

Development of Models for Zika Virus Infection in Mice and Rhesus Macaques Using a Contemporary Virus Strain

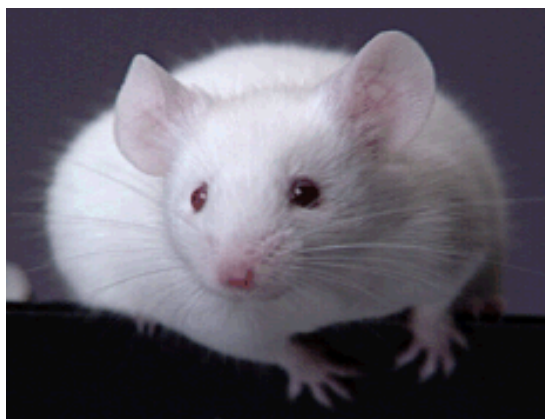
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Background and Animal Model Development

- First formal description of Zika virus was published in 1952.
 - ⦿ Rhesus macaques model in the 1950s generated the first Zika isolate, MR 766.
 - ⦿ Small rodents such as mice, guinea pigs, and rabbits.
 - ⦿ 17 serial passages required to manifest consistent disease in adult white mice
- In humans, Zika infection is self-limiting febrile illness associated with rash, arthralgia, and conjunctivitis, though most infections are asymptomatic.
- Guillain-Barré syndrome and microcephaly
- Ultimate goal is to develop appropriate animal models that recapitulates human disease

