Table S1. Average number of plaques per duplicate well observed from serum samples collected from immunocompromised IFNαβR$^{-/-}$ mice surviving to 21 days post CHIKV infection and calculated $PRNT_{80}$ titer.

Group	Animal Cage # [a]	Animal ID[b]	Dilution 1:20	1:40	1:80	1:160	1:320	1:640	$PRNT_{80}$[c]
2 [d]	2M	1L	0	0	4	3	4	4	40
	2M	1R	0	0	1	3	3	6	160
	2M	2L	0	0	2	2	2	6	320
	2M	1L2R	0	0	0	1	2	8	320
	2M	N	0	0	1	1	4	5	160
	2F	1L	2	1	3	4	5	5	80
	2F	1R	0	2	4	4	9	5	40
	2F	2L	0	0	4	5	3	4	40
	2F	1L2R	0	1	3	5	2	4	80
	2F	N	0	0	2	4	5	7	40
3 [e]	3M	1R	0	0	1	2	5	6	160
	3M	2L	0	0	1	4	3	5	80
	3M	1L2R	0	0	1	1	5	7	160
	3M	N	0	1	1	1	3	3	320
	3F	2L2R	0	0	0	0	3	7	320
	3F	1R	1	2	2	2	4	7	160
	3F	2L	0	2	3	6	9	8	80
	3F	1L1R	0	1	1	1	6	5	160
	3F	N	0	1	2	3	11	8	160
Positive Mouse Control			0	1	2	4	3	7	80
Negative Mouse Control			7	11	13	13	--	--	<20

a All animals in cages with the suffix "M" were males, all animals in cages with the suffix "F" were females. b 1L = one left ear punch; 1R = one right ear punch; 2L = two left ear punches; 1L2R = one left ear punch and two right ear punches; N = no ear punches. c Defined as the reciprocal of the highest dilution where the average number of plaques per well did not exceed the calculated cut-off value of three plaques per well. d 100 mg/kg CHIKV-EIG qd X 5, i.p., beginning 5 ± 1 h after infection. e 100 mg/kg CHIKV-EIG qd X 5, i.p., beginning 22 ± 2 h after infection.

Table S2. Mean percent change in body weight from baseline in immunocompromised IFNαβR$^{-/-}$ mice by study day, treatment group and gender.

Study Day	Treatment Group	Gender	Mean (95% Confidence Interval)
1	1 [a]	Female Only	1.83 (1.25, 2.41)
		Male Only	−3.76 (−5.37, −2.16)
		Female + Male	−0.97 (−2.88, 0.95)
	2 [b]	Female Only	1.54 (−3.15, 6.23)
		Male Only	0.65 (−1.49, 2.79)
		Female + Male	1.10 (−0.64, 2.83)
	3 [c]	Female Only	−0.25 (−6.58, 6.08)
		Male Only	−2.8 (−6.8, 1.2)
		Female + Male	−1.52 (−4.15, 1.11)
2	1	Female Only	2.53 (−0.17, 5.23)
		Male Only	−4.41 (−6.63, −2.19)

