SASTA OLIPHANT SCIENCE AWARDS

Prize Winner

Science Writing

Year 11-12

Mark Gul

Glenunga International High School

Science as a Human Endeavour Task
The Development of mRNA-based Vaccines

By ***Mark Gul***

Introduction:

On New Year's Eve of 2019, the world woke up to the news of a local viral outbreak in Wuhan, caused by an unknown Virus (WHO, 2019). The situation escalated and by February, the disease had spread to 21 different countries including the United States, Australia, Germany, United Kingdom, India, and many others (WHO 2019, Kantis 2021). It was officially declared a pandemic by WHO on March 11, 2020, and was averaging more than 80,000 daily new cases and 6,000 daily deaths during April (WHO 2021, Worldometer 2021). Now known as the COVID-19, this pandemic has caused extensive economic and social disruption; businesses and factories closed down, schools stopped running, international trades came to a halt. The International Monetary Fund (IMF) estimated global costs due to COVID-19 was approximately USD $28,000,000,000,000 (Elliott, 2020). The government urged the development of vaccines in order to suppress and eliminate COVID-19. A vaccine would typically take 10 years to develop due to its complex process, however, COVID-19 was spreading at a rapid rate and the world couldn't afford to wait 10 years (Bollmann, 2018). Introduced by necessity, mRNA-based vaccines were among the first COVID-19 vaccines to be commercialized. Within three months, both Moderna's mRNA vaccine and Pfizer/BioNTech's mRNA vaccine had moved to solidarity clinical trials (WHO, 2021). In the fight against the COVID-19 pandemic, mRNA vaccines have emerged as the main vaccination technique. This report will explore the biology behind mRNA-based vaccines, how it was developed, and the interactions between this technology and society.

Biology of mRNA-based Vaccines:

In a live infection of COVID-19, the virus uses SARS-CoV-2 spike proteins to infect and damage the body's cells, preventing it from performing its regular functions (Newswire, 2021). To build up the body's immunity to COVID-19, mRNA-based COVID-19 vaccines work by simulating a live infection of COVID-19. The mRNA contains instructions to produce the same protein from a live infection of COVID-19 (THL, 2021). The mRNA is given to the body's cells, causing them to produce the virus and triggering a T-Cell response and antibody production from the immune system. The mRNA is injected into the upper left muscle and travels through the bloodstream to the immune cells (Newswire 2021). Once it reaches them, it sends instructions to the immune cells to produce SARS-CoV-2 spike proteins (THL, 2021). Some of the spike proteins are displayed on the cell membrane, known as immunogens, which triggers the production of antibodies from plasma B-cells (Newswire, 2021). The immunogens also stimulate the production of cytotoxic T-Cells, which binds to infected cells and neutralizes them, preventing the viral protein from spreading between cells (Newswire, 2021). At the end of the process, the body gains active immunity to COVID-19 and learns how to protect itself against future infections.

