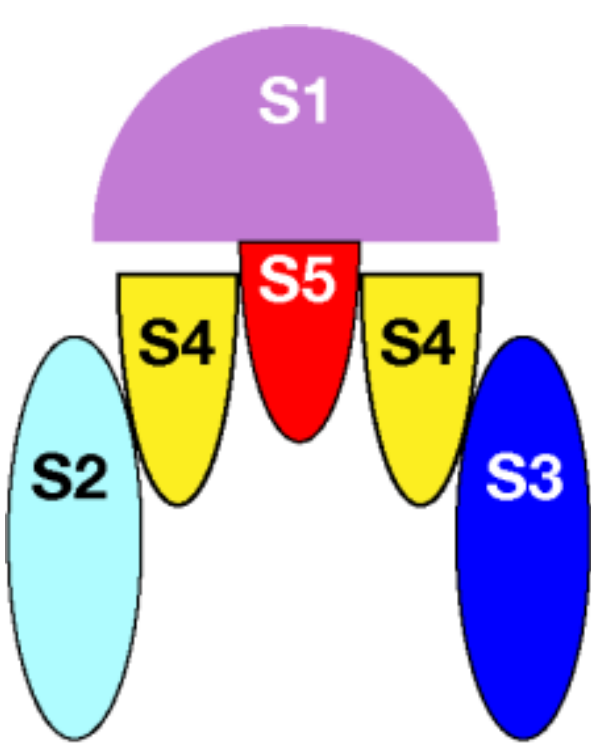
Vaccines based on genetically detoxified PT-9K/129G

