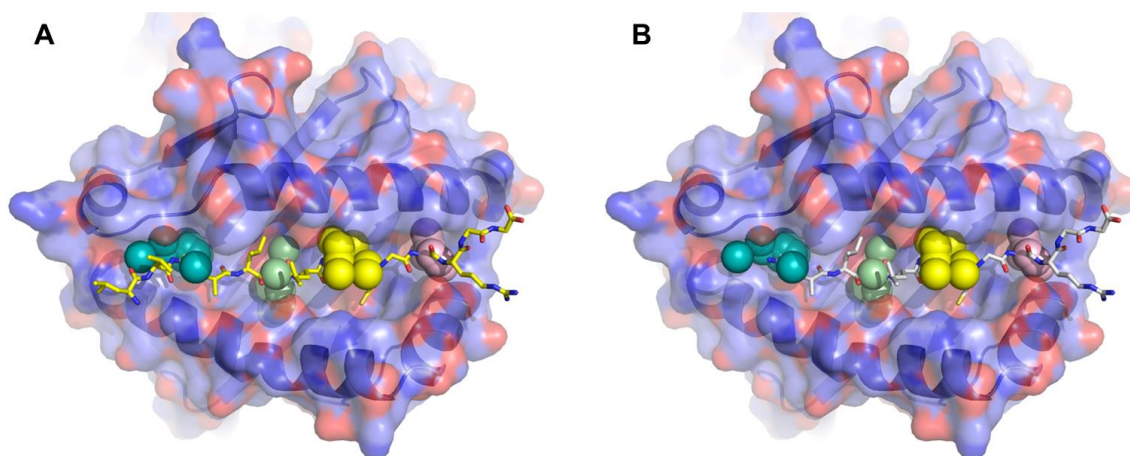
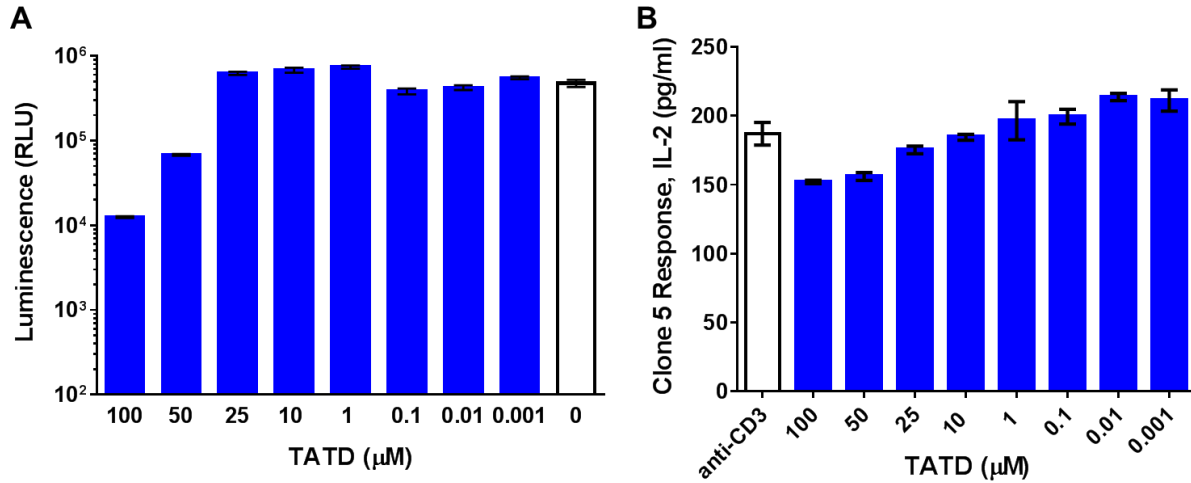


SUPPLEMENTARY DATA

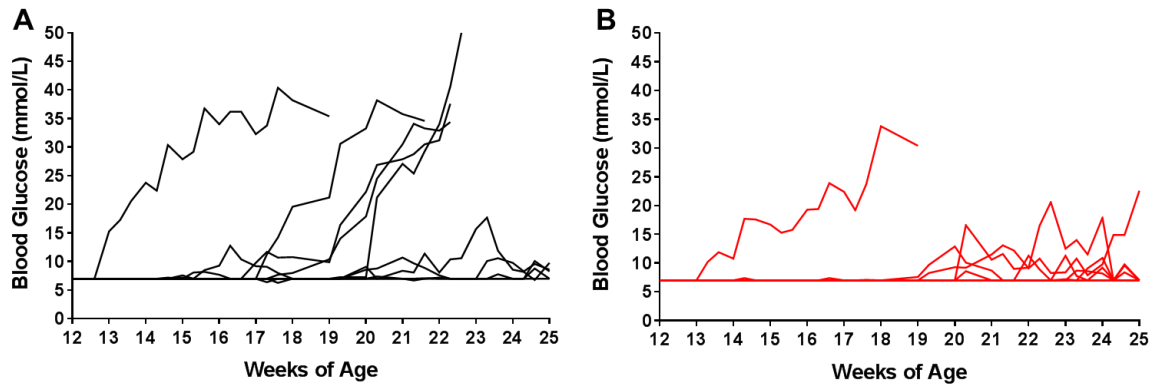
**Supplemental Figure 1. Molecular models of insulin B chain peptides bound to HLA-DQ8.**

(A) Insulin B chain amino acids 11-23 (B:11-23) and (B) B:13-23 bound to DQ8. The sites of interaction between the amino acids of the peptide to DQ8 are identical for both insulin peptides.

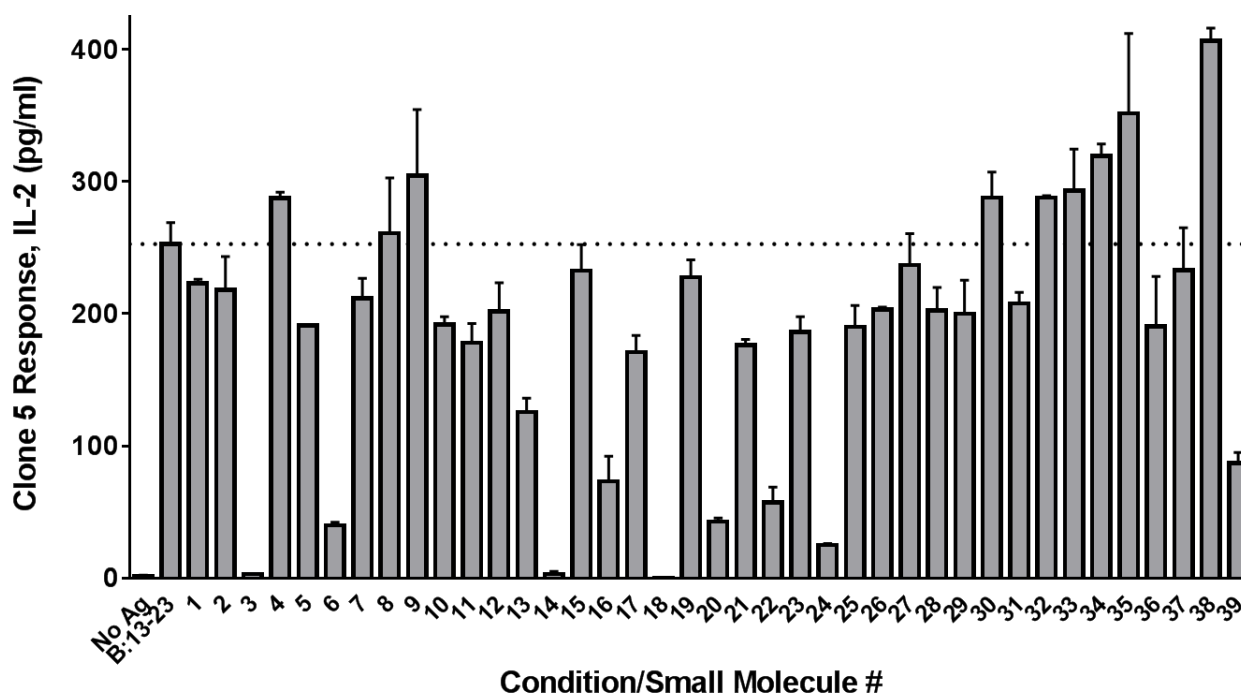
Pockets 1, 4, 6 and 9 are depicted by colored spheres.



