

Figure S1. Partial correlation network structure and predictions for IV-BCG vaccinated macaques.

A) Observed correlation matrix between all immune features. **B)** Partial correlation matrix of the PCN. **C)** Predicted correlation matrix from PCN. **D)** Comparison of correlations observed empirically from the data versus predicted by the PCN. Entries are only included if there was no edge in the PCN

corresponding to that pair. **E)** Dependence of lung and lymph node CFU on IV-BCG dose. Spearman correlation, one-tailed.

Partial correlations using single or multiple data modes

S: Single Mode P: Predicted Single Mode M: Multiple Modes

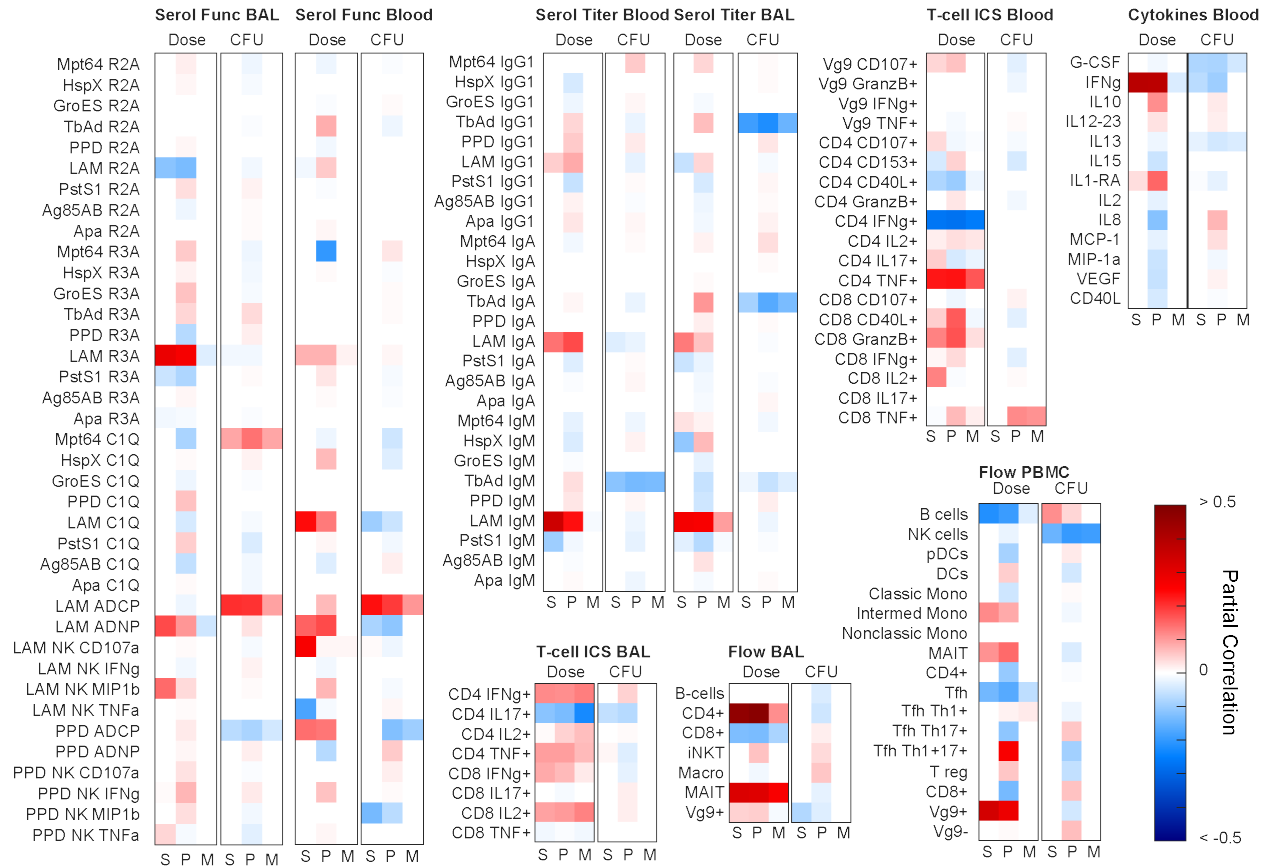


Figure S2. Comparison of partial correlations for single- and multi-modal PCNs. Same as Figure 2G, but for each data mode.

