

# Effectiveness of mRNA Vaccines on Cancer with and Without Immune Treatments

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## ABSTRACT

Recently, due to the COVID-19 pandemic's prevalence across the entire world, scientists pioneered the usage of a new medical technology to fight it and grant humans immunity towards the disease: mRNA vaccines. These vaccines were heavily effective as they prevented a majority of the population from getting COVID-19. This caused scientists to research how mRNA vaccine technology could be utilized for other areas of medicine and disease, especially the world of cancer. This review article will delve into the ways scientists are utilizing the powers of mRNA vaccines to provide treatment to patients with pre-existing cancer, and how they engineered the mRNA vaccine to primarily influence the T-cells to better spot cancer cells, with and without the addition of supportive immunological therapies. It was found that the mRNA vaccines of all types reviewed in this paper were effective against the cancerous tumors, and with supportive immune treatments, the vaccines' effects were further amplified to varying degrees. However, these vaccines may not translate their results for all types of cancer cells and bodies, though. This is why it is recommended that research must be done on more reliable mouse cell models with more trials to further confirm the effectiveness of the vaccine treatments on the cancerous tumor cells once and for all.

## Introduction

In America, there are an estimated 1.9 million cancer cases in the year 2023 alone, with an estimated over 32 percent of these cases leading to death (estimated 609,820 people) (American Cancer Society, 2023)). This alone proves that cancer is an all-too-prevalent and devastating disease, indiscriminately affecting even the most medically-advanced countries like America or others. This, of course, inspired heavy efforts by scientists globally to find an all encompassing treatment to the disease, to varying degrees of success. However, there have been new avenues opened up for a possible treatment to cancer in the unconventional direction of mRNA vaccines. mRNA vaccines have been famously used to prevent COVID-19 disease in patients across the globe, and now, scientists are finding out about how mRNA vaccines could also be utilized to engineer the T-cells in the human body to attack cancer cells of many different kinds. The main question rising from all of this now is how this vaccine will not only kill cancer, but also help prevent cancer from happening by training the body to remember to do so. This paper will contribute knowledge of how these mRNA vaccines work to kill off tumors in human bodies, and may work towards a total cure for cancer of all kinds in the near future.

## mRNA and mRNA Vaccines

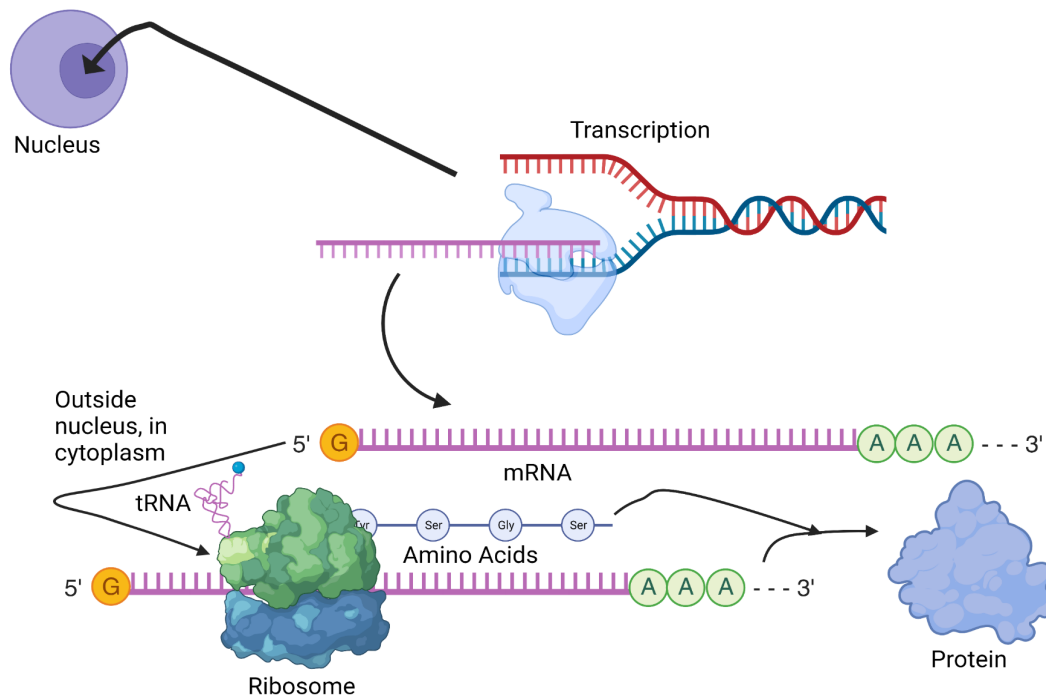
This section discusses the process of the creation of natural mRNA within the human body, and how that contributes towards protein manufacturing to keep the body healthy. Then, it discusses how mRNA vaccines essentially "hijack" this process by making the ribosomes manufacture antigenic proteins to induce a more memorable immune system training response and eventual inoculation.

## How mRNA Works

But first, in order to understand this research paper, one must understand what mRNA exactly is. mRNA is a type of RNA (ribonucleic acid) that serves a role in the genetic transcription and translation process within the cells of our bodies. DNA is read and transcribed by RNA polymerase, a protein within the DNA that unwinds the DNA to place an RNA sequence on the DNA template, within a process called “transcription”. This RNA that is then generated is called “mRNA”, or “messenger RNA”.