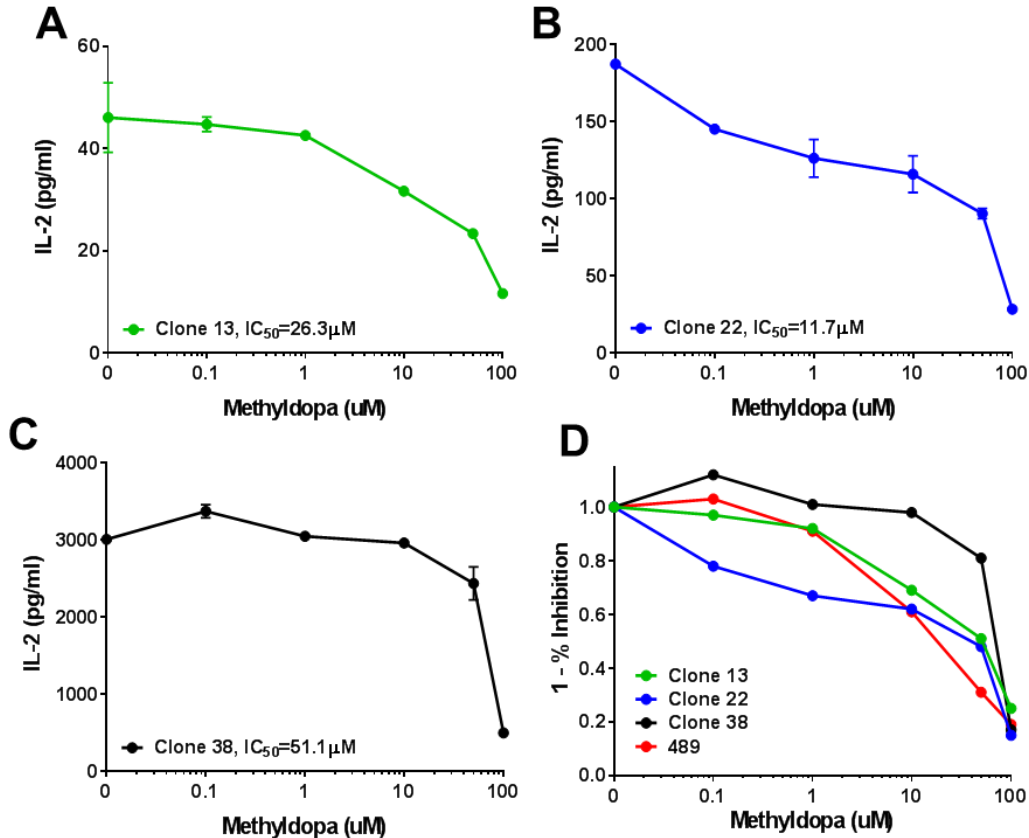
Supplemental Figure 2. Effects of TATD on in vitro cell viability and on CD3 stimulated T-cells. (A) The T-cell receptor transductant (Clone 5) was cultured in the presence of DQ8-transgenic spleen cells, insulin B:13-23 peptide and different concentrations of TATD. Cell viability was assessed with a luminescence assay that detects viable cells in culture. RLU = relative light units. (B) Clone 5 was cultured with an anti-CD3 stimulating monoclonal antibody in the presence and absence of TATD. After overnight culture, secreted IL-2 was measured in the supernatant. Data are shown as mean \pm SEM and are representative of at least three independent experiments.



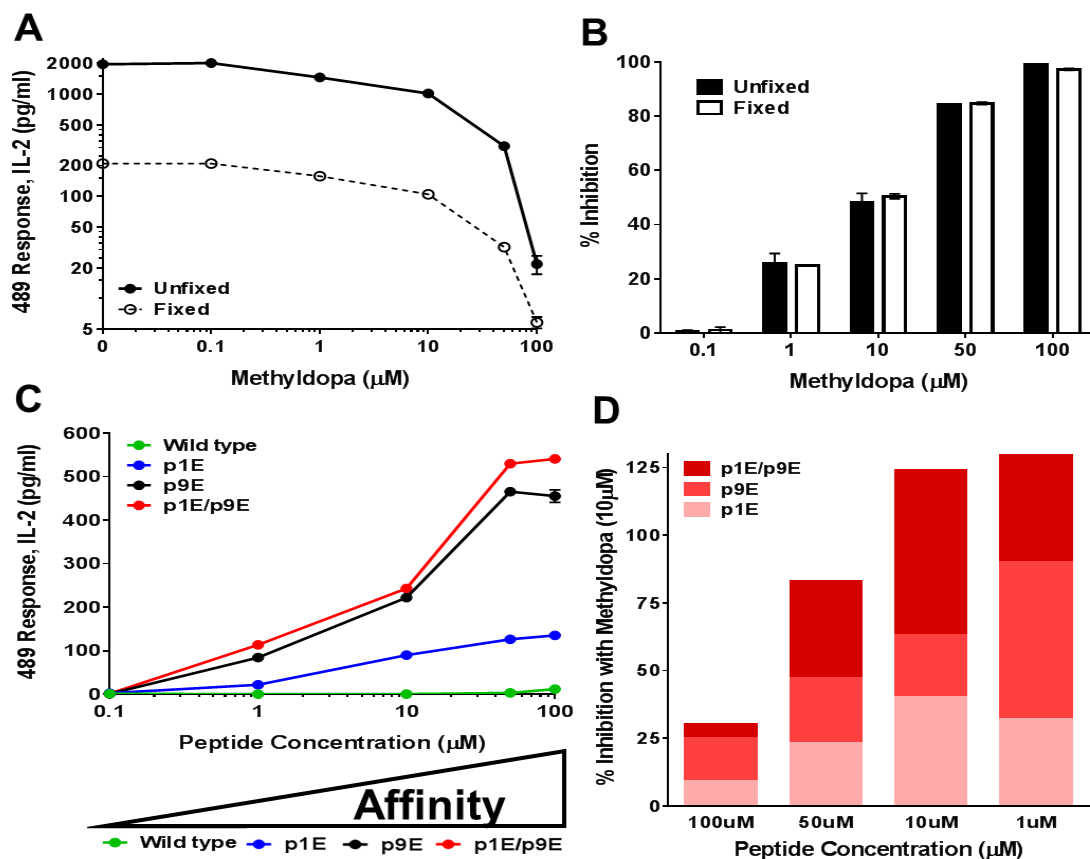
Supplemental Figure 3. TATD treatment late in the NOD disease course maintains normal blood glucose levels. Individual blood glucose data for female mice treated with (A) PBS (n=10) by intraperitoneal injection twice weekly or (B) TATD (n=9) 30mg oral gavage daily beginning at 12 weeks of age and concluding at 25 weeks. In the PBS group 6/10 mice developed overt diabetes, while 3/9 TATD treated mice developed diabetes; diabetes is defined as consecutive blood glucoses >14 mmol/L. Each line represents an individual mouse.



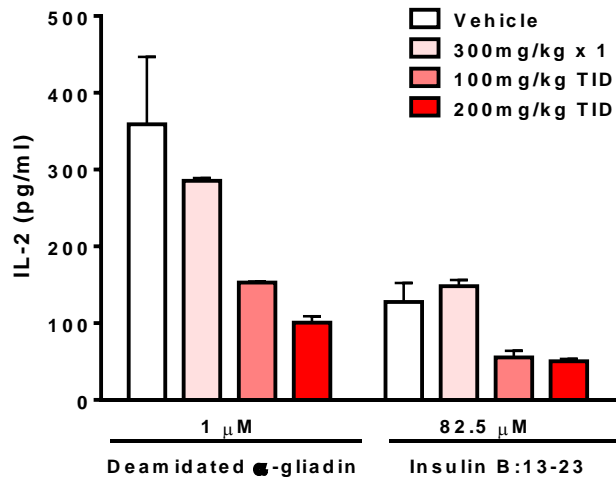
Supplemental Figure 4. In vitro screening of Food and Drug Administration (FDA) approved drugs to pocket 6 of HLA-DQ8. Clone 5 was cultured with insulin B:13-23 peptide plus individual small molecule drugs at 100 μ M in the presence of DQ8-transgenic mouse splenocytes as antigen presenting cells. Secreted IL-2 was measured in the cell culture supernatant after overnight culture using a highly sensitive ELISA assay. Numbers 1-39 depict tested compounds and responses are shown as mean \pm SEM; chemical structures are listed in Supplemental Table 5. No Ag = no antigen. Dotted line is at the IL-2 response to insulin B:13-23 alone.



