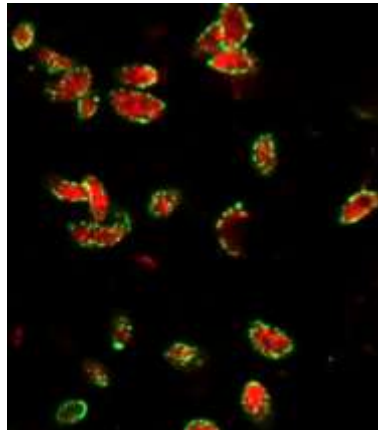


# Role of Natural Killer Cells in Chronic *Toxoplasma gondii* Infection

Ryan Krempels and Dr. Jason Gigley

# *Toxoplasma gondii*

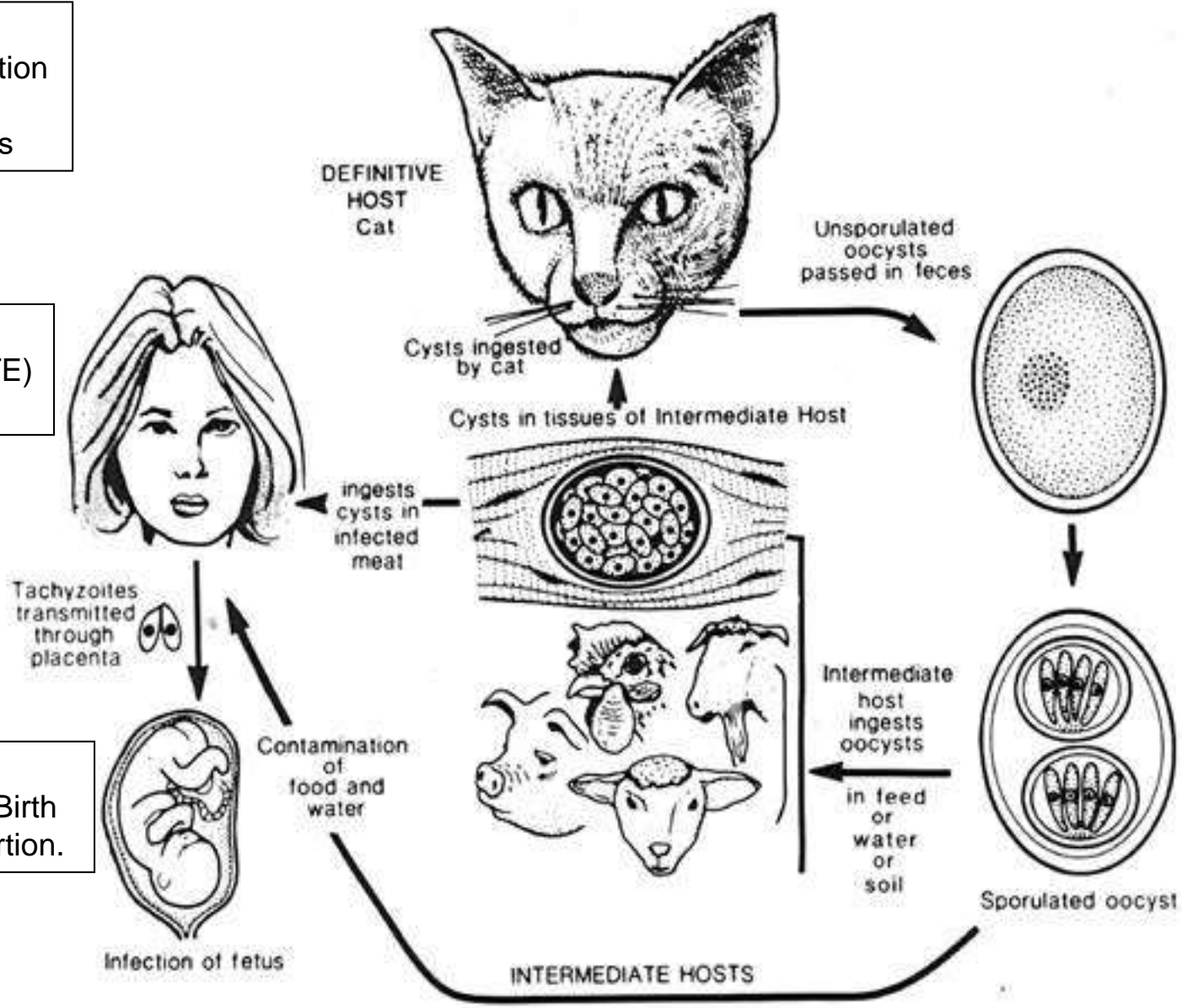
- Obligate intracellular parasite.
- Generally asymptomatic in healthy individuals.
- Up to 60 million Americans infected.
- 2<sup>nd</sup> largest cause of death from food borne illness.



