

**Development of a Bivalent Lyophilized VesiculoVax™
Vectored Vaccine for the Prophylaxis of Chikungunya
(CHIKV) and Zika (ZIKV) Virus Infection**

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VesiculoVax™ Vectored Vaccines

SS/NS/NS RNA Viruses

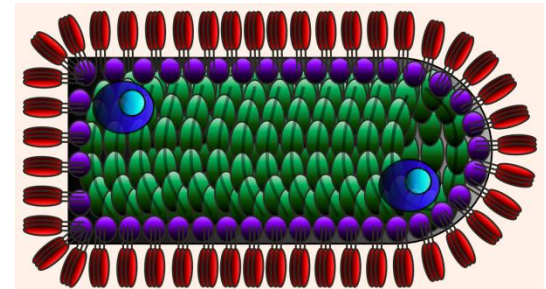
- Small genomes, but capacity for inserting multiple foreign genes
- Not considered to be human pathogens

Immunogenicity

- Replication competent vectors
- Target antigen-presenting cells
- Attenuating mutations **increase** immunogenicity

Vector Immunity

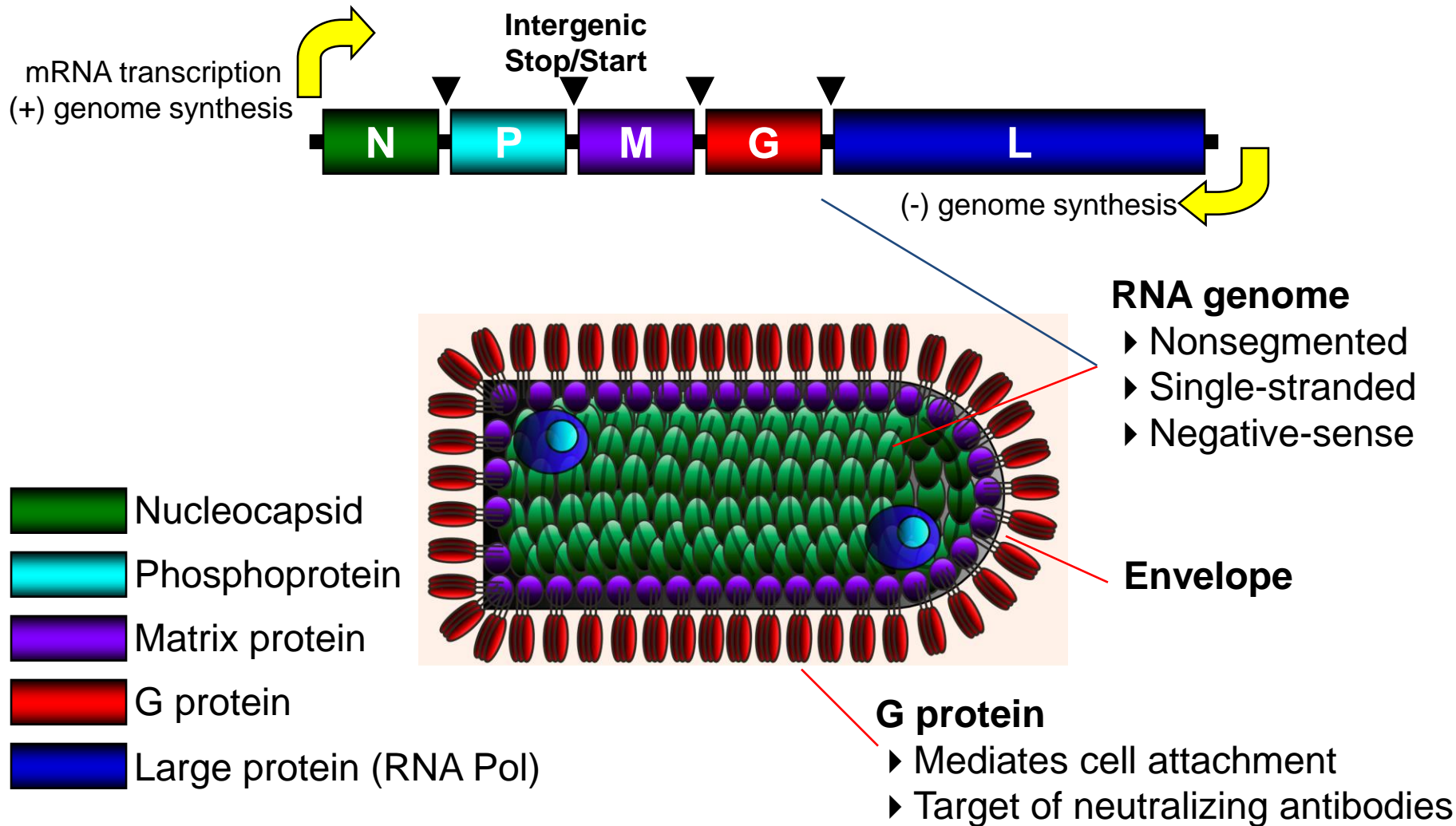
- Little pre-existing immunity in the human population



