Bundesinstitut für Impfstoffe und biomedizinische Arzneimittel
Federal Institute for Vaccines and Biomedicines

Paul-Ehrlich-Institut

// (Re-)Balancing of T cell memory to *Staphylococcus aureus* by delivery of *in vitro* transcribed antigens //

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Background

Rapid spread of methicillin-resistant *S. aureus* strains (MRSA) and limited therapeutic options clarify the need for alternative therapies[1]. So far, all vaccine trials failed during clinical stages due to lack of safety or efficacy[2]. In terms of successful vaccine development, characterization of adaptive immunity towards *S. aureus* has to be defined more deeply. Here, we present a novel mRNA-based approach for the analysis of staphylococcal antigen-specific human T cell responses highlighting the presence of a $CD4^+$ and $CD8^+$ T cell memory repertoire[3].

Methods

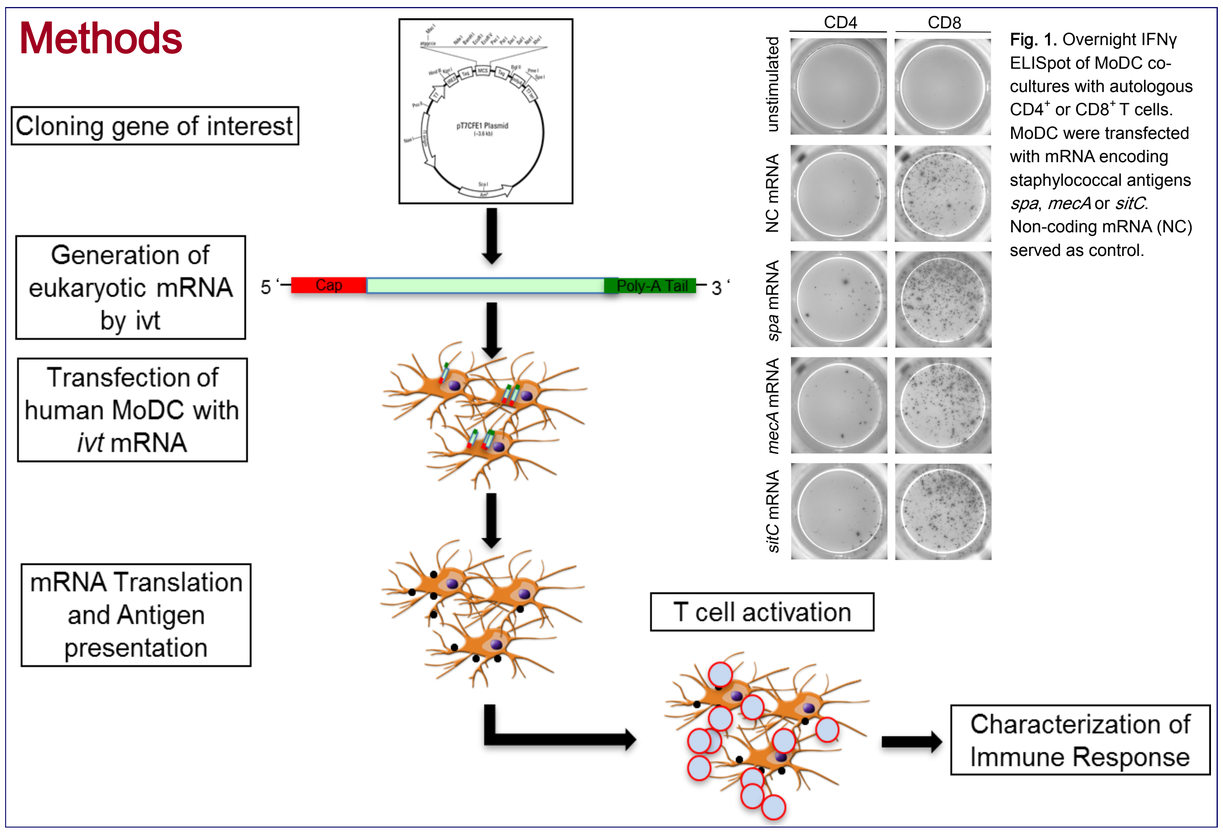

Fig. 1. Overnight IFNγ ELISpot of MoDC co-cultures with autologous $CD4^+$ or $CD8^+$ T cells. MoDC were transfected with mRNA encoding staphylococcal antigens *spa*, *mecA* or *sitC*. Non-coding mRNA (NC) served as control.

