352 TARGETING GLIOBLASTOMA WITH A TCR SPECIFIC TO THE HLA-A*02-RESTRICTED, GLIOBLASTOMA-ASSOCIATED ANTIGEN PTPRZ1

[1,2,3]Yu-Chan Chih*, [1]Philipp Koopmann, [1]Amelie Christina Dietsch, [1,2,4]Dennis A Agardy, [1,2,3,5]Alice De Roia, [3,6,7]Alexandros Kourtesakis, [1,2]Michael Kilian, [1,2]Christopher Krämer, [1]Edward Wilhelm Green, [8]Agnieszka Blum, [8]Victor Murcia Pieńkowski, [6,9]Wolfgang Wick, [10,11,12,13,14]Michael Platten, [10,13,14]Lukas Bunse. *[1]German Cancer Consortium (DKTK) Clinical Cooperation Unit (CCU) Neuroimmunology and Brain Tumor Immunology, German Cancer Research Center (DKFZ), Heidelberg, BW, Germany; [2]Department of Neurology, Mannheim Center for Translation Neuroscience (MCTN), Medical Faculty Mannheim, Heidelberg University, Mannheim, BW, Germany; [3]Faculty of Biosciences, Heidelberg University, Heidelberg, BW, Germany; [4]German Cancer Research Center (dkfz), Heidelberg, Germany; [5]DNA Vector Laboratory, DKFZ, Heidelberg, BW, Germany; [6]Neurology Clinic, Heidelberg University Hospital, Heidelberg, BW, Germany; [7]DKTK CCU Neurooncology, DKFZ, Heidelberg, BW, Germany; [8]Ardigen, Kraków, Małopolskie województwo, Poland; [9]Clinical Cooperation Unit (CCU) Neurooncology, German Cancer Research Center (DKFZ), Heidelberg, Germany; [10]DKFZ Hector Cancer Institute at the University Medical Center Mannheim, Mannheim, Germany; [11]Immune Monitoring Unit, National Center for Tumor Diseases (NCT), Heidelberg, Germany; [12]Helmholtz Institute of Translational Oncology (HI-TRON), Mainz, Germany; [13]Mannheim Center for Translation Neuroscience (MCTN), Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany; [14]DKTK (German Cancer Consortium) Clinical Cooperation Unit (CCU) Neuroimmunology and Brain Tumor Immunology, German Cancer Research Center (DKFZ), Heidelberg, Germany*

Background T cell therapy against glioblastoma (GBM) remains challenging. This is attributed, among other features, to a comparatively low mutational burden and resulting paucity of immunogenic, tumor-specific target antigens. To overcome these challenges, our study leveraged vaccine-induced T cell responses uncovered from the Glioma Actively Personalized Vaccine Consortium (GAPVAC) trial. In GAPVAC, human leukocyte antigen (HLA)-A*02$^+$ GBM patients were vaccinated with peptides encompassing glioblastoma-associated antigens (GAA), including protein tyrosine phosphatase receptor type Z1 (PTPRZ1). PTPRZ1 is upregulated in GBM, particularly in GBM stem cells. Therefore, we set out to target PTPRZ1 in GBM using T cell therapy.

Methods From a GAPVAC trial patient who experienced a favorable clinical outcome, autologous PTPRZ1-reactive T cells were expanded *in vitro*, sorted and single-cell sequenced. The dominant T cell receptors (TCRs) were evaluated using Jurkat reporter cells. Subsequently, a PTPRZ1-reactive TCR was selected and tested for cross-reactivity against predicted off targets using ARDitox. Next, the TCR was transduced into primary human T cells, and the resulting TCR-T cells were co-cultured with HLA-A*02$^+$ tumor cells. Flow cytometry and LDH release assay were employed to examine TCR activation and cytotoxicity. The *in vivo* therapeutic efficacy of PTPRZ1-TCR-transgenic primary human T cells was evaluated in immunodeficient NSG mice inoculated with tumor cells.

Results Of the sorted PTPRZ1-reactive T cells, the repertoire was oligoclonal. After testing the top expanded TCRs in Jurkat reporter cells, one TCR exhibited strong reactivity to tumor cell lines. To investigate potential cross-reactivity, the PTPRZ1-reactive TCR underwent rigorous testing against *in silico* predicted off targets, showing no cross-reactivity. Subsequently, primary human TCR-T cells were generated and co-cultured with target cell lines, demonstrating significant antigen-specific activation and cytotoxicity. Although CD8$^+$ T cells primarily serve as effectors, the assistance of CD4$^+$ T cells maximized the cytotoxicity. To assess the therapeutic potential of the TCR-T cell product, tumor-bearing NSG mice received adoptive transfer of primary human T cells transduced with the PTPRZ1-reactive TCR. PTPRZ1-TCR T cell transfer resulted in regression of established tumors with 30% complete regression and remarkably prolonged survival.

Ethics Approval Animal experiments were performed in compliance with the laboratory animal research guidelines and were approved by the government authority (animal protocols: G37/18 and G170/21, regional administrative authority, Regierungspräsidium Karlsruhe, Germany). The animals are housed at the specific pathogen-free/SPF animal facility of DKFZ Heidelberg.

Conclusions We identified a patient-derived, vaccine-induced, TCR reactive against an HLA-A*02-restricted epitope of the GAA PTPRZ1, and confirmed its therapeutic efficacy *in vivo*. In light of these promising results, a phase 1 clinical trial, Intraventricular T cell receptor transgenic T cell therapy to treat glioblastoma (INVENT4GB), is in preparation and aims to assess the feasibility and safety of intravenous and intracerebroventricular PTPRZ1-TCR-transgenic T cells in patients with recurrent GBM.

http://dx.doi.org/10.1136/jitc-2023-SITC2023.0352