Constance Brinckerhoff, Ph.D.: Incurably curious

By Laura Stephenson Carter

Grew up: Swampscott, Mass. (north of Boston)

Education: Smith College '63 (B.A. in biology); SUNY Buffalo '68 (Ph.D. in microbiology and immunology)

Training: Postdoctoral fellowship (in microbiology, with a focus on tumor immunology) at Dartmouth

First paid job: Babysitting

First job in science: Lab technician at the Rockefeller Institute in New York City between college and grad school

Where she met her husband: At summer camp in Maine, when she was 11 and he was 13; they started dating when she graduated from high school and got married right after she graduated from college

Favorite nonwork activities: Biking on Martha's Vineyard, where there are fewer hills; walking; going to the beach

Success in science, believes Brinckerhoff, is "a matter of really loving what you're doing, really being curious."

Once upon a time, Connie Brinckerhoff had no interest at all in tadpoles. But today she's a leader in the study of matrix metalloproteinases (MMPs)—a field launched by the discovery of how tadpoles lose their tails.

It was in 1962 that two Massachusetts General Hospital scientists—Jerome Gross, M.D., a developmental biologist, and Charles Lapierre, M.D., a dermatologist—found an enzyme that made tadpole tails decompose during metamorphosis. Tadpole tails are made of collagen, so they called the enzyme collagenase; it was the first identified MMP. Soon, other scientists determined that collagenase is a zinc-containing enzyme that, in people suffering from rheumatoid arthritis, can destroy collagen and other kinds of connective tissue such as cartilage, the tissue that surrounds joints. By the early 1970s, researchers had identified a whole family of MMPs. Today MMPs are considered therapeutic targets in several diseases, including rheumatoid arthritis, periodontitis, and cancer.

Little did Brinckerhoff know back in 1962 that MMPs would define her career. That in the early 1990s, she'd cochair the first Gordon Research Conference devoted to MMPs. That in the late 1990s, she'd receive a prestigious National Institutes of Health MERIT (Method to Extend Research in Time) Award, which recognizes superior scientists and funds their work for up to 10 years.

Brinckerhoff began her career studying autoimmune diseases as a graduate student at the State University of New York at Buffalo. After completing her Ph.D. in microbiology and immunology, she moved with her husband (who'd just finished his Ph.D. in philosophy) to southern Vermont and spent the next few years teaching at Windham College, working part-time in a clinical lab at Brattleboro Memorial Hospital, and raising their three children. In 1972, she decided to do a postdoctoral fellowship at DMS with Martin Lubin, M.D., Ph.D. For the next four years, she focused on tumor cell biology.

Finally, in 1976, she began working with MMPs when a leading rheumatologist—Edward Harris, M.D., a 1960 graduate of DMS who was then a member of the Dartmouth faculty—recruited her to work in his lab to do research on connective tissue disease. "It was really exciting and inspiring to observe how enthusiastic she was," says Harris, now an emeritus professor at Stanford.

"For the next six years," Harris continues, "we worked together and she became one of the thought and action leaders in the lab." With Brinckerhoff's help, Harris's team made important discoveries about how metalloproteinases are synthesized and how they degrade joints as rheumatoid arthritis progresses.

Brinckerhoff loved the work, often returning to the lab late at night to check on experiments. "We lived only four miles from the lab," she says. "I would set up experiments, go home, put on my nightgown, and . . . come back, park my car, walk into the lab, and float around in my nightgown." She laughs. "I did that many a night."

"She has an optimism and a buoyant personality," says Harris. But that's "not to say that she [was] totally immune to self doubt," he adds. In 1978, for instance, Brinckerhoff was preparing to give her first big presentation—about lab-generated multinucleated giant cells that spontaneously make collagenase—at a plenary session of the American College of Rheumatology. "She was extraordinarily nervous," Harris recalls. "We all had to sort of prop her up and assure her that she'd do a wonderful job, which of course she did."

"I remember this *very* well," says Brinckerhoff. "I was terribly nervous and . . . very relieved when it was all over." That presentation may have been over, but there were many more to come as Brinckerhoff's career began to soar. By the time Harris left DMS in 1983 to become chair of medicine at Rutgers, Brinckerhoff had her own funding. "She's moved well beyond my place in the field into new methodologies that [are] very modern and up-to-date," says Harris.

As Brinckerhoff continued to investigate collagenases, she began looking into their genetic underpinnings. She collaborated with Dartmouth biology professor Robert Gross, Ph.D., to learn new molecular biology techniques that have helped her lab isolate genes for collagenase and related enzymes. She studied MMP-1 and found DNA alterations that instructed the cell to produce too much of the enzyme; although collagenase can be useful, such as in helping to heal

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JON GILBERT FOX

Brinckerhoff studies a family of enzymes involved in rheumatoid arthritis and cancer.

wounds, too much of it can be destructive, which is the case in rheumatoid arthritis.

The lab wasn't to be her sole province, however, for leadership roles began coming her way. She was acting chair of the Department of Biochemistry from 1989 to 1991, and in 1991 she was named associate dean of science, a position she still holds.