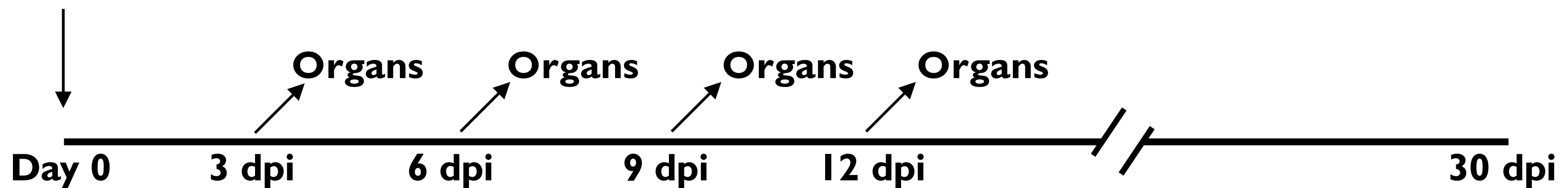
Zika Mouse Study Design



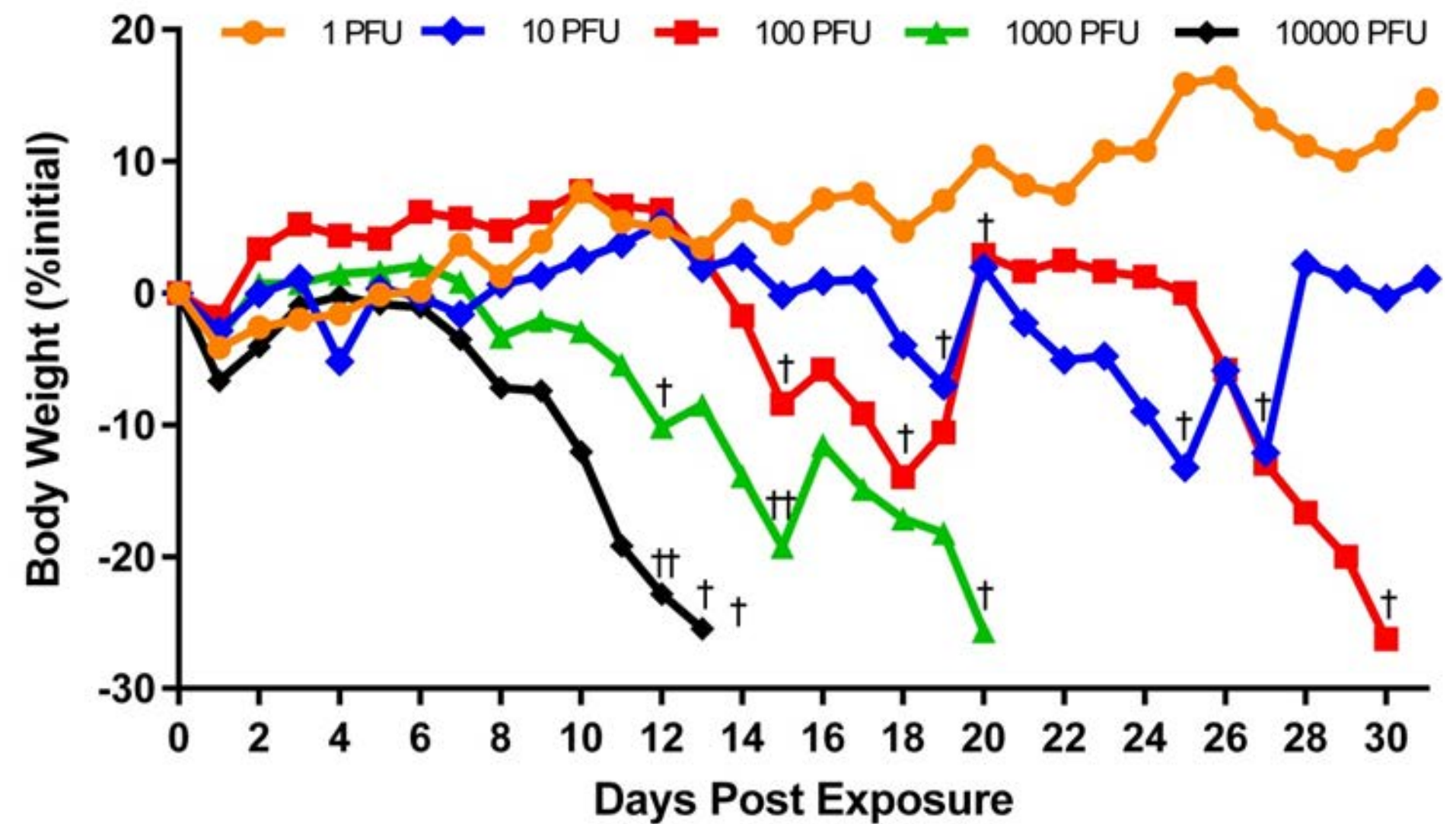
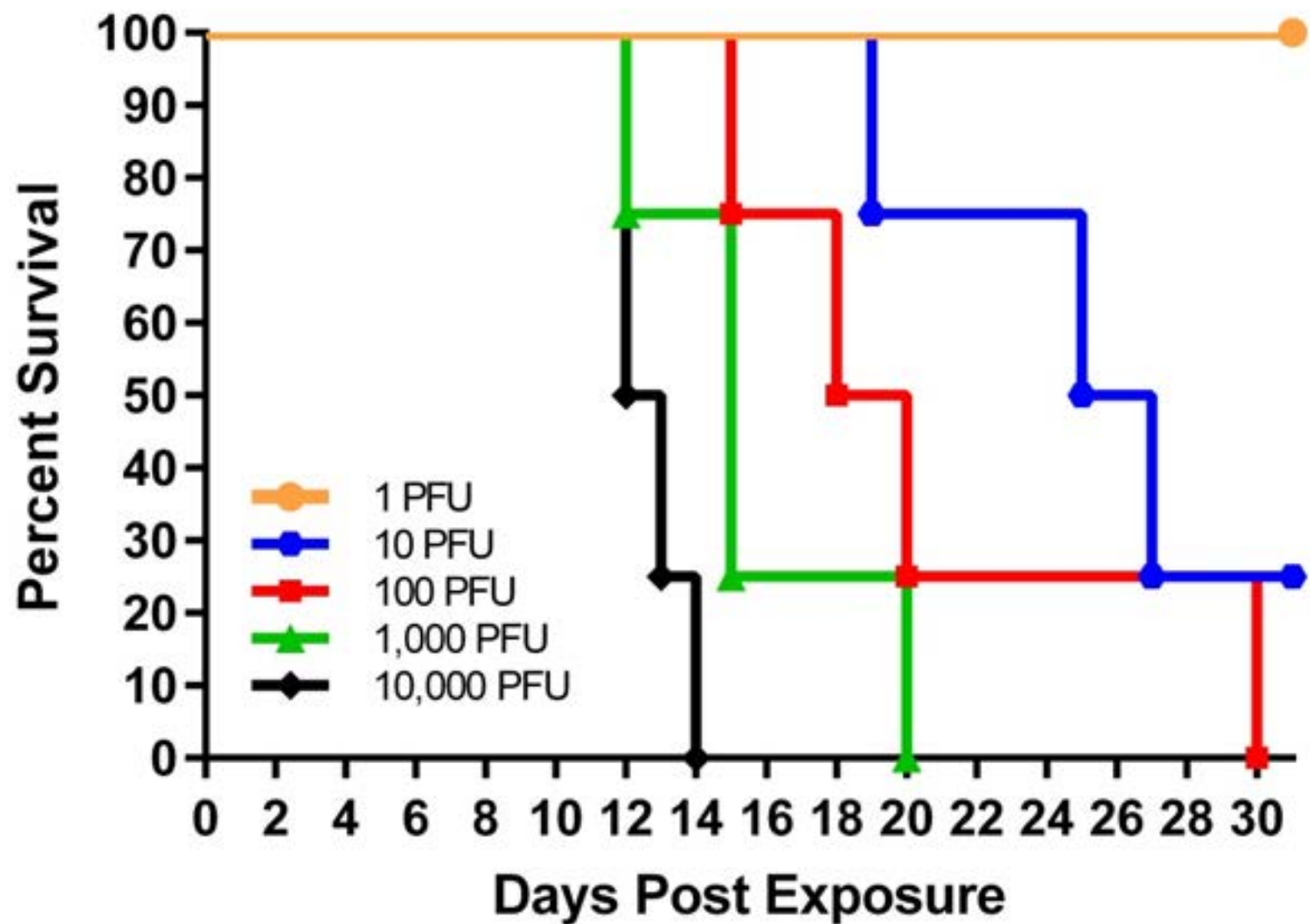
AGI29
(IFN α / β / γ R-/-)
Zika: PRVABC-59

- Group 1: 1 PFU**
- Group 2: 10 PFU**
- Group 3: 100 PFU**
- Group 4: 1000 PFU**
- Group 5: 10000 PFU**

