Are we there yet?

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I have devoted my entire scientific career to the field of RNA processing, beginning as a graduate student during its fledgling early days and continuing through its expansion to a size and complexity that can barely be accommodated in a single meeting. As this issue will undoubtedly include many accounts of such recent discoveries as microRNAs, I decided to write a subjective/anecdotal account of the events leading up to the founding of the RNA Society and the journal we are honoring at the close of its second decade. As an entering PhD student at Yale, I was very excited about enzymology but, by my second rotation, was hooked on RNA and became the first graduate student to join Alan Weiner's lab. The original goal of my project was to use the developmental program of the cellular slime mold *Dictyostelium discoideum* to shed light on the recently discovered U-class snRNAs. Although the actual body of work I completed involved more chemistry than biology, the seed planted then finally took root in my own research, which in recent years has focused on changes in RNA processing during meiotic progression in the fission yeast *Schizosaccharomyces pombe*.

Looking back many decades later, I feel extremely fortunate to have stumbled into this amazing field. Over the course of my graduate career (1976–81), introns were discovered in all three classes of RNA known at the time, and work began in earnest to elucidate the mechanisms through which they were spliced out to form mature mRNAs, tRNAs, and rRNAs. One memorable winter afternoon in New Haven, I received a phone call from a young assistant professor at the University of Colorado named Tom Cech, who was investigating splicing of the large subunit rRNA in *Tetrahymena*. We discussed the possibility that one of the small RNAs I had characterized in *Dictyostelium*, which included an ortholog of U3 snoRNA subsequently implicated in directing pre-rRNA cleavage, might be involved. The answer, of course, was no, and a decade later Tom was awarded the Nobel prize for showing that the RNA processing reaction he was studying proceeds through a completely unanticipated mechanism, self-splicing. On the other side of the Yale campus, Sid Altman's lab was characterizing the first *trans*-acting catalytic RNA, for which he shared the prize. A few years later,

Phil Sharp and Rich Roberts won a trip to Stockholm for discovering pre-messenger RNA splicing, unaccompanied by a Yale professor who ruefully acknowledged at a departmental retreat that he kept sending his postdocs back to re-analyze SV40 mRNAs because their sequences did not match the DNA.

The development of better and faster analytical tools for RNA research did not keep pace with the rapidly expanding conceptual horizons of the field. After becoming proficient at the labor-intensive techniques available at the time to determine a paltry few nucleotides of sequence, I eagerly embraced molecular cloning, which allowed RNA (and protein) primary structures to be deduced from DNA sequences. The Weiner lab secured a pre-publication protocol for Maxam-Gilbert sequencing, which employed a combination of mutagens and rocket fuel, and also routinely carried out chemical RNA sequencing, which required even more dangerous chemicals. Thankfully, these methods were soon supplanted by Sanger sequencing, which formed the basis for protocols still in use today. My main achievement as a graduate student, described in a 1980 paper published in *Cell*, was to clone the first gene encoding a snoRNA. During the mid-1990s, I responded to my own graduate student's incredulity that the journal's standards were so low even back then with a detailed description of the months of effort required to prepare a probe of sufficient specific activity to perform colony hybridization on a genomic library gridded by hand on agar plates poured in giant plastic trays from the cafeteria. His response: why didn't you just use PCR? The answer, of course, is that it had not yet been invented, and a complete genome sequence for any organism was still nearly two decades off. Alan's introduction to my thesis seminar mentioned how brave I was, prompting fear that he was about to repeat the story of how I foiled an attempted robbery at gunpoint while walking to my car with another student in the lab. Instead, he was referring to my selection of an organism arguably more primitive than *Dictyostelium*, *Saccharomyces cerevisiae*, for my postdoctoral research.

