Rong Li

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The old joke is that biologists were science majors who couldn't do the math. The new paradigm in biology? Quantify, quantify and then do the mathematical modeling. "That puts Rong Li at the leading edge," says Andrew Murray, about the career of his very first graduate student. Li is now an Investigator at the Stowers Institute for Medical Research in Kansas City. "I think Rong is one of those ahead of the curve," Murray says, "in her ability to interact with quantitative scientists and biologists."

"Rong Li's been a very successful scientist who's made real contributions to understanding how the cytoskeleton is organized," Murray continues. He is now at Harvard University. In 1989 Murray was a newly minted assistant professor at the University of California, San Francisco (UCSF). Later, Murray and Li were colleagues at Harvard, though on different sides of the Charles River, until Li's move last fall to the Stowers.

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Murray points to Li's recent collaborations on cell polarity in yeast cells with mathematicians Lani Wu and Steve Altschuler. Murray explains, "Yeast cells, when they make a bud, have to decide where on their surface to make that bud. There's been a lot of work on the elaborate series of historical marks that are laid down, one after another, and how this sequence tells cells to polarize. What Li did was to ask what happens if you break that system. She asked mathematicians how a spontaneous process could break symmetry. Together they came up with some very interesting answers."

"Rong Li's ability to ask difficult questions across disciplinary boundaries was a key reason for recruiting her," says Robb Krumlauf, Scientific Director at Stowers. With a $2 billion endowment from American Century Investments founders, Jim and Virginia Stowers, the Institute is a freestanding research organization. It has a scientific business model and an ambitious basic research agenda similar to that of the Howard Hughes Medical Institute. Its first 600,000 square foot research facility opened in 2000, and the Stowers plans to double in size by 2010.

Krumlauf thought Li would be a perfect fit. "Rong's very much a lateral thinker," Krumlauf says. "She's interested not only in her own projects but in the research of others. We need that synergy in an institution like ours …because all science is becoming interdisciplinary. To truly integrate biology, genetics, and biochemistry with computational science requires some uniquely qualified individuals," says Krumlauf. "Even if you have teams with individual expertise, it's not easy for them to say to another group, 'Please solve this problem for me.' You need someone like Rong Li who can bridge the gap just to know what question is being asked."

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"Rong is able to talk with mathematicians, help them understand the nature of the problem, and then take their solutions and translate them into things that can be tested experimentally." Krumlauf continues that Li brings similar skills to collaborations with the institute's imaging technologists: "This is not cookbook science. This is real integrative science where scientists and technologists sit down together. That makes Rong a great scientist for the Stowers and a great colleague."

"This is just a dream place for science," says Li, who made the move last fall. She admits that Stowers and Kansas City itself took her by surprise. "When they first invited me here, I thought to myself, 'Kansas City? Cornfields? Dusty streets?' So I said okay, but I would just give a seminar. I flew in on the day of my seminar because I didn't want to spend any extra minutes. But after I'd only been here half a day, I was impressed." She was impressed by the facilities, the intramural funding and, most of all, by the seriousness of the research staff. "When I gave my seminar, I knew that there weren't that many people in my field. But the seminar was a surprise. I had a ton of good questions."

A drive around the Plaza neighborhood of Kansas City, Missouri, that surrounds the Institute left Li impressed by the old prairie-style houses with stone porches, wide yards, and big shade trees. "Then I found out about the

cost of houses and the cost of living compared to Boston. Wow. But first I had to convince my family." Li's husband was unenthusiastic at first until Li "dragged" him to Kansas City for a visit.

Her husband, Dan Sun, is a China-trained physician who did his primary care residency in Boston but always dreamed of getting into a cardiology program. "He'd given up," says Li, "so this was a dream come true for him." Sun will start a cardiology fellowship next fall at the Mid America Heart Institute in Kansas City. Meantime, their two children, Olivia, 6, and Gregory, 3, are settling into their "new" 100-year-old house in the Plaza area. It's half the price and twice the size of their Boston house, says Li. And it's a ten-minute walk to her lab. "Just by not driving, I gained two hours a day at work," Li says.

Rong Li has come a long way to Kansas City. In 1984, Li was the first high school graduate from the People's Republic of China admitted to Yale College. She got into Yale, Li says, by writing a letter. She was born in Beijing, but went to high school in Wuhan in Hubei Province where both her parents were academic geologists. She came of school age just as the Chinese educational system was waking from the long nightmare of the Cultural Revolution. Like most bright Chinese high school students, Li was channeled toward a Chinese science university. Unlike most, Li had other plans. "I was obsessed with the idea of going to school in the U.S., but I had no idea of how to do it," she recalls.

At the time, only graduate students were leaving China for the U.S. Li got the names of American undergraduate colleges from the foreign English teachers who were just arriving at her parents' university. Li recalls, "They told me a whole bunch, but the only one of the names that I remembered was Yale because it was short." She wrote a letter to Yale's admissions office that began, "I am a high school student in China, and I want to come to Yale to study but I have no money."

