# A leap forward in research on CAR T cell therapy

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In cancer immunotherapy, cells in the patient's own immune system are activated to attack cancer cells. CAR T cell therapy has been one of the most significant recent advances in immunotherapies targeted at cancer.

In CAR T cell therapy, T cells are extracted from the patient for genetic modification: a chimeric antigen receptor (CAR) is transported into the cells using a viral vector, helping the T cells better identify and kill cancer cells. When the antigen receptor cells identify the desired surface structure in the patient's cells, they start multiplying and killing the target cells.

CAR T cell therapy was introduced to Finland in 2018, and the treatment form has been used in support of patients suffering from leukemia and lymphomas.

So far, the application of CAR T cell therapy to solid tumors has been difficult: targeting the therapy at just the tumor is difficult when the cancer type is not associated with any specific surface structure. In many cancer types, there is an abundance of a specific protein on the tumor's surface, but as the protein also occurs in low numbers in normal tissue, CAR T cell therapy is not able to discriminate between target protein levels. This is why genetically modified cells are quick to attack also healthy cells and organs, which can result in fatal adverse effects associated with the treatment.

A study recently published in the *Science* journal has found a solution to applying CAR T cell therapy to solid tumors as well: through collaboration, American and Finnish researchers identified a new way of programming CAR T cells so that they only kill cancer cells, leaving

alone healthy cells that have the same marker protein as cancer cells.

## New technique based on ultrasensitive identification of HER2 cells, further investigation underway

HER2 is a protein characteristic of, among others, breast cancer, ovarian cancer and abdominal cancers. The protein can also occur in great numbers on the surface of tumor cells, since, as a result of gene amplification, HER2 expression can be multiplied in tumors.

A new CAR T cell engineering technique developed by the researchers is based on a two-step identification process of HER2 positive cells. Thanks to the engineering, the researchers were able to produce a response where CAR T cells kill only the cancer cells in the cancer tissue.

"Our solution requires the preliminary identification of the surface structures associated with the cancer. When the preliminary recognition ability that induces the CAR construct is adjusted to require a binding affinity that is different from the affinity used by CAR to direct the killing of these cells, an extremely accurate ability to differentiate between cells based on the amount of target protein on their surface can be programmed in this two-step 'circuit' which controls the function of killer T cells," says Professor of Virology Kalle Saksela from the University of Helsinki.

Further studies for the application of the technique are already ongoing. Postdoctoral Researcher Anna Mäkelä, who works at Professor Saksela's laboratory, is coordinating a project funded by the Academy of Finland investigating the use of CAR T cell therapy on various cancer types and their surface structures.

"We are very excited about these results, and we are currently developing the technique so that it could be used to treat ovarian cancer. As the work progresses, the aim is to apply the technique itself and the targeting molecules of CAR constructs even more broadly to malignant solid tumors. Our goal is to develop 'multi-warhead missiles', against which cancer cells will find it difficult to develop resistance," Mäkelä says.

**More information:** Rogelio A. Hernandez-Lopez et al, T cell circuits that sense antigen density with an ultrasensitive threshold, *Science* (2021). DOI: 10.1126/science.abc1855

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