Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

potential as well as the phenotypic and functional characteristics of post-REP TIL were then evaluated.
Results: While DAC treatment led to a decrease in TIL expansion and an increase in the $CD4^+$ to $CD8^+$ ratio, this coincided with an increase in the frequency of central memory-like cells ($CD45RA^-CCR7^+$) as well as the expression of IL-7R and the transcription factors TCF1, Eomes, and KLF2, suggesting a shift towards a more memory-like phenotype. Additionally, DAC treatment increased the expression of CD25, CD28, and ICOS while reducing the expression of inhibitory receptors like PD-1 and TIGIT. Following stimulation, DAC-treated TIL showed increased degranulation and a higher frequency of $IFN\gamma^+TNF\alpha^+$ cells, which translated into increased cytotoxicity.
Conclusions: DAC treatment during TIL expansion can shift the balance away from effector differentiation and towards a more memory-like phenotype, while conferring increased expression of co-stimulatory receptors, reduced expression of inhibitory markers and improved functionality. Inhibiting DNA methylation programs during TIL expansion could represent a useful approach for modifying the epigenetic landscape of TIL, imprinted prior to ex vivo expansion and introduced during the expansion process itself, to improve their therapeutic potential.

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High Throughput Cloning of T Cell Receptors (TCRs) from Single Cells Reveals That TCRs Recognizing the Minor Histocompatibility Antigen HA-1 Have a Range of Affinities Despite Canonical Beta Chain Usage

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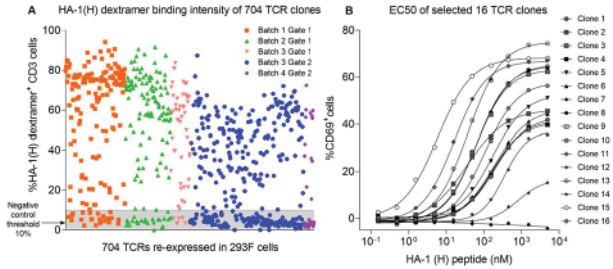
Minor histocompatibility antigens (miHAs) relatively restricted to hematopoietic cells are attractive targets for adoptive T cell immunotherapy in the context of allogeneic stem cell transplantation (alloSCT), as T cells that target them can mediate graft-versus-leukemia and promote engraftment with a low risk for graft-vs-host disease. We employed a novel high-throughput technology for cloning TCRs from single cells to isolate multiple receptors reactive against the hematopoietic cell-restricted miHA, HA-1, from a parous woman who was naturally immunized to HA-1 through pregnancy.
We identified an HLA-A*02:01 woman homozygous for the non-immunogenic HA-1 (R/R) allele who delivered three children with an HA-1 heterozygous (H/R) HLA-A*02:01 father. TCRs were cloned from single-cell-sorted HA-1 dextramer$^+$ ($dex^{HA\text{-}1+}$) CD8 T cells from unstimulated peripheral blood mononuclear cells (PBMCs) and subsequently from $CD8^+$ T cells co-cultured for one week with HA-1 peptide-pulsed antigen-presenting cells (APCs). TCRs were reexpressed in reporter cells using lentivirus vectors and analyzed for dextramer binding and CD69 upregulation after culture with HA-1(H) peptide-pulsed APCs. We also performed gene sequencing of cloned TCRs to understand TCR diversity.
We cloned 16 unique HA-1-reactive TCRs from 48 sorted $dex^{HA\text{-}1+}CD8^+$ T cells from unstimulated PBMCs. 704 additional TCRs were cloned from HA-1 peptide-stimulated CD8 cells. 440 of them, when re-expressed, bound HA-1(H) dextramer with various intensities that broadly matched the dextramer MFI lower limit of the sort gates (Figure A; each symbol is a reexpressed TCR). From these set, 6 additional unique anti-HA-1 TCRs were identified. anti-HA-1 TCRs had a broad range of EC50s despite all using TRBV7-9 (Figure B) and when expressed in primary $CD8^+$ T cells, killed $HA\text{-}1^+$ target cells. These data highlight the wide range of TCR affinities that can arise from a natural immune response against a single allopeptide/HLA complex (VLHDDLLEA/HLA-A*02:01). We aim to apply this approach to clone and characterize TCRs targeting other hematopoietically restricted miHAs for development of miHA-TCR transduced adoptive T cell therapy in alloSCT.



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Cellular and Humoral Responses from Sars-Cov-2 Specific CD45RA- Memory T Cells from Convalescent and Naive Donors. Clinical Application As an Adoptive Cell Therapy for COVID-19

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SARS-CoV-2 has caused a worldwide pandemic with millions of deaths and countless economic losses. Some vaccines are available but their long-term efficacy is not proved, and no fully effective treatment has being described. We present here a treatment based on an adoptive cell therapy using SARS-CoV-2 specific CD45RA- memory T cells from COVID19 convalescent donors. Our preliminary studies have shown that SARS-CoV-2 specific memory T cells can be detected, collected and stored for clinical studies. In a phase I clinical trial we proved the safety of infusing SARS-CoV-2 specific memory T cells to hospitalized COVID19 patients. We also determined the recommended dose for phase II, already on going. But some questions remained unanswered. Dexamethasone is the current standard of care for these patients and it is a corticoid well known for inhibition of T cell activity with a potential negative role in treatment effectiveness. Our results showed that current concentrations of dexamethasone used in the clinic do not have a huge effect on CD45RA- memory T phenotype, proliferation and IFN-g releasing capacity. We studied the cellular response of SARS-CoV-2 specific memory T cells from recovered patients and controls and their humoral responses at different time points after the disease in the first group, and after two doses of mRNA vaccination in both. Our data show that cellular responses from memory T cells against

