

Consumer: Need statement - how do we want quantitative modelling to improve TB vaccine dose/regimen selection?

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# Vaccine Dose finding - history

- No formal recommendations by any regulatory agency on how to determine vaccine dose (-“vaccine dose selection is not a major concern of regulators whose job it is to objectively review proposed studies and development plans for compliance with regulations”).
- No publications prior to 2017 on quantitative methodologies for dose finding
- No previously published confidence intervals on dose (How sure am I that I have the right dose? How much of that is the assay variability or the biologic response?)
- Method- SMART approach- use known responses of similar vaccines, do dose escalation in animals based on that data, generally assume that the response is sigmoidal and that the highest safe dose, given a margin, is the “Right Dose”
- This approach has worked well historically for vaccine responses based on binding antibodies
- Is this true for T cell responses, neutralizing antibodies, new platforms?

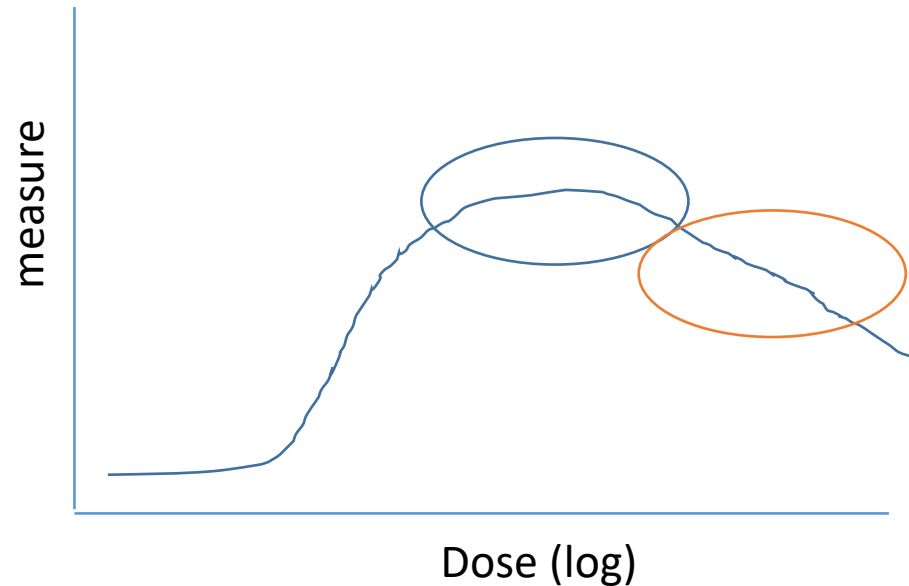
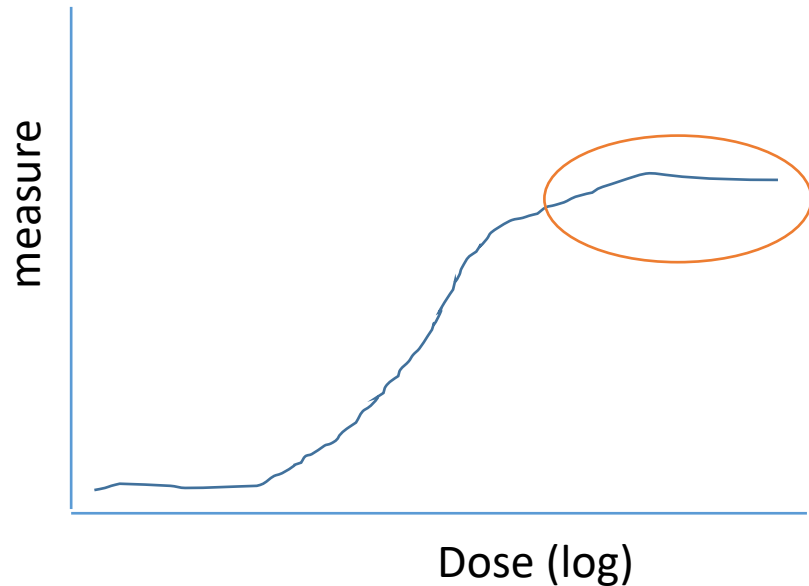


SMART- SMart people sitting  
ARound the Table approach

# Shortcomings of the present method- is there a problem

**We usually never check to see if the dose is right, so we usually don't know if there is a problem**

- RTS,S vaccine based on human challenge models
- IC31 and other adjuvanted TB vaccines- based on T cell activity was done incorrectly
- QS-21 adjuvanted HIV envelope proteins
- Neutralizing antibody competing with immunodominant binding antibodies
- Induction of CD4+ T cell responses by adenoviral vectors
- Yellow fever and inactivated polio fractionation



