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mRNA VACCINES: USING TINY PARTICLES TO FIGHT VIRUSES

Inbal Hazan-Halevy, Edo Kon, Lior Stotsky-Oterin and Dan Peer *

Laboratory of Precision Nanomedicine, Shmunis School of Biomedicine and Cancer Research, George S. Wise Faculty of Life Sciences, Tel Aviv University, Tel Aviv, Israel

YOUNG REVIEWER:

HILEL

AGE: 13

Nanoparticles are tiny containers that scientists create to carry molecules. How tiny? Let us say that a nanoparticle is about 100,000 times smaller than a single M&M candy. Scientists use special nanoparticles to treat specific diseases. For example, the mRNA vaccines that protect people from COVID-19 contain nanoparticles that are packed with mRNA molecules from the virus. In this article, we will answer some interesting questions: What are nanoparticles made of and how do they work? What are the mRNA molecules that are packed inside the nanoparticles of the COVID-19 vaccine? How do scientists create mRNA vaccines, and how do they protect us from COVID-19?

HOW VACCINES WORK

All vaccines work in a similar way. The idea behind any vaccine is to introduce into the body weakened viruses or bacteria (or even just a piece of a disease-causing virus or bacteria), that will be harmless but will still stimulate the body's immune system. This way, the body

can "practice" on a harmless form of the disease-causing organism and become prepared to protect us when the actual, dangerous form of the virus or bacteria arrives. The immune system is very accurate and has a type of memory. For example, if you are vaccinated against a virus, your immune system generally recognizes and protects you against that virus for a long time after vaccination. Mostly, the immune system recognizes proteins on the surface of a bacterium or virus. For the rest of this article, we will focus specifically on viruses, although much of what we will tell you also applies to bacteria.

ANTIBODIES

Proteins produced by B cells of the immune system to fight invading viruses and bacteria.

The immune response is complicated and includes several types of cells, including T cells that can bind to and destroy cells that are infected by viruses, and B cells that can produce proteins called **antibodies**. Antibodies help protect the body by recognizing and attaching to viruses and marking them for destruction. Once produced, antibodies remain in the body as a type of immune memory, to help the immune system respond quickly if exposed to the virus again.

mRNA LIPID NANOPARTICLE (MRNA-LNP) VACCINES

Vaccines made of lipid nanoparticles containing mRNA that codes for a viral protein.

The first vaccines that were created gave people's immune systems a chance to react against viral proteins by introducing whole weakened or dead viruses into their bodies. But technology has advanced, so today's scientists can create vaccines based on the exact proteins they want the immune system to react to, without introducing the entire virus into the body. While there are several methods to do this, we will focus on how scientists use **mRNA lipid nanoparticle (mRNA-LNP) vaccines**, which have been very effective in the fight against COVID-19 [1]. mRNA-LNP vaccines are made of two main components: the mRNA and the lipid nanoparticle. We will first describe the role of the mRNA molecule.

FROM DNA TO PROTEIN

NUCLEIC ACIDS

Molecules made out of units called nucleotides, come in two naturally occurring varieties: deoxyribonucleic acid (DNA) and ribonucleic acid (RNA).

RIBOSOME

A cellular "factory" that makes proteins.

MESSENGER RNA (mRNA)

An RNA molecule that carries a gene's code from the DNA in the nucleus to the ribosome in the cytoplasm, to produce a protein.

NUCLEOTIDES

Building blocks that form nucleic acids.

Both RNA and DNA are molecules called **nucleic acids**. DNA is a very stable nucleic acid that codes for the production of proteins. However, DNA is located within the nucleus and the production of proteins takes place in the cytoplasm—outside of the nucleus—in a molecular factory called the **ribosome**. A molecular messenger called **messenger RNA (mRNA)** carries the code from the DNA in the nucleus to the ribosomes in the cytoplasm. Therefore, each mRNA molecule is a copy of a DNA gene containing the instructions (message) to make a specific protein. How does this code work?

Nucleic acids are made of chains of molecules called **nucleotides**. DNA is made up of four types of nucleotides: adenine (A), thymine (T), guanine (G), and cytosine (C), linked one to the other to form two long strands. The two DNA strands are connected by a pairing of the nucleotides (A with T, and G with C; for more details about nucleic acids and the process of creating proteins, see this Frontiers for Young Minds article). RNA molecules also have four types of nucleotides,

three of which are the same as DNA: A, G, and C; but instead of T, RNA molecules contain uracil (U). Combinations of three nucleotides in a row code for specific **amino acids**. For example, if RNA contains the code GUU, the ribosome will incorporate an amino acid named valine into the protein chain, while if GCU is coded for, the ribosome will incorporate an amino acid named alanine into the chain. Proteins are long chains of amino acids. Human cells contain 20 different kinds of amino acids that ribosomes can link together in various combinations and lengths, to create unique proteins.

