THE RIGHT CHEMISTRY

HHMI INVESTIGATOR CAROLYN BERTOZZI FOUND HER CALLING IN A COLLEGE COURSE IN ORGANIC CHEMISTRY. "I LOVED SOLVING THE PROBLEMS," SHE SAYS. SHE STILL DOES.

By
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Photographs by
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When Carolyn R. Bertozzi was 12 she saw a roller skater doing a fancy jump. She thought it looked easy enough, her father recollects, so she tried it. The double spiral fracture of her leg that resulted kept her in a cast and on crutches for six months. ¶ "That's typical of Carolyn," says William Bertozzi, a professor of physics at the Massachusetts Institute of Technology (MIT). "If she sees something interesting she goes over, takes a look, and then tries it. Her high school soccer coach used to call her 'fearless.'" ¶ Fast-forward a couple of decades, and the same pluck that Carolyn Bertozzi demonstrated at the roller rink is in evidence in her current preoccupation—chemistry. An HHMI investigator and professor of chemistry and molecular and cell biology at the University of California, Berkeley, Bertozzi prides herself on choosing projects that many other chemists would consider too risky. ¶ "We like to do things that some people might say are really 'out there,'" says Bertozzi with a laugh. Her predilection for heading down untrod paths is very much at home in the progressive culture at Berkeley, and it attracts adventurous students with bright ideas of their own, which she makes a point of encouraging. Typical is her recent response to a visiting postdoctoral candidate who reported having a research proposal dinged by reviewers for being "premature." "All the more reason to do it," she urged.

Bertozzi's lab group, whose size has swelled past 50 this year, including 30 Ph.D. students and postdoctoral fellows, occupies most of the cramped eighth floor of the main campus's chemistry building and has spilled over to a satellite location at the Lawrence Berkeley National Laboratory (LBNL), nestled in the surrounding hills nearby. Most members of this tight-knit group have a background in chemistry but have come to Bertozzi's lab specifically because it applies the tools of chemistry to help answer biological questions related to human health and disease. Their raft of projects includes efforts to investigate cell-surface interactions involved in cancer, inflammation, and bacterial infection; to develop biomimetic materials, such as bone substitutes; and to define some of the basic elements of glycobiology, the study of carbohydrates.

Bertozzi, a founder and co-director of Berkeley's graduate program in chemical biology, now in its fourth year, is a leader in this burgeoning new field. She is also one of five directors of the Molecular Foundry—an interdisciplinary institute, now under construction at LBNL, that will focus on nanoscience and nanotechnology.

How does she find the energy to keep so many plates spinning at the same time? Nick Agard, a third-year graduate student working in her lab, has a two-word explanation.

Peanut butter.

CARBO-LOADING

By Agard's estimate, which others in the lab corroborate, Bertozzi goes through "at least two or three jars a week."

There is, in fact, a certain symmetry to Bertozzi's reliance on a carbohydrate-rich food source like peanut butter as her energy mainstay. The heart of her research is a focus on the carbohydrates that dot the landscape of cell surfaces. Also called sugars or polysaccharides, these branched and variously sized molecules hang from most of the proteins ("glycoproteins") and many of the fats ("glycolipids") lodged in the cell's membranes. Glycoproteins and glycolipids serve as beacons for communicating with other cells in the vicinity. The message might be that things are fine or it might be a call for help if the cell is damaged or under attack by a pathogen.

Bertozzi has long been fascinated by what polysaccharides do. As far back as 20 years ago, scientists observed that as tumors develop there are changes in glycosylation (the process by which proteins or other molecules are modified by the addition of sugars) that are characteristic of those tumors. Similarly, sugars change in distinctive ways during embryonic development. Bertozzi realized that if it were possible to correlate polysaccharide structure with disease state, this could provide a diagnostic or even prognostic marker.

She had been thinking for years that if she could develop a way to monitor glycosylation and measure it quickly, simply, and noninvasively in living animals, "that would be a really transforming modality." Such an approach might help researchers to gain fundamental and practical knowledge about how cell-surface sugars contribute to both health and illness.

It now appears that Bertozzi and her group have begun meeting what she calls this "major challenge of my professional life." Details of their glycosylation-reporting technique, which involves remodeling the cell-surface sugars in mice, were published in the August 19, 2004, issue of *Nature*.

