get tested. Admittedly, the test is not always accurate. I would remind everyone that a number of people who have BRCA 1 or 2 do not get breast cancer—and even if you do get it, you can take care of it if you find out early.

I'm all for genetic engineering, but we need to make sure that it doesn't harm the environment. I'm all for finding out what kind of genes people have but at the same time educating them about what this information means. I'm also all for diversity. In other words, I think it's very important for people to realize that the implications of these things are not simple. We must preserve our creativity, diversity, and three-dimensional way of thinking.

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Q: Can laws to control the use of genetic information be effective?

DR. BISSELL: I don't see why not. If laws are created in consultation with scientists and the scientific societies, they could make sense and could work. If we end up with politicians telling scientists and society what to do, it's not good.

I'm not saying that scientists should run amok. They are like anybody else: They need to police themselves, and they need to exercise a certain degree of control. Science, like all other professions, has its portion of crooks, yet I don't think that scientists are unscrupulous. A lot of scientists are arrogant, and we are susceptible to the same kinds of problems as anyone else. It's just that if you're a scientist, in the same way as if you're a doctor, you have an additional obligation to try to uphold the truth, whatever that may be.

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Q: How does the funding system for a national laboratory impact your research?

DR. BISSELL: The way that biology is funded in national labs is different from how scientists get funded at the National Institutes of Health [NIH] in-house laboratories. The latter have their funding and salaries provided. This was never the case in national labs for biology. People don't understand that all of our funding, including the scientists' salaries, are on "soft money," so we have to constantly compete.

Also, most people don't realize that researchers supported by the Department of Energy [DOE] have contributed tremendously to some of the boldest ideas in biology in the United States. They are the ones who started the Human Genome Project. They are the ones who supported the first studies on DNA repair, which now has become a huge field. They are the ones who supported Bruce Ames when he developed the Ames Test. At the time, he couldn't get money from the NIH.

In addition, the DOE has developed a huge amount of technology that has come out of national labs. It has allowed individual scientists a degree of freedom to do what they like. I was fortunate enough to have run into a few men in the DOE who appreciated that I was passionate about what I was doing, and they felt that I was an original thinker. They gave me enough freedom to move a little in other directions. I am totally indebted to the Office of Biological and Environmental Research and to the DOE. I think the NIH is a magnificent and well-run system, but people don't appreciate how important it is in science to have multiple sources of funding. Without funding for bold research, creativity really gets stifled. Scientists and artists have a lot in common: Good scientists have an artistic streak, and requiring them to accept the conventional wisdom would stifle their creativity. Scientists should be encouraged to push the envelope.

Funding organizations ought to allow scientists some freedom to be able to explore things that are not fashionable. One of the worries I have about how biotechnology and biology get developed these days is that we kind of clone ourselves: You go to a study section and they say, "Oh, but you don't have the

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background," or "Your ideas don't agree with what's published. How could your ideas be true?" That's one of the reasons we should support the NIH as well as the National Science Foundation [NSF]. We should support the DOE's Office of Biological and Environmental Science, but also NASA's biological office. It's crucial in a free society that we don't rely on just one giant organization, even when it works so very well. I'm a passionate advocate of multiple funding sources. It's important for originality, and I'm delighted to see that the NIH now includes originality as a criterion for supporting research. Also, it is wonderful that people as prominent as Harold Varmus—the very successful and brilliant past director of the NIH—are now calling for doubling the funding also for the NSF and for the Office of Science of the DOE.

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Q: Let's turn to your own "developmental matrix." How did growing up in Iran shape your perspective about your career?

DR. BISSELL: People often ask me how a woman from the Middle East has been able to come to this country, go to Harvard, and be successful in creating and directing a huge division. I remind them that hundreds of thousands of women are out there who have done the most amazing things. The United States is full of such immigrants, but I think I have done what I have done precisely because I come from Iran.

When I was growing up, Iran was a class-divided society, very much like the old England. In fact, class was more important than gender. I was fortunate enough to come from a well-to-do and educated family and to have a stable background. Basically, I grew up telling people what to do and was encouraged to express myself. I was encouraged by my mother especially, although my father also expected us to have higher education and to achieve. Women of my family's class did exactly as they pleased because they had a "room of their own"! Women had children, but they also had servants, so they were more free to pursue careers and their own interests.

My sister does not buy this explanation. She says, "But you also were the top high school student in the country. You were number one in most or all subjects." But I think that thousands of kids out there could be top students if they had the same opportunities.

