Animal models for Zika

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Key applications

- Longitudinal sampling
- Kinetics of virus replication and antiviral immunity
- Invasive tissue sampling
- Preclinical evaluation of interventions
- Rapid results

Ongoing research

- Evaluating antivirals (BioCryst, UTMB)
- Vaccine immunogenicity (Inovio Pharmaceuticals Inc, UTMB)
- Natural history in pregnant and non-pregnant NHP (CNPRC, ONPRC, TNPRC, WNPRC, YNPRC)
- Correlates of protective immunity in NHP (WNPRC)
- Pathogenesis of different virus isolates (CNPRC, WNPRC)

UTMB murine model

Shannan Rossi
Robert Tesh
Sasha Azar
Antonio Muruato
A. Jonathan Auguste
Rose Langsjoen
Slobodan Paessler
Nikos Vasilakis
Scott Weaver

Kathryn Hanley

scientists in blue are at this meeting

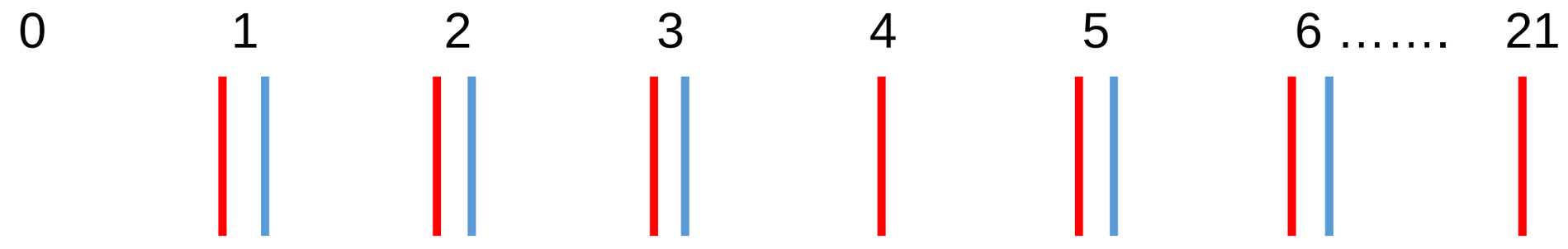
Characterization of a Novel Murine Model to Study Zika Virus

Shannan L. Rossi,* Robert B. Tesh, Sasha R. Azar, Antonio E. Muruato, Kathryn A. Hanley, Albert J. Auguste, Rose M. Langsjoen, Slobodan Paessler, Nikos Vasilakis, and Scott C. Weaver

Institute for Human Infections and Immunity, University of Texas Medical Branch, Galveston, Texas; Department of Pathology, University of Texas Medical Branch, Galveston, Texas; Institute for Translational Science, University of Texas Medical Branch, Galveston, Texas; Department of Microbiology and Immunology, University of Texas Medical Branch, Galveston, Texas; Sealy Center for Vaccine Development, University of Texas Medical Branch, Galveston, Texas; Department of Biology, New Mexico State University, Las Cruces, New Mexico

published today in Am. J. Trop. Med. Hyg.

ZIKV infection of immunocompromised mice



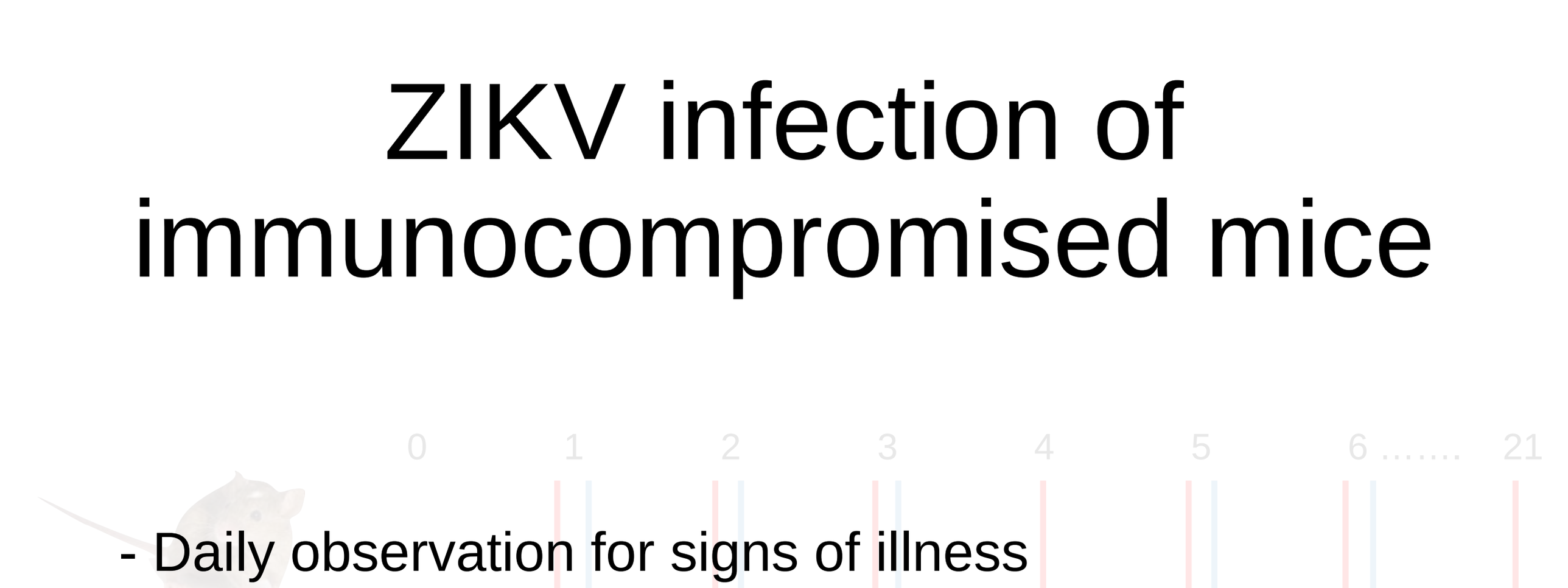
3-, 5-, 11-week old A129
$1x10^5$ pfu/mouse
ZIKV FSS13025 isolate
(Cambodia 2010)
Intraperitoneal injection

