SUPPLEMENTAL INFORMATION

Article title:

Mogamulizumab for adult T-cell leukemia-lymphoma: A multicenter prospective observational study

Kentaro Yonekura,[1,2]* Shigeru Kusumoto,[3]* Ilseung Choi,[4]

Nobuaki Nakano,[1] Asahi Ito,[3] Youko Suehiro,[4,5] Yoshitaka Imaizumi,[6] Makoto Yoshimitsu,[7] Kisato Nosaka,[8] Eiichi Ohtsuka,[9] Michihiro Hidaka,[10] Tatsuro Jo,[11] Hidenori Sasaki,[12] Yukiyoshi Moriuchi,[13] Masao Ogata,[14] Hiro Tatetsu,[8] Kenji Ishitsuka,[7] Yasushi Miyazaki,[6] Ryuzo Ueda,[15,16]

Atae Utsunomiya,[1] Takashi Ishida[3,16]

***K.Y. and S.K. contributed equally to this study.**

Institutions:

[1]Department of Hematology, and [2]Department of Dermatology, Imamura General Hospital, [3]Department of Hematology and Oncology, Nagoya City University Graduate School of Medical Sciences, [4]Department of Hematology, and [5]Department of Cell Therapy National Hospital Organization Kyushu Cancer Centre Hospital, [6]Department of Hematology, Nagasaki University Hospital, [7]Department of Hematology and Rheumatology, Kagoshima University

Graduate School of Medical and Dental Sciences, [8]Department of Hematology, Kumamoto University Hospital, [9]Department of Hematology, Oita Prefectural Hospital, [10]Department of Hematology, National Hospital Organization Kumamoto Medical Center, [11]Department of Hematology, Japanese Red Cross Nagasaki Genbaku Hospital, [12]Division of Medical Oncology, Hematology, and Infectious Diseases, Department of Medicine, Fukuoka University Hospital, [13]Department of Hematology, Sasebo City General Hospital, [14]Department of Hematology, Oita University Hospital, [15]Department of Tumor Immunology, Aichi Medical University School of Medicine, [16]Department of Immunology, Nagoya University Graduate School of Medicine

Correspondence:

Takashi Ishida, M.D., Ph.D.

Department of Immunology,

Nagoya University Graduate School of Medicine

65 Tsurumai-cho, Showa-ku, Nagoya, Aichi 466-8560, Japan.

Phone: +81-52-744-2135;

Fax: +81-52-744-2972;

E-mail: itakashi@med.nagoya-u.ac.jp

Supplemental Methods

Patients and study design

The "**M**onitoring of **i**mmune responses following **moga**mulizumab-containing treatment in patients with ATL" (**MIMOGA**) study is a multicenter prospective observational study (**UMIN000008696**). The primary end-point was to clarify the immune dynamics of various different lymphocyte subsets including Treg cells in blood following mogamulizumab-containing treatment. The secondary end-point was to explore the immunological and molecular mechanisms determining the efficacy of treatment and provocation of AE by mogamulizumab in ATL patients. Taking these findings together, the ultimate goal of the study was to establish the most effective and safe treatment strategy using mogamulizumab in ATL patients. Diagnoses and assignment of clinical subtypes of ATL in the MIMOGA study were made according to the criteria proposed by the Japan Lymphoma Study Group.[19-21] Inclusion criteria were patients ≥ 20 years of age with CCR4-positive ATL planned to receive mogamulizumab-containing treatment. Exclusion criteria were having received previous mogamulizumab or allogeneic hematopoietic stem cell transplantation (HSCT).[22,23] After enrollment, the treatment strategy which included mogamulizumab was not determined by protocol, but at each investigator's clinical discretion. The population evaluable for efficacy consisted of patients who received one or more doses of mogamulizumab. Efficacy assessments were performed by each investigator in each institution according to international consensus response criteria for ATL.[20] The enrolled patients were monitored for multiple immunological parameters before, during, and after mogamulizumab

treatment according to the protocol. For this study, patients' samples collected at different time points from the enrollment were preserved according to the protocol. At the initiation of the MIMOGA study, patients bearing the HLA alleles HLA-A2, HLA-A11 or HLA-A24 were selected in order to evaluate human T-cell lymphotropic virus type 1 (HTLV-1) Tax- and cytomegalovirus (CMV) pp65-specific CD8+ T cell responses, before, during, and after mogamulizumab treatment by HLA class I tetramer staining. However, this requirement was relaxed at interim revision of the protocol in order to accelerate patient enrollment.

Immune monitoring

For evaluating CCR4 expression by ATL cells in PBMC, PE-conjugated anti-CCR4 (clone 1G1), PerCP-conjugated anti-CD4 (SK3), APC-conjugated anti-CD25 (2A3), and the appropriate isotype control antibodies were used. For quantifying Treg phenotype of ATL cells in PBMC, FITC-conjugated anti-CD45RA (ALB11), PE-conjugated anti-FOXP3 (PCH101), PerCP-conjugated anti-CD4 (SK3), APC-conjugated anti-CD25 (2A3), and the appropriate isotype control antibodies were used. The Treg phenotype was determined by FOXP3 and CD45RA expression levels, according to the earlier studies.[17,22] Patients whose HTLV-1 provirus load in peripheral blood mononuclear cells (PBMC) was < 80.0 copies/1,000PBMC were considered "Treg-unclassified", because there were too few HTLV-1-infected ATL cells in PBMC to allow evaluation of their Treg phenotype. PC-5-conjugated anti-CD4 (13B8.2), anti-CD13 (IMMU103.44), anti-CD19 (J4.119), FITC-conjugated

anti-CD8 (SFCI21Thy2D3 [T8]), and PE-conjugated HLA-A*02:01/Tax11-19, HLA-A*11:01/Tax88-96 or HLA-A*24:02/Tax301-309 tetramers were used for evaluating HTLV-1 Tax-specific CD8+ T cells. For CMV pp65-specific CD8+ T cells, the tetramers were HLA-A*02:01/CMVpp65 495-503, HLA-A*11:01/CMVpp65 501-509 or HLA-A*24:02/CMVpp65 341-349. For evaluating the distribution in T cells, B cells, NK cells and monocytes within PBMC, a test namely “Malignant lymphoma analysis, CD45 gating, test for hematopoietic malignant tumor cell” (CODE : 2496 1, SRL, Inc., Tokyo, Japan) was performed. The scheme for immune monitoring is shown in Figure 1. All flow cytometry analyses were performed by SRL Hachioji Laboratory **(**SRL, Inc.). The acquired flow cytometry data were analyzed by FlowJo software (Tree Star, Inc., Ashland, OR). The HTLV-1 provirus load in PBMC and serum sIL-2R concentration were also quantified by SRL, Inc.

Statistical analysis

Survival estimates were calculated using the Kaplan-Meier method. Progression-free survival (PFS) was defined as the time from the first dose of mogamulizumab to progression, relapse, or death resulting from any cause, whichever occurred first. Overall survival (OS) was measured from the day of the first dose to death resulting from any cause. Allogeneic HSCT is a drastic strategy in which hematopoietic and immune systems are completely replaced by healthy donor-derived cells. Therefore, in some cases in the present study, the survival estimate was calculated with all transplanted patients (n = 15) censoring at the day of allogeneic HSCT. The data cut-off date in the present

study was 31st December, 2017. Survival times were compared using the log-rank test. Correlations between two variables were assessed using the Spearman rank correlation coefficient (Rs). Differences between two groups were examined with the Mann–Whitney U test or Fisher´s exact test. Clinically meaningful cut-off values for immune cells in PBMC, such as Tax-specific cytotoxic T lymphocytes (Tax-CTL), CMV pp65-specific cytotoxic T lymphocytes (CMV-CTL), CD2-CD19+ B cells, CD3+CD8+ T cells, CD16+CD56+ NK cells, or CD11c+ monocytes, have not been determined thus far. Hence, we attempted to divide ATL patients into two groups according to the percentages of these cells. The cut-off values for each cell population were tested at 7 different percentiles (20, 30, 40, 50, 60, 70, and 80th percentiles). Univariate analysis for survival was performed by the Cox proportional hazards regression model for each parameter at each of the 7 cut-off points. In the present study, the cut-off point yielding the minimum *P* value was chosen as the most meaningful cut-off value. Multivariate analysis using Cox proportional hazards regression models were applied to evaluate variables potentially affecting OS. All analyses were performed with SPSS Statistics 17.0 (IBM Corporation, Armonk, NY). In this study, $P < 0.05$ (two-sided) was considered significant.

Study oversight

All investigators were responsible for contributing to the study design. The protocol was approved by the Institutional Review Board at each participating site, and all patients provided written informed consent before enrollment according to the Declaration of Helsinki.

Supplemental Figure Legends

Supplemental Figure 1. Progression-free survival (PFS) and overall survival (OS) of the ATL patients according to clinical responses to mogamulizumab. (A) PFS according to clinical responses. Median PFS in patients with complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD) was 17.2, 8.3, 3.0, and 1.1 months, respectively. **(B)** OS stratified according to clinical responses. Median OS in patients with CR, PR, SD, and PD was 60.7, 18.8, 8.0, and 4.0 months, respectively. **(C)** PFS where patients were censored at the day of allogeneic HSCT, according to clinical responses. Median PFS in patients with CR, PR, SD, and PD was 17.2, 8.3, 3.0, and 1.1 months, respectively. **(D)** OS after HSCT censoring according to clinical responses. Median OS in patients with CR, PR, SD, and PD was 60.7, 18.8, 8.0, and 4.0 months, respectively. PFS and OS was compared using log–rank testing and the *P*-values calculated are indicated in the lower panel.

Supplemental Figure 2. PFS and OS of patients stratified according to their clinical parameters (A) PFS of previously treated and untreated patients. **(B)** OS of previously treated and untreated patients. **(C)** OS of previously treated patients according to their most recent treatment regimen. Median OS of those whose latest regimen was mLSG15-like, CHOP-like, or others was 18.1, 19.7, and 10.6 months, respectively. “Others” included gemcitabine-, sobuzoxane-, or procarbazine-based regimens, etc. OS was compared using log–rank testing and the *P*-values calculated for mLSG15 versus CHOP-like,

mLSG15-like versus others, and CHOP-like versus others were 0.521, 0.245, and 0.208, respectively. **(D)** OS in previously treated patients according to second or other line-setting of the present mogamulizumab-containing treatment. The median OS of patients receiving mogamulizumab in the second line setting versus third line setting or later was 22.6 and 7.5 months, respectively. **(E)** OS of patients treated with mogamulizumab monotherapy or combination therapy. **(F)** OS of patients treated with mogamulizumab combination therapy according to the regimen. The median OS of patients receiving mogamulizumab combined with the mLSG15-like, CHOP-like, or other regimens was 11.1, 13.2, and 12.8 months, respectively. Other regimens included gemcitabine, sobuzoxane, or procarbazine, etc. OS was compared using log–rank testing and the *P*-values calculated for mLSG15 versus CHOP-like, mLSG15-like versus others, and CHOP-like versus others were 0.347, 0.687, and 0.432, respectively. **(G)** OS of patients with acute, lymphoma, or unfavorable chronic subtype versus favorable chronic or smoldering subtype.

Supplemental Figure 3. Immunological status of the ATL patients at enrollment. Flow cytometry data of PBMC from all ATL patients enrolled in the present study, except patient number 080, which are missing. The lymphocyte population was determined by FSC-H and SSC-H levels (upper middle panel). Of these, CD4+ cells are plotted according to FOXP3 (x-axis) and CD45RA (y-axis) positivity (lower left panel). Regulatory T (Treg) cell phenotypes of the ATL cells were determined based on these data. The Treg phenotype is indicated above the chart in each case. CD4-positive cells are also plotted

according to CCR4 expression (x-axis) and CD25 (y-axis) positivity (lower left second panel). CD4 and CD25 double-positive cells are stained with anti-CCR4 mAb (open histograms) or isotype control mAb (solid histograms) in order to show CCR4 expression level in ATL (CD4- and CD25-double positive) cells (lower middle panel). Patients with an HTLV-1 provirus load in PBMC of <80.0 copies/1,000 PBMC were categorized as “unclassified” (Nos. 013, 016, 023, 024, 029, 030, 039, 042, 043, 044, 048, 050, 051, 056, 062, 065, 068, 070, 071, 075, 081, 083, and 101), and their histogram plots for CCR4 expression by ATL cells are not presented. The HTLV-1 provirus load in PBMC of each case is indicated in the panel. Within the lymphocyte population determined by FSC-H and SSC-H levels (upper middle panel), CD4-, CD13-, and CD19-negative cells are plotted according to HTLV-1 Tax tetramer (x-axis) and CD8 (y-axis) positivity (lower panel second from right), or CMV pp65 tetramer (x-axis) and CD8 (y-axis) positivity (lower right panel). Data for staining with these tetramers are missing for patients no. 069, 071, 074, 077, 078, 089, and 090. The percentages of Tax-specific cytotoxic T cells (Tax-CTL) and CMV-CTL within PBMC were determined based on these analyses. Patient number is indicated in the upper-left corner in each column.

Supplemental Figure 4. CD2-CD19+ B cells, CD3+CD8+ T cells, CD16+CD56+ NK cells and CD4+ cells in PBMC of the ATL patients at enrollment. Flow cytometry of PBMC from ATL patients enrolled in the present study (n = 102). The lymphocyte population was determined by FSC-H and SSC-H levels (upper left panel). Of these, CD45+ cells are plotted

according to CD2 (x-axis) and CD19 (y-axis) positivity, and these B cells are gated by quadrant (lower left panel); also plotted are CD3+ (x-axis) and CD8+ (y-axis) cells, gated by quadrant (lower second from left panel); CD16+ (x-axis) and CD56+ (y-axis) NK cells, gated by quadrant (lower second from right panel); and CD4+ (x-axis) and CD25+ (y-axis) cells plotted as CD4+CD25+$^{dim\text{-}high}$ cells gated by quadrant (lower right-hand panel). The percentages of CD2-CD19+ B cells, CD3+CD8+ T cells, and CD16+CD56+ NK cells within all lymphocytes were determined based on these analyses. Patient number is indicated in the upper-left in each column.

Supplemental Figure 5. CD11c+ monocytes in PBMC of the ATL patients at enrollment. Flow cytometry of PBMC from ATL patients enrolled in the present study (n = 102). The monocyte population was determined by FSC-H and SSC-H levels (upper left panel). Of these, CD45+ cells (upper right panel) are plotted according to CD20 (x-axis) and CD11c (y-axis) positivity, and CD11c+ monocytes are gated by quadrant (lower right panel). The percentages of CD11c+ monocytes among the whole monocyte population were determined based on these analyses. Patient number is indicated in the upper-left corner in each column.

Supplemental Figure 6. OS according to the Treg phenotype of the ATL cells. (A) OS after HSCT censoring according to the ATL phenotypes eTreg, non-Treg, other and unclassified. **(B)** OS of patients with eTreg + non Treg, other, and unclassified.

Supplemental Figure 7. OS according to the percentage of Tax-CTL or CMV-CTL in previously treated patients. OS was estimated after all transplanted patients were censored at the day of allogeneic HSCT. **(A)** OS according to higher or lower percentages of Tax-CTL within all lymphocytes (median OS, 19.7 vs. 7.4 months, *P* = 0.008). **(B)** OS according to higher or lower percentages of CMV-CTL in all lymphocytes (median OS, 13.2 vs. 19.6 months, *P* = 0.147). **(C)** OS according to higher or lower percentages of Tax-CTL within CD8+ lymphocytes (median OS, 19.7 vs. 7.1 months, *P* = 0.001). **(D)** OS according to higher or lower percentages of CMV-CTL within CD8+ lymphocytes (median OS, 15.7 vs. 18.1 months, *P* = 0.181).

Supplemental Table 1. Correlations among CD2-CD19+ B cells, CD3+CD8+ T cells, CD16+CD56+ NK cells and CD11c+ monocytes in ATL patients

	CD3+CD8+ T cells*	CD16+CD56+ NK cells*	CD11c+ monocytes#
CD2-CD19+ B cells*	Rs = 0.125	Rs = 0.139	Rs = 0.197
	P = 0.210	*P* = 0.163	*P* = 0.047
CD3+CD8+ T cells*		Rs = 0.778	Rs = 0.600
		P < 0.001	*P* < 0.001
CD16+CD56+ NK cells*			Rs = 0.516
			P < 0.001

*** percentage among whole lymphocytes; # percentage among whole monocytes; ATL, adult T-cell leukemia-lymphoma**

Supplemental Table 2. Univariate Cox proportional hazard analysis for overall survival* according to Tax specific CTL/whole lymphocytes

		Tax-CTL /lymphocytes (%)	No	HR	95% CI	*P* value
20 percentile		≤ 0.001	19	1.000		Ref.
		> 0.001	74	0.604	(0.305-1.194)	0.147
30 percentile		≤ 0.002	28	1.000		Ref.
		> 0.002	65	0.523	(0.290-0.942)	0.031
40 percentile		≤ 0.005	37	1.000		Ref.
		> 0.005	56	0.860	(0.488-1.518)	0.603
50 percentile		≤ 0.011	47	1.000		Ref.
		> 0.011	46	0.869	(0.495-1.523)	0.623
60 percentile		≤ 0.018	56	1.000		Ref.
		> 0.018	37	0.841	(0.472-1.498)	0.557
70 percentile		≤ 0.031	65	1.000		Ref.
		> 0.031	28	0.843	(0.452-1.571)	0.591
80 percentile		≤ 0.100	74	1.000		Ref.
		> 0.100	19	1.085	(0.564-2.087)	0.806

CTL, cytotoxic T lymphocytes; No, number; HR, hazard ratio; CI, confidence interval; Ref, reference; *The patients were censored at the day of allogeneic hematopoietic stem cell transplantation.

Supplemental Table 3. Univariate Cox proportional hazard analysis for overall survival* according to CMV-CTL/whole lymphocytes

	CMV-CTL /lymphocytes (%)	No	HR	95% CI	*P* value
	≤ 0	30	1.000		Ref.
	> 0	63	0.807	(0.451-1.444)	0.470
40 percentile	≤ 0.0012	37	1.000		Ref.
	> 0.0012	56	0.885	(0.502-1.560)	0.674
50 percentile	≤ 0.0030	47	1.000		Ref.
	> 0.0030	46	0.809	(0.461-1.420)	0.460
60 percentile	≤ 0.0125	56	1.000		Ref.
	> 0.0125	37	1.056	(0.596-1.871)	0.853
70 percentile	≤ 0.0450	65	1.000		Ref.
	> 0.0450	28	1.483	(0.810-2.716)	0.202
80 percentile	≤ 0.0730	74	1.000		Ref.
	> 0.0730	19	1.490	(0.788-2.816)	0.219

CMV, cytomegalovirus; CTL, cytotoxic T lymphocytes; No, number; HR, hazard ratio; CI, confidence interval; Ref, reference: *The patients were censored at the day of allogeneic hematopoietic stem cell transplantation.

Supplemental Table 4. Univariate Cox proportional hazard analysis for overall survival* according to Tax-CTL/CD8 lymphocytes

		Tax-CTL/CD8 (%)	No	HR	95% CI	*P* value
20 percentile		≤ 0.0200	19	1.000		Ref.
		> 0.0200	74	0.478	(0.240-0.952)	0.036
30 percentile		≤ 0.0418	28	1.000		Ref.
		> 0.0418	65	1.092	(0.574-2.075)	0.789
40 percentile		≤ 0.0750	37	1.000		Ref.
		> 0.0750	56	0.864	(0.487-1.534)	0.618
50 percentile		≤ 0.1930	47	1.000		Ref.
		> 0.1930	46	0.793	(0.451-1.394)	0.421
60 percentile		≤ 0.3500	56	1.000		Ref.
		> 0.3500	37	0.988	(0.558-1.748)	0.966
70 percentile		≤ 0.5000	65	1.000		Ref.
		> 0.5000	28	1.000	(0.550-1.819)	1.000
80 percentile		≤ 0.8500	74	1.000		Ref.
		> 0.8500	19	0.980	(0.500-1.920)	0.953

CTL, cytotoxic T lymphocytes; No, number; HR, hazard ratio; CI, confidence interval; Ref, reference;
***The patients were censored at the day of allogeneic hematopoietic stem cell transplantation.**

Supplemental Table 5. Univariate Cox proportional hazard analysis for overall survival* according to CMV-CTL/CD8 lymphocytes

		CMV-CTL/CD8 (%)	No	HR	95% CI	*P* value
		≤ 0	30	1.000		Ref.
		> 0	63	0.807	(0.451-1.444)	0.470
40 percentile		≤ 0.018	37	1.000		Ref.
		> 0.018	56	0.922	(0.523-1.626)	0.780
50 percentile		≤ 0.063	47	1.000		Ref.
		> 0.063	46	0.910	(0.519-1.597)	0.742
60 percentile		≤ 0.150	56	1.000		Ref.
		> 0.150	37	1.107	(0.628-1.953)	0.724
70 percentile		≤ 0.350	65	1.000		Ref.
		> 0.350	28	1.685	(0.931-3.050)	0.085
80 percentile		≤ 0.800	74	1.000		Ref.
		> 0.800	19	1.719	(0.892-3.312)	0.105

CMV, cytomegalovirus; CTL, cytotoxic T lymphocytes; No, number; HR, hazard ratio; CI, confidence interval; Ref, reference; *The patients were censored at the day of allogeneic hematopoietic stem cell transplantation.

Supplemental Table 6. Univariate Cox proportional hazard analysis for overall survival* according to CD2-CD19+ B cells/whole lymphocytes in PBMC

	CD2-CD19+ B cells /lymphocytes (%)	No	HR	95% CI	*P* value
20 percentile	≤ 0.150	20	1.000		Ref.
	> 0.150	81	0.458	(0.241-0.868)	0.017
30 percentile	≤ 0.240	30	1.000		Ref.
	> 0.240	71	0.502	(0.276-0.913)	0.024
40 percentile	≤ 0.390	40	1.000		Ref.
	> 0.390	61	0.509	(0.287-0.903)	0.021
50 percentile	≤ 0.620	51	1.000		Ref.
	> 0.620	50	0.697	(0.402-1.211)	0.201
60 percentile	≤ 1.205	62	1.000		Ref.
	> 1.205	39	0.650	(0.369-1.144)	0.135
70 percentile	≤ 1.850	72	1.000		Ref.
	> 1.850	29	0.867	(0.490-1.537)	0.626
80 percentile	≤ 3.100	81	1.000		Ref.
	> 3.100	20	0.984	(0.530-1.824)	0.958

No, number; HR, hazard ratio; CI, confidence interval;
***The patients were censored at the day of allogeneic hematopoietic stem cell transplantation.**

Supplemental Table 7. Univariate Cox proportional hazard analysis for overall survival* according to CD3+CD8+ cells/whole lymphocytes in PBMC

	CD3+CD8+ T cells /lymphocytes (%)	No	HR	95% CI	*P* value
20 percentile	≤ 1.65	20	1.000		Ref.
	> 1.65	81	0.577	(0.307-1.085)	0.088
30 percentile	≤ 3.00	30	1.000		Ref.
	> 3.00	71	0.768	(0.420-1.406)	0.392
40 percentile	≤ 4.70	40	1.000		Ref.
	> 4.70	61	0.873	(0.498-1.528)	0.634
50 percentile	≤ 8.60	51	1.000		Ref.
	> 8.60	50	0.947	(0.552-1.624)	0.842
60 percentile	≤ 12.70	62	1.000		Ref.
	> 12.70	39	1.154	(0.670-1.989)	0.606
70 percentile	≤ 17.00	72	1.000		Ref.
	> 17.00	29	1.116	(0.625-1.991)	0.710
80 percentile	≤ 20.00	81	1.000		Ref.
	> 20.00	20	1.363	(0.725-2.561)	0.337

No, number; HR, hazard ratio; CI, confidence interval;
***The patients were censored at the day of allogeneic hematopoietic stem cell transplantation**

Supplemental Table 8. Univariate Cox proportional hazard analysis for overall survival* according to CD16+CD56+ NK cells/whole lymphocytes in PBMC

	CD16+CD56+ NK cells /lymphocytes (%)	No	HR	95% CI	*P* value
20 percentile	≤ 1.36	20	1.000		Ref.
	> 1.36	81	0.550	(0.279-1.082)	0.083
30 percentile	≤ 1.90	30	1.000		Ref.
	> 1.90	71	1.050	(0.568-1.940)	0.876
40 percentile	≤ 3.10	40	1.000		Ref.
	> 3.10	61	0.974	(0.554-1.711)	0.926
50 percentile	≤ 5.00	51	1.000		Ref.
	> 5.00	50	1.069	(0.619-1.848)	0.810
60 percentile	≤ 7.80	62	1.069		Ref.
	> 7.80	39	0.924	(0.533-1.602)	0.779
70 percentile	≤ 9.50	72	1.000		Ref.
	> 9.50	29	0.788	(0.437-1.420)	0.427
80 percentile	≤ 15.00	81	1.000		Ref.
	> 15.00	20	0.769	(0.398-1.488)	0.436

No, number; HR, hazard ratio; CI, confidence interval; *The patients were censored at the day of allogeneic hematopoietic stem cell transplantation.

Supplemental Table 9. Univariate Cox proportional hazard analysis for overall survival* according to CD11c+ monocytes/whole monocytes in PBMC

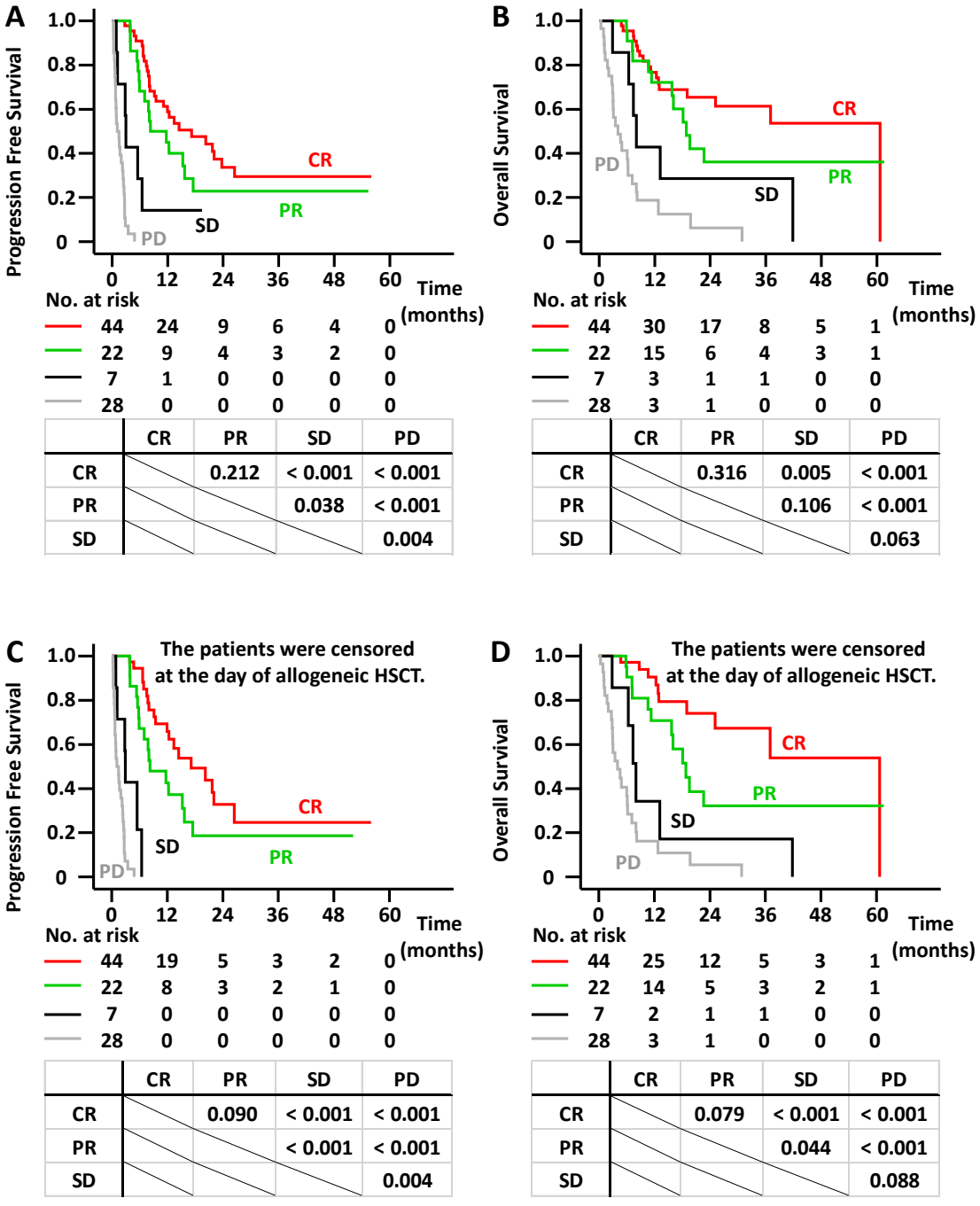
	CD11c+ monocytes /monocytes (%)	No	HR	95% CI	*P* value
20 percentile	≤ 15.5	20	1.000		Ref.
	> 15.5	81	0.690	(0.360-1.325)	0.265
30 percentile	≤ 35.0	30	1.000		Ref.
	> 35.0	71	0.984	(0.532-1.819)	0.958
40 percentile	≤ 50.5	40	1.000		Ref.
	> 50.5	61	1.059	(0.602-1.865)	0.841
50 percentile	≤ 61.0	51	1.000		Ref.
	> 61.0	50	0.974	(0.567-1.674)	0.923
60 percentile	≤ 71.5	62	1.069		Ref.
	> 71.5	39	0.905	(0.523-1.566)	0.721
70 percentile	≤ 80.0	72	1.000		Ref.
	> 80.0	29	0.874	(0.487-1.567)	0.651
80 percentile	≤ 88.5	81	1.000		Ref.
	> 88.5	20	0.863	(0.432-1.723)	0.677

No, number; HR, hazard ratio; CI, confidence interval;
***The patients were censored at the day of allogeneic hematopoietic stem cell transplantation.**

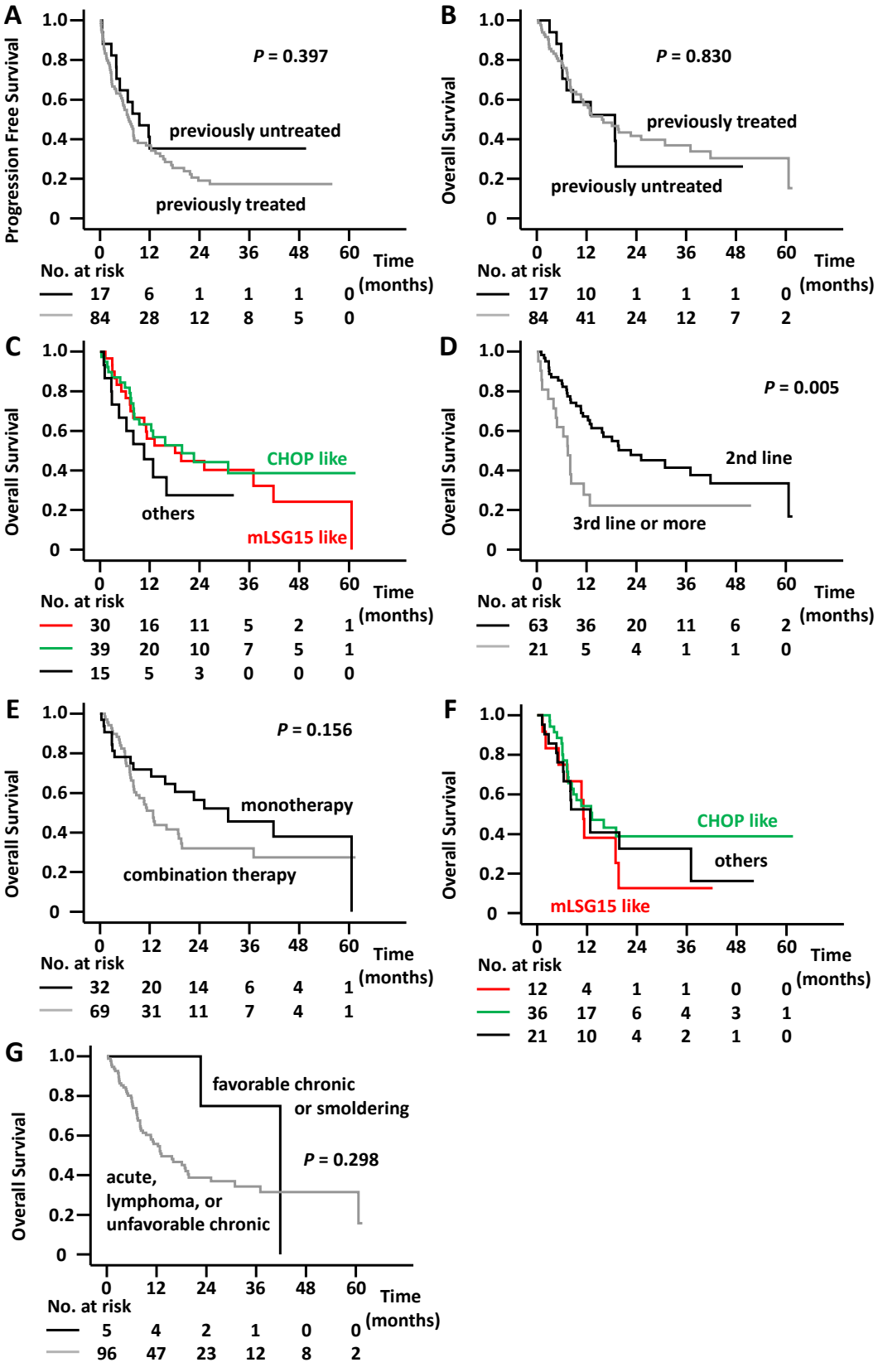
Supplemental Table 10. Multivariate analysis for overall survival* in previously treated patients with adult T-cell leukemia-lymphoma

Variables	Number	Hazard Ratio	(95% CI)	*P* value
Sex				
male	50	1.000		Reference
female	34	0.688	(0.344-1.373)	0.289
Age, years				
≤ 70	57	1.000		Reference
> 70	27	1.085	(0.561-2.098)	0.809
Clinical subtype				
chronic, smoldering	11	1.000		Reference
acute, lymphoma	73	1.903	(0.509-7.118)	0.339
ECOG PS				
0,1	62	1.000		Reference
2,3,4	22	2.094	(1.046-4.193)	0.037
sIL-2R (U/mL)				
≤ 20,000	71	1.000		Reference
> 20,000	13	10.081	(4.324-23.502)	< 0.001
CD2-CD19+ cells (%)#				
> 0.15	66	1.000		Reference
≤ 0.15	18	2.305	(1.066-4.984)	0.034
CD3+CD8+ cells (%)#				
> 1.65	71	1.000		Reference
≤ 1.65	13	6.415	(1.764-23.321)	0.005
CD16+CD56+ cells (%)#				
> 1.36	67	1.000		Reference
≤ 1.36	17	0.873	(0.286-2.667)	0.812
CD11c+ monocytes (%)$				
> 15.5	69	1.000		Reference
≤ 15.5	15	0.607	(0.219-1.678)	0.336

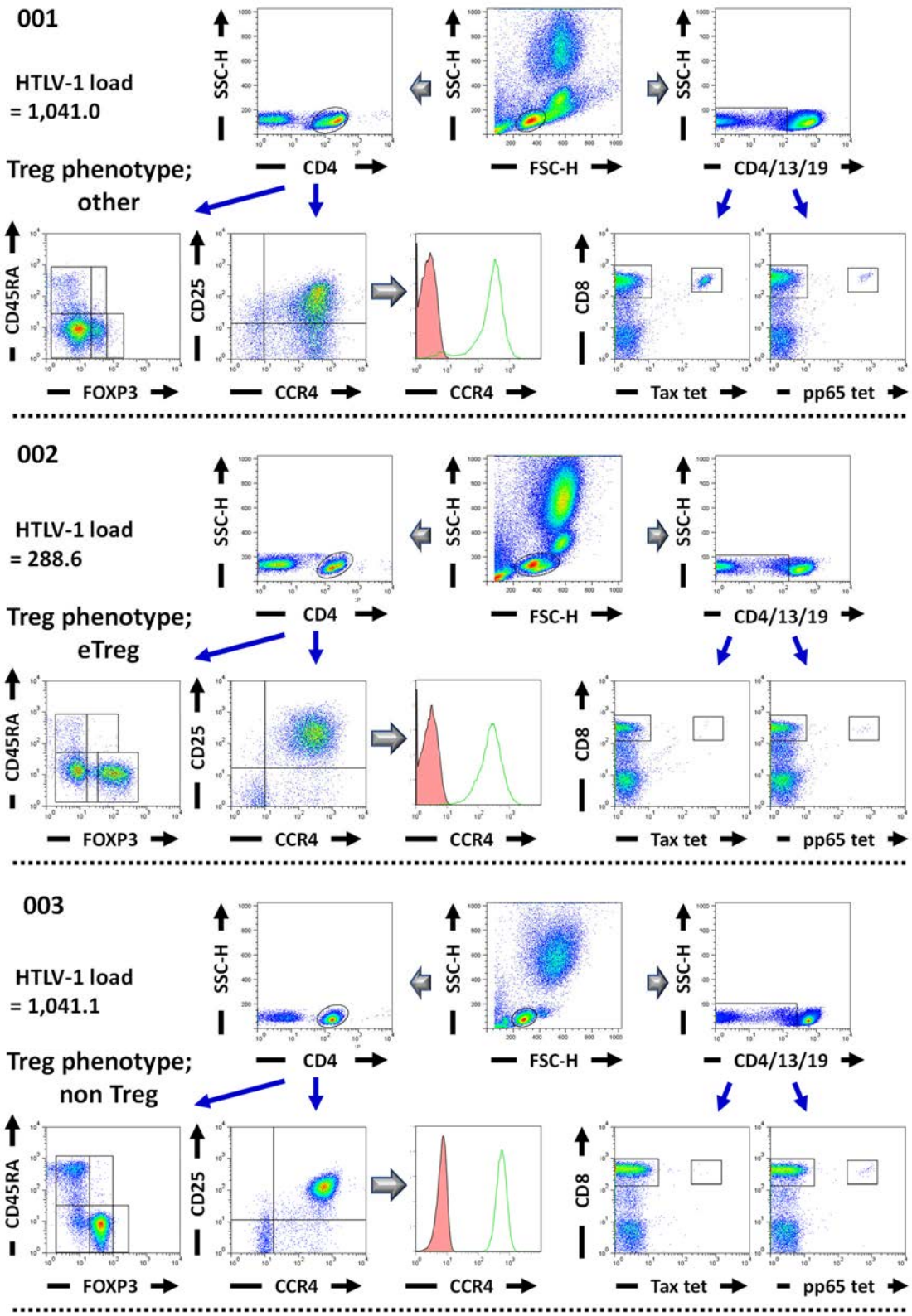
CI, confidence interval; *The patients were censored at the day of allogeneic hematopoietic stem cell transplantation.; # the percentage among whole lymphocytes in peripheral blood mononuclear cells (PBMC); $ the percentage among whole monocytes in PBMC