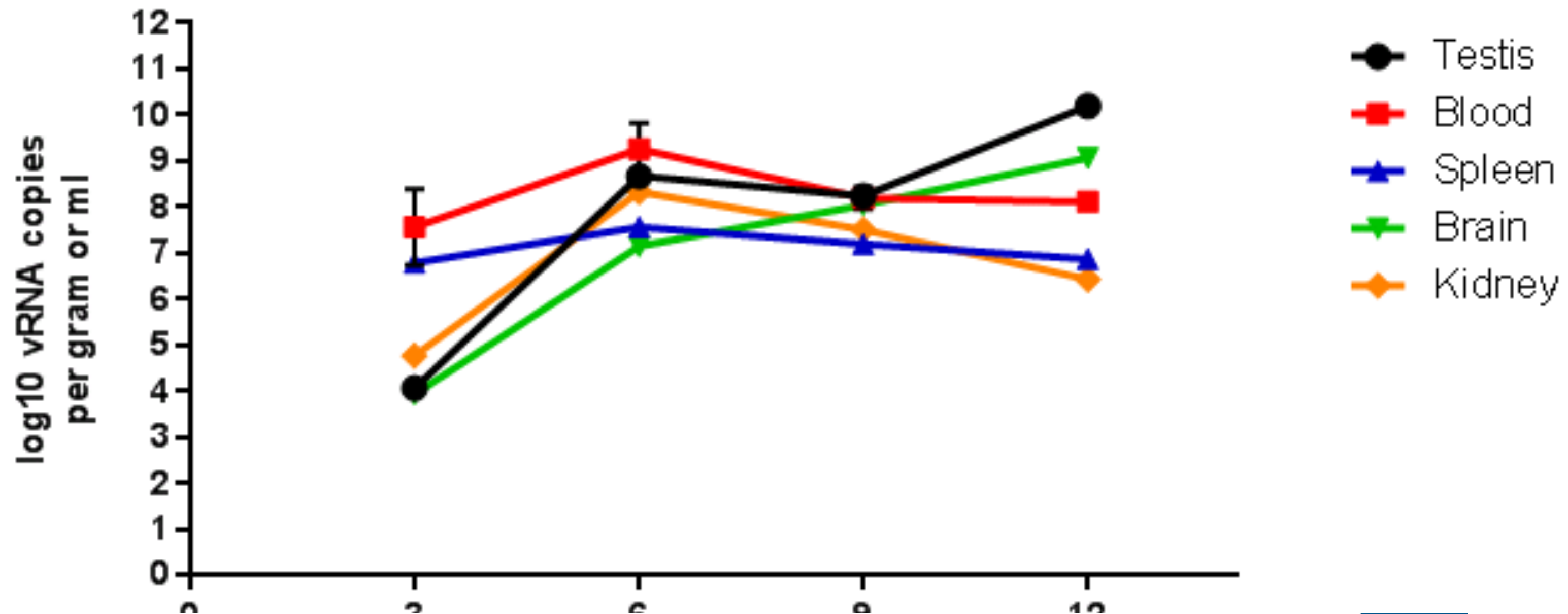
Monitored body weights, temperatures daily
Performed necropsy on days 3, 6, 9 and 12 post challenge



Mouse Body Weight and Survival



Mouse Zika Titers (qPCR)



Article

Cell

Vaginal Exposure to Zika Virus during Pregnancy Leads to Fetal Brain Infection

Laura J. Yockey,¹ Luis Varela,² Tasfia Rakib,¹ William Khoury-Hanold,¹ Susan L. Fink,^{1,3} Bernardo Stutz,² Klara Szigeti-Buck,² Anthony Van den Pol,⁴ Brett D. Lindenbach,⁵ Tamas L. Horvath,² and Akiko Iwasaki^{1,6,7,*}

