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Clinical response rates have been observed with therapies offering immediately accessible cell therapies to patients. High-dose therapies continue to be developed. This Go-Rex platform will advance preclinical assessment of T cell products as well as provide a novel discovery platform for new therapeutic opportunities.

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EVALUATION OF NON-GENE EDITED ALLOGENEIC “OFF-THE-SHELF” V61 γδ CAR T CELLS TARGETING CD20 FOR B CELL MALIGNANCIES
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Keywords: CAR T therapy, Allogeneic Therapy, Lymphoma.

Background & Aim: Background. Off-the-shelf, allogeneic CAR T cell therapies offer immediately accessible cell therapies to patients. High clinical response rates have been observed with γδ CAR T therapies, but opportunities for improvement remain. Strategies for investigating alternative cytotoxic effector cells that possess intrinsic tumoricidal activity, like γδ T cells, may improve depth and breadth of CAR T responses. Tumor targeting by allogeneic γδ CAR T therapy is complemented by innate and adaptive mechanisms. Studies have reported that tumor infiltrating γδ T cells are significantly correlated with patient survival and that V61 subset, primarily resident in peripheral tissues, can recognize and kill tumor cells through MHC-independent antigens. Aim. Here we describe extended preclinical evaluation, including gene-edited derivatives, of ADI-001, a non-gene edited allogeneic CAR V61 γδ T cell therapy targeting CD20 designed for the treatment of B cell lymphomas.

Methods, Results & Conclusion: Methods. Healthy donor-derived PBMCs were used to activate, expand, and genetically engineer V61 γδ T cells to express a second-generation CAR targeting CD20 in an established manufacturing process. In vitro phenotype and cytokine release assays were performed, including cell-based assays. Human tumor xenograft models in immunodeficient mice were used to evaluate in vivo efficacy. Additional characterization of gene-editing approaches to augment host versus graft influences were also compared to unmodified γδ T cell processes to evaluate relative susceptibility for host targeting. Results. PBMC-derived V61 γδ T cells were successfully activated, expanded, and genetically engineered using established manufacturing processes. ADI-001 demonstrated a predominantly naïve-like T cell memory phenotype and expressed multiple chemokine and natural killer cell receptors. ADI-001 exhibited robust in vitro and in vivo tumor growth inhibition in multiple human lymphoma cell lines. No xenogeneic GvHD or other toxicities were induced by ADI-001. Lastly, comparison of gene-edited derivatives to ADI-001, including B2Mδ0 with or without HLA-E overexpression, did not effectively limit elimination as compared to unmodified ADI-001. Conclusion. In summary, these findings demonstrate preclinical proof-of-concept for ADI-001 as an allogeneic CAR-T therapy. A phase 1 trial using ADI-001 to treat R/R B cell NHL patients is currently under investigation (NCT04735471).

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TIMING OF DONOR SELECTION ON CD45RA-MEMORY T CELLS AS ADOPTIVE CELL THERAPY FOR COVID-19
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Keywords: SARS-CoV-2 specific Memory T lymphocytes, Lymphopenia, COVID-19.

Background & Aim: The COVID-19 pandemic has resulted in significant morbidity and mortality worldwide. The vaccines had dramatically decreased infection rates, number of deaths, and hospitalizations, but they are not 100% effective and immunity is lost gradually over time. We have previously shown how we are able to detect, isolate and produce at clinical scale SARS-CoV-2-specific T cells within CD45RA-memory T cells from COVID-19 convalescent donors. In a phase I clinical trial we have proved that treatment with these cells of hospitalized patients with moderate/severe COVID-19 is safe and feasible. Understanding the durability and the level of cellular immunity within the CD45RA-memory T cells and how changes with immunization are critical for the development of a biobank of living drugs to treat future COVID-19 patients. We performed a longitudinal exploratory analysis of the SARS-CoV-2 specific humoral and cellular immunity within the memory CD45RA- T cells in naïve and previously infected individuals at different time points after two doses of BNT162b2 BioNTech/Pfizer vaccine