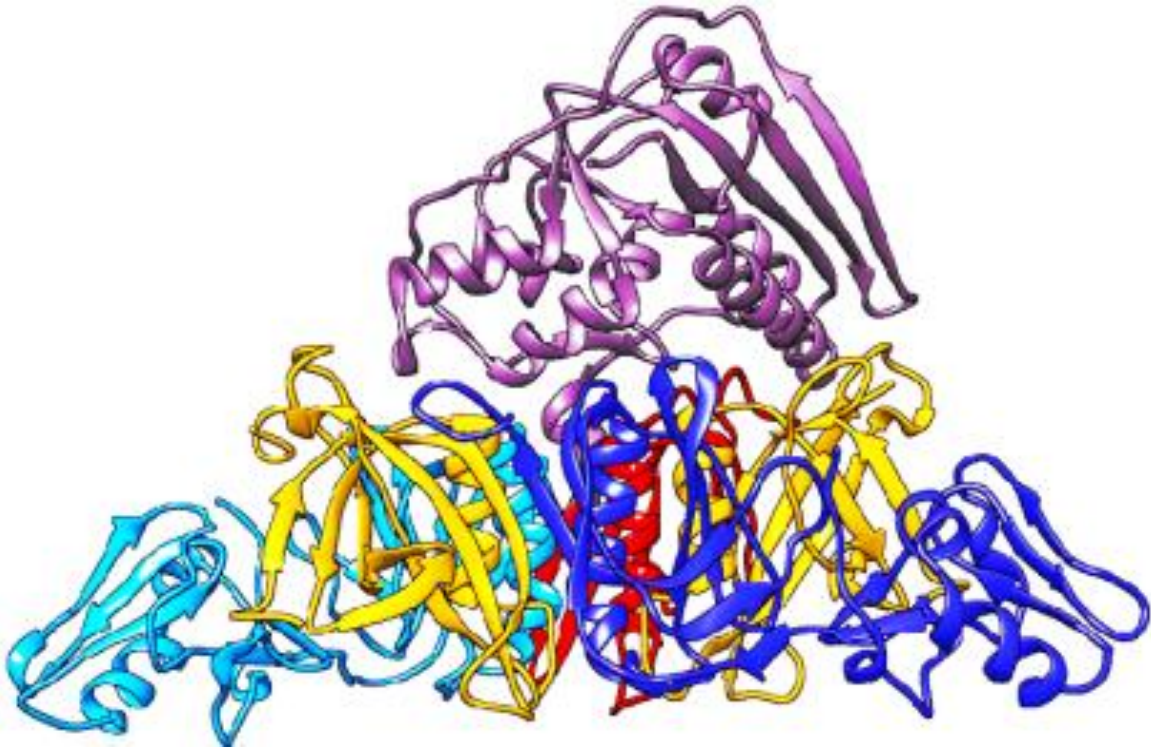
Mariagrazia Pizza

Pertussis:biology, epidemiology and prevention

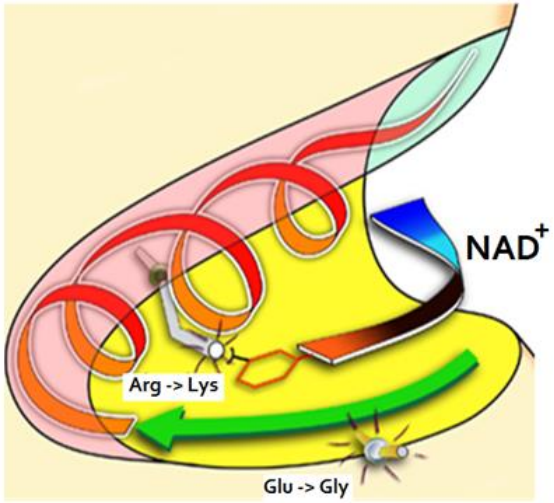
Annecy, Nov 13th, 2015

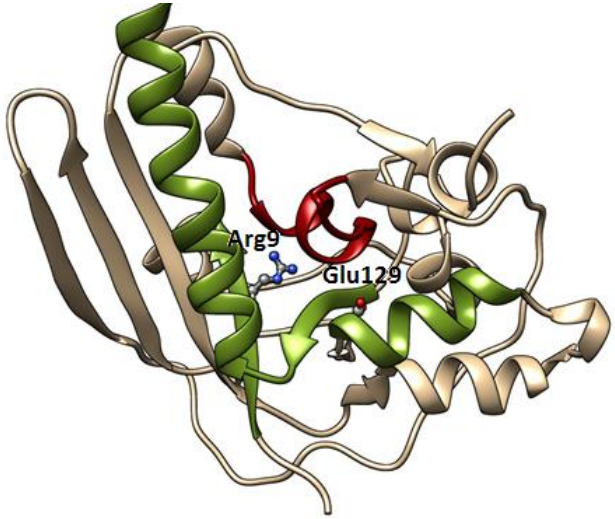
3D organization of PT structure

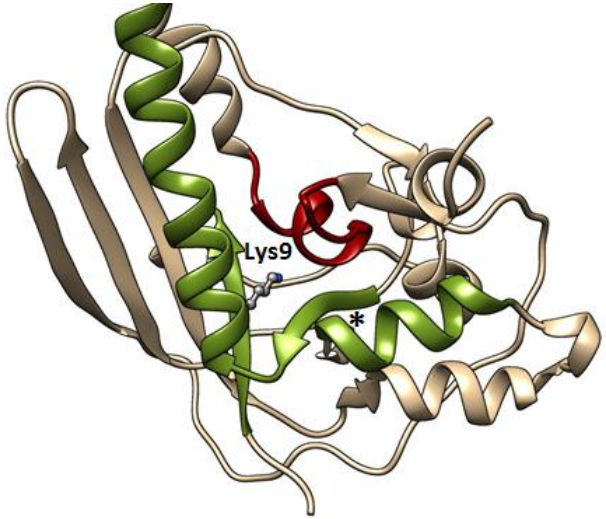




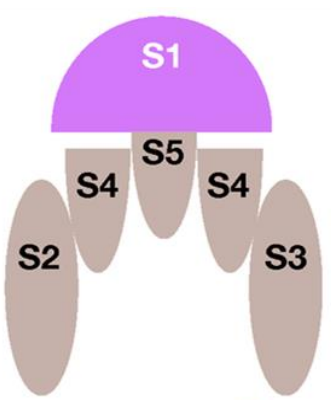
Catalytic residues in wild type (Arg 9 and Glu 129) and mutated S1 (Lys 9 and Gly 129)

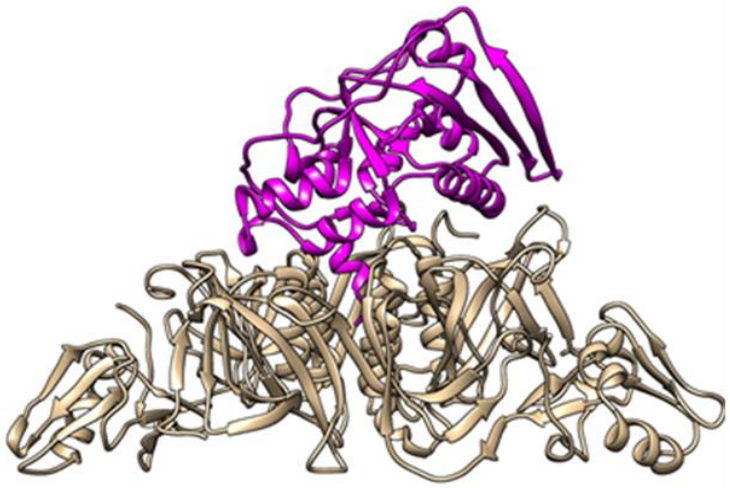




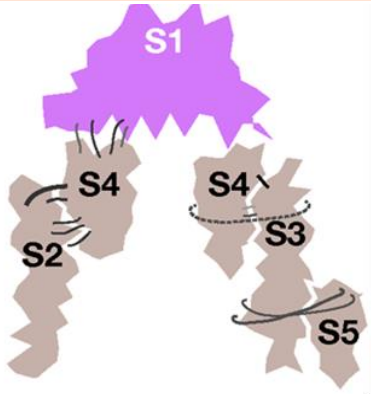


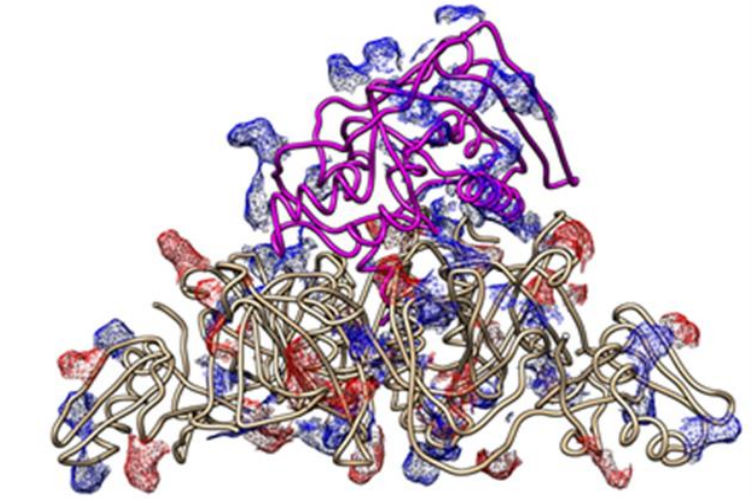
Predicted effects of detoxification on PT structure