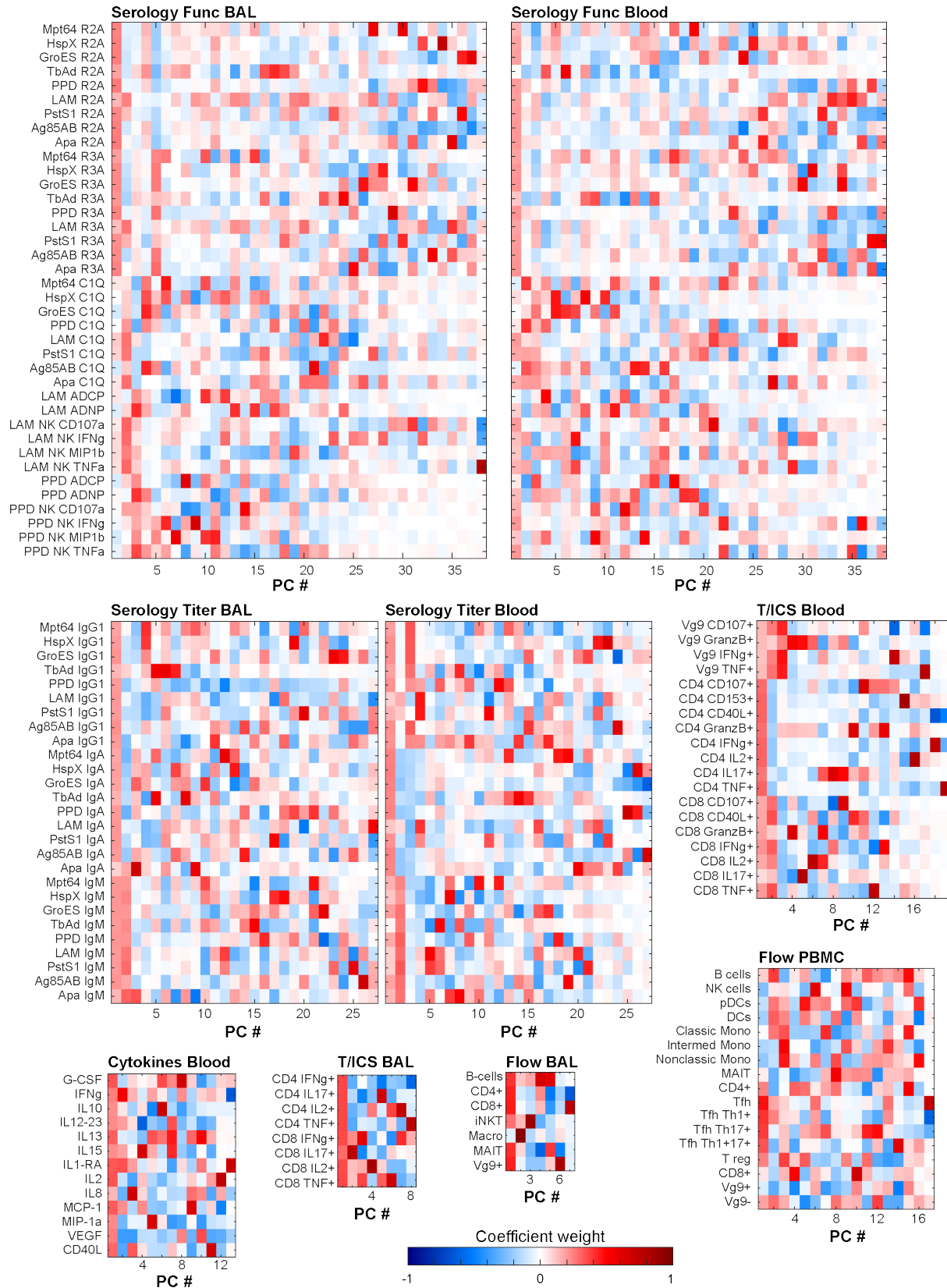
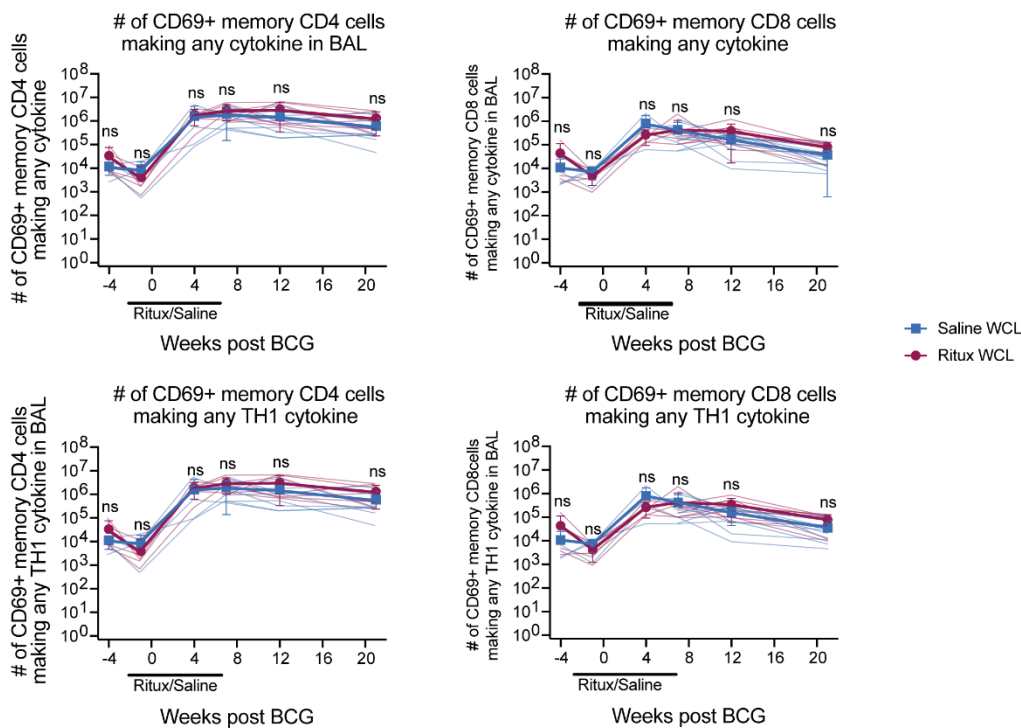
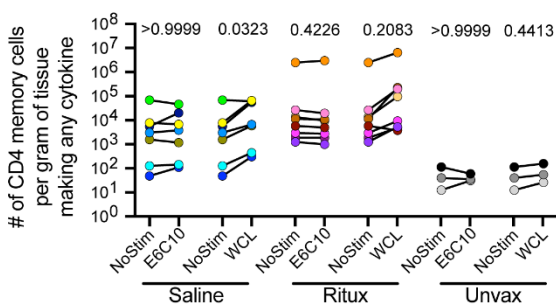


