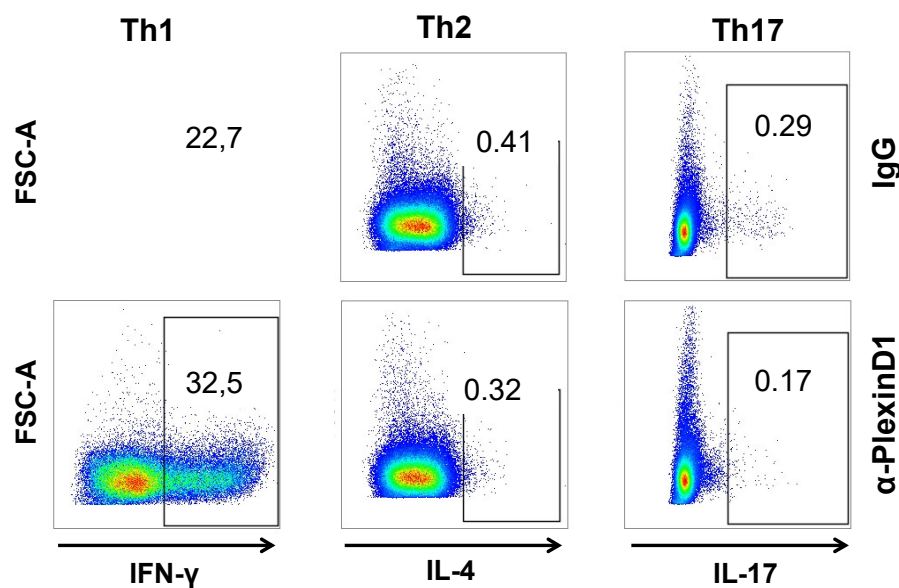
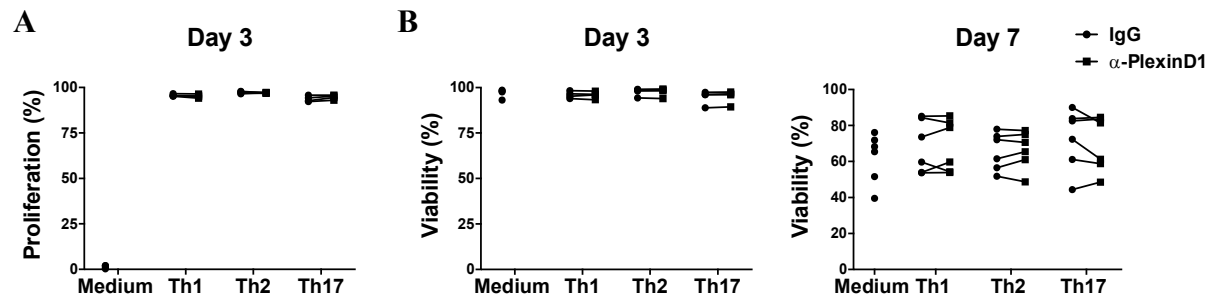


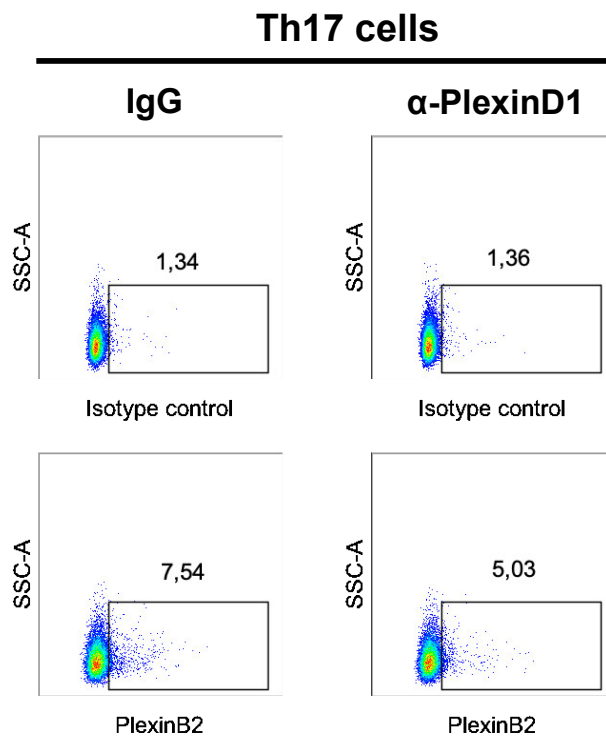
Supplementary Figure S1. Sema4A-PlexinD1 axis inhibits Th1 and promotes Th2 and Th17 differentiation. Cytokines mRNA expression in naïve CD4⁺ T cells differentiated either in medium (Med), Th1, Th2 or Th17 differentiation cocktails in the presence of an anti-PlexinD1 antibody or its respective isotype control for 3 days (n=4). Data is presented as connected dots. * p<0.05. # p<0.05 and ## p<0.01 compared to medium.



