Perspectives on Research

jur interviews David Goldfarb, Ph.D.

Dr. David Goldfarb, Professor in the Biology Department and a respected cell biologist discusses some of the oft-ignored, nontraditional aspects of a career in basic research, and the role of undergraduates in his laboratory.

jur: What kind of research are you involved with?

Goldfarb: I lead a group of molecular cell biologists. We are cellular mechanics who study the thousands of different parts in a cell and how they work in concert to facilitate various processes like energy production, motility, and replication. Most of the processes we study are fundamental—they occur in all animal and plant cells—but are somewhat esoteric and virtually unknown to non-aficionados. These processes are more complex than a series of linked chemical reactions, which might involve the concerted action of several proteins. The functioning of an automobile engine is an example of a cell-like process: the engine makes the car go. What makes cells move? Thousands of papers have been published on this one question. Like an engine that contains many parts, most cellular processes involve a large number of individual parts, most of which are proteins. Some of these proteins are structural, like a chassis. Other parts are functional, like pistons, and still others are regulatory, like gas and brake pedals. Processes also occur between different compartments in the cell, by analogy to the passenger compartment and under the hood. But cellular parts are very small—about 100 million times smaller than an engine—and are mixed together in an aqueous solution with thousands of other parts. Most proteins are exceedingly delicate, so they are easily damaged during experiments. Many proteins have lifetimes on the order of minutes or hours before they are degraded and replaced. Cells are dynamic entities. The cell body is continuously turning over and renewing itself. I think cells are better viewed as shifting patterns, like a waterfall, rather than static objects, like an engine. This, I think, is a beautiful concept: the cell is a paradigm of impermanence.

A typical task for cell biologists is to identify and catalogue all the parts that contribute to a particular process. While many of our working hours are spent identifying and characterizing the parts, we also enjoy guessing how the entire process might work. Processes begin as black boxes sometimes we have but a few pieces of the jigsaw puzzle to guess from. The job is analogous to giving a group of 18th century mechanical engineers the fuel injector and catalytic converter from a late model car and asking them to explain their function and the nature of the machine they belong to. Needless to say, I am really impressed with people who claim to be able to reconstruct an entire dinosaur from a single neck bone or tooth. So, you might imagine how satisfying it must be to figure out anything at all about cells. Some of the motivation comes from the fact that the questions we ask need only be solved once in the history of science, or at most a few times if different labs are working independently on the same project. It is rewarding to be the first person who discovers even the most trivial fact of life.

I will admit to being something of a mystic. I believe that the cells we study harbor mind-boggling secrets; if you read the journals you know this to be true. Moreover, every new fact induces a subtle shift in our conceptual landscape, changing our perception of the cell and ourselves. This is a process as slow as molasses, but it flows inexorably forward. This is why biology is a nice field to grow old in. Perspective helps.

jur: Aside from the personal rewards that come from solving these extremely difficult problems, why is it important to study cell biology?

Goldfarb: The ‘biomedical’ answer is what my parents and relatives want me to give them when they ask, “What is it good for?” Over the years our research has been funded by agencies like the American Cancer Society, March of Dimes, and National Institutes of Health, whose missions are to prevent or cure human suffering. Lucky for me, these agencies appreciate that gaining a basic understanding of how healthy cells and bodies work is an important part of reaching these goals. Any (good) automobile mechanic knows it’s next to impossible to diagnose and fix a sick engine if you don’t know how the darn thing is supposed to work when it’s healthy. This is not to deny the utility of time-tested empirical approaches to both medicine and mechanics: “Eat this root, it helped me,” or “Kick the tire and bang on the hood.” But I don’t know of any other way than the scientific method to elucidate cell mechanisms. There is no empirical approach to understanding vesicular dynamics. A strong suit of science is its calloused willingness to destroy our most beautiful and cherished ideas. The physicist Richard
Feynman said, “Science is the art of not fooling yourself.”