Many factors entered into my decision to join Christine Guthrie's lab at UCSF. First and foremost was a seminar visit to Yale by the woman herself, which took place within a year

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after two fascinating talks by scientists with related research interests. John Abelson's tales of chasing down the mechanism of tRNA splicing fueled my desire to remain in the RNA processing field, while Gerry Fink provided a compelling introduction to the awesome power of yeast genetics. I was particularly eager to apply the newly developed tools of reverse genetics to analyzing RNA processing mechanisms. The final vote was cast by Joan Steitz, a member of my thesis committee whom I admired greatly for combining a brilliant mind with an outlook so unwaveringly positive that, after hearing her speak, one could not help but feel inspired to go forth and push back the frontiers of knowledge. Over the years, my regard for Joan has continued to grow as she made room in her incredibly busy life to serve as an advocate for women.

Although Yale was certainly a high-powered research institution, the atmosphere there was positively bucolic in comparison to UCSF, which had just given birth to the biotech industry. When I arrived in the spring of 1981, the Guthrie group was still quite small, yet my five lab mates included two future RNA Society presidents, David Tollervey and Roy Parker. These guys, along with Christine and her technician, Harold Swerdlow, were also remarkable for towering over me by more than a foot. In spite of the height disparity, I played basketball with Roy and squash with David, who stood calmly in the middle of the court while I bounced around like a pinball. At meetings, I gravitated towards Anita Hopper, a friendly competitor and beacon of positive energy with similar vertical challenges. Even though my first project produced no publishable data, I spent just over three years as a postdoc, quite brief by today's standards. Taking advantage of the expertise I'd developed as a graduate student, I began to work with the group searching for spliceosomal snRNAs in *S. cerevisiae*. We did not achieve our central goal (because it turns out that yeast snRNAs are unexpectedly large as first shown by Manny Ares), but discovered dozens of snoRNAs and disrupted the gene encoding one of these.

Upon publication of these results in back to back *Cell* papers, it seemed like a good time for an academic job search. Upon assuming a faculty position at the University of Illinois at Champaign-Urbana, my plan was to continue a project begun during my final year as a postdoc, to dissect the RNA component of Signal Recognition Particle using reverse genetics. However, we were stymied by the unusually large size of the *S. cerevisiae* RNA (shown several years later by another lab) and decided to switch organisms rather than con-

tinuing to beat our heads against the wall. The wisdom of choosing *S. pombe* based on a report from Norbert Kaüfer and Paul Nurse that it could accurately splice a pre-mRNA of mammalian origin (unlike *S. cerevisiae*, reported earlier by Jean Beggs) seemed clear from our first gel, which revealed a small RNA profile indistinguishable from HeLa. We were embraced by the fission yeast community but alas, not the secretion field, and splicing soon came to the forefront once again.

Over the next several years, our research program was successful enough that I was invited to organize the 1993 and 1995 RNA Processing Meetings at Cold Spring Harbor and to become an Executive Editor of *Nucleic Acids Research*. However, having been abandoned by Olke Uhlenbeck soon after I arrived at UIUC (though I certainly can't blame him for moving to Colorado) and facing a general lack of appreciation for the importance of RNA biology from my remaining colleagues (who nevertheless granted me tenure and applauded my work on the SRP54 GTPase), I decided to seek a position elsewhere. Fortunately, Tim Nilsen, who chaired the splicing mechanisms session at the 1993 CSH meeting, was hiring several faculty members into what would soon become the Center for RNA Molecular Biology. My arrival at Case in 1994 coincided with the *RNA* journal's inception, and I cannot emphasize enough how fortunate I feel to have access to an editor of Tim's caliber to read my papers before submission, and to be part of the collegial group of faculty members he has assembled. Even beyond the Nobel prize-winning discoveries, the past two decades of RNA research have impacted our understanding of biology as a whole far more profoundly than I could possibly have imagined as a naïve graduate student. A few notable examples are broad acceptance of the concept that RNA served as the sole information carrier and catalyst in ancient cells, the revelation that the genetic complexity of humans is due largely to alternative RNA processing, and the growing appreciation for the roles of non-coding RNAs both large and small. Will we continue to uncover secrets as amazing as these over the next two decades? At the very least, I hope to win my bet with Tim about co-transcriptional gene silencing, in which nuclear siRNAs target nascent transcripts as part of a complex that interacts with RNA polymerases and associated RNA processing factors. Whether this pathway, first discovered and best understood in fission yeast, occurs in metazoans is currently controversial. Only time will tell who's right!

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