

## SUPPLEMENTAL FIGURES AND FIGURE LEGENDS

**Supplemental Table 1.** Ex vivo  $^{18}\text{F}$ -FDG uptake, represented as %ID/g, in tissues following terminal biodistribution study in (A) treatment-naïve (vehicle) mice, and (B) celgosivir-treated mice following lethal S221 DENV2 inoculation. LN = Lymph nodes.

### A

Tissue	Naive			1 d DENV2 (Vehicle)			2 d DENV2 (Vehicle)			3 d DENV2 (Vehicle)			4 d DENV2 (Vehicle)		
	Mean	SD	n	Mean	SD	n	Mean	SD	n	Mean	SD	n	Mean	SD	n
Blood	0.55	0.11	12	0.42	0.09	6	0.36	0.03	6	0.47	0.1	12	0.86	0.48	12
Heart	6.63	5.75	12	10.2	4.35	6	16.96	8.48	6	10.5	6.86	12	4.82	1.55	12
Lungs	3.13	0.52	12	2.59	0.17	6	2.71	0.36	6	3.63	0.55	12	4.94	1.37	12
Kidney	1.83	0.62	12	1.14	0.22	6	1.3	0.34	6	1.57	0.29	12	2.66	1.47	12
Spleen	2.6	0.48	12	2.63	0.55	6	3.15	0.46	6	10.56	2.65	12	12.6	2.33	12
Liver	1.33	0.22	12	1.17	0.32	6	0.98	0.08	6	1.66	0.22	12	2.06	1	12
Stomach	2.84	0.91	12	2.48	0.43	6	2.65	0.38	6	3.02	0.49	12	5.15	2.19	12
Pancreas	1.45	0.27	12	1.05	0.18	6	1.3	0.25	6	1.23	0.2	12	1.91	0.4	12
S.Int.	2.91	0.77	12	1.91	0.36	6	1.78	0.36	6	6.34	2.38	12	38.28	8.19	12
L.Int.	5.11	0.89	12	3.76	0.58	6	3.85	0.63	6	5.81	1.68	12	14.4	4.95	12
Mesenteric LN	2.51	0.77	12	1.44	0.89	6	1.14	0.98	6	4.92	2.56	12	4.96	1.09	12
Muscle	3.47	2.8	12	5.93	1.62	6	5.12	2.96	6	5.7	3.59	12	2.38	1.41	12
Bone	2.55	0.8	12	2.21	0.73	6	3.39	1.45	6	5.03	1.39	12	5.1	1.6	12
Thyroid*	6.5	2.44	12	7.12	0.76	6	8.39	1.81	6	8.61	2.24	12	5.29	1.38	12
Brain	8.76	2.32	12	6.69	1.81	6	5.04	0.75	6	12.56	3.67	12	10.1	1.89	12

