STRUCTURAL BIOLOGY

From ribosome to Royal Society

Georgina Ferry enjoys Venki Ramakrishnan's account of his road to the Nobel Prize.

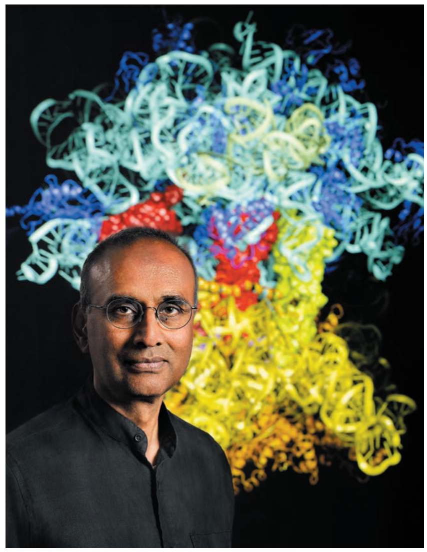
In 1968, the molecular biologist James Watson electrified the staid world of scientific biography by publishing *The Double Helix*, his memoir of the discovery of DNA's structure. Its irreverent style shocked and delighted readers in equal measure. And it changed how many think about science, by presenting it as a race in which winners got Nobel prizes and losers got nothing.

Fifty years later, structural biologist, Nobel laureate and Royal Society president Venki Ramakrishnan tells the story of his own marathon. In *Gene Machine*, he thoughtfully embeds his trajectory in a wider meditation on how scientists make the decisions that lead to success or failure — and on how they struggle to solve complex problems. "Scientists will collaborate or compete depending on what is in their self-interest," he writes, adding that competition can be "good for science, even if it isn't so great for scientists."

Ramakrishnan recognizes from the outset that, although most people today have at least a vague idea that DNA is the carrier of genetic information, the ribosome barely registers. Yet, without it, life as we know it would not have evolved. Every living cell contains millions of these complex structures, each consisting of a large and small subunit and incorporating a few dozen proteins and long strands of RNA. They are themselves protein factories. Each ribosome works along a molecule of messenger RNA, reading its copy of the genetic instructions encoded in DNA. Guided by this, ribosomes assemble protein chains that then float off to do the work of building and running the body.

This much was already known when Ramakrishnan began to work on the ribosome in 1978 — although, as he writes, "we had no idea how it did even one of the many complicated steps involved in making a protein". The race for the ribosome would reframe it as an intricate machine with numerous working parts — which you can now watch in action on YouTube.

Indian-born, with academic parents, Ramakrishnan studied physics at the University of Baroda (now Vadodara) in Gujarat. In 1971, he went to Ohio University in Athens for graduate work in theoretical physics. By the time he had submitted his thesis, he had decided to switch to biology. Reading around a subject about which he knew almost nothing, he picked the ribosome on the strength of a *Scientific American* article co-authored by biologist Peter Moore. Within a few years he was on the starting blocks, as a postdoc in Moore's laboratory at



MAX ALEXANDER/SPL

Venki Ramakrishnan.

Yale University in New Haven, Connecticut.

It was clear that the only way to understand the ribosome was to solve its 3D structure at the resolution of individual atoms. Ramakrishnan retrained in X-ray crystallography, then the preferred technique of structural biologists.

Structural biologists face near-impossible challenges. These include making floppy, irregular proteins form crystals to bombard with X-rays; obtaining a diffraction pattern from the irradiated crystals before the structures disintegrate; and solving the ever-present 'phase problem', the ambiguity in a diffraction pattern caused by peaks in an X-ray wave giving the same intensity as troughs. Eventually, software generates maps of electron density at high-enough resolution to 'see' the individual atoms. For the big, complicated ribosome, many research teams in different countries worked on each of these problems successively or simultaneously.

The acknowledged founder of the ribosome field is Israeli crystallographer Ada Yonath. She, with colleagues at the Max Planck Institute for Molecular Genetics in Berlin, published the first successful crystallization of a ribosomal subunit in 1980. An unwritten rule in crystallography at the time was that once someone had a crystal, everyone else would leave it to them to progress to atomic resolution. Ramakrishnan writes that the ribosome was different because of its importance, and the fact that years had gone by "without much apparent progress towards an actual structure". By 1995, four groups around the world were in competition, and several others were contributing key techniques to improve crystallization or locate atoms.

Gene Machine: The Race to Decipher the Secrets of the Ribosome
VENKI RAMAKRISHNAN
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In 1999, Ramakrishnan moved to the mecca of structural biology, the Medical Research Council Laboratory of Molecular Biology in Cambridge, UK. Scientists at this one lab had already garnered seven Nobel prizes. The institution has now racked up 11 — more than some scientifically advanced nations. Ramakrishnan focused on the smaller of the ribosome's subunits, which decodes mRNA before the larger subunit assembles the protein.

By 2000, he and his colleagues had solved its structure, finishing neck and neck with the team of Thomas Steitz at Yale, which had solved the large subunit. Previously seen as a rank outsider, Ramakrishnan was propelled into the limelight. A Nobel for the ribosome work was being openly discussed. There were up to six potential contenders for a prize that can be split only three ways. James Watson twice told Ramakrishnan that he shouldn't mind not being one of the three when the time came. Yet, in 2009, the time did come. Yonath, Ramakrishnan and Steitz shared that year's Nobel Prize in Chemistry.

Ramakrishnan credits his wife, the artist Vera Rosenberry, with keeping him grounded: on hearing of his prize, she said, "I thought you had to be really smart to win one of those!" He reflects on the disproportionate status such recognition brings. Suddenly, you're showered with other honours, and expected to pronounce sagely on everything from climate change to human cloning.

Some readers might take issue with how events or personalities are presented in *Gene Machine*. Yonath's pioneering work is fully acknowledged, for example. Yet, as Ramakrishnan's principal competitor, she sometimes appears in an unfavourable light. This is not an objective history of the field, but a highly personal account. As such, anyone who wants to know how modern science really works should read it. It's all here: the ambition, jealousy and factionalism — as well as the heroic late nights, crippling anxiety and disastrous mistakes — that underlie the apparently serene and objective surface represented by the published record. ■

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