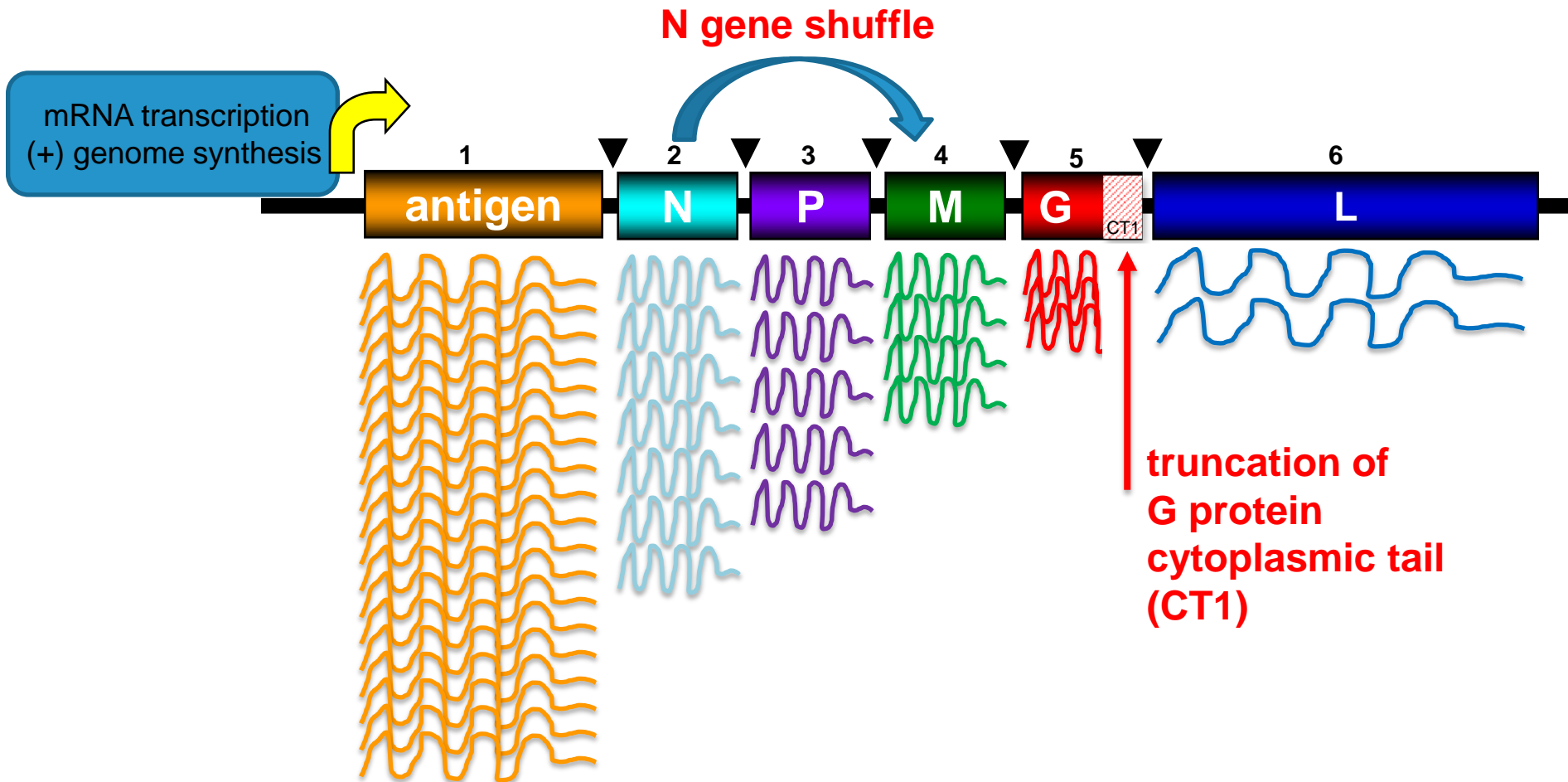
Clinical Testing (Phase 1)

- Attenuated (N4CT1) rVSV-HIV and rVSV-Ebola vaccine candidate were safe, well tolerated and immunogenic.

