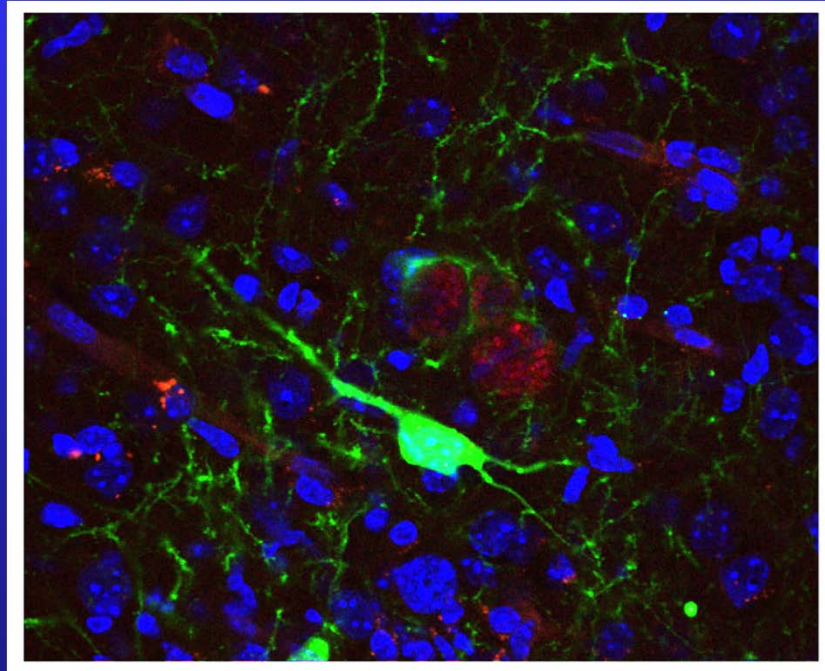


Avoiding neuroinflammation: how the co-evolution between the mammalian brain and the parasite *Toxoplasma gondii* might help us maintain high levels of cognition



Anita Koshy, M.D.

October 23, 2013

Evelyn F. McKnight Brain Institute Meeting

University of Arizona

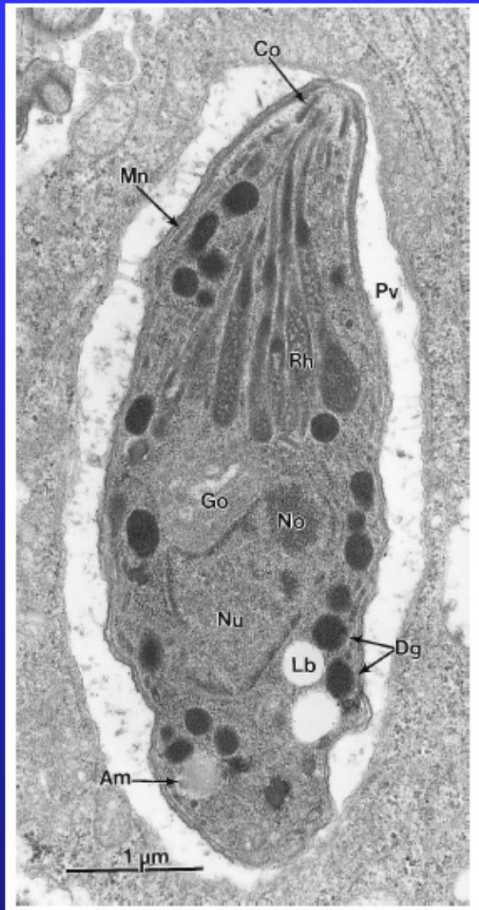
Aging & Cognition

- Aging associated brain changes
 - Increased pro-inflammatory state
 - Declining cellular functions (autophagy)
- Neuroinflammation:
 - Immune cells and cytokines in the brain
 - Dynamic interplay between immune cells and cells of the brain (astrocytes, neurons)
- If we can improve the brain environment/
inflammatory state, can we improve normal
cognition?

Exploiting the CNS-*Toxoplasma* interaction

- Harness evolution
 - Humans and microbes have interacted for 1000s of years
 - Co-evolution
 - Are there microbes that persist in the brain?
 - Brain “commensals”

Toxoplasma gondii



Dubey et al Clin Rev Micro 1998

Intermediate Host

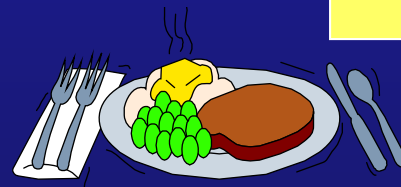


Carnivorism/
Contaminated water

Bradyzoites
(tissue cysts)



Tachyzoites



ASEXUAL

Koshy Lab

- Understanding CNS-*Toxoplasma* interaction
- Defining these interactions will give us insights into mediators of CNS immune responses
 - Role of neurons and astrocytes
- These insights will lead to better ways to manipulate neuroinflammation

How might *Toxoplasma* manipulate the CNS?

