Logbook Science Fair: Breakthrough of mRNA cancer vaccines to cure Pancreatic Ductal Adenocarcinoma

2023-2024, Sukrutha Jambur Sachin

December 13, 2023:

Today, I decided upon the basic idea for my science fair project.

- Being interested in biology, and oncology, I wanted to research new treatment methods for cancer by looking at data from a specific clinical study. I came across a study conducted by pharmaceutical company BioNtech using mRNA cancer vaccines for Pancreatic Cancer.
- I became intrigued by this because I was familiar with the mechanism of mRNA vaccines, as these were used to fight the COVID-19 virus and I thought it would be interesting to see how these would be able to fight cancer.

December 16, 2023:

- Today I came up with the driving question/main focus of my project. I also created three guiding for my project as these would help me narrow down my research into a specific topic.:

How can personalized mRNA neoantigen vaccines treat patients with Pancreatic Ductal Adenocarcinoma?

- What is the function and parts of the pancreas, and where does Pancreatic Ductal Adenocarcinoma occur?
- Why are traditional forms of immunotherapy such as immune checkpoint inhibitors ineffective against Pancreatic Ductal Adenocarcinoma?
- How do neoantigens stimulate the immune system of patients with Pancreatic Ductal Adenocarcinoma?

Since I was not very familiar with Pancreatic cancer, and the function of the pancreas in general, I started my research about the structure and functions of pancreas.

- The pancreas is a gland that is located in the abdomen and plays a key role in converting the food that we consume into fuel.
- The pancreas has two main functions, known as the exocrine and the endocrine functions.
- **Exocrine**:Means that this part of the gland secretes hormones through a ductal system and onto an epithelial surface.
- **Endocrine**: Means that this part of the gland secretes hormones directly into the bloodstream.

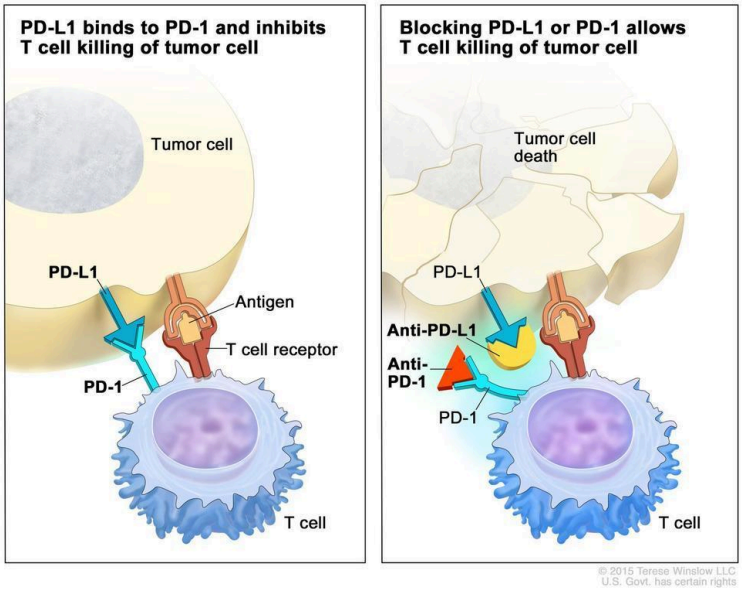
January 03, 2024:

Today, I did research about how tumors develop in the pancreas gland and why a type of traditional immunotherapy known as immune checkpoint inhibitors are ineffective against Pancreatic Ductal Adenocarcinoma.

- Pancreatic tumors are malignant or cancerous, because pancreatic cancer cells have mutations which cause them to outcompete the growth of healthy cells.
- 95% of pancreatic cancers occur in the exocrine glands, and the most common type of pancreatic cancer is Pancreatic Ductal Adenocarcinoma (PDAC).
- PDAC occurs when cancer cells line the pancreatic duct, and compress the bile duct, which blocks the flow of bile out of the liver.
- PDAC can spread rapidly to other parts of the body.
- It also has a high mortality rate, and until now, the only method used to treat it is an intense form of chemotherapy which is not effective as oftentimes, pancreatic tumors are chemotherapy-resistant.

To know about why a type of traditional immunotherapy known as immune checkpoint inhibitors are ineffective against Pancreatic Ductal Adenocarcinoma, I researched how immune checkpoint inhibitors work.

