
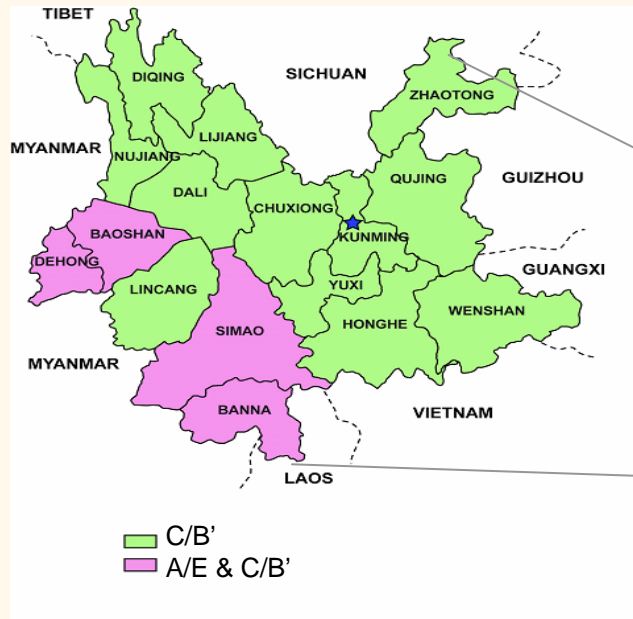
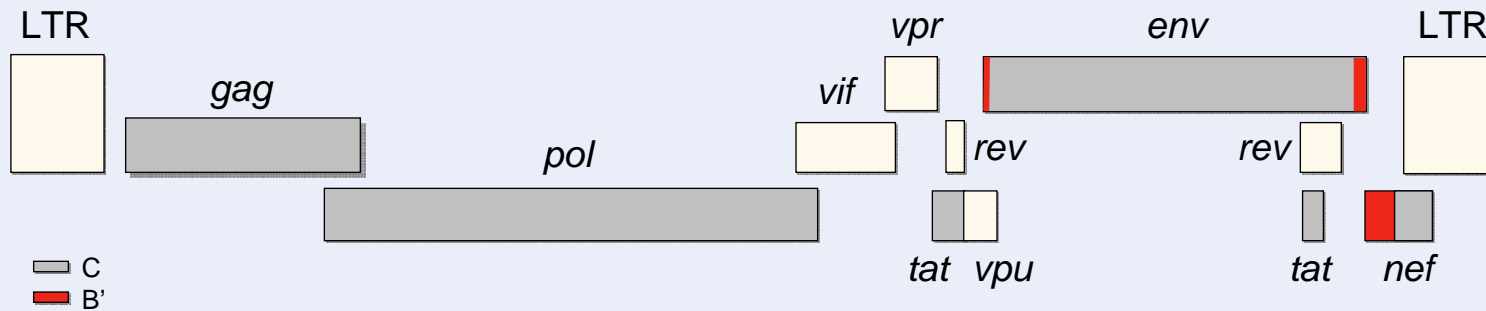


Cellular and Humoral Immunogenicity of ADMVA, a Clade C/B' MVA-Based HIV-1 Candidate Vaccine, in Healthy Volunteers

