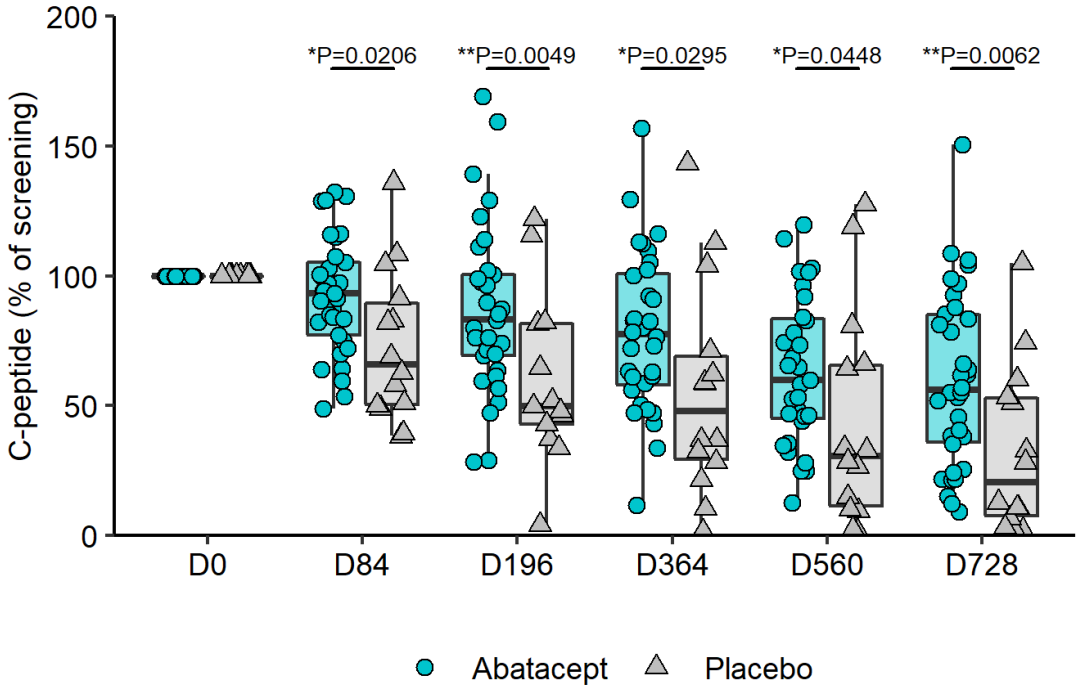
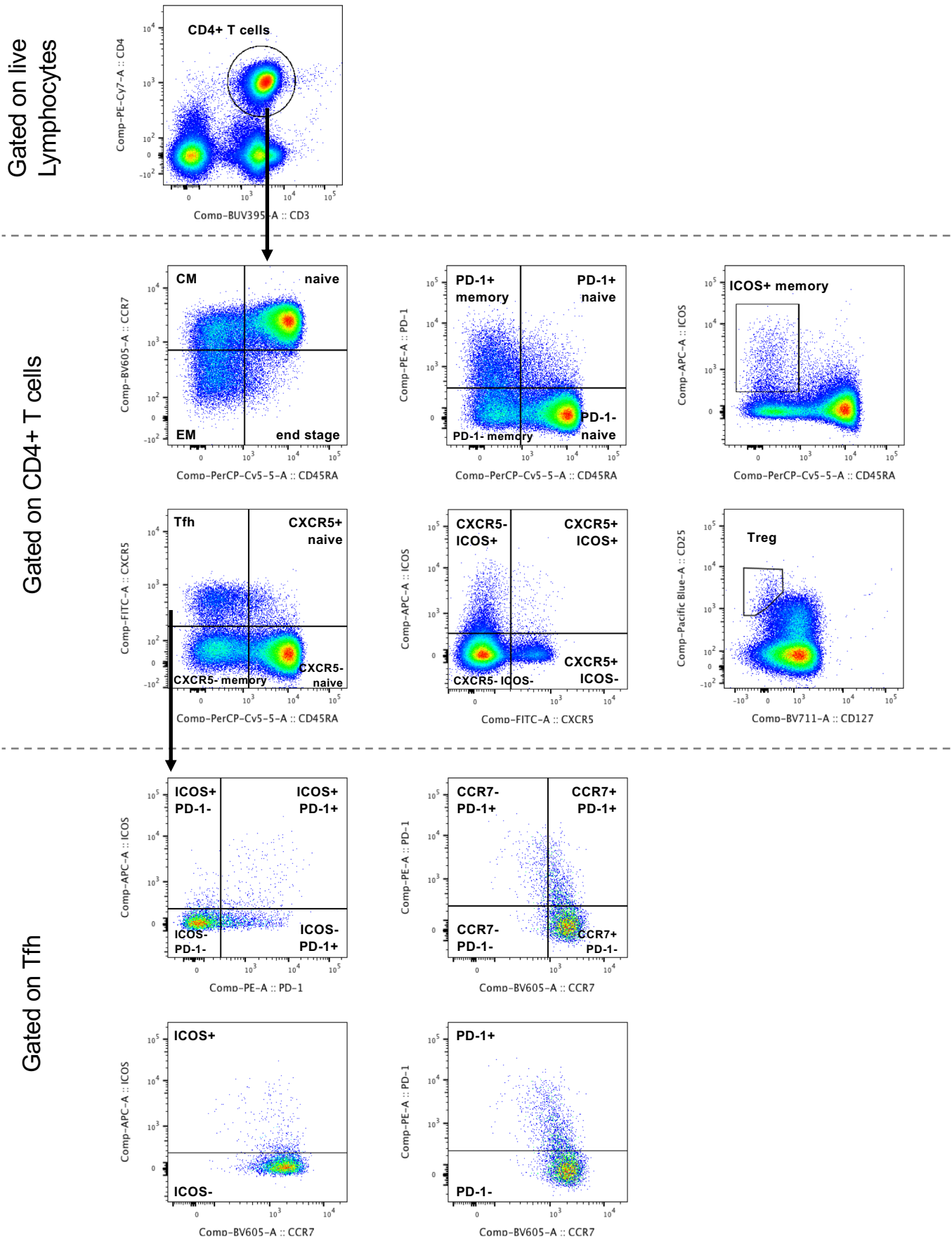