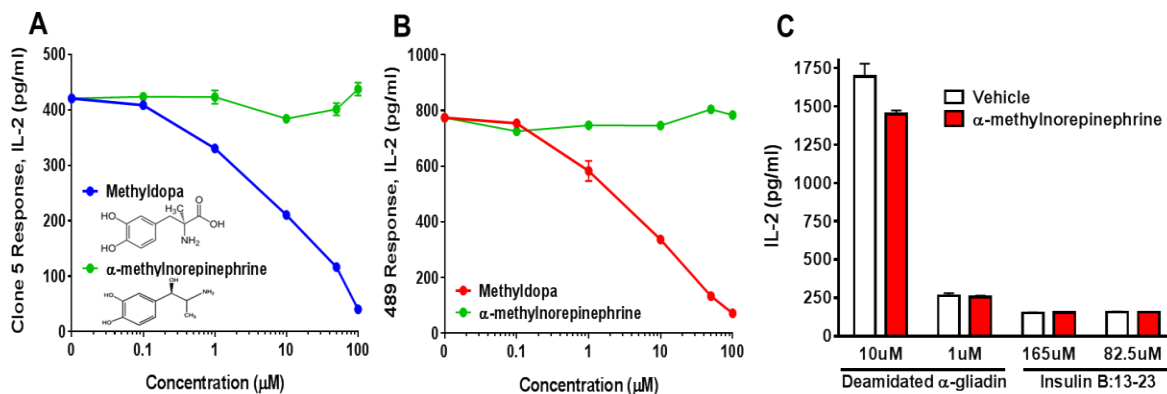
Supplemental Figure 5. Methyldopa inhibits multiple T-cell receptor (TCR) transductants restricted to the same peptide/DQ8 complex. TCR transductants were produced from the TCR α/β gene sequences for T-cell clones restricted to α -gliadin₂₂₈₋₂₄₀/DQ8; all TCR transductants respond to the double deamidated peptide SGE \underline{G} SFQPSQ \underline{E} NP. **(A)** Clone 13, **(B)** Clone 22 and **(C)** Clone 38 are all inhibited with the in vitro addition of methyldopa to varying degrees (different IC₅₀ values) despite different levels of IL-2 response to α -gliadin/DQ8. **(D)** Comparison of percent inhibition with methyldopa for the four TCR transductants including 489 with that inhibition curve depicted in Fig. 3C. Data is shown as mean \pm SEM and representative of at least three independent experiments.



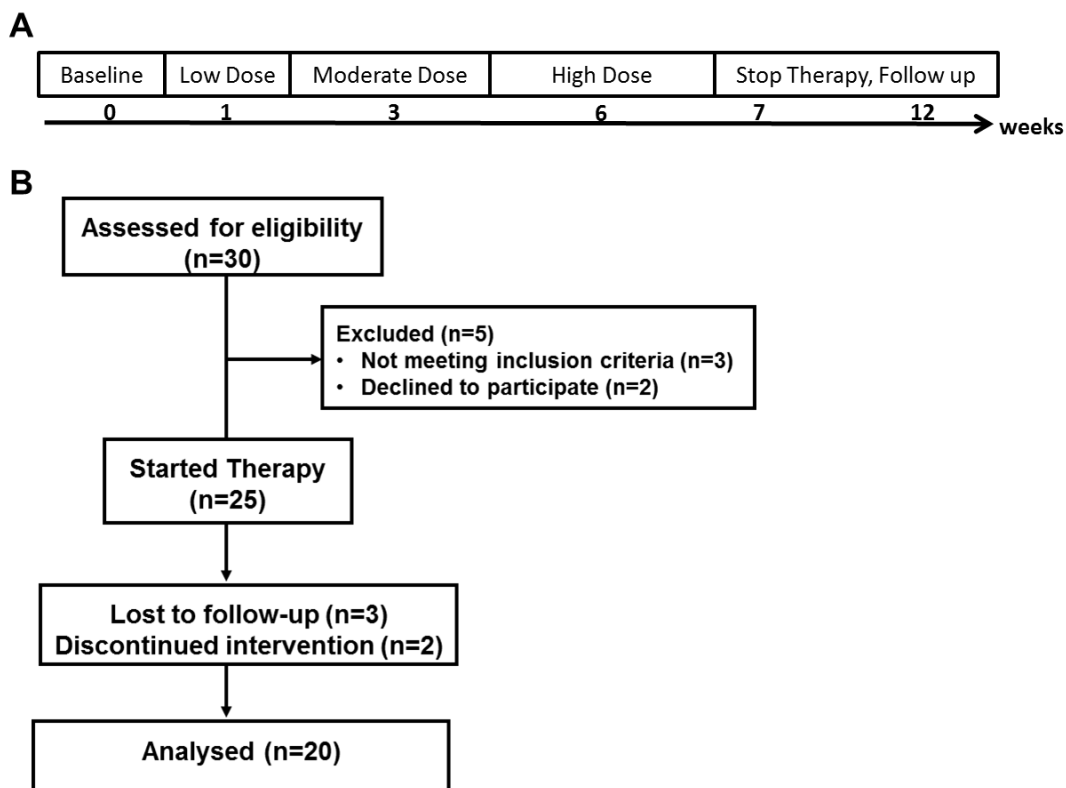
Supplemental Figure 6. Methyldopa acts on the cell surface to inhibit a TCR response based upon peptide affinity for DQ8. Artificial antigen presenting cells (APCs) expressing DQ8 (murine B cell line, M12C3, transduced with DQ8) were fixed with glutaraldehyde to prevent intracellular antigen processing. **(A)** Methyldopa inhibits 489 response in the presence of deamidated α -gliadin (10 μM) with both fixed and unfixed APCs. **(B)** The percentage of inhibition is similar between fixed and unfixed APCs. **(C)** 489 responds to a dose titration of α -gliadin₂₂₈₋₂₄₀ peptides presented by unfixed DQ8 APCs with a hierarchy of response based upon the number and position of deamidations (Q \rightarrow E). **(D)** 489 was cultured in the presence of DQ8 APCs with different peptide concentrations plus a fixed amount of methyldopa (10 μM); the percentage of inhibition for a given peptide is depicted at each in vitro concentration. Data is shown as mean \pm SEM representative of at least three independent experiments.



Supplemental Figure 7. In vivo dose finding studies with methyldopa in DQ8-transgenic mice. DQ8-transgenic mice were gavaged with vehicle or defined dose(s) of methyldopa in a 24 hour time period (n=2 per group). Ex vivo splenocytes were then used as APCs to present a deamidated α-gliadin peptide or insulin B:13-23 to 489 or Clone 5, respectively, with secreted IL-2 measured as the readout. No methyldopa was added to the in vitro culture. The concentration of in vitro added peptide is shown on the graph. Data are shown as mean ± SEM.

