

## **Electronic Supplementary Material (ESM)**

### **Slow progressors to type 1 diabetes lose islet autoantibodies over time, have few islet antigen-specific CD8<sup>+</sup> T cells and exhibit a distinct CD95<sup>hi</sup> B cell phenotype**

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### **Abbreviations**

HD	healthy donors
LS	long-standing type 1 diabetes
ND	newly diagnosed type 1 diabetes
SP	slow progressors

ESM Table 1

a

	Number	Mean age (yrs)	Age range (yrs)	Mean disease duration (yrs)	Range of disease duration (yrs)
HD male	14	34.6	18–72	-	-
HD female	9	34.2	20–55	-	-
SP male	6	34.5	28–69	-	-
SP female	4	43.3	33–55	-	-
ND male	12	31.3	19–45	0.4	0.1–1.0
ND female	6	29.0	18–50	0.4	0.1–0.9
LS male	10	38.4	20–48	23.1	3–38
LS female	8	34.1	18–49	18.9	3–36

b

	Gender	Age (years)	HLA Class II DRB1 genotyping		GADA (DK units/ml)	IA-2A (DK units/ml)	ZnT8A (units/ml)	IAA (units/ml)
HD1	M	52	*0701-0702	*0901	4.15	0.00	0.41	0.00
HD2	M	26	*0401-0422	*0805-0801	0.00	0.00	0.49	0.00
HD3	M	34	*0401-0422	*1302-1305/1303-1304	0.00	0.00	0.34	0.00
HD4	M	37	*0701-0702	*1001	0.33	0.00	0.33	0.00
HD5	M	72	*0101-0103	-	0.00	0.00	1.01	0.00
HD6	M	41	*0401-0422	*0701-0702	0.00	0.00	0.49	0.00
HD7	M	18	*1501-1505	*0701-0702	0.00	0.00	0.46	0.00
HD8	M	29	*0401-0422	*1302-1305/1303-1304	0.00	0.00	0.31	0.00
HD9	M	34	*1501-1505	*0701-0702	24.53	0.00	1.01	0.00
HD10	M	29	*0301	-	0.00	0.00	0.21	0.00
HD11	M	22	*1101-1121	*1302-1305/1303-1304	0.00	0.00	0.29	0.00
HD12	M	21	*1501-1505	-	0.00	0.00	0.40	0.00
HD13	M	24	*0401-0422	*0701-0702	0.00	0.00	0.45	0.00
HD14	M	46	*0101-0103	*0301	4.49	0.00	0.29	0.00
HD15	F	21	*0701-0702	-	0.00	0.00	0.32	0.00
HD16	F	49	*0301	*0701-0702	0.00	0.00	0.39	0.00
HD17	F	24	*1501-1505	*0701-0702	0.00	0.00	0.43	0.00
HD18	F	20	*0301	*0701-0702	0.00	0.00	0.72	0.00
HD19	F	38	*0101-0103	*0401-0422	0.00	0.00	0.54	0.00
HD20	F	44	*0401-0422	*1101-1121	nk	nk	nk	nk
HD21	F	33	*0301	*0805-0801	0.00	0.00	0.15	0.00
HD22	F	55	*1302-1305/1303-1304	-	0.00	0.00	0.45	0.00
HD23	F	24	*0401-0422	-	nk	nk	nk	nk
SP1	M	28	*0101-0103	*0301	309.30	0.00	0.38	0.00
SP2	M	41	*0301	*0401-0422	176.00	8.20	6.70	0.00
SP3	M	69	*0401-0422	*1201-1203	82.25	0.00	92.86	0.00
SP4	M	53	*0401-0422	*0701-0702	715.30	5.96	0.44	0.82
SP5	M	46	*0401-0422	*1501-1505	55.01	0.00	0.47	0.00
SP6	M	31	*0301	*0401-0422	146.59	0.00	4.34	0.00
SP7	F	33	*0101-0103	*0301	267.26	0.00	0.70	0.00
SP8	F	44	*0401-0422	*1101-1121	205.75	25.74	11.88	0.00
SP9	F	55	*0101-0103	*0401-0422	456.13	0.00	0.25	0.30
SP10	F	41	*0401-0422	*1001	362.95	228.42	7.13	0.00