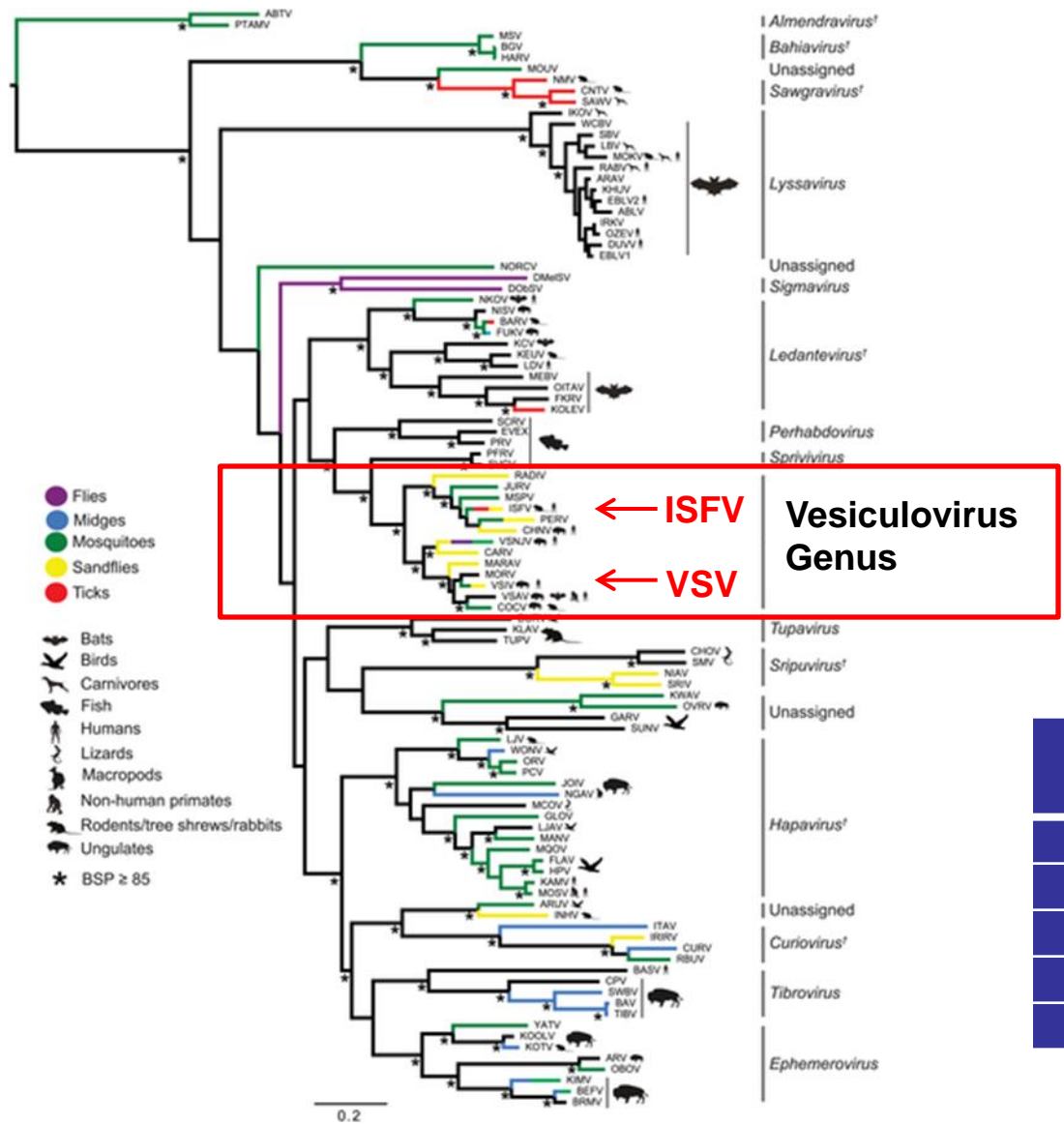
VesiculoVax™: A Family of Virus Vaccine Vectors



