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Book Review

Gene Machine: The Race to Decipher the Secrets of the Ribosome by Venki Ramakrishnan, Basic Books, 2018

Peter R. Bahn*

Bahn Biotechnology Company, 10415 E. Boyd Rd., Mt. Vernon, IL 62864, USA

****Corresponding author:*** Peter R. Bahn, Bahn Biotechnology Company, 10415 E. Boyd Rd., Mt. Vernon, IL 62864, USA; **E-mail:** pbahn@mvn.net

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Book Review

When I was a Yale Graduate student in the Department of Molecular Biophysics and Biochemistry, from 1972 to 1978, there were several notable scientists in the department including Joan Steitz, her husband Tom Steitz, Don Engelman, Peter Moore, and Sidney Altman. In 1978, just as I received my Ph.D. from Yale, a new postdoctoral student named Venki Ramakrishnan was starting work in Peter Moore's lab. Joan Steitz was studying ribosomal RNA binding sequences. Tom Steitz was using X-ray crystallography to study the three dimensional structure of large proteins like hexokinase. Don Engelman and Peter Moore were using neutron diffraction to study distances between deuterated pairs of ribosomal proteins. Sidney Altman was investigating the chemical properties of tRNAs. Venki Ramakrishnan's work with Peter Moore on the ribosome would, three decades later, lead to a path of Ramakrishnan winning the Nobel Prize in Chemistry, along with Tom Steitz and Ada Yonath.

Finding Ramakrishnan's book for sale at Barnes & Noble, and knowing some of the principals involved in this story, I had to read it. It is a beautifully written, riveting book. In some ways, *Gene Machine* bears similarities to another seminal scientific memoir *The Double Helix* written by James Watson, describing his race with his partner Francis Crick to decipher the secrets of DNA. In other ways, Ramakrhishnan's narrative is different.

As related by the author in his book, Ramakrishnan received his undergraduate degree from Baroda College in India and his Ph.D. from the University of Ohio. After his post doc in Moore's lab, Ramakrishnan landed his first independent job as a biophysicist at Brookhaven National Laboratory in 1983. In 1988, to learn X-ray crystallography, he took a two-week course in the subject at Cold spring Harbor Laboratory. In 1989, to learn more about crystallography, Ramakrishnan took a sabbatical year at, and several years later, took a staff position in the famous MRC Laboratory of Molecular Biology (LMB), where Watson and Crick had deduced the structure of DNA after Watson had looked at her Rosalind Franklin's X-ray photographs of DNA, and for which Watson and Crick won a Nobel Prize shared with Franklin's supervisor Maurice Wilkins in 1962. Sadly, Franklin died before that Nobel Prize was given.

In the early 1980s, Sidney Altman and Tom Cech discovered that RNA can catalyze chemical reactions much like protein enzymes, for which they won a Nobel Prize. Such RNA catalysts are called ribozymes and led to the speculation that life on earth originated in a RNA World where the first catalysts were ribozymes instead of proteinacious enzymes

Also, in the 1980s, Harry Noller at the University of California, Santa Cruz, was noticing that the ability of the ribosome to translate the genetic code written in messenger RNA into proteins seemed to be largely resistant to enzymes that cut up the ribosomal proteins, implying that ribosomal synthesis of protein from amino acids was catalyzed by ribozymes within the ribosome rather than ribosomal proteins. It was also around this time that Ada Yonath, of the Weizmann Institute in Israel, demonstrated that it was possible to obtain crystals of the ribosome which produced X-ray diffraction patterns. From these it would be theoretically be possible to determine the precise three dimensional map of the structure of the ribosome to atomic scale precision.

Finally, in this period, Tom Steitz and Peter Moore teamed up to begin studying the three dimensional structure of the ribosome by X-ray crystallography.