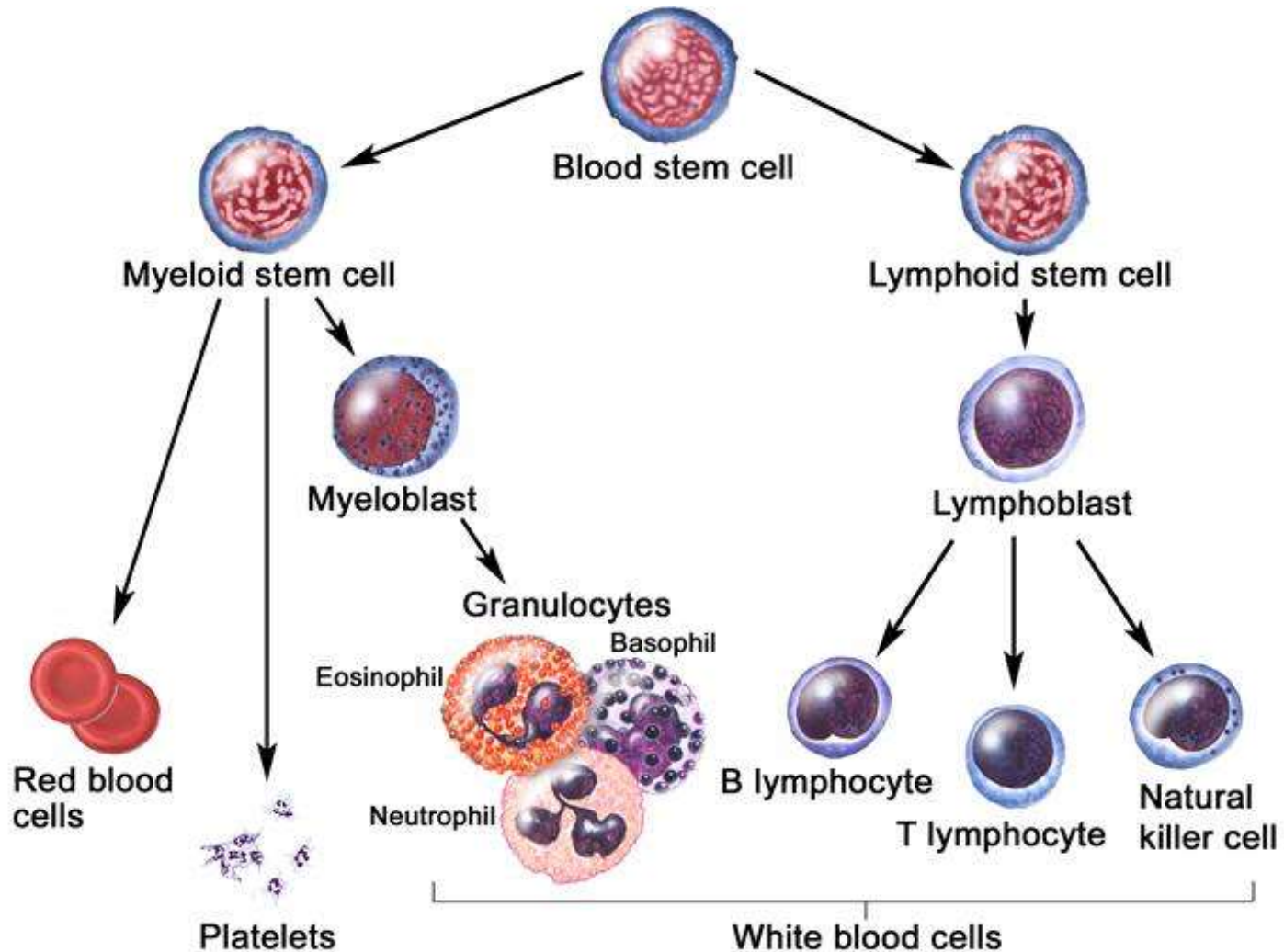
Immunocompetent  
Persistent life long infection  
Behavioral changes,  
Dementia, Alzheimer's

Immunocompromised  
Toxoplasmic encephalitis (TE)  
Death.

Fetal transmission  
Blindness, Hydrocephaly, Birth  
Defects, Spontaneous abortion.



# The Immune System



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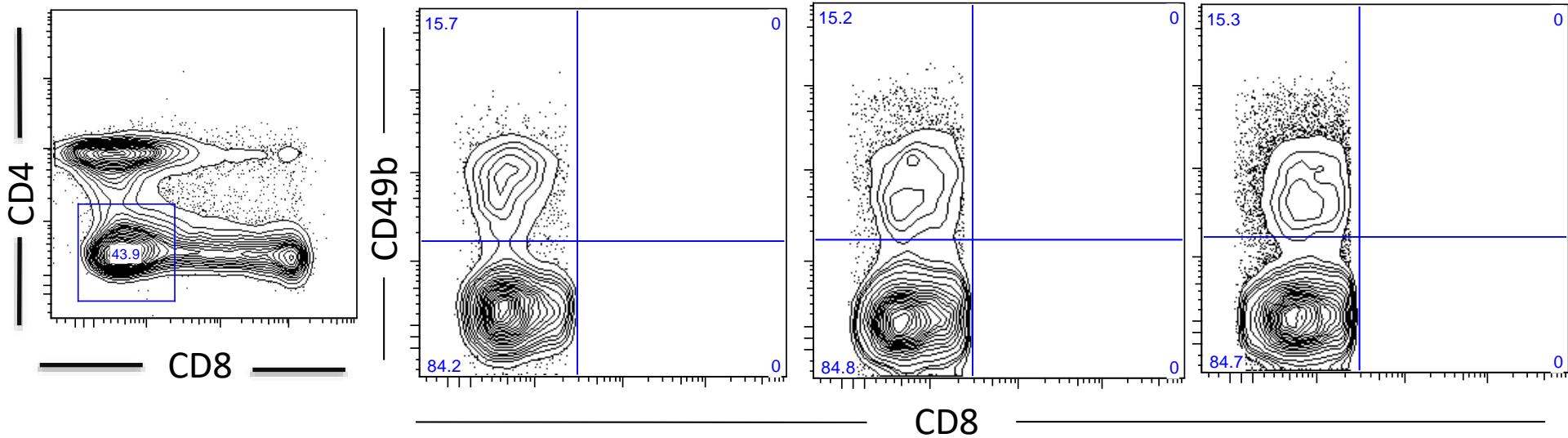
# NK Cells

- Innate immunity during acute infection.
  - Cytotoxicity
  - T-cell activation
- Recently shown to provide a memory immune response.