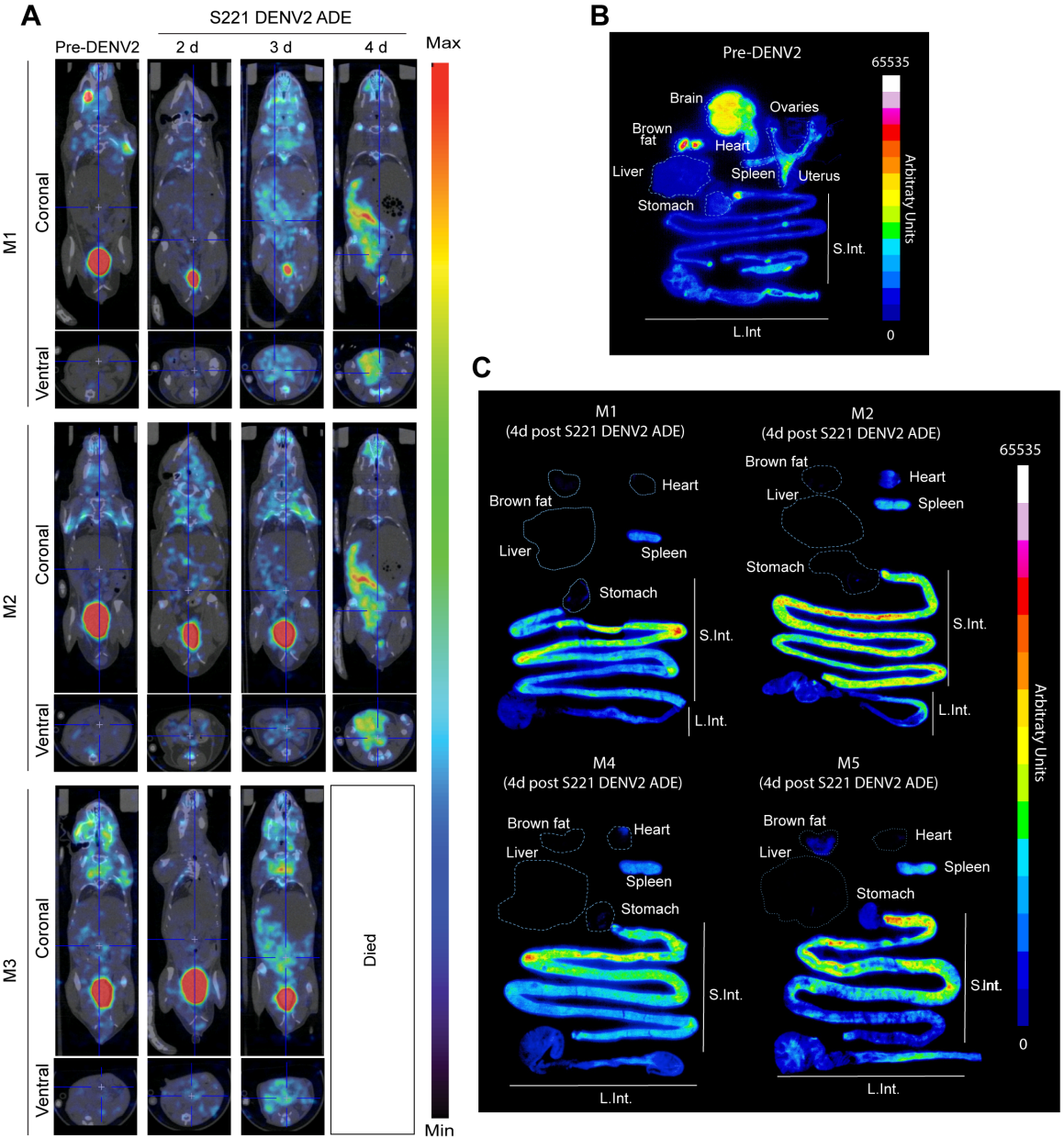
\* Represented as % ID/Org

### B

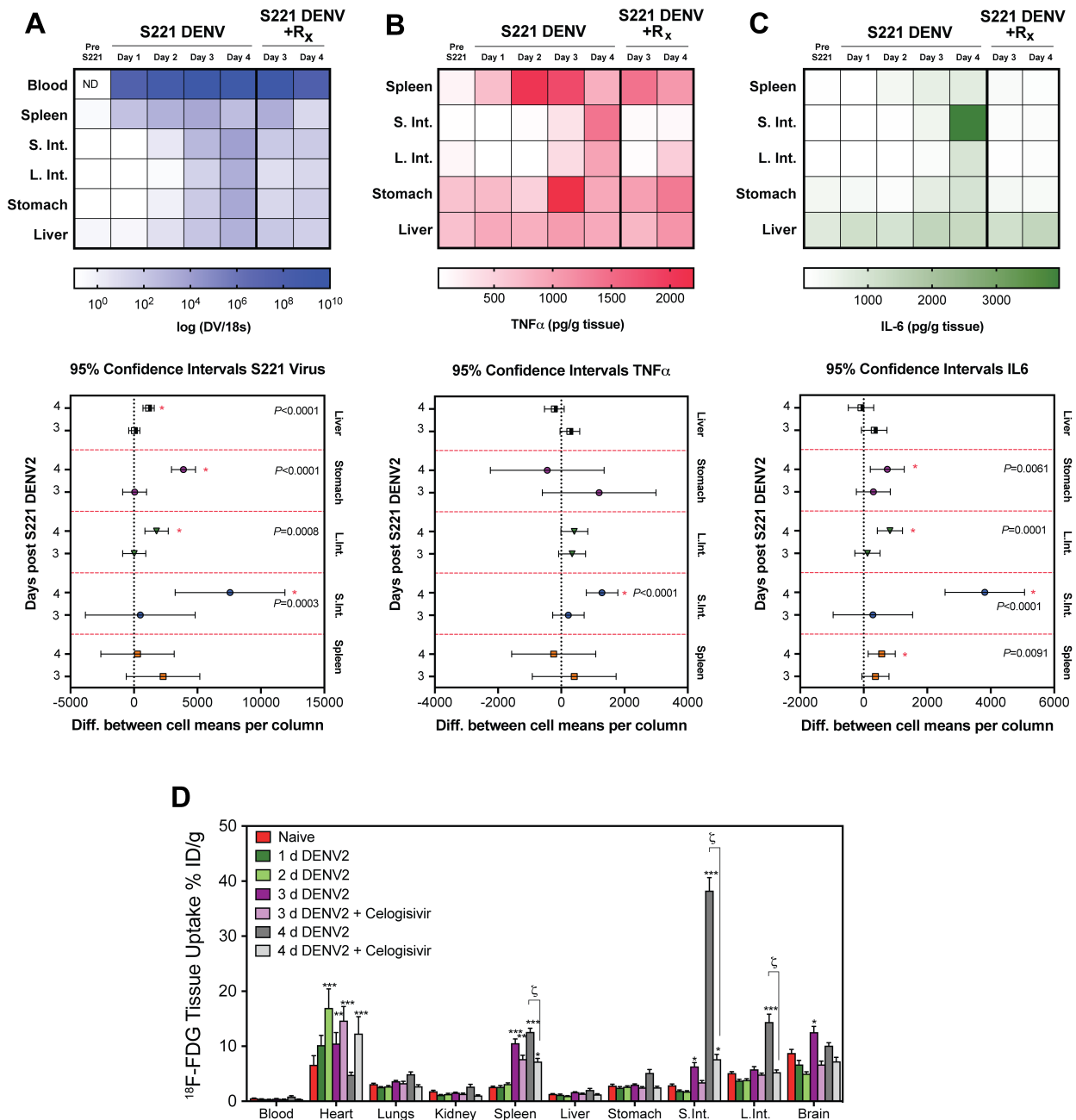
Mean	3 d DENV2 (Celgosivir)			4 d DENV2 (Celgosivir)		
	Mean	SD	n	Mean	SD	n
Blood	0.39	0.06	6	0.38	0.08	6
Heart	14.67	6.25	6	12.29	7.52	6
Lungs	3.31	0.78	6	2.72	0.67	6
Kidney	1.34	0.35	6	1.06	0.24	6
Spleen	7.67	1.72	6	7.22	1.41	6
Liver	1.38	0.24	6	1.24	0.33	6
Stomach	2.52	0.37	6	2.54	0.45	6
Pancreas	1.27	0.16	6	1.09	0.25	6
S.Int.	3.44	0.78	6	7.64	2.18	6
L.Int.	4.87	0.62	6	5.29	1.00	6
Mesenteric LN	2.90	1.61	6	2.89	1.36	6
Muscle	5.44	3.36	6	8.72	3.26	6
Bone	4.09	0.91	6	5.42	1.20	6
Thyroid*	9.36	1.54	6	9.82	2.53	6
Brain	6.70	1.46	6	7.26	1.76	6

\* Represented as % ID/Org

**Supplemental Figure 1.** (A) Serial in vivo  $^{18}\text{F}$ -FDG-PET/CT imaging of three representative mice M1, M2, and M3 ( $n=3$  mice per cohort, with treatment naïve (vehicle control) group performed three independent times), followed by (C) ex vivo  $^{18}\text{F}$ -FDG DAR imaging in M1, and M2, and spare mice M4 and M5, 4 days post DENV2 infection ( $n=4$  mice per cohort). (B) Ex vivo  $^{18}\text{F}$ -FDG DAR in representative control pre-DENV mice ( $n=2$  mouse per cohort).