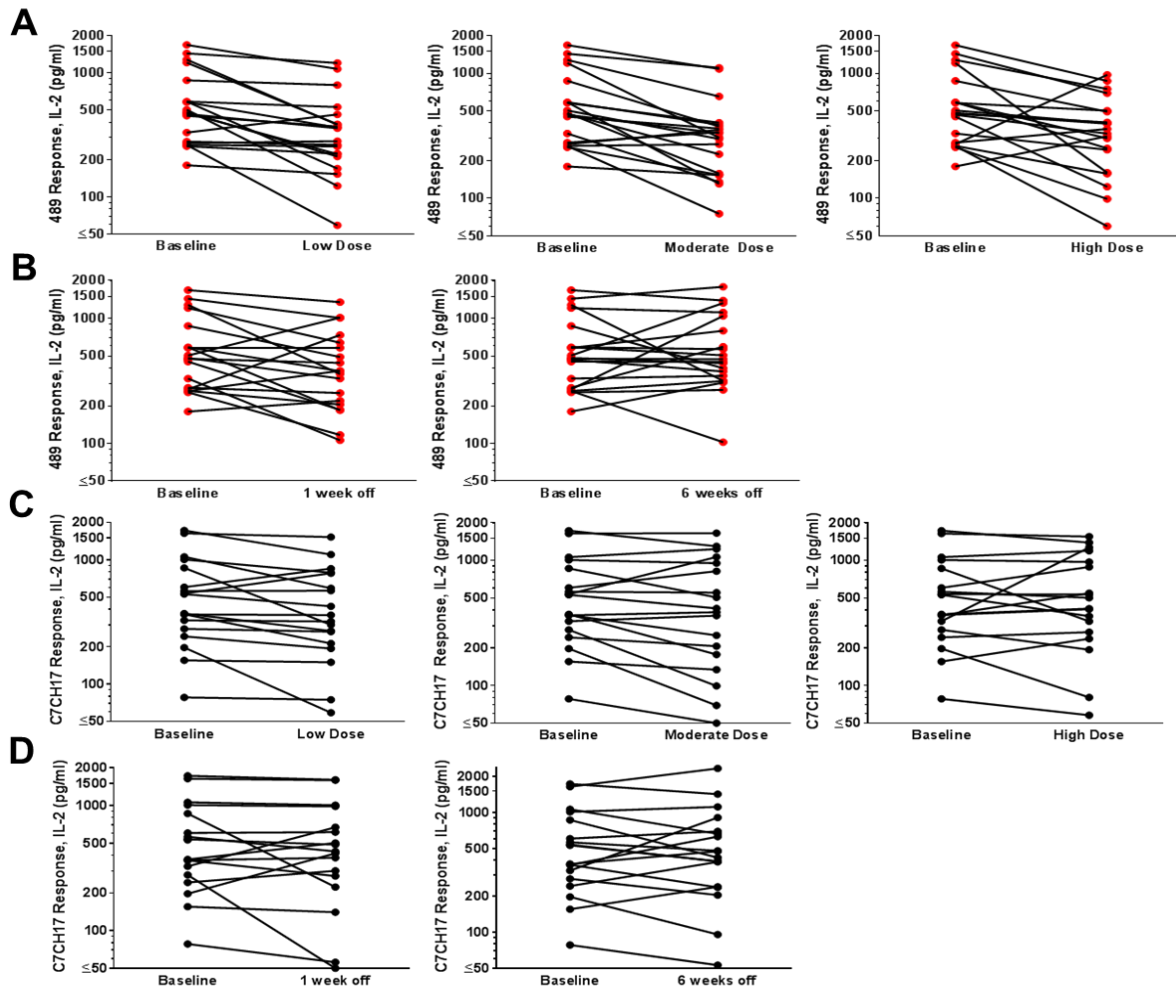


Supplemental Figure 8. A metabolite of methyldopa, α -methylnorepinephrine, does not block DQ8 restricted T-cell responses in vitro or in vivo. α -methylnorepinephrine is a major metabolite of methyldopa, which agonizes central α_2 adrenergic receptors resulting in blood pressure lowering. The metabolite is structurally similar to methyldopa but does not block (A) Clone 5 or (B) 489 when dose titrated into T-cell receptor transductant stimulation assays. Dose titrations of methyldopa were performed in the same assays. Data is shown as mean \pm SEM and representative of at least three independent experiments. (C) DQ8-tansgenic mice were gavaged with vehicle (n=4) or 50mg/kg α -methylnorepinephrine (n=3) three times daily for four days. Their ex vivo splenocytes were used as APCs to present different concentrations of deamidated α -gliadin or insulin B:13-23 to 489 or Clone 5, respectively. Data is shown as mean \pm SEM.

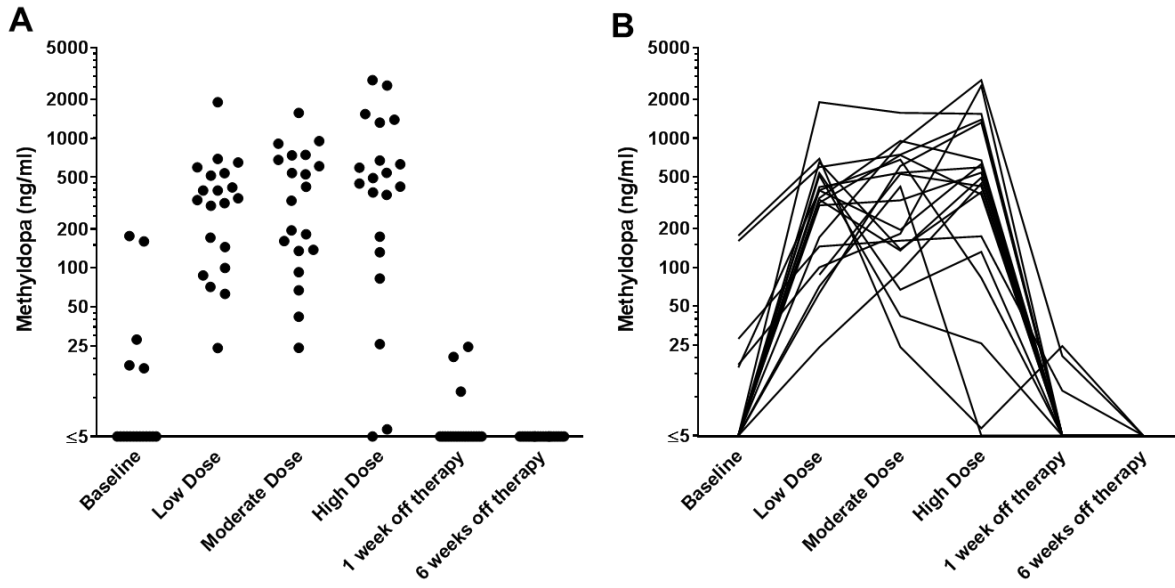


Supplemental Figure 9. Schema of study design with visits and consort flow diagram. (A)

The methyldopa intervention study was designed as a single-arm open-label dose escalation trial. Main inclusion criteria included American Diabetes Association diagnostic criteria for type 1 diabetes within the last 2 years, ages 18-45 years old, HLA-DQ8 (DQA1*03:01-DQB1*03:02) present and random C-peptide ≥ 0.1 ng/ml (a measure of residual endogenous insulin production). Each study participant served as their own control and there were 6 visits over a 12-week time period. All participants self-administered oral methyldopa (Aldomet) 500mg tablets at three separate doses: low dose = 500mg twice daily, moderate dose = 500mg three times daily and high dose = 2-3 grams divided daily. These doses did not exceed the maximum recommended doses for use as an antihypertensive agent. **(B)** Consort diagram of study participants assessed for eligibility, allocated to treatment, follow-up and analyzed. Three study participants were lost to follow-up and two withdrew from the study due to time constraints.

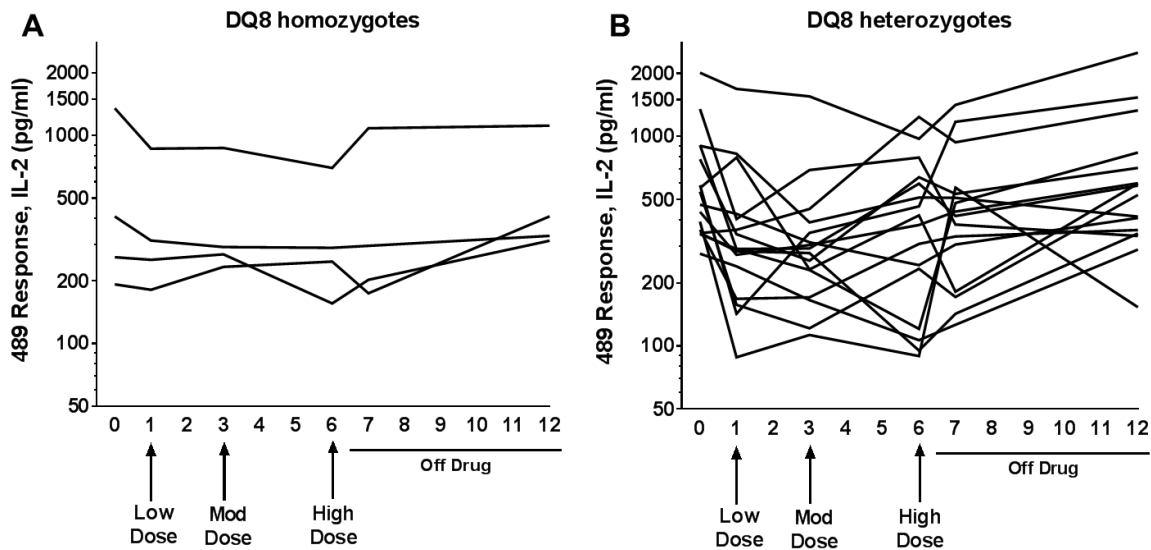


Supplemental Figure 10. Methyldopa treatment specifically blocks DQ8 antigen presentation in peripheral blood mononuclear cells from recent-onset type 1 diabetes patients with the DQ8 allele. Participants' cryopreserved peripheral blood mononuclear cells were used as antigen presenting cells to present cognate peptide to a given T-cell receptor (TCR) transductant. Secreted IL-2 after overnight culture was measured with a sensitive ELISA assay. Individual study subject responses to (**panel A**) 489 (TCR transductant restricted to deamidated α -gliadin/DQ8) comparing baseline to different drug doses and (**panel B**) baseline to time points off drug. Individual subject responses to (**panel C**) C7CH17 (TCR transductant restricted to HA₃₀₆₋₃₁₈/DR4) comparing baseline to drug doses and (**panel D**) baseline to time points off drug. Data are shown as a mean from triplicate wells at each time point during the study. Lines connect the same study participant.