This mRNA sequence slithers out of a pore within the nucleus, where all of the DNA is located, and then tries to locate, within the cell, a ribosome that is willing to utilize the mRNA strand to generate some proteins. A ribosome is essentially a protein-making machine either floating around in the cell or near your cell’s rough endoplasmic reticulum (rough ER). When the mRNA inserts itself inside the ribosome, the ribosome starts to translate the mRNA in a process called ‘translation’. The ribosome, while translating this mRNA, calls tRNA also floating around within the cell to attach to the mRNA and build a protein.

The tRNA (transfer RNA) has amino acids attached to the top of each tRNA vesicle, with three little prongs that act as anticodons. Anticodons are groups of 3 RNA coding pieces (bases) that are within each tRNA vesicle. These anticodons attach to groups of three bases on the mRNA strand (codon). If they click together and match, the protein starts to form with the clicked-together amino acids. The ribosome “calls” over some rRNA (ribosomal RNA) to check with the codons that make up these amino acids to make sure that this protein is all correct and good to go. All of these help make up the new protein which is then either kept in the cell or packaged in a vesicle by the Golgi apparatus and sent out to a different part of your body to help keep the body healthy.



**Figure 1.** A simplified figure of how the protein manufacturing process works inside a cell. Note the essential role mRNA has in the creation of proteins.

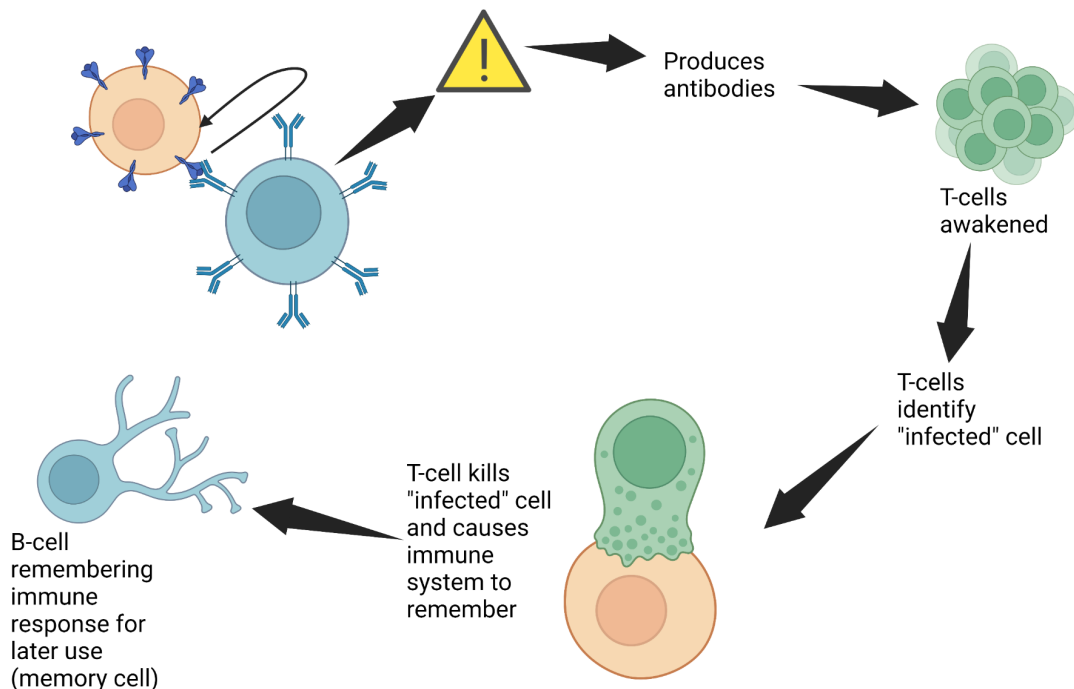
## Function of mRNA Vaccines

The mRNA vaccine works by injecting this mRNA so a cell can present antigenic proteins, thus triggering the immune system to attack and therefore train itself. The body cell uses this mRNA (usually the mRNA used by viruses, bacteria, or cancerous cells in this case) to create proteins or signaling proteins presented by these pathogenic agents, thus creating a proper antigen (disease-causing target) that the antibodies of the immune system (targeting molecules) can latch onto and mark for the immune system to destroy, thus recognizing what kinds of diseases have these kinds of antigens and proteins. This was utilized most famously and recently for the COVID-19 disease, where the cells presented the COVID-19 virus' spike proteins, training the immune system to recognize and destroy these agents, thus preparing it for the COVID-19 disease if it ever happens, giving the body some immunity against the disease. In people who took the vaccine administration, it was a success as people with the vaccines had much longer immunity than those without vaccine inoculation.

## mRNA Vaccines and Cytotoxic T-Cells

After mRNA vaccine administration and delivery, the mRNA influences primarily the T-cells to induce the body to train and recognize these harmful pathogens through the B-cells creating disabling antibodies (for the mRNA influenced proteins) to better force the T-cells to recognize the afflicted cells and then destroy them. This also practically translates into cancer causing cells as well. Since the T-cells (and B-cells, in a way) now know what cancerous cells practically look like due to the mRNA vaccines, they, theoretically, at least, should attack the cancerous cells with utmost efficacy.

Let's explore some examples of this cancer-focused mRNA vaccine being used within some mouse models. We have two experiments with very similar circumstances, both mouse models injected with comparable mRNA vaccine treatments. These treatments had similar processes, though, as they activated the immune system and induced it to attack the cancerous cells presented within these experiments. But the ways they approached them will be what we will discuss in the following paragraphs.

