



The image shows a microscopic view of a cell with several TLR11 receptors (dark, beaded structures) on its surface. Below the cell, there are several clusters of signaling molecules labeled MyD88, IRAK, TRAF6, and NFκB. The background is a dark, textured surface.

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MyD88

Innate immune defense to
Toxoplasma gondii

IRAK

TRAF6

NFκB

Pathogen recognition by innate immune cells



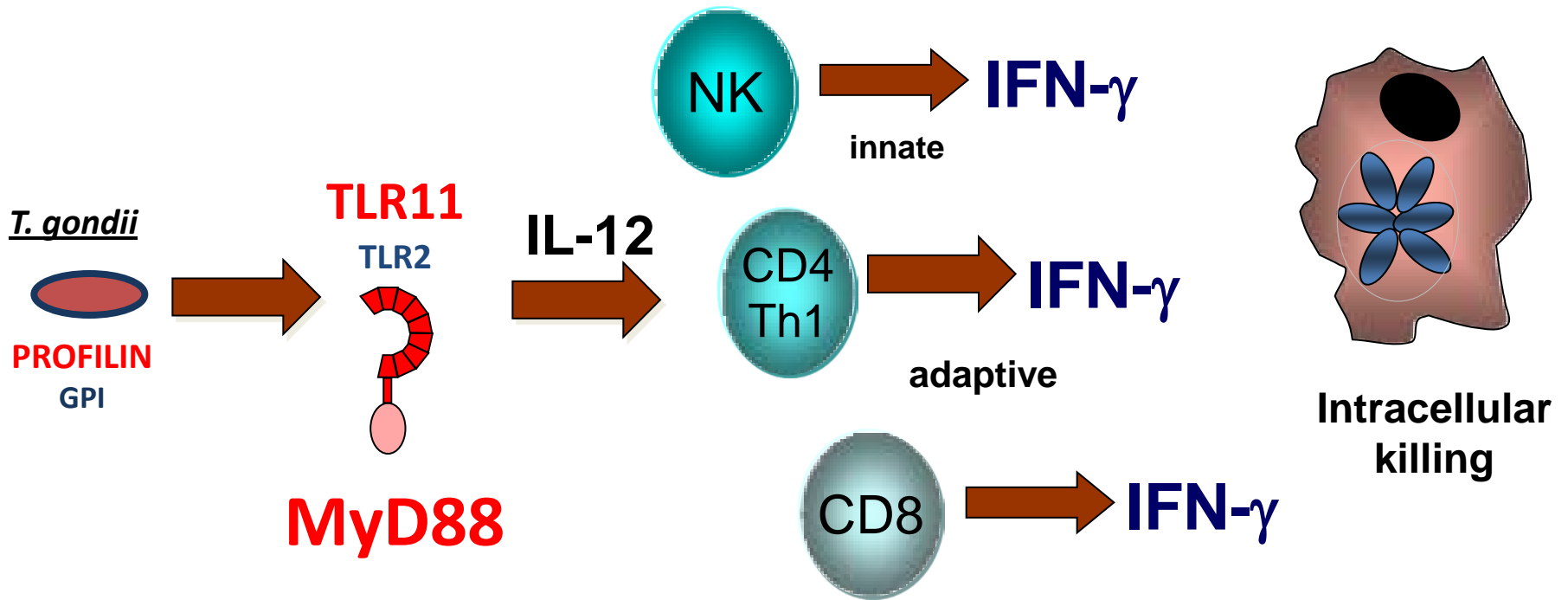
Major questions in the Lab:

- **What are the molecular mechanisms of innate recognition of parasites?**
- **How does innate recognition define host protection from infectious diseases?**

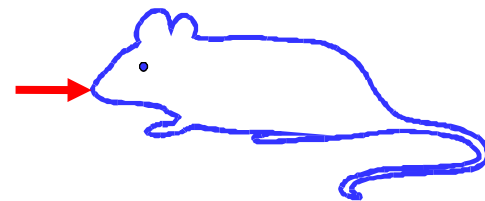
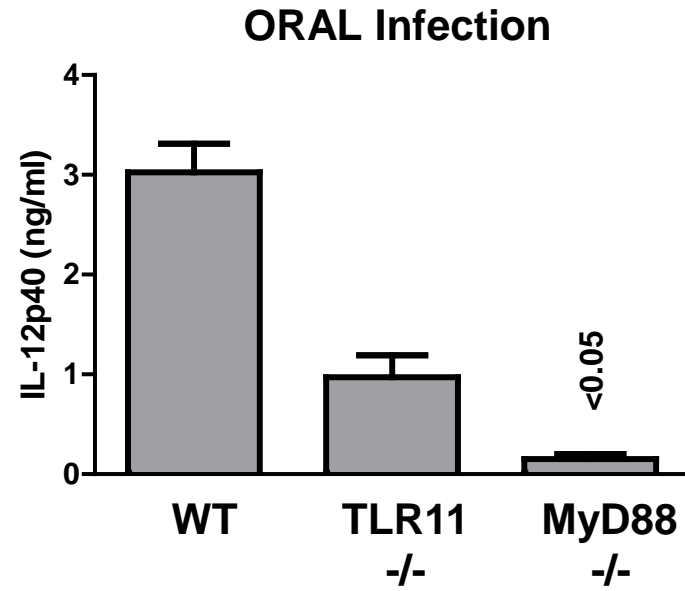
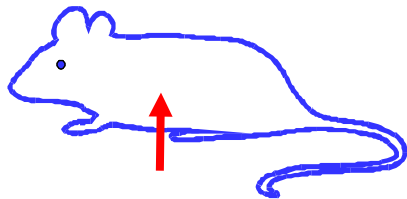
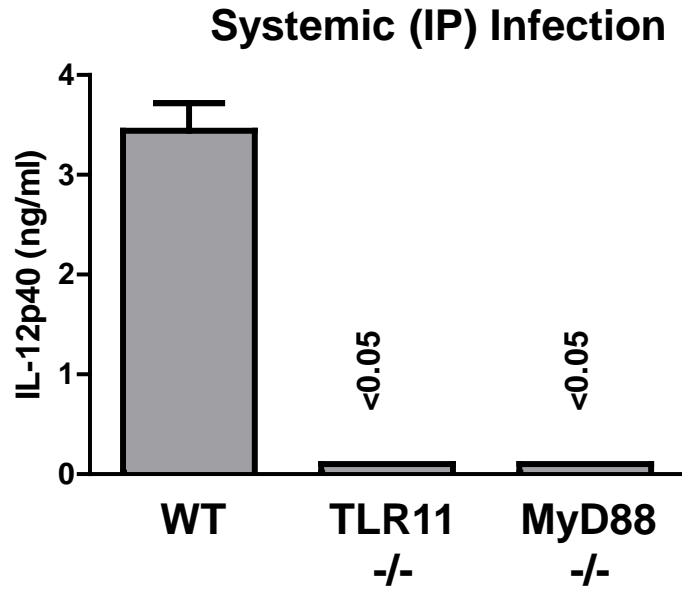
The central role for TLR11 and MyD88 in IL-12 mediated immunity against *T. gondii*

Pattern recognition
(pathogen-decoding)

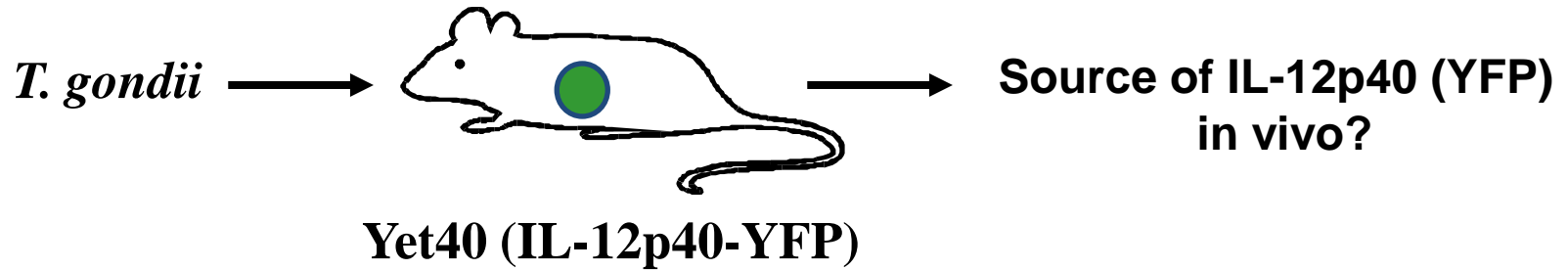
Effector phase



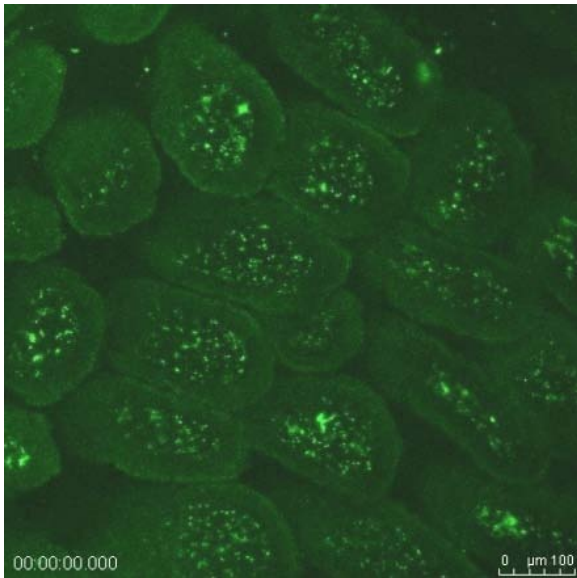
The mucosal immune system can initiate an immune response against *T. gondii* in the absence of TLR11



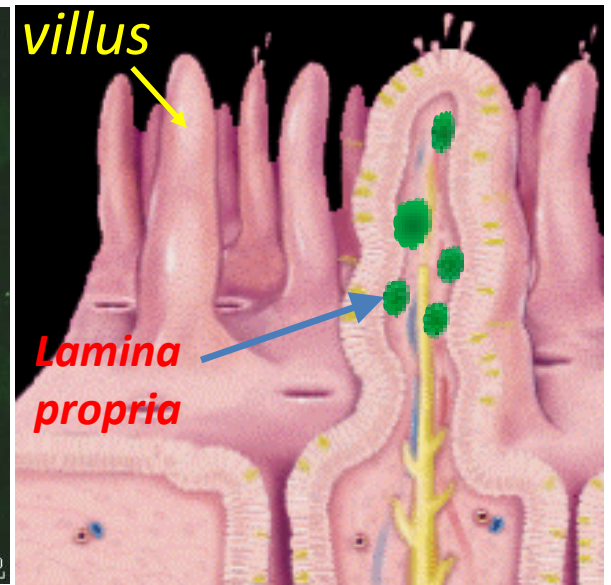
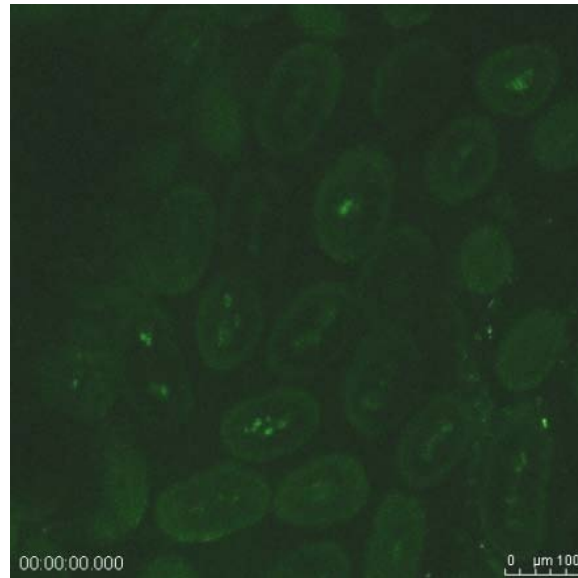
Visualization of IL-12-positive cells during *T. gondii* infection



