Licence to kill – the enormous potential of CAR T cells

With 6 million euros of EU funding, the CARAT project aims to optimise a technology called CAR T that is used to equip T cells with antibody fragments and specifically direct them to destroy cancer cells. The CARAT consortium comprises a multinational team of experts from the Institute for Cell- and Gene Therapy at the Freiburg University Medical Center led by Prof. Dr. Toni Cathomen and seven partner institutions. Cathomen's team is developing the gene scissors required for the technology.

Cancer is a leading cause of mortality and morbidity. In Germany alone, around half a million people are diagnosed with cancer every year. Some tumours are dangerous, others relatively harmless. The Centre for Cancer Registry Data estimates that 51 percent of men and 43 percent of women will develop cancer during their lifetime. However, the type of cancer a person develops depends on many unknown factors and cancer is usually only diagnosed when it is already in an advanced stage. This is because cancer has no real "face". However, there are a few features that can reveal the presence of a tumour.

Every oncologist is aware of the hallmarks of cancer published by the scientists Douglas Hanahan and Robert Weinberg in the journal Cell at the turn of the millennium. It remains one of the most cited papers worldwide. The original list of cancer hallmarks (sustaining proliferative signalling, evading growth suppressors, resisting cell death, enabling replicative immortality, inducing angiogenesis and activating invasion and metastasis) has now been expanded eleven years later. Inflammatory stimulation, genomic instability and deregulation of the cellular energy balance, evasion of immune system attacks by camouflage and defence strategies have been identified as new hallmarks. The latter prevents tumour cells from being destroyed by host T cells.

Over the past few years, researchers around the world have been developing preventive and curative therapies to fight cancer. Of these, cancer immunotherapy is considered the greatest beacon of hope. In addition to the three classical cancer therapies (surgical removal of the tumour, radiation and chemotherapy), a few complex immunotherapeutic approaches are available. Immunotherapies usually involve the use T lymphocytes (T cells), which are essential for the human immune system and patrol the body to destroy foreign cells. The goal is to activate the immune system, which is generally weakened in cancer patients. The T cells are recruited to the tumour cells and destroy them. Other immunotherapies use antibodies to mark tumour cells and block their survival strategies (i.e. the release of immunomodulators), so that the tumour cells are no longer able to evade immune system attacks. "Over the past few years, huge progress has been made in cellular immunotherapies, which are therapies involving antibodies and kinase inhibitors," says Prof. Dr. Toni Cathomen from the Institute for Cell- and Gene Therapy at the Freibrug

University Medical Center.

Adoptive cell transfer: CAR T technology

Prof. Dr. Toni Cathomen is developing the gene scissors required by the CARAT project for inserting the new receptors into T cells.
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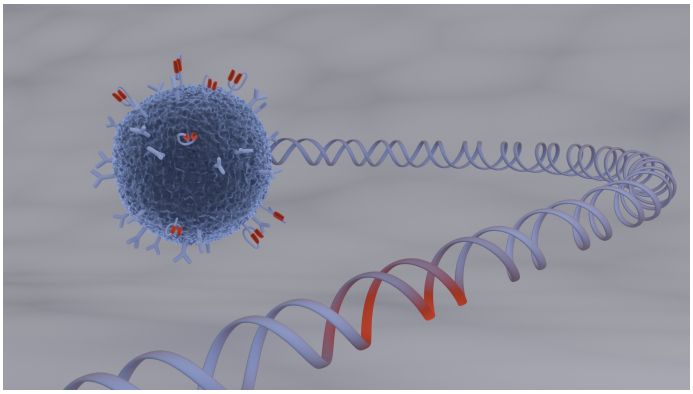
Adoptive cell transfer methods involve removing cells from a patient's blood, modifying, expanding and re-introducing them into the patient's body. As outlined above, the methods preferentially use T cells due to their immunological importance. Outside the body, the T cells that have been withdrawn are sensitised against tumour cells. Adoptive cell transfer has become increasingly important in cancer treatment over the past few years. In numerous studies, chimeric antigen receptor T cell therapy (CAR T cell therapy) has demonstrated its efficacy in leukaemia treatment. The T cells are collected from the leukaemia patient, and genetically engineered to produce so-called chimeric antigen receptors (CARs) that enable T cells to kill cancer cells. CAR T cells recognise a specific antigen on tumour cells and act as recognition molecules in the same way as T cell receptors (TCR) or antibodies. The target structures on the tumour cell surface are thus no longer recognised by the complete T cell receptor, and interactions with T cells are no longer dependent on major histocompatibility complex (MHC) molecules, which normally present fragments of foreign antigens to T cells and are necessary for a specific immune response to occur. CAR T cell therapy is based on the attachment of an antibody that is directed against a tumour cell antigen (or paratope that enables the recognition of target structures) to the intracellular domain of the TCR, parts of which remain as scaffolds.