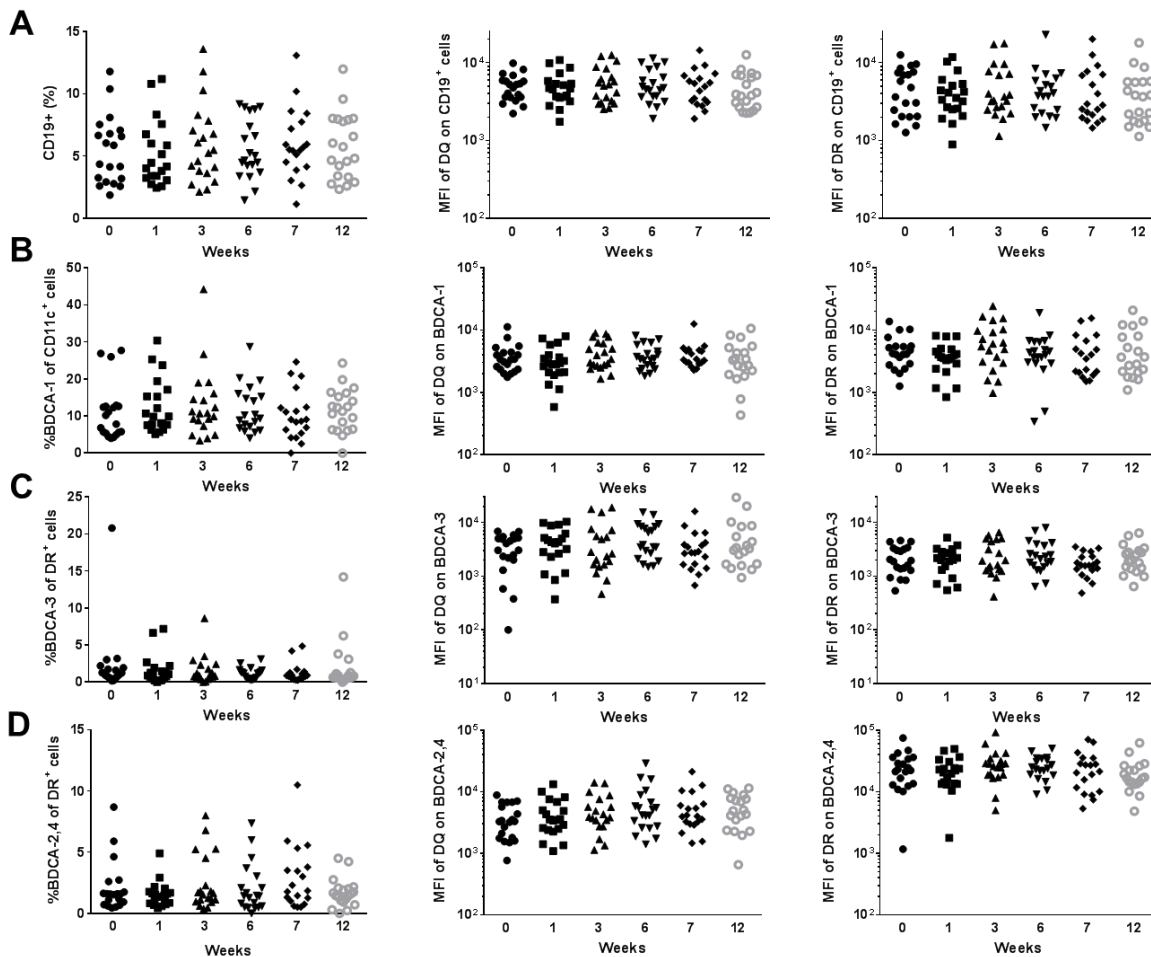


Supplemental Figure 11. Methyldopa levels measured from plasma of study participants.

Using liquid chromatography tandem mass spectrometry (LCMS), standard curves were generated for methyldopa and positive ion electrospray ionization mass spectra were obtained for each study sample (1:1 phosphate buffered saline diluted plasma). Sample collection was not timed to the last study drug administration; these assays were done to assess compliance with taking methyldopa during the study. **(A)** Methyldopa levels from study subjects at each of the six study visits. **(B)** Individual measurements throughout the study. Lower limit of detection ≤ 5 ng/ml. Low dose = 500mg twice daily, moderate dose = 500mg three time daily and high dose = 2-3 grams divided daily.

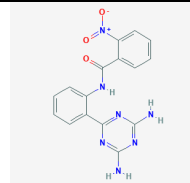
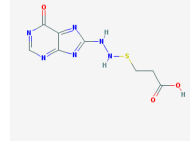
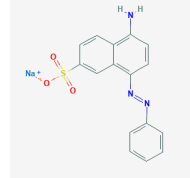
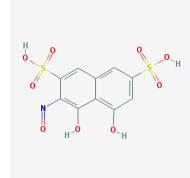
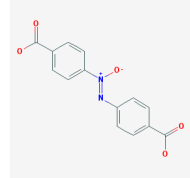
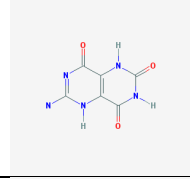
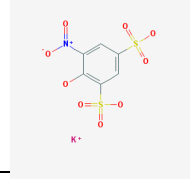
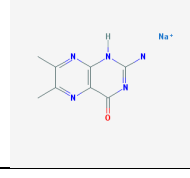


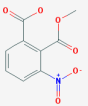
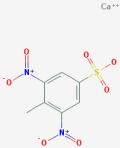
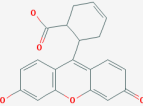
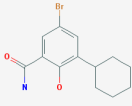
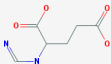
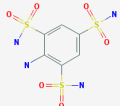
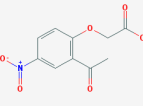
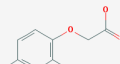
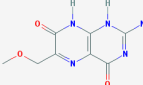
Supplemental Figure 12. DQ8 dose effect on the ability to block DQ8 antigen presentation in methyldopa treated study participants. Comparison of (A) DQ8 homozygotes (n=4) to (B) heterozygotes (n=16) in terms of response to the 489 T-cell receptor (TCR) transductant, which is restricted to deamidated α -gliadin/DQ8, throughout the study. Participants' cryopreserved peripheral blood mononuclear cells were used as antigen presenting cells to present cognate peptide to the 489 TCR transductant. Secreted IL-2 after overnight culture was measured with a sensitive ELISA assay. Each line represents an individual study participant.

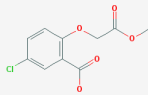
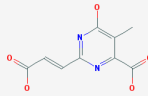
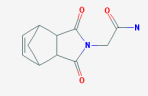
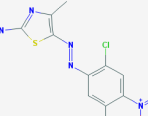
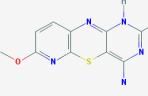
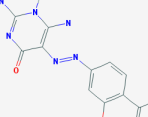
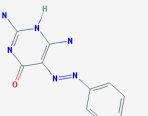
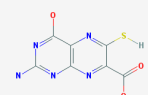
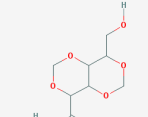



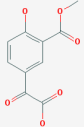
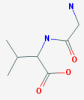
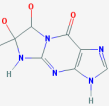
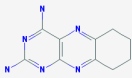
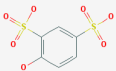
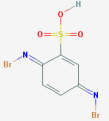
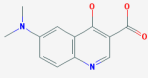
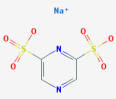
Supplemental Figure 13. Flow cytometry analysis of antigen presenting cells in the peripheral blood of methyldopa treated subjects throughout the study. Freshly isolated peripheral blood mononuclear cells were stained for cell surface markers corresponding to (**panel A**) B-cells, (**panels B, C**) myeloid dendritic cells and (**panel D**) plasmacytoid dendritic cells. Each panel shows the percentage of antigen presenting cells, followed by the mean fluorescent intensity of DQ and DR on the cell population.

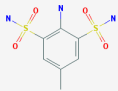
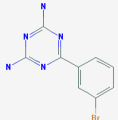
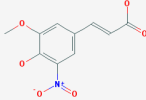
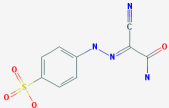
Supplemental Table 1. HLA-DQ8 pocket 1 top scoring in silico small molecules from the NIH Developmental Therapeutics Program chemical repository that were screened in vitro.

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1	138669		421786	-35.6 (#2)
2	46611		5856603	-34.3 (#3)
3**	45552		23679260	-32.8 (#4)
4	68045		412541	-32.4 (#5)
5	24947		68494	-31.3 (#7)
6	96656		262721	-31.3 (#8)
7	166346		54602266	-31.2 (#9)
8	146785		54608366	-31.2 (#10)

9	52151		243002	-31.2 (#11)
10	29033		54609354	-31.0 (#12)
11	157411		291857	-30.8 (#13)
12	7420		222105	-30.7 (#14)
13	334078		909	-30.6 (#15)
14	25857		230714	-30.5 (#16)
15	624899		361681	-30.5 (#17)
16	402434		53598	-30.4 (#18)
17	18694		227247	-30.2 (#19)

18	168957		297698	-30.2 (#20)
19	236671		5458452	-30.2 (#21)
20	241483		315734	-30.2 (#22)
21	137635		54610224	-30.1 (#23)
22	194985		73007	-30.1 (#24)
23	84120		6143498	-30.1 (#25)
24	1582		5921960	-29.9 (#26)
25	265215		5244562	-29.8 (#28)
26	16675		408896	-29.8 (#29)

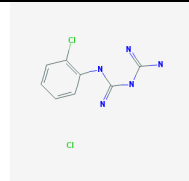
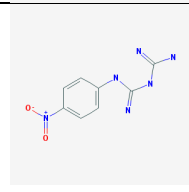
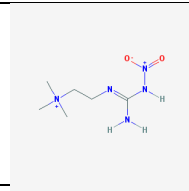
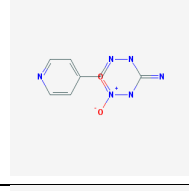
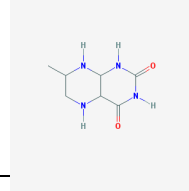
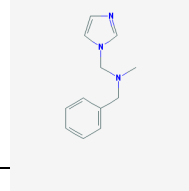
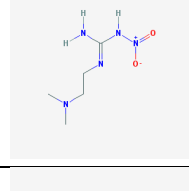
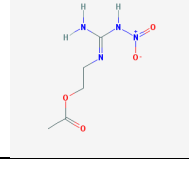
27	53040		243357	-29.7 (#30)
28	47043		240618	-29.8 (#31)
29	83255		97417	-29.6 (#32)
30	310778		5384166	-29.6 (#33)
31	501532		349999	-29.5 (#34)
32	9798		66787	-29.5 (#35)
33	344501		9573814	-29.4 (#36)
34	366390		339510	-29.4 (#37)
35	156622		54610506	-29.4 (#38)