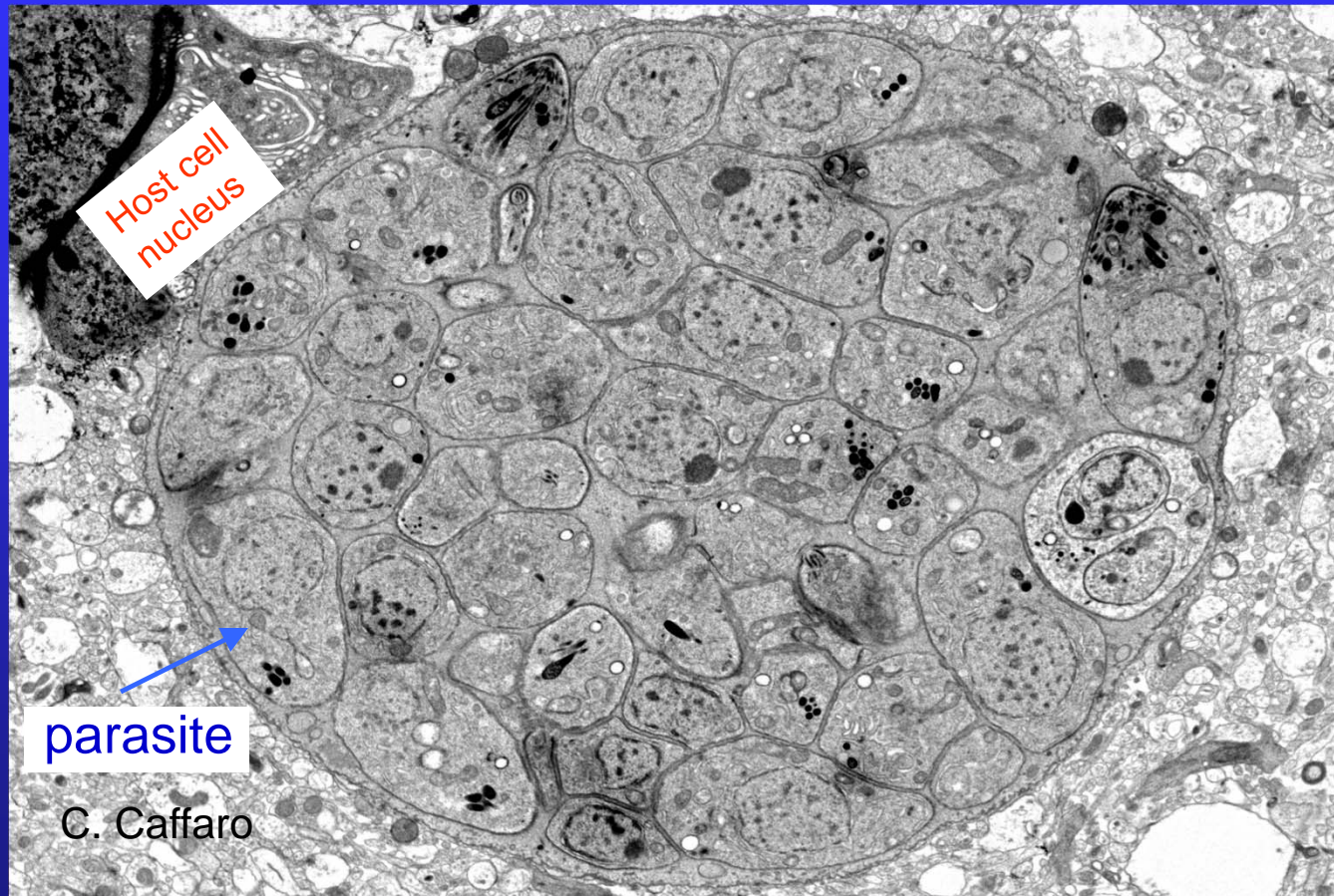
■ Direct effects

- *Toxoplasma* known to inject effector proteins into cells it invades
- Cell infected with *Toxoplasma* are highly manipulated (including neurons in which *Toxoplasma* persists)

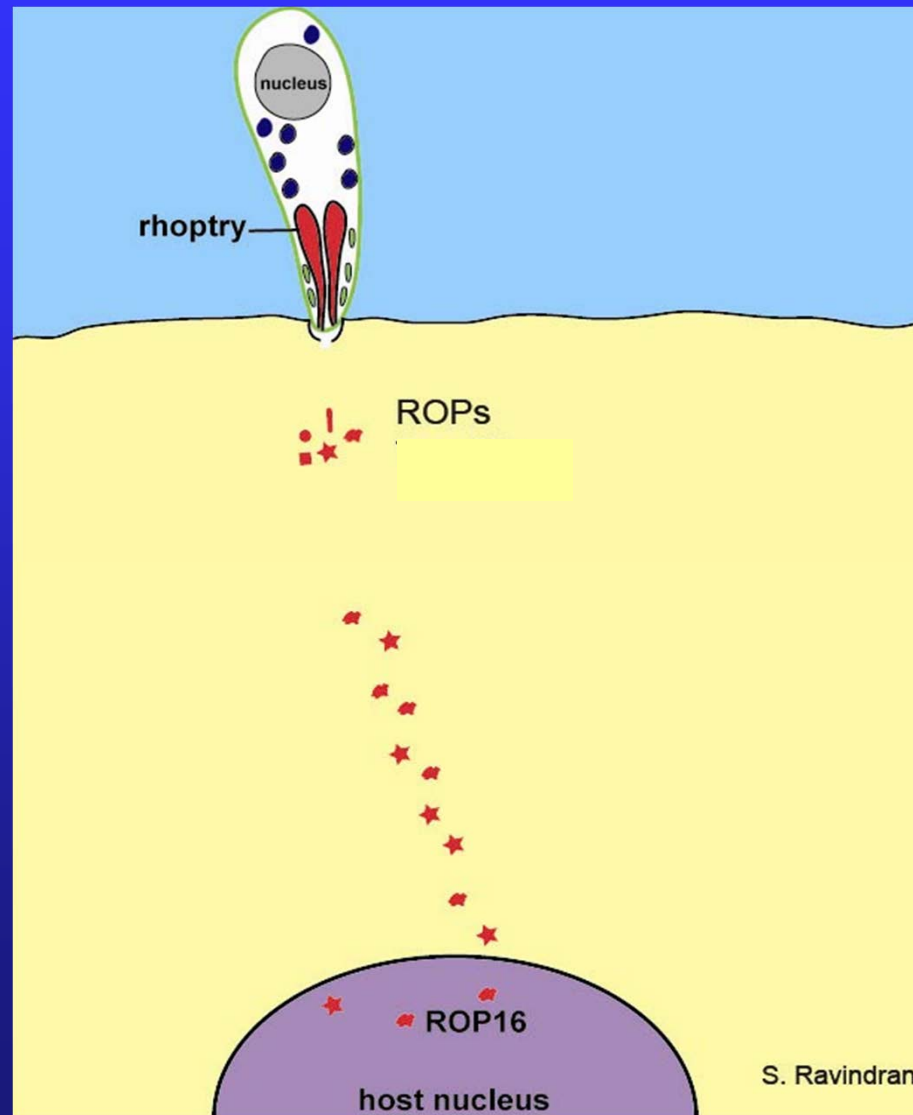
■ Indirect effects

- Immune response to *Toxoplasma* may change astrocyte/neurons/microglia

How does *Toxoplasma* persist in the CNS?