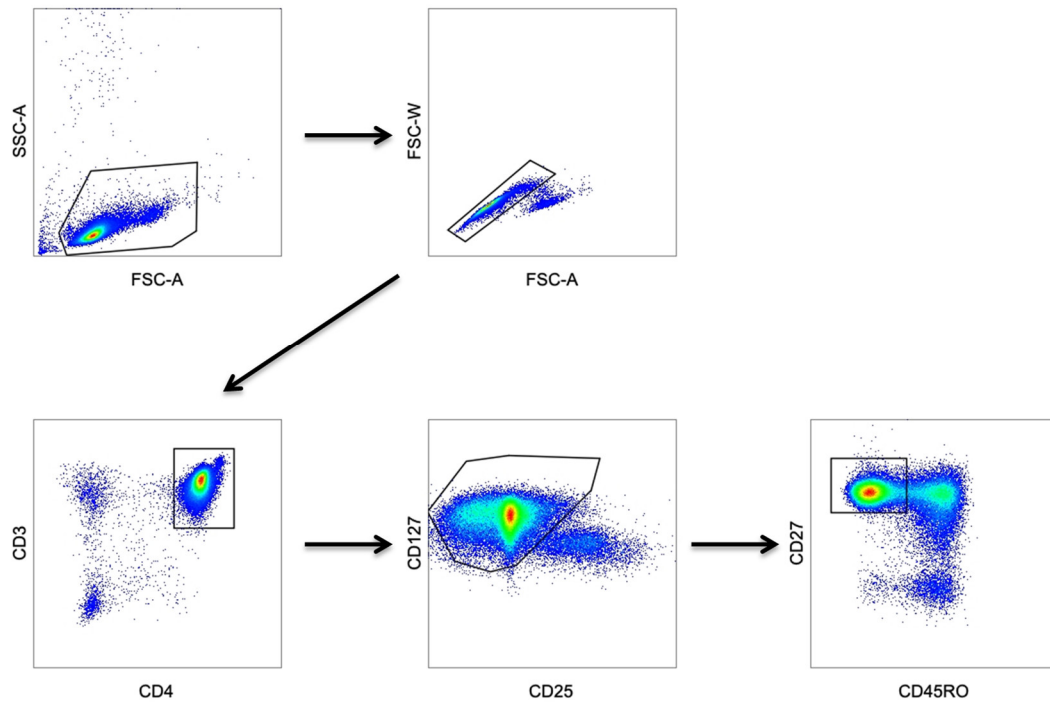
Supplementary Figure S2. Sema4A-PlexinD1 axis inhibits IFN-γ and promotes IL-4 and IL-17 production. Representative plots of intracellular cytokine production in naïve CD4⁺ T cells differentiated with Th1, Th2 or Th17 differentiation cocktails in the presence of an anti-PlexinD1 antibody or its respective isotype control for 7 days.



Supplementary Figure S3. Sema4A-PlexinD1 axis blockade does not affect cell proliferation and viability. Cell proliferation (A) and viability (B) in naïve CD4⁺ T cells differentiated in medium or Th1, Th2 or Th17 differentiation cocktails in the presence of an anti-PlexinD1 antibody or its respective isotype control for 3days (n=4) or 7 days (n=6). Data is presented as connected dots.



