PRESS RELEASE

CAR-T-Cell-Immunotherapy: Teaching the CAR to steer and brake

(Vienna, 20.08.2020) In the Christian Doppler Laboratory for Next Generation CAR T Cells, another important step towards improved cancer therapy has been achieved. Scientists from the St. Anna Children's Cancer Research Institute and the University of Natural Resources and Applied Life Sciences, Vienna, designed a platform with completely novel CAR prototypes. With these new CARs, immune cells can be directed even more specifically against tumor cells and are also reliably switched on and off. This reduces the risk of CAR T cells attacking healthy tissue. A safe and broad application in many types of cancer is thus coming closer. These promising results were published in the renowned scientific journal Nature Communications.

Cancer therapy with Chimeric Antigen Receptor (CAR) T cells attacks tumor cells and has already been successfully applied to certain types of blood cancer. Researchers at the Christian Doppler Laboratory for Next-Generation CAR T Cells in Vienna have now shown how this treatment can be used more precisely against tumor cells while mostly sparing healthy tissue. For this purpose, they designed a platform with newly constructed CAR T-cell prototypes that can be switched on and off and attack tumor cells even more specifically.

CARs are artificially produced receptor molecules. White blood cells, the so-called T-lymphocytes, of a patient are genetically modified so that they carry these receptor molecules on their surface. The blood cells artificially "armed" in this way are called CAR T cells. They are injected into the patient and now carry the new receptor (CAR) on their surface. These immune cells then recognize and attack tumor cells that have the corresponding docking sites for the CAR receptors. These docking sites, namely tumor-associated antigens, are often also present on healthy body cells. If non-tumor cells are also attacked, it can have fatal side effects (=on-target/off-tumor toxicity).

To control artificial killer cells by exploiting avidity

In order to direct the therapy more specifically against cancer cells, the scientists developed avidity-controlled CARs (AvidCARs). For this purpose, they used antigen binding sites for their CARs, whose binding strength (affinity) to the antigen is significantly reduced. This reduced binding strength requires a two-fold (=bivalent) interaction, i.e. a binding of the receptor to two antigen molecules in order to be activated. This procedure makes use of the so-called avidity, i.e. the greatly multiplied binding strength that results from double binding between the binding partners.
In addition, the CAR design has been improved so that certain subunits of the CARs can be combined (dimerized) in a controlled manner. This enables a targeted on and off-switching of the CAR function.

This controlled assembly and the use of avidity enables several control mechanisms. These were developed and preclinically tested by the team led by Dr. Manfred Lehner, St. Anna Children´s Cancer Research Institute and Dr. Michael Traxlmayr, University of Natural Resources and Applied Life Sciences, Vienna (see figure):
- CARs with a controllable on/off-switch can be switched on by the administration of a drug via combining two identical CAR subunits (homodimerization).
- AND-gate CARs, which consist of two different subunits and specifically recognize combinations of two different antigens. These CARs are only activated when they encounter a cell that shows both antigens on the surface simultaneously. The new mechanism of these CARs makes it possible for the first time to specifically kill only tumor cells without attacking neighboring healthy cells that carry only one of the two antigens. In addition, the two different subunits can be combined (heterodimerized) by administration of a drug and thus additionally controlled in their function.

Outlook: Targeted use also for other tumours

First author of the study, Dr. Benjamin Salzer from St. Anna Children's Cancer Research Institute summarizes: "The key lies in an improved CAR design. Our highly potent avidity-controlled CARs depend on bivalent antigen binding and are based on two principles: controlled assembly of two CAR units and low affinity antigen binding".

Lehner adds: "The car can now be steered more precisely and in addition, we can accelerate at different intensities. This makes it attractive for a wide range of tumors."