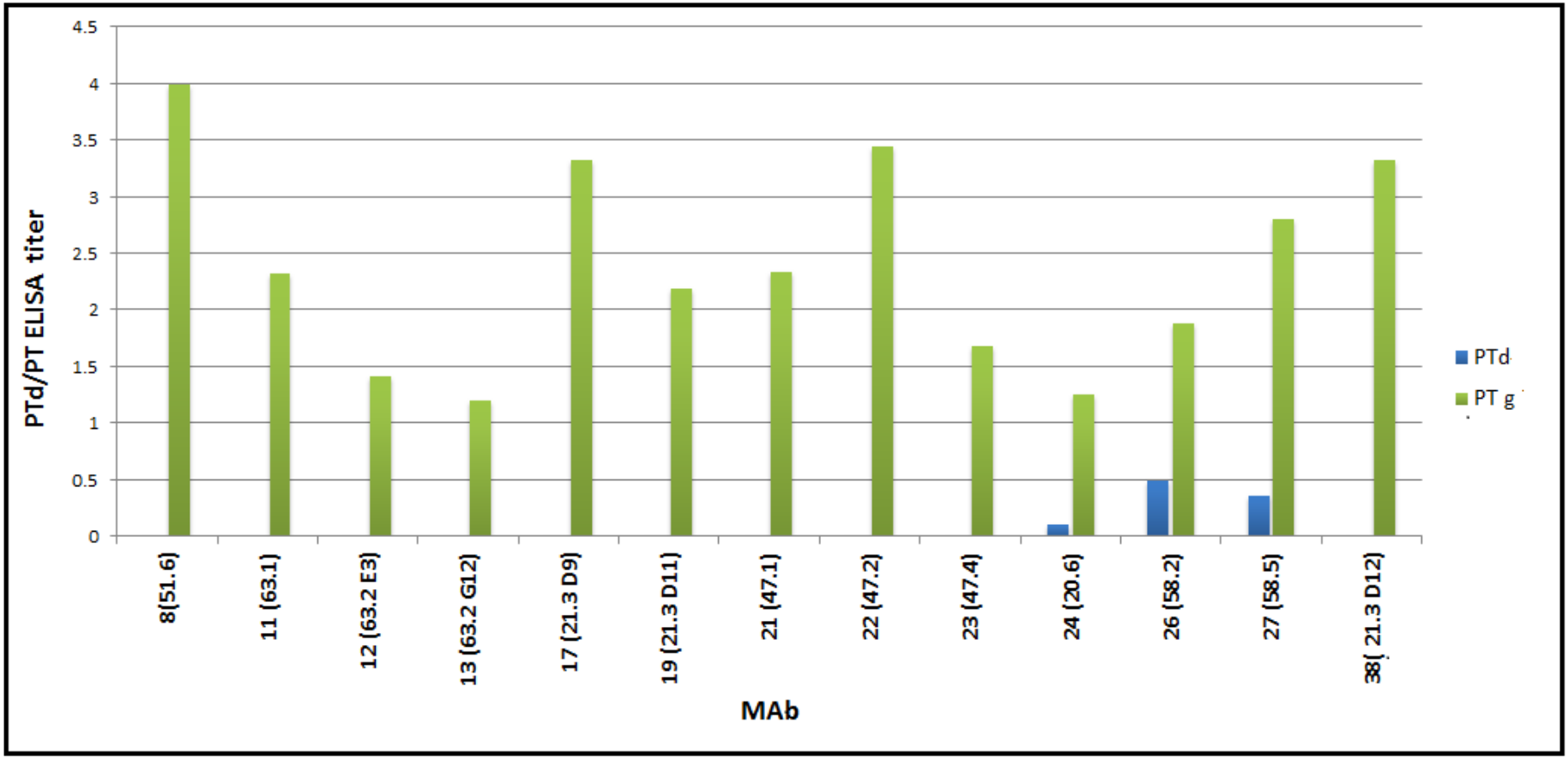
- No reversion to toxicity
- B and T cell epitopes conserved
- Higher immunogenicity





Arg and Lys residues, blue and red respectively

Recognition of genetically or chemically detox. PT by neutralizing MAbs

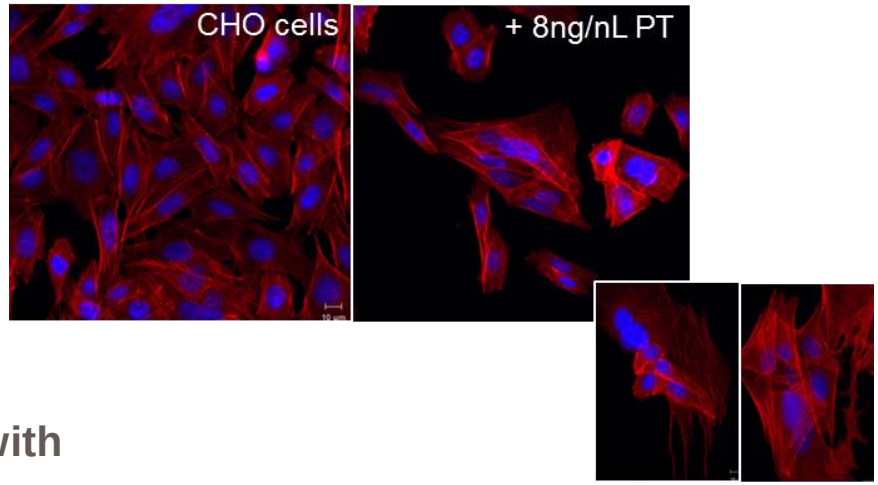


Titers are expressed as anti-detoxified PT ELISA to anti-native PT ELISA ratio. PTd = PT detoxified by 0.35% formaldehyde treatment; PTg = PT genetically detoxified (PT-9K/129G). *Ibsen, P. H. (1996). Vaccine.*

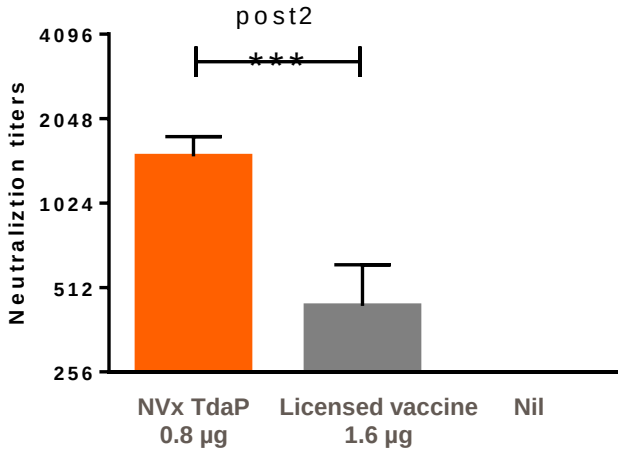
PT neutralization assay confirms the superiority of genetically detoxified PT

PT neutralization assay

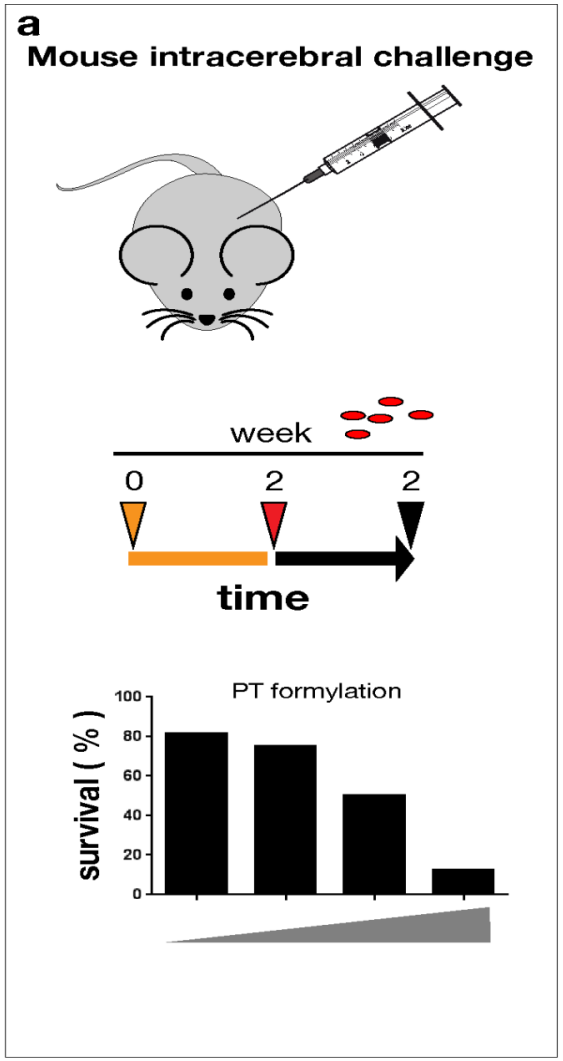
- Active PT induces a clustered phenotype in CHO cells
- aP antibodies are able to inhibit the clustering
- Titers: reciprocal of the highest dilution able to inhibit cell clustering