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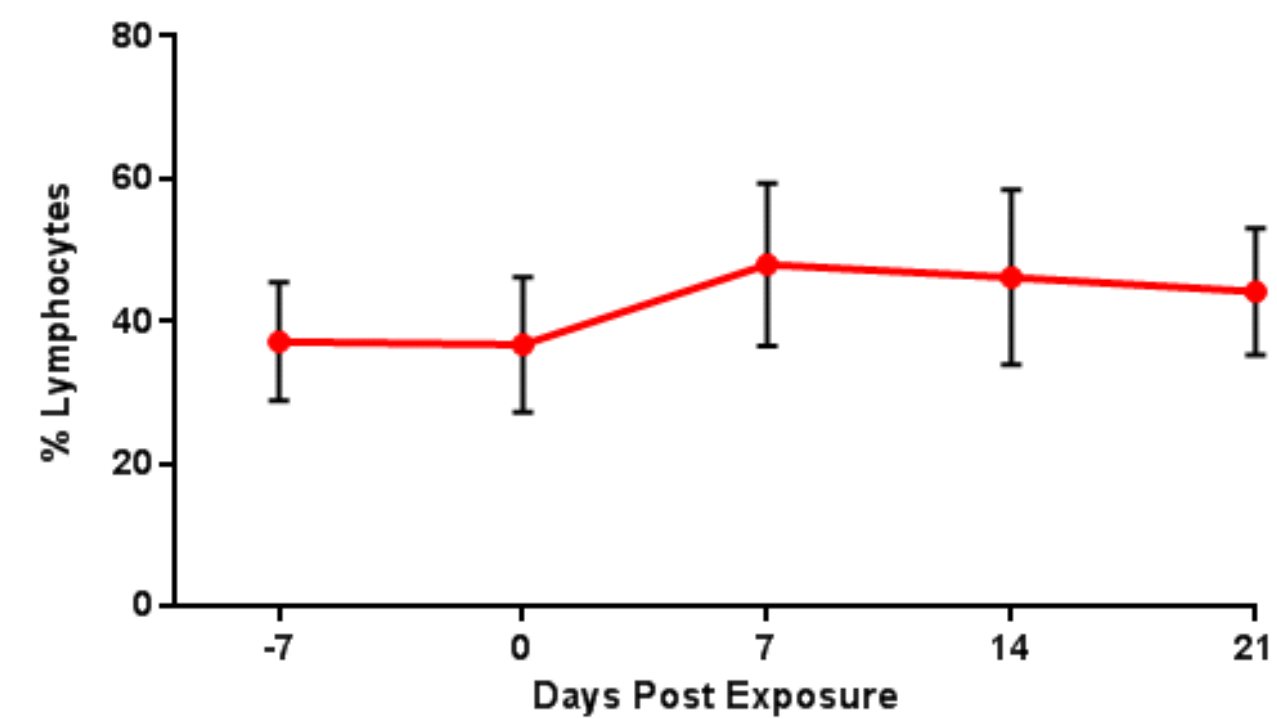