This method had its genesis back in 1996, when Bertozzi joined the Berkeley faculty. "One of the ideas I wanted to pursue was that you could tap into the metabolic pathways that produce polysaccharides," she says. Polysaccharides are polymers of monosaccharides, which come from the simple sugars that we eat, such as glucose and galactose. From these dietary sugars we generate a number of building-block monosaccharides, which get assembled into polysaccharides attached to proteins or lipids. Finally, those glycoconjugates go through a secretory process and are ultimately presented on the cell membrane.

"So I was thinking, what if you modified those simple dietary sugars with a chemical-reporter group, something that you can visualize?" says Bertozzi. "If you could get that sugar metabolized and integrated as a cell-surface glycoconjugate, now the reporter group would be resident on the cell surface and would provide a read-out for the presence of that sugar."

Bertozzi's group was the first to accomplish this feat, publishing their results in 1997 in the journal *Science.* Essentially, they figured out a way to feed cells a sugar decorated with a small functional group, the ketone, which then could then be tagged with probes for visualization on the surfaces of living cells. Later, the technique was refined for applications to living animals. In a subsequent publication in *Science* in 2000, Bertozzi's group demonstrated that another small functional group called an azide, made up of only three atoms of nitrogen, also could be delivered to cell surface glycoconjugates by the metabolism of simple sugars. The azide takes up a tiny volume of space, says Bertozzi, but it has a huge amount of chemical potential. Once implanted in a cell-surface sugar, it is available to form a very strong covalent bond with another reagent, called a phosphine, without interfering with the sugar's ability to carry out its normal signaling function.

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Bertozzi's group developed a key reaction by which the azide and phosphine can be linked together, which they termed the Staudinger ligation. Named after a German chemist and Nobelist, this chemical reaction was called "a gift to chemical biology" in a review published in 2004 in *Angewandte Chemie*, a highly respected chemistry journal, because of its elegance and general usefulness in the field. Bertozzi's group has now modified this reaction to create a reporter system in living animals. Aside from its scientific merit, this project has been a rare career-building opportunity as well, according to Jenn Prescher, a graduate student who was first author on the *Nature* paper. "Not too many graduate students ever have the experience of being able to master some aspect of organic chemistry and then work with it all the way into animals," she says.

Currently, the group is working with physician-scientists at Stanford and Johns Hopkins medical schools to test how well different imaging systems can monitor various reporter molecules in mice. They are also devising other chemical modifications of the Staudinger ligation and are look-

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ing at ways to label more than one sugar on a cell to capture even more biological information. "That's the Holy Grail," says Bertozzi.

BORED OF EDUCATION

Now 38, Bertozzi was born in Lexington, Massachusetts, a suburb of Boston, the middle daughter between older sister Andrea and younger sister Diana. Having a father who was a nuclear physicist at MIT, the girls were accustomed to seeing interesting gadgets like magnets and gyroscopes migrate from his lab to their home. And being "MIT kids," the sisters went to summer day camp and, later on, had summer jobs at MIT. So it was no big surprise when they showed leanings toward math and science, inclinations that eventually took root. Andrea is now a math professor at UCLA, and Diana is an occupational therapist practicing in New Jersey.

"It was clear from very early on that my older sister was a math genius," says Bertozzi. "For me, it wasn't clear until later what I would be. I was not a kid who was brilliant at one thing. I was just kind of a normal kid, but I could be pretty good at something if I worked hard at it."

Bertozzi managed to distinguish herself in other ways. "Music became my thing," she says, "and I was very athletic in high school—I played soccer and softball." And she played very well, according to her mother, Norma, who says Bertozzi's performance as defenseman in soccer garnered her the honor of being named a Middlesex County League All-Star. At the piano, her father reports, Bertozzi showed unusual talent. "She took some lessons, but she didn't want to practice because it was boring," he says. "She preferred to figure out how to play the songs she knew, playing by ear, two-handed, which to me was sort of astounding." For a time, Bertozzi seriously considered a career in music. Today, her keyboard is her refuge. "After a long, difficult day, if I need to unwind I'll plug in my headset and just bang on the piano," she says.