Figure S3. Principal components of single data modes. Weights of original features of principal components for each data mode.

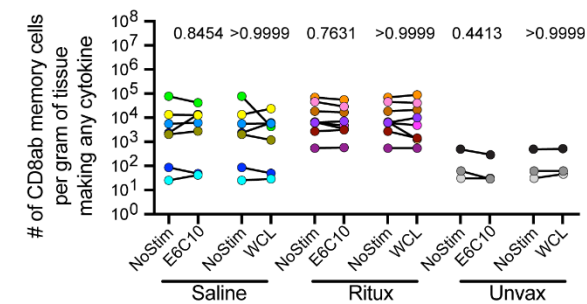
A T cell responses in airways



B CD4 memory T cell response in lungs



C CD8 memory T cell response in lungs



D Total cell counts in lungs

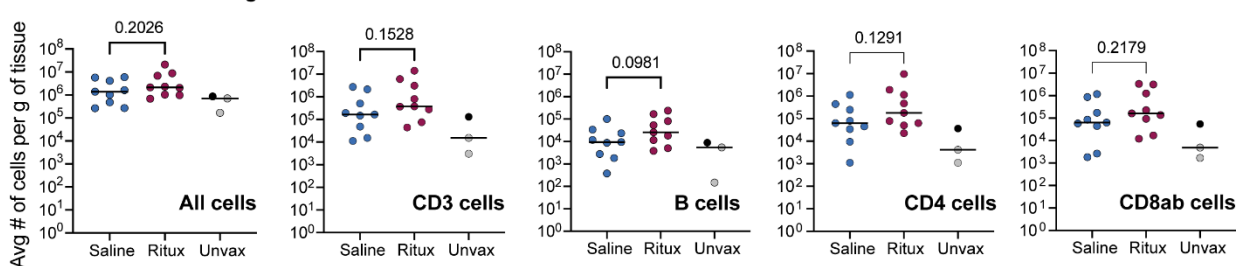


Figure S4. T cell responses upon B cell depletion. A) Number of CD4 memory cells in BAL using CD45RA and CD28 to differentiate memory cells via flow cytometry. Rituximab treated animals are shown in blue while saline treated animals are shown in red. Mean and SD shown. Statistics: Multiple Mann-Whitney Tests with Holm-Šidák method adjusted p-values reported: ns - $p > 0.05$. B, C) CD4 and CD8ab memory T cells making any cytokine (IFN γ , IL-2, TNF α or IL-17) in the lung at time of necropsy. Cells were unstimulated or stimulated with ESAT-6/CFP10 peptides or Whole Cell Lysate (WCL). Each point (colored by animal) represents a median from 3 separate lung lobes from each animal.

Saline group consists of 7 animals, Ritux group 8, and Unvax group 3. Statistics: Friedman test (for paired data) with Dunn's multiple comparison adjusted p-values reported. **D**) Cell counts from hemacytometer count of single cell suspensions at time of necropsy and as measured from cell surface markers during flow cytometry. Statistics: Unpaired t test p-values shown. **B-D**) Black circle represents clinically uninfected animal.