Using the Vesiculovirus mRNA Transcriptional Gradient to Attenuate the Vector and Overexpress a Gene of Interest



Rhabdovirus phylogenetic tree (Walker et al., 2015)



VSV_{IN} – ISFV Comparison

Gene	VSV _{IN} /ISFV % AA Conservation
N	52
P	20
M	32
G	16
L	58



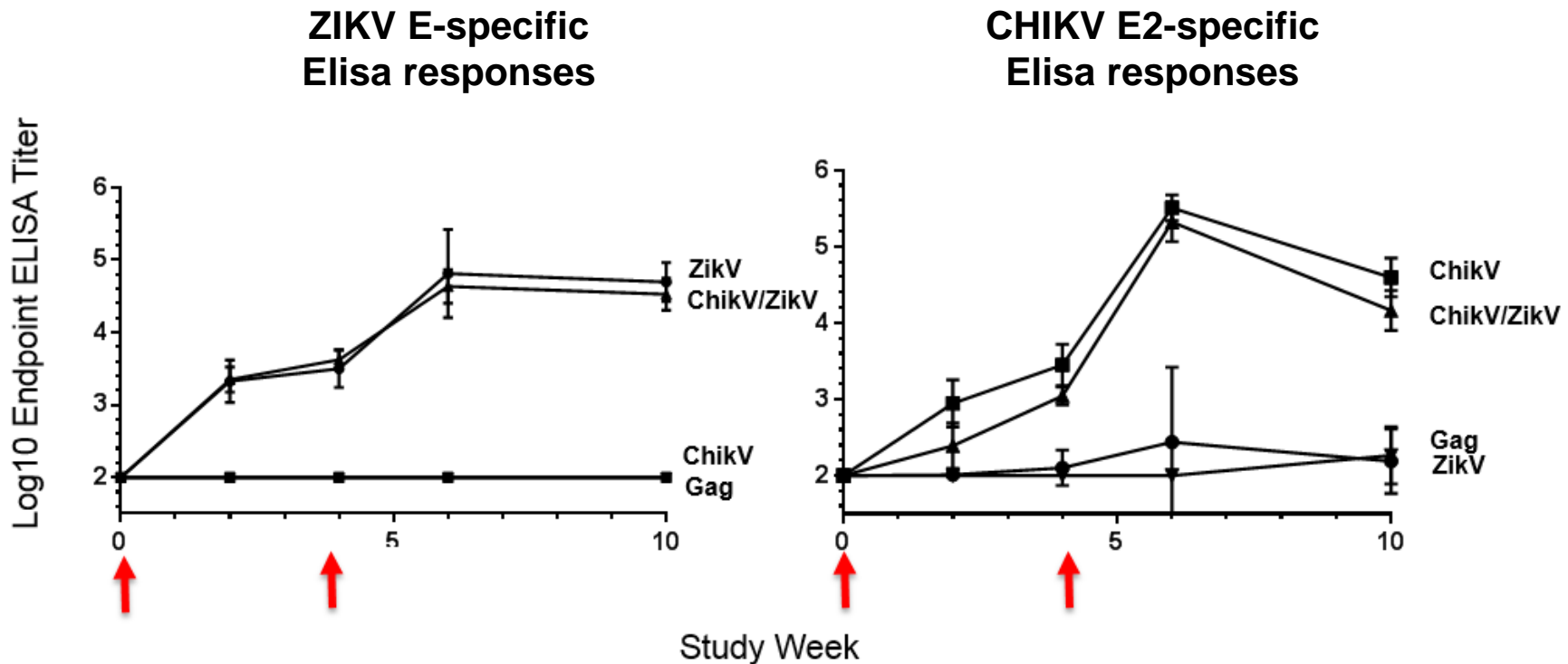
The rISFV-CHIKV and rISFV-ZIKV Vaccines Candidates

- The rISFV-ZIKV vaccine candidate encodes **ZIKV prM-E**.
- The rISFV-CHIKV vaccine candidate encodes **CHIKV E3-E2-6K-E1**.

rISFV-vectored CHIKV and ZIKV Vaccine Candidates Demonstrate a Lack of Neurovirulence After Intracranial Inoculation of Swiss Webster Mice