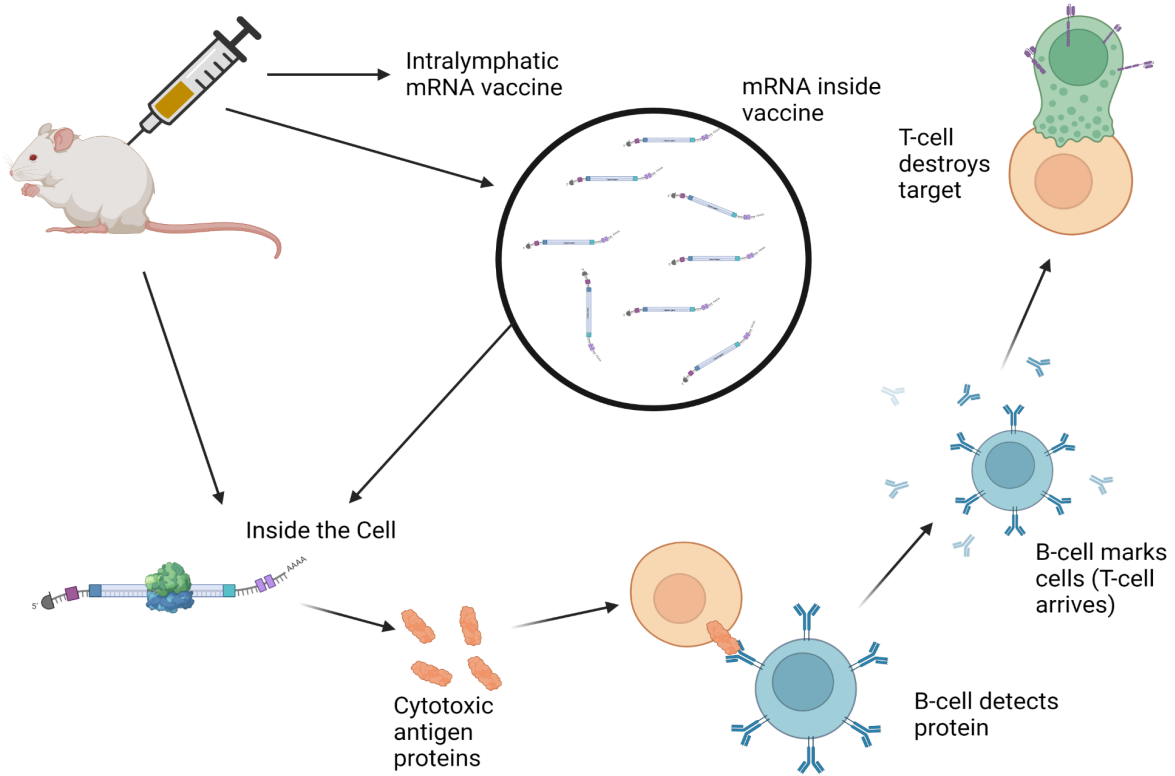


**Figure 3.** A simplified look into how the immune system utilizes the vaccine's spike proteins, especially via the B-cells and the T-cells. The B and T cells work in conjunction with each other to target and destroy a harmful antigen, especially once-healthy cells that have now turned cytotoxic (harmful to the surrounding cellular environment).

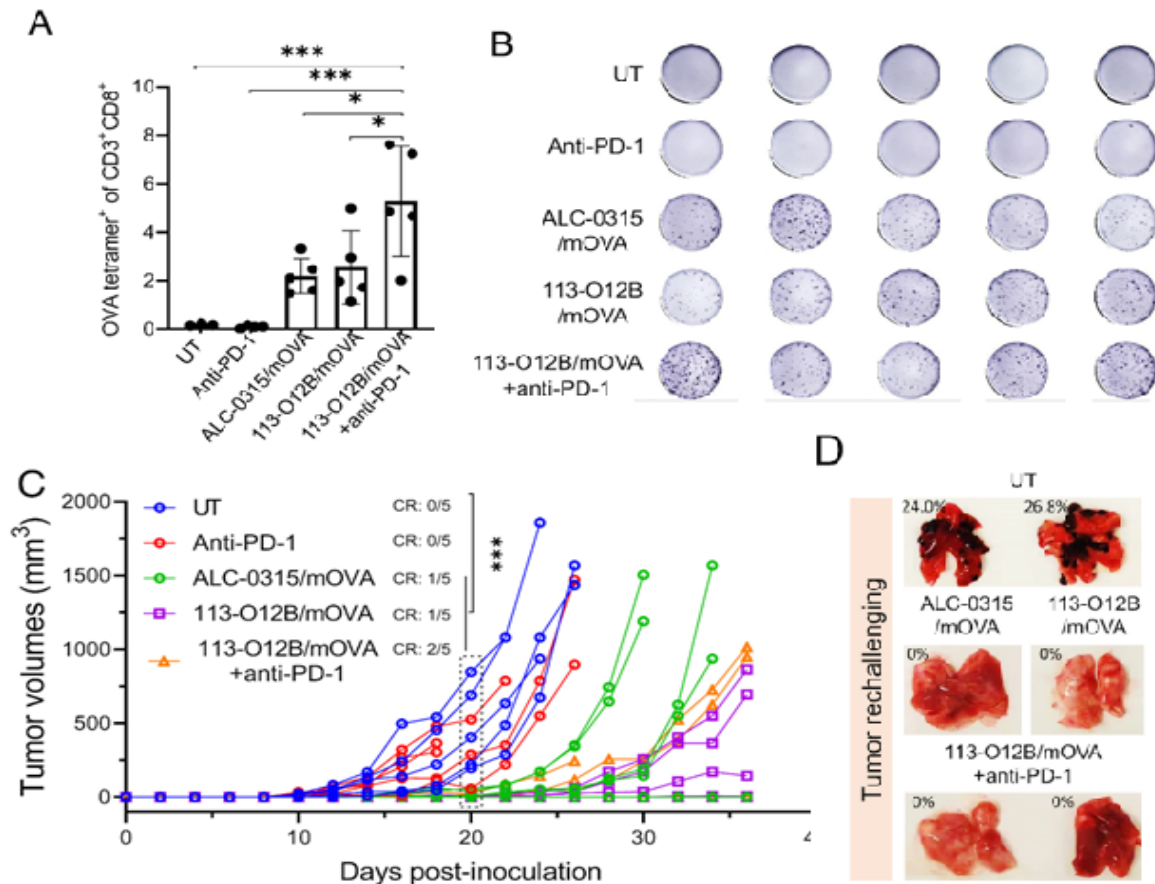
### mRNA Cancer Vaccines in Experimental Mouse Models

