P06 Cell Therapy in Solid Tumors

P06.01 αβ-T CELLS ENGINEERED TO EXPRESS γδ-T CELL RECEPTORS CAN KILL NEUROBLASTOMA ORGANOIDS INDEPENDENT OF MHC-I EXPRESSION

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Background Currently ~50% of patients with the diagnosis of high-risk neuroblastoma will not survive due to relapsing or refractory disease. Recent innovations in immunotherapy for solid tumors are highly promising, but the low MHC-I expression of neuroblastoma represents a major challenge for T cell-mediated immunotherapy. Here, we propose a novel T cell-based immunotherapy approach for neuroblastoma, based on the use of TEG002, αβ-T cells engineered to express a defined γδ-T cell receptor, which are thought to recognize and kill target cells independent of MHC-I. In this pilot project we have tested the potential efficacy of TEG002 therapy as a novel treatment for neuroblastoma, with tumor organoids.

Materials and Methods Effector cells were created from healthy donor peripheral blood T cells. The TEG002 cells were engineered by transducing αβ-T cells with a defined Vγ9Vδ2-T cell receptor. Both the untransduced αβ-T cells and the endogenous Vγ9Vδ2-T cells from the same healthy donor were used as controls in all experiments. Activation and killing of TEG002 was tested in a co-culture setting with neuroblastoma organoids. Supernatant of the co-culture was collected at 24 hours for IFNγ ELISA to measure activation of TEG002. The dynamics of cytotoxicity were analyzed over time from 0 till 72 hours, using the live-cell imaging system IncuCyte from Sartorius®. Killing was quantified using a Caspase3/7 Green dye and the IncuCyte software. Transcriptional profiling of the neuroblastoma organoids was done by RNA sequencing and MHC-I expression of the neuroblastoma organoids was determined by flow cytometry.

Results We showed that 3 out of 6 neuroblastoma organoids could activate TEG002 as measured by IFNγ production. Transcriptional profiling of the neuroblastoma organoids showed that this effect correlates with an increased activity of processes involved in interferon signaling and extracellular matrix organization. Analysis of the dynamics of organoid killing by TEG002 over time confirmed that organoids which induced TEG002 activation were efficiently killed independently of their MHC-I expression. Of note, efficacy of TEG002 treatment was superior to donor-matched untransduced αβ-T cells or endogenous γδ-T cells.

Conclusions We demonstrated that 50% of tested neuroblastoma organoids can effectively activate TEG002 and that killing of the organoids is independent of MHC-I expression. Hence, this pilot study identified TEG002 as a promising novel cellular product for immunotherapy for a subset of neuroblastoma tumors, warranting further investigations into its clinical application.

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P06.02 CANCER-SPECIFIC DIFFERENCES OF TERTIARY LYMPHOID STRUCTURES AND CELLULAR RESPONSES AGAINST FREQUENTLY EXPRESSED CANCER TESTIS ANTIGENS

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Background Tertiary lymphocyte structures (TLS) can be detected in the tumor microenvironment across a wide range of cancer types and are associated with increased patient survival and susceptibility to immune checkpoint inhibition. However, evidence for the functional significance of TLS on humoral and cellular immunity is scarce. In this study, we combine assessment of abundance and spatial distribution of TLS with expression levels of 10 tumor associated antigens (TAAs) and functional analyses of T cell responses to these antigens.

Materials and Methods 52 treatment naïve cancer patients across 5 tumor types (NSCLC, CRC, RCC, HCC and BCA) were included. Presence and localization of TLS was assessed in immunohistochemical stainings (CD20) of whole section slides from FFPE embedded tumor samples. B cell clusters were quantified in the whole tumor region and in two different tumor margins (300 µm, 2000 µm). A panel of 30 cancer testis antigens was selected via GEPIA software (TCGA Database) and their expression in our cohort was determined using NanoString based RNA expression analysis of tumor samples and patient-matched healthy tissue. The 10 peptide pools with the largest cross-cancer overlap were selected based on our NanoString results. 2-color Fluorospot assays (IFN-γ and IL-2) were applied to assess the frequency of tumor-specific T-cell responses in patient PBMCs (triplicates for each TAA).

Results CD20 immunohistochemistry and enumeration of intra- and peritumoral TLS revealed different distribution patterns of TLS/mm^2 with the largest proportion in the 300 µm margin ($p < 0.01$) in most of the cancer types. This effect was particularly observed in patients with non-small cell lung cancer (NSCLC). The 10 tumor antigens CEP55, CT83, GAGE1, IGF2BP3, MAGEA1, MAGEA3/6, PBK, PRAME, Survivin and TTK were selected as they showed the highest overlap across different cancer types and the most pronounced differential expression between tumor and matched normal tissue. While 31/52 (59.6%) patients showed an IFN-γ, only 11/52 (21.2%) patients exhibited an IL-2 response against at least one of the tested CTAs. Survivin was the CTA presenting the highest frequency of responses (18/52 IFN-γ and 5/52 IL-2 responses). PBMCs of patients with NSCLC showed the highest frequency of T-cell responses (83.3% with at least one IFN-γ response)