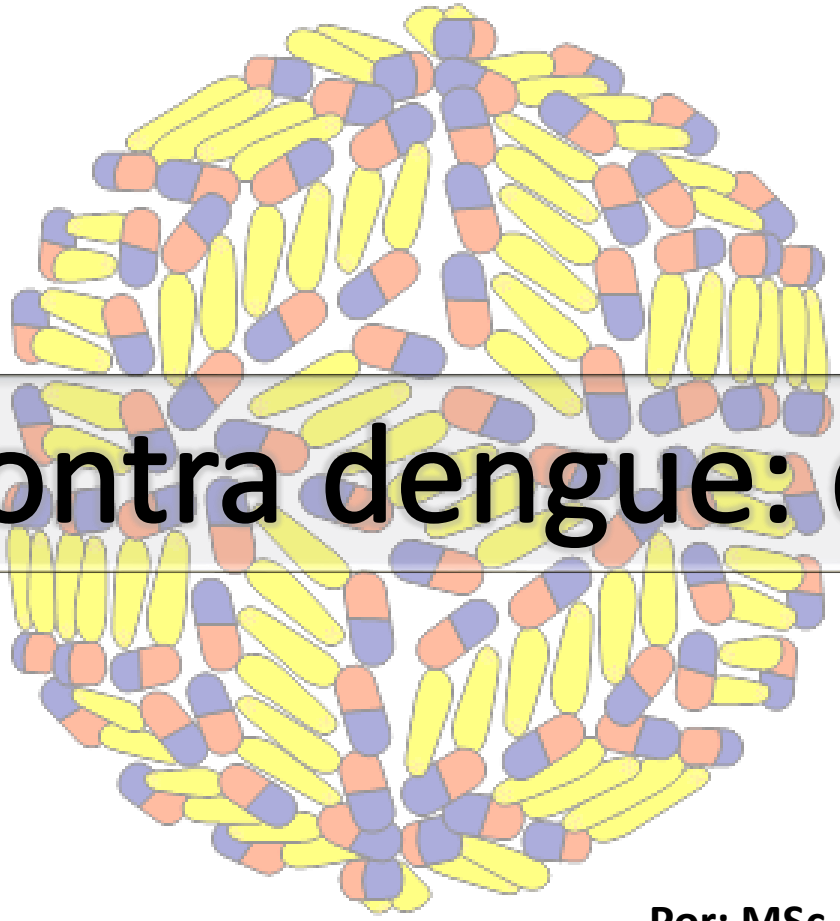


Vacina contra dengue: quando?

Por: MSc. Rúbens Prince Alves

Novembro/2015

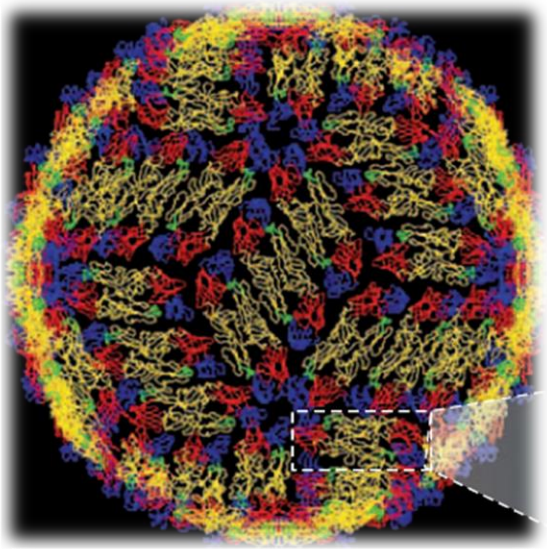
Dengue a doença

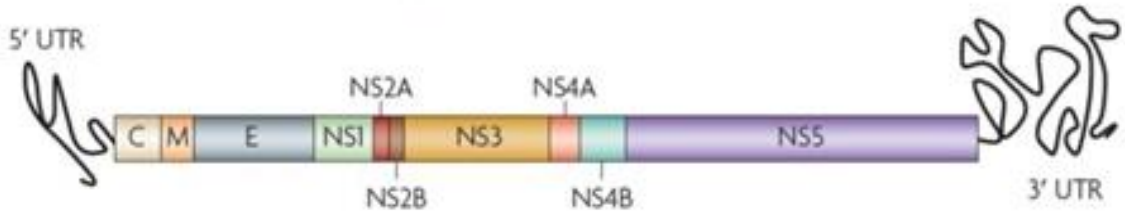
- ~390 milhões de casos no mundo por ano;
- 96 milhões de casos com algum sinal de gravidade;
- ~30 mil mortes por ano;
- Milhões de dólares gastos ou perdidos com hospitalizações, absenteísmo no trabalho e prejuízos ao turismo.

OMS, 2015; Baht et al, Nature 2013.

Vírus da Dengue

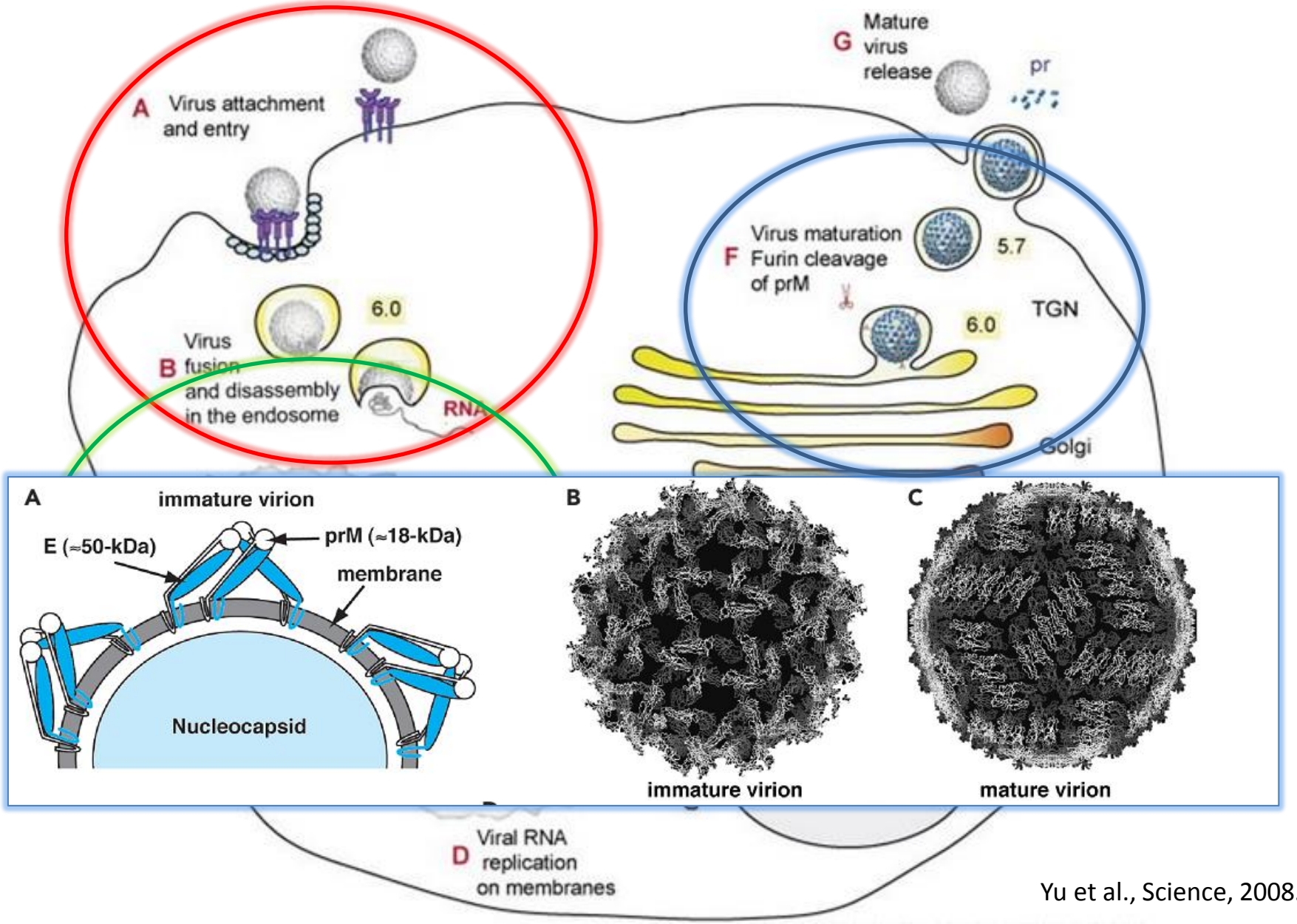
- Vírus dengue:
- Arbovírus (arthropod born virus)
- *Flaviviridae*
- Vírus de RNA
- RNA (+) de fita simples
- Esférico
- Envelopado





WHITEHEAD , S. S. *et al.* Nature Reviews. 2007; MURRELL *et al.*, 2011.