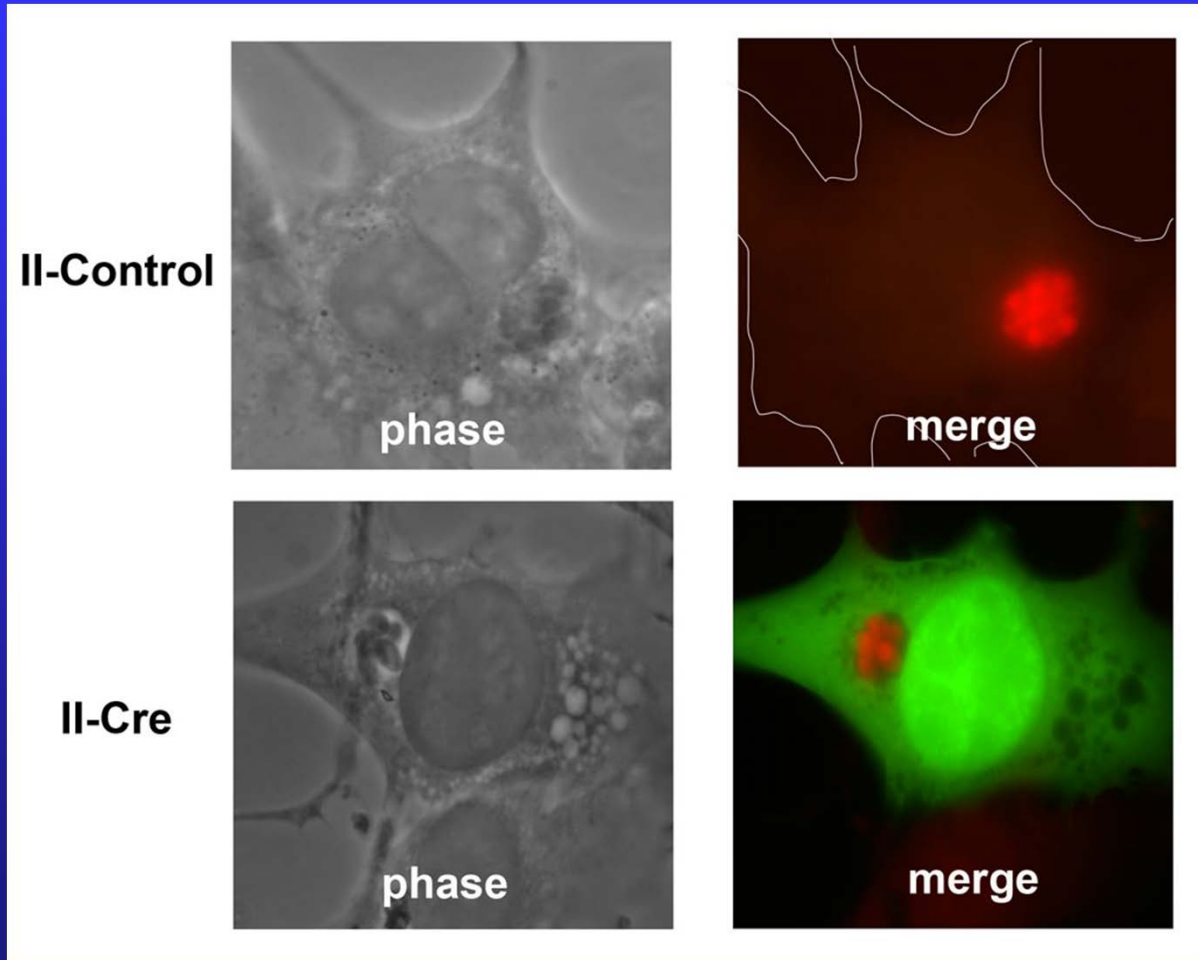


Toxoplasma inject effector proteins when it invades a host cell

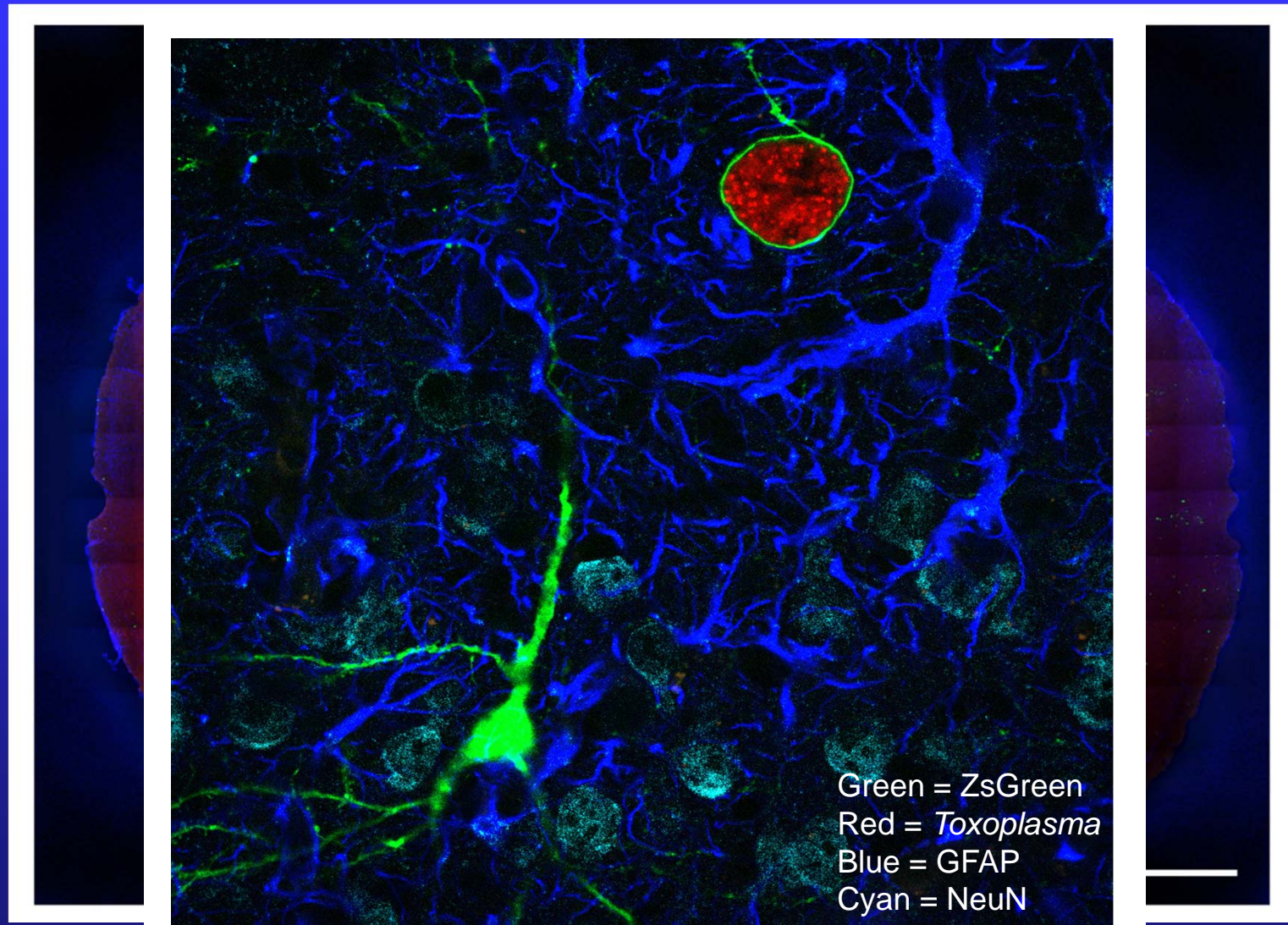