Results I – mRNA antigens induces more IFNγ than protein antigens

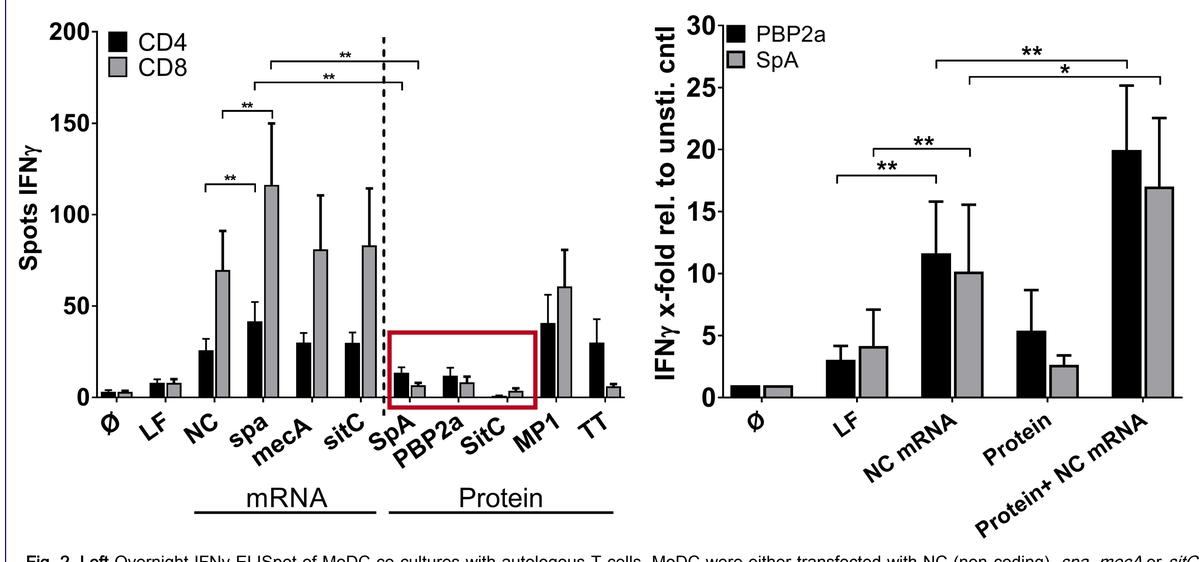

Fig. 2. Left Overnight IFNγ ELISpot of MoDC co-cultures with autologous T cells. MoDC were either transfected with NC (non-coding), *spa*, *mecA* or *sitC* mRNA, stimulated with corresponding proteins SpA, PBP2a or SitC. **Right**. or stimulated simultaneously with NC mRNA and protein antigen. n=8

Adjuvant effect of mRNA facilitates the induction of IFNγ secreting $CD8^+$ T cells overnight

Results II – mRNA induces high T_h1 immune response

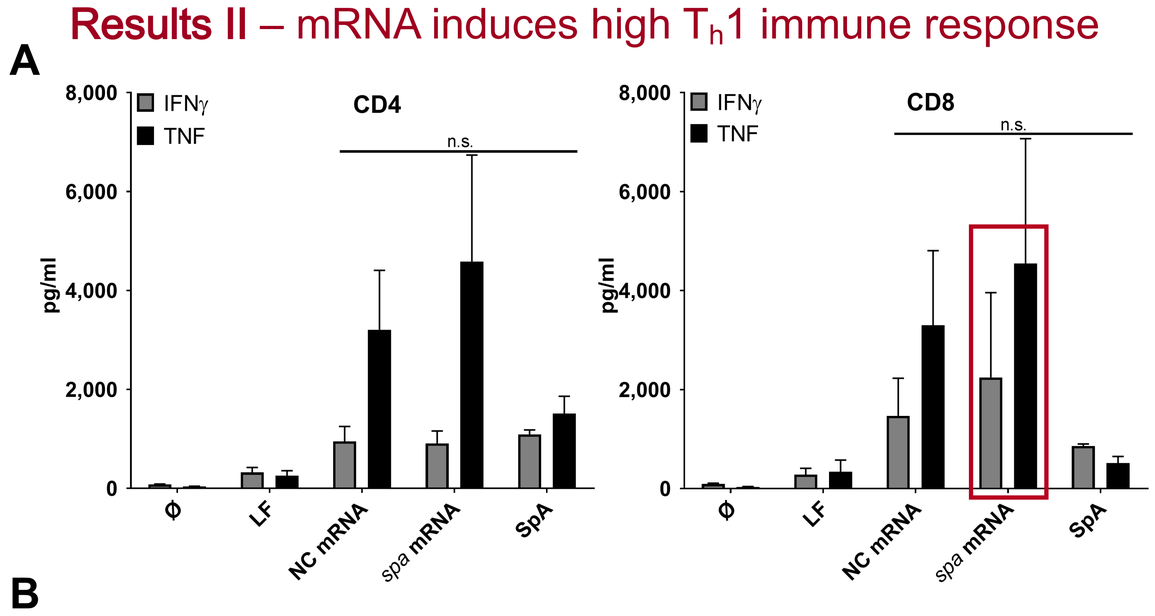

Fig. 3. Cytokine Multiplex Assay after 5 days of MoDC stimulated with mRNA or protein-delivered antigens in co-culture with $CD4^+$ (left) or $CD8^+$ T cells (right). **A** IFNγ and TNF and **B** IL-5, IL-13 are displayed as mean of n=6 different donors.