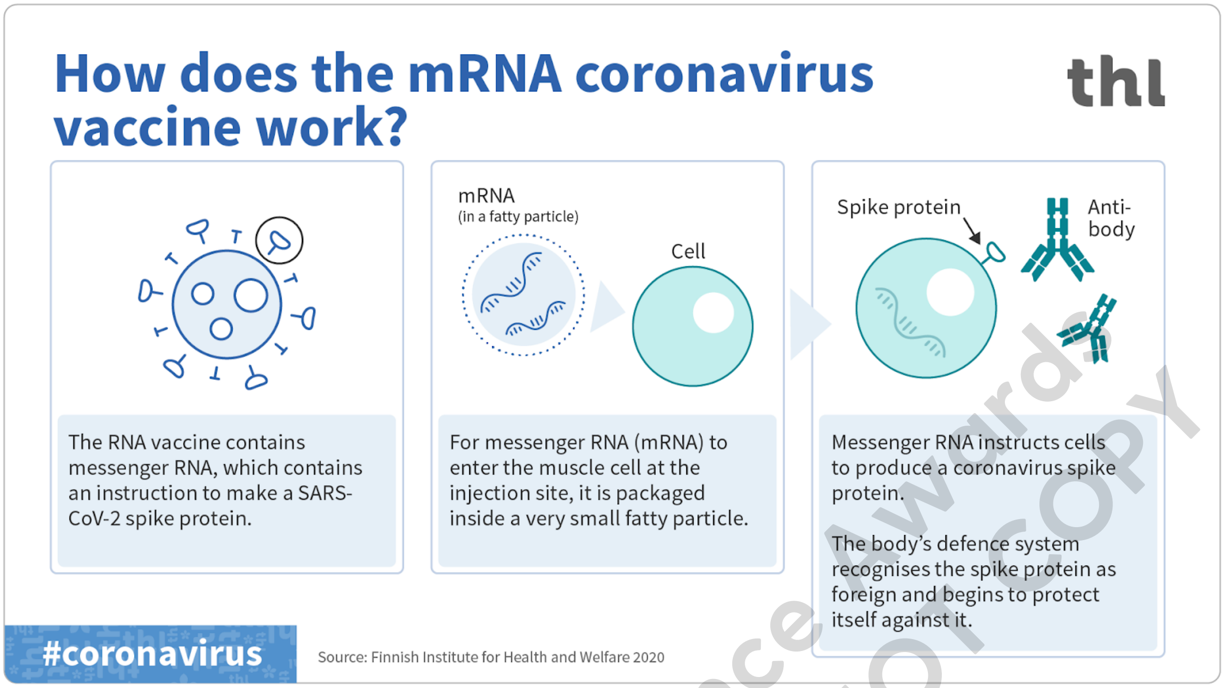

Figure 1: How does the mRNA coronavirus vaccine work? (Finish Institution for Health and Welfare, 2021)

Development of mRNA-based Vaccines:

Traditional vaccines depended on physically growing the live virus, which could take several years. But COVID-19 was rapidly spreading between countries threatening human lives and the economy on a global scale. Developing a vaccine in the shortest amount of time was of the utmost importance, thus the utilization of mRNA-based vaccines. Research in mRNA technology over the past 50 years has made mRNA vaccines possible. The first research started in 1971 when scientists from the University of Cambridge were studying protein production. They put mRNA from a rabbit into frog egg cells, which led to the frogs' cells producing rabbit versions of that protein (Gurdon, 1971).

In the early 1990s, researchers started using mRNA as a potential Vaccine (Cuiling, 2019). They encountered the first problem where the mRNA was too immunogenic, causing it to be destroyed before it could send the message to the cells. After 12 years of research, this problem was solved by Katalin Karikó and her longtime partner Drew Weissman at the University of Pennsylvania (Garde, 2020). Similar to DNA, the RNA is composed of four nitrogenous bases: adenine, cytosine, uracil, and guanine (Ruairi, 2020). When the arrangement of these four bases was slightly altered, it made the RNA less recognizable to the immune system, which decreased the immunogenicity (Pardi 2013). These modifications allowed the mRNA to be customizable so that scientists could find the perfect amount of immunogenicity that still triggers the immune system but not so much that it destroys the vaccine too soon. In 2013, researchers at the University of Pennsylvania were able to successfully modify the stand of RNA so that the immune system didn't react too soon (Pardi 2013).

The next problem was that the mRNA molecule was very unstable and struggled to pass through the cell membrane. It was very inefficient to send RNA to the cell as the free-floating RNA would split apart before reaching its destination. However, in 2016, research done by the Massachusetts Institute of Technology and Harvard Medical School found the solution to this problem was to coat the mRNA with an LNP layer (Reichmuth, 2016). LNP's have a positive charge which allows them to stick to the negatively charged cell membrane (Reichmuth 2016). The LNP then undergoes a process known as endocytosis; a process where cells take in substances outside the cell by engulfing them into a vesicle (Reichmuth 2016).

