T cell mediated immunity elicited in volunteers following immunization with the live oral *Salmonella* Paratyphi A attenuated vaccine strain CVD 1902

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Background

- ***S.* Paratyphi A infection (paratyphoid A fever) has emerged as a health problem in enteric disease endemic areas.**
- **Disease caused by *S.* Paratyphi A strains showing resistance to multiple clinically-relevant antibiotics are common.**
- **Well-tolerated effective licensed vaccines are available to prevent *S.* Typhi disease (typhoid fever) but those do not provide effective cross-protection against paratyphoid A or B fevers.**
- **Currently no vaccine is available to prevent *S.* Paratyphi A disease**
- **Development of a vaccine against *S.* Paratyphi A is a public health priority.**

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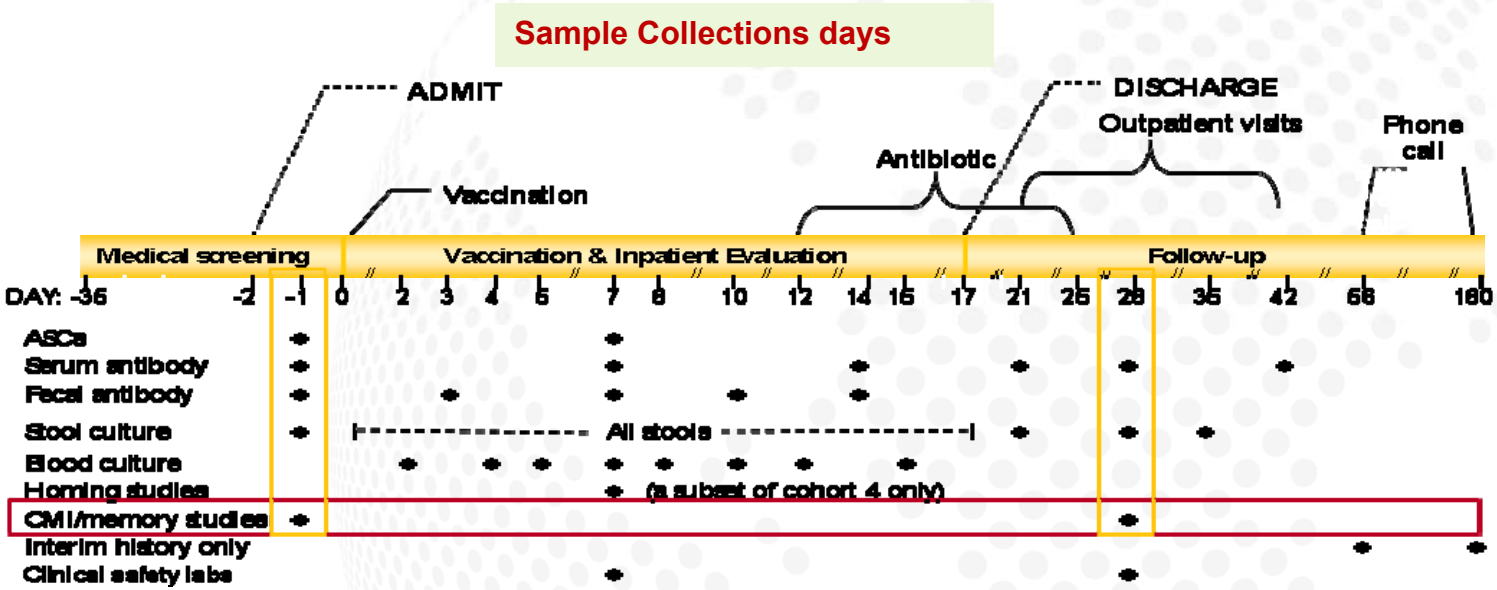
Candidate vaccines against *S.* Paratyphi A developed at CVD-Maryland

- **Subunit vaccine:** *S.* Paratyphi A O polysaccharide linked to carrier proteins.
- **Live oral vaccine:** CVD 1902: A wild type *S.* Paratyphi A strain attenuated by
  - Introducing deletions in the *guaBA* chromosomal operon (which impairs the biosynthesis of guanine nucleotides).
  - An additional mutation in the clpX gene (encodes a chaperone ATPase) for safety and enhanced expression of flagellar antigen.
  - **Pre-clinical study**: CVD 1902 immunized mice were protected against intraperitoneal wt-type *S.* Paratyphi A challenge.
  - **Dose-escalating phase 1 clinical trial in healthy adults**: Single doses as high as 10^9 and 10^{10} CFU were well tolerated and immunogenic.