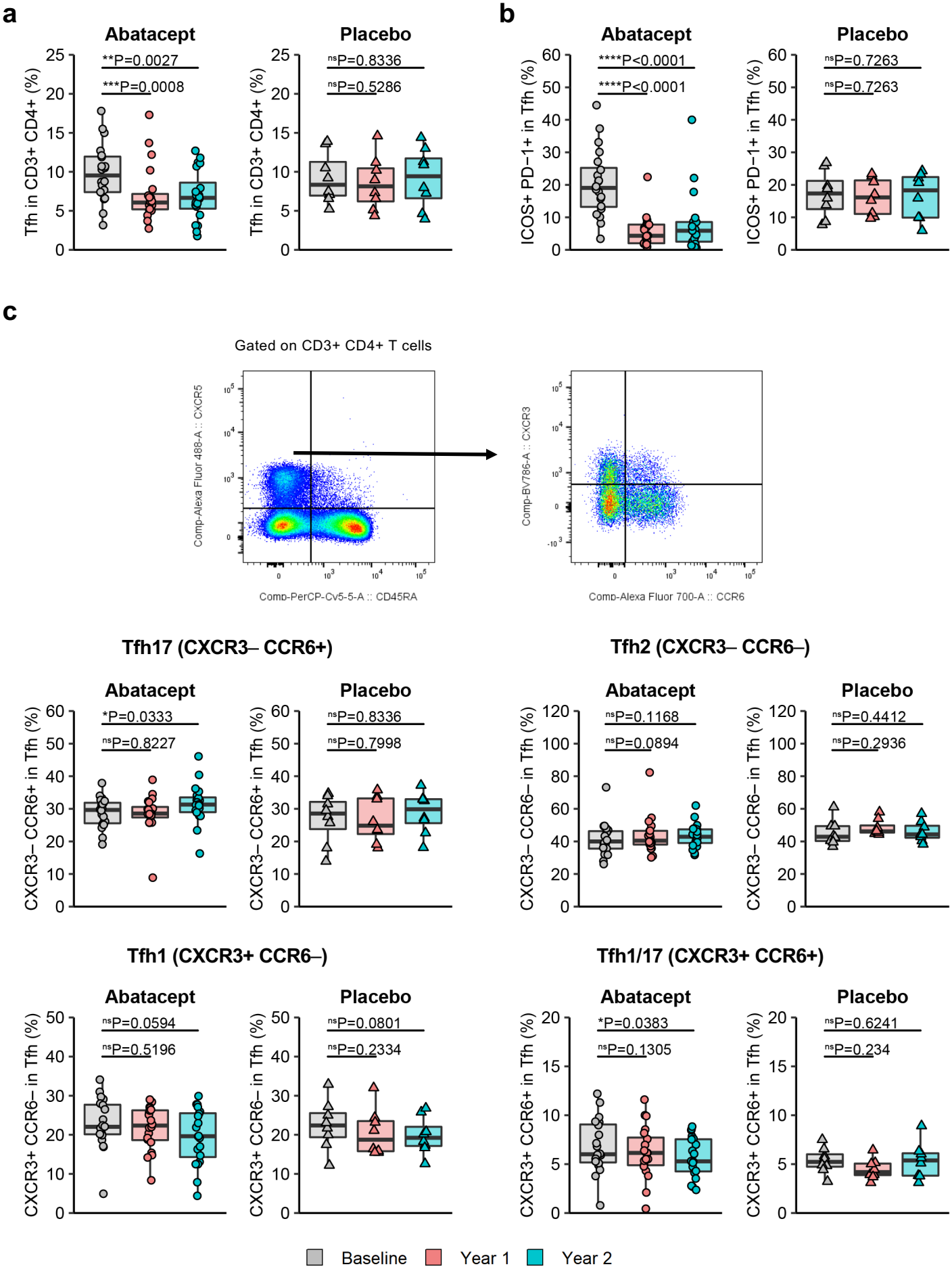
Supplementary Figure 1. Preserved C-peptide response in patients receiving Abatacept