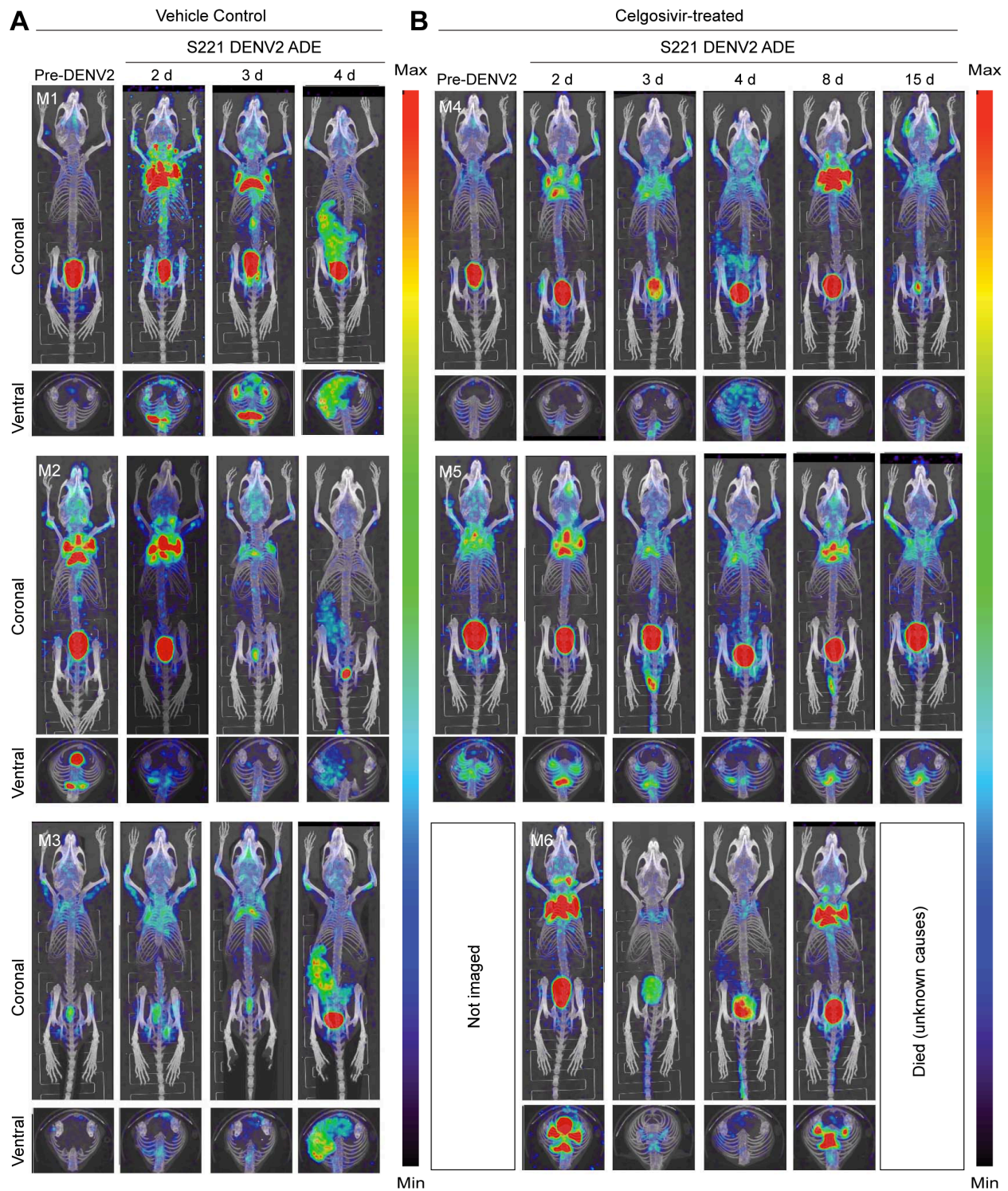


**Supplemental Figure 2.** Ex vivo characterization of tissue-specific **(A)** virus and **(B)** TNF- $\alpha$  and **(C)** IL-6 cytokine levels lethal IC DENV2 murine model infected with mouse-adapted S221 DENV2 strain following treatment with vehicle control ( $n=12$ ), and with celgosivir q.i.d. ( $n=6$ ). Between Day 3 and Day 4 treatment-naïve and celgosivir-treated groups: \*,  $P<0.05$ . **(D)**  $^{18}\text{F}$ -FDG tissue uptake, represented as mean %ID/g  $\pm$  SEM; Mean values compared by two-way ANOVA with multiple comparisons; Versus Naïve: \*\*,  $P<0.001$ , \*\*\* $P<0.0001$ ; Versus Rx:  $\zeta$ ,  $P<0.001$ .





**Supplemental Figure 3.** Representative panel of serial  $^{18}\text{F}$ -FDG-PET/CT MIP images of lethal S221 infected mice that are (A) treatment-naïve (vehicle control) or (B) had celgosivir treatment q.i.d. at day 2 post-infections ( $n=3$  mice per imaging arm; with imaging of treatment-naïve group performed three independent times).





**Supplemental Table 2.** Ex vivo  $^{18}\text{F}$ -FDG uptake in tissues, in (A,B) non-lethal and (C,D) lethal EDEN2 DENV2 ADE at different time points post-infection compared to naïve non-infected control, represented as %ID/g (A,C) and as Localization Ratio (LR), following normalization to non-infected mice (B,D). LN = Lymph nodes.

**A**

	Naive			1 d Non-Lethal			2 d Non-Lethal			3 d Non-Lethal			4 d Non-Lethal			5 d Non-Lethal		