In the first experiment, which we will call mouse model 1, an intralymphatic mRNA vaccine was inserted into mouse models to tell the immune system's clinically-relevant lymph-nodes to target the clinically-relevant cancer cells for this experiment, the cervical cancer cells. The research in question brings into question the efficacy of the mouse models utilized during this experiment. When the mRNA is injected into the mouse model's cell bodies, the cells start to present antigens that the mouse B-cells recognize via the usage of antibodies. These start to act as markers for clinically relevant Cluster of differentiation 8+ T-cells. CD8 is a receptor protein that aids in the process of T-cell immune system defense. These 'CD8+ T-cells' are T-cells that are important in the regulation of the immune cell differentiation response and the fight against cancerous cells. These specific T-cells are equipped with surface protein receptors that target these antigens specifically, making the whole target practice much easier for the T-cells and immune system in general.

These T-cells need to work hard to find cancerous and/or toxic cells, though, and most of the time it's far too late when these cells finally target and attack the cancerous cells, usually at the stage where aggressive chemotherapy treatment is needed. This mRNA vaccine, though, prevents this stage from happening by making the cells present the antigens that the cervical tumor's cells present, thus allowing the T-cells to recognize the cancerous cells much more quickly, thus increasing efficacy and immunity. The antigenic proteins essentially tell the T-cells what kind of cells they should be looking for, so they can now more quickly find tumor nests and then biologically smash them into pieces. This causes effective tumor regression in these models, comparable to what might happen in patients.



**Figure 4.** A figure that illustrates the aforementioned experiment, but highlights how the mRNA causes the immune system-neoantigen interaction. Note that the mRNA programs “neoantigens”, which are antigens that arise from mutations or new forms of tumors.



**Figure 5.** This entire image shows the effects and results of the vaccination upon the Lymph Node tumors in question. Section A's graph highlights the flow percentages of CD3+ and CD8+ T-cell receptors binding to the vaccine's antigens. Section B highlights the T-cell secretions with and without the vaccine. In the petri dishes, the researchers analyzed the amount of detected T-cells active per treatment mode within this experiment. Section C highlights the tumor volumes, establishing a comparison between with and without vaccine. Finally, Section D highlights the lungs collected from the mouse models 18 days after initial injection. Note the discoloration is less present within the vaccinated lung cells rather than the UT control cells. [Images and datasets from 'Lipid nanoparticle-mediated lymph node-targeting delivery of mRNA cancer vaccine elicits robust CD8+ T cell response', Chen et. al., *PNAS*.]