It didn't occur to me that I—or anyone—couldn't do what I did. I came to the United States all by myself, when I was barely 18. I had won a big scholarship and landed in New York. I went to college, got married, and had a child the first year of graduate school. This was 35 years ago, when only 3 of the 200 students at Harvard Medical School were women. Everybody immediately assumed I would quit. Maybe I was being naive, because I didn't realize how difficult things could be: I didn't have servants; I didn't have my mother next door; we were living on student salaries. But it didn't occur to me even once to quit.

People would say, "Of course you are quitting. What is

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your mother going to say?" You know what my mother said? She called from Iran and said, "You're not quitting, are you?" and she came to help for a few months. Now how many American mothers, 35 years ago, would say this to their daughters? They would make you feel guilty—they would say, "You have to stay home and take care of your kid." I'm not saying that people shouldn't do that. People should stay home and take care of their kids full-time, if they want to. But with my energy level when I was that young, if somebody had forced me to stay home I probably would have jumped off the roof. I probably would have driven my kids crazy. (I'm sure they thought I drove them crazy anyway!) I have a wonderful daughter and a wonderful son. Both are well educated and in good shape. They're now both married, and I'm a grandmother.

I had my daughter during my first year of graduate school, and my son the second year of postdoc, and I just continued to work. I never stopped. Now I look back and realize how difficult it was. I keep thinking, "How on earth did I do it?" But in the end it was worth it.

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FEATURED SCIENTIST

Mina J. Bissell, Ph.D.

Q: Even with all your energy, it must have been challenging to raise a family, earn your degree, and work all at the same time. How did you manage to give appropriate time and energy to each commitment?

DR. BISSELL: It was even harder because I was doing very unconventional science. That didn't help. I didn't have a regular mentor; I didn't have a club to which I belonged. At the time, I didn't know that what I was doing was so hard; I just didn't see it that way. Again, that's part of this whole background situation. People don't realize how much our background shapes us. Some very powerful men in science think I'm a little too outspoken, or that I say inappropriate things. Sometimes I wish I wouldn't say certain things to my colleagues, but it comes from my background. I was never punished for speaking my mind; I was encouraged. If I had been punished, I probably would have gotten so depressed that I would not have developed the same way. But cultural backgrounds play a big role in how people behave.

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"People don't realize how much our background shapes us."

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FEATURED SCIENTIST

Mina J. Bissell, Ph.D.

Q: How has being a woman scientist in the United States affected you? Has it been a detriment?

DR. BISSELL: Oh, it has. In my generation, being a woman really was a handicap in science. But believe it or not, I didn't recognize that until after graduate school. After my postdoc I got my first job here at Berkeley. I realized when I started the job that a male colleague of mine—who was younger, had fewer publications, and hadn't done half as much as I—had been hired into a better position with a much higher salary: He was my boss. I wasn't used to that kind of discrimination. I couldn't understand it, and the injustice of it really affected me. I looked at the situation and thought, "Huh?" Of course it made me angry and caused problems, because I can't be as creative when I'm dealing with anger. Nevertheless, I managed to move on. As I moved higher and higher up, things became more and more difficult. In retrospect, it could have been partly my fault—I may have appeared to feel entitled, which isn't right. But part of it was simply frustration.

But I think I lucked out in many different ways, partly because of sheer force of energy. Now I feel very grateful, and I'm sure I could have done things differently had I realized the cultural differences. I'm grateful to many people, including my current director at the Lawrence Berkeley National Laboratory, Chuck Shank; the people in the Department of Energy's Office of Biological and Environmental Research; and a few other colleagues across the United States who have been very supportive. Unfortunately, even though younger women may not have as much trouble, I do think that a lot of discrimination still goes on, even though people think it has been eliminated.

I'm pleased to see how many gains women have made in science, but I still see the difference between being a man and being a woman in the field. Very often, I'm the only woman in the room. In a lot of cases, I'm the only one who speaks up. And often, when I speak up too much, it causes trouble. Of course, men can also get themselves in trouble if they speak up, yet there is *still* a big difference.

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"I'm pleased to see how many gains women have made in science, but I still see the difference between being a man and being a woman in the field."

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FEATURED SCIENTIST

Mina J. Bissell, Ph.D.

Q: Do you think that any of the relatively new areas of genomic research are "friendlier" to women?

DR. BISSELL: Yes and no. People say, for example, "We have enough women in biology because it is the study of nature and is intuitive for women. We don't have enough women in physics because women don't think that way." I was surprised to notice years ago that some of the best physicists in this country are women of Italian origin, and I always wondered why so many brilliant female physicists come from Italy. Then I found out that in Italy, physics is considered a fine art. Men go into politics and finance, and women are encouraged to do math and physics along with painting and music!

I think our family's expectations as we are growing up have a lot to do with the career we end up in. It is my hope that the genomic sciences will remain more open to women. Diversity and different points of view are good for science. It's not just because 50 percent of this society is made up of women—I think that women do bring different insights to science.