Saeij J.P.J., Coller, S. et al. *Nature* 2007

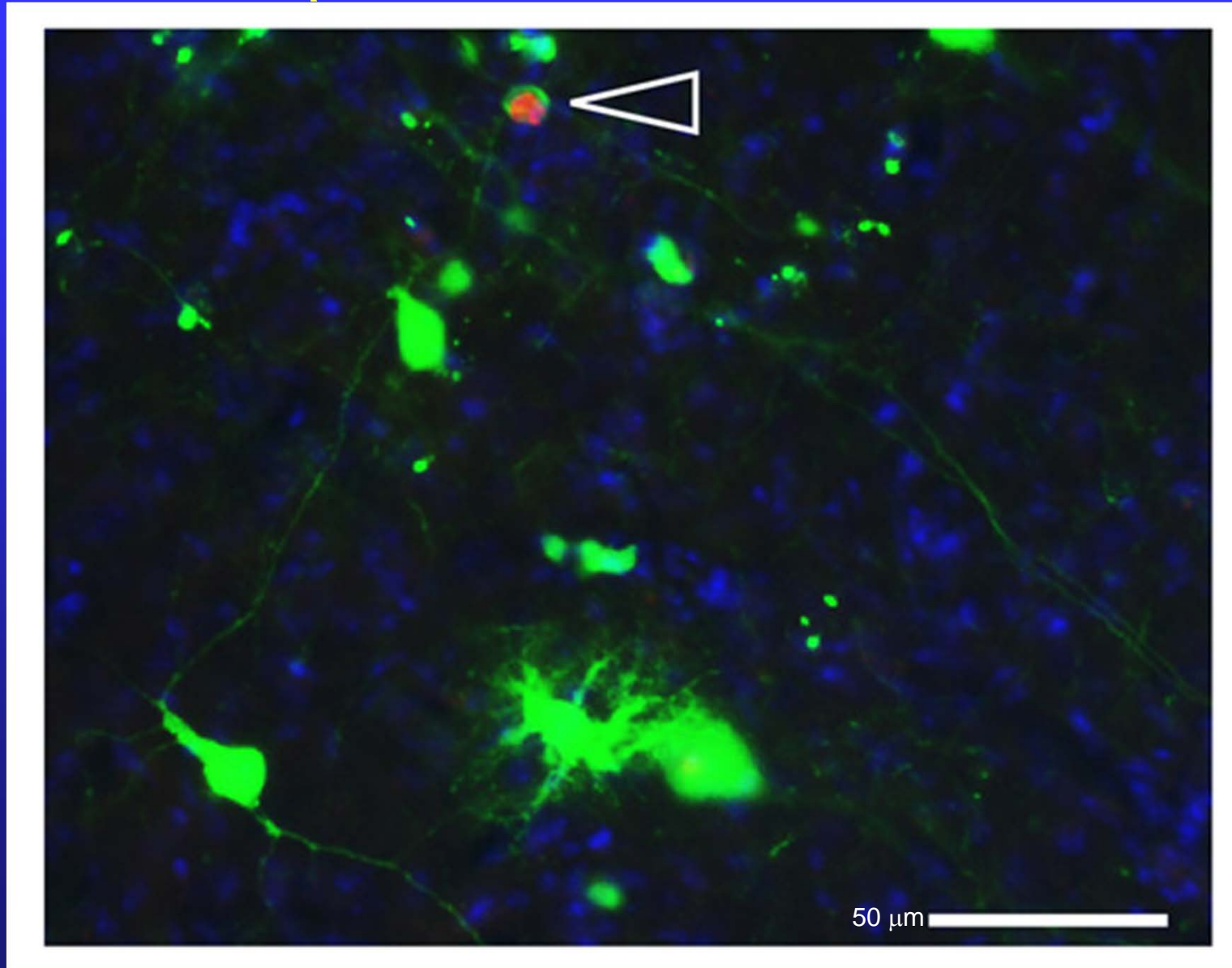
Toxoplasma-Cre system marks host cells that have interacted with *Toxoplasma*