Dose-escalating phase 1 clinical trial with CVD 1902 in healthy adults

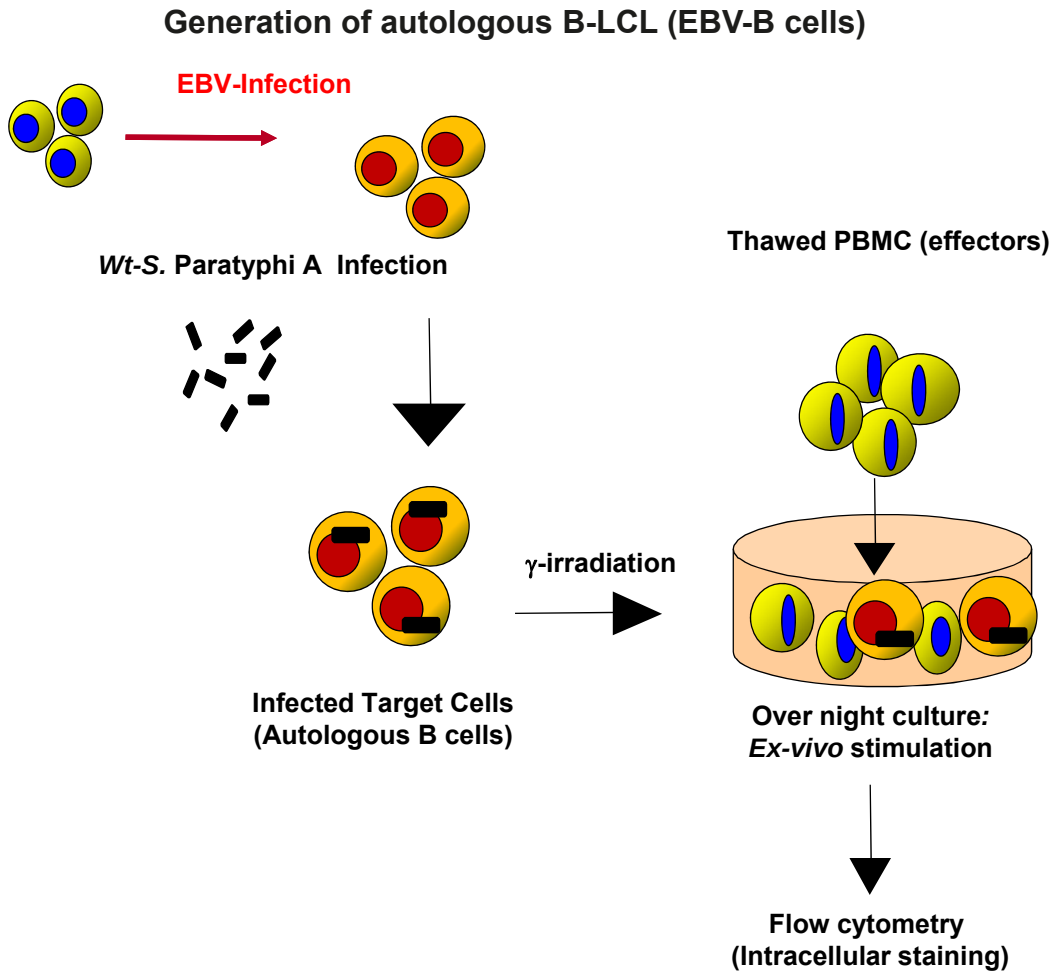
Study Groups and Vaccine Doses				
Cohort	**Setting**	**Vaccine Inoculum size**	**No. of subjects**	
			CVD 1902 vaccine	**Placebo**
1	**Inpatient**	**10^6 CFU**	**6**	**2**
2	**Inpatient**	**10^7 CFU**	**6**	**2**
3	**Inpatient**	**10^8 CFU**	**6**	**2**
4	**Inpatient**	**10^9 CFU**	**6**	**2**
5	**Inpatient**	**10^{10} CFU**	**6**	**2**