C-peptide AUC per time point and treatment as % of screening C-peptide AUC for all patients. Shown are boxplots with black horizontal line denoting median value, while box represents IQR (Q1-Q3 percentile) and whiskers show minimum (Q1– 1.5 * IQR) and maximum (Q3 + 1.5 * IQR) values. Abatacept, n=31 (D560), 32 (D364), 33 (D84, D196) or 34 (D0, D728) patients; Placebo, n=13 (D196) or 14 (all other time points) patients. Two-tailed Mann–Whitney U test; **, $p < 0.01$; *, $p < 0.05$.



Supplementary Figure 2. Gating strategy

Representative gating strategy for patient samples stained for flow cytometry. PBMC samples were thawed and stained as described in the methods. Following an initial singlet gate and a live cell gate (not shown), populations were gated as presented. Names indicated are those used in downstream analysis. CM: central memory; EM: effector memory.



Supplementary Figure 3. Minimal impact of Abatacept treatment on Tfh skewing
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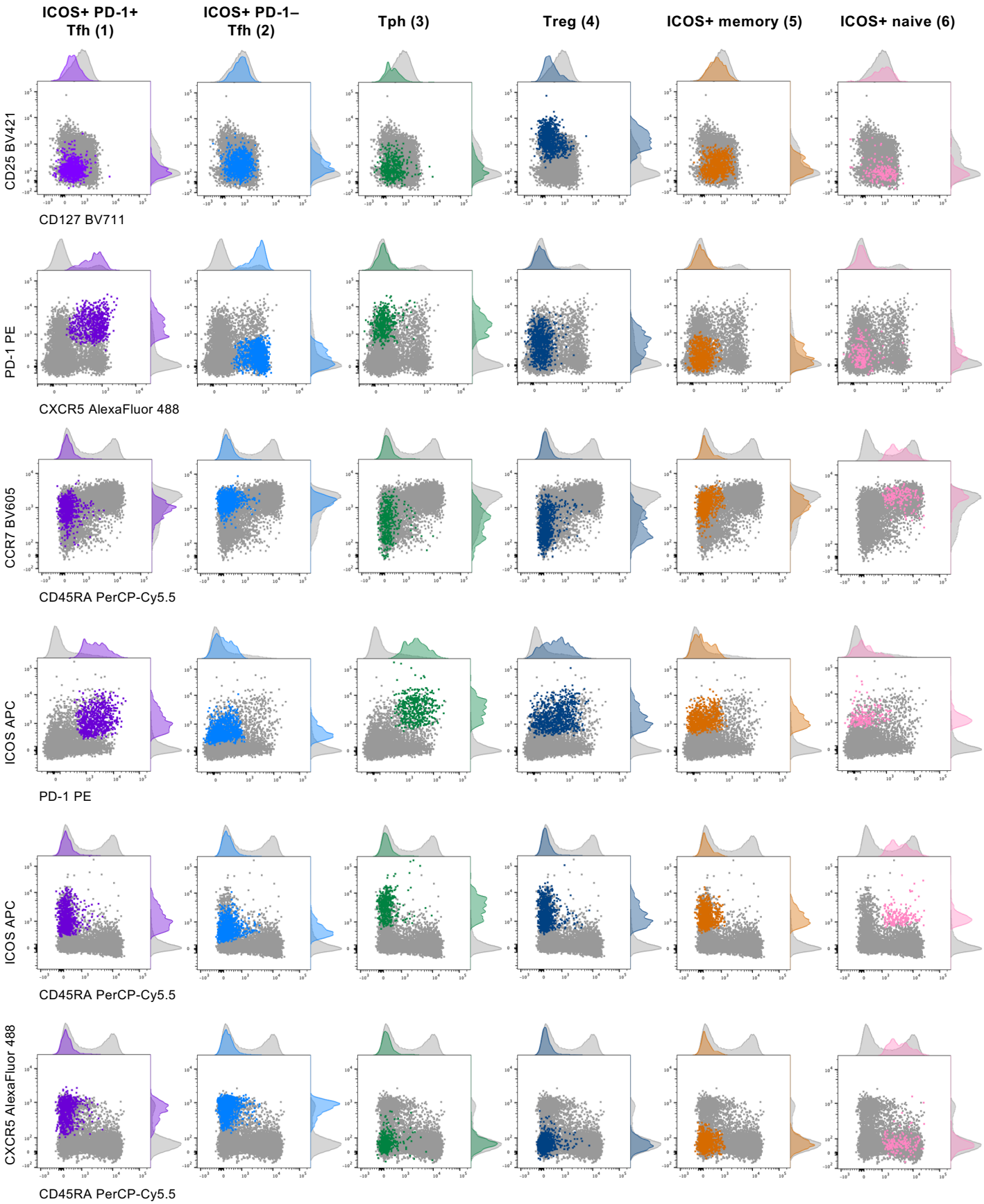
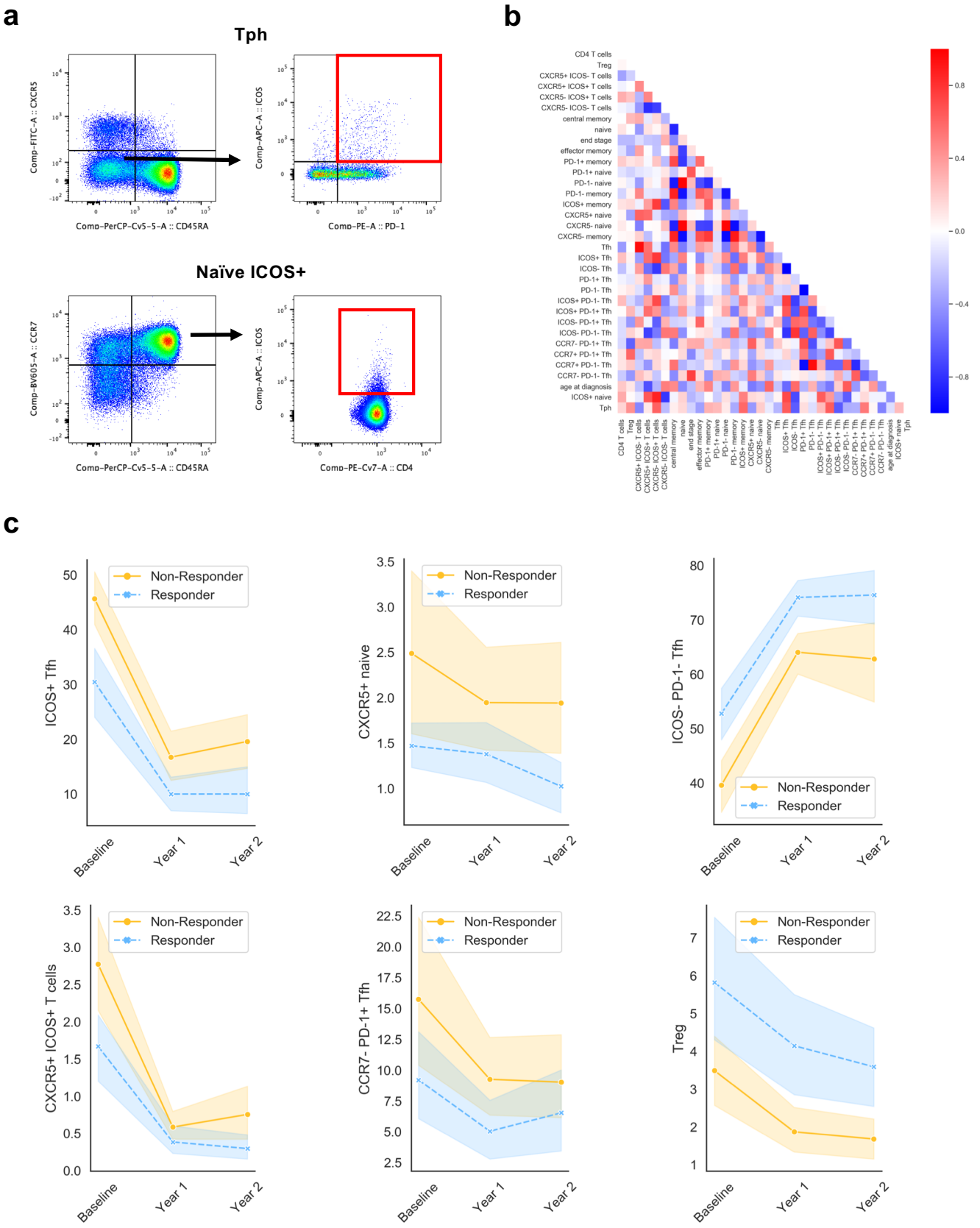
Supplementary Figure 3. Minimal impact of Abatacept treatment on Tfh skewing
Additional frozen PBMC samples from recent onset T1D patients that received Abatacept or placebo were thawed and stained for flow cytometry analysis of Tfh skewing. **(a)** Collated data for Tfh ($CD45RA^-$ $CXCR5^+$) frequencies in $CD3^+$ $CD4^+$ cells from recipients of Abatacept (left) or placebo (right) in new cohort. **(b)** Collated data for $ICOS^+$ $PD\text{-}1^+$ frequencies in Tfh cells from recipients of Abatacept or placebo in new cohort. **(c)** Representative gating strategy (top) and collated data (bottom) for frequencies of indicated populations of CXCR3 and CCR6 expressing Tfh cells in Abatacept and placebo treated individuals. Shown are boxplots with black horizontal line denoting median value, while box represents IQR (Q1-Q3 percentile) and whiskers show minimum (Q1– 1.5 * IQR) and maximum (Q3 + 1.5 * IQR) values. Abatacept, n=20 patients; Placebo, n=8 patients. Two-tailed Wilcoxon signed-rank test; ****, $p < 0.0001$; ***, $p < 0.001$; **, $p < 0.01$; *, $p < 0.05$; ns, not significant.



