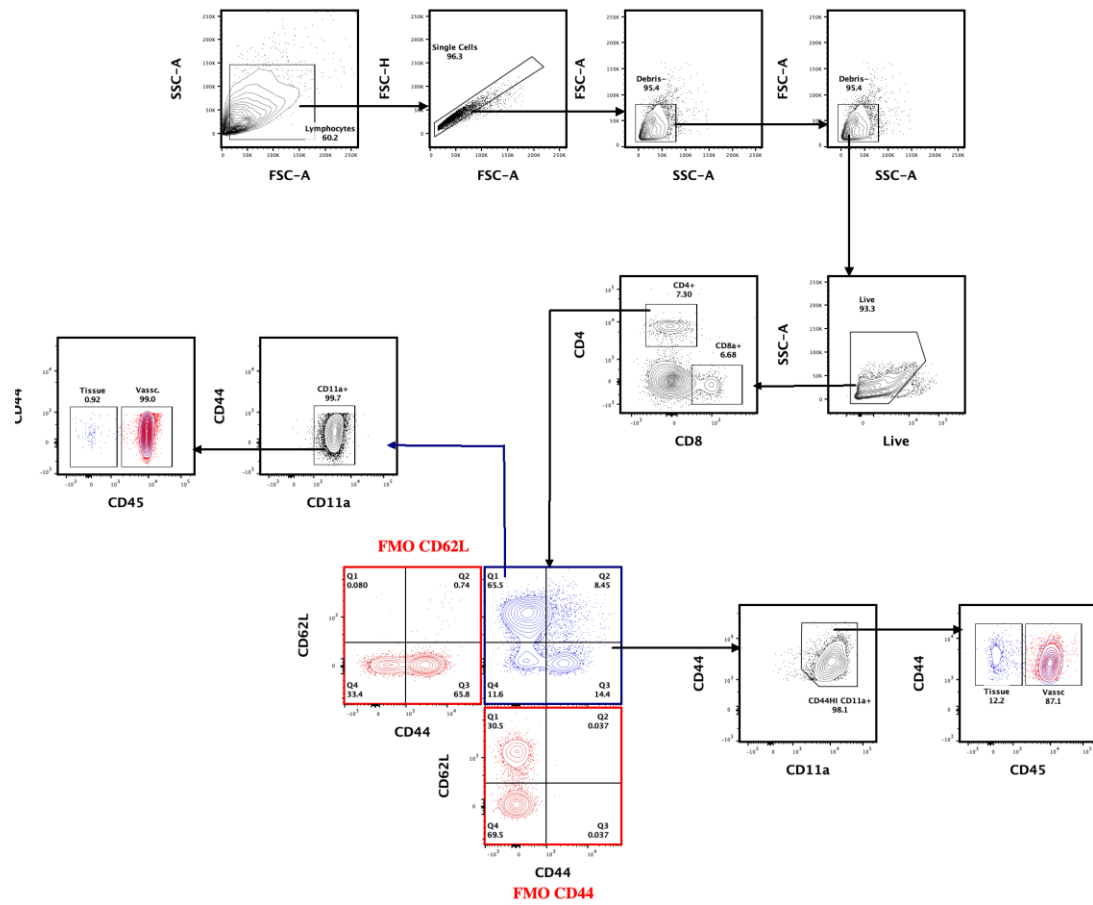