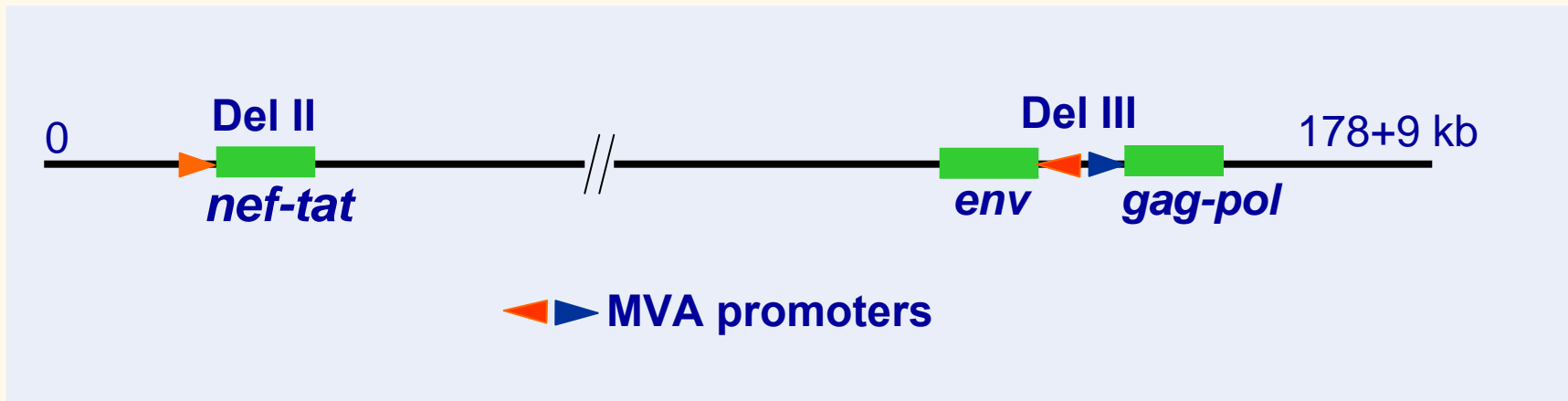


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ADMVA was constructed using an HIV-1 subtype C/B' strain dominant in Yunnan, China



ADMVA: a recombinant vaccinia vector (MVA) containing five HIV-1 genes



