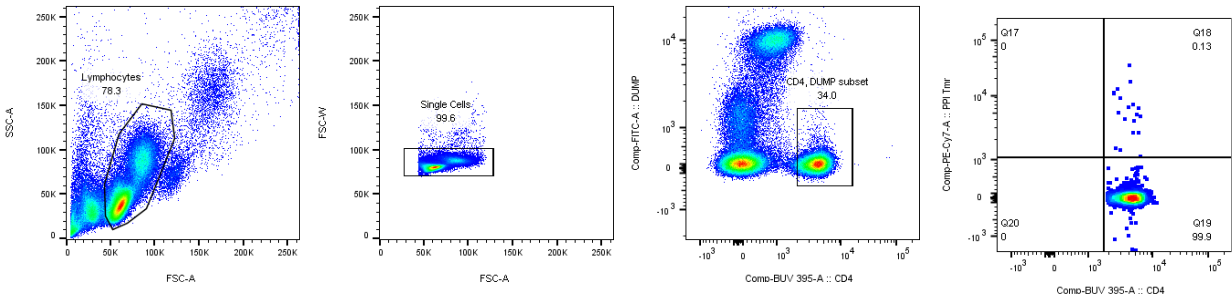
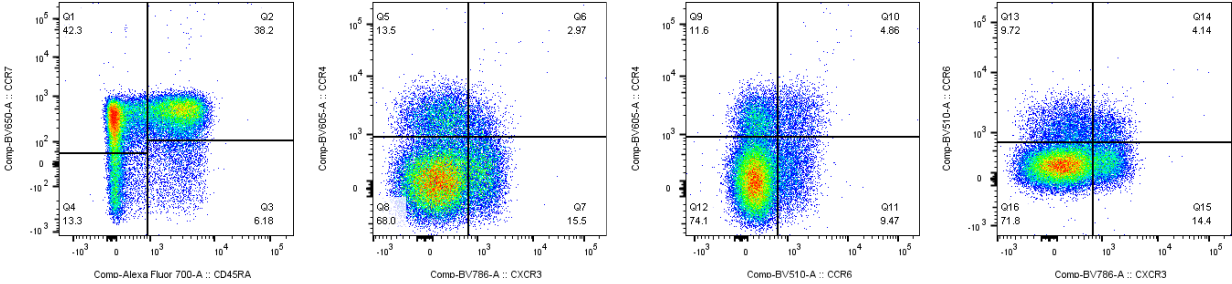


A



B



Supplemental Figure 1 – Surface marker gating for T cell analysis. FACS plots from a representative subject with T1D show the gating scheme used for CD4 T cell analysis. **A:** We sequentially gated lymphocytes (FSC-A versus SSC-A), single cells (FSC-A versus FSC-W), and viable CD4+ T cells (CD4 versus Dump). For viable CD4+ T cells, positive thresholds were then set for each tetramer channel, as shown for the representative PE-Cy7 labeled PPI tetramer. **B:** For viable CD4+ T cells, positive thresholds were also set to define naïve and memory subsets (CD45RA versus CCR7) and positive thresholds for CXCR3, CCR4, and CCR6. Using these threshold MFI values, sequential gating was then applied to define Th1-like (CXCR3+, CCR4- and CCR6-), Th2-like (CXCR3-, CCR4+ and CCR6-), Th17-like (CXCR3-, CCR4+ and CCR6+), Th1/17-like (CXCR3+, CCR4- and CCR6+), Th1/2-like (CXCR3+, CCR4+ and CCR6-), or Th1*-like (CXCR3+, CCR4+ and CCR6+) lineages.

Supplemental Table 1. DRB1*4:01+ subjects with type 1diabetes used for in vitro assays

Subject ID	Age ^a	Sex	Time Since Diagnosis ^a	Auto-antibody status ^b
T1D #1	29	Male	4.3 years	IAA, IA2, ZnT8
T1D #2	20	Female	1.9 years	GAD, IAA, IA2, ZnT8
T1D #3	26	Female	1.4 years	GAD, IAA, IA2
T1D #4	31	Female	5.1 years	GAD, IA2, ZnT8
T1D #5	30	Female	3.2 years	GAD, IAA, IA2, ZnT8
T1D #6	32	Female	7.3 years	GAD, IAA, IA2, ZnT8
T1D #7	29	Male	9.9 years	IAA, IA2
T1D #8	31	Female	3.1 years	IAA, IA2
T1D #9	37	Male	7.1 years	GAD, IAA, IA2, ZnT8
T1D #10	29	Female	12.6 years	GAD, IAA, IA2
T1D #11	32	Male	7.1 years	IAA
T1D #12	39	Female	27.9 years	GAD, IA2
T1D #13	40	Female	4.4 years	GAD
T1D #14	31	Female	3.5 years	GAD, IAA
T1D #15	36	Female	31.5 years	IAA, IA2

^aThe mean age of patients was 31.5 years. The mean time since diagnosis was 8.7 years.