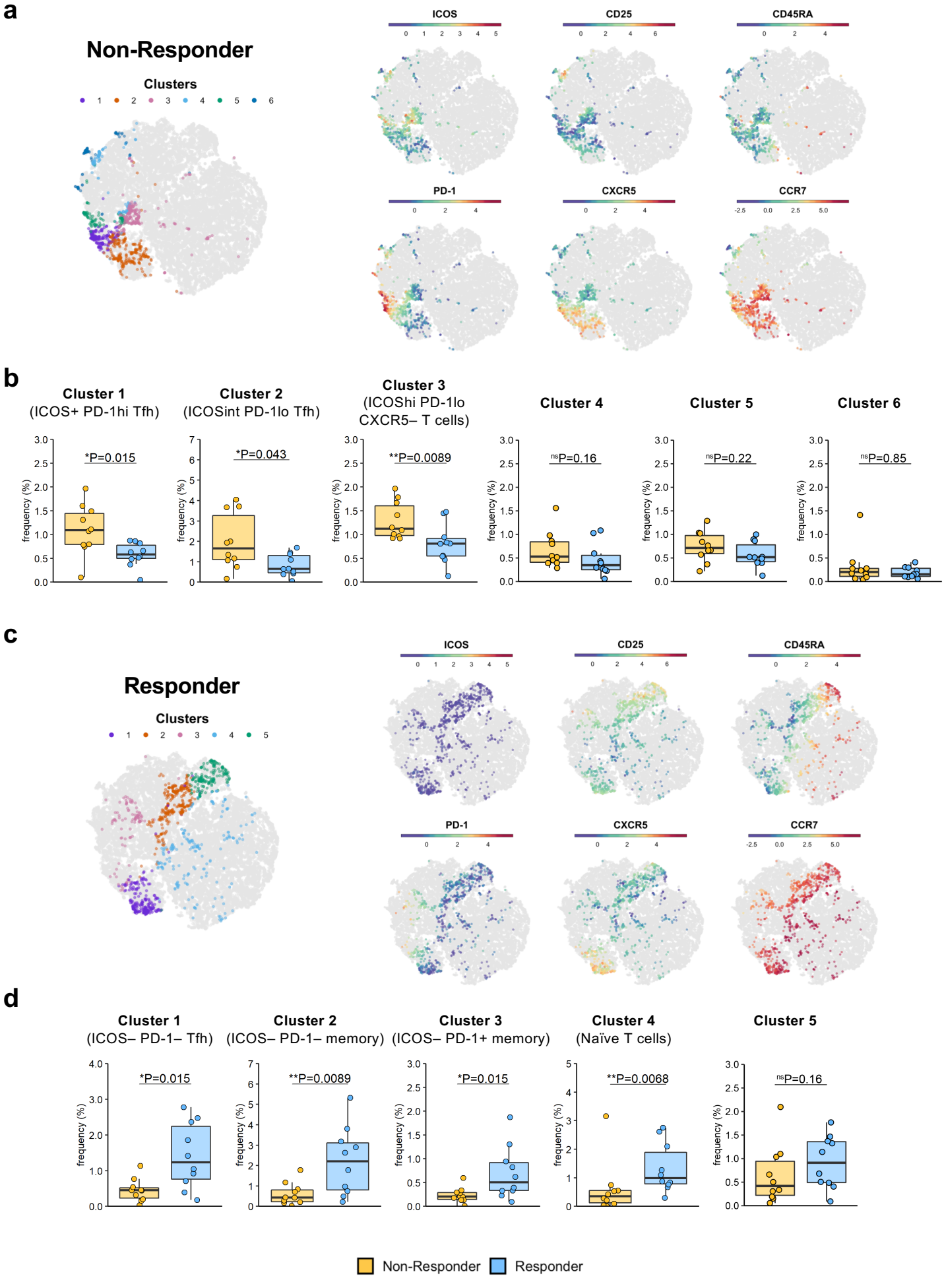
Supplementary Figure 4. Cell clusters identified by data-driven analysis correspond to known cell subsets