Constructed by Z. Chen based on an MVA strain provided by B. Moss (NIH)

Strong promoters: Psyn and PH5

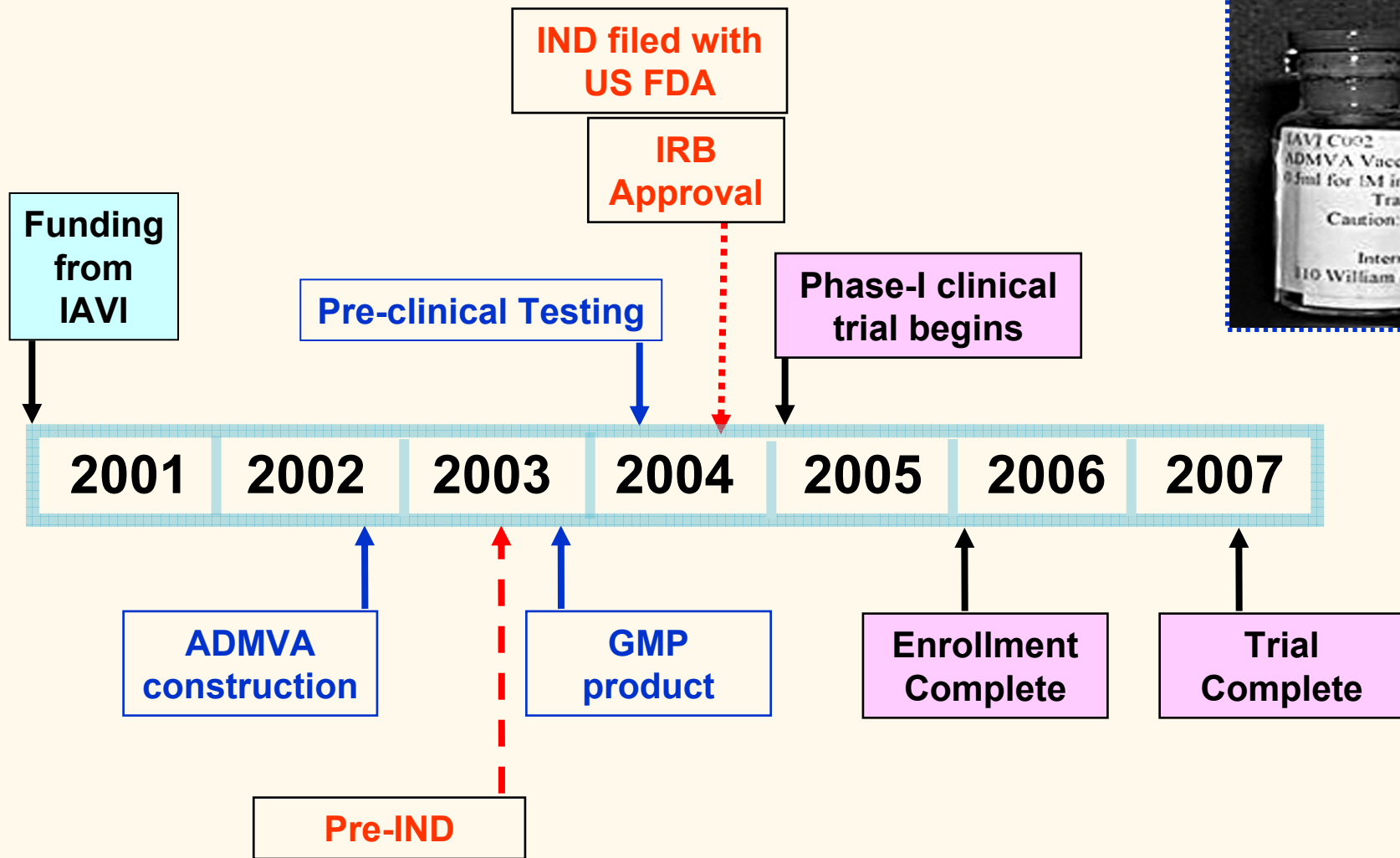
Mutations that render PR, RT, IN, Tat, and Nef non-functional

