New research results explore the safety of short-term cultivated CAR T cells in cancer immunotherapy

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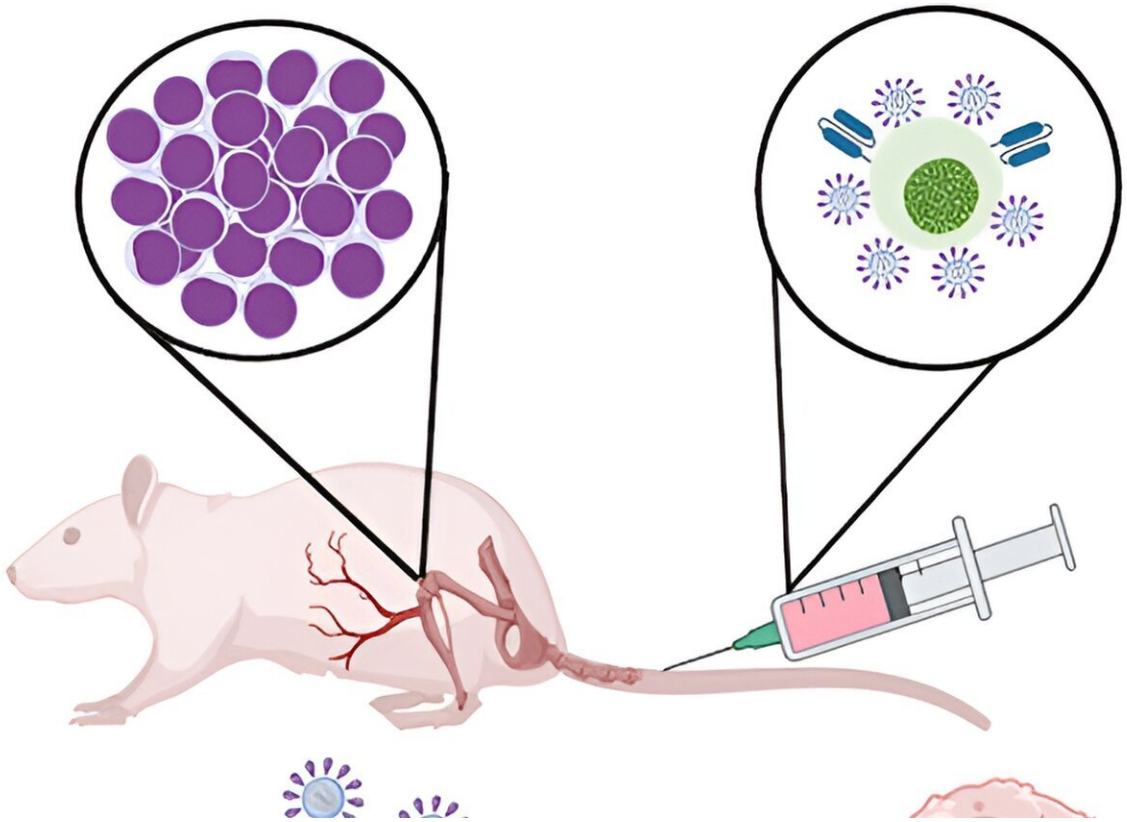

To make CAR T cells available to all patients, various strategies facilitating the manufacturing process are followed. Short-term (st) CAR T cells are administered shortly after exposure to lentiviral vector (LV) particles. Here, their preclinical safety was assessed ex vivo and in vivo. Credit: *EMBO Molecular Medicine* (2024). DOI: 10.1038/s44321-024-00055-9

Chimeric antigen receptor T cells—CAR T cells for short—are immune cells (T cells) that are taken from the body and genetically modified outside the body in the laboratory using transport vehicles for the genes to be transmitted (vectors). After being returned to the patient, these CAR T cells can specifically target and kill cells that contain defined antigens.

CAR T cells provide treatment options for patients with certain forms of blood cancer (B-cell leukemias and lymphomas) that have not responded to other therapies. Impressive treatment results have been achieved in some cases.

Lengthy production time for CAR T cells prevents prompt treatment

An issue that arises with the application of this technology is the complex and lengthy cell production process, which prevents timely treatment of patients. A new strategy has been developed as a potential solution to the problem. In this new approach, patients' T cells are returned very soon after exposure to vector particles that transmit the chimeric antigen receptor (CAR). Although these short-term cultivated CAR T cells are available faster, their safety has not yet been sufficiently tested.

There has been a lack of preclinical models that make it possible to predict the risk of developing cytokine release syndrome (CRS). CRS is a severe, potentially life-threatening complication of CAR T cell therapy, in which large amounts of immune system messenger substances are released, possibly leading to a disruption of the immune system.

Test systems to assess the safety of newly developed

CAR T cell therapies

A research team formed by Professor Christian Buchholz, head of the Molecular Biotechnology and Gene Therapy Research Group at the Paul-Ehrlich-Institut, addressed the issue surrounding short-term cultivated CAR T cells. Using an easily accessible mouse model and a cell-based test, the researchers demonstrated that short-term cultivated CAR T cells bear a significantly higher risk of inducing cytokine release syndrome compared to conventional CAR T cells.

Their study has also shown that the release of CRS-relevant cytokines is independent of the presence of tumor cells. Instead, residual components of the lentiviral vector particles on the surface of the short-term cultivated CAR T cells were identified as causative.

The findings underline the need to pay particular attention to the induction of CRS after the clinical application of short-term cultivated CAR T cells while also having direct test systems available for a risk assessment of the cells before clinical application.

Producing CAR T cells in a manner that makes them quickly available for treatment is an important goal to give more patients access to this potentially life-saving treatment. The test systems detailed above can help make this treatment option accessible to patients without disproportionate risks.

The research is published in the journal *EMBO Molecular Medicine*.

More information: Arezoo Jamali et al, Early induction of cytokine release syndrome by rapidly generated CAR T cells in preclinical models, *EMBO Molecular Medicine* (2024). DOI:

10.1038/s44321-024-00055-9