People & Ideas

Louis Reichardt: The long climb to science's summits

From the highest mountains to biology's own Everest—the brain—Reichardt tackles the biggest challenges of climbing and biology.

Louis Reichardt's scientific career has spanned the simple and the complex. As a graduate student, Reichardt helped to uncover the now renowned DNA regulatory mechanisms that allow one of the simplest life forms, lambda phage, either to hide within a cell or to make its presence known via massive replication (1).

Letting his curiosity for the unknown guide him, Reichardt then forayed into a much more intricate system, the brain. As a postdoc, he showed that growth conditions influenced which neurotransmitters are synthesized by isolated neurons (2). Later, as a professor at UCSF, he discovered synaptotagmin, using the first monoclonal antibody that defined a synaptic vesicle membrane protein (3), showed that expression levels of nerve growth factor in target tissues correlate with the density of innervation (4), and characterized the properties of mice lacking genes encoding the neurotrophins and their Trk receptors (5, 6).

Now a professor and director of the Neuroscience Program at UCSF, Reichardt's laboratory still studies the interface of cell biology and neurobiology, including the involvement of cell adhesion molecules in synaptic development (7). He explains that science is not so different from his favorite hobby, mountain climbing.

THE CALL OF THE MOUNTAIN

Your Wikipedia page describes you as a noted mountain climber, who, by the way, is also a scientist. Tell us about your trailblazing climbs.

Well, we had the opportunity to do some things that hadn't been done before, so, as in science, you grab them. That was at a time, in the late '60s to early '80s, when things were much more remote, so these could be long trips; on our successful Everest trip, I was gone for two and a half months.

For Everest, Richard Blum—California Senator Dianne Feinstein's husband—had gotten a permit and asked me to be involved. I did a little reading and realized that nobody had even visited the east face of the mountain since 1921, and it had never been climbed. There are some wonderful words of George Mallory's in a 1921 book describing the route. The gist of it was, "Others more foolish might try this, but it was not for us." When I realized that, I thought, "We'll obviously have to try it."

If it's there, you have to climb it?

It was clear we were going to be the first group the Chinese let in to do this sort of thing, so we should try something that was new and different. But we did not have very good pictures of the mountain, and when we arrived, half the team just wanted to go around to the north side.

But we had Edmund Hillary in the tents telling us, "Well, of course you could do the north side, but it would have no significance." We actually got up what I'd call the difficult part but didn't go on because we had terrible weather. People were clearly very scared. When we went back two years later in 1983, it was an El Niño year. In Tibet, that means a drought, so we did not have any of the problems with storms, and it went remarkably smoothly. Nobody's gone back to repeat that route since.

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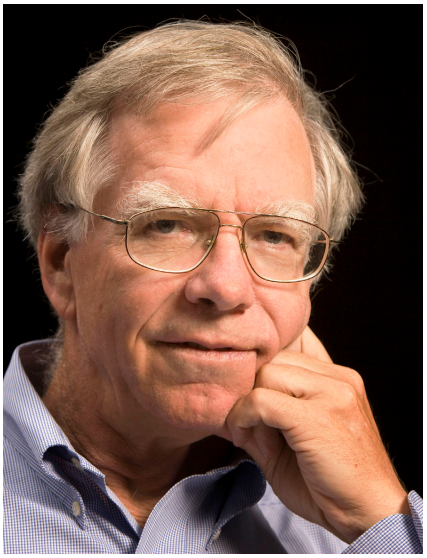
How about the K2 trip?

I think at the time we went, there had been six previous unsuccessful American expeditions to K2, and there was a history of sagas and tragedies. The Italians came in 1954 and knocked the thing off, which annoyed everybody, with a huge expedition of about 100 people. So, when we went in '78, we felt like we really needed to do it.



Louis Reichardt

That involved a lot of politics. Jim Whittaker had been turned down by the Pakistanis, but he knew Senator Ted Kennedy quite well, who intervened with the Prime Minister, Ali Bhutto, Benazir Bhutto's father. By the time we arrived, Bhutto was in jail, and the Pakistanis didn't really want us.

They said we could only come in the summer, which is the worst time. So we were there a long time, 68 days at or above our base camp. We got very lucky at the end, had a few days of good weather and were able to climb it. But my buddy stayed on the summit longer than I did and ended up extremely sick. In the end, he had to get carried out.

