Enhancing CAR-T cell therapy to treat childhood leukemia

Professor Marco Herold and Dr Emily Lelliott

Leukemia is a cancer that arises from abnormal white blood cells. It is the most common cancer diagnosed in children, accounting for approximately 35% of all childhood cancers. CAR-T-cell therapy is an innovative therapy recently approved to treat childhood leukemia. This therapy involves collecting the patient's T cells (a type of immune cell) and engineering them to selectively seek out and destroy cancer cells. It is generally used for high-risk leukemias as a last line treatment after traditional treatments, such as chemotherapy, have failed. It has been remarkably successful, leading to remission in ~90% of patients, however, sadly, around half of these patients will eventually relapse and succumb to the disease.

With the generous support of the Australian Lions Childhood Cancer Foundation, WEHI researchers Prof Marco Herold and Dr Emily Lelliott are developing a new generation of CAR-T cells that will overcome this challenge and more effectively treat childhood leukemia. The team are taking an innovative, two-part approach that will lead to lower rates of relapse whilst ensuring that those children who do relapse have access to the follow-up treatment, they need to make a full recovery:

Part 1: Identify genes that can be edited to generate CAR-T cells with optimal and long-term cancer-fighting ability

Unlike traditional cancer treatments, such as chemotherapy, CAR-T cells are generated from a patient's biologically living T cells. As a result, the effectiveness of CAR-T cells can vary greatly between patients. Many CAR-T cells can only kill cancer cells for a short time before they become ineffective, while other long-lived CAR-T cells can survive and function for long periods of time and are very efficient at killing many cancer cells. This project will apply unique high-throughput CRISPR/Cas gene editing technology to simultaneously test thousands of genes and efficiently identify those that can be edited to generate long-lived CAR-T cells with optimised cancer-fighting

Dr Emily Lelliott

ability.

Part 2: Develop and test new therapeutic technology that enables CAR-T cells to be engineered directly inside the body

CAR-T cell therapy currently relies on complex procedures where T cells are collected from the patient and genetically engineered *outside the body* in a specialised laboratory. This approach has been highly successful in treating some patients, however, removing cells from the body and manipulating them in a laboratory significantly reduces their cancer-fighting function once transferred back into the patient. It is also expensive, with the total cost of each treatment reaching up to $1,000,000. This project will utilise lipid nanoparticle (LNP) technology, recently developed as a delivery tool for COVID-19 mRNA vaccines, that will allow CAR-T cells to be engineered inside the body. This approach has the potential to not only optimise the quality of CAR-T cells, but significantly reduce the cost of therapy, making it more accessible to patients.

Thank you to the Australian Lions Childhood Cancer Research Foundation and the broader Lions community for their invaluable support of this important research project.