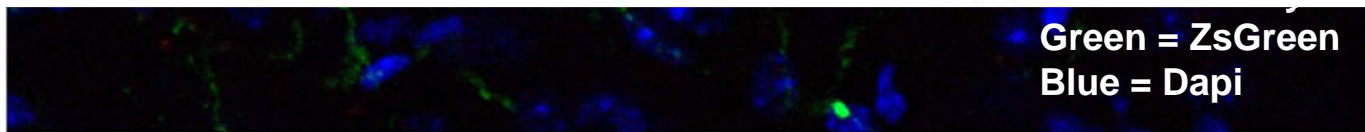
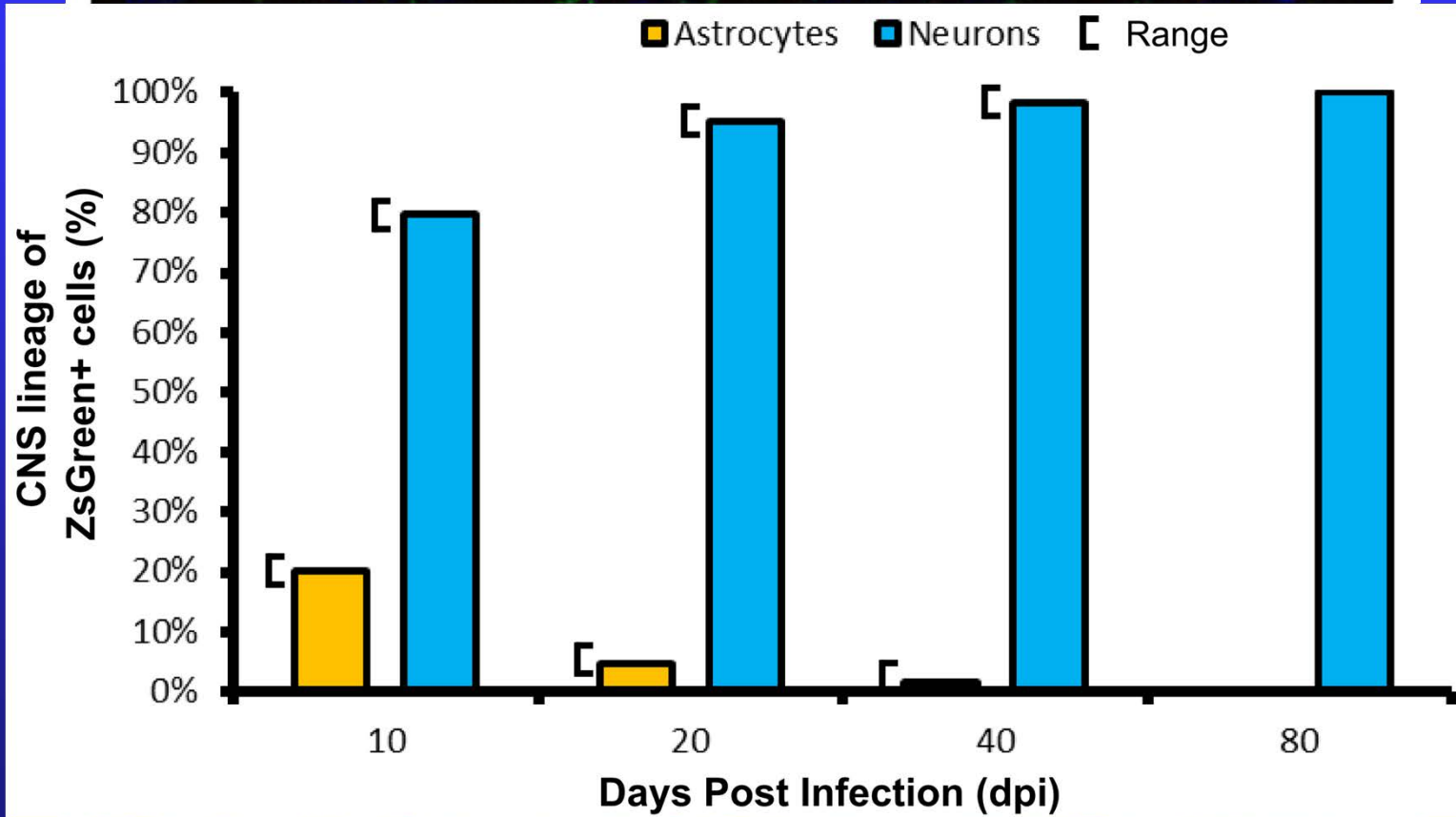
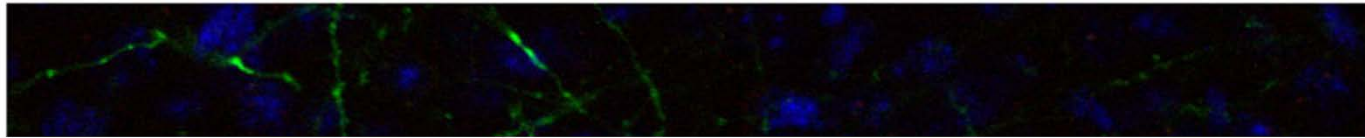
Toxoplasma-Cre marks CNS cells even weeks after infection



