Illuminating the Code Reader*

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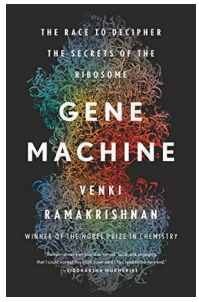

Gene Machine: The Race to Decipher the Secrets of the Ribosome
Author: Venki Ramakrishnan
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In January of 2016, IISER Mohali community, including me, was all geared up about the upcoming visit of Nobel Laureate Venkatraman "Venki" Ramakrishnan. I was particularly excited to hear his lecture on the Nobel Prize-winning work. It was one of the most effective introductions of a scientific topic that I had heard, and which has stayed with me all this time. To introduce us to his groundbreaking work, Venki showed profile pictures of world-famous influential people, the likes of Mozart who had died at a young age because of infectious diseases. He asked the audience to imagine how much our lives would be enriched and beautified by their unique and unmatched talent, had they not succumbed to these infections. This led on to the topic of antibiotics and their role in combating bacterial infections and the common cellular target to which many of these antibiotics bind–the ribosome.

Now in his memoir, Gene machine, Venki Ramakrishnan provides a candid, engaging and witty account of his scientific journey and of the race to solve the atomic structure of ribosome. The structure of the ribosome has been central to our current understanding of how this molecular machine mediates the translation of messenger RNA (mRNA) into protein.

Ramakrishnan's journey in science was anything but straightforward or easy. As a young researcher, there must be several occasions where it appears to the reader that he should have given up or let the status quo be as it is. For instance, realizing that he was not excited about research in the area of condensed matter physics, or not getting faculty job interviews, let alone an offer, after applying to more than 50 different institutes or the one that he did accept eventually at Oak Ridge National Lab did not provide support to test his ideas. As Ramakrishnan notes, "Looking back, it still astonishes me that my career worked out at all after so many false starts and dead ends. My beginnings were not promising. There were so many times when I could have fallen off the edge and disappeared from the world of science, a fate I only avoided by changing track

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or starting over again". Indeed, the readers observe that a common theme in Ramakrishnan's scientific journey was his determination to follow his passion and that he is not scared to make wrong choices.

At Brookhaven National Lab where he eventually established his independent research group, it was clear to Ramakrishnan that neutron scattering, a technique he had used during postdoctoral training with Peter Moore at Yale, was never going to lead to an atomic map of ribosome crystals. This prompted him to collaborate with colleague and crystallographer by training, Steven White, to determine the X-ray crystallographic structures of purified ribosomal proteins. However, as Ramakrishnan elaborates "I didn't want to just sit back and watch Steve solve them. I wanted to learn how to solve them myself." And thus, he got himself trained in the technique by attending a short course on X-ray crystallography at Cold Spring Harbor Laboratory and subsequently taking a year of sabbatical with Aaron Klug at the MRC-Laboratory of Molecular Biology in Cambridge. Reading this part in the memoir, I was both struck and inspired, as the immediate focus of many early and mid-career researchers as myself, is to establish a track record of publications rather than solving a fundamental problem in science. Indeed as Ramakrishnan also notes, "What I didn't quite realize then was that my sabbatical had changed forever both my attitude towards science and how I would approach the ribosome. When I returned, I found I was no longer satisfied with making solid but incremental advances and instead wanted to attack the big questions in the field." This part of the book also narrates the history of protein crystallography in a lucid manner, which should enable understanding of the fundamental principles of X-ray crystallography to both scientists and non-scientists.

