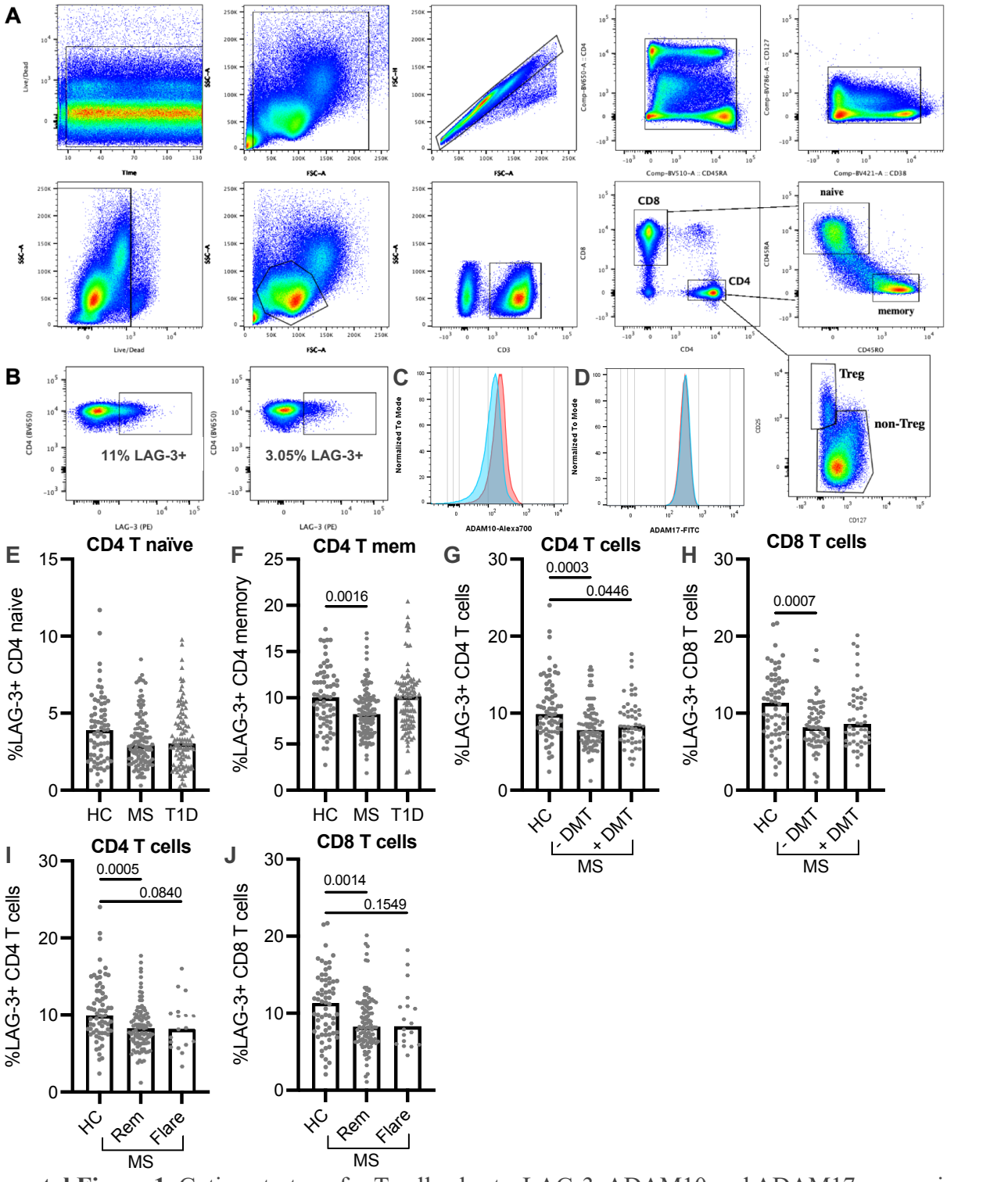
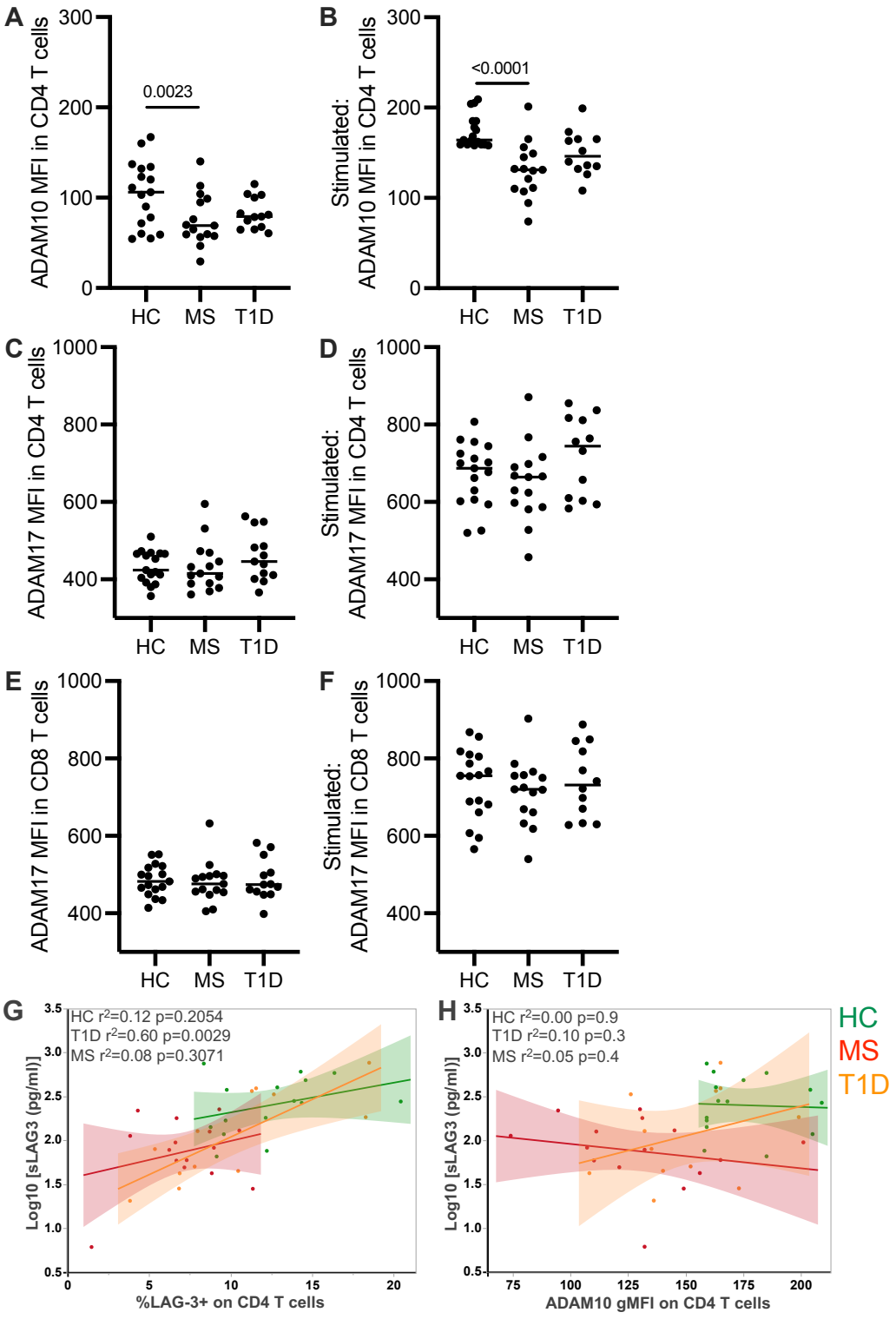
Supplemental Table 1: Patient cohort characteristics

	Cohort 1			Cohort 2		
Characteristics	**HC**	**T1D**	**RRMS**	**HC**	**T1D**	**RRMS**
Subject N	62	104	121	19	15	20
Age median (range)	31 (22-47)	42 (12-76)	42 (19-75)	43 (23-58)	34 (26-41)	42.5 (27-57)
