**Messenger-RNA delivers a Nobel**

**Zareena, Mookayi and Mari**

Mari was slowly cycling home from the nearby Post Office after sending a letter. She was lost in thought. What a fascinating story it had been about **Kariko**. She had recently learnt that this year’s Nobel prize in medicine or physiology was given for the work on **messenger-RNA**. Yes, the same messenger-RNA which was used to develop vaccines for *Covid-19*. She had looked up about **Katalin** **Kariko** and **Drew** **Weissman** who had shared the Nobel prize.

But what had fascinated her had been the story of Kariko. What a human story of one who never gave up her ideas though she faced so many difficulties. And yet she was so cheerful and had no ill feeling towards anyone in her interviews.

There was a familiar shout and she crashed into someone. She fell down and got up dusting herself looking around to see what happened an­d found she had crashed into Zar. She found her friend Mooks grinning at her while trying to lift up her cycle.

Zar was scowling and picking up the scattered books saying, “Look what you have done. The library books I was bringing to your house are all covered in dust”. Mari lost her cool. “You made me fall and you are blaming me!” Mooks tried to pacify them both “Now, now…these things happen. Nobody is hurt, the cycle is not broken and the books are not damaged. So you both stop this. Luckily this happened just outside Mari’s house”.

Just then Usha called out from the house. “Mari, Mooks and Zar, come inside. Have the *mixture* and *badusha* which I just made. Then I will get you some tea and we can discuss the article you are planning to write. Did you get the books on Kariko I told you about, Zar?”

Zar looked at the books and she replied to Usha. “Yes, I got them. The librarian said you had called and told her”. Then scowling at Mari added in a low voice “And now Mari by her riding without looking has made them fall down and get all dusty!” Then she carefully cleaned them with her kerchief.

Once inside, like birds on a banyan tree making a lot of racket, they ate what Usha had put on the table. They quieted only when they started drinking the tea. Usha checked the books Zar had placed on the table. Both were as she asked. One was a beautifully illustrated children’s book by Debbie Dadey called “*Never Give Up: Dr. Kati Karikó and the Race for the Future of Vaccines*” and the other was a delightful memoir by Katalin Karikó herself: “*Breaking Through: My Life in Science*”. She had seen these books in the meeting she went to and had found them unfortunately expensive. Luckily she got her friend to recommend the University Library to get them which they did very quickly. She made sure the books were not damaged and set them down again on the table. She went to the other room to call her friend the librarian and thank her.

Usha came back and found the three animatedly discussing and browsing the books. She sat down with them. “OK. Now you three read these two books and we will meet after a day to discuss about the article for ***Jantar Mantar***”.

Zar said without stopping, “I already know about how Kariko after she did her PhD in Hungary had to leave the country, and ended up in the US. She went through so much difficulty but kept pursuing her working on using mRNA for medicine. She found that just a simple change of using modified **Uracil** in synthetic mRNA could prevent the immune system from attacking it. This way you can prevent unwanted allergy-type reactions. This made it possible to use mRNA with *modified bases* to make vaccines when Covid happened!”

Mooks said to Zar when she paused to catch her breath, “Oh.. here is Ms Know-It-All again”. Mari quickly butted in before a fight began, “Hey guys,...I also saw the news and some of the reports. But let us read these books and then talk about our article. So come on, let’s go sit outside. It is such a nice day! Amma, can Zar and Mooks stay for lunch and go in the evening?” Usha smiled and said “Of course. They can help you cook some additional rice later. We already made quite a bit of *sambar* and *kootu* in the morning.”

*Two days later...*

Mari, Mookayi and Zari came to Usha and told her ,“We read the books and have come up with an outline of an article. Can we discuss it with you?” Usha put aside the paper and smiled. “Of course. Let’s start”.

Mari said, “We first introduce vaccines using Covid-19 as an example. Let’s see. These are (see Box for explanations):

- The inactive SARS-Cov2 virus used in Covaxin,

- The modified replication deficient adenovirus carrying the optimised DNA of the spike protein of SARS-Cov2 as in Covishield,

- The receptor binding domain of the spike protein of SARS-Cov2 used in Corbevax,

- The Pfizer/Moderna modified base containing mRNA of the SARS-Cov2 spike protein.

**BOX on Types of Vaccines**

Most Covid-19 vaccines target or use the spike or S protein which resides in the envelope of the SARS-Cov2 virus.

**Covaxin** was developed by a traditional method of vaccine formulation, which is **composed of adjuvanted inactivated viral particles**. This means that Covaxin contains (6µg of) the entire Covid virus, but in an inactivated form. An **adjuvant** is an ingredient used in some vaccines that helps create a stronger immune response so the vaccines work better.

**Covishield** is a r**ecombinant, replication-deficient chimpanzee adenovirus vector**. This means that the basic entity is an *adenovirus* that causes cold and flu. A chimpanzee adenovirus, as the name suggests, causes cold and flu in chimpanzees which are biologically closely related to humans. The word *recombinant* means that the adenovirus has a portion of it replaced with some foreign protein. In this case, the protein which is inserted is that found in the spikes of the SARS-CoV-2 virus. Finally, *replication-deficient* means that the virus is not able to replicate by itself in the host. The spike protein part of the vaccine generates the immune response in the human being.