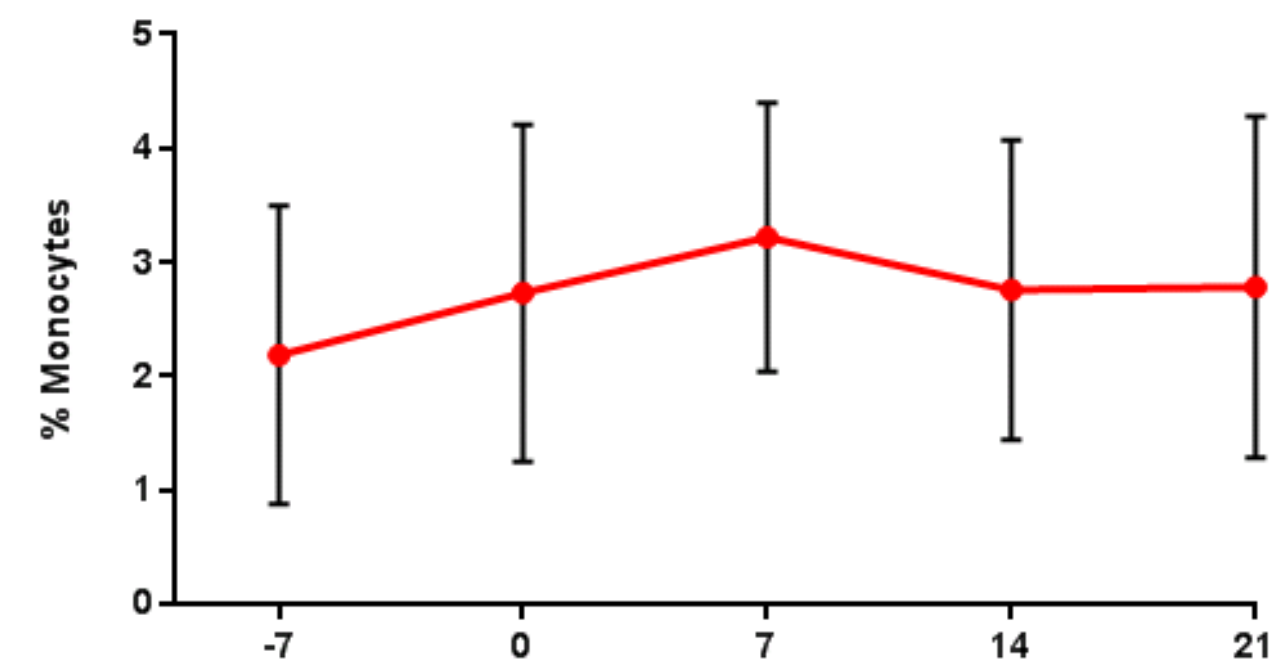
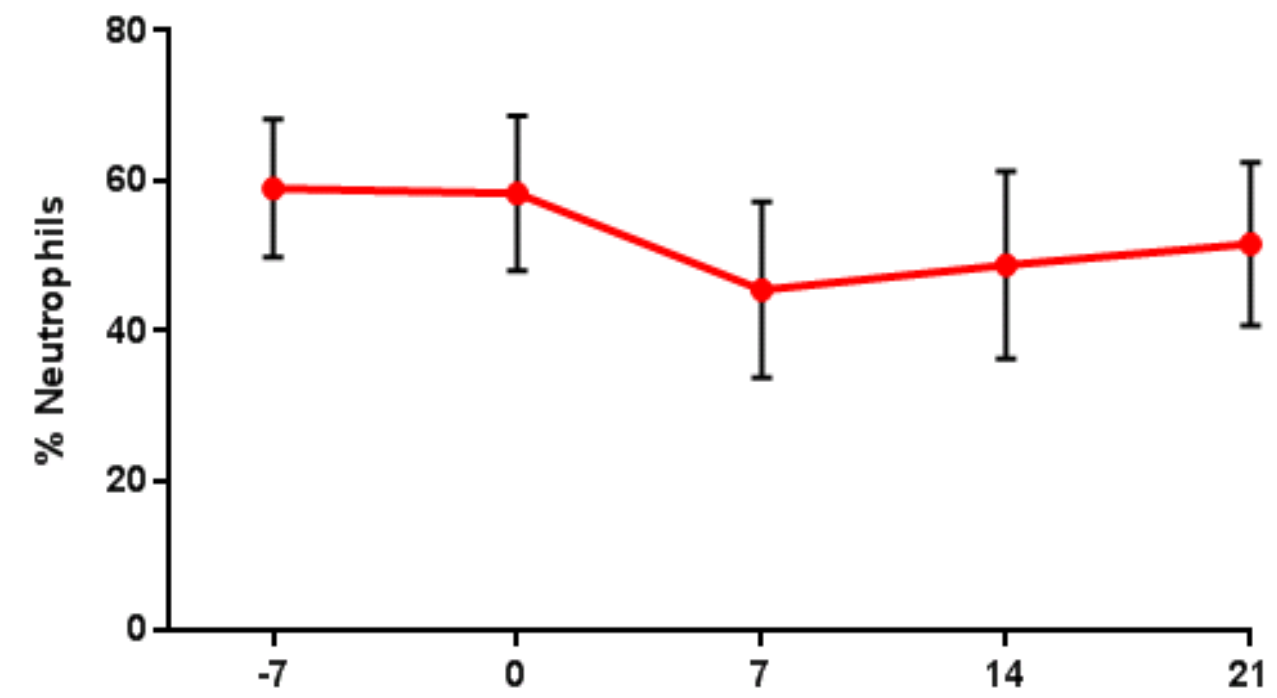