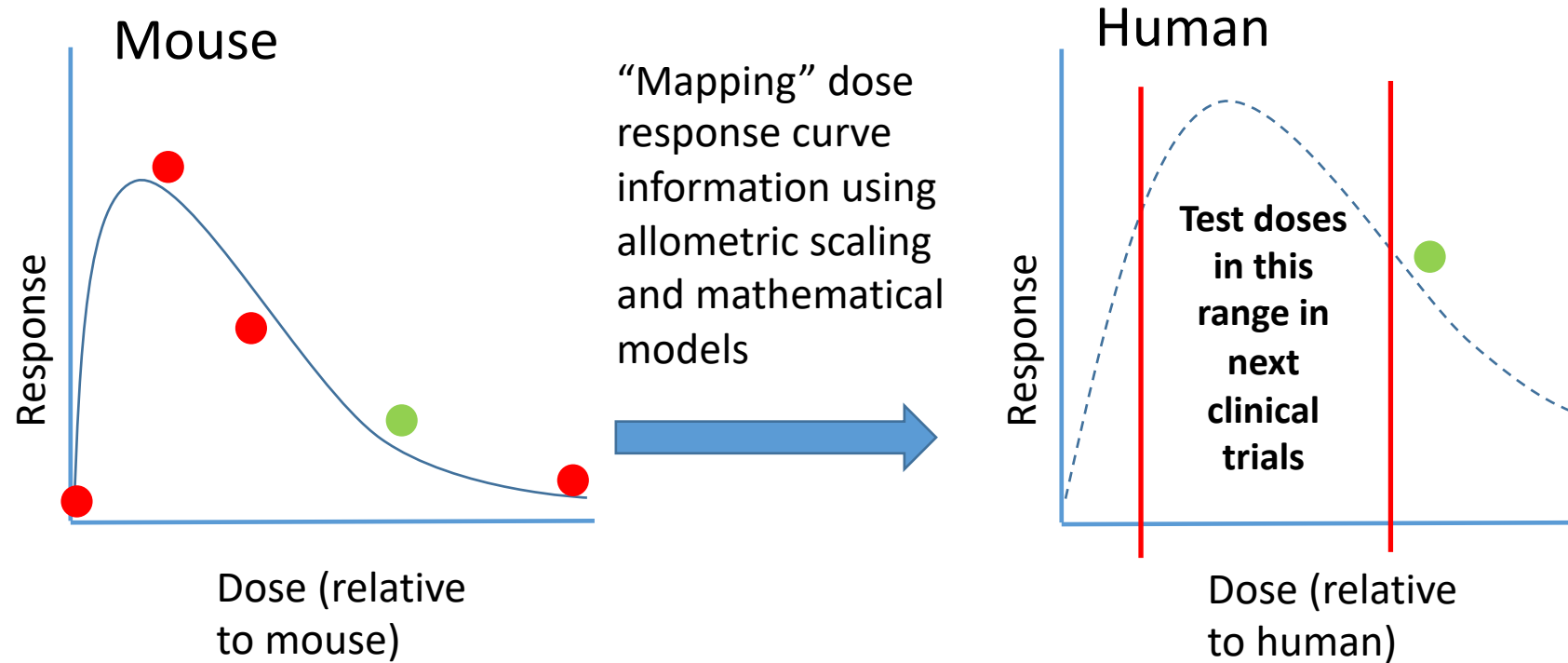
# Potential approaches to these issues

- Larger and greater number of doses and increased N in dose-finding studies
- Iterative dose finding studies
- Adaptive dose finding studies

Note that the intrinsic, natural bias toward magnitude in vaccine dose selection is VERY SLOWLY being replaced with a focus on known correlates of protection or functionality- (neutralizing or ADCC Ab vrsus titer for RSV and CMV, T cell affinity, memory, or tissue functionality instead of T cell magnitude in PBMCs)

Solution in drugs- use PK/PD results from animals to generate a model, use allometric scaling to choose doses in man, and do adaptive studies in which doses are chosen during the ongoing study

# Translating dose



- “Map” dose response information between mouse and human at specified time point
- Could utilize a mechanistic model (Immunostimulation/Immunodynamics) to characterize the immune response (T cell) response over time to compare, map and predict dose information between mouse and human, and design trial to maximize the information gained

