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Reporting Summary

Nature Portfolio wishes to improve the reproducibility of the work that we publish. This form provides structure for consistency and transparency in reporting. For further information on Nature Portfolio policies, see our Editorial Policies and the Editorial Policy Checklist.

Statistics

For all statistical analyses, confirm that the following items are present in the figure legend, table legend, main text, or Methods section.

n/a	Confirmed	
☐	☒	The exact sample size (*n*) for each experimental group/condition, given as a discrete number and unit of measurement
☐	☒	A statement on whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
☐	☒	The statistical test(s) used AND whether they are one- or two-sided *Only common tests should be described solely by name; describe more complex techniques in the Methods section.*
☐	☒	A description of all covariates tested
☒	☐	A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons
☐	☒	A full description of the statistical parameters including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) AND variation (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals)
☐	☒	For null hypothesis testing, the test statistic (e.g. *F*, *t*, *r*) with confidence intervals, effect sizes, degrees of freedom and *P* value noted *Give P values as exact values whenever suitable.*
☒	☐	For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings
☒	☐	For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes
☒	☐	Estimates of effect sizes (e.g. Cohen's *d*, Pearson's *r*), indicating how they were calculated

Our web collection on statistics for biologists contains articles on many of the points above.

Software and code

Policy information about availability of computer code

Data collection	The clinical trial management system OnCore was used to collect individual patient case record forms.
Data analysis	SAS v9.4 and R v4.4.2 were used for assessment of clinical response rates and survival rates. Descriptive statistics were used for data analysis (Microsoft Excel 2016). Kaluza Analysis v2.1 (Beckman Coulter) was used for flow cytometry data analysis. CellQUEST and DIVA (Becton Dickinson) were used for flow cytometry data analysis. Aperio ImageScope v12.4 was used for IHC slide visualization. shinyCircos v2.0 was used for circos plots generation. HTML and JavaScript code were used leveraging the D3.js library for graphics (https://d3js.org/) and Grok 3-beta for code generation and refinement (https://x.com/i/grok) for Sankey style data visualization (ribbon plots). Cell Ranger, Loupe Browser and Loupe VDJ Browser (https://10xgenomics.com) were used for scRNA sequencing data processing. The Seurat R package was used to run principal components analysis (PCA), t-stochastic neighbor embedding (t-SNE), and k-means clustering algorithms to visualize clustered cells in a two-dimensional space.

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors and reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Portfolio guidelines for submitting code & software for further information.

Data

Policy information about availability of data

All manuscripts must include a data availability statement. This statement should provide the following information, where applicable:

- Accession codes, unique identifiers, or web links for publicly available datasets
- A description of any restrictions on data availability
- For clinical datasets or third party data, please ensure that the statement adheres to our policy

Data generated during the study is maintained in electronic format on a database housed by the Center for Cell and Gene Therapy, Baylor College of Medicine. Clinical data is stored in our clinical trials management system (OnCore). All data used in the analysis of the findings in the present study are included in the manuscript and the Supplementary Information and are also provided as source data. The TCRvβ deep sequencing data are available in ImmuneACCESS (DOI: 10.21417/BLMC2025NM). The raw sequencing data and processed scRNA-seq expression matrices generated in this study are publicly available in the Gene Expression Omnibus (GEO) under accession number GSE307914. All other data (raw or analyzed) are available from the corresponding authors (B.L.M. or A.M.L.) on reasonable request.

Research involving human participants, their data, or biological material

Policy information about studies with human participants or human data. See also policy information about sex, gender (identity/presentation), and sexual orientation and race, ethnicity and racism.

Reporting on sex and gender	Sex and gender were not considered in study design since they were not relevant to the topic of the study. Overall, 19 female and 18 male subjects were treated (sex being defined based on biological attributes).
Reporting on race, ethnicity, or other socially relevant groupings	Race, ethnicity or other socially relevant groupings were not considered in study design. Based on self-reported ethnicity, 30 non-hispanic subjects, 6 hispanic and 1 subject of unknown ethnicity were treated in the study.
Population characteristics	37 treated adult patients: their characteristics are described in the manuscript and in Supplementary Materials
Recruitment	Patients were recruited based on study eligibility criteria (described in Methods and in the clinical protocol) and after informed consent (H-40378).
Ethics oversight	The protocol and amendments were approved by the Baylor College of Medicine and Houston Methodist Hospital Institutional Review Boards, and the study was conducted under an IND approved by the FDA (H-40378, NCT03192462), in accordance with the principles of the Declaration of Helsinki and the International Conference on Harmonization of Good Clinical Practice guidelines.