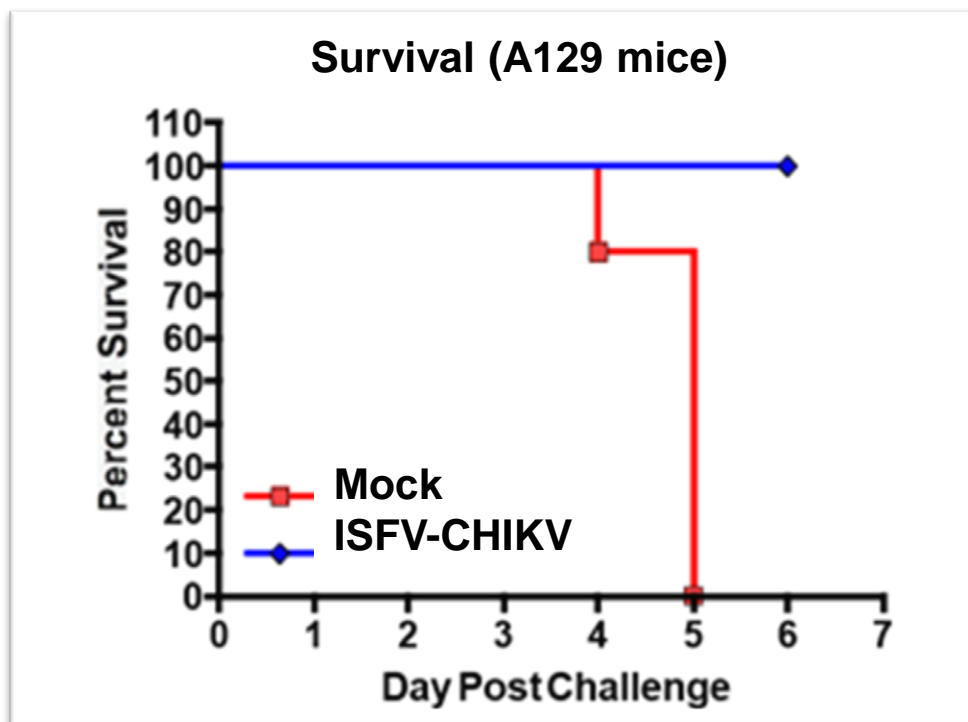
Inoculum	Test Article Dose (log PFU)	Survival	
		24h	14 days
rISFV/WT	3	100%	0%
	2	100%	20%
	1	100%	10%
rISFV/ZIKV	7	100%	100%
	6	100%	100%
	5	100%	100%
rISFV/CHIKV	7	100%	100%
	6	100%	100%
	5	100%	100%
rVSV _{IN} (HIVGag)5	2	100%	0%
PBS	---	100%	100%

Immunogenicity of Attenuated rISFV-vectored CHIKV and ZIKV Vaccine Candidates in Balb/c Mice