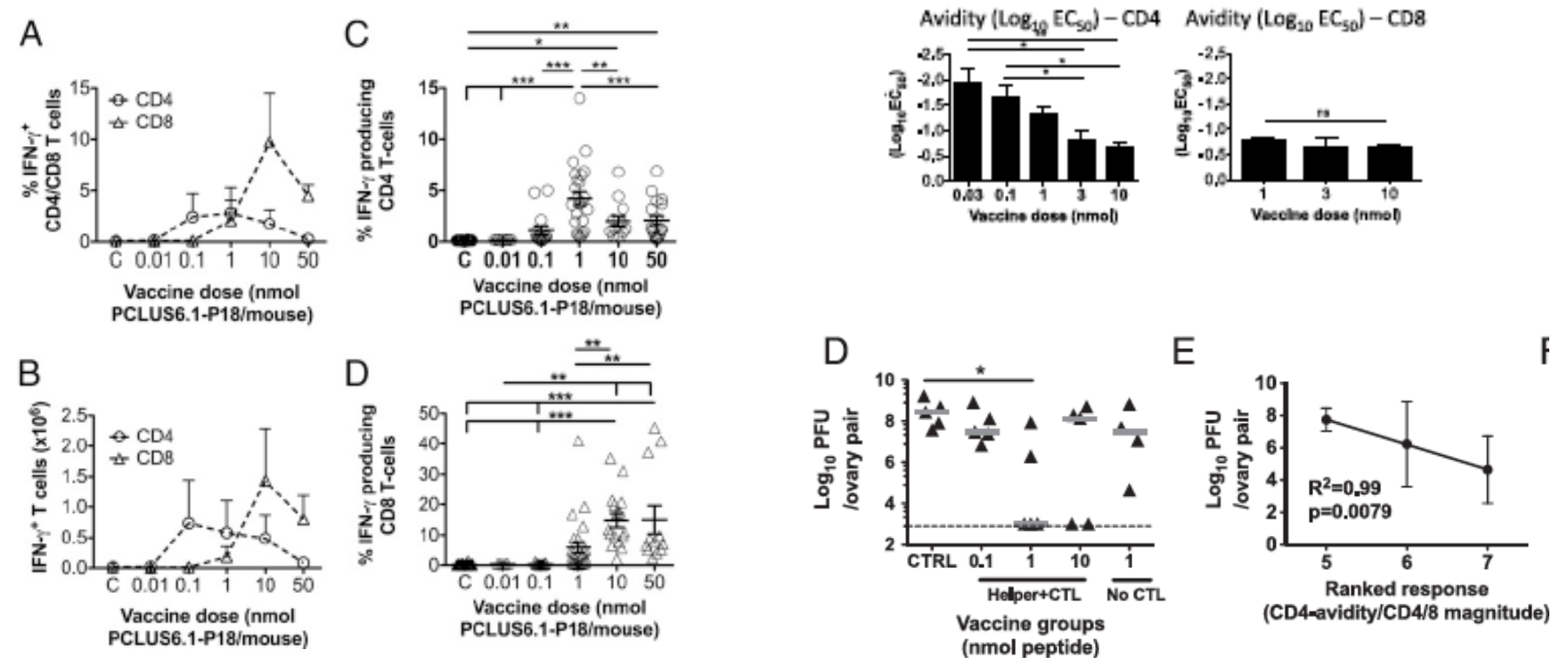
# Do we need modelling compared to our “usual methods”

Advantages	Disadvantages
Use of fewest subjects to find the best dose	No regulatory guidance
Able to use pre-defined confidence intervals to determine the N	Not accepted in the field
Extensive work in immunologic models from which to choose	No allometric scaling tools available
Relies on quantitative assessments rather than opinions	New field with no history and little talent to date

# Example- Induction of CD4/CD8 in mice

Billeskov et al. J Immunol 2017

- Vaccinia challenge model following protein/CAF09 immunization
- Found CD4 number and avidity affected by dose
- Found protection correlated strongly with a ranked response index that included CD4 avidity and CD4 and CD8 magnitude, despite protection being dependent on CD8 T cells
- Best protection was not at the highest dose



(CD4 Inf- $\gamma$  MFI appeared to be a reasonable substitute for avidity)

