Immunotherapy Narrative Script:

In order to understand immunotherapy, there are a few things we need to get straight in our heads first. The first thing we need to get a general understanding of is what cells are, how they work, why they're so important, and what is it that happens in cancer that turns our own cells against us.

So, to begin with, cells are what make us us. They are the building blocks for absolutely all living things. Whether it is humans, dogs, jellyfish, spiders, flowers, or seaweed. But we are going to be focusing on humans in this scenario.

In all of our bodies there are billions of cells, with a bunch of different jobs. In fact, there are actually over 200 different kinds of cells in our bodies, all with their own important function. But these cells can't just sit around by themselves, or else nothing would ever happen. They need to work together and cells team up and become something bigger called a tissue.

Then from here, similar tissues work together to make an organ which carries out a certain function. A number of organs can then work together to make a system. So in this example, the stomach is part of the digestive system, which is responsible for getting the nutrients out of the food we eat and spreading these nutrients around the body, where they can be used to keep us alive. This system is made up of things like the stomach, the intestines and the liver. But it doesn't stop there. Systems work together to make what we call an organism; like us! Not only do we have a digestive system, we also have a circulatory system, a nervous system and many more.

From this, it's easy to see how every little cell we have is extremely important, as they are ultimately what allow everything else to work properly.

In order to keep us all healthy and have everything working properly, the cells in our bodies also need to grow and divide. But it is very important that they don't grow and divide too much. Unfortunately, this is what happens in cancer. Something goes wrong in a cell and it starts to grow and divide too much, and actually begins to take over. This is essentially what a cancer cell is. It's totally out of control. When this starts to happen, the rogue cells usually group together – forming a tumour. Tumours are able to destroy the normal cells that surround it, which leads to tissue damage and then disruption of the organ in which the tumour is located. So this change that happens at a cellular level actually prevents the organ from carrying out its job properly, which can lead to further health complications.

Sometimes these cancer cells are even able to move around. They separate from the tumour and travel through the blood, before finding a new place in the body where they can

settle down and start growing and dividing at an uncontrolled level again. The spread of cancer to a new area of the body is called metastasis.

The next thing we need to get a bit of knowledge about is genes. Everyone knows that genes are what we get from our parents. Your blue eyes, your curly hair, your funny smile, your dimples. But what actually are they? Well, genes are made up of DNA, and are used as instructions to make the different molecules and proteins that make you you. DNA is found in every single cell of your body, and genes are responsible for the proteins that are found in each cell, which control the function of the cell, how quickly the cell grows, how often the cell divides, and even how long the cell lives for. So, it therefore makes sense that if there is a mistake in a gene, there will also be a mistake in the protein that the gene codes for, which could potentially lead to protein being unable to carry out its job properly. This is essentially how all cancers start; a dysfunctional gene that has some sort of mutation, or mistake, that leads to the protein it codes for either not being made at all, or being made in a faulty way that stops it from working properly. Sometimes such a mutation can lead to the cell multiplying uncontrollably, and becoming cancerous.

There are two basic kinds of mutations that can happen to genes: germline mutations and acquired mutations.

Germline mutations are mutations that get passed down directly from a parent to a child. In this kind of mutation, the mutation is found in every single cell of the body. However, these types of mutation are not a very common cause of cancer, accounting only for about 5 – 10% of all cancers.

Acquired mutations on the other hand, are the most common cause of cancer. These mutations build up throughout a person's life, or are 'acquired' throughout their lifetime. Acquired mutations do not get passed on to the next generation. Instead, we get these mutations through things such as tobacco, ultraviolet light (or the sun), occasionally certain viruses, and just from getting old in general. Cancer that is caused by acquired mutations is known as sporadic cancer.

Now, something you may not have previously associated with cancer is your immune system. Your immune system is what usually keeps us safe from things that we call pathogens. Pathogens are things like viruses or bacteria that try to infect us and make us sick. The immune system has lots of different cell types that all work together to rid the body of things that don't belong there. What you might not know, is that our immune system can also recognise cancer cells and get rid of them before they begin to cause us any harm. Unfortunately, this doesn't always happen. There are a few reasons why the immune system sometimes can't detect cancer cells.

One reason is that some cancer cells are actually able to disguise themselves to look like normal healthy cells, thus evading being killed by the immune system, as it can't see that anything is wrong.

Another reason for the immune system not killing cancer cells is that the cancer is actually just too strong, and overpowers our immune response.

And last, but not least, some cancer cells actually release substances called cytokines that subdue the cells of the immune system, so that they no longer are a threat to the cancer cells.

Now that we all understand the different aspects of cancer, we can now move onto the different treatments that are available.