		Female + Male	−0.94 (−3.49, 1.61)
	2	Female Only	2.27 (−0.63, 5.18)
		Male Only	2.03 (−3.37, 7.43)
		Female + Male	2.15 (0.11, 4.19)
	3	Female Only	−1.07 (−8.83, 6.7)
		Male Only	−0.09 (−4.35, 4.17)
		Female + Male	−0.58 (−3.54, 2.39)
3	1	Female Only	−3.28 (−6.11, −0.45)
		Male Only	−8.68 (−9.89, −7.48)
		Female + Male	−5.98 (−8.02, −3.94)
	2	Female Only	0.03 (−3.11, 3.17)
		Male Only	0.03 (−4.4, 4.46)
		Female + Male	0.03 (−1.77, 1.84)
	3	Female Only	−0.69 (−7.29, 5.9)
		Male Only	−0.7 (−4.2, 2.8)
		Female + Male	−0.69 (−3.18, 1.79)
4	1	Female Only	−4.49 (−7.03, −1.94)
		Male Only	−9.24 (−10.31, −8.17)
		Female + Male	−6.86 (−8.67, −5.06)
	2	Female Only	1.55 (−2.53, 5.62)
		Male Only	2.05 (−4.39, 8.5)
		Female + Male	1.80 (−0.74, 4.34)
	3	Female Only	2.12 (−5.49, 9.72)
		Male Only	−0.91 (−3.96, 2.13)
		Female + Male	0.60 (−2.30, 3.50)
5	1	Female Only	−5.29 (−10.63, 0.05)
		Male Only	−11.05 (−11.91, −10.2)
		Female + Male	−8.17 (−10.78, −5.56)
	2	Female Only	2.58 (−2.23, 7.39)
		Male Only	2.86 (−4.15, 9.86)
		Female + Male	2.72 (−0.11, 5.55)
	3	Female Only	2.38 (−4.15, 8.91)
		Male Only	−2.14 (−8.14, 3.85)
		Female + Male	0.37 (−2.89, 3.63)
6	2	Female Only	0.36 (−3.54, 4.26)
		Male Only	−3.73 (−13.64, 6.18)
		Female + Male	−1.69 (−5.47, 2.10)
	3	Female Only	1.55 (−2.99, 6.1)
		Male Only	−5.49 (−12.56, 1.58)
		Female + Male	−1.58 (−5.03, 1.87)
7	2	Female Only	−2.52 (−9.29, 4.24)
		Male Only	−9.7 (−16.16, −3.24)
		Female + Male	−6.11 (−10.01, −2.21)
	3	Female Only	−3.8 (−13.34, 5.75)
		Male Only	−8.53 (−20.41, 3.34)
		Female + Male	−5.90 (−10.82, −0.98)
8	2	Female Only	−3.26 (−10.85, 4.32)
		Male Only	−12.13 (−19.2, −5.06)
		Female + Male	−7.70 (−12.20, −3.19)
	3	Female	−3.31 (−11.37, 4.75)
		Male	−11.13 (−25.75, 3.49)

			Female + Male	−6.78 (−12.24, −1.33)
9	2		Female Only	−2.97 (−9.39, 3.46)
			Male Only	−9.84 (−18.92, −0.76)
			Female + Male	−6.40 (−10.73, −2.08)
	3		Female Only	−3.34 (−9.78, 3.11)
			Male Only	−9.8 (−23.49, 3.89)
			Female + Male	−6.21 (−10.96, −1.46)
11	2		Female Only	−1.9 (−6.34, 2.53)
			Male Only	−8.17 (−16.1, −0.25)
			Female + Male	−5.04 (−8.69, −1.38)
	3		Female Only	−11.75 (−17.76, −5.74)
			Male Only	−6.74 (−16.97, 3.48)
			Female + Male	−9.53 (−13.34, −5.71)
12	2		Female Only	0.66 (−2.11, 3.43)
			Male Only	−2.22 (−9.7, 5.27)
			Female + Male	−0.78 (−3.60, 2.04)
	3		Female Only	−0.58 (−7.22, 6.07)
			Male Only	−5.08 (−14.0, 3.85)
			Female + Male	−2.57 (−6.26, 1.11)
14	2		Female Only	0.12 (−3.46, 3.71)
			Male Only	−0.48 (−4.72, 3.75)
			Female + Male	−0.18 (−2.04, 1.68)
	3		Female Only	1.73 (−6.33, 9.79)
			Male Only	−3.31 (−10.34, 3.72)
			Female + Male	−0.51 (−4.40, 3.38)
21	2		Female Only	6.64 (3.68, 9.6)
			Male Only	9.0 (0.47, 17.53)
			Female + Male	7.82 (4.72, 10.92)
	3		Female Only	6.28 (−8.32, 20.88)
			Male Only	6.18 (−5.16, 17.52)
			Female + Male	6.24 (0.10, 12.37)

a 100 µL PBS (vehicle) qd X 5, i.p., beginning 22 ± 2 h after infection. b 100 mg/kg CHIKV-EIG qd X 5, i.p., beginning 5 ± 1 h after infection. c 100 mg/kg CHIKV-EIG qd X 5, i.p., beginning 22 ± 2 h after infection.

Table S3. Summary of percent change in right footpad swelling (from left footpad) at 5 dpi to 9 dpi in CHIKV infected immunocompetent DBA/1J mice by treatment group.