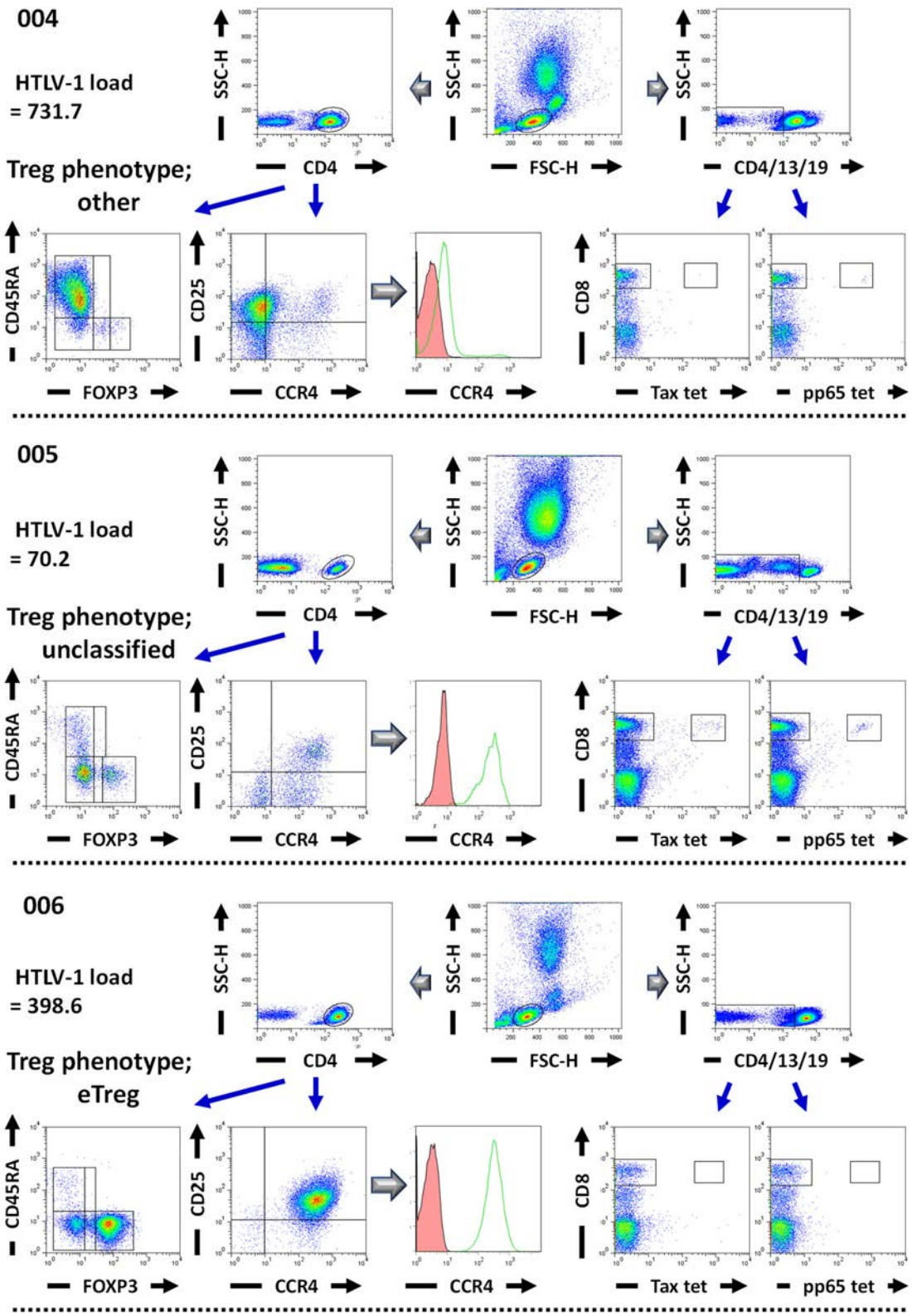
Supplemental FIGURE 1



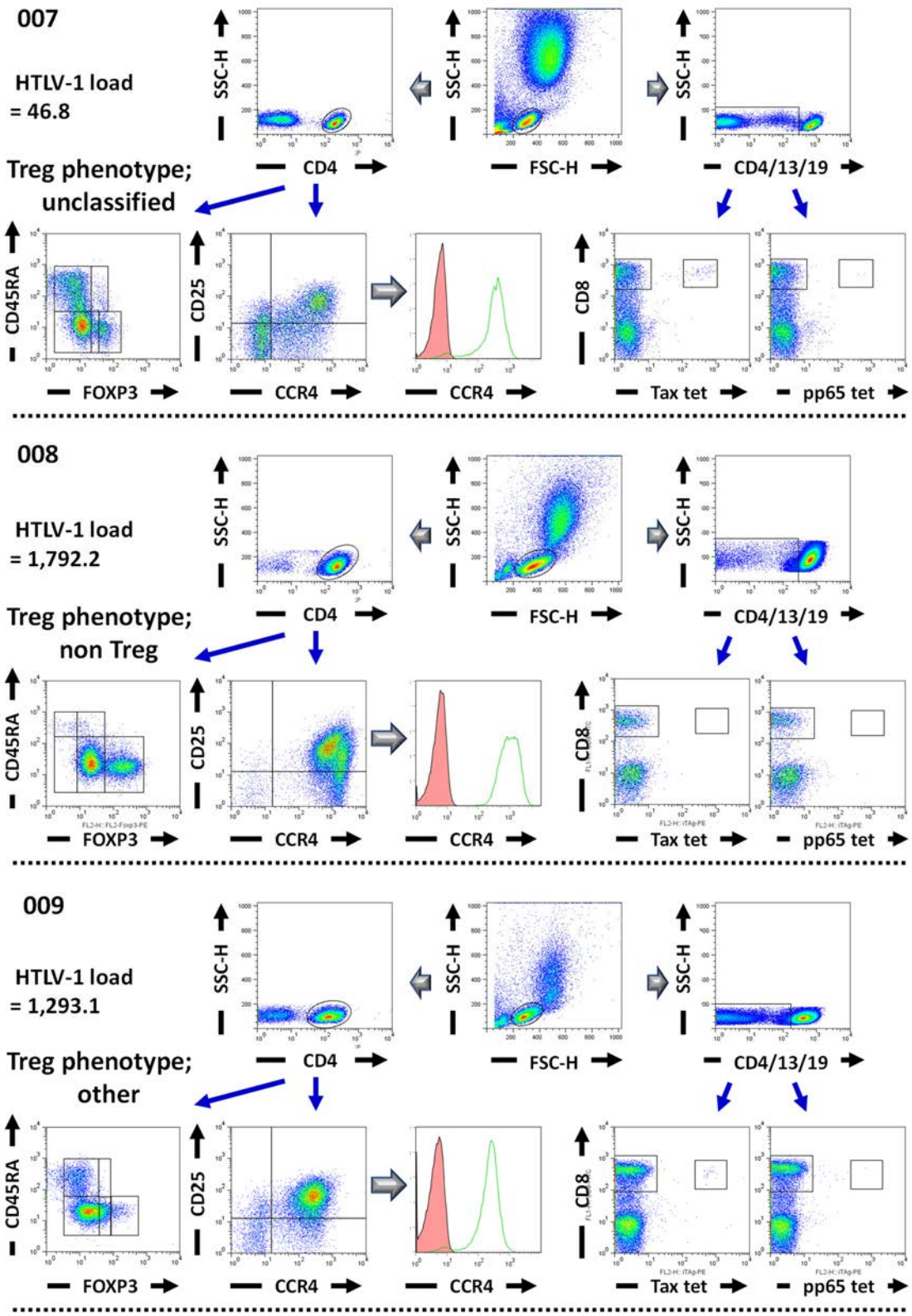
Supplemental FIGURE 2



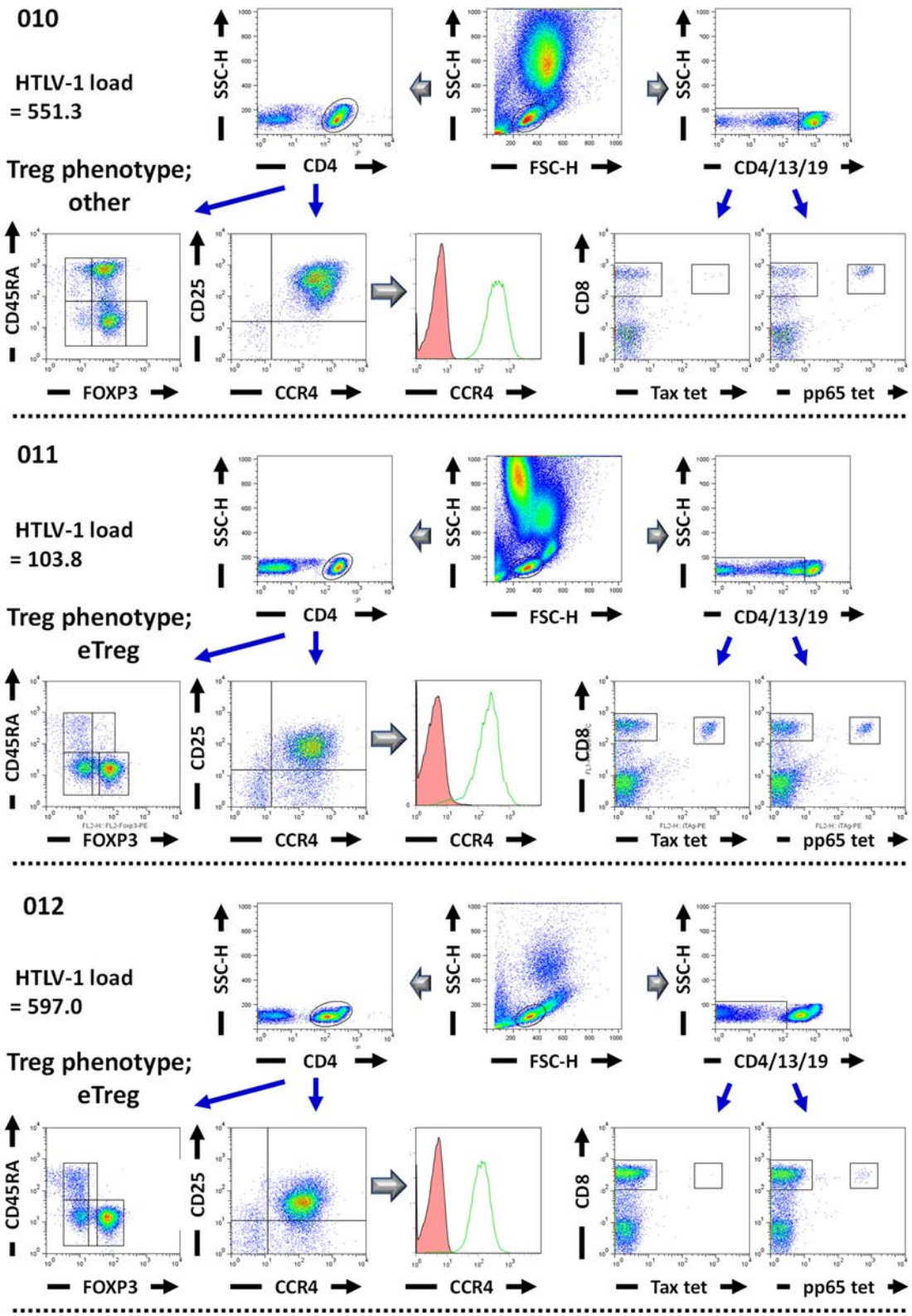
Supplemental FIGURE 3



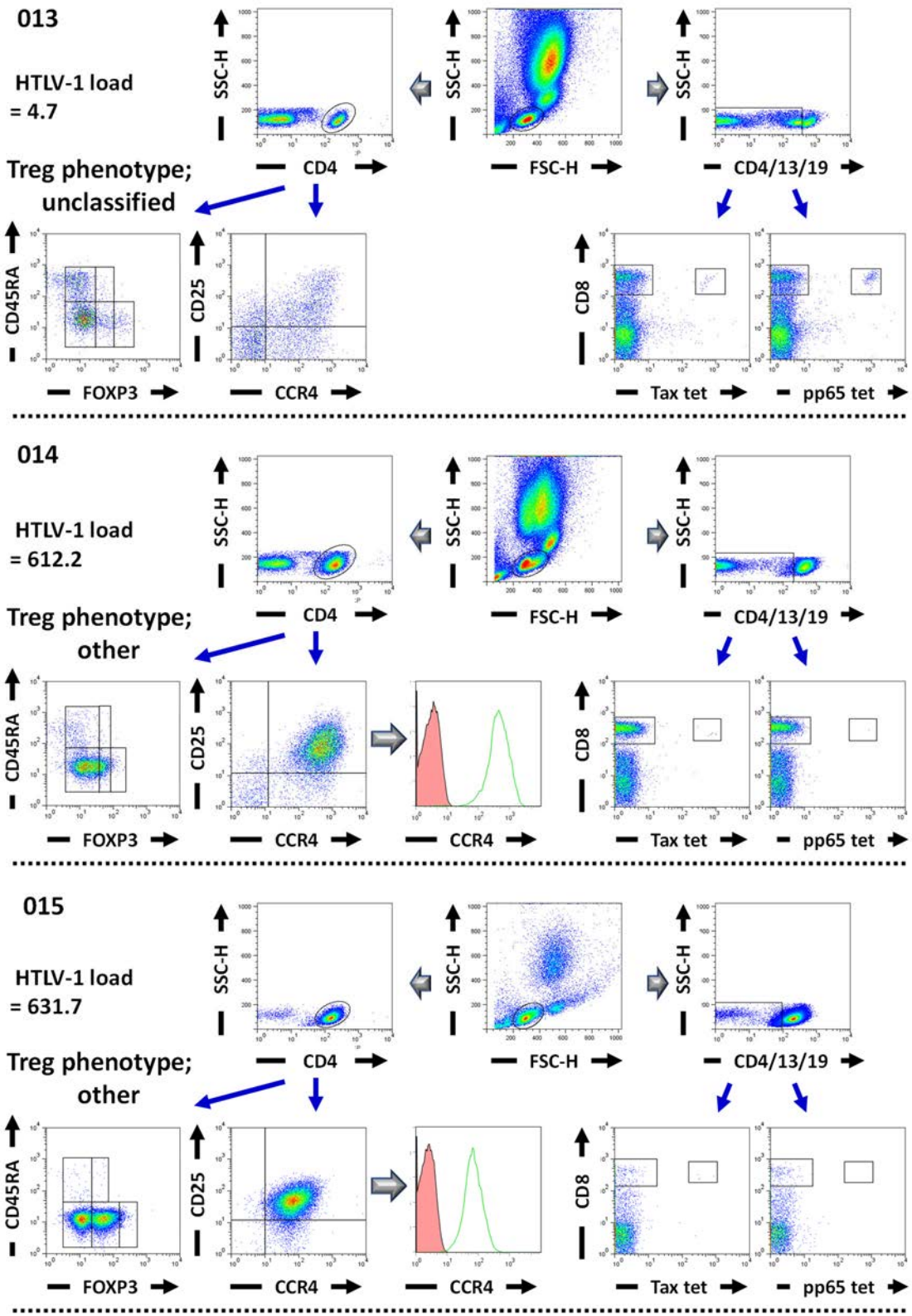
Supplemental FIGURE 3



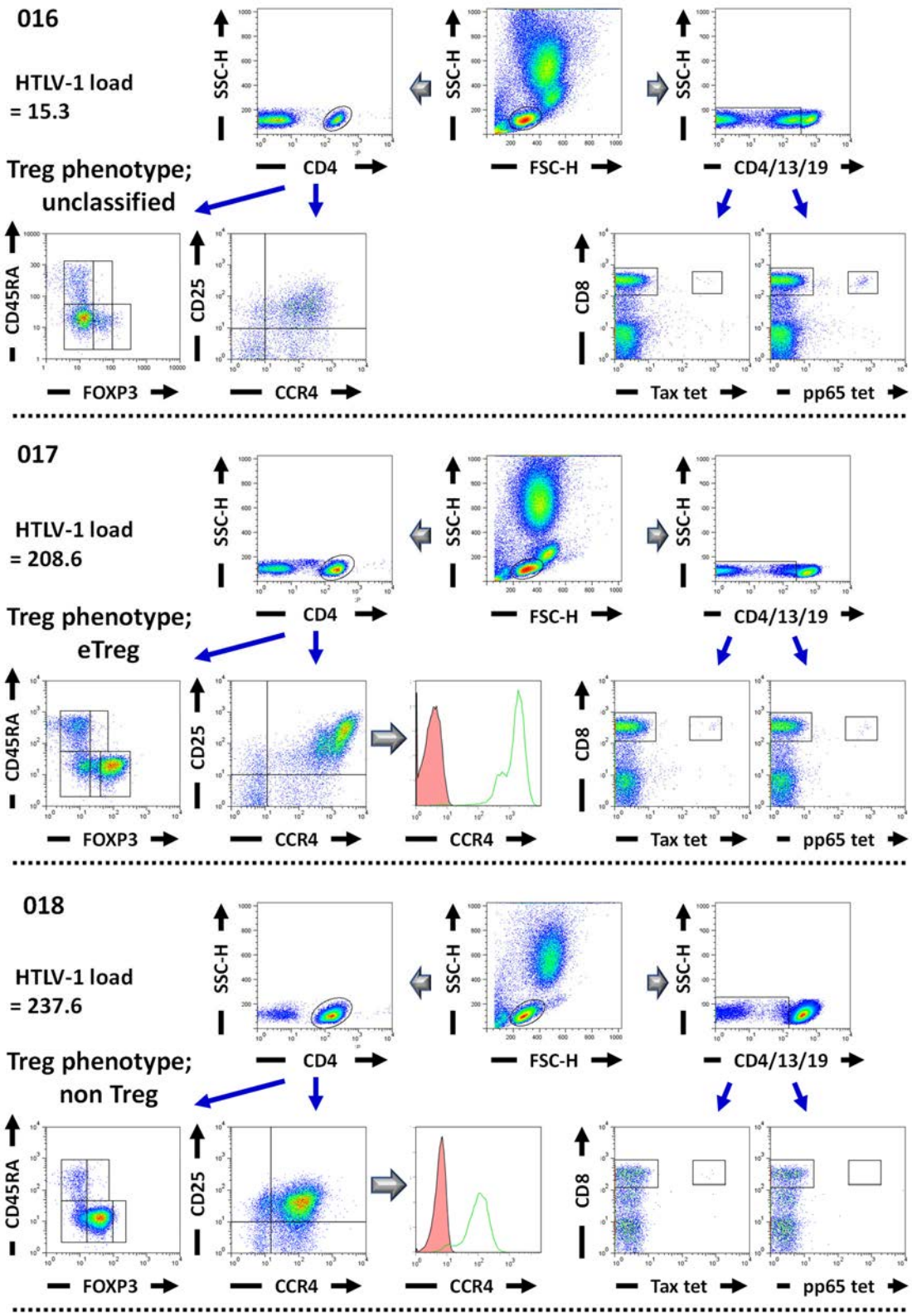
Supplemental FIGURE 3



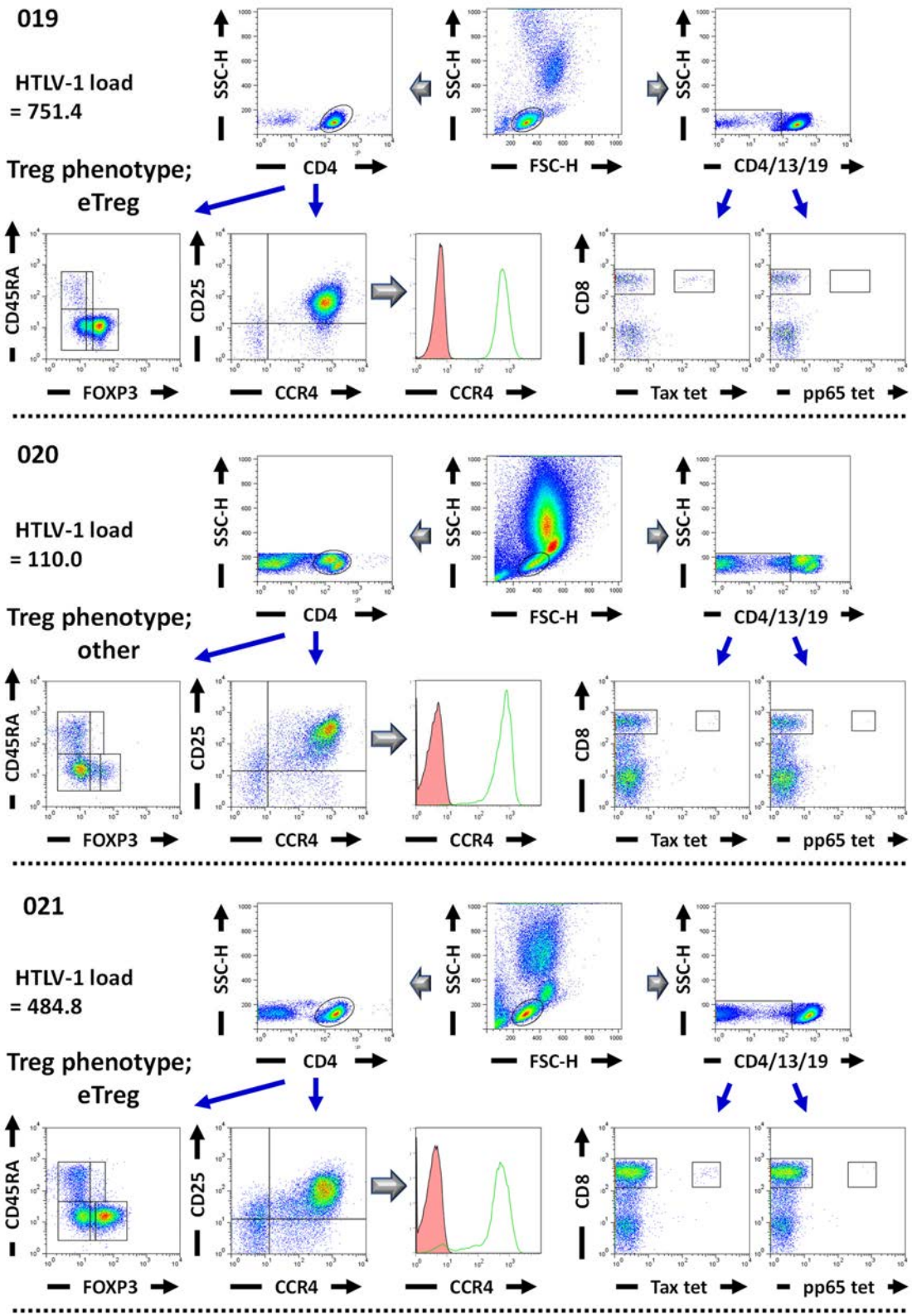
Supplemental FIGURE 3



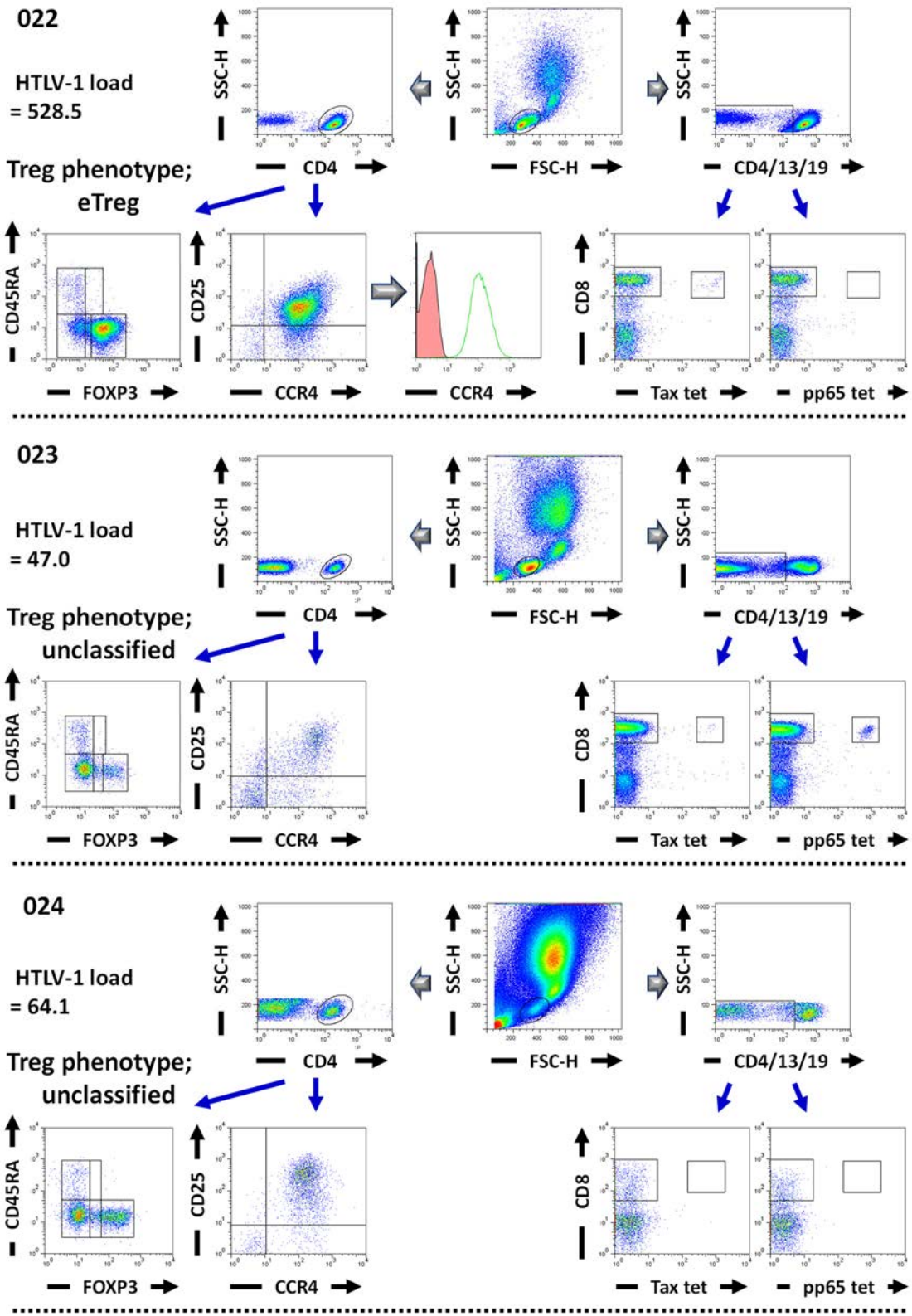
Supplemental FIGURE 3



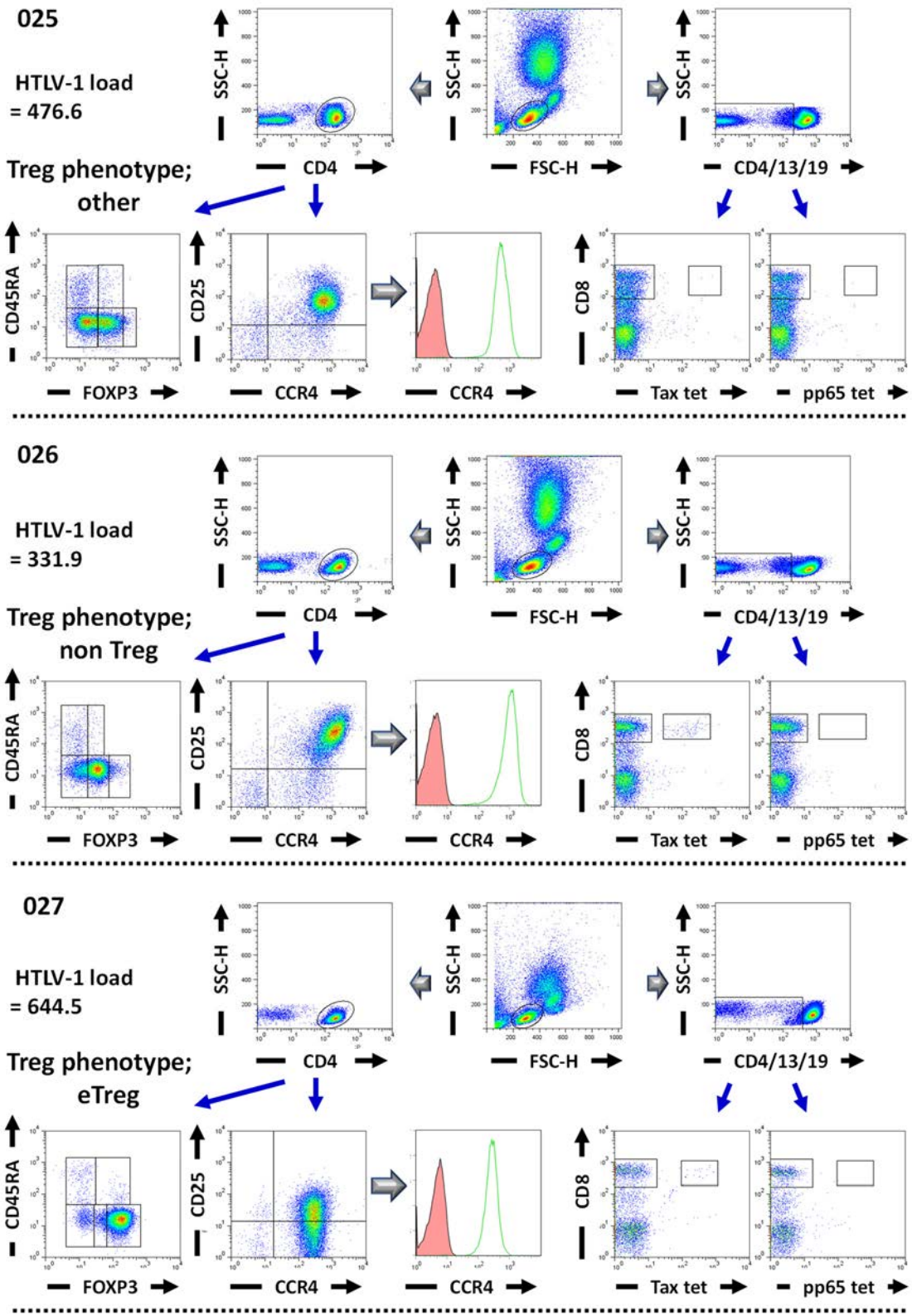
Supplemental FIGURE 3



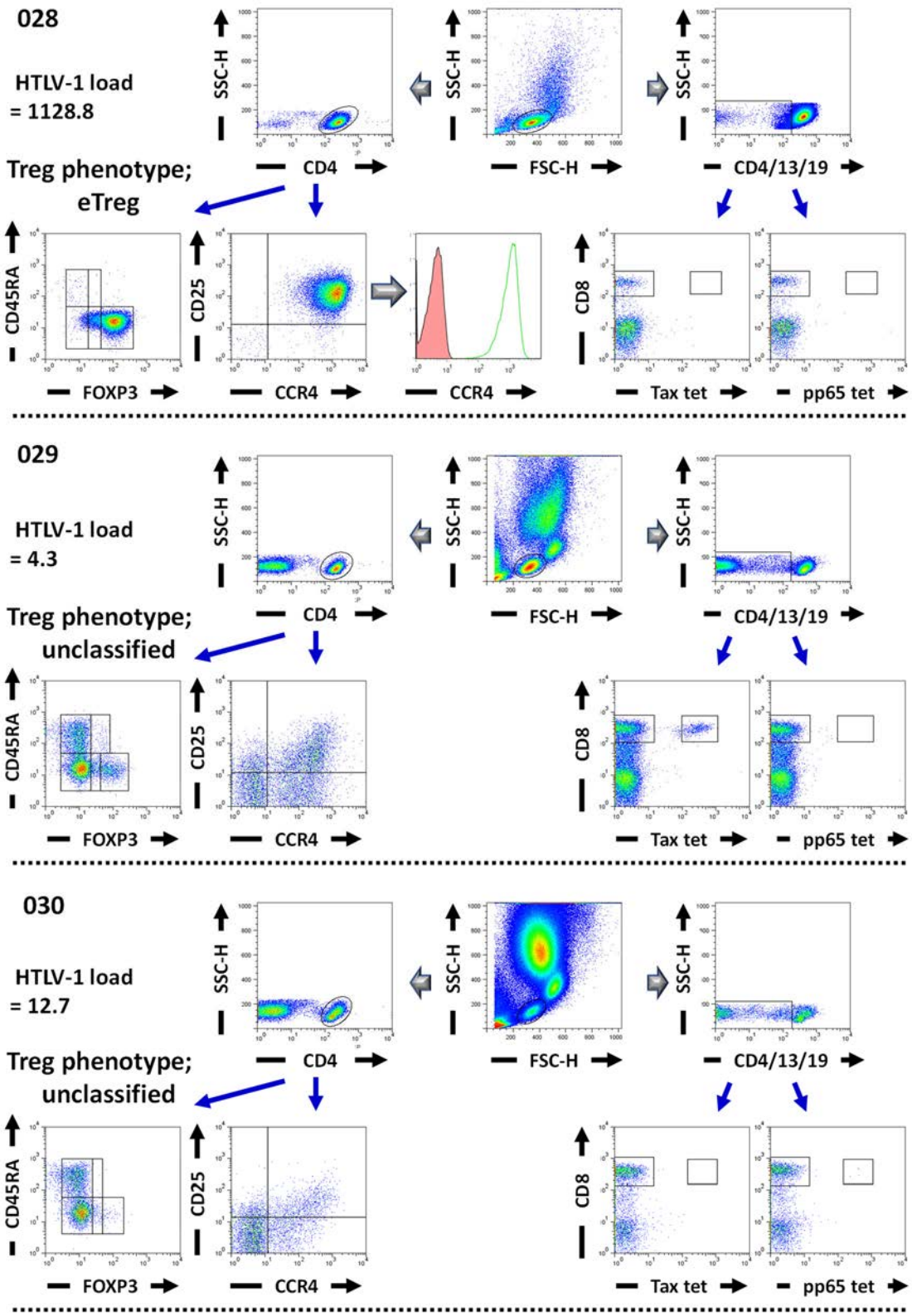
Supplemental FIGURE 3



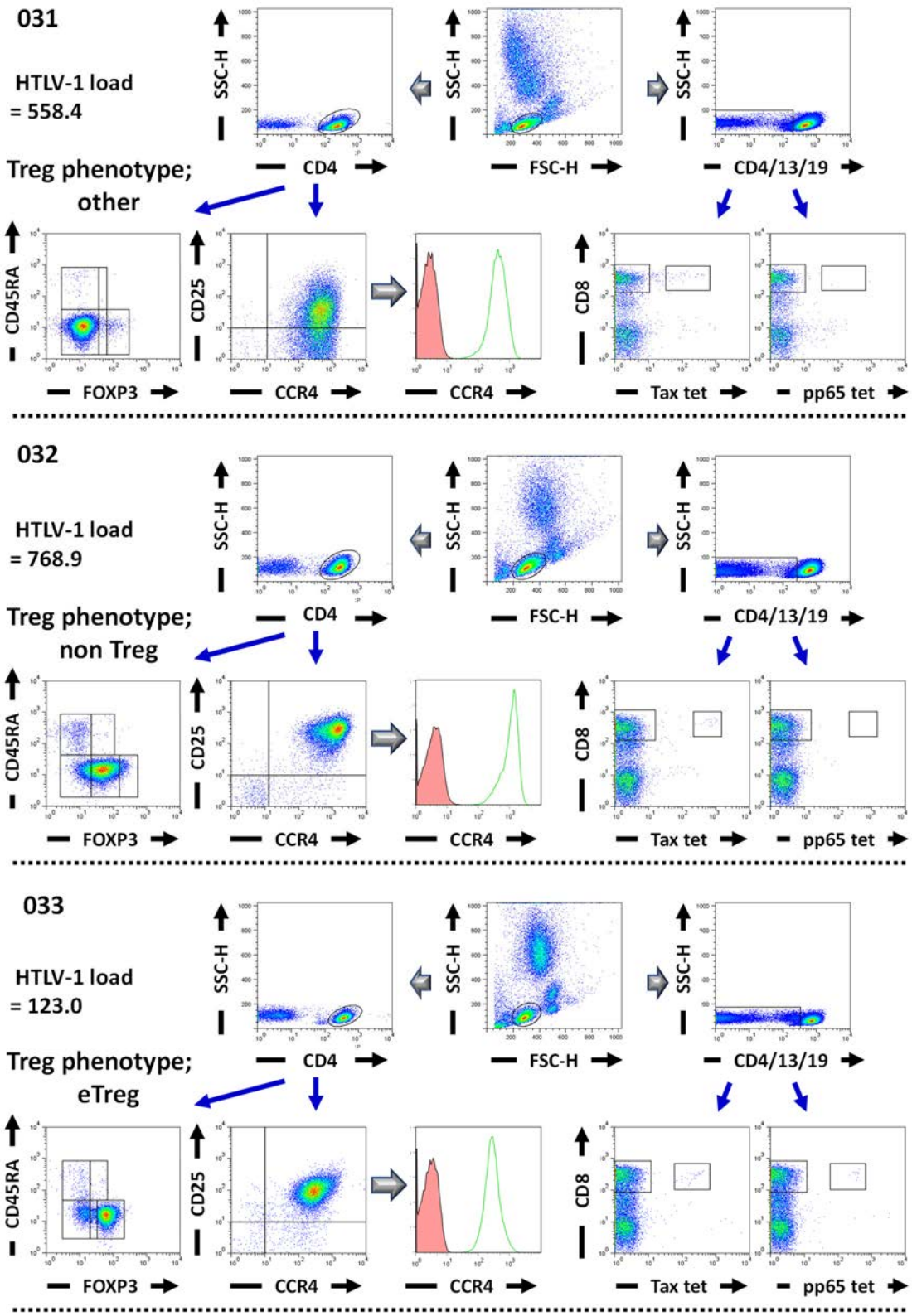
Supplemental FIGURE 3



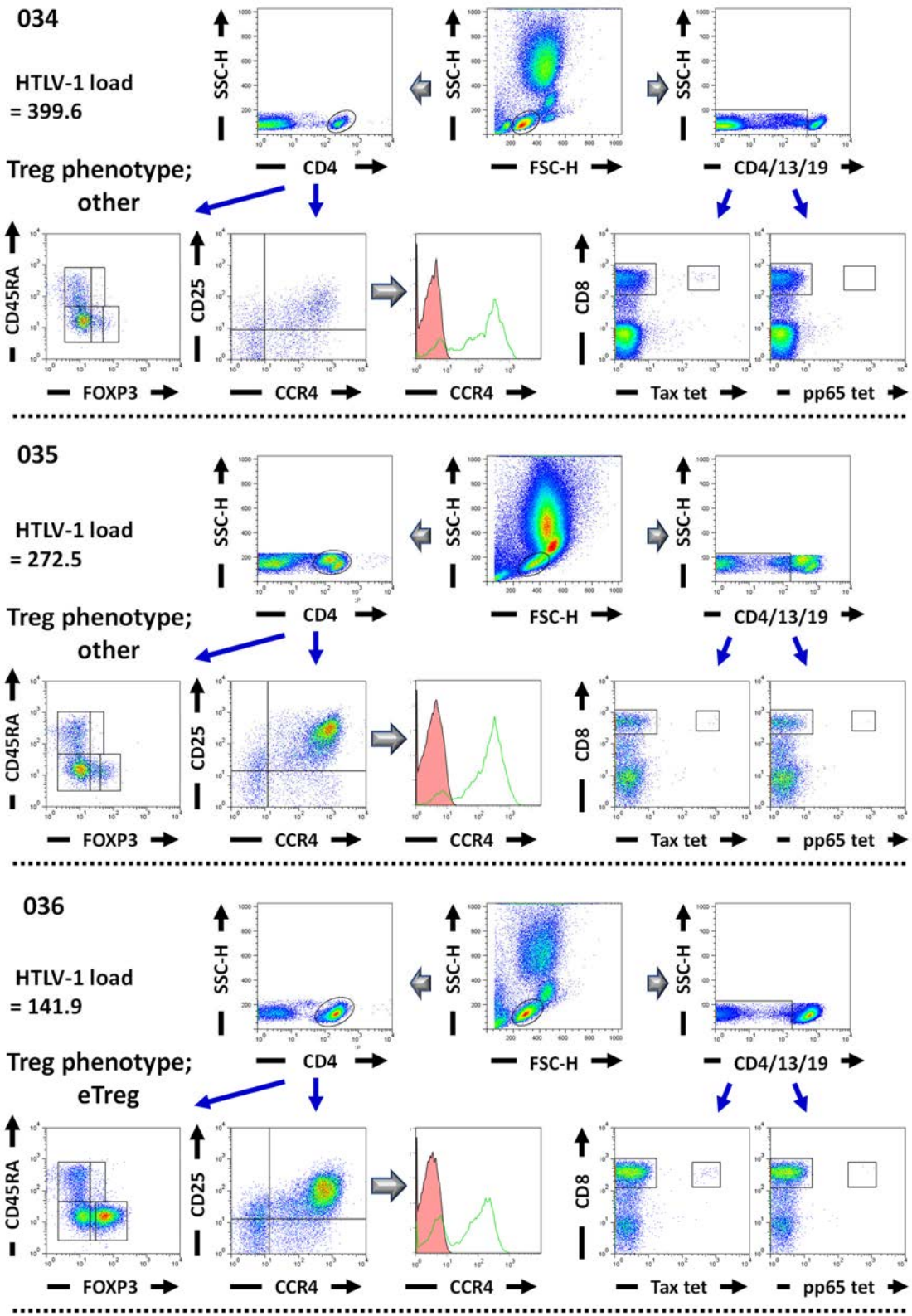
Supplemental FIGURE 3



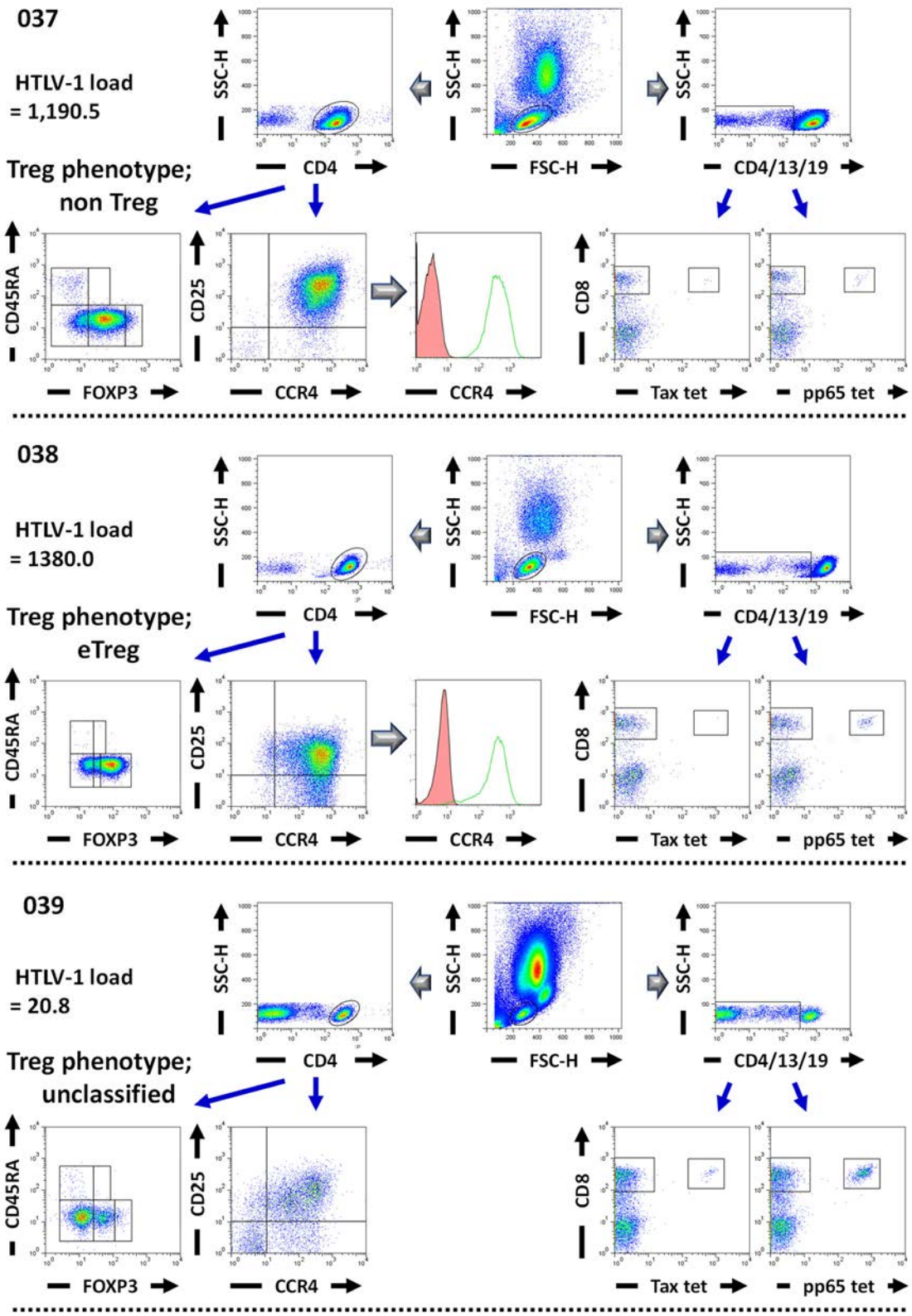
Supplemental FIGURE 3



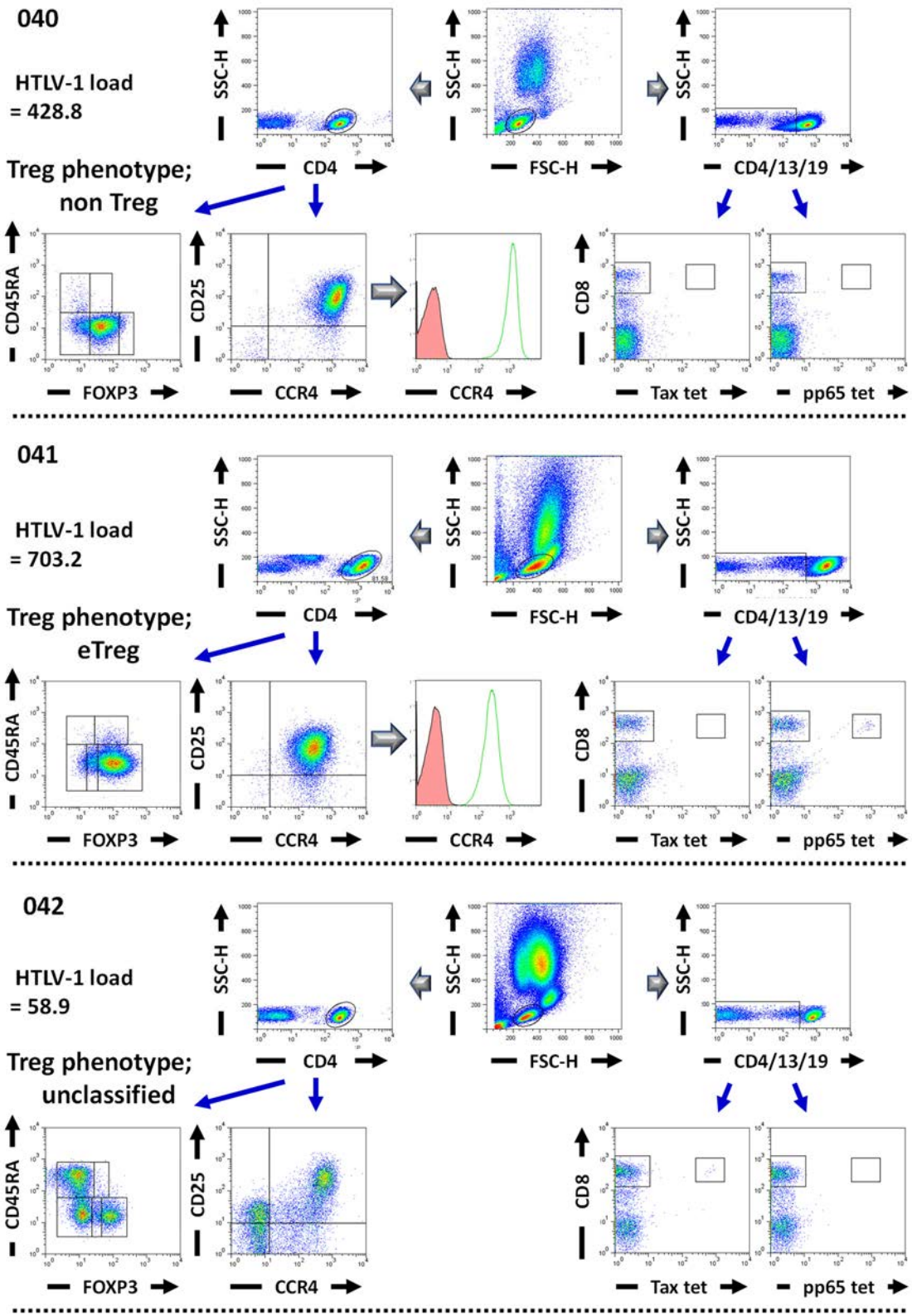
Supplemental FIGURE 3



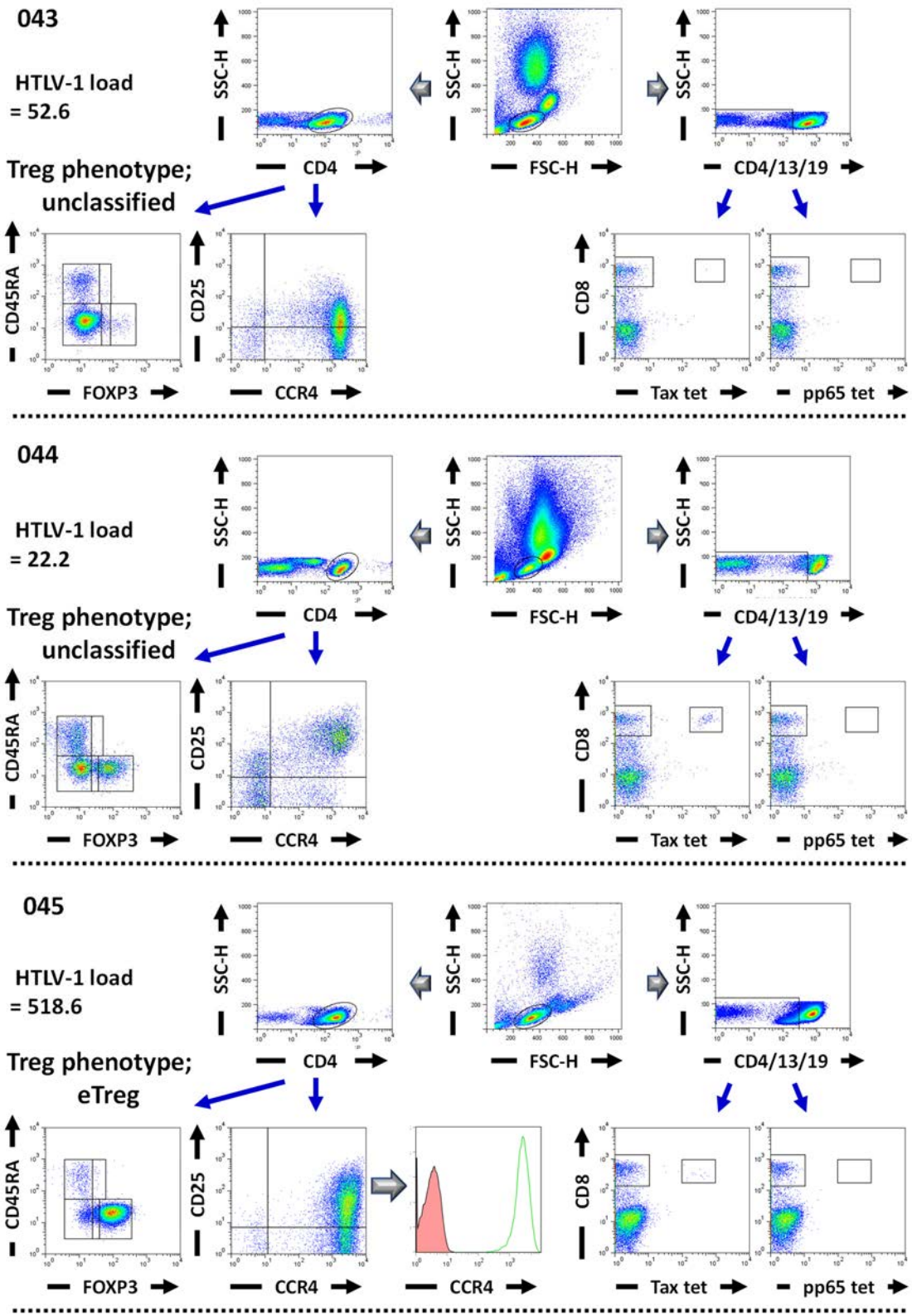
Supplemental FIGURE 3



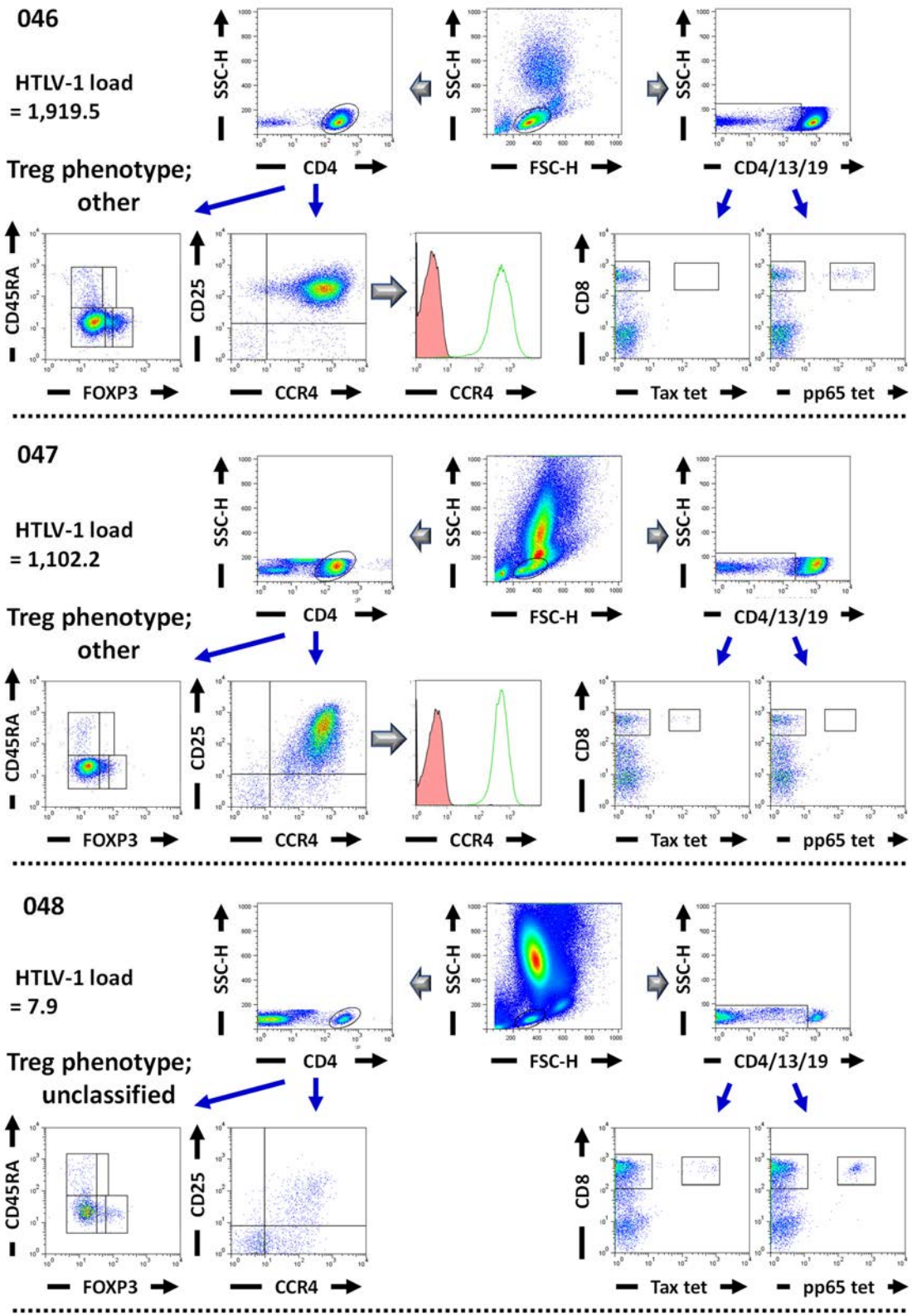
Supplemental FIGURE 3