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FEATURED SCIENTIST

Mina J. Bissell, Ph.D.

Q: You've said that you had difficulty choosing between pursuing chemistry or literature. Do you feel that you made the right decision?

DR. BISSELL: I think I did, although literature—and having taken what I believe was one of the best English classes this country had to offer, at Bryn Mawr College—has stood me in terrific stead. I still read a tremendous amount of literature. Colleagues ask where I find the time, but I read just before I go to bed. I love good writing. It's such a pleasure.

I eventually chose chemistry because I figured that I can read on my own but I can't study chemistry on my own. I'm glad I did science. I absolutely love what I do. My enthusiasm and love of science is what has carried me through all these years. It is like doing jigsaw puzzles and getting paid for it!

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FEATURED SCIENTIST

Mina J. Bissell, Ph.D.

Q: Is it important for scientists to study literature and take other courses not related to science?

DR. BISSELL: Absolutely; I think so. Scientists are not being taught enough social sciences or enough literature. These are very important subjects, and I think that a liberal-arts education is a very good background for scientists. Too many people are being trained to be straight-A premed students. They cram, but they don't become full human beings.

From time to time, we have scientific geniuses who are really weird and are social misfits. What we also want are creative scientists who can also be nice human beings and interact with society. This is one of the problems that scientists have: Often, they are not articulate enough to express themselves or speak to the public, or they don't care to do so. I'm delighted to see scientists involved in politics. Bruce Alberts, who is the president of the National Academy of Sciences and an inspiration in many areas, including science education, recently returned from Iran with the other two National Academy presidents. They went to Isfahan, where 6 out of the 12 members of the city council apparently were medical doctors. He said that this would never happen in the United States.

In societies like Iran's, scientists are revered. This year, even under the Islamic regime, Iranian women make up 60 percent of the medical school class, and the figures are similar in science, engineering, and architecture. We need more of that in this country. We need a marriage between politics and science, and we need multifaceted scientists. Fine arts, literature, and the rest of the liberal-arts curriculum should be introduced into science. It would help shape scientists' ways of thinking and allow us to better understand biology. The reverse is also true: Society needs scientific education. We must encourage our children not to be afraid of science.

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FEATURED SCIENTIST

Mina J. Bissell, Ph.D.

Q: Has your liberal-arts background made you more open to an "environmental" view of cells and their regulation?

DR. BISSELL: Absolutely. But at the same time, it's important not to be afraid of physics, math, and computers. It's crucial that we educate minorities and women in those areas, because it's easy to be scared of math, science, and physics. People need to overcome their fear of these subjects. But they need teachers who encourage them. I had wonderful math and physics teachers in high school, and some were bright and inspiring women.

Ultimately, society needs to create multifaceted individuals to think in multifaceted ways. But, we have to study science to understand the complexity of what we face in the new millennium.

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FEATURED SCIENTIST

Mina J. Bissell, Ph.D.

Q: The existing intense collaboration between industry and academia represents a huge change in the research environment since the early 1970s. Has the change been good for biology?

DR. BISSELL: In general, it's been good. In any case, we can't stop it. The part that worries me is what worries everybody else—that patent laws and secrecy affect researchers' ability to talk about their work. A lot of scientists say, "I won't talk about it until I can patent it," and they aren't as willing to share their research material. It's difficult to get information from companies. These attitudes can be harmful.

The good news, of course, is that [industrial-academic collaboration] has brought a lot of very intelligent and capable people into research. They realize they don't have to go to the stock market to make money: They can go into biology to make money! [*Chuckles.*] It also has created a bigger job market for biologists. We need to watch for the dangers and increase the benefits. Cooperation and interaction with industry is good, as long as it doesn't muzzle us too much.

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FEATURED SCIENTIST

Mina J. Bissell, Ph.D.

Q: Looking to the future, what areas of biology and genomic research should researchers be focusing on?

DR. BISSELL: Opinions vary, and some areas are rather obvious, but something I really would like to see emphasized more in biology—and in combination with genomics—is the science of imaging. It's important for people to really think about where genes are expressed. I want to see companies and universities paying a lot more attention to imaging because we will not understand the nature of tissue and organ specificity unless we know exactly the microenvironments of these proteins within the cells and tissues. I would like to see a combination of genomics and imaging being developed. That's another reason I'm in a national lab—it allows a multifacetedness that until recently didn't exist in universities.

I'd also like to see larger and more equal teams of people collaborating and bringing different disciplines together. At the national laboratories, biologists are working next to informatics experts, engineers, and physicists. We encourage multiteam investigations. This is the way of the future in biology.

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