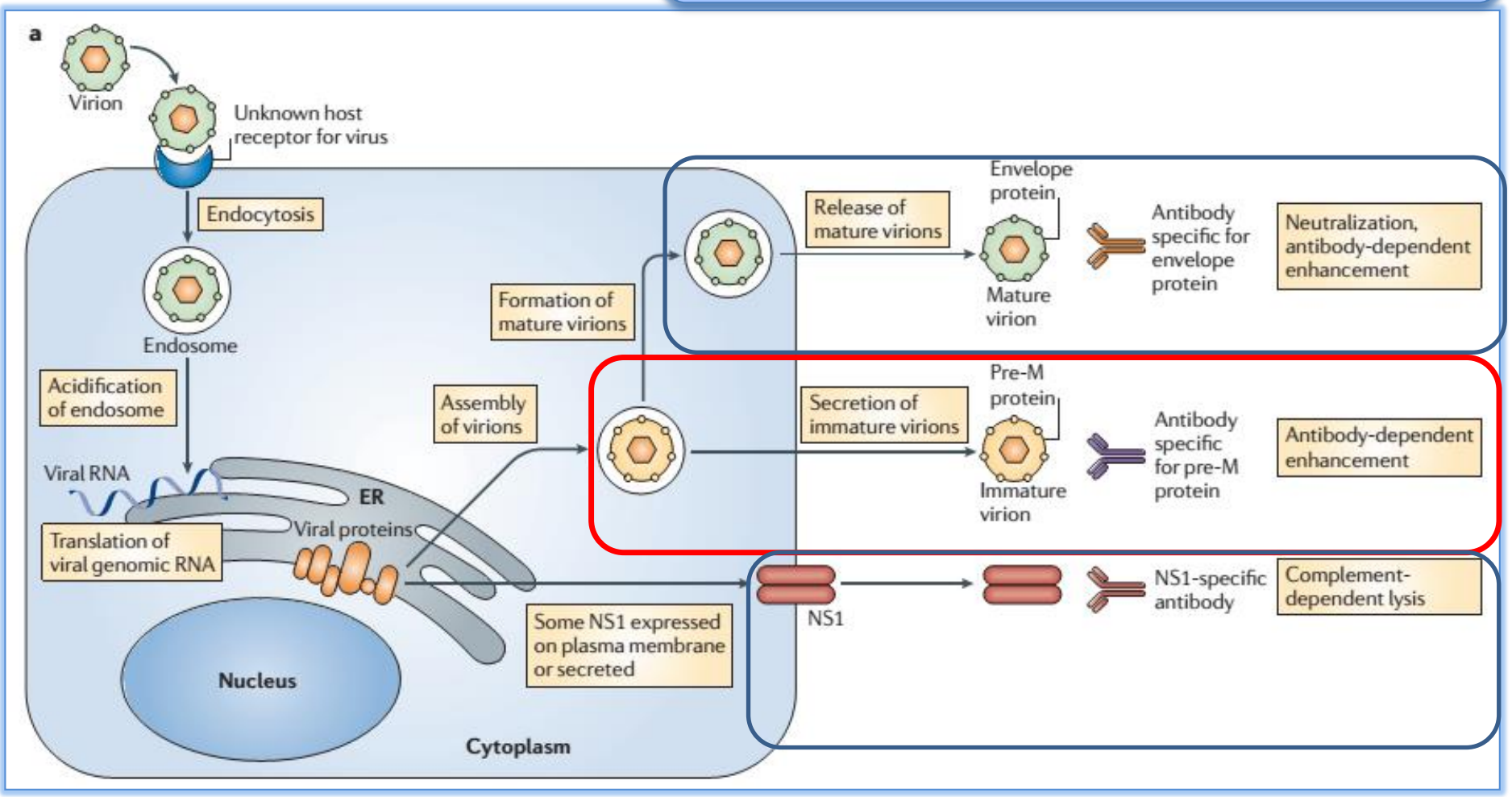
Multiplicação viral x alvos vacinais



Yu et al., Science, 2008.

Resposta Imunológica contra dengue

Resposta imunológica humoral

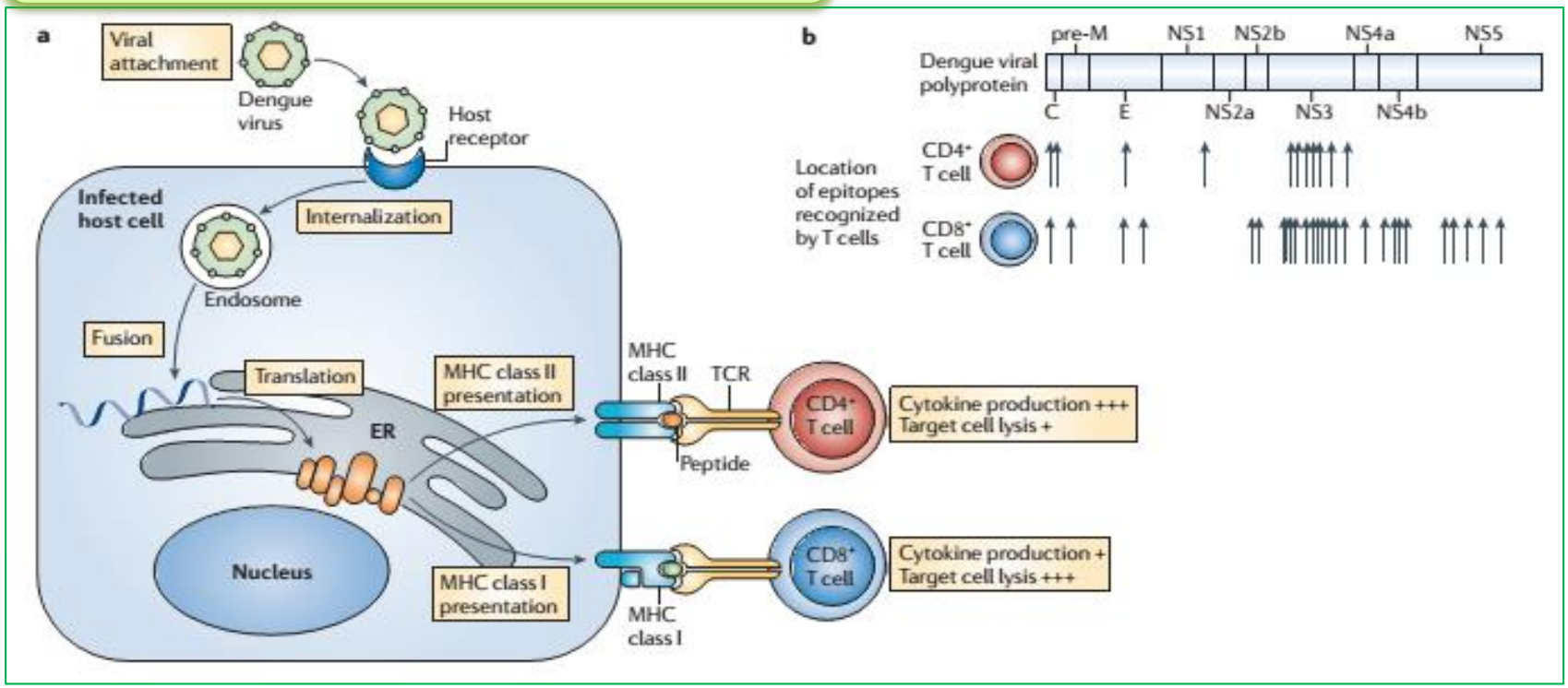


Rothman, Nature Immunol, 2012.