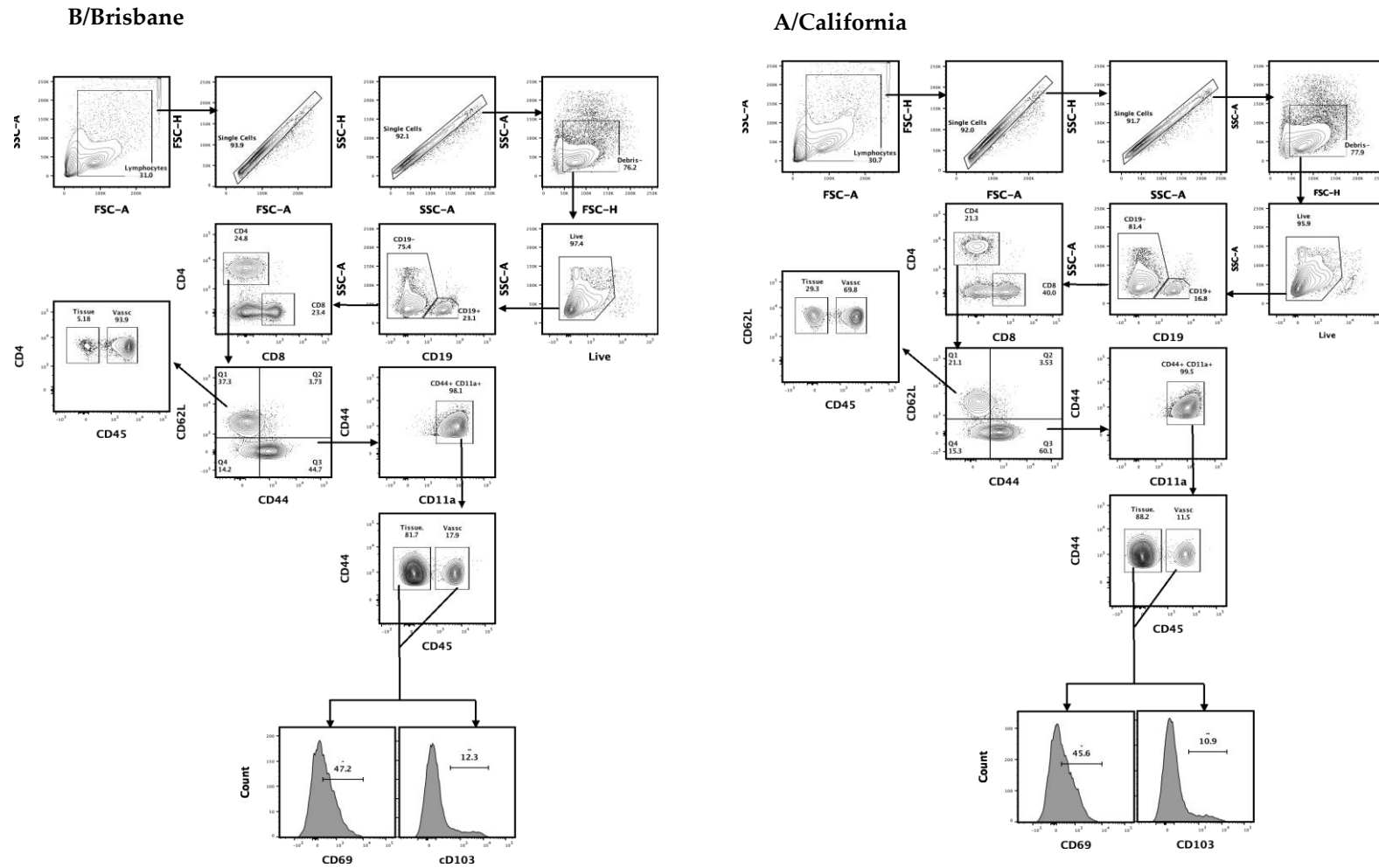