Female	34/62 (54.8%)	66/104 (63.5%)	85/121 (70.2%)	12/19 (63.2%)	6/15 (40%)	13/20 (65%)
Statistical Analysis: Age		*p* <0.0001	*p* <0.0001		*p* =0.0006	*NS*
Sex		*NS*	*p =0.0393*		*NS*	*NS*
Overlap with Cohort 1				2/19	0/15	15/20
Clinical measures						
Disease duration (yrs) mean (range)	-	23.6 (1.2-55)	8.2 (0-32.4)	-		9.1 (0-29.4)
Active MS Flare	-	-	18/121 (14.9%)	-	-	19/20 (95%)
DMT*	-	-	51/121 (42.1%)	-	-	16/20 (80%)

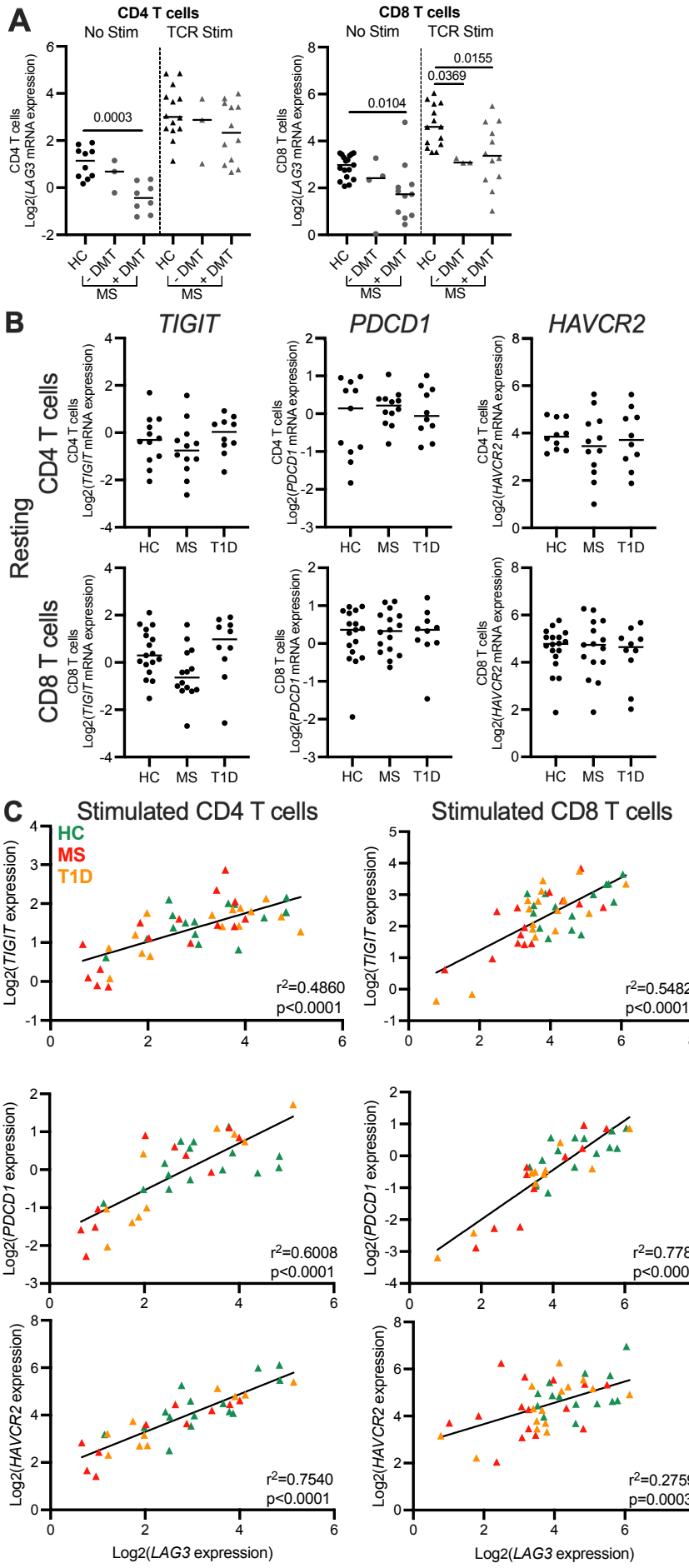
*DMT = natalizumab, glatiramer acetate, dimethyl fumarate, interferon beta-1a and 1b; NS, not significant. P values are from one-way ANOVA (age) and chi-squared (sex).