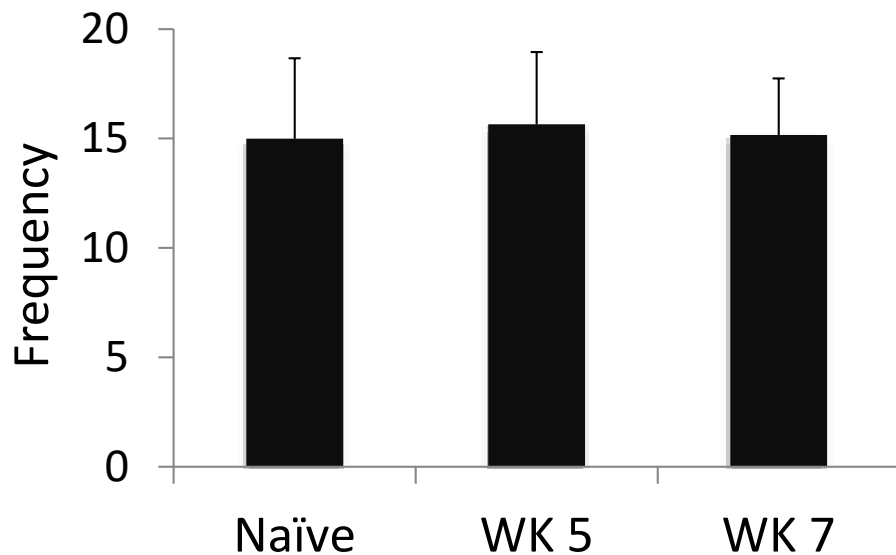
# Specific Aims

- Aim 1: Demonstrate that NK cells play a role in controlling chronic *T. gondii* infection
- Aim 2: Determine the functionality of NK cells during chronic *T. gondii* infection

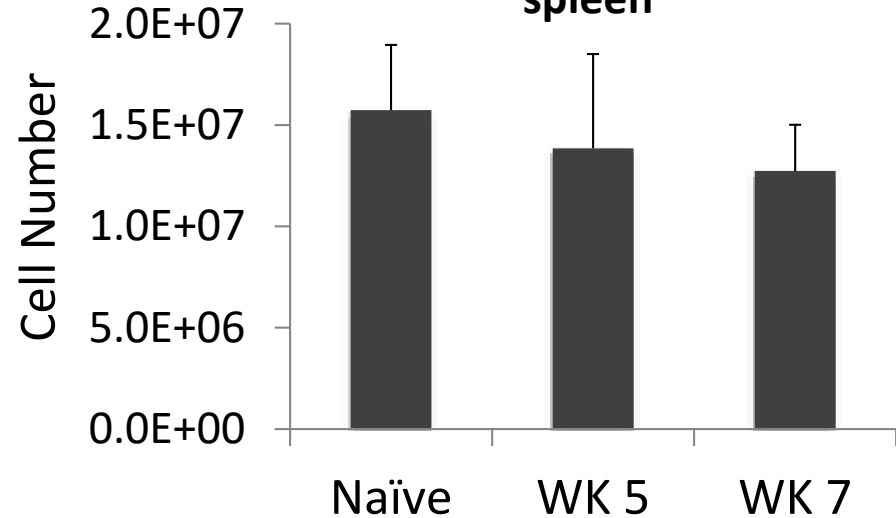
There is no change in the number of NK cells in the spleen of chronically infected mice.



