Robert Barker/CU

CU

Barbara Baird
Chemistry and Chemical Biology
Nanobiotechnology Center

CU

Barbara A. Baird

HAVING A FRAMEWORK

A Search for Answers

How do cells respond to external stimuli? How does a molecular signal from the outside engage a cell surface receptor, and how does that cause the cell to respond? This is my research. I like to have a framework in which to think about a problem and to hang pieces of information from that framework as they become available. I start with what I know—with an idea or reasonable explanation about how a system works. As I get more information I change the idea so that it becomes consistent with the information. If I see that the framework really isn't the right one, then I adjust it. This is what science is: trying to figure out how things work. It's rarely a linear process, in which one problem is solved and then the next one. Information comes from every direction—biological and physical. The work in my lab is highly interdisciplinary, and we try to understand how all the pieces fit together.

Take our work in immunology. We study the cell surface receptor involved in the allergic immune response. An allergen triggers an allergic reaction by engaging the receptor. This initiates transmembrane signaling, which causes the cells to respond. The cells degranulate to release histamine and other mediators that cause the allergic reaction.

Cells and stimulated inflammatory responses are involved in this process. Similar receptor-mediated responses occur in other cells in the immune system and throughout physiology. What fascinates me about this problem is that it's a very general problem, and yet I can zoom in on a single type of cell, a single receptor, and begin to solve it in a very detailed way. As I move in from the angle of the medical problem or the cell biology problem, I come very quickly to where I want to address the problem at the most fundamental molecular mechanisms. We know that receptors are distributed over the cell surface. We know that when a particular molecule engages from the outside, a signal has to get across the membrane. How does this happen? How do we explain all the processes in terms of the participatory molecules? We are searching for how the signal gets across the plasma membrane and through the cell.

We use a variety of measurements to get information. The approach that has continued to be very helpful is fluorescence. Fluorescence microscopy enables us to see tiny amounts of labeled components in a complex environment, which is the situation with cells. For example, we label the receptors with fluorescence and observe how the fluorescence redistributes when we add the stimulating molecule. Prior to this addition

there is a uniform distribution, and afterward the receptors bunch up into clusters all over the cell surface. What is the underlying mechanism? When we labeled other molecules on the cell surface, some of them bunched up together with the receptor and some didn't. This provided evidence that the stimulating molecule affected not only the receptor itself, but also other components within the plasma membrane in a selective way that initiates the transmembrane signal.

WE STUDY THE CELL SURFACE RECEPTOR INVOLVED IN THE ALLERGIC IMMUNE RESPONSE. AN ALLERGEN TRIGGERS AN ALLERGIC REACTION BY ENGAGING THE RECEPTOR.

This is enlightening because it says that when we begin to engage a cell surface receptor, other parts of the cell become part of the process almost immediately. This tells me, the biophysical chemist, that if I really want to study biology and molecules in biology, I can't take a key molecule out of its natural system. Even if we can learn the details of biomolecular structure or the function in isolation, we can't really understand how it's working within the cell unless we look at it there.

Our studies make us realize that we have to help develop tools that enable us to look at molecules within a living cell. I want to answer many debated questions about the cellular process we're addressing, but I also want to help develop techniques that will enable this process.

Suffering with Allergies?

My mother puts the question to me this way: "What are you doing for the taxpayers?" Most people can relate to allergies. I explain that the very fundamental basis of allergies comes from cells that release histamines causing allergic reactions. If we can understand well enough how this works, then we can help in the development of a drug that can prevent it at the initial stage rather than treating the symptoms. Current antihistamines, for example, have side effects. That's because they may be hitting the target, but they're hitting other components as well. As we know the system in greater detail, we can offer more precise treatments to replace drugs that cause drowsiness or other secondary responses.

Putting the Pieces Together

Constructing a framework to understand a cellular process is a very deliberate, rational exercise. What are the facts? How can we put them together so that they can best explain what we see? How can we bring in more facts to fill the gaps? Not everything is going to be right, so we sort through the data and hang the facts on the framework and continue to develop it. Sometimes we have an experiment that was done for a different purpose, and it gave us information that we didn't understand at first, but suddenly it helps to explain many other things that are hanging on the framework. Things click into place, and we can take a jump rather than proceed in an incremental process. These experiences are some of the most delightful to have as a scientist.