Supplemental Figure 1. Gating strategy for T cell subsets, LAG-3, ADAM10 and ADAM17 expression, frequency of LAG-3+ naïve and memory CD4 T cells, and MS subjects stratified by therapy and disease activity. (**A**) Gating strategy for CD3+ CD4+ and CD8+ T cells, memory (CD45RA-CD45RO+), naïve (CD45RA+CD45RO-), regulatory CD4 T cells (CD25+CD127low) and conventional CD4 T cells (CD25-CD127low). (**B**) Representative gating for frequency of LAG-3+ CD4 T cells. Representative histogram of ADAM10 (**C**) and ADAM17 (**D**) in resting CD4 T cells (HC red; RRMS blue). Frequency of LAG-3+ CD4 (**E**) naïve (CD45RA+CD45RO-) and (**F**) memory (CD45RA-CD45RO+) T cells from HC (69), T1D (104), and RRMS (121) subjects. LAG-3+ frequency in CD4 and CD8 T cells when stratifying RRMS subjects by treatment with disease-modifying therapies (DMT, 51) (**G, H**) and disease activity (18 flares) (**I, J**). Lines shown are median, and *p* values are shown after a one-way ANOVA. Results shown from 25 independent experiments.



Supplemental Figure 2. ADAM10 and ADAM17 expression on T cells. The gMFI of ADAM10 **(A)** before and **(B)** after a 48-hour TCR stimulation in CD4 T cells**.** The geometric MFI of ADAM17 before and after stimulation in (**C, D**) CD4 and (**E, F**) CD8 T cells. **(G)** Correlation between surface LAG-3 expression and sLAG3 concentration after TCR stimulation in CD4 T cells (all subjects $p<0.0001$, $r^2=0.4150$). **(H)** Correlation between CD4 ADAM10 gMFI and sLAG3 concentration after TCR stimulation (all subjects p=0.0490, $r^2=0.0093$). Results from two independent experiments, HC (green) n=17, RRMS (red) n=15, and T1D (orange) n=13. Lines shown are median, and p-values are shown after a one-way ANOVA **(A-F)** or a Spearman correlation test **(G, H).**



Supplemental Figure 3.
Transcriptional expression of additional inhibitory receptors in RRMS and T1D. (**A**) *LAG3* mRNA expression in CD4 and CD8 T cells stratified by RRMS subjects taking disease-modifying therapies (DMT, 4). **(B)** In resting CD4 (top) and CD8 T cells (bottom) *TIGIT, PDCD1*, and *HAVCR2* mRNA levels were not different in RRMS and T1D subjects. **(C)** In CD4 and CD8 T cells, *LAG3* mRNA levels positively correlate with *TIGIT* (top), *PDCD1* (middle) and *HAVCR2* (bottom) expression after TCR stimulation. qRT-PCR for *HAVCR2, PDCD1* and *TIGIT* was normalized to the ribosomal gene *RPL36A* and reported relative to a Jurkat cell line. HC green, n=20; RRMS red, n=20; T1D orange, n=15. Results shown are from three independent experiments. Lines shown are median, and *p* values are shown after a one-way ANOVA. Linear regressions are shown with Pearson correlation coefficient.