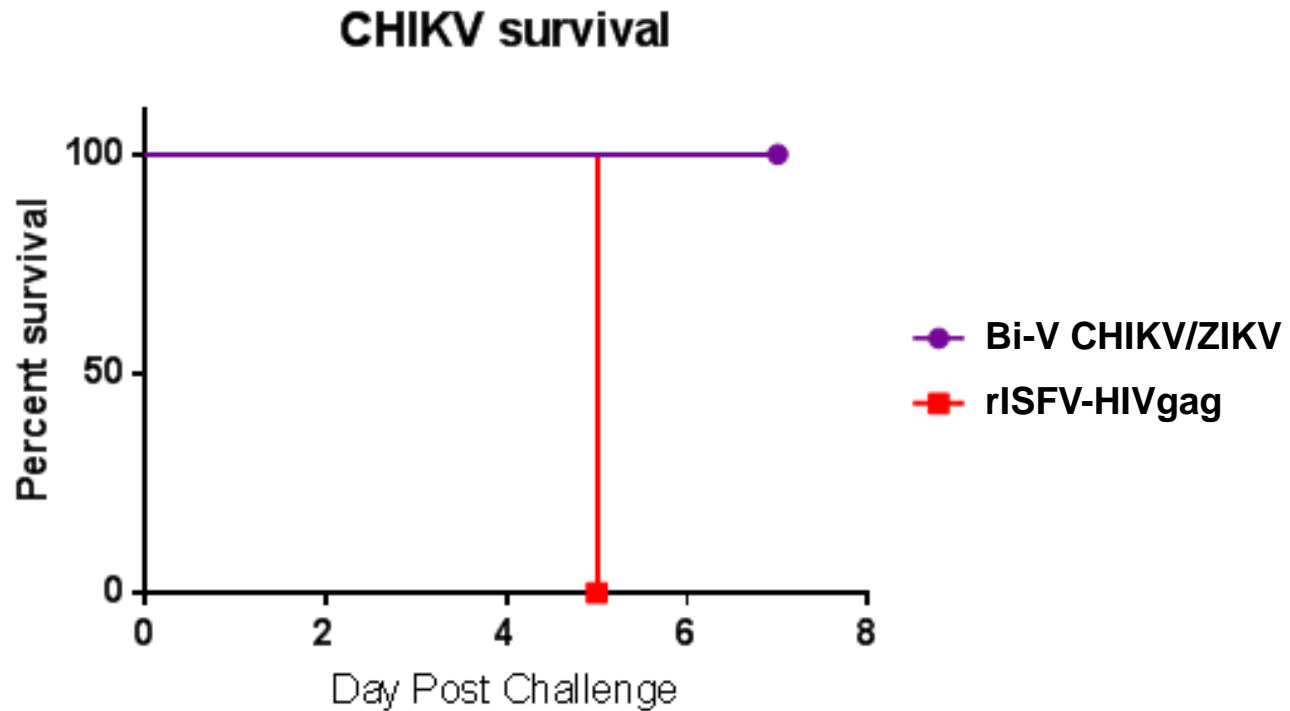
- IM vaccination for Balb/c mice (n=5/group):
- 1×10^7 PFU of each of the monovalent CHIKV or ZIKV vaccine candidates
 - 2×10^7 PFU of the bivalent CHIKV/ZIKV vaccine.

Monovalent Attenuated rISFV-CHIKV Vaccine Provides **Single Dose Protection Against CHIKV-Induced Morbidity in Normal C57Bl/6 and Mortality Immune Compromised A129 Mice, respectively.**



Challenge of A129 mice by footpad injection with 1×10^4 PFU of CHIKV (LaReunion strain) at day 28 post vaccination with 1×10^7 PFU of the rISFV-ChikV candidate.

Single dose Attenuated Bivalent CHIKV/ZIKV Vaccine Protects A129 IFN α R^{-/-} Mice Against Lethal CHIKV Challenge



Single-Dose Attenuated Bivalent CHIKV/ZIKV Vaccine
 Completely Protects A129 IFN α R^{-/-} Mice from **CHIKV**
 Viremia on Day 2 Post Challenge

Mouse ID	Vaccine	CHIKV Titer in Blood (PFU/mL)
1	Bivalent rISFV CHIKV/ZIKV	<LOD
		<LOD
2		
3		<LOD
4		<LOD
5	<LOD	
1	rISFV HIVgag	1.7x10 ⁶
2		1.7x10 ⁶
3		2.1x10 ⁶
4		4.0x10 ⁶
5		2.0x10 ⁶