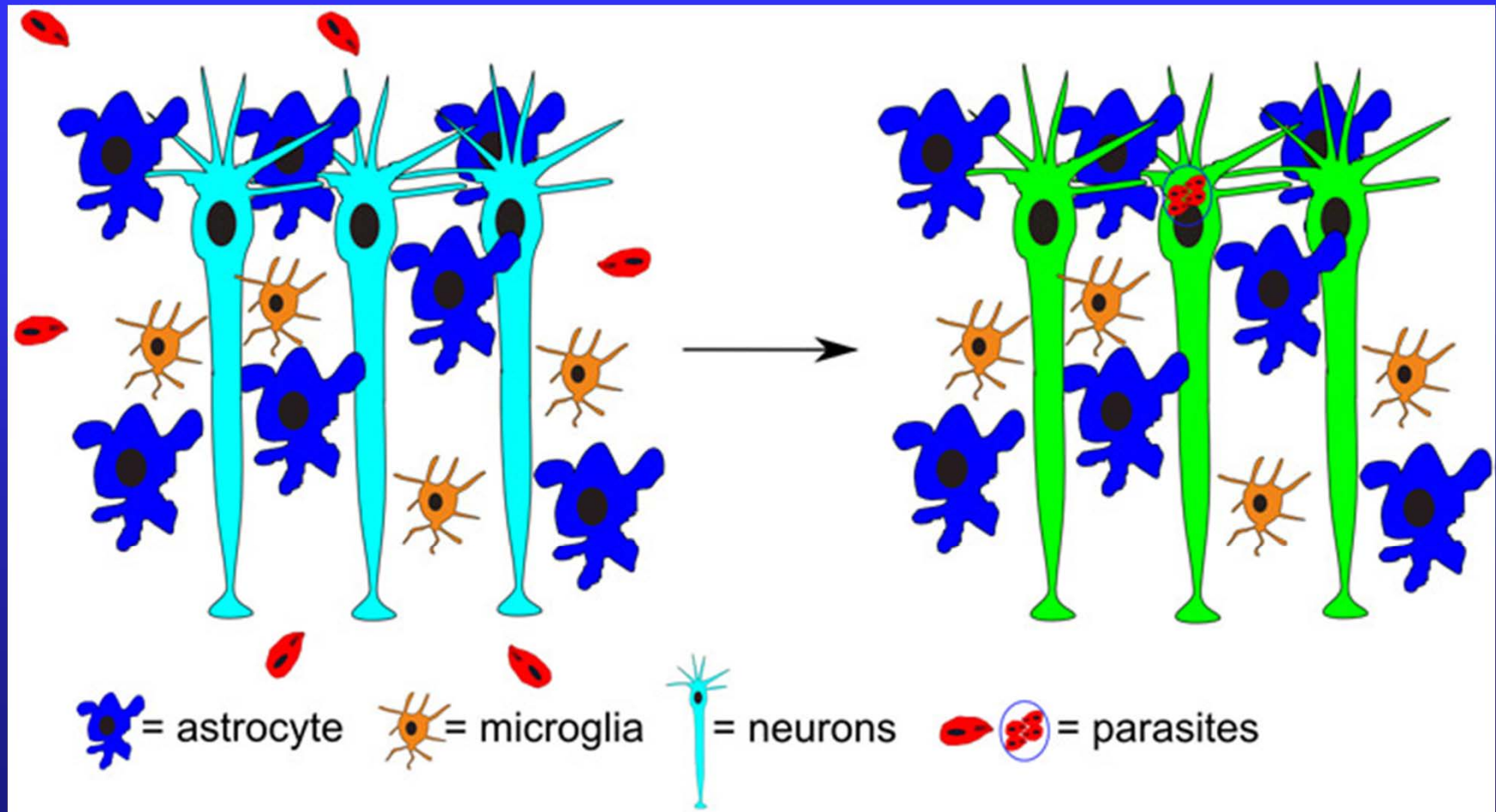
Many more uninfected-interacted CNS cells compared to infected cells



Most uninfected CNS cells consistent with neurons



How are uninfected-interacted neuron arising?



*Pilot grant to see if neuronal autophagy involved

Summary

- *Toxoplasma*-CNS interactions can be used to understand fundamental neurobiology
- Neurons may be able to clear *Toxoplasma*
 - Stimulation of neuronal autophagy?
- What is the effect of chronic toxoplasmosis on the global CNS environment?
- Ultimate goal: improve overall brain health

