THE immune system is the body’s defence against disease and infection. Lymphocytes, a group of white blood cells, are a major portion of our immune system. There are two types of lymphocytes – B lymphocytes (B-cells) and T lymphocytes (T-cells).

B-lymphocytes make antibodies to “coat” the antigens on the invading cells, marking them as targets for T-cells. T-cells are distinguished by a special protein on their surface, known as the T-cell receptor (TCR). These receptors can bind to these antigens (also proteins) present on the marked cells and kill them. However, in most circumstances the body’s natural immune system seems unable to identify cancer as a foreign invader.

In diseases such as acute lymphatic leukaemia (ALL), chronic lymphatic leukaemia (CLL) and non-Hodgkin’s lymphoma (NHL), the immune B cells themselves become cancerous. While 85% of these cancers are successfully treated by standard chemotherapy, in the remaining 15% chemotherapy works only temporarily or not at all. To treat such cases researchers are trying over the past two decades to reengineer the T-cells so that they can recognise some specific receptors on the cancerous B-cells and attack them.

The hallmark of all B-cells, cancerous or otherwise, is the presence of an antigen known as CD19 on their surface. So the idea is to genetically engineer the patient’s own T-cells such that they can express a chimeric antigen receptor (CAR) on their surface, which can bind to CD19 and destroy the cancerous B-cell.

Producing CAR T-cells

Now, how is this done? Blood sample is taken from the patient’s body through an intravenous (IV) catheter in one arm into a machine which separates out the T-cells from the rest of the blood, using a process known as Leukopheresis. The remaining blood returns to the body through an IV on the other arm. About 1% of the body’s T-cells are extracted so that the patient’s immune system is not compromised.

The extracted T-cells are then purposely infected with a disabled virus carrying a gene that encodes for a protein on the surface of the T-cells that can specifically recognise and bind to the antigen CD19 on the B-cells. The virus also triggers the T-cell to multiply vigorously in a culture medium. Such genetically engineered T-cells are known as chimeric antigen receptor T-cells (CAR T-CD19 cells).

These are then multiplied to billions in the laboratory over a period of about two weeks and infused back into the patient’s body in large numbers. The CAR T-CD19 cells when once inside the patient’s body go on hunting for the cancerous B-cells and destroy them. CAR T-cells can be designed with other antigen receptors too to target other cancers. For example, CAR T-CD123, CAR T-CD38 CAR T-CS1 cells target myeloid leukemia.

Clinical trials of CAR T-cell therapy at various centers have produced impressive results in patients with blood cancers like leukemia and lymphoma. More recent versions of CAR T-cell technologies incorporate mechanisms for further amplifying T-cell activation or dampen it in case of over reaction by introducing by what are called “suicide switches”. Carl June an immunologist at the University of Pennsylvania has developed the so called “armored” CAR T technology, which is designed to attack even solid tumors.
CAR T-19 cells and also did not mediate any graft versus host reaction. The biggest advantage of UCAR T-cells is that they can be manufactured on an industrial scale with standardised techniques. Cells taken from just one healthy donor can be engineered and multiplied billions of times and preserved frozen in aliquots to treat thousands of patients over a period of time. This would also bring down the cost of treatment considerably.

A demonstration of the proof-of-concept of UCAR T-19 cells in an actual clinical setting was the recent case of a one-year-old girl Layla Richards. Layla Richards was diagnosed with Acute Lymphoblastic leukaemia when she was just three months old. It is a disease in which cancerous stem cells from the bone marrow release vast number of immature immune B-cells into the blood. Doctors at the Great Ormaond Street Hospital, London, had tried all the established procedures like chemotherapy and bone marrow transplant without much success. In her case, autologous CAR T-cell therapy could not be attempted because chemotherapy had obliterated her immune system and no T-cells were left.

Just before Layla’s first birthday, the disease had reached end stage. Left with no choice other than palliative care, doctors tried UCAR T-19 cell therapy. Layla was given an injection of UCAR T-19 cells (4.5X 10^6 cells per kilogram body weight) in June 2015. Doctors kept their fingers crossed. But, miraculously, within weeks after the treatment her condition improved. A short time after the treatment her condition improved. A short time after the treatment her condition improved. A short time after the treatment her condition improved. By November 2015 doctors announcing on her announced that her leukemia was under remission.

Encouraged by the results, doctors plan safety trials this year with 10 to 12 patients using Universal CAR T-cells. If all goes as planned, they say that the technique can become a treatment of choice for a number of hematological cancers and other diseases.

Universal CAR T-cells

One of the basic limitations of the CAR-T cell technology is that it is autologous. That is, the patient’s own T-cells are used. This means they have to be produced on a “patient-by-patient” basis, which takes a long time, will not have any standard production procedure from center to center and is expensive.

In response to these limitations, researchers at the National Cancer Institute, USA and many other centers have been developing standardised procedures to generate “off-the-shelf” CAR T-cells taking T-cells from third-party healthy donors, which can be used to treat any patient.

The problem with allogenic T-cells, cells taken from a healthy donor, is that when injected into a recipient, who is not a perfect match, they would recognize the recipient’s cells as foreign and attack them leading to what is known as “graft versus host reaction”. To prevent this, researchers at Callectis, a bioengineering company at Paris, use precise gene-editing tools like Transcription Activator-like Effector Nuclease (TALEN) to knock out two genes – the TCR alpha gene and the CD52 gene in the donor T-cells.

Knocking out the TCR gene would eliminate the TCR expression and abrogate the donor T-cell’s potential for graft versus-host disease. Inactivating a gene like the CD52 would protect the donor T-cells from being destroyed by the anticancer drugs the patient may be receiving.

Finally, just as in autologous CAR T-cell production, they introduced a new gene through a virus vector to produce a chimeric antigen receptor protein on the donor cell surface, which can bind to the antigen on the cancer cell. These “Universal CAR T (UCAR T) cells” can also be engineered to target different tumors, be compatible with specific medical regimens that the patient may undergo and also equipped with a suicide gene through which they can be eliminated in case of any unintended reactions.

In mouse models, UCAR T-19 cells thus produced exhibited antitumor activity equivalent to that of autologous CAR T-19 cells and also did not mediate any graft versus host reaction.

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