Resposta Imunológica contra dengue

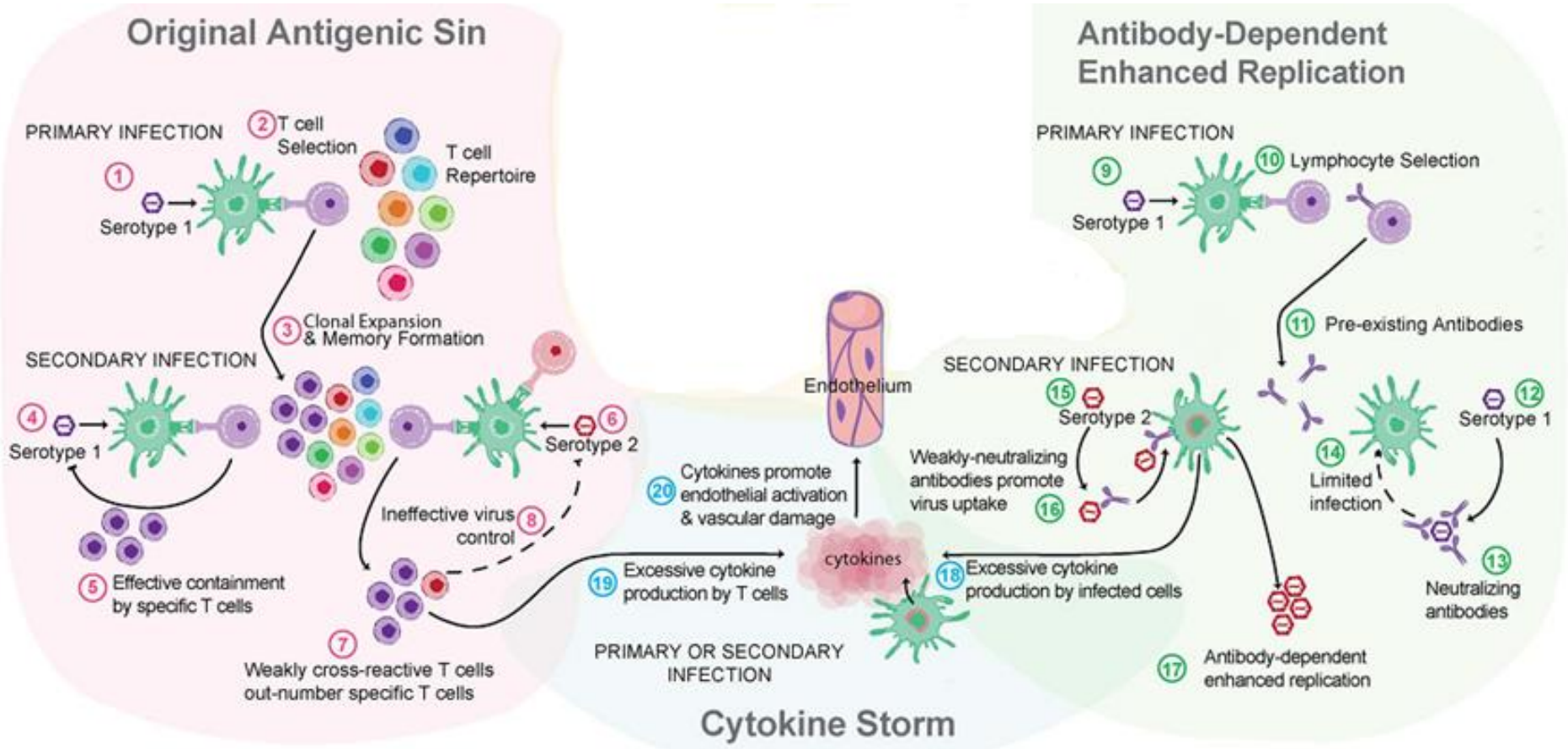
Resposta imunológica celular

Rothman, Nature Immunol, 2012.



Dificuldades no desenvolvimento de vacinas

Principal: Necessidade de **TETRAVALÊNCIA**



St John, PLoS Pathog, 2013.

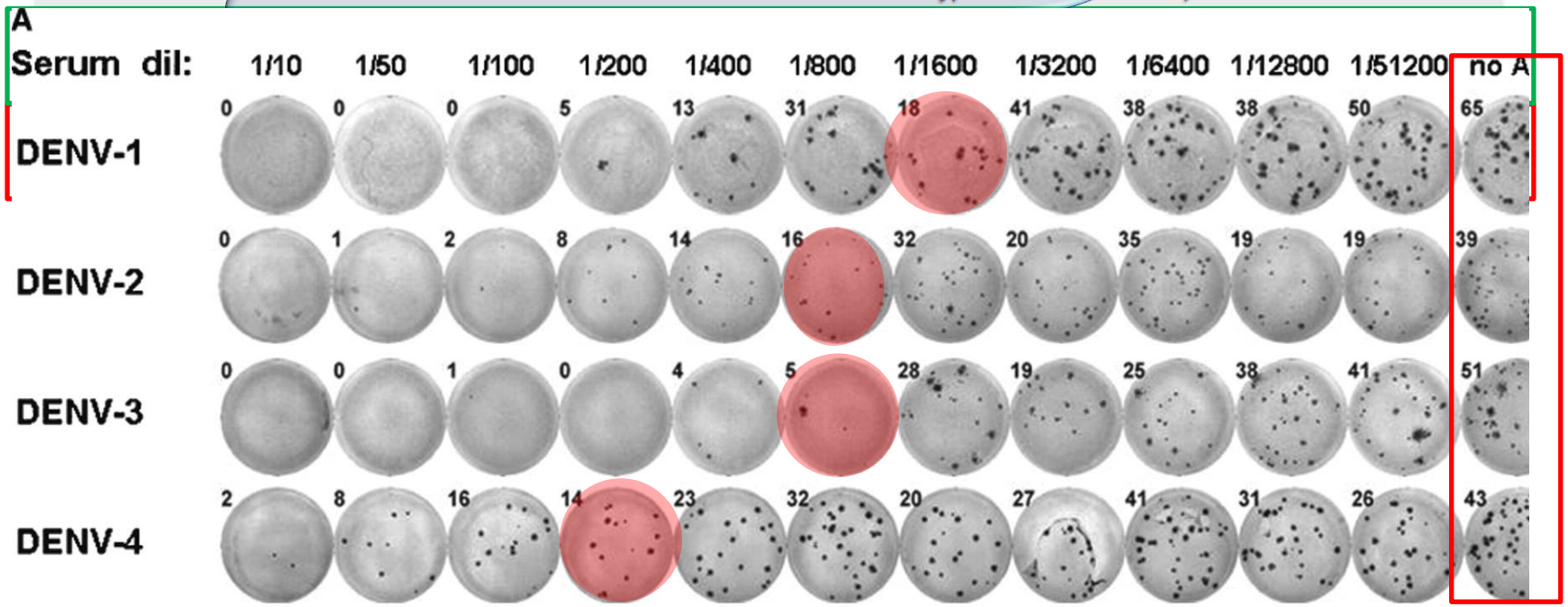
Vacinas em desenvolvimento

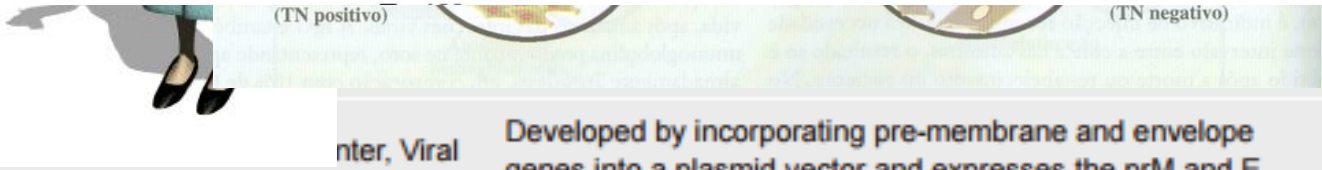
Produção de anticorpos neutralizantes

OPRNT – Plaque Reduction Neutralisation Test

PROTEÇÃO?

Developer	Product description	Stage
Takeda Pharmaceuticals / Inviragen	PDK-53 virus and DEN/DEN intertypic chimeric viruses)	Phase 2





		Phase 1
nter, Viral & Rickettsial Diseases Department	Developed by incorporating pre-membrane and envelope genes into a plasmid vector and expresses the prM and E genes of DENV-1	Phase 1

Wei, et al., Virologica Sinica 2014.