**C**

	Gender	Age (years)	Disease duration (yrs)	HLA Class II DRB1 genotyping		GADA (DK units/ml)	IA-2A (DK units/ml)	ZnT8A (units/ml)
LS1	M	48	32.0	*0301	*0401-0422	122.21	106.47	13.91
LS2	M	33	3.0	*0301	-	183.84	81.25	0.47
LS3	M	39	30.0	*0301	*0401-0422	13.48	0.00	0.44
LS4	M	20	13.0	*0101-0103	*0301	1.73	0.00	0.29
LS5	M	35	22.0	*0301	*0701-0702	51.32	0.00	0.39
LS6	M	29	13.0	*0301	-	67.57	239.50	41.41
LS7	M	48	36.0	*0401-0422	-	175.45	0.00	0.88
LS8	M	45	31.0	*0401-0422	*0701-0702	3.00	0.00	0.65
LS9	M	43	13.0	*0101-0103	*0301	5.14	1.74	0.88
LS10	M	44	38.0	*0101-0103	*0401-0422	0.00	0.00	0.31
LS11	F	33	17.0	*0101-0103	*0401-0422	86.75	0.00	0.37
LS12	F	44	14.0	*0301	-	900.07	0.00	0.36
LS13	F	34	31.0	*0401-0422	*1302-1305/1303-1304	0.00	0.08	0.49
LS14	F	37	13.0	*0401-0422	*1101-1121	79.94	2.10	0.24
LS15	F	34	25.0	*0301	*0401-0422	1.51	3.31	0.95
LS16	F	24	12.0	*0301	*0401-0422	5.37	0.00	0.41
LS17	F	49	36.0	*0301	*0401-0422	16.61	0.00	0.52
LS18	F	18	3.0	*0301	*0401-0422	1,018.96	0.00	0.51
ND1	M	36	0.3	*0401-0422	-	11.68	0.00	0.25
ND2	M	28	0.1	*1501-1505	*0401-0422	0.00	0.00	0.46
ND3	M	36	0.3	*0401-0422	*1302-1305/1303-1304	221.12	271.26	170.31
ND4	M	27	0.3	*0401-0422	-	193.87	29.82	0.41
ND5	M	37	0.1	*0101-0103	*0301	869.57	267.67	126.84
ND6	M	34	1.0	*0101-0103	*0401-0422	15.31	0.00	0.50
ND7	M	45	0.9	*0301	*0701-0702	69.99	201.51	0.54
ND8	M	21	0.4	*1501-1505	-	0.00	0.00	0.21
ND9	M	24	0.7	*0301	*0401-0422	314.61	124.11	0.28
ND10	M	24	0.2	*0101-0103	*0701-0702	345.06	0.00	0.49
ND11	M	45	0.3	*0301	*0701-0702	458.91	0.00	0.57
ND12	M	19	0.3	*0301	*0701-0702	1,015.09	300.97	0.41
ND13	F	18	0.3	*0301	*0401-0422	0.00	2.54	69.83
ND14	F	50	0.7	*0301	*0401-0422	0.00	0.00	1.97
ND15	F	23	0.3	*0401-0422	-	500.65	280.68	106.96
ND16	F	23	0.9	*0301	*0401-0422	517.54	0.00	0.26
ND17	F	36	0.3	*0301	*0701-0702	663.30	110.65	0.68
ND18	F	24	0.1	*0401-0422	*1302-1305/1303-1304	173.03	3.68	4.30