That allowed her to address something that had always bothered her—the lack of attention given to graduate students in the biomedical sciences. "I really felt strongly that it was important to recognize graduate students as much as possible to the same degree as medical students were recognized," she says. She felt the disparity especially keenly at graduation, when prizes were handed out to the top M.D. graduates. So with support from then-Dean Andrew Wallace, M.D., "we initiated the Strohbehn Award, which is given to the graduate student with the best research track record. It's not just about research. It's about being a good scientific citizen. . . . I'm actually fairly proud of that."

Brinckerhoff began to accumulate honors herself, too. In 1991, she became the first woman at DMS named to an endowed chair—the Oscar M. Cohn 1934 Distinguished Professorship of Molecular Medicine. In 1993, she was appointed to the Nathan Smith Professorship—a chair previously held by a revered former dean, S. Marsh Tenney, M.D. That same year, she cochaired the prestigious Gordon Research Conference, the first one devoted to MMPs. In 1996, she was invited to give Dartmouth's Presidential Lecture—an honor bestowed each year on a single faculty member; she spoke about her favorite topic in a lecture titled "Collagenase and gene expression in arthritis: Does too much of a good thing make joints ache?"

By then, Brinckerhoff had begun to study the way cancer cells may use collagenase to travel to other parts of the body. "It's ironic, because it was just about the same time that I was diagnosed with breast cancer," she says. "I had decided, 'Okay, we've been working with arthritis for a long time, these enzymes are doing more than just destroying joints in arthritis. They're important in mediating tumor invasion and metastasis.' So we started branching out." Her voice drops to a near-whisper. "And that was about the same time that my sister died from breast cancer and I was diagnosed with breast cancer." Brinckerhoff got her own diagnosis just a week after her sister's death and four months after delivering the Presidential Lecture.

Fortunately, a year of chemotherapy and radiation banished her cancer. And the honors continued to pile up. In 1998, she served for a year as acting provost, succeeding James Wright after he was named president of Dartmouth. Since 2003, she has been the executive editor of the *Journal of Cellular Physiology*. One of her favorite awards came in 2003, from her undergraduate alma mater: the Smith College Medal for "distinction in teaching and research." Later this year, she'll be designated an American College of Rheumatology Master, one of the organization's highest honors.

Brinckerhoff admits that scientific research requires patience but insists that her curiosity, excitement, and love for her work have driven her success. "I think it's a matter of really loving what you're doing, really being curious, and just being satisfied by a small piece of information that is enlightening," she says. "And then when you hit a roadblock, [you try] to figure out how you get around that, what's really going on, what are the data telling you."

Anyone who goes into research solely to find new treatments is "probably going to be doomed to failure," she cautions. "It's not going to happen that quickly." So Brinckerhoff looks for and nurtures a sense of curiosity in students, too. "If they don't have it, it's going to be very difficult for them to succeed," she says. "That motivation has to come from within . . . and it's got to be sustained through an awful lot of potentially negative experiences—grants rejected, papers rejected. You have to learn not to take it personally. You've just got to say, 'Okay, what do they want me to do? How can I fix it? What's next?' Living with rejection is part of being a scientist."

But at the same time, she also realizes that "it's important to recognize the strengths that each individual student has and try and develop those rather than clone yourself."

Though Brinckerhoff now spends less time in the lab than she used to, she recently published a paper in *Cancer Research* on MMPs and melanoma, the most virulent form of skin cancer. Her lab found that

continued on page 60

Constance Brinckerhoff

continued from page 53

in mice injected with human melanoma cells, inhibiting MMPs prevented the melanoma from metastasizing.

She also advises students, teaches, and gives talks. And she spends a lot of time writing and reviewing grants and papers, trying to impress on students and colleagues the importance of good writing. She's a very good writer herself. An article she wrote for the March 2002 issue of *Nature Reviews Molecular Cell Biology*—"Matrix metalloproteinases: a tail of a frog that became a prince"—is a compelling story of two scientists who discovered how tadpoles lose their tails . . . ■

Paul Zamecnik

continued from page 55

can bind to a complementary nucleotide sequence on the mRNA strand. The result is double-stranded mRNA, which is unable to translate genetic information into proteins. Zamecnik then used the antisense technique to stop the growth of a virus by blocking a gene essential to its replication.

Zamecnik "might be considered the father of antisense technology," says Dr. Marcus Horwitz, a tuberculosis (TB) expert at the University of California, Los Angeles. Horwitz has been collaborating with Zamecnik for 12 years to use antisense technology against *Mycobacterium tuberculosis*, the bacterium that causes TB.

The bacterium's nearly impregnable cell wall is an important factor in TB's virulence, so it is an obvious target for fighting the disease. In 2000, Zamecnik and Horwitz showed that it is possible to employ antisense technology to hinder the growth of the cell wall. By 2002, they had identified targets in the bacterium's genome that might be vulnerable to antisense therapy. They have continued to refine their approach and last year published an article reporting success in inhibiting the growth of *M. tuberculosis*.

Zamecnik says there's still progress to be made before the findings can be translated into effective treatments, but he thinks the goal is within reach. With so much work to do, he sees no reason to stop now. "As long as you can be competitive," he says, "you might as well do what you like." ■