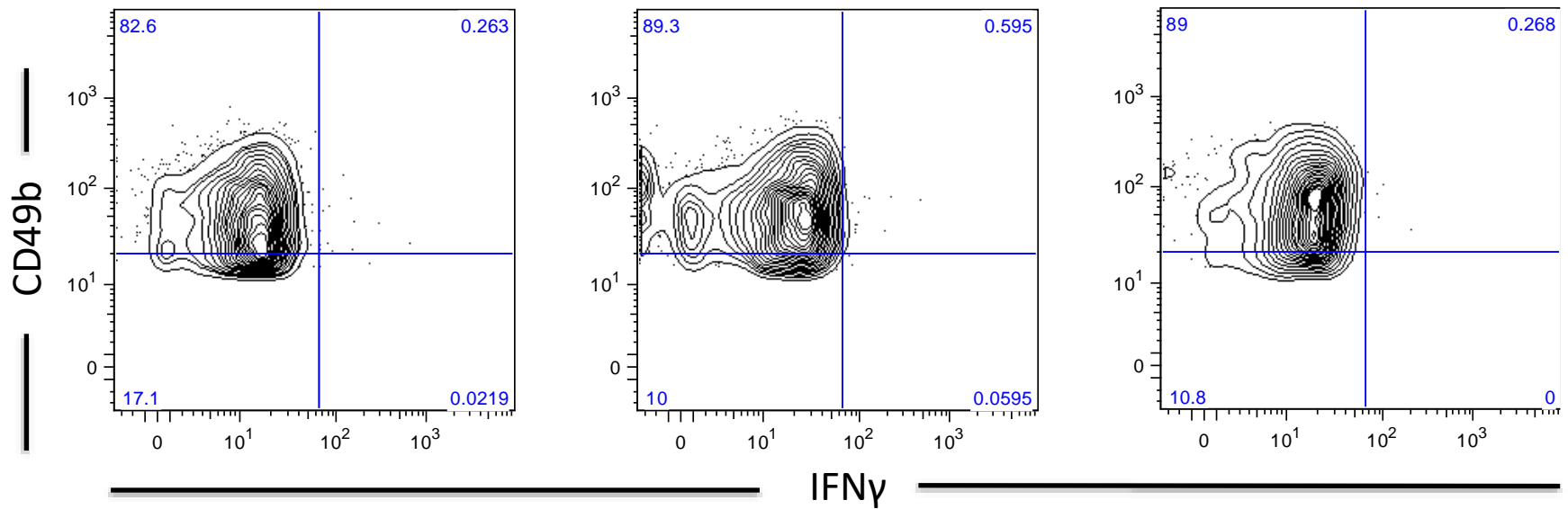
Frequency of NK cells per spleen



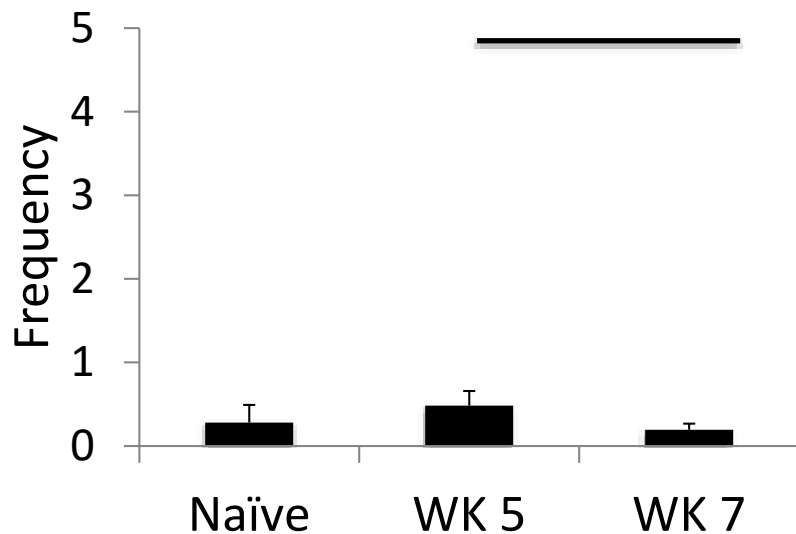
Absolute Number of NK cells per spleen



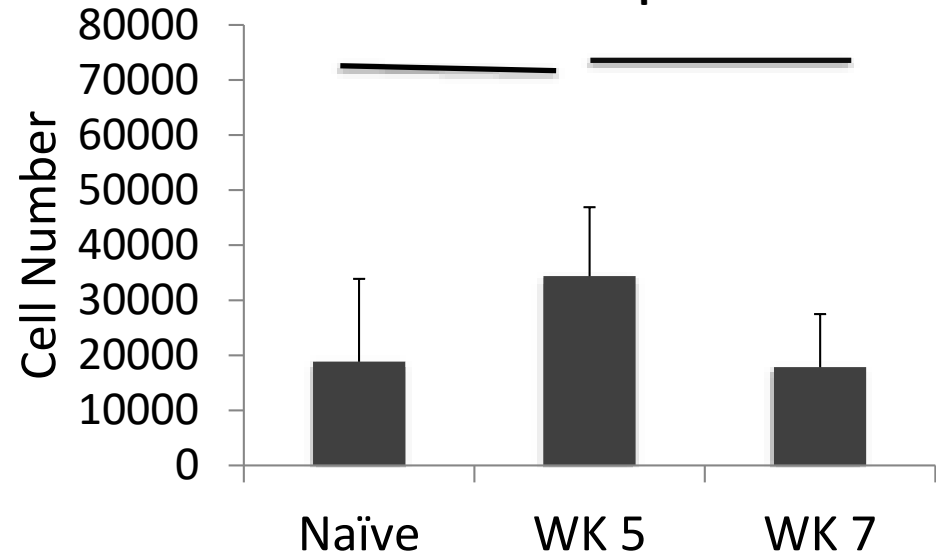
# IFN $\gamma$ expression decreases during *T. gondii* reactivation.