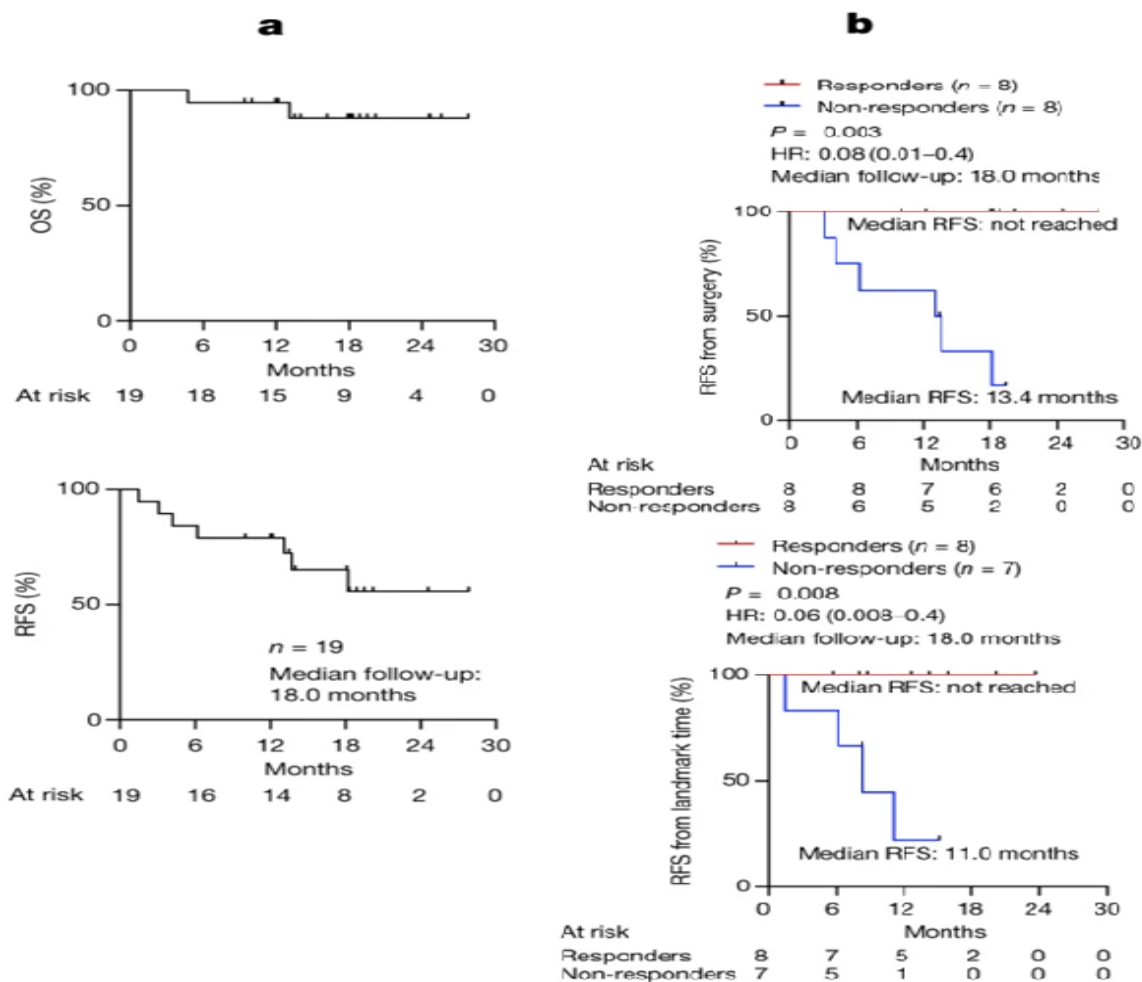
The vaccines here in question delivered Lymph Node Targeting nanoparticles (LNPs) called 113-O12B through mOVA (ovalbumin) based vaccines. ALC-0315 is a synthetic lipid garnered from the COVID-19 vaccines utilized as a comparison model for the effects of the different vaccine types. As shown in the above picture, the 113-O12B mRNA vaccines aided in excellent tumor regression as the vaccines helped increase T-cell response, thus improving the effectiveness of the tumor model. When combined with PD-1 therapy (anti-programmed death 1), where the vaccine LNPs are encapsulated with TRP-2 peptides instead of protein nanoparticles, the response gained from these LNPs also had excellent and heavily improved tumor inhibition, with complete response of 40% in the tumor model, showing that peptides also work alongside the originally protein-based vaccine (Chen et. al., 2022). All the mice showed immune memory for the tumors, preventing metastatic

lung tumors in the future tests that followed after this experiment. This experiment highlights the next generation of mRNA vaccines being for cancer treatments and therapies, and this is proven heavily through this collected data.

### mRNA Neoantigen Cancer Vaccines in Experimental Cancer Patients

The above experiment was within a mouse model. What about in active human models as well? In another experiment we shall explore today, researchers tested out a neoantigen mRNA vaccine in patients with PDAC, a form of pancreatic cancer that is the most common form as well as the most deadliest (88% mortality rate). Neoantigens are forms of antigens that develop on some cancer cells that develop after genetic mutations within the cancerous tumor cells. This mRNA vaccine is part of an experiment that works in a similar fashion to the vaccine and booster administrations for COVID-19.

The vaccine essentially had lots of theory and calculations behind it, with the scientists essentially making a prediction based upon evidence that they found during studies of the PDAC cells and their mutations. However, it seemingly paid off at the end, as they injected the experimental vaccine into a group of PDAC treatment patients, and compared with those that did not receive the vaccine, after 18 months, the patients with the neoantigen vaccine had their tumors regress much more than the control patients.





**Figure 6.** Graphs detailing tumor relapse rates of PDAC tumors in patients after surgery after initial priming of treatment and spotting of the tumor. Section A shows the rate of survival and the relapse rate initially in patients without vaccine priming. Section B shows the rates of relapse in patients who received the vaccine treatment and got their PDAC tumors removed. Note the decreasing relapse for the patients that were administered vaccines within the row labeled ‘B’. [Images and datasets from ‘Personalized RNA neoantigen vaccines stimulate T cells in pancreatic cancer’, Rojas et. al., *Nature* Issue 618, 144-150.]