- An important type of white blood cells in our bodies are T-cells which help to fight against foreign elements in the body like cancer cells.
- T cells have proteins called checkpoint proteins on their surface which regulate the immunogenicity of the T-cells, and are responsible for switching off T-cells when required.
- Cancer cells, however, usually have special types of receptors which can increase the presence of
- checkpoint proteins on T-cells and therefore weaken the immune systems. Immune checkpoint inhibitors work by blocking these receptors on cancer cells, therefore protecting T-cells and the immune system from the immunosuppressive nature of tumor cells. This image here illustrates this. PD-1 is a type of checkpoint protein on immune cells, and PD-L1 is an antigen on tumor cells. PD-L1 usually binds to PD-1 and suppresses the immune system. However, an anti PD-L1 blocker, which is an immune checkpoint inhibitor, stops this immunosuppressive effect.

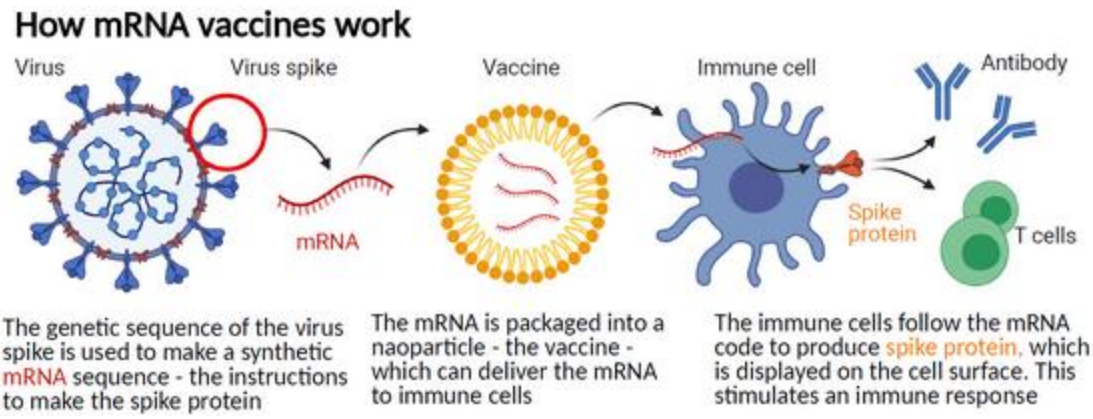


- The main reason why immune checkpoint inhibitors are ineffective against PDAC is because PDAC is a type of cancer with low mutations.
- In order for immune checkpoint inhibitors to be effective, they need to be able to bind to a very specific target on the tumor cells.
- On PDAC tumors, recognizing these specific targets becomes difficult for checkpoint inhibitors.
- This, therefore, results in a reduced sensitivity of PDAC tumors against checkpoint inhibitors.

January 06, 2024:

Today, I researched about how mRNA vaccines are effective against Pancreatic Ductal Adenocarcinoma.

- The human immune system normally fights infections by using white blood cells which have a memory of different foreign organisms such as pathogens. These white blood cells then build antibodies against foreign cells in the body, and can use these antibodies to defend themselves against foreign cells. However, the reason that this is ineffective against cancers is because immune cells do not have the ability to build the necessary antibodies against cancer cells. mRNA cancer vaccines use a special type of antigen known as neoantigens to help the immune system build the necessary antibodies against cancer cells. Neoantigens are a type of tumor specific antigens which are only present on the surface of tumor cells. mRNA vaccines introduce these neoantigens on the surface of the immune system's T-cells, as shown in this image, therefore enabling the T-cells to recognize the cancer cells and build the needed antibodies against them.



- Also, I researched specifically about the way mRNA neoantigen vaccines are used to treat patients with PDAC. To do this, I used research and data collected from a recent phase 1 study conducted by BioNtech to test mRNA cancer vaccines against PDAC tumors. In this trial, the 16 patients who were enrolled had their tumor removed, or resected surgically, through a process known as the whipple procedure. This is a surgical procedure used to remove pancreatic tumors. Within 72 hours after the tumor was resected, it was sent to a manufacturing facility where exome sequencing was performed on it. The human genome is divided into two parts known as the intron and the exome. The exome is the part of the genome which contains information to code proteins. Most mutations in cancer lie in this part of the genome. Therefore, exome sequencing scans for mutations in the nucleic bases of the exome. Exome sequencing can effectively recognize the parts of the exome which contain the information to code the neoantigens on the mutated tumors.