So, the study of basic cell processes is important because it benefits the work of biomedical and medical researchers and physicians. Although cell biology is partly a game or just a career for some people, it is ultimately a compassionate endeavor, at least in my opinion. We can track these benefits by using a web-based tool that displays all the publications that reference our papers; such citation records provide interesting insight into the 'life' of a result. Back in 1993 we published a paper with another group that explained how HIV-1 gets into the nucleus to do its dirty work. As of this week, the most recent of 454 papers to cite the HIV-1 study is titled, “Lentivirus-mediated gene transfer to the respiratory epithelium: a promising approach to gene therapy of cystic fibrosis.” Who knew? Another of our papers also published in 1993 has been cited 154 times, but only by other basic research papers. A 1997 paper on the evolutionary origin of certain proteins—it doesn't get more basic than this—has been cited 60 times, most recently by a paper titled, “Nuclear transport and cancer: From mechanism to intervention.” So it goes.

There’s something else to say about the HIV-1 paper, though. Our contribution to that paper was technically and conceptually relatively trivial compared to our core research efforts, but the result attracted radio and television attention. I appeared on the 10 o’clock news and was interviewed on local National Public Radio. One caller challenged me to defend the charge that the US government was using the AIDS virus to attack African American communities. I wish I had been better prepared. The important point here is that this ‘trivial’ but relevant result could not have been discovered had not we and many others been sequestered away for years with our little tubes and pipettes, like monks in their monasteries performing esoteric rituals. Behind every headline proclaiming this or that shortcut, some people, it is ultimately a compassionate endeavor, at least in my opinion. We can track these benefits by using a web-based tool that displays all the publications that reference our papers; such citation records provide interesting insight into the ‘life’ of a result. Back in 1993 we published a paper with another group that explained how HIV-1 gets into the nucleus to do its dirty work. As of this week, the most recent of 454 papers to cite the HIV-1 study is titled, “Lentivirus-mediated gene transfer to the respiratory epithelium: a promising approach to gene therapy of cystic fibrosis.” Who knew? Another of our papers also published in 1993 has been cited 154 times, but only by other basic research papers. A 1997 paper on the evolutionary origin of certain proteins—it doesn't get more basic than this—has been cited 60 times, most recently by a paper titled, “Nuclear transport and cancer: From mechanism to intervention.” So it goes.

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happy that my group can do interesting work without harming (many) laboratory animals. We stopped using frogs, mice, rats, and rabbits over a decade ago. We had a holdover from those years, a pet *Xenopus laevis* frog. She died a few weeks ago at the ripe old age of 13 years, and she has been replaced with one we rescued from the experimental tanks on the third floor.

My general guideline is to avoid experimenting on animals with nervous systems. It used to be “animals with faces,” but I thought that made a mockery of a serious situation. Recently, a student in my lab had good reason to work with fruit flies, so we ended up killing lots of them. I can rationalize using flies, even though I know they have lives too. One recurring problem is that we can’t get all of our work done without using antibodies raised in rabbits (antibodies are sometimes raised in hamsters, mice, chickens and even goats). These animals suffer and ultimately die during the production of antibodies, so I am mindful of where our antibodies come from and try to use them judiciously. So I do break the rule. There is a disconcerting amount of blood, sweat, and tears in research aimed at reducing suffering.

*jur*: Was there some particular event that made you decide to stop using animals in your research?

Goldfarb: The decision to stop using vertebrates in the lab was influenced by events long ago. My very first day in a research lab as a freshman at the University of San Diego included watching the beheading, with a nifty miniature guillotine, of twenty or thirty mice. The objective was to harvest fresh pituitary glands, which were plopped unceremoniously into liquid nitrogen. I still remember the odor associated with the slaughter, and the memory still evokes the repulsion I felt when I saw their heads gasp for air. I also remember being ashamed at being repulsed. Later, during my senior year, I made a huge gaffe and accidentally put 200 mice in rat cages. The bars were too widely spaced to contain the mice. During the night many of the mice escaped their cages and had a big party in the animal facility. By morning there was no way to tell which mice belonged to which group. The project was ruined, and it fell to me to euthanize all 200 mice by CO₂ asphyxiation. This episode affected me deeply. For this and other reasons (including lessons learned from shooting at animals and the influence of positive relationships with cats, dogs, and horses) I no longer eat anything with a nervous system.

*jur*: Since your interaction with undergraduate research tends to be through students in your lab, could you tell us about undergraduate research in the laboratory context?