AMINO ACIDS

Building blocks that form a protein.

After scientists discovered the genetic code, they could create the instructions for *any* protein, by making the mRNA molecules that code for that protein. In the case of mRNA-LNP vaccines, the mRNA codes for a surface protein of a virus—the structure on which scientists want the immune system to practice. The challenge with mRNA molecules, however, is that they are fragile and difficult to get inside of cells. For this reason, scientists invented the second component of the mRNA-LNP vaccines—the lipid nanoparticles, which both protect mRNA molecules and transport them into cells.

WHAT ARE LIPID NANOPARTICLES?

Nanoparticles are any tiny particles that range between 1 and 100 nanometers (nm) in size. 1 nm is a million times smaller than 1 mm (1 mm is the average size of a grain of coarse sand). Nanoparticles are so small that they cannot be seen by the human eye or even using a light microscope. They require very advanced microscopes, called electron microscopes, to see of them (Figure 1). Electron microscopes produce images that have much more detail than those produced by standard light microscopes (Figure 2). Over the years,

NANOPARTICLES

Small particles that range from 1 to 100 nm in size; a nm is one-millionth of a mm.

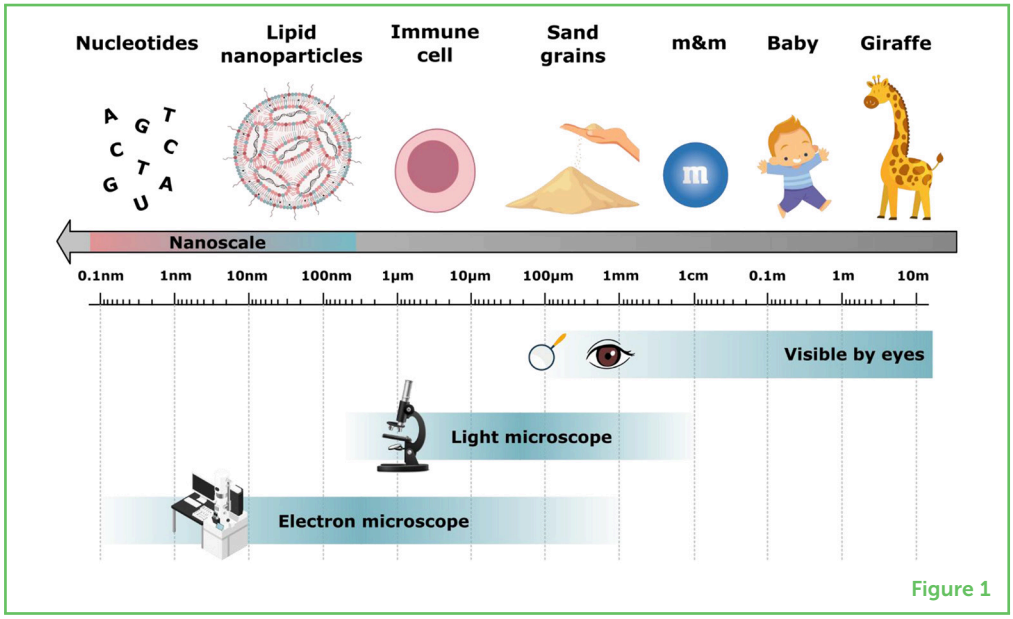

Figure 1

The nanoscale includes the range between 1 and 100 nanometers. Lipid nanoparticles are about 100,000 times smaller than an M&M candy.