Deletion of the V2 loop in Env

Demonstrated high-level co-expression of all HIV-1 antigens *in vitro*

Excellent immunogenicity *in vivo* (mice and rabbits)

ADMVA Development Timeline



Clinical Trial Design

Objectives

Primary—safety (including cardiac safety)
Secondary—immunogenicity

Trial Sites

Rockefeller University Hospital (2/3)
University of Rochester Medical Center (1/3)

Study Subjects

Male or female healthy volunteers, age 18-40 years
Negative for HIV by antibody and PCR testing
Practicing safe sex, and effective birth control if female
No HBV, HCV, STD, or other active infections
No commercial sex work

Dose-Escalating Design

Immunization schedule (IM)	Weeks 0, 4, 24
Dose groups	1×10^7 ; 5×10^7 ; 2.5×10^8 pfu
Group size	16: 12 vaccine, 4 placebo (saline)
Follow up	18 months

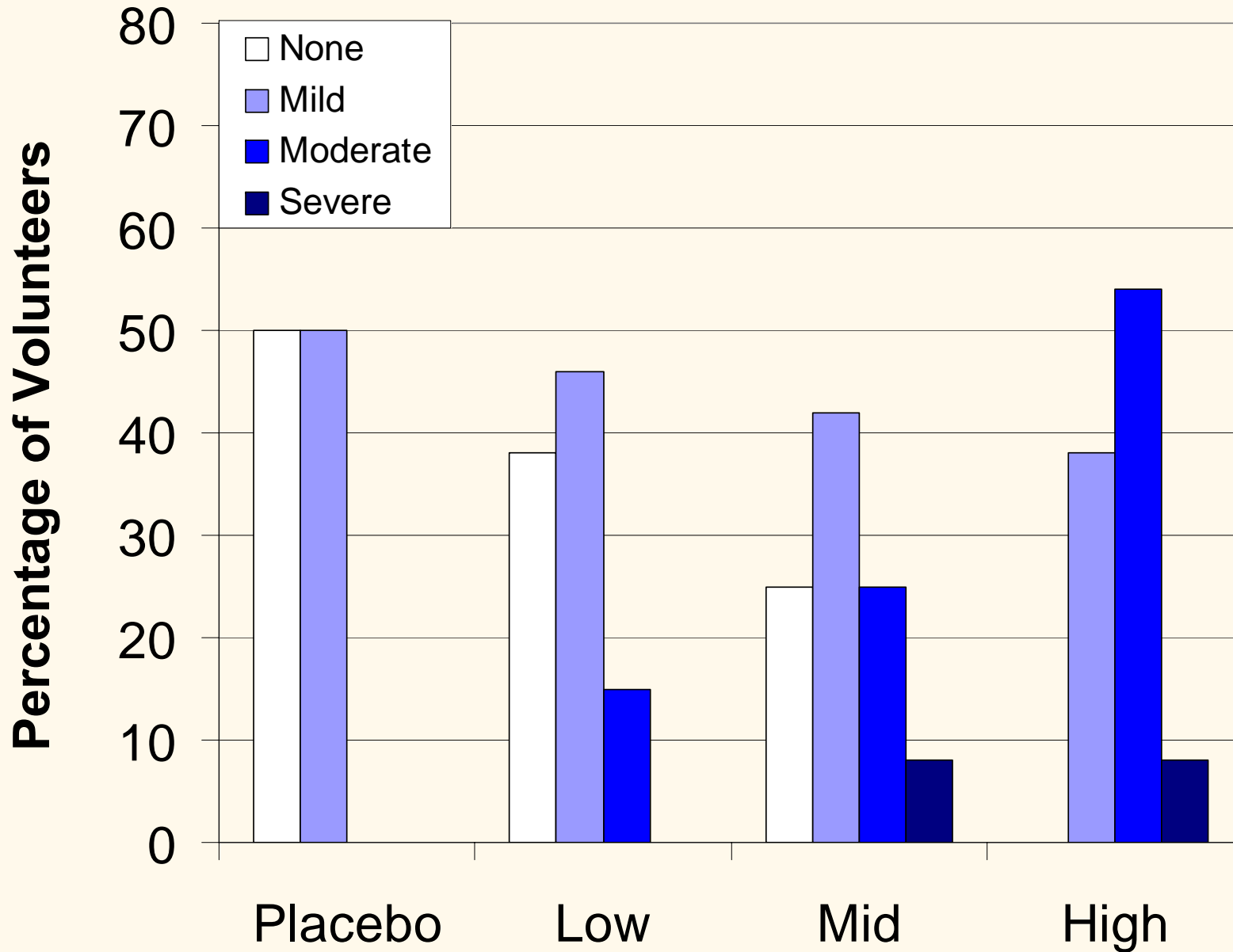
ADMVA Safety Profile

Subjects: 26 men & 24 women
age range 18-40 years, mean 26

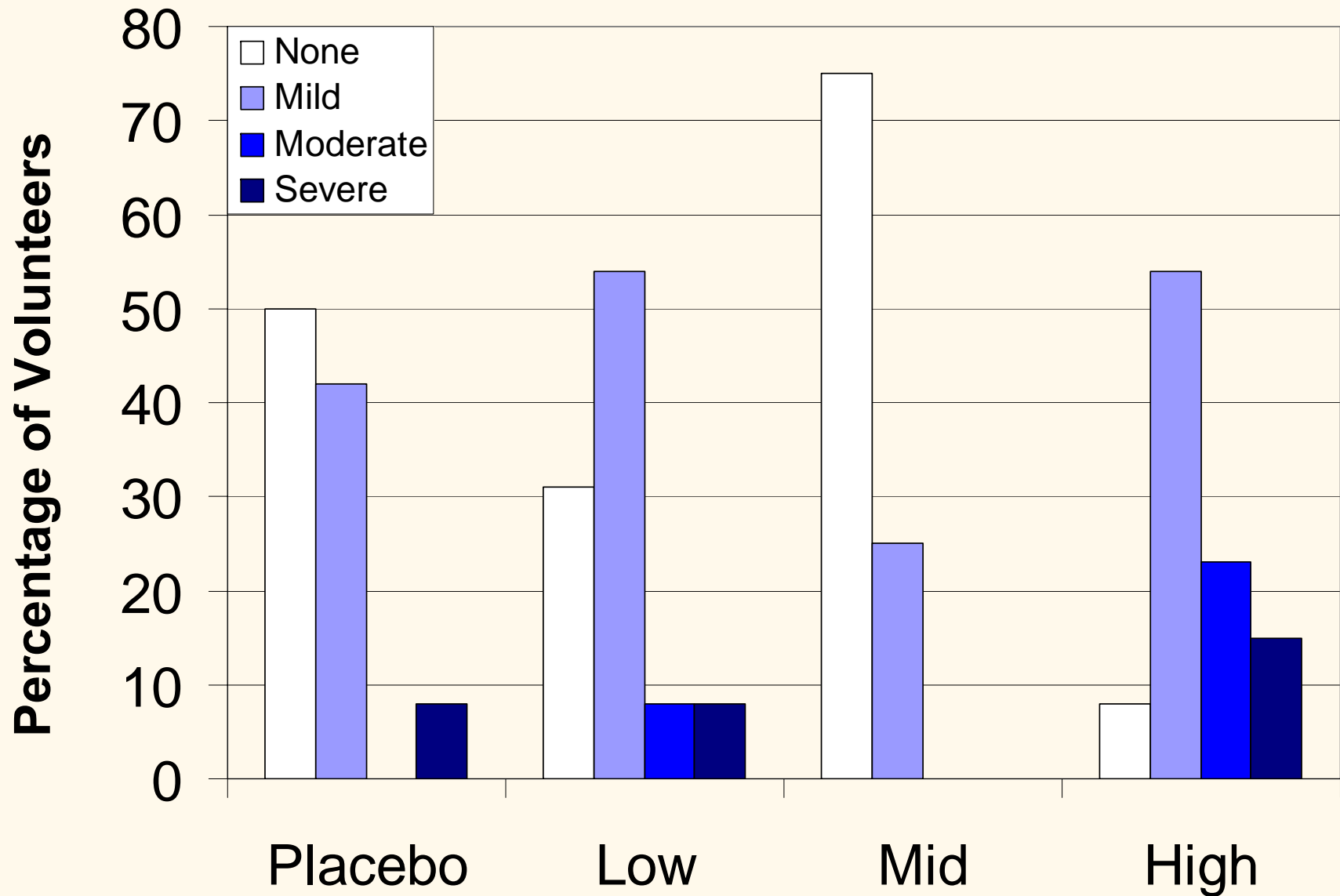
No vaccine related serious adverse events

No evidence of peri- or myocarditis

Local Reactogenicity



Systemic Reactogenicity



Immune monitoring assays

- **Validated IFN- γ ELISpot assays by the IAVI Core Lab**

Run in quadruplicate with 6 peptide pools of 15mers overlapping by 11aa that cover Gag, Pol, Env, Tat, and Nef

An assay is considered positive if four criteria are met:

- 1) Coefficient of variation between wells <70%
- 2) Mean count > 4 times mean mock
- 3) Mean mock < 55 sfu/10⁶ cells
- 4) > max percentile from the distribution of pre-vaccination and placebo response for a given peptide pool