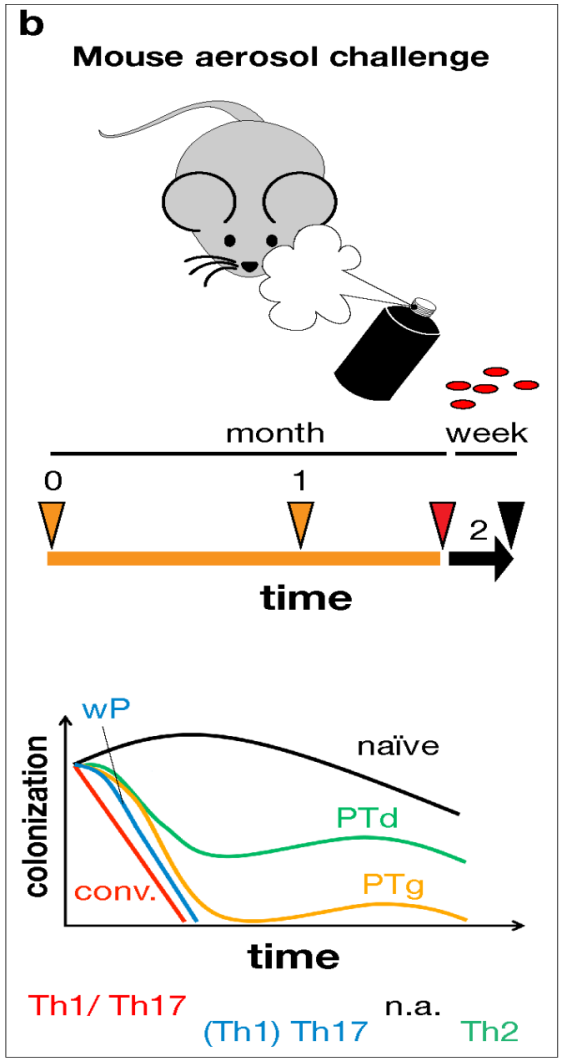
Genetically detoxified PT elicits antibodies with higher neutralizing activity (mouse)