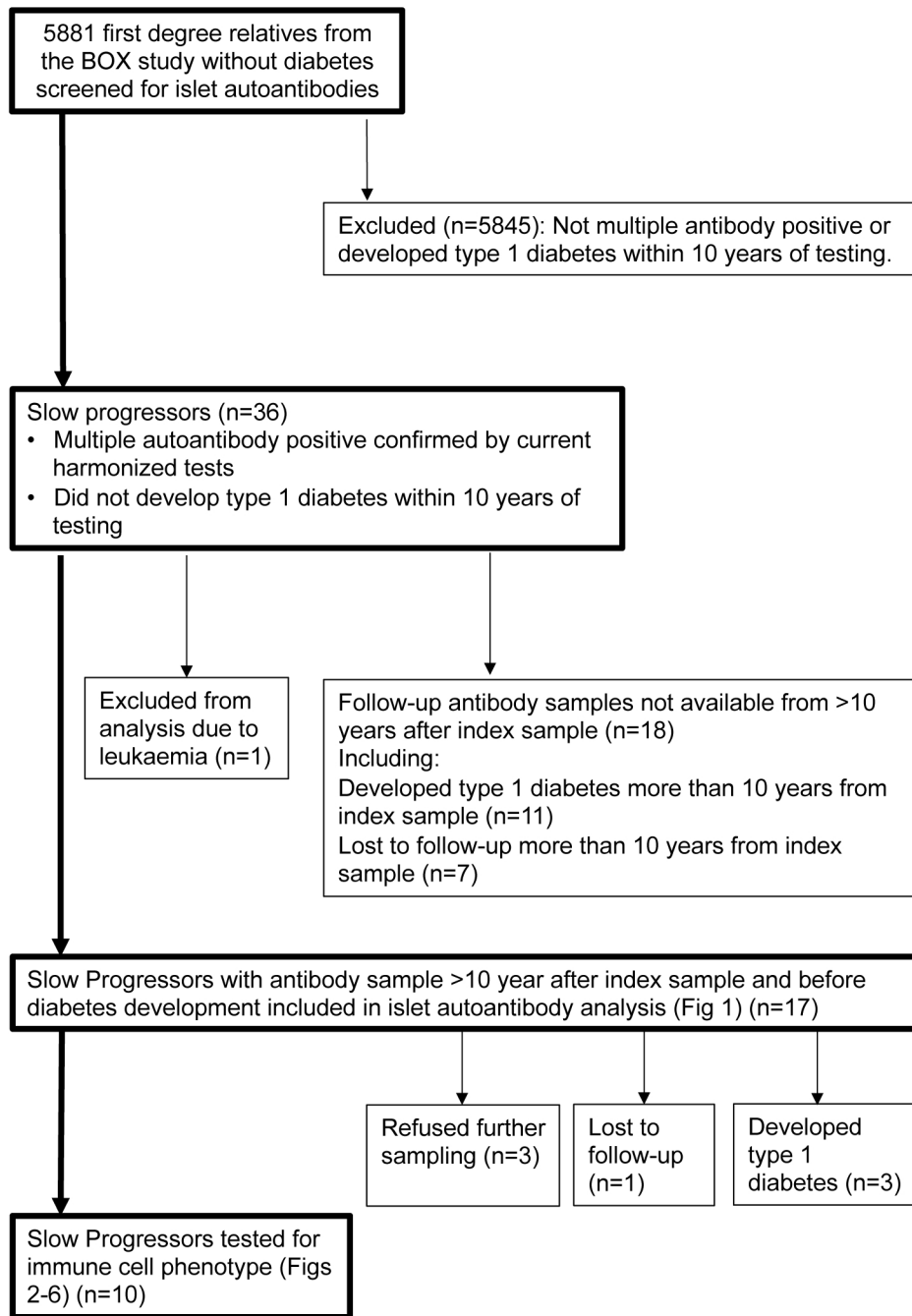
**ESM Table 1. Clinical, demographic, and immunological characteristics of SPs, people with ND or LS type 1 diabetes, and HDs.** (a) Summary table of demographics (b) HDs' and SPs' demographic and immunological characteristics (c) Clinical, demographic, and immunological characteristics of people with newly diagnosed or long-standing type 1 diabetes. nk: not known. SP6 had autoimmune thyroid disease. Thresholds for seropositive islet autoantibody titres: GADA  $\geq$  33 DK units/ml; IA-2A  $\geq$  1.4 DK units/ml; ZnT8A  $\geq$  1.8 units/ml; IAA  $\geq$  0.2 units/ml. HD, healthy donors; LS, long-standing type 1 diabetes; ND, newly diagnosed type 1 diabetes; SP, slow progressors