days post infection

bleed

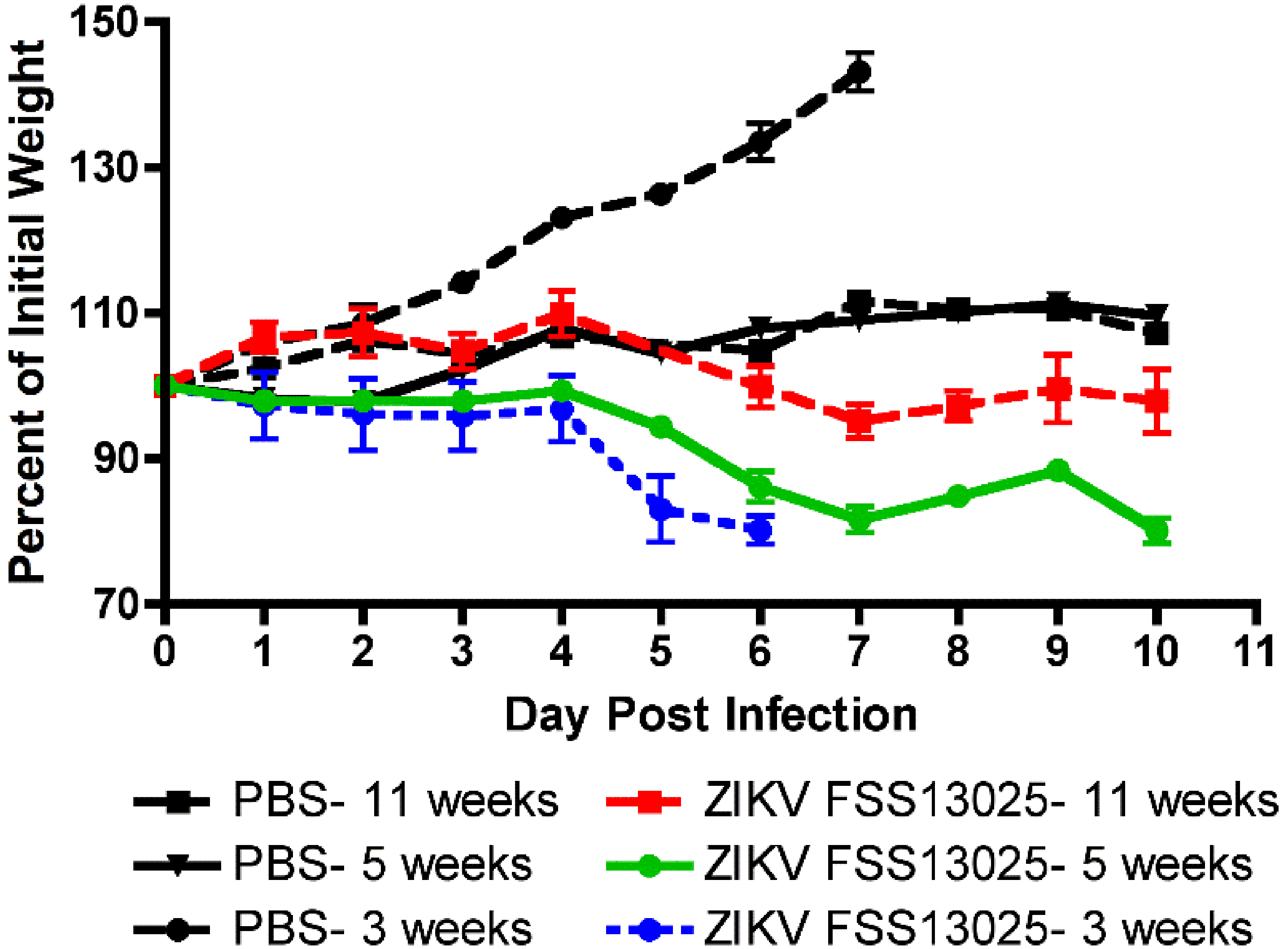
PBS perfusion and/or necropsy

ZIKV infection of immunocompromised mice



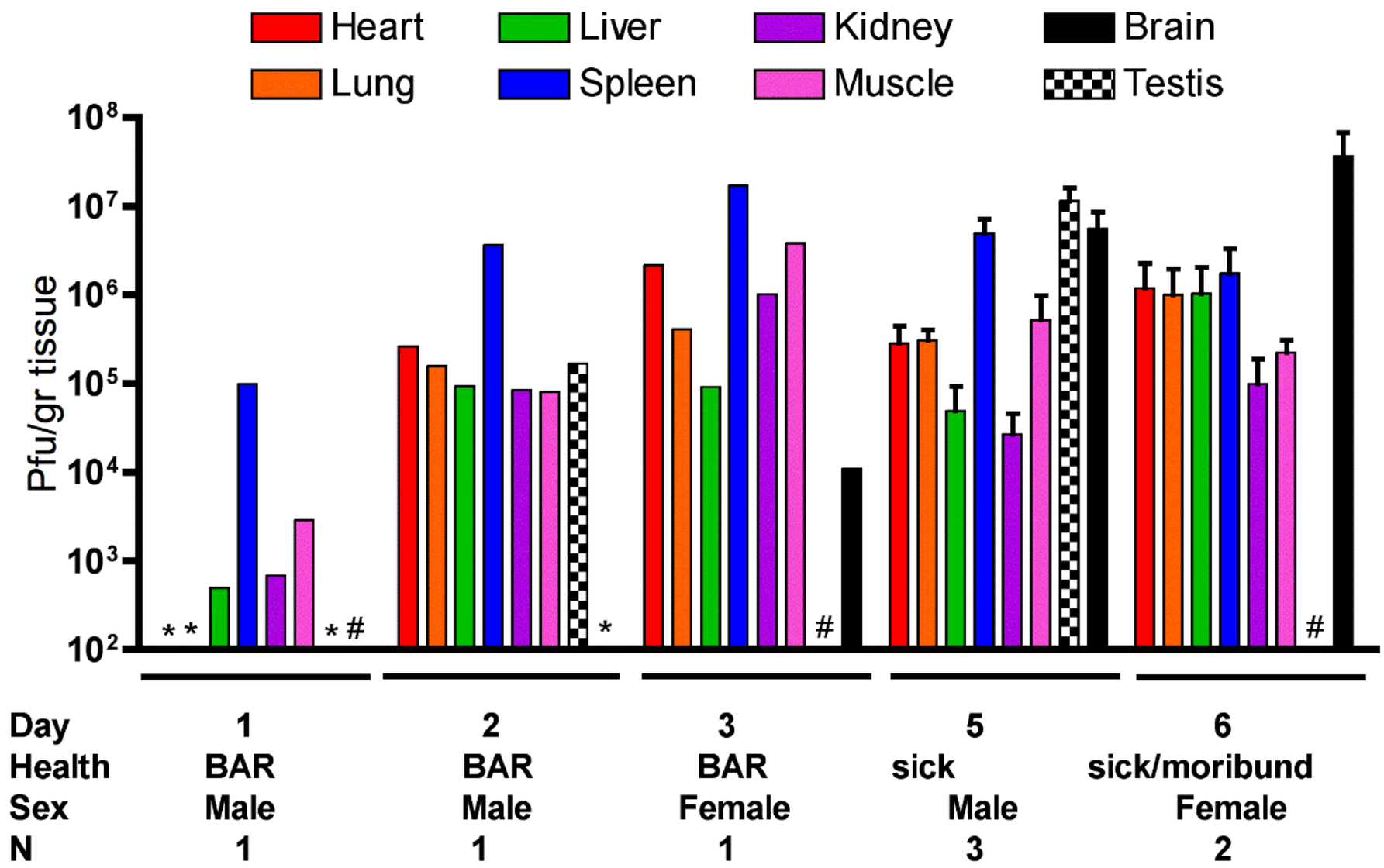
- Daily observation for signs of illness
- Weight taken
- RO bleeds for viremia and/or seroconversion (pending)
- Necropsies for predetermined and moribund mice

Disease in A129 mice is age-dependent



more weight loss in younger mice
higher mortality in younger mice

ZIKV titers in tissues of 3-week A129 mice



(BAR = bright, alert, responsive to stimuli)

ZIKV titers in tissues of 3-week A129 mice

- High titers observed in spleen, testes and brain

- Mild splenomegaly observed on day 3

- Neurologic disease (tremors, loss of balance, partial hind limb paralysis) observed moribund mice

