vacuolization was achieved in peptide-treated groups, and substantial correction for bone pathology was observed in all Gene Therapy-treated groups.

Conclusion: The results of our study support the concept of combining antigen-specific oral tolerance with gene therapy to prevent unwanted immune responses against therapeutic transgene products. The induction of oral immune tolerance with AAV9 gene therapy provides a sustainable enzyme supply that improves bone pathology in MPS IVA mice without the elevation of anti-GALNS antibodies. Early diagnosis of MPS IVA is achievable through newborn screening programs in various countries. Therefore, this oral treatment will be applied to the affected newborns. A novel approach to *in vivo* GT using oral immunogenic peptides will provide a new paradigm of therapeutic options for MPS IVA patients. It will have a wide range of applications for other types of MPS, lysosomal storage diseases, and genetic diseases.

2046 Tour de Tumor: scRNA Uncovers CD4+ Cycling State & CD8+ Finish Line Linked to Enhanced Anti-Tumor Efficacy and Decreased Dysfunction in Solid Tumors

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Chimeric Antigen Receptor (CAR) T cell therapies face significant challenges in targeting solid tumors due to the immunosuppressive tumor microenvironment. In this study, we engineered CAR T cells to express the interleukin-9 receptor (IL-9R), enabling IL-9 signaling, and analyzed their functionality using single-cell RNA sequencing (scRNA-seq) and trajectory analyses under antigen stress conditions. Our findings reveal that IL-9 signaling profoundly alters CAR T cell differentiation, steering CD8+ T cells toward memory and effector states while promoting the cycling of CD4+ T cells.

Trajectory and RNA velocity analyses demonstrated enhanced multipotency in IL-9-signaling CAR T cells, avoiding dysfunctional fates and favoring central memory T cell phenotypes. Differential transcription factor activation identified STAT1 and STAT4 as key drivers of these transitions. Additionally, single-cell transcriptomics highlighted the upregulation of chemokine receptors (CXCR3, CCR5) and cytotoxic effectors (IFNG, PRF1), reinforcing the enhanced antitumor potential of IL-9-signaling CAR T cells.

These insights into the molecular mechanisms underlying IL-9-mediated CAR T cell reprogramming showcase its promise in enhancing the efficacy and persistence of CAR T cell therapies for solid tumor treatment.