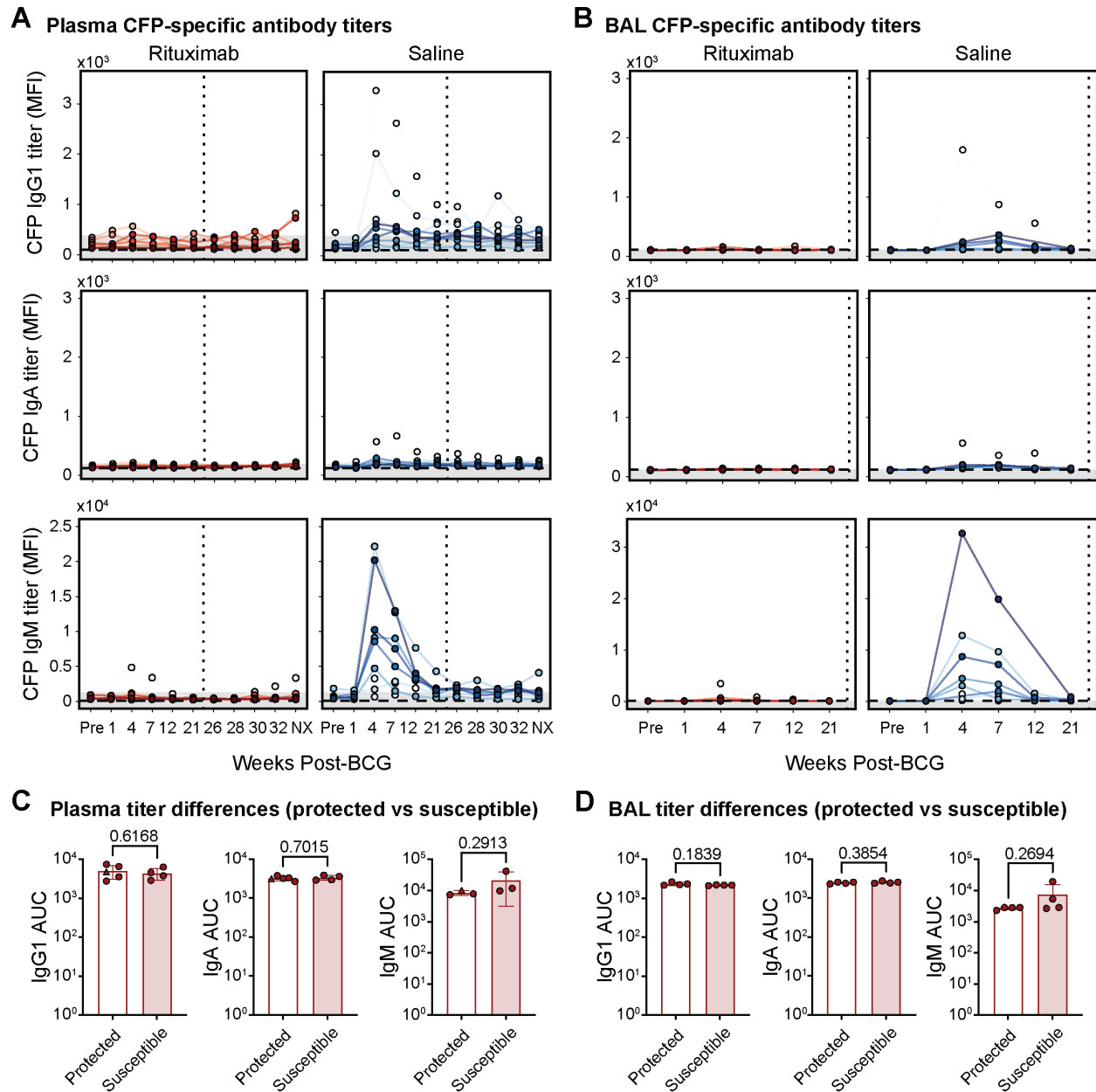


Figure S5. CFP-specific antibody responses. **A, B** IgG1 (top), IgA (middle), and IgM (bottom) antibody titers present in the **(A)** plasma, and **(B)** BAL, of each macaque following IV BCG vaccination specific to CFP measured via Luminex. Y-axis is median fluorescence intensity (MFI). X-axis shows time

in weeks, including pre-vaccination at week -4 (Pre) and necropsy at week 38 (NX). Each point represents the duplicate average from a single macaque at the corresponding timepoint. Rituximab-treated macaques are red (left) and saline-treated macaques are blue (right). Vertical dotted line indicates the time of challenge (week 23). Horizontal dashed line is the PBS control. Grey shaded area is the background level set to 2 standard deviations above the mean MFI of the pre-vaccination samples. Measurements at least 2 standard deviations above the mean MFI of the pre-vaccination samples are considered to be above the limit of detection. **C, D**) Comparison of CFP-specific antibody titers between protected (total Mtb CFU = 0) and susceptible (total Mtb CFU > 0) Rituximab-treated macaques in the (C) plasma, and (D) BAL. Area under the curve (AUC) values were calculated using longitudinal Luminex MFI data from the following timepoints: Pre-vaccination (Pre), week 4, 7, 12, and 21. Macaque with 0 Mtb CFU, but residual BCG present in a peripheral lymph node (12620) is represented by the triangle marker. Unadjusted p-values resulting from two-tailed Mann-Whitney U tests are indicated