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Field-specific reporting

Please select the one below that is the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

☒ Life sciences ☐ Behavioural & social sciences ☐ Ecological, evolutionary & environmental sciences

For a reference copy of the document with all sections, see nature.com/documents/nr-reporting-summary-flat.pdf

Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	Refer to the clinical protocol for sample size estimates; in brief, the assigned sample size was 15 patients in each study Arm with the primary goal of assessing the safety and feasibility of administering 6 mTAA-T cell infusions.
Data exclusions	No data were excluded from the analysis
Replication	Experiments were performed independently on individual patient samples.
Randomization	Not relevant to this study
Blinding	Not relevant to this study

Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

Materials & experimental systems

n/a	Involved in the study
☐	☒ Antibodies
☒	☐ Eukaryotic cell lines
☒	☐ Palaeontology and archaeology
☒	☐ Animals and other organisms
☐	☒ Clinical data
☒	☐ Dual use research of concern
☒	☐ Plants

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☐	☒ Flow cytometry
☒	☐ MRI-based neuroimaging

Antibodies

Antibodies used

Antibody /Catalog # /Vendor / Clone
CD3 AF 750 /A66329/ Beckman Coulter /UCHT1
CD4 KO /A96417 /Beckman Coulter /13B8.2
CD8 PB /A82791 /Beckman Coulter /B9.11
CD56 PE /IM2073U /Beckman Coulter /N901
CD16 PE /IM1238U /Beckman Coulter /3G8
CD62L ECD /IM2713U /Beckman Coulter /DREG56
CD45 RO APC /340438 /Becton Dickinson /UCHL1
CD197 (CCR7) FITC/ 561271 /Becton Dickinson /150503
CD69 PerCP /340548/ Becton Dickinson/ L78
CD279 (PD-1) FITC /557860 /Becton Dickinson /MIH4
CD3 PerCP /347344 /Becton Dickinson /SK7
CD8 APC /IM2469U /Beckman Coulter /B9.11
IFN-gamma FITC /340449 /Becton Dickinson/ 25723.11
TNFa PE /340512 /Becton Dickinson /6401.1111
CD137 (4-1BB) PE /555956 /Becton Dickinson /4B4-1
CD154 (CD40L) APC/ 648887 /Becton Dickinson /89-76
CD107a FITC /555800 /Becton Dickinson /H4A3
CD223 (LAG3) PerCP-Cy5.5/ 369312/ Biolegend /11C3C65

Validation

Validation of antibodies used in the study was performed according to Standard Operating Procedures of the GMP facility at the Center for Cell and Gene Therapy, Baylor College of Medicine. Furthermore, validation statements can be found on manufacturers' websites.

Clinical data

Policy information about clinical studies

All manuscripts should comply with the ICMJE guidelines for publication of clinical research and a completed CONSORT checklist must be included with all submissions.

Clinical trial registration	NCT03192462
Study protocol	The full study protocol can be found in Supplementary Materials
Data collection	Collected in OnCore (as stated above), from January 21, 2018 until July 14, 2025 in Houston, Tx.
Outcomes	Specified in Methods and in the supplied clinical protocol

Plants

Seed stocks	n/a
Novel plant genotypes	n/a
Authentication	n/a

Flow Cytometry

Plots

Confirm that:

☒ The axis labels state the marker and fluorochrome used (e.g. CD4-FITC).

☒ The axis scales are clearly visible. Include numbers along axes only for bottom left plot of group (a 'group' is an analysis of identical markers).

☐ All plots are contour plots with outliers or pseudocolor plots.

☒ A numerical value for number of cells or percentage (with statistics) is provided.

Methodology

Sample preparation	Sample preparation is described in Methods.
Instrument	FACScan and FACS-Canto II (Becton Dickinson) and Gallios (Beckman Coulter)
Software	The software used to collect and analyze flow cytometry data is specified in Methods
Cell population abundance	Cell sorting was not performed. Details on number of collected events are provided in Methods (50,000 viable cells)
Gating strategy	Initial gating was performed based on FSC/SSC properties of the tested cell population. Subsequently, viable cells were selected, a CD3 gate was applied to include the CD3+ population and further subgating was performed within the CD3+ gate.

☐ Tick this box to confirm that a figure exemplifying the gating strategy is provided in the Supplementary Information.