Publication

Engineering AvidCARs for combinatorial antigen recognition and reversible control of CAR function
B Salzer, C M Schueller, C U Zajc, T Peters, M A Schoeber, B Kovacic, M C. Buri, E Lobner, O Dushek, J Huppa, C Obinger, E M Putz, W Holter, M W Traxlmayr*, M Lehner*, Nature Communications 20th August 2020, https://www.nature.com/articles/s41467-020-17970-3
* Corresponding Authors

Funding

This research work was supported by the Austrian Federal Ministry for Digital and Economic Affairs, the Christian Doppler Research Association (Christian Doppler Laboratory for Next Generation CAR T Cells), the Austrian Science Fund (FWF Doctoral Program Biomolecular Technology of Proteins, BioToP, W1224; FWF Individual Project P32001-B, Eva König neé Putz) and donations to the St. Anna Children's Cancer Research Institute. Johannes Huppa and Timo Peters received support from the Horizon 2020 Framework Programme of the European Union (Marie Skłodowska-Curie grant agreement no. 721358). Omer Dushek was supported by a Wellcome Trust Senior Research Fellowship (207537/Z/17/Z).

About St. Anna Children´s Cancer Research Institute (CCRI)

The CCRI is an internationally renowned multidisciplinary research institution with the aim to develop and optimize diagnostic, prognostic, and therapeutic strategies for the treatment of children and adolescents with cancer. To achieve this goal, we combine basic research with translational and clinical research and focus on the specific characteristics of childhood tumor diseases in order to provide young patients with the best possible and most innovative therapies. Dedicated research groups in the fields of tumor genomics and epigenomics, immunology, molecular biology, cell biology, bioinformatics and clinical research are working together to harmonize scientific findings with the clinical needs of physicians to ultimately improve the wellbeing of our patients.
Further information: https://science.ccri.at, christian-doppler.ccri.at

About the University of Natural Resources and Applied Life Sciences, Vienna

The University of Natural Resources and Applied Life Sciences Vienna is one of the leading life science universities in Europe. The combination of natural sciences, technology as well as social and economic sciences characterizes its research and teaching. In addition to sustainability and the use of resources, medical biotechnology is an important research focus.
Further information: www.BOKU.ac.at

About Miltenyi Biotec

Miltenyi Biotec is a global provider of products and services that advance biomedical research and cell therapy. The innovative instruments support research at every level - from basic research to translational research and clinical application. The technologies are used by scientists and clinicians around the world and include techniques for sample preparation, cell isolation, cell sorting, flow cytometry and cell culture. The company's 30 years of experience extends to research areas such as immunology, stem cell biology, neuroscience and cancer. Today, Miltenyi Biotec employs over 3,000 people in 28 countries - all with the goal of helping researchers and clinicians make a greater impact on science and health.
Further information: www.miltenyibiotec.com

About the Christian Doppler Laboratories of the Christian Doppler Research Association

In Christian Doppler Laboratories application-oriented basic research is carried out at a high level. Outstanding scientists cooperate with innovative companies. The Christian Doppler Research Association is internationally

regarded as a best practice example for the promotion of this cooperation. Christian Doppler Laboratories are jointly financed by the public sector and the participating companies. The most important public funding body is the Austrian Federal Ministry for Digital and Economic Affairs (BMDW).
Further information: www.cdg.ac.at

Figure (adapted from original publication, Nature Com 2020): Avidity-conrolled Chimeric Antigen Receptors (AvidCARs)

Picture: Dr. Benjamin Salzer working on new CAR prototypes in the lab of the St. Anna Children´s Cancer Research Institute
Copyright: St. Anna Children´s Cancer Research Institute

Scientific contact
Manfred Lehner
M: +43 (1)40470-4087
St. Anna Kinderkrebsforschung/ST. ANNA CHILDREN'S CANCER RESEARCH INSTITUTE
1090 Wien, Zimmermannplatz 10
manfred.lehner@ccri.at

Press contact
Lisa Huto
St. Anna Kinderkrebsforschung/ST. ANNA CHILDREN'S CANCER RESEARCH INSTITUTE
1090 Wien, Zimmermannplatz 10
Telefon: +43 (1) 40470-4006
E-Mail: lisa.huto@kinderkrebsforschung.at