Day	Treatment Group	n	% Change in Right Footpad Swelling (From Left Footpad)		
			Mean (SD)	Median (25th, 75th Percentile)	Min, Max
5	1 [a]	10	−1.635 (5.648)	−3.56 (−5.07, −0.48)	−7.45, 11.11
	3 [b]	9	2.245 (5.545)	0.48 (−2.39, 5.77)	−4.91, 11.43
	5 [c]	10	3.193 (6.249)	2.56 (−1.37, 8.08)	−6.05, 14.50
	7 [d]	10	1.078 (6.846)	1.18 (−4.37, 2.38)	−6.87, 17.81
	9 [e]	10	20.588 (17.416)	24.89 (11.90, 32.37)	−8.68, 48.69
	11[f]	10	15.304 (12.433)	16.48 (8.60, 25.12)	−7.49, 32.39
6	1	10	2.298 (4.435)	0.00 (0.00, 5.00)	−4.55, 9.09
	3	9	3.989 (9.552)	4.35 (0.00, 10.00)	−12.00, 19.05
	5	10	2.304 (5.344)	2.27 (−1.32, 7.01)	−5.44, 9.52
	7	10	−0.238 (5.285)	−0.66 (−5.06, 2.13)	−6.41, 8.33

	9	10	4.654 (7.788)	0.86 (−0.90, 12.78)	−3.56, 18.78
	11	10	24.429 (16.292)	18.17 (11.81, 42.68)	4.44, 45.89
7	1	3	1.329 (4.916)	4.17 (−4.35, 4.17)	−4.35, 4.17
	3	2	−4.348 (6.149)	−4.35 (−8.70, 0.00)	−8.70, 0.00
	5	3	3.235 (6.913)	4.35 (−4.17, 9.52)	−4.17, 9.52
	7	3	0.000 (0.000)	0.00 (0.00, 0.00)	0.00, 0.00
	9	3	19.769 (13.769)	22.73 (4.76, 31.82)	4.76, 31.82
	11	3	50.922 (10.462)	54.55 (39.13, 59.09)	39.13, 59.09
8	1	3	1.515 (2.624)	0.00 (0.00, 4.55)	0.00, 4.55
	3	2	−2.165 (9.795)	−2.16 (−9.09, 4.76)	−9.09, 4.76
	5	3	9.596 (12.476)	14.29 (−4.55, 19.05)	−4.55, 19.05
	7	3	4.414 (4.349)	4.55 (0.00, 8.70)	0.00, 8.70
	9	3	50.412 (11.025)	47.83 (40.91, 62.50)	40.91, 62.50
	11	3	21.465 (12.548)	22.73 (8.33, 33.33)	8.33, 33.33
9	1	3	0.000 (0.000)	0.00 (0.00, 0.00)	0.00, 0.00
	3	2	2.489 (9.948)	2.49 (−4.55, 9.52)	−4.55, 9.52
	5	3	−4.282 (7.645)	−8.70 (−8.70, 4.55)	−8.70, 4.55
	7	3	1.515 (2.624)	0.00 (0.00, 4.55)	0.00, 4.55
	9	3	34.327 (17.264)	26.09 (22.73, 54.17)	22.73, 54.17
	11	3	5.863 (6.621)	4.55 (0.00, 13.04)	0.00, 13.04

p.i. = post-infection; SD = standard deviation. a 100 mg/kg/d CHIKV-EIG qd X 5, i.p., beginning 4 h before infection. b 50 mg/kg/d CHIKV-EIG qd X 5, i.p., beginning 4 h before infection. c 25 mg/kg/d CHIKV-EIG qd X 5, i.p., beginning 4 h before infection. d 100 mg/kg/d CHIKV-EIG qd X 3, i.p., beginning 4 h before infection. e 2 mg/kg/d methotrexate qd X 5, s.c., beginning 1 day before infection. f 100 µL PBS (vehicle) qd X 5, i.p., beginning 4 h before infection.

Table S4. Analysis of percent change in right footpad swelling (from left footpad) at 5 dpi and 6 dpi in CHIKV-EIG treated immunocompetent DBA/1J mice.

