Junying Yuan

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The graduate student who arrived for a rotation in neurobiologist Robert Horvitz's Massachusetts Institute of Technology (MIT) lab was from an exotic place then called "Mainland China." As hard as it is to fathom today, Chinese graduate students were incredibly rare in American universities in 1982. Junying Yuan was one of the first recruited through the China–United States Biochemistry Examination and Application (CUSBEA) program. CUSBEA was an American-administered competitive exam to find the very brightest science students emerging from China's newly revived universities after the Cultural Revolution. Yuan came in second out of 25,000 who took the CUSBEA that first year.

Another thing that made Yuan stand out in an MIT lab was the fact that she was a Harvard Medical School (HMS) graduate student, Horvitz recalls, still chuckling at the memory. "Junying was a Harvard student who managed to persuade Ed Kravitz [the head of Harvard's Program in Neuroscience] to be allowed to rotate in my lab at MIT with Harvard paying for it. She then managed to persuade someone at Harvard to pay for her entire education at MIT, which I took to be a sign of someone unusual."

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Horvitz had other indications that Yuan was unusual. "When Junying first arrived, I defined a rotation project for her that I figured would keep her busy for the next two years. And then about two weeks later, Junying came back to me and said, 'That's done. What can I do next?'.... Then she got interested in the problem of cell death genes."

To Stockholm

Her timing was perfect. Twenty years later, the experiments that Yuan performed in his lab on programmed cell death would lead to a Nobel Prize in Medicine or Physiology for Horvitz. When Horvitz went to Stockholm in December 2002 to accept the Nobel Prize that he shared with Sydney Brenner and John Sulston, he insisted that Yuan join his official party. Other lab members made key contributions, but in his Nobel lecture Horvitz singled out Yuan for mounting the first experimental look at the molecular mechanism of cell death.

The success of that work gave Yuan the momentum to skip a postdoc after finishing her Ph.D. with Horvitz in 1989 and set up her own lab at Harvard's Massachusetts General Hospital. In 1996, Yuan moved back to where she had started as a graduate student fresh off the plane from China—the HMS Longwood campus in Boston—when she joined the HMS cell biology department. In four years, she rose to full professor. Today Yuan's hugely productive HMS lab pursues cell death on a number of fronts, including its role in neurodegenerative diseases and inflammation, its possible regulation by small molecules, and its role as an amplifier of cell transduction signals. Yuan has also proposed a third cell death pathway somewhere between programmed apoptosis and catastrophic cell necrosis. She calls its "necroptosis."

It all began with a worm. In the early 1980s, *Caenorhabditis elegans* was nearly as rare as Chinese grad students on American campuses. Horvitz had brought the worm back to Cambridge, MA, from Cambridge, UK. There he'd learned *C. elegans* genetics from its experimental champions, Brenner and Sulston. They'd chosen *C. elegans* as a new model organism because it has exactly 959 cells. On its developmental path from a single fertilized egg cell to 959-cell adulthood, *C. elegans* loses exactly 131 cells. The process by which they vanish is apoptosis. Self-vanishing cells are a normal feature of embryonic development, removing unnecessary cells such as the webbing between human fetal fingers or budding neurons that fail to wire up properly. But apoptosis in mammals was difficult to study, let alone control. The 959-cell worm with its missing 131 cells seemed more tractable.

Null for Cell Death

Just before Yuan's arrival, the Horvitz lab found its first *C. elegans* mutant that was null for cell death. These mutants would develop into adult worms with the normal complement of cells plus 131 extra ones that should have been stricken off by apoptosis. (Lab members called the mutant's extra cells "the undead.") The mutants gave the researchers two leading gene candidates for cell suicide directors, *ced-3* and *ced-4.* Horvitz quickly switched his fast-working grad student to *ced* genes.

According to Horvitz, "Junying was the one who showed that *ced-3* and *ced-4* are suicide genes. She did the experiments that showed these genes acted within the cells that are going to die. They do not send out signals, as many people thought, to other cells to commit suicide."

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It was Yuan who also helped make the experimental connection between a cell death gene in worms and a cell death mechanism in humans, says Horvitz. Working with fellow grad student Shai Shasham (now at Rockefeller University), Yuan discovered that *ced-3* in *C. elegans* encoded a protein that turned out to be similar to a human protease, interleukin-1-β converting enzyme (ICE). The ICE-derived protein in humans and the CED-3 protein in worms were the first in a family of cell death proteases now known as the caspases. "That was the first caspase, and to this day the best demonstration of the mechanistic basis of apoptosis," Horvitz declares. "Junying discovered that first caspase while she was still in my lab. She brought it into mammals, literally and figuratively. That was one-third of the Nobel right there," he maintains.

The First Caspase

Horvitz continues, "Everything she did [in my lab] was golden. That's continued through her whole career, and she's just done a whole litany of things. She's had a whole series of breakthrough studies in cell death, and then she turned to human disease and has done some work on Huntington's and Alzheimer's that is just spectacular. She's the ultimate innovative scientist, the real pioneer, because she keeps doing things that are new."

