Overcoming the limits of immunotherapies

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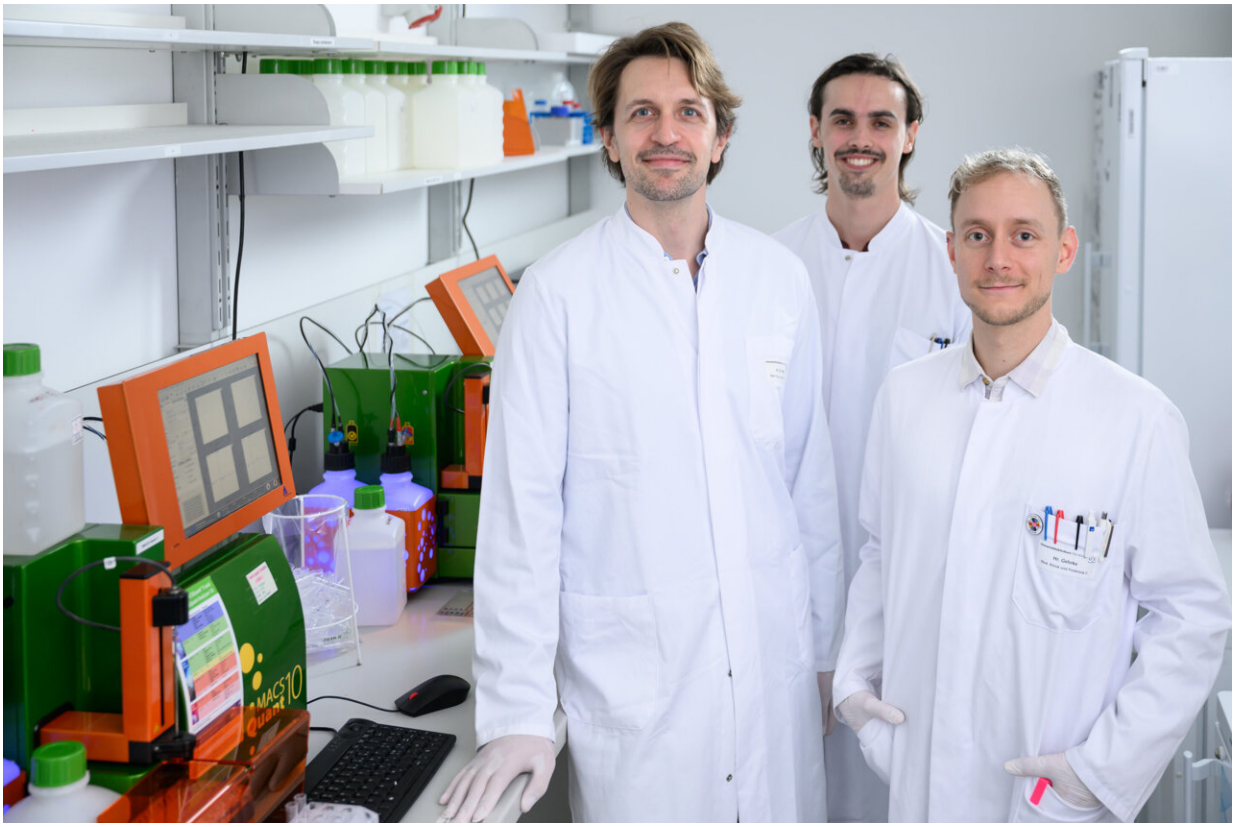

Karl Petri (left) is setting up an Emmy Noether research group at the University Hospital of Würzburg with the support of the German Research Foundation. Alexandre Trubert (centre) and Leon Gehrke (right) are already part of the team. Credit: Daniel Peter

CAR-T cells are highly effective in treating selected blood cancers. However, challenges remain with this new therapy, which was first

approved in 2017 in the U.S. and a year later in Europe for treating acute lymphoblastic leukemia (ALL). For instance, no effective CAR-T cell therapies for solid tumors exist. Furthermore, CAR-T-induced remissions are not always durable, and the production of CAR-T cells is slow and laborious.

Dr. Karl Petri of the University Hospital Würzburg (UKW) / Julius-Maximilians-University Würzburg aims to address these issues using an advanced CRISPR method to increase the efficiency of cancer-directed immunotherapies.

Prime-CAR inspection project

His project is called Prime-CAR Inspection. "Prime" stands for the CRISPR 2.0 method CRISPR Prime Editing, which allows for targeted and programmable incorporation of DNA changes into therapeutic T cells; "CAR" stands for chimeric antigen receptor, which equips the patient's own T cells to recognize and target specific surface molecules of cancer cells; "Inspection" refers to the safety validation of new gene-editing methods using advanced molecular diagnostics.

"While the conventional CRISPR-Cas9 method introduces a double-strand break into the DNA molecule, the CRISPR Prime Editing method requires only a single-strand break, allowing for more precise genome modifications," explains Dr. Petri. All 12 possible base pair substitutions, as well as small insertions and deletions, can be precisely incorporated into the T cell genome using CRISPR Prime Editing.

Dr. Petri states, "If CRISPR-Cas9 is described as DNA scissors that can selectively knock out gene functions, then Prime Editing is comparable to an eraser and pencil that can be used to rewrite DNA precisely."

In addition to optimizing gene-editing techniques, the Prime-CAR

Inspection project also aims to standardize the safety validation of new gene-editing techniques to facilitate clinical translation and ultimately provide more effective CAR-T cell products for patients with multiple myeloma and other cancers.

Improving cancer-targeted CAR-T cells with safety-validated CRISPR prime editors

"Currently, CAR-T cell therapy is approved for selected blood cancers. Our goal is to expand the application of CAR-T cell therapies and improve their effectiveness so that solid tumors can also be effectively treated with CAR-T cells. We also want to modify CAR-T cells to achieve longer and more durable remissions," says Dr. Petri.

His research also focuses on allogeneic CAR-T cells, modified T cells from healthy donors. "With CRISPR 2.0 editing, certain molecules on CAR-T cells could be modified so that the immune system does not reject the foreign cells. This way, larger quantities of CAR-T cells can be produced more cost-effectively."

For CAR-T cell therapy, white blood cells are separated from the rest of the blood components through leukapheresis from the patients' blood. The cells are genetically modified in the laboratory and reintroduced to the patients as a living drug via a ten-minute infusion. A single "activated" T cell can destroy 1,000 tumor cells. Ideally, the T cells remain in the body for life, eliminating hidden or newly emerged tumor cells.

Provided by University of Würzburg