INSIDE every living cell, tens of thousands of tiny machines churn out cargos of amino acids with mind-boggling speed and precision. This tiny machine the size of one millionth of an inch routinely helps turn genes into flesh and blood or as we biologists say translates the genetic code into functional proteins.

Research revealed ribosome to be a factory more than a machine. When this complex molecule was first glimpsed under an electron microscope, it looked somewhat inconsequential, with three different RNA molecules and more than 50 different proteins. In the watery interior of the cells, these pieces form two parts, called the 30/40S and the 50/60S subunits, which drift apart and together based on ionic concentration.

The small subunit is the “brain” of the ribosome, which reads the genetic code; its “heart”, where proteins are made, is bigger. Intense research on various aspects of this VIP organelle were credited with three Nobel Prize discoveries starting with Theodor Svedberg for ultra-centrifugation that characterised the subunits, Palade for its discovery and Steitz, Yonath and Venki Ramakrishnan for unveiling its ultra-structures. This article unveils some possible queries addressed in recent years in ribosome research in the form of a fictitious interview.

1. Mr Ribosome, let’s start with origin. We have all read about the debate whether DNA or RNA came first and with evidence and logic we support the RNA world hypothesis. If so, can ribosomes also act as a record of evolution?
Yes, let me enlighten you a bit on this. In June 2014, NASA astrobiologists compared three-dimensional structures of me by digitally peeling back my layers isolated from a variety of species of varying complexity (humans, yeast, bacteria, etc.) and they found distinct fingerprints and the presence of a basic skeleton where the complexity was added to my surface without altering my core. They concluded that I must have originated over 3 billion years ago before the Last Universal Common Ancestor (LUCA). It was also inferred that my core was the same, but expanded and became complicated as species gained complexity. So, ribotyping is usually carried out nowadays for phylogenetic classification.

2. You are a superhero who churns out proteins according to the cell’s need, at an immense rate and precision. Do you apply brakes in between?
Yes, of course. I translate the three letters (codon) at a time into the proteins that run most of the working of the cell. I glue the amino acids together and shove the growing protein chain out through the exit tunnel in my back. Researchers used to ask me whether I move at a constant rate. Though the speed of translation affects folding and localisation of the final protein product, my speed is majorly based on the abundance of specific tRNA or majorly due to mRNA secondary structures. Due to these secondary structures, I have to plough through the tangled segments of transcripts, which slows me a bit. Finally, when I translate positively charged amino acids like
lysine, arginine and histidine the positive charges interact electrostatically with the negative lining of my exit tunnel, gumming it up and hence some time act as sand traps for me (Roberts, 2013).

3. If so can we trap ribosomes in their footsteps?
Ok you mean, catch me if you can? Oh yes. In the year 2016, Baranov and Loughran at Cork University mentioned a powerful enhancement technique known as translation complex profile sequencing (TCP-seq) which helps to get a snapshot by scanning and further mapping of ribosomal complexes.

4. What is your life span? How are you degraded in the cell?
It’s natural to die as to be born. Again, it is the cell’s need and its balance of synthesis, degradation, and recycling of cellular products that decides my birth and death. I am selectively degraded through ribophagy – eating of ribosomes. Ubiquitin-specific protease 3 (Ubp3) and Ubp3-associated cofactor Bre5 are the proteins that mainly assist in my recycling during starvation (Kamilla et al., 2009) and later when required my biogenesis happens.

5. We consider you as nature’s miracle. Can we artificially synthesise ribosomes?
Even though the initial attempts to mimic my structure and function were utter failures, recently a few great minds of the North Western University & Harvard University tried an approach of ‘one-pot’ synthesis in which they tossed the genes encoding ribosomal RNA, natural ribosomal proteins and additional enzymes of an E. coli cell together and succeeded to an extent in giving birth to me. This in vitro birth can transform the ability to engineer novel forms and bio-catalytic ensembles for useful purposes. Me being a chef, I hope they are planning to make ‘brand new chefs’ and can alter them to do new things too.

6. Recently we heard of robotic ribosomes. We are so excited. What are they?
Yes, my role in translating genetic material to the workhorses was ascertained by a group of scientists at the University of Manchester and was considered as a mechanical marvel. These are not my substitutes but they are nanomachines that can produce short chunks of protein (peptides). Structurally they mimicked me using rotaxane based large molecular ring threaded onto another molecule that acts as an axle. The axle is linked to three and a chain of three more amino acids hangs from the outer edge of the ring. Cysteine is attached to the ring and heating prompts the thiol to pluck an amino acid from the axle and transfer it to the end of the chain of amino acids attached to the ring. This trick can be repeated, and later unthreaded or broken off to release the peptide. But it’s too slow compared to me; I heard it takes about 12 h to attach each amino acid where I attach about 15-20 amino acids per second (Lewandowski et al., 2013).

One of my friends, Ribo-T (first human-made) was created in the laboratories of Alexander Mankin at Center for Biomolecular Sciences, UIC College of Pharmacy along with Michael Jewett of Northwestern University. Unlike me, his subunits won’t separate. He was tuned to produce unique and functional polymers for exploring ribosome functions or producing designer therapeutics (https://news.uic.edu/researchers-design-first-artificial-ribosome).

7. We know that you are the target for most of the antibiotics, but can we tackle some complex diseases caused by ‘prions’ through you?
Recent reports suggest my role in preventing prion diseases like mad cow and Creutzfeldt-Jakob also. Let me first clarify that they are targeting my protein folding activity, which is most likely involved in prion propagation. Two prion inhibitors 6-aminopentanidine and guanabenz acetate implement antiprion activity by binding to ribosomal RNA and inhibiting PFAR. An in vitro PFAR assay has been developed and can be used as a platform for screening prion inhibitors in a high-throughput fashion.

It was wonderful to know more about you. I think the coming years will unravel your qualities further for the betterment of the living world. Thank you Mr. Ribosome.

Veda Krishnan and Anchara Sachdev are with the Division of Biochemistry, Indian Agricultural Research Institute, Pusa, New Delhi-110012. Email: vedabiochem@gmail.com
Biju Dharmapalan is with the Mar Althanasios College for Advanced Studies (MACFAST), Kerala.