Steven Shapin

Gene Machine: The Race to Decipher the Secrets of the Ribosome
by Venki Ramakrishnan.
Oneworld, 272 pp., £20, September 2018, 978 1 78607 436 2

RNA gets no respect. It's similar in make-up to its charismatic chemical cousin, with small structural variations. DNA is a very large double-stranded helix while many RNA forms are single-stranded; one of the four nitrogenous bases in DNA is different from its equivalent in RNA; and the base-bearing backbone in RNA contains the five-carbon sugar ribose, while that in DNA has one less oxygen atom – hence deoxyribose (so RNA is 'ribonucleic acid' while DNA is 'deoxyribonucleic acid'). It's the physiological role of these small differences that accounts for RNA being the Cinderella of the nucleic acid family. No corporate mission statement says that 'innovation is in our RNA' (CommBank) and no automobile advertisement claims that 'adventure is in our RNA' (Land Rover). When the much-missed Arsène Wenger said that Arsenal was 'an attacking team', he didn't announce that this aggressive style of play was 'in our RNA'. And you can't find a dictionary definition explaining that 'Your RNA is what makes you uniquely you.' One of the most instantly recognisable graphic icons of modern bioscience, or indeed of modernity itself, is a schematised DNA double-helix, but, if you aren't a biochemist or geneticist, you'll have no idea what RNA looks like and little notion of its role in the scheme of life.

When Watson and Crick discovered the structure of DNA in 1953 – bounding into a Cambridge pub and bragging that they had solved 'the secret of life' – the molecular basis of heredity was immediately apparent. The sequence of bases in one strand of DNA was shown to be complementary to that of the other, meaning each strand could be a template for reproducing its mirror-image twin, yielding chemically identical double-helical progeny. This is the molecular mechanism by which like produces like. It was also apparent – though the biochemical pathways were not then understood – that the sequence of bases along the DNA strands might constitute a functional code – a blueprint detailed enough to instruct cellular mechanisms how to go about building the structures and conducting the processes of life. But the structures themselves either contained proteins or required those proteins called enzymes to be constructed, ordered and regulated. There are a lot of proteins in living organisms – maybe ten million differ-

ent forms – each made up from a palette of twenty amino acids and each assuming specific three-dimensional configurations that allow it to perform its vital function. The emerging research agenda of molecular biology was, therefore, a problem of translation. What were the processes and structures through which DNA code became protein reality? How did sequences of four DNA bases specify each of the twenty amino acids, and how were these amino acids then assembled into proteins? One agenda for post-Watson-Crick molecular biology was to crack the code; another was to discover the molecular mechanisms of code-translation.

Some years after the 1953 discovery, Crick and Watson announced the so-called Central Dogma of Molecular Biology, a widely-circulated version of which stated that DNA makes RNA and that RNA makes protein. The DNA code, they said, was read by forms of 'messenger RNA' (mRNA) which then carried those coded instructions from the cell nucleus to extra-nuclear sites where proteins were constructed. The amino acid building blocks carried there by particular types of 'transfer RNA' (tRNA). The role of DNA in both heredity and in coding for proteins was solved in principle, and all that remained for molecular biology was the problem of how all this worked in practice. For some scientists, the theoretical solution was the great prize and the work that remained to be done was regarded as a series of mopping-up operations or mere puzzle-solving, what the historian Thomas Kuhn called 'normal science'.

By that time it had become clear that the cellular organelle where proteins were manufactured was the ribosome – given its name by an American microbiologist. The ribosome was known to be an extremely complex structure. But what was its atomical architecture? How did its molecular bits and pieces fit together? How did it work in protein manufacture? You couldn't tell very much about ribosomal structure by seeing it directly, for example, by electron microscopy: the maximum resolution was far from good enough. The question for scientists was whether there were available techniques – or whether new techniques could be developed – that would allow them to infer and represent its detailed structure, each atom in its proper place.

That is where Venkatraman Ramankrishnan comes into the story. An Indian from Tamil Nadu who had done his doctoral work in physics at an unexceptional university in the American Midwest, Ramankrishnan didn't set out to discover the 'secret of life' or even to work on biological subjects. His early story, as he tells it in *Gene Machine*, is not one of vision and vocation but of drift and accident. Molecular biology was founded in the mid-20th century largely by physicists who had wandered into biology, and Ramankrishnan strayed in too, drawn by the excitement following on the Watson-Crick discovery. In 1976 – physics doctorate in hand, newly married and with two young children – he decided to take up biological research, the precise nature of which remained to be determined. It had nothing to do with ribosomes, and what he knew about them at the time wasn't appealing. The distinguished South African mo-

lecular biologist Sydney Brenner had said that discovering the structure of the ribosome was a 'trivial problem' while Watson reckoned that the structure was so dauntingly complicated – experimentally the opposite of 'trivial' – that it might never be worked out. But as a post-doc at Yale, Ramakrishnan came into the orbit of researchers who believed that various forms of radiation, including those produced by new types of particle accelerators, might help to establish how atoms were arrayed in the ribosome – and they were determined to do it.

A few things were already known about its structure and about the functions of its parts. Unlike nuclear DNA, the ribosome is not one molecule but many, comprising about a million atoms. It is made up of around two-thirds ribosomal RNA (rRNA) and one-third protein, of more than fifty different types. The ribosome itself has two physically separable sub-units: the 'small sub-unit', which 'reads' the mRNA, and the 'large sub-unit', where the amino acids are assembled into the polypeptide chains of proteins. In the 1980s, ribosome research became defined by the search for its structure: it was thought that this discovery would explain how the ribosome read the DNA code and made proteins. The drive to discover this went beyond disinterested biological understanding. There implications for commercial pharmacology: it was already known, for instance, that antibiotics act on the microbial ribosome, disrupting protein synthesis. (Ramakrishnan doesn't seem to have been consumed by practical problems of drug-action, but pharmaceutical concerns ultimately affected the availability of funding for research into ribosome structure.)