^bGAD denotes glutamic acid decarboxylase 65, IAA denotes (micro) insulin, IA2 denotes tyrosine phosphatase-related islet antigen 2, ZnT8 denotes zinc transporter 8. Autoantibody data is historical and was not in done conjunction with the current study.

Supplemental Table 2. DRB1*4:01+ subjects with type 1 diabetes used for direct staining

Subject ID	Age ^a	Sex	Time Since Diagnosis ^a	Auto-antibody status ^b
T1D #1	23	Female	4.8 years	IAA, IA2, ZnT8
T1D #2	70	Female	14.5 years	IAA
T1D #3	29	Male	5.6 years	GAD, IAA
T1D #4	53	Male	37.8 years	GAD, IAA
T1D #5	56	Female	42.6 years	IAA
T1D #6	25	Male	2.3 years	IAA, IA2, ZnT8
T1D #7	34	Female	31.6 years	IAA
T1D #8	63	Male	48.8 years	No results
T1D #9	42	Male	12.7 years	GAD, IAA
T1D #10	59	Female	14.1 years	GAD

^aThe mean age of patients was 45.4 years. The mean time since diagnosis was 21.4 years.

^bGAD denotes glutamic acid decarboxylase 65, IAA denotes (micro) insulin, IA2 denotes tyrosine phosphatase-related islet antigen 2, ZnT8 denotes zinc transporter 8. Autoantibody data is historical and was not in done conjunction with the current study.

Supplemental Table 3. DRB1*04:01 healthy subjects used for direct staining

Subject ID	Age	Sex
Control #1	62	Male
Control #2	58	Female
Control #3	53	Male
Control #4	42	Female
Control #5	22	Female
Control #6	67	Female
Control #7	34	Female
Control #8	46	Male

The mean age of controls was 48 years.

Healthy subjects under the age of 18 could not be recruited.

Supplemental Table 4. Organ donor with diabetes used for study

Case ID ^a	Age	Sex	Time Since Diagnosis	HLA-DR Type
nPOD 6472	10	Female	4 years	DRB1*03:01/04:04

^aCD4+ T cell lines were isolated from vibratome slices of pancreas tissue from this organ donor (Cat# nPOD_6472, RRID:SAMN15879525).

Supplemental Table 5. Splice Variant and Secretory Granule Peptides with Predicted DR0401 Binding Motifs

Peptide	Sequence	Measured IC ₅₀ (μM) ^{a,b}
CCNI-008 p1	SEILRMERIILDKLN	>50
CCNI-008 p2	MERIILDKLNWDLHT	>50
CCNI-008 p3	KLNWDLHTATPLDFL	>50
CCNI-008 p4	HTATPLDFLHIMDSSQLIH	7.2
CCNI-008 p5	ATPLDFLHIMDSSQ	>50
CCNI-008 p6	DFLHIMDSSQLIH	20.1
CCNI-008 p7	LHIMDSSQLIHCRE	15.1
CCNI-008 p8	SSQLIHCRELVAHHL	>50
CCNI-008 p9	RELVAHHLSTLQSSL	11.4
CCNI-008 p10	LSTLQSSLPLNSVYV	>50
GAD2-003 p1	LKYAIKTGIVSSKII	37.3
GAD2-003 p2	KTGIVSSKIIKLFFR	>50
GNAS-002 p1	AQQWRRARHNYNDL	>50
GNAS-002 p2	GRRAATALLWLSCSI	>50
GNAS-002 p3	ATALLWLSCSIALLRAL	>50
GNAS-002 p4	SCSIALLRALATSNA	>50
GNAS-002 p5	IALLRALATSNAARAQ	0.02
GNAS-002 p6	AQVPESPESEDHE	>50
GNAS-002 p7	ELSLPECLEYEEEFD	>50
GNAS-002 p8	LEYEEEFDYETESE	>50
GNAS-002 p9	EEFDYETESETESE	>50
GNAS-002 p10	EFDYETESETESEIE	>50
GNAS-002 p11	ESEISETDFETEPE	>50
GNAS-002 p12	ETDFETEPETAPTTP	>50
GNAS-002 p13	GPVVPKHSTFGQSLT	>50
GNAS-002 p14	HSTFGQSLTQRLHAL	>50
GNAS-036 p1	DKQLQDEKMGYMCTH	>50
GNAS-036 p2	DEKMGYMCTHRLLL	>50
GNAS-036 p3	THRLLLLGAGESGKS	>50
GNAS-036 p4	LLGAGESGKSTIV	>50
GNAS-036 p5	STIVKQMRILHVNGF	>50
GNAS-036 p6	MRILHVNGFNGDEKA	>50
GNAS-036 p7	LKEAIETIVAAMSNL	>50
GNAS-036 p8	IETIVAAMSNLVPPV	0.15
GNAS-036 p9	ENQFRVDYILSVMNV	0.17
GNAS-036 p10	RVDYILSVMNVPDFD	10.9
GNAS-036 p11	DFDFPPEFYEHAKAL	>50
GNAS-036 p12	PEFYEHAKALWEDEG	>50
GNAS-036 p13	KALWEDEGVRACYER	>50