Also, for repeat vaccination, low dose key at **priming**

# Application- Proposed approach in adenoviral programs

- Explore at least 5 doses in mice to determine shape of curve of ChAdOx1
- Score the **readout** in CD4 magnitude/functionality (using Gamma interferon MFI) and CD8 magnitude/polyfunctionality (multiple potential indexes published -Darrah, Larsen, Derrick)
- (Be prepared by filling at  $10^9$  and  $10^{11}$  (often a limiting factor), and need rapid correlate turnaround)
- In man, use 3+3 protocol to generate same data at (perhaps)  $10^7, 10^8, 10^9, 10^{10}, 10^{11}$  (N=15)
- Use modeling simulations to determine how to best define the shape and peak of the “curve”
- Do iterative groups that are given by modelling group (usually 3 doses) around putative best dose (N=16)
- Set as a goal a CI of 0.5 log for the vaccine dose – achievable with 60 subjects in 8 months
- Explore the methodology in other systems, in which effect of dose on recruitment ( $\delta$ ) and  $\beta_{cm}$  can be studied (see et al. Nature, 2017); i.e., does dose affect the rate of transition to the different populations that affect outcome?



# Dose ranging study, N=60

May		June				July					Aug				Sep				Octobe
20	27	3	10	17	24	8	15	22	29	5	12	19	26	2	9	16	23	30	7
N=3 10*8		PBMC		PBMC															
N=3 10*9		PBMC		PBMC															
N=3 10*10		PBMC		PBMC		example													
N=3 10*11		PBMC		PBMC															
						N=8 5x 10*9	MVA 10*7	PBMC			PBMC								PBMC
						N=8 5x 10*9	MVA 10*8	PBMC			PBMC								PBMC
						N=8 10*10	MVA 10*7	PBMC			PBMC								PBMC
						N=8 10*10	MVA 10*8	PBMC			PBMC								PBMC
						N=8 5x 10*10	MVA 10*7	PBMC			PBMC								PBMC
						N=8 5x 10*10	MVA 10*8	PBMC			PBMC								PBMC

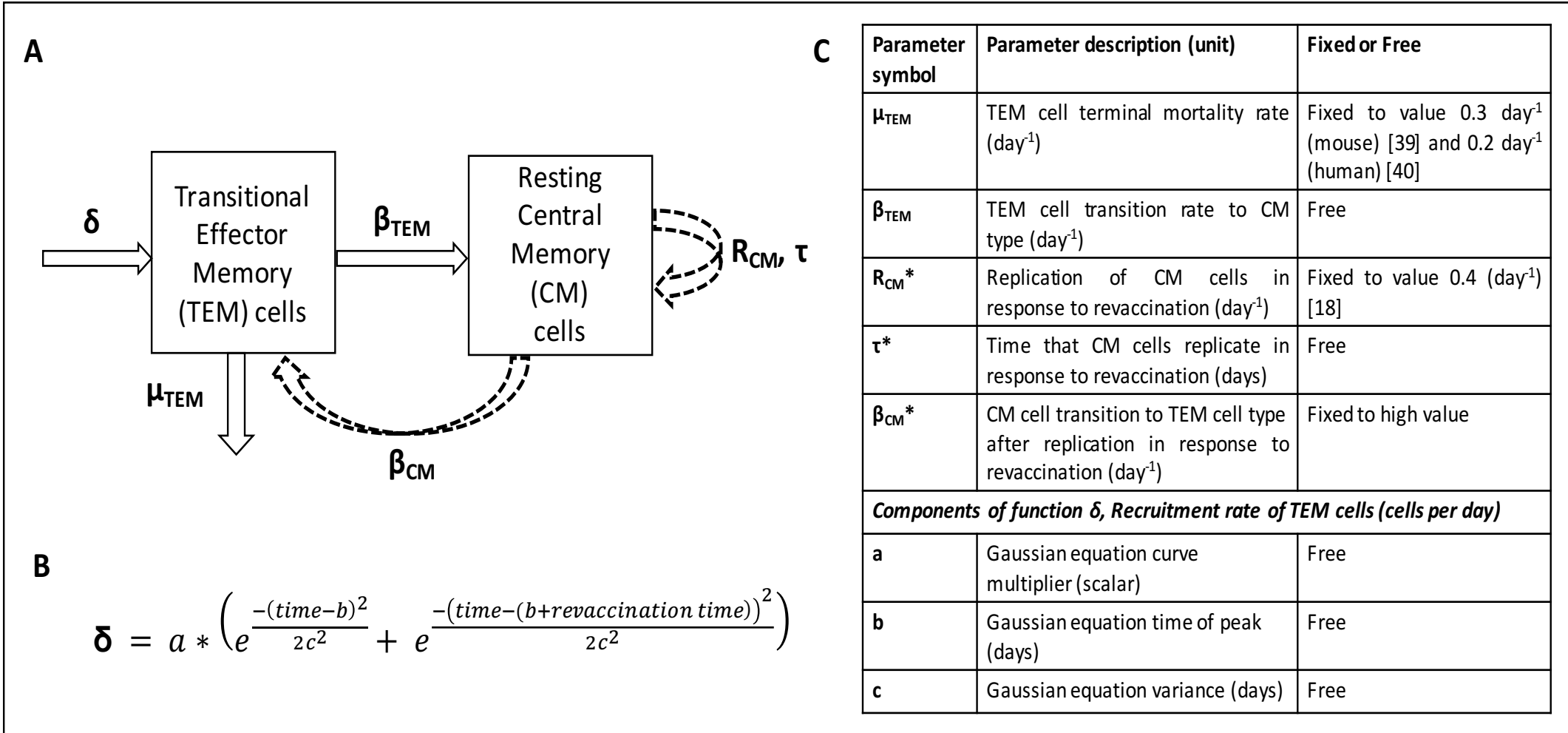
- FPFV May- two weeks to enroll initial 12 subjects
- Select phase 2 doses from day 14
- Two months to recruit 48 at two sites
- Use peak data to select dose and confirm using one month and 3 month data

