Using a TCR-transgenic CD4 T cell Approach to Guide Rational Chlamydia Vaccine Design

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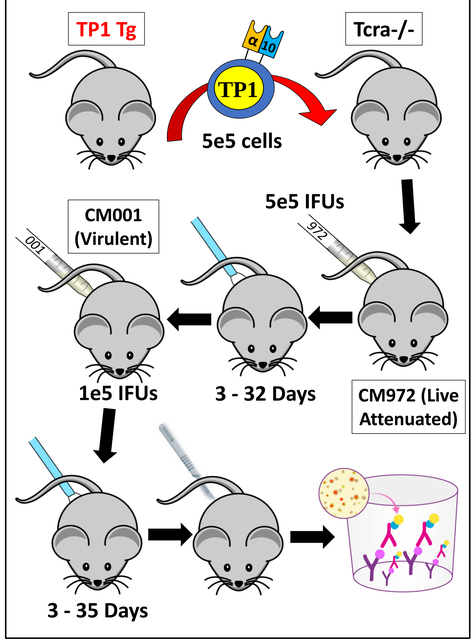
INTRODUCTION

- *Chlamydia trachomatis* is the most prevalent sexually transmitted bacterial infection globally.
- In 2018, there were 129 million new cases worldwide[1].
- 70% of women and 50% of men are asymptomatic, which can lead to late or no treatment[2].
- Untreated chlamydia can lead to serious symptoms such as pelvic inflammatory disease and infertility[3].
- Previous research demonstrates that CD4+ T cells are critical for protection against infection.
- We developed a novel TCR transgenic mouse (TP1) model to investigate the protective capability of a monoclonal CD4+ T cell response to genital infection[4].
- To determine this, we immunized TP1 recipient mice with live-attenuated *Chlamydia muridarum* (CM972) and later intravaginally challenged CM972-immunized mice with a virulent strain (CM001)[5].

METHODS



HYPOTHESIS

Memory TP1 cells specific for a single epitope will significantly reduce bacterial burden compared to naïve controls.