mRNA antigens shift the immune response to *S. aureus*

Results III – Protein antigens induce T_{reg}-associated cytokines

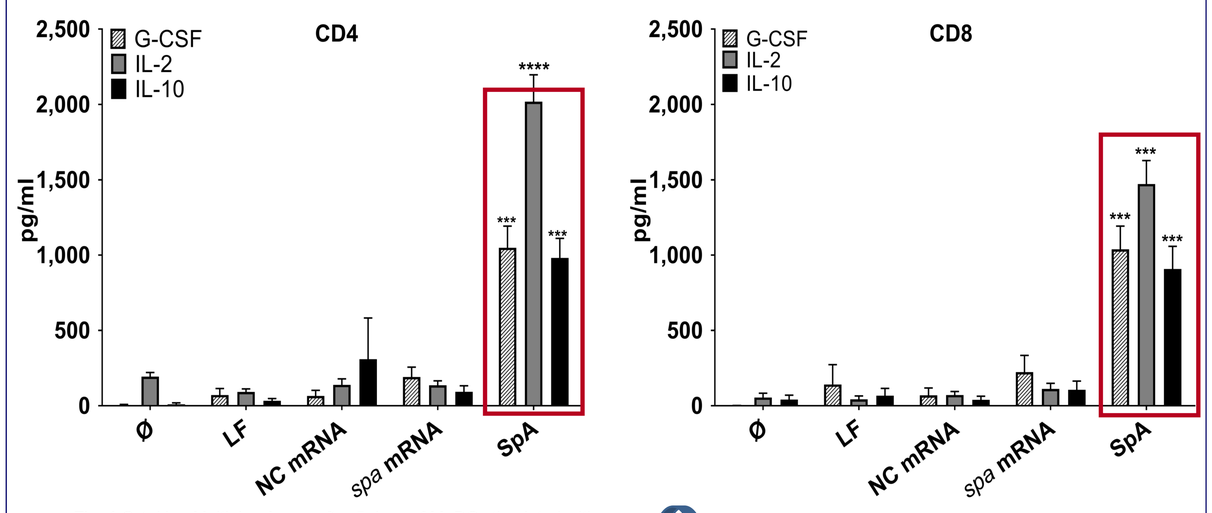

Fig. 4 Cytokine Multiplex Assay after 5 days of MoDC stimulated with mRNA or protein-derived antigens in co-culture with CD4+ (left) or CD8+ T cells (right). IL-2, IL-10 and G-CSF are presented as mean of n=6 different donors.

Protein antigens induce immune tolerance

Results IV – Protein antigens activate memory T cells

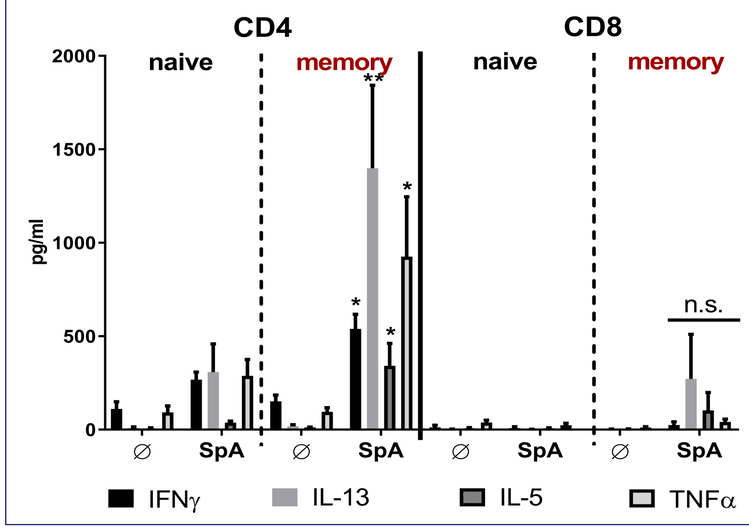

Fig. 5. Cytokine Multiplex Assay of n= 8 donors after 5 days. MoDC loaded with SpA protein in co-culture with $CD4^+CD45RO^-CD45RA^+$ (naive) and $CD4^+CD45RO^+$ $CD45RA^-$ (memory) cells (sorted by Aria Fusion).

Existence of a human $CD4^+$ and $CD8^+$ memory T cell repertoire

Conclusion

The mRNA-based delivery of staphylococcal antigens enables the induction of high IFNγ responses by human memory and naive T cells due to the mRNA's adjuvant effect. While staphylococcal protein antigens induce a T_h2/T_{reg} - biased cytokine profile, *in vitro* transcribed antigens shift the endogenous T cell response towards a T_h1-like phenotype. Our data therefore presents mRNA as a promising new Th1-polarizing adjuvant in the development of protective vaccine formulations against *S. aureus*.

1 Fowler & Procotr. Clin Microbiol Infect. 2014 May 20;5:66-75.

2 Giersing *et al.* Vaccine. 2016 Jun 3;34(26):2962-6

3 Uebele *et al.* PLoS Pathog. 2017 May 25; 13(5):e1006387

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