Cell clusters identified by CellCnn and k-means clustering to be significantly reduced in samples from Abatacept-treated individuals were overlaid onto flow cytometry data in order to infer identity. Plots show representative overlays of k-means clusters (colour) on original flow cytometry data (grey). Examples shown derive from a baseline sample.



Supplementary Figure 5. Feature selection for gradient boosting model and dynamic analysis of cell populations

(a) Representative flow cytometry plots depicting manual gating strategy for the additional populations added prior to development of a predictive model. These two populations, Tph (top) and naive ICOS⁺ T cells (bottom), were added since they were identified by CellCnn and k-means clustering to be altered in Abatacept-treated individuals. **(b)** Pairwise Pearson correlation comparison of all features used in gradient boosting model. A threshold of 0.95 was used to eliminate highly correlated features. **(c)** Time-series plots of flow cytometry gated populations contributing to gradient boosting model. Mean and 95% confidence interval are plotted (n=10 patients in each group).

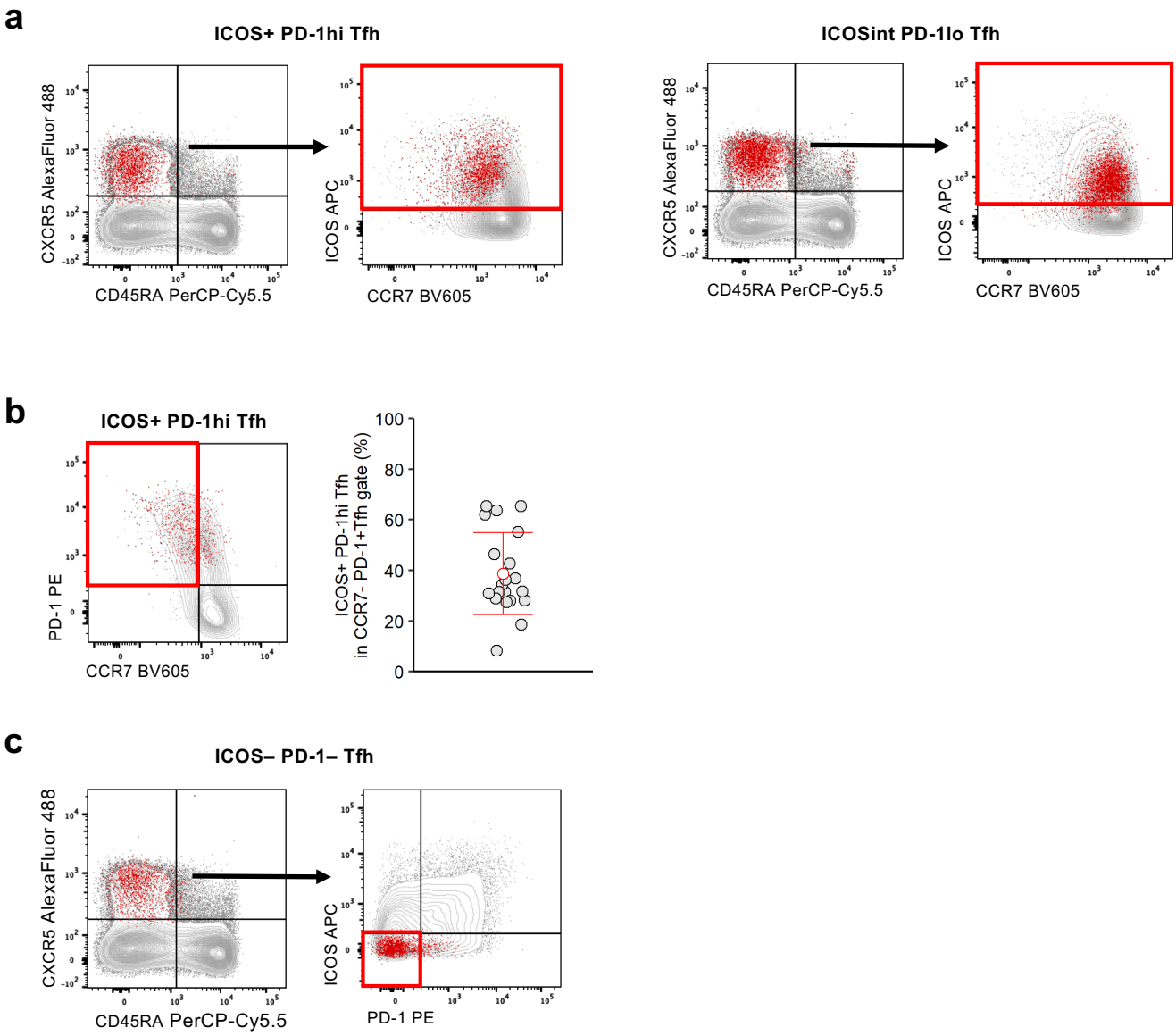


Supplementary Figure 6. Visualisation and frequencies of clusters identified by CellCnn that are linked to clinical response to Abatacept

See following page for full legend.

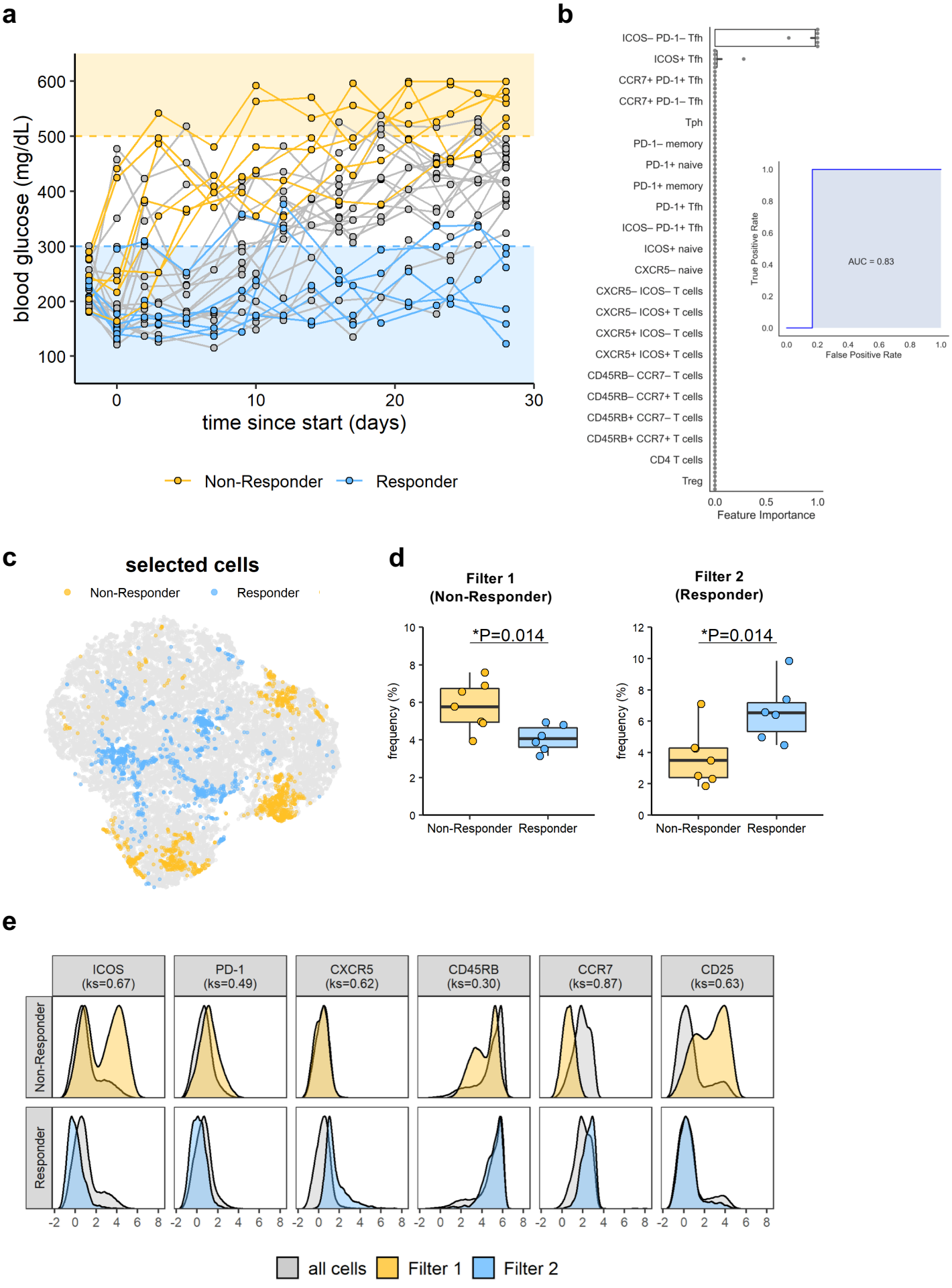
Supplementary Figure 6. Visualisation and frequencies of clusters identified by CellCnn that are linked to clinical response to Abatacept