WT (Yet40)

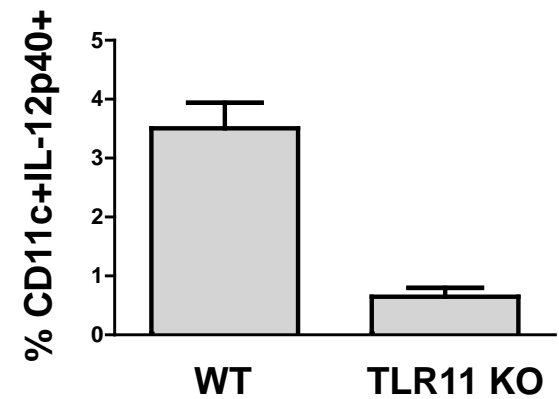
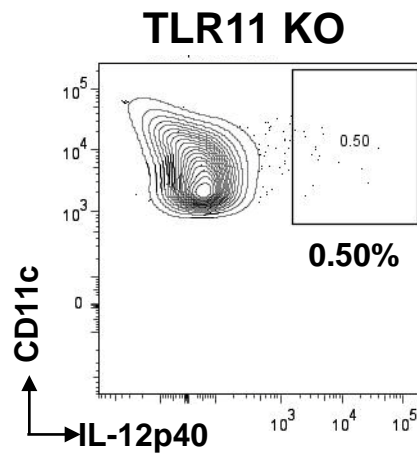
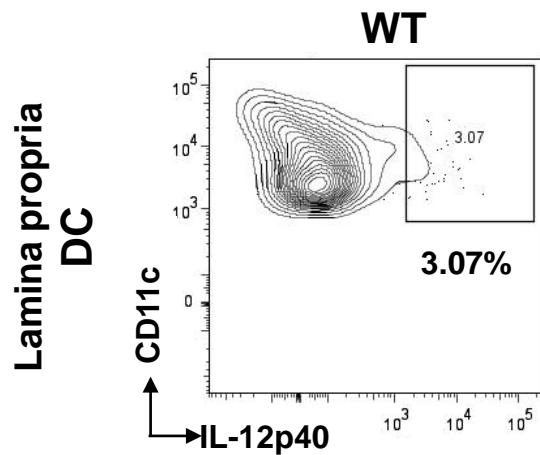
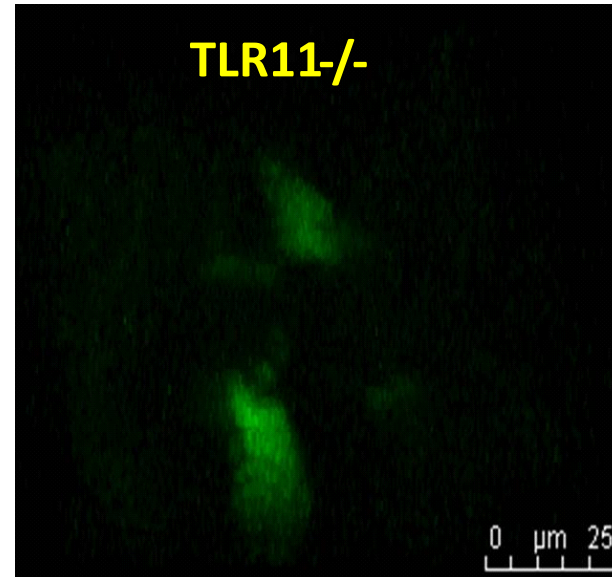
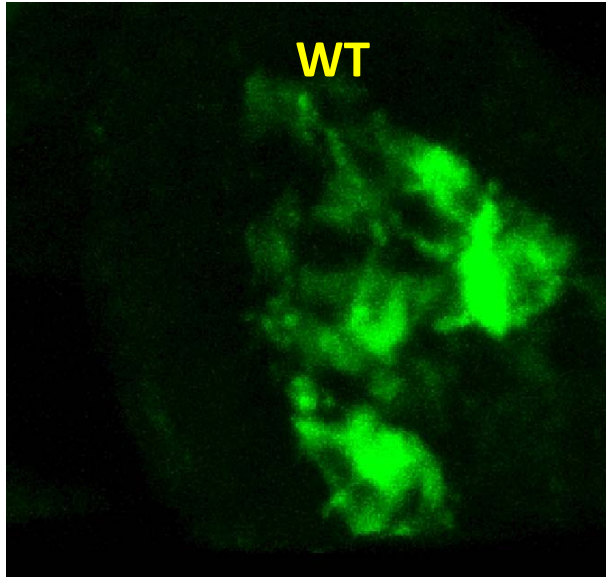


TLR11^{-/-} Yet40

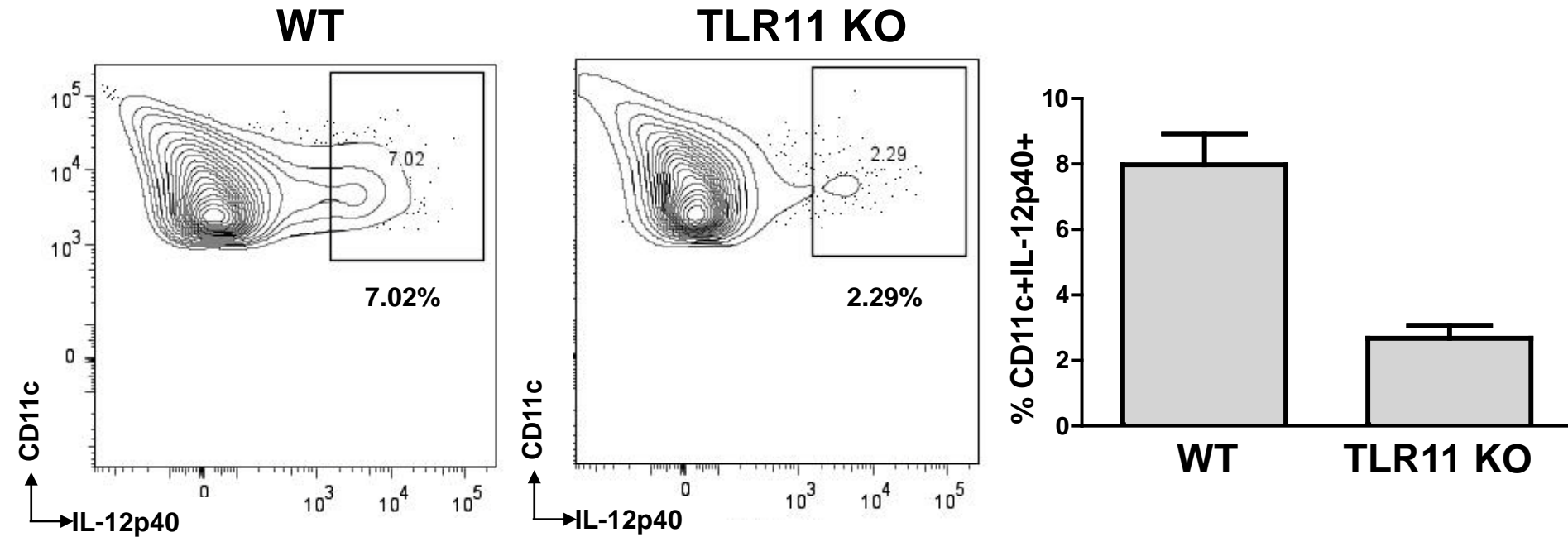


Adapted from Ganz (2000), *Nat. Immunol*

Visualization of IL-12-positive cells during *T. gondii* infection

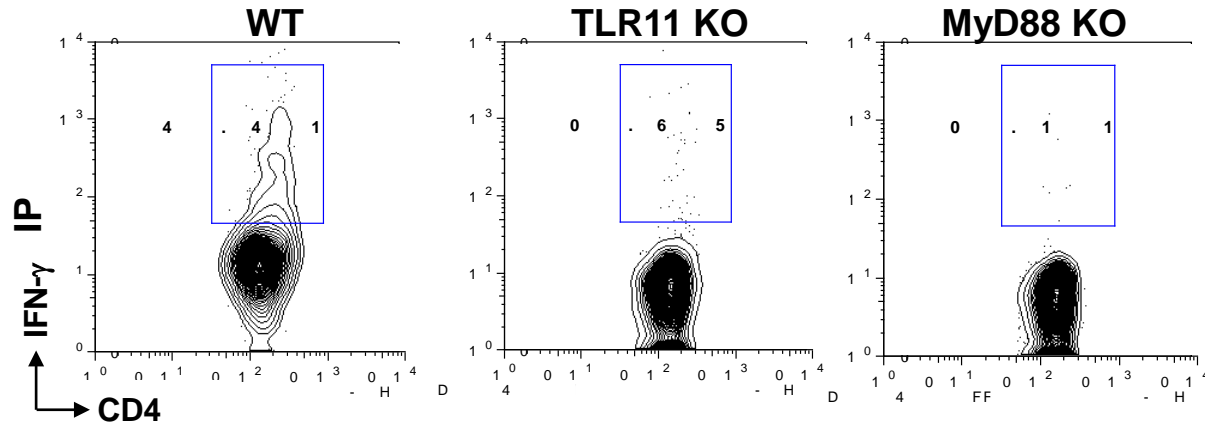
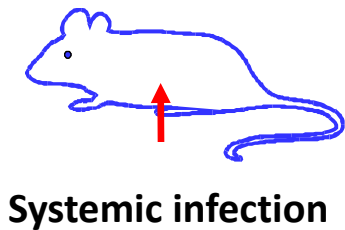
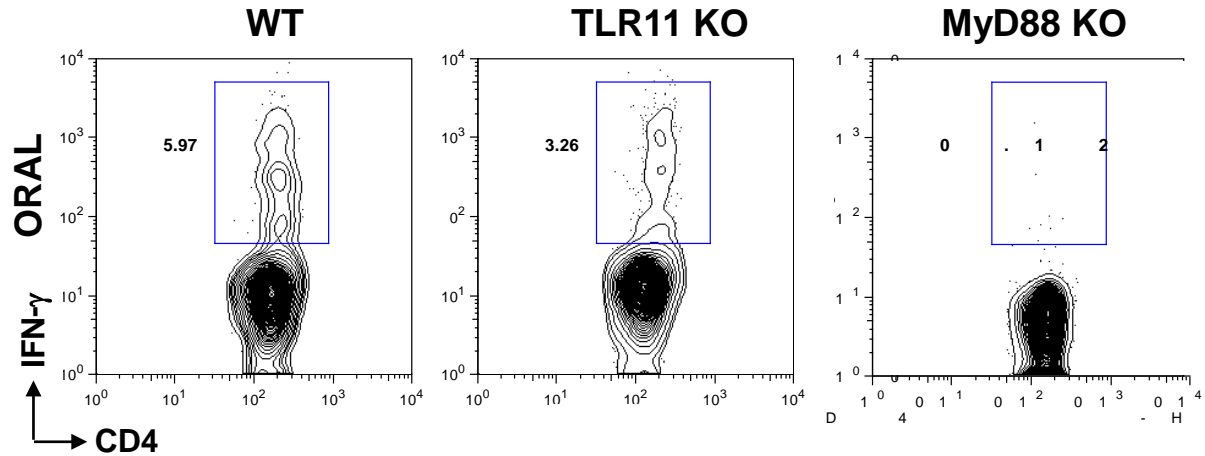