GNAS-036 p14	RACYERSNEYQLID	>50
GNAS-036 p15	SNEYQLIDCAQYFLD	38.6
IAPP-002 p1	SVALNHLKATPIERQ	25.4
IAPP-002 p2	IPVLSRNILLELRGA	>50
IAPP-002 p3	KSKVIRWKSGNATLP	>50
PTPRN-021 p1	AAGVKLLEILAEHVVH	>50
PTPRN-021 p2	KLLEILAEHVHMSSGS	0.02
PTPRN2-005 p1	LPPRVLPAAAPSSVPR	>50
PTPRN2-005 p2	GCLLEEGLCGASE	>50
REXO2-020 p1	ALWIVKYYSRNSVHE	>50
REXO2-020 p2	VKYYSRNSVHEDKKF	>50
SCG5-009 p1	YEKMKGGERRRK	>50
SCG5-009 p2	TRAWLDCCGDAWSFLS	>50
SCG5-009 p3	GDAWSFLSGAVNRLK	>50
SCG5-009 p4	WSFLSGAVNRLKPSL	>50
SCG5-009 p5	AVNRLKPSLVGKSQN	>50
SLC30A8-002 p1	MEFLERTYLVNDKAA	>50
SLC30A8-002 p2	RTYLVNDKAAKMYAF	0.08
SLC30A8-002 p3	AKMYAFTLESVELQQK	0.03
SLC30A8-002 p4	GGMYHCHSGSKPTEK	6.0
IAPP trans-S p1	QVFLIVLSVALKLQVF	19.9
SCG5 p1	MVSRMVSTMLSGL	2.4
SCG5 p2	SRMVSTMLSGLLFWL	>50
SCG5 p3	SGLLFWLASGWTPAF	>50
SCG5 p4	LLFWLASGWTPAFAY	>50
SCG5 p5	EADIQRLLHGVMEQL	>50
SCG5 p6	QRLLHGVMEQLGIAR	16.9
SCG5 p7	RVEYPAHQAMNLVGP	>50
SCG5 p8	HEGLQHLGPFGNIPN	>50
SCG5 p9	LQHLGPFGNIPNIVA	>50
SCG5 p10	LGPFGNIPNIVAEIT	>50
SCG5 p11	IPNIVAEITGDNIPK	>50
SCG5 p12	PKDFSEDQGYDPDPN	>50
SCG5 p13	TAEFSREFQLHQHLF	0.05
SCG5 p14	SREFQLHQHLFDPEH	>50
SCG5 p15	QHLFDPEHDYPGLGK	>50
SCG5 p16	KLLYEKMKGGERRRK	>50
SCG5 p17	NVVAKKSVPHFSDDED	>50
UCN3 P1	PVHFLLLLLLLLLGG	16.8
UCN3 P2	PHKFYKAKPIFSCLN	33.4
UCN3 P3	KPIFSCLNTALSEAE	0.34
UCN3 P4	KRSFHYLRSRDAS	>50
UCN3 P5	SFHYLRSRDASSGEE	0.94
UCN3 P6	KKTFPISGARGGARG	>50