Day	Treatment Group	Wilcoxon Rank-Sum Test *p* Value	
		Versus Vehicle Control	Versus Methotrexate Control
5	1 [a]	0.006 *	0.015 *
	3 [b]	0.025 *	0.020 *
	5 [c]	0.031 *	0.017 *
	7 [d]	0.021 *	0.009 *
6	1	0.970	0.001 *
	3	0.838	0.008 *
	5	0.677	0.001 *
	7	0.162	<0.001 *

* Denotes significant p-value (≤ 0.05). a 100 mg/kg/d CHIKV-EIG qd X 5, i.p., beginning 4 h before infection. b 50 mg/kg/d CHIKV-EIG qd X 5, i.p., beginning 4 h before infection. c 25 mg/kg/d CHIKV-EIG qd X 5, i.p., beginning 4 h before infection. d 100 mg/kg/d CHIKV-EIG qd X 3, i.p., beginning 4 h before infection.

Table S5. Summary statistics of cytokine levels at 6 dpi in right hind limb tissue cytokine levels in immunocompetent DBA/1J mice and comparison between CHIKV-EIG treatment groups and vehicle and methotrexate controls.

Cytokine	Treatment Group	Mean (SD)	Median (25th, 75th percentile)	Min, Max	Wilcoxon Rank-Sum Test	
					vs Vehicle	Vs Methotrexate
GMCSF	1 [a]	20.717 (54.811)	0.00 (0.00, 0.00)	0.00, 145.02	0.391	1.000
	3 [b]	0.000 (0.000)	0.00 (0.00, 0.00)	0.00, 0.00	1.000	0.391
	5 [c]	0.000 (0.000)	0.00 (0.00, 0.00)	0.00, 0.00	1.000	0.391

	7 [d]	0.000 (0.000)	0.00 (0.00, 0.00)	0.00, 0.00	1.000	0.391
	9 [e]	0.000 (0.000)	0.00 (0.00, 0.00)	0.00, 0.00	--	--
	11[f]	0.774 (2.048)	0.00 (0.00, 0.00)	0.00, 5.42	--	--
IFNγ	1	125.937 (40.193)	128.23 (87.16, 150.88)	68.76, 190.96	0.523	0.523
	3	123.775 (20.436)	125.04 (117.96, 142.29)	82.87, 143.45	0.250	0.371
	5	119.751 (29.265)	131.01 (91.15, 136.21)	74.43, 159.72	0.798	0.523
	7	75.814 (6.689)	77.19 (72.67, 78.64)	63.15, 84.84	0.002*	0.018*
	9	117.522 (16.300)	115.63 (105.63, 122.59)	95.24, 147.30	--	--
	11	110.480 (24.099)	109.70 (83.32, 132.12)	75.78, 137.68	--	--
IL10	1	102.453 (133.102)	17.10 (0.00, 188.36)	0.00, 336.72	0.229	0.642
	3	77.480 (101.994)	0.00 (0.00, 153.97)	0.00, 245.72	0.372	1.000
	5	99.388 (122.262)	76.08 (0.00, 186.35)	0.00, 334.37	0.133	0.513
	7	22.622 (59.852)	0.00 (0.00, 0.00)	0.00, 158.35	0.722	0.180
	9	23.040 (39.556)	0.00 (0.00, 73.63)	0.00, 87.65	--	--