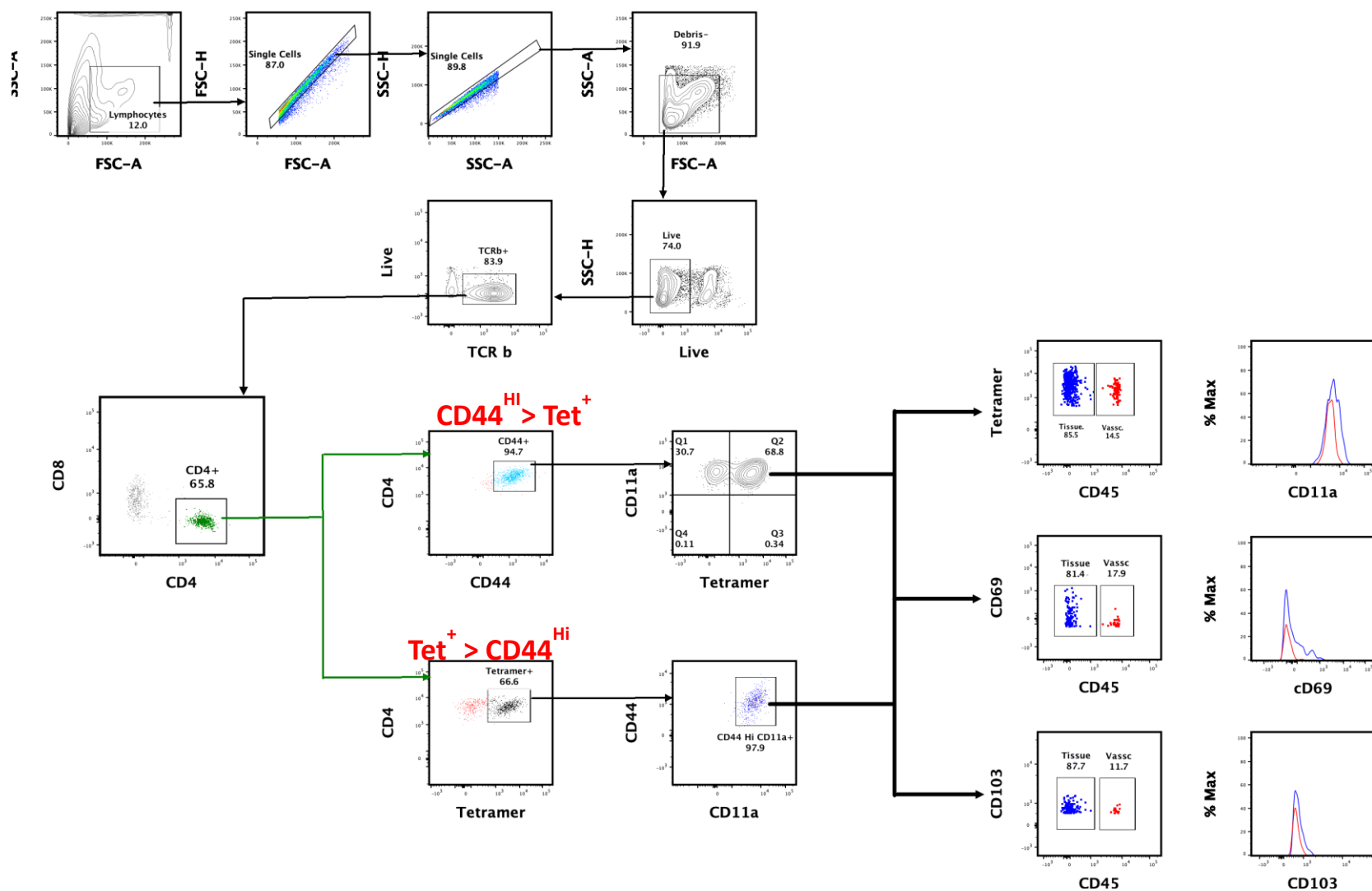
Supplemental Data



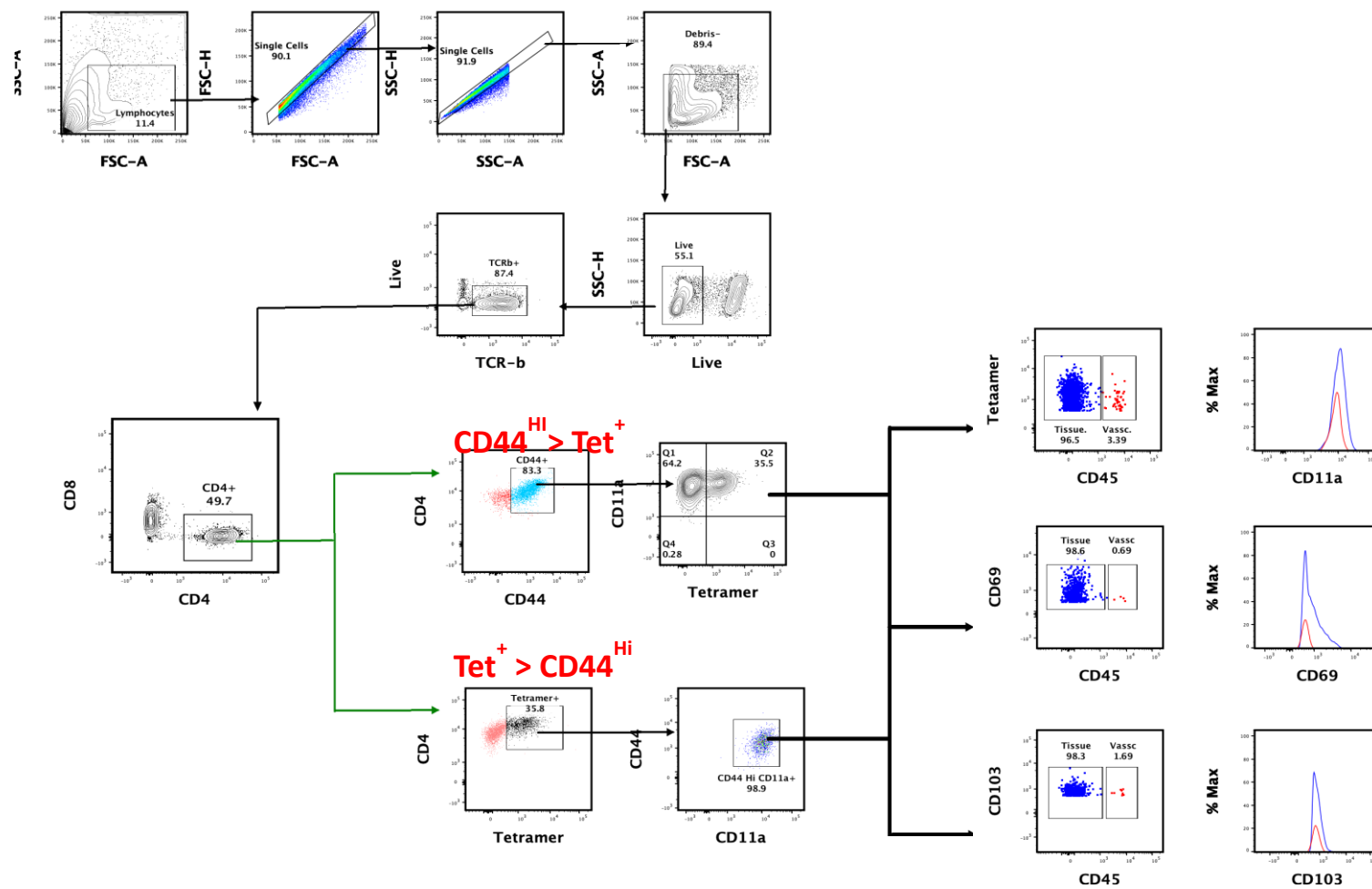
Supplementary Figure S1. Gating scheme to quantify naïve ($CD44^- CD62L^+$) and $CD44^{hi} CD4$ T cells in uninfected mice shown for data in Figure 5.



Supplemental Figure S2. Gating scheme for analyses of polyclonal CD4 T cells in lung. A sequential gating scheme as shown was used to identify antigen experienced CD4 T cells in the lung vasculature and tissue and to quantify surface markers (CD11a, CD69 and CD103, as shown).



Supplementary Figure S3A. Flow cytometry gating scheme using MHC class II: peptide tetramers from lung CD4 T cells that were isolated from influenza B infected mice. Shown is the sequential gating scheme used to identify peptide epitope-specific CD4 T cells using the I-A^b:HA-23 peptide tetramer (see Supplemental Table S1).



Supplementary Figure S3B. Flow cytometry gating scheme using MHC class II: peptide tetramers from lung CD4 T cells isolated from influenza A infected mice. Shown is the sequential gating scheme used to identify peptide epitope-specific CD4 T cells using the I-A^b:NP-263 peptide tetramer (see Supplemental Table S1).

Supplemental Table S1. Peptide nomenclature and sequences.