January 10, 2024:

Today, I continued the research on the steps of using mRNA vaccines to treat Pancreatic Ductal Adenocarcinoma.

- The surgically resected tumors underwent a process known as RNA sequencing in which the total content of the RNA, known as the transcriptome, was scanned to search and identify the locations .of the parts of the RNA which coded for the neoantigens on the surface of the PDAC tumors of each of the patients. These neoantigens were then packaged within the mutated mRNA to form the personalized neoantigen mRNA vaccines.
- During this manufacturing process of the mRNA vaccines, patients enrolled in the trial were given a targeted therapy drug known as atezolizumab, which is an anti PDL-1 blocking antibody.
    - Atezolizumab is a monoclonal antibody (man made antibody) which binds to a protein present on many tumor cells known as PD-L1 (Programmed Cell Death - Ligand 1) and blocks interactions with a protein known as PD-1 which is present on T-cells. PD-1 is a protein on T-cells which plays an important role in inhibiting immune responses and regulates self-tolerance. In pancreatic cancer, a protein known as PD-L1 exists on the tumor cells which will bind to the PD-1 protein and

increase the production of T-cells with increased expression of the PD-1 protein. This way, the immune system is weakened as the increased expression of PD-1 proteins inhibits the T-cells' ability to target tumor cells. Atezolizumab blocks the interactions between PD-1 and PD-L1, as seen from the image below, so that the immune response is not inhibited by the high proliferation of PD-1 expressing T-cells.

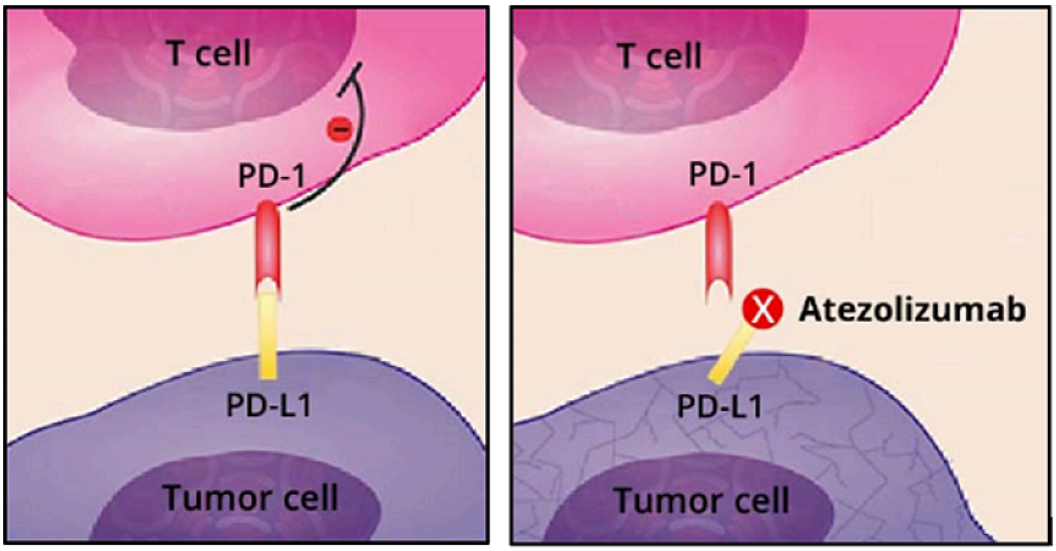


Image Source

- The patients then received 8 consecutive priming doses of their personalized mRNA vaccines, each of which contained about 20 neoantigens. A priming dose refers to the initial dose of a vaccination, and has the aim of stimulating the immune system of the patient by introducing the neoantigens on the surface of the T-cells of the immune system. These doses aim to increase the activation and expansion of neoantigen-expressing immune T-cells which can then attack the PDAC tumors.
- Following this, the patients received an aggressive form of chemotherapy known as FOLFIRINOX. This is a type of chemotherapy which targets rapidly dividing cancer cells. Chemotherapy is often used before mRNA vaccines as it is effective in debulking mass tumors and reducing the number of cancer cells which the immune cells have to target.

