P141

Emergence of a Unique T Cell Population Associated with Cladribine Tablet Treatment in Multiple Sclerosis

Claudia Cantoni[1], Michael A. Paley[2], Kenneth Lee[1], Robert C. Axtell[3], Amber Salter[4], Julie Korich[5], Lori A. Lebson[5], Gabriel Pardo[3], Olaf Stuve[4], Amit Bar-Or[6], Anne H. Cross[1], Brian T. Edelson[7], Gregory F. Wu[1]

Departments of [1]Neurology and [2]Medicine, Washington University in St. Louis; [3] Department of Arthritis and Clinical Immunology Research, OMRF; [4] Department of Neurology, University of Texas Southwestern Medical Center; [5] EMD Serono, Rockland, MA, USA; [6]The Center for Neuroinflammation and Experimental Therapeutics and the Department of Neurology, University of Pennsylvania

Acknowledgments: This study was sponsored by EMD Serono, Inc., Rockland, MA, USA (CrossRefFunder ID: 10.13039/100004755), who reviewed and provided feedback on the poster. Presented at ACTRIMS Forum 2023 | February 23–25, 2023 – Copyright © 2023 remains with the authors

Background: Cladribine tablets (CladT) are efficacious for relapsing multiple sclerosis (RMS). However, the mechanisms by which cladribine exert favorable outcomes in MS have not been exhaustively identified and its effects on compartmentalized inflammation within the central nervous system remain unknown.

Objectives: To determine the extent, diversity, and phenotype of leukocyte infiltration within the cerebrospinal fluid (CSF) of RMS patients before and after treatment with CladT.

Methods: Blood and CSF samples from two individuals with RMS before and one year after treatment, plus another participant 10 weeks after start of CladT, were used to examine immune cell changes by transcriptomics. Transcriptional profiles of immune cells were obtained by single cell RNA sequencing, which served as the basis for uniform manifold approximation and projection (UMAP) visualization.

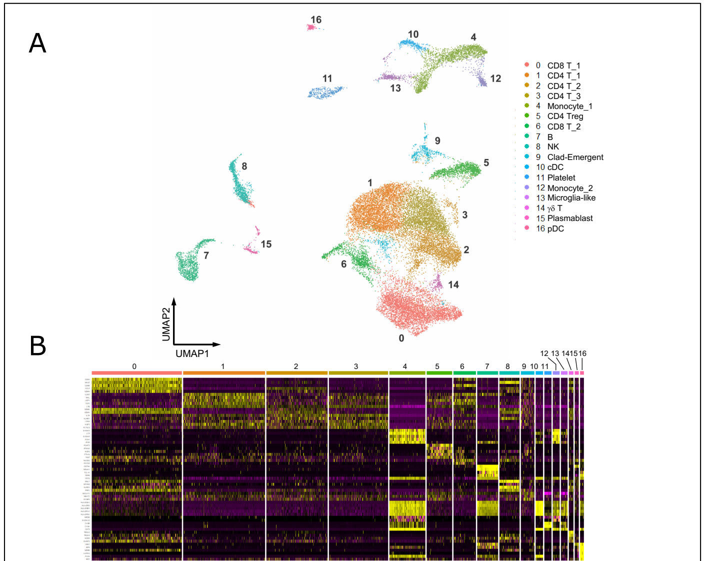
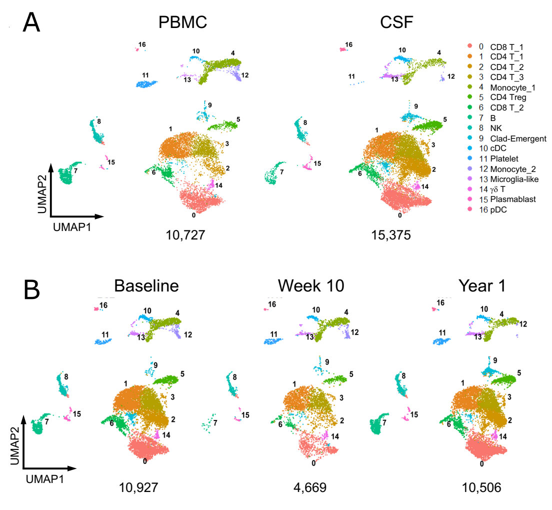


Figure 1. Immune cell landscape within the blood and CSF of RMS patients treated with CladT. (A) Composite UMAP of 26,102 peripheral blood (PBMC) and CSF immune cells from all participants at all timepoints. (B) Heatmap representation of the top 5 genes expressed by each cluster.

Figure 2. Spatial architecture and proportion of blood and CSF immune cells in RMS patients treated with CladT. (A) UMAP of immune cells from the blood (PBMC, left) and CSF (right) from all individuals combined. (B) UMAP of blood and CSF immune cells combined at baseline (left), week 10 following treatment (middle), and one year following treatment (right) from both blood and CSF.



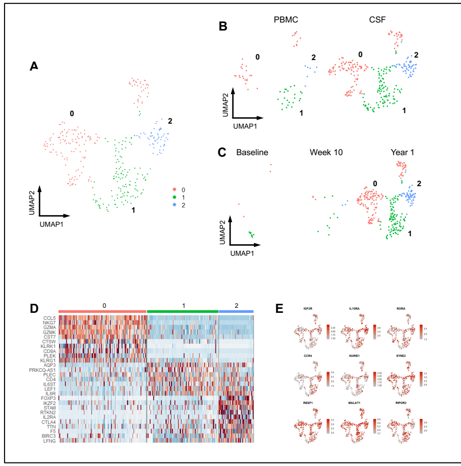


Figure 3. Transcriptional features of a unique CD4 T cell population associated with CladT. (A) Sub-cluster analysis of Clad_Emergent T cells identifies 3 sub-clusters (0, 1, 2). (B) UMAP of Clad_Emergent T cell sub-clusters in PBMC (left) and CSF (right). (C) UMAP of Clad_Emergent T cell sub-clusters in the blood and CSF at baseline (left) and 10 weeks (middle) or 1 year (right) post-treatment with cladribine. (D&E) Expression of selective upregulated genes expressed by sub-clusters of Clad_Emergent T cells by heatmap (D) and displayed by UMAP (E).