Supplementary Figure S4. Sema4A-PlexinD1 axis inhibition reduces the expression of PlexinB2 in Th17 cells. (A) Representative flow cytometry plot of PlexinB2 expression in Th17-differentiated CD4⁺ T cells in the presence of an anti-PlexinD1 antibody or its respective isotype control for 3 days.



Supplementary Figure S5. Analysis strategy of sorted naïve CD4⁺ T cells. Flow cytometry gating strategy analysis to sort naïve CD4⁺CD25⁻CD27⁺CD45RO⁻ T cells.

Supplemental Table S1. List of T helper cell differentiation cocktails.

Th1 differentiation	Company	Concentration
IL-12	Biolegend	5 ng/ml
Anti-IL4	R&D systems	1 µg/ml

Th2 differentiation	Company	Concentration
IL-4	R&D systems	10 ng/ml
Anti-IFN γ	R&D systems	1 µg/ml

Th17 differentiation	Company	Concentration
IL-1 β	R&D systems	10 ng/ml
IL-6	Immunotools	10 ng/ml
IL-23	R&D systems	10 ng/ml
TGF- β 1	Biolegend	10 ng/ml
Anti-IL4	R&D systems	1 µg/ml
Anti-IFN γ	R&D systems	1 µg/ml

Supplementary Table S2. Characteristics of SSc patients.

	SSc (n=8)
Age (years)	66 (58-72)
Female: n (%)	6 (75)
Disease duration (years)	7 (4.5-8.5)
ANA positive: n (%)	6 (75)
ACA positive: n (%)	6 (75)
Scl70 positive: n (%)	1 (12.5)
mRSS	5 (1-9)
DMARDs: n (%)	1 (12.5)
Biologicals: n (%)	0 (0)

Data is presented as the median (interquartile range) or number (percentage). ANA: antinuclear antibodies; ACA: anticentromere antibodies; Scl70: antitopoisomerase antibodies; mRSS: modified Rodnan Skin score; DMARDs: disease-modifying antirheumatic drugs.

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Supplemental Table S3. List of primers.

Gene	Primer forward	Primer reverse
<i>IL17</i>	5'CCGTGGGCTGCACCTGTGTC3'	5'GGGAGTGTGGGCTCCCCAGA3'
<i>IL22</i>	5'GCTGGCTAAGGAGGCTAGCTT3'	5'CATACTGACTCCGTGGAACAGTTT3'
<i>IFNγ</i>	5' GCAAGGCTATGTGATTACAAGGC3'	5'GTGAAATAAACACACAACCCATGG3'
<i>TNF</i>	5'TCTTCTCGAACCCCGAGTGA3'	5'CCTCTGATGGCACCACCAG3'
<i>IL4</i>	5'AGCAGTTCCACAGGCACAAG3'	5'ACTCTGGTTGGCTTCCTTCAC3'
<i>IL5</i>	5'ACTGCTTTCTACTCATCGAACTCTG3'	5'TTGACTCTCCAGTGTGCCTATTC3'
<i>TBX21</i>	5'TCCAACACGCATATCTTTACTTTCC3'	5'AGCTGAGTAATCTCGGCATTCTG3'
<i>GATA3</i>	5'CAGACCACCACAACCACAC3'	5'TGCCTTCCTTCTTCATAGTCAG3'
<i>RORC</i>	5'AAGACTCATCGCCAAAGCAT3'	5'TCCACATGCTGGCTACACA3'
<i>PLEXIND1</i>	5'GGCCGAGTGAAAGACTTGGA3'	5'GGTGAGACTTCTTGGGCTCC3'
<i>PLEXINB1</i>	5'CTGCAGAAGTTCGTGGATGA3'	5'GAGGCAAGCTGTTGGTCTTC3'
<i>PLEXINB2</i>	5'TCTCAGTCAAGGGCACACTG3'	5'GCGGTAAGCTGTTTCGTCTTC3'
<i>NRP1</i>	5'GAAAAATGCGAATGGCTGAT3'	5'AATGGCCCTGAAGACACAAC3'
<i>ILT4</i>	5'TGCTGATCTGAGTCTGCCTG3'	5'CTTGGGGATGGTCCCTGTCT3'
<i>B2M</i>	5'GATGAGTATGCCTGCCGTGT3'	5'TGCGGCATCTTCAAACCTCC3'