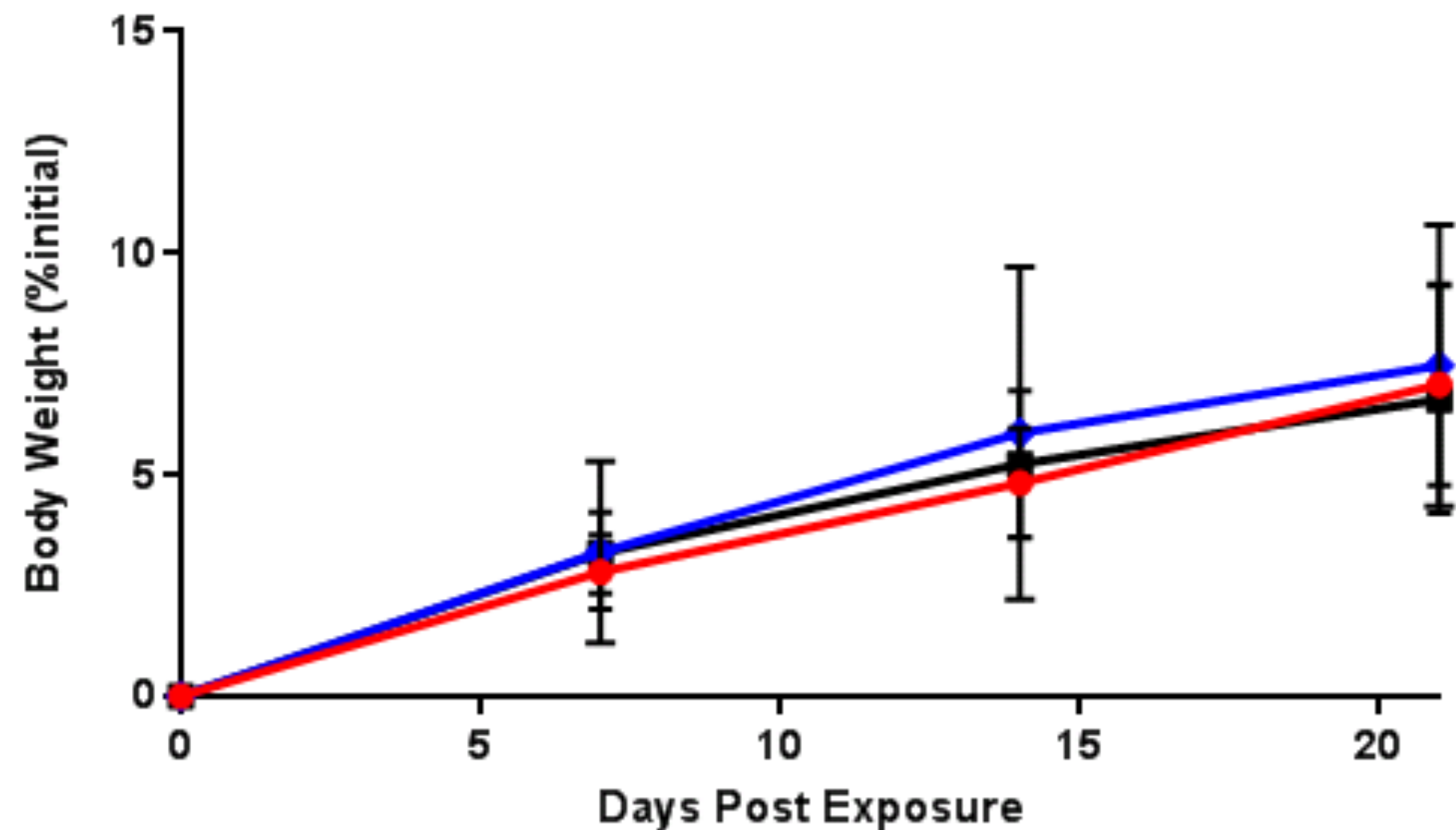
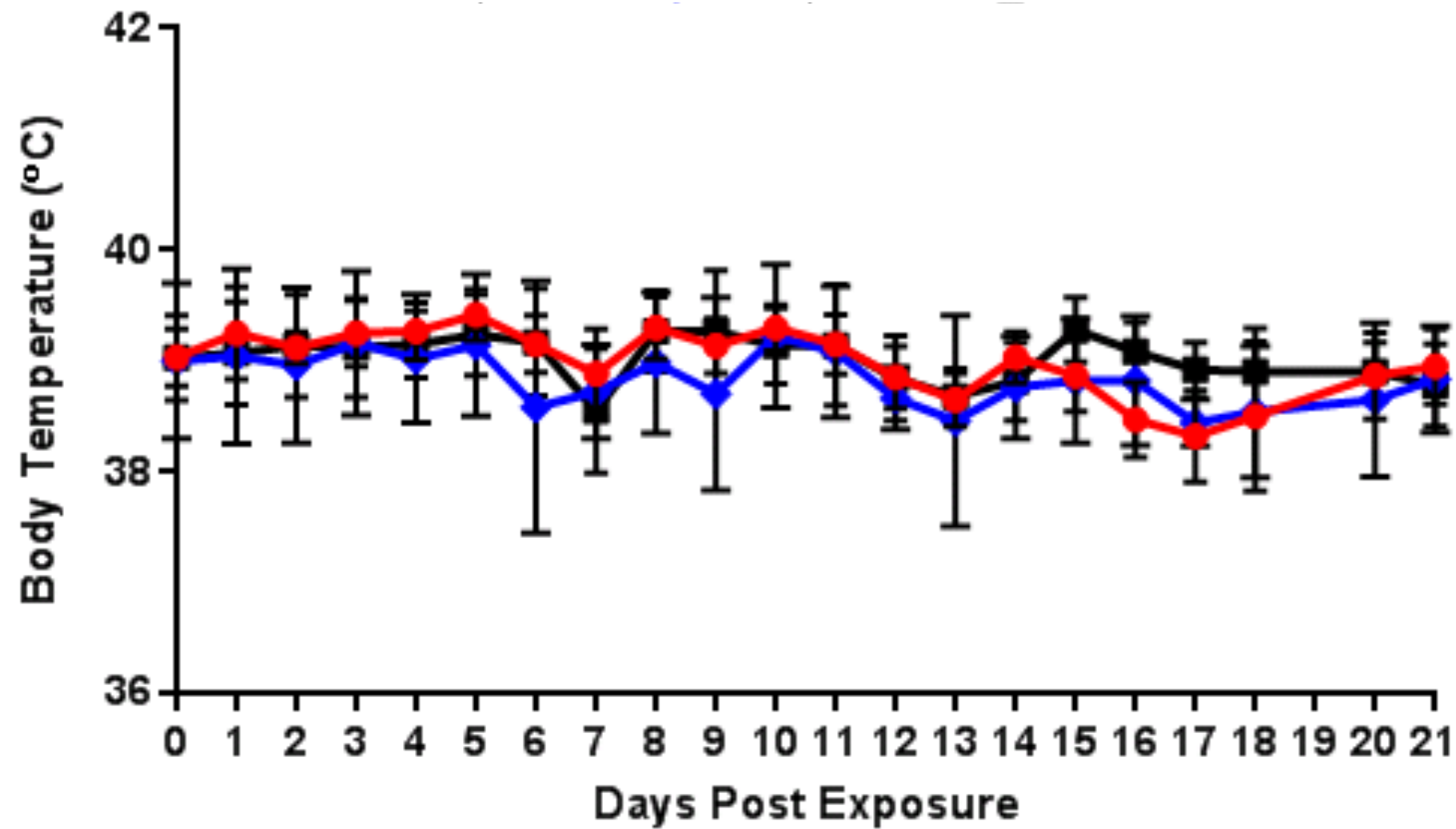
Zika Rhesus Study Design