- Neurologic disease more severe in 3-week-old AG129 (“toe-walking” and loss of motor coordination) but otherwise similar disease and virulence

CNPRC NHP model

Graham Simmons
Mike Busch
Marion Lanteri
Eliza Bliss-Moreau
Lark Coffey
Koen Van Rompay

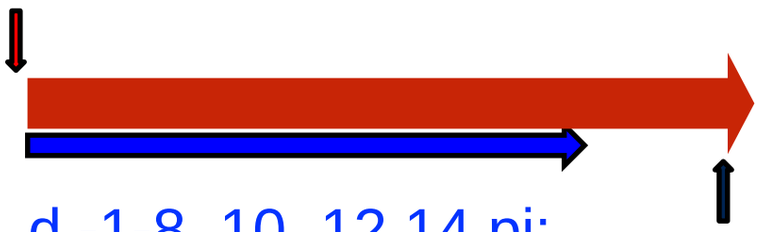
scientists in blue are at this meeting

NHP model using Brazilian plasma virus

STUDY 1
(in progress)

Non-pregnant rhesus macaques
n=2

Zika virus (2015 Brazilian plasma, P1) intravenous inoculation
10^5 PFU



d -1-8, 10, 12,14 pi: sample blood, urine, saliva

14 d euthanasia, detailed virologic and tissue analysis

STUDY 2
(planned)

Pregnant rhesus macaques
n=4

Zika virus (2015 Brazilian plasma, P1) intravenous and intra-amniotic inoculation at 4 different gestational days (1 per animal)

NHP model using Brazilian plasma virus

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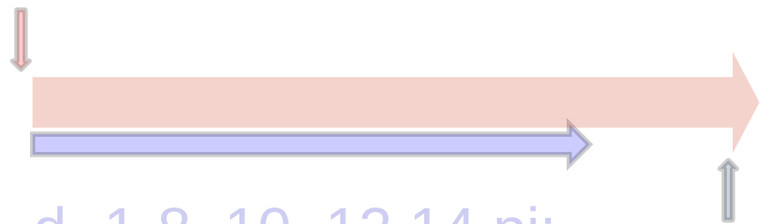