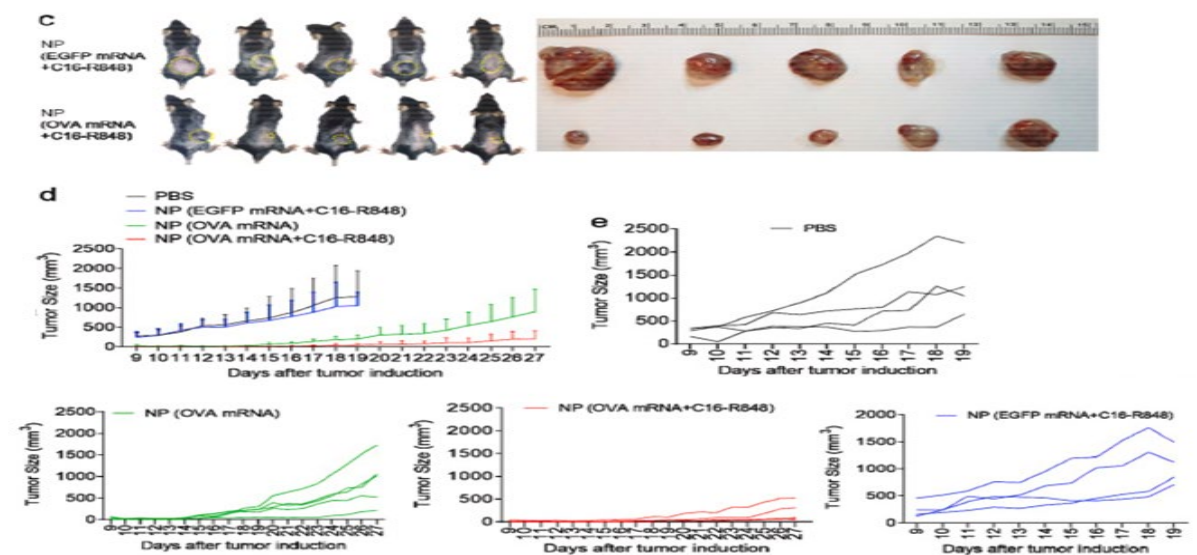
As highlighted in the picture above, the patients not only had higher regression rates as time went by, but the patients also had lower relapse rates when the tumor was removed after vaccine priming, which basically means after the vaccine was administered. The neoantigen-based vaccine helped the T-cells damage the tumors much more, causing more weakness in the tumors, thus preventing the more severe relapse of them (Rojas et. al., 2023).

## mRNA and Combined Therapies

We observed the effects of the vaccines themselves so far, but what about combined therapy? This is where the vaccines are paired with adjuvant-pulsed immunotherapies and their effects, theoretically, at least, are amplified. In similar fashion to the above, we will explore two experiments that utilized this revolutionary new medical delivery technology. Both will be similar in the sense that they utilize immunotherapeutic nanoparticles to enhance effectiveness, but both will utilize different treatment mechanisms.

### Adjuvant-Pulsed Immunotherapeutic Nanoparticles

In a mouse-model based experiment, researchers wanted to discover the effects of adjuvant-pulsed combined therapy on an initial mRNA vaccine treatment. The scientists injected OVA (ovalbumin, aka egg-based vaccine treatments) mRNA vaccines into the tumor cells in the mouse models, and then held the experiment. The cells were segregated into primary groups, where one group was treated with just the vaccine while another group was treated with the vaccine plus the adjuvant-pulsed treatment. Adjuvant is the additional treatment after initial chemotherapy delivery, and pulsation simply means intermittent drug delivery.





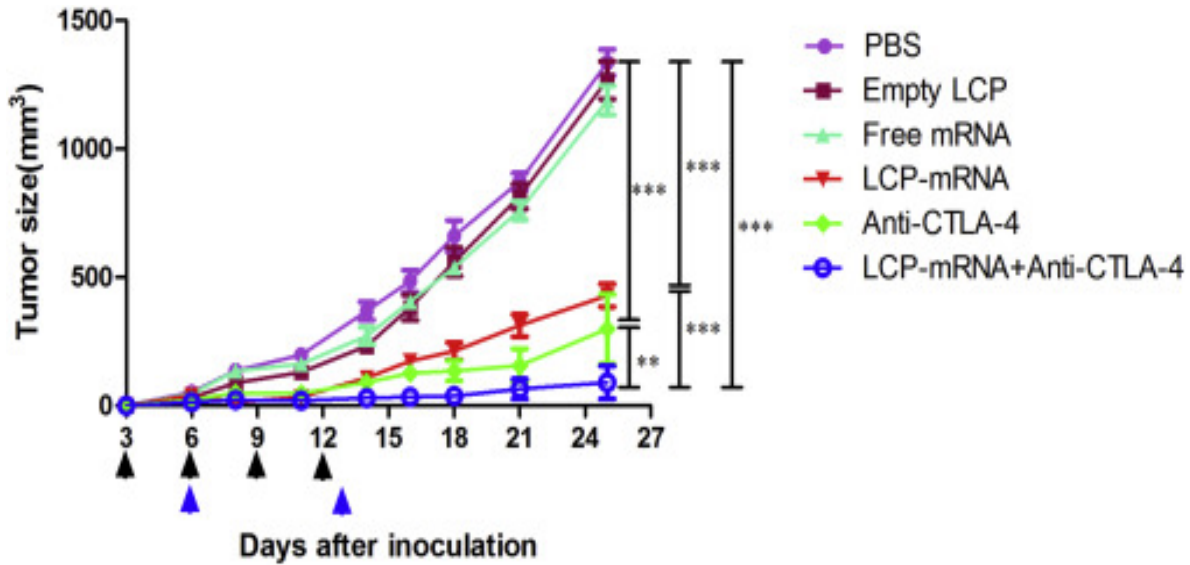
**Figure 7.** Graphs and pictures highlighting the effectiveness of the vaccine combined with an adjuvant-pulsed-based immunotherapy NP treatment. All of the figures talk about tumor regression to some degrees based upon the type of treatment delivered. All caused some form of tumor regression. However, the C16-R848 NP treatment bonded with the OVA-delivered mRNA vaccines caused the highest amount of tumor size loss and regression, proving clinically significant in this case. Images of rats show the effectiveness of the vaccine treatments upon their bodies and respective sicknesses. [Images and datasets from ‘Adjuvant-pulsed mRNA vaccine nanoparticle-support for immunoprophylactic and therapeutic tumor suppression in mice’, Islam et. al., *Bio-materials* Volume 266.]