Identification of IL-12p40 producing cells in peripheral lymphoid organs during oral infection with *T. gondii*.



mLN, day 5 post infection

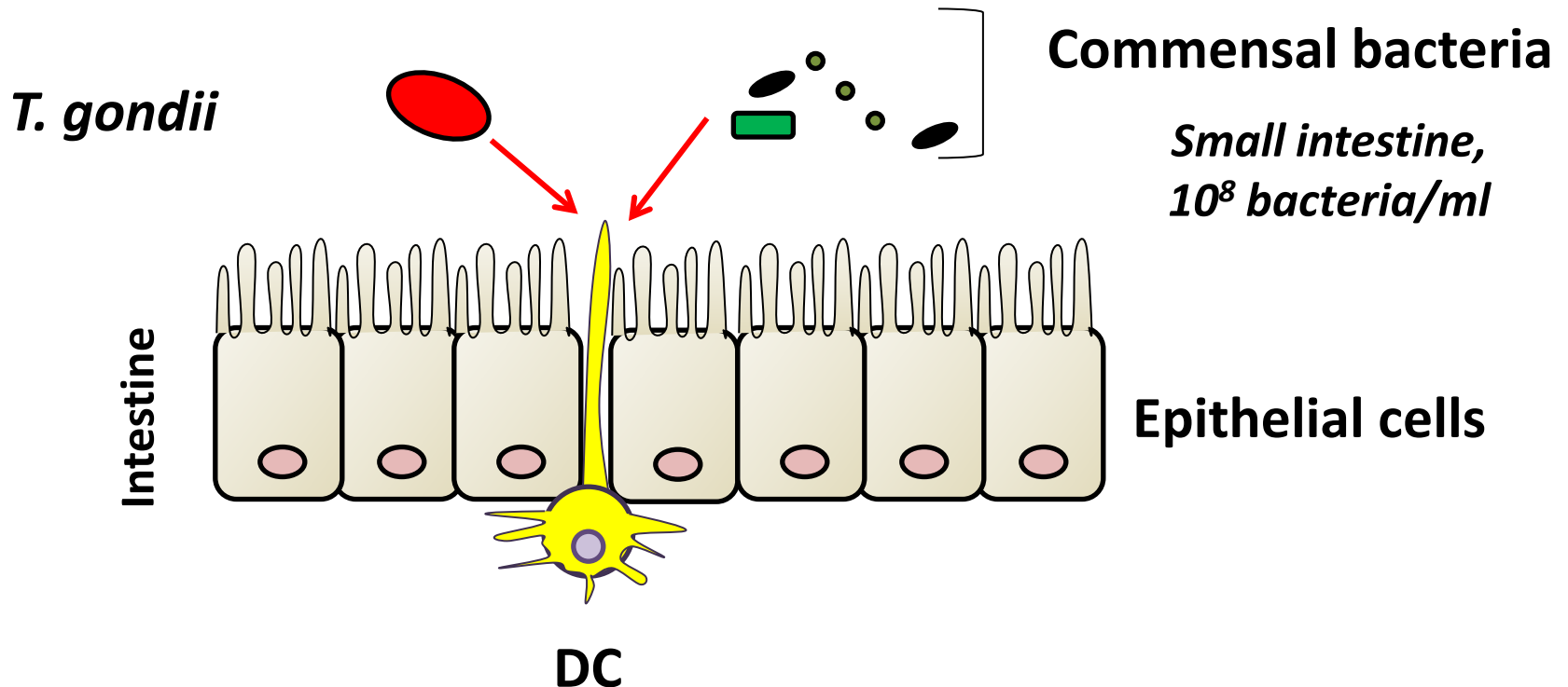
Natural route of the *T. gondii* infection results in TLR11-independent Th1 responses to the parasite



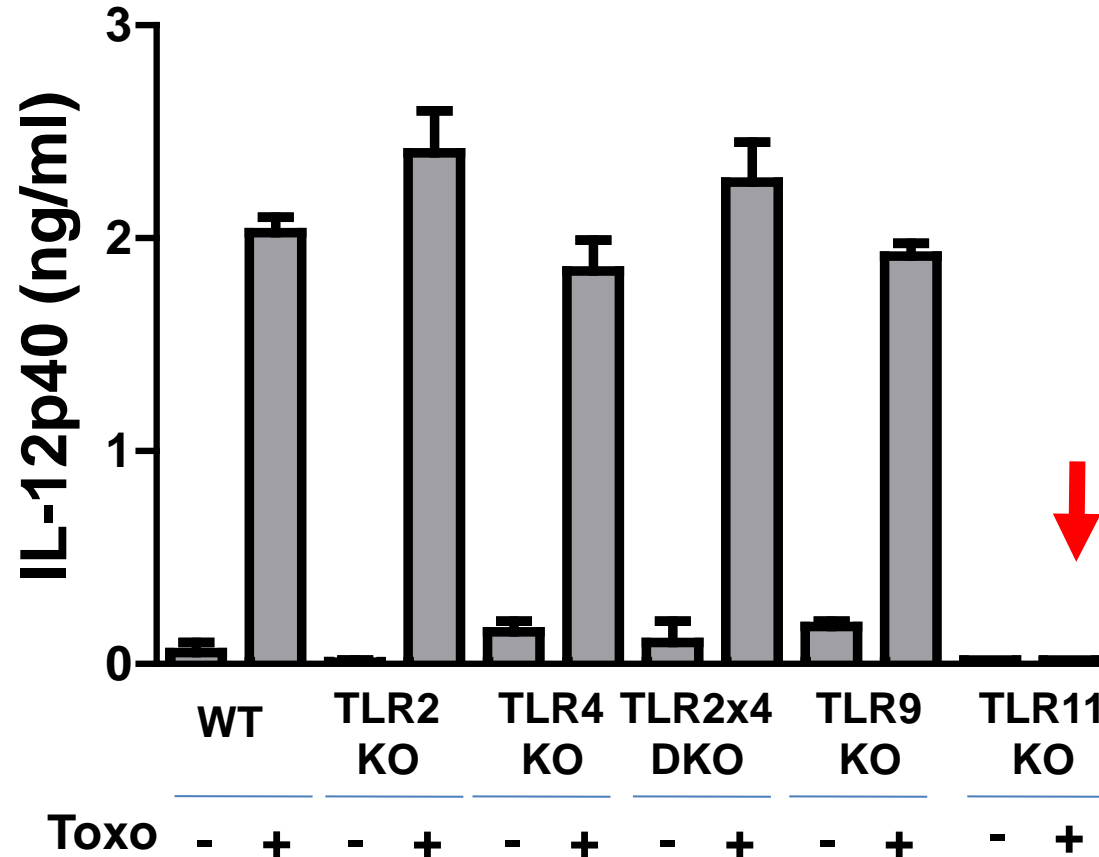
Two possible models

Mucosal DC directly recognize *T. gondii* through a TLR11-independent mechanism that governs IL-12 production

The mucosal microbial environment is responsible for indirect stimulation of anti-parasitic responses

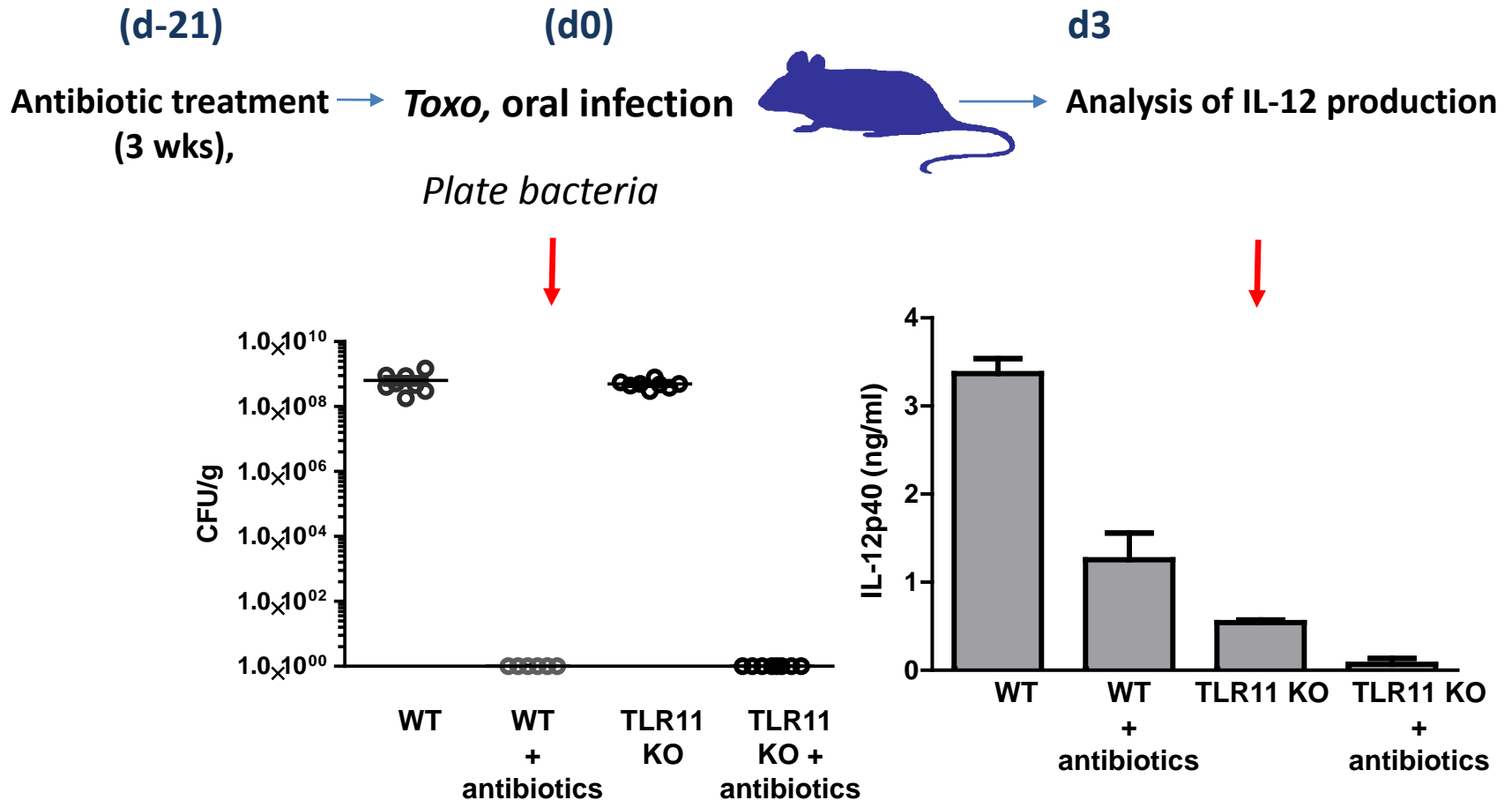


Can mucosal DC directly recognize *T. gondii* through a TLR11-independent mechanism ?