Dose-escalating phase 1 clinical trial with CVD 1902 in healthy adults



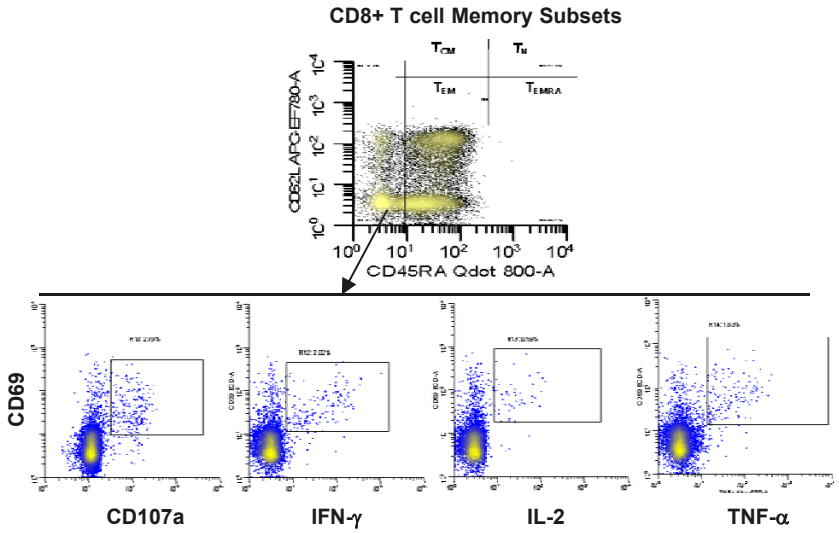
- Volunteers were immunized with a single dose of 10^9 (n=6) or 10^{10} (n=6) CFU or placebo (n=4) of CVD 1902
- Blood samples were drawn before (day 0) and 28 days after vaccination
- Purified PBMC were cryo-preserved until used in CMI assays

Experimental Design



Experimental Design

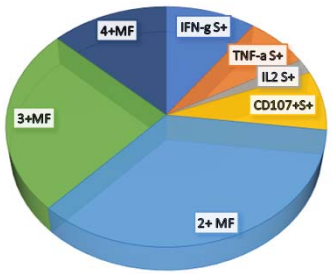
Flow Cytometry assay



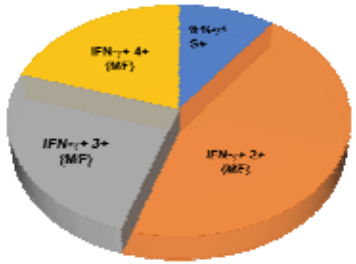
FCOM analysis

Single (S+) cells : Expressing / producing only one of the functions measured
Multifunctional (MF) cells: Concomitantly producing two or more functions