Tissue	Mean	SD	n	Mean	SD	n	Mean	SD	n	Mean	SD	n	Mean	SD	n	Mean	SD	n
Blood	0.62	0.09	8	0.41	0.06	8	0.38	0.06	8	0.37	0.05	8	0.54	0.08	8	0.60	0.19	8
Heart	2.78	1.15	8	18.29	8.19	8	12.36	6.79	8	12.99	7.00	8	5.23	1.47	8	7.82	4.82	8
Lungs	2.58	1.09	8	2.99	0.30	8	3.12	0.51	8	3.70	1.00	8	3.81	0.62	8	4.20	0.70	8
Kidney	1.39	0.53	8	1.23	0.12	8	1.37	0.35	8	1.29	0.16	8	1.51	0.18	8	1.40	0.24	8
Spleen	3.35	2.31	8	5.48	0.82	8	6.89	1.27	8	8.96	1.74	8	16.42	8.49	8	10.32	1.06	8
Liver	2.85	4.53	8	1.30	0.14	8	1.48	0.19	8	1.08	0.11	8	1.03	0.15	8	1.31	0.30	8
Stomach	2.26	0.90	8	2.30	0.57	8	2.49	0.56	8	2.60	0.61	8	4.56	1.19	8	3.17	0.79	8
Pancreas	7.36	12.10	8	1.17	0.81	8	0.83	0.19	8	0.98	0.18	8	2.22	1.04	8	2.63	0.78	8
S.Int.	2.49	0.88	8	1.98	0.24	8	2.69	0.52	8	6.69	2.00	8	13.77	3.89	8	3.92	1.31	8
L.Int.	4.89	0.62	8	4.58	0.67	8	4.58	0.81	8	4.88	0.74	8	15.21	3.35	8	9.67	3.25	8
Mesenteric LN	2.71	2.90	8	3.12	1.17	8	4.37	1.72	8	3.69	1.54	8	30.00	58.75	8	5.58	3.04	8
Muscle	2.50	4.42	8	2.01	1.05	8	2.52	1.50	8	1.40	0.80	8	1.46	1.27	8	4.85	2.38	8
Bone	2.69	4.35	8	5.03	7.33	8	3.38	1.20	8	2.56	0.48	8	5.79	3.82	8	3.37	0.79	8
Thyroid*	5.05	1.21	8	5.86	7.35	8	8.34	1.55	8	8.67	3.27	8	12.62	4.25	8	8.21	2.50	8
Brain	10.13	4.05	8	9.28	1.38	8	10.09	1.72	8	10.33	2.69	8	13.92	1.43	8	5.69	0.93	8