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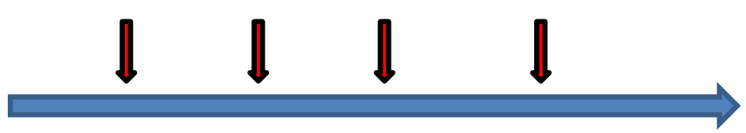
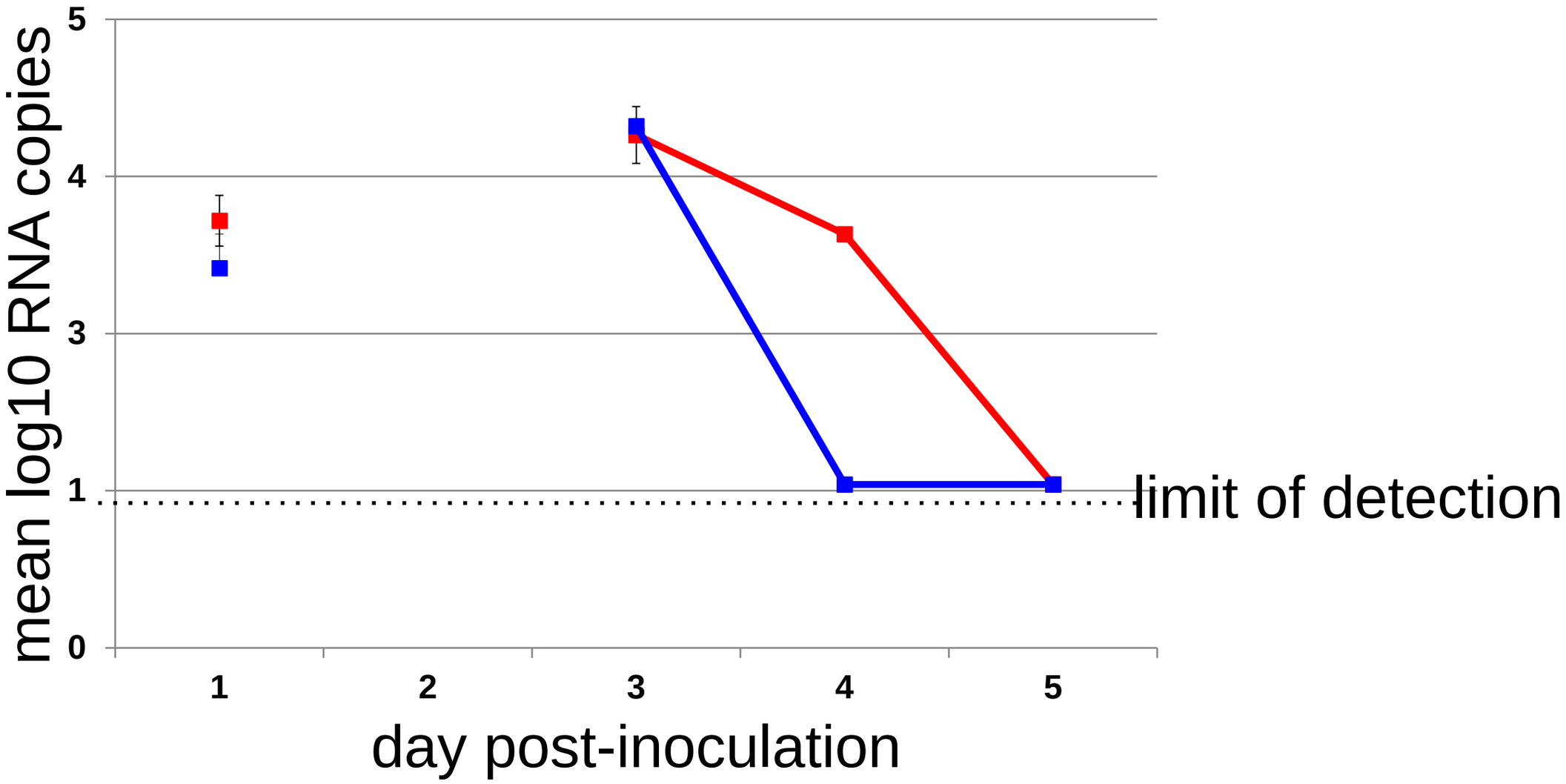


Detection of plasma viral RNA



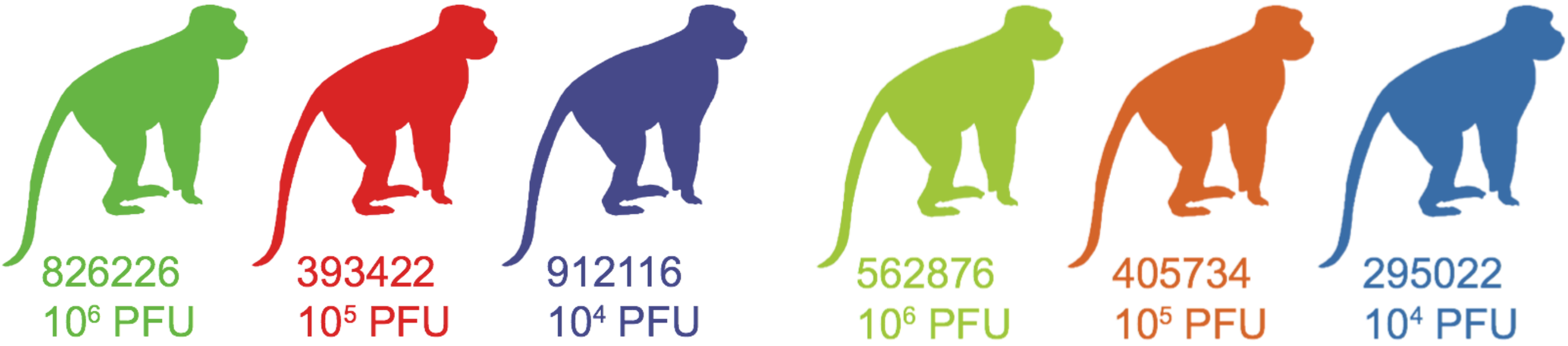
successful infection with peak viremia ~3 days

Zika experimental science team (ZEST)

- Dawn Dudley, Emma Mohr, Christina Newman, Mariel Mohns, Meghan Breitbach, Mustafa Rasheed, Kristi Hall, Adam Ericsen, Adam Bailey
- **Tom Friedrich**, Andrea Weiler, Gabrielle Lehrer-Brey, Louise Moncla
- **Ted Golos**, Greg Wiepz, Igor Iruretagoyena
- **Jorge Osorio**, Matt Aliota
- **Shelby O'Connor**, Dane Gellerup
- **Eva Rakasz**, Kim Weisgrau
- **Sallie Permar**, Tony Moody, Josh Eudailey (@ Duke University)
- **WNPRC:** Buddy Capuano, Nancy Schultz-Darken, Heather Simmons, Jen Post, Sandra Boehm
- **Brazil:** Esper Kallas, Renato Aguiar, Amilcar Tanuri, Carlos Moreira
- **Funding**: NIH supplement 3R01AI116382-01A1S1 and WNPRC P51 pilot funds