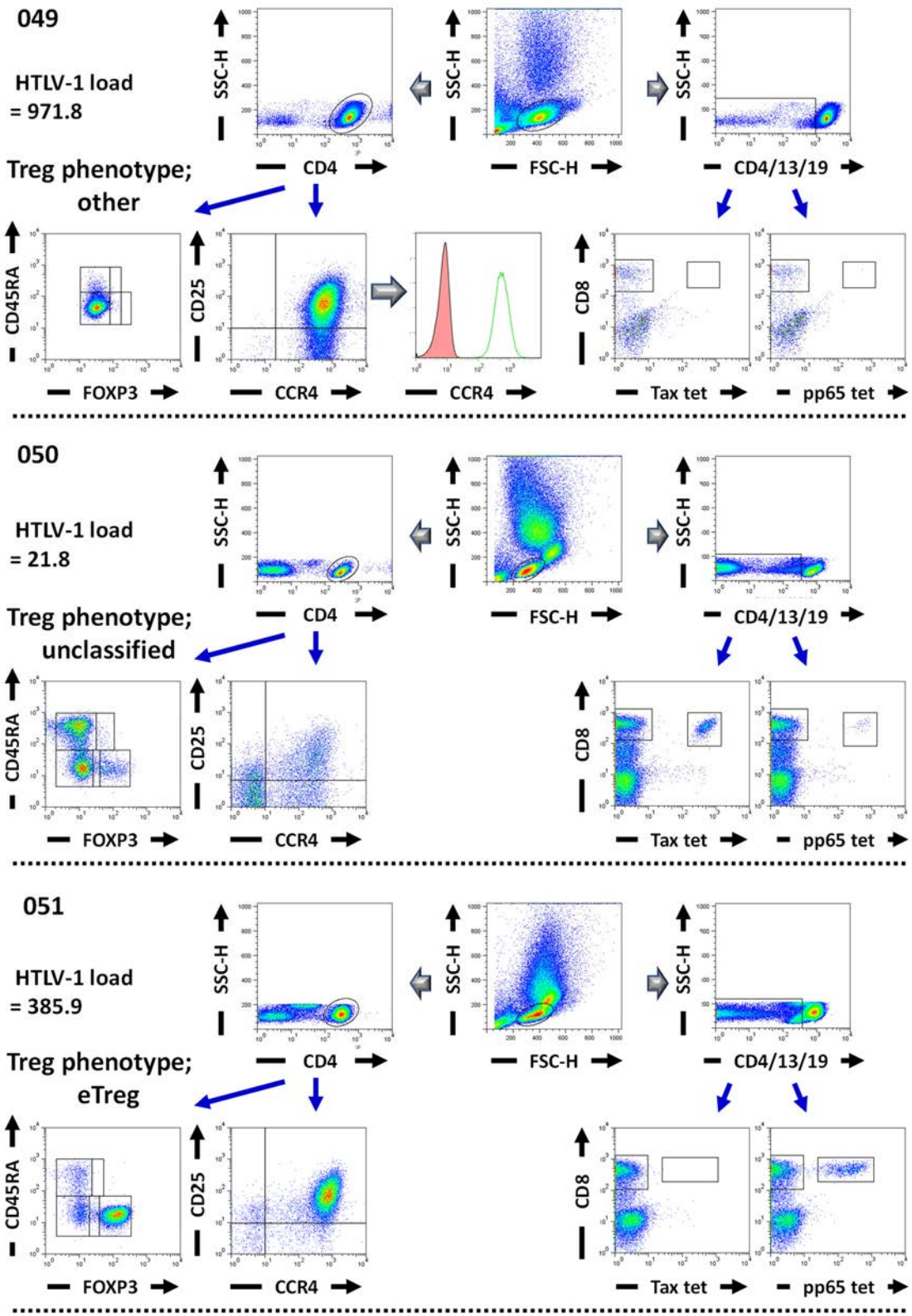
Supplemental FIGURE 3



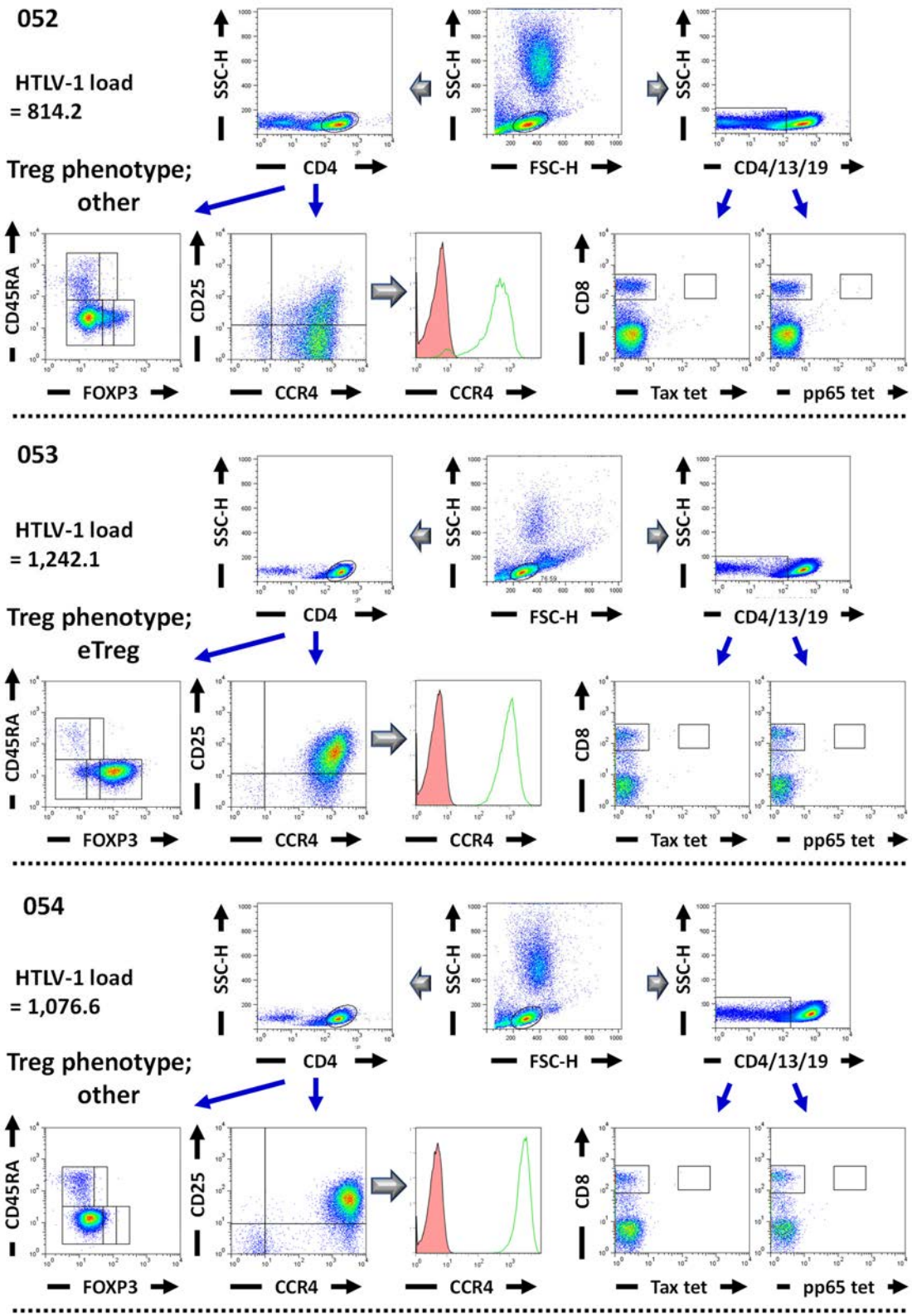
Supplemental FIGURE 3



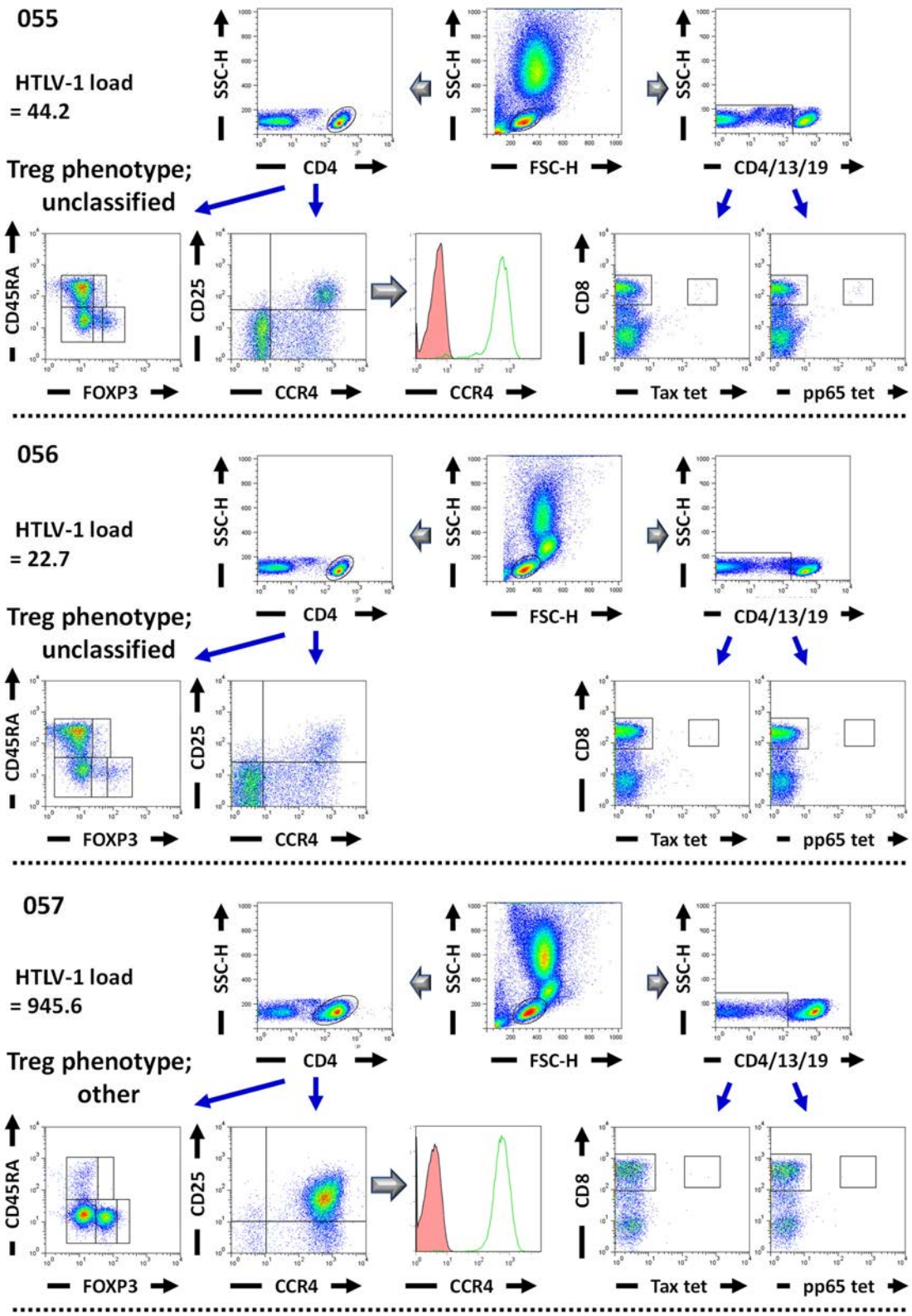
Supplemental FIGURE 3



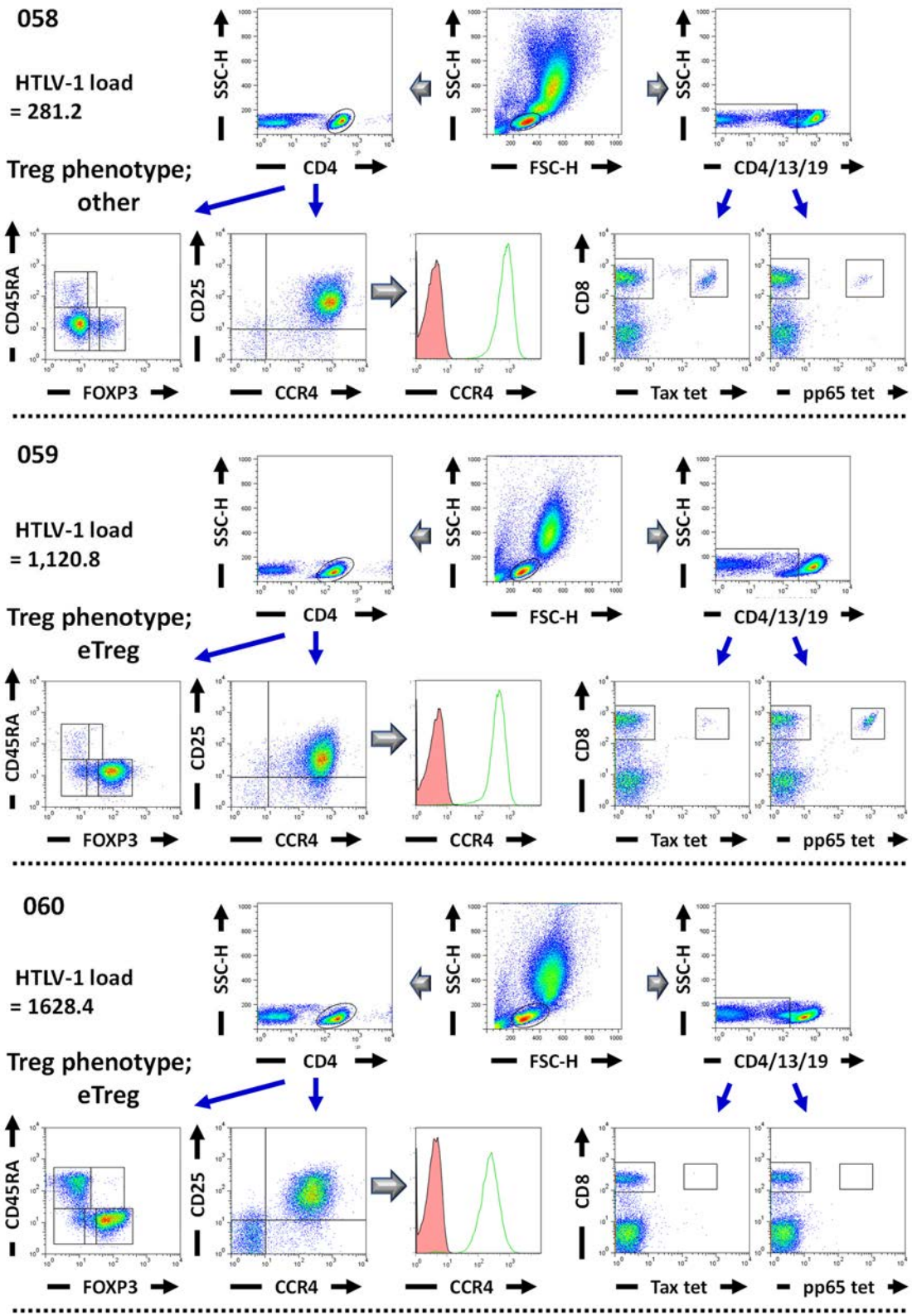
Supplemental FIGURE 3



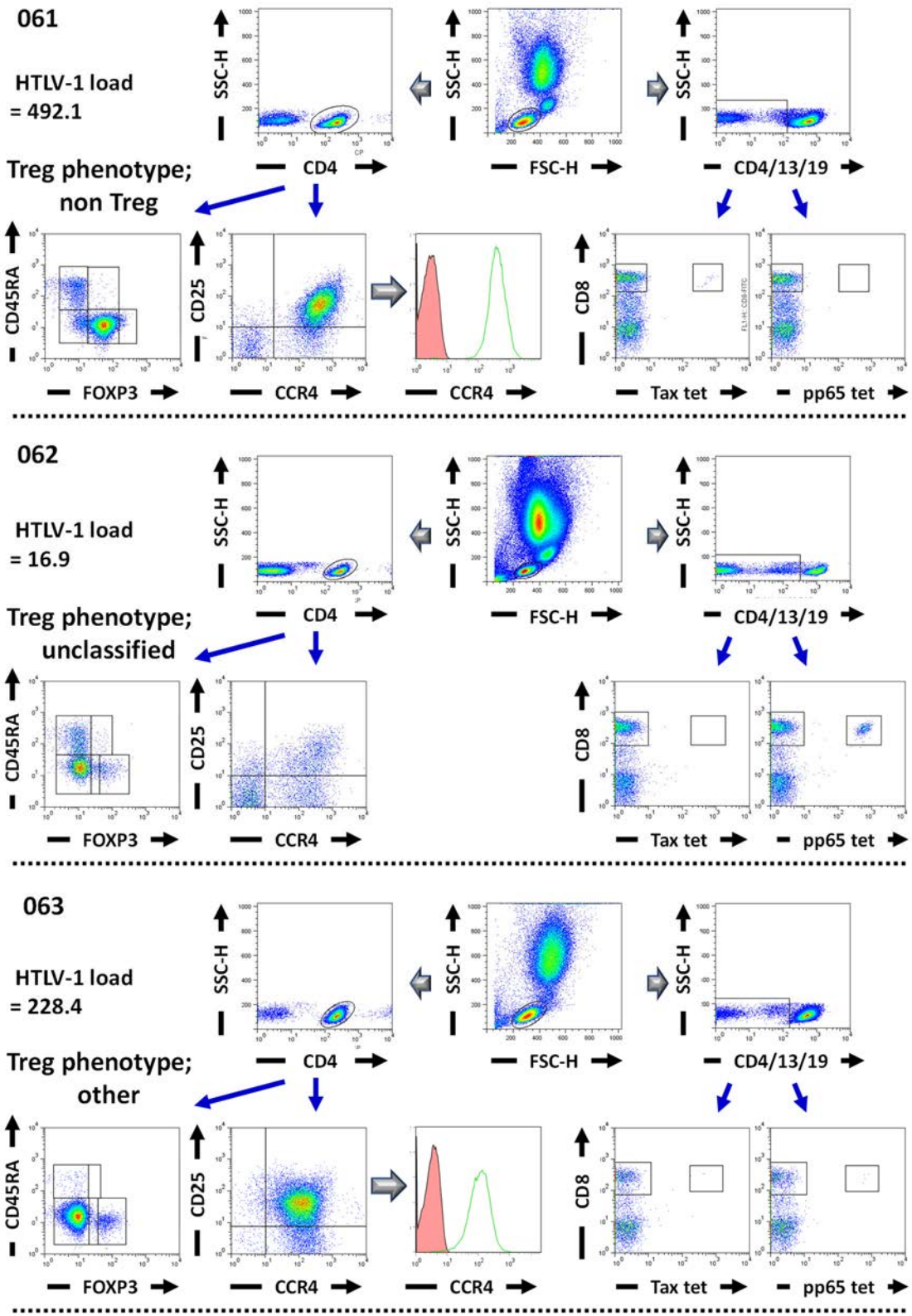
Supplemental FIGURE 3



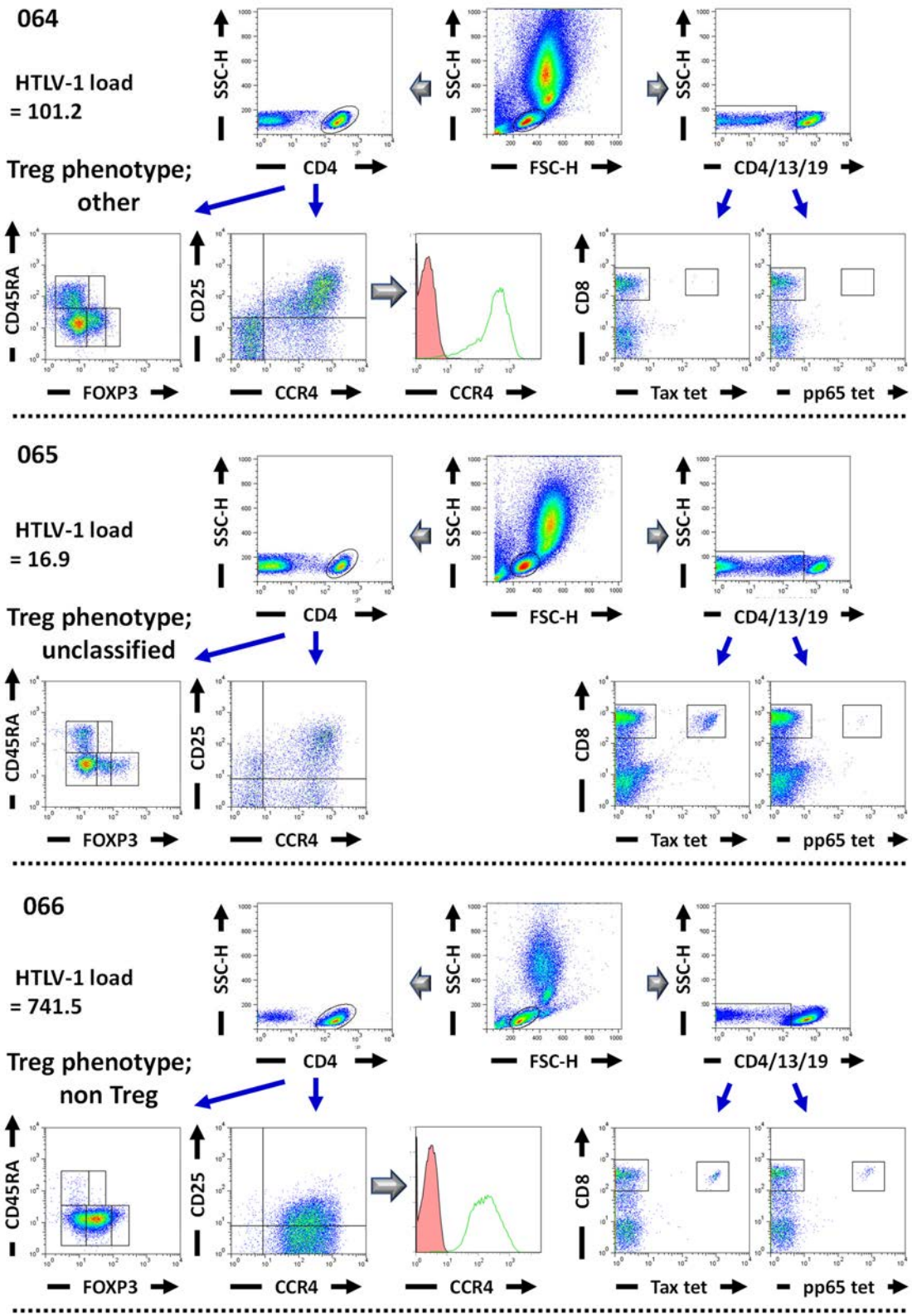
Supplemental FIGURE 3



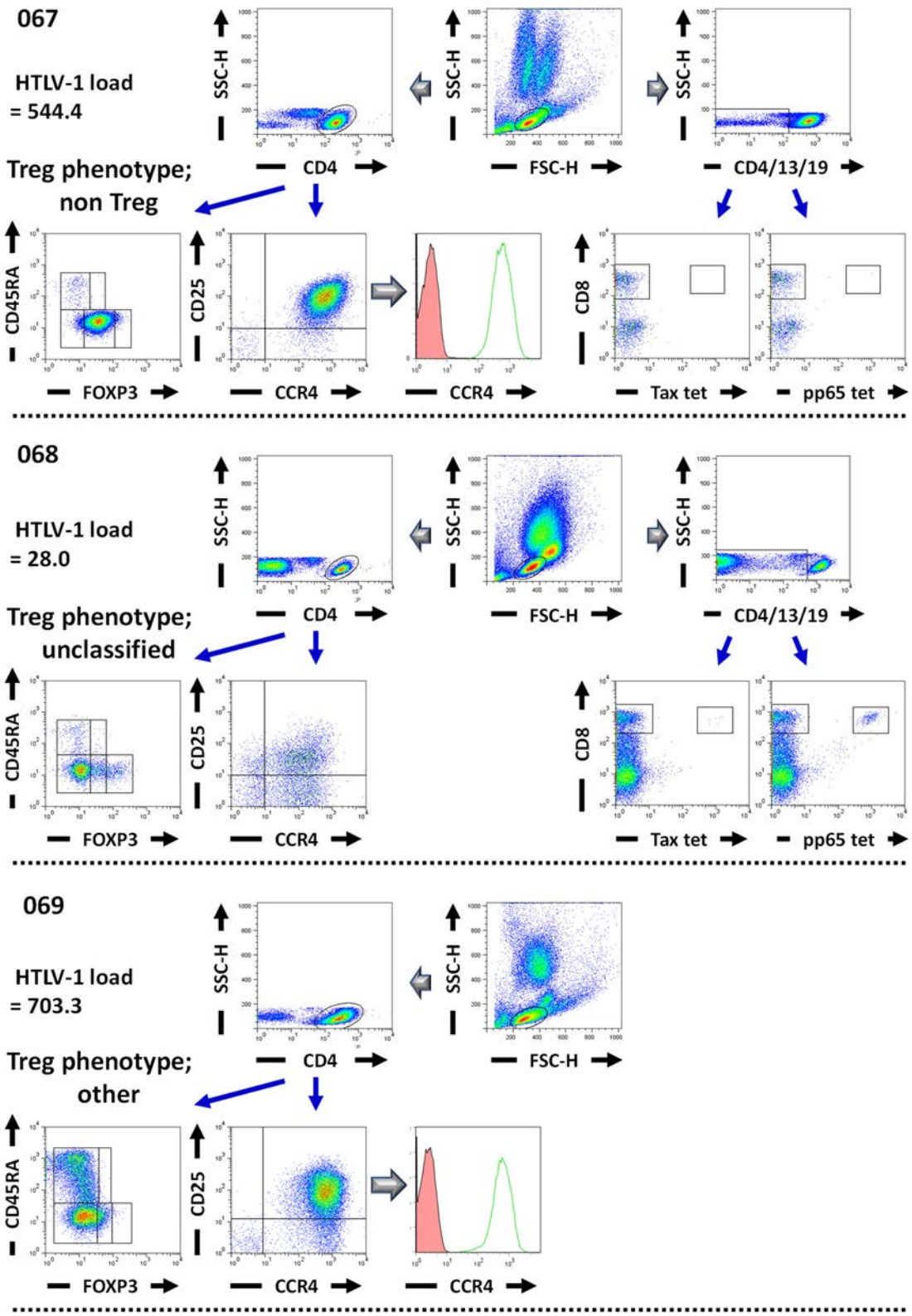
Supplemental FIGURE 3



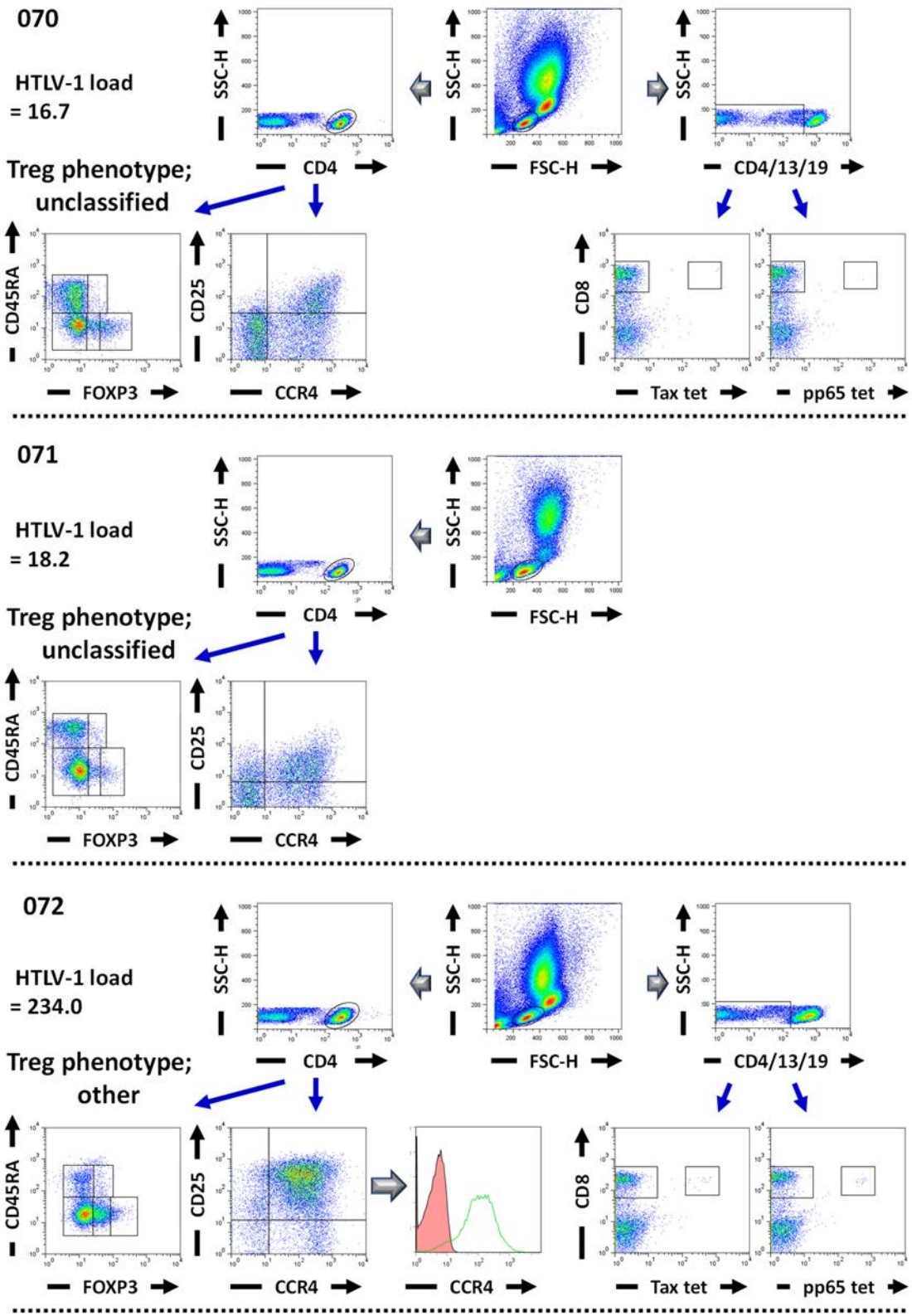
Supplemental FIGURE 3



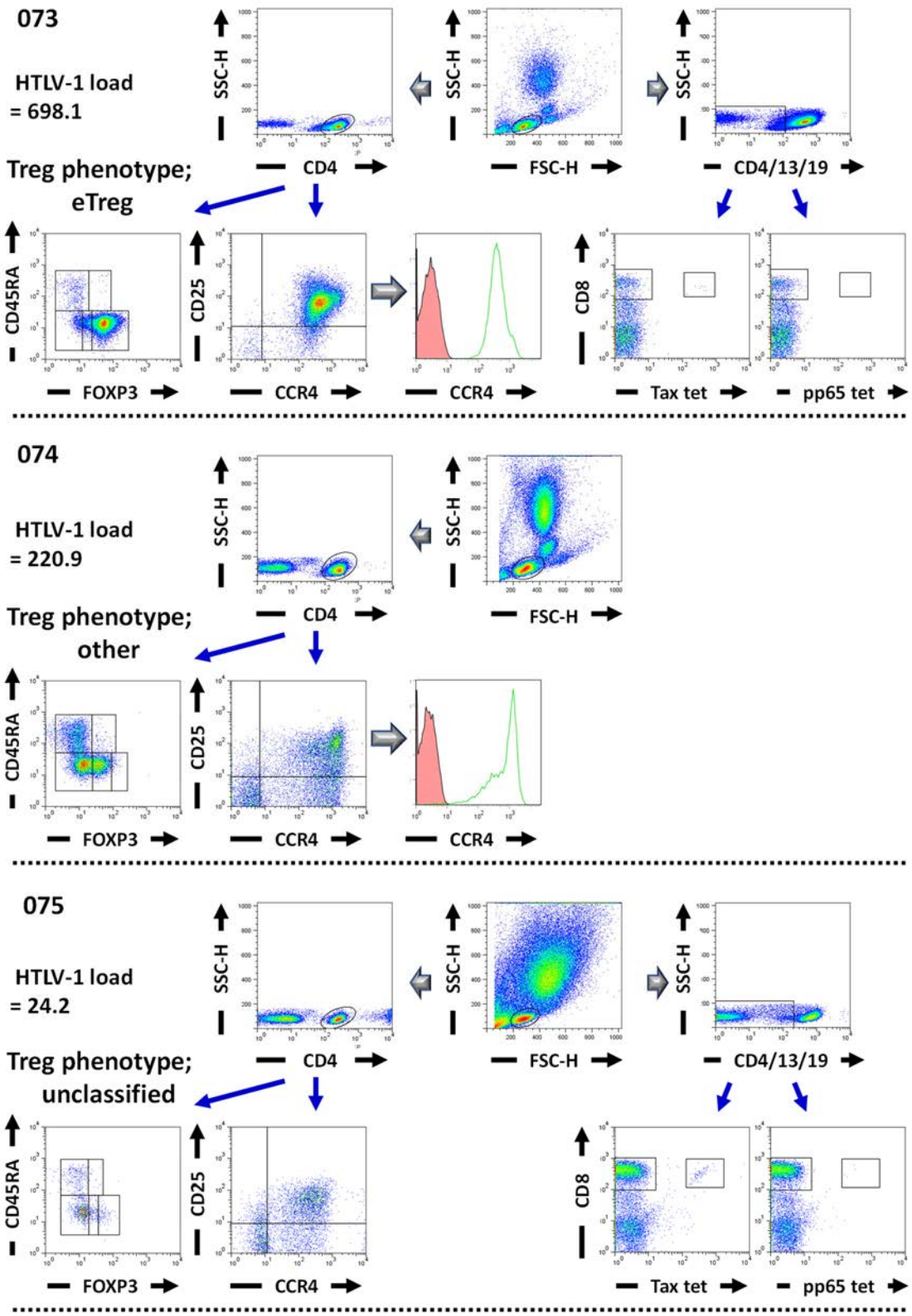
Supplemental FIGURE 3



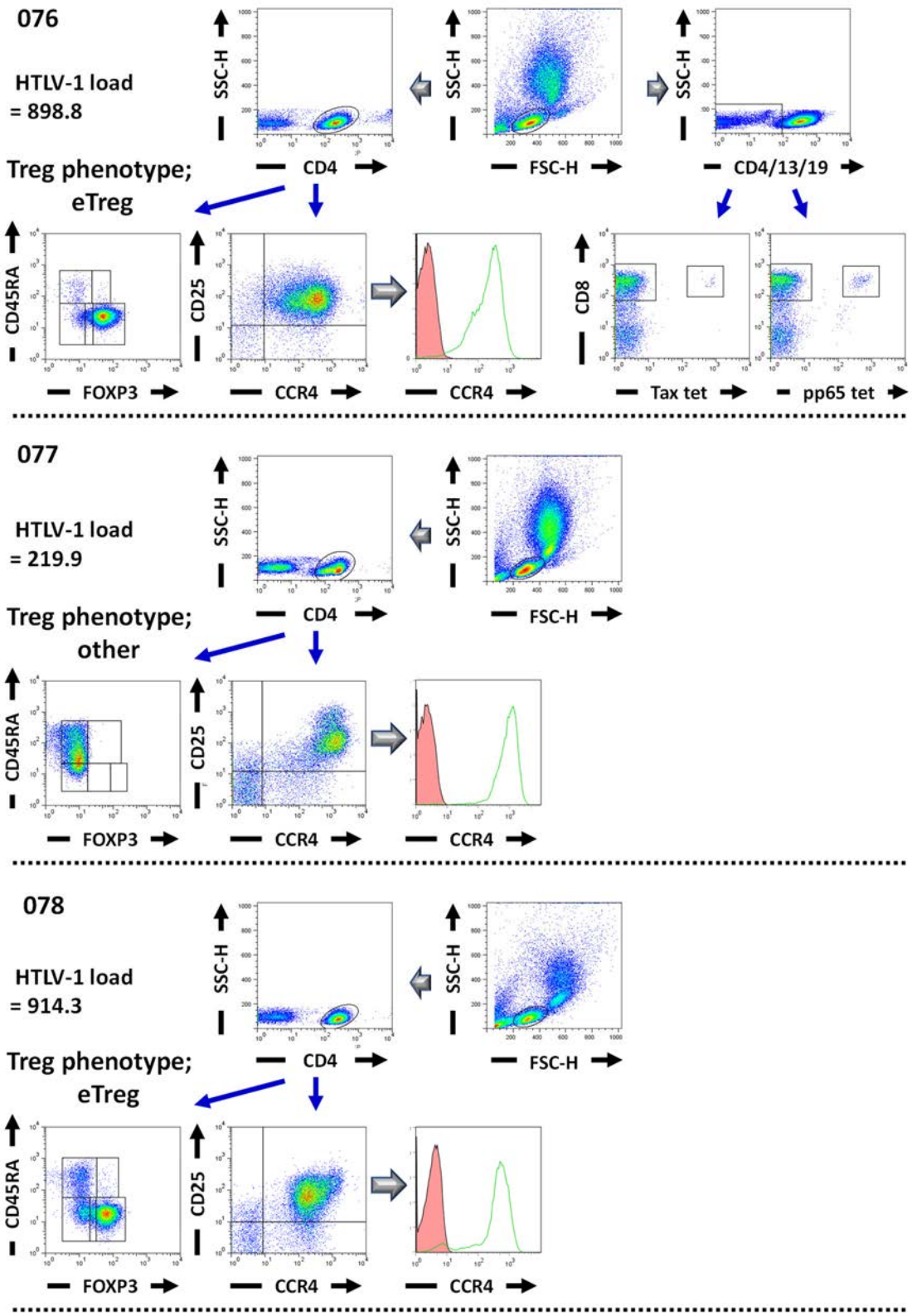
Supplemental FIGURE 3



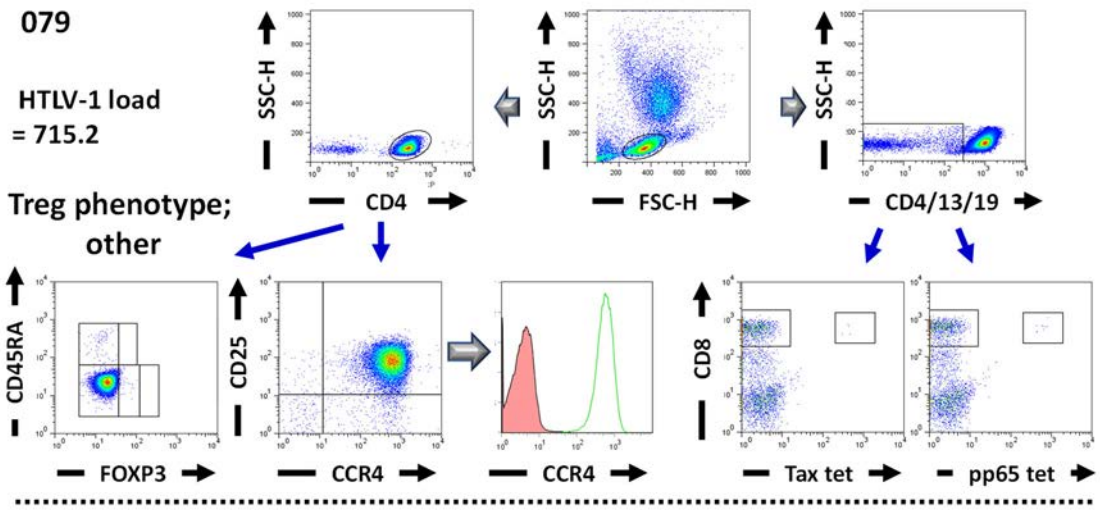
Supplemental FIGURE 3



Supplemental FIGURE 3

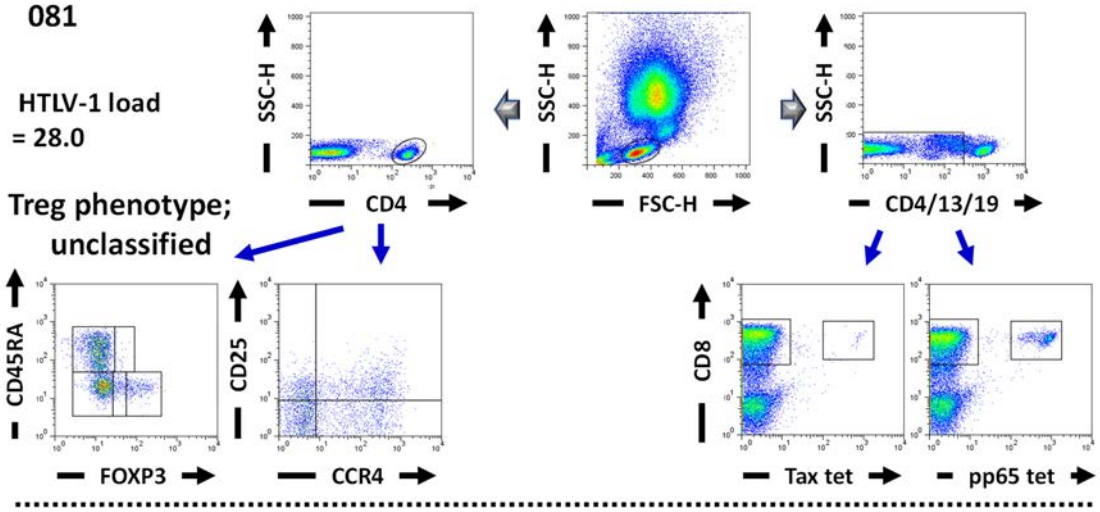


Supplemental FIGURE 3

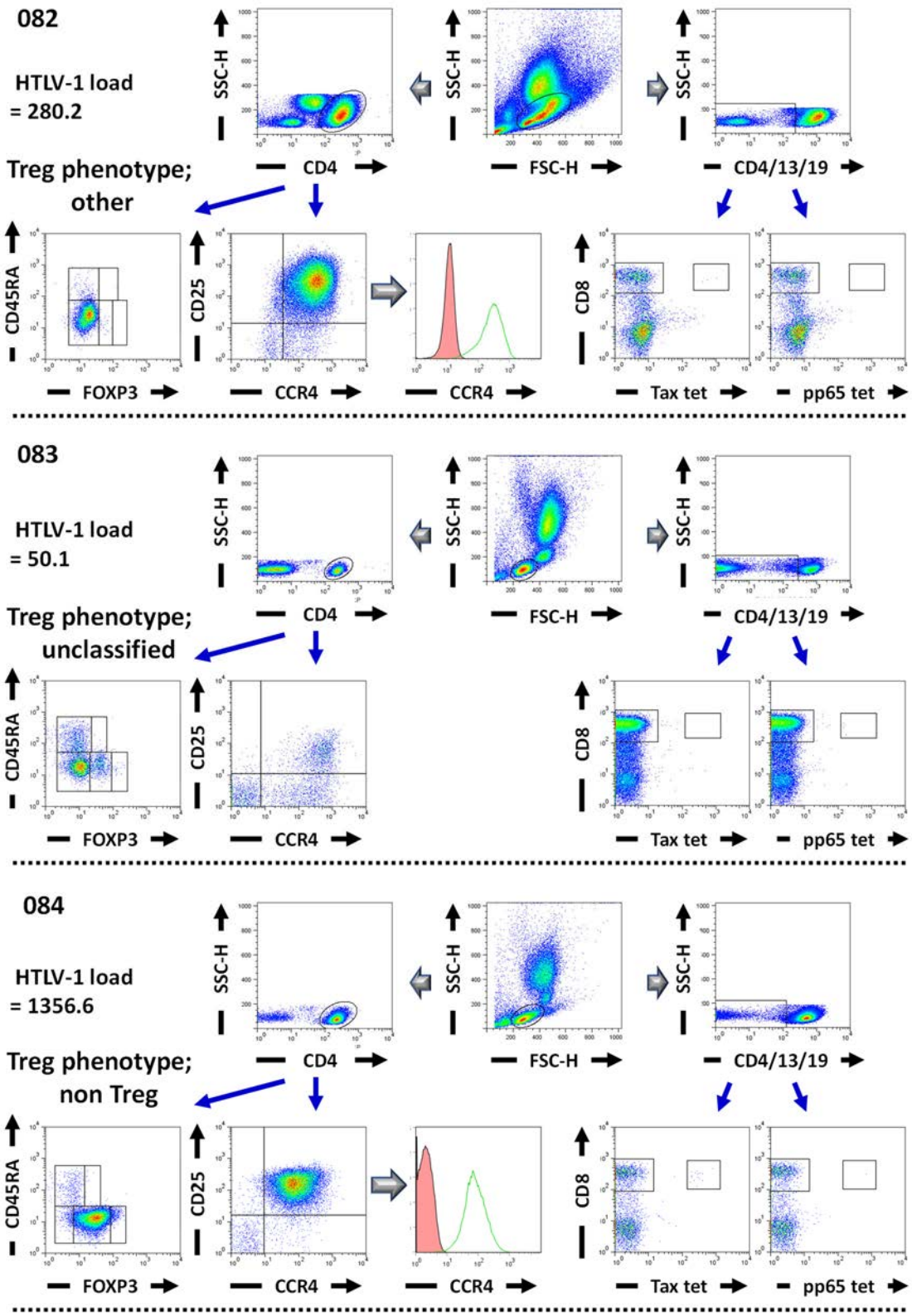


080

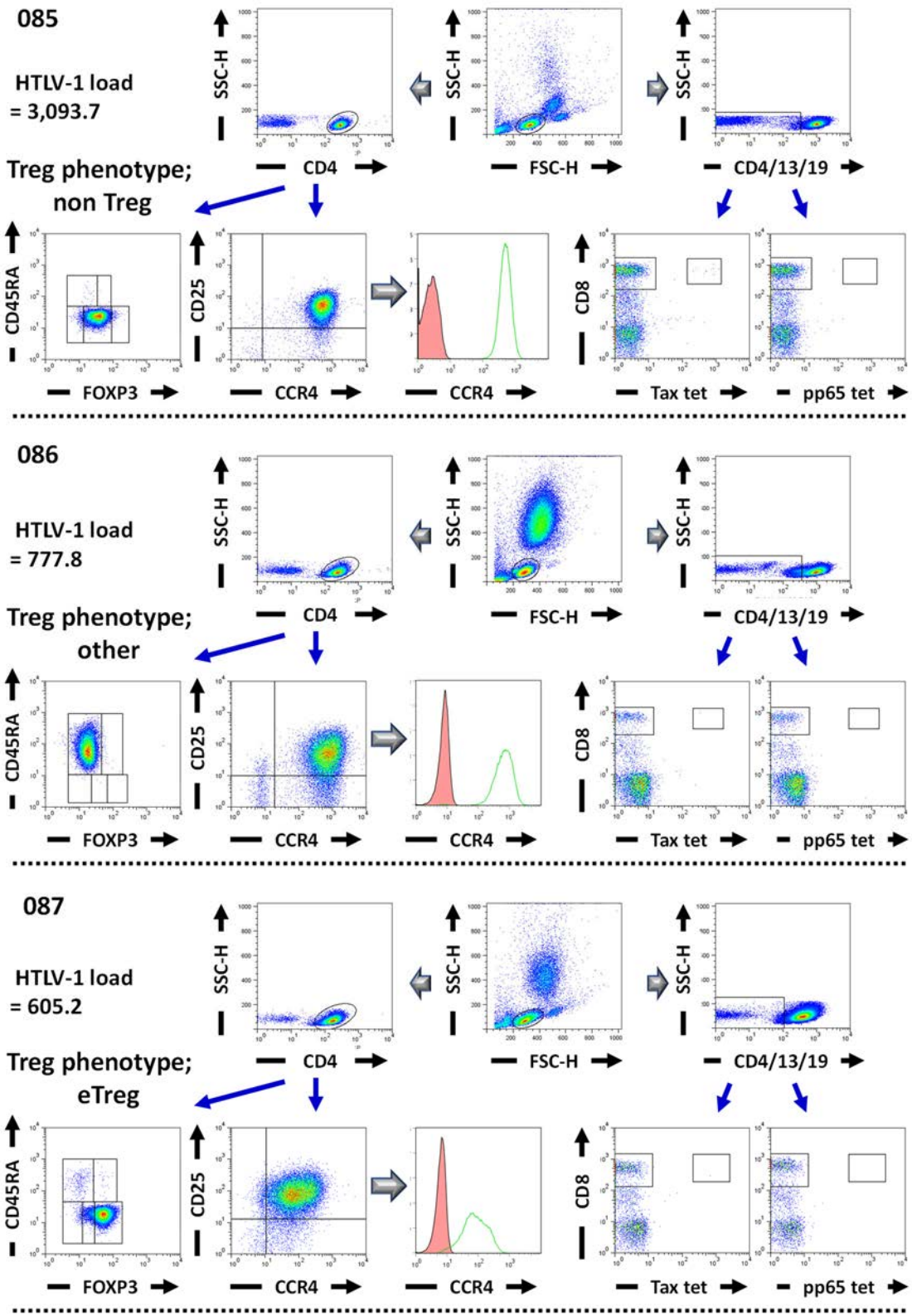
HTLV-1 load
= 382.1



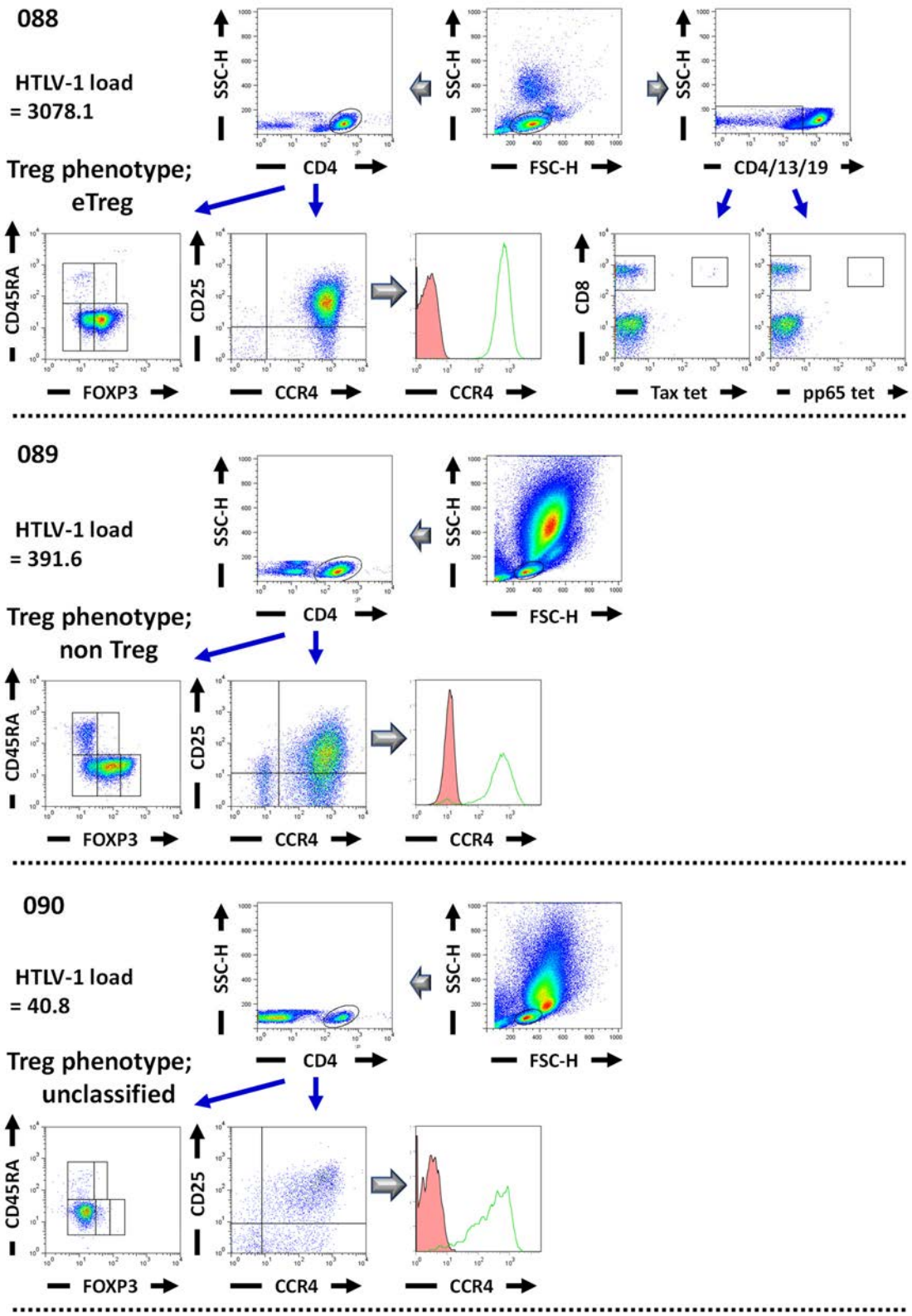
Supplemental FIGURE 3