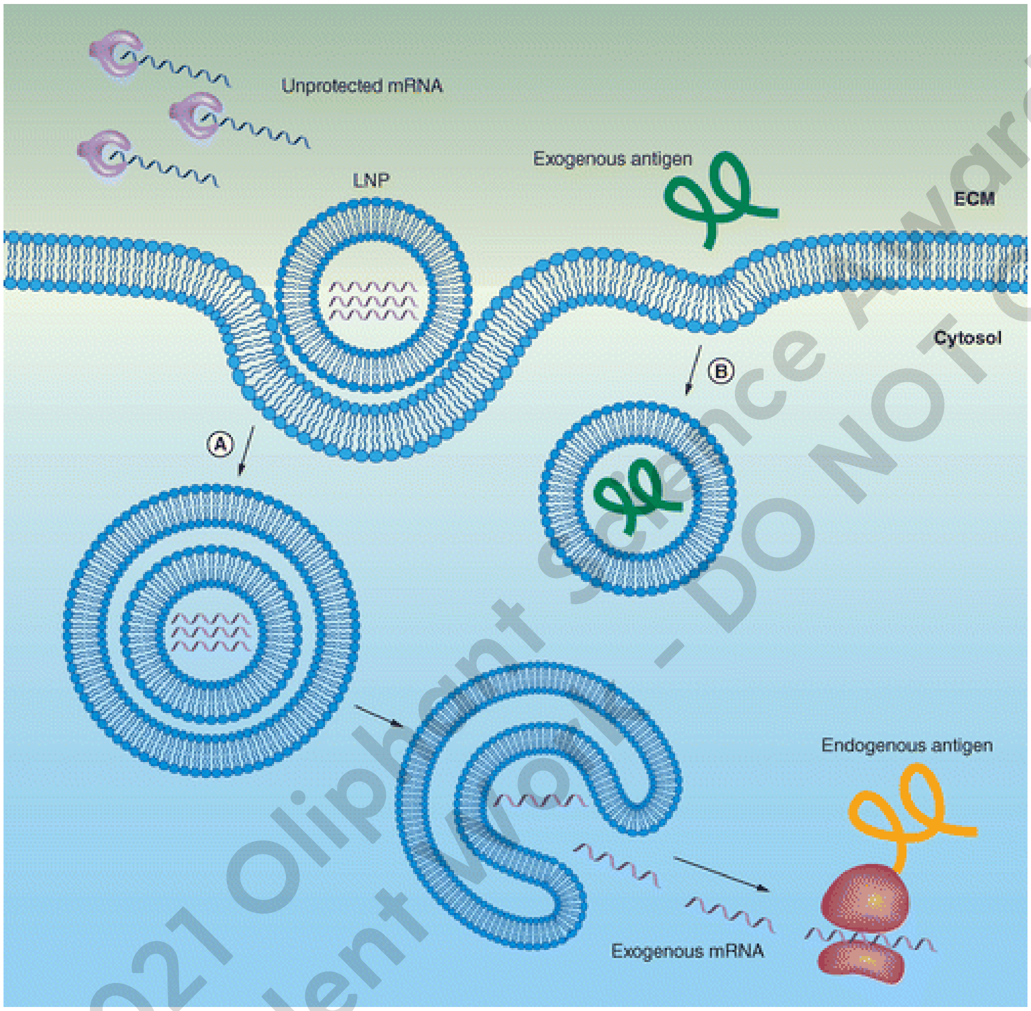

Figure 2: Endocytosis of a cell (Andreas M Reichmuth, 2016)

By packaging the vaccine inside of the LNP, it allows the mRNA to pass through the cell membrane efficiently without breaking apart and reach inside the cell where it can send the message (Reichmuth, 2016). In 2018, the Food and Drug Administration approved the first RNA medicine that involved LNPs (FDA, 2018).