Clustering results of CellCnn Responder vs Non-Responder comparison. t-SNE plot of marker expression and cluster assignment on selected cells (Responder vs Non-Responder comparison). **(a, c)** t-SNE projection of down-sampled, pooled flow cytometry data of all samples used for CellCnn analysis. K-means clusters or indicated marker expression of non-responder **(a)** and responder **(c)** filter-specific cells are highlighted. **(b, d)** Frequency of cluster-specific cells in each analysed sample for non-responder **(b)** and responder **(d)** filters. Shown are boxplots with black horizontal line denoting median value, while box represents IQR (Q1-Q3 percentile) and whiskers show minimum (Q1– 1.5 * IQR) and maximum (Q3 + 1.5 * IQR) values. n=10 patients in each group; two-tailed Mann-Whitney U test; **, $p < 0.01$; *, $p < 0.05$; ns, not significant.



Supplementary Figure 7. Cell clusters identified by data-driven analysis overlay manually gated cell populations

CellCnn and k-means clustering were used to identify populations that differed between individuals showing a good or poor response to Abatacept. Identified populations were then overlaid onto manually gated flow cytometry plots. **(a)** Representative overlays of cells belonging to ICOS^{+} PD-1^{hi} Tfh (left) and ICOS^{int}PD-1^{lo} Tfh (right) CellCnn clusters (red) on manual gating for ICOS^{+} Tfh cells (grey). **(b)** Representative overlay of ICOS^{+} PD-1^{hi} Tfh CellCnn cluster (red) on CCR7^{-}PD-1^{+} Tfh gate (grey) (left). Collated data showing frequency of CellCnn cluster ICOS^{+} PD-1^{hi} Tfh that falls within manual CCR7^{-}PD-1^{+} Tfh gate (right). n=20 patients. Mean ± SD are plotted in red. **(c)** Representative overlay of cells belonging to ICOS^{-}PD-1^{-} Tfh CellCnn cluster (red) on manual gating for ICOS^{-} PD-1^{-} Tfh cells (grey). Examples shown are from a baseline sample.



Supplementary Figure 8. Analysis of response to Abatacept in mouse model of autoimmune diabetes reveals similar trends to human data

See following page for full legend.

Supplementary Figure 8. Analysis of response to Abatacept in mouse model of autoimmune diabetes reveals similar trends to human data

Blood glucose of DO11.10 x RIP-mOVA mice was monitored and mice with blood glucose between 180 and 290 mg/dL were treated with Abatacept every two to three days for four weeks. Blood glucose was monitored, and responder and non-responder mice were identified based on final blood glucose reading. **(a)** Blood glucose readings of all treated mice over the treatment period. Responders and non-responders are highlighted in blue and yellow, respectively. Cut-offs used are highlighted in corresponding colour. **(b)** Baseline bleeds were stained for flow cytometry analysis and gated in a similar way to human samples, substituting CD45RB for CD45RA. The gradient boosting model used in Fig.7 was applied to this data after removal of highly correlated features. Features ranked by importance (bar shows mean and black lines represent 95% confidence intervals) and ROC curve of the predictive model are shown. **(c,d,e)** CellCnn analysis was applied to baseline samples of responders and non-responders. t-SNE projection of down-sampled, pooled flow cytometry data of all samples used for CellCnn analysis **(c)**, frequencies of filter-specific cells in each sample for Responder and Non-Responder filter **(d)** and histograms of marker expression of filter-specific cells (yellow; non-responder, blue; responder) or all cells (grey) **(e)** are shown. In **(d)** boxplots are shown with black horizontal line denoting median value, while box represents IQR (Q1-Q3 percentile) and whiskers show minimum (Q1– 1.5 * IQR) and maximum (Q3 + 1.5 * IQR) values. **(a)** n=31 mice; **(b-e)** n=6 (responder) or 7 (non-responder) mice; **(d)** two-tailed Mann–Whitney U test; **(e)** two-tailed Kolmogorov-Smirnov (ks) test; *, $p < 0.05$.