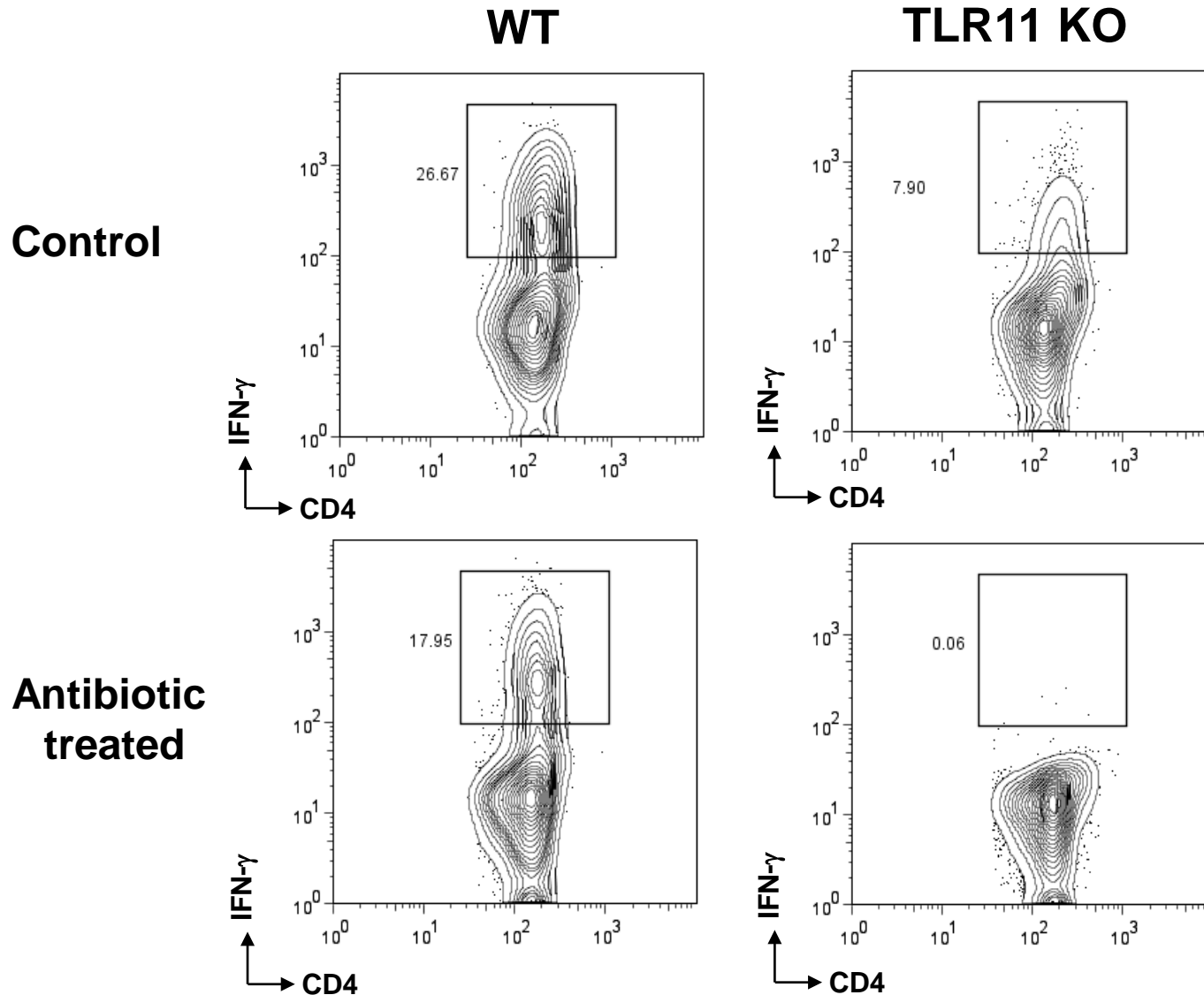
Mucosal DC IL-12 responses in vitro depend on TLR11

Is the mucosal microbial environment responsible for indirect stimulation of anti-parasitic responses?

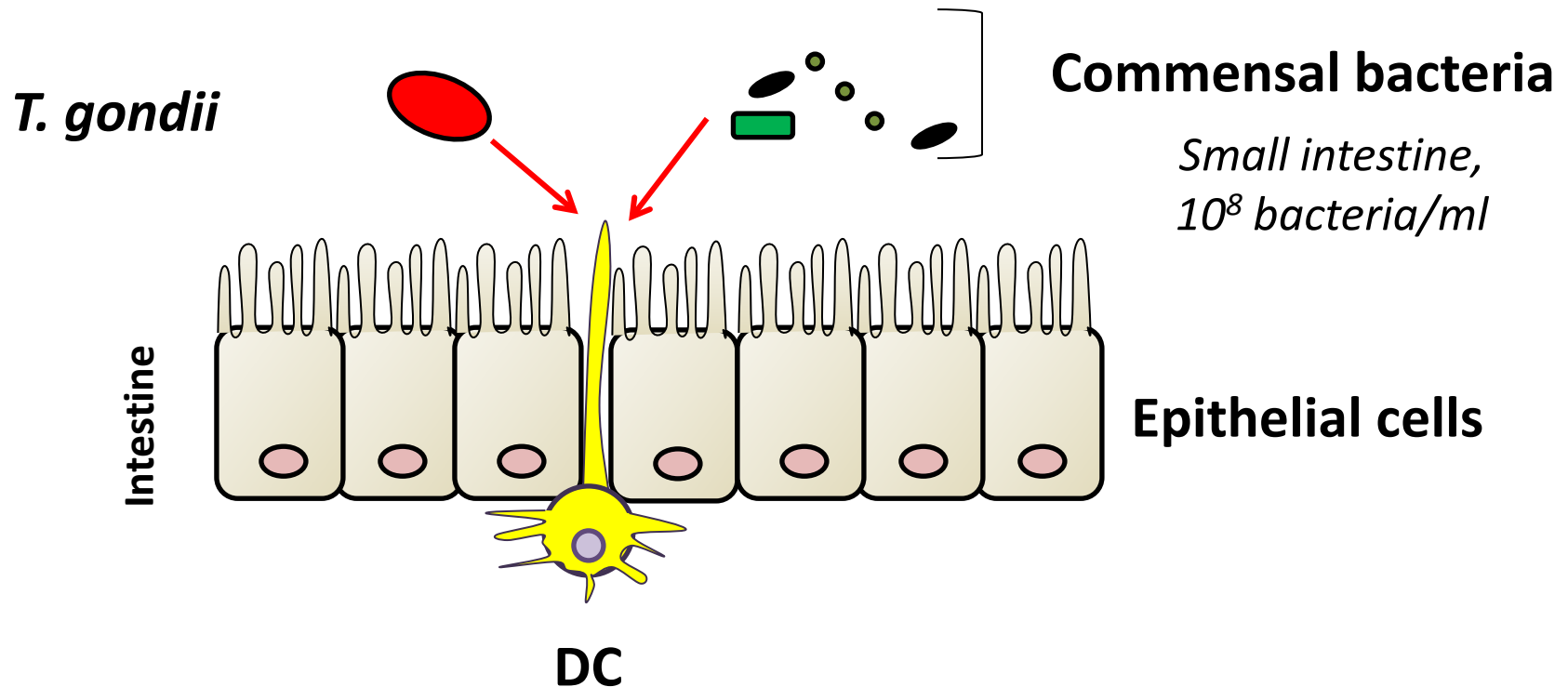


Commensal bacteria are required for IL-12 production in response to *T. gondii* in the absence of TLR11

Commensal bacteria are essential for Th1 immunity during oral infection with *T. gondii* in the absence of TLR11



Gut commensal bacteria direct a protective immune response against human pathogen *Toxoplasma gondii*



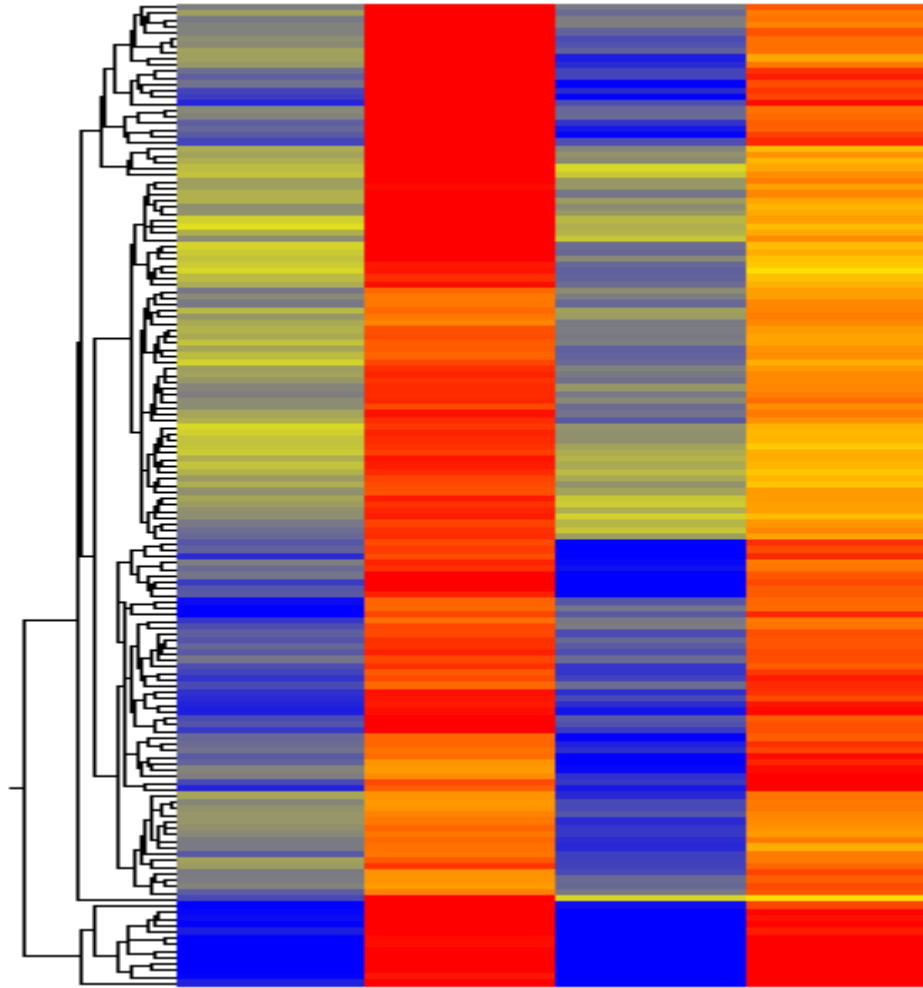
***T. gondii*: invasion and tissue damage**

***Micro flora*: a molecular adjuvant**

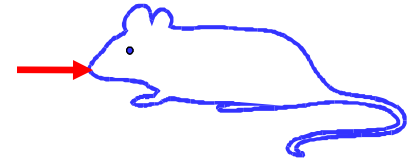
Gut commensal bacteria regulate a protective immune response against *Toxoplasma gondii*

TOXO
antibiotics

- + - +
- - + +



Peroral infection



(+/- Abx)

Conclusions (1)

A novel function for commensal bacteria:

protection against pathogens

- gut commensal bacteria function as a molecular adjuvant during parasitic infections, providing TLR-dependent immunostimulatory signals

Pathogen recognition by innate immune cells

pathogen → Initiator sensor cell → Innate immune response

?

Dendritic cell

Epithelial cell

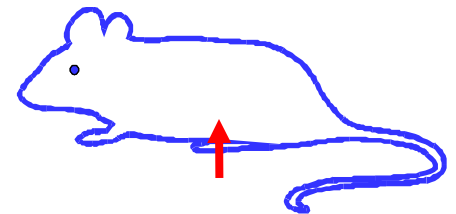
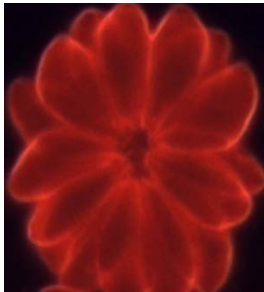
Macrophage

Monocyte

Neutrophil

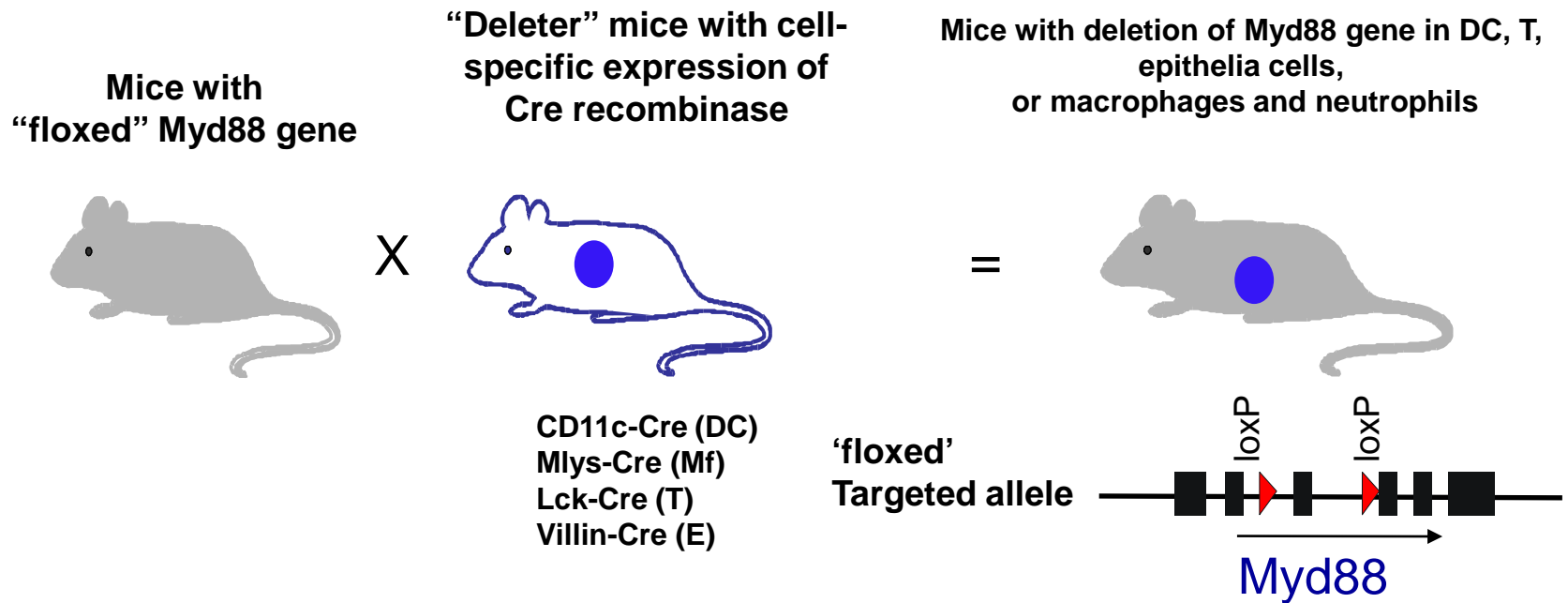
Mast cell

Toxoplasma

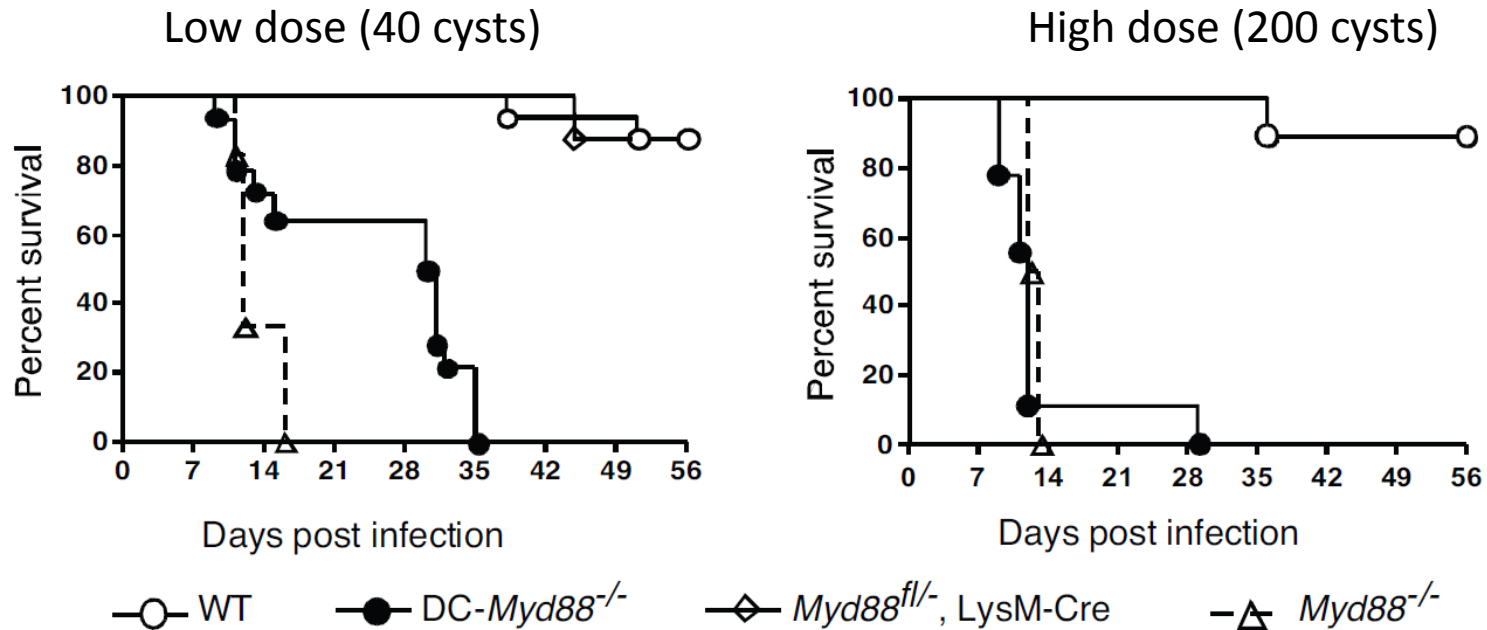


Systemic infection

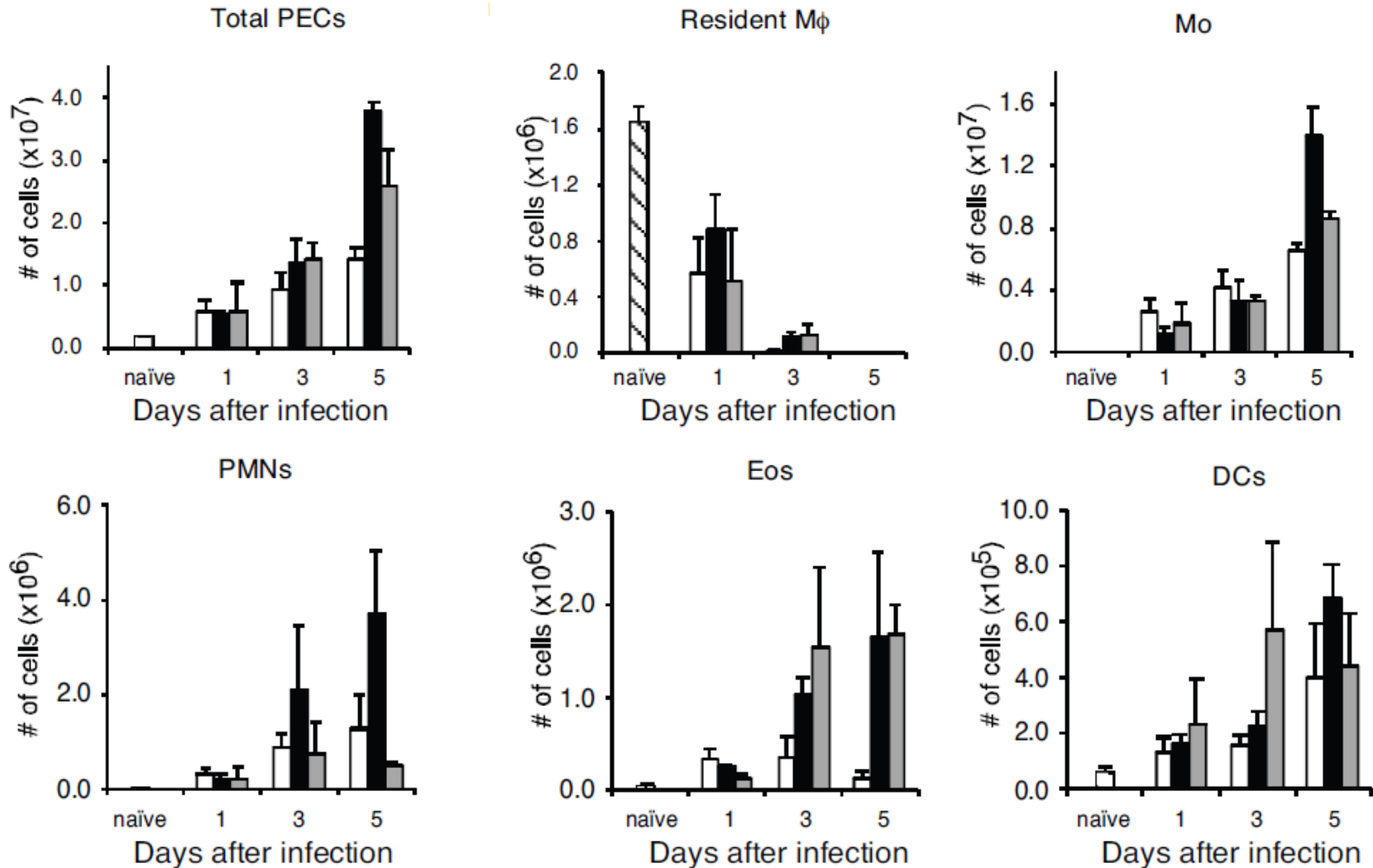
Cell-specific MyD88-dependent regulation of immunity