There's actually a play inspired by this expedition, which describes two guys on a ledge, one of whom is a scientist and the other a lawyer. Depending on the end of the play, they either both die on the ledge, or one guy walks off. [Laughs] Actually, it's a very good play; it won a Tony Award.

Do you see a link between climbing and science?

Yes, a lot of my friends who are serious climbers are scientists, particularly engineers or physicists, more than biologists. I think it's because each involves solving problems. Climbing a route is in some ways like designing an experiment.

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And there's a lot of focused energy and intelligence in making decisions in climbing.

A CULTURE OF DISCOVERY

How did you get interested in science?

I went to Harvard for undergrad, and I think it was this combination of hearing some very exciting lectures about what was going on in molecular biology—it wasn't many years after people realized mRNA existed—and books coming out, like C.P. Snow's *The Two Cultures*, which were very influential. And it was the time of Sputnik. So you felt science was really important. Even now, biology and astrophysics are still the two really exciting areas, it seems to me.

> "Climbing a route is in some ways like designing an experiment. Each involves solving problems."

Why does biology appeal to you?

Because biology is something that you can actually do yourself.

Astrophysics is incredibly exciting in terms of what people are learning about the origins of the universe, but the truth is you can't easily do an experiment. I think you must have to be a better politician than Barack Obama to get time on one of the big telescopes. In biology, a graduate student can make a discovery just by thinking about something and doing a cool experiment. You go to the bench and find out something about how you form a limb, the brain, etc.

Where did you go after Harvard?

For my graduate work, I went to Stanford, which was very influential; the biochemistry department was the center of everything. Arthur Kornberg had discovered DNA polymerase; Dale Kaiser and David Hogness were working on phage lambda.

Lambda was the model developmental system, in a sense. Once it infects bacteria, it makes this simple decision: kill the cell and make tons of phage, or integrate and stay along for the ride.

My advisor, Dale, got the Lasker Award, in recognition of work by a graduate student I shared a bench with, Peter Lobban, who used enzymes purified at Stanford to link pieces of DNA together, starting modern molecular biology.

For my thesis, I purified the lambda repressor, made good antibodies and used these in assays to measure the lambda repressor levels. Once you had a way to measure repressor, it was very simple to figure out what all of our mutants were doing. It was a beautiful story—two promoters and a repressor stimulating its own synthesis—a model network for a binary decision.

SCALING SCIENCE'S HEIGHTS

How did you get from such a simple system to the complexities of the brain?

At that point, the faculty at Stanford were beginning to look for new pastures: Paul Berg went into tumor virology; David Hogness became interested in *Drosophila*; Dale Kaiser switched and ever since has worked on myxobacteria; Arthur Kornberg was also very interested in membranes. I think we all felt since our professors were doing this, we should too. And if you wanted to branch out, to go as far away as you could, the brain was the perfect place. [Laughs] It was kind of crazy, but I think I assumed that development would be just "lambda squared."

And are there similarities?

It's similar in the sense that there are circuits; when you go down one path, you reinforce mechanisms for either turning on or off a particular gene. That's basically what happens with lambda—you have an unstable circuit and the organization of the circuit forces you in one direction or another.

For your postdoc work, you ended up back at Harvard?

Harvard had the first department of neurobiology, founded by this amazing, creative person, Steve Kuffler. It was a remarkable and a very self-centered department. I was told that Jim Watson once visited the department to discuss starting neurobiology courses at Cold Spring Harbor. He talked about who should organize some courses there, and one of the Harvard neurobiology faculty apparently told him, "Well, you wouldn't want to talk to anybody outside of this room." [Laughs]

There, I tried to explain this very simple switch that sympathetic neurons make between producing acetylcholine or epinephrine.

The brain must have really intrigued you, because you've worked in that area for 30 years, even still at UCSF.

Yes, there's always some new discovery. New technologies keep opening up possibilities. Now, with fluorescent proteins, you can actually look at single neurons and their dendrites and ask what happens in animals.

And UCSF, in addition to being one of the great places for science, has also been terrific in trying to help society. Bruce Alberts catalyzed formation of a Science Education Partnership with the San Francisco Public School District. With some colleagues, I have been working very hard on the Special Neuroscience Research Program at the University of Alaska Fairbanks. There, a lot of the prizes for the best student in chemistry, etc., go to underrepresented minorities, usually Native Americans. And a lot of these kids have gone on to do great things, gone to medical school or become scientists. The NIH has supported what we're doing, and it's been terrific. There's no better place to reach your potential as a scientist and as a citizen of this planet.

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Reichardt at the summit of K2.