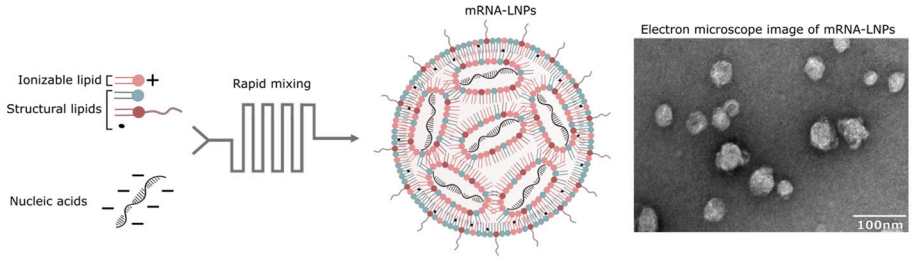

Figure 2

Lipid nanoparticles (LNPs) are made of nucleic acids (mRNA) and lipids that are rapidly mixed. Ionizable lipids have a positive charge, while mRNA molecules (and other nucleic acids) have a negative charge, therefore they stick together to create tiny clumps of mRNA molecules surrounded by ionizable lipids. Other lipids, named structural lipids, also participate in creating these clumps and are responsible for creating an outer layer surrounding the mRNA clumps, forming the LNPs. An electron microscope can be used to see the structures of mRNA-LNPs and measure their size.

scientists have engineered many types of nanoparticles, made of various materials.

Lipid nanoparticles (LNPs) are made by mixing building blocks that can be found in nature: lipids (fats) and nucleic acids. Both lipids and nucleic acids exist in every cell of the body. Lipids are the main component of the cell membrane. If you look at the LNP structure, you will notice that the RNA molecules are enclosed within the lipid structure (Figure 2).

The main component in LNPs is a type of lipid called an **ionizable lipid**. Ions are charged molecules—they can have positive (+) or negative (–) charges. In nature, positively charged molecules are attracted to negatively charged molecules and they stick together. To form LNPs, ionizable lipids are rapidly mixed with mRNA molecules. In this mixture, the ionizable lipids have a positive charge while the mRNA molecules are negatively charged; therefore, a combination of these two components is formed. Each molecule of mRNA is attracted to several ionizable lipid molecules. In this way, tiny clumps of mRNA molecules become surrounded by lipids. The other lipids in the mixture (called structural lipids) organize these structures and create a capsule (outer coating) around them [2]. When we look at LNPs with an electron microscope, we can see that LNPs have a circular structure with a size of about 60–100 nm, and they are filled with masses of lipids and nucleic acids (Figure 2).

LIPID NANOPARTICLES

Nanoparticles made of lipids and nucleic acids.

IONIZABLE LIPID

A class of lipid molecules that has the ability to gain a positive charge or remain neutral.

RNA MOLECULES AS MEDICINES

Combining mRNA and LNPs in this way, scientists can now efficiently create any protein they want inside cells. LNPs can also be used to transport other types of nucleic acid molecules. For example, the first LNP drug, approved in 2018, delivered interfering RNA (RNAi) molecules that as opposed to mRNA, prevent the formation of proteins in the liver cells of patients who suffer from a liver disease called amyloidosis. Recently, two mRNA-LNP vaccines have been approved to protect the population from COVID-19. These vaccines use LNPs to deliver mRNA molecules coding for a specific protein found on

SPIKE PROTEIN

Protein that expresses on the surface of SARS-COV2 viruses and allows them to penetrate host cells.

the surface of the COVID-19 virus, called the **spike protein**, for the immune system to practice on [3].

HOW DOES THE mRNA VACCINE AGAINST COVID-19 WORK?

mRNA-LNP vaccines are injected into the muscle, where they are swallowed by muscle and immune cells. After entering the cells, the mRNA-LNPs release their mRNA molecules into the cells' cytoplasm. In the cytoplasm, ribosomes "read" the code on the mRNA, using it to create the viral spike protein.

When the spike protein breaks down inside cells, small pieces of it are moved to the cell membrane, where they are "shown" to T cells and B cells. These immune cells recognize the spike protein as foreign (not from a human) and create an immune response, including antibodies against it. Eventually, the mRNA from the vaccine breaks down and all that remains is the immune system's memory (Figure 3) [4].