- **ICS assays on ELISpot Responders**


- **Anti-gp120 binding antibodies by ELISA and IFA**

- **HIV-1 neutralization assays by Monogram Biosciences**

- **Anti-vaccinia antibodies by V-Bio**

IFN γ ELISPOT Responders

ADMVA Vaccinations

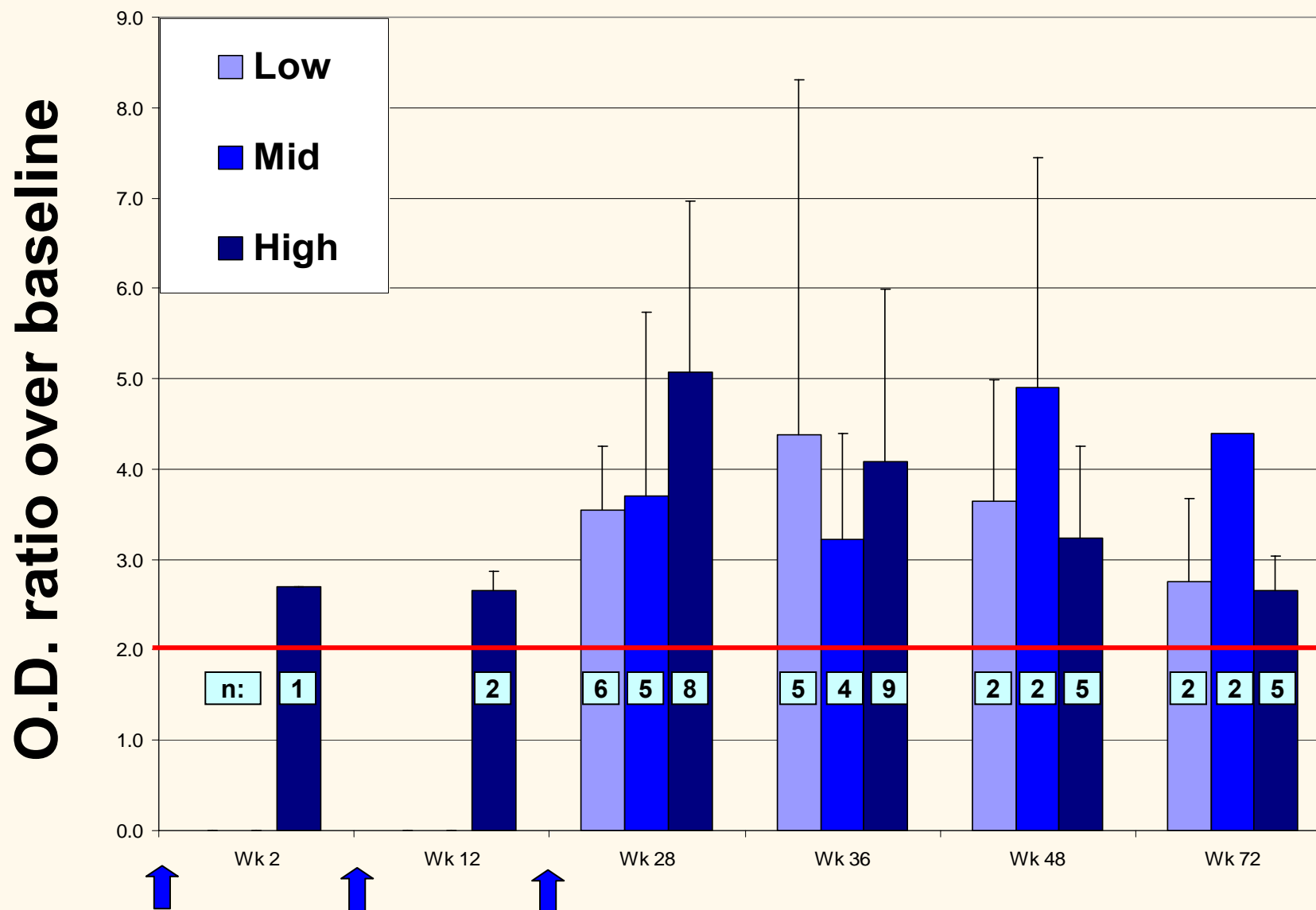


	W0	W1	W2	W5	W6	W24	W26	W28	W36	W52	W78
Low Dose 3/12 (25%)					Env 57						
							Env 60	Env 138	No visit	No visit	No visit
								Env 99	N/A		
Mid Dose 5/12 (42%)					Env 55		Env 69	Pol 84			
							Gag 60 Pol 59		N/A		N/A
			Gag 58 Nef-Tat 75			Gag 48			Nef-Tat 85	Nef-Tat 275	Nef-Tat 394
					Env 93,75		No visit				
											Env 60
High Dose 8/13 (62%)		Pol 73 Env 184,86	Env 275 Nef-Tat 125		Env 95		Env 59		Env 71		Env 51
			Env 55		Env 59						Env 101
					Pol 42		No visit			ND	
		Env 175 Nef-Tat 93									
					Pol 120						ND
		Env 93						N/A			ND
			Env 220								
			Env 58				Env 49	Env 60 NefTat163			ND