January 12, 2024:

- Today, I researched various forms of data to illustrate the role that mRNA cancer vaccines play in treating Pancreatic Ductal Adenocarcinoma. This first chart is a table of the results from two clinical trials testing immune checkpoint inhibitors against PDAC. In the first trial, out of 27 patients, only 1 had any response to immune checkpoint inhibitors, and in the second trial, out of 14 patients, none of them had immune response to the checkpoint inhibitors.

Table 1. Single-agent trials of checkpoint inhibition in PDAC to date.

Reference	Phase	Design	*N*	Results	Toxicity
Royal and colleagues[8]	II Locally advanced/ metastatic PDAC	CTLA-4 inhibitor ipilimumab	27	One patient had a delayed objective response	11% patients experienced grade ⩾3 immune-related adverse events
Brahmer and colleagues[9]	I Multiple tumours, advanced PDAC	Anti-PD-L1 (BMS-936559)	14	0 PDAC patients had an objective response	9% patients across all tumour types had grade ⩾3 immune-related adverse events

PDAC, pancreatic ductal adenocarcinoma; PD-L1, programmed death ligand 1.

- Image Source
- This next data from the BioNtech clinical trial testing mRNA pancreatic cancer vaccines against PDAC talks about the safety. One of the primary endpoints of this trial testing mRNA vaccines on patients with PDAC was safety. As seen from the graph below, this endpoint was met as a small percentage (less than 10%) of the patients in the Autogene Cevumeran which is the name of the mRNA vaccine, faced Grade 3 Adverse Events (AEs), specifically fever and hypertension. As well, 0% of the patients had Grade 3 AEs for atezolizumab. Both of these recorded levels were well within the study threshold of 25% indicated by the blue dotted line in the graph.

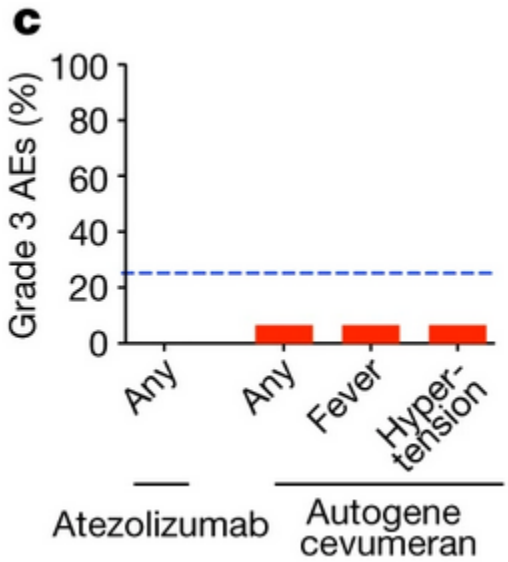


Image Source

- This study also tested the immunogenicity of the neoantigen mRNA vaccines, or whether

or not these vaccines were able to stimulate a response in the patients' T cells. The study found that 8 out of the 16 patients (50%) had T-cells which were able to develop the tumor-specific neoantigens that the autogene cevumeran mRNA vaccine introduced to the patients' immune system. These patients were classified as responders, and meet the secondary endpoint of this study which is the immunogenicity of the neoantigen mRNA vaccines is met by this.

- From the graph, it can be seen that in the responders a certain number of the neoantigens in the autogene cevumeran vaccine were immunogenic and were able to stimulate the patient's immune system (coloured yellow in the graph).

