RESEARCH NEWS

Cellular immunotherapy

Advances in Cancer Treatment: CAR T Cells Fight Solid Tumors

A new generation of CAR T cell therapy is bringing hope in the fight against cancer, targeting not only blood cancers but also solid tumors such as ovarian and breast cancer. Fraunhofer researchers teamed up with the University Hospital of Würzburg to streamline the complicated process of manufacturing these therapies as well. This could make them much more available.

Cellular immunotherapy has been one of the most effective methods of treating cancer for several years now. The immune system's defensive cells, known as T cells, undergo genetic modifications that make them able to recognize tumor cells and attack them specifically. In CAR (Chimeric Antigen Receptor) T cell therapy, the T cells are equipped with a receptor programmed for the specific surface molecules (antigens) found in certain tumor cells. Once they bind to the tumor antigens, they are activated and destroy the cancer cells. Even in people who have completed radiation and chemotherapy and are considered to have run out of treatment options, CAR T cell therapy still offers good treatment options and potentially the prospect of being cured.

Working together, the Fraunhofer-Institute for Cell Therapy and Immunology IZI and the University Hospital of Würzburg have made crucial next steps in advancing this form of treatment. The new therapy version is intended to make it possible to treat solid tumors such as ovarian and breast cancer or adrenocortical carcinoma, not just blood cancers. This represents significant progress, since solid tumors are much more common than hematological tumors arising in the blood, bone marrow or lymph nodes.

The research project is being led at the University Hospital of Würzburg and the Fraunhofer IZI branch lab in Würzburg by Michael Hudecek, a pioneer in immunotherapy who helped to develop the first generation of CAR T cells. At Fraunhofer IZI, the team headed by Kati Kebbel and Gerno Schmiedeknecht, head of the GMP Cell and Gene Therapy department (GMP stands for "good manufacturing practices"), is in charge of producing the therapeutic agent.

Enzymes for genetic change

The tyrosine kinase-like orphan receptors (RORs), which are found on the surface of cancer cells, are key to advancing the research of treating solid types of cancer. These

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molecules only play a role during human embryonic development, when they contribute to tissue growth and cell renewal. Adults hardly have any RORs — except if they have cancer. The team of researchers has modified the T cells so that their CAR receptors specifically recognize these RORs.

As part of the joint project, the researchers are also working to make the complicated process of producing them more efficient. An enzyme called the "Sleeping Beauty" transposase helps with this by making it possible to integrate therapeutic genes into the genome of cells. The team of researchers uses the enzyme as a substitute for viruses to genetically modify the immune cells. This technology was developed by Zoltan Ivics, who is now also doing research at Fraunhofer IZI in Leipzig. "This method has safety advantages and helps to reduce the amount of work and cost involved in production," Hudecek explains.

Cleanroom production

Fraunhofer IZI has years of experience with developing and producing cell and gene therapeutics. For the current project, the experts have developed a robust, reproducible production process. "In terms of pharmaceutical quality and safety, the process meets the strict standards that apply to the approval of drugs for use in clinical trials. This enables translation into the clinic and first treatment of patients.", Schmiedeknecht says.

The CAR T cells are produced from patients' blood. The white blood cells (leukocytes) are enriched in a circulatory process at the medical center. This ultimately results in a leukocyte concentrate that serves as the basis for production, which takes place in the cleanroom at Fraunhofer IZI.

Schmiedeknecht explains the cleanroom production steps: "The first step is to isolate the T cells. We add paramagnetic particles to the leukocyte concentrates, and the T cells bond to those. They stick to a magnetically charged column, while all the other components are rinsed away. This leaves T cells with purity of up to 98 percent."

The cells recover in a cell culture medium after they are isolated. Then comes the crucial step: The CAR receptor is inserted into the T cells. The researchers use the Sleeping Beauty technology for this. The CAR T cells can be harvested after another ten days in the cell culture medium. They are delivered to the hospital frozen in liquid nitrogen.

The therapeutic agent is administered to patients via infusion. "We've already treated a number of patients with it, and initial results are promising. This is truly a glimmer of hope for patients with solid tumors," Hudecek says."
Even so, he adds, "We still have a long road ahead of us through clinical development and then, if the trial results are positive, ultimately to the approval stage."

"Our research in this field demonstrates that here in Germany, we are able to develop even highly ambitious medical therapies and put them into clinical practice quickly and to the very highest standards of quality," Hudecek says.

The further developed CAR T cell therapy is paving the way for better treatment options in the future, not only for a wide variety of different types of cancer but also for other diseases such as autoimmune disorders and infections.

CAR T cell therapy, made in Germany

The Fraunhofer Institute for Cell Therapy and Immunology IZI has been supporting the development of this CAR T cell therapy since 2018. As part of a pilot project, the researchers have already completed the preclinical studies to evaluate the treatment's safety and efficacy and established the pharmaceutical production methods needed. This laid the foundations for the clinical study.

The Fraunhofer institute, which has locations in Leipzig and Würzburg, conducts research across the entire cell and gene therapy development cycle. The institute supports its partners up to the approval stage, from the basic concept to preclinical testing and process development and through to production in line with GMP standards and clinical trials.

Fig. 1 Fraunhofer IZI employees work in the cleanroom at the Leipzig location to produce a CAR T cell preparation for the clinical study in Würzburg.

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Fig. 2 The patient's immune cells and the genetic material for the ROR-1 receptor are combined in a cuvette. The genetic information enters the cell's genome through the application of electrical impulses.

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