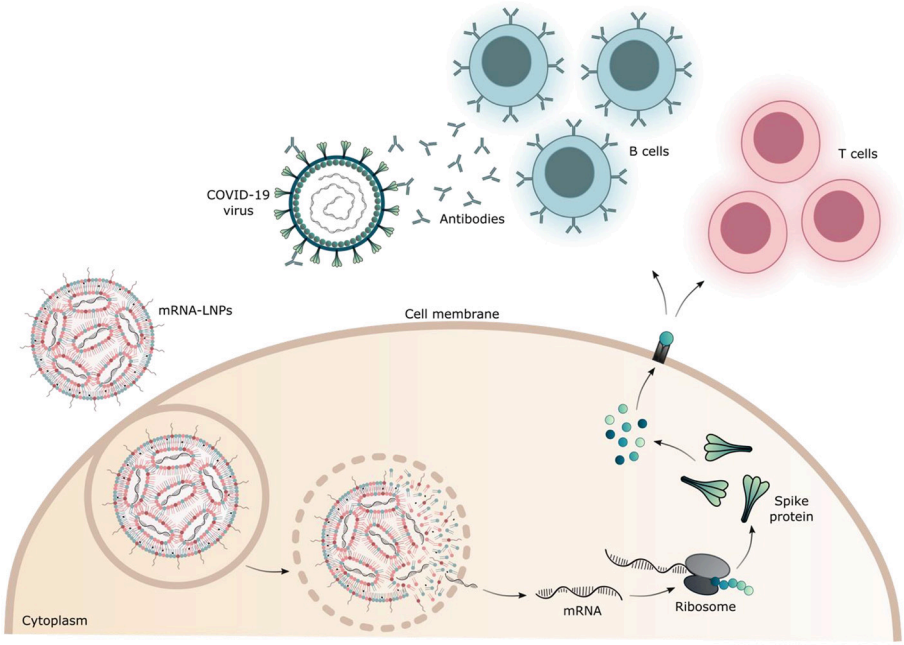

Figure 3

The immune response to mRNA-LNP vaccines. mRNA-LNPs are swallowed by muscle or immune cells. The genetic code in the mRNA is translated by the ribosome to create the spike protein. When the spike protein breaks down, pieces of it travel to the cell membrane where they can trigger the T and B cells of the immune system, "training" them to fight against the COVID-19 virus.

WHY ARE mRNA-LNP VACCINES A BREAKTHROUGH?

mRNA-LNP vaccines are relatively safe, very effective, and can be produced quickly. Scientists can simply make any desired mRNA that codes for a specific protein, and pack it within the LNPs. That makes LNPs a very useful tool. Also, since the mRNA molecules are destroyed in the cytoplasm, do not enter the nucleus, and do not affect the DNA, these vaccines are safe. This type of vaccine is the result of many years

of research invested by great scientists who were very helpful in the fight against the COVID-19 pandemic.

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YOUNG REVIEWER

HILEL, AGE: 13
I live in Tel Aviv. I study in a gifted student class and love combining art and science. I won national math competitions and participated in Tel Aviv University's DaVinci

Project. Piano playing has been a passion of mine from a young age, I compose, play different instruments, and sing in a musical ensemble.

AUTHORS

INBAL HAZAN-HALEVY
Inbal is a researcher at the Laboratory of Precision Nanomedicine at Tel Aviv University, Israel. After completing her Ph.D. studies in Israel, she did postdoctoral training in Houston, Texas, USA. In the laboratory, she is developing lipid nanoparticles to deliver therapeutic RNA molecules to cancer cells, specifically blood cancers. She enjoys practicing Pilates, reading, and spending her free time with her family.

EDO KON
Edo Kon completed his Ph.D. studies at Tel Aviv University, where he developed new mRNA-lipid nanoparticle (LNP) vaccines. In his research, he studied how mRNA-LNP vaccines work against viruses and how to also make them work against bacterial infections. He is now attempting to create new RNA-LNP-based therapies to treat many diseases. In his free time, he enjoys spending time with his family, reading, and watching old movies.

LIOR STOTSKY-OTERIN
Lior is a Ph.D. student in Dan Peer's Laboratory of Precision Nanomedicine at Tel Aviv University, Israel. Her research focuses on developing potential new therapies for a type of blood cancer called mantle cell lymphoma. She is interested in learning more about genes involved in cancer pathology and hopes to use this knowledge to develop new strategies for improved cancer therapy. In her free time, Lior enjoys spending time with her family, including their beloved dog Luka and making delicious desserts—mostly brownies.

DAN PEER
Dan Peer is the director of the Laboratory of Precision Nanomedicine at Tel Aviv University, Israel. The Peer lab is designing novel techniques to change cells' function, using targeted and safe lipid nanoparticles, the most advanced technology for the delivery of nucleic acids into cells. His lab is using nanotechnology tools to create novel therapeutic strategies for inflammatory diseases, rare genetic diseases, and cancers. In his free time, he likes to travel and make wine. *peer@tauex.tau.ac.il