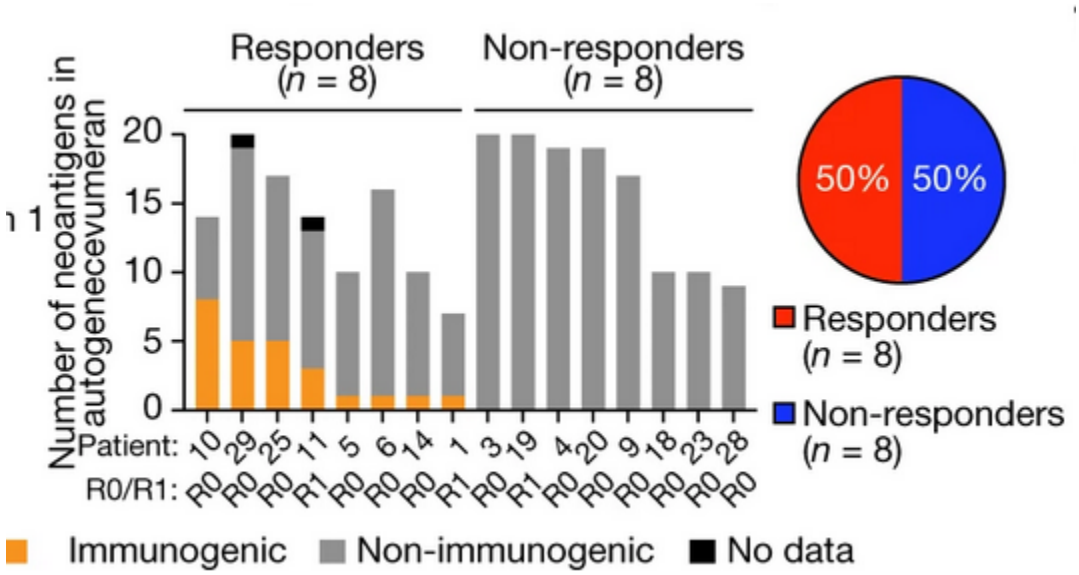


Image Source

January 16th, 2024:

Today, I continued to collect data for the BioNtech clinical trial. I specifically looked at a graph which represented the median recurrence free survival of responders vs non responders to the mRNA neoantigen vaccines:

- The graph below shows the median recurrence free survival (RFS) for the responders (red) and the non-responders (blue). We can see that the non-responders had a median RFS of 13.4 months, meaning that they had a recurrence of the cancer after 13.4 months. However, the responders have not yet reached a median RFS. This means that 24 months after receiving the mRNA cancer vaccine, these patients have not had a relapse of the cancer, and have a 100% relapse free survival. This shows that having a response to the neoantigen vaccine results correlates to delayed Pancreatic Ductal Adenocarcinoma recurrence.

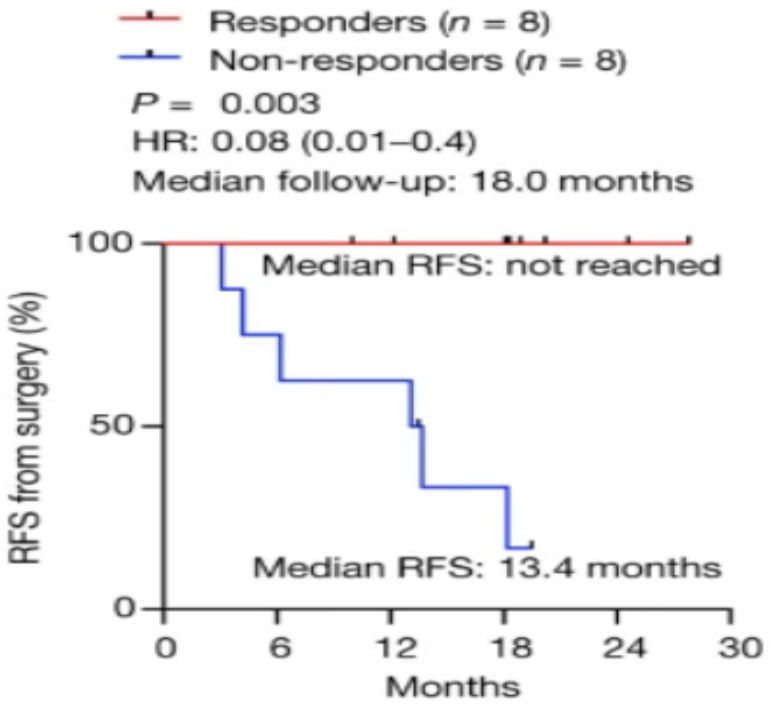


Image Source

January 20th, 2024:
Today, I wrote a conclusion/discussion for my project:

Pancreatic Ductal Adenocarcinoma is lethal in 88% of its patients, and Until recently, traditional immunotherapy methods such as immune checkpoint inhibitors have been ineffective against it. However, personalized neoantigen mRNA vaccines have shown promising results against PDAC.