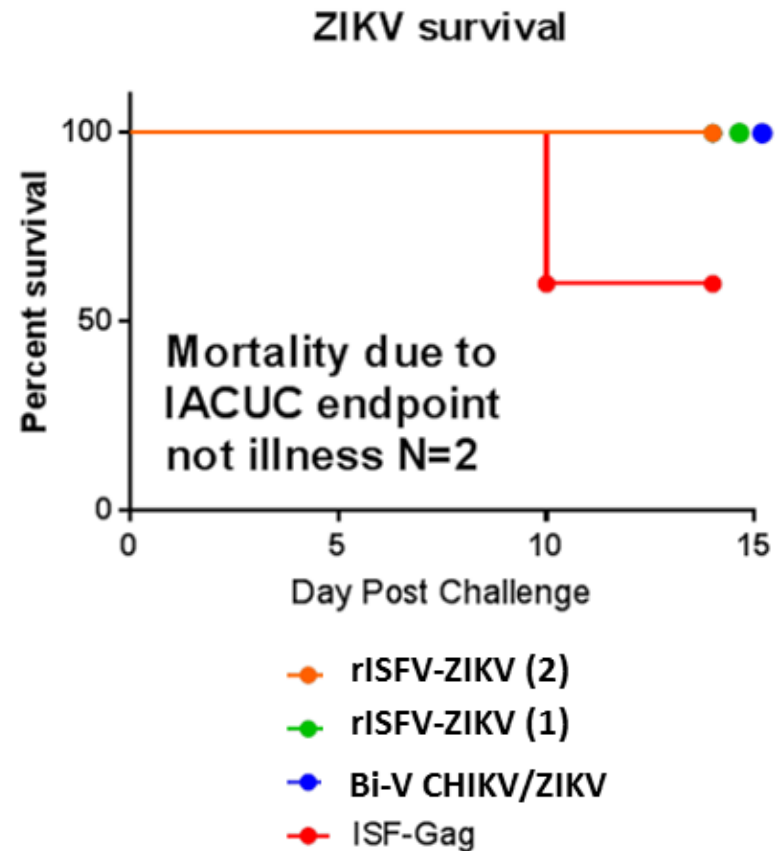
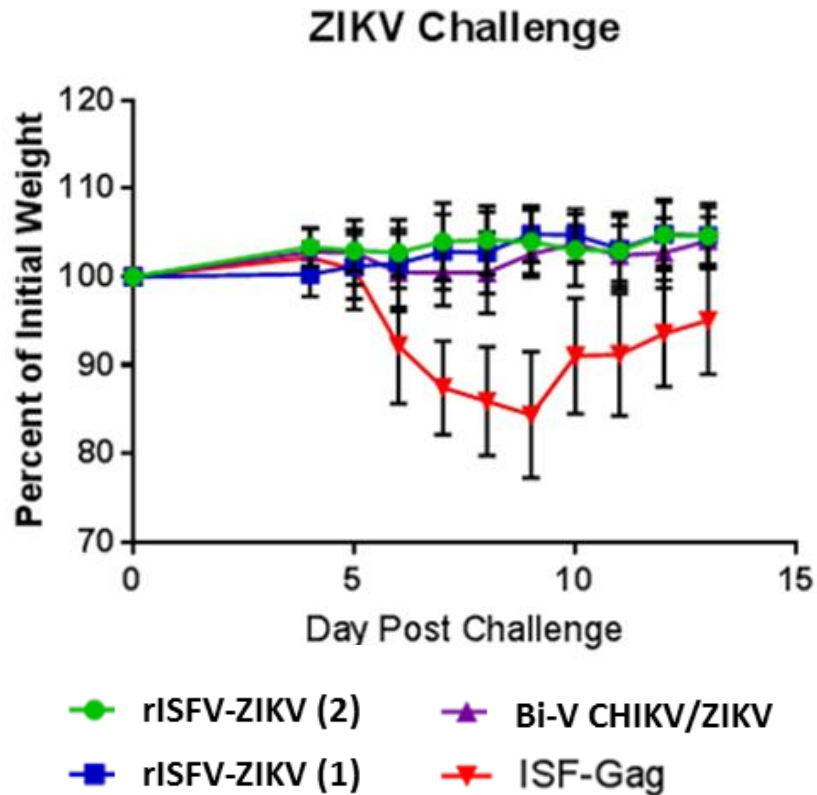
Efficacy of a **Single Dose** Attenuated Vaccine Against CHIKV/ZIKV Challenge in A129 IFN α R^{-/-} mice

Group #	# mice	Vaccine	Vaccine dose
1	5	rISF-ZIKV (2)	10 ⁷ pfu
2	5	rISF-ZIKV (1)	10 ⁷ pfu
3	10	rISF-CHIKV + rISF-ZIKV (1)	10 ⁷ pfu + 10 ⁷ pfu
4	10	rISFV N4(GdeltaCT25) (HIV-1 Gag-SDE)1	10 ⁷ pfu