Eventually, it seems that specialized scientific meetings in the field of ribosome biology gave the author some insights into where the field stands at the time and the realization "that rather than just contributing to the effort, I had a chance to make the next real breakthrough." More importantly, while it appeared that there was intense competition between the various research groups including that of Thomas Steitz and Ada Yonath, the other two winners of the Prize with Ramakrishnan, it also convinced the author that his "idea of using special atoms with synchrotrons to solve the structure using anomalous scattering still seemed to be the only way forward". As the author notes "In the end, what really swayed me was the realization that the structure of the ribosome was the most important goal in my field. There seemed a narrow window of opportunity, and since I had a clear idea of how to attack the problem, it would be a mistake to be dissuaded by this new development." And the rest, as they say, is history. Ramakrishnan's group would go on to attain the atomic resolution structures of the small or 30S ribosomal subunit and then of the complete 70S ribosome, providing fundamental insights into how ribosome ensures accurate reading of the codon and why mismatches

are allowed at the third base of the codon. Further, the atomic structure also allowed Venki's group to determine the binding sites of several antibiotics (including the clinically relevant antibiotic, tetracycline) on the small subunit of the ribosome.

In Gene machine, Ramakrishnan makes a commendable effort to describe his fellow scientists–quirky and funny facts about their personalities, their family history and their academic careers, which makes the narrative interesting and humorous and also lets the readers become involved in Ramakrishnan's journey. The text also captures the human face of scientific research, the disappointments of the failed experiment, adrenaline rush of whether the new approach has worked and the excitement of building the model and seeing the beauty of your discovery in its full glory. As Ramakrishnan sums it up in the book "THE ATOMIC STRUCTURES OF THE subunits were amazing. It was like landing on a new continent and encountering completely new and different terrain." While Ramakrishnan's work revealed the structure of the smaller 30S subunit, Thomas Steitz, in collaboration with Venki's postdoc advisor, Peter Moore, uncovered the structure of the larger 50S subunit. Yonath's work paved the way for these studies by creating the first crystals of a molecule as large as the ribosome, consisting of a million atoms.

For their discovery of the structure of this fundamental macromolecule central to life itself, Ramakrishnan, Steitz and Yonath would share the Nobel Prize in Chemistry in 2009. A common question asked to most Laureates is how they felt when they came to know, to which Venki has accurately and with all honesty summed up "It certainly did not bring the immediate burst of excitement that made Brian and me do high fives at the Brookhaven synchrotron when we saw peaks from the tungsten clusters, or when we saw our anomalous peaks in Argonne and knew the structure had been cracked." Indeed, no award or recognition can match up with the feeling of discovering something for the first time.

It was clear that the Nobel committee chose these three winners as their discovery of the atomic structure was central to the understanding of how ribosome functions. However, as Ramakrishnan also notes "Unlike in sport, the distinction between competition and collaboration is not so clear cut in science: even when scientists are competing, they are actually using one another's advances to make progress and are thus collaborating, albeit involuntarily." Two other key figures in this race were Harry Noller who showed that ribosome is a ribozyme i.e. the RNA component is responsible for the peptide bond formation catalyzed by the ribosome and Joachim Frank who captured the images of ribosome in different stages using electron microscopy. Indeed, Noller would go on to receive the Breakthrough Prize in 2016 "*for discovering the centrality of RNA in forming the active centers of the ribosome*" and Joachim Frank was awarded the Nobel Prize in Chemistry in 2017 "*for developing cryo-electron microscopy for the high-resolution structure determination of*

biomolecules in solution."

Towards the end of this memoir, Ramakrishnan shares his views on the nature of science, "When we have a clear goal in mind, we think we are struggling to reach a summit. But there is no summit. When we get there, we realize we have just climbed a foothill, and there is an endless series of mountains ahead still to be climbed." Ramakrishnan devotes the epilogue to share his views on being the chosen one and receiving the ultimate Prize "Science never emerges from a vacuum. Rather, advances are made when certain ideas are in the air, and the state of understanding in a field and developments in technology reach a stage where those ideas can be pursued. When that happens, one or more people happen to see the next possible advance a little before everyone else.....So I don't subscribe to the heroic narrative of science. Rather, some of us are fortunate enough to be the agents of important discoveries that would have been made anyway, sometimes not even that much later.....So even if discoveries are inevitable, we recognize that it is individuals who make them happen, and we like to honour those who took that first leap into the unknown, to go just beyond what was thought to be possible."

Gene machine is a highly interesting and thoughtful account of a momentous discovery in science that will captivate the attention of readers driven by the curiosity towards the inner workings of our natural world.

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