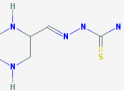

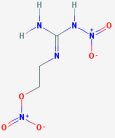
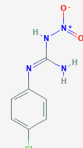

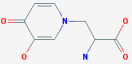
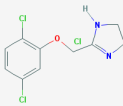
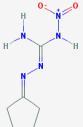
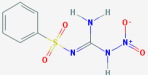
36	163632		294715	-29.3 (#39)
37	118753		273483	-29.3 (#40)
38	16686		5354666	-29.3 (#41)
39	176297		6377127	-29.3 (#42)

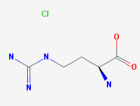
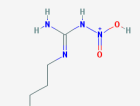
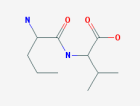
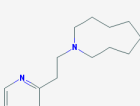
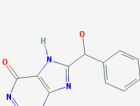
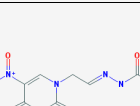
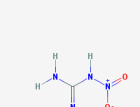
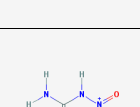

*NSC (National Service Center) identifiers for substances submitted to the National Cancer Institute, Developmental Therapeutics Program. Website to obtain further compound information (<https://dtp.cancer.gov/dtpstandard/ChemData/index.jsp>).

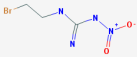
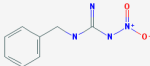
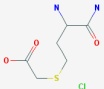

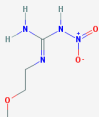
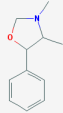
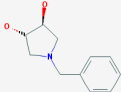
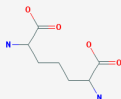
**Increased T-cell response in the screening assay above that of insulin peptide alone; presence of peptide was necessary to elicit an IL-2 response.

Supplemental Table 2. HLA-DQ8 pocket 4 top scoring in silico small molecules from the NIH Developmental Therapeutics Program chemical repository that were screened in vitro.

Number	NSC Identifier*	Chemical Structure	PubChem CID	Molecular docking score (rank)
1	44456		2730222	-37.9 (#1)
2	34785		20322	-35.9 (#2)
3	172832		425320	-35.8 (#3)
4	1529		54611695	-35.4 (#4)
5	129578		279241	-35.0 (#5)
6	116532		272244	-35.0 (#6)
7	206150		427023	-34.7 (#7)
8	35895		411794	-34.7 (#8)

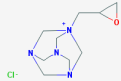
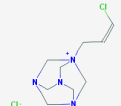
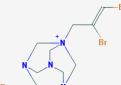
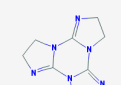
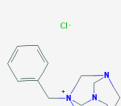
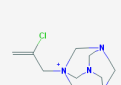
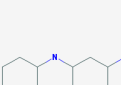

9	91090		9552109	-34.0 (#10)
10	62497		3053359	-33.5 (#11)
11	40588		412620	-33.4 (#12)
12	132372		40466	-33.2 (#13)
13	112772		24190696	-33.1 (#14)
14	69188		3862	-33.1 (#15)
15	167746		24194385	-33.1 (#16)
16	157959		5717606	-33.0 (#17)
17	137950		24192331	-32.9 (#18)

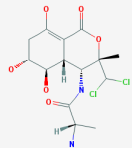
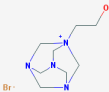

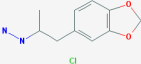
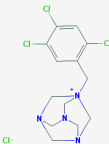
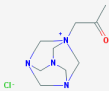
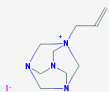


18	374666	 <chem>NC(=O)NCCCl</chem>	24200451	-32.9 (#19)
19	35894	 <chem>NC(=O)NCCCl</chem>	6332033	-32.8 (#20)
20	319055	 <chem>NC(=O)NCCCl</chem>	330454	-32.7 (#21)
21	19006	 <chem>NC(=O)NCCCl</chem>	227431	-32.6 (#22)
22	85786	 <chem>NC(=O)NCCCl</chem>	5127022	-32.5 (#23)
23	89799	 <chem>NC(=O)NCCCl</chem>	9568312	-32.3 (#24)
24	137952	 <chem>NC(=O)NCCCl</chem>	421691	-32.2 (#25)
25	137975	 <chem>NC(=O)NCCCl</chem>	5752031	-32.1 (#27)
26	49798	 <chem>NC(=O)NCCCl</chem>	413577	-32.1 (#28)



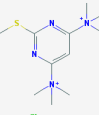
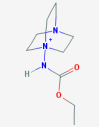


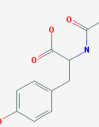


27	36872		412037	-31.9 (#29)
28	10386		79438	-31.9 (#30)
29	320034		24199275	-31.7 (#31)
30	24527		12562407	-31.5 (#33)
31	34697		411483	-31.5 (#34)
32	354435		434666	-31.5 (#35)
33	603628		353977	-31.5 (#36)
34	206289		865	-31.4 (#37)


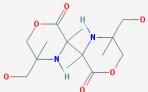


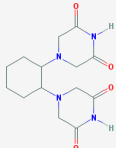
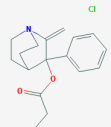
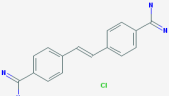
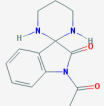
*NSC (National Service Center) identifiers for substances submitted to the National Cancer Institute, Developmental Therapeutics Program. Website to obtain further compound information (<https://dtp.cancer.gov/dtpstandard/ChemData/index.jsp>).

Supplemental Table 3. HLA-DQ8 pocket 6 top scoring in silico small molecules from the NIH Developmental Therapeutics Program chemical repository that were screened in vitro.

Number	NSC Identifier*	Chemical Structure	PubChem CID	Molecular docking score (rank)
1	177979		24195292	-40.3 (#2)
2	172971		6435993	-39.9 (#3)
3	168615		54612368	-39.2 (#5)
4	53040		243357	-39.2 (#6)
5	10408		12645659	-38.9 (#7)
6	172855		59114	-38.6 (#8)
7	667746		381308	-38.0 (#9)
8	30049		10355477	-38.0 (#10)

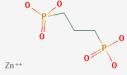
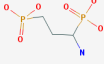
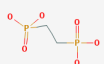

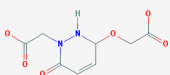
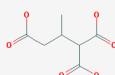
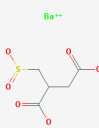
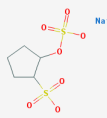
9	325014		54676871	-37.8 (#11)
10	206142		24195918	-36.7 (#13)
11	203305		24195881	-36.5 (#14)
12	23429		54608325	-36.5 (#15)
13	155877		21144519	-36.4 (#16)
14	177977		24195291	-35.9 (#17)
15	5062		2827274	-35.7 (#18)
16	130818		279615	-35.4 (#20)
17	163897		54606769	-35.4 (#21)


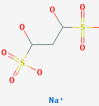
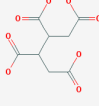
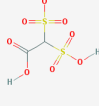
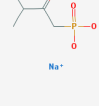
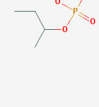
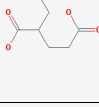
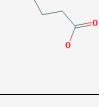
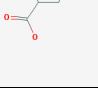
18	137877		283346	-35.3 (#22)
19	100731		86889	-35.2 (#23)
20	49716		54609783	-35.1 (#24)
21	259711		429590	-34.7 (#25)
22	302851		327510	-34.4 (#26)
23	404874		346598	-34.4 (#27)
24	83260		256410	-34.3 (#28)
25	179805		24195325	-33.7 (#30)
26	7308		64159	-33.7 (#31)

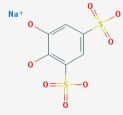

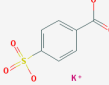

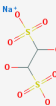

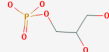
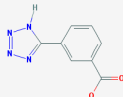

27	621512		359895	-33.7 (#32)
28	372109		127384	-33.6 (#33)
29	4436		87571	-33.6 (#34)
30	193502		303819	-33.5 (#35)
31	134695		281808	-33.5 (#36)
32	170540		24194660	-33.4 (#37)
33	35605		54601068	-33.4 (#38)
34	124145		276387	-33.4 (#39)

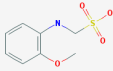

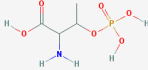

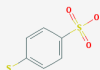
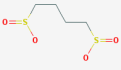
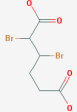
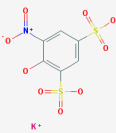
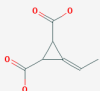
*NSC (National Service Center) identifiers for substances submitted to the National Cancer Institute, Developmental Therapeutics Program. Website to obtain further compound information (<https://ntp.cancer.gov/ntpstandard/ChemData/index.jsp>).