## ESM Table 2

Peptide	Sequence	QDot 1	QDot 2	Panel
CMV	NLVPMVATV	585	800	A
EBV	GLCTLVAML	655	800	A
non-interfacing	GLFGGGGGV	585	605	A
INS b10-18	HLVEALYLV	605	655	B
PI 15-24	ALWGPDPAAA	585	655	B
GAD 114-123	VMNILLQYVV	655	800	B
IA-2 797-805	MVWESGCTV	585	605	B
IGRP 265-273	VLFGLGFAI	605	800	B
pplAPP 5-13	KLQVFLIVL	585	800	B

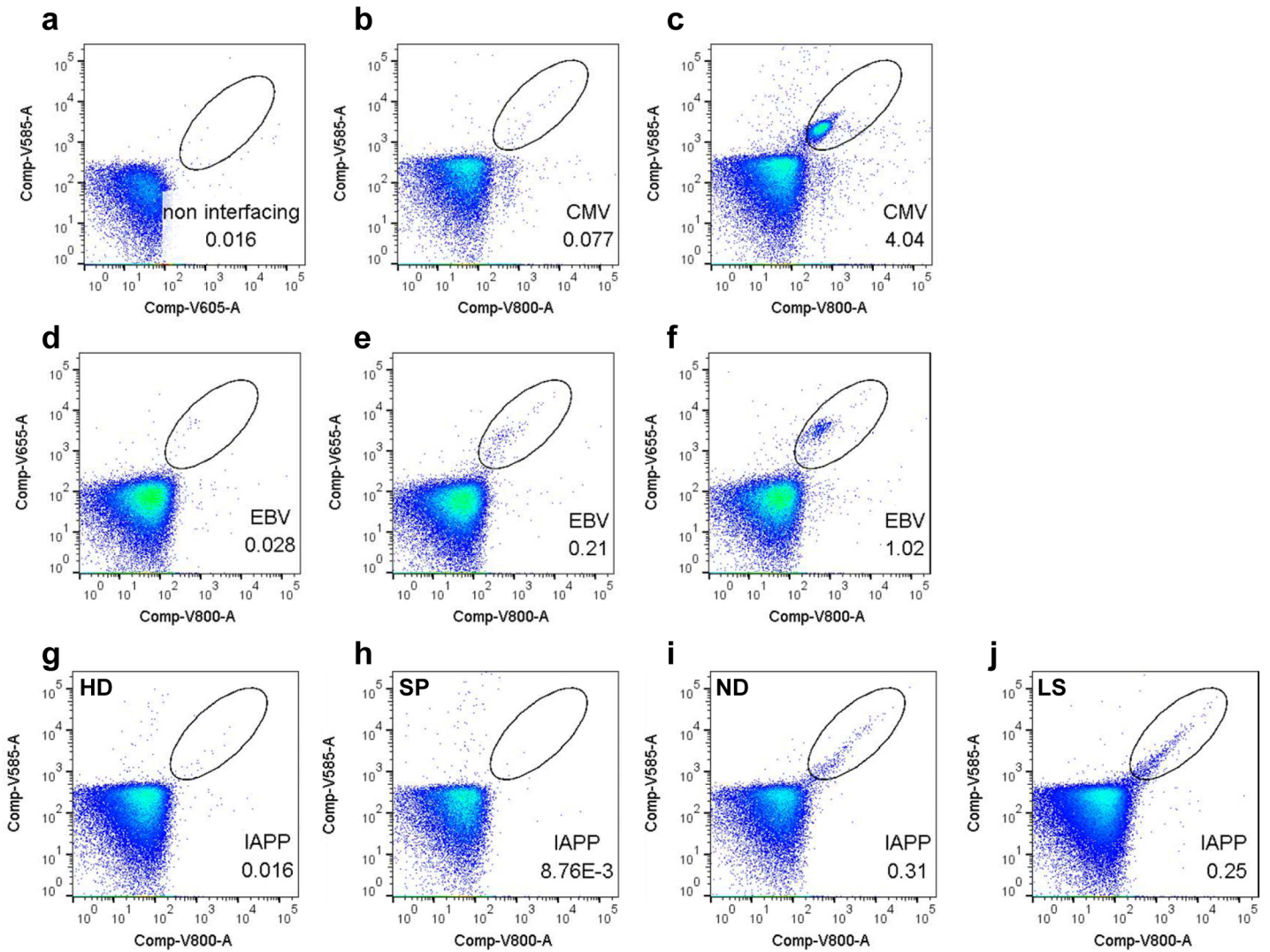
**ESM Table 2. Peptide-HLA-A2 tetramers used in this study.**