Estratégia

SANOFI PASTEUR

Phase III Efficacy Latin America

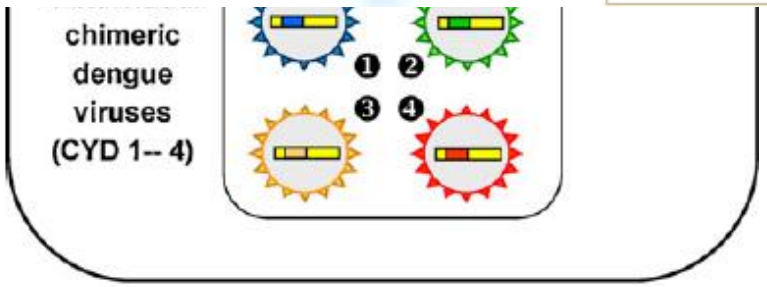
- Countries: Colombia, Mexico, Honduras, Puerto Rico, and Brazil
- Age group: 9-16 years
- Sample Size: 20,875

Phase III Efficacy Asian

- Countries: Thailand, Indonesia, Malaysia, Viet Nam, Philippines
- Age group: 2-14 years
- Sample Size: 10,278

Phase IIb Efficacy study Thailand

- Country: Thailand
- Age group: 4-11 years
- Sample size: 4,002

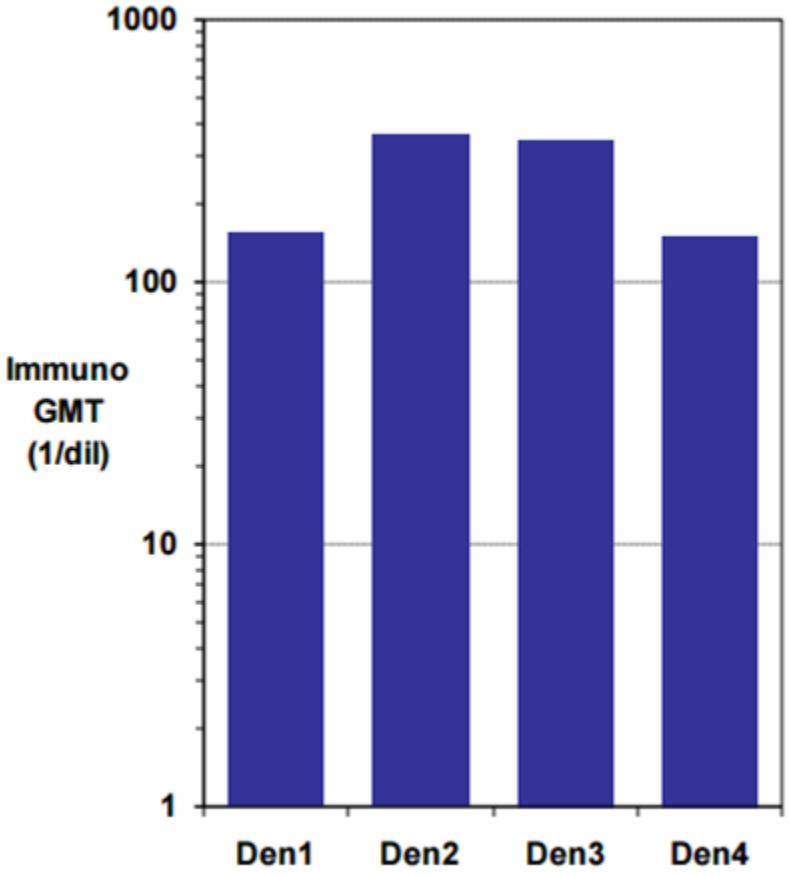


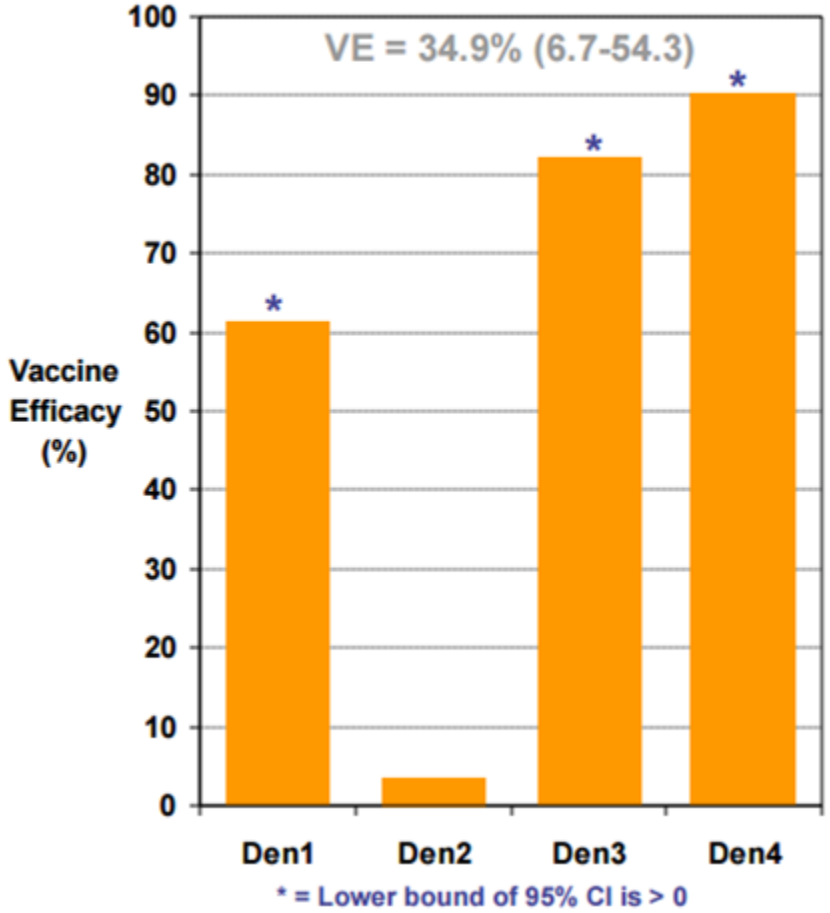
- 10^5 doses infecciosas (salina 0,4%)
- Placebo = salina 0,9%

} subcutâneo

GUYA, B. *et al*. Vaccine, 2011.

Fase 3 – Resultado na Ásia





Fase 3 – Resultado na América Latina

The NEW ENGLAND JOURNAL of MEDICINE

Table 3. Serotype-Specific Vaccine Efficacy.

Variable	Vaccine Group			Control Group			Vaccine Efficacy (95% CI)
	Cases	Person-Yr at Risk	Incidence Density (95% CI)	Cases	Person-Yr at Risk	Incidence Density (95% CI)	
	no.		*no./100 person-yr*	*no.*		*no./100 person-yr*	%
Modified per-protocol analysis*							
Serotype 1	66	12,478	0.5 (0.4–0.7)	66	6,196	1.1 (0.8–1.4)	50.3 (29.1–65.2)
Serotype 2	58	12,495	0.5 (0.4–0.6)	50	6,219	0.8 (0.6–1.1)	42.3 (14.0–61.1)
Serotype 3	43	12,514	0.3 (0.2–0.5)	82	6,213	1.3 (1.1–1.6)	74.0 (61.9–82.4)
Serotype 4	18	12,522	0.1 (0.1–0.2)	40	6,206	0.6 (0.5–0.9)	77.7 (60.2–88.0)
Unknown	6	12,540	<0.1 (0.0–0.1)	3	6,268	<0.1 (0.0–0.1)	0.0 (–517.8–78.6)
Intention-to-treat analysis							
Serotype 1	99	27,016	0.4 (0.3–0.4)	109	13,434	0.8 (0.7–1.0)	54.8 (40.2–65.9)
Serotype 2	84	27,035	0.3 (0.2–0.4)	84	13,461	0.6 (0.5–0.8)	50.2 (31.8–63.6)
Serotype 3	55	27,060	0.2 (0.2. 0.3)	106	13,459	0.8 (0.6–1.0)	74.2 (63.9–81.7)
Serotype 4	32	27,063	0.1 (0.1–0.2)	83	13,442	0.6 (0.5–0.8)	80.9 (70.9–87.7)
Unknown	15	27,079	<0.1 (0.0–0.1)	14	13,514	0.1 (0.1–0.2)	46.5 (–19.6–75.9)

Reflexões

Por que esta estratégia vacinal não foi completamente efetiva?

Será que neutralização viral é capaz, por si só, de induzir proteção duradoura contra o DENV?

Há envolvimento das proteínas não-estruturais na indução de proteção duradoura contra o DENV?

