

Lynne E. Maquat

In a science relentlessly driven by data, cell biologists still rely on the “story” to keep things straight. The story of messenger RNA (mRNA) was until recent years fairly straightforward, except for one glaring hole in the cellular plot. In organisms with a cell nucleus—e.g., humans—RNA is the go-between. It’s the molecule that assembles inside the nucleus as a mirror image of an unfolding DNA strand. That molecule, says the story, is pre-mRNA. It must undergo processing to cut out the noncoding stretches called introns. It must also splice together the parts called exons that specify useful proteins. Once spliced, mRNA is ready for dispatch through the gates of the nuclear pore complex and into the wider world of the cytoplasm. There, protein-assembling ribosomes await their instructions. A hole in the messenger RNA story was what happened to the nonsense. Lynne Maquat filled in that hole. A frame shift or nonsense mutation in mRNA is a mistake in the three-nucleotide code that causes the ribosome to read a premature stop codon. This yields a truncated, improperly working, and potentially dangerous protein. Given the vast number of cellular mRNA syntheses, many of which involve pre-mRNA splicing at alternative sites, why aren’t there more nonsense proteins floating around?

Tidying Up the Nonsense

Maquat demonstrated that in mRNA, the nonsense tidied up after itself through a process called nonsense-mediated mRNA decay (NMD). She is at the School of Medicine and Dentistry, University of Rochester, in upstate New York.

The problem goes “way back,” explains Joan Steitz of Yale. “But I consider Lynne the pioneer—and it took her a number of years—in figuring out this mysterious process called nonsense-mediated mRNA decay.” Nearly everyone working with mRNA realized that somehow cells can tell when a premature stop

codon has been inserted into an open reading frame. Yet no one had an explanation of what happened to these nonsense proteins. “There’s nothing different about a premature stop codon. It’s one of the three stop codons in an open reading frame, and there didn’t seem to be any sequence context that made a difference,” says Steitz.

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According to Steitz, the big leap came when Maquat figured out that introns must leave a mark on newly synthesized mRNA. Working with Melissa Moore in the late 1990s and early 2000s, Maquat identified that mark—the exon junction complex (EJC). It is an RNA-binding protein tag that normally sits approximately 20–24 nucleotides upstream from the spot on the mRNA where the intron was cut out. After pre-mRNA splicing, mRNAs with EJCs marking the splice points will move out of the nucleus for protein synthesis. In the first or “pioneer” round, the ribosome machinery will literally knock off the EJC tag as it goes along.

EJC Marks the Spot

But if there is a mistake in the mRNA—either in the genome or acquired during pre-mRNA splicing—chances are that it will manifest as a premature stop codon upstream of an EJC. The ribosome’s surveillance complex will recognize the premature stop codon as aberrant because of the downstream EJC.

Anita Hopper of Ohio State remembers hearing for the first time about the pioneer round of translation when Maquat presented a talk at a 2001 RNA Society meeting. “When I heard that talk, I was just sitting there with my jaw open. Wow. It was really true that you could have heard a pin drop in that audience.”

According to Hopper, Maquat’s NMD mechanism showed that a pioneer round of protein synthesis not only occurs but supports NMD. An mRNA gets used many times by ribosomes to make many proteins, Hopper explains. “Everyone assumed that when mRNA



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engaged with the ribosome, it would undergo exactly the same process. Lynne showed that wasn’t true. The first time the RNA message gets translated is different from all the subsequent rounds. The first time, the message is tested to see if it’s a good message. If it’s not, it gets destroyed. If it’s a good message, it gets changed—the proteins associated with it are altered—and it can be translated many, many times.”

NMD fills out the mRNA story, but it has wider biological implications, according to Steitz. Because premature stop codons are the cause of many human genetic disorders, NMD helps explain why heterozygous carriers of a genetic disease can survive with harmful nonsense codons that otherwise would be dominant. Says Steitz, “If these messages weren’t destroyed, they would cause a dominantly inherited disease.”

Of Maquat’s relentless pursuit of NMD, Steitz declares, “I consider it just a beautiful story of how persistence and always asking the right question and not giving up until you have the partial answers eventually gives you the real answer.”

Work in “A” Lab?

Giving up, though, was exactly what Maquat wanted to do in her first research lab experience. She was an undergraduate at the University of Connecticut (UConn) at Storrs. “I was terribly shy,” Maquat confesses. “I know that nobody who knows me today believes that, but I really was very shy.”

As a UConn sophomore, she’d desperately wanted to join the lab of her cell biology professor, Stu Heywood. She tells the story. “I approached him about working in ‘a’ lab. He said, ‘A lab?’ And I kind of squeaked out, ‘Your lab?’ And he said, ‘Sure.’”

Maquat loved the bench work on protein synthesis in embryonic chick muscle, but as the only undergraduate, she felt out of her depth. Finally she resolved to quit. Maquat waited outside the science building for Heywood to arrive, as usual, on his motorcycle. As they walked in together, Maquat was still fumbling with her resignation speech. Heywood suddenly said, “You know, Lynne, I think you’re doing among the best science in my lab.” Maquat laughs at the memory. “I burst out crying, and he was flabbergasted: ‘What did I say? What did I say?’”