Thank you

Koshy Lab

Hans Dietrich

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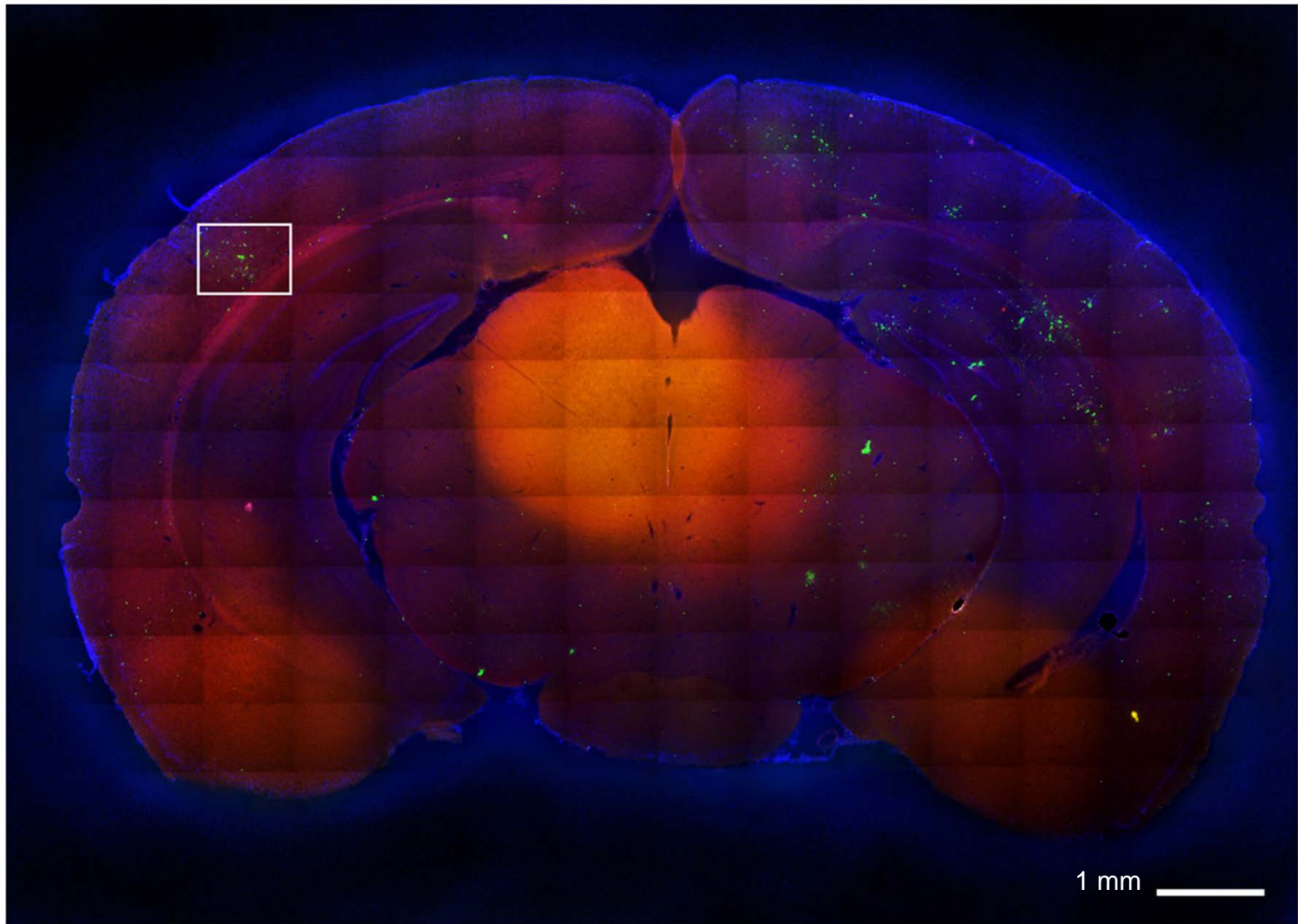


Boothroyd lab

John Boothroyd

To numerous to mention





Hygiene Hypothesis

- Human evolution: humans and microbes highly interactive
 - Last 100+ years, antibiotics, improvement in hygiene has decreased this interaction in developed countries
 - Our immune system now lacks the interaction for which it evolved → increased incidence of auto-immune diseases, asthma/atopy in developed countries
 - Treating auto-immune diseases with parasites
- How about brain-microbe interaction affecting the inflammatory state of the brain?