Li arrived in New Haven in 1984 with little more than pocket change. Her airport shuttle fare took most of the $25 in U.S. currency that Beijing customs officials allowed her. Yale, though, was waiting with support services, an American host family, and a series of campus jobs to cover her living costs beyond her full academic scholarship.

"My English was lousy," Li remembers. "The first semester was extremely frustrating." She went everywhere with a large English-Chinese dictionary and had to convince instructors to

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allow her to have it during exams. Fortunately, her Chinese high school science and math classes had carried her beyond the Yale freshman level. "Even though I couldn't understand a lot of the English, I could at least recognize the equations," Li recalls.

Yale opened unexpected possibilities for Li. "When I was a kid, I loved art but studying art was never a possibility in China. After the Cultural Revolution, all the talented students in school were going into science. There was no choice. When I got to Yale, I was feeling liberated and decided I would take an art class. I ended up taking as many art courses as science courses…and declared a double major in Art and in Science. For a while, I thought of becoming a professional artist."

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Two summers at Cold Spring Harbor and a year in the Yale lab of Dieter Soll working on tRNA processing tipped her back into biology. In 1988, she arrived at UCSF to begin graduate school in a Cell Biology program that included Marc Kirschner, Bruce Alberts, Ira Herskowitz, and Tim Mitchison.

In the end, Li joined the Murray lab at UCSF, which didn't exist yet. Murray was finishing up as a Kirschner postdoc but already plotting his new lab's strategy to get at the so-called mitotic checkpoint. Then it was a theoretical mechanism which stops cells with damaged DNA by arresting the cell cycle before mitosis. Murray wanted to screen for yeast mutants defective in cell cycle arrest and study them as surveillance monitors. "Andrew didn't even have a lab, but I knew I wanted to work with him," Li recalls.

As Murray's only grad student, Li particularly enjoyed the early days at UCSF, unpacking boxes, scrounging bench space, and foraging for supplies. Soon, the Murray lab and Li's yeast screen got on their feet. "We were very lucky to come up quickly with a set of mutants that affected their ability to arrest at the mitotic checkpoint," she recalls. They called the mutant genes "MAD" for "mitotic arrest defective." MAD mutants proceeded blithely toward mitosis—and cell death—even though they lacked a proper spindle apparatus to separate sister chromatids successfully The Li & Murray paper on the MAD genes and their role in the mitotic checkpoint appeared in the same issue of *Cell* as a paper from Andrew Hoyt's lab. Hoyt's paper described a complementary set of yeast "checkpoint" genes called "bub." Both papers are considered landmarks in the history of cell cycle research.

Awarded her PhD in 1992, Li moved across the Bay to University of California, Berkeley, for a postdoc with David Drubin, another new PI whose actin cytoskeleton lab was just getting going. Here Li developed an *in vitro*

permeabilized cell assay to detect the assembly of the cortical actin cytoskeleton in budding yeast. In 1994, Li decided to throw her hat into the ring for a faculty position at UCSF. She called Marc Kirschner who had just moved to HMS in Boston to ask for a recommendation. Kirschner responded with an invitation to apply at Harvard. She joined Kirschner's Cell Biology Department at HMS in 1995.

Jumping from postdoc to PI, Rong Li had a hard landing. Her first two NIH grant applications at HMS were rejected. "That was probably the hardest time in my life," Li recalls. "It was much harder than my first year at Yale." Without NIH funding in those early days, it was hard to attract postdocs. Without postdocs, Li was working at the bench most days and writing grants most nights. It took three rounds of NIH applications before she finally succeeded. Li attributes her eventual success to her talented graduate students and the identification of the yeast analog of WASP, a mutated protein first discovered in a human genetic disorder called Wiskott-Aldrich Syndrome, and the yeast version of the Arp2/3 complex, which at the time was suspected to nucleate actin filaments. Through both genetic and biochemical experiments, they were able to connect these protein in a conserved pathway for assembling actin filaments at cell plasma membrane.

"NIH extramural funding is central to any cell biology laboratory," says Li, "and the NIH Study Section system is valuable in its own right." But Li says that there are always new questions and new ideas on how to ask them that won't fare well in the NIH system. Coming to Stowers with its intramural funding and intramural advanced technology base will let her focus on the symmetry/asymmetry riddle underlying cell morphogenesis using model systems that she had little experience with and technology she could only dream about before, Li says. "There is no longer any excuse not to do something special."

The current explanation of polarization is that cells react to protein signals that cue polarity, says Li. "But we know that isn't the whole story, because if you take away a lot of these cues, cells can still polarize. However, they polarize in random directions."

Protein signaling may bias polarity, but it doesn't explain the underlying symmetry breaking mechanism. Says Li, "the analogy I make is that when you're hungry, you may get up and go to the cafeteria. But that doesn't mean the cafeteria is the reason you eat. The cafeteria is convenient. It biases where you go to eat." By this analogy her approach is to first understand the internal urge and then ways different food sources control this urge. ■

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