\* Represented as % ID/Org

**B**

	1 d Non-Lethal			2 d Non-Lethal			3 d Non-Lethal			4 d Non-Lethal			5 d Non-Lethal		
Tissue	Mean	SD	n	Mean	SD	n	Mean	SD	n	Mean	SD	n	Mean	SD	n
Blood	0.66	0.05	8	0.61	0.05	8	0.60	0.04	8	0.87	0.06	8	0.97	0.12	8
Heart	6.58	1.42	8*	4.45	1.08	8*	4.67	1.12	8*	1.88	0.33	8	2.81	0.74	8*
Lungs	1.16	0.18	8	1.21	0.19	8	1.43	0.25	8	1.48	0.24	8	1.63	0.26	8
Kidney	0.88	0.12	8	0.99	0.16	8	0.93	0.13	8	1.09	0.15	8	1.01	0.15	8
Spleen	1.64	0.41	8	2.06	0.52	8	2.67	0.68	8*	4.90	1.49	8*	3.08	0.76	8*
Liver	0.46	0.26	8	0.52	0.29	8	0.38	0.21	8	0.36	0.20	8	0.46	0.26	8
Stomach	1.02	0.17	8	1.10	0.18	8	1.15	0.19	8	2.02	0.34	8	1.40	0.23	8
Pancreas	0.16	0.10	8	0.11	0.07	8	0.13	0.08	8	0.30	0.18	8	0.36	0.21	8
S.Int.	0.80	0.11	8	1.08	0.15	8	2.69	0.44	8*	5.53	0.88	8*	1.57	0.27	8
L.Int.	0.94	0.06	8	0.94	0.07	8	1.00	0.07	8	3.11	0.28	8*	1.98	0.25	8
Mesenteric LN	1.15	0.46	8	1.61	0.65	8	1.36	0.55	8	11.07	8.73	8*	2.06	0.87	8
Muscle	0.80	0.52	8	1.01	0.66	8	0.56	0.37	8	0.58	0.41	8	1.94	1.26	8
Bone	1.87	1.44	8	1.26	0.74	8	0.95	0.55	8	2.15	1.33	8	1.25	0.72	8
Thyroid	1.16	0.52	8	1.65	0.18	8	1.72	0.27	8	2.50	0.37	8*	1.63	0.22	8
Brain	0.92	0.14	8	1.00	0.15	8	1.02	0.17	8	1.37	0.20	8	0.56	0.09	8

\*,  $P < 0.05$ ; relative to '1' (i.e. naïve (%ID/g)/naïve (%ID/g))

**C**

	1 d Lethal			2 d Lethal			3 d Lethal			4 d Lethal			5 d Lethal		
Tissue	Mean	SD	n	Mean	SD	n	Mean	SD	n	Mean	SD	n	Mean	SD	n
Blood	0.48	0.1	6	0.42	0.03	8	0.5	0.09	8	1.28	0.62	8	1.15	1.03	3
Heart	10.19	7.39	6	13.71	7.08	8	7.11	4.26	8	4.09	0.87	8	11.01	6.19	3
Lungs	3.06	0.51	6	3.51	0.63	8	3.57	0.9	8	4.8	1.33	8	5.01	0.65	3
Kidney	1.34	0.26	6	1.78	0.79	8	1.3	0.24	8	5.12	5.82	8	2.66	1.16	3
Spleen	5.67	0.91	6	6.19	1.13	8	12.52	6.05	8	13.62	5.26	8	13.17	1.5	3
Liver	1.34	0.32	6	1.54	0.18	8	1.1	0.22	8	2.04	0.65	8	2.6	0.7	3
Stomach	2.62	0.82	6	2.41	0.63	8	2.41	0.67	8	4.4	1.41	8	4.15	2.65	3
Pancreas	1.21	0.27	6	0.95	0.25	8	1.65	0.89	8	3.22	0.77	8	22.14	35.12	3
S.Int.	2.09	0.37	6	4.33	0.9	8	18.61	6.97	8	27.61	7.76	8	13.78	8.38	3
L.Int.	4.67	1.18	6	4.37	0.56	8	8.59	3.28	8	19.65	7.46	8	17.54	9.47	3
Mesenteric LN	2.52	0.63	6	4.17	2.05	8	4.47	2.18	8	12.3	17.9	8	5.17	0.64	3
Muscle	1.73	0.71	6	2.26	1.6	8	2.61	2.06	8	1.24	0.62	8	2.11	1.76	3
Bone	2.16	0.61	6	4.38	3.96	8	7.91	13.49	8	6.86	5.84	8	4.03	1.6	3
Thyroid*	9.82	1.9	6	11.11	2.67	8	14.72	14.46	8	7.52	1.67	8	13.43	0.8	3
Brain	11.25	2.28	6	12.33	3.14	8	11.57	2.62	8	13.87	5.86	8	10.54	8.12	3