scientists in blue are at this meeting

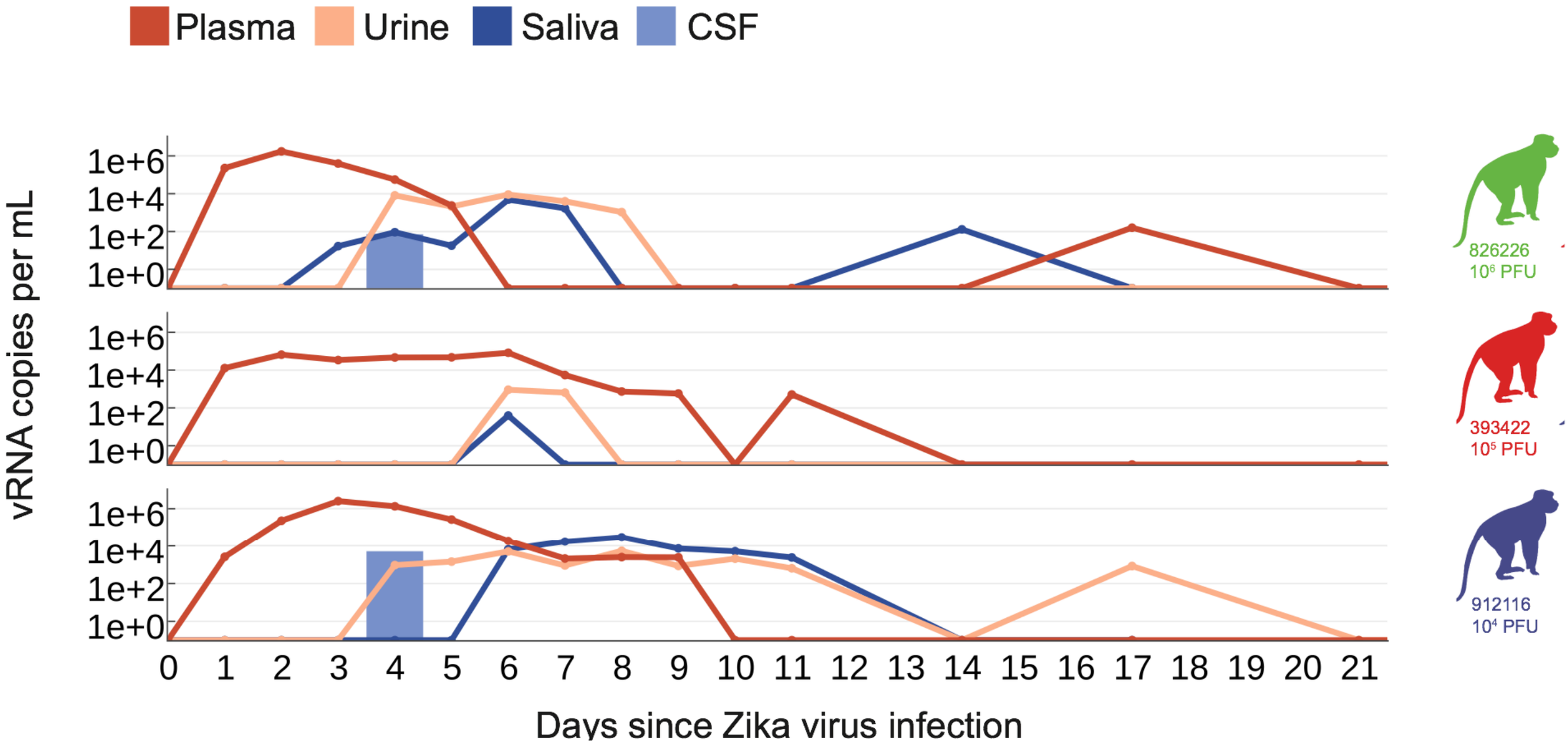
Asian and African Zika virus infects rhesus macaques



Zika virus/H.sapiens-tc/FRA/2013/
FrenchPolynesia-01_v1c1

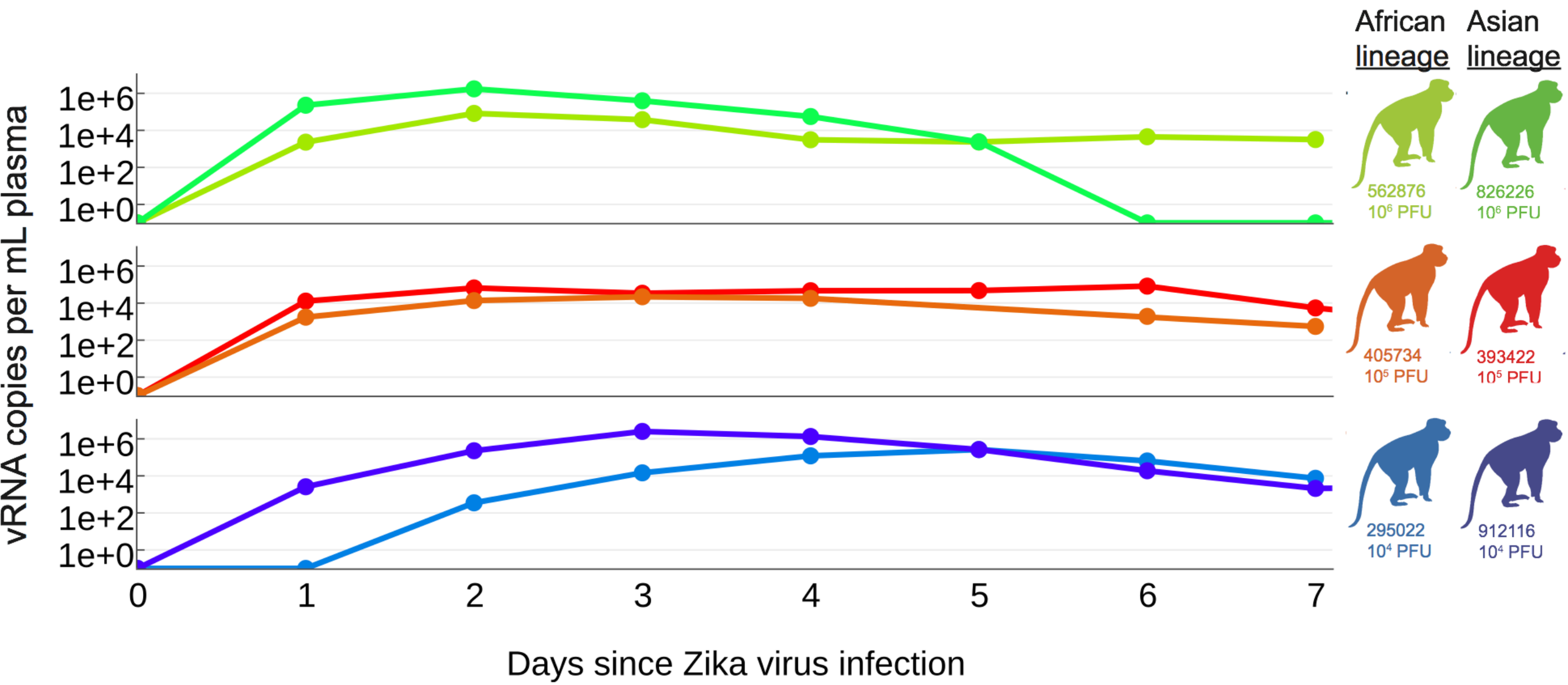
Zika virus/R.macaque-tc/UGA/1947/
MR766-3329