RESULTS

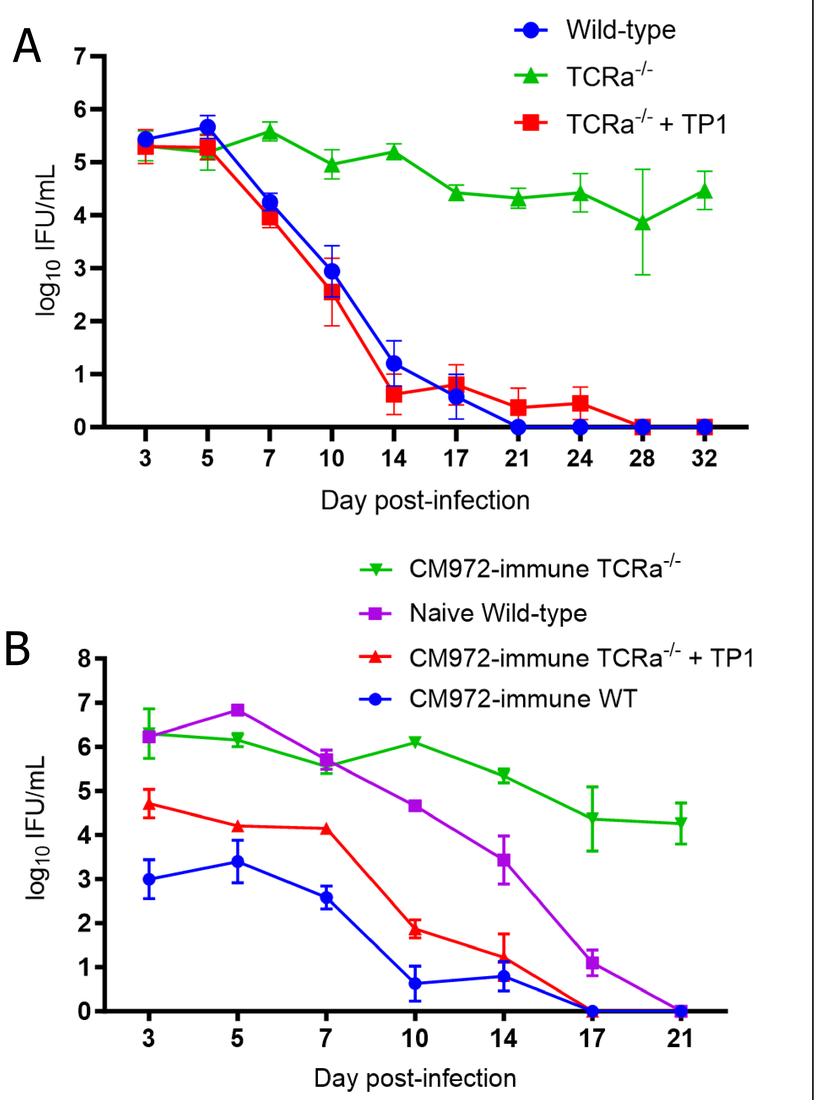


Fig. 1. Memory TP1 cells reduce chlamydial burden in genitally challenged mice. Wild type (WT), TCRa$^{-/-}$, and TCRa$^{-/-}$ with adoptively transferred TP1 cells were inoculated with *C. muridarum* strain CM972. (A) CM972 infection was monitored by IFU assay and mice were treated with doxycycline post-clearance. Mean +/- SEM of 4-5 mice per group depicted. WT vs. TCRa$^{-/-}$ + TP1 (p=0.9280), TCRa$^{-/-}$ + TP1 vs. TCRa$^{-/-}$ (-2.8 logs), p<0.0001 by 2-way repeated measures ANOVA. (B) Naïve and CM972-immune mice were challenged with strain CM001. Infection was monitored as above. Immune WT vs. Immune TP1 (-0.82 log), p=0.0076; Immunized TP1 vs. Naïve WT (-1.7 log), p<0.0001; Immunized TP1 vs. Immunized TCRa$^{-/-}$ (-3.1 logs), p<0.0001; Immunized WT vs. Naïve WT (-2.5 logs), p<0.0001, all by 2-way repeated measures ANOVA.

RESULTS

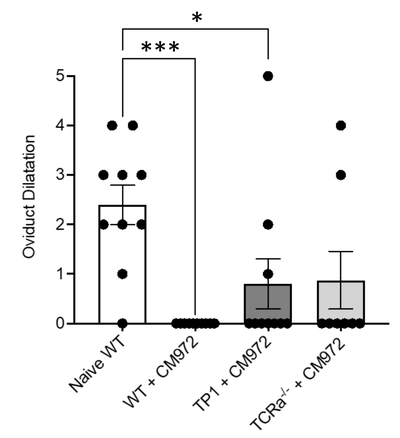


Fig 2. Memory TP1 cells reduce severity of oviduct pathology. Mice from Fig 1B were sacrificed at 35 days post-secondary infection. Oviduct dilatation scores were determined by a pathologist blinded to the study design (n=8-10 oviducts per group). WT + CM972 vs. Naïve WT, p<0.0001; TP1 + CM972 vs. Naïve WT, p<0.01, by Kruskal-Wallis test.

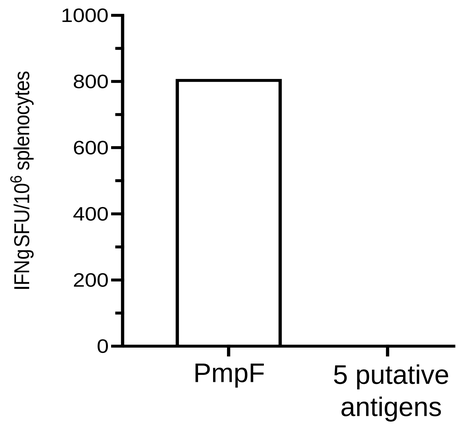


Fig 3. TP1 cells are specific for polymorphic membrane protein F (PmpF). Splenocytes from TCRa$^{-/-}$ mice that received TP1 cells followed by CM972 and CM001 infections were screened against a panel of Chlamydia antigens (MOMP, OmcB, PmpG, CPAF, Hsp60) by interferon-gamma ELISpot assay. SFU = spot-forming units.

CONCLUSIONS & FUTURE DIRECTIONS

- Memory TP1 cells significantly reduced chlamydial burden compared to naïve wild-type T cells but were not as efficacious as memory wild-type T cells.
- Despite reducing burden by over 2-logs compared to naïve controls, memory TP1 cells did not prevent oviduct hydrosalpinx compared to immune controls.
- Antigen screening revealed that TP1 cells are specific for polymorphic membrane protein F (PmpF), an adhesin important for Chlamydia entry.
- We will next determine the specific PmpF peptide recognized by TP1 cells and perform preliminary PmpF vaccine studies.

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