An area of research like this can't be done in isolation. The whole cellular system is too complicated. We can't do all of the experiments, so we must be aware of other work published in this and related fields and how that work relates to our research. We talk to other scientists. Many of our experiments depend

on collaborations with other experts. Collaborative research has been a source of success and great enjoyment in the kind of science my lab does. Getting input from other sources forces us to try different perspectives—to view it as an engineer or as an immunologist. Taking a variety of approaches is part of the fun.

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To Kindle Insight

Most scientists always have their scientific problems in the background, regardless of what we're doing. Sometimes insight comes from something else we're dealing with, thinking about, or doing. Music is an example. It relaxes the mind, particularly when bearing down on a problem and trying to put the pieces together. Nature is another example. Anything that lifts and relaxes one—anything that takes the knot away—allows one to go back to the problem in different way. It's important to me to have opportunities to stand back and not always work directly toward solving a problem.

Teaching provides a different opportunity. An academic scientist is forced to examine the ideas, examine the presentation, and ensure accuracy and coherence, so that the subject is conveyed in a way that students can understand it. It's easy for me to know what I'm thinking, but in teaching, I have to communicate these thoughts. With coworkers I can be less precise because they already know what I'm talking about. Students may be facing this material for the first time, and I want to give them information and ideas in the clearest way I can.

From Lab to Center

I'm a faculty researcher, and I'm director of the Nanobiotechnology Center, a science and technology center supported by the National Science Foundation (NSF). The combination brings a wide range of scientific problems to me. In my research lab, our problems are related to the big picture of how molecules interact in the context of a cell. However, there are many aspects surrounding this general problem, as well as many other parts of a cell that we try to work on. There are not only structures, but also dynamics and specific functions that are involved. We want to understand how this all fits together. We have about 10 ongoing projects in my lab. More than half of these are collaborative with researchers outside my lab, who are often involved in new techniques that we can apply to our research.

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Then there's the set of problems that goes with the center—some are administrative. The enjoyable part of being a center director is experiencing other people's research without being directly involved. I'm able to see how other researchers approach problems. Because I continue to think about my research area, I can see how it may impact what others are doing and vice versa. There may be a new technique that I can apply or a new concept that may be related to what my research group is doing. There is a definite reward in being exposed to and thinking about what other researchers are doing, whether or not it has any direct bearing on what we do in our lab.

When I present what's happening in the center, I'm often presenting other people's research. I have to understand their research well enough to be credible. When I represent the center, I'm representing individuals who are wonderful scientists and engineers. So I put a lot of effort into understanding their research. Because I like to think about scientific problems, this is a rewarding experience.

A Passion for Science

I have an innate drive as a scientist to figure things out, to understand the pieces and how they fit together, and then appreciate how they work. I'd be happy just thinking about these things; it's satisfying. Digging in and understanding them, I become aware that with the knowledge, I can do research that may help society in some way.

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A Fascination with Cell Biology Problems

I'm most proud of our steady advance in our research area—bringing a physical characterization to complex biological problems. This perspective isn't prevalent on the biological side.

My husband, David Holowka (senior scientist), runs the lab with me. He brings a different perspective and a healthy tension that can be energizing. By training he's a biochemist, and I'm a chemist. Both of us are fascinated with cell biology problems. I try to make a problem as simple as possible—to narrow it down to a few parameters to understand. His inclination is to put it in a biological context. He can't forget that there are other factors playing a role, even though this makes it messier and more difficult to approach.

A Discovery Is Made

There are many chemicals in the cell providing an amazing number of functions, and somehow the cell has to be able to regulate those functions. It does so by taking advantage of the cell structure and dynamics. We discovered the important role that the plasma membrane plays in receptor-mediated signaling: regulating the signal and providing a target. It wasn't a single eureka-type moment, although there was some of that feeling. It was an accumulation of knowledge from our lab and other labs, which began to fit together and point to this role of the plasma membrane, starting with simple observations and building on them. It was recognizing the role that the membrane structure plays in organizing functional components of the cellular response.