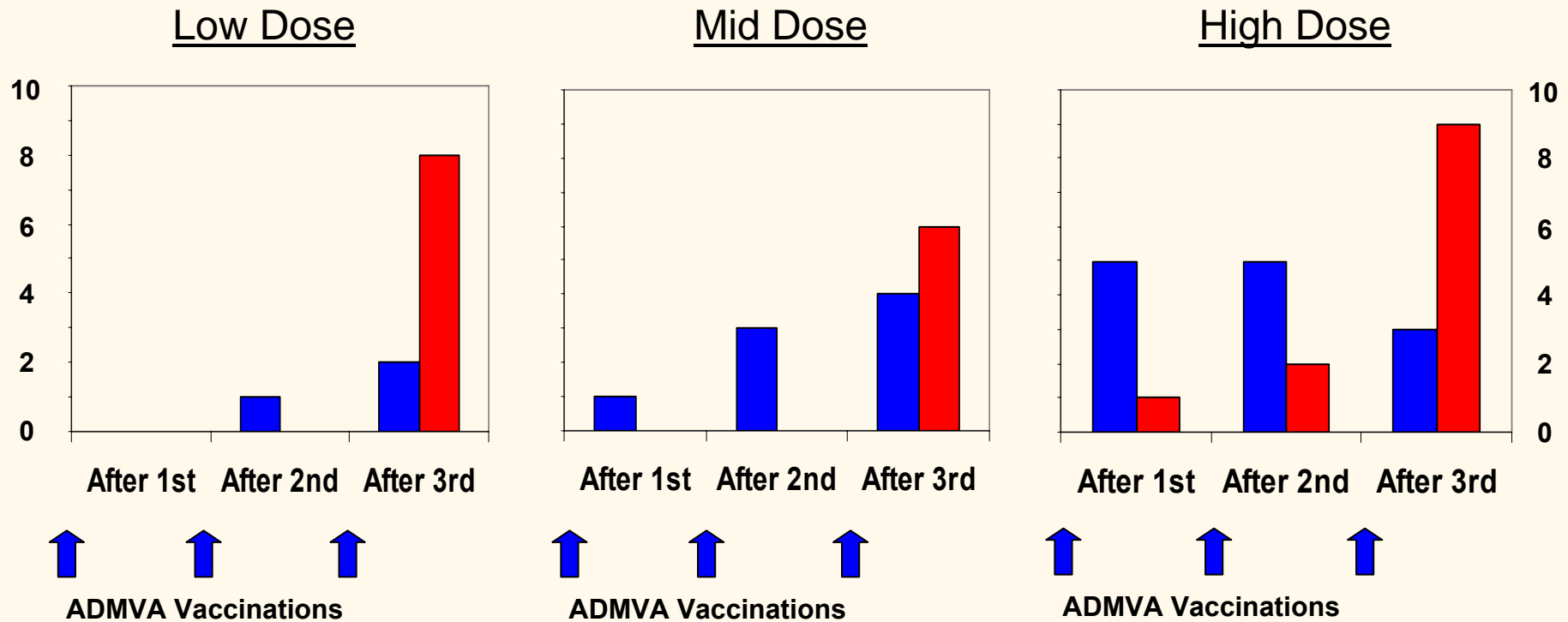
Summary of ADMVA Immune Response Rate

<u>Vaccine dose (pfu)</u>	<u>By IFN-γ ELISpot</u>	<u>By anti-gp120 Ab's</u>	<u>By either assay</u>
Placebo	0/12 (0%)	0/12 (0%)	0/12 (0%)
1.0 x 10 ⁷	3/12 (25%)	8/13 (62%)	10/13 (77%)
5.0 x 10 ⁷	5/12 (42%)	6/12 (50%)	7/12 (58%)
2.5 x 10 ⁸	8/13 (62%)	10/13 (77%)	11/13 (92%)