### Frequency of IFN $\gamma$ <sup>+</sup> NK Cells

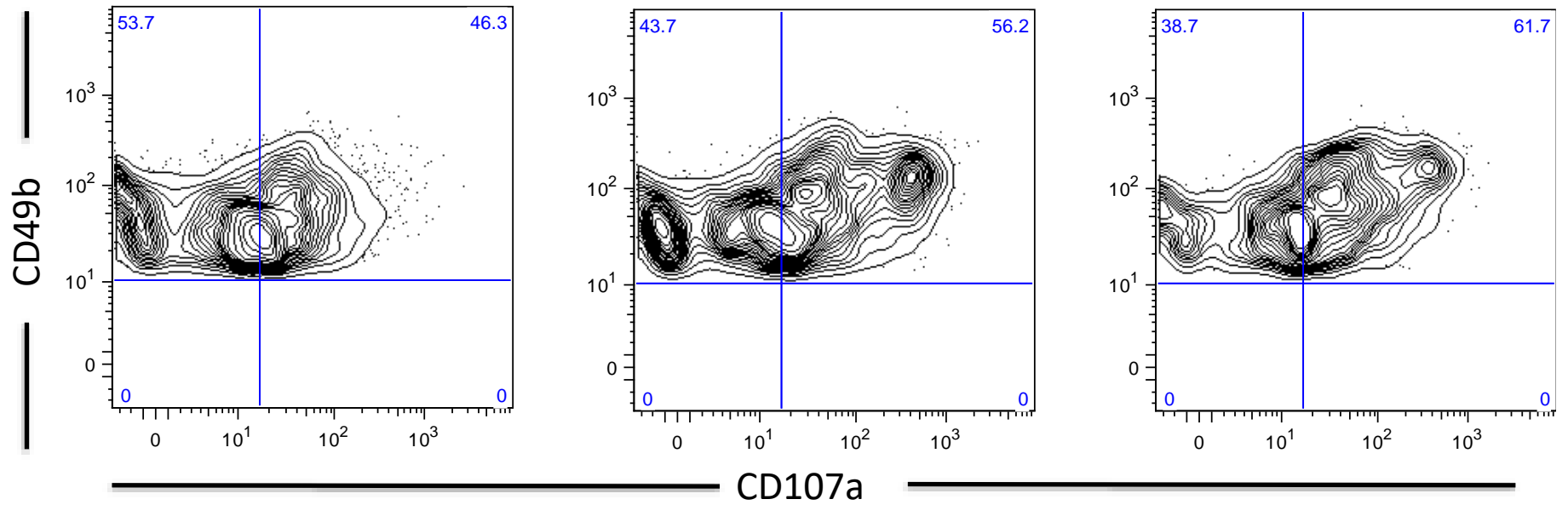


### Absolute Number IFN $\gamma$ <sup>+</sup> NK Cells

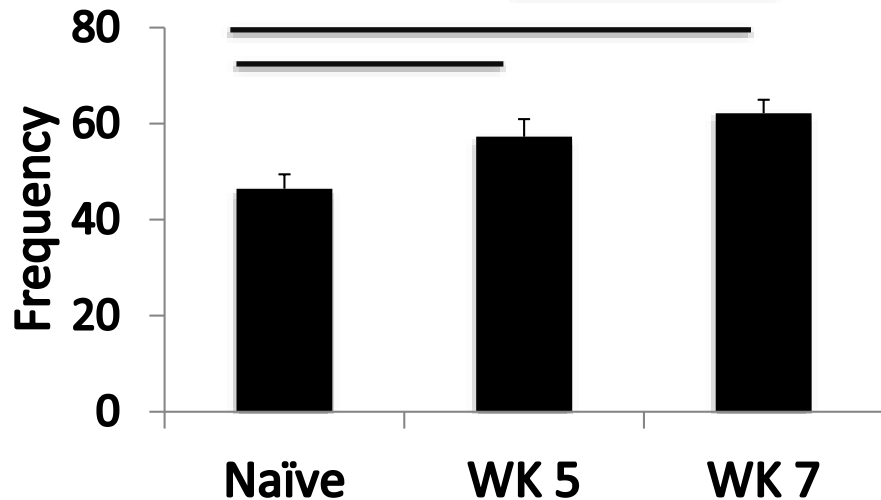




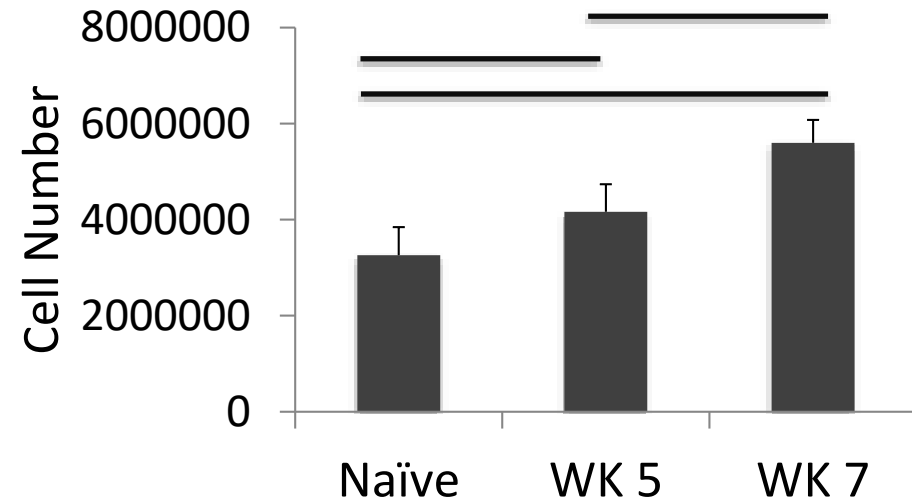
# CD107a expression increases during *T. gondii* reactivation.



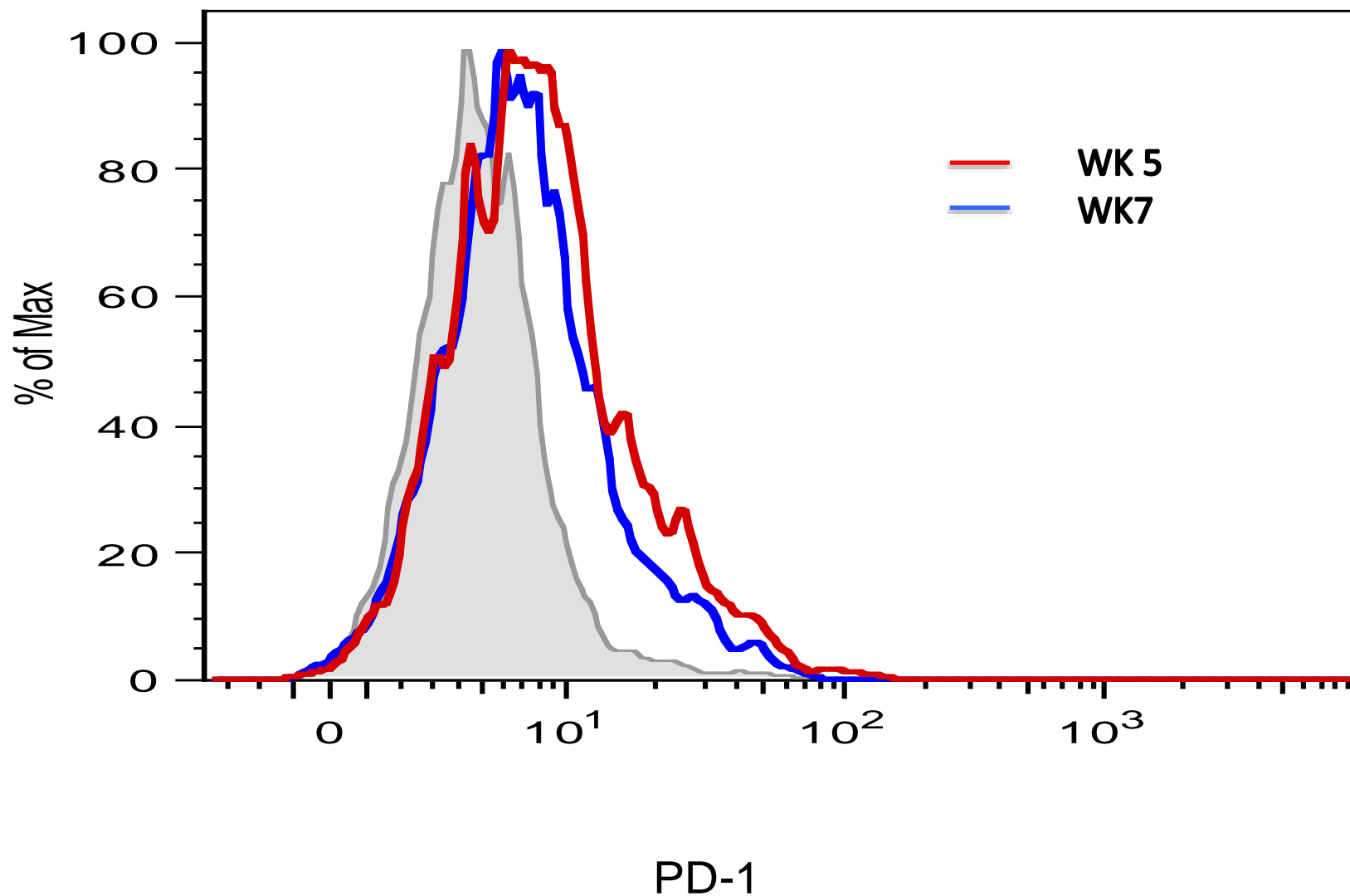
### Frequency CD107a<sup>+</sup> NK Cells