	11	45.418 (61.555)	27.84 (0.00, 81.60)	0.00, 167.52	--	--
IL12p70	1	169.855 (45.912)	187.92 (127.64, 193.58)	86.60, 219.16	0.250	0.798
	3	148.145 (24.442)	151.95 (147.49, 160.39)	96.83, 175.43	0.482	0.250
	5	156.580 (34.342)	171.03 (128.89, 181.65)	91.64, 184.41	0.307	1.000
	7	99.459 (17.726)	97.37 (91.64, 102.70)	77.76, 135.49	0.030*	0.030*
	9	143.567 (34.775)	149.09 (126.20, 158.26)	81.46, 196.44	--	--
	11	168.940 (55.993)	166.05 (114.90, 226.91)	88.97, 246.32	--	--
IL17	1	18.568 (45.699)	0.00 (0.00, 7.99)	0.00, 121.98	0.936	0.594
	3	0.000 (0.000)	0.00 (0.00, 0.00)	0.00, 0.00	0.173	0.391
	5	0.000 (0.000)	0.00 (0.00, 0.00)	0.00, 0.00	0.173	0.391
	7	0.000 (0.000)	0.00 (0.00, 0.00)	0.00, 0.00	0.173	0.391
	9	3.656 (9.414)	0.00 (0.00, 0.59)	0.00, 25.00	--	--
	11	2.142 (5.666)	0.00 (0.00, 0.00)	0.00, 14.99	--	--
IL1a	1	3920.307 (1903.751)	4165.18 (2868.63, 5284.86)	529.98, 6250.17	0.523	0.898
	3	5521.166 (1690.683)	5792.18 (4399.35, 7121.65)	2895.17, 7750.56	0.055	0.160
	5	3715.351 (1197.770)	3015.20 (2908.35, 4451.52)	2572.84, 5918.00	0.609	0.898
	7	2548.967 (950.348)	2380.09 (1872.76, 2745.72)	1767.11, 4556.69	0.125	0.25
	9	3773.296 (1884.169)	3467.39 (2455.56, 3996.84)	2147.15, 7718.30	--	--
	11	3877.762 (1808.493)	4836.24 (1649.27, 5269.20)	1576.16, 5939.99	--	--
IL1b	1	157.959 (40.677)	160.92 (134.75, 194.64)	85.52, 202.61	0.798	0.798
	3	163.063 (34.780)	173.20 (142.44, 187.74)	94.96, 195.10	0.443	0.701
	5	195.598 (61.430)	202.33 (142.44, 255.27)	95.87, 256.47	0.125	0.160
	7	98.453 (19.975)	91.51 (83.88, 109.20)	78.29, 137.67	0.015*	0.084
	9	152.341 (34.745)	159.57 (130.36, 184.73)	93.71, 194.92	--	--
	11	145.542 (50.605)	167.03 (91.51, 190.32)	78.64, 203.76	--	--
IL2	1	6.656 (12.414)	0.00 (0.00, 14.65)	0.00, 31.94	0.722	0.722
	3	14.931 (23.047)	0.00 (0.00, 24.38)	0.00, 61.77	0.337	0.424
	5	2.887 (7.639)	0.00 (0.00, 0.00)	0.00, 20.21	1.000	1.000
	7	0.000 (0.000)	0.00 (0.00, 0.00)	0.00, 0.00	0.391	0.391
	9	7.300 (19.315)	0.00 (0.00, 0.00)	0.00, 51.10	--	--
	11	13.172 (34.849)	0.00 (0.00, 0.00)	0.00, 92.20	--	--