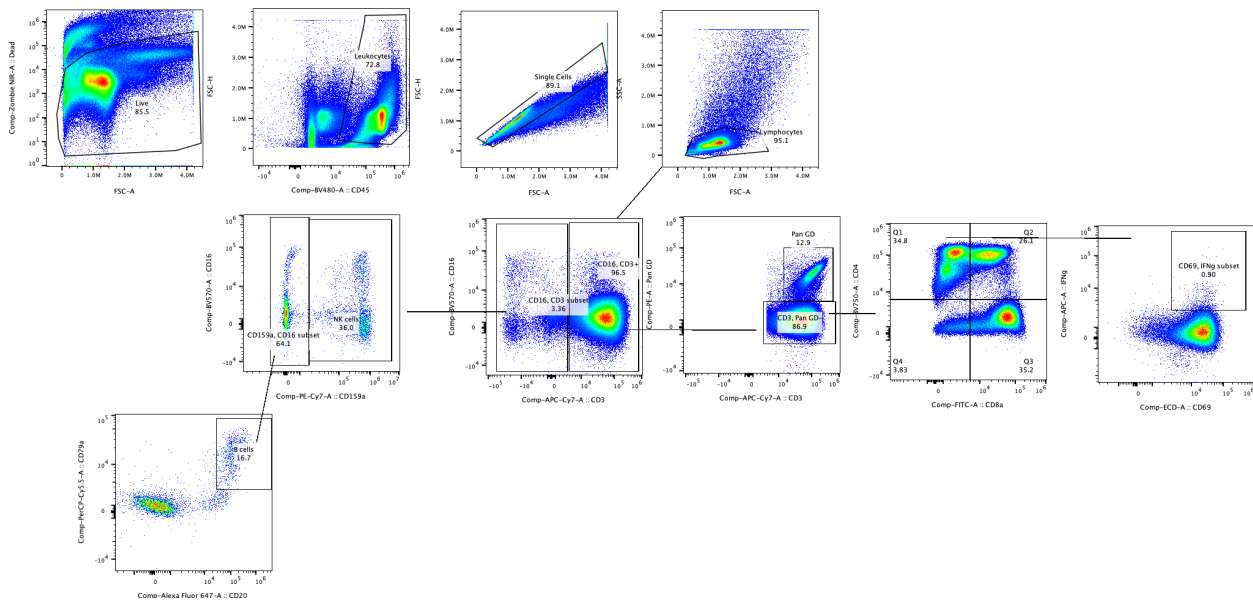


Figure S6. Gating strategy of BAL for flow cytometry

Ber-ACT8	CD103	BV711	V13	Biolegend	350222	cohort 1 week 7-week 20
6b11	iNKT	BV711	V13	Biolegend	342922	cohort 1 week -4-20 only
L200	CD4	BV750	V14	BD Biosciences	747202	cohort 1 and 2 all time points
DK25	CD8a	FITC	B2	Agilent Technologies	F076501-1	cohort 1 and 2 all time points
HM47	CD79a	PerCP-Cy5.5	B9	ThermoFisher Scientific	45-0792-42	cohort 1 and 2 all time points
3D12	CCR7	PerCP-eFluor710	B10	ThermoFisher Scientific	46-1979-42	cohort 1 and 2 all time points
5A6.e9	Pan gd	PE	YG1	ThermoFisher Scientific	MHGD04	cohort 1 and 2 all time points
TP1.55.3	CD69	ECD	YG3	Beckman Coulter	6607110	cohort 1 and 2 all time points
19.2	CD206	PE-Cy5	YG5	BD Biosciences	551136	cohort 1 and 2 all time points
Z199	CD159a	PE-Cy7	YG9	Beckman Coulter	B10246	cohort 1 and 2 all time points
2H7	CD20	AF647	R2	Biolegend	302318	cohort 1 and 2 all time points
H4A3	CD107a	AF700	R4	BD Biosciences	561340	cohort 1 week 22, cohort 2 pre BCG
LN3	HLA-DR	AF700	R4	ThermoFisher Scientific	56-9956-42	cohort 1 week -4-4 only
27E10	Calprotectin, biotin	AF700 (2 step)	R4	ThermoFisher Scientific	MA1-40314	cohort 1 week 7-12 only
SP34-2	CD3	APC-Cy7	R7	BD Biosciences	557757 (bulk order 624072)	cohort 1 and 2 all time points
-	L/D	ZombieNIR	R8	Biolegend	423106	cohort 1 and 2 all time points