### Absolute Number CD107a<sup>+</sup> NK Cells

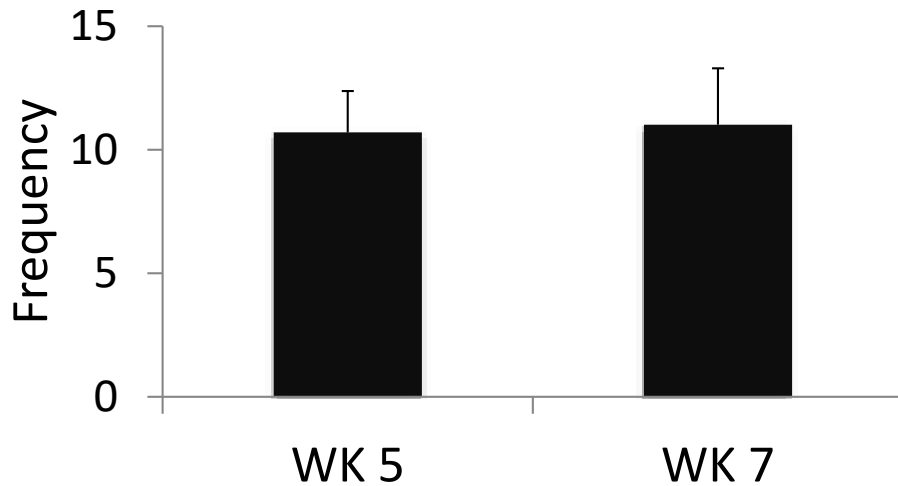


PD-1 is upregulated in infected mice but does not change between weeks five and seven post infection.

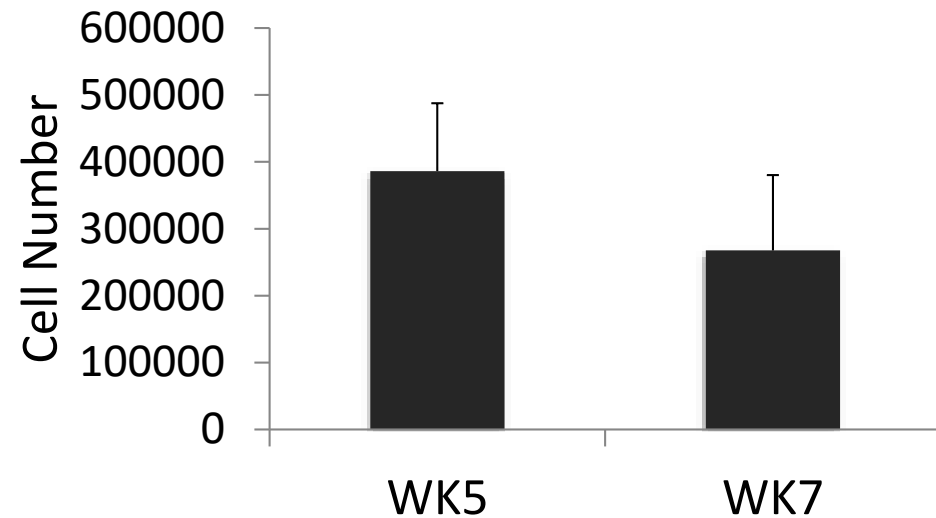


# NK cells maintain their ability to proliferate after chronic infection.

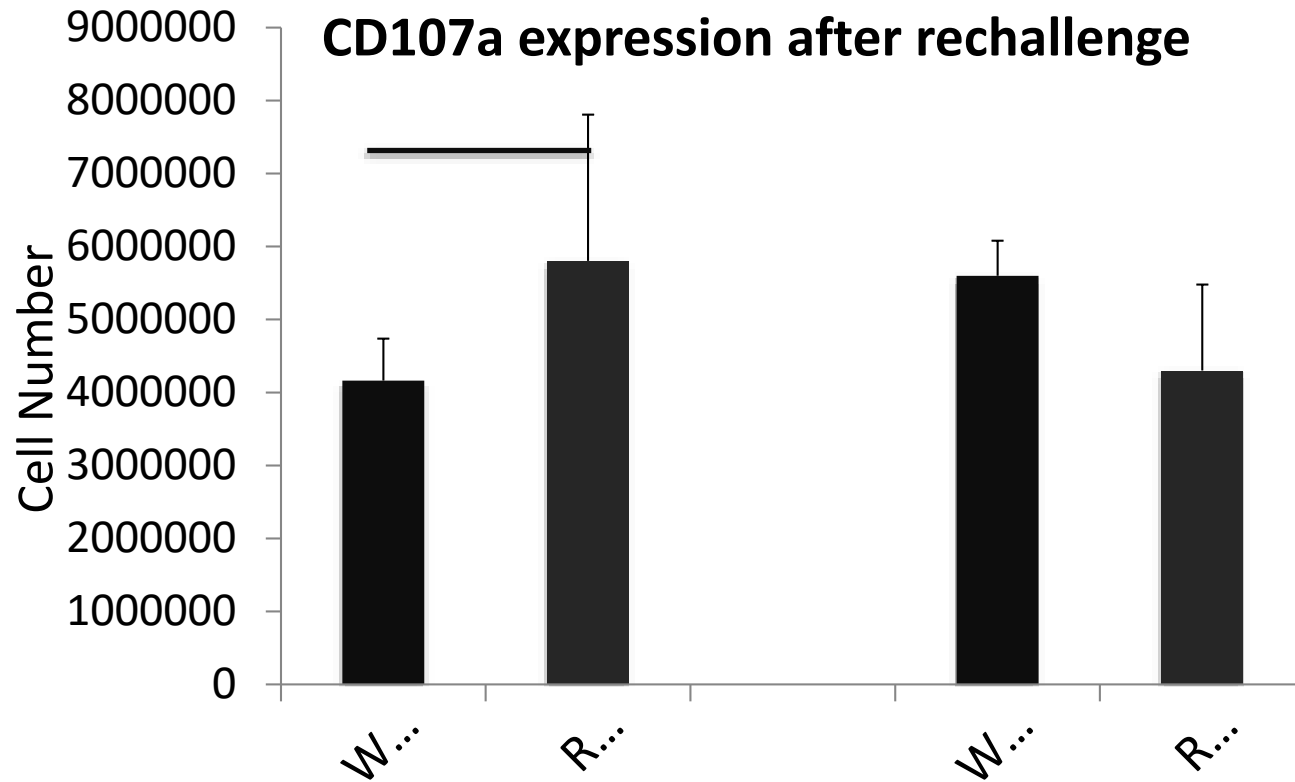
## Frequency ki67 expression in NK cells