IL3	1	67.514 (18.788)	66.47 (56.29, 81.17)	33.87, 89.92	0.898	0.250
	3	68.173 (13.759)	72.76 (64.35, 77.76)	39.62, 78.45	0.701	0.160
	5	65.490 (24.156)	63.13 (41.68, 72.31)	38.18, 111.27	1.000	0.482
	7	41.479 (4.208)	41.18 (39.62, 44.22)	35.00, 48.68	0.030 *	0.523
	9	67.407 (21.927)	65.92 (54.52, 81.96)	33.33, 103.20	--	--
	11	54.798 (19.205)	52.76 (37.72, 76.03)	32.81, 77.60	--	--
IL4	1	61.200 (18.187)	62.70 (51.91, 79.00)	27.35, 81.80	0.097	0.055
	3	48.214 (7.590)	49.87 (47.99, 52.99)	32.00, 54.88	0.798	0.898
	5	54.154 (17.839)	52.79 (43.85, 55.41)	30.84, 89.55	0.443	0.749
	7	30.756 (1.680)	30.84 (29.24, 32.00)	28.27, 33.25	0.030 *	0.084
	9	49.105 (14.004)	48.96 (42.80, 54.62)	26.92, 73.69	--	--
	11	45.764 (14.253)	47.93 (30.84, 60.16)	26.50, 60.17	--	--
IL5	1	142.396 (36.042)	153.11 (98.32, 172.96)	88.81, 177.39	1.000	0.523
	3	157.817 (24.655)	164.06 (155.82, 172.05)	103.89, 174.88	0.443	0.097
	5	160.181 (49.235)	167.00 (100.11, 197.19)	98.32, 227.86	0.898	0.337
	7	107.396 (27.942)	100.11 (91.77, 107.96)	83.42, 168.23	0.073	0.482
	9	158.177 (44.612)	152.94 (135.39, 211.73)	87.40, 216.71	--	--
	11	143.066 (71.313)	126.50 (86.03, 161.93)	84.71, 288.93	--	--
IL6	1	69.056 (17.820)	73.38 (55.25, 77.88)	41.03, 96.62	0.522	0.798
	3	71.961 (11.116)	74.82 (72.00, 79.50)	48.00, 81.08	0.084	0.481
	5	84.762 (23.765)	83.62 (72.00, 94.95)	46.25, 125.04	0.041 *	0.201
	7	59.162 (29.948)	48.00 (42.40, 61.09)	38.55, 125.04	0.125	0.030 *
	9	66.108 (12.038)	70.67 (62.56, 74.28)	40.38, 74.82	--	--
	11	74.243 (12.529)	71.67 (66.36, 76.00)	62.23, 100.48	--	--
MCP1	1	42.941 (14.645)	41.93 (34.24, 46.36)	22.10, 70.16	0.003 *	0.002 *
	3	124.345 (185.652)	52.91 (41.16, 73.43)	40.28, 544.33	0.055	0.030 *
	5	47.151 (23.062)	39.04 (36.82, 47.56)	24.46, 96.48	0.005 *	0.002 *
	7	52.455 (61.163)	26.86 (25.85, 45.70)	24.46, 190.17	0.021 *	0.005 *
	9	151.587 (75.680)	154.49 (91.17, 169.41)	54.90, 295.74	--	--
	11	286.985 (124.803)	286.91 (187.82, 440.06)	129.56, 447.13	--	--
MIP1a	1	92.162 (243.837)	0.00 (0.00, 0.00)	0.00, 645.13	1.000	1.000
	3	11.278 (22.547)	0.00 (0.00, 19.17)	0.00, 59.77	0.594	0.477
	5	17.817 (26.403)	0.00 (0.00, 36.93)	0.00, 68.26	0.200	0.200
	7	0.000 (0.000)	0.00 (0.00, 0.00)	0.00, 0.00	0.391	0.391
	9	2.741 (7.251)	0.00 (0.00, 0.00)	0.00, 19.19	--	--
	11	2.692 (7.122)	0.00 (0.00, 0.00)	0.00, 18.84	--	--
RANTES	1	26.707 (62.312)	0.00 (0.00, 19.94)	0.00, 167.01	0.019 *	0.006 *
	3	34.377 (42.678)	17.58 (0.00, 88.76)	0.00, 98.74	0.040 *	0.005 *
	5	59.635 (23.654)	59.09 (40.28, 88.39)	30.68, 89.54	0.250	0.007 *
	7	726.037 (1848.792)	23.57 (0.00, 83.96)	0.00, 4918.20	0.125	0.041 *
	9	156.005 (162.435)	90.68 (46.79, 311.21)	19.03, 451.27	--	--
	11	160.056 (56.369)	176.47 (130.71, 193.49)	62.38, 240.15	--	--
TNFα	1	54.051 (28.722)	49.98 (41.65, 68.34)	11.97, 106.59	0.609	0.201
	3	39.885 (17.517)	30.44 (26.04, 53.45)	22.58, 69.90	0.609	0.523
	5	57.227 (18.711)	51.87 (43.36, 76.53)	29.96, 80.30	0.307	0.125
	7	138.426 (265.366)	33.66 (13.25, 90.61)	12.37, 736.87	0.798	0.898
	9	53.565 (36.467)	46.68 (31.33, 51.28)	22.46, 132.94	--	--

11	39.505 (29.853)	30.86 (17.48, 45.81)	16.53, 101.38	--	--

* Denotes significant p-value (≤ 0.05). p-values are not adjusted for multiple comparisons. a 100 mg/kg/d CHIKV-EIG qd X 5, i.p., beginning 4 h before infection. b 50 mg/kg/d CHIKV-EIG qd X 5, i.p., beginning 4 h before infection. c 25 mg/kg/d CHIKV-EIG qd X 5, i.p., beginning 4 h before infection. d 100 mg/kg/d CHIKV-EIG qd X 3, i.p., beginning 4 h before infection. e 2 mg/kg/d methotrexate qd X 5, s.c., beginning 1 day before infection. f 100 μL PBS (vehicle) qd X 5, i.p., beginning 4 h before infection.