Asian ZIKV detected in multiple fluids



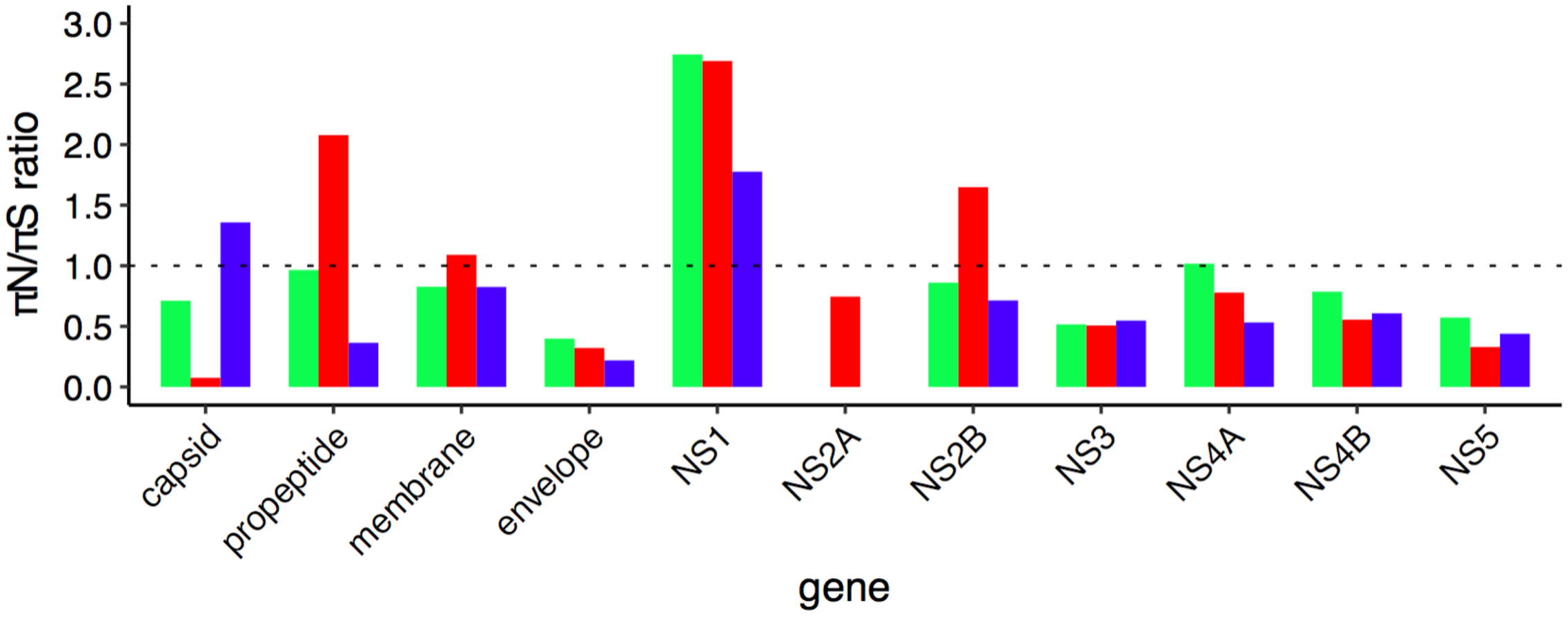
ZIKV detected in CSF in two macaques four days post infection