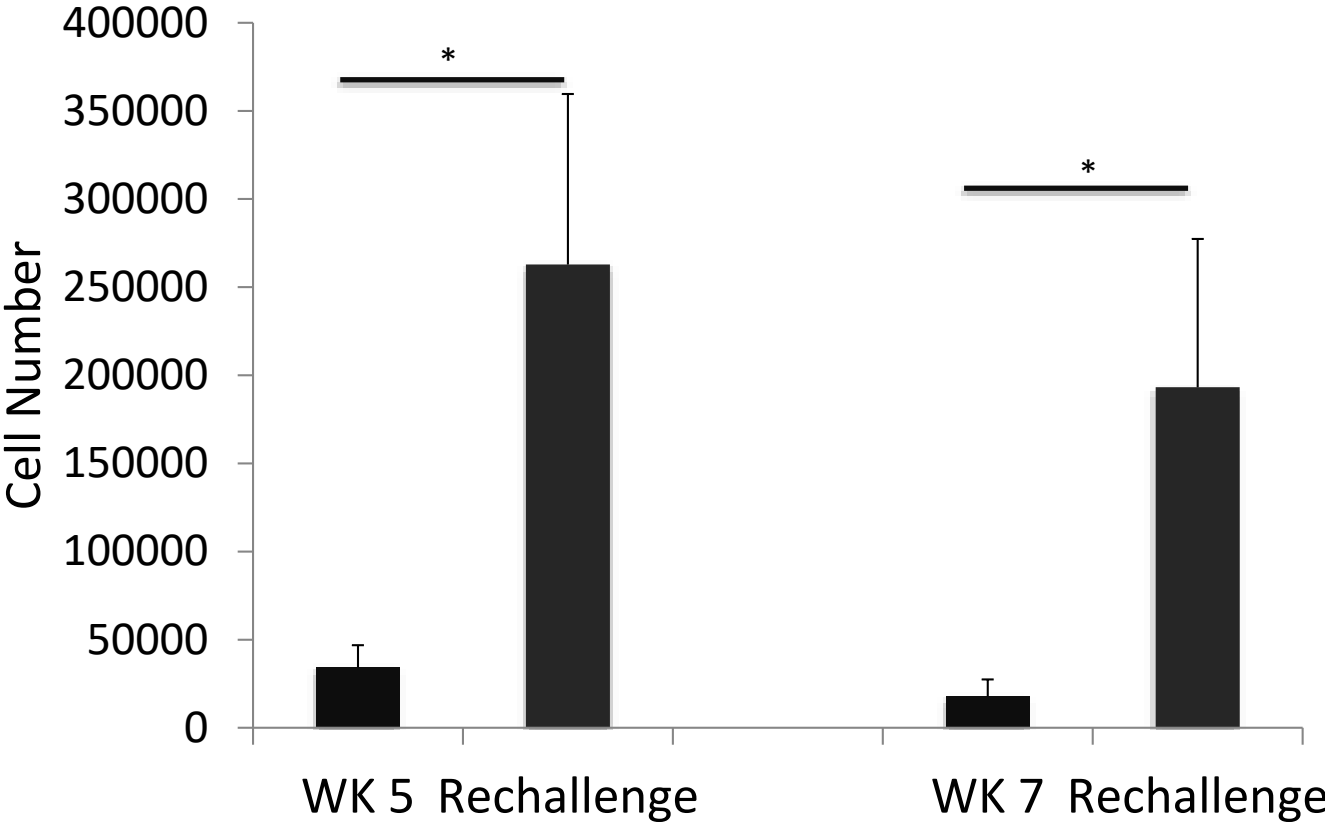
## Absolute Number ki67 expression in NK cells



An increased number of NK cells express CD107a when rechallenged five weeks after initial infection, but fewer NK cells express CD107a when rechallenged after seven weeks of infection.