Reflexões

frontiers in IMMUNOLOGY

EDITORIAL
published: 18 February 2015
doi: 10.3389/fimmu.2015.00075

Protective immune responses to dengue virus infection and vaccines: perspectives from the field to the bench

Scott B. Halstead*[1] *and Simona Zompi*[2,3] *

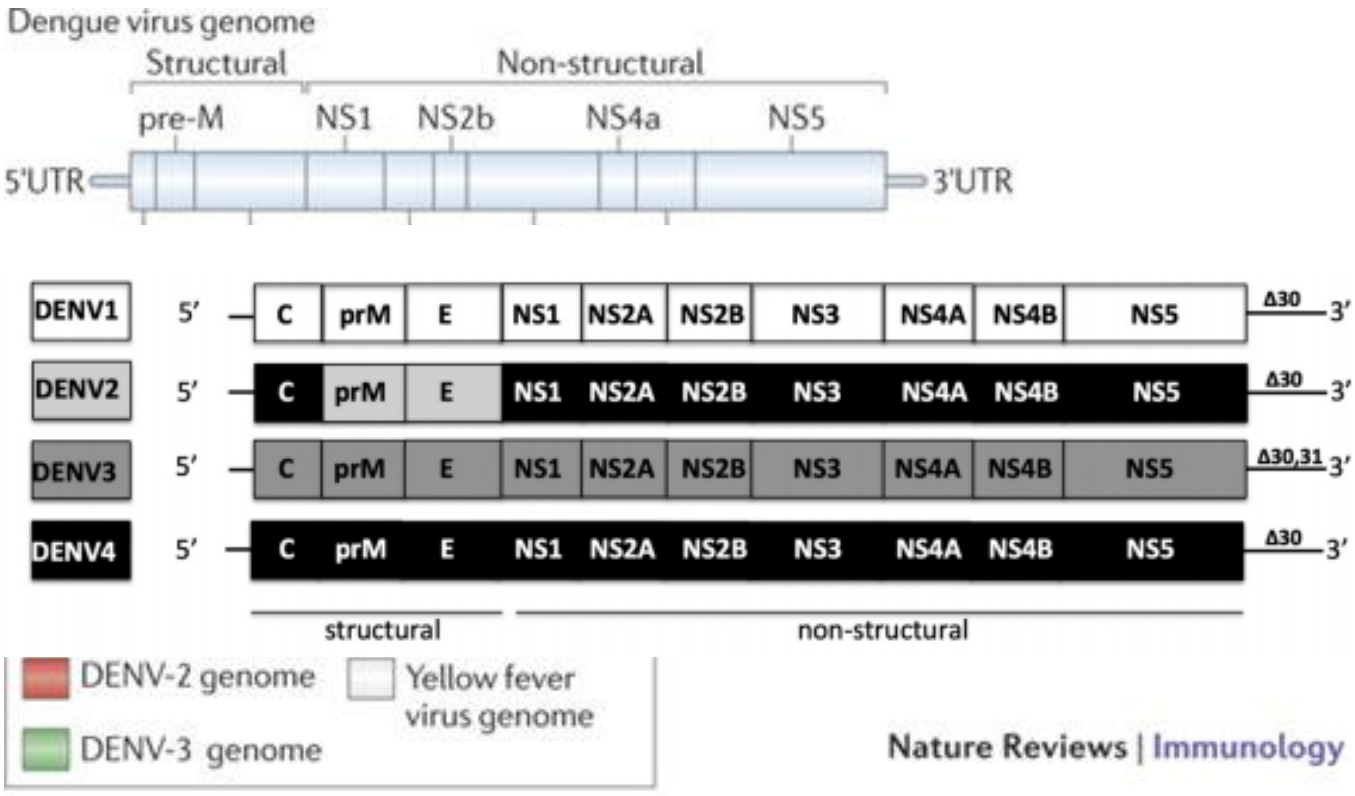
Dengue

Maria G Guzman, Eva Harris

Dengue viruses have spread rapidly within countries and across regions in the past few decades, resulting in an increased frequency of epidemics and severe dengue disease, hyperendemicity of multiple dengue virus serotypes in many tropical countries, and autochthonous transmission in Europe and the USA. Today, dengue is regarded as the most prevalent and rapidly spreading mosquito-borne viral disease of human beings. Importantly, the past decade has also seen an upsurge in research on dengue virology, pathogenesis, and immunology and in development of antivirals, vaccines, and new vector-control strategies that can positively impact dengue control and prevention.

Lancet 2015; 385: 453–65
Published Online
September 14, 2014
http://dx.doi.org/10.1016/
S0140-6736(14)60572-9

Estratégia

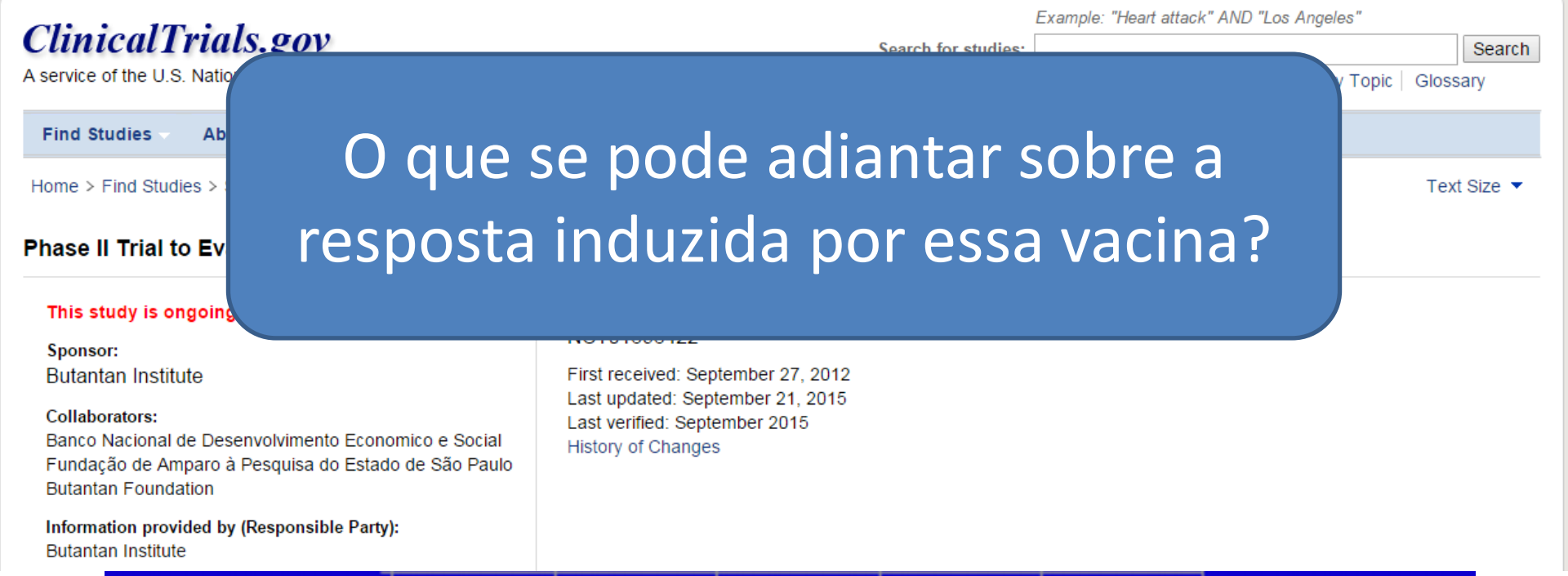


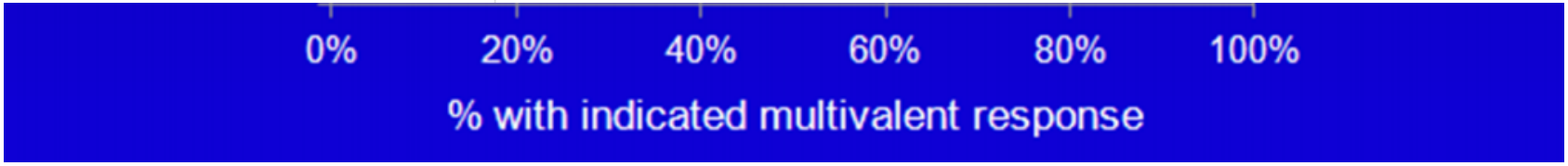
Rothman, A. L. *Nat Rev Immunol*, 2011; Weiskopf et al., *J Virol*, 2015

Resultados da fase I

Vaccine	N	% seroconverted ($PRNT_{50} \geq 10$)				Mean titer (GMT) ($PRNT_{50} \geq 10$)			
		DEN1	DEN2	DEN3	DEN4	DEN1	DEN2	DEN3	DEN4

O que se pode adiantar sobre a resposta induzida por essa vacina?