***S.* Paratyhi A specific CD8+T_{EM} cells**

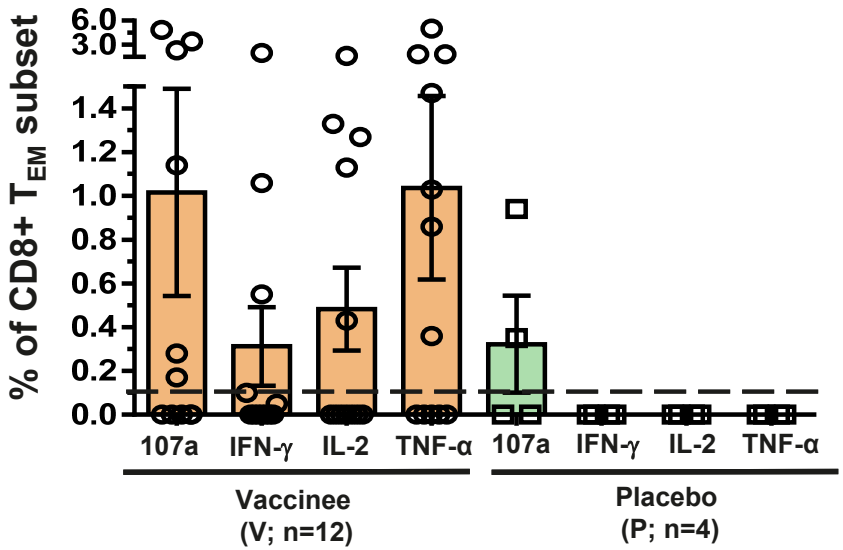


IFN-γ producing T cells



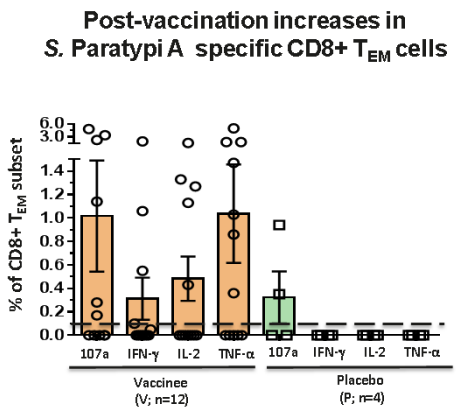
CVD 1902 elicited *S.* Paratyphi A specific CD8+ T_{EM} Responses

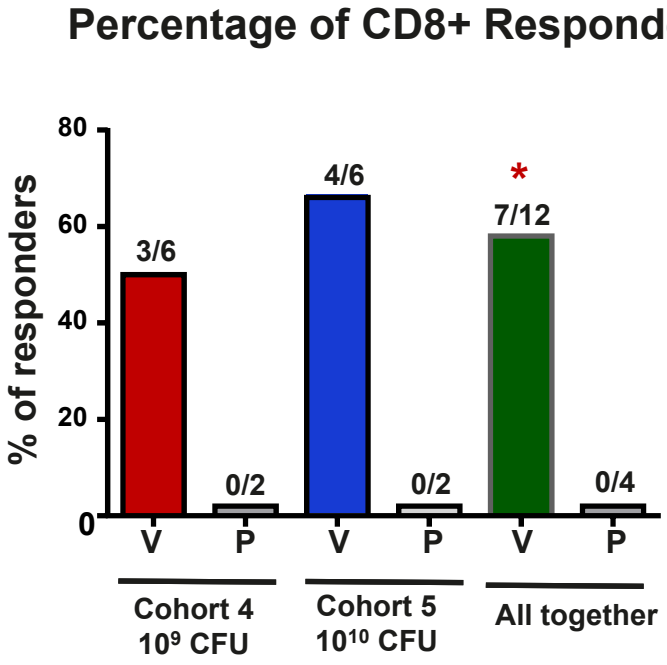
Post-vaccination increases in *S.* Paratypi A specific CD8+ T_{EM} cells



Post-vaccination increase: Post-vaccination (day 28) minus Pre-vaccination (day 0) levels

CVD 1902 elicited *S.* Paratyphi A specific CD8+ T_{EM} Responses





CD8+ vaccine responders: Volunteers showing post-vaccination increases of ≥0.1% in PA target-specific CD8+ CD69+ T_{EM} cells producing and/or expressing at least 2 functions (IFN-γ, TNF-α, IL-2 and/or CD107a)

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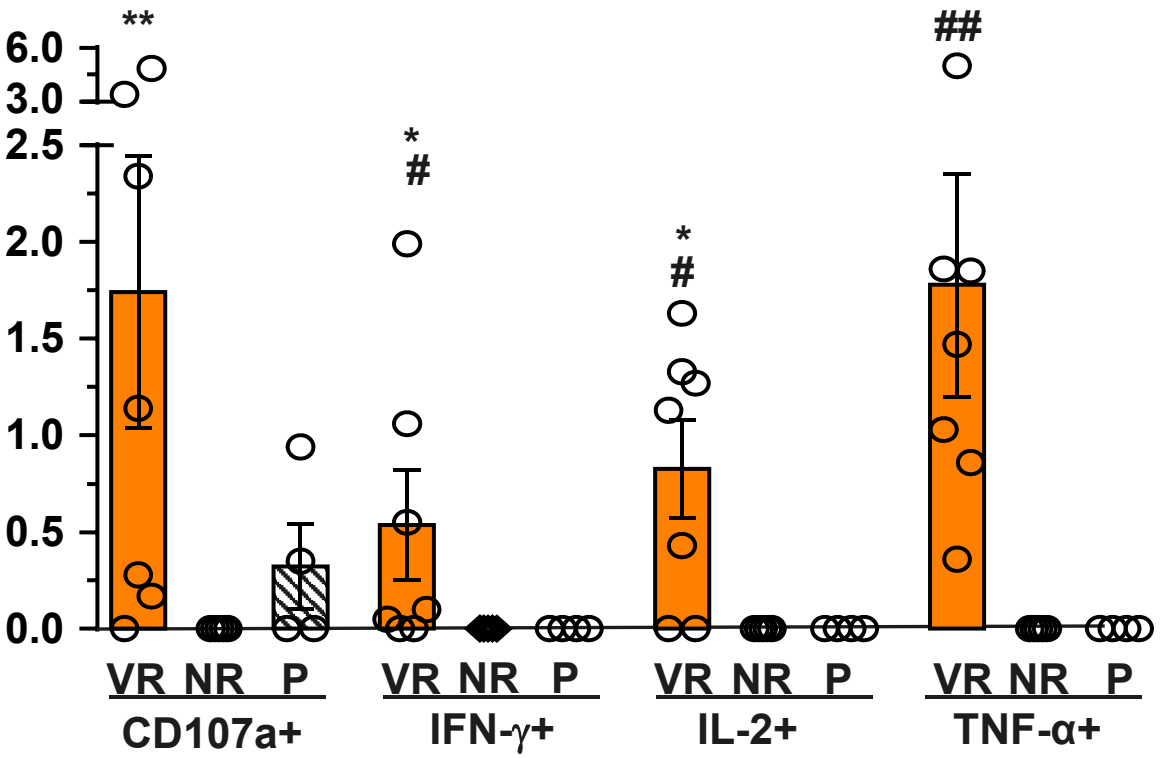
Comparisons of vaccine elicited responses in CD8+ responders vs non-responders or placebo



Mann-Whitney test, Compared with NR (*, p<0.05; **, p<0.01) or P (#, <0.05, ## p<0.01)

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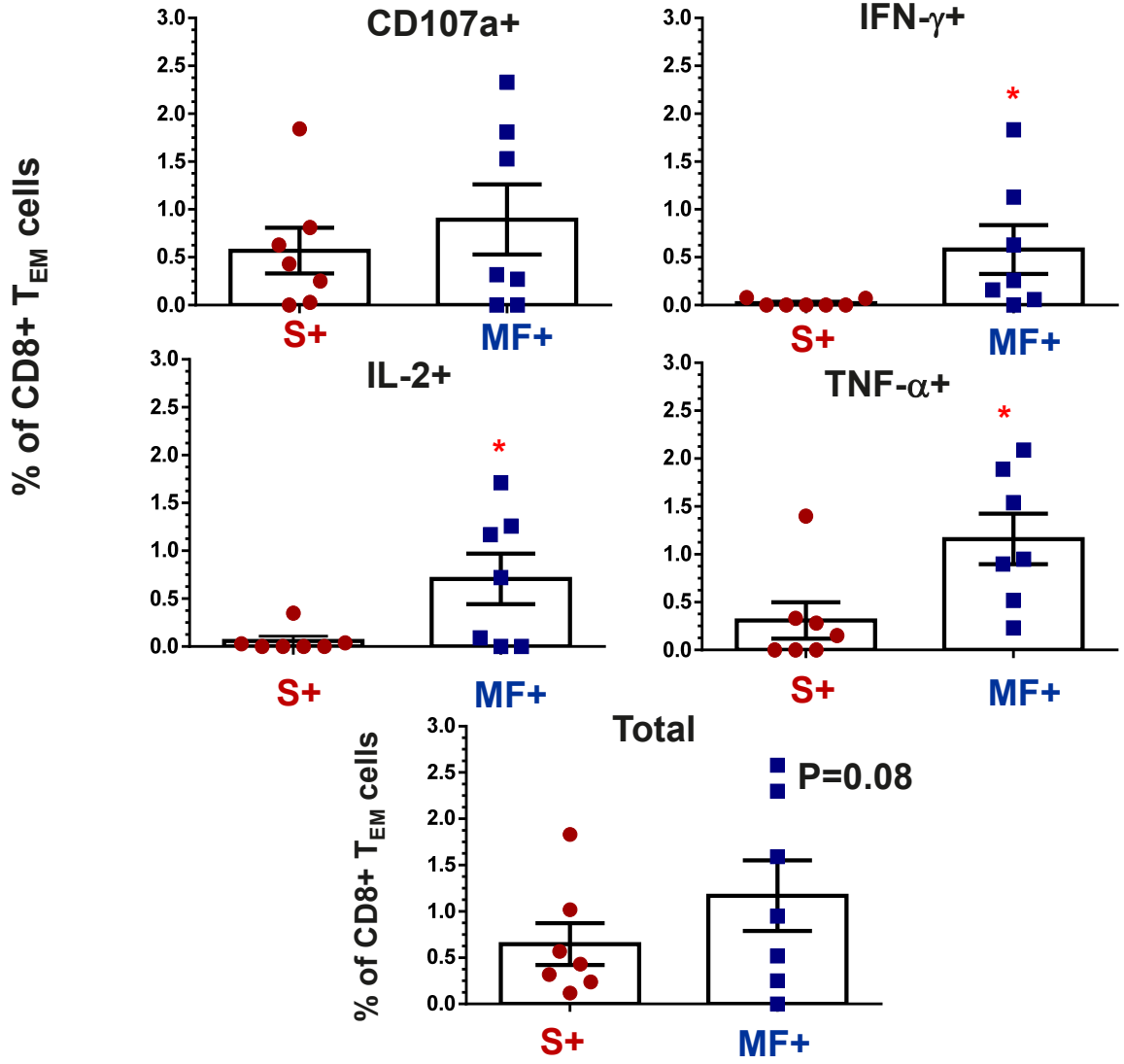
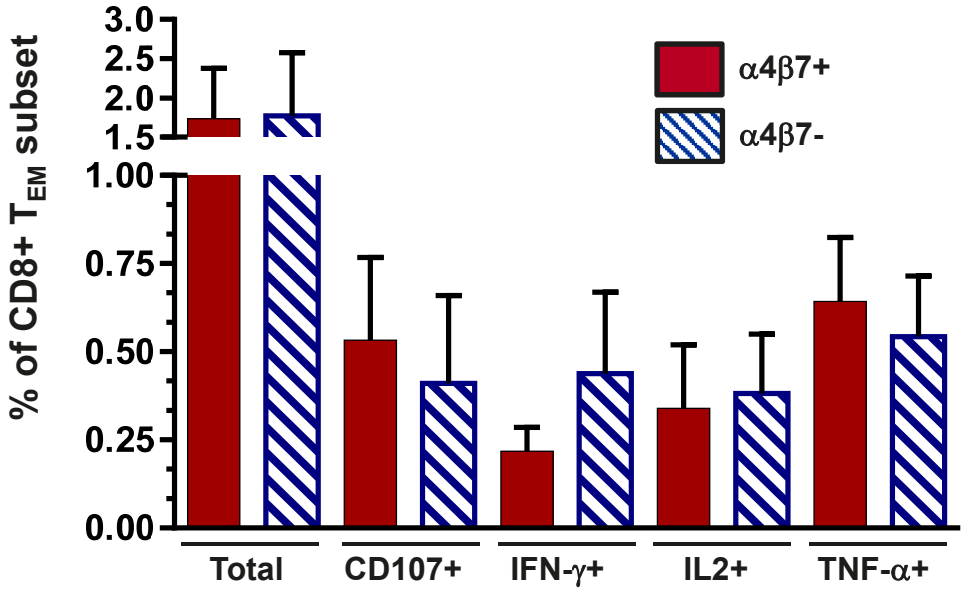
Multifunctional Characteristics of the CVD 1902 CD8+ T_{EM} cell responses in CD8+ responders



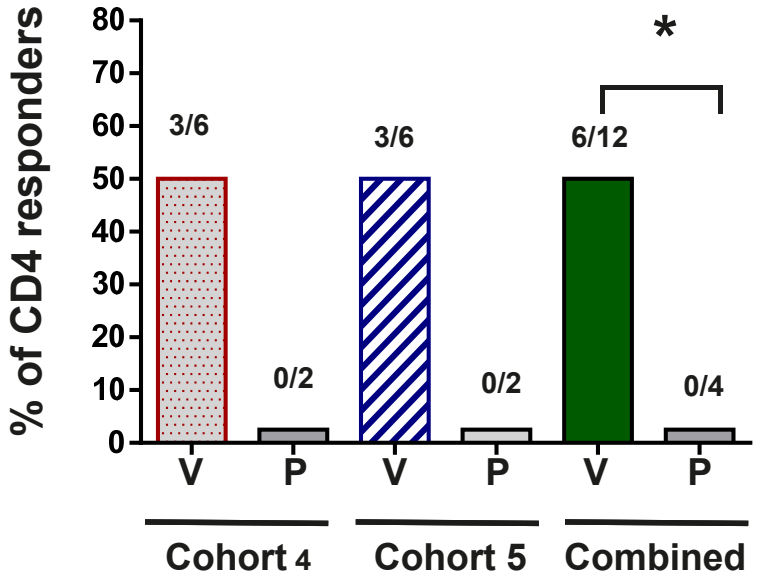
*p<0.05 compared to respective S+ cells: Wilcoxon paired test

Gut homing potential of CVD 1902 elicited multifunctional CD8+ T_{EM} cells in CD8 vaccine responders

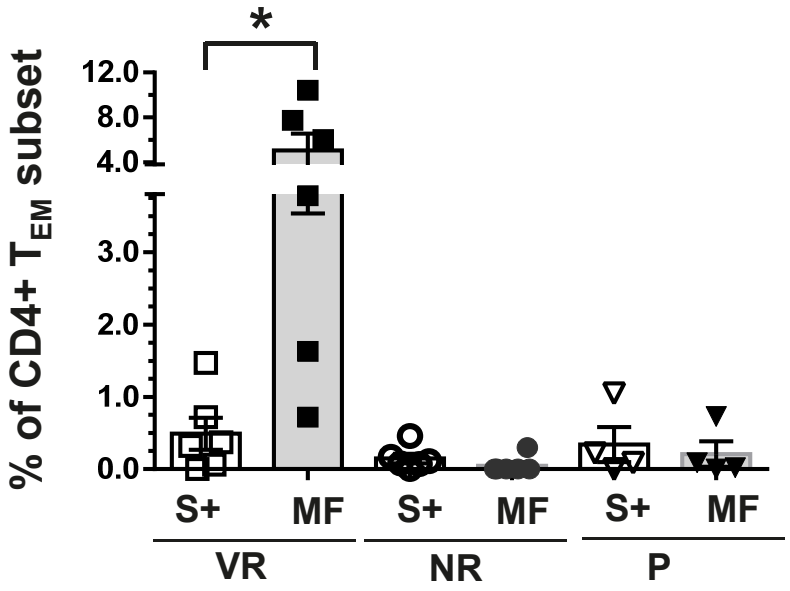


Induction of multifunctional (MF) CD4+ T_{EM} cells following immunization with CVD 1902