- Challenge virus 2015 Puerto Rico, strain PRVABC-59
- N=18

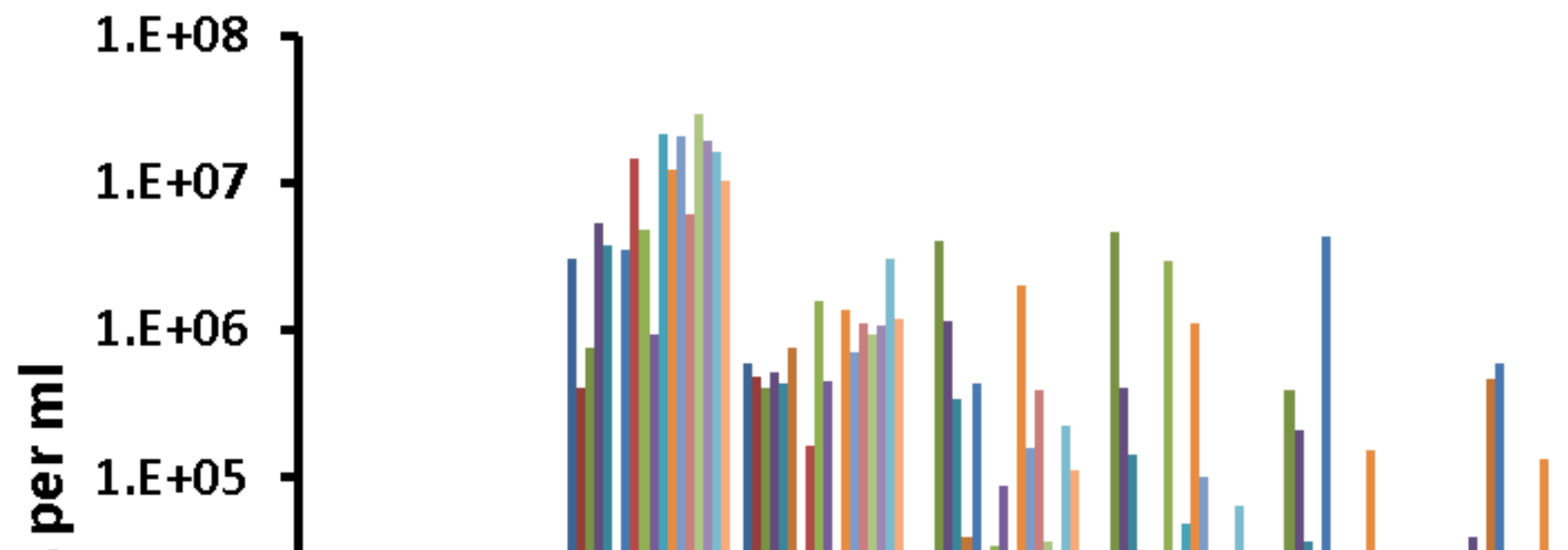


Day	-7	-3	-2	-1	0	1	2	3	4	5	6	7	8	9	10	11	14	17	21
Zika Challenge					X														
RT-q-PCR for Zika							X	X	X	X	X	X	X	X	X	X			
Health condition observation	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight	X				X							X					X		X
Temperature	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood collection	X				X							X					X		X
Urine collection	X				X							X					X		X
Hematology	X				X							X					X		X
Clinical chemistry	X				X							X					X		X