The plasma membrane can form domains or compartments. Compartments allow selection, and they provide a target. When receptors are engaged by an external signal, they gather with molecules in the plasma membrane. Once a compartment is formed, certain molecules can go in, and other molecules go out. The ones that go in are the signaling molecules. When key molecules are accumulated, they build on themselves, and what results is a combination of regulation and targeting. The concept helps us to understand how signaling proceeds, in many cases, with various types of receptors and molecules. It provides an explanation for how pathogens are able to infect cells. They hijack the same processes. Once we have this understanding, then we can apply it. We can learn about the molecules involved. We can find a way to prevent the process or enable it, if it's not happening properly. We can ponder the concept: if that's how a cell does it, what happens if we put these same kind of molecules together? Perhaps we can make a new, highly tunable device—a sensor and actuator.

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Challenges and Frustrations

Challenges are positive, but frustrations are discouraging. Our frustrations as scientists come when we're so discouraged from continuing our work by outside sources that it's very hard to keep going. If we can't get grant money or if our papers aren't accepted by critics, we might begin to think, what's the point? It takes external and internal resources to do research. I am very grateful for the support my research group has received from the National Institutes of Health (NIH) over the years, and I understand our obligation to use this money well.

The challenges are the juggling and the balancing. Academic scientists are committed to many responsibilities, including research, teaching, and often some type of administration. To any one of them, we'd like to give 100 percent of our time, but we have to balance our time, and that's challenging. At the same time, we need to accept it, but it's difficult to know how to get it right. However, there are some good things that come out of this. For example, it forces us to change our perspectives, and when we do, all of our responsibilities are enriched. As we move from one thing to the next, a role we play in one area gives us a perspective that's helpful in the other areas.

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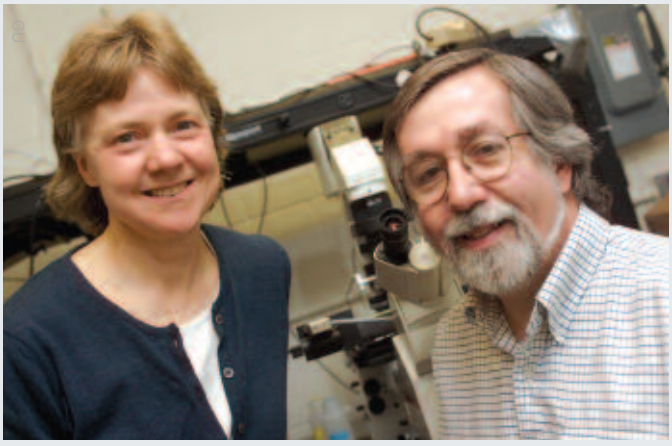

Barbara Baird and graduate student Stephanie Hammond

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Science from Start to Finish

It seems as if science has always been with me. I had many positive influences early in my life. Although my father was a lawyer and my mother was a nurse with an interest in the social sciences, they appreciated problem-solving skills—going after a problem, being challenged, not giving up, and feeling rewarded by the hard effort that led to a good outcome. This was pervasive in my family. We also enjoyed exploration as family vacations.

I had good teachers in grade school, who offered challenges. I had an excellent chemistry teacher in high school. I also participated in programs sponsored by the NSF that enabled high school kids to go to college campuses for the summer. This offered adventure away from my hometown, and I enjoyed the intellectual aspects as well as the fun aspects.

Physical chemistry in college motivated a greater passion in me to understand things. Material that seemed very difficult suddenly became understandable after I spent time thinking about it. I realized that this is the subject, this is the approach, and this is the set of tools that I enjoy.

I also had an interest in biology, but in college, it wasn't a pleasant experience. In those days it was a lot of memorizing and a lot of competition among the premeds. By the time I rediscovered biology in my senior year, I had studied a good amount of chemistry and had the perspective of molecules and how things work together according to a plan or an equation and how they could be quantified to make predictions. This is when I clicked with biology. I could approach biology in this way.