PT9K/129G induces higher protection in the animal models

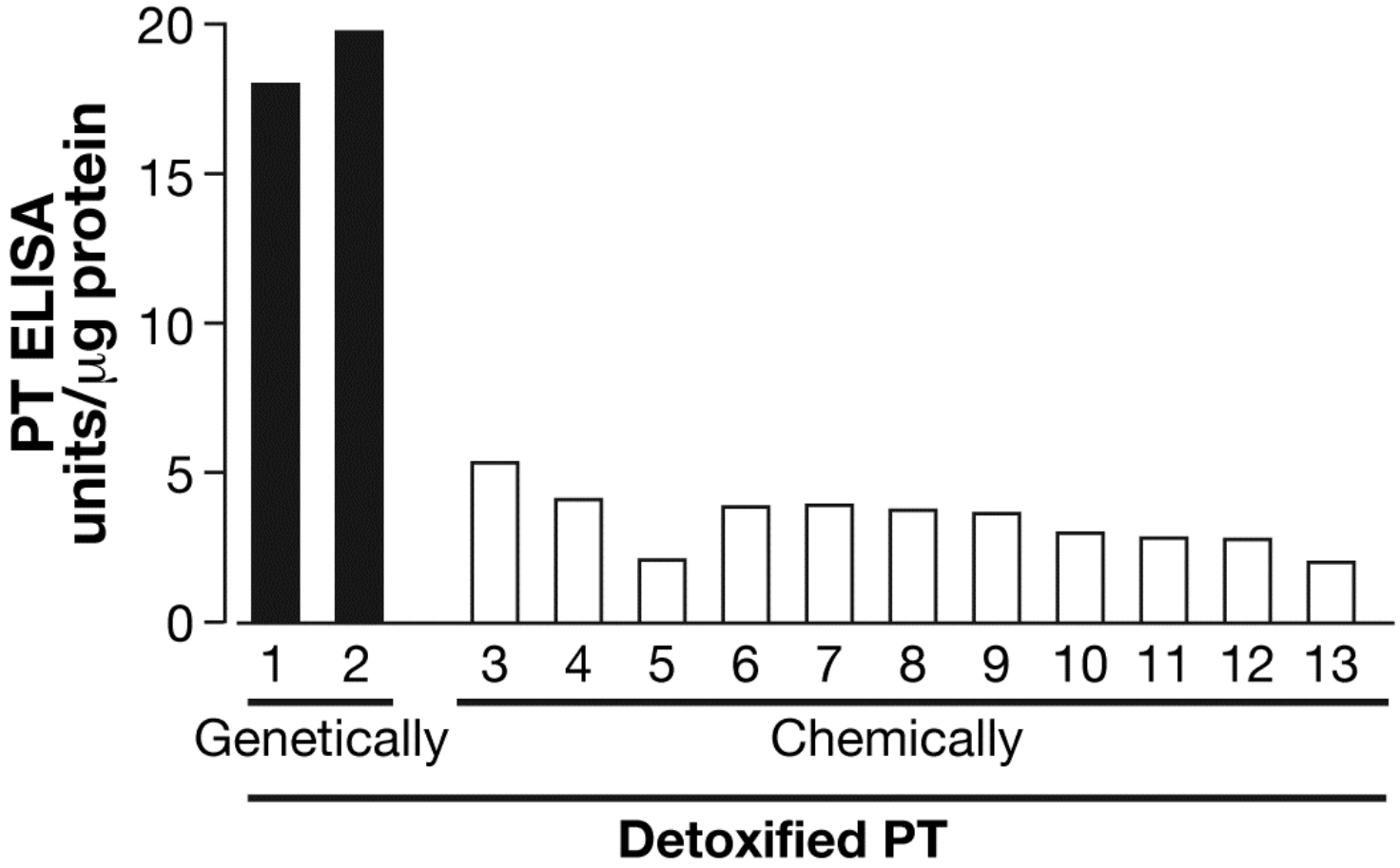


aP-mediated protection depends on degree of formylation of the vaccine antigens

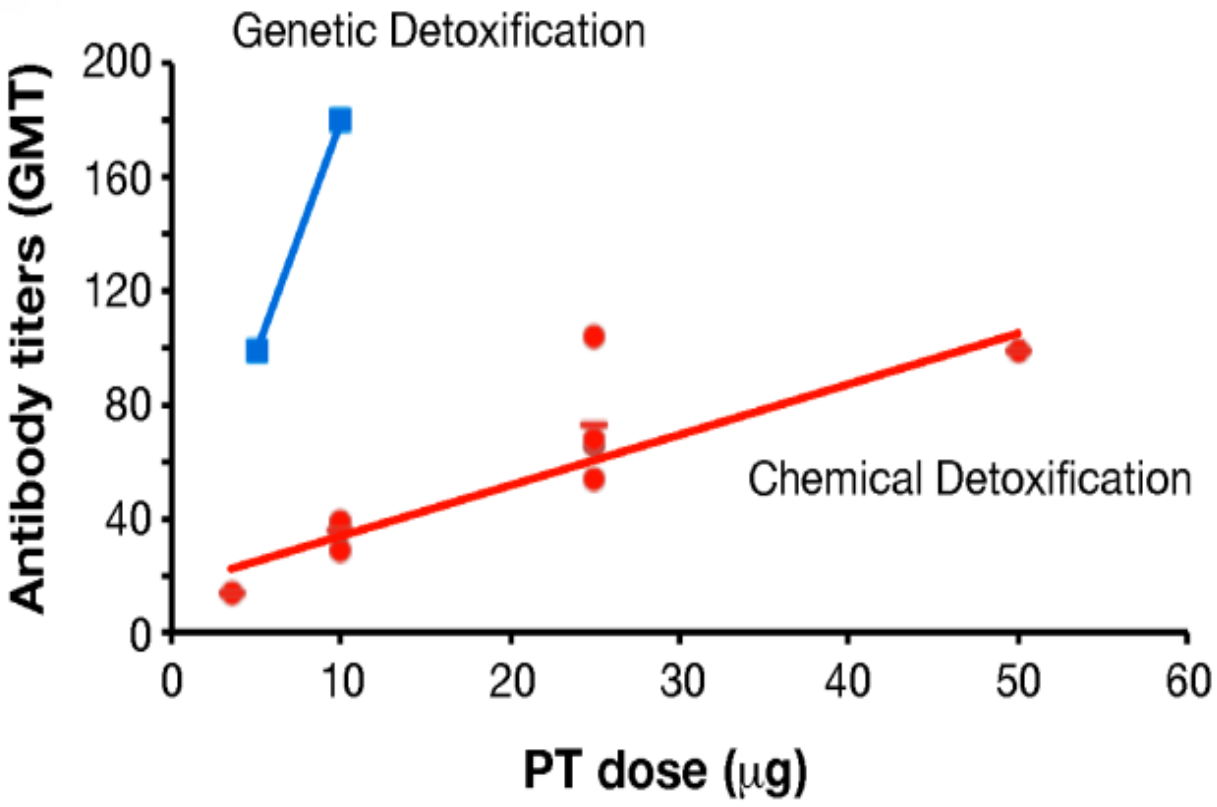


protection from colonization correlates with vaccine efficacy;
protection mediated by Th1/ Th17- dependent mechanisms

PT immunogenicity in humans: NIH trial



PT immunogenicity NIH trial: dose response



Increasing PTg dose will lead to a superior vaccine

1990s Italian Efficacy Study: Design

N° of subjects enrolled = 14751; Multicenter trial: 62 centers - in 4 regions; Schedule: 2-4-6-months.

Component	SmithKline DTaP	Biocine DTaP	Connaught (US) DTwP	Biocine DT (Control)
PT: Inactive Pertussis Toxin (μg)	25	**5** (genetically)	Pertussis*	--
FHA: Filamentous hemagglutin (μg)	25	**2.5**	Pertussis*	--
PRN: Pertactin (μg)	8	**2.5**	Pertussis*	--
D: Diphtheria Toxoid (flocculation units)	25	**25**	6.65	25
T: Tetanus Toxoid (flocculation units)	10	**10**	5	10
Aluminum-Salt Adjuvant	Aluminum Hydroxide	Aluminum Hydroxide	Aluminum Phosphate	Aluminum Hydroxide
Weight of ionic Al (mg)	0.5	0.35	0.15	0.7
Preservative	2-Phenoxyethanol	Thimerosal	Thimerosal	Thimerosal
Weight (mg)	2.5	0.05	0.05	0.05

*5.7 IU per dose by mouse intracerebral challenge test, as determined by manufacturer

Greco D et al. NEJM 1996)

1990s Italian Efficacy Study: Immunogenicity

ASSAY	SmithKline DTap		Biocine DTaP		Connaught (US) DTwP		Biocine DT (control)	
	GMT (95% CI)	RESPONSE (%)	GMT (95%CI)	RESPONSE (%)	GMT (95%CI)	RESPONSE (%)	GMT (95%CI)	RESPONSE (%)
EIA for IgG to **PT** (units/ml)	**51.3**	94.5	**94.4**	96.7	*1.2*	*4.2*	1.0	--
EIA for IgG to **FHA** (units/ml)	147.0	85.1	52.6	60.5	*5.2*	*13.1*	1.5	--
EIA for IgG to **PRN** (units/ml)	274.2	96.6	136.6	95.9	*9.9*	*37.9*	1.6	--
PT neutralization by CHO	**230.0**	67.8	**787.6**	93.6	*23.0*	*1.7*	22.0	--
D		96.6		98.8		*92.9*		98.8
T		99.8		100		*99.1*		100