Several generations of CARs of differing intracellular, co-stimulatory domain composition are now available. Binding a T cell to a tumour cell with a CAR triggers a specific immune response. The potential of CAR T cells has been demonstrated over the past few years and such treatments have proven to be very successful. For example, in a clinical trial of B cell leukaemia, more than 90% of patients showed complete remission, i.e. complete absence of disease symptoms. This is a world first in the field of tumour medicine. The fact that these patients were resistant to all other therapies, encourages the researchers to further develop CAR T cell therapy.

CARAT has several objectives

The CARAT project (chimeric antigen receptors for advanced therapies), involving eight partners from four countries and financed with 6 million euros of EU funding, aims to further develop CAR T



Researchers involved in the EU project CARAT equip T cells with chimeric antigen receptors (CAR) that can recognise tumour cells on the basis of their surface structures and induce an immune response.
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into a comprehensive platform and facilitate the manufacture of CAR T cells and delivery of safe cell therapies. “Here in Freiburg, we use designer nucleases to insert CAR genes at specific sites in the T cell genome. This enables us to predict their expression and ensures that no other important genes are activated or interrupted,” explains Cathomen. “This helps us minimise the risk of gene transfer-induced leukaemia.” For further security, the Freiburg researchers equip the surface of their CAR T cells with epitopes with which they can be deactivated using epitope-specific antibodies.

CAR T cell therapies are currently very expensive and labour-intensive: the T cells need to be collected from patients via apheresis (a process during which blood is withdrawn and one or several blood components removed before being put back into the patient). Then they need to be genetically engineered to produce chimeric antigen receptors on their surface, activated to become cytotoxic CD8 T cells, enhanced and frozen, and, when there are sufficiently high numbers of CAR T cells, infused into the patient. “CAR T cells are a product made exclusively for each individual patient. This is highly personalised medicine,” says Cathomen. The overall goal of the project is automation. “We are hoping to develop devices that will enable all hospitals to produce CAR T cells from patients’ own T cells. No supplier will be needed and the product will be ready for re-injection into the patient the day after the removal of the cells.”

Studies confirm the potential

The technology is currently not used for the treatment of solid tumours as T cells are unable to penetrate the stroma surrounding such tumours. This problem is also being addressed as part of the project. The immunomodulators released by the tumour target specific receptors on the T cells. Cathomen plans to selectively switch off these receptors. He comments: “Switching off these natural breaks makes the T cells more aggressive. The parallel incorporation of security aspects is therefore of the utmost importance.”

Clinical data gained from treating patients with acute lymphoblastic leukaemia have shown that relapsed and treatment-resistant patients are cancer-free after receiving CAR T cell therapy. “Over the past two to three years, the successful use of CAR T cells for the treatment of leukaemia has demonstrated the enormous potential of the therapy,” says Cathomen optimistically. “I am sure that over the next few years many more CAR T cells will be used for the personalised treatment of tumours, perhaps also in combination with antibodies or inhibitors.”

Will CAR T cell therapy be able to cure cancer? Cathomen is hopeful: “There are still a few years to go before this becomes possible. But I am sure we will get there.”

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Further information

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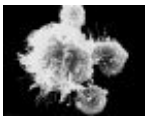
- CARAT - Chimeric Antigen Receptors (CARs) for Advanced Therapies

The article is part of the following dossiers



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