ESM Figure 1



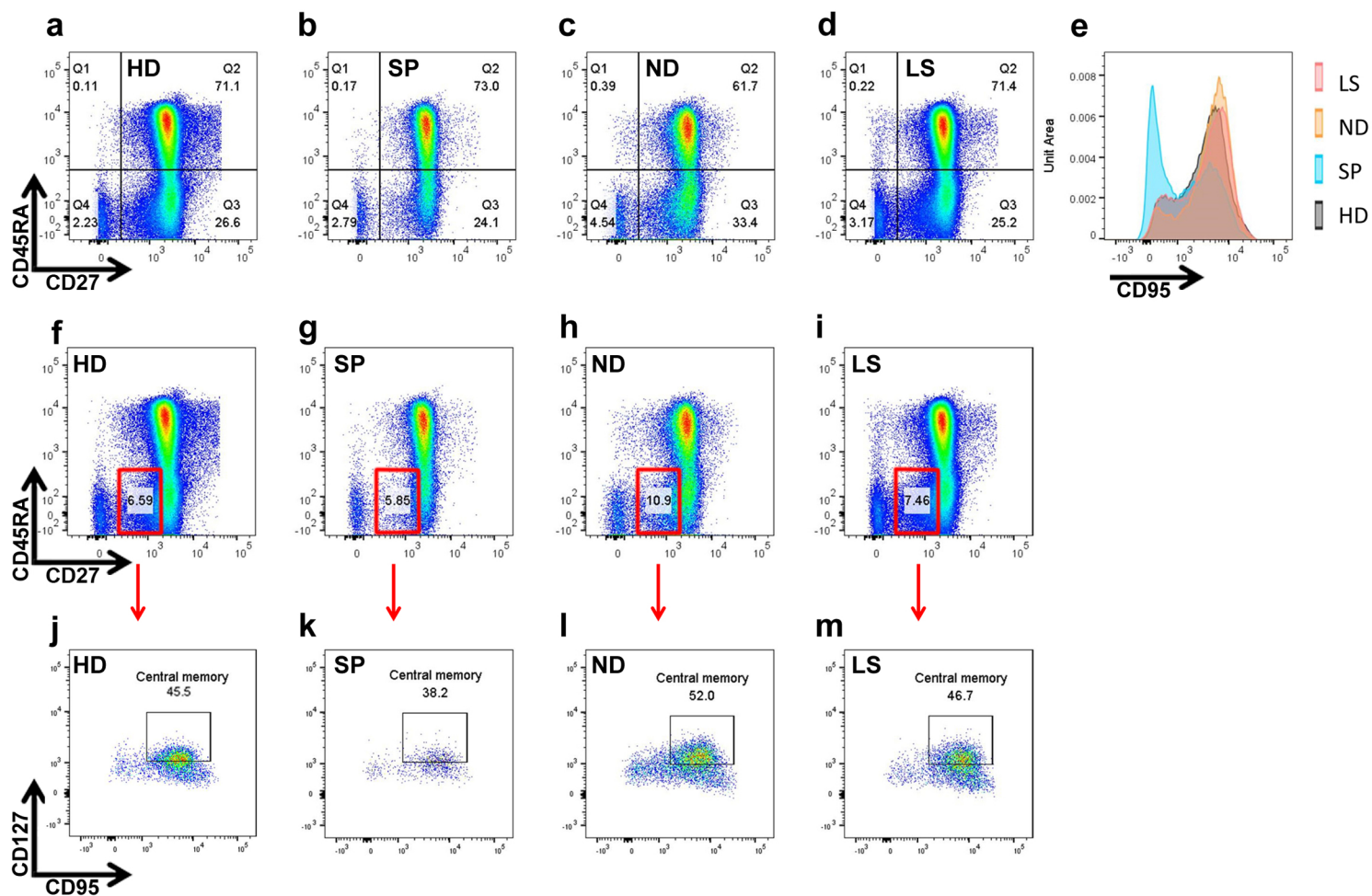
ESM Figure 1: Consort diagram of slow progressors.