Explorando o papel da imunidade celular

JVI Journals.ASM.org

Received 18 July 2014 Accepted 1 October 2014 Editor: M. S. Diamond
Accepted manuscript posted online 15 October 2014

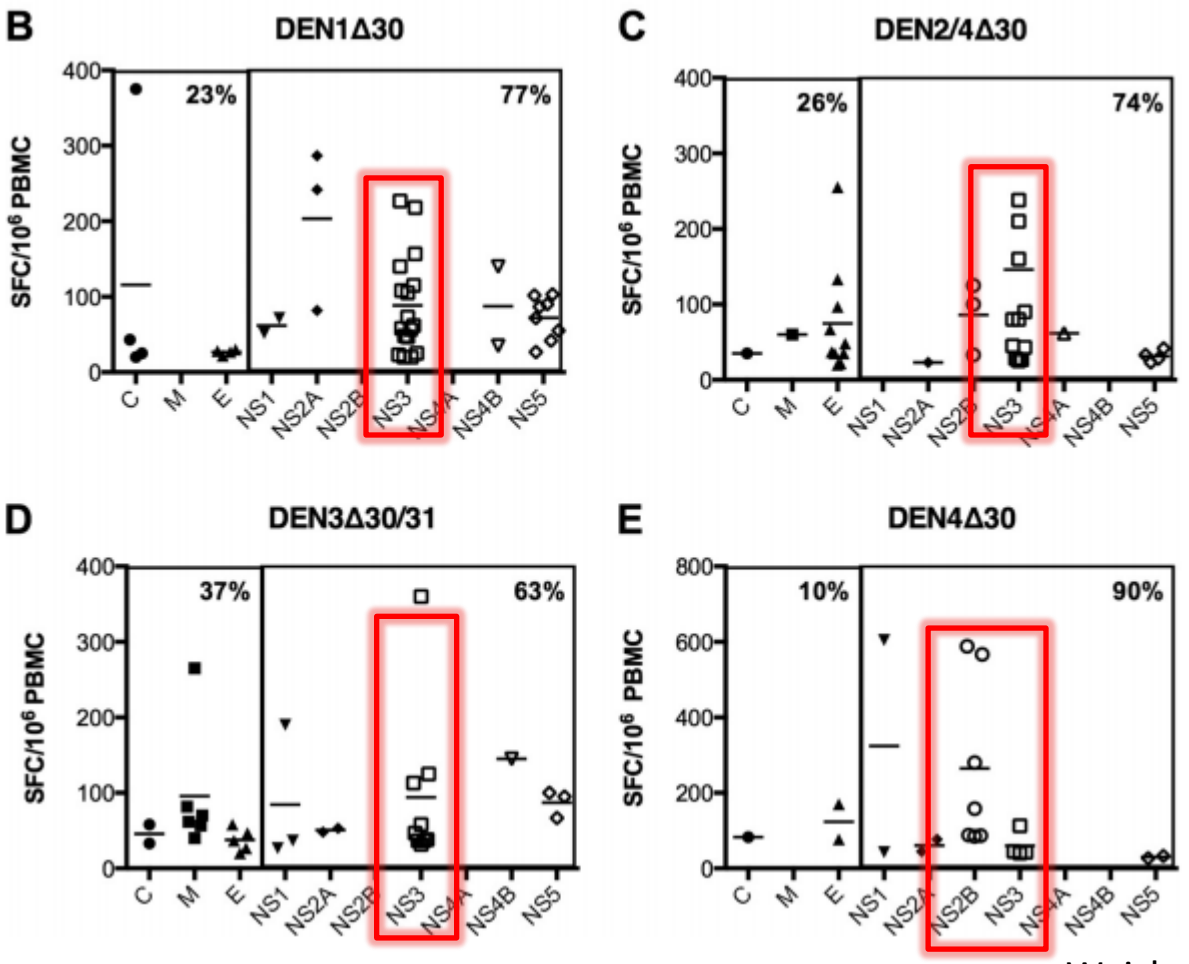
The Human CD8$^+$ T Cell Responses Induced by a Live Attenuated Tetravalent Dengue Vaccine Are Directed against Highly Conserved Epitopes

Daniela Weiskopf,[a] Michael A. Angelo,[a] Derek J. Bangs,[a] John Sidney,[a] Sinu Paul,[a] Bjoern Peters,[a] Aruna D. de Silva,[a,e] Janet C. Lindow,[b] Sean A. Diehl,[b] Stephen Whitehead,[c] Anna Durbin,[d] Beth Kirkpatrick,[b] Alessandro Sette[a]

Division of Vaccine Discovery, La Jolla Institute for Allergy and Immunology, La Jolla, California, USA[a]; University of Vermont College of Medicine and Vaccine Testing Center, Burlington, Vermont, USA[b]; National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland, USA[c]; Johns Hopkins University Bloomberg School of Public Health, Baltimore, Maryland, USA[d]; Genetech Research Institute, Colombo, Sri Lanka[e]

Explorando o papel da imunidade celular

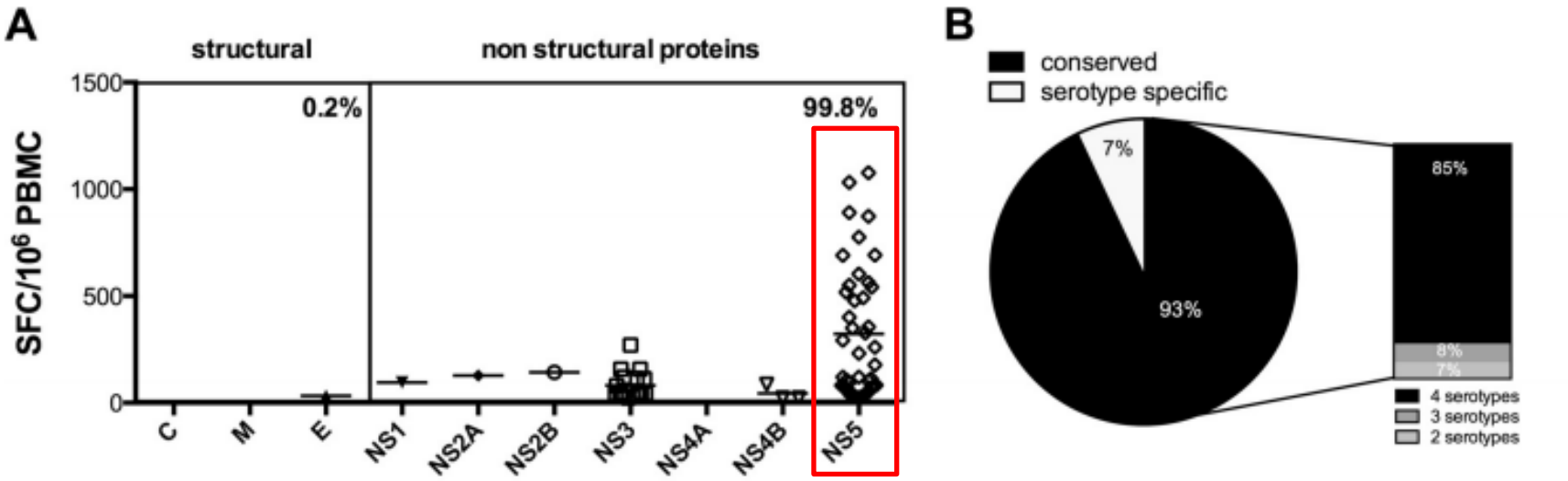
Padrão de resposta celular para formulações monovalentes



Weiskopof et al., *J Virol.* 2015

Explorando o papel da imunidade celular

Padrão de resposta celular para a formulação tetravalente



Weiskopf et al., *J Virol.* 2015

Explorando o papel da imunidade celular

frontiers in IMMUNOLOGY

REVIEW ARTICLE
published: 07 March 2014
doi: 10.3389/fimmu.2014.00093

T-cell immunity to infection with dengue virus in humans

*Daniela Weiskopf * and Alessandro Sette*

Divis

Human CD8$^+$ T-Cell Responses Against the 4 Dengue Virus Serotypes Are Associated With Distinct Patterns of Protein Targets