At the time Ramakrishnan entered the field, however, ribosome research was unfashionable, and so was he. In 1981, having finished his post-doc, Ramankrishnan sent out over fifty applications for academic jobs, all of which were rejected. Some universities apparently doubted whether his English was good enough for teaching purposes; others were sceptical about his qualifications for doing serious biological research; still others seemed to share the view that ribosome work just wasn't going anywhere. He was rescued by the high-energy physics institutions established during the Cold War, whose research involved using radiation beams to investigate ribosome structure. Several years later, having spent some time at the Oak Ridge National Laboratory in Tennessee, Ramankrishnan was offered a position as staff scientist at the Brookhaven National Laboratory on Long Island, where he remained for 12 years before moving on to the Laboratory of Molecular Biology at Cambridge. In 2000, Ramakrishnan's team at Cambridge solved the structure of the small sub-unit. Shortly after, scientists at Yale worked out the large sub-unit, then in 2007 a structure for the whole ribosome was revealed. What followed were the rewards expected for achievement of that scope and significance: a share of the 2009 Nobel Prize in chemistry, a knighthood, honorary degrees, India's highest civilian honour and in 2015 the presidency of the Royal Society.

There were several approaches to solv-

ing the ribosome, but the young Ramakrishnan banked on crystallography. The technique was simple to state, but extremely difficult to execute. You make a crystal – that is, a purified regular latticed structure of the molecule or molecular aggregate in question – and then subject it to various forms of radiation, notably X-rays. [How and why do you make crystals? Because the ribosome can't withstand the X-ray?] The diffraction patterns then obtained reveal where the constituent atoms are arranged in space. Rosalind Franklin's 'Photo 51' of crystallised DNA – which Watson and Crick famously obtained without her knowledge or permission – was used as crucial evidence of its double-helical structure; the idea was to do the same with RNA. But RNA is a far more complex molecule and obtaining X-ray crystallographic images of it proved to be an entirely different matter.

The practical complexity of solving ribosome structure through X-ray crystallography matched the complexity of the structural target. First, you needed to find ribosomes stable enough even to attempt crystallisation: these were discovered by researchers in Israel, Germany and Russia working on micro-organisms living in extremely hot or salty water. Then you had to get these organisms to grow in lab conditions, to extract and purify the ribosomes, to get the sub-units – and eventually entire ribosomes – to form crystals good enough to work with, to ensure that crystal-making procedures that worked in one lab also worked in other labs and in other researchers' hands, to devise techniques ensuring that the ribosomes weren't damaged by the same X-rays used to produce diffraction patterns, to write software programmes to interpret those patterns and finally to achieve the extraordinarily high resolutions that would allow the determination of atom-by-atom structure. Ribosome crystal-growing, crystal-image-interpreting, the writing of appropriate software and devising conventions for the graphic representation of molecular structure are as messy, delicate, time-consuming and complex as anything in modern science. Watson and Crick modelled the structure of DNA; solving the structure of the ribosome would mean seeing it.

To Ramakrishnan, the ribosome is a machine, but you can also think of it as a factory – an organised system of machines – and ribosome discovery, like so much present-day science, was itself done through factory-like divisions of technical labour. No one scientist, nor any one type of scientist, could solve the problem on their own. Some researchers could engineer the right sort of ribosome crystals; some could produce the diffraction patterns; others could write the computer programmes to make sense of the patterns; and a few others – especially Ramakrishnan himself – had the networking skills to bring together the findings of dispersed research groups and the drive and imagination to attempt goals that others thought impossible. Samples circulated around the world and researchers moved from lab to lab, learning the unique skills on offer at each establishment. Ramakrishnan's account of the the discovery of the ribosome has aspects of the picaresque. Almost every step towards

the solution involved movements of people from one lab to another and from one international ribosome conference to the next, between coffee-table-talks in scientific establishments around the world.

Gene Machine comes advertised as 'a personal story', perhaps gesturing to James Watson's *The Double Helix: A Personal Account of the Discovery of the Structure of DNA*. But it's 'personal' in a different way. There are 'personalities': one of Ramakrishnan's assistants keeps himself motivated in the achingly cold conditions need to grow ribosome crystals by playing Johnny Cash CDs; a Ferrari-owning Californian RNA scientist names his computers after Italian Grand Prix drivers. Ramakrishnan himself is a vegetarian, 'near teetotaller' family-man and there are no Jim Watson-style chases after 'popsies'. The young Ramakrishnan admits to being ambitious, but also despairs that his contributions will ever be properly recognised and chides himself for caring about what he calls the 'politics' of scientific recognition and scientific prizes. There are passages in *Gene Machine* when secrets are securely shielded from rivals or in which restricted distribution is requested, but on the whole information and ideas flow freely. A few of the ribosome researchers get on each others' nerves; but there are only a few thorough-going jerks and none of the Watson-Franklin animosity, coming close to bodily violence, that animated *Double Helix*. Instead the excitement resides in Ramankrishnan's descriptions of the often-frustrating extended labour of ribosome research and the dogged persistence of ribosome researchers, year after year, decade after decade. □