**Corbevax** also uses the S-protein in the spike of the SARS-Cov-2 virus to generate immunity.

Pfizer/Moderna are names of the two companies that make **mRNA vaccines**. Such vaccines use a special type of RNA called messenger-RNA or mrNA. Instead of containing a piece of the virus, it uses the mRNA to direct the human cells to produce copies of SARS-Cov-2 spike protein, which then generates an immune response.

**END OF BOX**

For those who have learned about DNA, Usha added more details. “First introduce the fact that DNA (deoxyribonucleic acid) has what are called **nucleic acid bases**. These form the “rungs” of the DNA “ladder”. These bases are used to make the mRNA or messenger RNA in the nucleus of the human cell. Then the mRNA is used by the ribosomes in the cytoplasm (outside the cell nucleus) to make the protein. The virus contains RNA which is converted to mRNA directly by an enzyme called RNA-dependent RNA-polymerase which is encoded in the viral RNA itself. The viral RNA also encodes the spike protein that is part of the viral coat protein.”

**Small BOX: messenger RNA (mRNA)**

Messenger RNA (abbreviated mRNA) is a type of single-stranded RNA (unlike DNA which is double stranded in the famous helical shape) involved in making or synthesis of proteins in cells. It is read by a *ribosome* to make proteins. So mRNA vaccines contain mRNA which makes proteins, for example the spike protein of the SARS-Cov2 virus. A special protein called R**NA-dependent RNA polymerase** (RdRp) or **RNA replicase** for short is also present. This is an enzyme that catalyzes or enables the replication of RNA from an RNA template. So the mRNA contains both the RNA that makes the protein as well as the instructions which tell it to make the protein! The human body then generates an immune response against this protein to protect us from severe infection.

**END OF BOX**

Zar added, “We should also mention the discovery of mRNA by **Brenner**, **Jacob** and **Messelson** in 1961”.

Mooks replied “Yes. We will do that. And also tell about how in all vaccines the spike protein is used to produce both types of immune response – antibody based and T-cell based - in the cell. Of course in the inactive virus all components of the virus are used to raise both antibodies and T-cell responses”. (See Box for explanation).

**BOX on Lymphocytes**

**Lymphocytes** or white blood cells play an essential role in your immune system. Your immune system fights infection-causing pathogens (viruses, bacteria, fungi and parasites) and harmful cells, like cancer cells.

Both B-cells and T-cells are a type of lymphocytes. They’re also called B and T lymphocytes.

Both types are part of your body’s defense. When your immune system detects **antigens** — markers that indicate a threat like a bacteria or virus has entered your body — your B-cells produce proteins called antibodies to fight the invader. T-cells protect you by destroying harmful pathogens and by sending signals that help control your immune system’s response to threats.

**END OF BOX**

Zar broke in, “But we must tell the advantage of an mRNA vaccine. That is, the mRNA can be in the cytoplasm of the cell and make many copies of itself as it has both the **spike protein** and the **RNA** **replicase** encoded”.

“I have an idea,” Mari said .“At this point, why not introduce the problem people faced earlier? That is, before the work of Kariko and Weissman of using mRNA for vaccine or therapeutics? I mean there is a tangled history to the use of and work on mRNA for vaccines and therapeutics since the first suggestion and trial by Malone in 1988. The mRNA that they used caused a lot of inflammation as side effect. It was only in 2005 when Kariko and Weissman showed that *modified mRNA* is not recognized by the body as foreign. So there was no inflammtion produced and only then that the use of mRNA really became feasible”.

Zar added “Yes, we can mention that Kariko and Weissman used **Uracil** as a substitute for a nucleic acid base. The body did not recognise this **modified** nucleic acid base in its messenger RNA as a foreign body but thought it was a self RNA. So it did not react and cause inflammation”.

Mari said “Then at the end we can bring in the story of Kariko. How she had to emigrate from Hungary as she lost her job there and by chance got an opening in USA. Later how she was almost sent back from USA due to the person who enabled her to come into the country complaining to immigration department that she was illegally there.”

“I know. How nasty of the person just because she got a job at another place without his help,” agreed Mooks.

Zar continued “We can then say how she moved to University of Pennsylvania but still she was harassed there because she continued to work on mRNA which did not get her grants. I mean she was asked to leave or to continue with lower pay”.

Mari went on, “Yes, how terrible. But she said she will work on mRNA there only and she continued without a proper lab. Luckily for her meeting Weissman by accident and their doing work together to use mRNA against HIV helped her find out that modified base containing mRNA is not seen by the body as foreign and did not trigger allergy response”.

Mooks said “We should add how Kariko did not look only for positive results , even though their experiment failed but she still worked on the problem and solved it”.

Usha tried to caution them, “Adding all this is nice, but just keep in mind that the article should not be too long or the Editor will cut your article short! In fact, it’s time you sat down now and wrote out the article!” So saying, Usha smiled and went back to her newspaper.

***Sources (including figures): Nobel archive at nobelprize.org and Wikipedia***