## Next steps

- Finish adenovirus first dose analysis and build T cell model
- Discuss adaptive dose ranging protocols with the Regulatory agencies
- Begin to analyze regimens to study boosting times
- Confirm CI hypotheses in the TB model
- Apply work to another area (malaria challenge studies or yellow fever)
- Encourage others to join our efforts

# Back-up

# Model structure to bridge animal to human

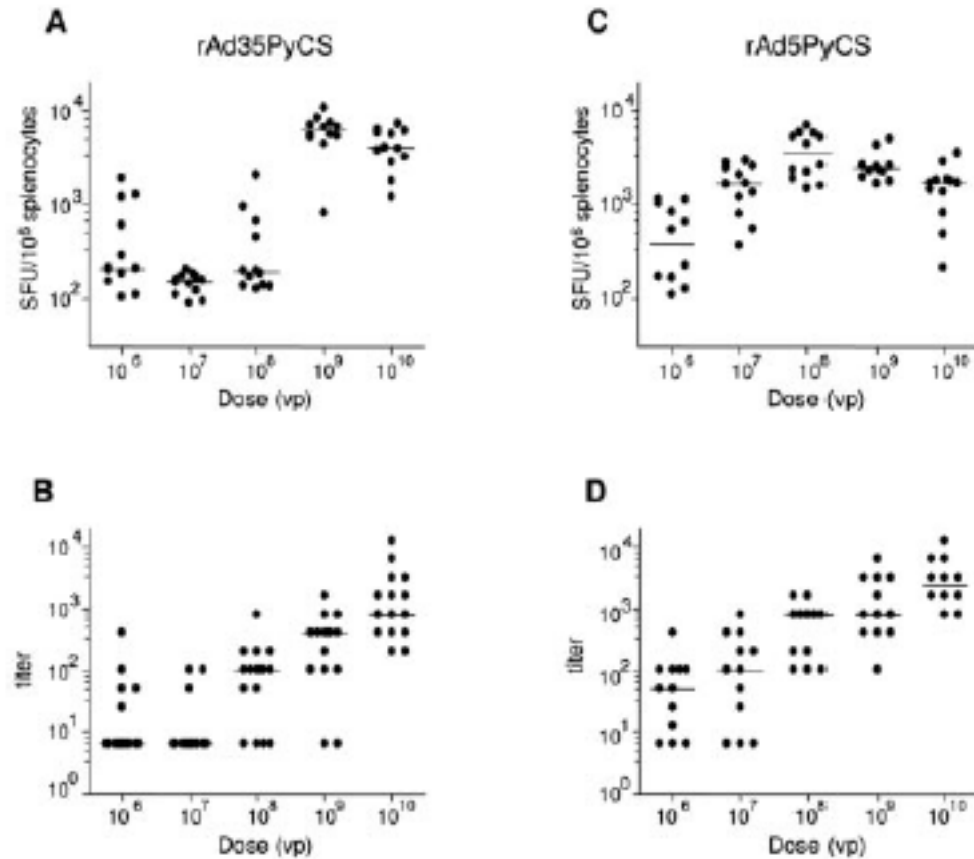


# Population parameters for mice and humans

- Estimated using NLMEM, using the SAEM algorithm fixed in Monolix (as per PK/PD)
- Final model selected using Bayesian Information Criteria Selection