Asian ZIKV establishes higher peak viremia



Peak viremia at least 10-fold higher in Asian ZIKV

ZIKV variation at day 4 by peptide



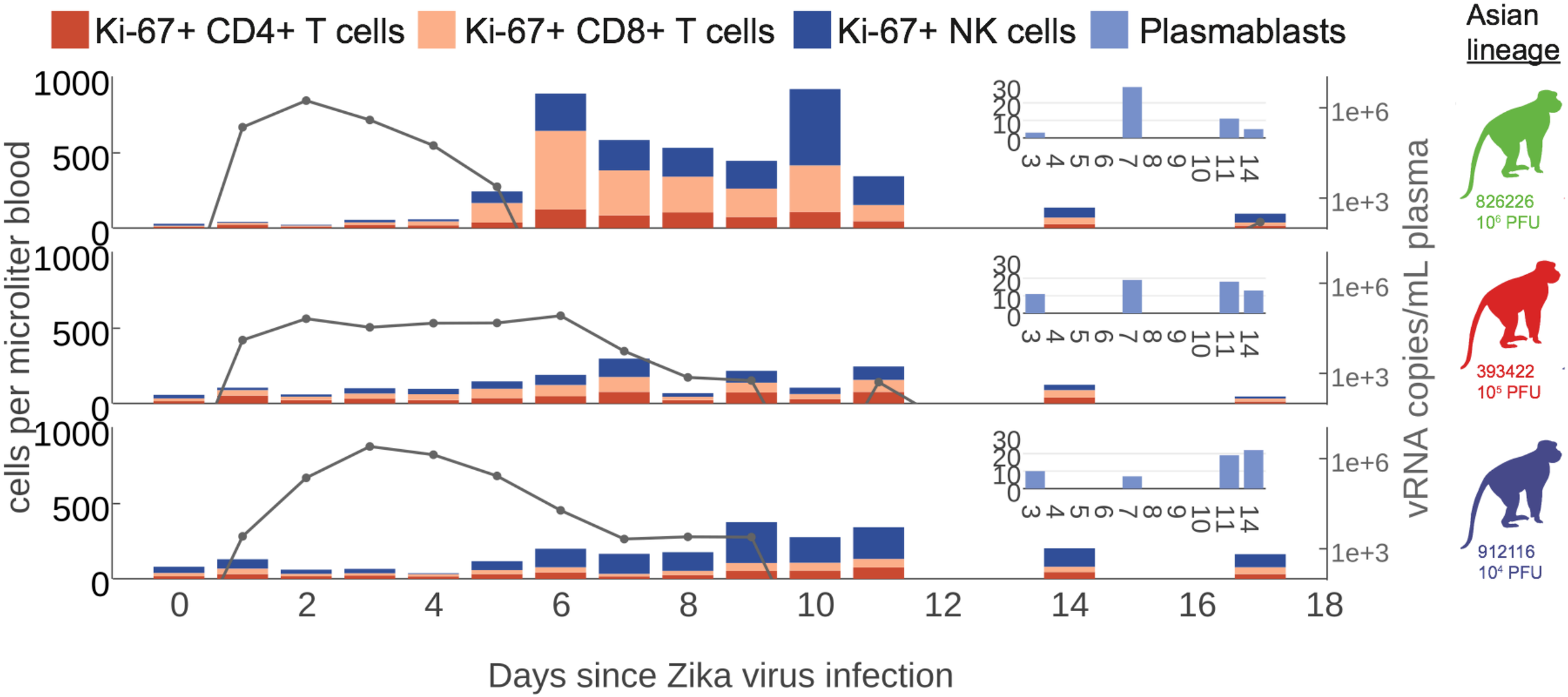
826226
10^6 PFU

393422
10^5 PFU

912116
10^4 PFU

Possible evidence for positive selection in NS1

Robust pathogen sensing by adaptive immune responses



will rechallenge with Asian ZIKV April 25 to assess protective immunity

Infection of pregnant macaque with Asian ZIKV

Zika virus/H.sapiens-tc/FRA/2013/
FrenchPolynesia-01_v1c1
mid-first trimester (~35d)

study pathology in mother and fetus

Development of fetus in ZIKV-infected mother

normal ultrasound as of March 18

For more information:

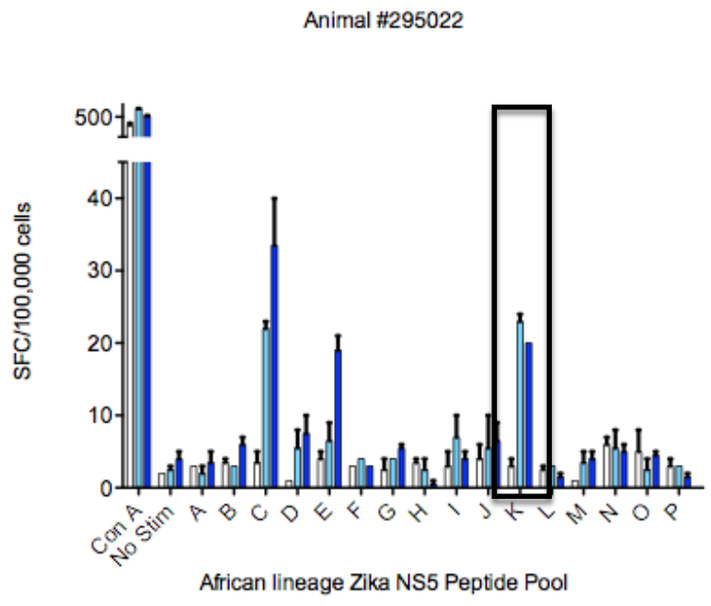
- Murine model: Characterization of a novel murine model to study Zika virus, Rossi et al., Am. J. Trop. Med. Hyg. (2016)

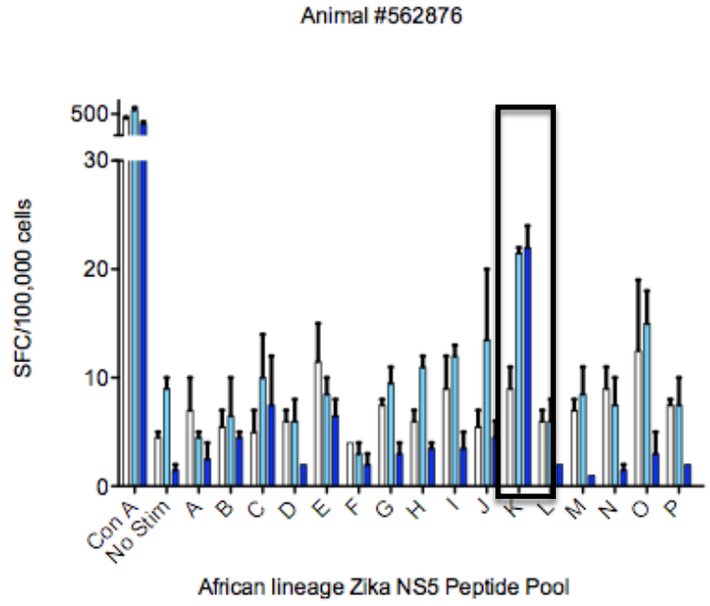
- CNPRC NHP studies: http://www.cnprc.ucdavis.edu/our-science/zika/zika-blog/