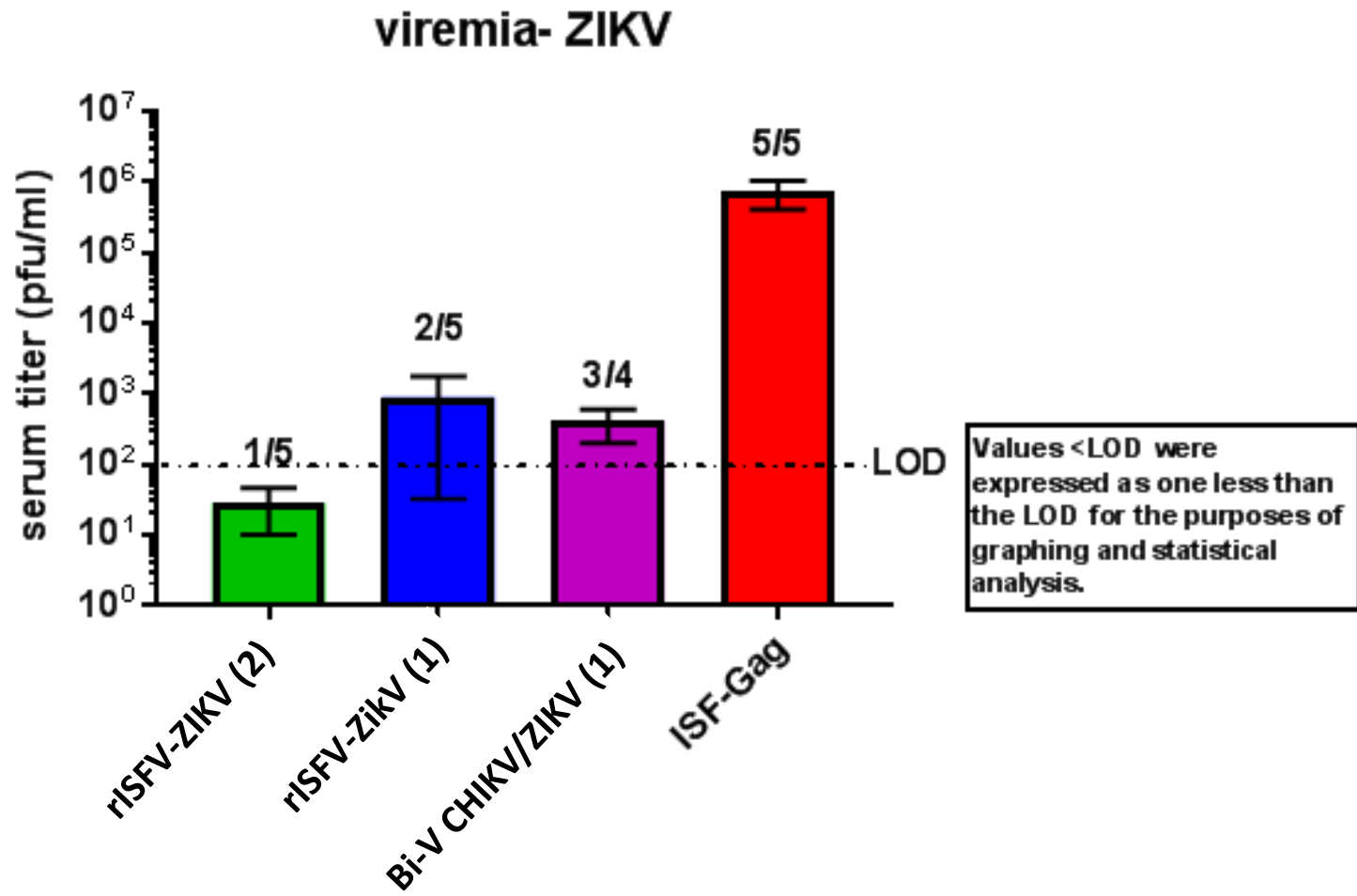
Challenge with:

- CHIKV: 1x10³ pfu in the footpad; LaReunion strain
- ZIKV: 1x10⁵ pfu IP; Cambodian strain (human isolate) FSS13025.

Single Dose Bivalent Attenuated CHIKV/ZIKV Vaccine Protects A129 IFN α R^{-/-} mice From Disease Following ZIKV challenge



Single Dose Monovalent ZIKV or Bivalent CHIKV/ZIKV vaccines significantly reduced ZIKV Viremia in A129 IFN α R^{-/-} mice day 2 post ZIKV challenge





Conclusions for the Bivalent Attenuated VesiculoVax™ CHIKV/ZIKV Vaccine:

Immunogenicity, Balb/c Mice:

- The CHIKV E2-specific and ZIKV E-specific IgG responses elicited by the bivalent CHIKV/ZIKV vaccine are equivalent to the responses elicited by monovalent vaccines.

Efficacy, A129 IFN α R^{-/-} Mice:

- Efficacy of the bivalent CHIKV/ZIKV vaccine against CHIKV or ZIKV challenge is equivalent to the efficacy demonstrated by monovalent vaccines.



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