Daniela Weiskopf,[1]
Françoise P. Sanch
Angel Balmaseda,[3]

[1]Division of Vaccine Disc
Health, University of Cali
[4]Sustainable Sciences Ins
Brazil; and [5]Genetech Re

Dengue virus infection elicits highly polarized CX3CR1$^+$ cytotoxic CD4$^+$ T cells associated with protective immunity

Daniela Weiskopf[a,1,2], Derek J. Bangs[a,1], John Sidney[a], Ravi V. Kolla[a], Aruna D. De Silva[a,b], Aravinda M. de Silva[c],

ech Research Institute, Colombo, 00800, Sri Lanka;
hapel Hill, NC 27599

March 25, 2015)

RESEARCH ARTICLE www.ScienceTranslationalMedicine.org 11 March 2015 Vol 7 Issue 278 278ra35

DENGUE

Virus-specific T lymphocytes home to the skin during natural dengue infection

Laura Rivino,[1,2]* Emmanuelle A. Kumaran,[1] Tun-Linn Thein,[3] Chien Tei Too,[1] Victor Chih Hao Gan,[3] Brendon J. Hanson,[4] Annelies Wilder-Smith,[5] Antonio Bertoletti,[2,6] Nicholas R. J. Gascoigne,[1] David Chien Lye,[3] Yee Sin Leo,[3,5] Arne N. Akbar,[7] David M. Kemeny,[1] Paul A. MacAry[1]

Reflexões

➔ O correlato de proteção baseado apenas em neutralização viral não é suficiente como indicador de proteção;

➔ O braço de resposta imunológica celular conta dengue tem importante papel na indução de proteção contra a infecção viral;

➔ Porém, mais informações sobre a imunidade celular contra a dengue deve ser estudada.

O que temos a dizer...

Vacinas para o controle da dengue: potencial vacinal da combinação das proteínas não estruturais na geração de resposta celular protetora em modelo experimental

Beneficiário: Rubens Prince dos Santos Alves

Instituição-sede da pesquisa: Instituto de Ciências Biomédicas (ICB). Universidade de São Paulo (USP). São Paulo, SP, Brasil

Pesquisador responsável: Luis Carlos de Souza Ferreira

Área do conhecimento: Ciências Biológicas - Microbiologia - Microbiologia Aplicada

Linha de fomento: Bolsas no Brasil - Doutorado

Processo: 15/02352-7

Vigência (Início): 01 de agosto de 2015

Vigência (Término): 31 de julho de 2018

➔ Estudar alvos em separado (Proteína não estrutural 1, 3 e 5);

➔ Associar padrões de resposta imunológica induzida com controle da multiplicação viral;

➔ Propor uma formulação vacinal que reúna antígenos corretos e que induzam padrões de resposta capazes de controlar a infecção

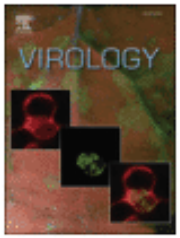
O que temos a dizer... Agora!

Virology 487 (2016) 41–49

Contents lists available at ScienceDirect

Virology

journal homepage: www.elsevier.com/locate/yviro



Antibodies are not required to a protective immune response against dengue virus elicited in a mouse encephalitis model

Jaime Henrique Amorim [a,*], Rúbens Prince dos Santos Alves [a], Raíza Bizerra [a], Sara Araújo Pereira [a], Lennon Ramos Pereira [a], Denicar Lina Nascimento Fabris [a], Robert Andreata Santos [a], Camila Malta Romano [b], Luís Carlos de Souza Ferreira [a,*]

[a] *Laboratório de Desenvolvimento de Vacinas, Departamento de Microbiologia, Universidade de São Paulo, Brasil*
[b] *Instituto de Medicina Tropical de São Paulo e Faculdade de Medicina, Departamento de Moléstias Infecciosas e Parasitárias (LIMHC), Universidade de São Paulo, Brasil*

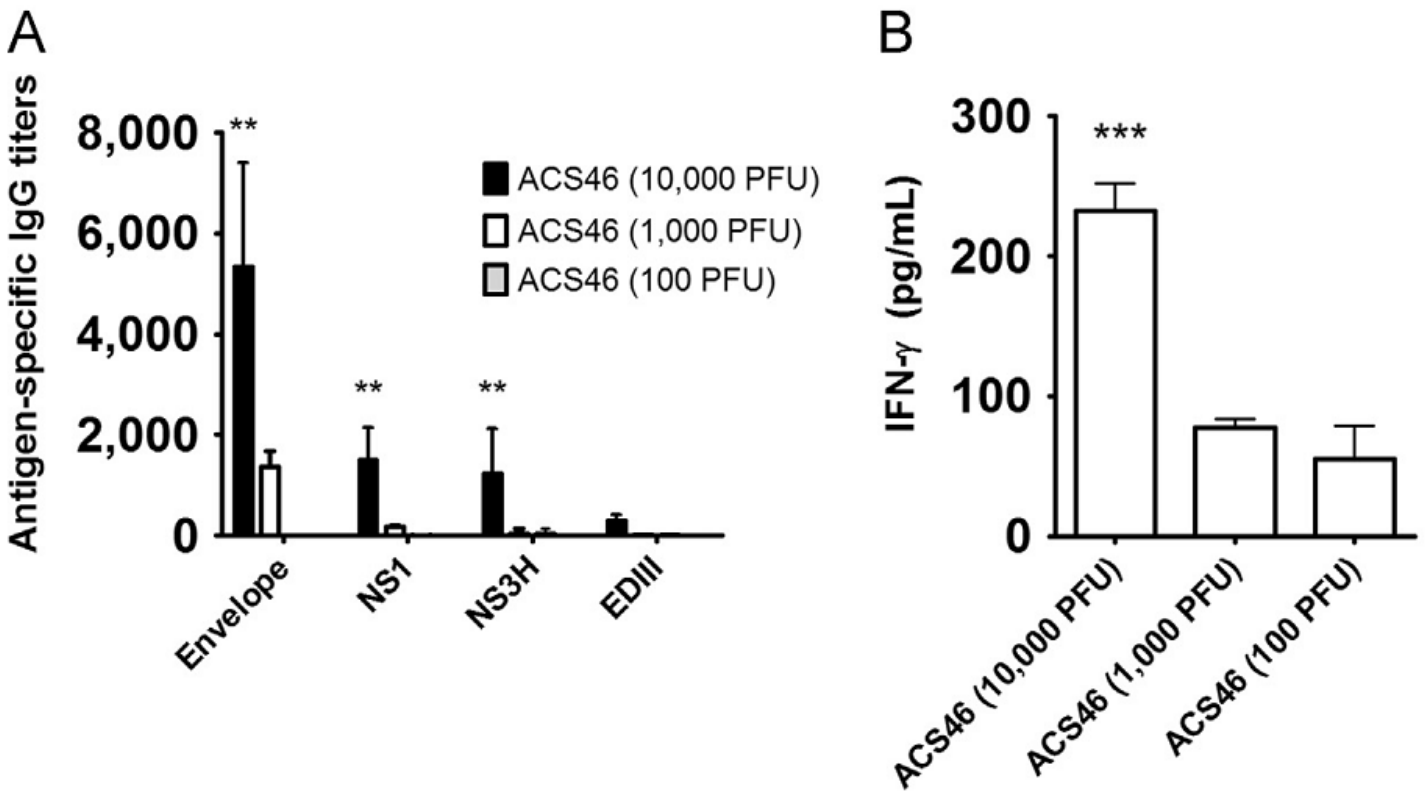
O que temos a dizer...