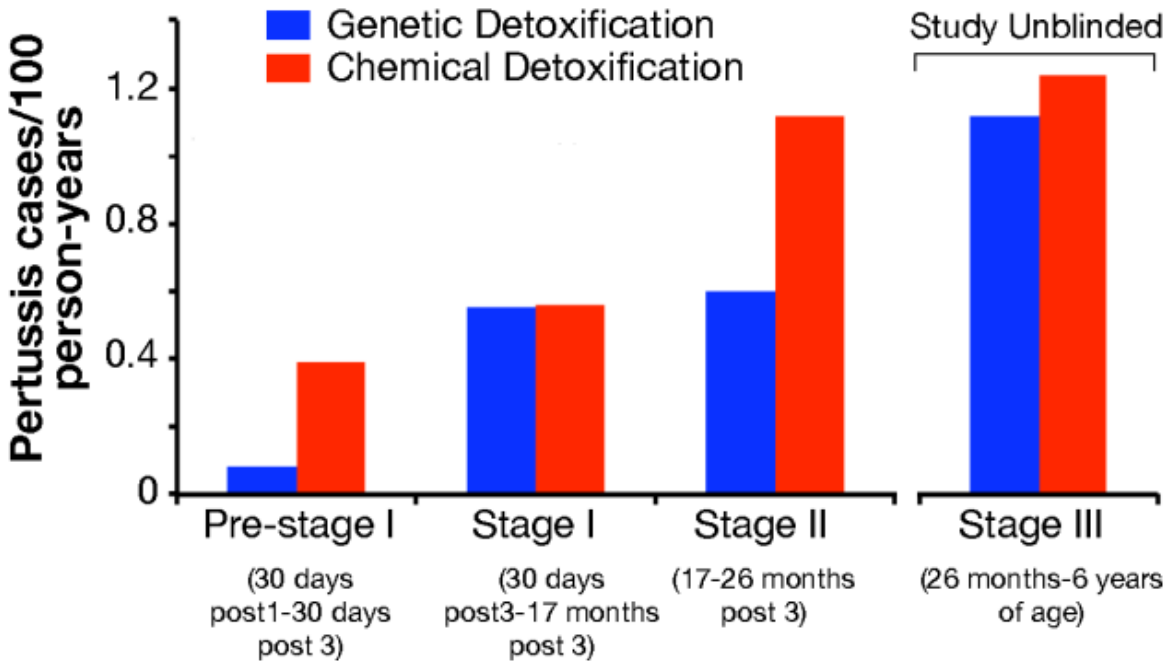
Greco DNEJM 1996.

EIA= enzyme linked immunoassay, CI= confidence interval, GMT= geometric mean titer, CHO= chinese hamster ovary assay

1990s Italian Efficacy Study: Efficacy

VACCINE	EFFICACY
Biocine DTaP	84.2 (76.2 – 89.7)
SmithKline DTap	83.9 (75.8 – 89.4)
Connaught (US) DTwP	36.1 (14.2-52.1)

1990s Italian Efficacy Study: key findings



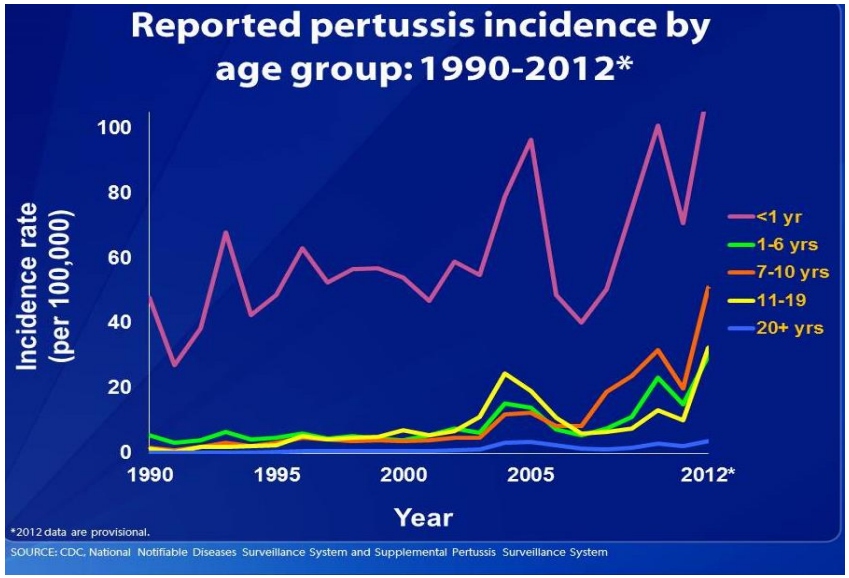
PT9K/129G (at a dose of 1/5 of the chemically detox PT) was able to induce

- earlier protection from disease, before completion of the full vaccination schedule
- longer protection, in the later phase, when the titers of circulating antibody are declining

The need of Pertussis Booster Vaccines

- Significant resurgence of notified pertussis in the past decade despite global vaccination with high uptake
- Highest burden in infants under 6 months and persons over 10 years

(Source: http://www.cdc.gov/pertussis/downloads/pertussis-surveillance-report.pdf)