Goldfarb: There are a number of good reasons for undergraduates to work in a real research lab. One of the good reasons for coming to the U of R is the opportunity to experience world-class research firsthand. Research is how we learn in the sciences and it’s also useful in the arts. Lab courses are one means we offer students to experience lab work, but some wish to go further. Even a brief apprenticeship in a lab can be a transforming experience. For some, it becomes clear after a few weeks that they are either not cut out for, or not interested in research. This is good to know. Others discover a love of the work and never look back.
I have no hard and fast rules about who gets to come into my lab. In my junior year at UCSD I was interviewed by Jonathan Singer for a position in his lab. Dr. Singer is famous for the fluid mosaic model of biological membranes. I remember him looking directly at me from across his vast desk and pronouncing that he saw nothing exceptional in my record. There was no place for me in his lab. That was a healthy dose of reality. Instead of climbing back down my hole, I joined the lab of Katsumi Miyai, who was less judgmental, but still a very serious scientist. I published my first paper in his lab. Now that I am the one sitting behind the desk, I don’t always look for something exceptional. Still, the students I invite into the lab usually do impress me with some personal quality, such as motivation, excellence in areas outside of school, or simply an engaging personality. However, there has to be evidence of an innate seriousness. Paradoxically, a goofy student can still be dead serious. Taking students with good grades—at least a strong ‘B’ average—is important for two reasons. First, there is a correlation between performance in coursework and performance in the lab, and it is fair to give students who have a future in research a chance. Second, students who are struggling with their classes usually cannot afford the commitment needed to work in a lab. However, there are exceptions; in fact I was an exception. Paul Saltman at UCSD invited me to work in his lab at the end of my freshman year because I was struggling with my coursework. His lab, which was a very supportive environment, helped me to gain a lot of confidence. With this new measure of confidence I found myself better able to invest in studying, since there was now hope for a good outcome. Because of this experience I periodically accept students who are struggling with their coursework. I have read or heard a lot of like-minded parables about horses or calligraphers or sons or daughters that attest to the deeper understanding or greater accomplishments of those who struggle in the beginning. Being truly gifted is not a ticket to success in research. Analytical skills never hurt, but they are neither sufficient nor necessary. Intangibles like showing up to work with eyes and ears open are the aces up many students’ sleeves. I have come to believe that a person’s unique personality is just as important in research as their intelligence and motivation.

jur: What are some of the obstacles that you face in your lab, and how do these affect undergraduates in particular?

Goldfarb: Students who enter the lab soon discover that it is not for the faint of heart. My lab has always been a pretty intense place; we are not fooling around. Those who enter the lab with the sole intention of adding to their resume or getting a recommendation rarely last very long. The work has to be intrinsically important to the student, which is something that cannot be manufactured. Persistence in the lab is a self-selecting trait. When things are not going well I might remind the student that “we are struggling with the beast.” By this I refer to the sensation that our yeast cells almost maliciously resist giving up their secrets, that they are designed by a greater power to be recalcitrant. Cells are extremely subtle entities. We can’t directly experience the inner workings of cells, so we need to develop sophisticated and imperfectly indirect methods. You should see some of the microscopes we use these days. We also develop our own cell-based assays. There are no kits for what we do. We usually start using these assays before the kinks have been removed, and sometimes even before we have the correct equipment for the job. There is no time to wait, since we really need to know the answer. Bailing out a boat with a sieve can be done, but it takes commitment.

I think it is also very important to note that having undergraduate researchers in my lab is great for me, even though undergraduates sometimes have trouble accepting how often, repeatedly, and miserably we fail. I have seen many students who couldn’t deal with this reality. The quality of falling down, picking oneself up, falling down again, and picking oneself up again is a regular experience for most people, at least in my lab. I believe this is the experience of anyone who strives to achieve excellence in any field. Many of our top undergraduates sail through their coursework and expect their independent research projects to be the same. Sometimes they are. Sometimes the project and the student just click and nothing could be easier. This is rare. But everyone eventually hits some kind of wall, and often they hit it hard. It takes a strong ego-structure to survive in the lab long-term. Maybe students are ultimately attracted to independent research because it feels real, it is real. An extremely gifted teacher of mine once signed a book of his over to me with the lines, “If not you, who? If not now, when?”

Further Reading List:


