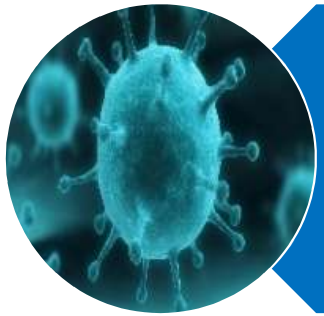
Recent TB vaccine developments

Willem Hanekom

BILL & MELINDA GATES foundation

Whole cell

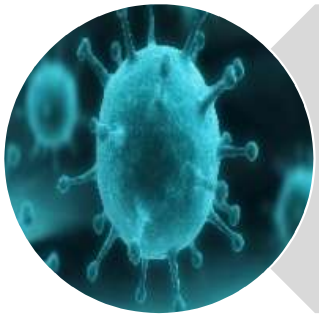


Viral vectored

Protein/ Adjuvant

Contingency!

Whole cell

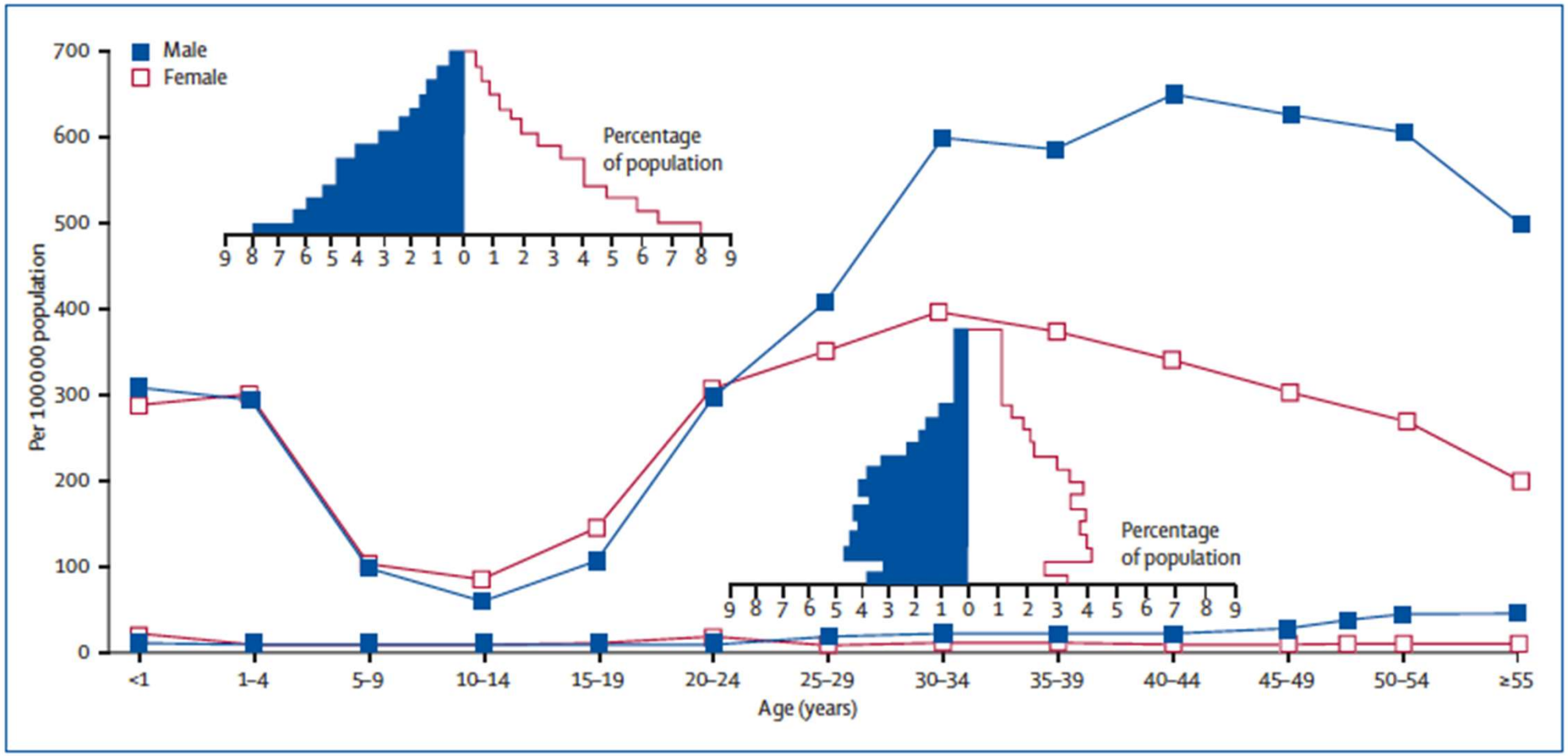


Viral vectored

Protein/ Adjuvant

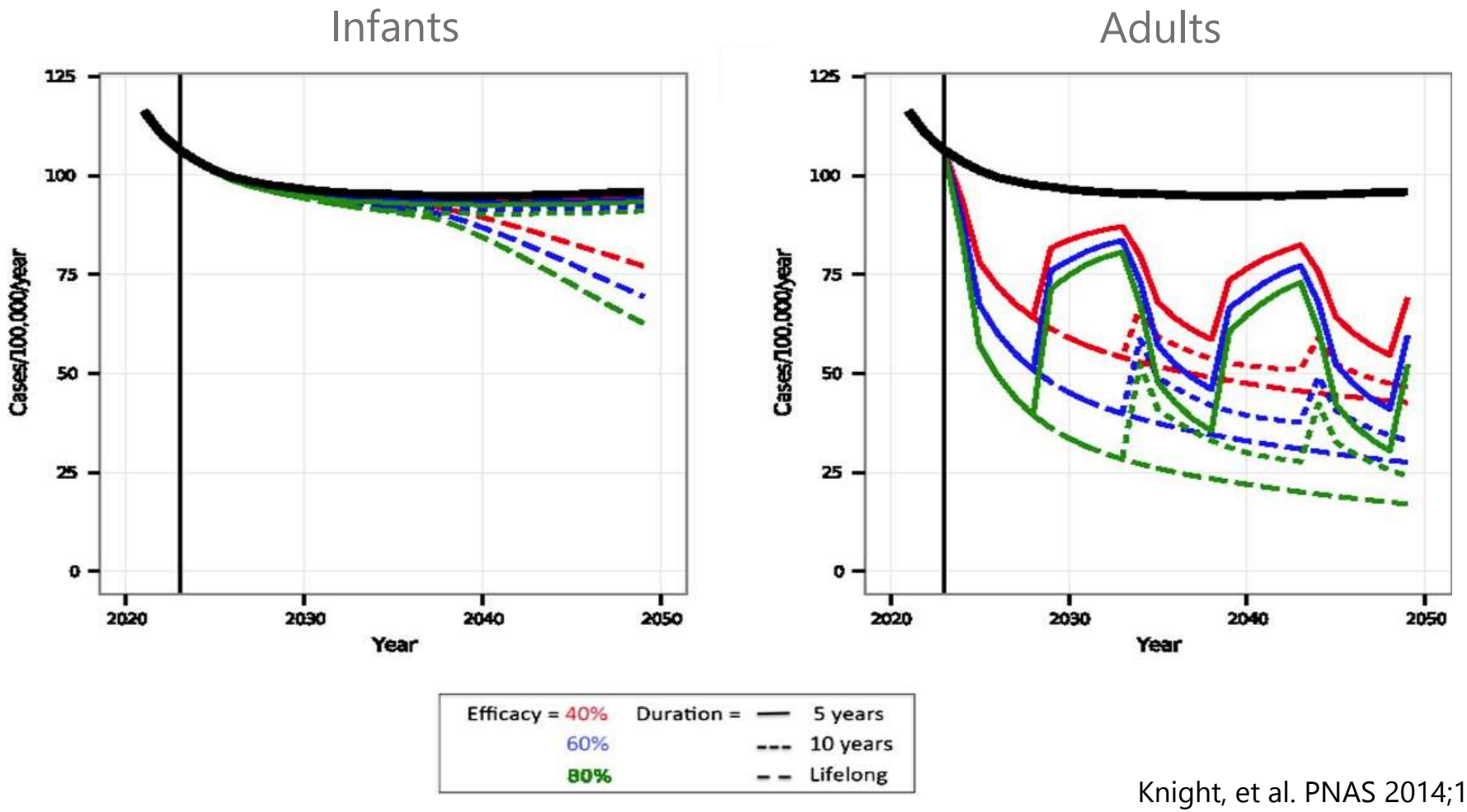

50%
20%
80%
BCG

For impact (even in children), target adolescents and adults



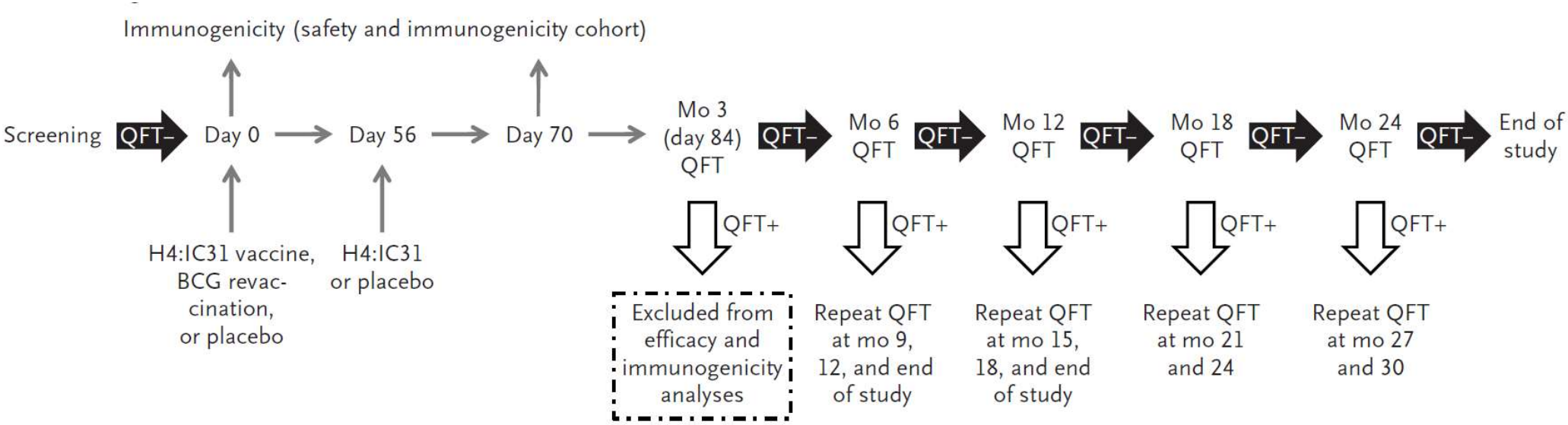
Donald, et al. IJTLD 2004;8:621.

Target (HIV-uninfected) adolescents and adults, first



Knight, et al. PNAS 2014;111:15520

Can H4:IC31 or BCG prevent Mtb infection in adolescents?

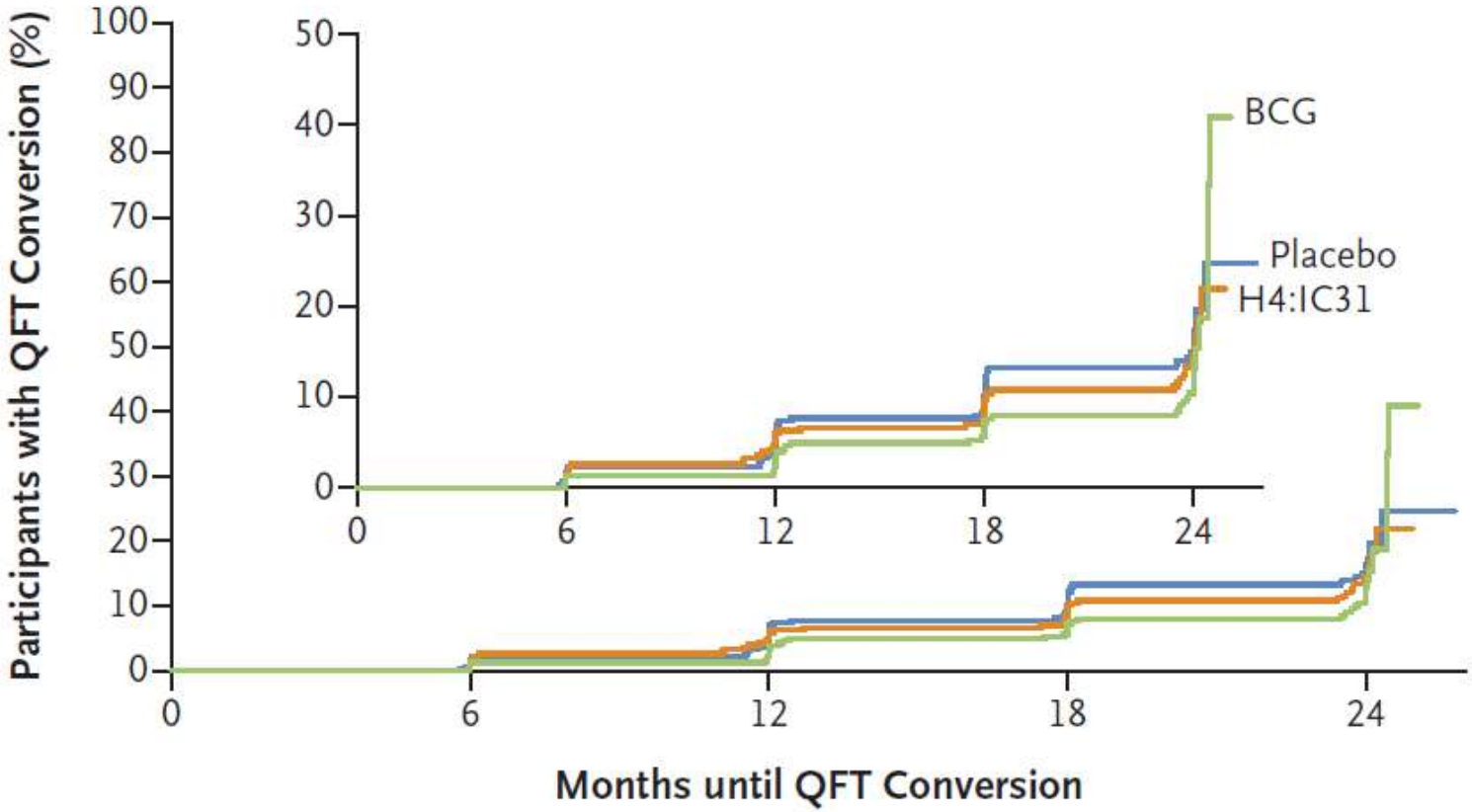


Inclusion criteria:
Healthy HIV-, QFT- adolescents
Exclusion criteria:
Previous/current TB disease, household TB contact

Nemes, et al. NEJM 2018;379:138

Can H4:IC31 or BCG prevent Mtb infection in adolescents?

Primary outcome: Any QFT conversions after day 84



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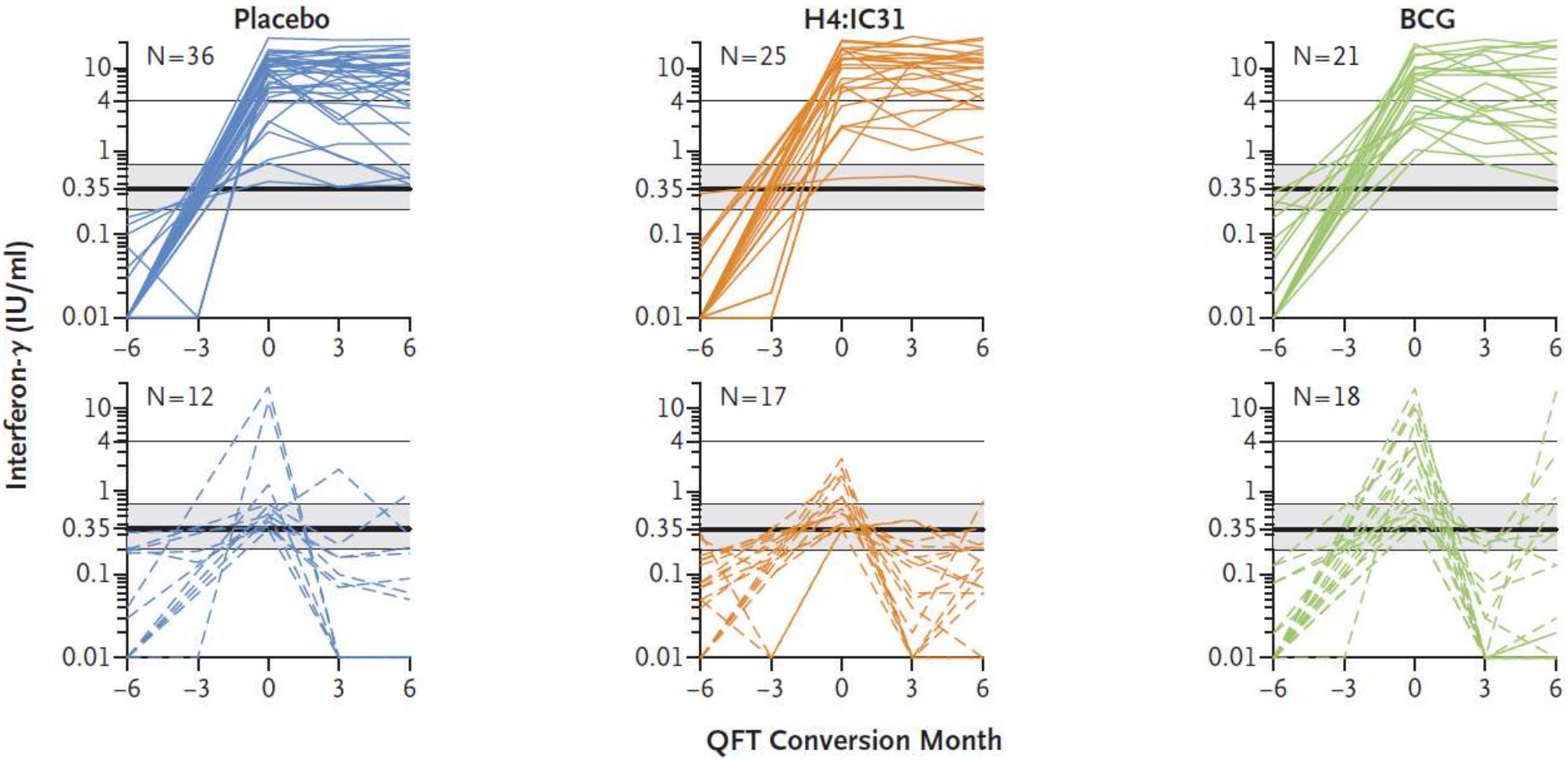
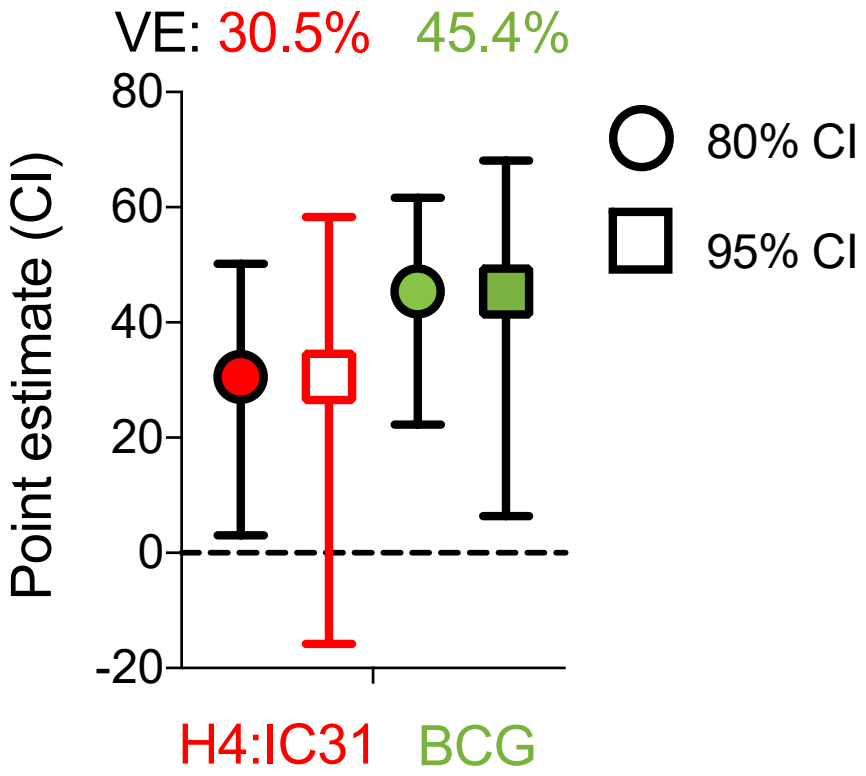


Nemes, et al. NEJM 2018;379:138

Can H4:IC31 or BCG prevent Mtb infection in adolescents?

Secondary outcome: Sustained QFT conversions (3x positive over 6 months)



Nemes, et al. NEJM 2018;379:138


50%
20%
80%
BCG

Would alternate routes or doses of BCG result in better protection against TB disease?

Group (NHPs)	Vaccine	Dose	Route	N (per cohort)
1	BCG	$5x10^5$	Low-ID	10 (5, 4, 1)
2	BCG	**$5x10^7$**	High-ID	8 (0, 4, 4)
3	BCG	**$5x10^7$**	AE	10 (5, 4, 1)
4	BCG	**$5x10^7$**	IV	10 (5, 4, 1)
5	BCG	$5x10^5$ + **$5x10^7$**	ID+AE	10 (5, 4, 1)
6	Unvaccinated			4 (0, 0, 4)

Low-dose TB challenge (10-15 CFU-Erdman): 6 months after immunization

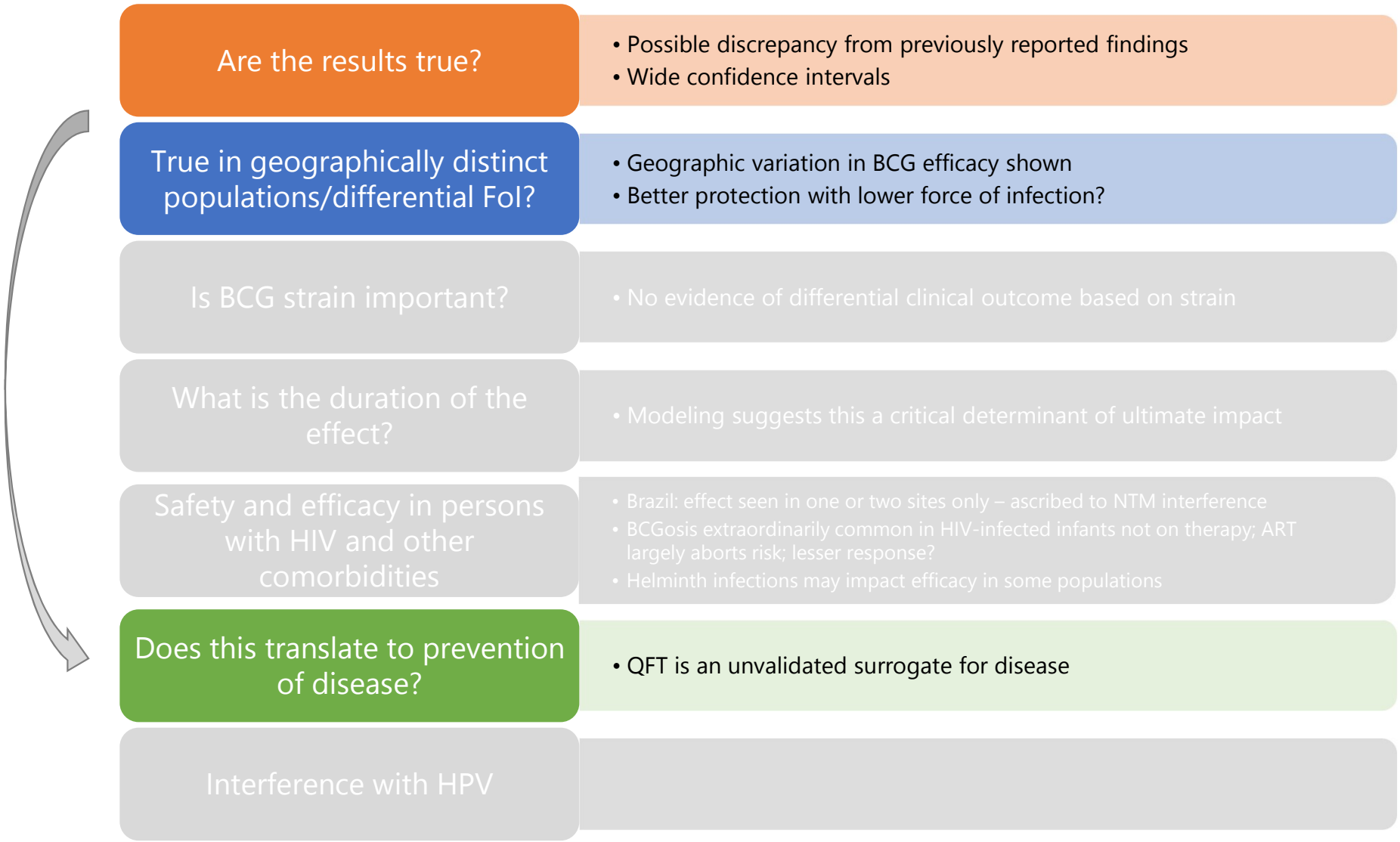
Endpoints: PET/CT imaging, Pathology/CFU

Tricia Darrah, Bob Seder, Mario Roederer, Joanne Flynn and colleagues, Aeras

Toward a comprehensive BCG strategy at the foundation

Optimal use of current BCG	Delineating mechanisms/correlates of protection	Next generation whole cell vaccines

• BCG revaccination	• Human (prevention of infection)
	• NHP (IV BCG)
		• BCG dose/route
		• Safer/more protective strains
		  • Fast followers
		  • Others
		• Guided by protective mechanisms


Are the results true?
• Possible discrepancy from previously reported findings
• Wide confidence intervals
True in geographically distinct populations/differential FoI?
• Geographic variation in BCG efficacy shown
• Better protection with lower force of infection?
Is BCG strain important?
• No evidence of differential clinical outcome based on strain
What is the duration of the effect?
• Modeling suggests this a critical determinant of ultimate impact
Safety and efficacy in persons with HIV and other comorbidities
• Brazil: effect seen in one or two sites only – ascribed to NTM interference
• BCGosis extraordinarily common in HIV-infected infants not on therapy; ART largely aborts risk; lesser response?
• Helminth infections may impact efficacy in some populations
Does this translate to prevention of disease?
• QFT is an unvalidated surrogate for disease
Interference with HPV

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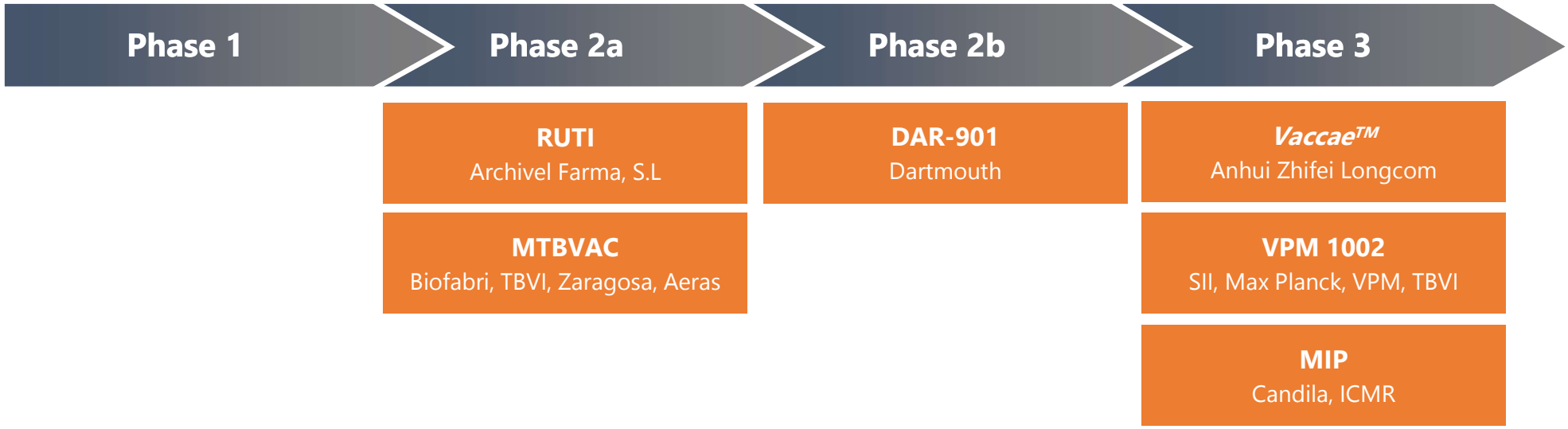
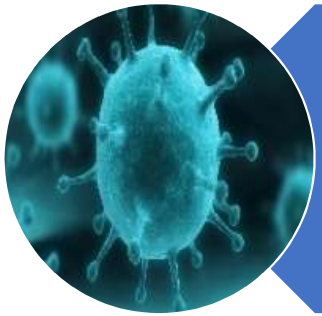
Clinical pipeline: whole cell vaccines



Whole cell



Viral vectored

Protein/ Adjuvant

Can CMV-TB protect against TB disease?

Two HCMV/TB vectors:

Both: UL82 (pp71) deleted and miR-124 (CNS tropism) restricted

Rhesus: greatly reduces pathogenic potential, while retaining immunogenicity

Modifications appear more attenuating in hCMV

Vector #1: UL128/UL130 and UL146/UL147 deleted

Rhesus: Unconventional CD8+ T cell responses

More attenuated due to absence of pentameric complex

Vector #2: UL128/UL130 and UL146/UL147 intact

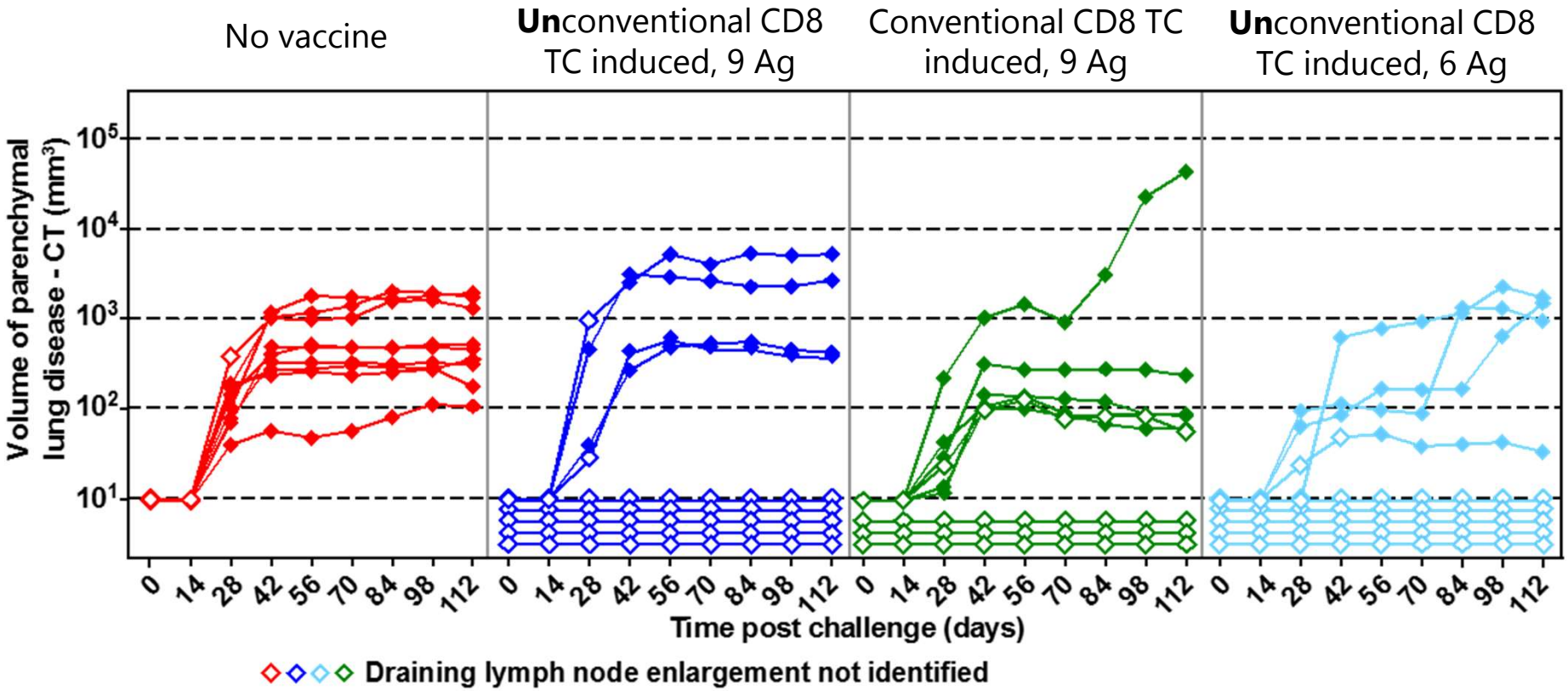
Rhesus: Conventional CD8+ T cell responses

Less attenuated: advantageous if UL82 deletion and miR-124 insertion is over-attenuating

Louis Picker and colleagues, Aeras, Vir

Can CMV-TB protect against TB disease?

CMV-TB: 68% (36-85%) protection in the non-human primate

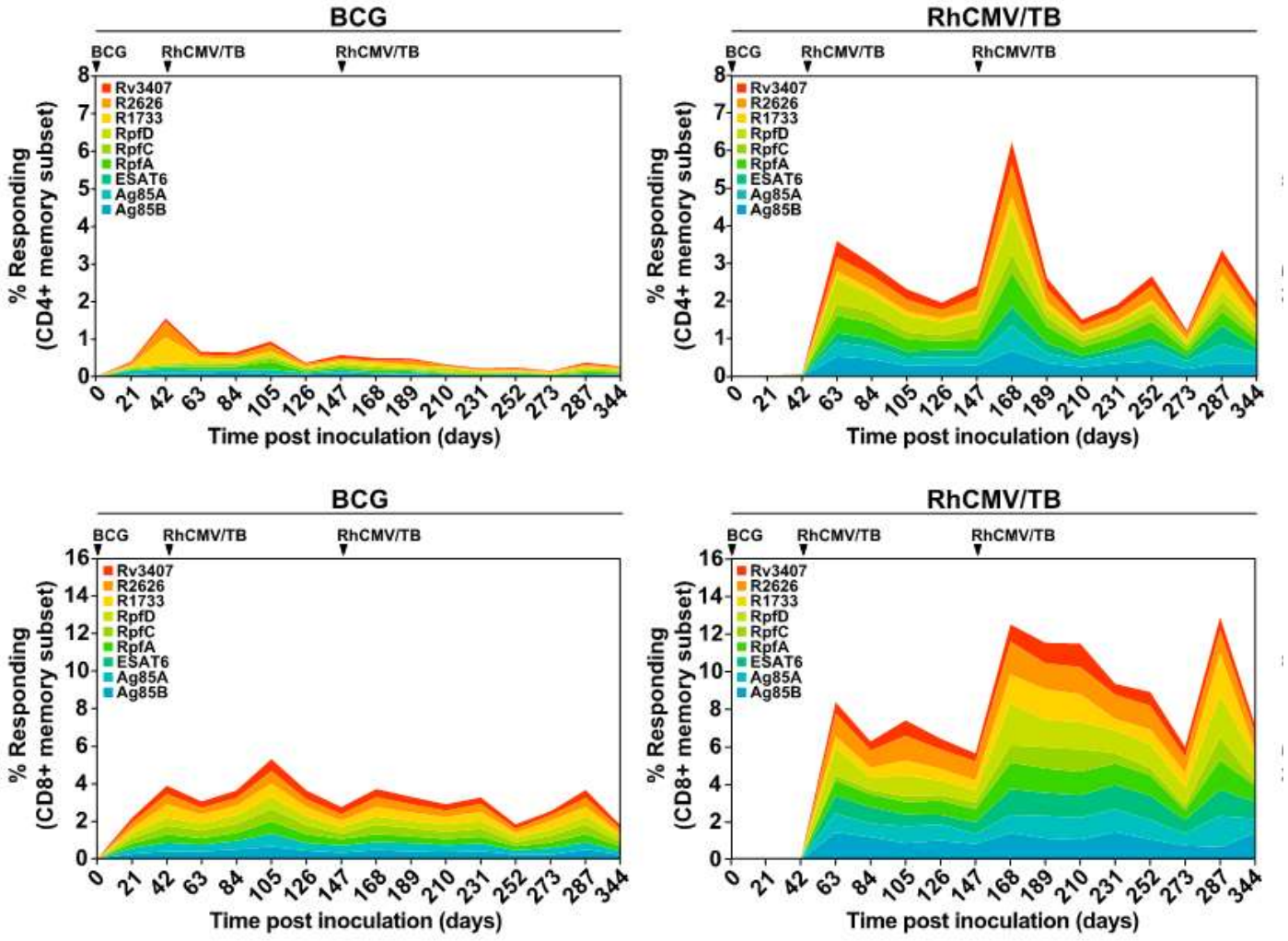


Louis Picker and colleagues, Aeras, Vir

Toward a comprehensive CMV strategy at the foundation

Development of human CMV-TB	Delineating mechanisms/correlates of protection	Next generation vaccines
• CMC • First in humans in 2020	• NHP	• Guided by protective mechanisms

CMV-TB: immunity differs from other vaccine approaches



Continuously replenished EFFECTOR memory T cells

Louis Picker and colleagues, Aeras

Toward a comprehensive CMV strategy at the foundation

Development of human CMV-TB	Delineating mechanisms/correlates of protection	Next generation vaccines
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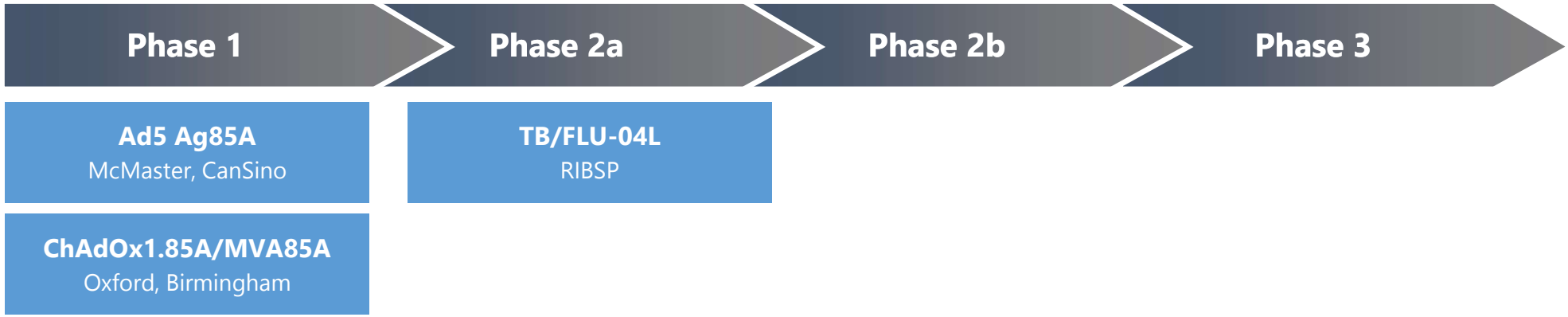
Clinical pipeline: viral vectored vaccines



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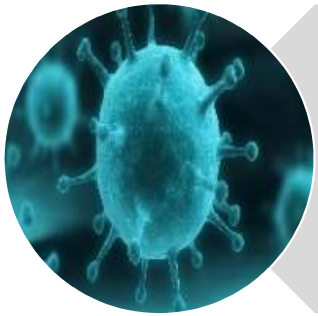
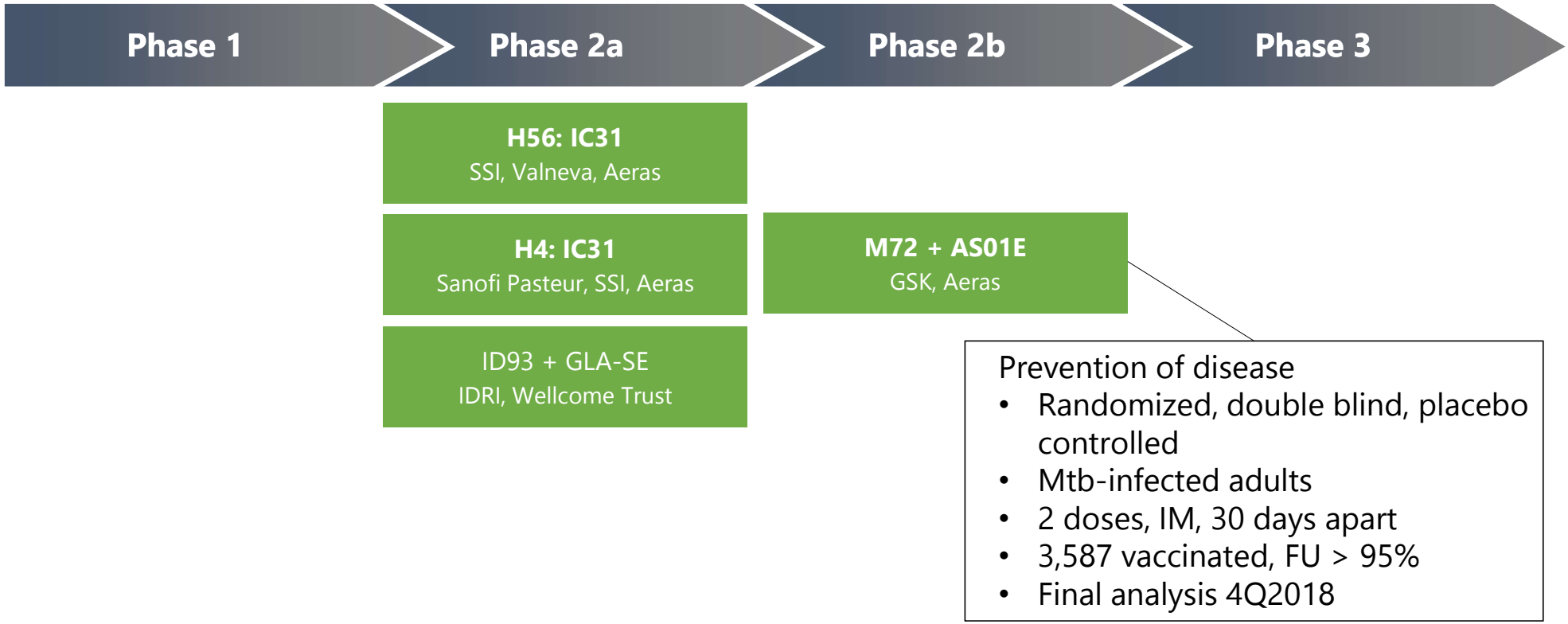


Viral vectored

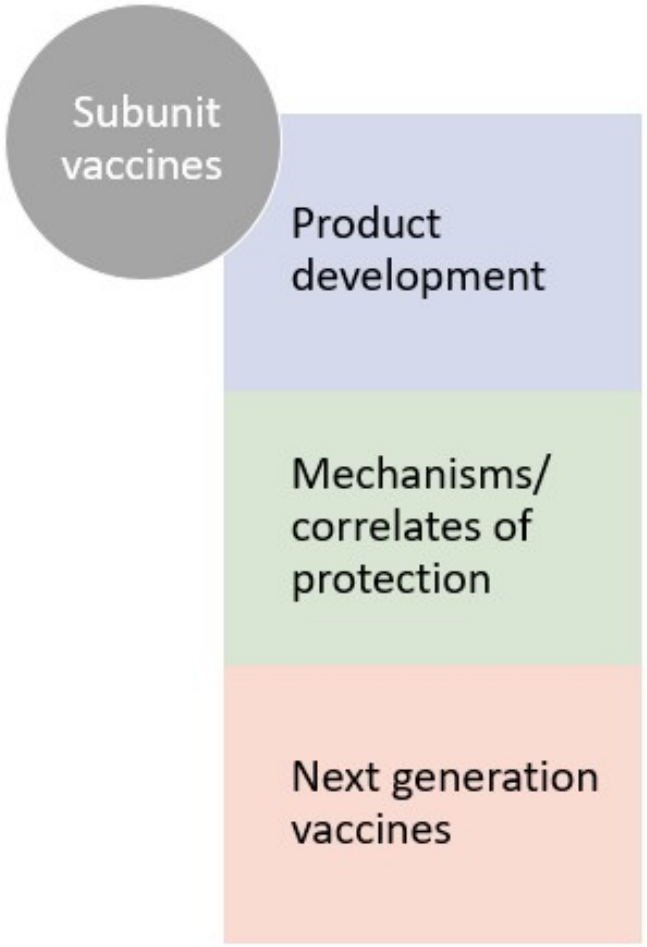
Protein/ Adjuvant

Clinical pipeline: protein/adjuvant vaccines



Aeras

Toward a comprehensive subunit vaccine strategy at the foundation



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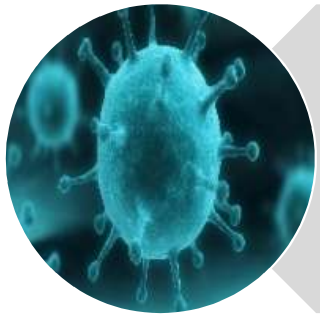


Viral vectored

Protein/ Adjuvant

Contingency!

A short list of **risks** of the BCG and CMV-TB projects

- BCG-induced protection against infection cannot be confirmed
- BCG-induced prevention of infection does not translate into prevention of disease
- BCG cannot be used in HIV-infected persons
- (IV BCG is not safe in humans)

- CMV-TB cannot be manufactured
- Observed protection in the NHP does not translate to the human
- CMV-TB is not safe

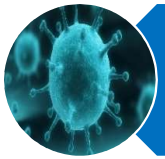
- Not enough money to do all

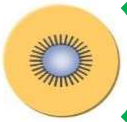
A robust preclinical space


Aerosol

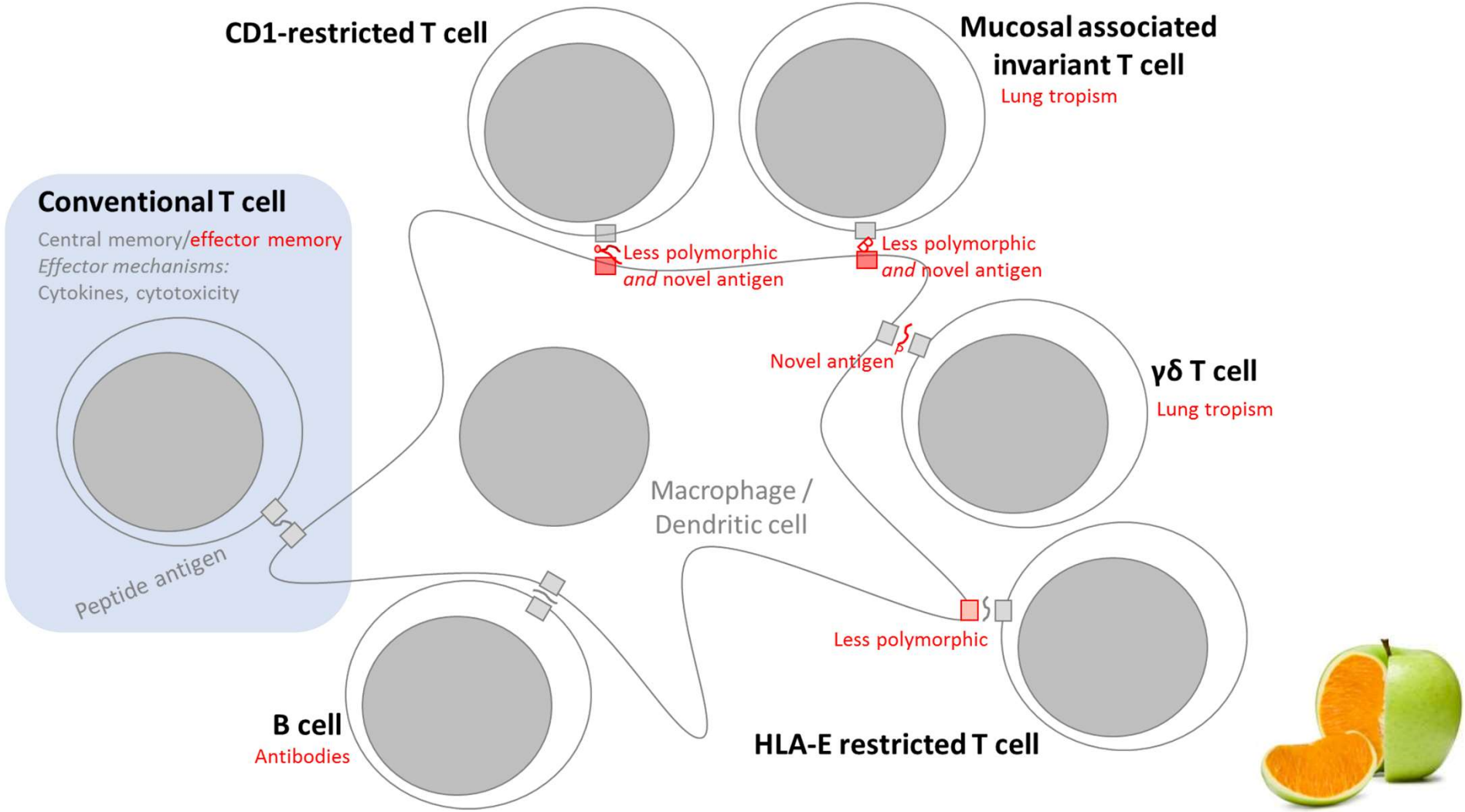

Combinations


Whole cell

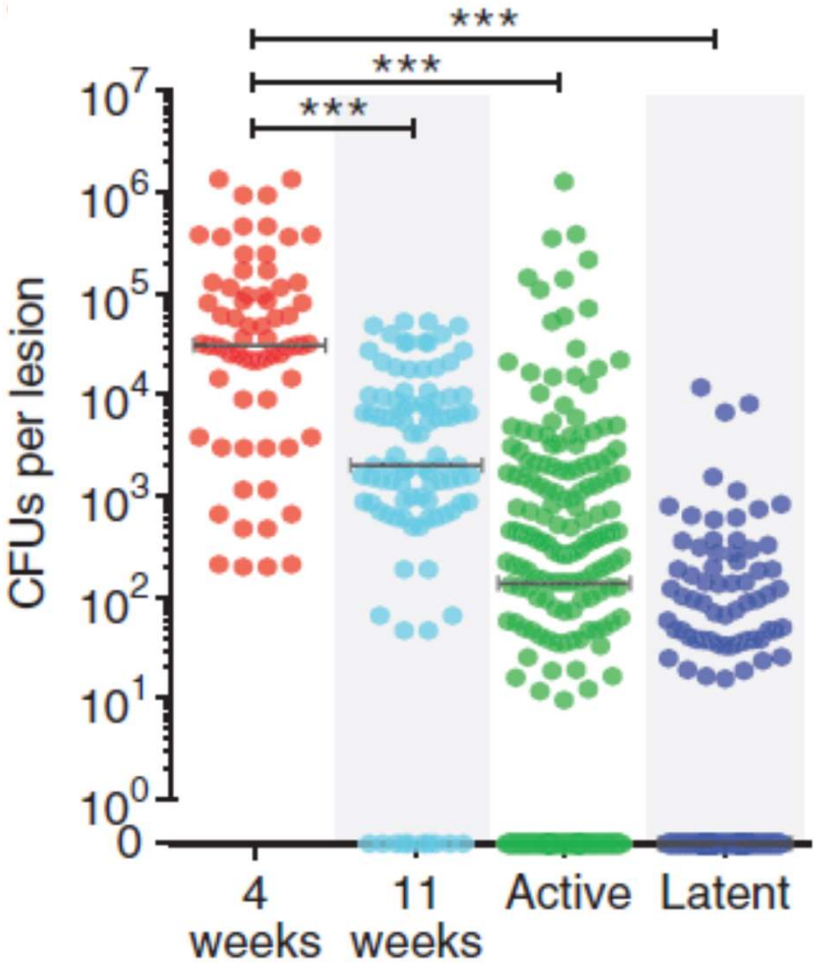

Viral vectored


Protein/ Adjuvant

Vaccine discovery: beyond conventional T cells



Understanding controlling and permissive TB granulomas in the NHP



And in the human…

UNIVERSITY OF KWAZULU-NATAL

Hannah Gideon, Ling Lin, Adri Steyn and colleagues

Conclusions: TB vaccines

- **We are on the verge of new vaccines and vaccination strategies with potential to save millions of lives.**

- **BCG** may be repurposed to protect against TB in adolescents and adults
  IV BCG in NHPs may allow delineation of correlates of protection

- **CMV-TB** induces the best protection seen in preclinical models to date
  Challenging development track

- Risks remain significant
  Development, especially discovery efforts, should continue

From this presentation: Four questions where modeling may help

1. How can infection be defined?
2. Would prevention of infection translate into prevention of disease?
3. What candidate specific dose and/or schedule characteristics are required for impact?
4. What characteristics would alternate whole cell, subunit or viral vector vaccines have to have for acceptable/greater safety or greater impact?
5. How can animal models be used to predict clinical outcome?