Magnitude of ADMVA Anti-gp120 Binding Antibodies Among Responders

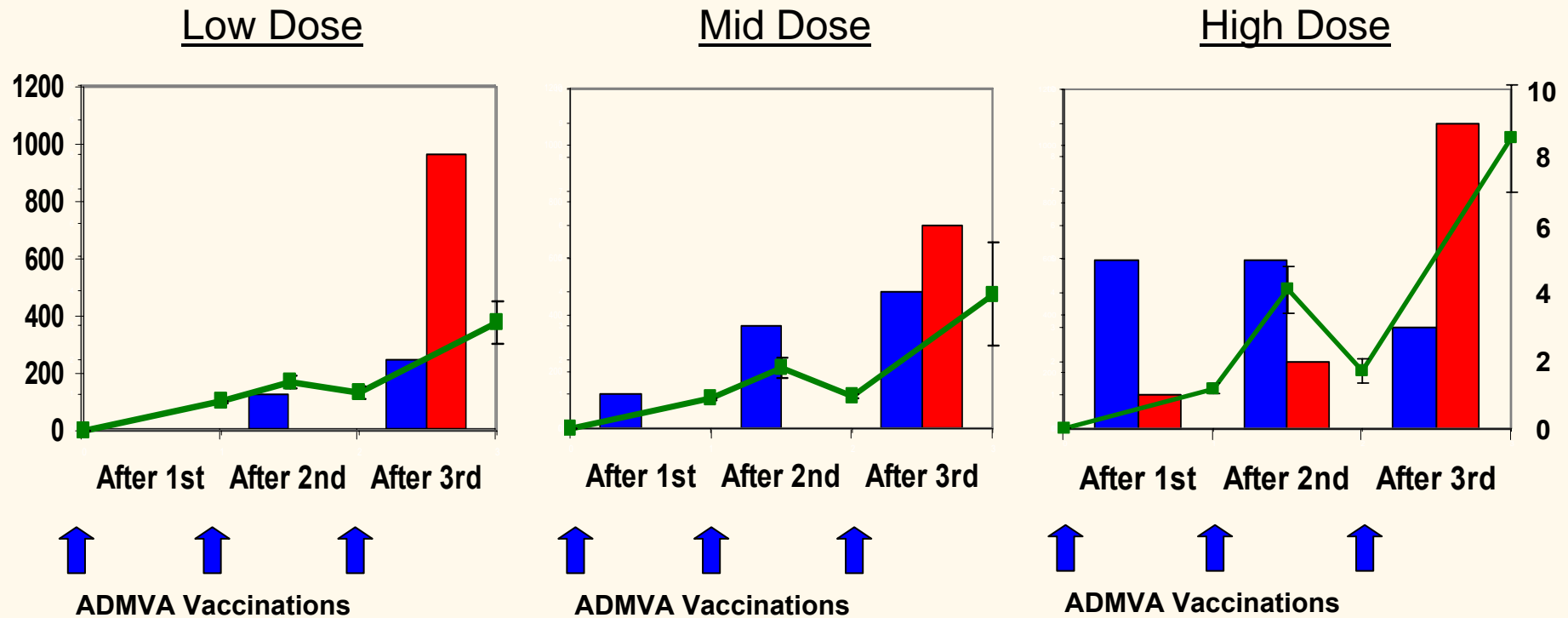


IFN γ ELISPOT and Anti-gp120 Responders After Each Vaccination



■ - IFN γ ELISPOT responses
■ - anti-gp120 binding antibody responses

Relationship of Immunogenicity with Anti-Vaccinia Binding Antibody Titers



- - IFN γ ELISPOT responses
- - anti-gp120 binding antibody responses
- - anti-vaccinia binding antibody titer

Additional Characterization of Humoral Responses

HIV-1 neutralization assays by Monogram Biosciences:

- Two volunteers exhibited weak neutralization to Chinese Clade C primary isolates
- Low-level neutralization to sensitive lab-strain virus (SF162) that was concordant with anti-gp120 binding:

	gp120+	gp120-
SF162+	18	1
SF162-	6	7

Clinical ELISA and Western Blot assays by New York City Department of Health:

- One high dose volunteer seroconverted after 3rd vaccination
- Western Blot positive for p24 and gp160
- HIV-1 PCR negative
- ELISA, Western Blot subsequently negative
- No clinical seroconversions at the end of the trial

Conclusions

ADMVA was safe and well tolerated in this study

ADMVA was immunogenic in humans, raising both antibody responses, and T-cell responses to all five HIV-1 genes encoded

Anti vector immunity was elicited in a dose-dependent fashion, but did not preclude immune responses to the third vaccination

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