UCN3 P7	RTKFTLSLDVPTNIM	7.3
UCN3 P8	SLDVPTNIMNLLFNI	>50
UCN3 P9	PTNIMNLLFNIAKAK	>50
UCN3 P10	LFNIAKAKNLRAQAA	0.05
UCN3 P11	AKNLRAQAAANAHLM	>50
PCSK2 p1	GGCVSQWKAAAGFLF	>50
PCSK2 p2	AAGFLFCVMVFASAE	>50
PCSK2 p3	GFLFCVMVFASAERP	>50
PCSK2 p4	RPVFTNHFLVELHKG	>50
PCSK2 p5	HFLVELHKGGEDKAR	0.32
PCSK2 p6	GFGVRKLPFAEGLYH	>50
PCSK2 p7	LYHFYHNGLAKAKRR	>50
PCSK2 p8	RVKMALQQEGFDRKK	>50
PCSK2 p9	KRGYRDINEIDINMN	>50
PCSK2 p10	RDINEIDINMNDPL	>50
PCSK2 p11	EIDINMNDPLFTKQW	>50
PCSK2 p12	DPLFTKQWYLINTGQ	>50
PCSK2 p13	TKQWYLINTGQADGT	0.13
PCSK2 p14	AEAWELGYTGKGVTI	>50
PCSK2 p15	GVTIGIMDDGIDYLH	>50
PCSK2 p16	HPDLASNYNAEASYD	>50
PCSK2 p17	ASNYNAEASYDFSSN	>50
PCSK2 p18	SYDFSSNDPYPYPRY	>50
PCSK2 p19	YPRYTDDWFNSHGTR	>50
PCSK2 p20	DDWFNSHGTRCAGEV	>50
PCSK2 p21	AGEVSAAANNNICGV	>50
PCSK2 p22	NNNICGVGVAYNSKV	>50
PCSK2 p23	QPFMTDIEASSISH	0.07
PCSK2 p24	MTDIEASSISHMPQ	>50
PCSK2 p25	ISHMPQLIDIYSASW	>50
PCSK2 p26	LIDIYSASWGPTDNG	>50
PCSK2 p27	SASWGPTDNGKTVDG	>50
PCSK2 p28	ELTLQAMADGVNKGR	>50
PCSK2 p29	SIYVWASGDGGSYDD	>50
PCSK2 p30	DGYASSMWTISINS	>50
PCSK2 p31	ASSMWTISINSAIND	>50
PCSK2 p32	MWTISINSAINDGRT	>50
PCSK2 p33	TALYDESCSSTLAST	0.04
PCSK2 p34	TTDLYGNCTLRHSGT	>50
PCSK2 p35	NCTLRHSGTSAAAPE	0.83
PCSK2 p36	AGVFALALEANLGLT	7.2
PCSK2 p37	GLTWRDMQHLLTVLTS	>50
PCSK2 p38	RDMQHLLTVLTSKRN	>50
PCSK2 p39	VHQWRRNGVGLEFNH	>50

PCSK2 p40	GLEFNHLFGYGVLDA	>50
PCSK2 p41	NHLFGYGVLDAGAM	>50
PCSK2 p42	GYGVLDAGAMVKM	>50
PCSK2 p43	AKDWKTVPERFHCVG	>50
PCSK2 p44	PERFHCVGGSVQDPE	>50
PCSK2 p45	TGKLVLTLTTDACEG	2.9
PCSK2 p46	KENFVRYLEHVQAVI	>50
PCSK2 p47	VRYLEHVQAVITVN	>50
PCSK2 p48	EHVQAVITVNATTR	>50
PCSK2 p49	QAVITVNATTRGDLN	8.1
PCSK2 p50	RGDLNINMTSPMGTK	20.1
PCSK2 p51	KVGFDKWPFMTTHTW	>50
PCSK2 p52	DKWPFMTTHTWGED	>50
PCSK2 p53	PFMTTHTWGEDAR	>50
PCSK2 p54	RGTWTLELGFGVSAP	2.8
PCSK2 p55	ELGFGVSAPQKGVLK	>50
PCSK2 p56	KGVLKEWTLMLHGTQ	>50
PCSK2 p57	KEWTLMLHGTQSAPY	>50

^aIC₅₀ represents the peptide concentration that displaces half of the reference peptide.

^bPeptides selected for in vitro studies (based on IC₅₀ values) are shown in boldface.