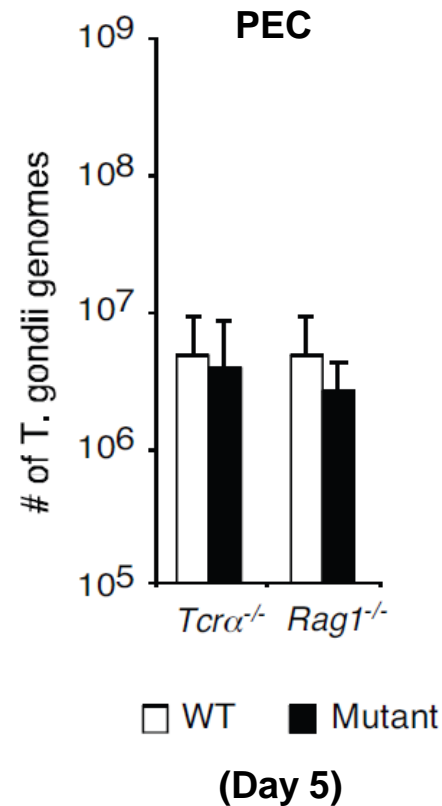
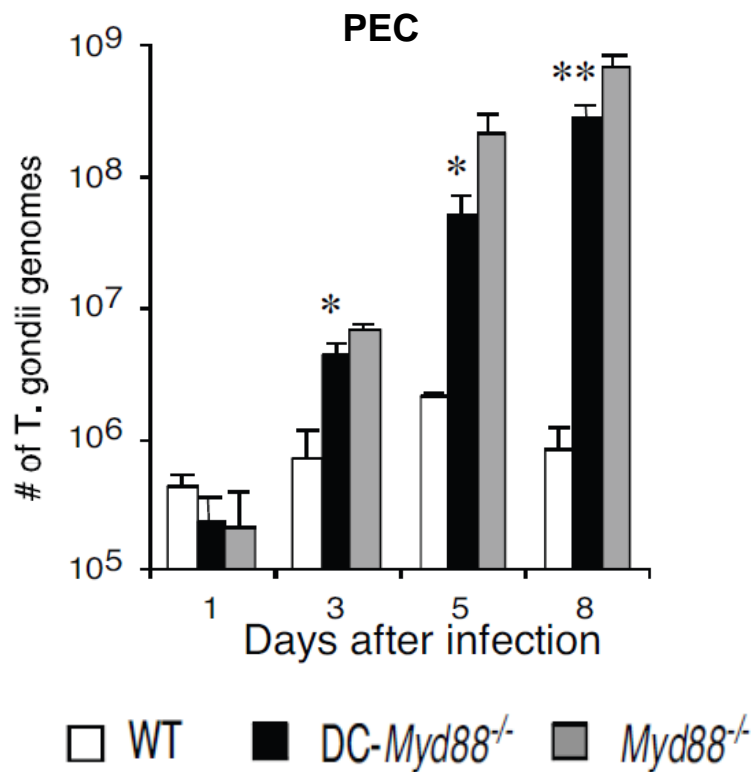
Role of MyD88 signaling in DCs for survival of mice upon *T. gondii* infection



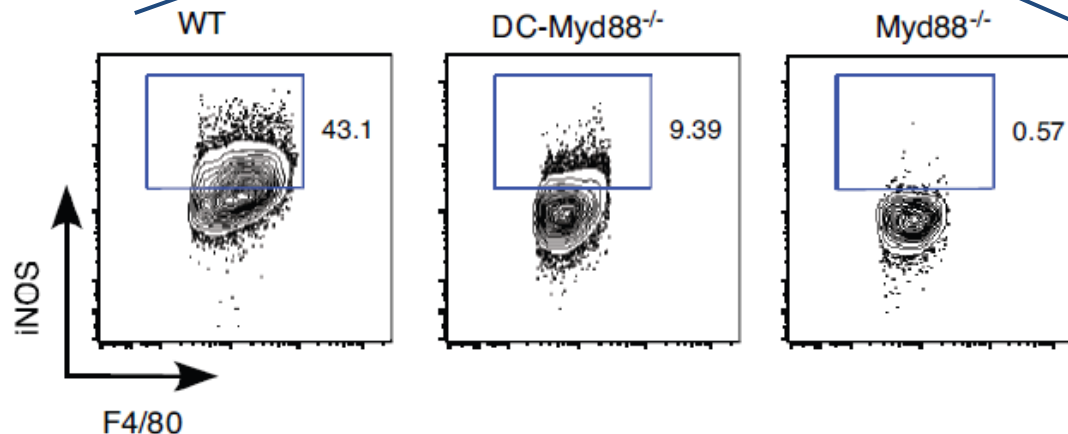
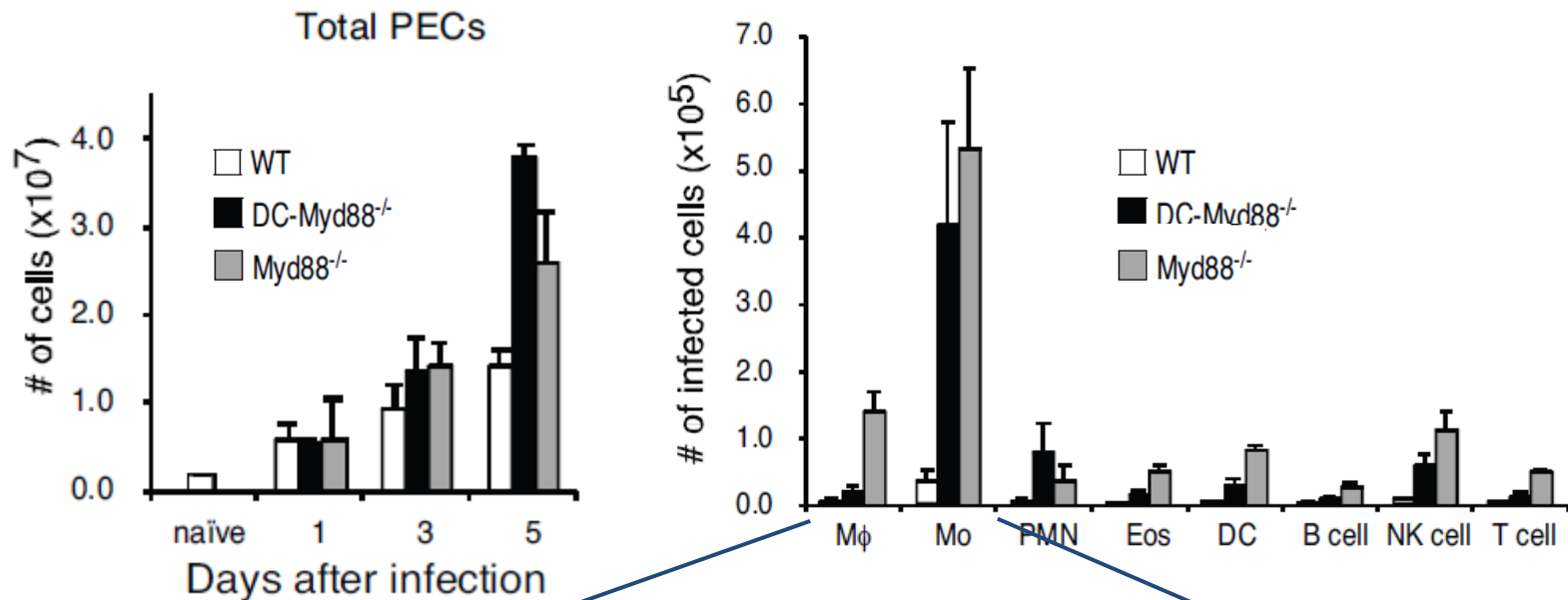
Role of MyD88 in DCs for the recruitment of inflammatory cells in acute *T. gondii* infection



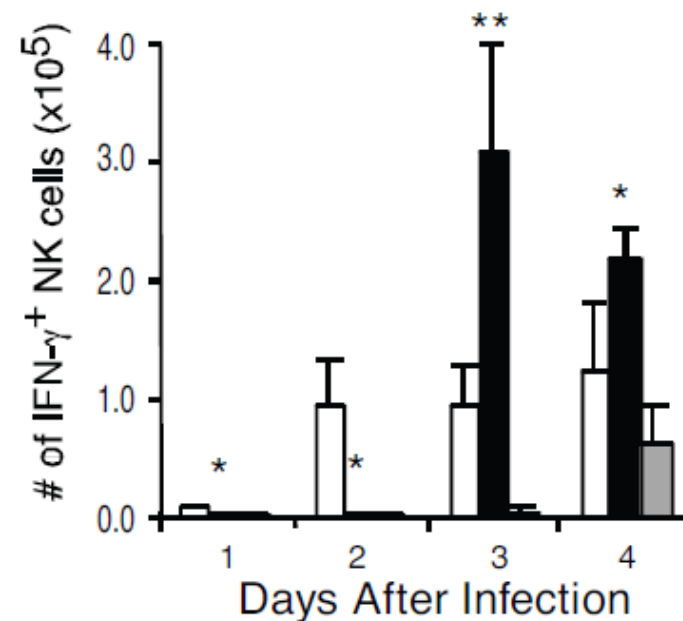
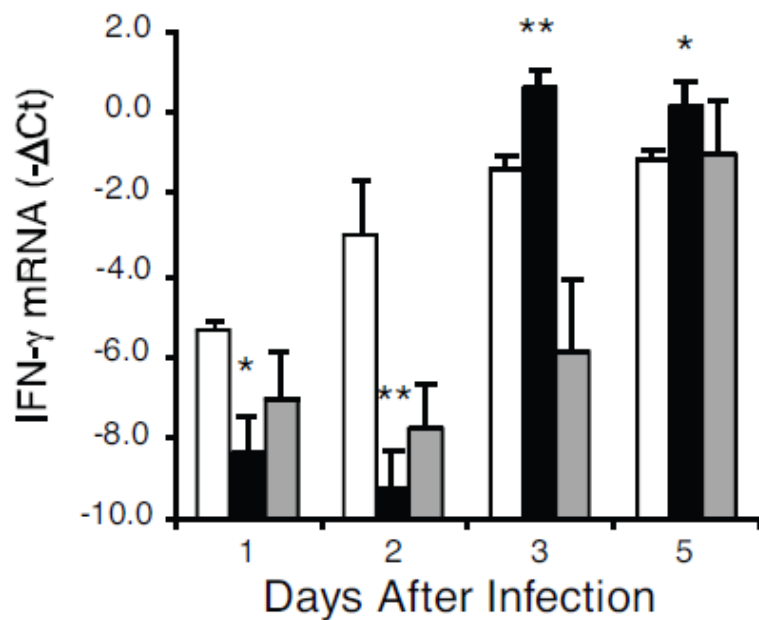
Expansion and dissemination of *T. gondii* in the DC-*Myd88*^{-/-} mice