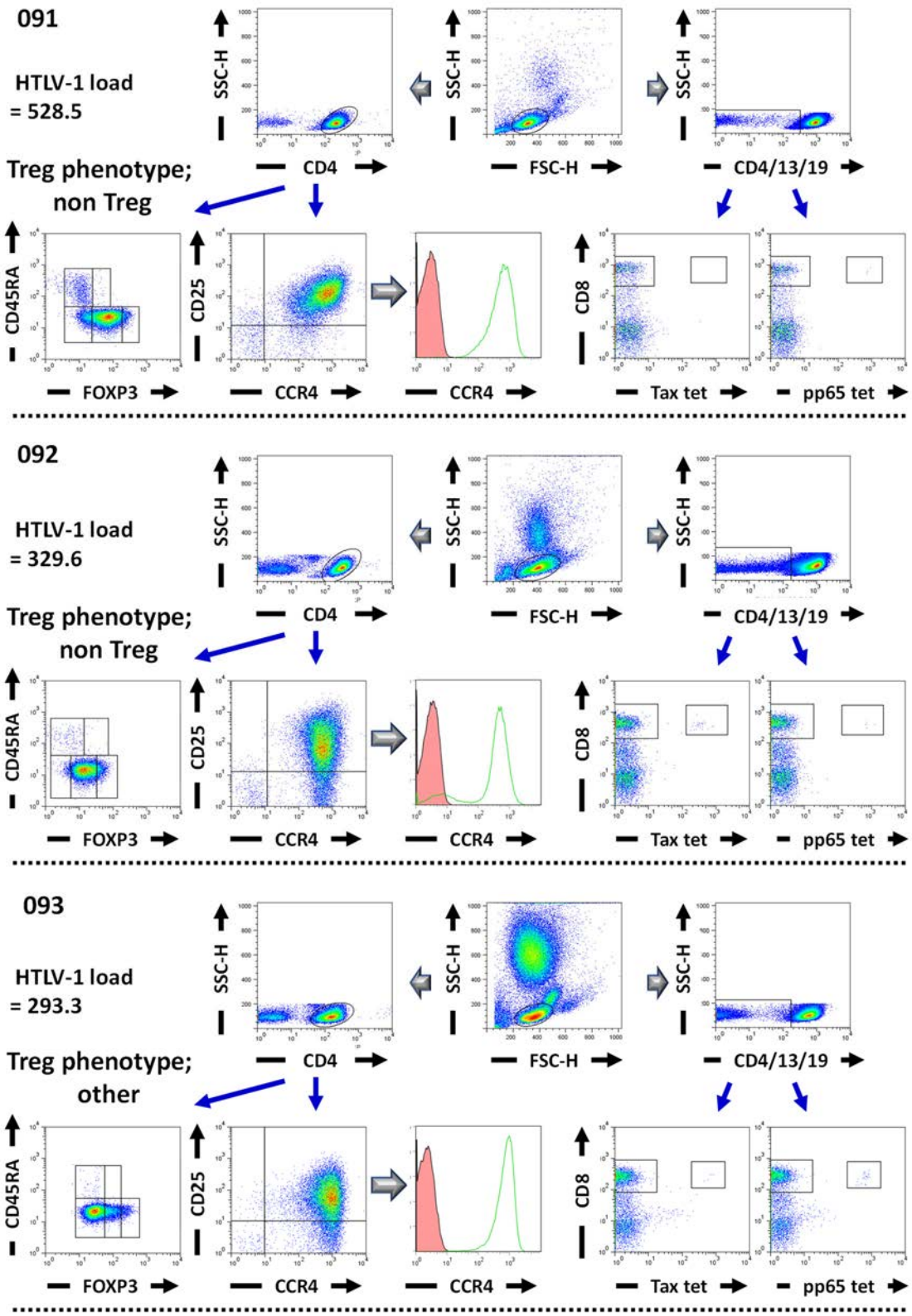
Supplemental FIGURE 3



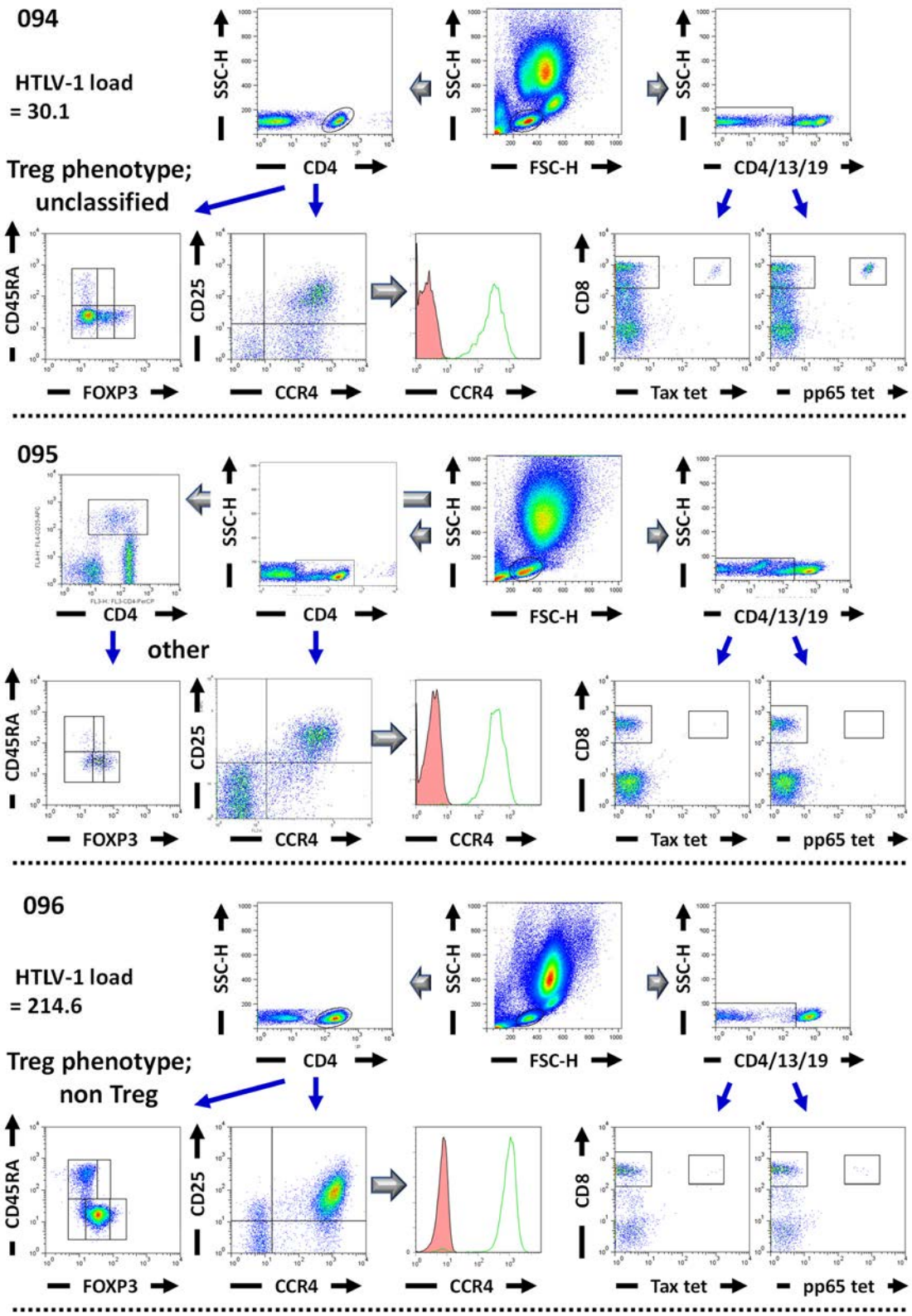
Supplemental FIGURE 3



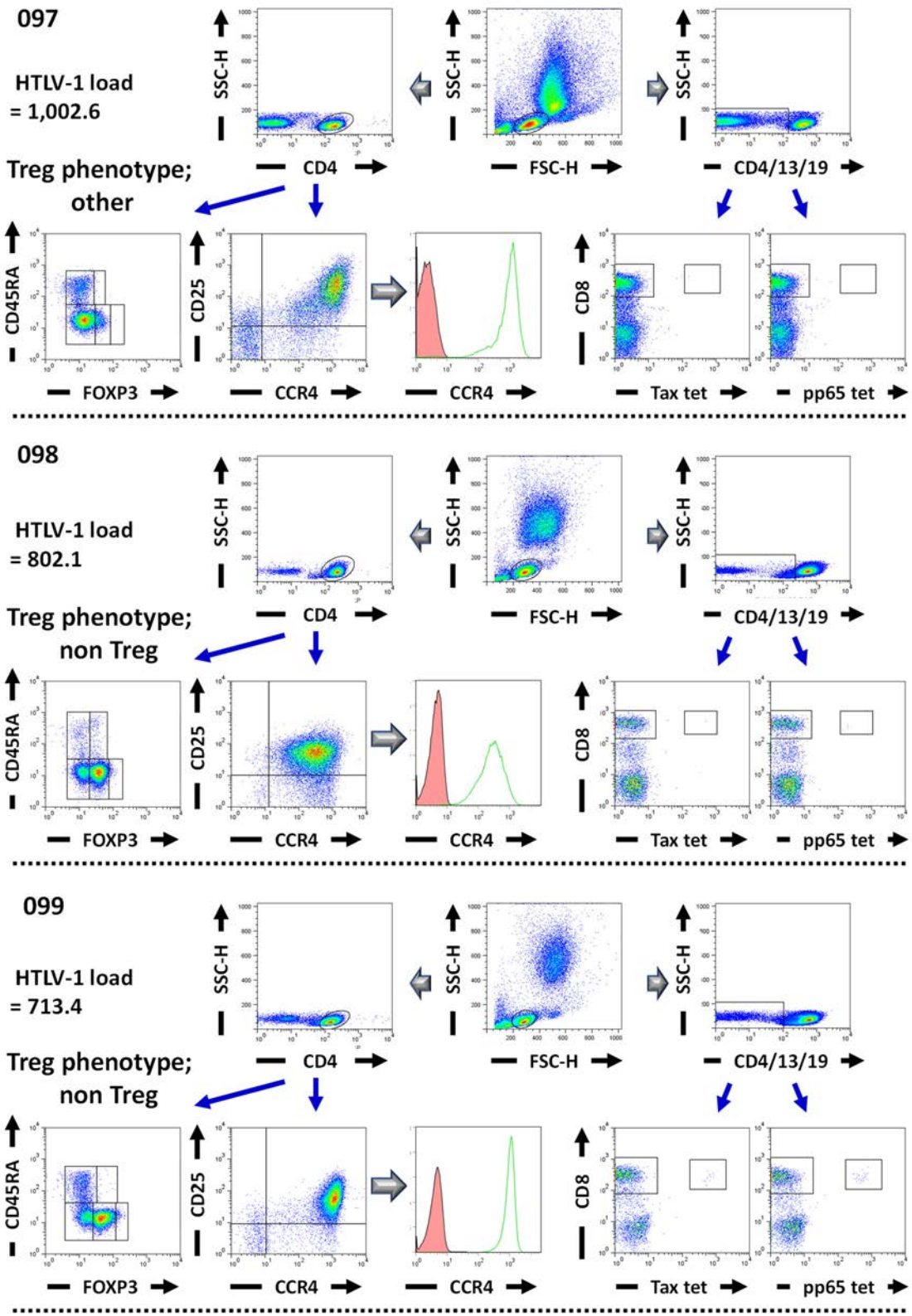
Supplemental FIGURE 3



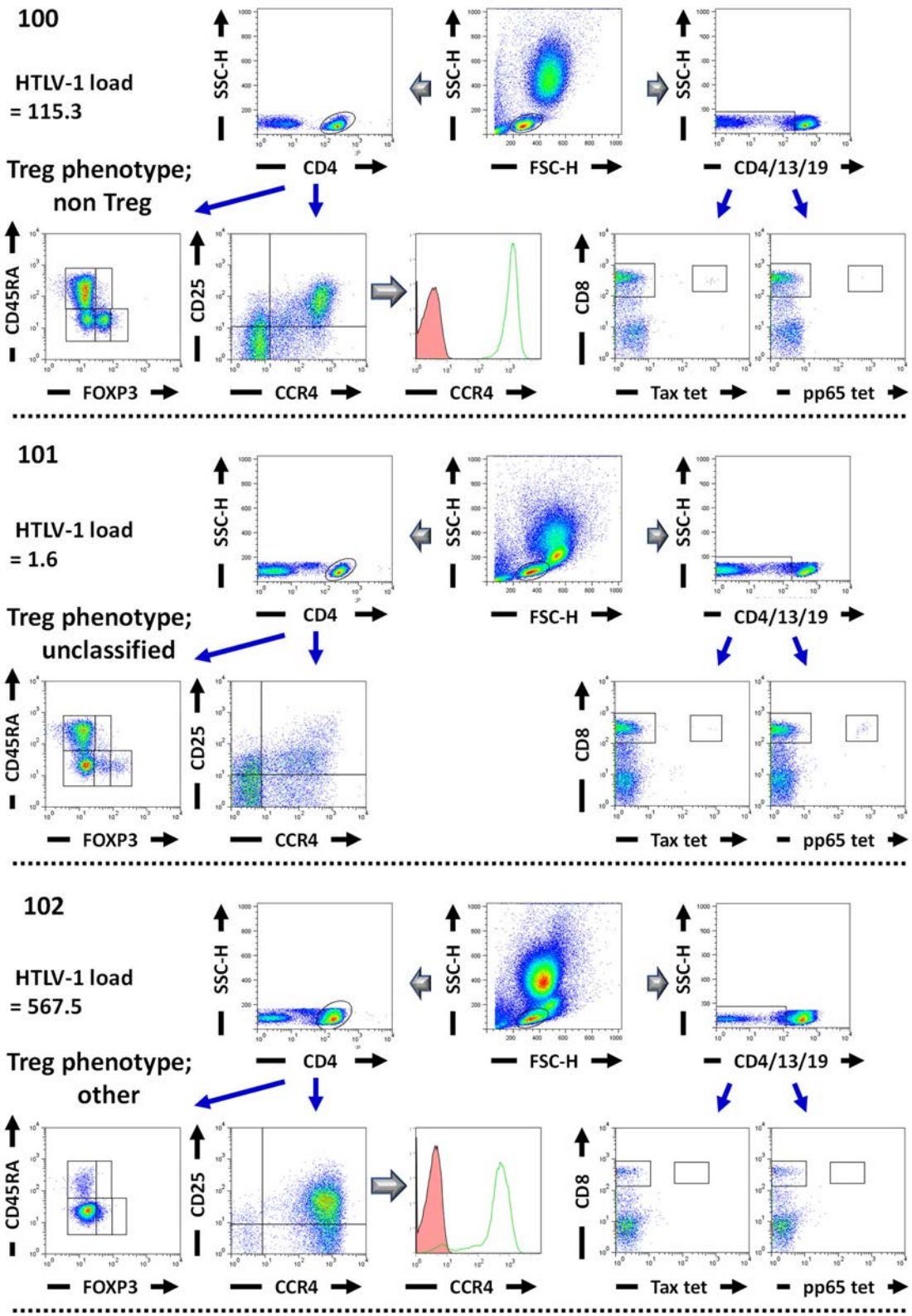
Supplemental FIGURE 3



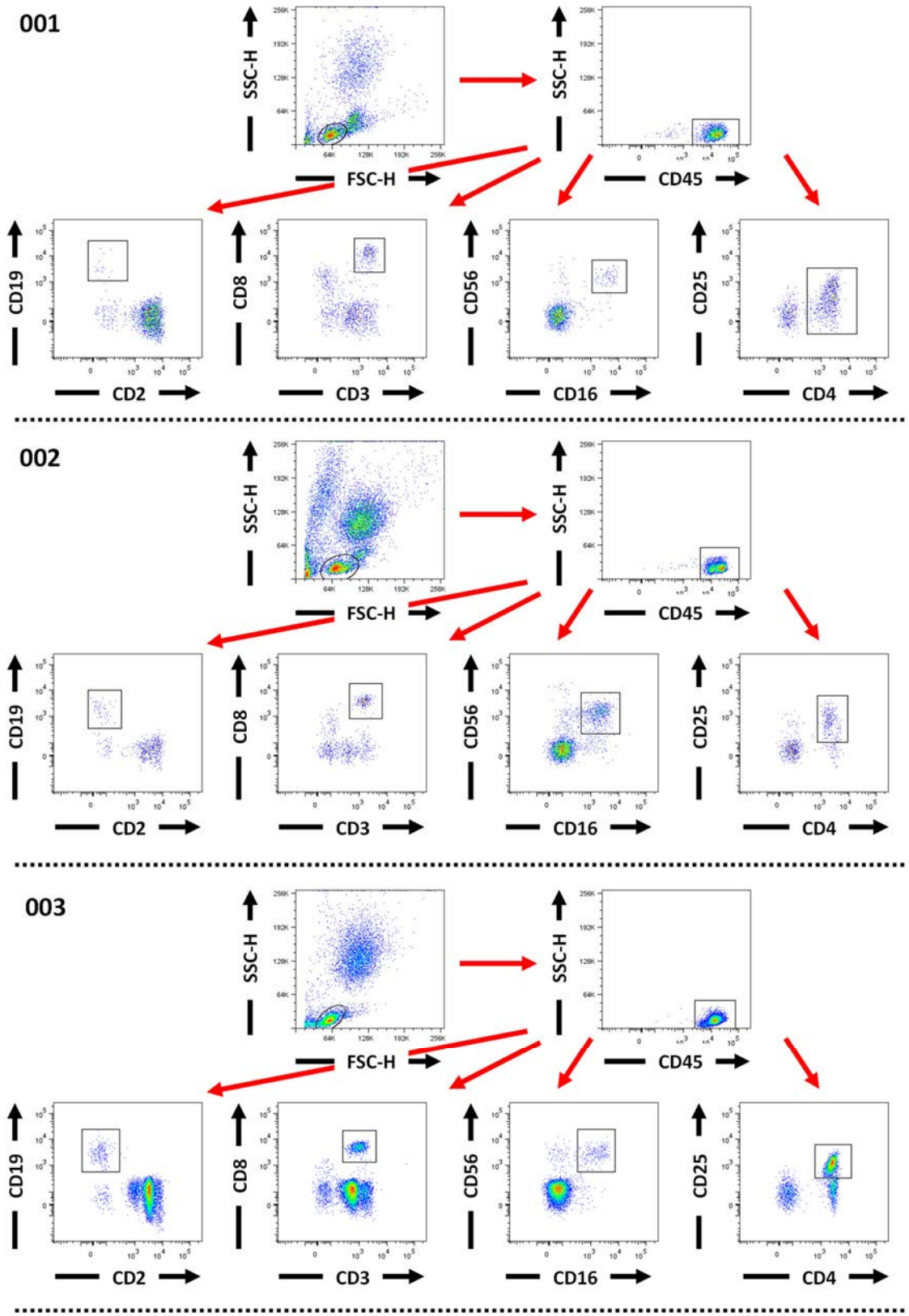
Supplemental FIGURE 3



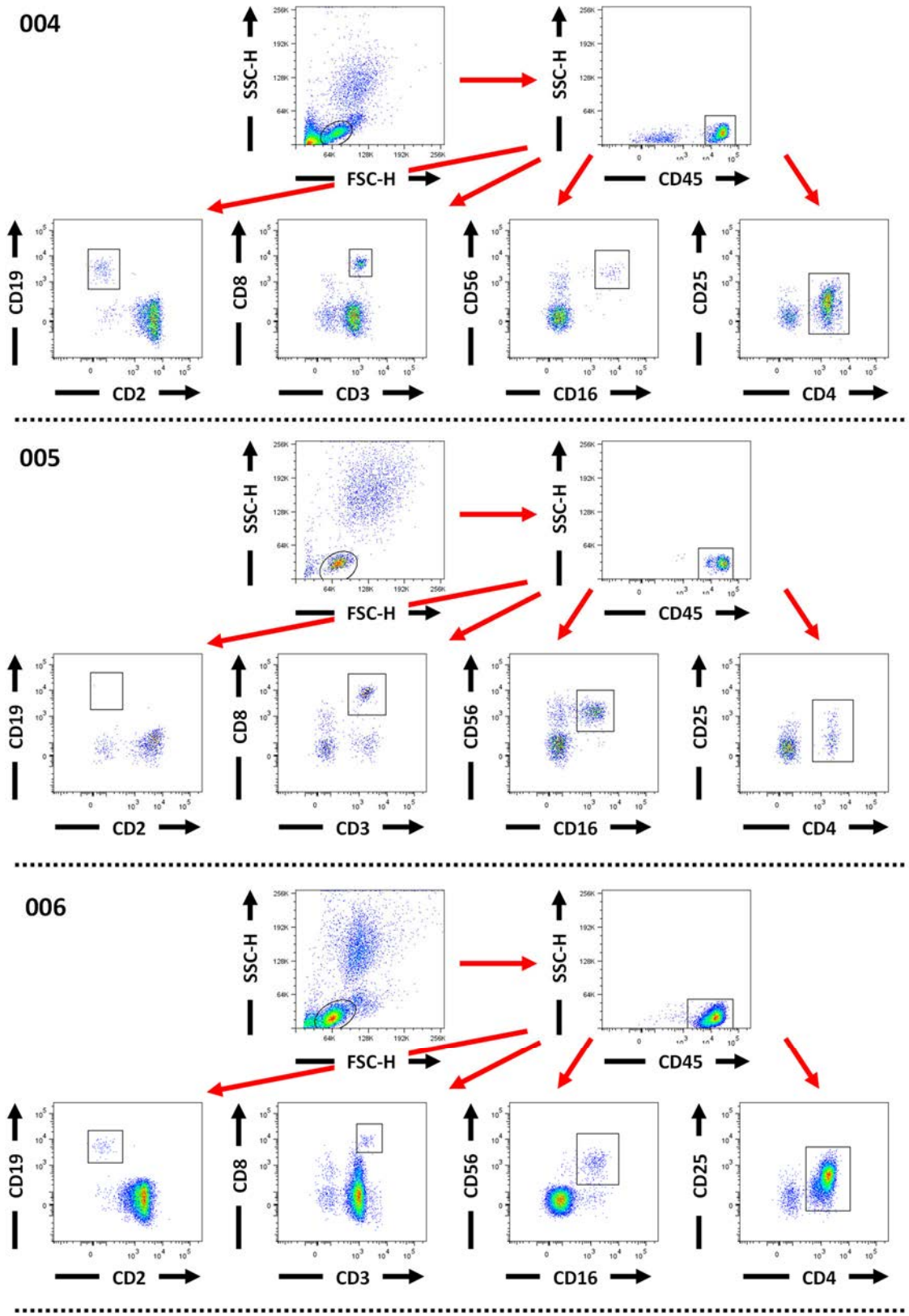
Supplemental FIGURE 3



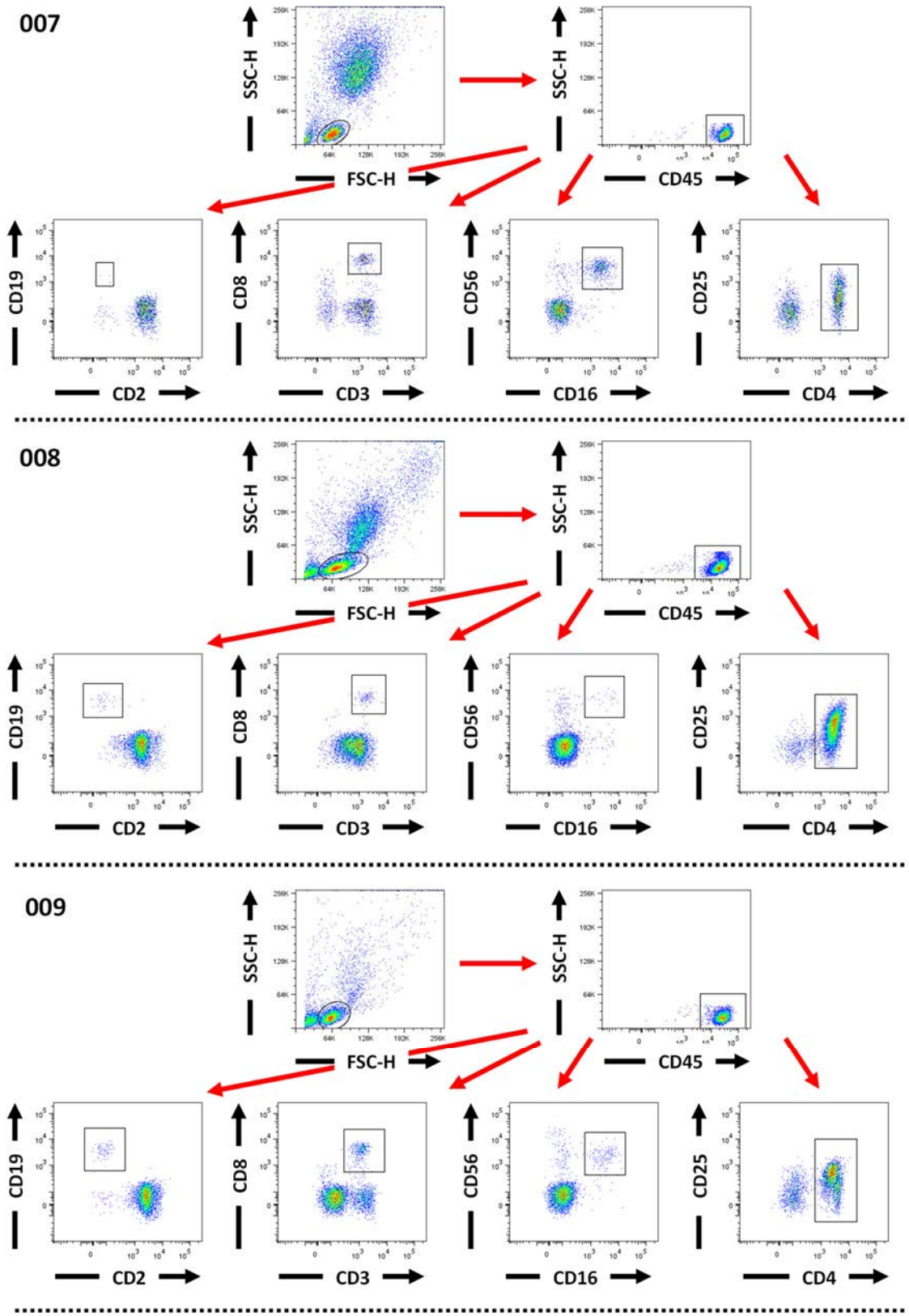
Supplemental FIGURE 3



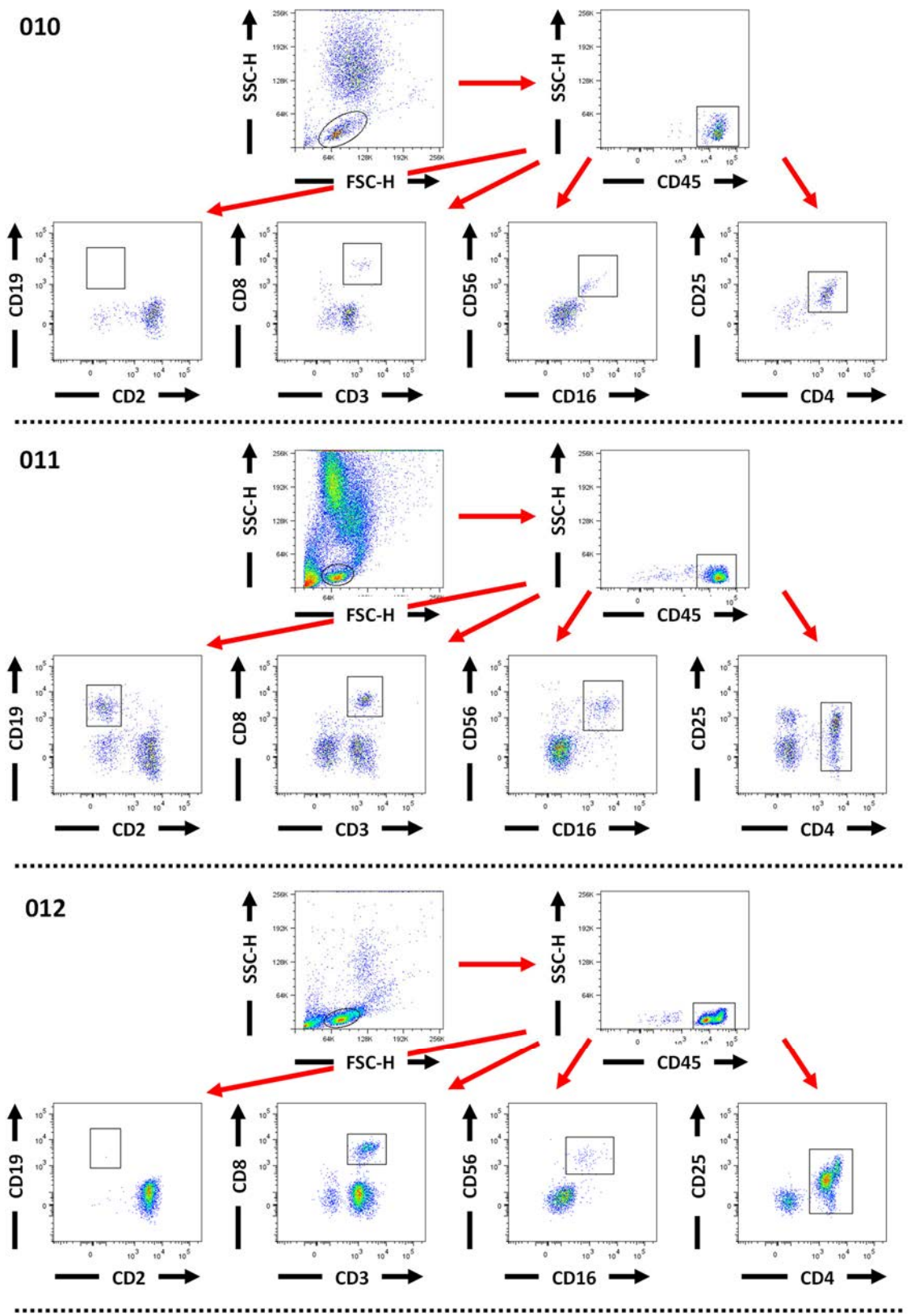
Supplemental FIGURE 4



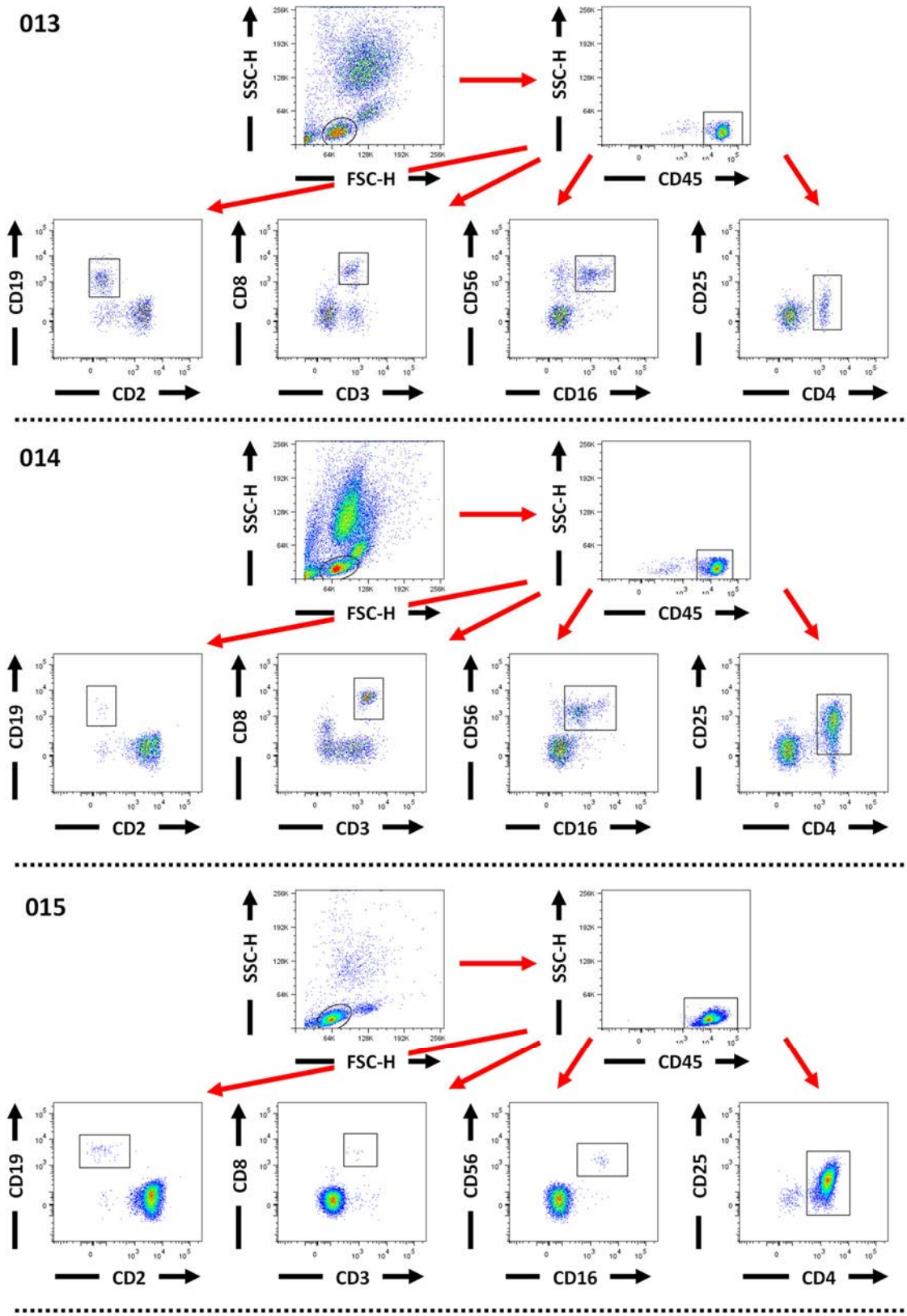
Supplemental FIGURE 4



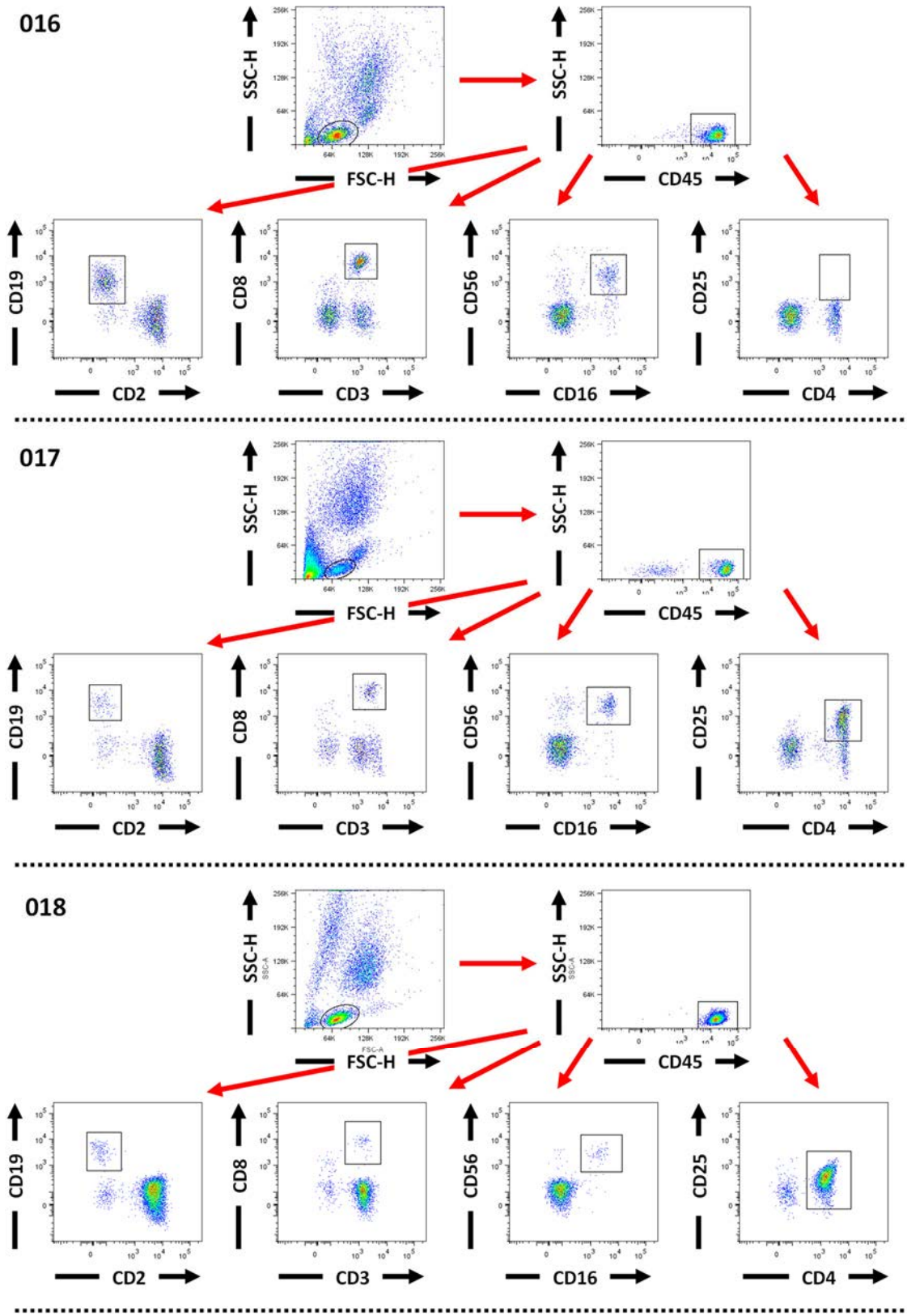
Supplemental FIGURE 4



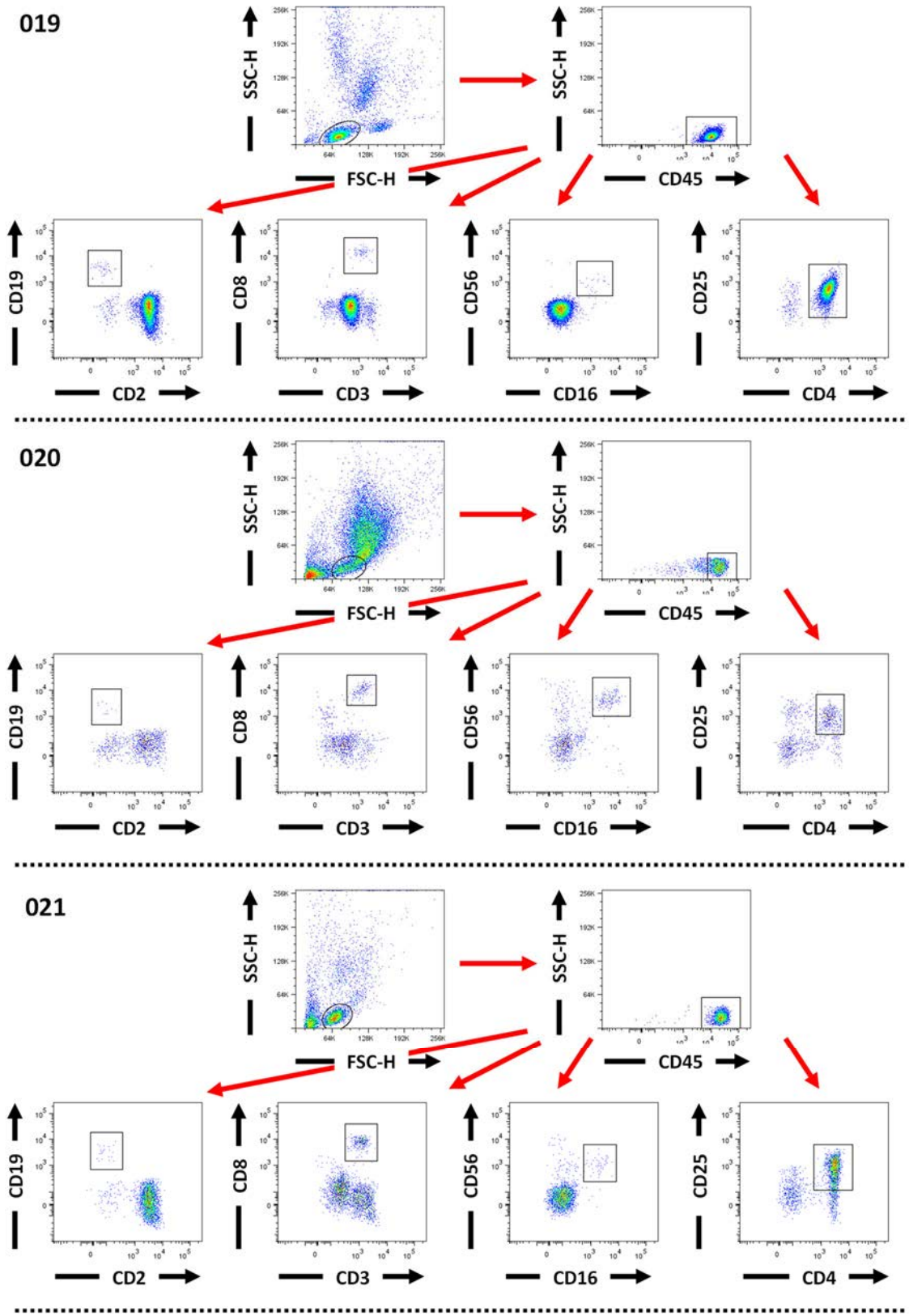
Supplemental FIGURE 4



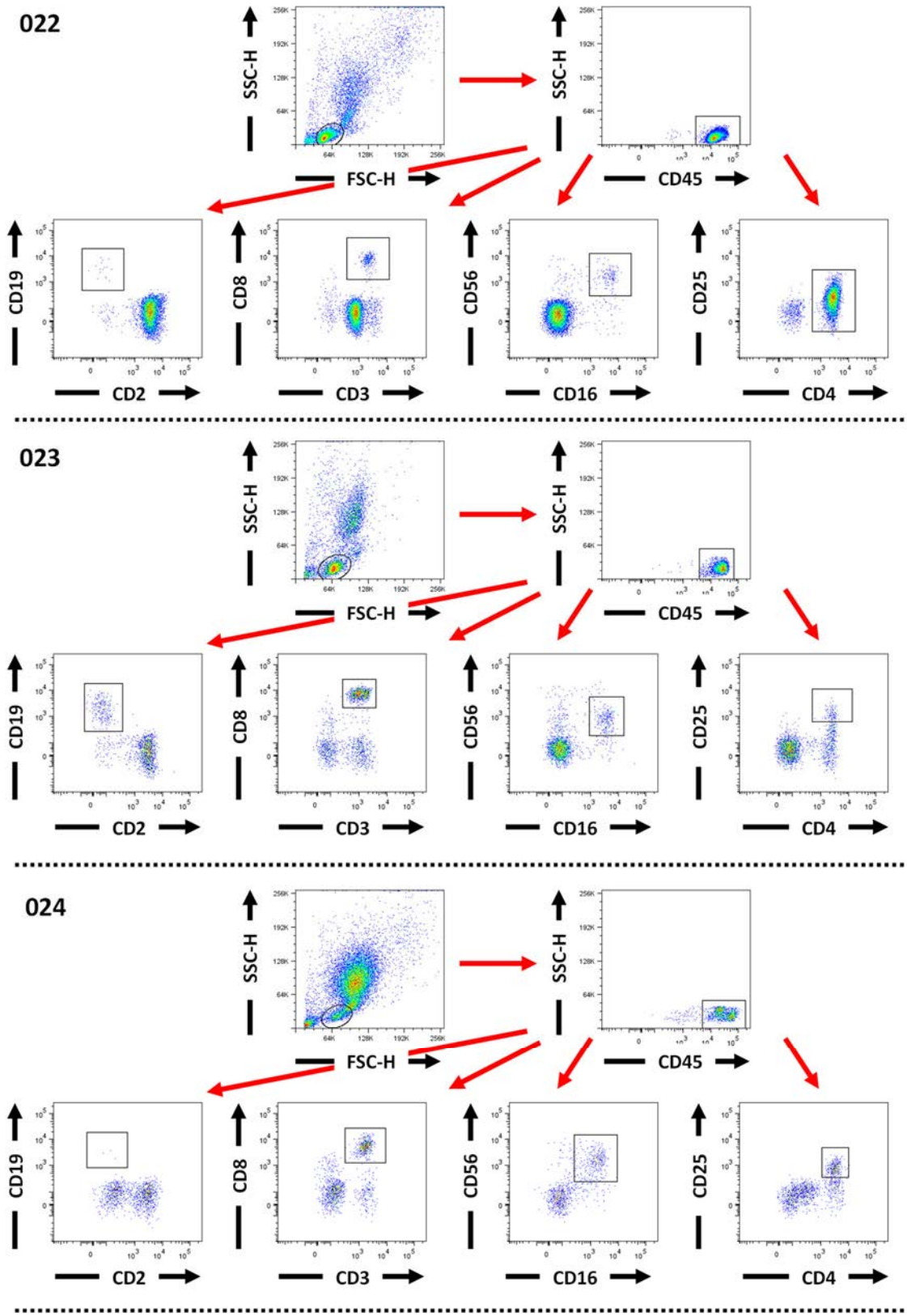
Supplemental FIGURE 4



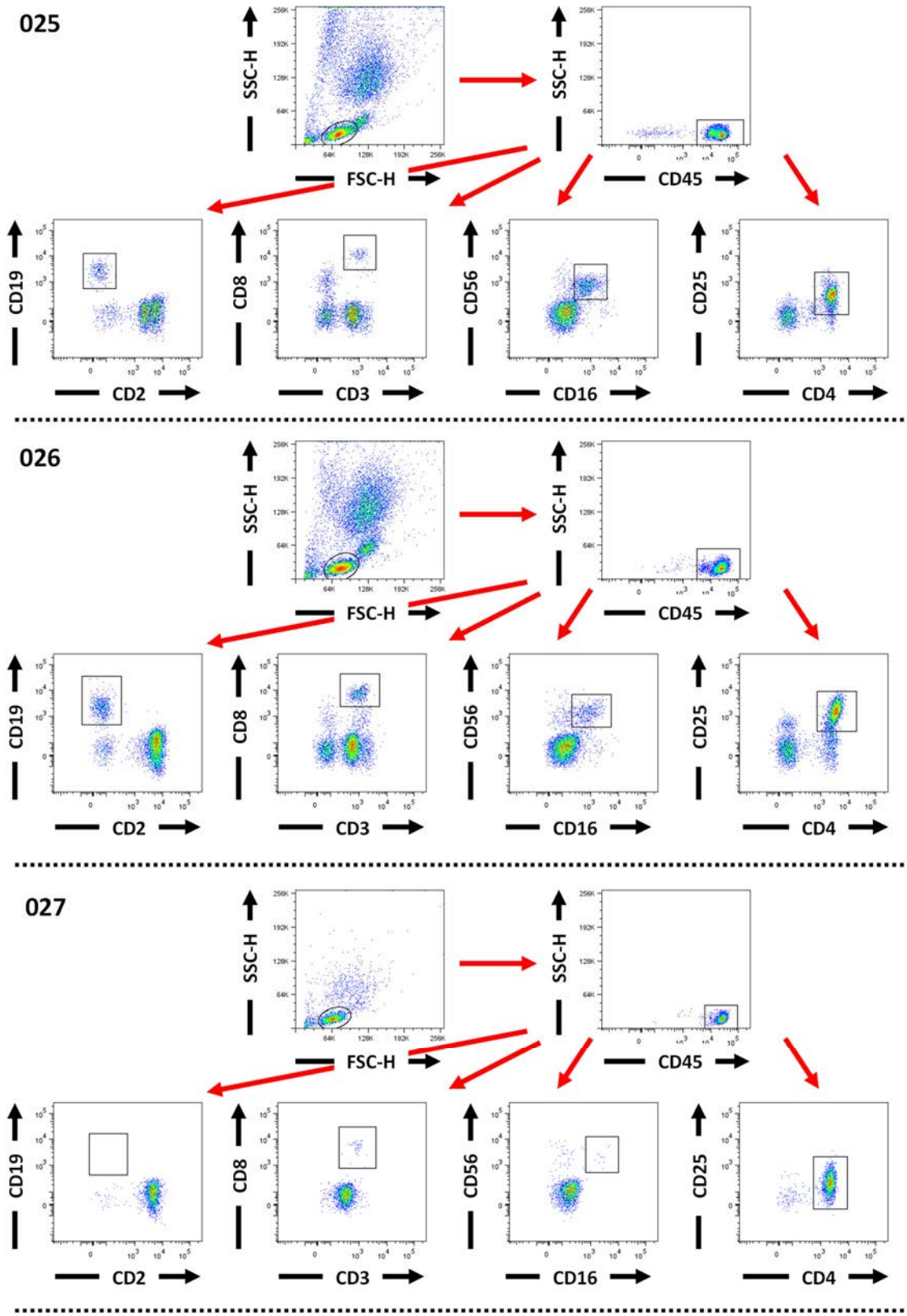
Supplemental FIGURE 4



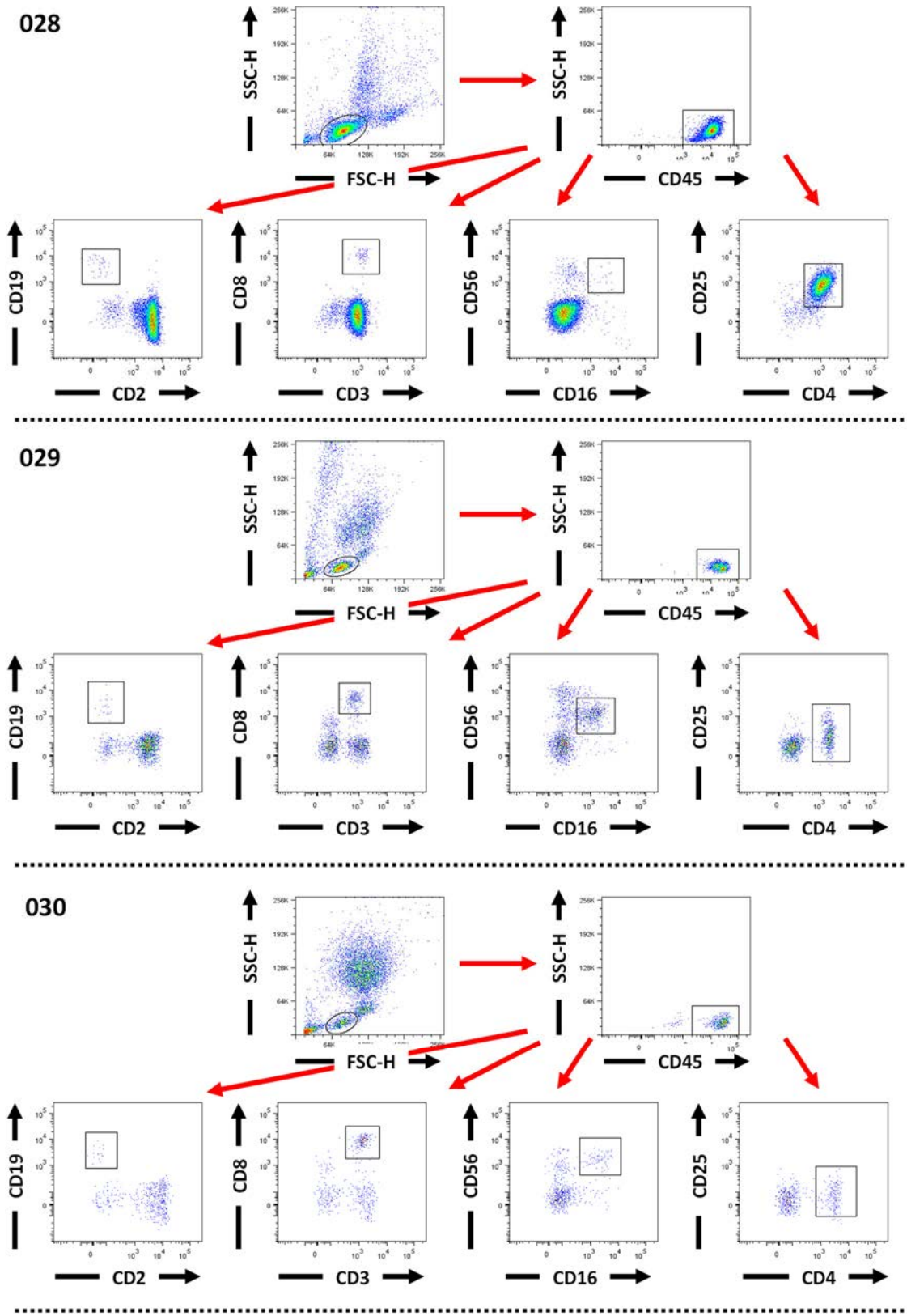
Supplemental FIGURE 4



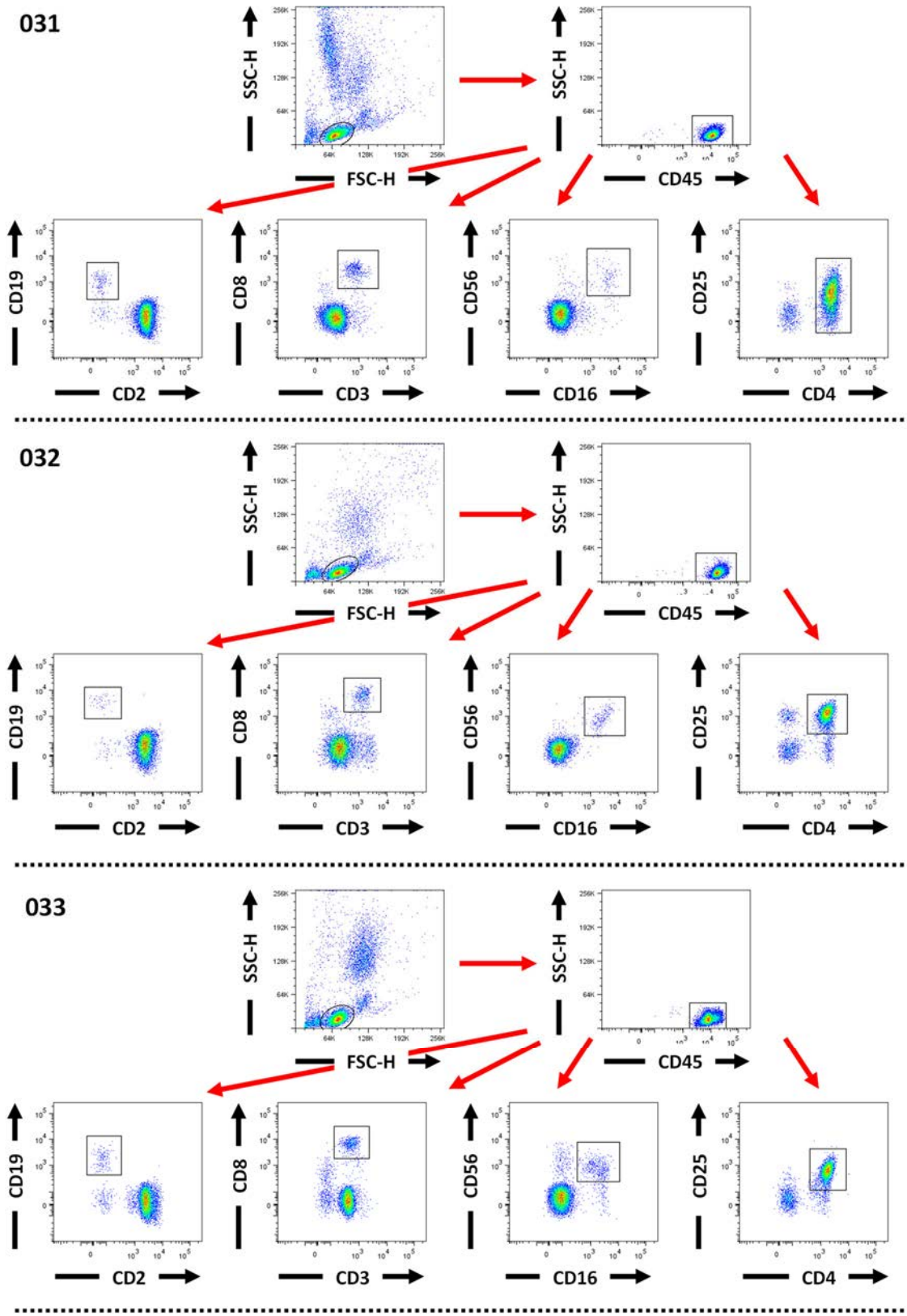
Supplemental FIGURE 4