Hematological patterns measured in mice inoculated with ACS46 or JHA1 DENV2 strains.[a]

Hematological parameters[b]	Infection groups			
	ACS46 (100 PFU)	ACS46 (1000 PFU)	ACS46 (10,000 PFU)	JHA1 (100 PFU)
HCT[c]	33.02 ± 0.90	32.02 ± 0.85	33.40 ± 1.25	43.74 ± 2.80**
RBC	9.12 ± 0.30	8.72 ± 0.22	8.42 ± 0.92	9.45 ± 0.20
WBC	8.11 ± 0.48	8.61 ± 0.68	9.21 ± 0.98	1.98 ± 0.61***
LYM	5.79 ± 0.54	5.98 ± 0.37	1.12 ± 0.78	1.06 ± 0.21***
NEU	1.50 ± 0.15	1.62 ± 0.25	0.89 ± 0.97	0.64 ± 0.28***
PLT	7.28 ± 0.45	7.68 ± 0.33	7.48 ± 0.33	6.56 ± 0.37
PT[d]	19.40 ± 1.55	20.30 ± 2.56	21.30 ± 3.06	263.60 ± 15.28***

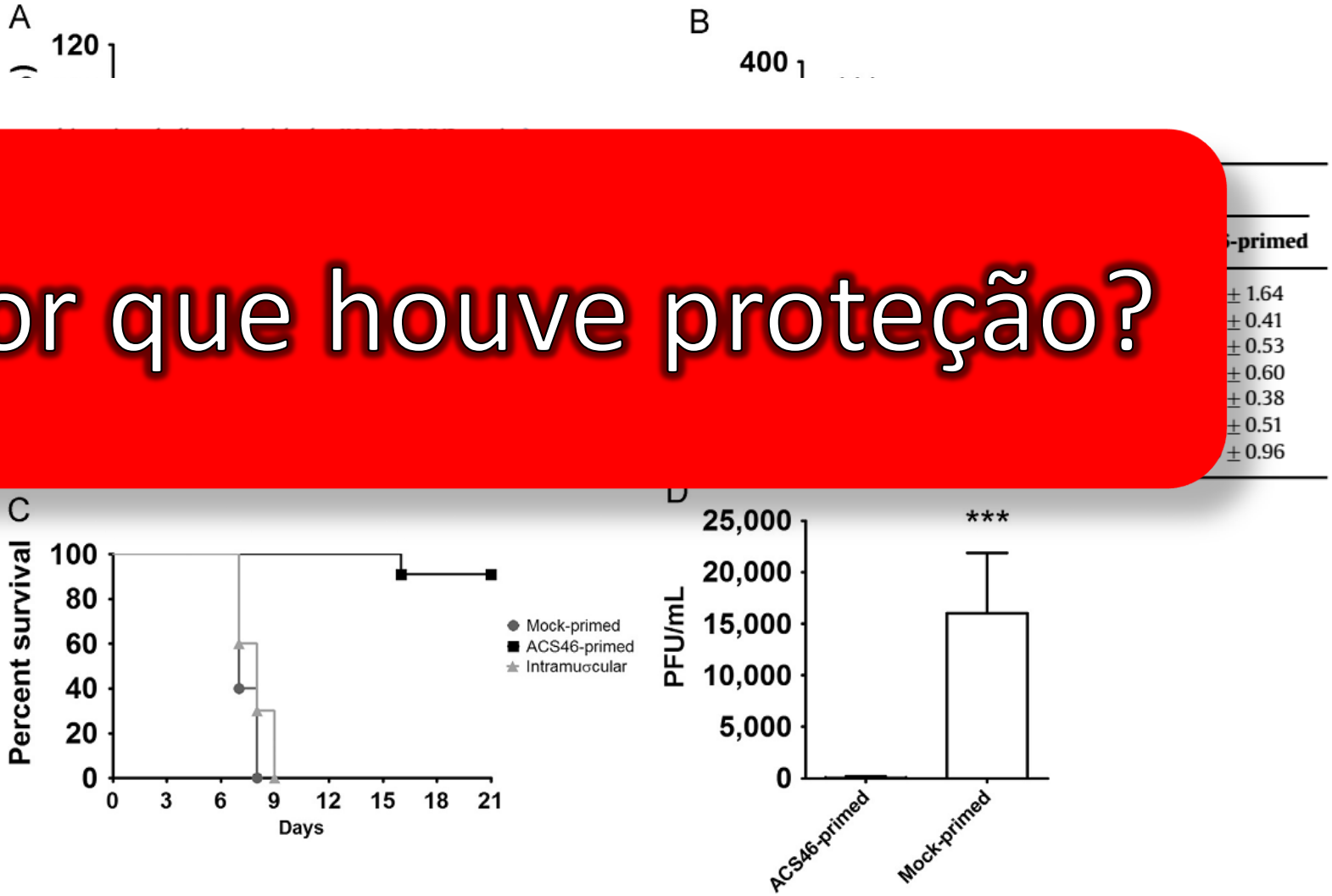
O que temos a dizer...

Resposta imunológica induzida pelo prime com ACS46



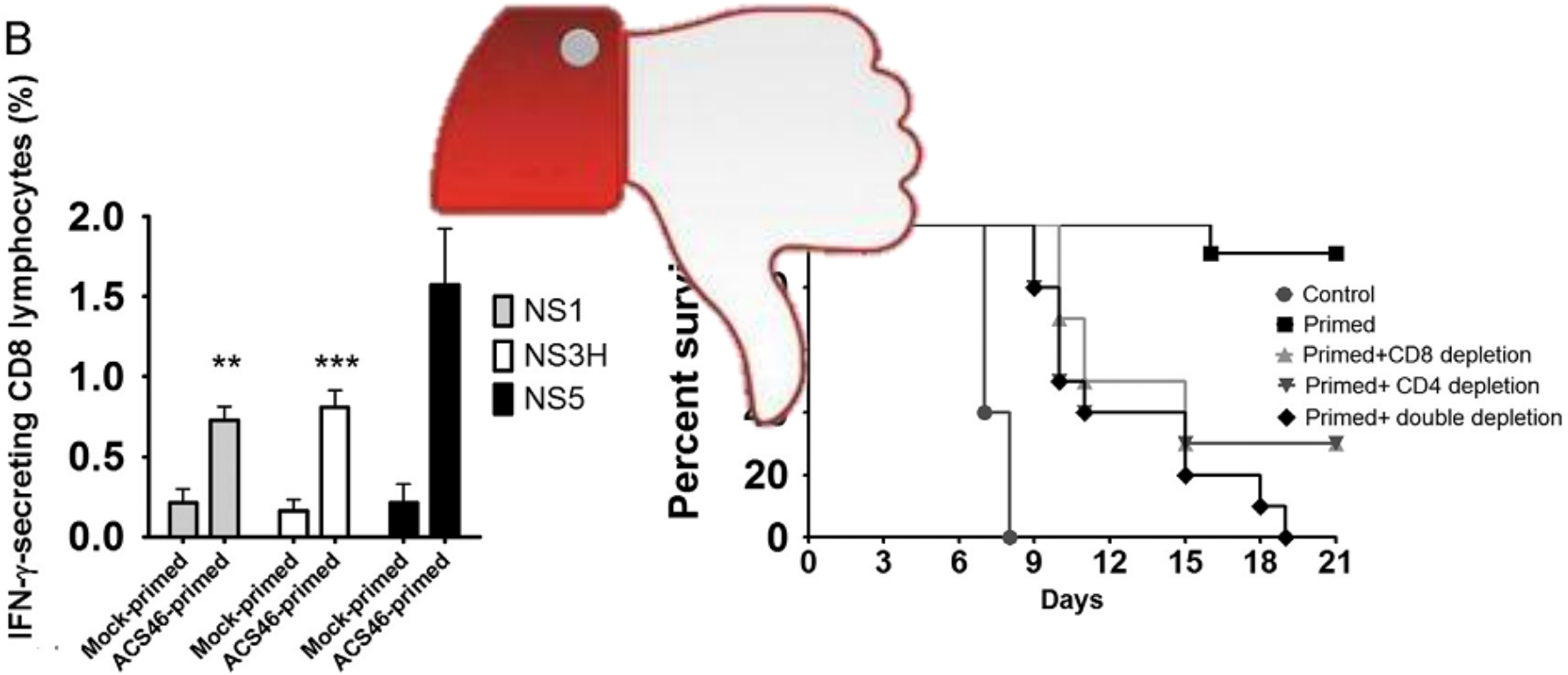
O que temos a dizer...

Proteção induzida pelo prime com ACS46



O que temos a dizer...

Provável resposta protetora celular



Conclusões...

- Não é simples... Abaixo o empirismo...
- Repensar o desenvolvimento de vacinas para controle da dengue;
- Associar padrões de resposta imunológica com controle da multiplicação viral;
- Estudar alvos em separado;
- Propor uma formulação vacinal que reúna antígenos corretos e que induzam padrões de resposta capazes de controlar a infecção.

Agradecimentos

LDV
LABORATÓRIO DE DESENVOLVIMENTO DE VACINAS

Laboratório de Desenvolvimento de Vacinas

FAPESP