\* Represented as % ID/Org

**D**

	1 d Lethal			2 d Lethal			3 d Lethal			4 d Lethal			5 d Lethal		
Tissue	Mean	SD	n	Mean	SD	n	Mean	SD	n	Mean	SD	n	Mean	SD	n
Blood	0.77	0.08	6	0.68	0.04	8	0.81	0.07	8	2.06	0.37	8	1.85	0.96	3
Heart	3.67	1.21	6*	4.93	1.15	8*	2.56	0.66	8*	1.47	0.24	8	3.96	1.41	3*
Lungs	1.19	0.19	6	1.36	0.22	8	1.38	0.24	8	1.86	0.33	8	1.94	0.32	3
Kidney	0.96	0.15	6	1.28	0.26	8	0.94	0.14	8	3.68	1.56	8*	1.91	0.55	3
Spleen	1.69	0.43	6	1.85	0.47	8	3.74	1.11	8*	4.07	1.14	8*	3.93	0.99	3*
Liver	0.47	0.27	6	0.54	0.30	8	0.39	0.22	8	0.72	0.41	8	0.91	0.53	3
Stomach	1.16	0.22	6	1.07	0.18	8	1.07	0.18	8	1.95	0.35	8	1.84	0.72	3
Pancreas	0.16	0.10	6	0.13	0.08	8	0.22	0.14	8	0.44	0.26	8	3.01	3.26	3*
S.Int.	0.84	0.12	6	1.74	0.25	8	7.47	1.36	8*	11.09	1.77	8*	5.53	2.06	3*
L.Int.	0.96	0.11	6	0.89	0.06	8	1.76	0.25	8	4.02	0.57	8*	3.59	1.13	3*
Mesenteric LN	0.93	0.36	6	1.54	0.64	8	1.65	0.69	8	4.54	2.90	8*	1.91	0.73	3
Muscle	0.69	0.45	6	0.90	0.61	8	1.04	0.71	8	0.50	0.32	8	0.84	0.67	3
Bone	0.80	0.47	6	1.63	1.07	8	2.94	2.44	8*	2.55	1.65	8*	1.50	0.92	3
Thyroid	1.94	0.23	6	2.20	0.26	8	2.91	1.04	8*	1.49	0.17	8	2.66	0.24	3
Brain	1.11	0.18	6	1.22	0.20	8	1.14	0.19	8	1.37	0.28	8	1.04	0.49	3

\*,  $P < 0.05$ ; relative to '1' (i.e. naïve (%ID/g)/naïve (%ID/g))

**Supplemental Figure 4.** Ex vivo characterization of tissue-specific **(A)** virus and **(B)** TNF- $\alpha$  and **(C)** IL-6 cytokine levels in non-lethal and lethal DENV2 murine model infected with clinical DENV2 isolate EDEN2. Mean values compared by two-way ANOVA with multiple comparisons; Non-lethal vs lethal: \*,  $P<0.05$ .