ESM Figure 2



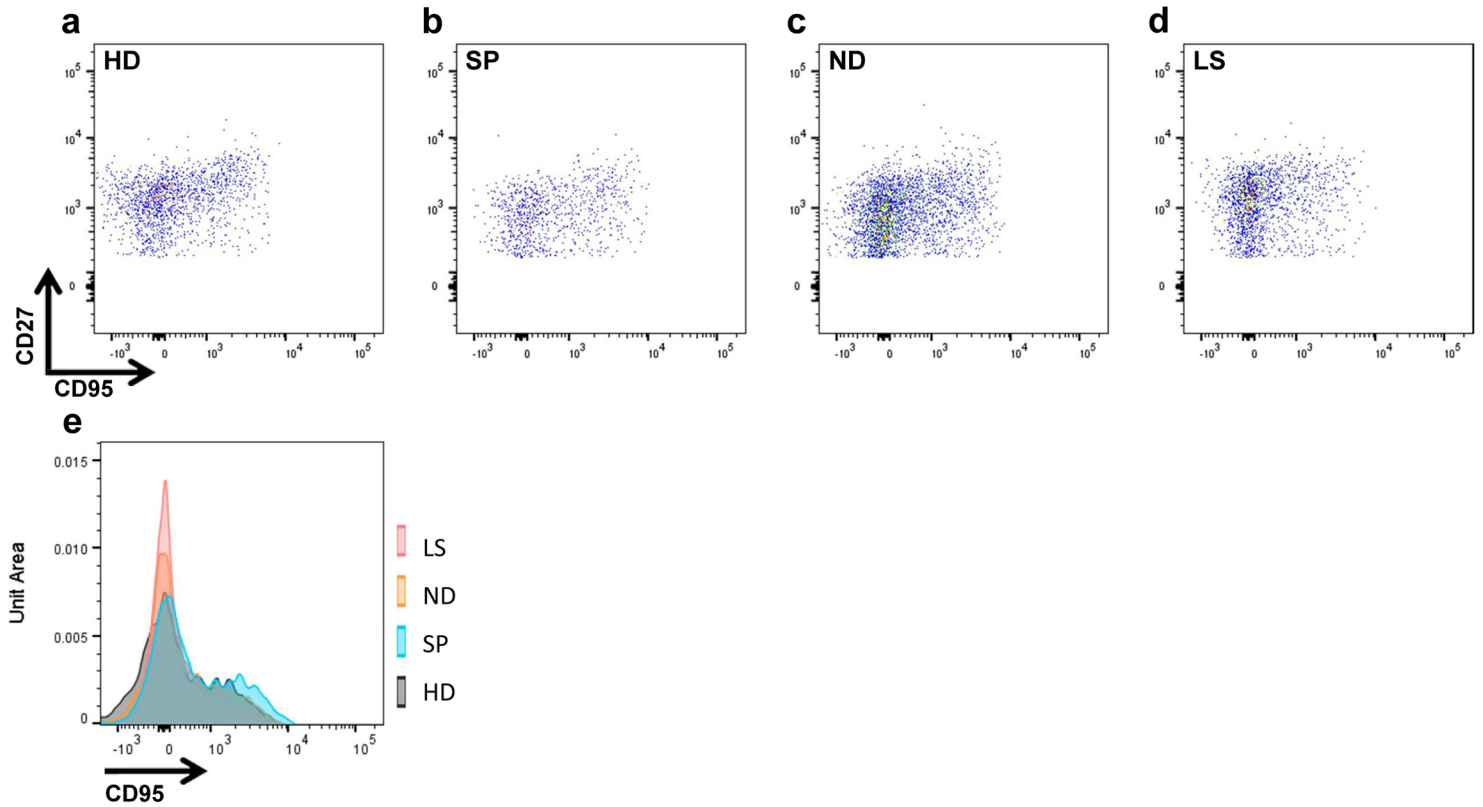
**ESM Figure 2: Representative flow cytometric plots from negative and positive control data in Figure 2, illustrating different levels of response: a. staining with non-interfacing peptide tetramer; b, c. staining with CMV peptide tetramer; d,e,f staining with EBV peptide tetramer; g. staining with IAPP peptide tetramer from HD; h. staining with IAPP peptide tetramer from SP; i. staining with IAPP peptide tetramer from ND; j. staining with IAPP peptide tetramer from LS. HD, healthy donors; LS, long-standing type 1 diabetes; ND, newly diagnosed type 1 diabetes; SP, slow progressors**

### ESM Figure 3



**ESM Figure 3: Representative flow cytometric plots from data in Figure 3.** Quadrant-gated CD4<sup>+</sup> T cells a. HD; b. SP; c. ND; d. LS; e. histogram overlay of CD95 expression in Q3 of the quadrant gated plots (CD27<sup>+</sup>CD45RA<sup>-</sup> T cells). f-i CD4<sup>+</sup> plots with a CD27<sup>int</sup>CD45RA<sup>-</sup> population box-gated manually in FlowJo f. HD; g. SP; h. ND; i. LS; j-m CD127 and CD95 expression in the box gated populations (parts f-i), indicating the central memory population that is analogous to cells shown in Fig 3d of the main text; j. HD; k. SP; l. ND; m. LS. HD, healthy donors; LS, long-standing type 1 diabetes; ND, newly diagnosed type 1 diabetes; SP, slow progressors