As highlighted in the image above, the vaccines of all types did some level of tumor regression during the experiment. However, the vaccine by itself didn’t do as much damage to the tumors as the treatments combined with adjuvant-pulsed NP therapies. The therapies in question were labeled as C16-R848, which is a palmitic acid-modified TLR7/8 agonist coated with a lipid-polyethylene glycol (lipid-PEG) shell. TLR7/8 are immune system receptors that detect single-strand RNA sequences, taking them in and then forging the target practice antigens on top of the impacted cell (ScienceDirect, n.d.). This C16-R848 acted as its agonist, meaning it supported the intake of the mRNA vaccine’s OVA-delivered mRNA sequences to more easily induce the creation of biological target practice dummies for the body’s T-cells to recognize the signs that make up a cancerous tumor cell. The OVA (not EGFP-control) vaccines combined with this treatment, delivered adjuvant-pulsed (periodically after initial cancer therapy like chemotherapy) after initial vaccine administration and immunotherapy, caused the highest amount of tumor regression and essential downsizing, speaking to the abilities that combined therapies have for already effective mRNA vaccines (Islam et. al., 2020). It’s also noted that remission was hampered down further by these combined treatment therapeutic vaccine types. This shows the valuable prospects of adjuvant-pulsed immunoprophylactic therapy, but what about the clever combination of immune checkpoint blocking NPs with these cancer vaccines? We shall discover this within the next experiment, which looks into this possibility of utilizing an essential ingredient in immune cell splitting and reproduction to the mRNA vaccine treatment’s advantage (via hijacking).

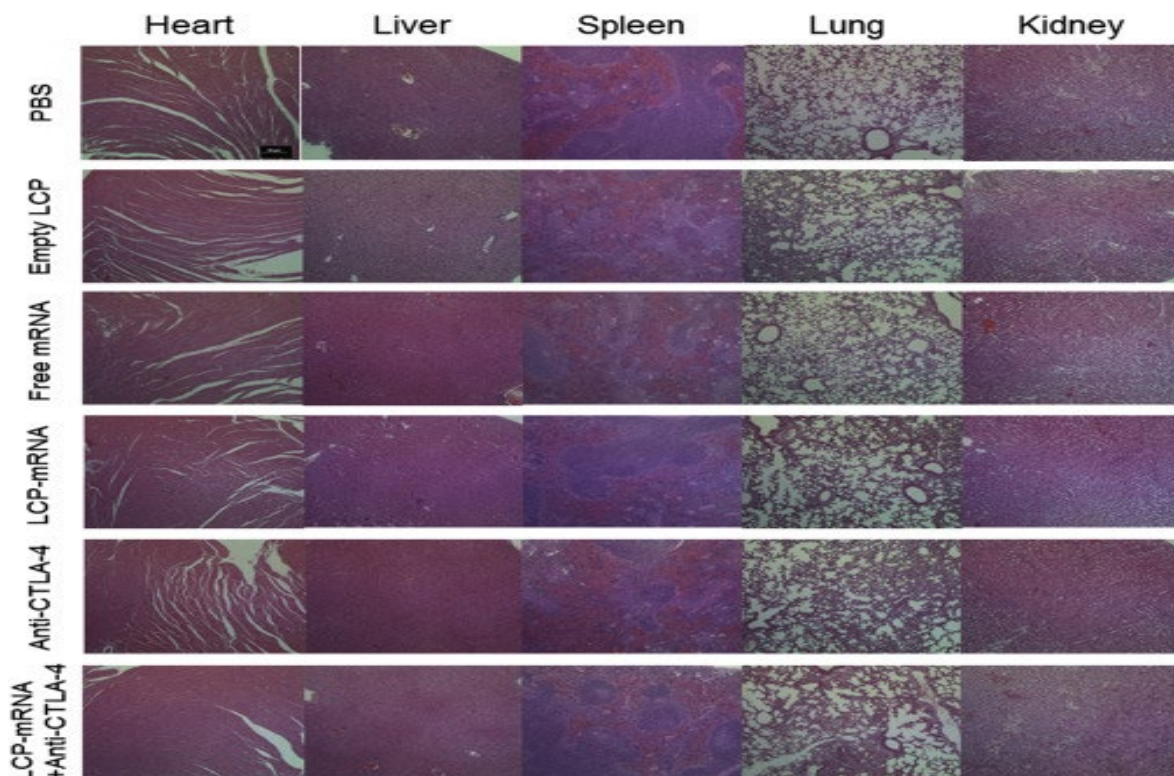
## Immune-Checkpoint Blocker Nanoparticles

In another very similar experiment, a group of researchers injected an experimental mRNA vaccine into a group of model cells with a type of breast cancer known simply as TNBC. TNBC (Triple-negative breast cancer) is a type of breast cancer that makes up 10 to 20 percent of all breast cancers, and is a particularly elusive breast cancer in the sense that it cannot be treated as easily as other breast cancers.