Neonates: most vulnerable

Infants: increasing incidence

*** Maternal Booster** → **neonates** → *** Infant Booster**

V113_01 Study: aP and TdaP booster

A Phase I, Randomized, Controlled,

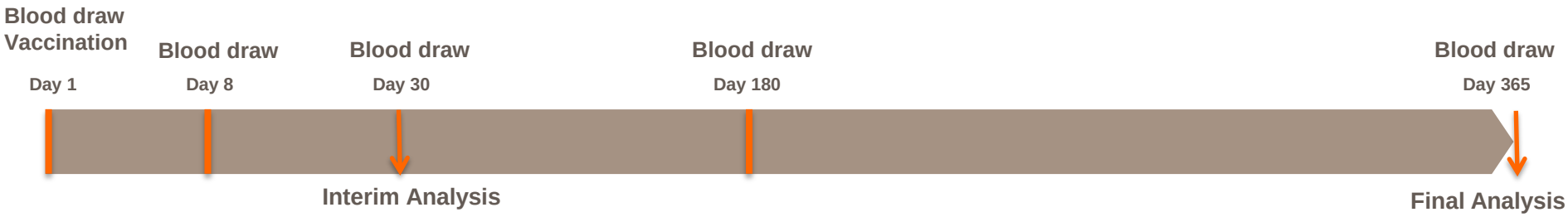
Observer-Blind,

Dose-Ranging Study of Acellular Pertussis and

Tetanus-Diphtheria-Acellular Pertussis Booster

Vaccines in Adults Aged 18 to 40 Years

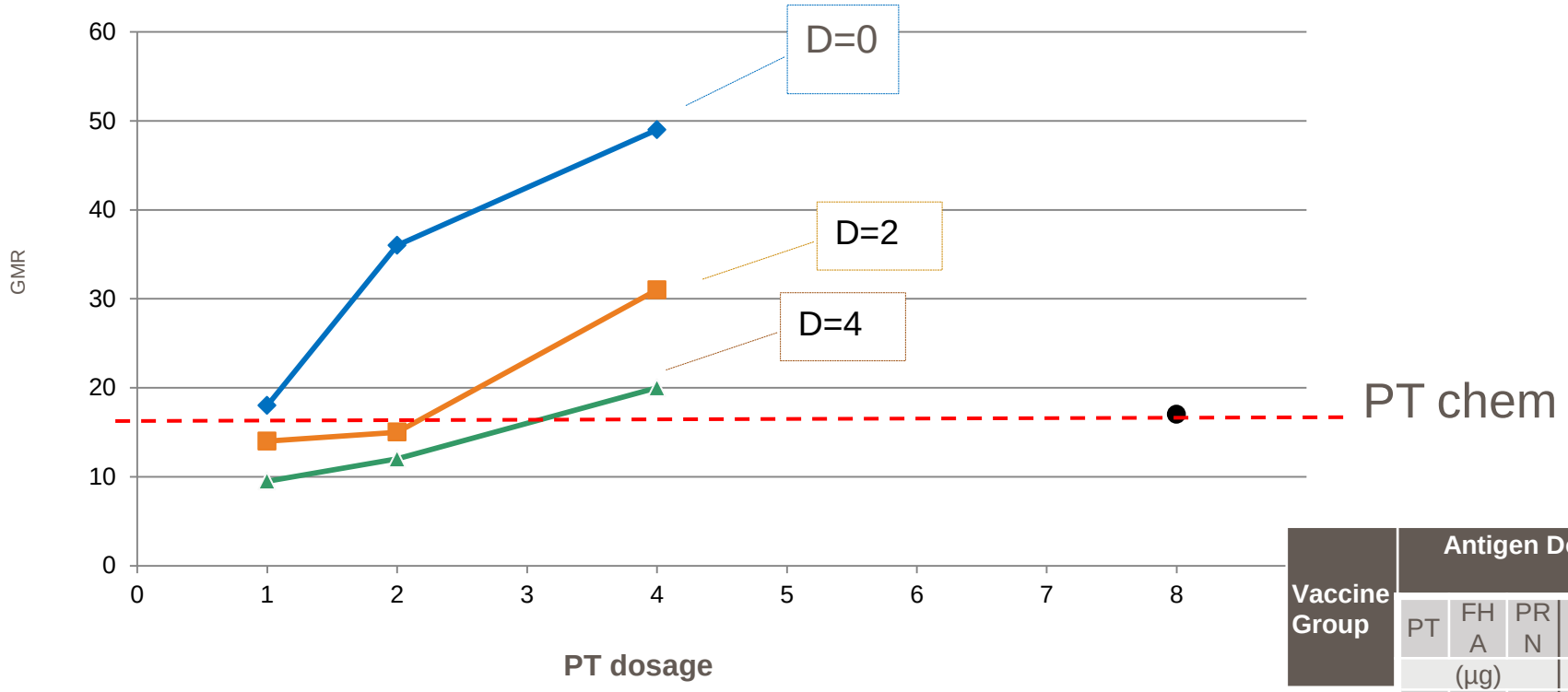
V113_01: Study design



Visit		DAY 1					DAY 30
Vaccine Group	No of Subjects	Antigen Doses					
		PT	FHA	PRN	D	T	
		(µg)			(Lf)		
1 (NVD aP booster)	42	1	1	2	0	0	Td-pur®
2 (NVD aP booster)	42	2	2	4	0	0	Td-pur®
3 (NVD aP booster)	42	4	4	8	0	0	Td-pur®
4 (NVD Tdap booster)	42	1	1	2	2	5	Saline
5 (NVD Tdap booster)	42	2	2	4	2	5	Saline
6 (NVD Tdap booster)	42	4	4	8	2	5	Saline
7 (NVD Tdap booster)	42	1	1	2	4	5	Saline
8 (NVD Tdap booster)	42	2	2	4	4	5	Saline
9 (NVD Tdap booster)	42	4	4	8	4	5	Saline
10 (Licensed comparator Tdap booster)	42	8	8	2.5	2.5	5	Saline