Some of Maquat’s earliest experiences with science were also daunting. Her mother was an operating room supervisor and brought up

her eldest daughter with an inordinate fear of microbes. In high school, Maquat watched in horror as her biology teacher enthusiastically dissected road kill in front of the class. “With my overly hygienic background, what struck me most was how he kept putting his hands that were just in an opossum’s gut in his pockets.” And yet, Maquat remembers dissecting *Planaria* on her own in the family basement.

After UConn, Maquat chose a biochemistry doctoral program at the University of Wisconsin (UW), Madison, partly because she thought the program would be challenging. “And it was *rigorous*,” she concedes. Working with Bill Reznikoff on the lactose operon in *Escherichia coli* was Maquat’s initiation to RNA synthesis. Staying all night alone in the old and creepy UW biochemistry building to tend an experiment—while trying not to imagine building ghosts—is a lasting memory.

Buffalo to Rochester

After a postdoc at the McArdle Laboratory for Cancer Research in Madison, Maquat set out on her own in 1982 at the Roswell Park Cancer Institute (which Maquat points out is the oldest comprehensive cancer care center in the U.S., named for Dr. Roswell Park, and is not a park per se). In 2000, Maquat moved to a faculty post in biochemistry and biophysics at the University of Rochester.

Maquat’s interest in RNA metabolism had accelerated during her postdoc with Jeff Ross in Madison. Then she proved for the first time that a human disease, the hemolytic anemia β^+ -thalassemia, could be due to a pre-mRNA splicing defect. In Madison and then Buffalo and Rochester, Maquat began exploring the fundamentals of β^0 -thalassemia and another anemia called triosephosphate isomerase deficiency. The approach led Maquat to uncover the mechanism of NMD. Its importance as a means of quality control keeps growing as the Maquat lab identifies new molecular players and maps out competing RNA decay networks, she reports. “It turns out that a third of all alternatively spliced transcripts are targeted for NMD because they are mistakes. When you think about it, that’s amazing because conservatively 75% of human genes encode pre-mRNAs that undergo alternative splicing.”

Among her many scientific memberships is the ASCB, where Maquat is finishing a long term on the Public Information Committee (PIC). As an editor for the PIC’s ASCB Annual Meeting press book, Maquat is renowned for

her tactful persistence and her ability to get a corrected manuscript back from a dithering author in 24 hours or less.

Maquat is also extremely active in the RNA Society, having held every elective office from Director to Secretary-Treasurer to President. She is soon to begin organizing the 2011 International RNA Society meeting in Osaka, Japan. But first she has taken on organizing a 2010 Gordon Research Conference in Newport, RI.

Back in Rochester, Maquat has been a prime mover behind the university's "strategic commitment" to a new Center for RNA Biology. She directs the center. She also chairs the University of Rochester Graduate Women in Science program. And she is PI on a new NIH T32 graduate student training grant.

Facing down the unknown is a theme in her life. It was a factor in her turning toward Buddhism, Maquat says. In 1992, she volunteered as the team geneticist on a Children's Hospital of Buffalo "medical trek" to isolated Himalayan communities in northern India. There and on a later trip to the Tibetan capital, Lhasa, Maquat came face to face with the Wrathful Deities. They are demonic but protective figures in Buddhist art who are supposed to guide sentient beings toward enlightenment. Maquat had dabbled in Eastern philosophies before, but the Wrathful Deities drove her to serious study with Buddhist teachers back home.

The Lab Lab

Maquat was also taken by the sheer adventure of trekking in the Himalayas. It turned out to be something she had in common with Mark Spall, a technology development manager she met in Rochester. He'd also hiked over the Kanji-La Pass at 17,500 feet in Ladakh. They were married in 2005 while traveling in Vietnam and promptly set out for Cambodia. "We really like adventure travel," says Maquat. "The Himalayas and Andes are especially wonderful." The couple also shares a condo on Rochester's East Avenue with a black Labrador named Lily. Lily is listed on the Maquat lab site as the "Lab Lab."

Maquat's résumé is clearly that of a "world-class scientist," insists Greg Petsko of Brandeis University. But it omits one aspect of her career: Maquat as science friend. They first met by phone about 25 years ago when Maquat called to discuss an enzyme, triosephosphate isomerase,

that Petsko was no longer working on. The friendship continued even as their research diverged. Petsko explains, "If you're lucky in life, you have friends with whom it doesn't matter how frequent your contacts are, whenever you do see them, you pick up as if time hadn't passed. Lynne's been one of those people. We do talk science, but we're likely to talk about almost anything."

Then in the last five years, Petsko began to study the structure of proteins involved in neurodegenerative diseases. Working in yeast, Petsko identified the gene for an RNA-binding protein that was toxic when overexpressed and then a second gene whose protein suppressed that toxicity. When he went to look up the human homolog, Petsko recalls, "I laughed out loud. It was Lynne's protein. Within 24 hours, I had her clones for the human proteins sitting in my office."

So more than 25 years on, they are finally going to collaborate, says Petsko. "For me, RNA processing is a new field, and when you're going into a new field, the problem is always, 'What can you trust? What's really reliable? Who are the people who are just going on assumptions?' With Lynne, I know I can take anything that she's done to the bank." ■

—John Fleischman

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