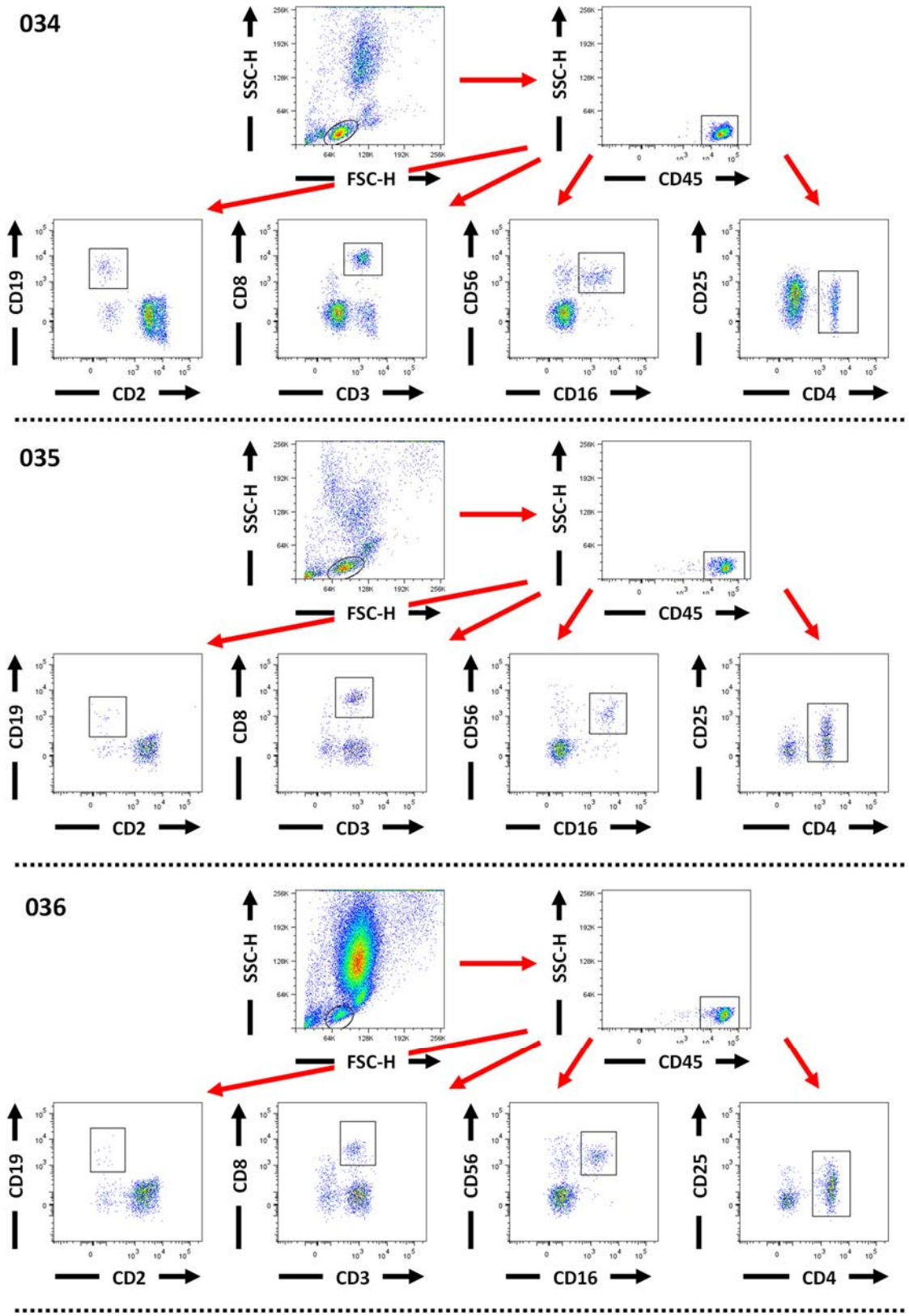
Supplemental FIGURE 4



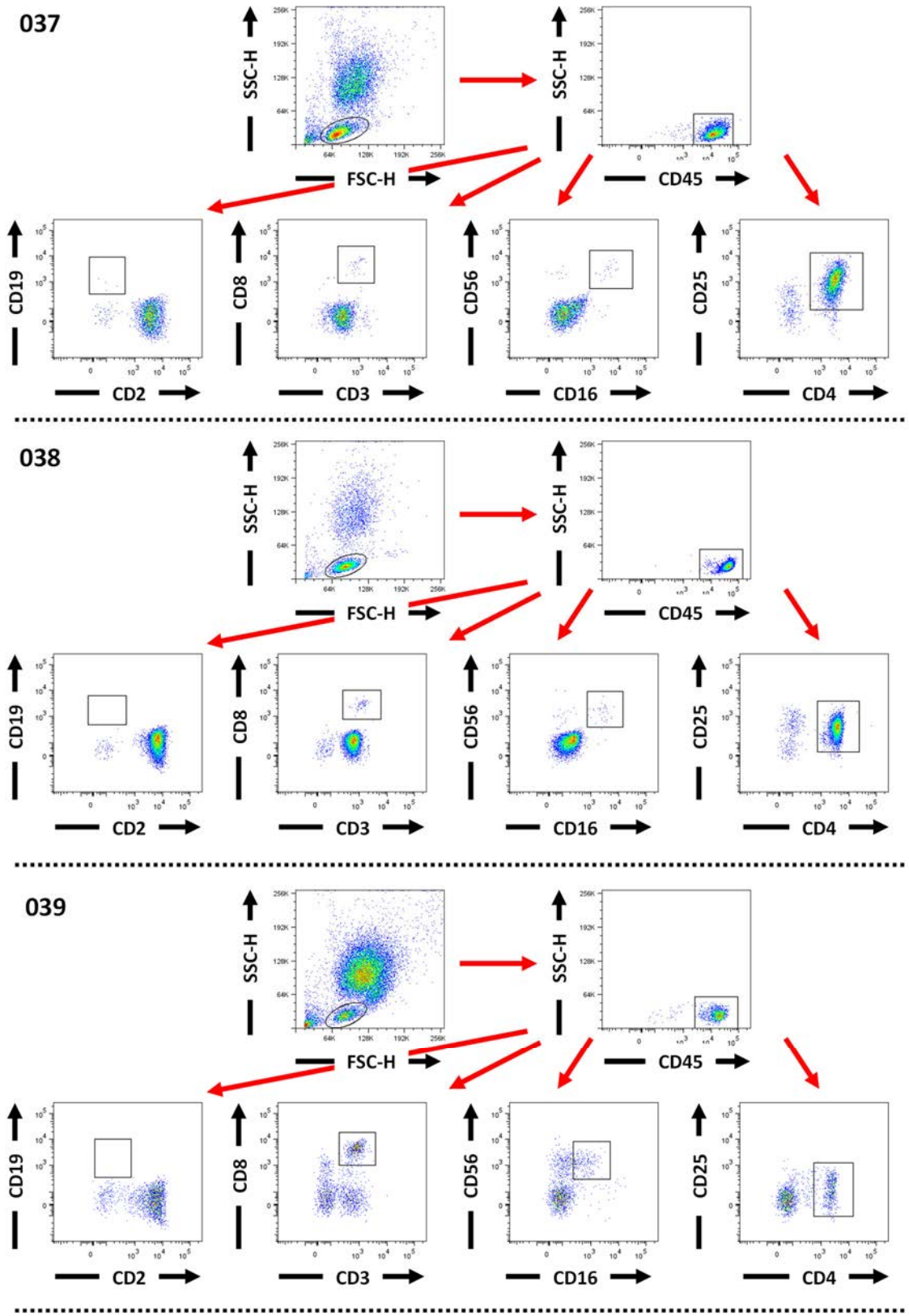
Supplemental FIGURE 4



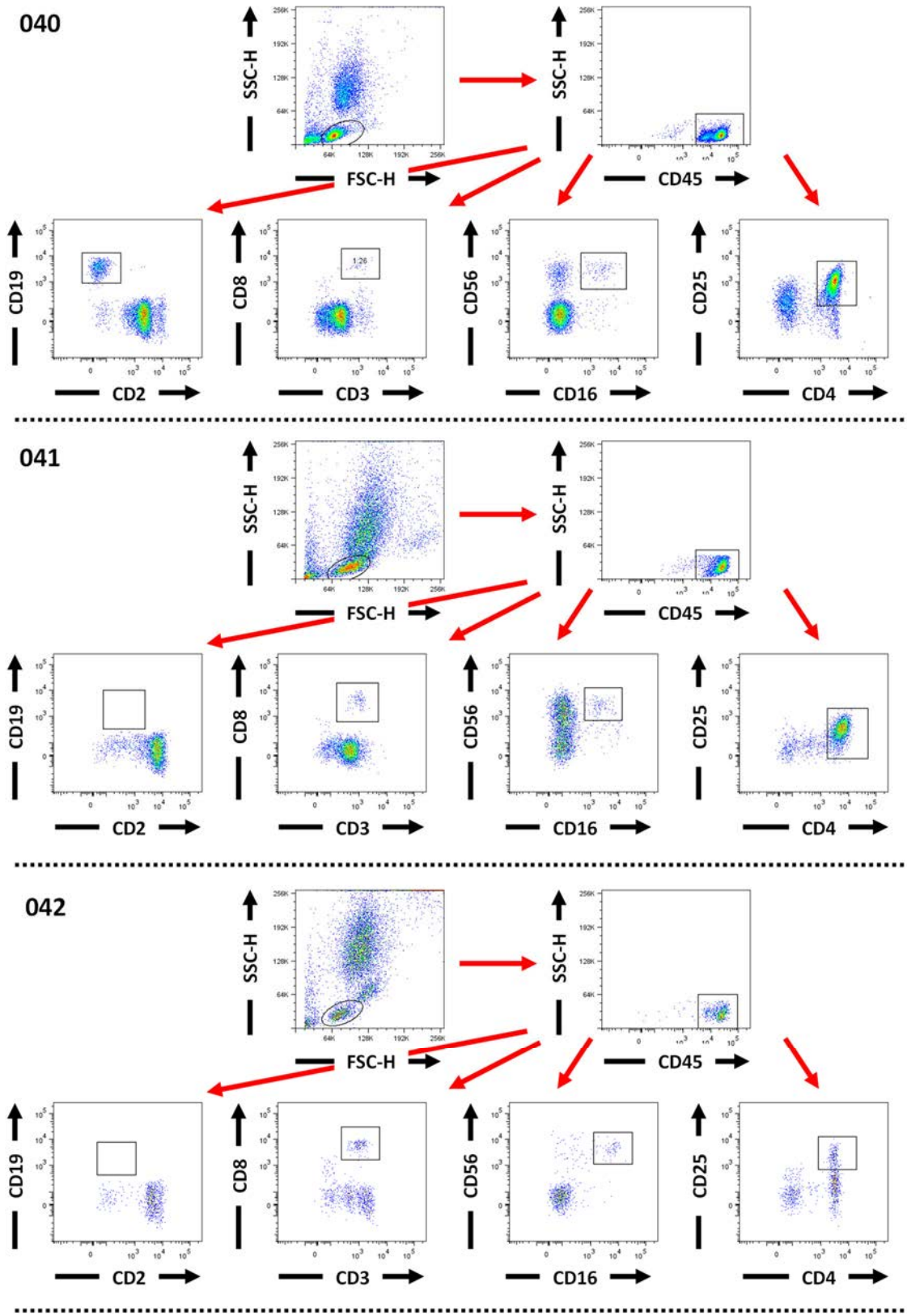
Supplemental FIGURE 4



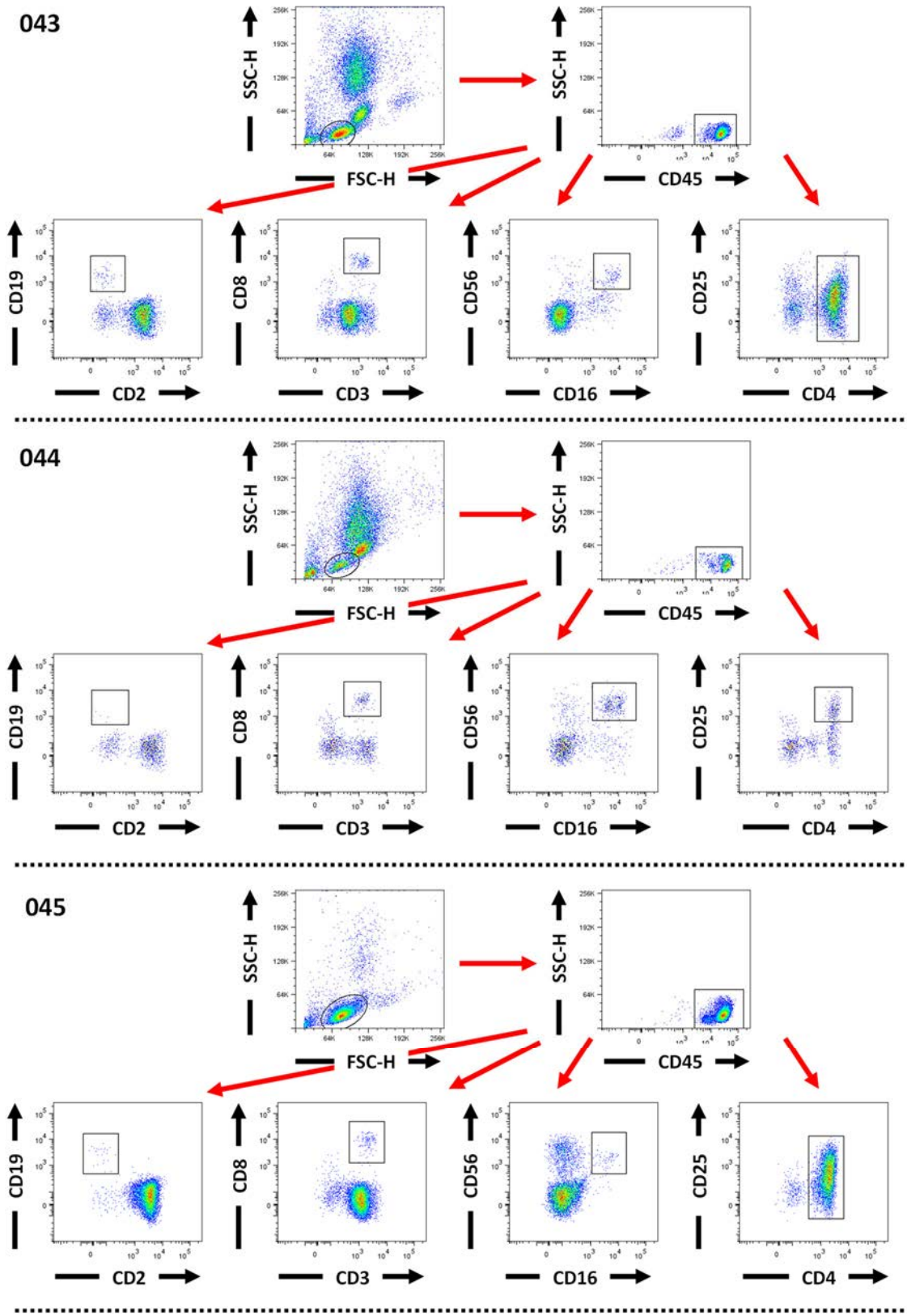
Supplemental FIGURE 4



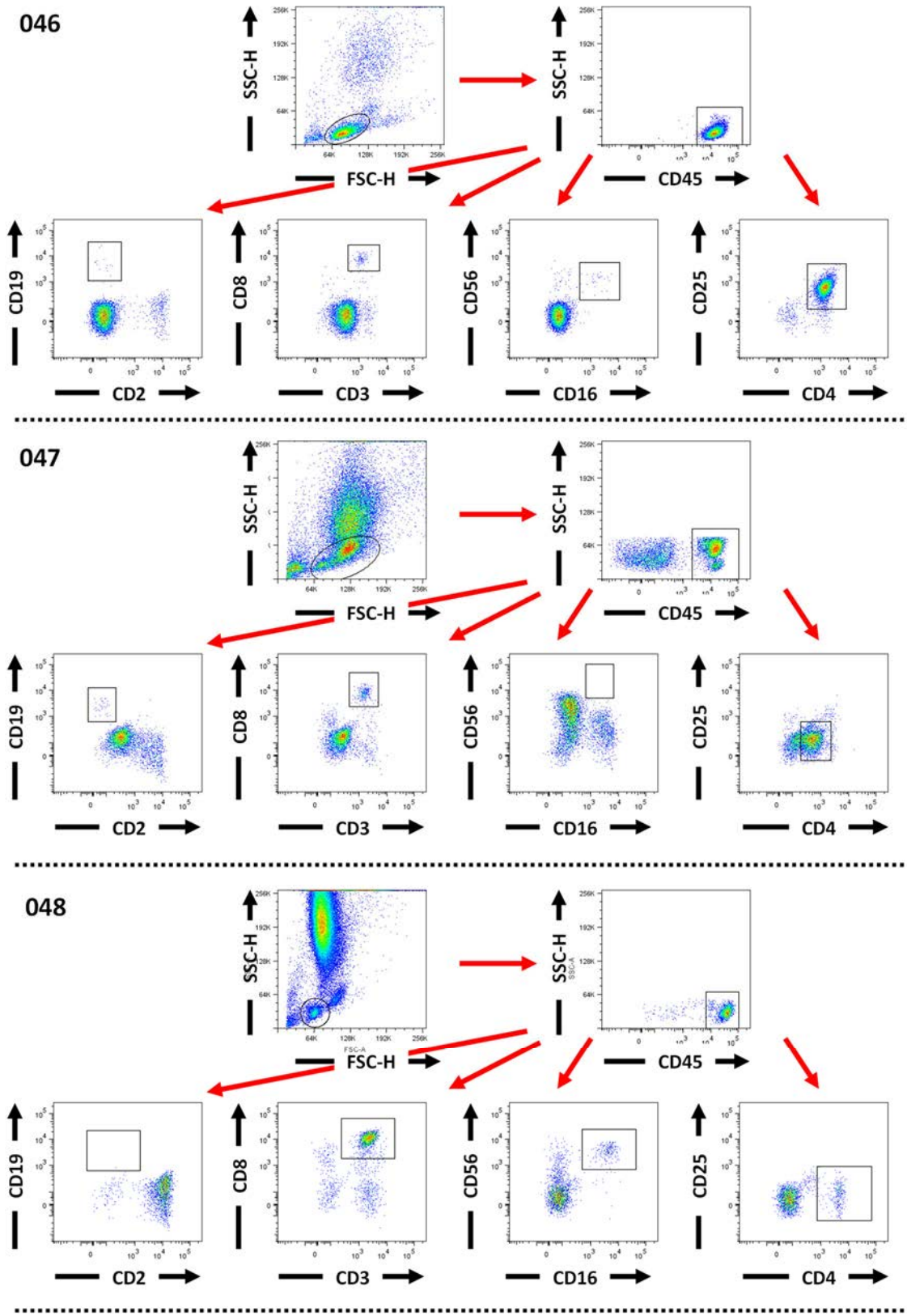
Supplemental FIGURE 4



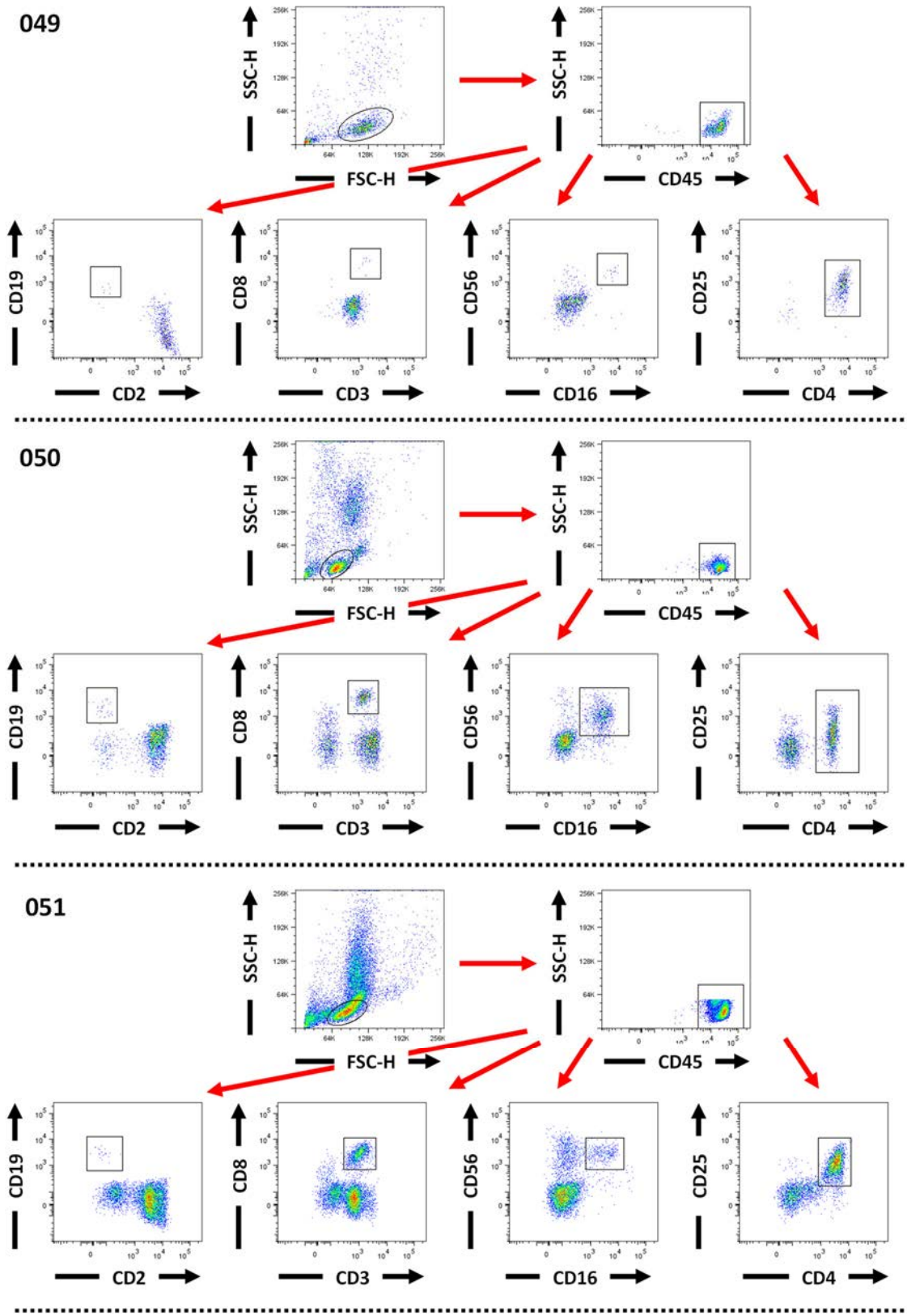
Supplemental FIGURE 4



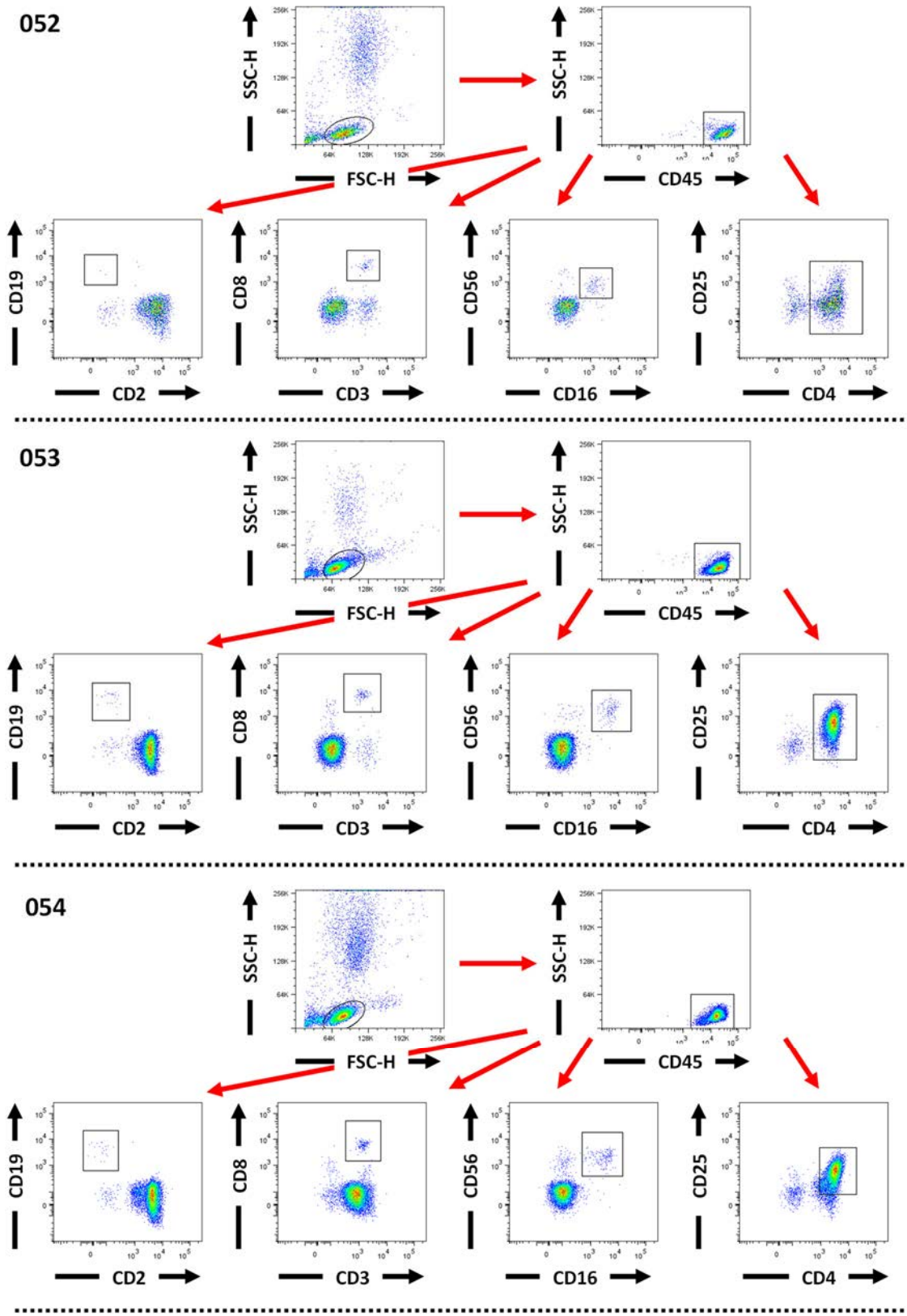
Supplemental FIGURE 4



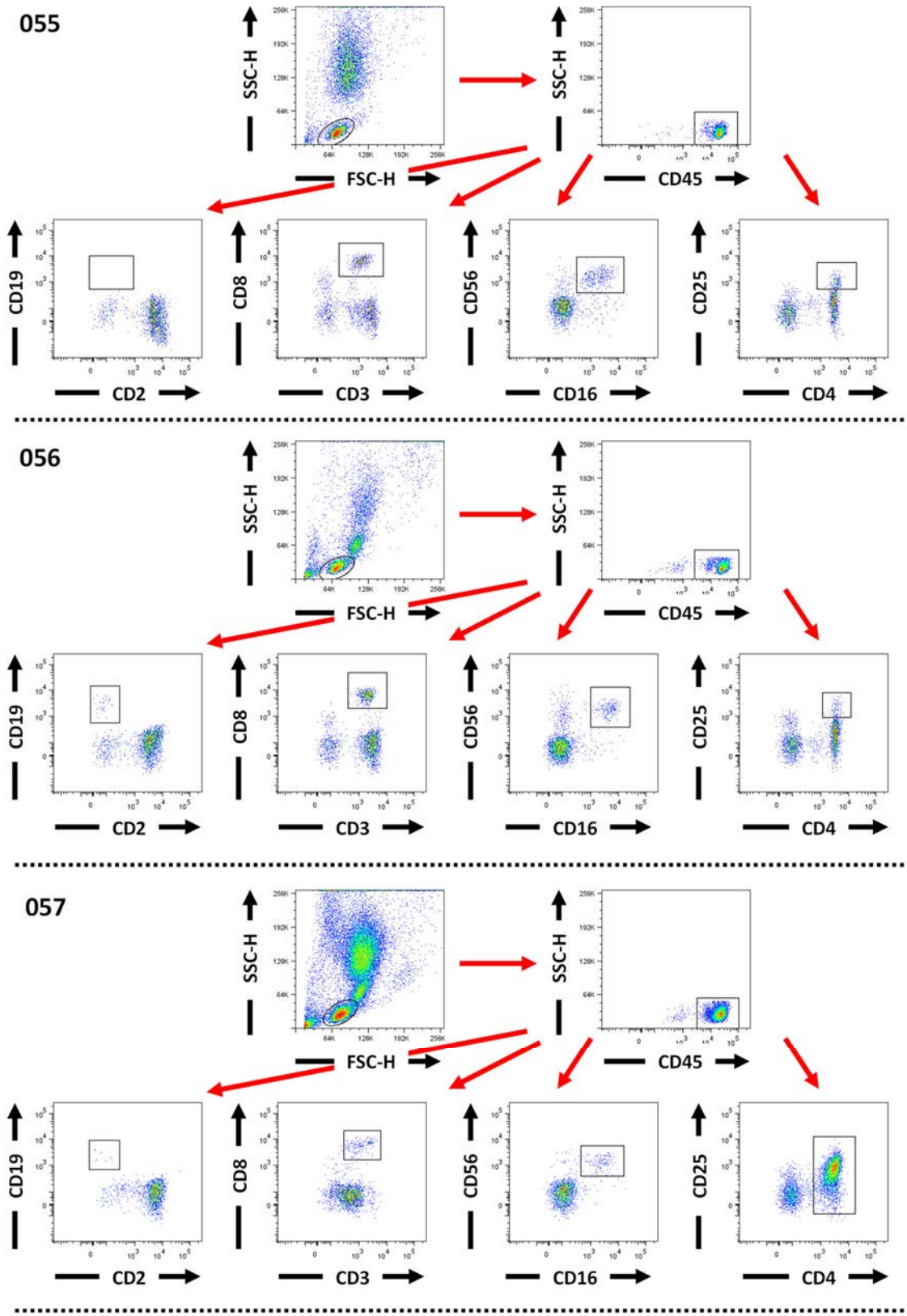
Supplemental FIGURE 4



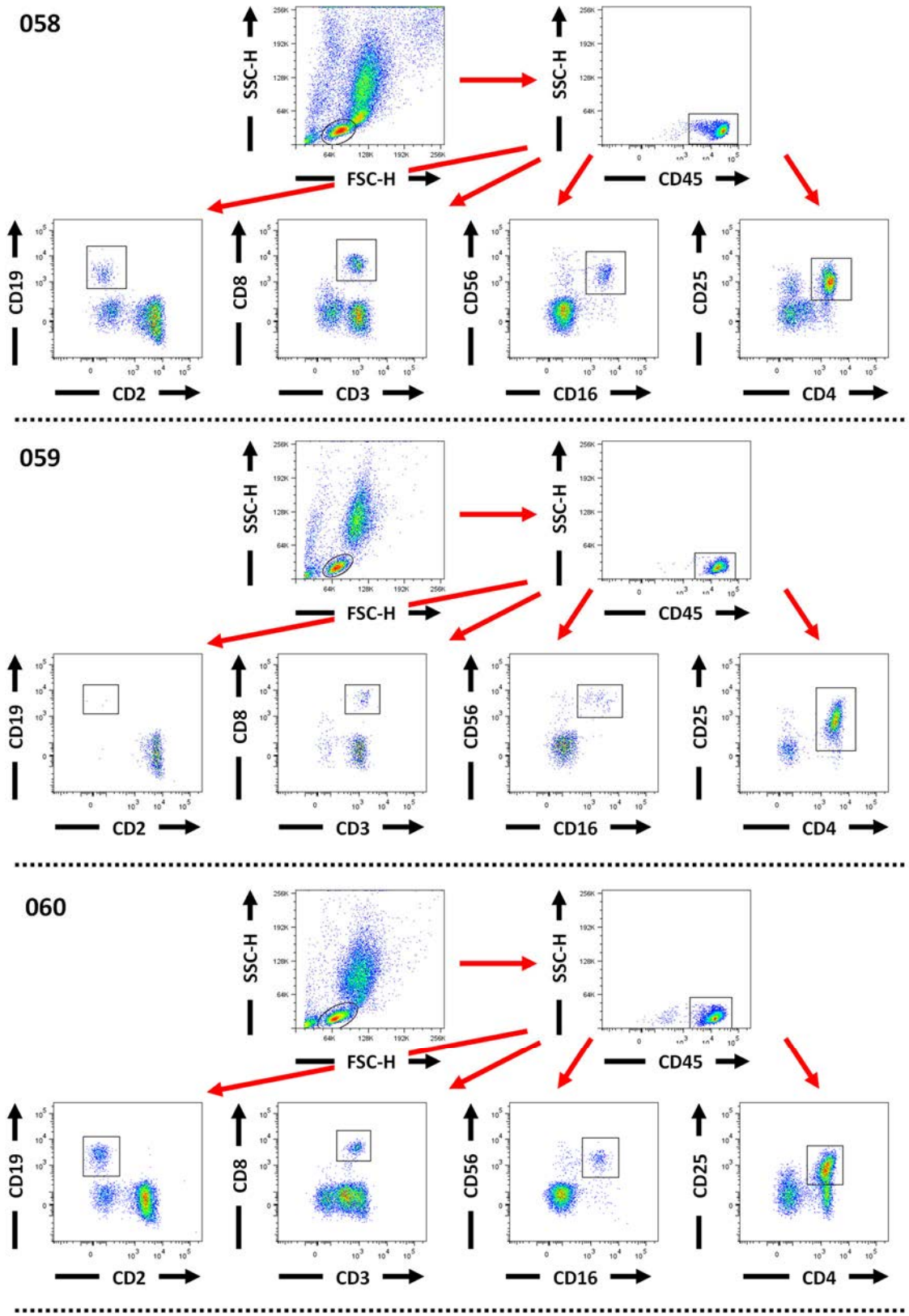
Supplemental FIGURE 4



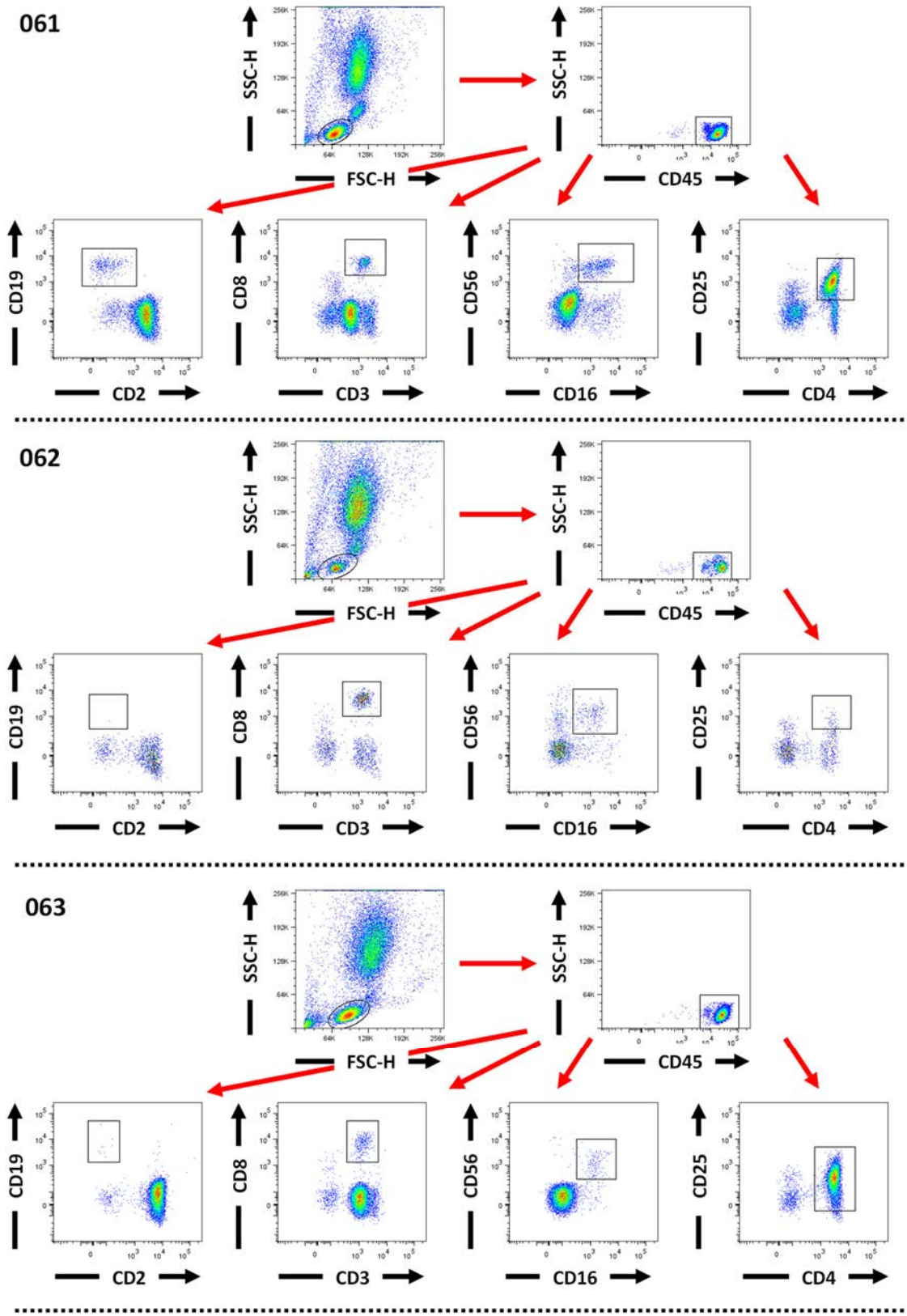
Supplemental FIGURE 4



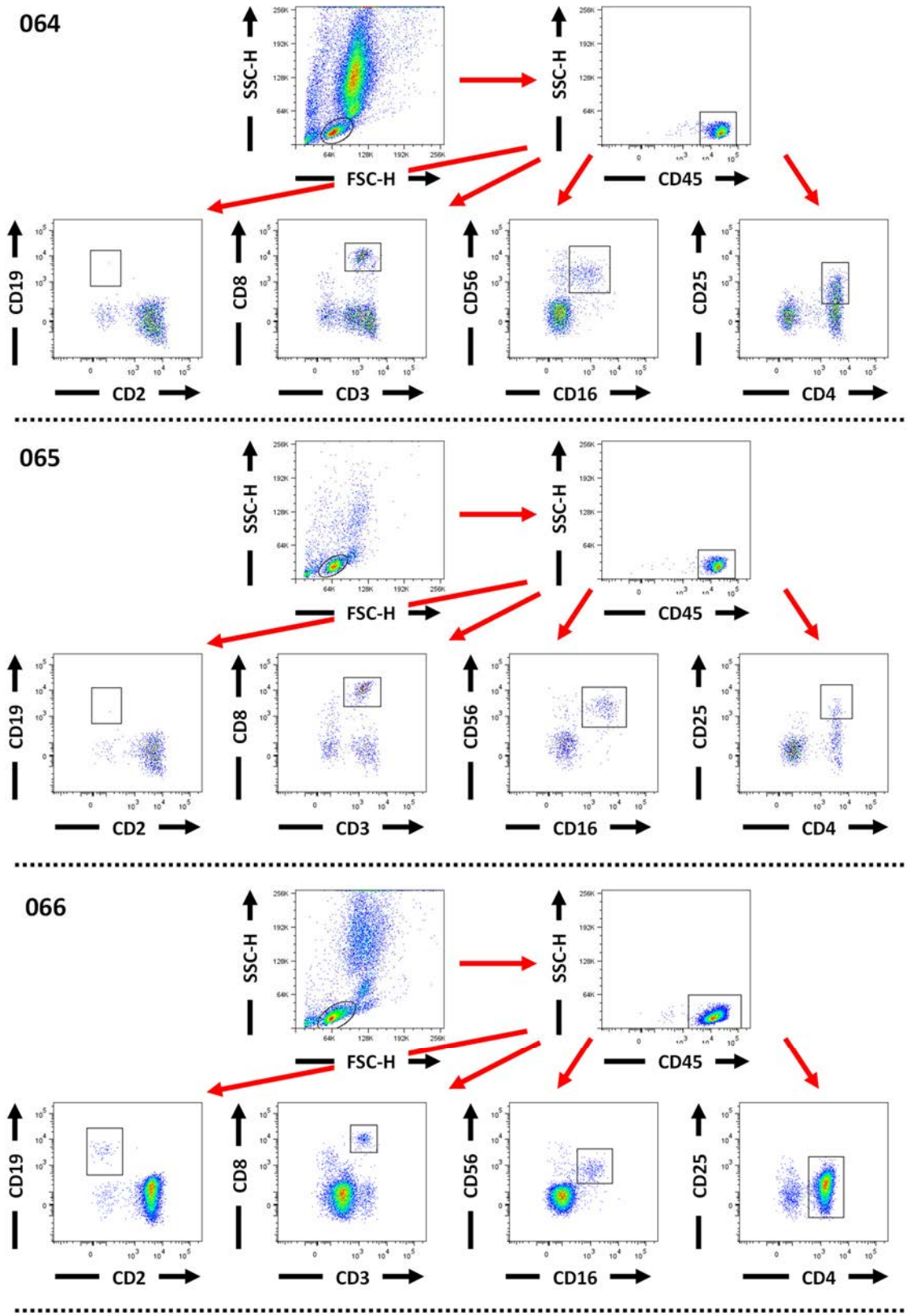
Supplemental FIGURE 4



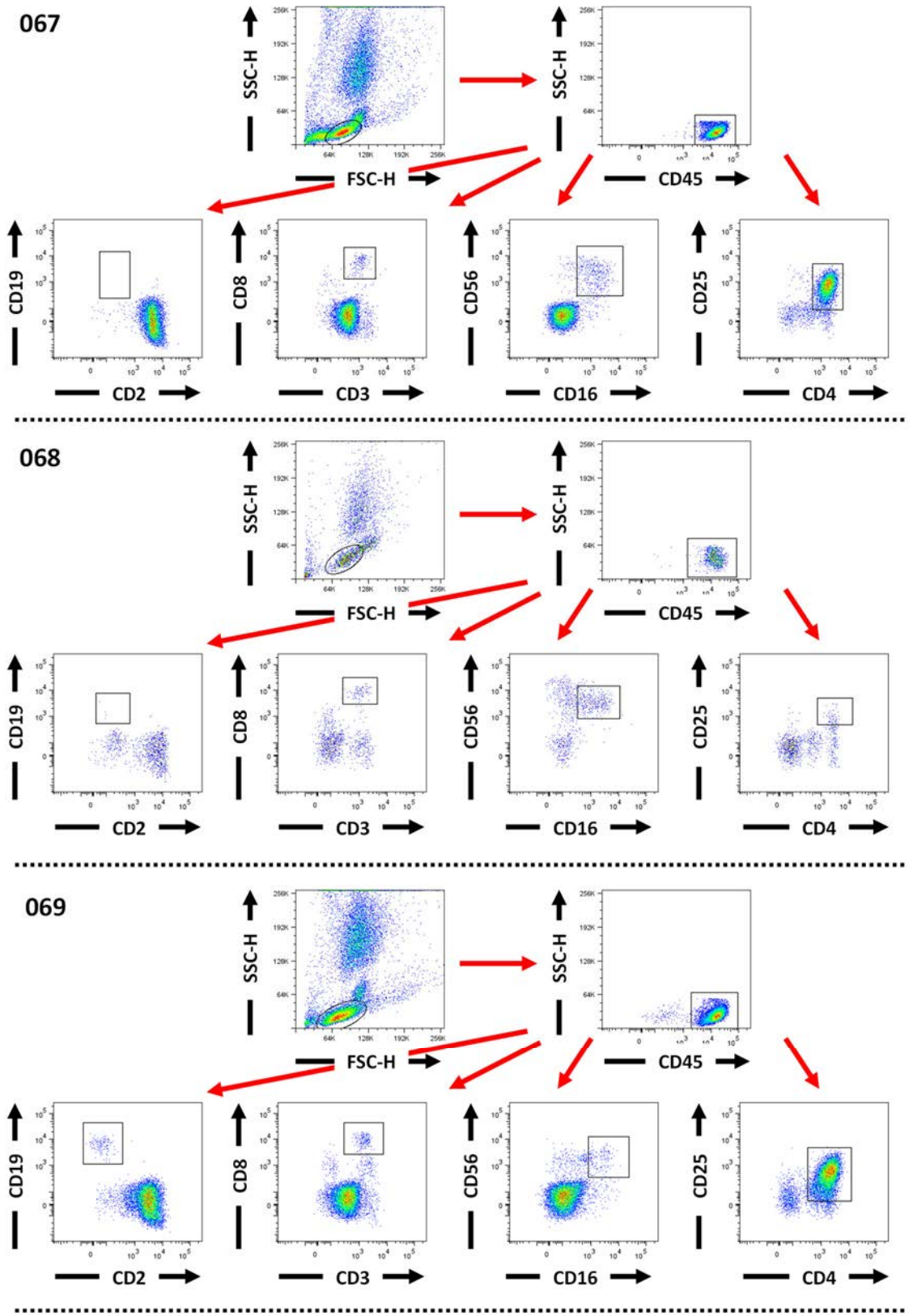
Supplemental FIGURE 4



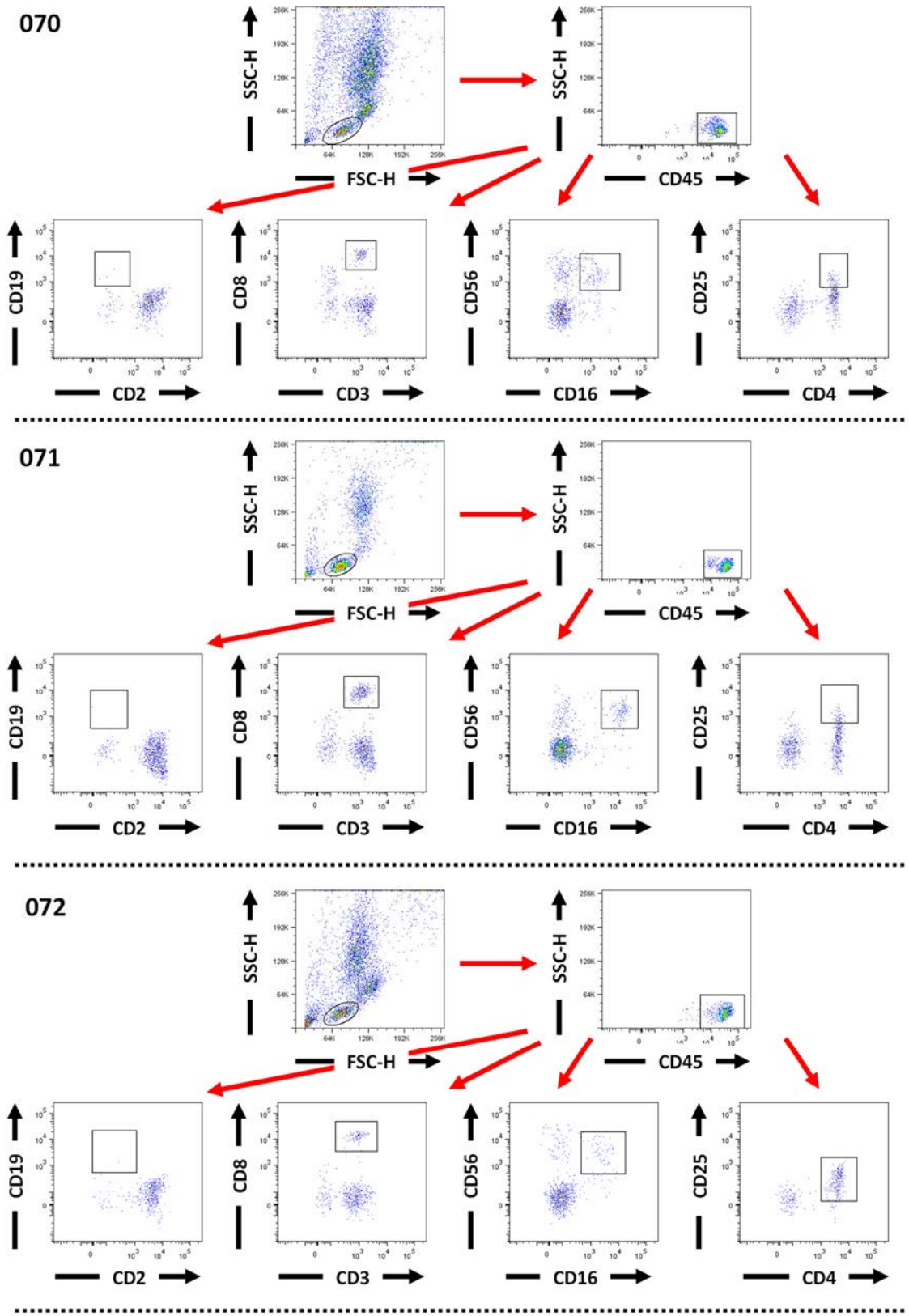
Supplemental FIGURE 4



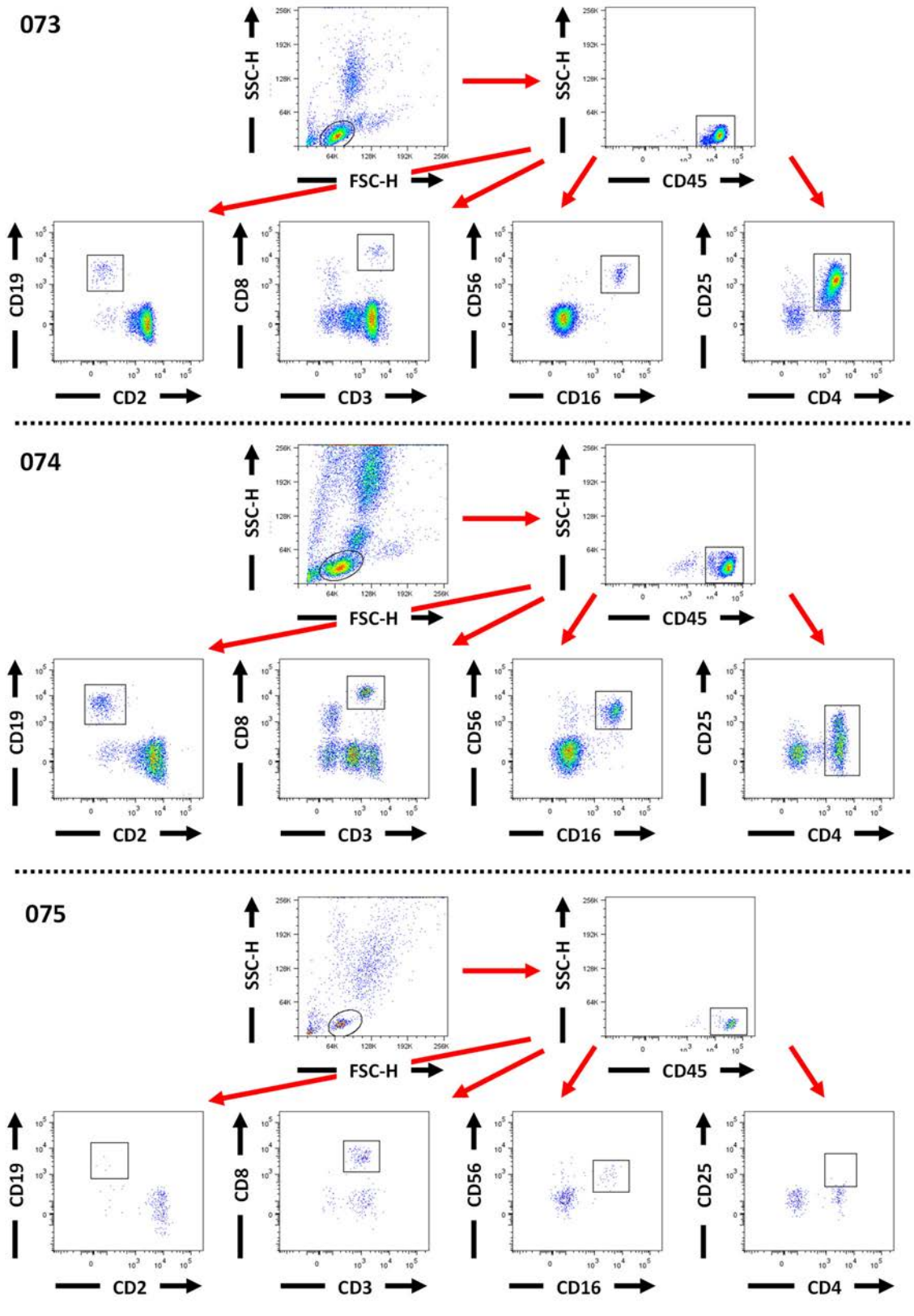
Supplemental FIGURE 4



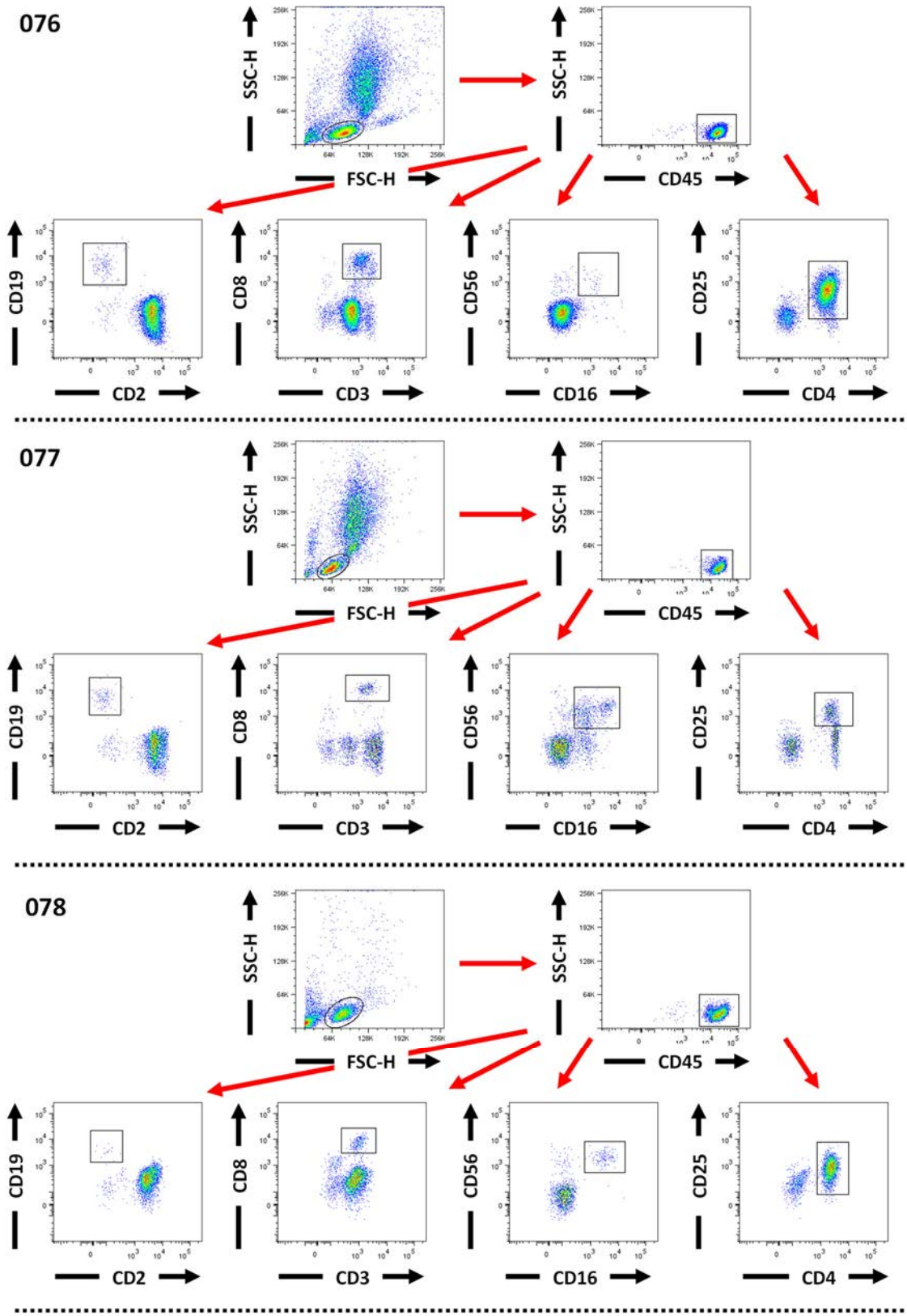
Supplemental FIGURE 4