Table 4. Flow cytometry antibodies for staining BAL in Cohorts 1 & 2

Clone	Marker	Fluor	Aurora Channel	Vendor	Catalog #	cohort/time point
5H9	CD45RA	BUV395	UV2	BD Biosciences	740315	cohort 1 week 7-22, all cohort 2
GHI/61	CD163	BUV395	UV2	BD Biosciences	745572	cohort 1 week -4 -4 only
ICRF44	CD11b	BUV563	UV9	BD Biosciences	741357	cohort 1 and 2 all time points
2ST8.5H7	CD8b	BUV737	UV14	BD Biosciences	748324	cohort 2 week 12, 22 only
3.9	CD11c	BV421	V1	BD Biosciences	565806	cohort 1 and 2 all time points
GB11	GranzymeB	V450	V3	BD Biosciences	561151	cohort 1 and 2 all time points
D058-1283	CD45	BV480	V4	BD Biosciences	566145 (bulk order (624248))	cohort 1 and 2 all time points
BL168	IL-17	BV510	V7	Biolegend	512330	cohort 1 and 2 all time points
3G8	CD16	BV570	V8	Biolegend	302036	cohort 1 and 2 all time points
CD28.2	CD28	BV605	V10	Biolegend	302968	cohort 1 and 2 all time points
Mab11	TNF	BV650	V11	BD Biosciences	563418	cohort 1 and 2 all time points
6b11	iNKT	BV711	V13	Biolegend	342922	cohort 1 week -4-20 only
BerACT8	CD103	BV711	V13	Biolegend	350222	cohort 1 week 22, cohort 2 pre BCG
L200	CD4	BV750	V14	BD Biosciences	747202	cohort 1 and 2 all time points
MQ1-17H12	IL-2	BV785	V15	Biolegend	500348	cohort 1 and 2 all time points
DK25	CD8a	FITC	B2	Agilent Technologies	F076501-1	cohort 1 and 2 all time points

HM47	CD79a	PerCP-Cy5.5	B9	ThermoFisher Scientific	45-0792-42	cohort 1 and 2 all time points
3D12	CCR7	PerCP-eFluor710	B10	ThermoFisher Scientific	46-1979-42	cohort 1 and 2 all time points
5A6.e9	Pan gd	PE	YG1	ThermoFisher Scientific	MHGD04	cohort 1 and 2 all time points
TP1.55.3	CD69	ECD	YG3	Beckman Coulter	6607110	cohort 1 and 2 all time points
19.2	CD206	PE-Cy5	YG5	BD Biosciences	551136	cohort 1 and 2 all time points
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B27	IFNg	APC	R1	Biolegend	506510	cohort 1 and 2 all time points
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SP34-2	CD3	APC-Cy7	R7	BD Biosciences	557757 (bulk order 624072)	cohort 1 and 2 all time points
-	L/D	ZombieNIR	R8	Biolegend	423106	cohort 1 and 2 all time points

Table 5. Flow cytometry antibodies for staining lung cells at time of necropsy in Cohorts 1 & 2

Clone	Marker	Fluor	Aurora Channel	Vendor	Catalog #	cohort/time point
5H9	CD45RA	BUV395	UV2	BD Biosciences	740315	cohort 1 and 2 all time points
ICRF44	CD11b	BUV563	UV9	BD Biosciences	741357	cohort 1 and 2 all time points

2ST8.5H7	CD8b	BUV737	UV14	BD Biosciences	748324	cohort 1 and 2 all time points
3.9	CD11c	BV421	V1	BD Biosciences	565806	cohort 1 and 2 all time points
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3G8	CD16	BV570	V8	Biolegend	302036	cohort 1 and 2 all time points
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DK25	CD8a	FITC	B2	Agilent Technologies	F076501-1	cohort 1 and 2 all time points
HM47	CD79a	PerCP-Cy5.5	B9	ThermoFisher Scientific	45-0792-42	cohort 1 and 2 all time points
3D12	CCR7	PerCP- eFluor710	B10	ThermoFisher Scientific	46-1979-42	cohort 1 and 2 all time points
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TP1.55.3	CD69	ECD	YG3	Beckman Coulter	6607110	cohort 1 and 2 all time points
H4A3	CD107a	PE-Cy5	YG5	BD	555802	cohort 1 and 2 all time points

Z199	CD159a	PE-Cy7	YG9	Beckman Coulter	B10246	cohort 1 and 2 all time points
B27	IFNg	APC	R1	Biolegend	506510	cohort 1 and 2 all time points
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