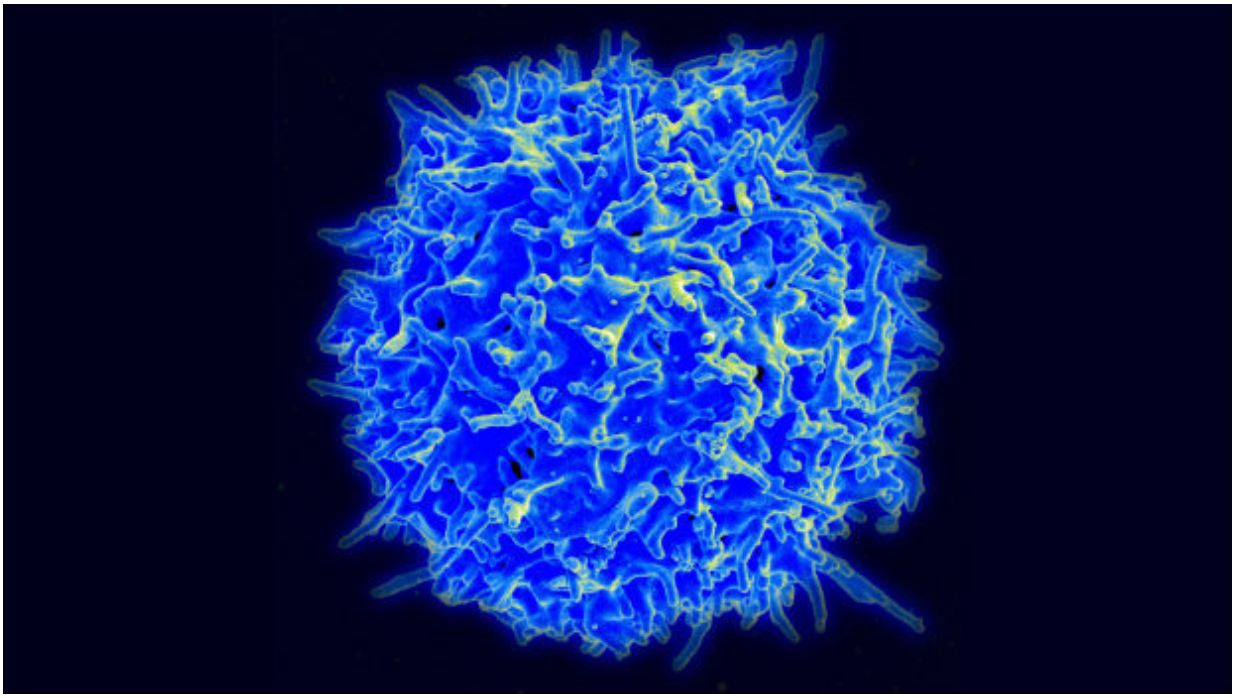
Testing a new immunotherapy treatment for neuroblastoma

May 3 2017, by Emma Smith



T cells are important fighters against disease. Credit: NIAID/NIH (public domain), via Wikimedia Commons

Immunotherapies are changing the outlook for many cancer patients.

Drugs that block cancer cells from deflecting an immune attack are now routinely used to treat advanced skin and kidney cancers, and are showing promise in other types of cancer too.

But cancers are complex and diverse – what works well against one type of cancer might have little effect against another. The immunotherapies available for some patients aren't a magic bullet that will work for everyone.

So researchers all over the world are looking into other potential treatments that unleash the immune system against cancer, and one of these approaches uses genetic engineering to modify our immune cells.

Professor John Anderson, a doctor and researcher who specialises in children's cancers, tells us more about a Cancer Research UK clinical trial that he's the leading doctor for.

It's an early stage clinical trial that we're running at Great Ormond Street Hospital and University College Hospital, testing the potential of a new type of immunotherapy to treat neuroblastoma – an aggressive type of cancer that most commonly occurs in young children.

What is the new treatment, and how does it work?

The treatment is based on genetically engineering a type of white blood cell in our immune system, called a T cell, to turn it into a cancer-killing cell.