Junying Yuan's career nearly didn't happen at all. Yuan jokes that if she had stayed in her first job as an inept factory worker in China, she would be retired now. But the story is no joke. Yuan comes from a Shanghai family of scientists. Her grandfather was an organic chemist. Her father was an anatomist, her mother a botanist and expert on traditional Chinese medicine. That made the family "intellectuals," and in the turmoil of the Cultural Revolution such a background made Junying Yuan ineligible to attend a university. After a patchy high school education, she was assigned to a factory that made heavy machinery. "I hated it," Yuan recalls. "Also I was no good at it, but fortunately the boss mostly let me sit there and watch."

A high school teacher who had seen Yuan's potential rescued her. Catching wind of a new competitive university entrance exam open to all, the teacher insisted that Yuan start cramming. Only there were no modern textbooks, Yuan recalls. Those that hadn't been burned by the Red Guards were locked away in schools. Her teacher broke into the high school library at night to steal the books Yuan needed. After four frantic months of self-tutoring, Yuan took the first open college entrance exam for a place at the reformed Fudan University. She placed first in Shanghai out of the more than 100,000 high school graduates who took the exam.

Arguing with Deans

Four years later, her CUSBEA exam scores caught the attention of Harvard biochemist Manfred Karnovsky. It was Karnovsky who brought Yuan's eye-popping results to HMS neurobiologist Ed Kravitz. Sight unseen, Kravitz offered Yuan a place. Kravitz was not disappointed when he met the quietly determined young woman from Shanghai that fall. Kravitz remembers, "Clearly, Junying was very smart but she was also thoughtful. You would not pick her out as a hyperaggressive person or as a super-shy one. She had her opinions and she wasn't shy in expressing them."

There was the matter of lab placements, Kravitz recalls. Harvard's new cross-campus neuroscience program sent her on three-month rotations through labs in the medical school and on the main campus in Cambridge. "Junying just couldn't find a lab to work in. She'd do a rotation and then come back and say, 'No, that's not the one.'"

Kravitz helped tip Yuan toward the question of cell death. He taught a survey course on neurodegenerative diseases and liked to start each week's discussion of a disease with a guest presentation from a leading Harvard clinician. Typically, the clinician would bring along a patient. Yuan remembers being impressed by the dignity of the patients but unimpressed by the eminent specialists. "They [the experts] really didn't know anything about these diseases," she recalls with indignation. "All they could do was tell us how they differentiated in diagnosis between Alzheimer's or Huntington's. But they had no treatments, and I thought that if I am a patient, it doesn't make much difference to me which way I am going to die."

Yet Yuan believed that there was a link between all these neurodegenerative diseases: They all involved selective die-off of neurons. Yuan couldn't find anyone who addressed her new interest until she heard Horvitz, then a junior faculty member from MIT, talk about his work with an unusual model organism on something called programmed cell suicide. So Yuan found her lab—with Horvitz at MIT—and Kravitz found himself arguing with various Harvard deans. "Obviously, it worked out," says Kravitz with pride. The rest is Nobel history, and today cell death is the central issue in a vast amount of research on subjects from cancer to spinal cord regeneration.

Have You Eaten?

Pushed into remembering, Yuan looks back on her first days in America and her arrival on the deserted Longwood campus in the last days of summer. She found herself virtually alone in her HMS dormitory with nothing to eat but Greek salad from the local delicatessen. Yuan was appalled. In the Chinese culinary tradition, raw salad is not food.

"At the end of three days, I was really starving," she recalls. "My mother had given me a package for a friend of a friend in Boston. I had the phone number, so I went to a phone booth and called. In Chinese, the normal greeting is 'Oh, have you eaten?' and when this man answered and said, 'Have you eaten?,' tears dropped down my face."

The couple rescued Yuan from starvation. "This family became my adopted family and every weekend they took me into their house to feed me," Yuan recalls. "Now they are retired, I feed them at my house."

That house is in nearby Newton where her daughter, Julia Yu, 16, is in high school. Her son, Albert Yu, 19, is taking a gap year after high school. Although his interests are in science, his parents await bulletins on his precise intentions. Yuan's husband, Qiang Yu, a biochemistry professor at Boston University, is back in Shanghai running the pharmaceutical company that he started there four years ago.

A member of the ASCB since 1999, Yuan has become increasingly concerned with women's issues in science. Last year she joined the Society's Women in Cell Biology Committee. "I have been very lucky in that I have had a lot of good mentors," Yuan explains. "But I've always thought that I should give back. Perhaps it's easier for me to connect to young women."

Like many high-performers, Yuan is a marvel of efficiency and fierce concentration. She says she never goes to an airport, a doctor's appointment, or a child's sports practice without her faithful bag of journals and manuscript drafts. She is a fervent user of the Blackberry, as her lab members soon discover. She replies almost instantly to their emails, even when she's in Shanghai on a visit home. "I feel nervous if I don't have my Blackberry," Yuan confesses, adding that she totally understood Barack Obama's reluctance to part with his after the election. "I feel very glad to share the same passion for the Blackberry as President Obama," says the professor of cell biology at HMS.

It is a statement that shows how far science, the world, and the Blackberry have come since Junying Yuan came to America. ■

—John Fleischman

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