

# Genital tract CD4<sup>+</sup> T cells for vaccination and protection against *Chlamydia trachomatis*

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## ABSTRACT

Vaccination strategies for protection against sexually transmitted diseases are lacking due to an incomplete understanding of genital tract T cell responses. This thesis dissects the generation of T helper subsets, including the recently discovered Th17 subset, during genital tract infection with a common sexually transmitted pathogen, *Chlamydia trachomatis*, and addresses vaccine requirements for the generation of genital tract CD4<sup>+</sup> T cell immunity.

Our studies demonstrate the presence of anatomically distinct T helper differentiation patterns in the genital tract. C57BL/6 mice were infected with *C. trachomatis* and the response in the upper genital tract (UGT) was found to be dominated by Th1 cells, whereas the lower genital tract (LGT) hosted Th2 cells in the presence of IL-10-producing DCs. Additionally, Treg and Th17 responses were demonstrated in both the UGT and LGT following infection.

For the generation of T cell-mediated immunity against infection, costimulatory signals through CD28 were critical. We found that T helper differentiation and Treg responses to infection were impaired in both the UGT and LGT of CD28<sup>-/-</sup> mice. In contrast, in the absence of ICOS-signaling we observed enhanced elimination of bacteria and the development of protective immunity. Here, intense Th1 cell differentiation dominated and we found reduced regulation through both IL-10 and FoxP3<sup>+</sup> Tregs. Paradoxically, in mice lacking both CD28 and ICOS molecules (DKO), primary infection with *C. trachomatis* was eliminated more rapidly than in CD28<sup>-/-</sup> mice. These mice failed to develop protective immunity against reinfection similarly to CD28<sup>-/-</sup> mice. As in ICOS<sup>-/-</sup> mice, Th1 differentiation in the LGT was enhanced in DKO mice. This indicated that ICOS costimulation modulates the immune response even in the absence of CD28-signaling, leading to augmented inflammatory immune responses in the genital tract during *C. trachomatis* infection.

The generation of CD4<sup>+</sup> T cell immunity is also key to vaccination against other STDs. Because of this we studied intravaginal (i.vag) immunization for priming of CD4<sup>+</sup> T cells in the genital tract. We investigated the requirements for progesterone or estradiol for successful immunization. Both intranasal and i.vag delivery of cholera toxin conjugated to ovalbumin peptide (CT-OVA) induced T cell responses in the draining lymph node, however, i.vag immunizations were absolutely required in order to attract T cells to the genital tract mucosa.

In conclusion, the results presented in this thesis provide evidence of anatomically divided T cell immune responses to *C. trachomatis* in the genital tract. Understanding of T cell responses in the genital tract has important implications for the generation of protective immunity and immunopathology.

Keywords: *Chlamydia*, T cell differentiation, costimulation, Th1, Th2, Th17, Tregs, vaccination.

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AKADEMISK AVHANDLING

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av

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Little Rock, Arkansas, USA

Avhandlingen baseras på följande delarbeten:

- I. **IL-10 producing vaginal DC inhibit Th1 responses to *Chlamydia trachomatis* infection.**  
Ellen Marks, Miguel Tam, Nils Lycke.  
*Submitted manuscript.*
- II. **Differential CD28 and inducible costimulatory molecule signaling requirements for protective CD4<sup>+</sup> T-cell-mediated immunity against genital tract *Chlamydia trachomatis* infection.**  
Ellen Marks, Martina Verolin, Anneli Stensson, Nils Lycke.  
*Infect. Immun.* 75(9):4638-47 (2007).
- III. **Th1 cell differentiation in the absence of CD28 and ICOS signaling rescues host immune responses to a primary genital tract infection with *Chlamydia trachomatis*.**  
Ellen Marks, Anneli Stensson, Woong-Kyung Suh, Nils Lycke.  
*Manuscript.*
- IV. **Vaccination of the genital tract for the generation of CD4<sup>+</sup> T cell immunity.**  
Ellen Marks, Anja Helgeby, Karin Schön, Nils Lycke.  
*Manuscript.*



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