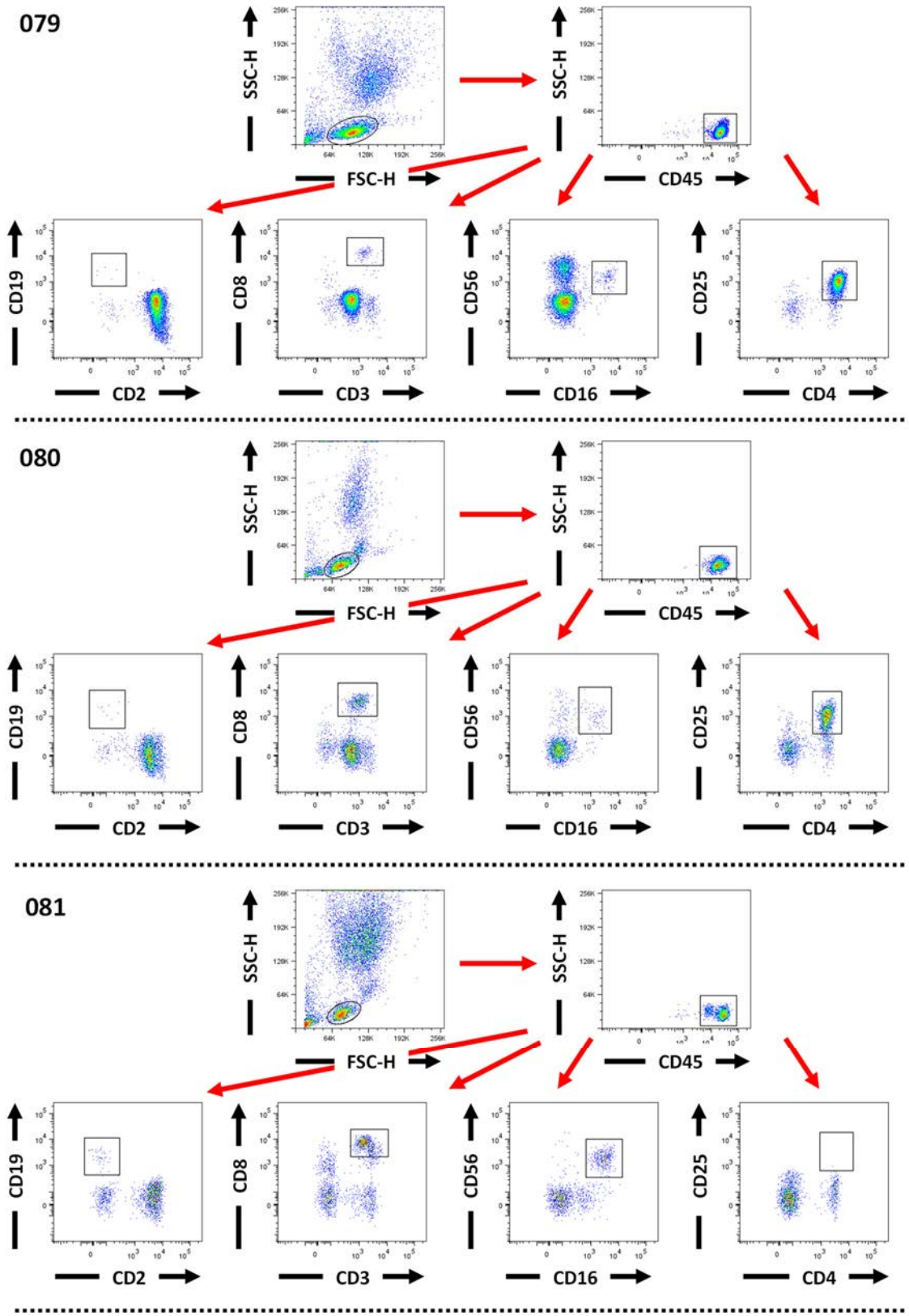
Supplemental FIGURE 4



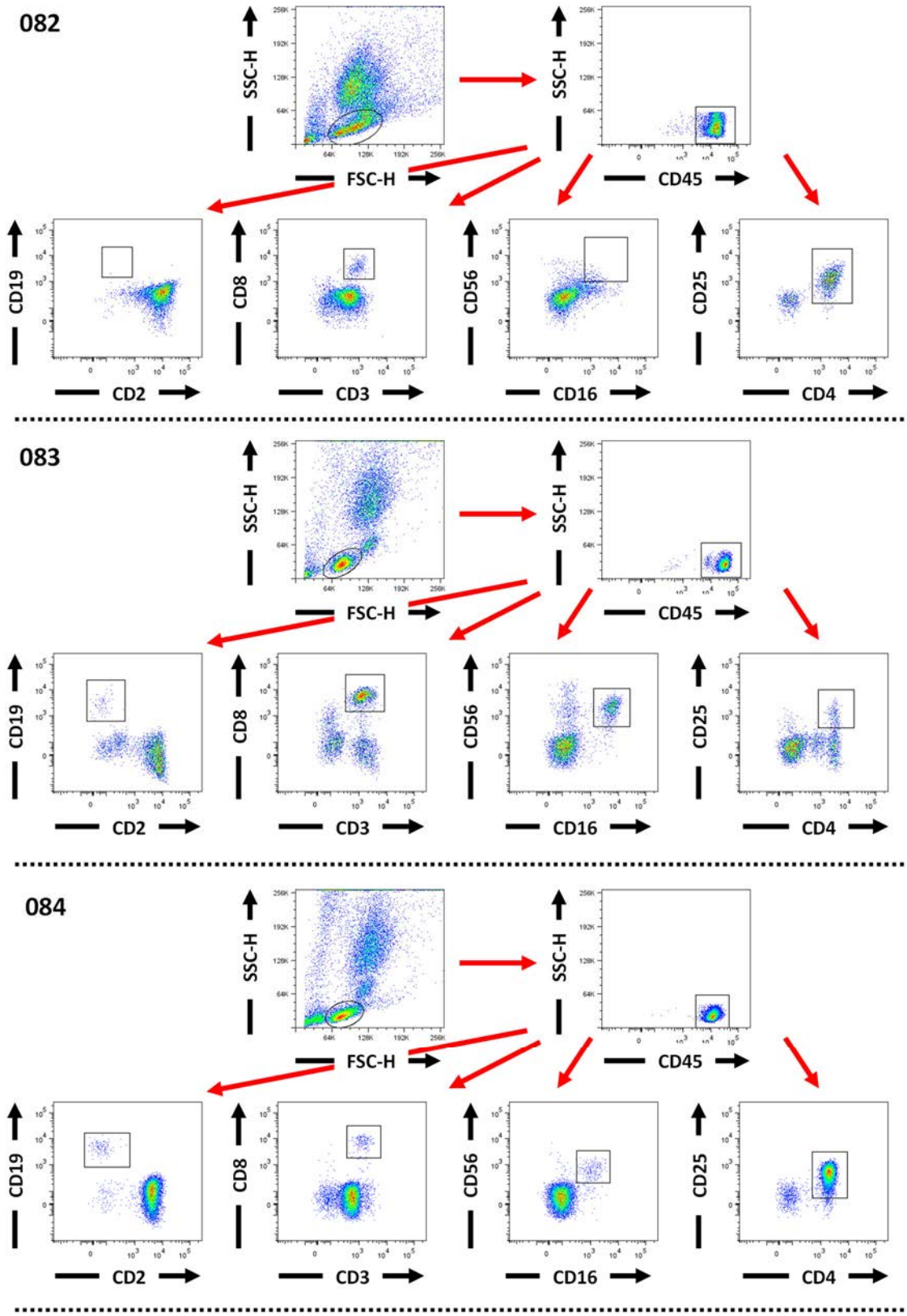
Supplemental FIGURE 4



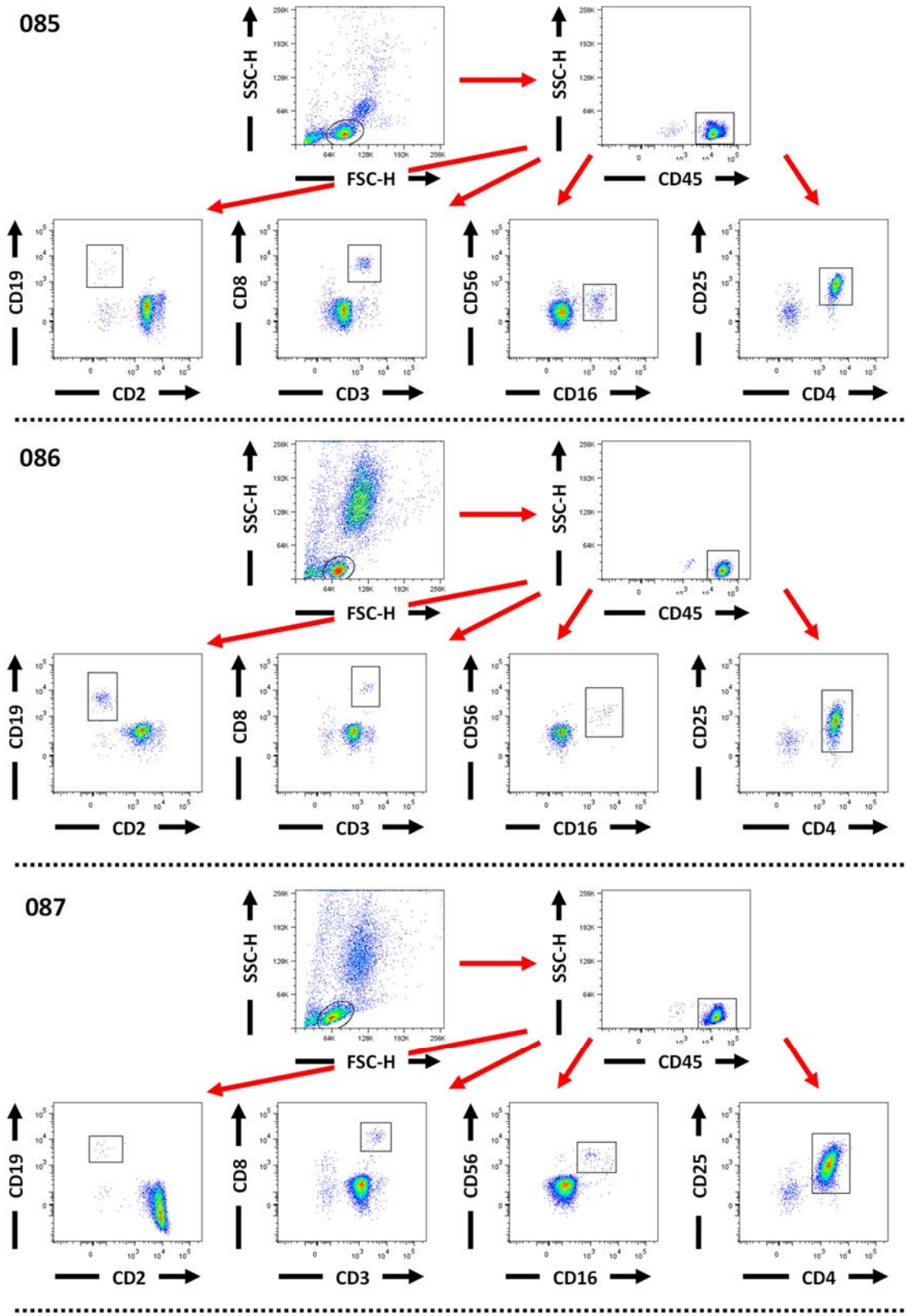
Supplemental FIGURE 4



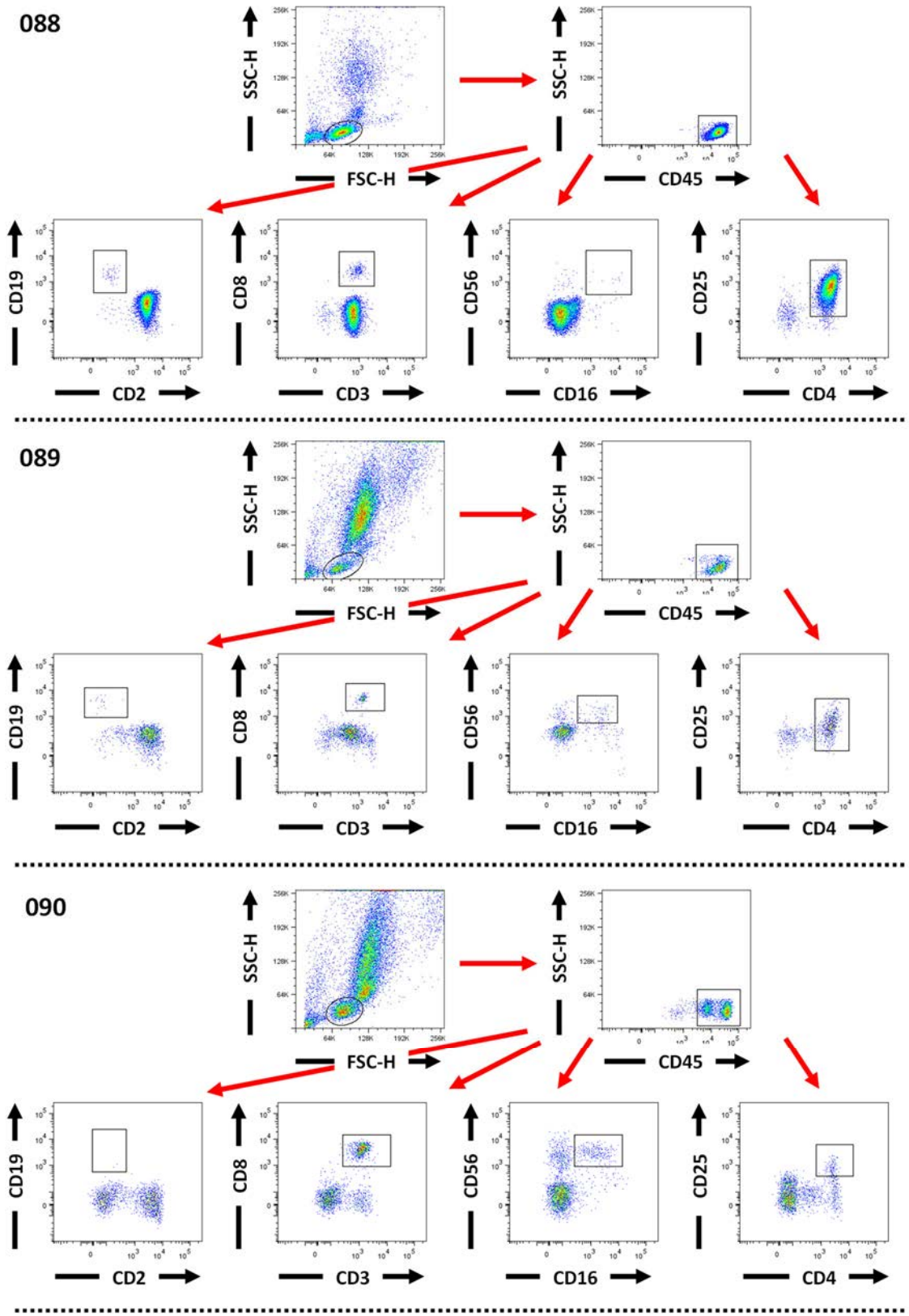
Supplemental FIGURE 4



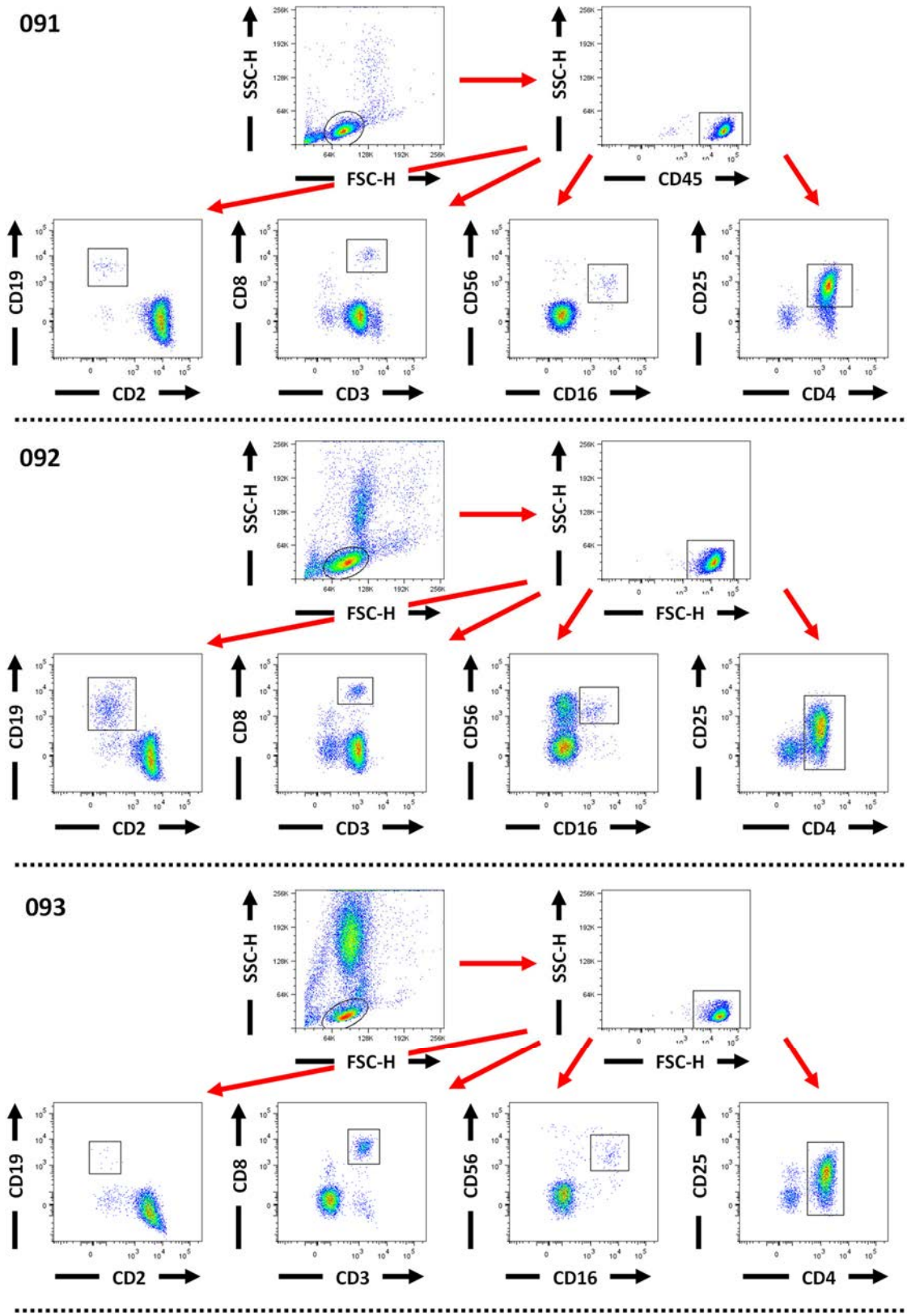
Supplemental FIGURE 4



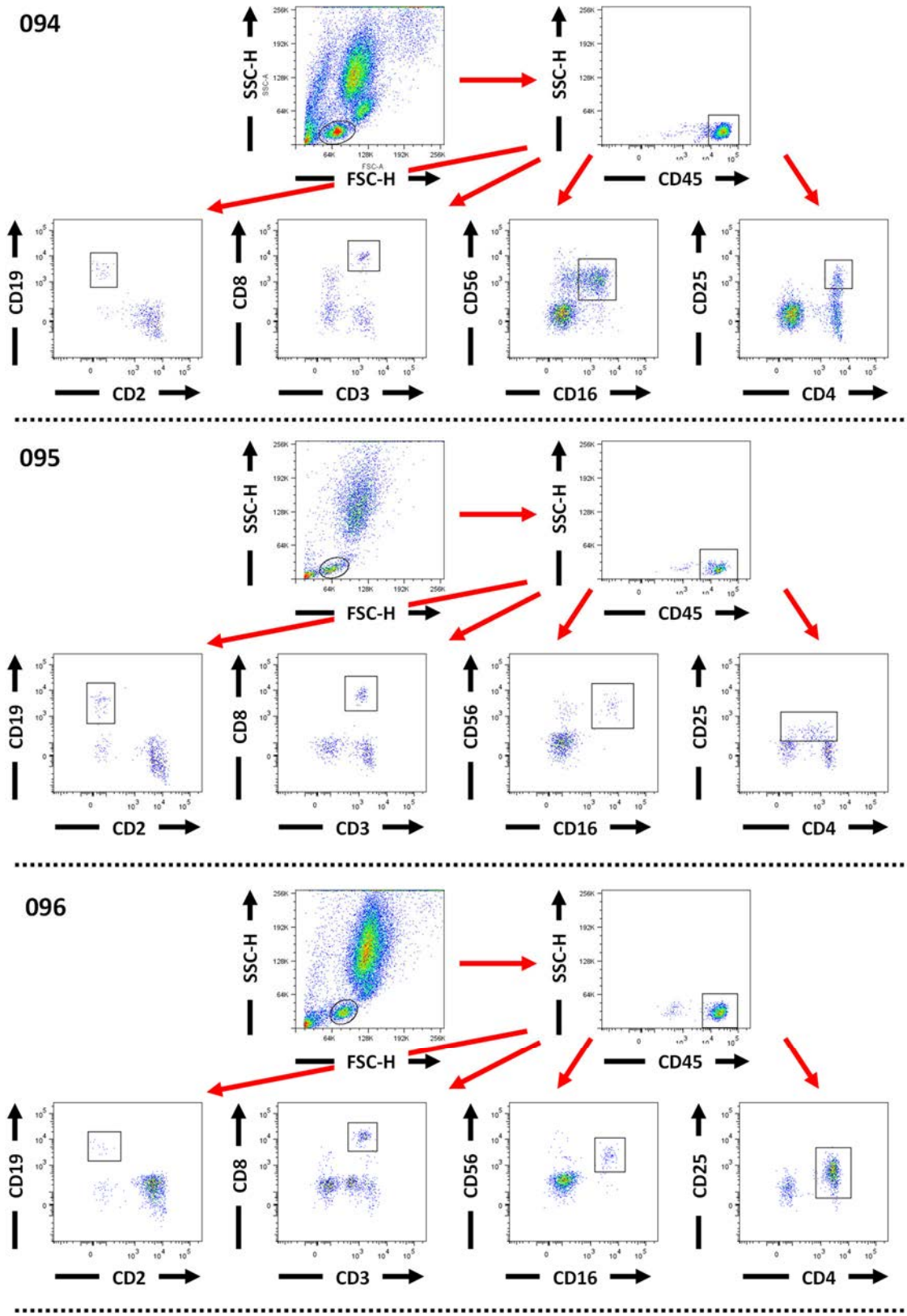
Supplemental FIGURE 4



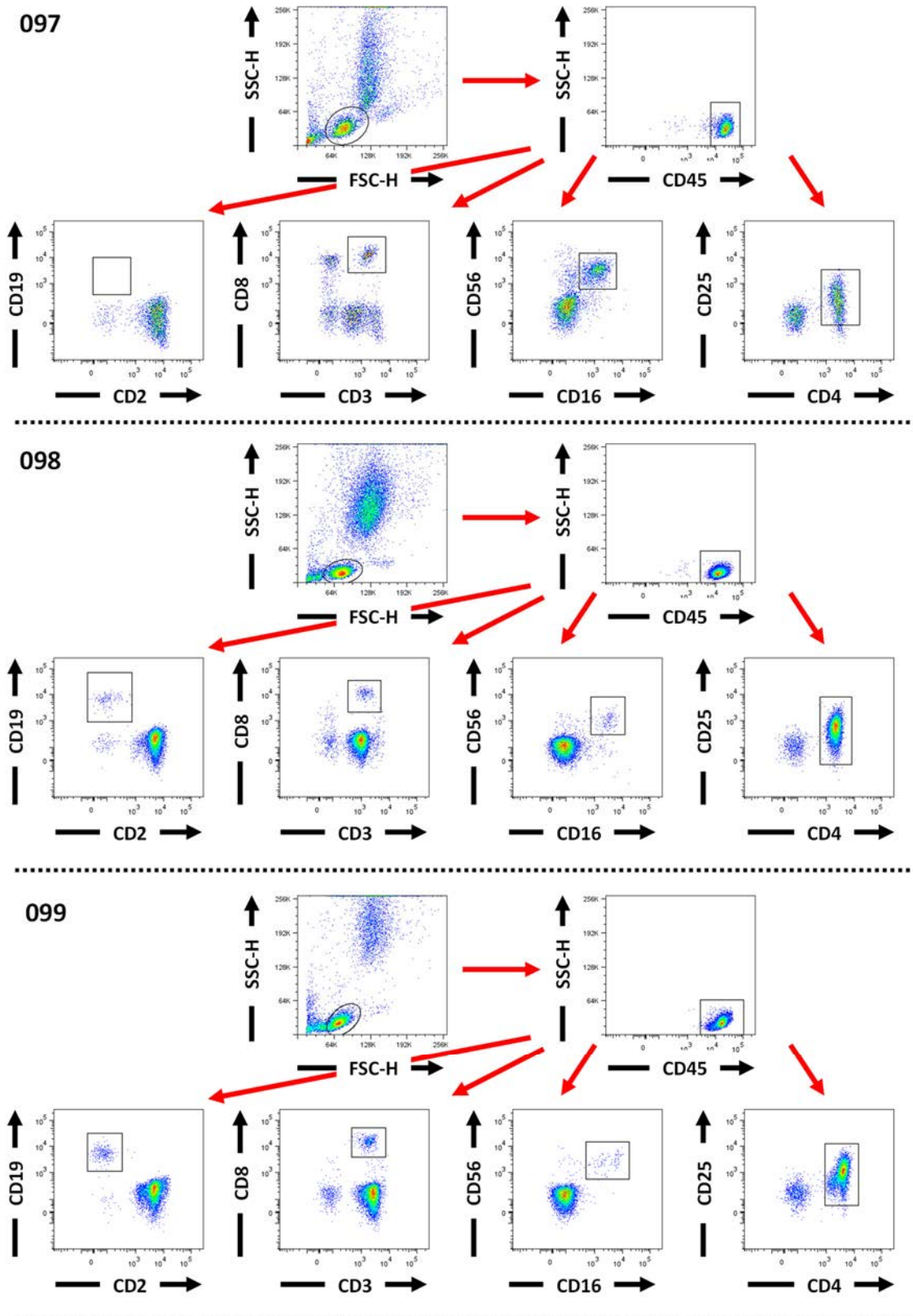
Supplemental FIGURE 4



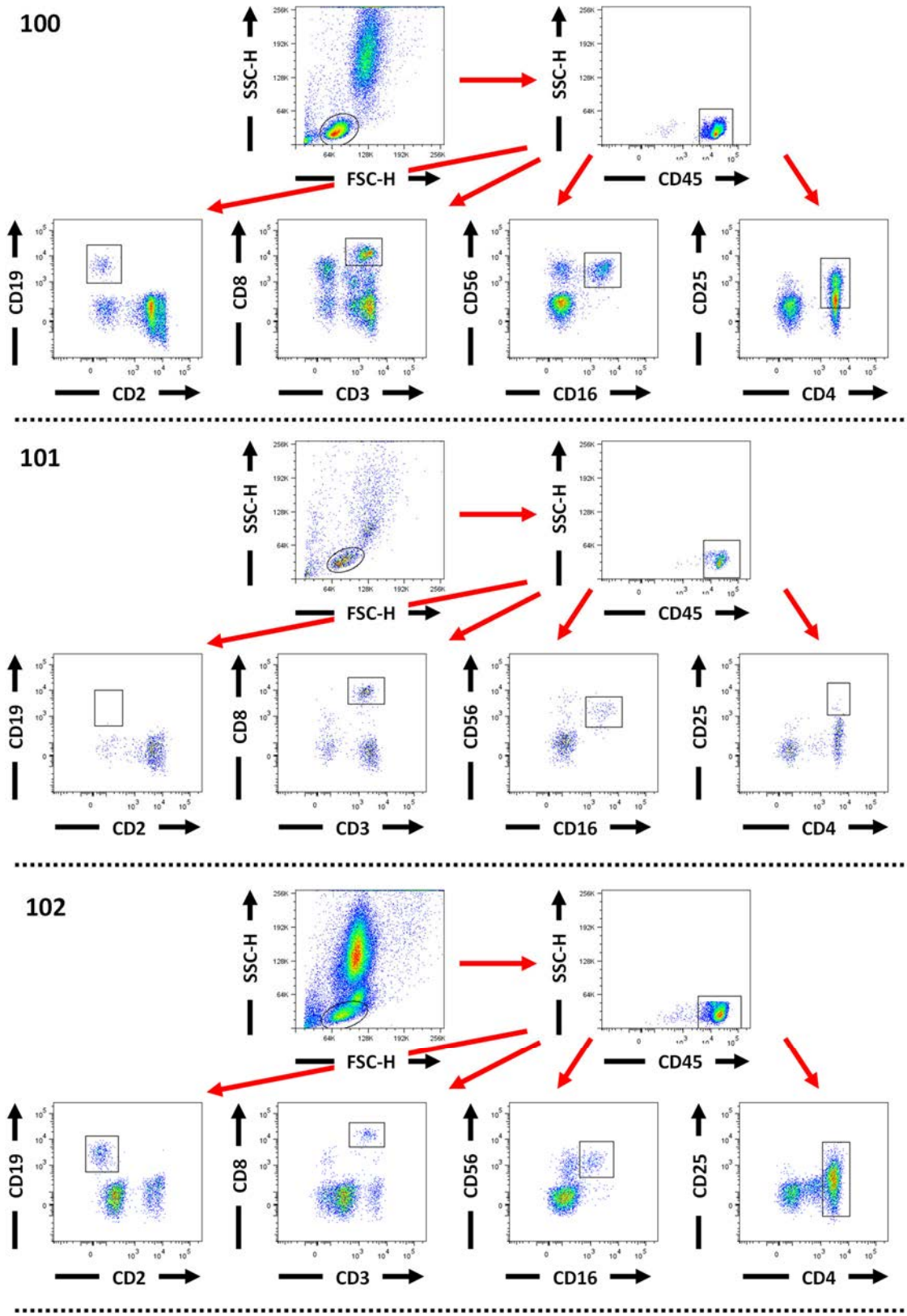
Supplemental FIGURE 4



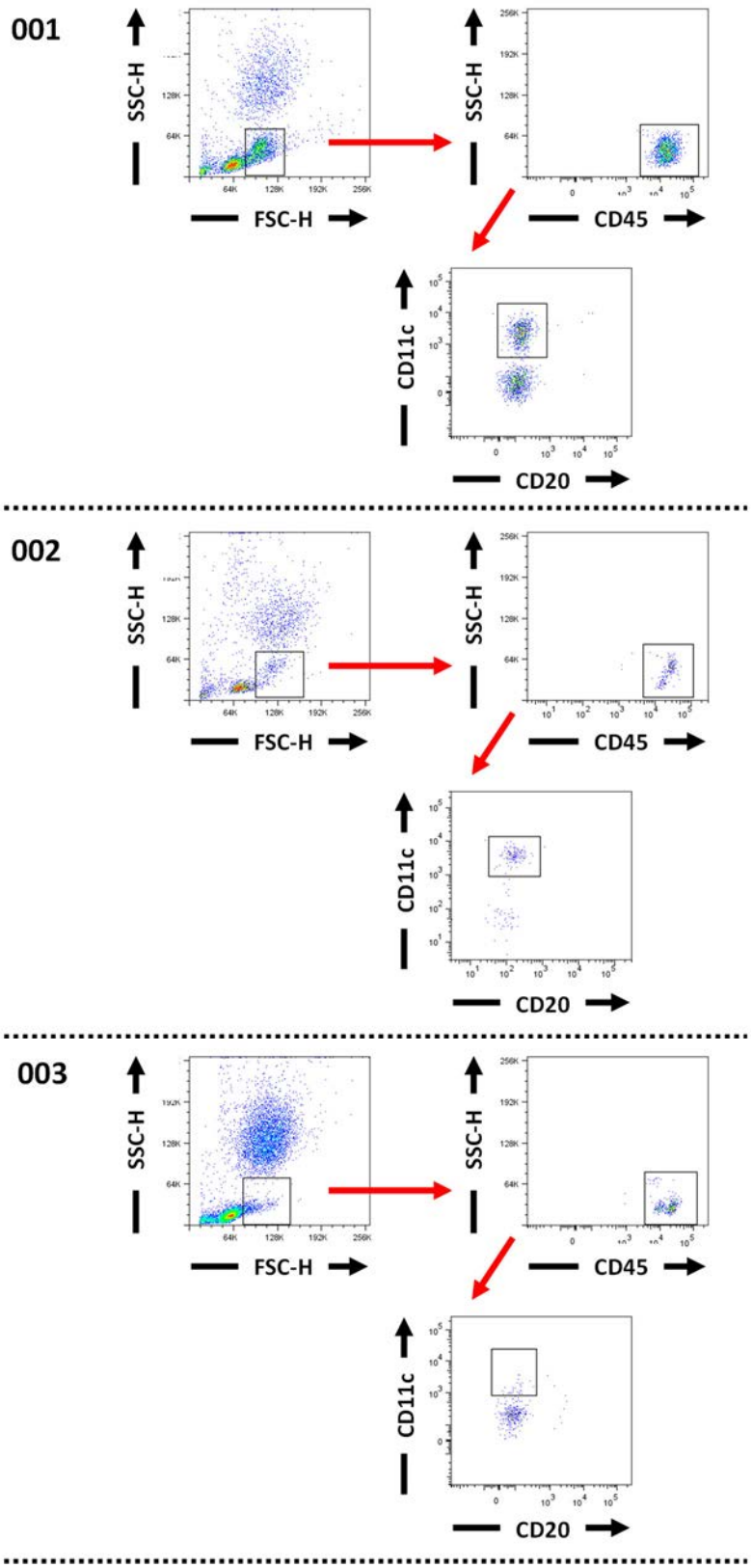
Supplemental FIGURE 4



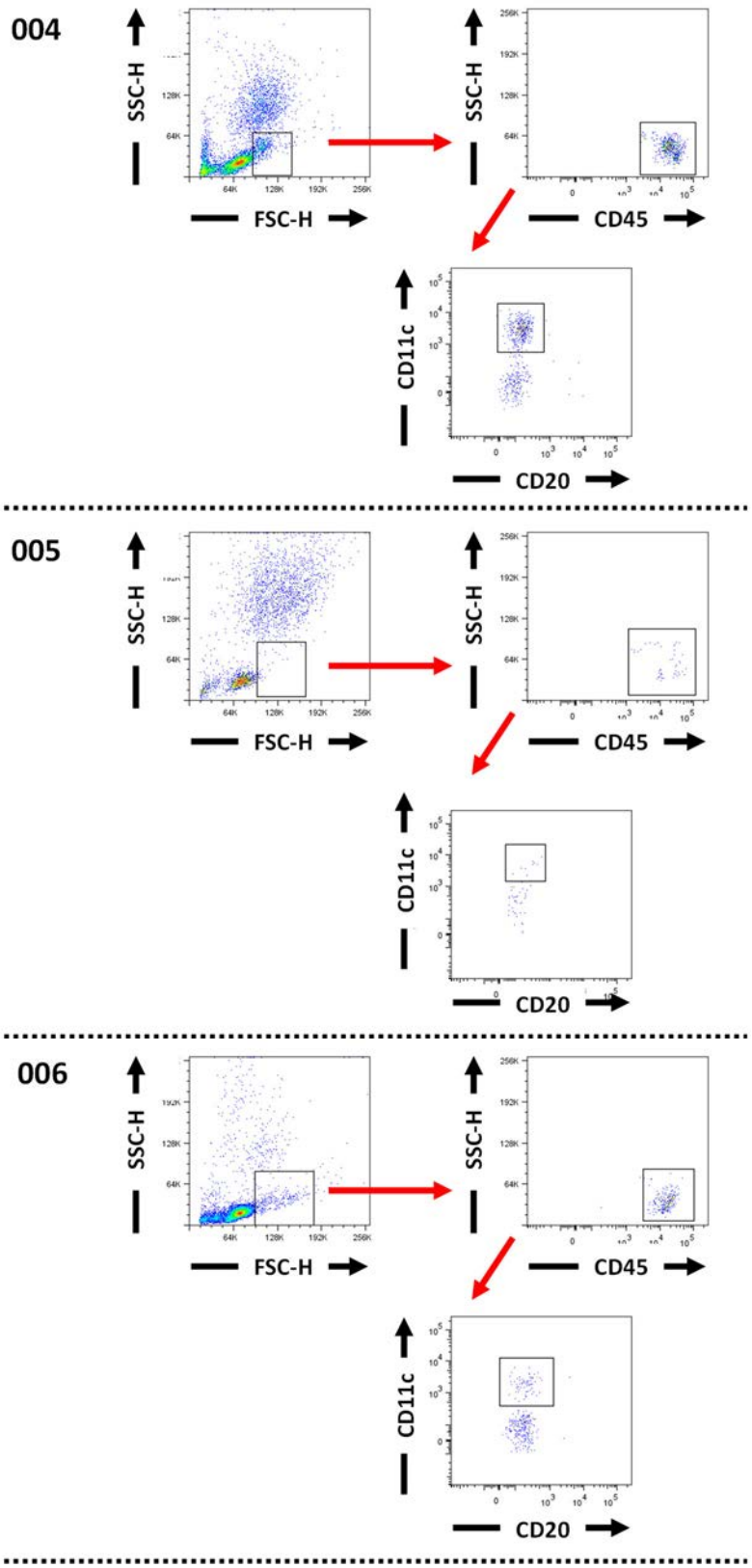
Supplemental FIGURE 4



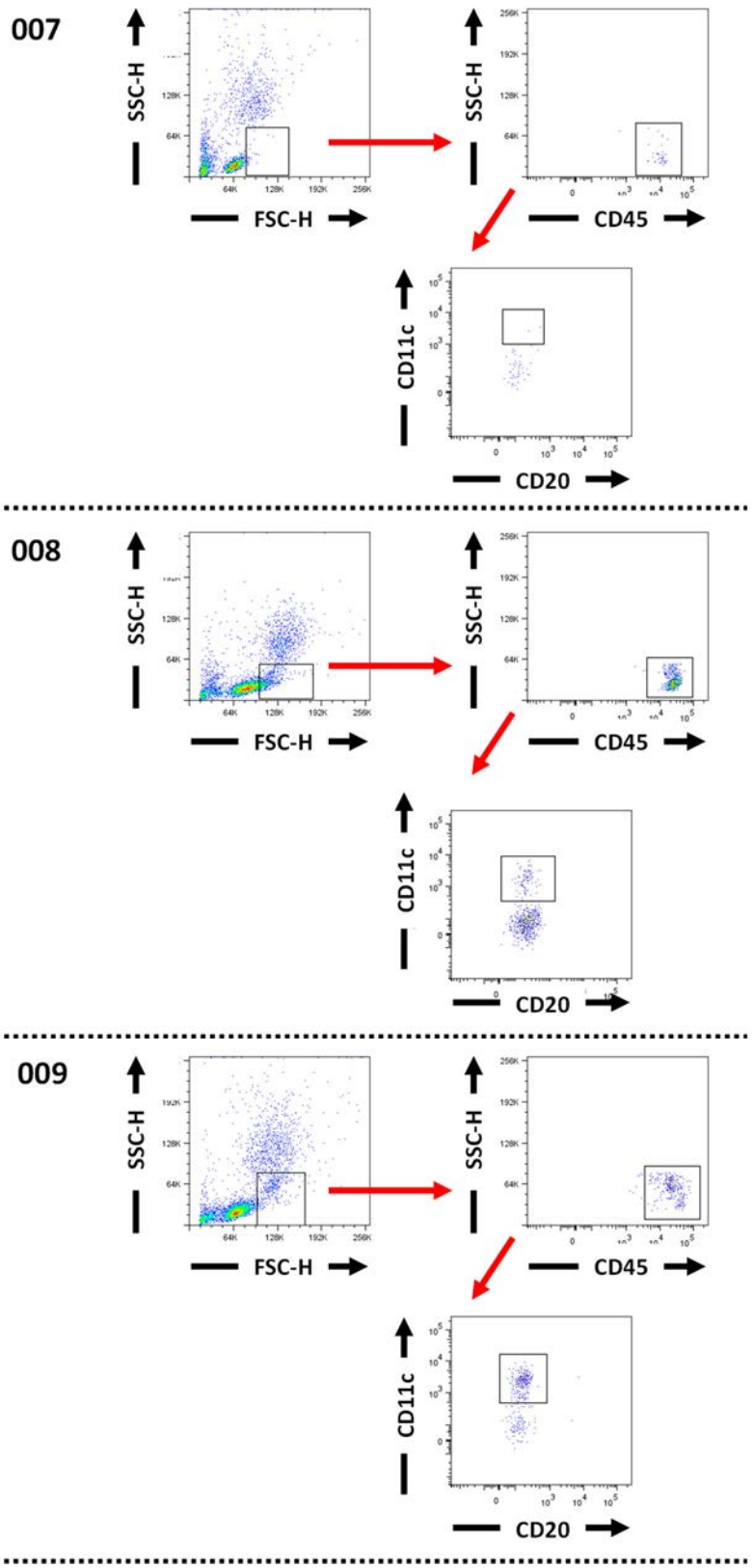
Supplemental FIGURE 4



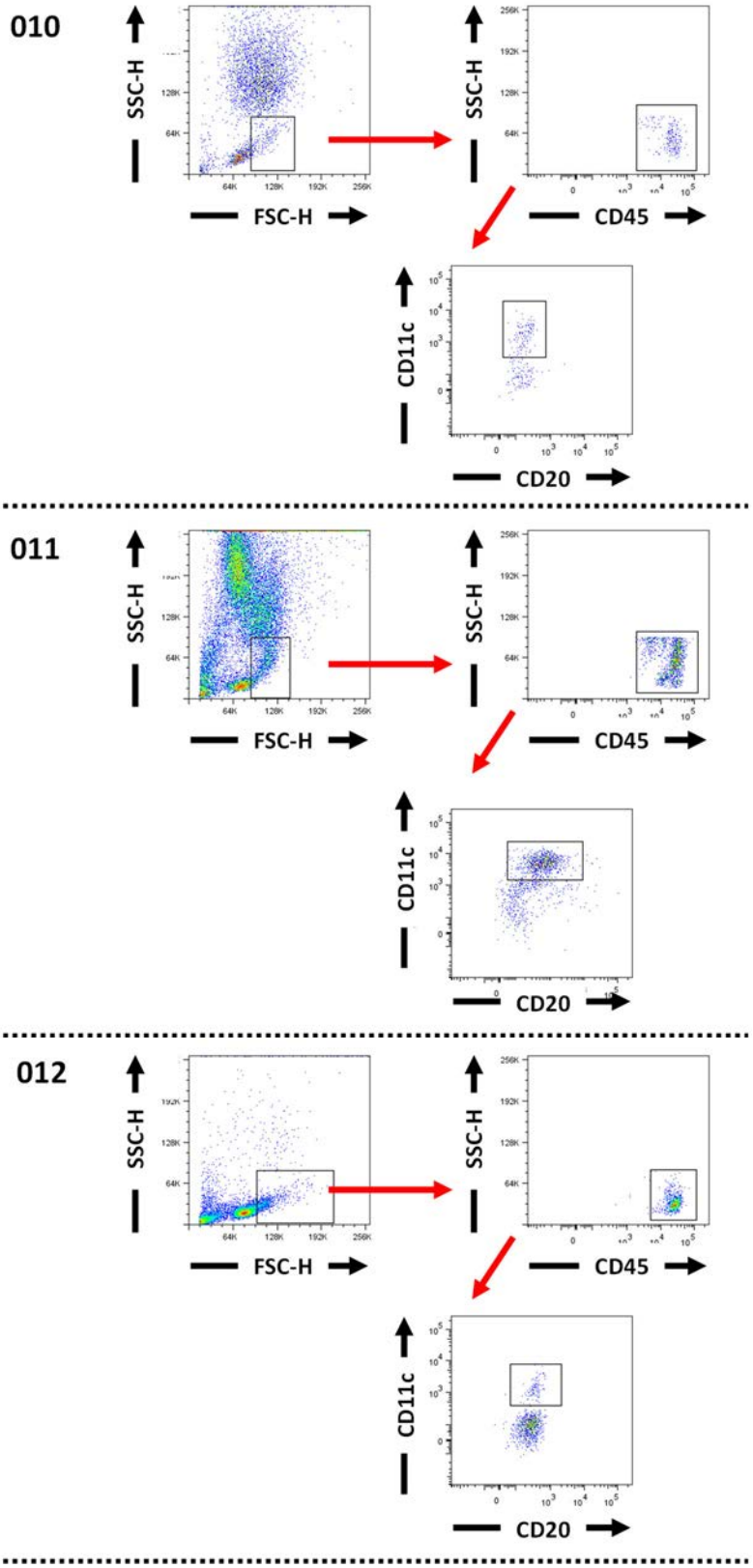
Supplemental FIGURE 5



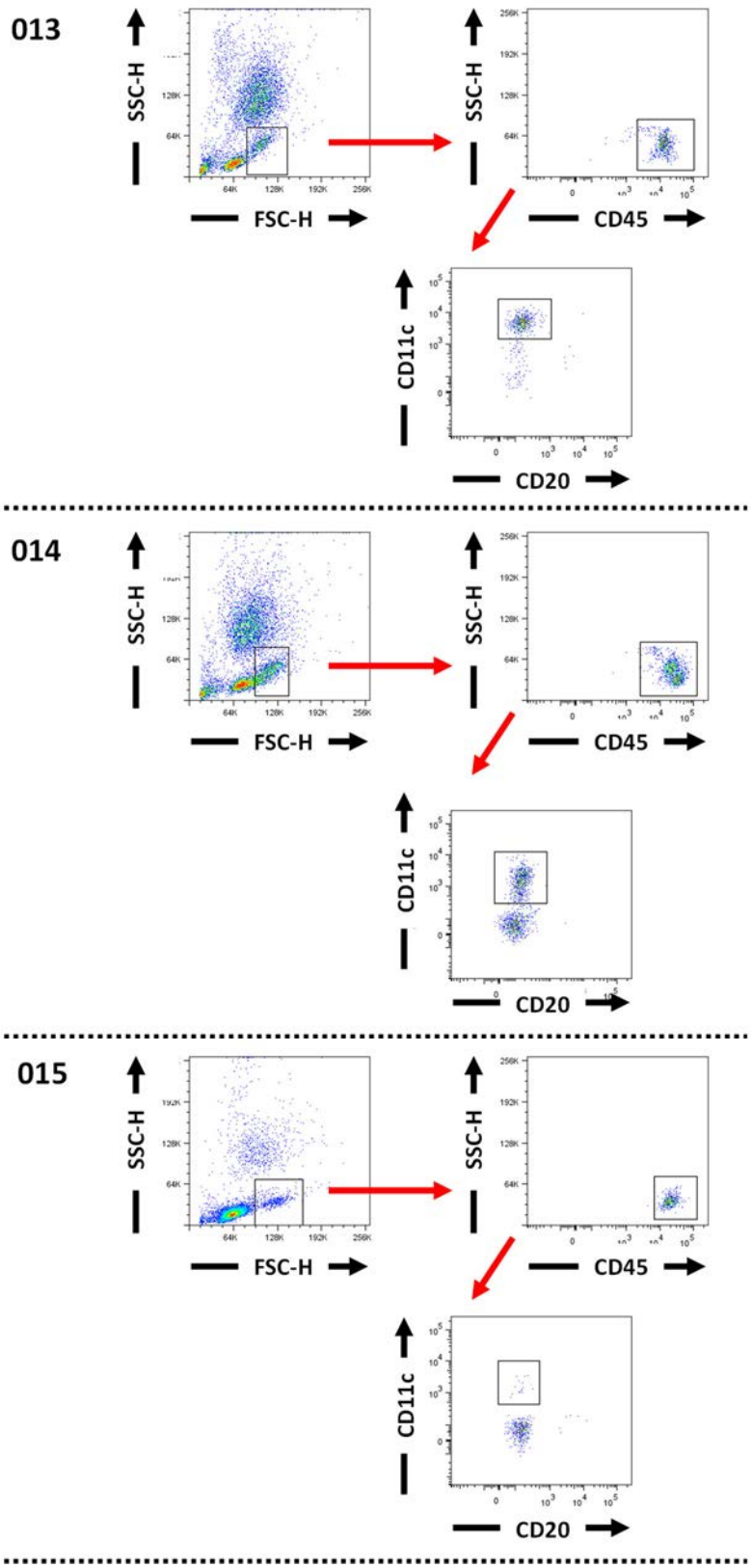
Supplemental FIGURE 5



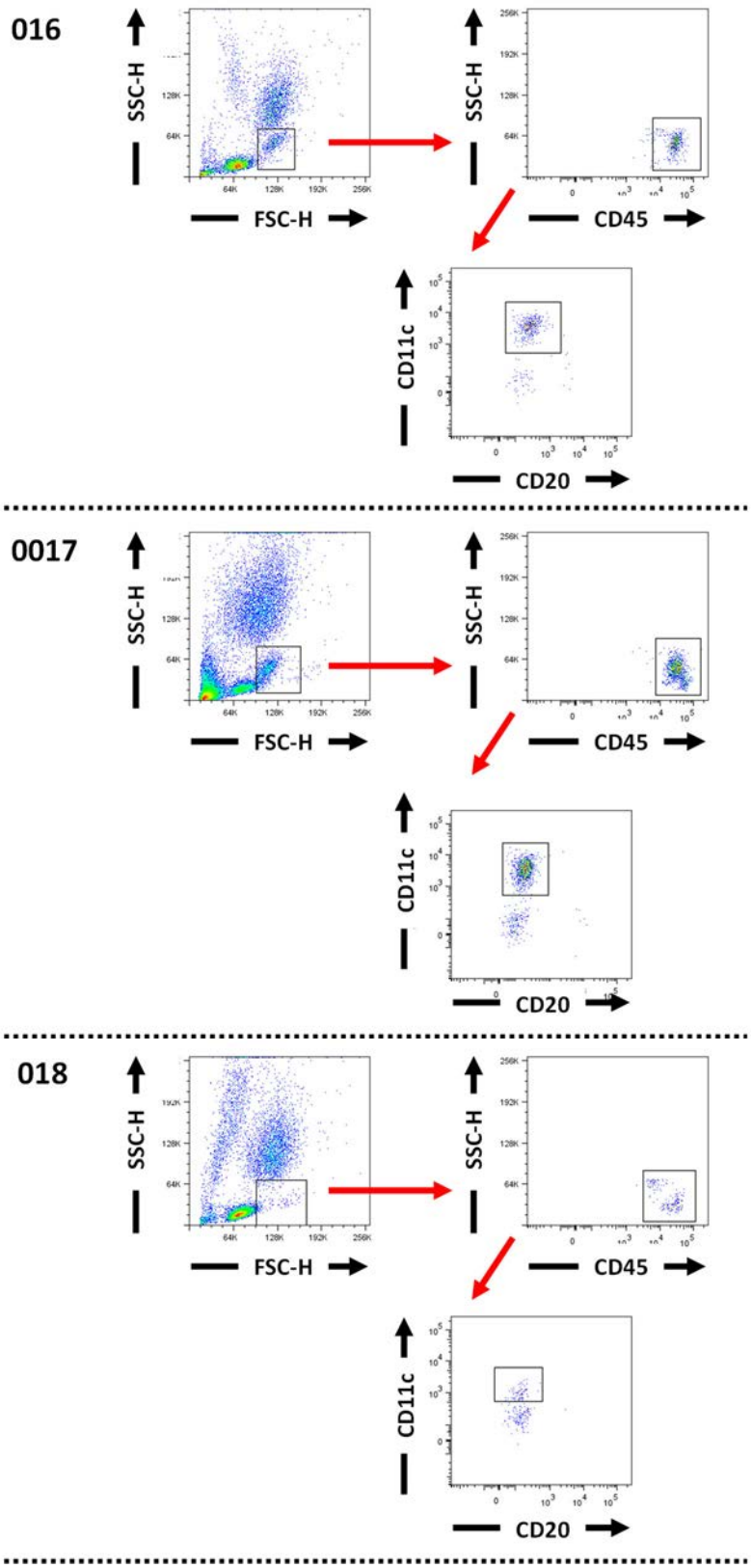
Supplemental FIGURE 5



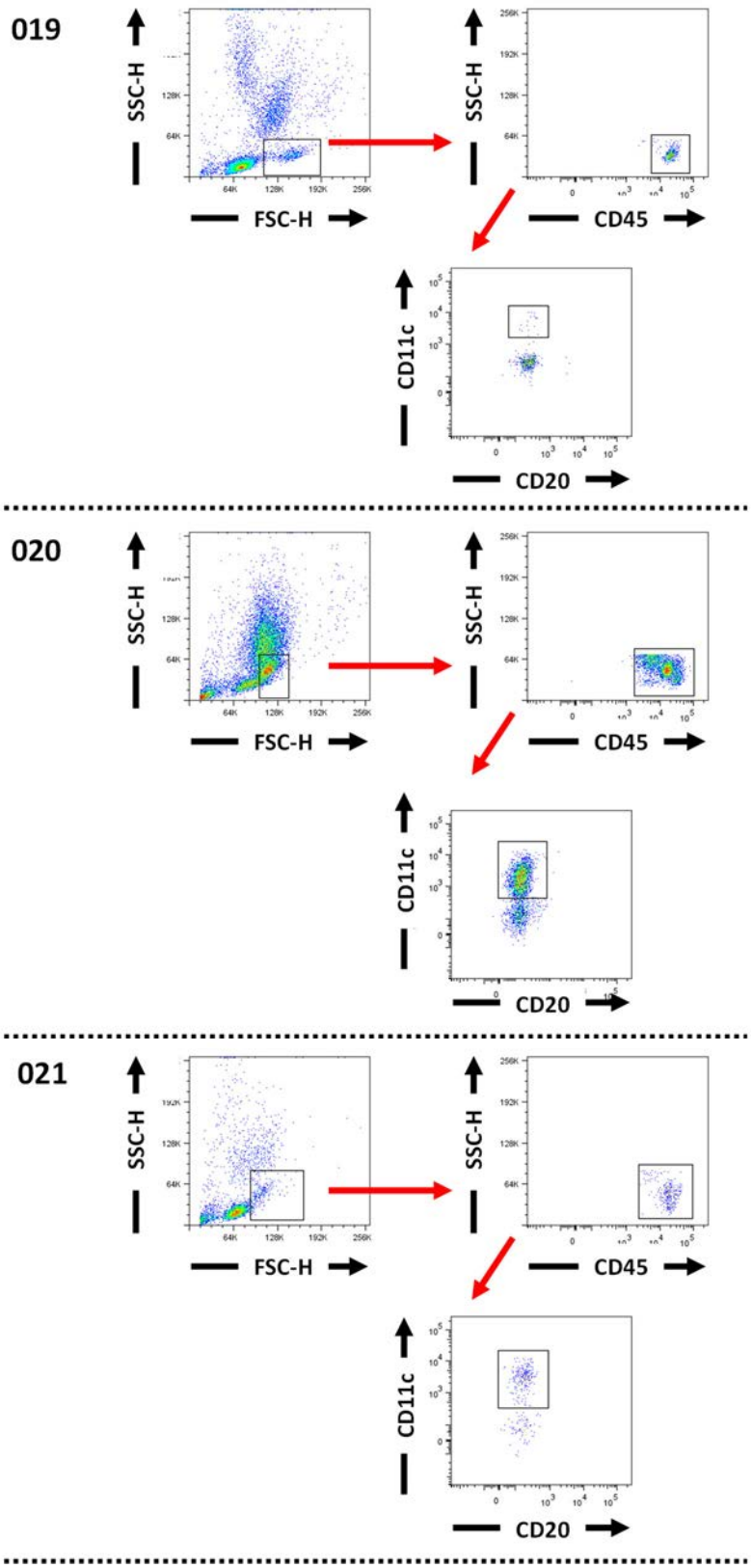
Supplemental FIGURE 5