The normal role of T cells is to protect us from infections, particularly viruses. Killer T cells can spot cells that are infected with a dangerous virus and destroy them, wiping out the infection. They can also spot cells that are damaged or faulty, and destroy them too.

Nearly all of our cells display small fragments of their contents on their surface as part of routine health checks. T cells wander through your body, using specialised scanners – called T cell receptors – to examine the fragments on cells as they pass by.

T cells are trained not to react to healthy cells. But when a cell is infected or damaged it usually causes changes to the fragments the cell displays, and these unusual fragments set off an alarm in T cells.

The immune system is very powerful so there are lots of checks and balances in place. But if T cells receive enough danger signals, they begin to multiply, attack and destroy the damaged or infected cells.

It's the T cell attack that forms the basis of the treatment we're testing. We're using genetic engineering to create designer T cells that focus the T cells' attack on the cancer cells. These engineered cells are called Chimeric Antigen Receptor T cells (CAR T cells).

The biggest challenge is finding a target to train the T cells to hunt, and there are two problems to tackle. Firstly, some cancers are very diverse, which means there are few, if any, targets that all the cancer cells share.

Secondly, the fragments on the surface of cancer cells are often very similar to those displayed by the same type of healthy cell, meaning that the T cells might attack healthy tissues as well, potentially causing side effects.

But in the case of neuroblastoma, there is a good target. Levels of a molecule called GD2 are high on most neuroblastoma cells, and it's not found on most healthy cells. So that's what we engineer the CAR T cells to target.

How do you genetically engineer someone's T cells?

The process starts by taking blood from a patient – either normally from a vein, or using a machine that only takes out the white blood cells.

In specialised labs, we stimulate the patient's T cells to start multiplying,

then we use an engineered virus to smuggle new genes into the T cell. One of these genes contains the instructions for the T cells to make the targeting molecule (CAR) that recognises GD2.

We grow the modified CAR T cells for a few days in the lab, freeze them in batches, test them for cancer killing ability, then give them back to the patient through an IV drip.

Who can join the trial?

This is the first time we've tested this treatment in patients, so our first priority is measuring safety.

The immune system is extremely powerful, so any immunotherapy has the potential to cause serious side effects, and in the most severe cases, can be fatal.

This is a phase I trial and our goal is to find out the new therapy's safety, and what doses we can give it to children without causing severe side effects.

Because we don't know yet if it will be effective, we're testing the CAR T cells in children who have run out treatment options. These are poorly children, whose neuroblastoma has come back and no longer responds to chemotherapy.

The trial will only include a small number of children at this stage. We predict in the range of 15 to 20 children.

The trial starts by simply giving the CAR T cells to the patient. If there are no bad reactions, then the next patients receive increasing doses of chemotherapy before giving them the CAR T cells. This will reduce the numbers of competing normal T cells and T cells that naturally dampen

down immune reactions, giving the CAR T cells a better chance of surviving and mounting an attack on the cancer cells.

We'll be monitoring the children very closely for side effects and to control the immune reaction if it gets out of hand.

Will this treatment be a big breakthrough for children with neuroblastoma?

We simply don't know yet. That's what we're trying to determine through clinical trials.

Like any new treatment, the CAR T cells need to go through a rigorous process of testing. This first phase is to find out if they're safe and what dose to use them at. We will also get some information on whether the CAR T cells start attacking the neuroblastoma cells, as they're designed to do.

If all goes well, then we can take the treatment into larger clinical trials to start working out how effective it is.

CAR T cells have been showing lots of promise in clinical trials testing them in people with blood cancers, including various types of leukaemia and lymphoma, with many patients going into complete remission.

But their deployment against solid tumours in adult cancers has had mixed success.

And there are still safety concerns associated with CAR T cells. Once they have been unleashed, it's hard to stop them, and an out of control immune reaction can cause death.

So we need to proceed with caution and make sure safety is at the top of our agenda. At the same time, the outlook for children with neuroblastoma that's not responded to treatment rarely survive for more than 2 years and we urgently need better treatments for these children.

Could CAR T cells be part of the answer? Only time will tell.

Provided by Cancer Research UK