Thus, at the end of the millennium, the stage was set for race to discover the complete three dimensional structure of the ribosome, the organelle inside the biological cell that translates the genetic code into proteins that form the structures and enzymes of each cell. As Ramakrishnan's scintillating narrative shows, this race was not going to be easy. In fact, all of the groups of researchers studying the structure and chemistry of the ribosome employed many grad students, post docs, and collaborators with enormous talents and skills in biomolecular analysis. The human character and brilliant contributions of these diverse molecular biologists are told with a considerable charm by Ramakrishnan in his book. Ramakrishnan is excellent at giving credit where credit is due, something which does not always happen in the modern competitive scientific world. It is very nice to see it here.

Not that there was any lack of tension in the race to the ribosome structure. Each of these researchers was working full speed in the hope of scooping the opposition. In the way that things worked out, the Steitz & Moore group concentrated on deciphering the structure of the 50S subunit of the ribosome, Ramakrishnan's group concentrated on the structure of the 30S subunit, while Noller's group

and Yonath's groups concentrated, by differing methods, on the whole 70S ribosome. All of these people who worked on the ribosome were friends and knew each other and met regularly to talk and compare notes at various conferences. Throughout his book, Ramakrishnan describes the honorable illuminating competition that goes on in science everyday and that is the glory of this subject. By the end of the millennium the thrilling race told by Ramakrishnan was essentially over, and the different research groups displayed their results in a really beautiful Volume LXVI of the Cold Spring Harbor Symposium in 2001.

The ribosome is one of the most complicated cell organelles ever studied. It is a monstrously complex concatenation of RNA and protein, having a diameter of approximately 200 Angstroms and a total molecular weight of about 3 million Daltons. It is comprised of 80 ribosomal proteins, making up 35% of its weight and 4 large ribosomal RNAs (rRNAs), making up 65% of its weight. A picture of the ribosome at atomic scale, shown on the cover of Ramakrishnan's book, looks like an extremely complicated tangle of spaghetti. Most of the proteins are on the surface of the ribosome. Most of the interior is comprised of RNA. Thus, the synthesis of most proteins that goes on in cells is catalyzed by ribozymes, not enzymes. In this regard, the RNA World currently lives on in every biological cell on Earth.

As is often the case, the Nobel Committee in Sweden took several more years, until 2009 to award the Nobel Prize in Chemistry to Tom Steitz, Venki Ramakrishnan, and Ada Yonath. The rules of the Nobel Foundation limit the prize to three recipients. If there were no such limitation, then Peter Moore and Harry Noller would undoubtedly also have also shared in the Nobel Prize. While appreciating the great honor given to him by his peers, Ramakrishnan takes distinctly philosophical point of view by pointing out that winning a Nobel Prize in science is largely a matter of luck and of being in the right place at the right time. He also points out that many prestigious science prizes now bestow much more money than the Nobel Prize. Still, I have to give Ramakrishnan much credit for writing a book that is as riveting as *The Double Helix* but told with a natural grace and honesty that is lacking in Watson's triumphal memoir.

Strangely enough, the classical era of X-ray crystallography in molecular biology that began with Watson and Crick's use of Rosalind Franklin's X-ray photographs of DNA in 1953 and ended with Ramakrishnan's X-ray photographs of the ribosome half a century later may finally be over. In 2015, I attended the 5th Zing Nucleic Acids conference in Tampa, Florida. I was amazed to see that on the slides of most presenters that the backgrounds of the nucleic acids shown always showed the immediate protein surroundings of the nucleic acids to atomic level resolution. Several scientists told me that such atomic scale resolutions of proteins (and nucleic acids) were now seen with atomic electron microscopes on single molecules without the need for crystals or X-rays. Biomolecular structures that used to take years by X-ray crystallography are now routinely being solved in weeks. In this sense, with the new millennium, molecular biology has entered a brand new era in which molecular biologists struggle to decipher the exceedingly intricate mechanism by which such complicated biomolecular machines as the ribosome operate.

I have just one complaint about *Gene Machine*. It lacks an index. Hopefully this will be added in future editions. Otherwise, it is a very fine book, well worth reading.

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