- As seen from the presented data, the mRNA vaccine tested in the Phase 1 clinical trial was able to create a strong immune response in 8 out of the 16 patients enrolled in the study.
- It is also supported by the data that immune response to the neoantigen mRNA vaccine correlates with delayed PDAC recurrence (longer RFS).
- Therefore, the research and data analysis show personalized neoantigen vaccines are a safe, feasible method to treat Pancreatic Ductal Adenocarcinoma as they are able to stimulate the immune system to recognize and screen out the tumor cells, and are related to delayed recurrence of the cancer.

January 25 2024:

- Today, I researched about future steps:

- One future step for the administration of mRNA neoantigen vaccines for Pancreatic Ductal Adenocarcinoma is a Phase 2 clinical trial. This trial was recently approved and would involve 260 patients from 80 sites around the world. While the Phase 1 trial tested whether the mRNA vaccine would be able to trigger an immune response in patients with Pancreatic Ductal Adenocarcinoma, this new trial would compare this treatment with the current treatment for PDAC which is surgery followed by chemotherapy. This would enhance learning and understanding of the benefits that mRNA neoantigen vaccines would offer, over current treatments.
- Another future step in the field of mRNA vaccine therapy is extending this therapy to other cancers such as lung and skin cancer. A recent clinical trial in the U.K. has been launched which uses therapeutic cancer immunotherapies that are tailored to a particular type of cancer, to treat patients who have been diagnosed with lung or skin cancers. It is being tested to see its capability to shrink tumors. mRNA cancer vaccines can provide a reliable and long term cure for patients with lethal cancers. The hope is that mRNA cancer vaccines can be extended to treat all types of cancers in the near future.

January 31 2024:

Today, I added my citations.

- *Checkpoint inhibitors*. Checkpoint inhibitors | Types of immunotherapy | Cancer Research UK. (2022, February 15). https://www.cancerresearchuk.org/about-cancer/treatment/immunotherapy/types/checkpoint-inhibitors
- Guardian News and Media. (2024, February 4). *First UK patients receive experimental messenger RNA cancer therapy*. The Guardian. https://www.theguardian.com/science/2024/feb/04/first-uk-patients-experimental-messenger-mrna-cancer-therapy-treatment
- Http://journals.sagepub.com/doi/abs/10.1177/0887302x07303626 | ... (n.d.). https://www.researchgate.net/publication/328039672_httpjournalssagepubcomdoiabs10117708873 02X07303626
- *The pancreas and its functions*. Pancreas Functions, Location & Disease | Columbia Surgery. (n.d.). https://columbiasurgery.org/pancreas/pancreas-and-its-functions
- Pancreatic Cancer Action. (2022, September 8). *Distal pancreatectomy & splenectomy*. https://pancreaticcanceraction.org/about-pancreatic-cancer/treatment-options-for-pancreatic-cancer/treating-pancreatic-cancer/surgery-for-operable-pancreatic-cancer/distal-pancreatectomy-splenectomy/
- *Pancreatic cancer treatment*. National Cancer Institute. (n.d.). https://www.cancer.gov/types/pancreatic/patient/pancreatic-treatment-pdq
- Rojas, L. A., Sethna, Z., Soares, K. C., Olcese, C., Pang, N., Patterson, E., Lihm, J., Ceglia, N., Guasp, P., Chu, A., Yu, R., Chandra, A. K., Waters, T., Ruan, J., Amisaki, M., Zebboudj, A., Odgerel, Z., Payne, G., Derhovanessian, E., ... Balachandran, V. P. (2023, May 10). *Personalized RNA neoantigen vaccines stimulate T cells in pancreatic cancer*. Nature News. https://www.nature.com/articles/s41586-023-06063-y

- *Whipple procedure*. Johns Hopkins Medicine. (2021, August 23). https://www.hopkinsmedicine.org/health/conditions-and-diseases/pancreatic-cancer/whipple-procedure
- YouTube. (2016, June 21). *What is pd-1? ask A scientist*. YouTube. https://www.youtube.com/watch?v=02ldbt50uWc
- YouTube. (2022, June 30). *Phase I trial of mrna neoantigen vaccines for pancreatic cancer*. YouTube. https://www.youtube.com/watch?v=7AlMcarXdBo&t=148s