SARS-CoV-2 peptides (M, N and S) reach a peak just after infection and then decrease over time. No significant statistical differences were observed between the first and second dose of mRNA vaccine in antigen-specific cellular responses in recovered and control individuals. Similarly, comparing both groups no differences in cellular responses were observed either. Regarding humoral response, after the vaccine we have observed antibody production in both groups (Nucleocapsid, NAB, RBD, S1 and S2), and it was higher than after COVID19 in recovered patients. After the second dose, there was a distribution statistically significant in antibodies production, being higher in recovered patients than in controls. To sum up, vaccination stimulates antibodies production while cellular responses decrease or remain similar with time. Regarding the therapy we propose, is feasible, safe and its antiviral properties are not affected by dexamethasone. The ideal donors would be individuals that have just recovered from the disease (1 to 2 months), but given the decrease in prevalence of COVID19 due to vaccination, SARS-CoV-2 memory T cells could also be obtained from recovered and immunized donors

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Ascorbate Deficiency Is Associated with Severity of Cytokine Release Syndrome Following Therapy with Chimeric Antigen Receptor T-Cells

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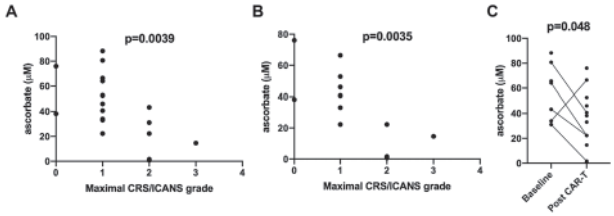
Introduction: CAR-T cell therapy is often associated with cytokine release syndrome (CRS), as well as immune effector cell-associated neurotoxicity syndrome (ICANS). Recent work has implicated ascorbate in the regulation of the activity of TET enzymes in hematopoietic cells (PMID: 28825709, PMID: 28823558). Given that TET2 deficiency has been associated with increased elaboration of inflammatory cytokines such as IL-6 and IL-1 by macrophages (PMID 3026882, PMID: 28104796, PMID: 28636844), we reasoned that ascorbate deficiency might predict for more pronounced cytokine release in pts leading to more severe CRS or ICANS.
Methods: We identified 13 pts receiving CAR-T cell at the UTSW. Plasma specimens were collected from pts at baseline prior to receipt of lymphodepleting chemotherapy and/or at two weeks following CAR-T cell infusion. We used an optimized protocol incorporating a C13-labeled ascorbate internal standard to obtain highly precise serum ascorbate measurements using liquid-chromatography mass spectrometry. CRS / ICANS were graded per ASTCT consensus criteria.
Results: We measured serum ascorbate in 7 baseline and 12 post CAR-T cell infusion specimens obtained from 13 patients, with a median age of 65 (range 53 to 77). The cohort included 8 pts with DLBCL and 2 pts with mantle cell lymphoma receiving CD19 CAR-T cells, as well as 3 pts with Myeloma receiving BCMA CAR-T cells. Eight pts developed grade one CRS, 3 pts developed grade two CRS, and 2 pts did not develop CRS. One patient developed grade one ICANS, 1 pt developed grade two ICANS, and 1 pt developed grade three ICANS. Eight pts received dexamethasone for CRS or ICANS, and 8 pts received tocilizumab. Five pts only received one dose of tocilizumab, while 2 pts received two doses and 1 pt received three doses.
Taking all pre- and post-CAR-T cell infusion ascorbate measurements into account, a significant correlation was found between having low serum ascorbate levels and a higher maximal grade of CRS or ICANS (Figure 1A, r^2=-0.64, p=0.0039). Post-infusion ascorbate measurements also demonstrated a significant correlation between low serum ascorbate levels and higher maximal CRS or ICANS (Figure 1B, r^2=-0.78, p=0.0035), while there was no correlation between pre-infusion ascorbate measurements and CRS or ICANS. Finally, we noted a significant decrease in serum ascorbate levels when comparing pre-infusion to post-infusion specimens (Figure 1C, p=0.048), including five paired specimens.

Figure 1



Conclusion: Low serum ascorbate levels may be associated with an increased risk for developing severe CRS and ICANS following CAR-T cell therapy. These data provide preliminary evidence that serum ascorbate levels may serve as a useful biomarker to predict severity of CRS and ICANS with future follow up studies in larger cohort. Furthermore, results suggest ascorbate

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A Pipeline for Optimizing miHA Specific TCR Therapy for Leukemia

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Introduction: Adoptive T cell therapy with $CD8^+$ T cells engineered to express T cell receptors (TCRs) that recognize hematopoietically-restricted minor histocompatibility antigens (miHAs) is an attractive approach for improving the efficacy of allogeneic hematopoietic stem cell transplantation.
Methods: We developed a mouse model to determine how to optimally implement anti-miHA T cell therapy, focusing on the key characteristics of anti-miHA TCRs that correlate with in vivo efficacy. We immunized B6 mice to the K^b-restricted miHA H60 and used a high throughput approach to amplify TCR α/β chains from single $CD8^+$ tetramer-$H60^+$ (Tet^{H60+}) cells. Cloning efficiency was high with both α and β chain cloned from