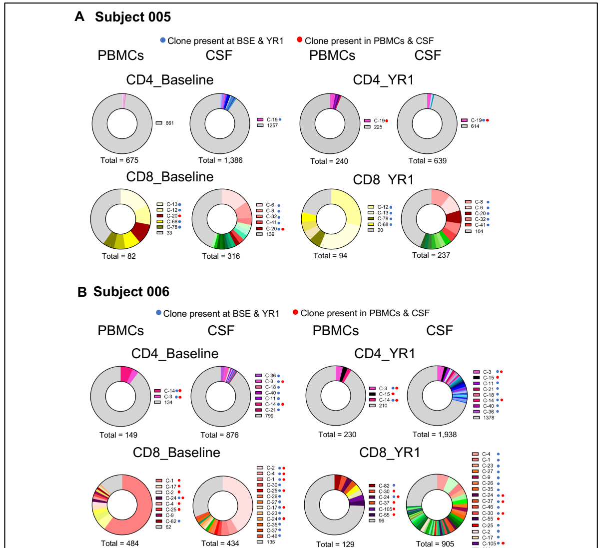

A Subject 005
Clone present at BSE & YR1
Clone present in PBMCs & CSF
PBMCs
CSF
CD4_Baseline
CD4_YR1
Total = 675
Total = 1,386
Total = 240
Total = 639
CD8_Baseline
CD8_YR1
Total = 82
Total = 316
Total = 94
Total = 237
B Subject 006
CD4_Baseline
CD4_YR1
Total = 149
Total = 876
Total = 230
Total = 1,938
CD8_Baseline
CD8_YR1
Total = 484
Total = 434
Total = 129
Total = 905

Figure 4. Antigen receptor clonality before and after CladT. Donut charts of paired single cell RNA-seq T cell receptor (TCR) VDJ analysis from PBMCs and CSF T cells in participants 005 (A), and 006 (B). Total number of CD4 (top) or CD8 (bottom) T cells sequenced is reported for each individual below each donut chart. Clones shared between baseline and year 1 (YR1) are denoted with blue dots, while clones shared between PBMCs and CSF TCRs at each time point are indicated by red dots. The grey portion of each chart indicates clones seen in one to four cells from a sample. Colors used for expanded CD4 and CD8 T cell clones from participants 005 and 006 are the same although no clonal sequences were shared between participants.

Conclusion: These results suggest an immune cell dynamic that is associated with CladT therapy for RMS, including the emergence of a unique subset of T cells one year after treatment. This study exemplifies the utility of CSF examination for identifying mechanisms of disease-modifying therapy for, as well as pathogenesis of, MS.

Disclosures: CC, KL and BTE have no disclosures. MAP receives research support from Lilly paid to the institution and received consultant fees from AbbVie, JK Market Research, and Priovant Therapeutics. RCA has consulted for Roche, EMD Serono, and Biogen Idec and is on the advisory board for Progentec Diagnostics Inc. AS receives research funding from Multiple Sclerosis Society of Canada, NMSS, CMSC and the US DOD and is a member of editorial board for Neurology. She serves as a consultant for Gryphon Bio, LLC. She is a member of the DSMB for PREMOD2, CAVS-MS, and CELLO. JK and LAL are employees of EMD Serono, Rockland, MA, USA. GP has received speaker honoraria and/or consulting fees from Alexion, Biogen Idec, Celgene/BMS, EMD Serono, Rockland, MA, USA, Horizon, Greenwich Pharmaceuticals, Novartis, Roche/Genentech, Sanofi-Genzyme, TG Therapeutics; and has received research support (to the institution) from Abbvie, Adamas, Alkermes, Biogen Idec, EMD Serono, Rockland, MA, USA, Roche/Genentech, Sanofi Genzyme, Novartis, and Teva. OS receives grant support from EMD Serono, Rockland, MA, USA, Genzyme, and Exalys. He serves on the editorial boards of Therapeutic Advances in Neurological Disorders, has served on data monitoring committees for Genentech-Roche, Pfizer, and TG Therapeutics without monetary compensation, and has advised EMD Serono, Rockland, MA, USA, Celgene, Genentech, Novartis, TG Therapeutics, and Genzyme. AB-O has Received fees for advisory board participation and/or consulting from Accure, Atara Biotherapeutics, Biogen, BMS/Celgene/Receptos, GlaxoSmithKline, Gossamer, Janssen/Actelion, Medimmune, EMD Serono, Novartis, Roche/Genentech, Sanofi-Genzyme; and has received grant support to the University of Pennsylvania from Biogen Idec, Roche/Genentech, EMD Serono and Novartis. AHC has consulted for Biogen, Bristol Myers Squibb, EMD Serono, Genentech/Roche, Horizon, Janssen, Novartis, Octave, TG Therapeutics. GFW has received consulting fees from Genentech and Sangamo, research support from EMD Serono, Biogen, and Genentech, and speaker fees from EMD Serono.