Supplemental Table 4. HLA-DQ8 pocket 9 top scoring in silico small molecules from the NIH Developmental Therapeutics Program chemical repository that were screened in vitro.

Number	NSC Identifier*	Chemical Structure	PubChem CID	Molecular docking score (rank)
1	407817		54607957	-42.1 (#1)
2	133881		281247	-38.2 (#3)
3	40837		80247	-37.9 (#4)
4	608071		355088	-36.8 (#5)
5	21415		228462	-36.5 (#6)
6	25950		230738	-36.4 (#7)
7	244047		54607157	-36.2 (#8)
8	101358		24190131	-35.6 (#9)

9	24681		230123	-35.4 (#11)
10	18259		54605027	-35.2 (#13)
11	21371		15560	-35.1 (#14)
12	243618		428822	-35.0 (#15)
13	320310		54601833	-34.9 (#18)
14	41912		237877	-34.9 (#19)
15	8447		222467	-34.6 (#20)
16	133883		98450	-34.5 (#21)
17	72272		14308	-34.5 (#22)

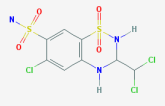
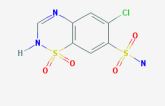
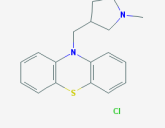
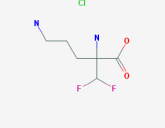
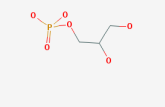
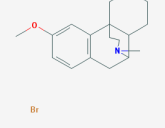
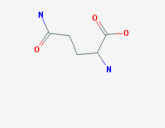
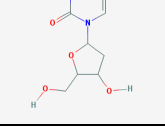
18	12861	 <chem>[Na+].[Na+].[O-]S(=O)(=O)c1ccc(cc1)[B-](O)(O)Oc2ccc(cc2)S(=O)(=O)[O-]</chem>	24181945	-34.3 (#24)
19	36997	 <chem>O=C(O)c1ccc(cc1)[B-](O)(O)Oc2ccc(cc2)C(=O)O</chem>	370	-34.1 (#25)
20	4862	 <chem>[K+].[O-]C(=O)c1ccc(cc1)S(=O)(=O)[O-]</chem>	19038728	-34.0 (#27)
21	35597	 <chem>[Na+].[O-]S(=O)(=O)c1c(I)cc(I)c(I)c1</chem>	54605355	-33.9 (#28)
22	18262	 <chem>[Na+].[O-]S(=O)(=O)c1ccc(cc1)[B-](O)(O)Oc2ccc(cc2)S(=O)(=O)[O-]</chem>	54602188	-33.9 (#29)
23	282051	 <chem>[Na+].[O-]C(=O)c1nc2c(n1)CC(S(=O)(=O)[O-])N2</chem>	54601982	-33.9 (#30)
24	9231	 <chem>[Na+].[O-]C(=O)c1nc2c(n1)CC(S(=O)(=O)[O-])N2</chem>	754	-33.8 (#31)
25	338094	 <chem>[Na+].[O-]C(=O)c1nc2c(n1)CC(S(=O)(=O)[O-])N2</chem>	333942	-33.8 (#32)
26	128066	 <chem>[Na+].[O-]C(=O)c1nc2c(n1)CC(S(=O)(=O)[O-])N2</chem>	278442	-33.8 (#33)

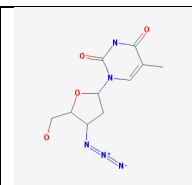
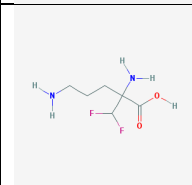
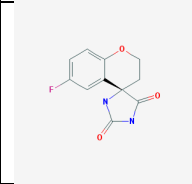
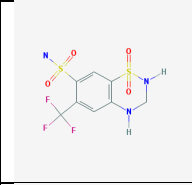
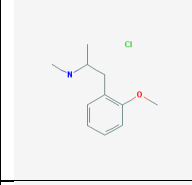
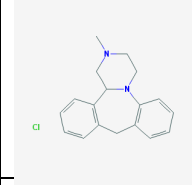
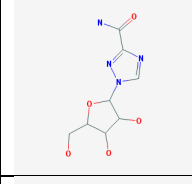
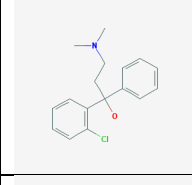
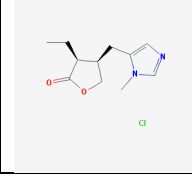
27	7549		7126	-33.8 (#34)
28	30078		3857	-33.7 (#35)
29	89296		1016	-33.7 (#36)
30	117802		272987	-33.6 (#37)
31**	127168		97488	-33.6 (#38)
32	51047		242438	-33.6 (#39)
33	133387		45072	-33.5 (#40)
34	166346		54602266	-33.4 (#41)
35	179410		301548	-33.4 (#42)

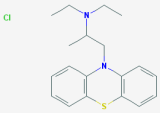

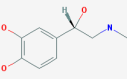
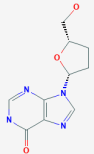

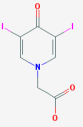
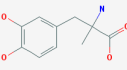
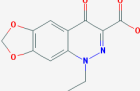

*NSC (National Service Center) identifiers for substances submitted to the National Cancer Institute, Developmental Therapeutics Program. Website to obtain further compound information (<https://dtp.cancer.gov/dtpstandard/ChemData/index.jsp>).

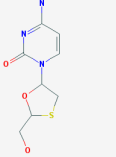
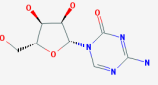
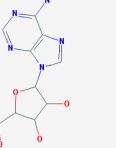
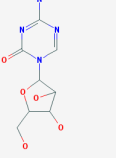
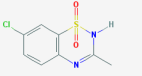
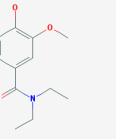
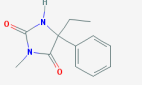
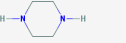
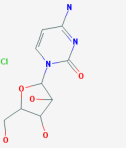
**Increased T-cell response in the screening assay without the addition of insulin peptide.

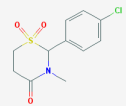
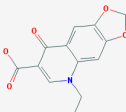
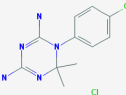
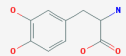
Supplemental Table 5. HLA-DQ8 pocket 6 top scoring in silico Food and Drug Administration (FDA) Approved small molecule drugs that were screened in vitro.

Number	NSC Identifier*	Chemical Structure	PubChem CID	Molecular docking score (rank)
1	61560		5560	-32.1 (#1)
2	25693		2720	-28.9 (#2)
3	169091		14676	-27.5 (#4)
4	270295		57004	-27.1 (#5)
5	9231		754	-27.0 (#6)
6	50381		11957506	-26.8 (#7)
7	27421		738	-26.7 (#8)
8	66259		3363	-26.5 (#9)

9	602670		5726	-26.1 (#10)
10	337250		3009	-25.7 (#12)
11	355082		337359	-25.6 (#13)
12	44627		3647	-25.4 (#14)
13	65644		9859211	-25.4 (#15)
14	292267		68551	-25.3 (#16)
15	163039		5064	-25.0 (#18)
16	113595		2795	-25.0 (#19)
17	5746		5909	-24.9 (#20)

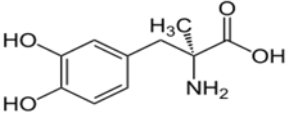
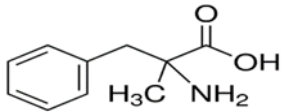
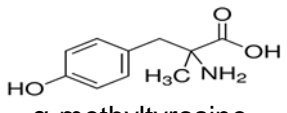
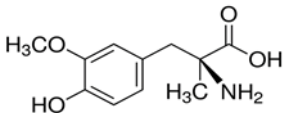
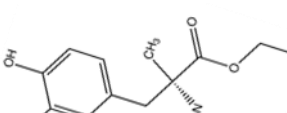
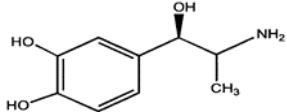
18	64074		122824	-24.7 (#21)
19	120735		4786	-24.5 (#22)
20	62786		247704	-24.4 (#23)
21	612049		50599	-24.2 (#24)
22	8704		3728	-24.1 (#26)
23	60718		9304	-24.1 (#27)
24	169916		4138	-23.9 (#28)
25	304467		2762	-23.8 (#29)
26	27690		231285	-23.7 (#30)

27	620753		3877	-23.7 (#31)
28	102816		9444	-23.6 (#32)
29	7652		191	-23.5 (#35)
30	281272		1805	-23.5 (#36)
31	76130		3019	-23.4 (#38)
32	406087		9363	-23.4 (#39)
33	34652		4060	-23.4 (#40)
34	474		4837	-23.4 (#41)
35	63878		63878	-23.3 (#42)

36	169108		2717	-23.1 (#45)
37	110364		4628	-23.1 (#47)
38	3074		9048	-23.0 (#48)
39	118368		836	-23.0 (#51)

*NSC (National Service Center) identifiers for substances submitted to the National Cancer Institute, Developmental Therapeutics Program. Website to obtain further compound information (<https://dtp.cancer.gov/dtpstandard/ChemData/index.jsp>).