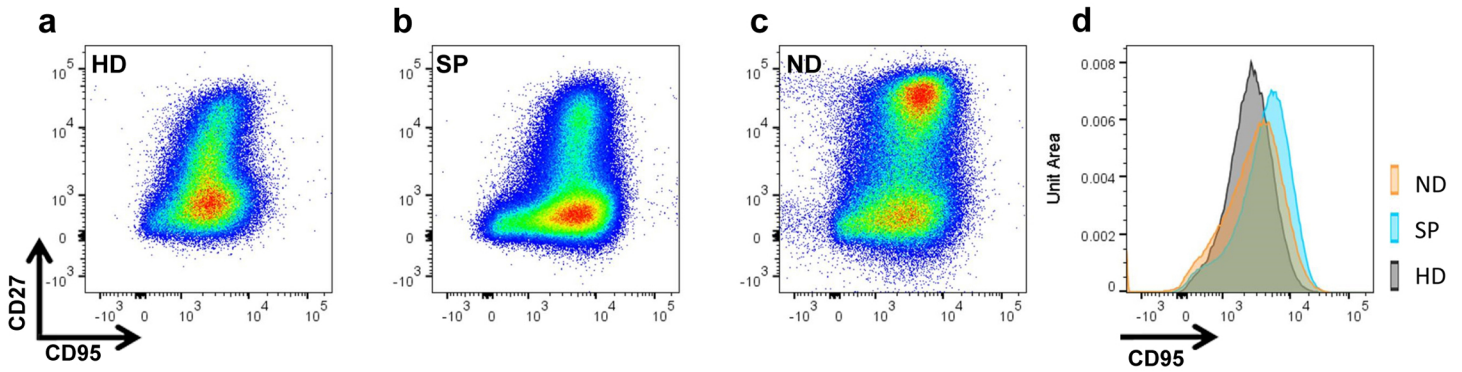
ESM Figure 4



**ESM Figure 4: Representative flow cytometric plots from data in Figure 4.** Switched memory B cells (CD27<sup>+</sup>IgD<sup>-</sup>) from freshly isolated PBMC, manually gated in FlowJo, showing expression of CD27 and CD95: a. HD; b. SP; c. ND; d. LS; e. a histogram of CD95 expression in the switched memory B cells. HD, healthy donors; LS, long-standing type 1 diabetes; ND, newly diagnosed type 1 diabetes; SP, slow progressors

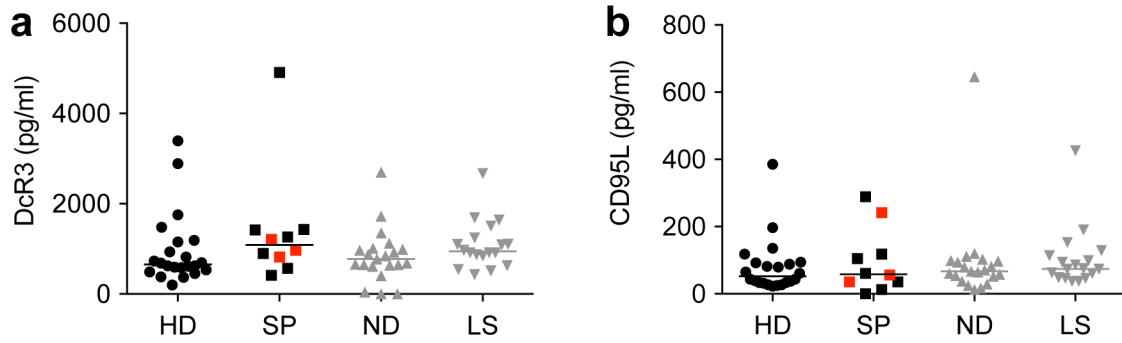


## ESM Figure 5



**ESM Figure 5: Representative flow cytometric plots from data in Figure 5. B cells following *ex vivo* stimulation showing expression of CD27 and CD95: a. HD; b. SP; c. ND; d. histogram overlay of CD95 expression in the switched memory B cells. HD, healthy donors; ND, newly diagnosed type 1 diabetes; SP, slow progressors**

ESM Figure 6



**ESM Figure 6: Serum levels of DcR3 and CD95L.** Serum concentrations of DcR3 and CD95L were measured using ELISAs. ELISA results are shown: a. DcR3; b. CD95L. Horizontal lines indicate median values. Red squares denote slow progressors who tested seropositive for a single islet autoantibody at the time of immune cell analysis. HD, healthy donors; LS, long-standing type 1 diabetes; ND, newly diagnosed type 1 diabetes; SP, slow progressors