CD4+ Vaccine responders



Multifunctionality of CD4+ Response



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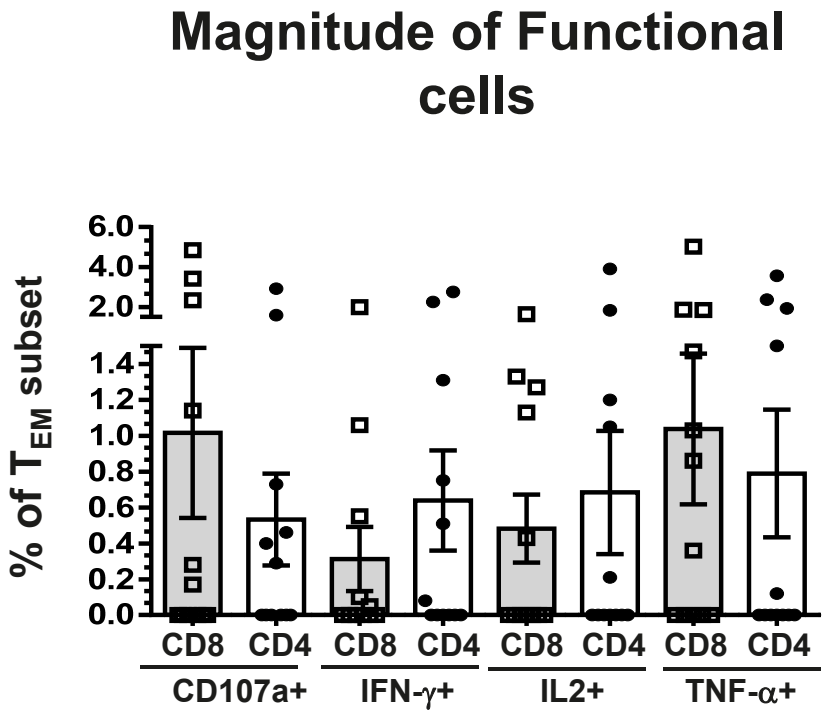
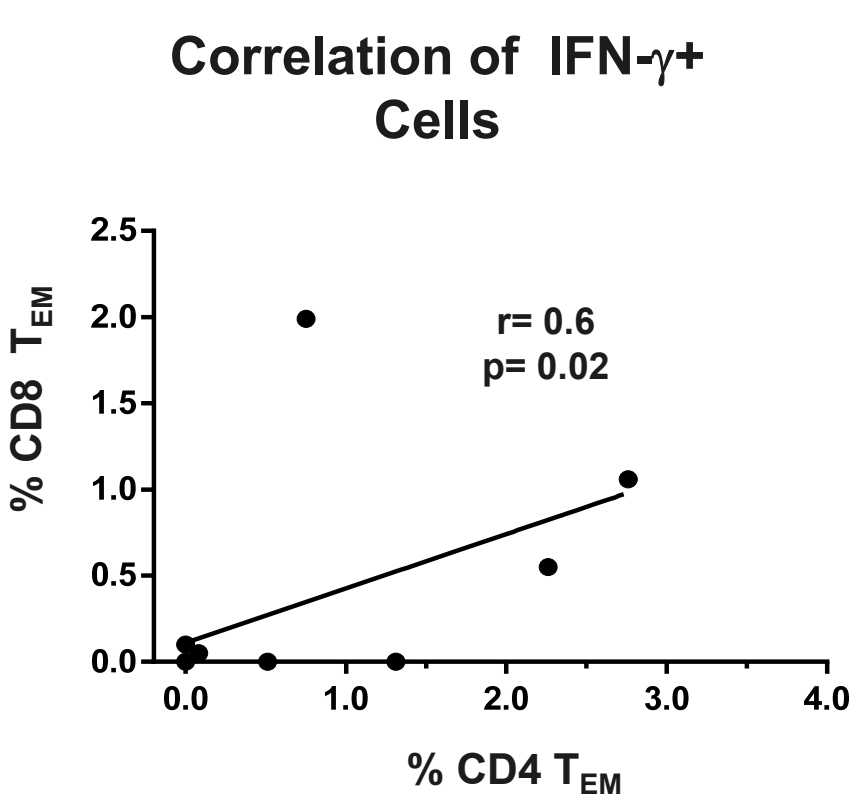
Comparisons of vaccine elicited CD8+ and CD4+ responses





Summary

- A single dose of either 10^9 or 10^{10} CFU of CVD 1902 elicited *S.* Paratyphi A specific T effector memory (T_{EM}) responses mediated by both CD8+ and CD4+ T cells in almost two third of the vaccinees
- CVD 1902 induced T-CMI predominately mediated by *S.* Paratyphi A specific-Multifunctional (MF) cells
- A significant proportion of CD8+ MF T_{EM} cells expressed the gut homing molecule integrin $\alpha 4\beta 7$
- Cytokine production patterns by both CD8+ and CD4+ cells are suggestive of robust Th1 responses
- Future challenge studies with wt *S.* Paratyphi A and field studies will establish the importance of these vaccine elicited T memory responses in protection
- These results, together with the observed safety and humoral immunogenicity data elicited by CVD 1902, suggest that a single or multiple doses have the potential to protect against *S.* Paratyphi A infection

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