Though math was not her strongest suit in school, academically Bertozzi fell into step behind Andrea, who was only 14 months older, faithfully tripping along in her shadow—taking the same classes, joining the math team—until college, when their paths diverged. Just before accepting an offer from Princeton, where Andrea was enrolled, Bertozzi made a last-minute decision to apply to Harvard. She got in and quickly settled into her new independence, starting toward a major in biology and playing keyboards and singing in a heavy metal "hair" band called Bored of Education.

But organic chemistry, which Bertozzi took during her sophomore year, proved life-changing. "I loved solving the problems," she says. "I wouldn't go out on weekends because I just wanted to read the book and see if I could work the problems." Realizing her calling, she switched her major from biology to chemistry and ended up graduating summa cum laude and winning the award for best senior thesis—which documented her design and construction of a laser-based photoacoustic calorimeter.

After college, Bertozzi did a summer internship at AT&T's Bell Laboratories in chemical physics. But she really wanted to work at the interface of chemistry and biology. So she chose Berkeley for her graduate studies, launching her career in carbohydrate chemistry by working with Mark Bednarski—she was one of his first graduate students—on the synthesis and biological activity of C-glycosides. Midway through her dissertation research, Bednarski was diagnosed with cancer and, in an epiphany, he left research to pursue a medical degree. Bertozzi turned what could have been a disastrous situation into an opportunity, rallying to finish her own thesis and advising his other students on theirs.

"In retrospect, it was actually good training," she says. "It was good experience in mentoring and in writing grants and papers, and I learned how to set up a lab and initiate projects from scratch. This accelerated things when I started my first faculty position." Because these lessons proved so valuable to her, Bertozzi says she now steers some of her own students into similar situations, encouraging them to initiate new projects and work with new professors if they get the chance.

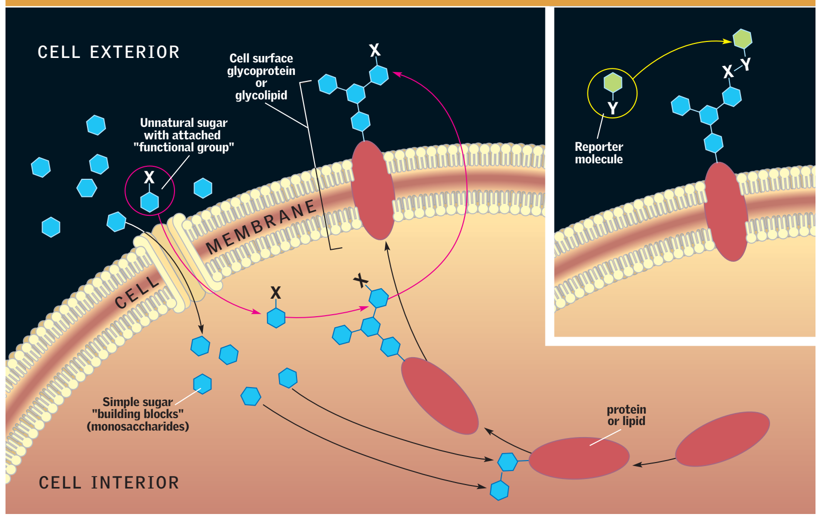
Another important step toward Bertozzi's career in glycobiology was her postdoctoral work in the laboratory of Steven D. Rosen at the University of California, San Francisco. She had become interested in the selectin family of adhesion molecules, which had just been discovered at that time (late 1980s and early 1990s). It was clear that selectins bind to certain carbohydrates, "and that the binding was important in inflammation and in the immune response generally," she says.

Rosen had cloned and characterized L-selectin, a molecule involved in the adhesion of blood-borne lymphocytes to endothelial cells within lymph tissue. When Bertozzi called Rosen to, in her words, "sell myself to him as an amateur biologist," it did not take much persuading. "We were taking on a structural problem at that time and I really needed someone who could help us with the standards," says Rosen. "She knew our work—knew the field—from having read about it, and it was clear there would be no deficit whatsoever in her getting on board. She fit in perfectly."

The research that Bertozzi did with Rosen—identifying the sulfated carbohydrates on endothelial cells that facilitate binding of L-selectin—continues to this day, he says. "That first project laid the foundation for a long and continuing interest in biological sulfation. It set the stage for a lot of other work in my lab, in her lab, and in many other labs." Rosen cites as particularly significant the work Bertozzi's group is doing on *Mycobacterium tuberculosis*, the causative agent in tuberculosis.