V113_01

Day 30 – Immunogenicity results

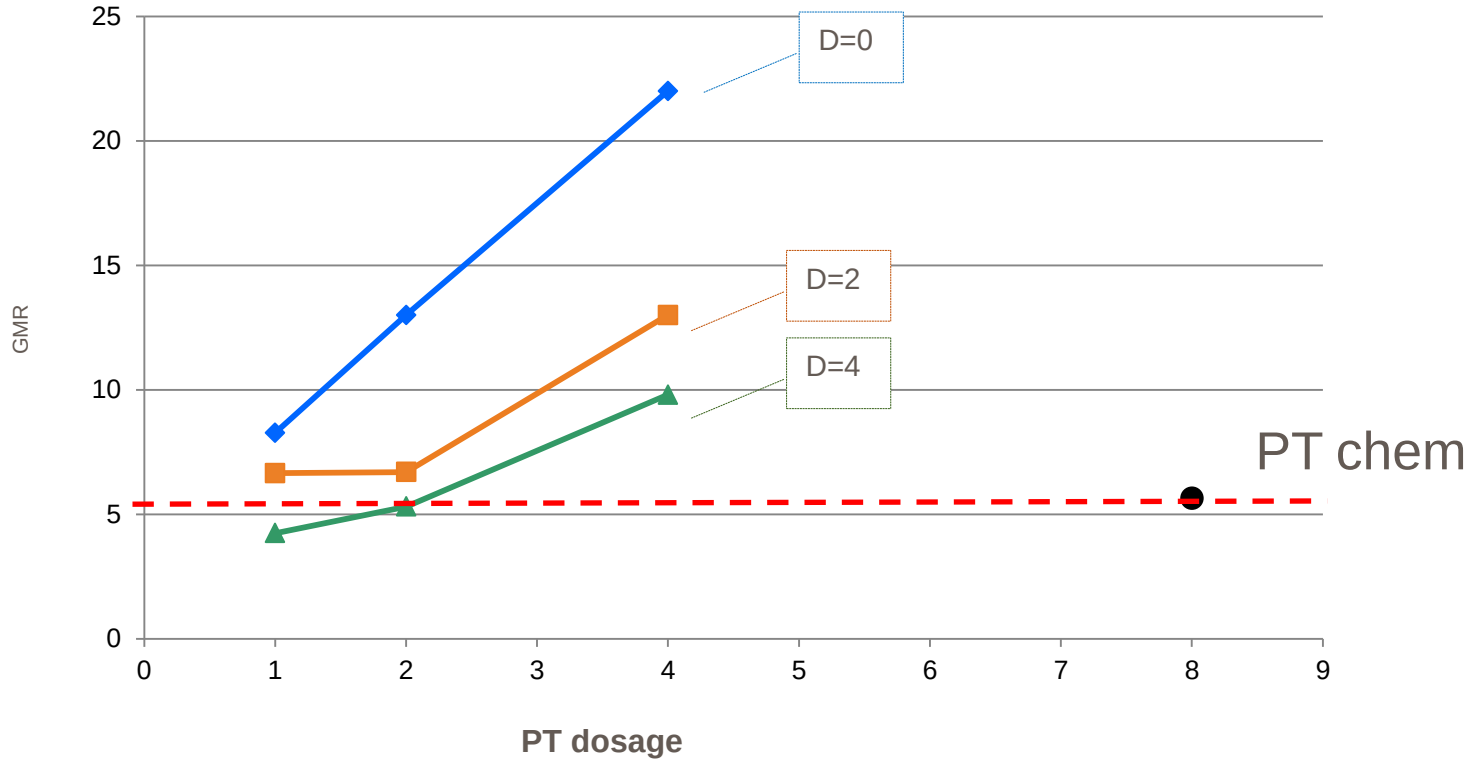


- ✓ **Non-inferiority**
- ✓ **Higher titers with less Ag**

Vaccine Group	Antigen Doses				
	PT	FHA	PRN	D	T
	(µg)			(Lf)	
aP1	1	1	2	0	0
aP2	2	2	4	0	0
aP4	4	4	8	0	0
T5D2aP1	1	1	2	2	5
T5D2aP2	2	2	4	2	5
T5D2aP4	4	4	8	2	5
T5D4aP1	1	1	2	4	5
T5D4aP2	2	2	4	4	5
T5D4aP4	4	4	8	4	5
Licensed vaccine	8	8	2.5	2.5	5

V113_01

Day 365 – Immunogenicity results

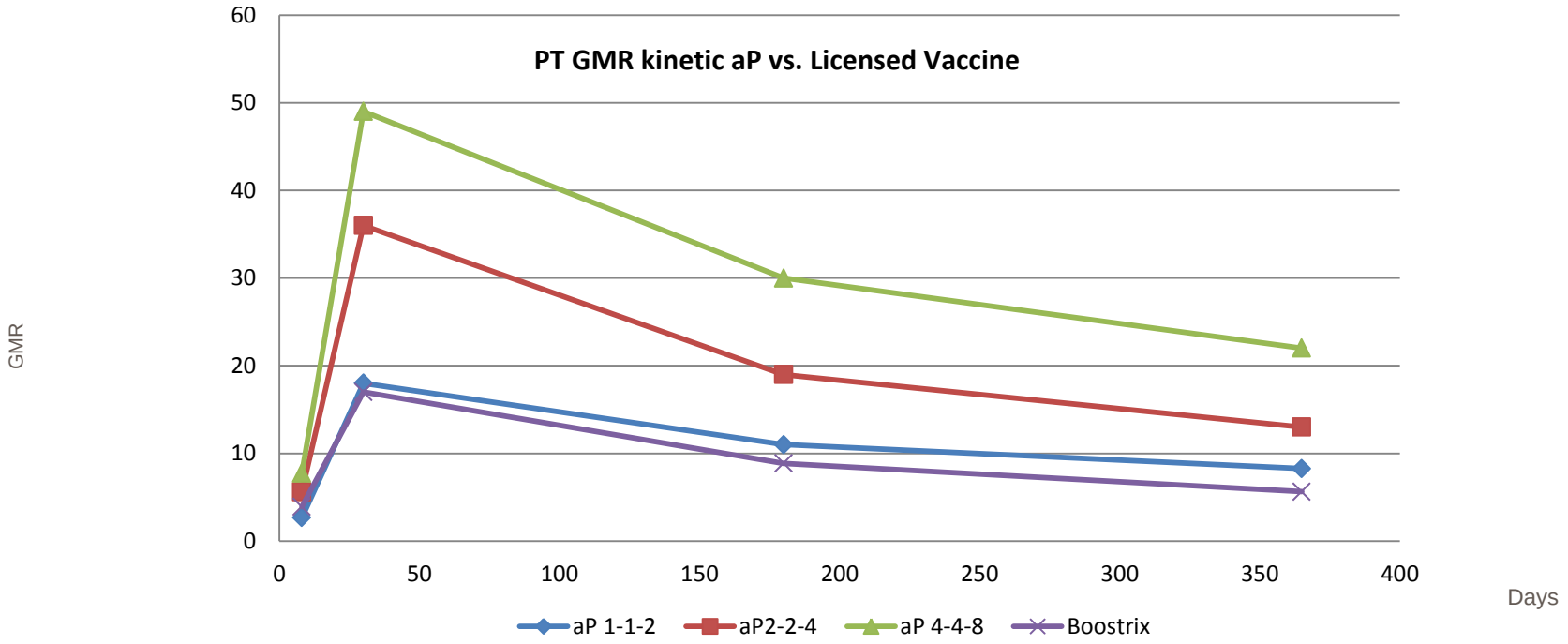


Key Learnings day 365

- PT: Novartis aP/Tdap groups showed more sustained antibody persistency as compared to a licensed booster vaccine . All 4 mcg PT 9K/129G dosages were statistically superior compared to PT chemically detoxified.

V113_01

Day 365 – aP kinetics over time



V113 Phase I study: Conclusions

- All investigational vaccines were well tolerated with no safety concerns identified.

- 30 days post-vaccination PT9K/129G formulations induced anti PT antibodies at higher level compared to the PT chem. detox., despite lower antigen doses.

- Antibody persistence (180/365 days) was evident in all groups, but waning of anti-PT antibodies was slower in PT9K/129G, as compared to the PT chem.detox. vaccinated subjects

Conclusions

- Only genetic inactivation of pertussis toxin leads to a vaccine antigen that maintains all neutralizing epitopes
- Vaccines containing PT9K/129G outperformed vaccines containing chemically inactivated PT in pre-clinical infection models and in clinical trials even at lower antigen concentrations
- Future pertussis vaccine formulations should include the genetically inactivated PT-9K/129G instead of its chemically activated counterparts

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