Role of MyD88 in DCs for the recruitment of inflammatory cells in acute *T. gondii* infection



Induction of IFN- γ in the *T. gondii*-infected DC-*Myd88*^{-/-} mice

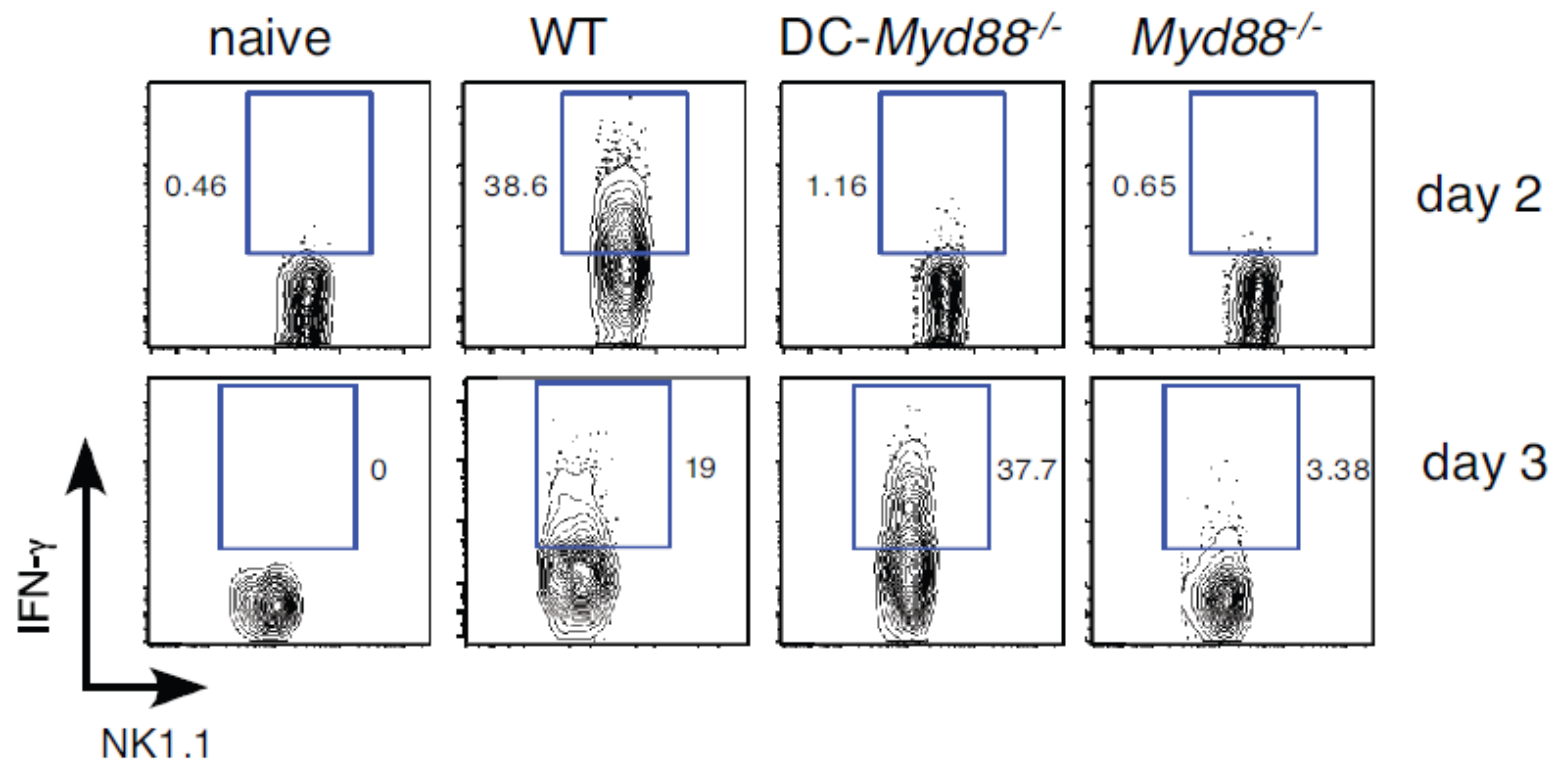


□ WT

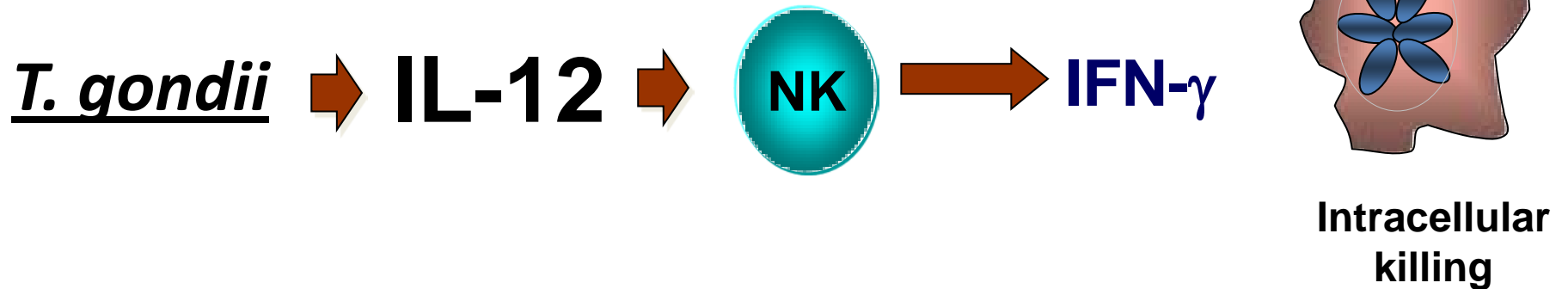
■ DC-*Myd88*^{-/-}

■ *Myd88*^{-/-}

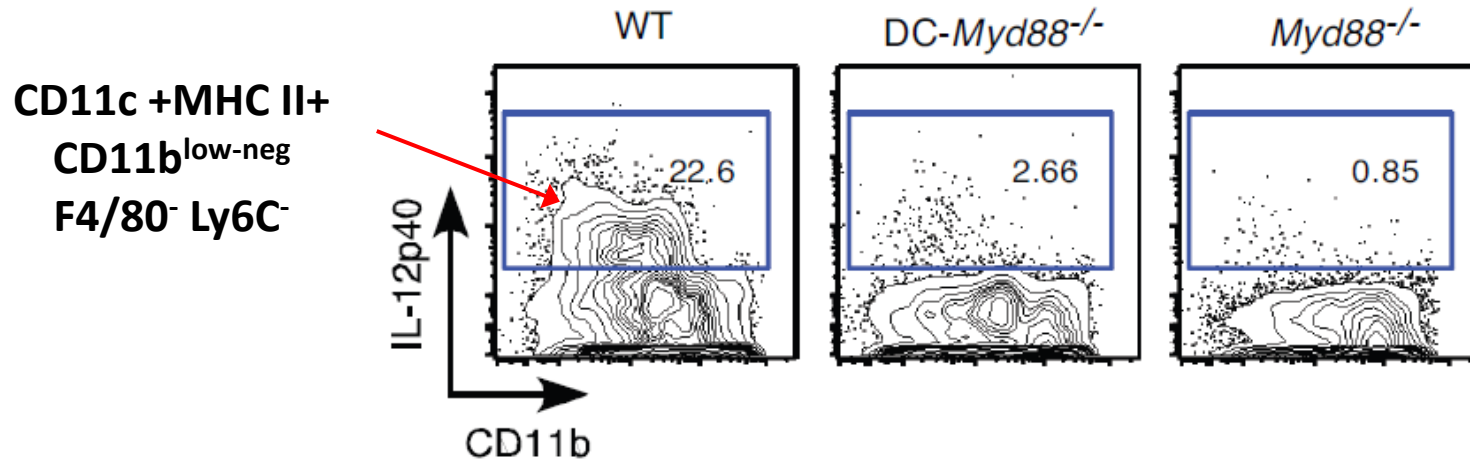
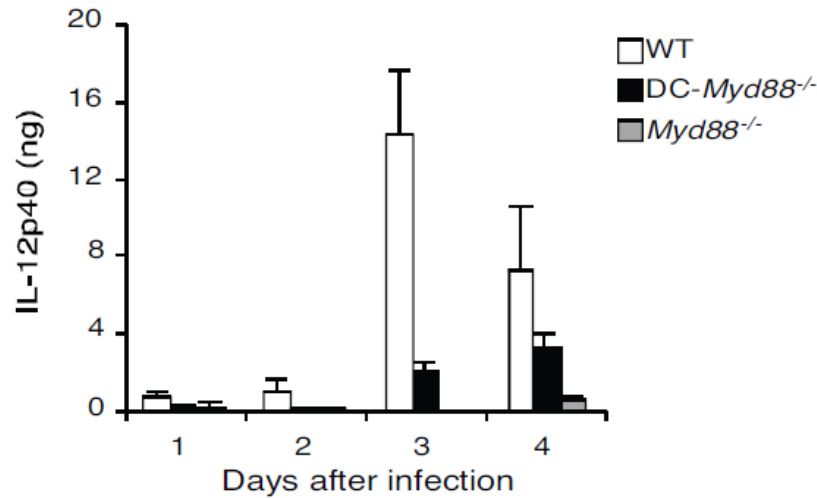
Induction of IFN- γ in the *T. gondii*-infected DC-*Myd88*^{-/-} mice