Zika Rhesus Clinical Signs



Zika Rhesus Viremia



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Research Paper

Characterization of a 2016 Clinical Isolate of Zika Virus in Non-human Primates



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May 11

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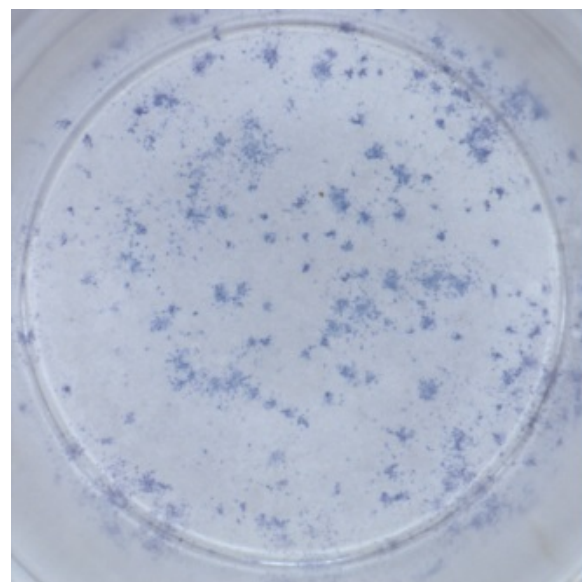
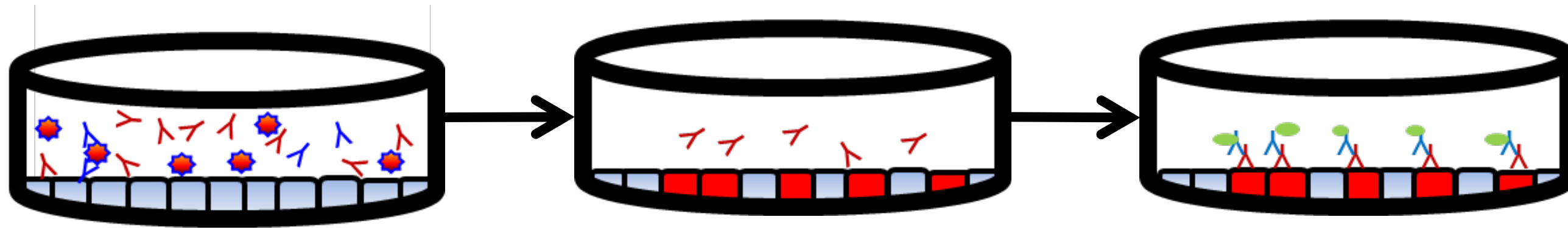
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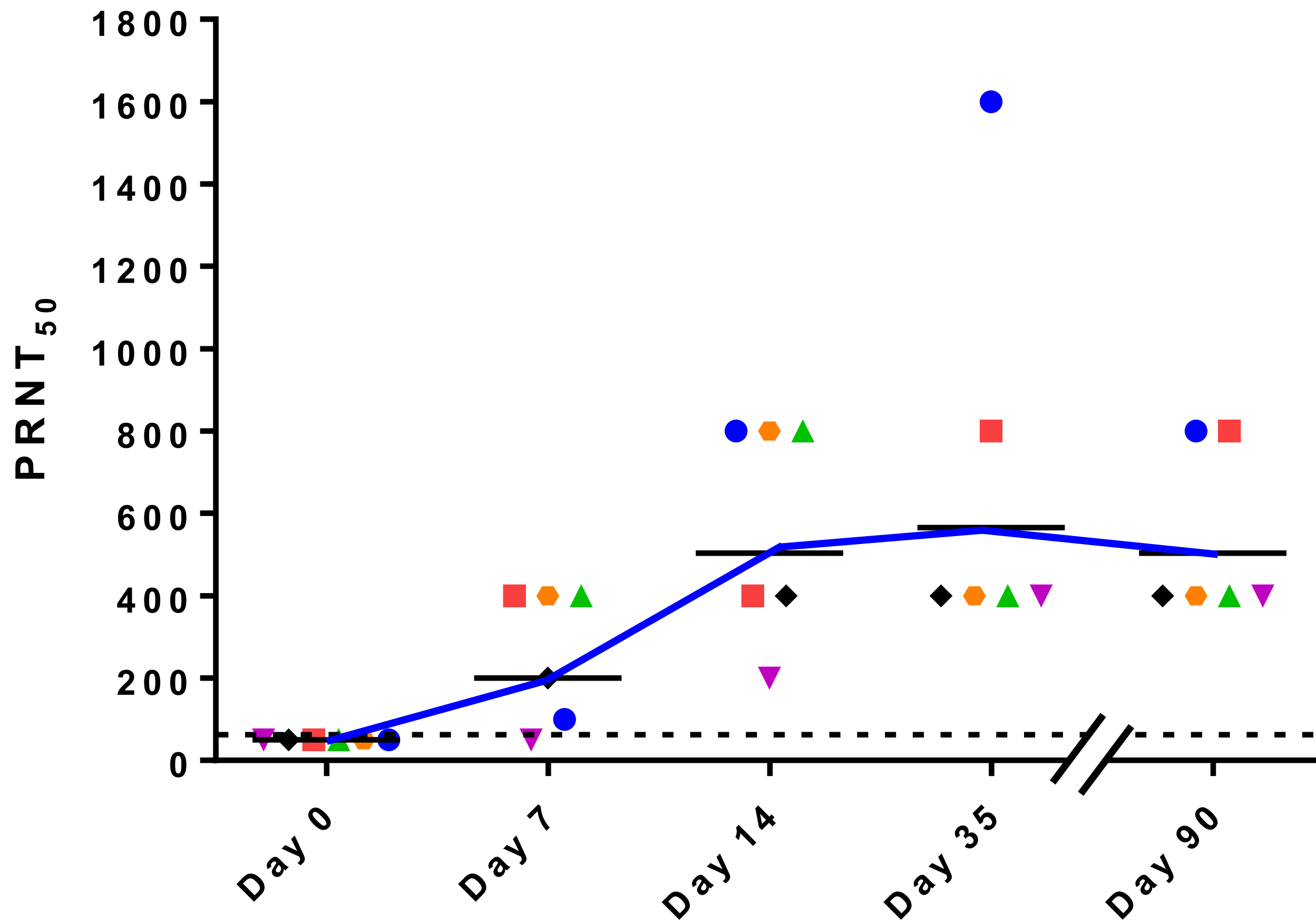
Zika Microneutralization Plaque Assay



a1	a2	a3	a4	a5	a6	a7	a8	a9	a10	a11	a12
79	62	81	84	72	85	48	69	94	92	86	94
b1	b2	b3	b4	b5	b6	b7	b8	b9	b10	b11	b12
47	45	75	74	48	47	70	58	111	62	96	91
c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12
32	12	18	33	37	27	44	51	47	50	59	68
d1	d2	d3	d4	d5	d6	d7	d8	d9	d10	d11	d12
11	17	15	29	38	29	37	71	67	30	59	46
e1	e2	e3	e4	e5	e6	e7	e8	e9	e10	e11	e12
7	11	13	5	8	15	18	58	13	28	15	12
f1	f2	f3	f4	f5	f6	f7	f8	f9	f10	f11	f12
5	7	8	3	7	5	12	20	6	7	8	7
g1	g2	g3	g4	g5	g6	g7	g8	g9	g10	g11	g12
7	3	4	5	3	7	7	4	4	4	2	21
h1	h2	h3	h4	h5	h6	h7	h8	h9	h10	h11	h12
3	6	0	6	1	2	6	7	3	6	3	22

For Help, press F1 Done.

Zika Microneutralization Plaque Titers



Summary and Conclusions

- IFN- $\alpha/\beta/\gamma$ KO mice
 - provide a small animal model for evaluating Zika virus pathogenicity
 - provide an initial platform for the in vivo screening of antivirals and vaccines for Zika virus.
- Rhesus macaques can be infected by the contemporary ZIKV strain.
- The Zika Rhesus model partly recapitulates some clinical features and viral kinetics in ZIKV-infected patients.
- Adaptive immune response offers protection from future reinfection.

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