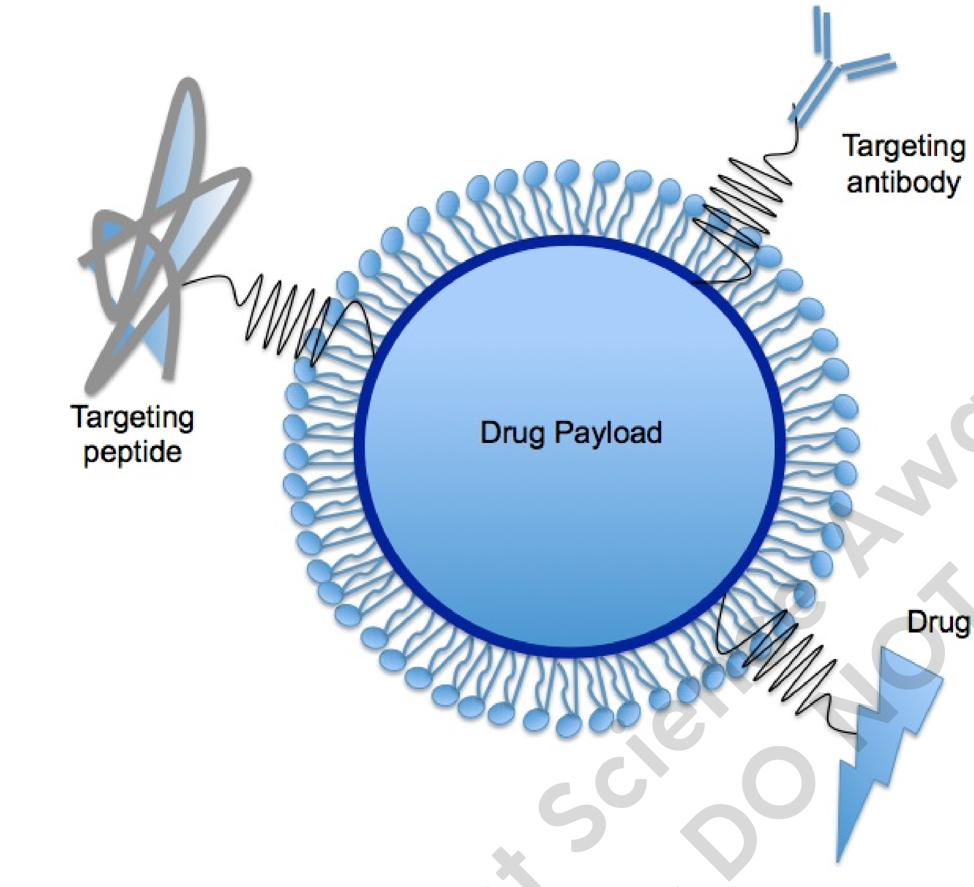

Figure 3: Diagram of LNP containing drug (Trementozzi A, 2013)

In January 2020, the genetic sequence of SARS-CoV-2 was released. Both Moderna's mRNA Vaccine and Pfizer/BioNTech's mRNA Vaccine were among the first COVID-19 vaccines to reach the human clinical trial phase. In July 2020, both companies were already conducting phase 3 clinical trials involving thousands of participants (WHO, 2021). The results from the clinical trials showed that both were approximately 95% effective in the prevention of COVID-19 (Lurie et al, 2021). By December, the U.S. Food and Drug Administration (FDA) authorized emergency use of these mRNA-based vaccines (Lurie et al, 2021).

Along with the technology of mRNA being ready and prior work on coronaviruses, such as MERS-CoV and SARS-CoV, there was a global effort in developing the vaccine. In response to the COVID-19 pandemic, Lynlee Burton, head of the center for vaccines and emerging diseases at PRA Health Sciences, decided that the government and companies should prioritize their resources to developing COVID-19 vaccines and treatments (Cassata, 2021). The Global Preparedness Monitoring Board USD allocated $8,000,000,000 in response to COVID-19 for research in vaccines (WHO, 2021). Additionally, clinical trials received huge involvement from the public. Trials for vaccines filled up faster than in previous years (Cassata, 2021). If it wasn't for this global effort, the development of mRNA vaccines may have been delayed by several years.

Interactions between science and society:

This technology has health, social, and economic impacts. Vaccinating the majority of people significantly reduces the likelihood of an outbreak, essentially achieving herd immunity. Along with protecting people's lives, this will allow travel restrictions, lockdowns, and closed schools to be lifted, increasing economical and social activity. The mRNA vaccine has significantly changed the way vaccines will be developed in the future. The traditional protein-based vaccine requires a live virus or bacteria. This involves growing the live virus/bacteria in eggs or cells which can take several years to do. With mRNA technology, scientists just need the composition of the virus to begin the development of the vaccine. This technology has greatly shortened the amount of time required to develop a vaccine, which allows quicker response times to pandemic threats. It reduces the amount of time countries spend in lockdown and allows the economy/social activity to be restored quicker. Now that a working mRNA vaccine has been made, when a new virus hits, scientists can simply swap out the message encoded on the mRNA for the new virus and the vaccine is ready. As of right now, multiple mRNA vaccines for bacterial diseases, viral diseases, and even certain cancers are undergoing clinical trials (Xu, 2020).

Conclusion:

The mRNA vaccine marks a new era in vaccinology. The vaccine was able to be developed in such a short time due to several decades of research from collaborations between major universities around the world such as the Massachusetts Institute of Technology, the University of Cambridge, and Harvard Medical School. If it wasn't for the global effort from the government, major companies, and public support, this vaccine would never have been developed as quickly as it was. Scientists and researchers are currently finding ways to make this vaccine more readily available through methods such as improving efficiency in production methods. The mRNA vaccine has left a significant impact on the future development of vaccines. With this technology, countries will be able to respond to future pandemic threats much faster and more effectively.