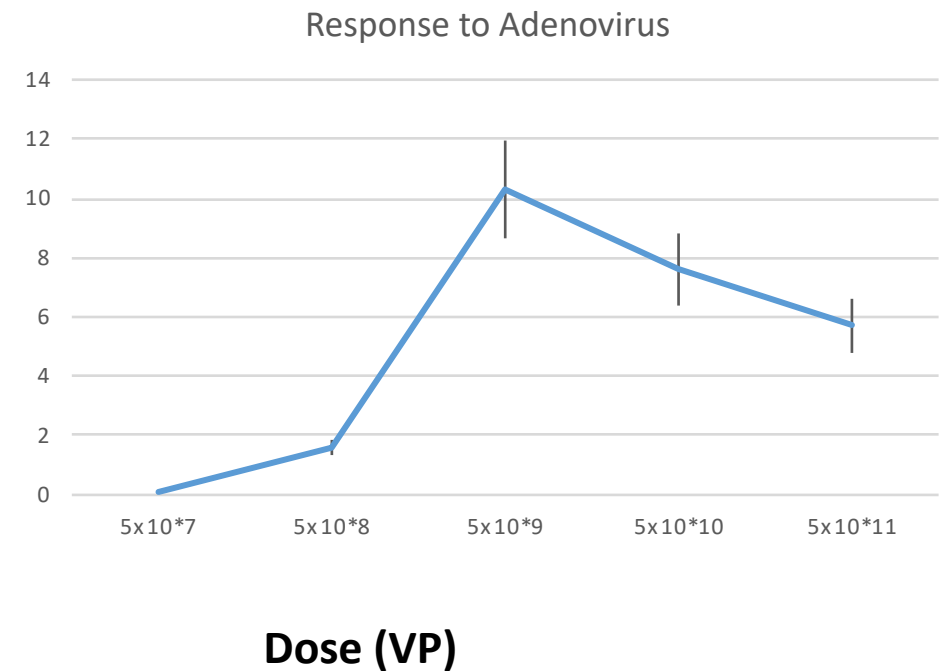
	Mouse					Human			
	Pooled (analysis 1i)		Dose covariate (analysis 1ii)			Pooled (analysis 2)		Predicting dose (analysis 3)	
Parameter (unit)	Value	RSE (%)	Dose group	Value	RSE (%)	Value	RSE (%)	Dose group	Value
Death rate of Transitional effector memory cells, $\mu_{TEM}$ (per day)	0.3 (F)*	-		0.3 (F)*	-	0.2 (F)**	-		0.2 (F)**
Transition rate from Transitional Effector to Central Memory cell type, $\beta_{TEM}$ (per day)	0.18 (E)	17	Low	0.23 (E)	14	0.022 (E)	31	Low	0.032 (P)
			Middle	0.15 (E)	23			Middle	0.022 (F')
			High	0.056 (E)	26			High	0.0074 (P)
Replication rate of Central Memory cells (per day), $R_{CM}$	0.4 (F)***	-		0.4 (F)***	-	0.4 (F)***	-		0.4 (F)***
Central Memory cell replication time, $\tau$ (days)	1.1 (E)	2		1.1 (E)	7	0.34 (E)	35		0.34 (F')
Transition rate from Central Memory to Transitional Effector type, $\beta_{CM}$ (per day)	10 (F) <sup>\$</sup>	-		10 (F) <sup>\$</sup>	-	10 (F) <sup>\$</sup>	-		10 (F) <sup>\$</sup>
Recruitment of Transitional Effector rate $\delta$ : Gaussian equation scalar, a (# cells)	92.9 (E)	14		103 (E)	13	51 (E)	23		51 (F')
Recruitment of Transitional Effector rate $\delta$ : Gaussian equation mean, b (days)	6 (E)	8		6.2 (E)	10	16.6 (E)	20		16.6 (F')
Recruitment of Transitional Effector rate $\delta$ : Gaussian equation variance, c (days)	0.91 (E)	15		0.89 (E)	7	5.7 (E)	13		5.7 (F')

# Selected evaluation of adenoviral dose responses



Here using immunodominant peptide  
*Ophorst et al Infect Immun 2006*

% CD8 response at peak time point



Also using immunodominant peptide  
*Pinto et al. J Immunol 2003*