METABOLIC ENGINEERING OF CELL SURFACE SUGARS

Sugars modified to bear reactive functional groups (circled in red), such as ketones or azides, can be "fed" to cells and incorporated along with natural sugars into glycoproteins or glycolipids lodged in the cell membrane. As shown in the inset, introduction of a reporter molecule (circled in yellow) — for example, a fluorescent imaging agent — that binds to the functional group provides a way of visualizing the pattern of sugars on that particular cell type.



Collaborative interaction, considered by many to be the *élan vital* of research, provides the spark and inspiration to head in new or unexpected directions. Bertozzi believes fervently in this principle, as her numerous collaborations with Rosen attest. Another of her collaborations, this one at LBNL with two other Berkeley researchers, fuses materials science with molecular biology and carbohydrate chemistry. The project's aim is to attach a small piece of DNA to the surface of living cells using Bertozzi's method for cell-surface engineering, explains Matthew B. Francis, a fellow chemistry professor and one of the collaborators. Then, a second, complementary piece of DNA is attached to the surface of a microchip. When a solution containing DNA-tagged cells is streamed across the microchip, "the cells go right to where the complementary DNA is bound," says Francis. "Ultimately, the idea is to build biosensors using this concept."

GIMME A "B"

Francis and Bertozzi collaborate on a grant, work in the same building, and serve on many of the same committees. About his colleague, Francis says, "You don't see too many people who work that hard and are that energetic about it. She truly loves what she does, and that's infectious. It's sort of like having a cheerleader in the department, although she probably wouldn't like me to make that comparison."

Regardless of metaphor, it is clear that people are drawn in by Bertozzi's palpable enthusiasm for her field and by her remarkable gift for explaining it simply. When she gives a presentation, she "makes it feel like she's talking just to you, as if it's a conversation across a table," says Jenny Czlapinski, a third-year postdoctoral fellow in the lab. Her first introduction to Bertozzi was a talk to an audience of synthetic chemists at Northwestern University. "It was amazing, the most well-attended organic seminar I attended during graduate school," says Czlapinski. "She exudes so much energy you get caught up in it. Even those people who hadn't even a smidgen of interest in biology were coming out of there saying it was just fantastic."

Bertozzi's talent for communicating science in the classroom has been recognized several times over by Berkeley administrators. Framed teaching award certificates line one wall of her office. The chemistry dean's office receives frequent requests for her as a speaker. She also makes time for periodic lectures to Berkeley undergrads and at Bay-area public schools. One of her commitments, for example, is to Nano*High, LBNL's once-a-month Saturday program for teaching high school students about nanoscience.

Mentoring the next generation of scientists is something that comes naturally to Bertozzi. As busy as she is, she maintains an open-door policy in her office and encourages drop-ins. She also clearly enjoys the camaraderie of the lab, to the point where the line between mentor and student often blurs. Recently, for instance, reluctant to accept the onset of age-related presbyopia, Bertozzi agreed to be fitted for glasses only if a posse from the lab went with her to help pick out frames. "I prefer being treated as a peer rather than *Herr Professor*," she says.

She has recruited her students into other adventures as well, including giving tennis lessons—until an inflamed foot tendon sidelined her. Still nursing the injury, these days she stays fit by cycling the hills between campus and her nearby house and working out in her home gym. She keeps her tennis elbow oiled, though, by late night practice batting the ball against the wall in the hallway outside her office. "She likes to fidget when she's writing," says grad student Jenn Prescher. "It helps her think."

Bertozzi, who in 1999 was one of the youngest scientists ever to receive a MacArthur "genius" award, remains humble. Characteristically, for example, she's quick to point out that her lab group is plenty sharp enough to keep her on her toes. "These people are phenomenal," she says. "I was a Berkeley student myself, but if I were a student now in my own group, I don't think I could keep up."

But Bertozzi's modesty, though sincere, belies the facts, says Steve Rosen. "Carolyn is really a great citizen on her campus, nationally, and internationally. She's a terrific scientist and teacher, and students flock to her because of her great work and her ability to convey excitement in the work that's going on," he says. "She's a star on an incredibly exciting trajectory." H

DAVID HERBICK