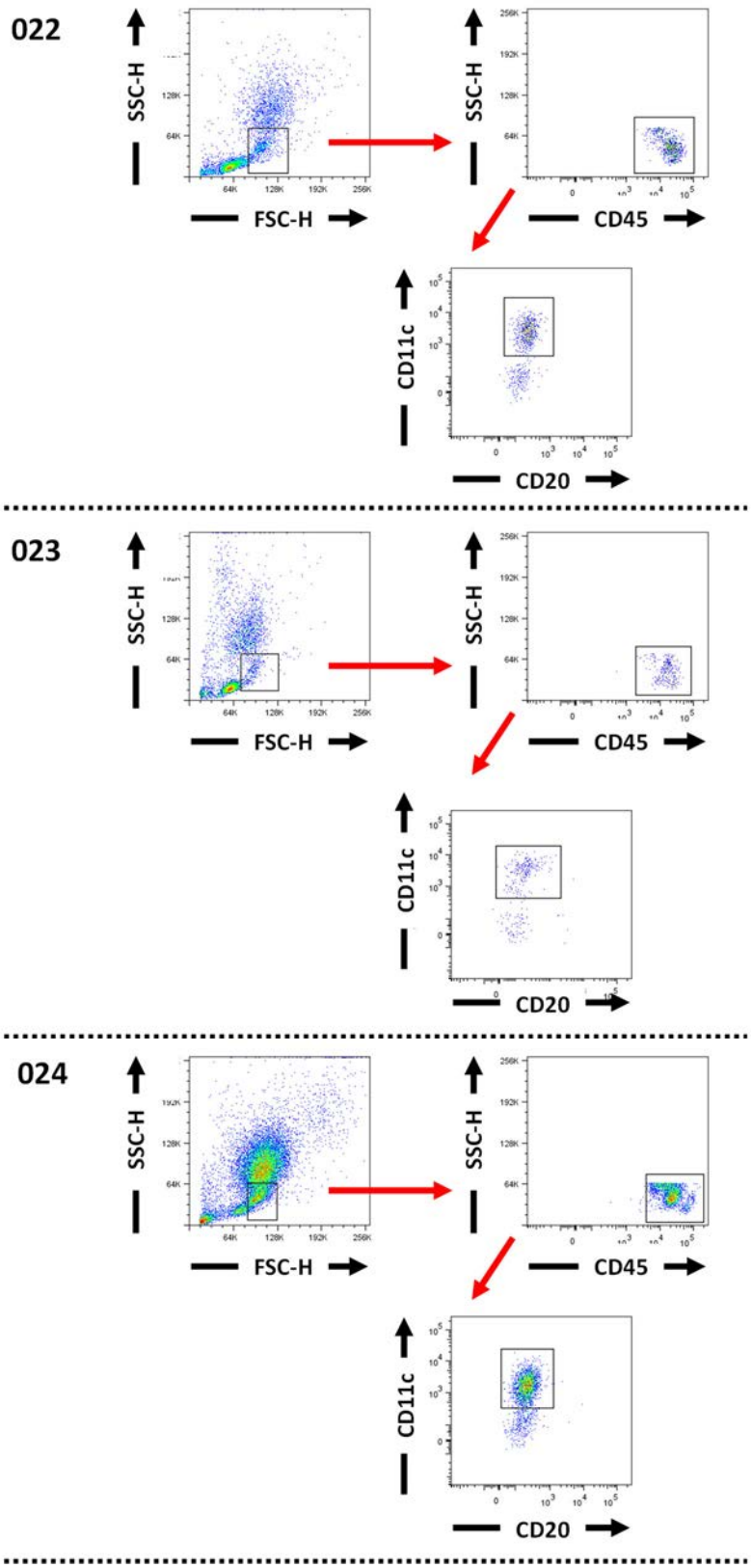
Supplemental FIGURE 5



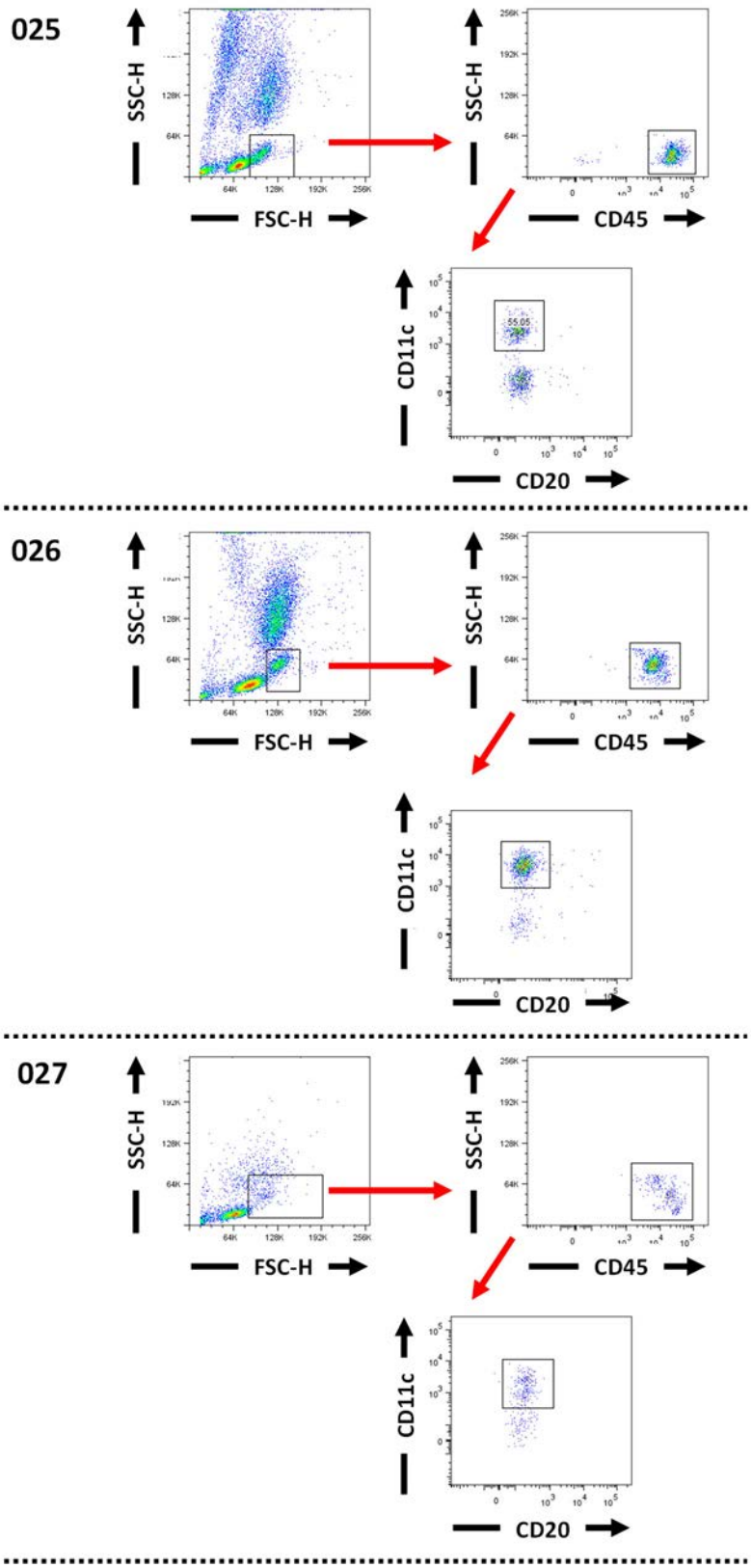
Supplemental FIGURE 5



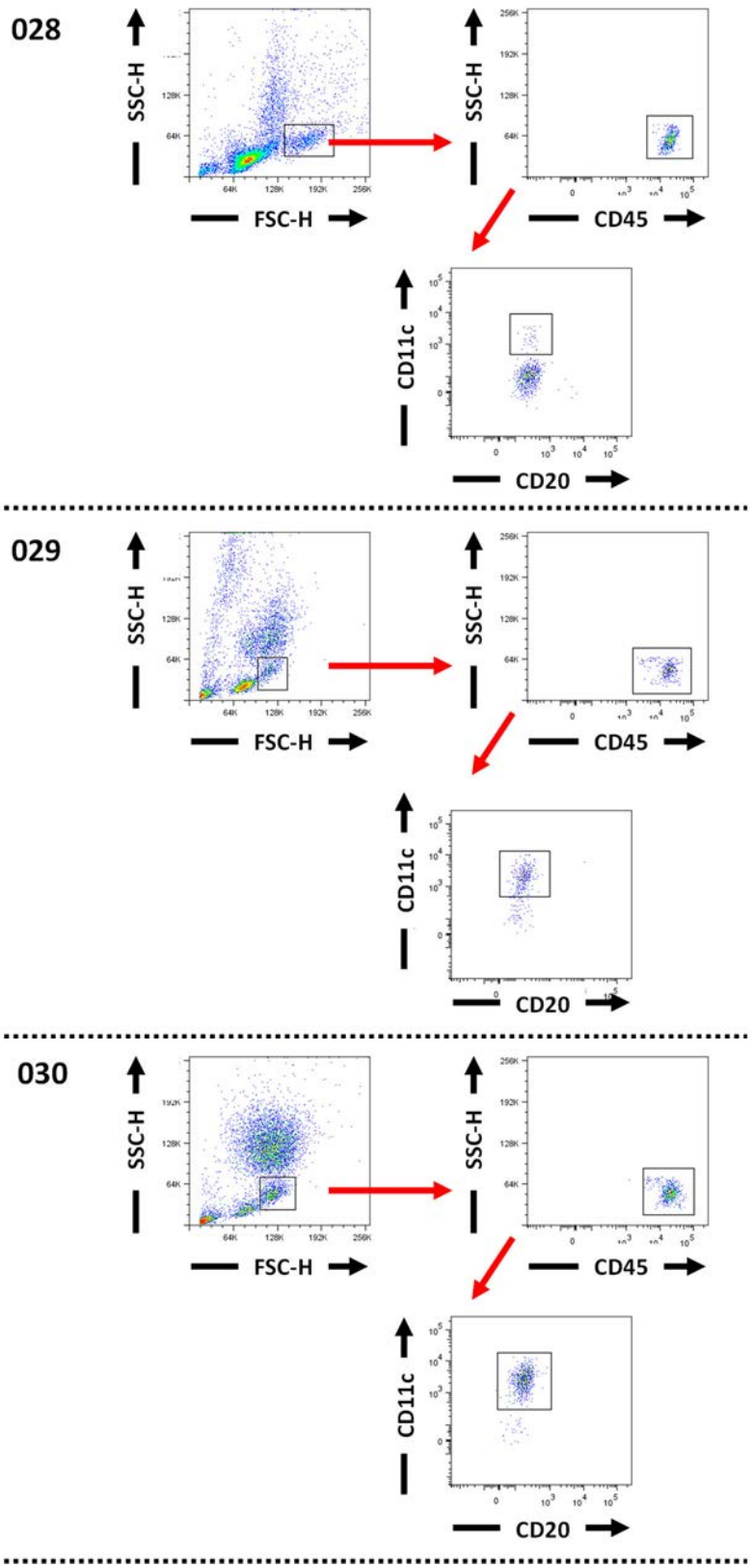
Supplemental FIGURE 5



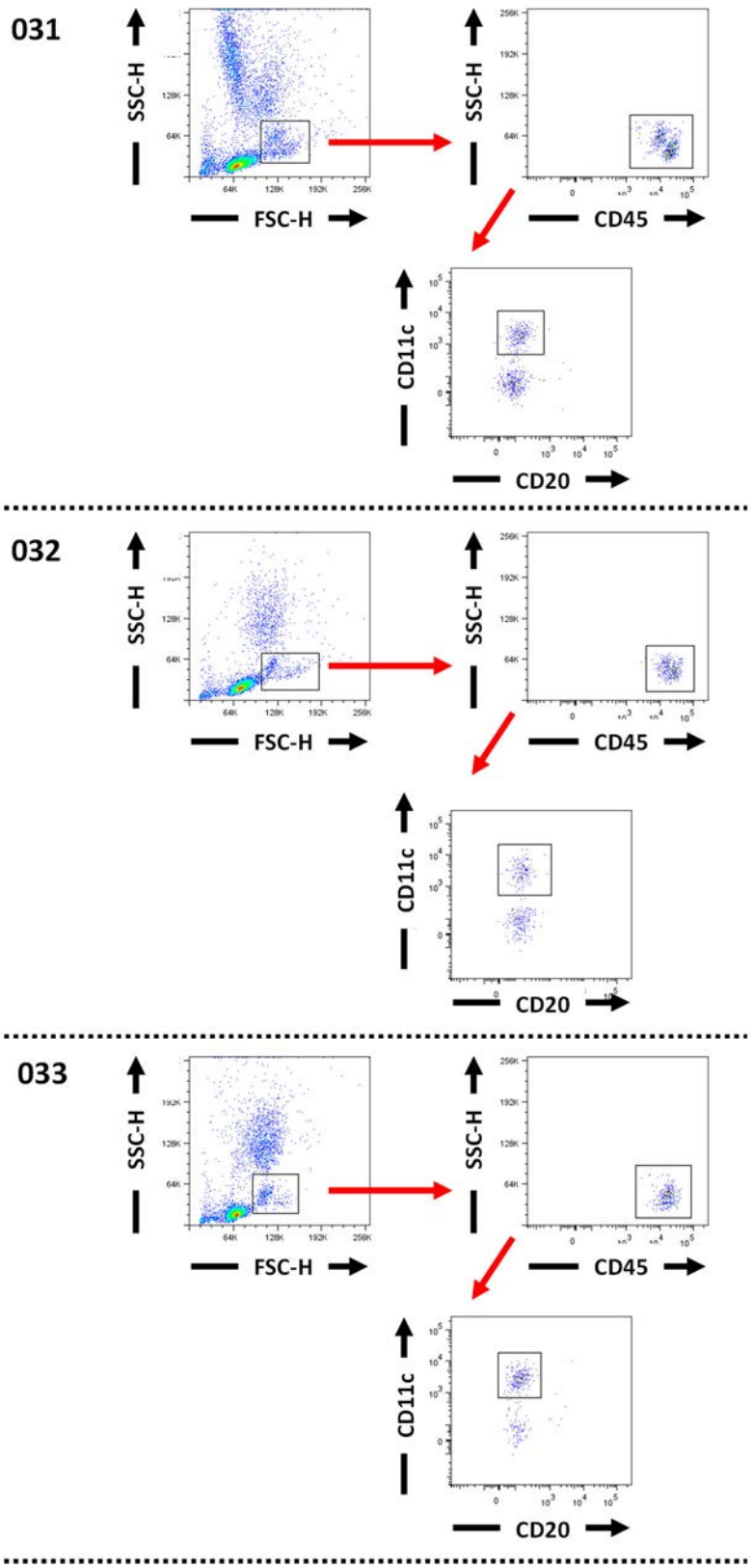
Supplemental FIGURE 5



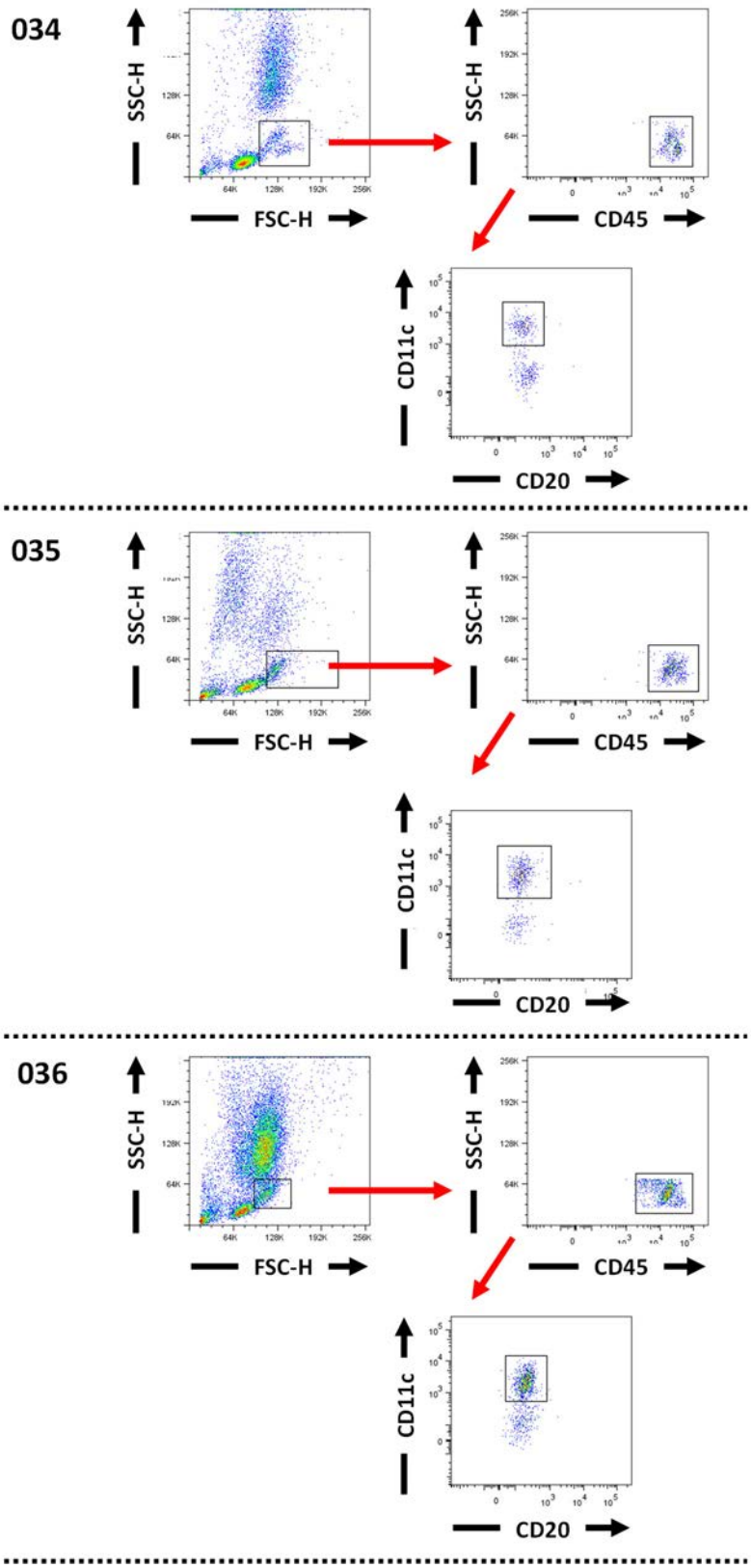
Supplemental FIGURE 5



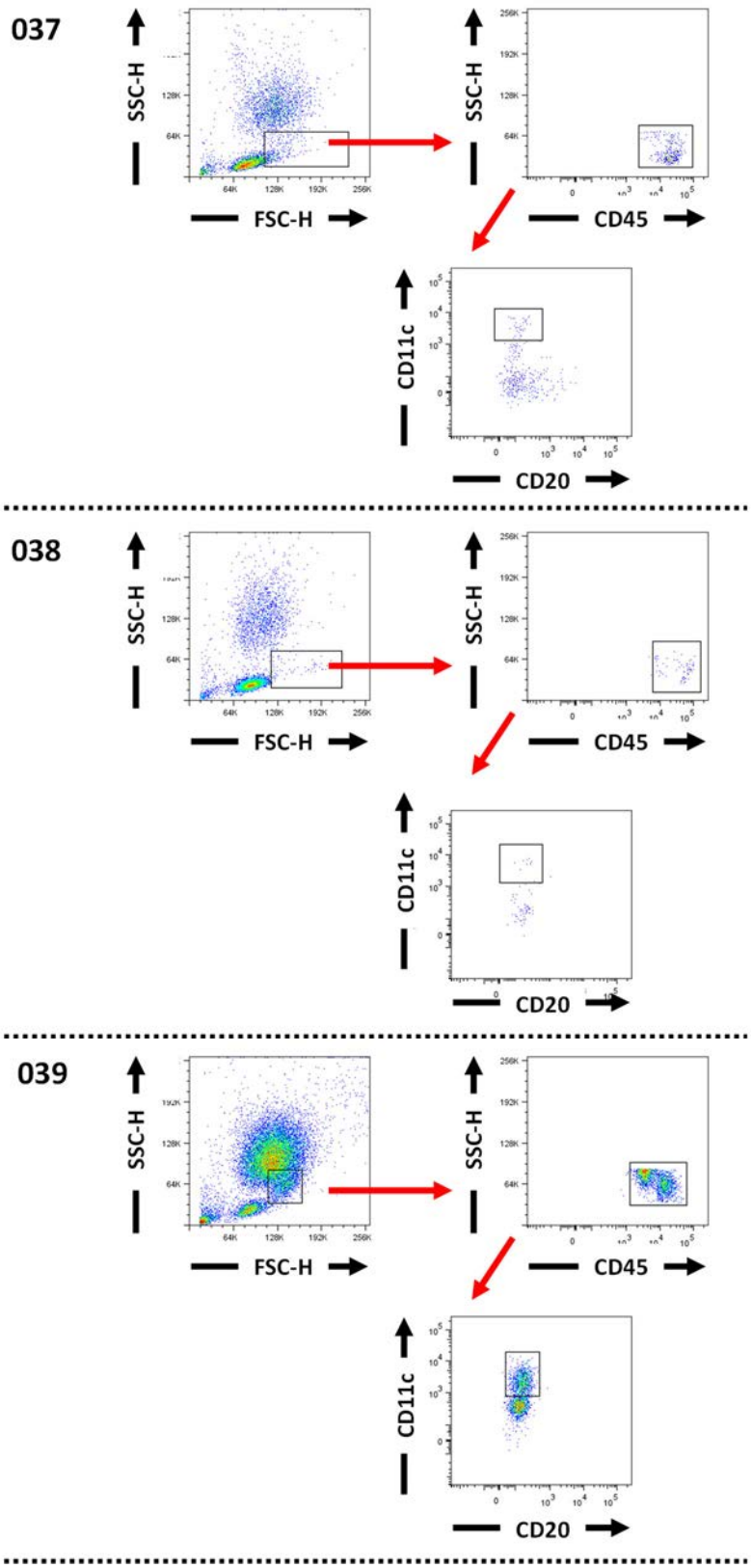
Supplemental FIGURE 5



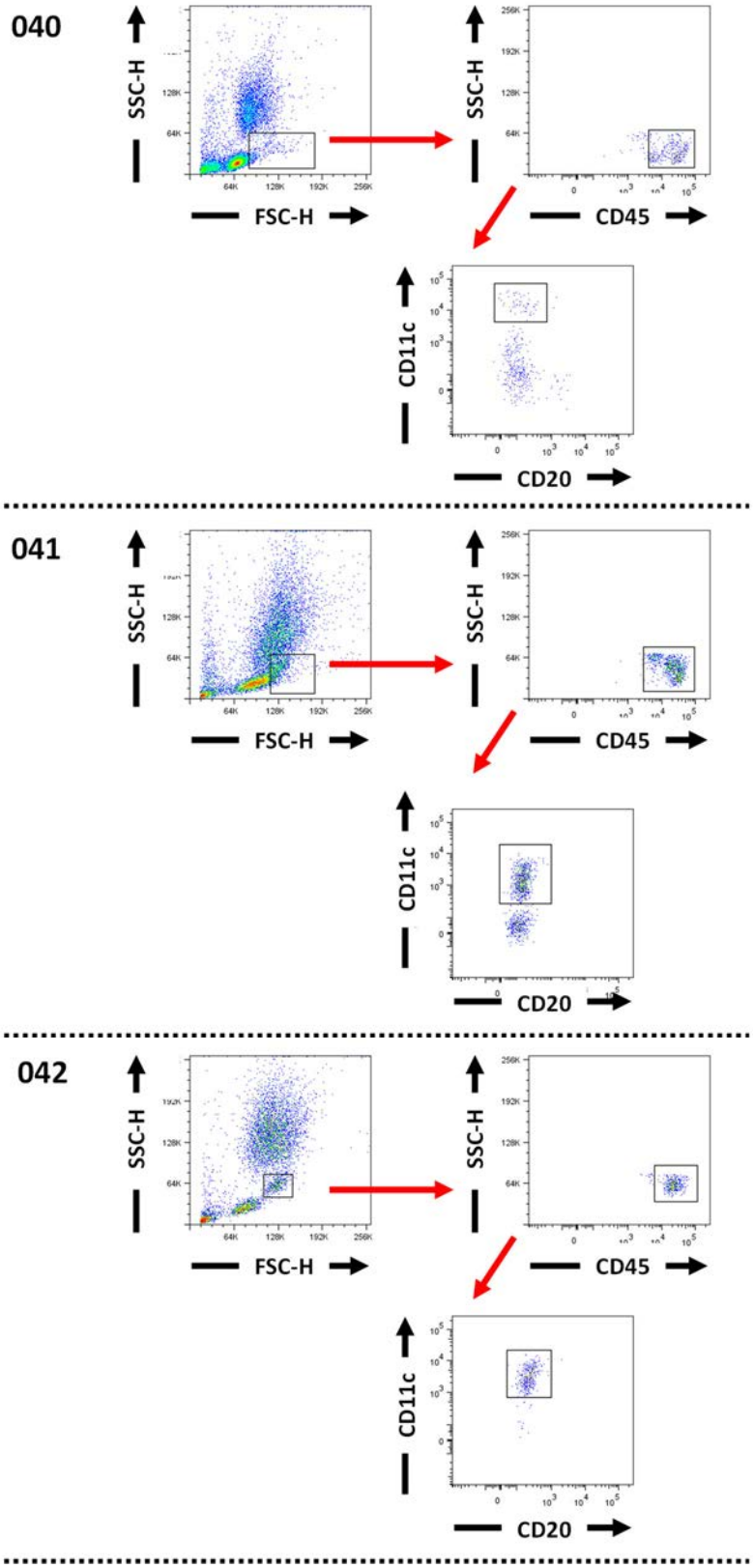
Supplemental FIGURE 5



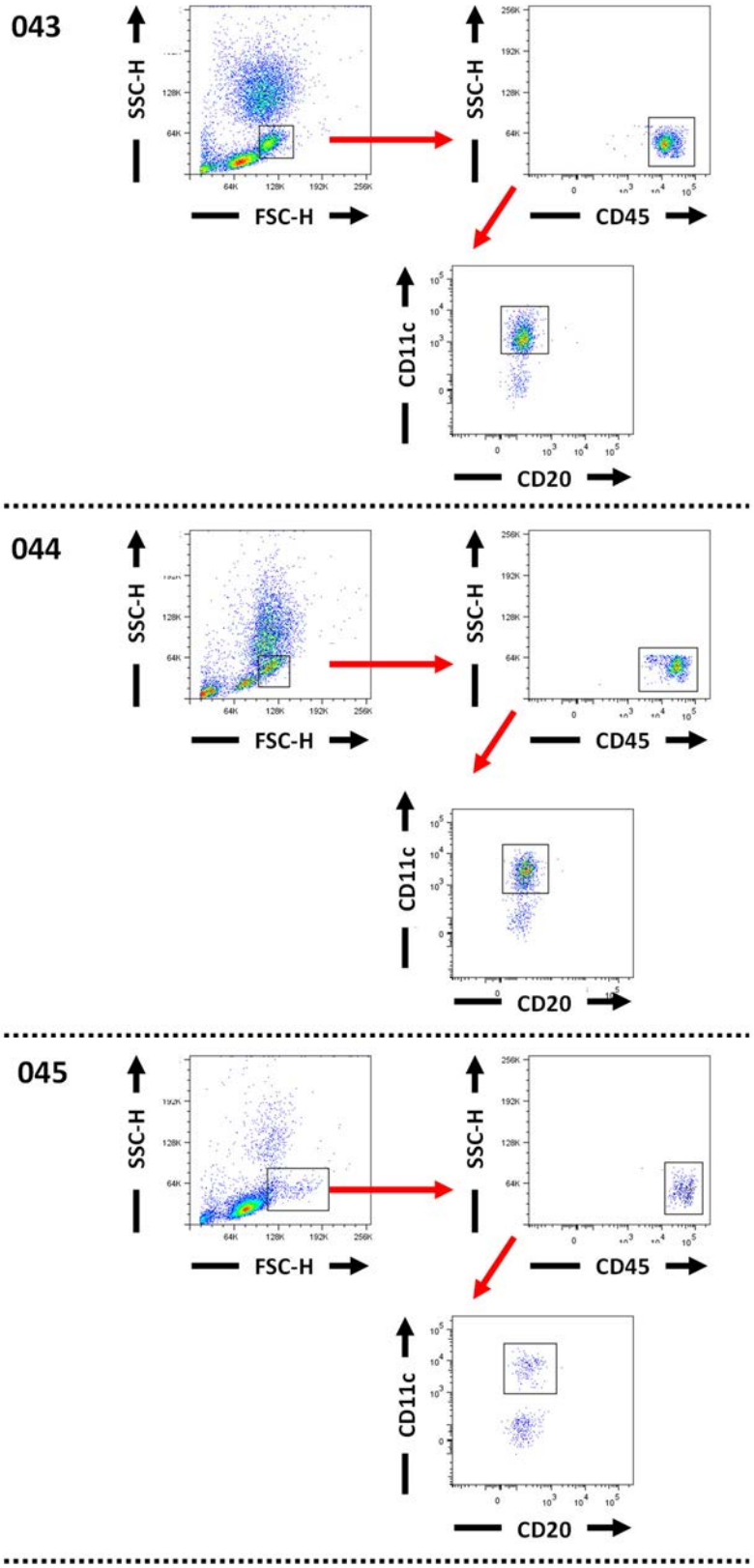
Supplemental FIGURE 5



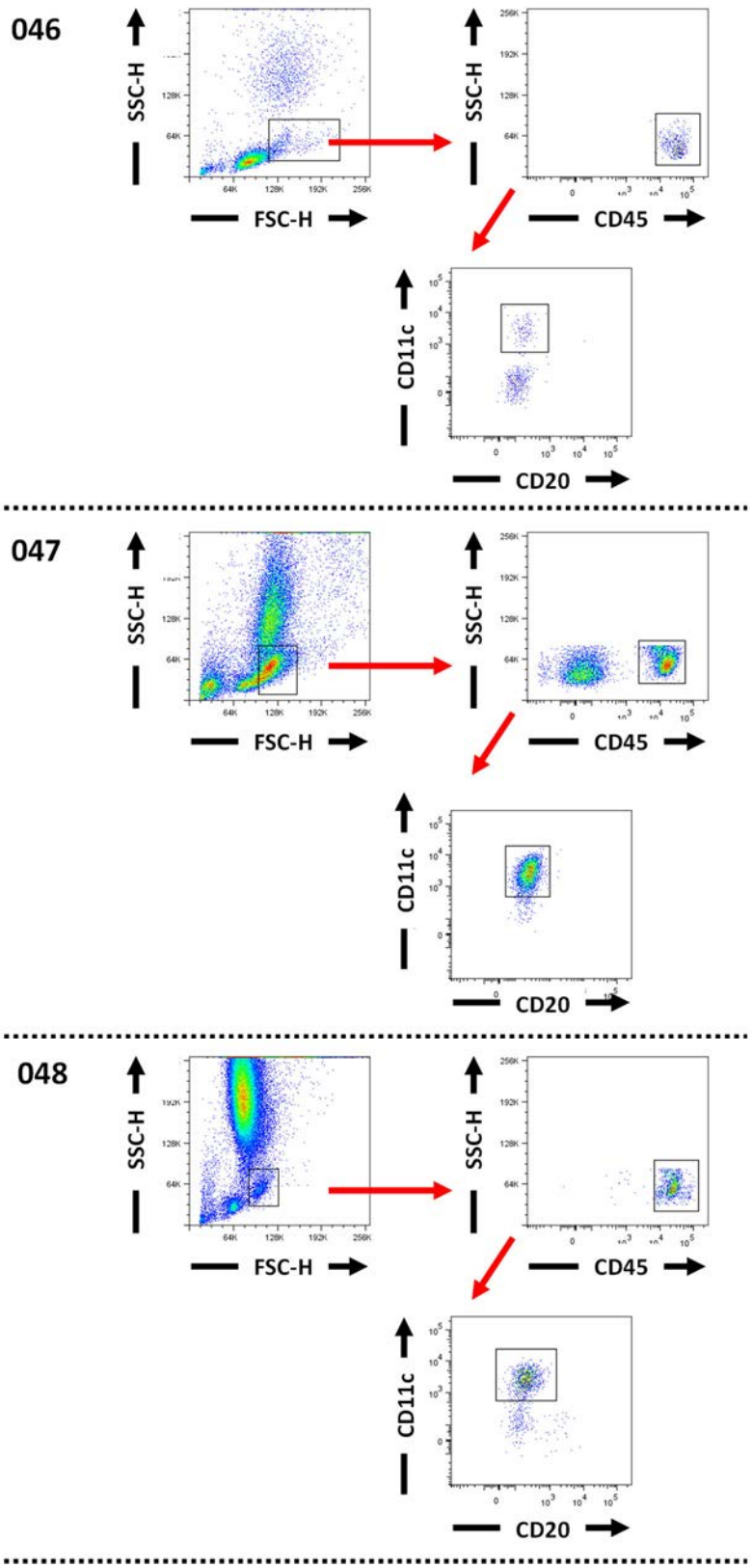
Supplemental FIGURE 5



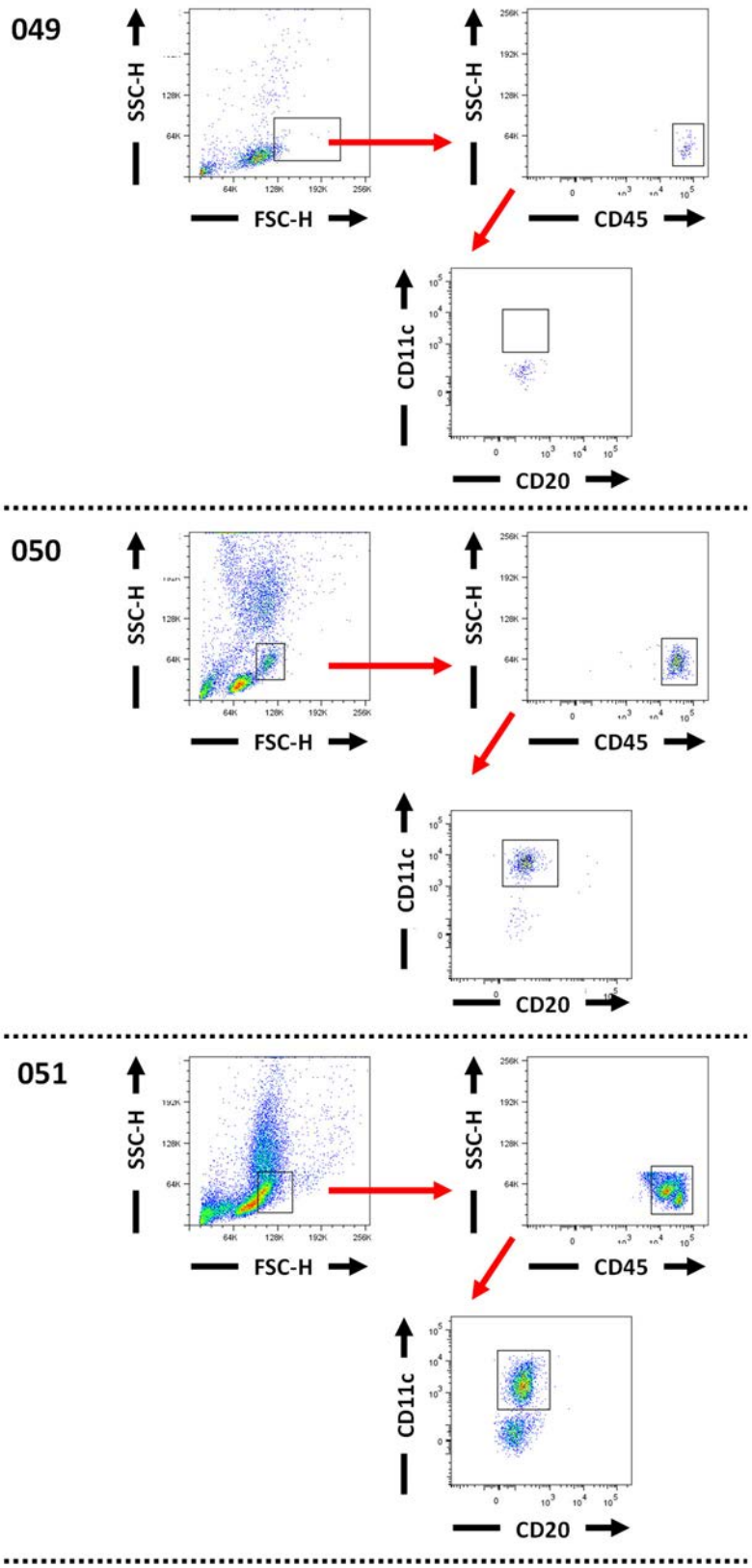
Supplemental FIGURE 5



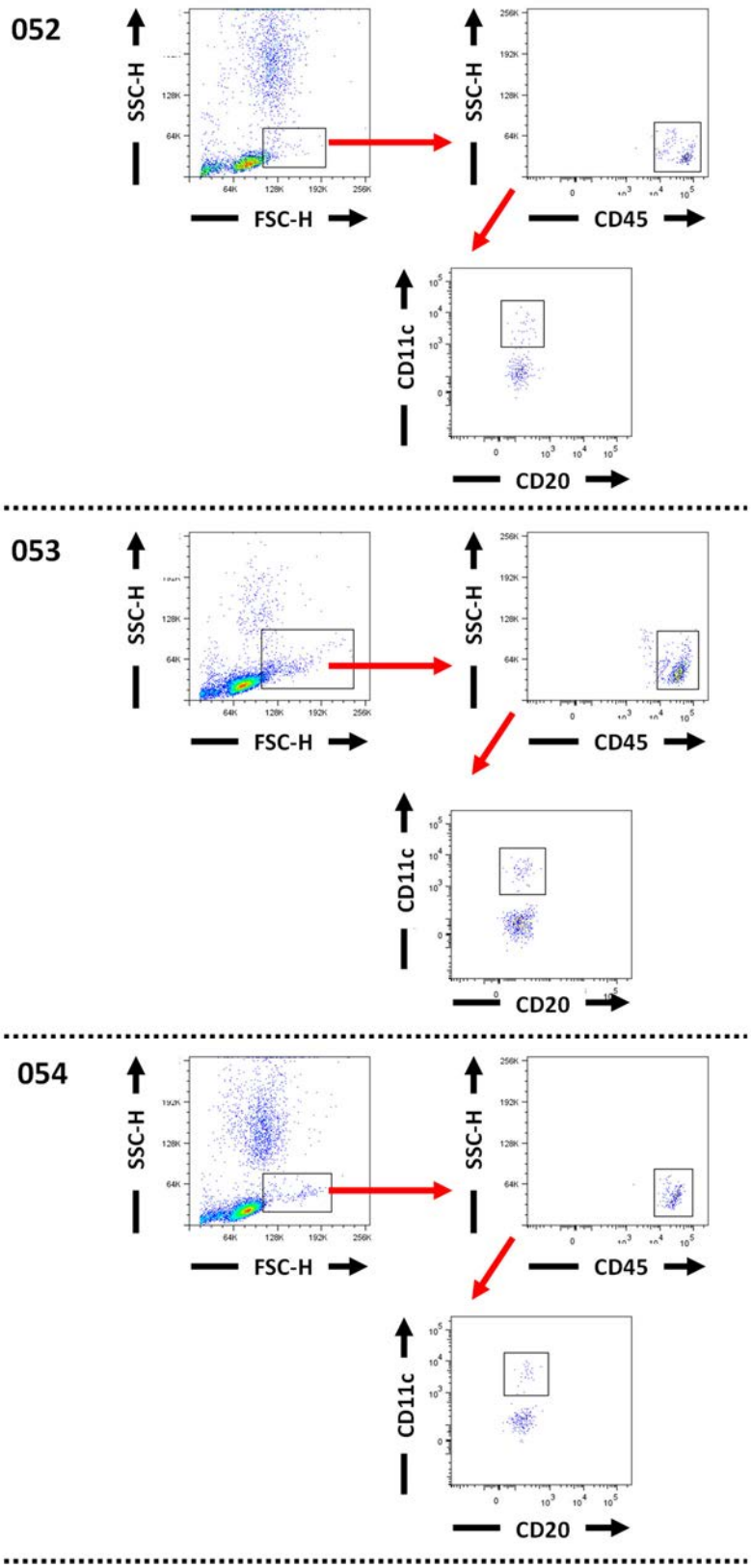
Supplemental FIGURE 5



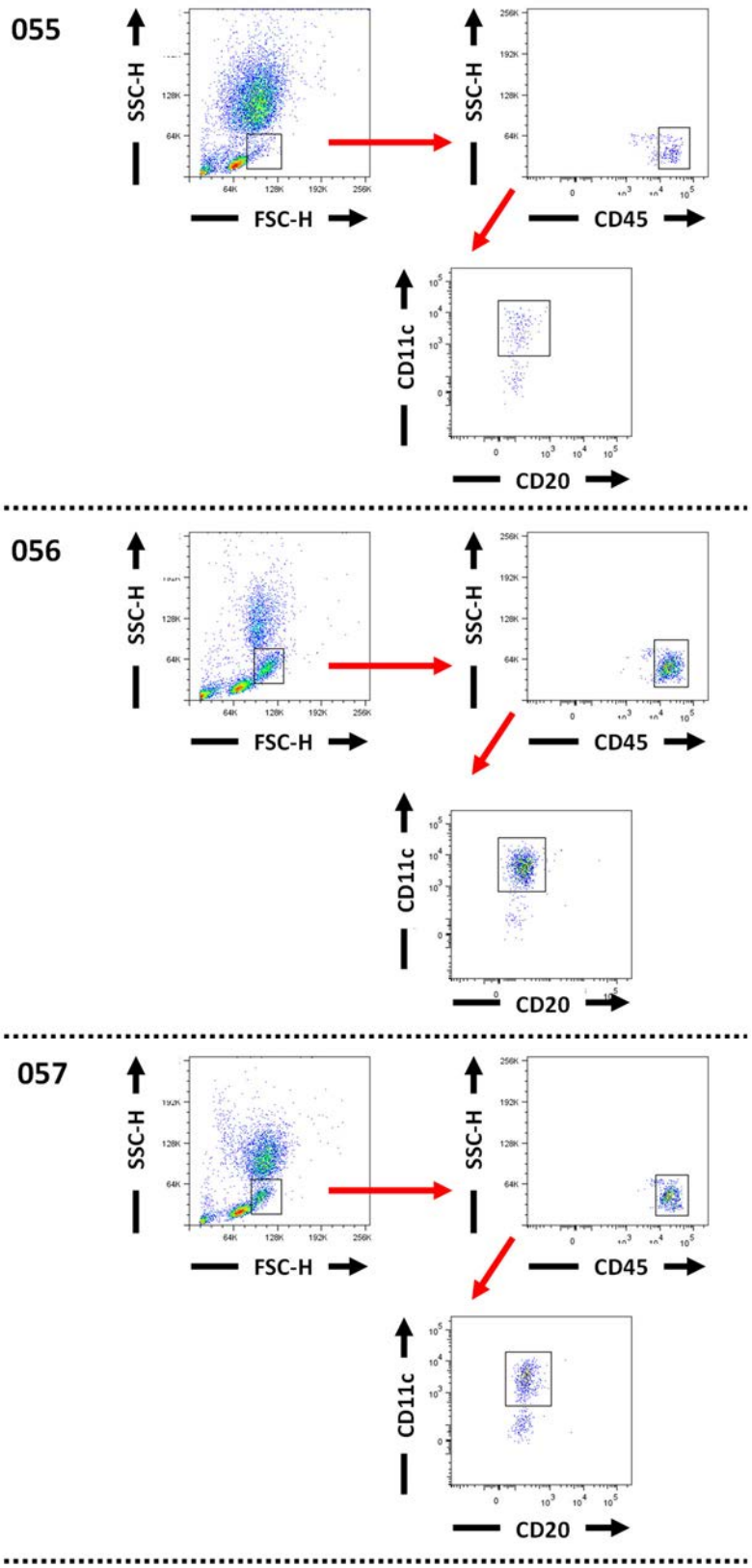
Supplemental FIGURE 5



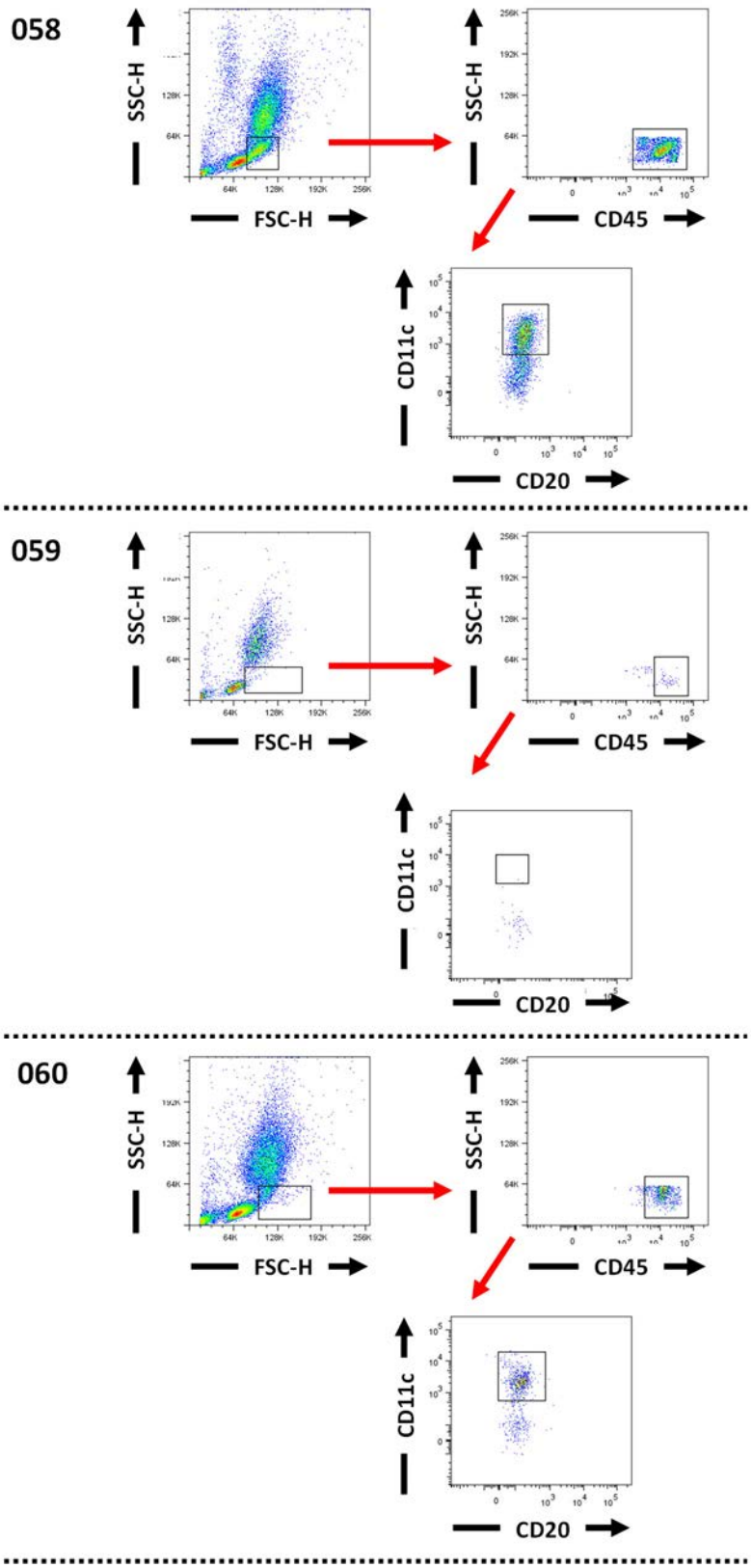
Supplemental FIGURE 5



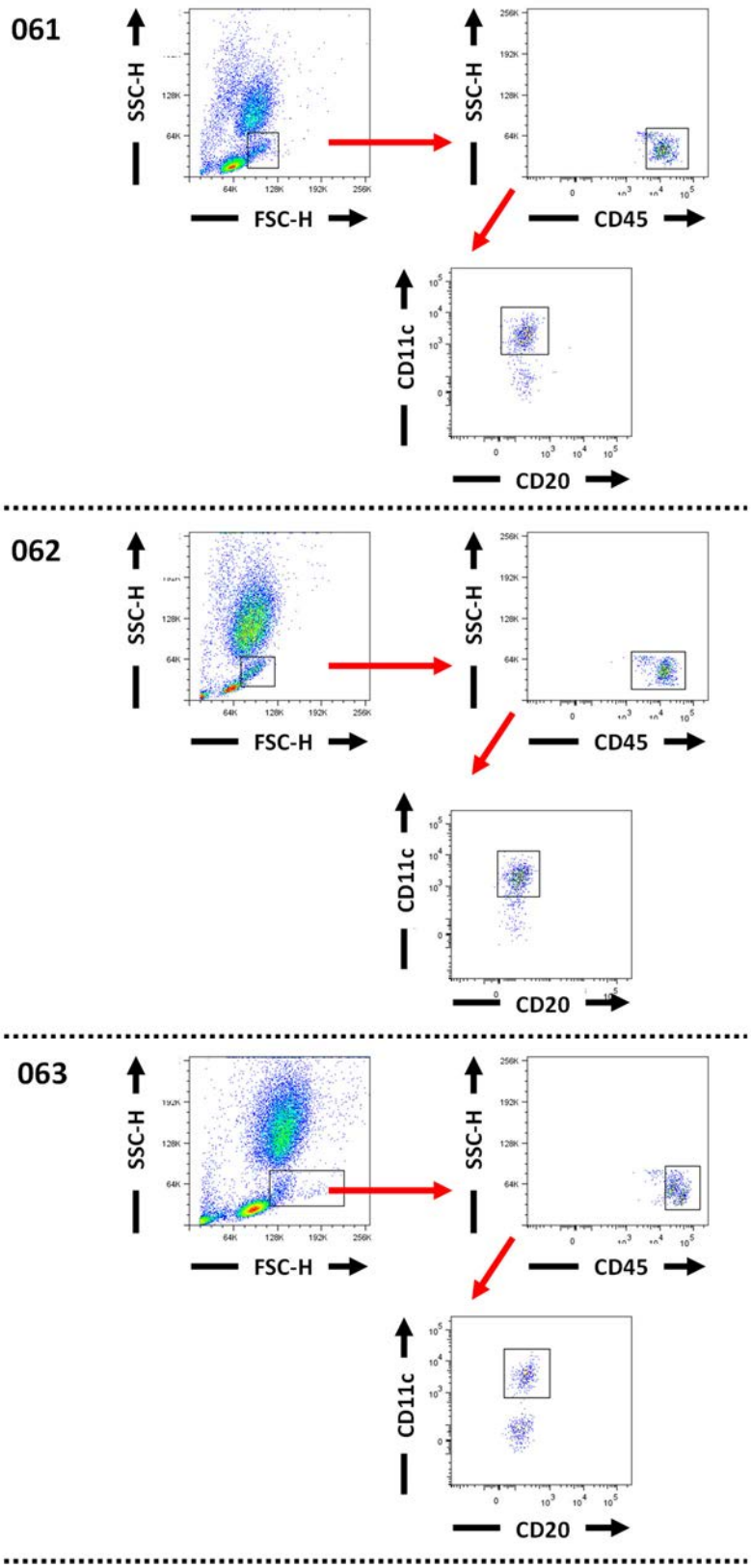
Supplemental FIGURE 5



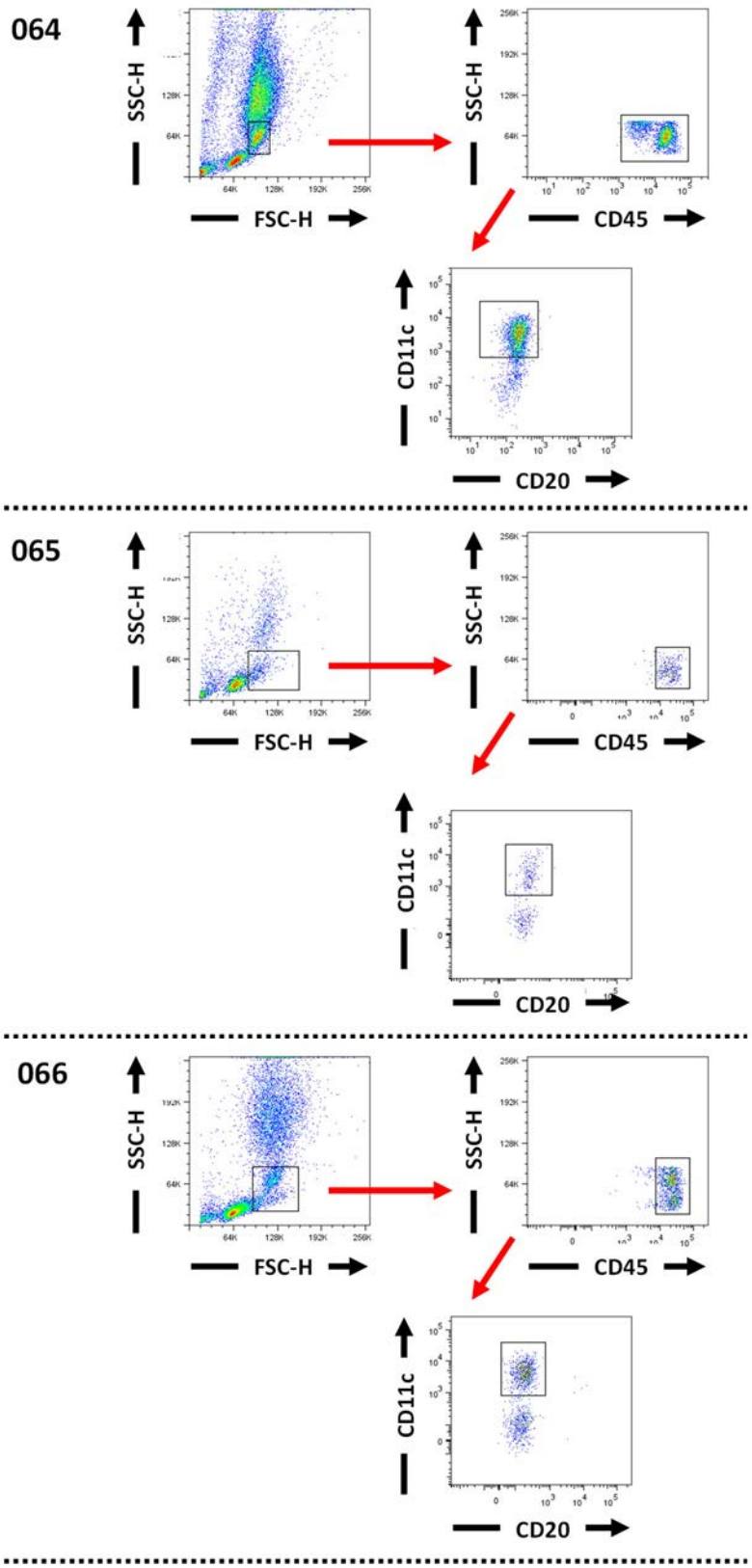
Supplemental FIGURE 5