A Framework Outside the Lab

My family is absolutely most important to me. My husband and I run a lab together, and this has worked well for us. We are fortunate. We have three sons: two are twins, now juniors in college, and the third is a sophomore in high school. We also have a couple of dogs. Our household can become rather chaotic when everyone is home. Although science is my work and my hobby, I like to take moments to step back and enjoy other things. I enjoy being outdoors and all the things I can do outdoors: walking, riding a bike, swimming. I like physical activities to relax the mind and to stay heathy, and Ithaca is a wonderful place for intellectual and outdoor activities.

WE DISCOVERED THE IMPORTANT ROLE THAT THE PLASMA MEMBRANE PLAYS IN RECEPTOR-MEDIATED SIGNALING: REGULATING THE SIGNAL AND PROVIDING A TARGET.

WE CAN PONDER THE CONCEPT: IF THAT'S HOW A CELL DOES IT, WHAT HAPPENS IF WE PUT THESE SAME KIND OF MOLECULES TOGETHER? PERHAPS WE CAN MAKE A NEW, HIGHLY TUNABLE DEVICE—A SENSOR AND ACTUATOR.

If They Try a Little Bit Harder

Teachers, especially in the early grades, are crucial to raising children's curiosity about science. K–12 educational activities are a very important part of the Nanobiotechnology Center. Our program, collectively called Main Street Science, is led by a wonderful education team here in the center, and they interact effectively with the local community. By engaging kids in an enjoyable way, we can excite them about science. Sometimes we have to entertain kids to attract them and keep them involved. We also have to help them understand that to really enjoy it, they have to work a little bit harder, and the harder they work, the more they get out of it.

From Girls to Women

Girls are no different from boys in abilities. It may be that girls have more distractions, especially in the middle and high school years. Those are the years that draw children, particularly girls, away from subjects such as the sciences. Our Nanobiotechnology Center offers science clubs for middle school students and summer internships for high school students. We also have many other activities to engage these groups. This is consistent with the mission of the NSF, which supports the center.

The other tough period for young women is after graduate school or postdoctoral studies. We've made tremendous advances in the number of women in science graduate programs. Our Department of Chemistry and Chemical Biology is an example; we have a good percentage of female students in the department. But the number of those who go on to faculty positions drops off dramatically. Again, there are distractions. An important factor is family, and there may be other opportunities that lead to career satisfaction without the grueling lifestyle of

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Barbara Baird and graduate student Alexis Torres

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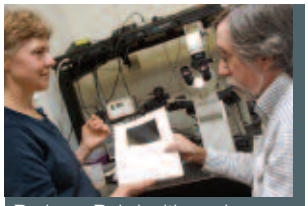
academia. Putting these factors together makes it harder, and the rewards may not be big enough for women in academic science. We need to figure out how to get around the barriers.

The key is flexibility. Let women, and all individuals, have the flexibility they need to do the best job they can. They will be driven by their own passion for their work. When someone gets to a faculty position, no one has to drive or push him or her to work. It's what they want to do. What is important is to give them the means to do it the way they need to do it. For women, that often means flexibility in working with their families and children. This is one reason that working with my husband has worked out well for our family and our department.

Getting It Right

We must be committed to communicating with the public about our research. What is the gain? What is the potential? At the same time, we must convey that most scientists are very concerned about conducting research in a way so that we address appropriately other unintended consequences that might result from our research. We also have to convey the effort it takes to make progress. Things don't happen overnight. Research is a lot of people working very hard; it's difficult work. We have to continue to draw the public into the process of how we do science, the potential rewards, and our concern for getting it right.



Barbara Baird with senior scientist David Holowka

The Proverbial Onion

In my research, the cell is like the proverbial onion. There are many layers that we need to understand, and we have a long way to go. Think about the progression that I've described: the molecules that directly interact and how they engage other molecules in other parts of the cell, and ultimately how that cell contributes to the tissue. Clearly there are many medical implications. Although my current focus is on the fundamental science, I am interested in how the research translates and in communicating more directly with the people who deal with the medical aspects. Communication, back and forth, is very helpful for both sides. I also feel a responsibility to help develop the technology. The challenges associated with understanding and intervening with biological systems are so difficult that, in addition to interdisciplinary collaborations, we need new techniques that are yet to be developed.

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For more information:

E-mail: bab13@cornell.edu
Website: www.chem.cornell.edu/bab13