In this experiment, similar to the above experiment, the researchers wanted to find out exactly how effective a combined cancer therapy is. They did a control (vaccine only) compared with an experimental group (vaccine + immune checkpoint blocker NPs). The NPs in question are the CTLA-4 immune checkpoint blockers. CTLA-4 immune checkpoint blockers are blockers that aid in the immune checkpoint process. This checkpoint process allows the prevention of certain cytotoxicity of the cells. However, in cancerous cells, this immune checkpoint molecule can upregulate and cause the constant proliferation of certain cancer cells, especially cells related to breast cancer cells. These blockers, as the name practically suggests, blocks this immune checkpoint from happening and upregulating the division of the cancer cells, thus supporting the attacks upon the tumor.



**Figure 8.** Graph that highlights the tumor sizes after different treatments of vaccines and controls. PBS is the original control (the untreated tumor cells). Empty LCP is the control LCP vaccine, or Lipid-Core-Peptide, which, as the name ‘empty’ implies, has no treatment inside of it. Free mRNA is mRNA delivered through traditional cancer therapy methods, like monoclonal antibodies. LCP-mRNA is delivered alongside LCP shells through the vaccines. Anti-CTLA-4, otherwise known as the CTLA-4 blockers, is shown to have a very significant effect upon the tumor size. The LCP-based mRNA vaccine combined with the Anti-CTLA-4 treatment caused the most decrease and regression in the tumor size and effects. [Images and datasets from ‘Combination Immunotherapy of MUC1 mRNA Nano-vaccine and CTLA-4 Blockade Effectively Inhibits Growth of Triple Negative Breast Cancer’, Liu et. al., *Molecular Therapy*, Volume 26, Issue 1.]



**Figure 9.** These images support the graph made during the results portion of this experiment. Mice were sacrificed to be dissected and take morphological looks within their organs. Each organ was analyzed for resultant cytotoxicity due to the metastasizing tumor. The top-most row, the untreated control, had very visible organ degradation and damage, while the bottom-most row, the vaccine combined with the immune blocker treatment, had relatively the least amount of damage to the organs and therefore had the least amount of cytotoxicity, in turn supporting the above graph on the resultant tumor sizes and surrounding bodily environmental damage. [Images and datasets from ‘Combination Immunotherapy of MUC1 mRNA Nano-vaccine and CTLA-4 Blockade Effectively Inhibits Growth of Triple Negative Breast Cancer’, Liu et. al., *Molecular Therapy*, Volume 26, Issue 1.]

As highlighted in the images above, researchers performed experiments utilizing all kinds of treatments and combined vaccines in order to find the most effective treatment, but at the end, they found that the LCP-mRNA vaccine plus the Anti-CTLA-4 treatment caused the most progressive damage to the tumors within the model. All of the data was marked as significant in different levels (Liu et. al., 2018). The CTLA-4 blocker NPs caused, in these *in vivo* studies on cytotoxic T-cells, more response against the tumor cells in question, the TNBC 4T1 cells. 4T1 is a cell line of mammary breast cells derived from the mice of this experiment. This comparatively significantly enhanced the immune response to the cancerous cells than the other treatments each alone, thus reinforcing the theory that combined drug therapies can further cause more powerful and efficient regression of the cancerous tumors.

## Conclusion

We can conclude that these vaccines, on the most part, work significantly well. These vaccines essentially program the immune system to, similar in fashion to the COVID-19 virus as the mRNA vaccines were originally intended for, recognize cancerous tumor cells and kill them before they do any more toxic damage to the surrounding cells of the organism.

The vaccine cannot perform miracles on its own, however, as it needs the power of teamwork to truly accomplish its goals. This is where the combined treatments come in. These treatments, usually delivered almost immediately (relatively) after the vaccine’s delivery, gives some biological oomph to the already effective vaccine treatment.

These immunity drugs help the tumor stay down, causing more efficient regression of the tumor’s severity. This further reduces the tumor and cytotoxicity, and gives a much better prognosis of the body with the cancer.

This shows how the future of vaccines is mRNA. mRNA vaccines are useful for viruses like COVID-19, but time and time again scientists are finding new ways to utilize revolutionary treatments like the vaccine for purposes not originally intended, which causes more efficient development and research than ever before. mRNA is a revolutionary technology, and this research very much highlights this fact. Now, the question lies in how efficient these vaccines are for the more broad world of cancer. How will this vaccine treat other kinds of cancer? How efficient will this vaccine be in terms of the other types of cancer? Will there be the need for boosters that administer these combined treatments like the COVID-19 vaccines? This and more questions are beckoned by this research, though the revolutionary ideals pushed by this research must not be understated. More experimentation on more accurate and efficient models must be needed, however, to ensure the most accurate results and the most encouraging news for usage in cancer patients.

## Limitations

This study had some limitations regarding the experiments that were performed during the creation of the vaccines and the testing of them. As stated above, more accurate and efficient models are needed for the proper collection of data. This includes more reliable mouse models, so the researchers would gather more reliable data. There could also be more experimentation on more types of cancerous cells, to further prove the reliability of the vaccine treatment for all different kinds of cancer apart from the ones stated in this research paper. Also, there could be more experimentation on more kinds of combined therapies to better support this resolution. However, it is an interesting prospect and field nonetheless that all cancer biology and medical researchers must look into if there is to be expected some progression within the near future.

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