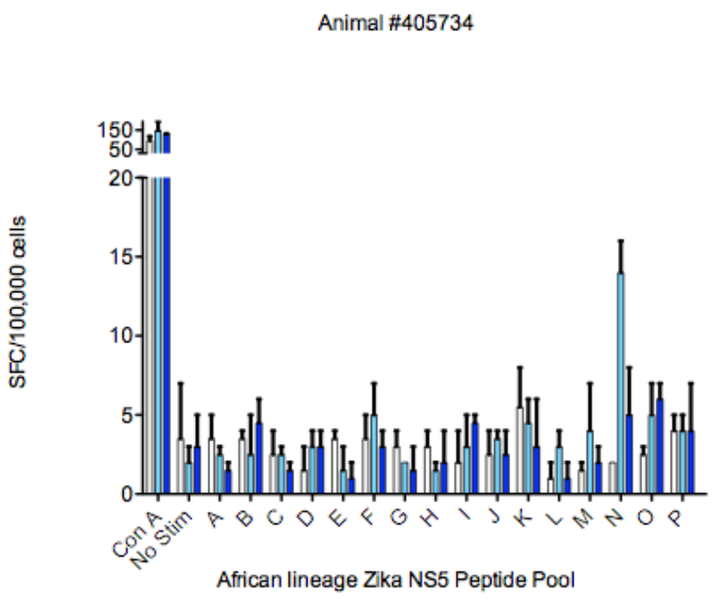
- ZEST studies: http://goo.gl/rmNCqf

- http://zika.labkey.com

ZIKV-specific cellular immunity to NS5







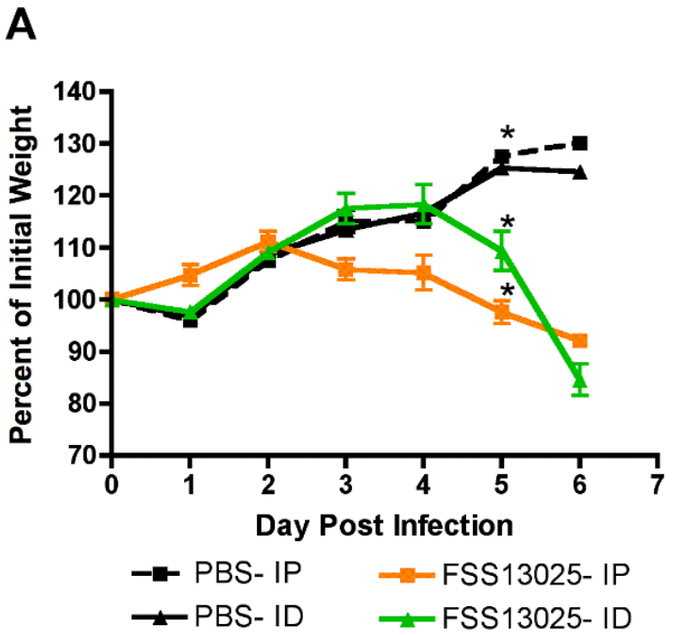
A006, A008, B045a, B-unk

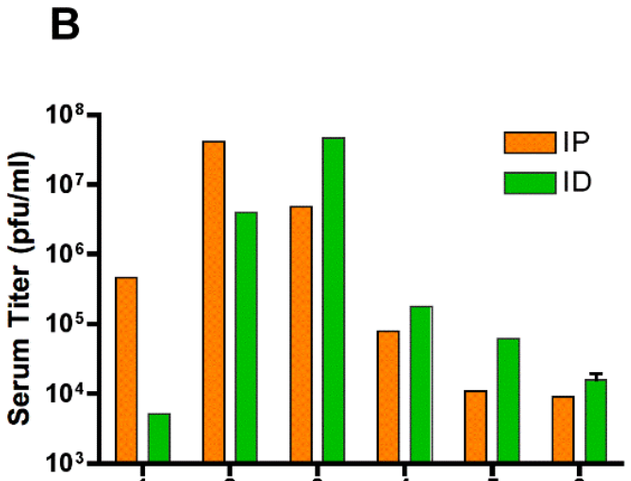
A006, A012, B012b, B048

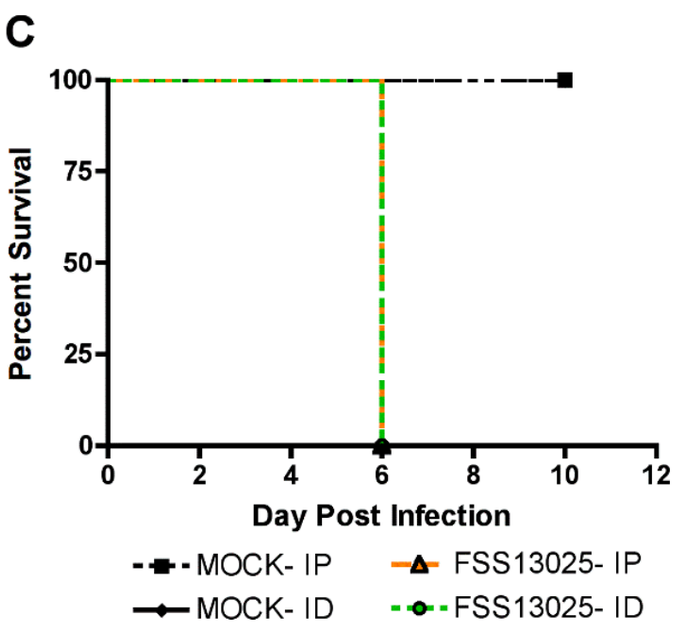
A002a, A004, B012b, B017a

T cell responses by 10d; possible class I restricted recognition

A129 and AG129 mice have similar kinetics







A129 and AG129 mice exhibit similar kinetics in terms of mean time to death and peak viremia titers

Mice infected by ID route show slightly delayed infection compared to IP route

All infected mice succumb to illness

AG129 mice do not show age-dependent phenotype