Word Count: 1394 Words

<u>Reference List:</u>

2018, *FDA approves first-of-its kind targeted RNA-based therapy to treat a rare disease*, FDA, viewed 22 May 2021, <https://www.fda.gov/news-events/press-announcements/fda-approves-first-its-kind-targeted-rna-based-therapy-treat-rare-disease>

2021, *mRNA vaccines: FAQ,* Finish Institution for Health and Welfare (THL), viewed 8 May 2021, <https://thl.fi/en/web/infectious-diseases-and-vaccinations/what-s-new/coronavirus-covid-19-latest-updates/transmission-and-protection-coronavirus/vaccines-and-coronavirus/mrna-vaccines-faq>

2021, *COVID-19 Coronavirus Pandemic Live Update*, Worldmeter, viewed 12 May 2021, <https://www.worldometers.info/coronavirus/>

2021, *COVID-19 vaccination – Information on COVID-19 Pfizer (COMIRNATY) vaccine*, Department of Health, Australian Government, viewed 18 July 2021, <https://www.health.gov.au/resources/publications/covid-19-vaccination-information-on-covid-19-pfizer-comirnaty-vaccine>

2021, *Timeline: WHO's COVID-19 response*, World Health Organisation (WHO), viewed 19 July 2021, <https://www.who.int/emergencies/diseases/novel-coronavirus-2019/interactive-timeline#!>

Bollmann et al 2018, *Vaccine Development, Testing, and Regulation*, The College of Physicians of Philadelphia, viewed 8 May 2021, <https://www.historyofvaccines.org/content/articles/vaccine-development-testing-and-regulation>

Cassata C 2021, *Here's How It Was Possible to Develop COVID-19 Vaccines So Quickly*, Healthline, viewed 8 May 2021, <https://www.healthline.com/health-news/heres-how-it-was-possible-to-develop-covid-19-vaccines-so-quickly>

Cuiling et al, 2019, *Advances in mRNA Vaccines for Infectious Diseases*, Frontiers in Immunology, vol. 10, viewed 18 July 2021, <https://www.frontiersin.org/articles/10.3389/fimmu.2019.00594/full#h5>

Elliot 2020, *IMF estimates global Covid cost at $28tn in lost output*, The Guardian, viewed July 19 2021, <https://www.theguardian.com/business/2020/oct/13/imf-covid-cost-world-economic-outlook>

Garde 2020, *The story of mRNA: How a once-dismissed idea became a leading technology in the Covid vaccine race*, STAT, viewed July 15 2021, <https://www.statnews.com/2020/11/10/the-story-of-mrna-how-a-once-dismissed-idea-became-a-leading-technology-in-the-covid-vaccine-race/>

Gurdon et al, 1971, *Rabbit haemoglobin synthesis in frog cells*, University of Cambridge, viewed 7 May 2021, <https://www.researchgate.net/publication/17998491_Rabbit_haemoglobin_synthesis_in_frog_cells_the_translation_of_reticulocyte_9_s_RNA_in_frog_oocytes>

Kantis et al, 2021, *Timeline of the Coronavirus*, Think Global Health, viewed 17 July 2021, <https://www.thinkglobalhealth.org/article/updated-timeline-coronavirus>

Lurie, N, Cramer, JP & Hatchett, RJ 2021, *The Vaccine Revolution.*, Foreign Affairs, vol. 100, no. 3, pp. 128–135, viewed 17 July 2021, <http://search.ebscohost.com/login.aspx?direct=true&db=khh&AN=149858533&site=ehost-live>

Pardi N et al 2013, *In vitro transcription of long RNA containing modified nucleosides*, University of Pennsylvania, viewed 5 May 2021, <https://doi.org/10.1007/978-1-62703-260-5_2>

Newswire 2021, *COVID-19 Welcomes a New Era in Vaccinology. mRNA Based Vaccines to Reach US$127.3 Billion by the Year 2027*, PR Newswire US, 29 June, viewed 17 July 2021, <http://search.ebscohost.com/login.aspx?direct=true&db=bwh&AN=202106290855PR.NEWS.USPR.LA25605&site=ehost-live>.

Reichmuth et al 2016, *mRNA vaccine delivery using lip nanoparticles*, MIT & Harvard Medical School, viewed 7 May 2021, <https://pubmed.ncbi.nlm.nih.gov/27075952/>

Ruairi J 2020, *DNA vs. RNA – 5 Key Differences and Comparison*, Technology Networks, viewed 9 May 2021, <https://www.technologynetworks.com/genomics/lists/what-are-the-key-differences-between-dna-and-rna-296719>

Reichmuth 2016, *mRNA vaccine delivery using lipid nanoparticles*, Future Science, viewed 9 May 2021, <https://www.future-science.com/doi/10.4155/tde-2016-0006>

Xu et al 2020, *mRNA Vaccine Era—Mechanisms, Drug Platform and Clinical Prospection*, NCBI, viewed 8 May 2021, <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7554980/>