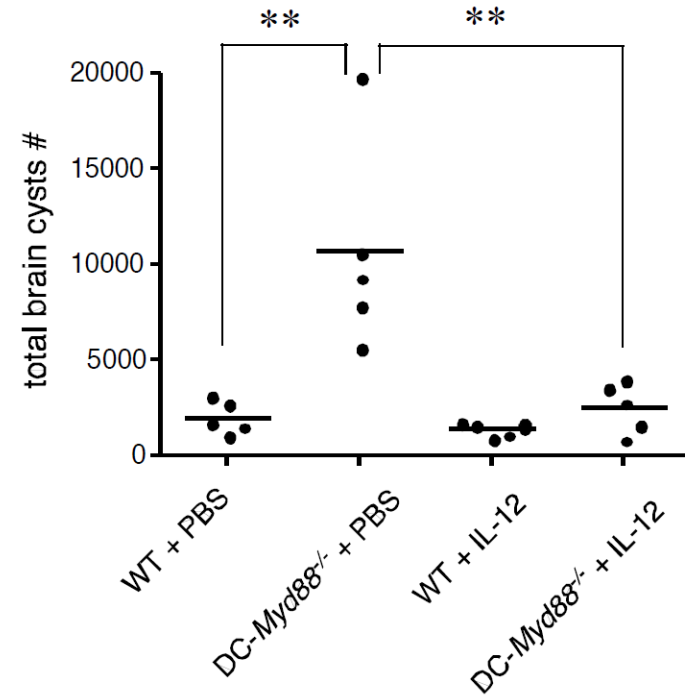
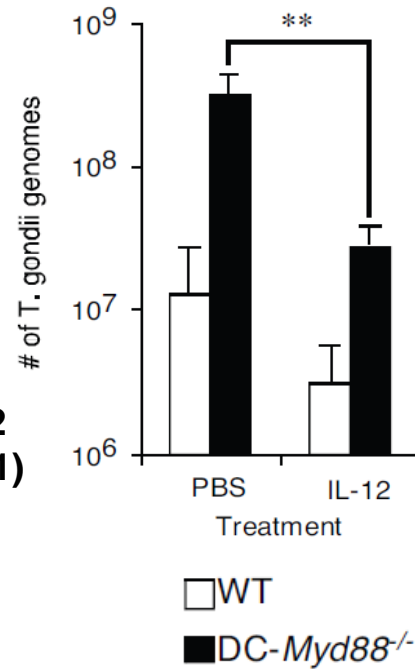
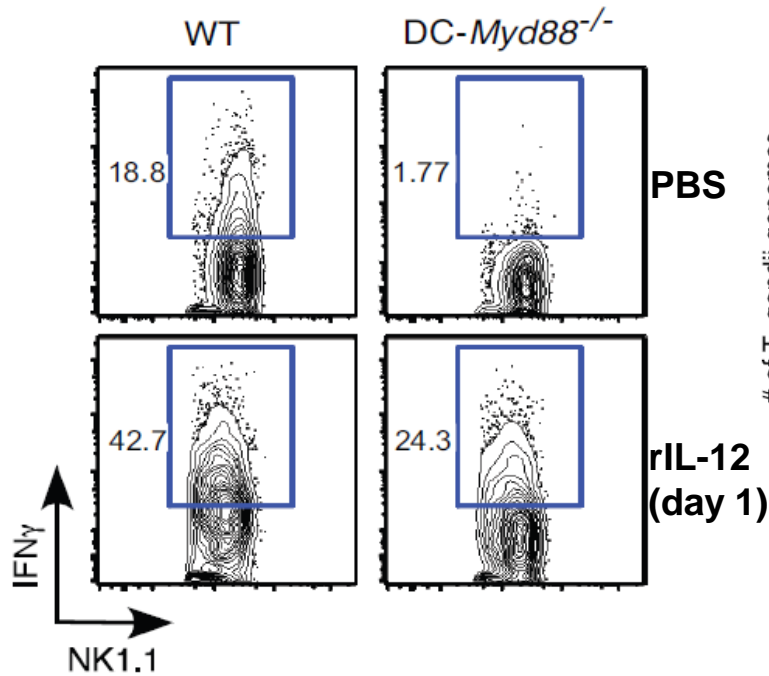
The central role for IL-12 in IFN- γ mediated immunity against *T. gondii*

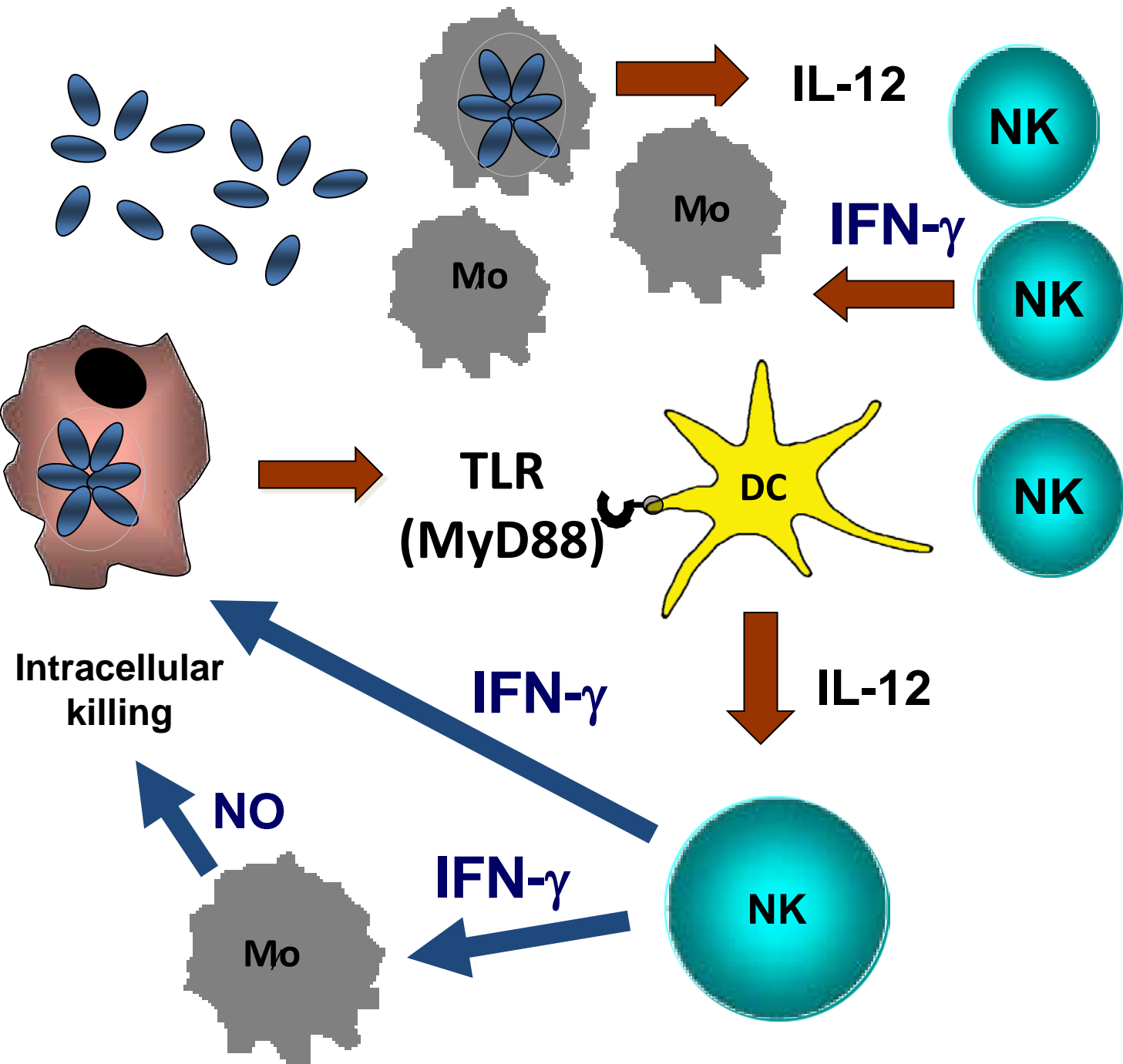


Defective IL-12 induction in *T. gondii*-infected DC-*Myd88*^{-/-} mice

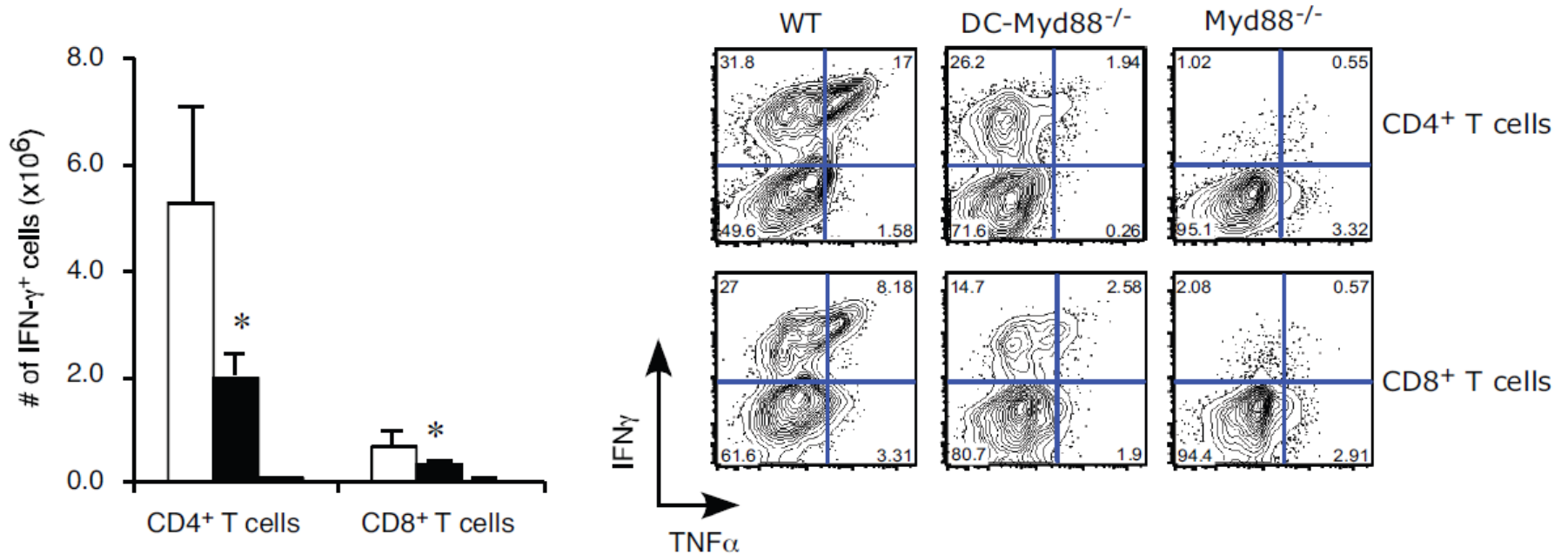


Induction of IL-12 in the *T. gondii*-infected DC-Myd88^{-/-} mice





Activation of T cells in the DC-*Myd88*^{-/-} mice



Acknowledgements

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