Firstly, the cancerous cells can simply be removed from the body through surgery. This is probably the easiest method to understand, although it is often either not possible, or not enough to rid the cancer fully. Other treatments, which you have probably heard about, include chemotherapy and radiation. However, while these treatments are often highly effective, they are not exactly specific to cancer cells; instead they target rapidly dividing cells, as cancer cells divide at a much faster rate than other cells in the body. However, for this reason, it also has some profound side effects, such as nausea and hair loss, as these cells also divide at a relatively fast rate (although not as fast as cancer cells).

A more recent line of treatment, which you may not have heard about, is something called 'cancer immunotherapy'. This is basically a broad term that means using or altering the immune system to fight cancer. There are a whole range of different cancer immunotherapies that all work in different ways, but that ultimately have the same effect – allowing the immune system to detect and destroy cancerous cells, when it was previously unable to do so.

We are going to discuss 5 cancer immunotherapy treatments.

The first cancer immunotherapy we are going to discuss is vaccines, of which there are two different kinds. These immunotherapy vaccines either prevent cancer, or help treat cancer. The preventative cancer vaccines do not actually prevent the formation of cancerous cells within your body. Instead, they prevent common viruses that are known to *cause* cancer from infecting us, thus preventing *them* from causing cancer within our bodies. Therapeutic cancer vaccines on the other hand do not prevent cancer at all. Instead they assist the immune system in ridding the body of cancerous cells once a patient has already been diagnosed with the disease. The way this works is that the vaccines help show the immune system what certain cancer cells actually look like so that the immune system can then recognise these cells as bad and target them for destruction.

Next we are going to talk about cell therapy. In certain individuals, immune cells called lymphocytes can infiltrate the tumour and help get rid of it. These cells are referred to as tumour infiltrating lymphocytes, or TILs. These TILs are already capable of targeting the cancerous cells and destroying them, but often there are not enough of them. In these

individuals, the TILs can be extracted from the tumour and grown externally in a lab. The cells are put in a T flask with media that provides them the necessary nutrients. Once these cells have multiplied, they are re-injected back into the patient, where they can then target the tumour but with more force, as there are more of them now, and destroy the cancerous cells.

Next up we will talk about something called cytokines as a cancer immunotherapy. Cytokines are chemical signals that naturally occur in our body all the time in response to different things. Some cytokines, such as interleukin 2 (or IL-2) and interferon alpha (IFN-α), help to boost our immune systems. Scientists have managed to make these cytokines outside of the body. These man-made versions can then be injected into the body to help boost the immune system. This is particularly useful in the scenario where the cancer cells have produced signals to subdue the immune system. The cytokines help override the signals from the cancer cells, meaning the immune system becomes fully active again and can start to target the cancer cells.

Another incredible invention in relation to cancer immunotherapy is something called 'monoclonal antibodies'. Antibodies are one of the things that our immune systems use to destroy things that are not meant to be in our body, such as bacteria or cancer cells. However, antibodies are very specific, and will only target what that the immune system has told it to target; furthermore, each antibody will only have one target. So although antibodies will sometimes naturally target cancer cells, this does not always happen. This is where monoclonal antibodies come into it all. Monoclonal antibodies are man-made antibodies that have been made to target specific cancer cell types, such as breast cancer. These monoclonal antibodies then attach to the cancer cells, acting as a signal to the rest of the immune system to come and kill the cells. Monoclonal antibodies can also be programmed to prevent cancer cells from growing, thus preventing further tumour growth.

Checkpoint inhibitors are the final cancer immunotherapy treatment we are going to discuss. Our immune systems have been programmed in such a way that they are usually able to differentiate our own, healthy cells from foreign or cancerous cells. It does this through something called 'checkpoints'. Our own healthy cells have certain indicators on their surface, or checkpoints, that lets the immune system know that everything is ay-okay. Unfortunately, some cancer cells evolve in such a way that they can keep these checkpoints on their surfaces and use them as a disguise. The immune system then sees them as a normal healthy cell and will not attack. Checkpoint inhibitors bind to checkpoints, thus preventing cancer cells from using such masks or disguises, meaning that they are then exposed to the full wrath of the immune system.

So which treatment is best? Unfortunately this is not really a question that can be answered. Cancer is not just one disease, it is more of an umbrella term for when cells divide and grow uncontrollably, which can happen for lots of different reasons. Due to this, no one treatment can be used for all cancers. Different treatments work best for different people and different cancer types. This is why it is so important to understand both the biology and immunology of cancer.

Some of the big questions that still need answered include:

1) Why do people respond differently to treatments?
2) Are there ways of predicting how a patient will react to a treatment?
3) Can we personalise treatments for individual patients?