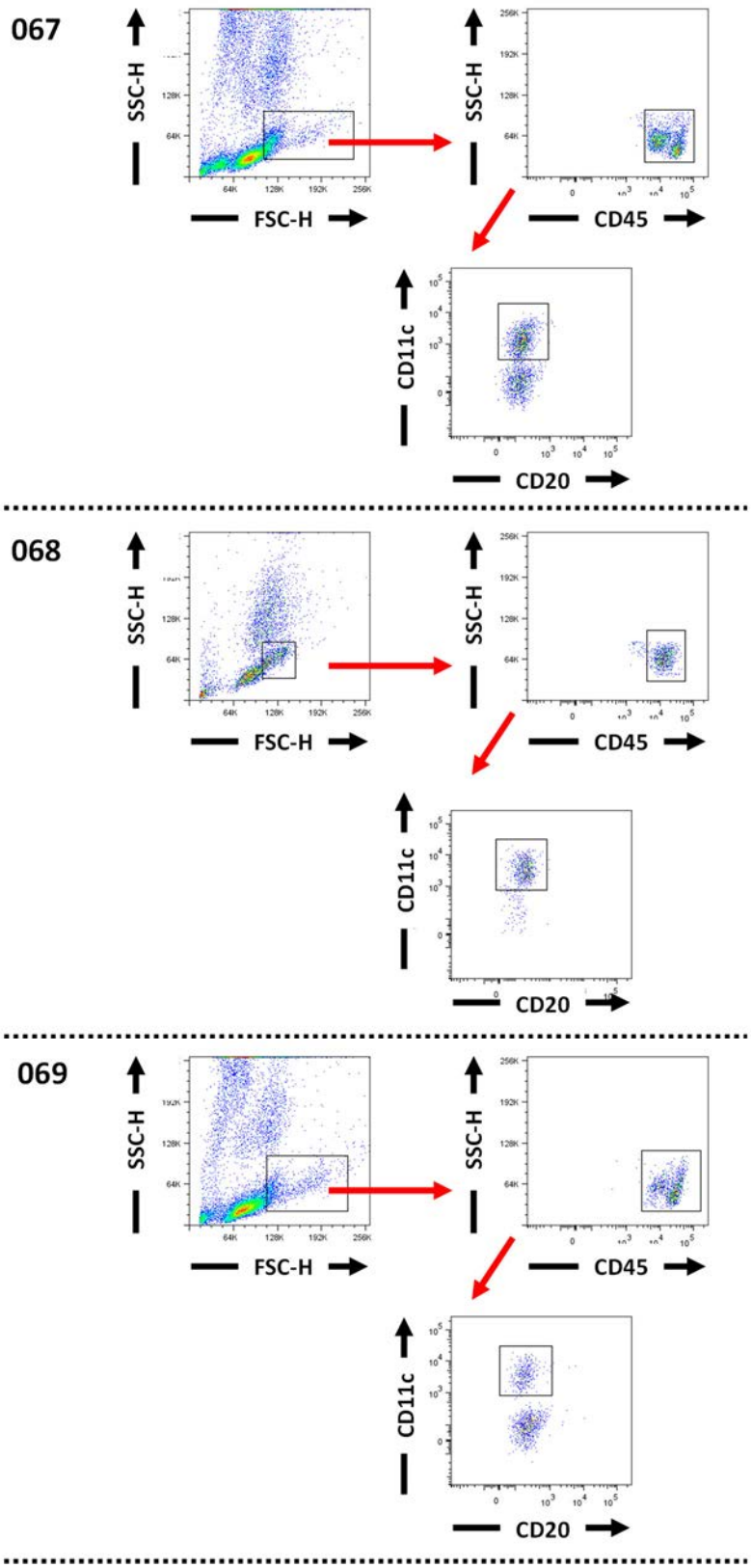
Supplemental FIGURE 5



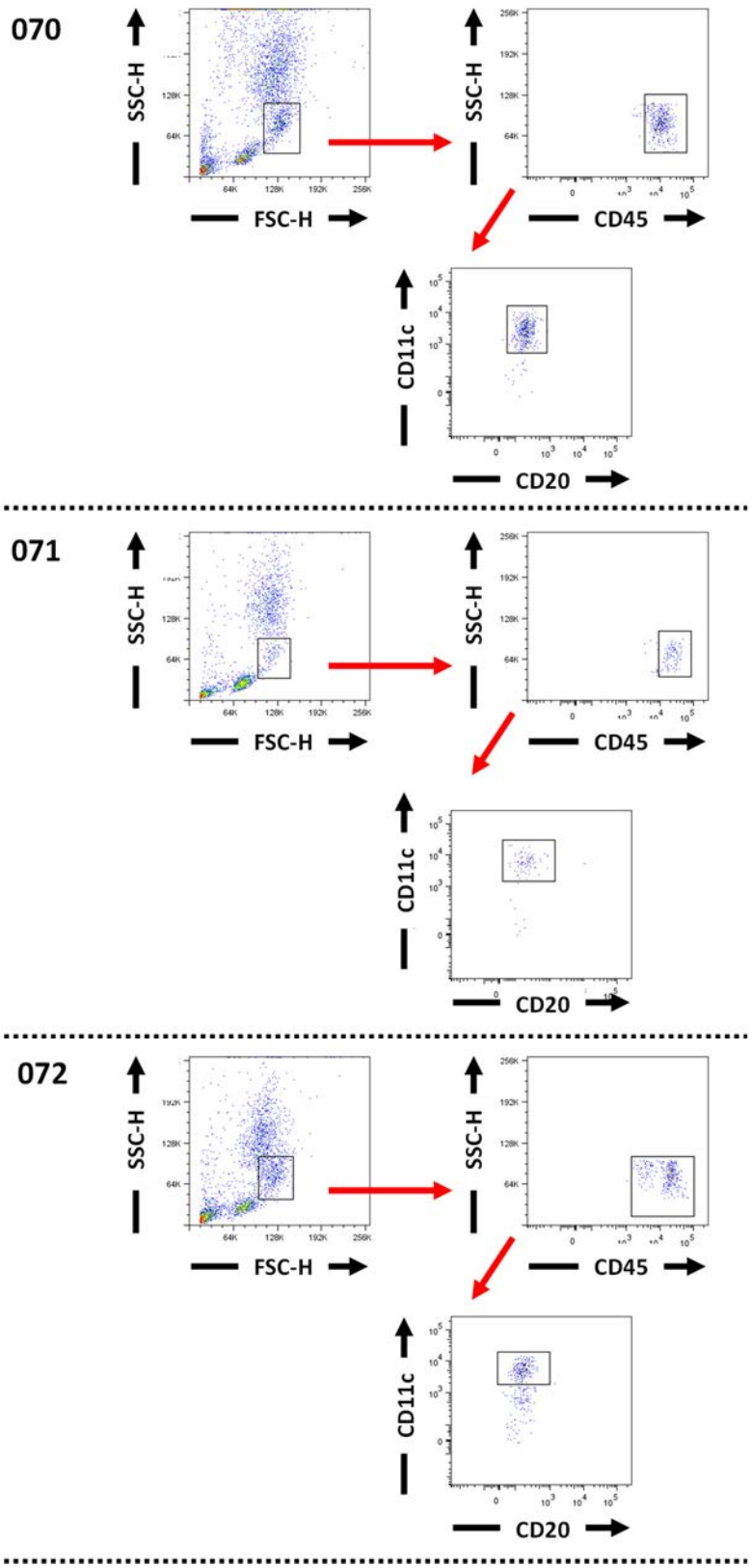
Supplemental FIGURE 5



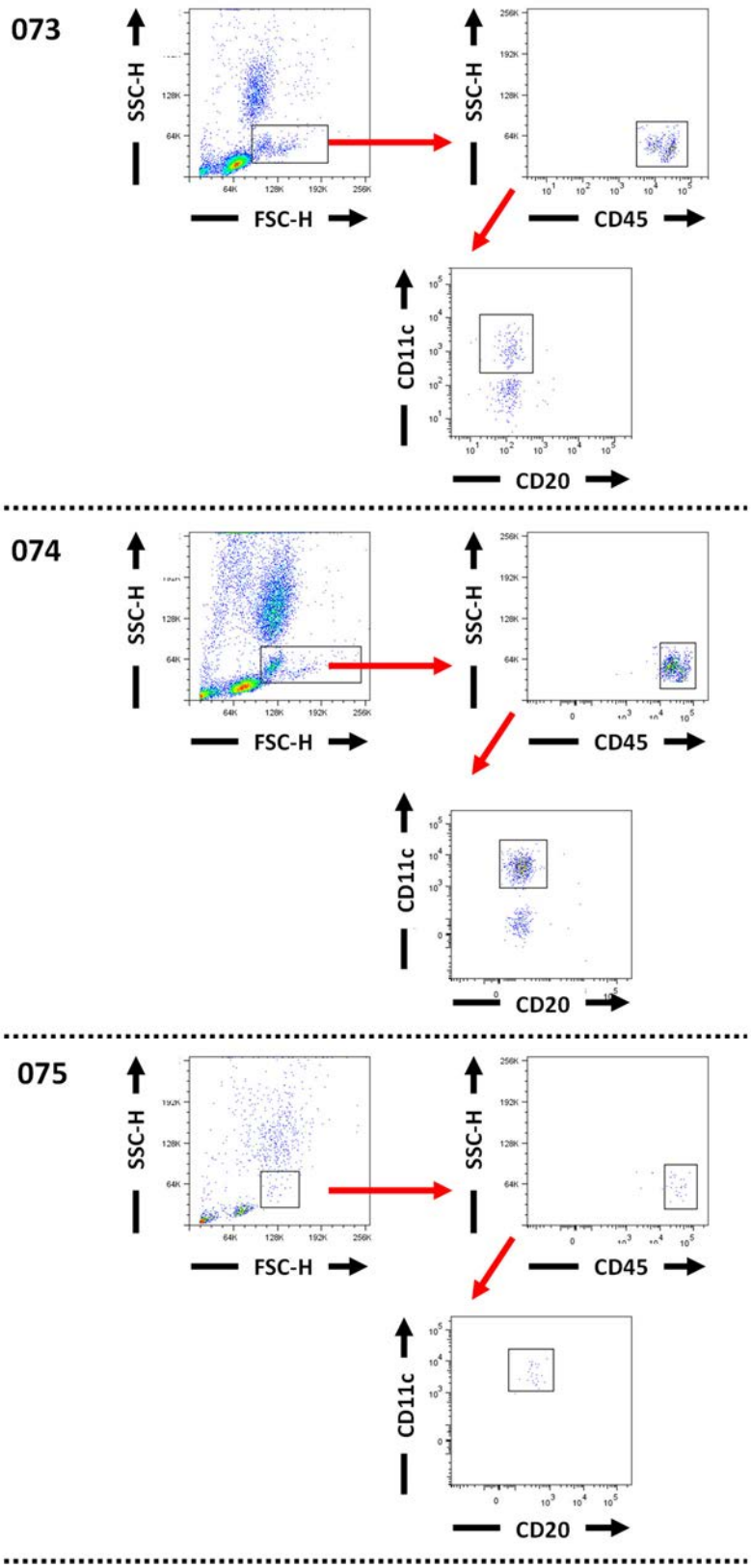
Supplemental FIGURE 5



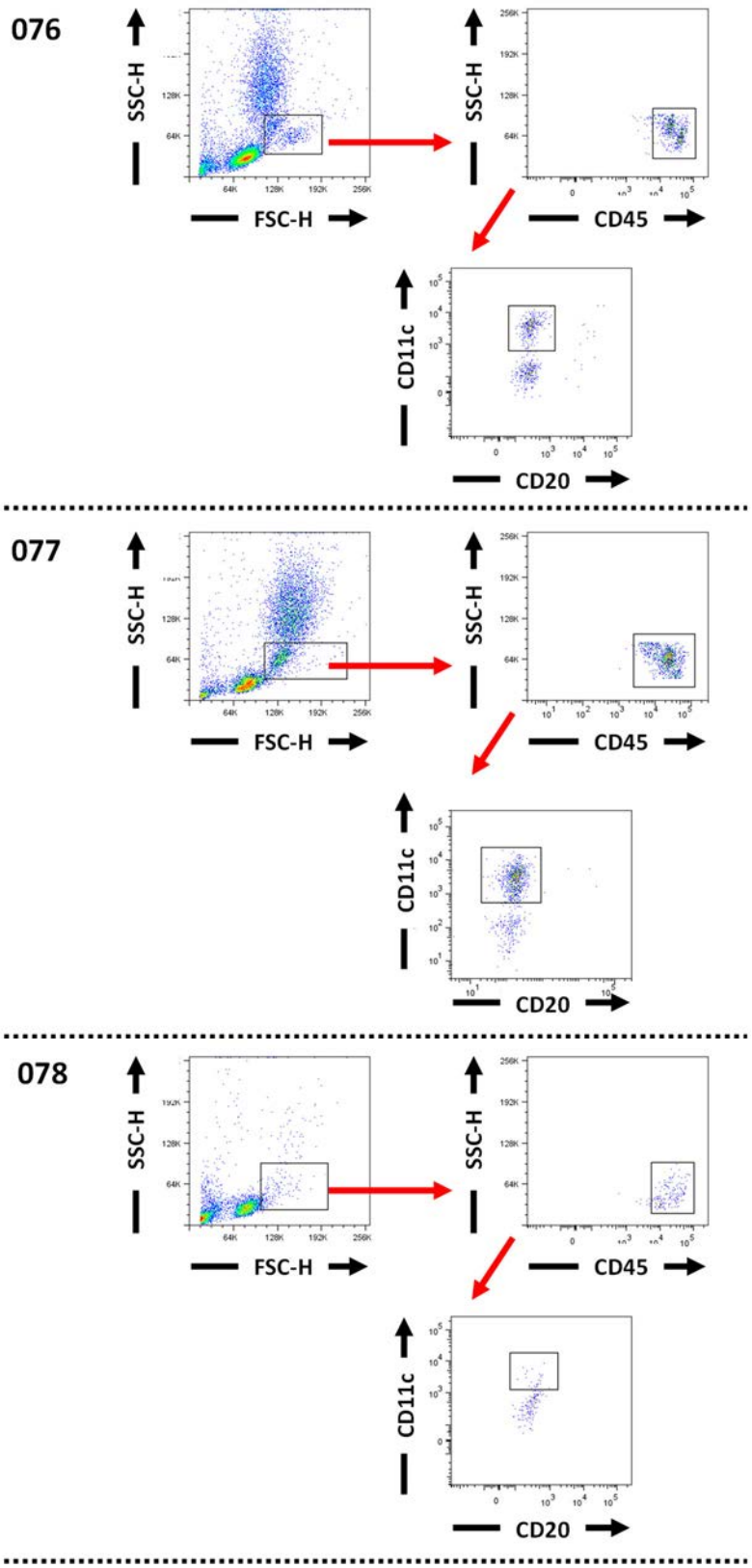
Supplemental FIGURE 5



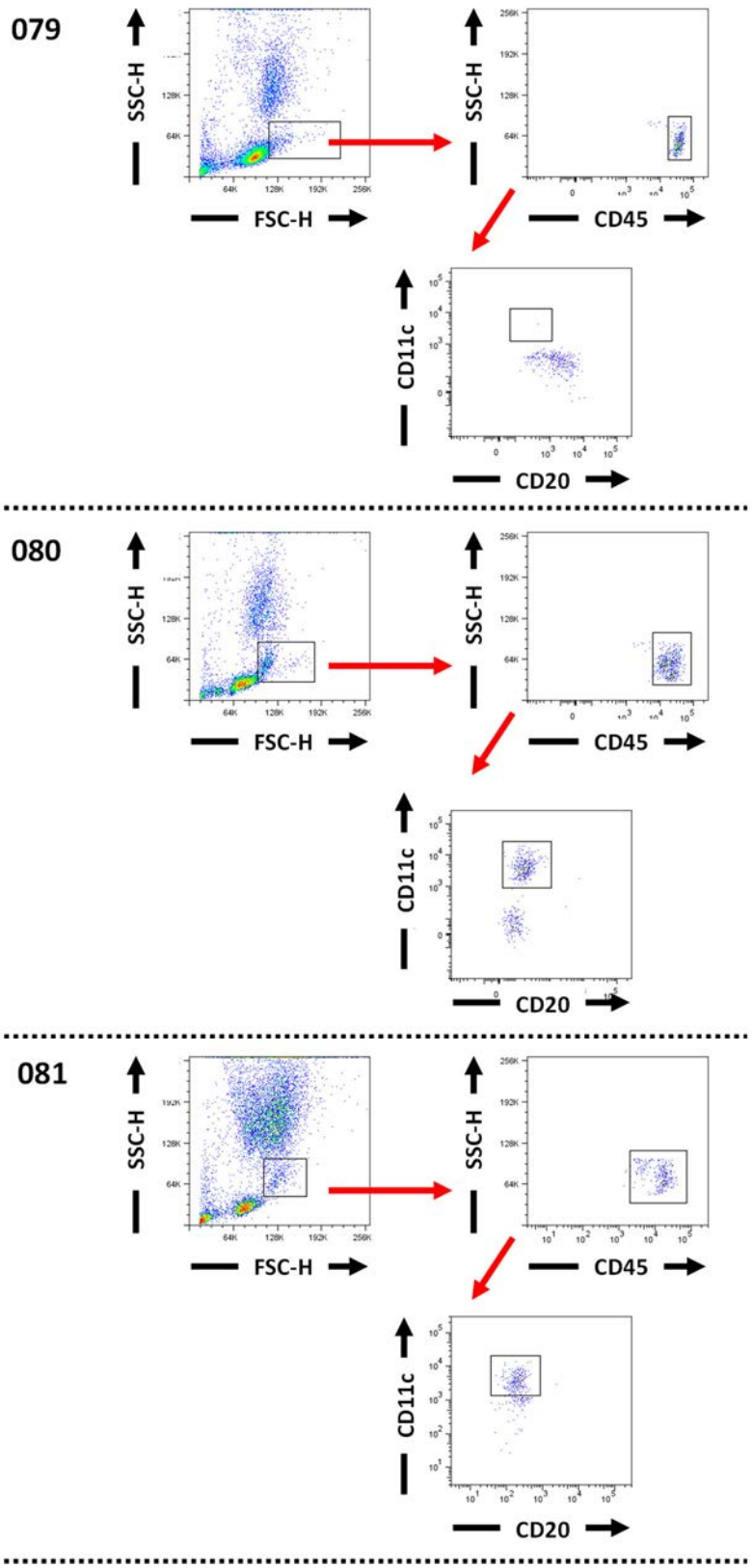
Supplemental FIGURE 5



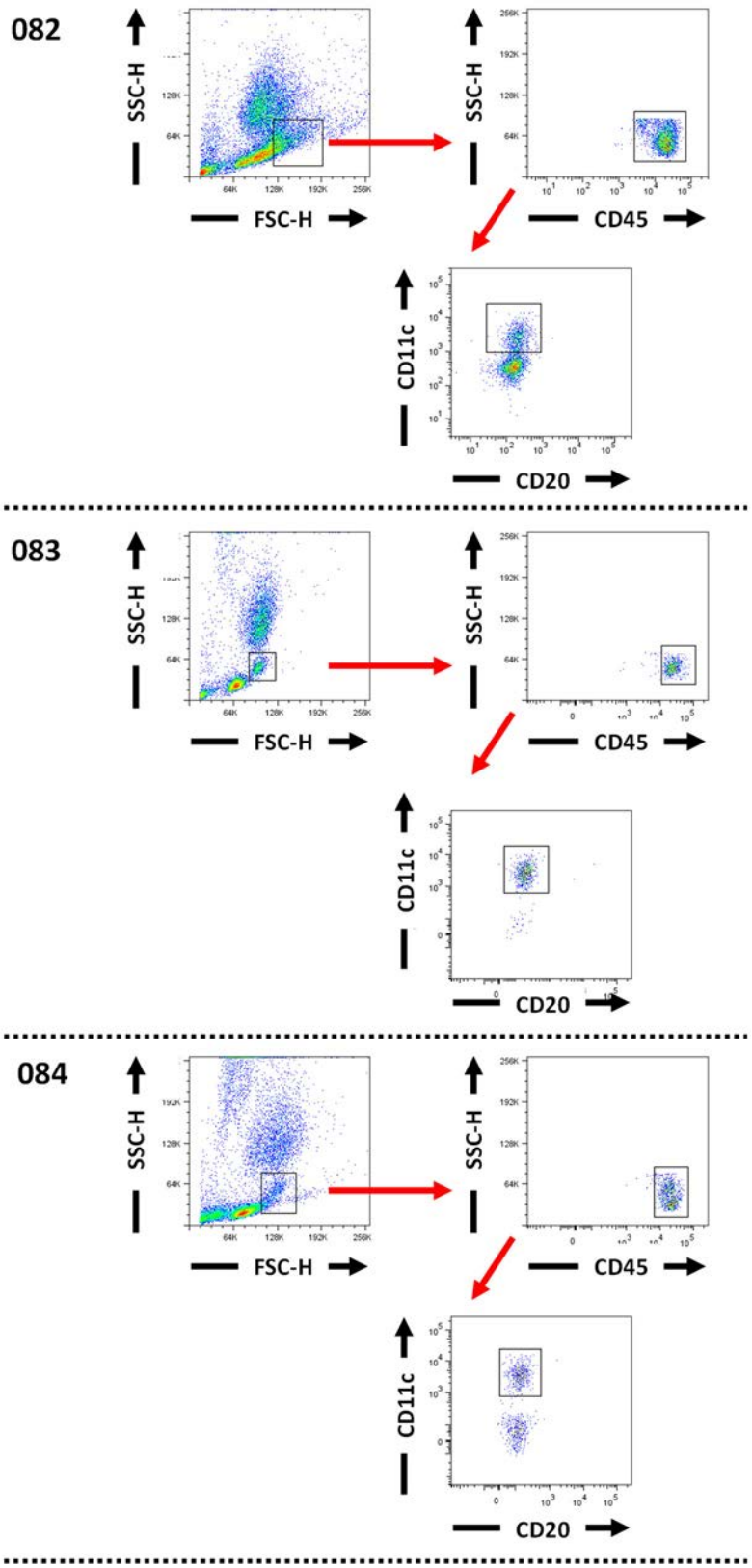
Supplemental FIGURE 5



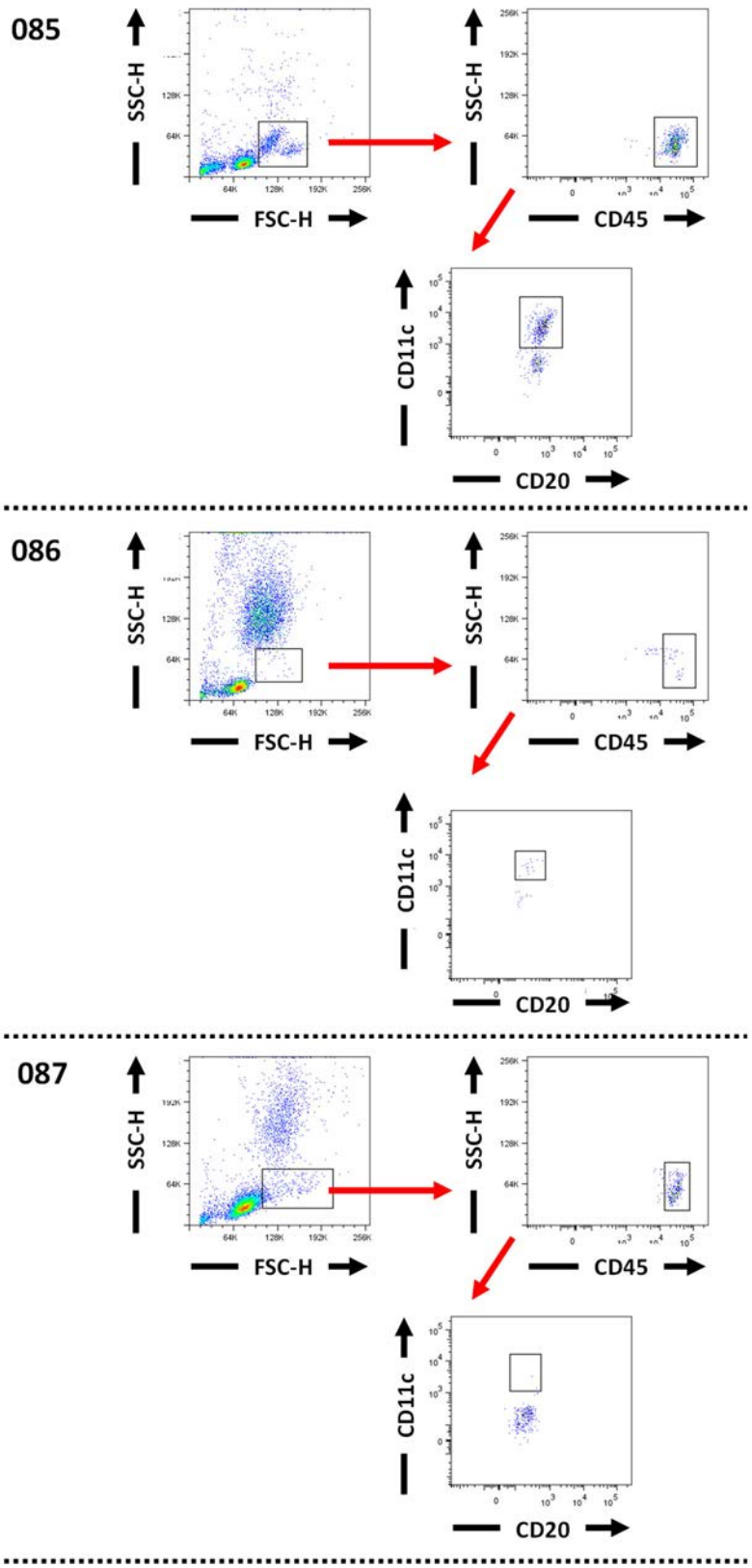
Supplemental FIGURE 5



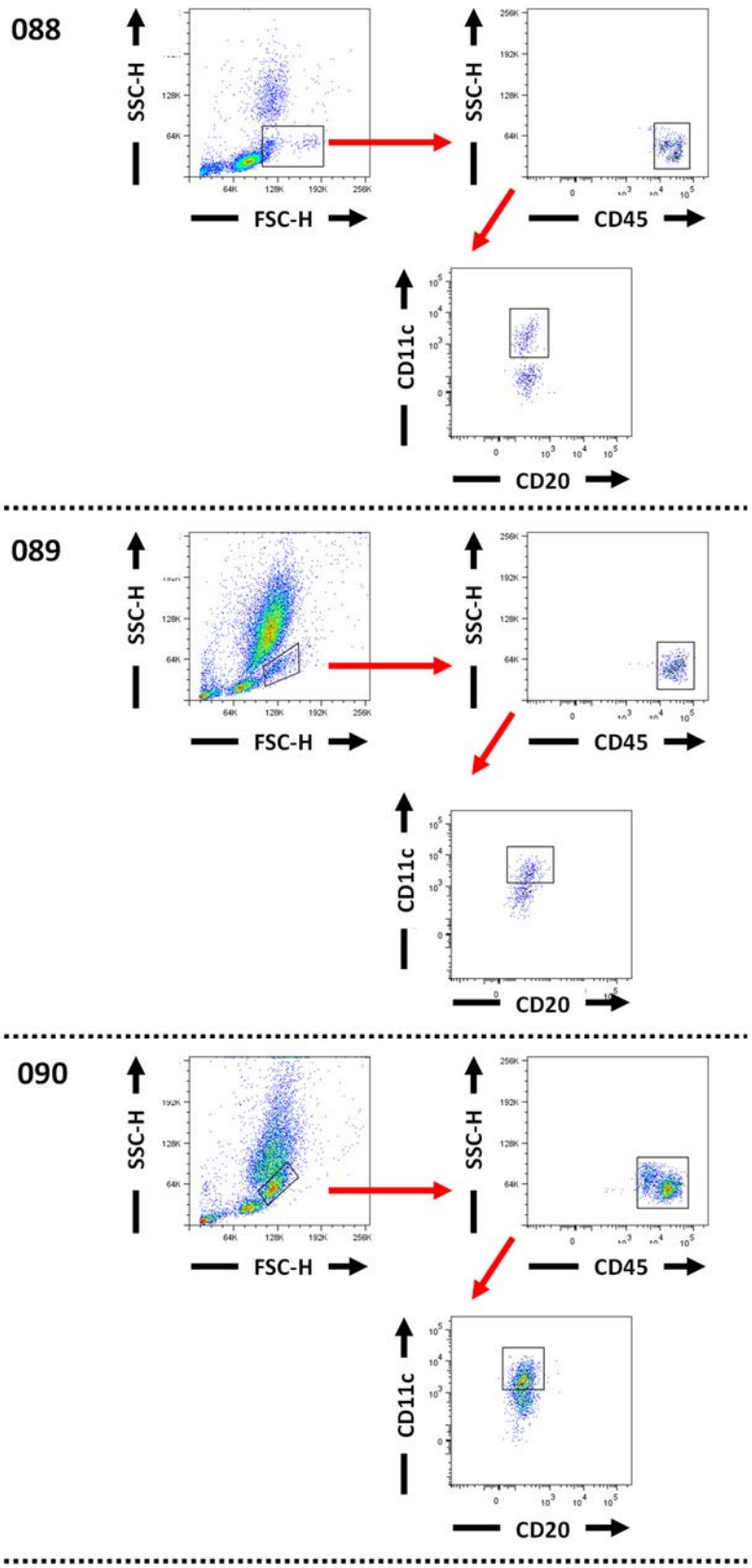
Supplemental FIGURE 5



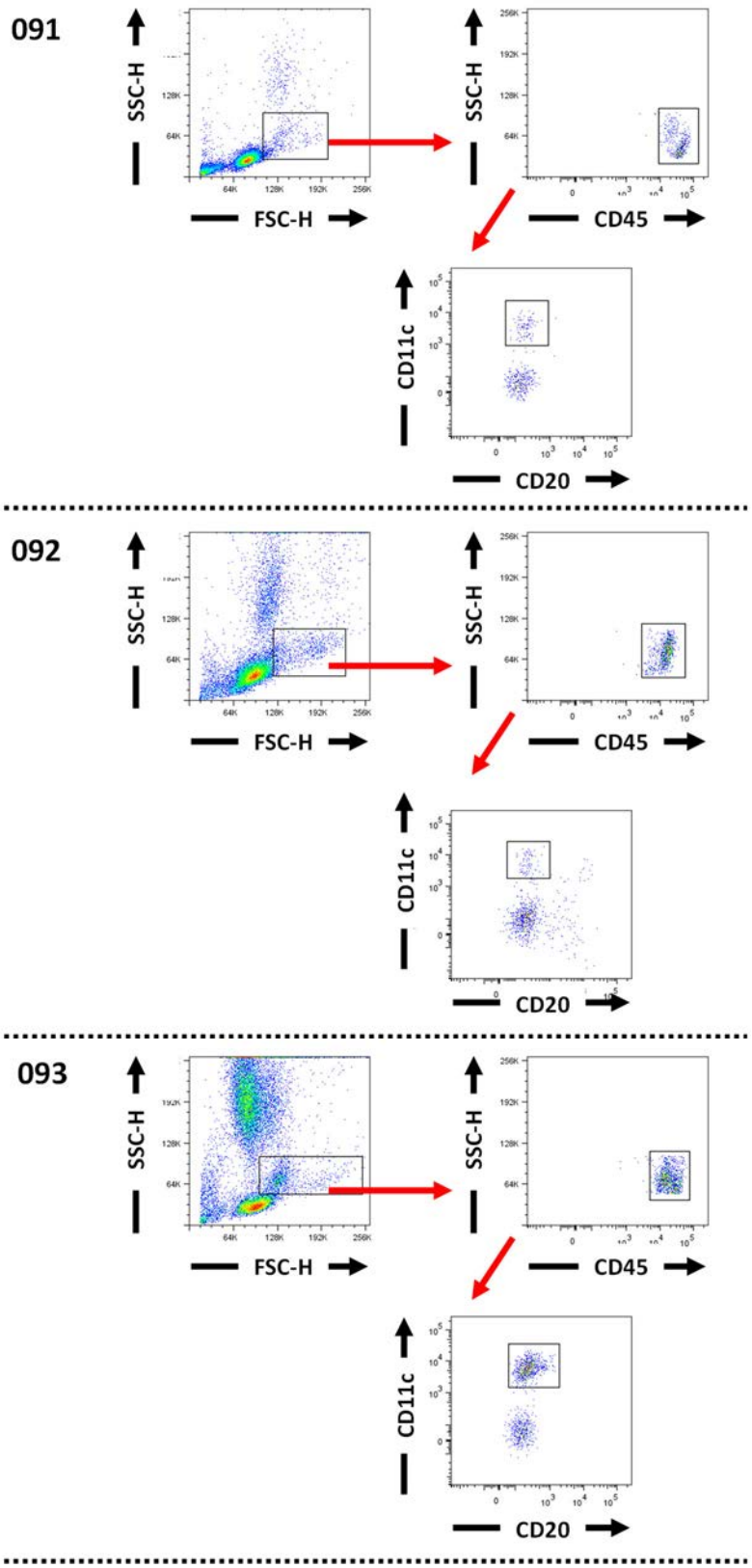
Supplemental FIGURE 5



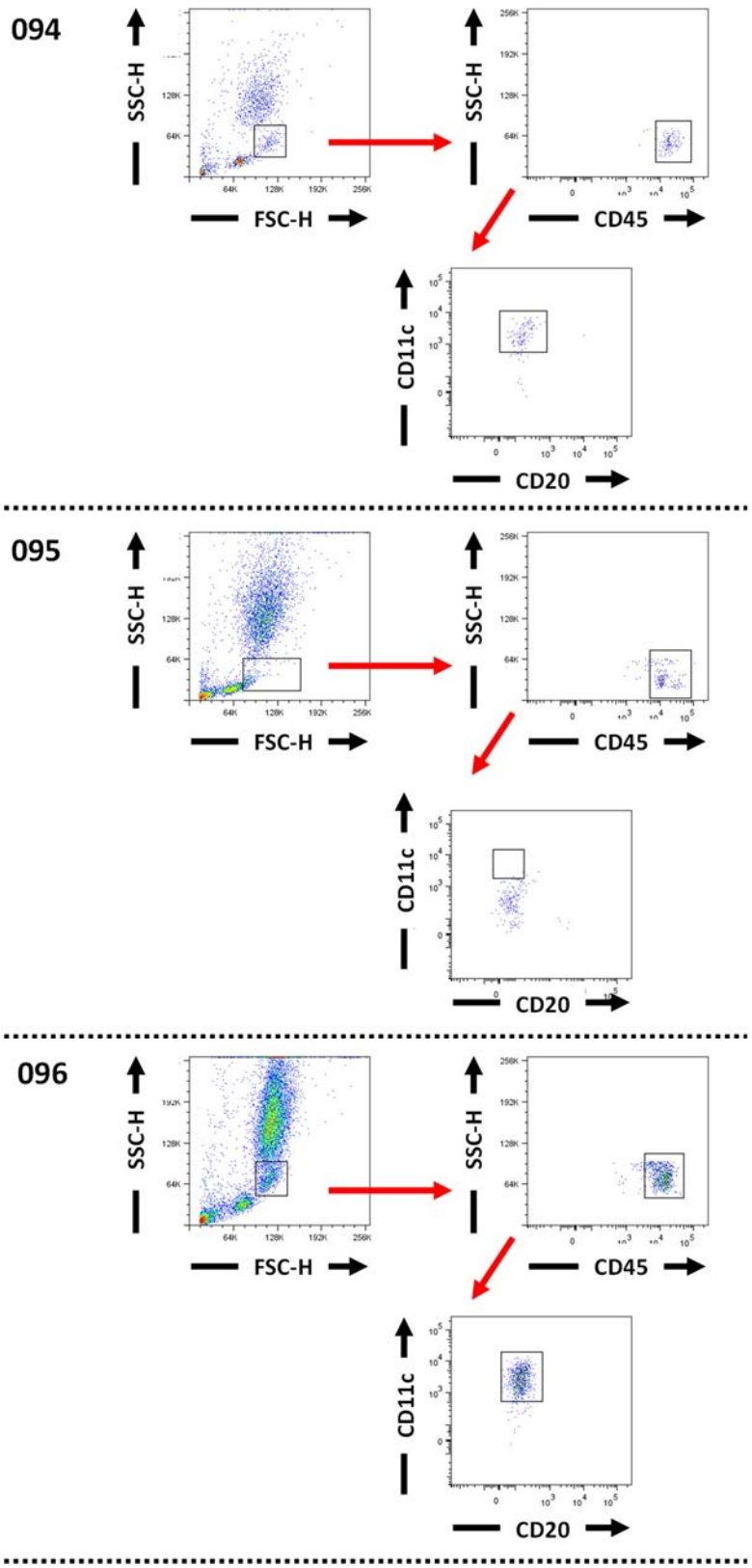
Supplemental FIGURE 5



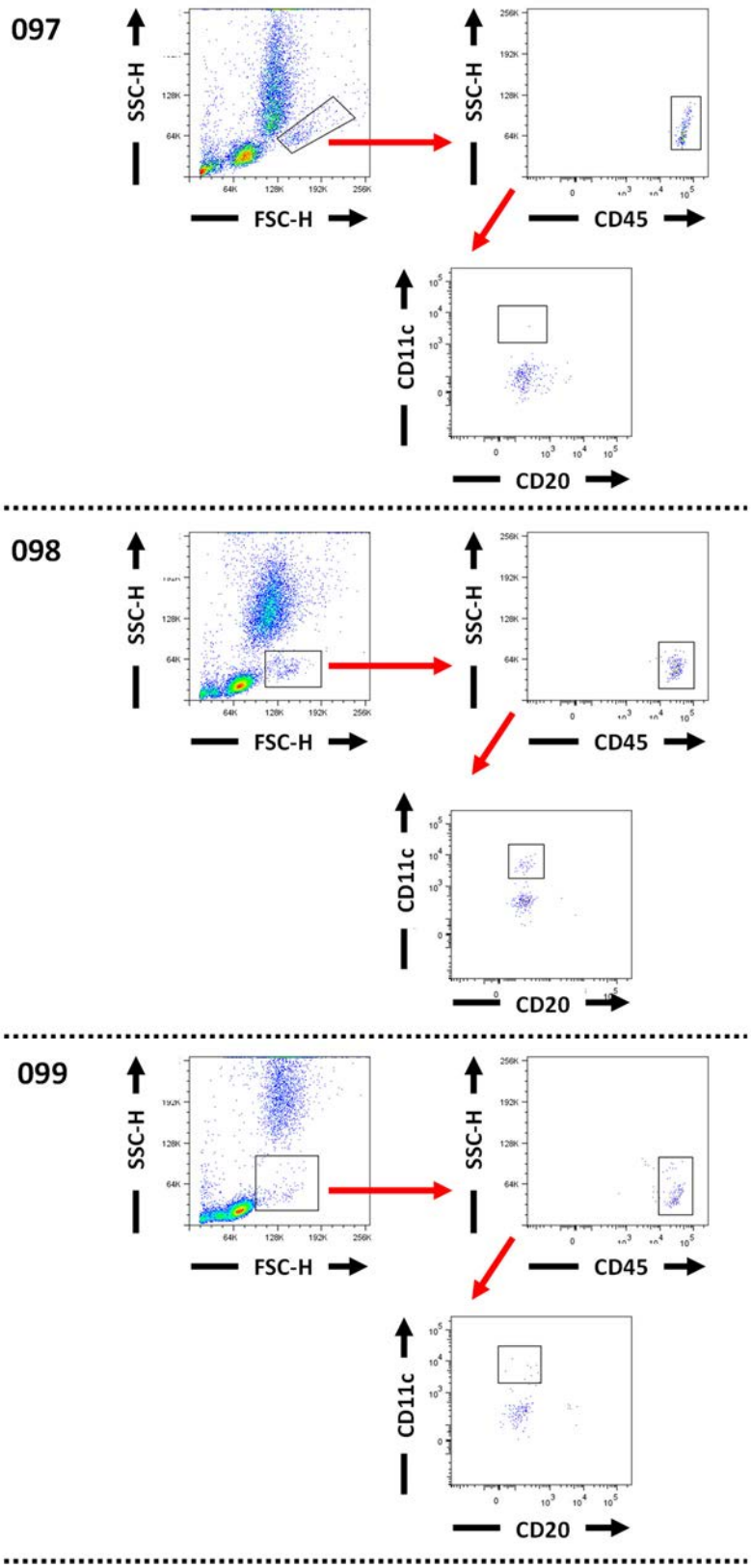
Supplemental FIGURE 5



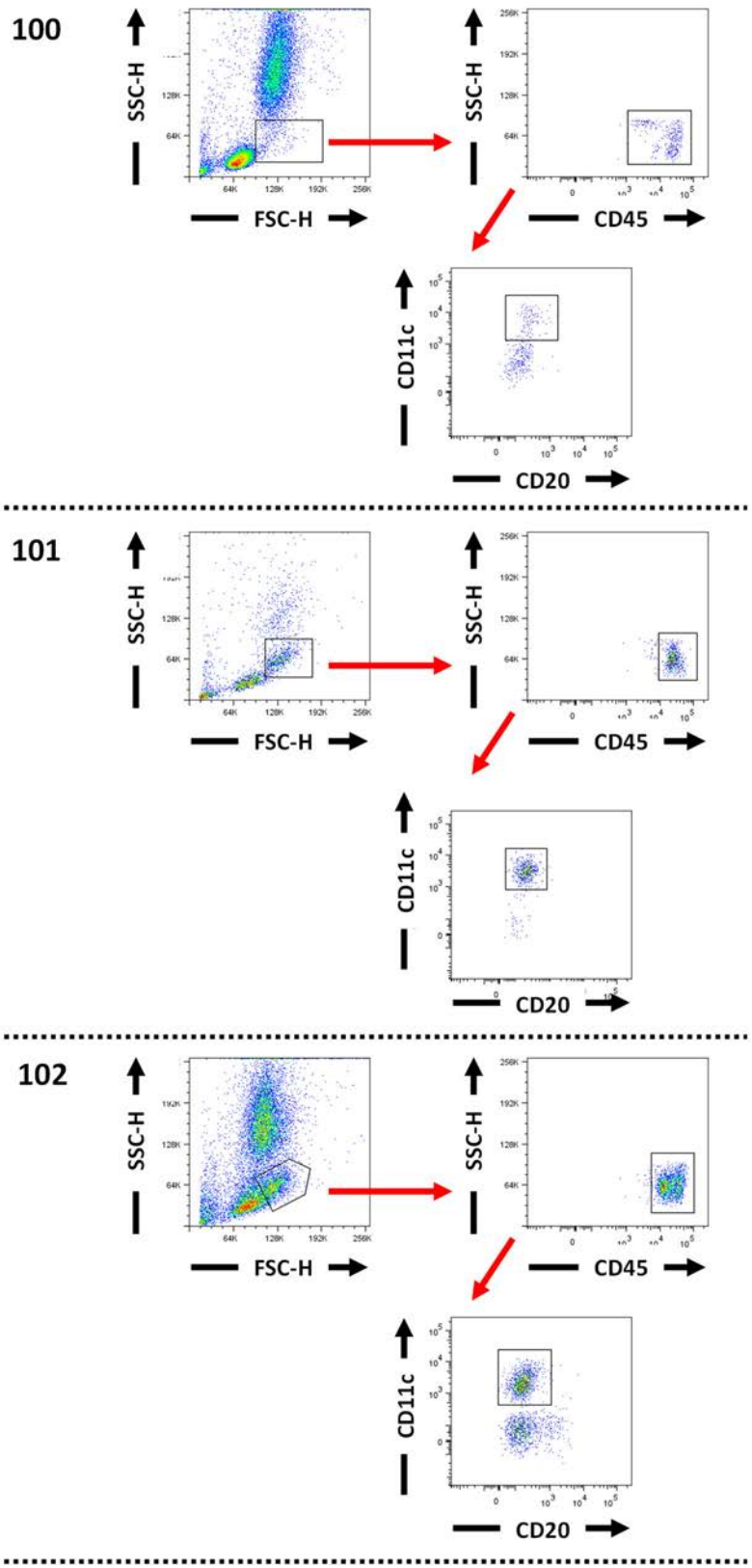
Supplemental FIGURE 5



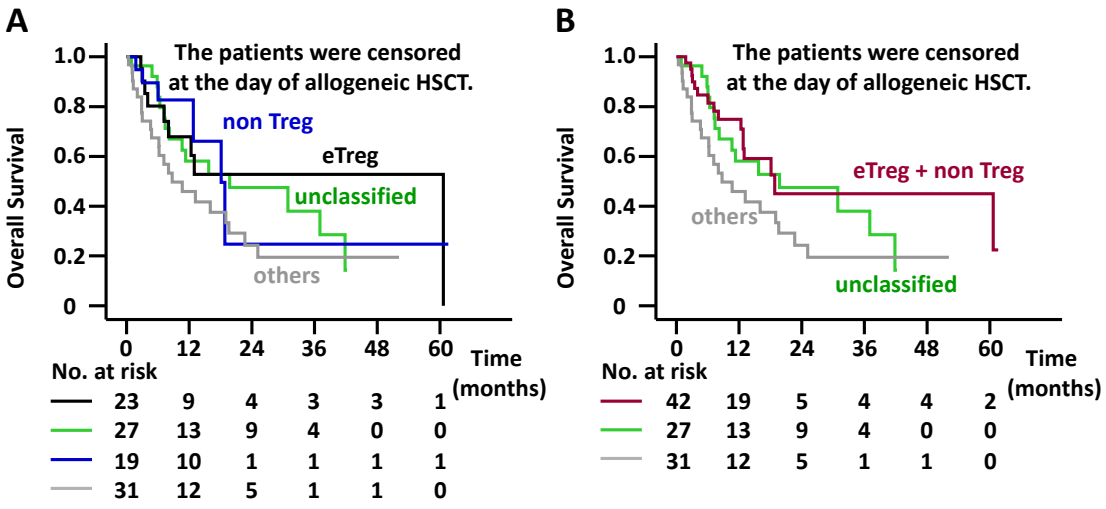
Supplemental FIGURE 5



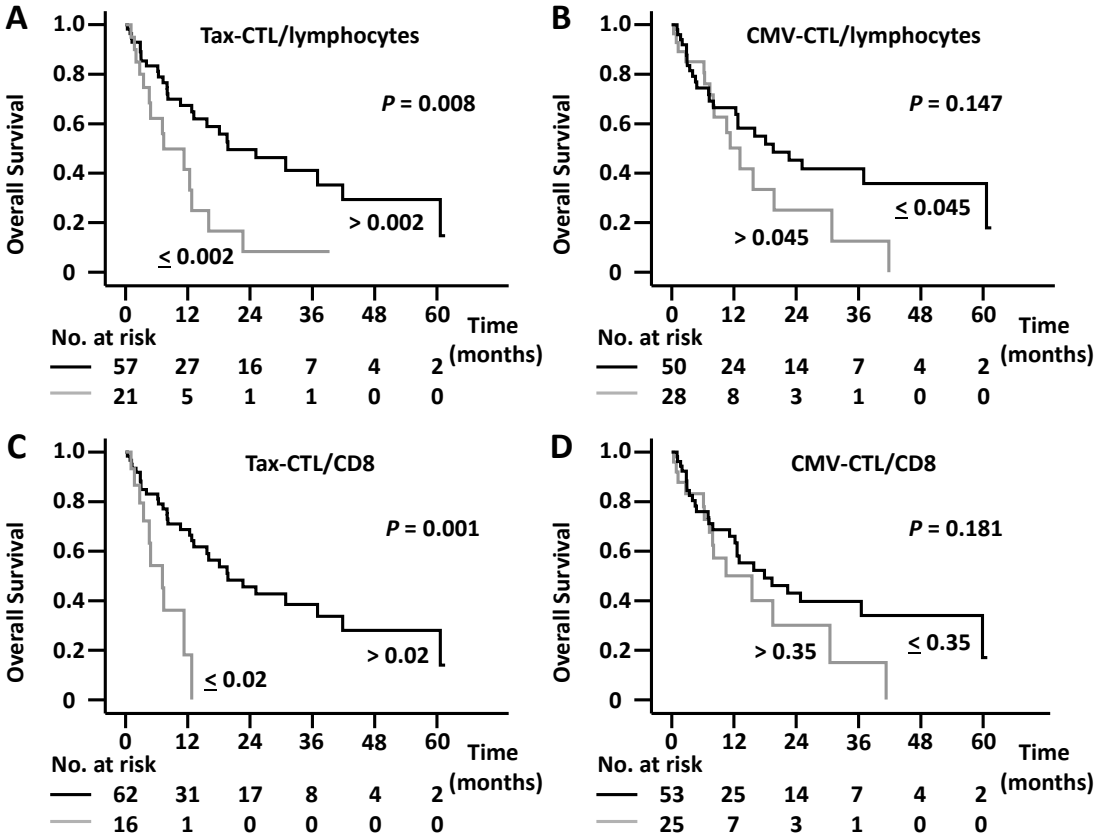
Supplemental FIGURE 5



Supplemental FIGURE 5



Supplemental FIGURE 6



Supplemental FIGURE 7