Supplemental Table 6. Structure of Methyl dopa and Derivatives

Chemical Structure and Name*	Clone 5 (insulin/DQ8)	489 (α -gliadin/DQ8)
 <p>α-methyl dopa, 2-amino-3-(3,4-dihydroxyphenyl)-2-methylpropanoic acid</p>	Inhibition	Inhibition
 <p>α-methylphenylalanine, 2-amino-2-methyl-3-phenylpropanoic acid</p>	No inhibition	No inhibition
 <p>α-methyltyrosine, 2-amino-3-(4-hydroxyphenyl)-2-methylpropanoic acid</p>	No inhibition	No inhibition
 <p>3-O-methyl methyl dopa, 2-amino-3-(4-hydroxy-3-methoxyphenyl)propanoic acid</p>	No inhibition	No inhibition
 <p>α-methyl dopa ethyl ester, Ethyl-2-amino-3-(3,4 dihydroxyphenyl)-2-methylpropanoate</p>	Inhibition	Inhibition
 <p>α-methylnorepinephrine, 4-(2-amino-1-hydroxypropyl)benzene-1,2-diol</p>	No Inhibition	No inhibition

*Common chemical name followed by International Union of Pure and Applied Chemistry (IUPAC) name.

Supplemental Table 7. Study Subject Demographics, Completion of Visits, Islet Autoantibody Status, and HLA Type

ID	Age (yrs)	Sex	T1D Duration (days)	Study Visits*						Islet AutoAb**				HLA Type***						DQ	DR
				1	2	3	4	5	6	GAD	IA-2	IAA	ZnT8	Allele 1			Allele 2				
														DRB1	DQA1	DQB1	DRB1	DQA1	DQB1		
003	25	M	210	X	X	X	X	X	X	96	3	0.279	0.002	0401	<u>0301</u>	<u>0302</u>	0401	<u>0301</u>	<u>0302</u>	8/8	4/4
006	23	M	148	X	X	X	X	X	X	71	2	0.015	0.039	0404	<u>0301</u>	<u>0302</u>	0701	0201	0202	8/2	4/7
007	43	F	103	X	X	X	X	X	X	126	205	0.077	0.065	0401	<u>0301</u>	<u>0302</u>	0701	0201	0303	8/9	4/7
008	23	M	40	X	X	X	X	X	X	144	16	0.002	0.001	0301	0501	0201	0401	<u>0301</u>	<u>0302</u>	2/8	3/4
009	20	M	50	X	X	X	X	X	X	16	201	0.003	0.709	0102	0101	0501	0401	<u>0301</u>	<u>0302</u>	5/8	1/4
011	21	F	25	X	X	X	X	X	X	921	368	0.035	0.095	0401	<u>0301</u>	<u>0302</u>	1302	0102	0604	8/6	4/13
012	20	M	43	X	X	X	X	X	X	99	311	0.002	0.239	0301	0501	0201	0401	<u>0301</u>	<u>0302</u>	2/8	3/4
014	25	F	122	X	X	X	X	X	X	885	116	0.092	0.001	0411	<u>0301</u>	<u>0302</u>	1602	0505	0301	8/7	4/16
015	28	M	105	X	X	X	X	X	X	707	432	0.482	0.671	0302	0501	0203	0405	<u>0303</u>	<u>0302</u>	2/8	3/4
016	42	F	141	X	X	X	X	X	X	673	382	0.001	0.323	0301	0501	0201	0401	<u>0301</u>	<u>0302</u>	2/8	3/4
018	18	M	65	X	X	X	X	X	X	7	215	0.001	0.073	0401	<u>0301</u>	<u>0302</u>	0401	<u>0301</u>	<u>0302</u>	8/8	4/4
019	20	F	73	X	X	X	X	X	X	496	0	0.001	0	0301	0501	0201	0402	<u>0301</u>	<u>0302</u>	2/8	3/4
022	23	M	21	X	X	X	X	X	X	15	0	0.02	0.009	0401	<u>0301</u>	<u>0302</u>	0404	<u>0301</u>	<u>0302</u>	8/8	4/4
023	33	F	566	X	X	X	X	X	X	7	102	2.224	0.007	0101	0101	0501	0401	<u>0301</u>	<u>0302</u>	5/8	1/4
024	19	M	92	X	X	X	X	X	X	0	326	0.004	0.005	0101	0101	0501	0401	<u>0301</u>	<u>0302</u>	5/8	1/4
025	19	F	486	X	X	X	X	X	X	71	174	0.071	0.023	0405	<u>0301</u>	<u>0302</u>	1316	0102	0604	8/6	4/6
026	35	M	159	X	X	X	X	X	X	119	0	0.978	0.000	0405	<u>0301</u>	<u>0302</u>	0701	0201	0202	8/2	4/7
027	20	M	53	X	X	X	X	--	X	45	0	0.001	0.003	0401	<u>0301</u>	<u>0302</u>	0404	<u>0301</u>	<u>0302</u>	8/8	4/4
028	20	M	78	X	X	X	X	X	X	469	190	0.002	0.294	0301	0501	0201	0401	<u>0301</u>	<u>0302</u>	2/8	3/4
029	18	M	88	X	X	X	X	X	X	38	61	0.105	0.021	0404	<u>0301</u>	<u>0302</u>	0801	0401	0402	8/4	4/8

*X denotes a completed study visit.

**Values highlighted in yellow denote positive values, normal values:

Glutamic Acid Decarboxylase (GAD) < 20 DK Units

Islet Antigen 2 (IA-2) < 5 DK Units

Insulin (IAA) < 0.011

Zinc Transporter 8 (ZnT8) < 0.021

***Underlined and bolded alleles represent HLA-DQ8.

Supplemental Table 8. IFN- γ ELISPOT responses to an insulin B chain mimotope, tetanus toxin and peptides

Subject ID*	IFN- γ Total ELISPOTS									
	Baseline					3 Months				
	No Ag	B:9-23 (B22E)	TT	TT 506-525	TT 922-941	No Ag	B:9-23 (B22E)	TT	TT 506-525	TT 922-941
007	9	25	83	17	17	1	1	4	1	5
014	0	21	19	2	6	6	11	35	4	75
015	14	42	332	10	101	8	18	196	8	72
022	0	5	2	96	8	5	6	183	62	61
023	24	51	264	51	101	41	49	407	82	276
025	2	9	38	0	5	32	32	62	32	55
026	4	15	76	7	8	3	4	94	5	10

*Only those subjects responding to the insulin B:9-23 (B22R \rightarrow E) mimotope at baseline were evaluated for responses to whole TT protein and peptides.

Supplemental Table 9. Individual TCR transductants, peptide and MHC restriction

TCR Transductant	Peptide and Amino Acid Sequence	MHC Class II Molecule
Clone 5	Insulin B:13-23 EALYLVCGERG	DQ8
489	α -gliadin ₂₂₈₋₂₄₀ SGEGSFQPSQENP	DQ8
Clone 13	α -gliadin ₂₂₈₋₂₄₀ SGEGSFQPSQENP	DQ8
Clone 22	α -gliadin ₂₂₈₋₂₄₀ SGEGSFQPSQENP	DQ8
Clone 38	α -gliadin ₂₂₈₋₂₄₀ SGEGSFQPSQENP	DQ8
DQ8-flu	HA ₁₀₂₋₁₁₈ PENGTCYPGYFADYEEL	DQ8
C7CH17	HA ₃₀₆₋₃₁₈ PKYVKQNTLKLAT	DR4
233	a-II-gliadin ₆₂₋₇₃ PQPELPYPQPQL	DQ2

*Bold amino acid represents a Q→E deamidation in α -gliadin.

Supplemental Table 10. Flow cytometry antibody clones and suppliers

Antigen	Clone	Manufacturer
CD19	HIB19	BD
HLA-DR	TU36	BD
HLA-DR	G46-6	BD
HLA-DQ	SK10	eBioscience
CD11c	S-HCL-3	BD
CD11c	3.9	BioLegend
CD123	6H6	BioLegend
CD1c (BDCA-1)	L61	BioLegend
CD303 (BDCA-2)	201A	BioLegend
CD141 (BDCA-3)	M80	BioLegend
CD304 (BDCA-4)	12C2	BioLegend
CD4	RPA-T4	BioLegend
CD8	SK1	BioLegend

BDCA = blood dendritic cell antigen