Methods, Results & Conclusion: We studied the cellular and humoral response of SARS-CoV-2 specific memory T cells from recovered patients and controls at different time points: 2 weeks after recovering from COVID-19, 9 months after the infection/just before mRNA immunization, and 65 days after full immunization. Detection of SARS-CoV-2 Specific Memory T Cells was performed by IFNγ assay after exposure of cells to the M, N, and S SARS-CoV-2 peptides. Our data shows that memory T cell responses within the CD45RA-memory T cell subpopulation and most of the subsets tend to be higher in recovered individuals at all time points. The cellular response produced by control individuals to the S peptide is like the one from recovered patients at the same time point. Humoral responses were higher in recovered individuals after full immunization. Antibodies titer was not boosted after the late vaccine time point. An exploratory analysis of non-parametric Spearman’s rho correlation of humoral and cellular responses shows a positive correlation after infection with the 3 peptides and 65 days after immunization. In conclusion: We have analyzed the SARS-CoV-2 specific T cells within the CD45RA-memory T cell subpopulation and the different subsets at different time points after infection.

Figure 1. Time points scheme for blood collection in recovered and control individuals.
infection and fully vaccinated. We claim that the best donors would be immunized individuals recovered from COVID-19 ideally in a time frame not higher than 6 months.

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DEVELOPING OFF THE SHELF T CELL THERAPIES FOR HIGH-GRADE GLIOMAS

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Keywords: T-Cell, Glioma, Immunotherapy.

Background & Aim: High-grade gliomas (HGG) often present with poor survival rates due to their resistance to current treatment strategies. T cell-based immunotherapies have been shown to penetrate the BBB and precisely target proteins unique to malignant cells. These therapies have shown promising results against other malignancies. However, some patients with HGG progress too rapidly to allow autologous T cell manufacture, and there is evidence to suggest that T cell dysfunction is present due to treatment as well as disease-related factors. An established bank of HGG antigen-specific T cells may circumvent these limitations. The use of “off the shelf” T cell therapies derived from allogeneic donors matched at one HLA allele or more have been successfully used for the treatment of viral infections. Therefore, we investigated the feasibility of developing an “off the shelf” PRAME-specific T cell therapy for HGG.

Methods, Results & Conclusion: T cells derived from healthy donors were harvested from peripheral blood and expanded in vitro. Mature dendritic cells (DCs) were pulsed with overlapping peptides spanning the PRAME protein and were used to stimulate the harvested T cells. The specificity and cytotoxicity of these expanded cells were tested using IFN-γ ELISPOT and chromium release assays, respectively. T cells expanded a mean of 82.6-fold after three stimulations with DCs and were specific for PRAME (348.1 ± 74.5 SFC/1x10⁵ cells) versus negative control (12.3 ± 4.4 SFC/1x10⁵ cells) in IFNγ ELISPOT assay. PRAME-specific T cell products HLA-matched with tumor targets at 4 of the tumor’s HLA class I alleles specifically killed glioma cells (13.56% killing at E:T ratio of 40:1). In comparison, non-specific T cells derived from the same donor did not show specific tumor killing (2.79%). PRAME-specific T cells that only matched at 1 HLA allele showed lower killing (6.72%). However, PRAME-specific T cell products that were completely HLA-mismatched with the tumor did not elicit any anti-tumor activity (0% at 40:1 E:T) despite showing robust cytolytic activity against PRAME expressing autologous PHA blasts (20.42%). In summary, our preclinical results suggest that “off the shelf” PRAME-specific T cell therapies are a potentially viable treatment option for HGG. Future work will focus on testing the in vivo function in an in vivo orthotopic mouse model as well as clinically (IND27716).

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GDA-301: ENGINEERED NAM-NK CELLS VIA CISH KNOCKOUT AND MEMBRANE-BOUND IL-15 EXPRESSION INCREASES CYTOTOXICITY AGAINST MALIGNANCIES

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