TABLE S1.1: Influenza B peptides

| Peptide name | Peptide sequence | Peptide length |
|--------------|----------------------------------|----------------|
| *HA 23 | 23 TSSNSPHVVKTATQGE 38 | 16 |
| HA 97 | 97 SILHEVRPVTSGCFP 111 | 15 |
| HA 483 | 483 KLKKMLGPSAVEIGN 497 | 15 |
| NP 316 | 316 LLARSMVVVRPSVASKV 332 | 17 |
| NP 321 | 321 MVVVRPSVASKVVLPI 337 | 17 |
| NP 346 | 346 GFNVEEYSMVGYEAMAL 362 | 17 |
| NP 358 | 358 EAMALYNMATPVSILRM 374 | 17 |
| NP 391 | 391 GAAYEDLRVLSALTGTE 407 | 17 |
| NP 465 | 465 SPVFAVERPIALSKQA 480 | 16 |
| NA 77 | 77 EPEWTPRLSCPGST 91 | 15 |
| NA 173 | 173 HMAAWSGSACHDGKE 187 | 15 |
| NA 177 | 177 WSGSACHDGKEWTYI 191 | 15 |
| NA 321 | 321 TYLDTPRPNDGSITG 335 | 16 |
| NS1 8 | 8 TTQIEVGPGATNATIN 22 | 16 |
| NS1 85 | 85 MKVLLFMNPSAGIEGF 100 | 16 |
| NS1 89 | 89 LFMNPSAGIEGFEPYC 104 | 16 |
| NS1 109 | 189 VNGTFLKHPNGYKSL 204 | 16 |

TABLE S1.2: Influenza A/California peptides

| | | | |
|--------|--------|-------------------------------------|----|
| NA 28 | NA 109 | 109-GSKGDVVFVIREPFIS-123 | 15 |
| NA 39 | NA 153 | 153-SPYRTLMSCPIGEVPS-168 | 16 |
| NA 45 | NA 177 | 177-VAWSASACHDGINWL-191 | 15 |
| NA 56 | NA 221 | 11515221-NNILRTQESECACVN-235 | 15 |
| NS1 3 | NS1 9 | 9-FQVDCFLWHIRKFA-23 | 16 |
| NS1 4 | NS1 13 | 13-CFLWHIRKRFADNGL-27 | 16 |
| NS1 13 | NS1 49 | 49-TLGLDIETATLVGKQ-63 | 16 |
| NS1 23 | NS1 89 | 89-YLSDMTLEEMSRDWF-103 | 16 |
| M1 35 | M1 137 | 137-TVTTEAAFGLVCATC-151 | 15 |
| M1 46 | M1 181 | 181-LASTTAKAMEQMAGS-195 | 15 |
| M1 47 | M1 185 | 185-TAKAMEQMAGSSEQA-199 | 15 |
| M1 53 | M1 209 | 209-TRQMVHAMRTIGTHPS-224 | 15 |
| M1 55 | M1 217 | 217-RTIGTHPSSSAGLKD-231 | 15 |

Supplemental Table S2. IFN γ EliSpot kinetics of CD4 T cell response in different tissues.

| Virus | B/Brisbane | | | | A/California | | |
|---------------|---------------------------|---------|--------|---------------|---------------------------|--------|--------|
| | CD4 T cells Spots/million | | | | CD4 T cells Spots/million | | |
| Viral Protein | Day 7 | Day 10 | Day 16 | Viral protein | Day 7 | Day 10 | Day 16 |
| Lung | | | | | | | |
| | | | | | | | |
| NA-B | 3490.0 | 11727.5 | 7628.5 | NA-A | 932.5 | 8080.0 | 6725.0 |
| NP-B | 2575.8 | 11715.0 | 7029.9 | NP-A | 3541.7 | 9082.5 | 7050.0 |
| | | | | | | | |
| mLN | | | | | | | |
| | | | | | | | |
| NA-B | 1535.8 | 2156.1 | 2138.8 | NA-A | 131.7 | 986.3 | 385.8 |
| NP-B | 1361.7 | 2693.3 | 2297.9 | NP-A | 322.3 | 1051.7 | 652.1 |
| | | | | | | | |
| Spleen | | | | | | | |
| | | | | | | | |
| NA-B | 2478.9 | 1670.6 | 1142.9 | NA-A | 1251.0 | 445.6 | 82.5 |
| NP-B | 2406.2 | 2115.6 | 1423.8 | NP-A | 2293.5 | 613.1 | 181.9 |