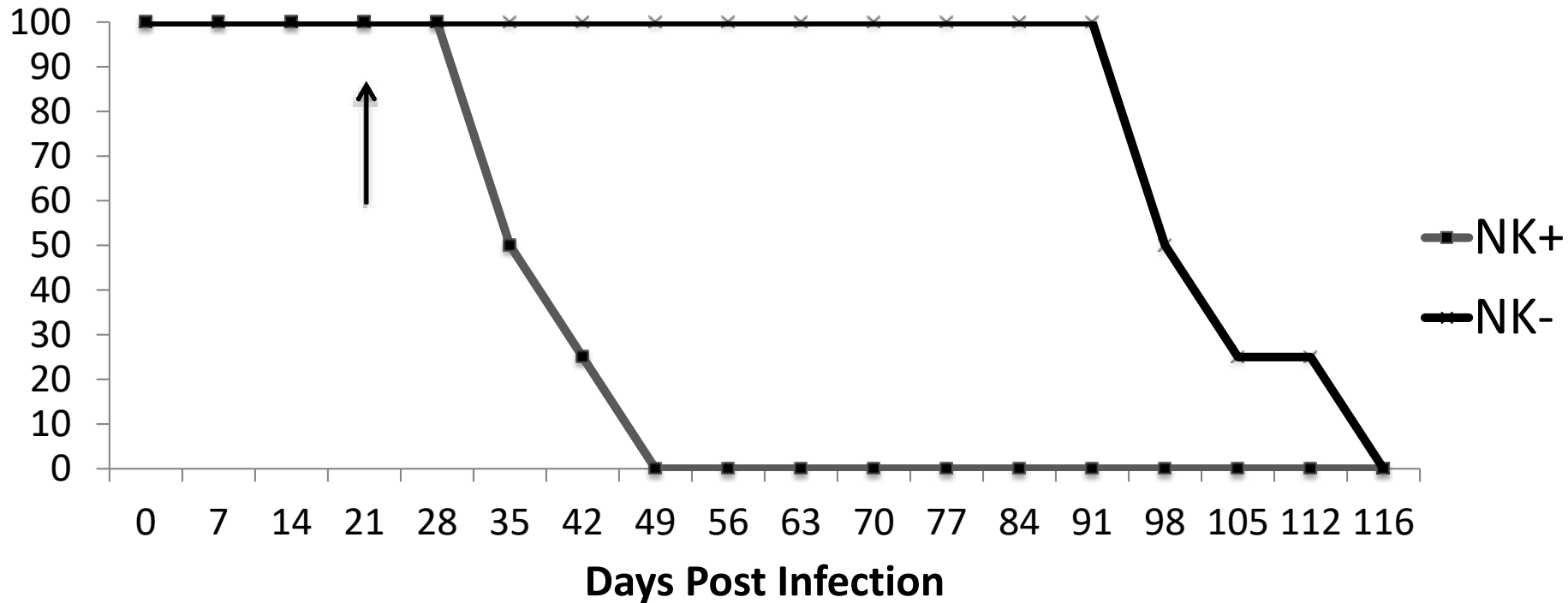


# IFN $\gamma$ expression increases significantly upon rechallenge with *T. gondii*



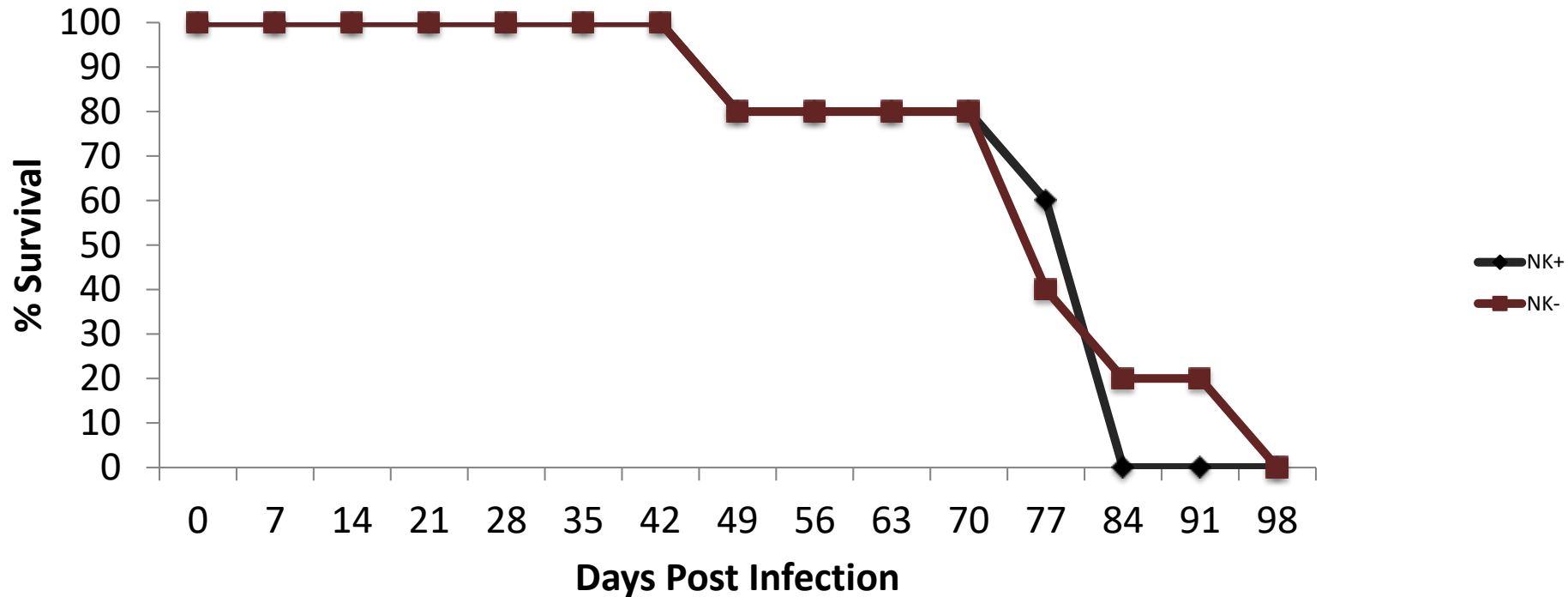
# Consistent depletion of NK cells during chronic *T. gondii* infection results in improved survival.

## Survival of Chronically Infected NK+/- Mice



Inconsistent depletion of NK cells leads to no change in survival.

Survival of Chronically Infected NK+/- Mice



# Conclusions

- NK cells negatively impact survival in chronically infected mice.
- NK cells switch from immunostimulatory to cytotoxic function during chronic infection.



# Future Directions

- Address the Mechanism of NK cell contribution to reactivation of *T. gondii*.
- Determine if NK cells are targeting and killing T-cells during chronic infection.

# References

- Prevention, CDC-Centers for Disease Control and. “CDC - Toxoplasmosis - General Information.” Accessed April 30, 2015.  
[http://www.cdc.gov/parasites/toxoplasmosis/gen\\_info/index.html](http://www.cdc.gov/parasites/toxoplasmosis/gen_info/index.html).
- Cooper, Megan A., Marco Colonna, and Wayne M. Yokoyama. “Hidden Talents of Natural Killers: NK Cells in Innate and Adaptive Immunity.” *EMBO Reports* 10, no. 10 (October 2009): 1103–10. doi:10.1038/embor.2009.203.
- Gigley, Jason P., Rajarshi Bhadra, Magali M. Moretto, and Imtiaz A. Khan. “T Cell Exhaustion in Protozoan Disease.” *Trends in Parasitology* 28, no. 9 (September 2012): 377–84. doi:10.1016/j.pt.2012.07.001.