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# Quality Over Quantity: New Insights into the Role of Specific CAR T Cells in Cancer Therapy

**CAR T-cell therapies are used successfully to treat certain blood cancers. However, while some patients respond even to low-dose treatment, others derive no benefit. Researchers from the Heidelberg Faculty of Medicine at Heidelberg University and the Berlin Institute of Health at Charité (BIH) investigated the reasons behind these differences in a collaborative research project. They identified a specific subgroup of CAR T cells that plays a key role in determining the success of low-dose therapies and could potentially serve as a biomarker in the future. The findings have now been published in Nature Communications.**

Immunotherapies strengthen the body's own anti-cancer defenses in a highly targeted manner. In therapies using so-called CAR T cells (chimeric antigen receptor T cells), a patient's immune cells are genetically engineered and directed against their individual cancer cells. Until now, it has remained unclear why even very low CAR T cell doses are effective in some patients, while others do not benefit from the treatment. A research consortium led by the Department of Medicine V at Heidelberg University Hospital, and the Berlin Institute of Health at Charité (BIH) has now identified key biological factors that influence the effectiveness of CAR T-cell therapy when lower cell doses are administered. These findings could help improve outcomes for individual patients, further personalize cancer treatment, and reduce treatment costs.

CAR T-cell therapies can be used in certain advanced blood and lymphatic cancers when other treatments, such as chemotherapy or radiation therapy, have failed or after disease relapse. For this approach, a patient's own immune cells are genetically modified in the laboratory so that they can recognize a specific target structure on the surface of cancer cells and selectively attack and destroy them. In many patients, cancer remains undetectable for extended periods following CAR T-cell therapy. The manufacturing and expansion of these therapeutic immune cells is complex and time-consuming. Moreover, it is not always possible to produce the intended, ideally large number of cells required for treatment. In such cases, patients either receive a therapy with uncertain prospects of success despite the risk of potentially severe side effects, or the manufactured CAR T-cell product is not administered at all because the cell yield is too low.

## Highly Functional CAR T Cells Determine Treatment Success

The study, now published in Nature Communications, is based on data and samples from the HD-CAR-1 trial, conducted by researchers from the Heidelberg Faculty of Medicine, the German Cancer Research Center (DKFZ), and at the National Center for Tumor Diseases (NCT). The scientists analyzed both original blood samples from patients with hematological malignancies and the CAR T-cell products generated from those samples. Using high-resolution single-cell analyses, they examined, among other aspects, the composition of CAR T-cell products administered at different dose levels, identifying the immune cell types they contained and assessing their functional activity. These findings were then compared between patients who responded to treatment and those who did not.

The researchers identified a subgroup of CAR T cells whose abundance was directly associated with the success of low-dose therapies. These cells are characterized by a molecular profile that makes them particularly effective at killing tumor cells, as well as by the absence of two specific surface markers that can be used to identify them. "The greater the number of these specific CAR T cells, the more effective the therapy was, even when the overall number of cells was relatively low," says Michael Schmitt, MD, Professor "Cellular Immunotherapy" at Heidelberg Faculty of Medicine, Heidelberg University, Head of the Cell and Immunotherapy Research Program within the Department of Hematology, Oncology and Rheumatology at Heidelberg University Hospital, and one of the study's two senior authors. "Our findings suggest that the absolute number of these highly functional cells could serve as a biomarker for predicting the success of low-dose CAR T-cell therapy."

"We also showed that treatment success does not depend solely on the CAR T cells themselves. Equally important is the state of a patient's immune system before cell manufacturing begins," adds Professor Simon Haas. Professor Haas conducts research at the Center of Genomic Medicine of the Berlin Institute of Health at Charité, the Max Delbrück Center for Molecular Medicine in Berlin, and Queen Mary University of London (United Kingdom), and is co-senior author of the study together with Professor Schmitt. "Patients whose blood contained larger numbers of functional immune cells were more likely to yield

effective CAR T-cell products." By contrast, when the original blood samples contained a high proportion of cells that suppress immune responses, fewer highly functional CAR T cells were generated, and patients were less likely to respond to treatment. "Our analyses show that indicators of how well the final CAR T-cell product will perform can already be detected in the patient's blood before manufacturing begins," summarizes Schayan Yousefian, a doctoral researcher in Professor Haas's group and first author of the study.

## New Opportunities for Personalized CAR T-Cell Therapies

According to the study authors, the findings represent an important step toward further personalization of cancer immunotherapies. "Further research is needed to better understand the underlying mechanisms, validate the biomarker, and ultimately integrate it into routine clinical practice," says Professor Schmitt. One of the key next steps will be to determine the minimum number of highly functional CAR T cells required for a therapy to have a reasonable likelihood of success.

Professor Haas notes that the findings also have implications for healthcare policy and economics. CAR T-cell therapies can cost several hundred thousand euros per patient. "If our findings are confirmed in further studies, CAR T-cell manufacturing could become much more targeted in the future. This would benefit not only patients but also help conserve healthcare resources."

**Publication**

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