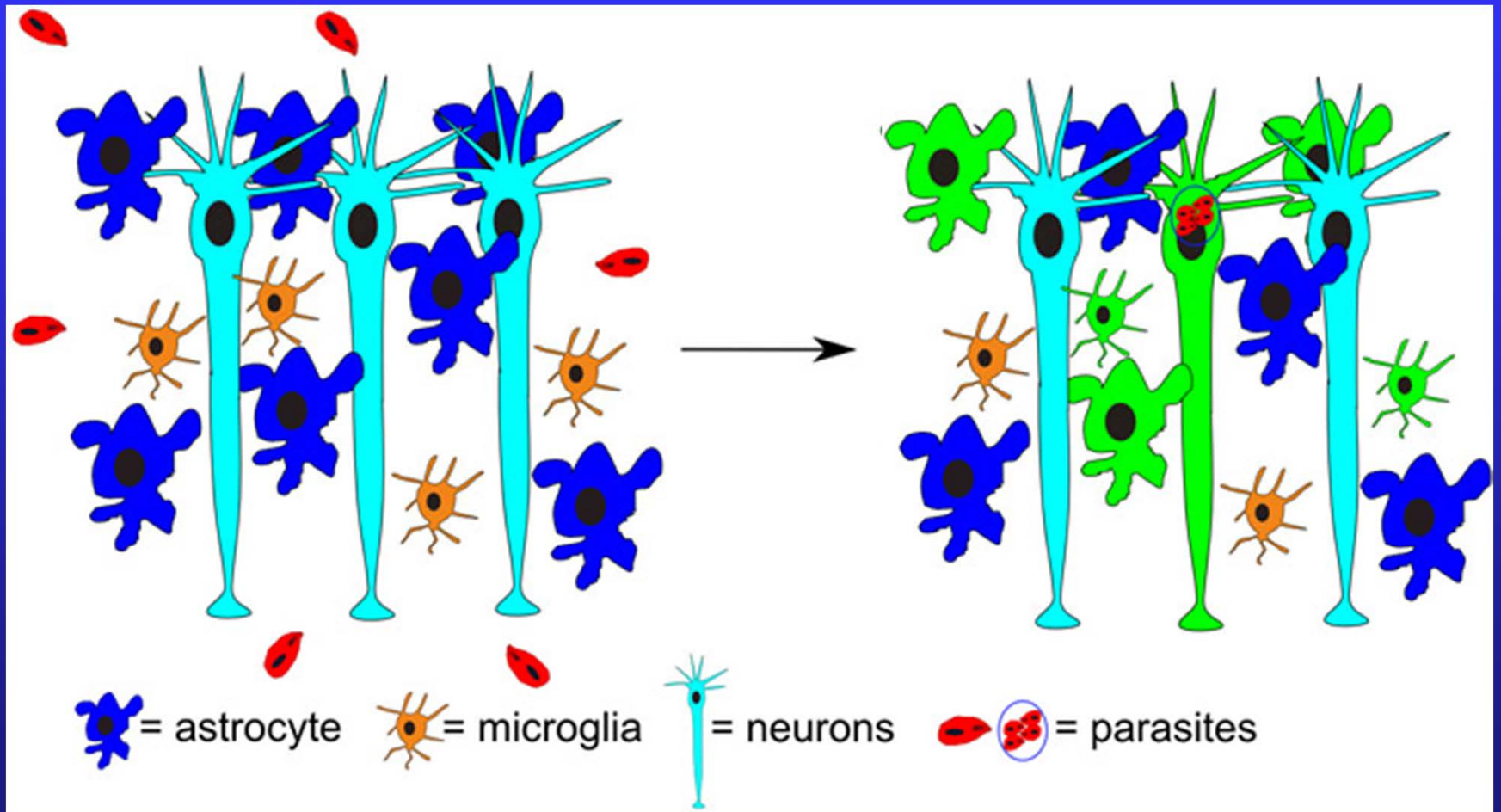
Future Directions

- Transcriptionally profile neurons that have cleared *Toxoplasma*
- Use distinct strains to understand how host cells are differentially manipulated
- Use distinct strains to define how *Toxoplasma* establishes a neuroprotective environment

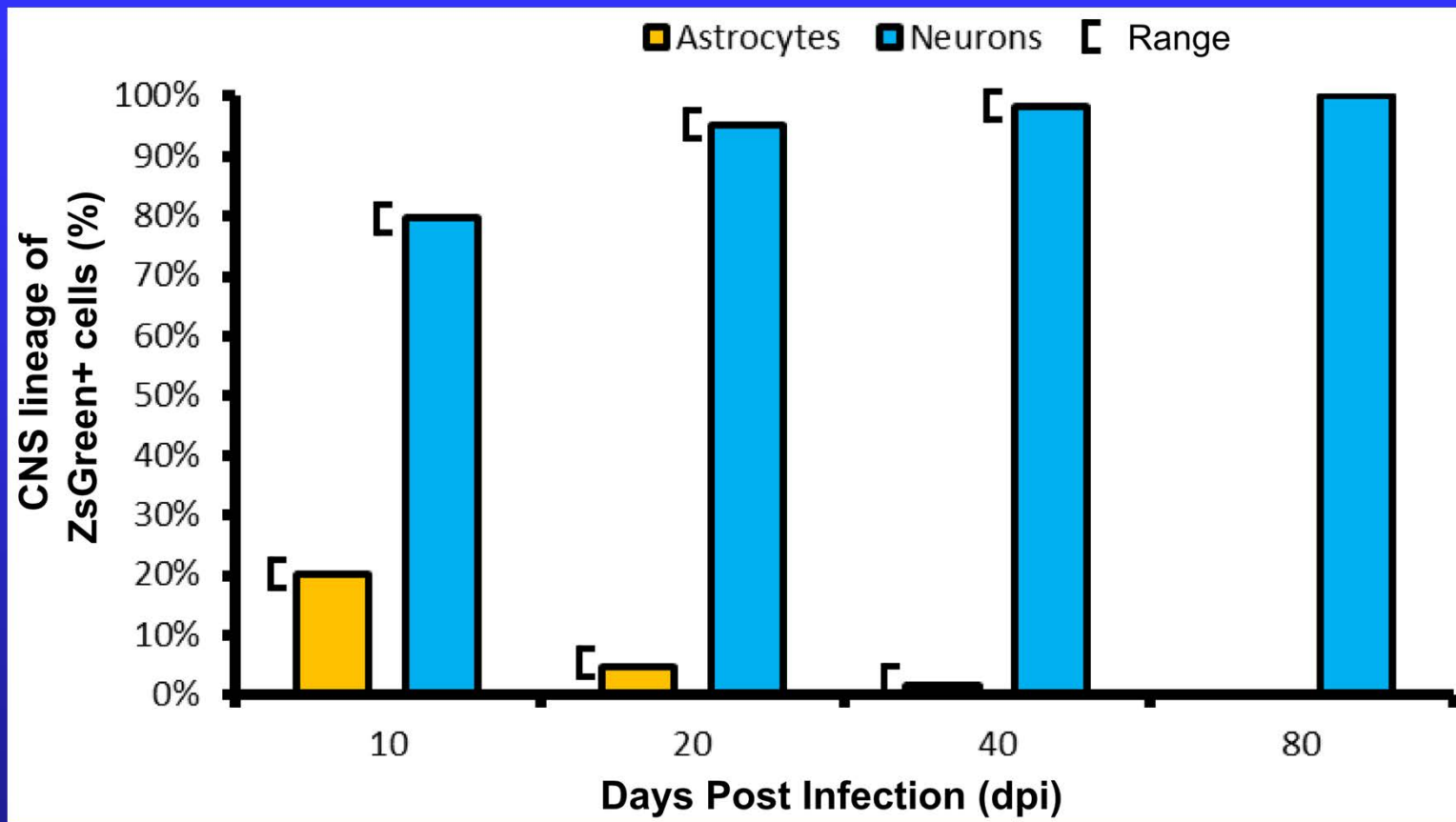
Evidence

- Alzheimer's disease:
 - Microglia “pro-inflammatory”
 - Ab exacerbates
 - Neuronal autophagy decreased → leads to inability to clear Ab
- Normal aging
 - C1q- component of complement system; increases in aging
 - Parabiosis of old and young: serum factor that improves aging
- Fix age-associated immune dysfunction, fix multiple diseases?

Toxoplasma infects all CNS cells but only persists in neurons



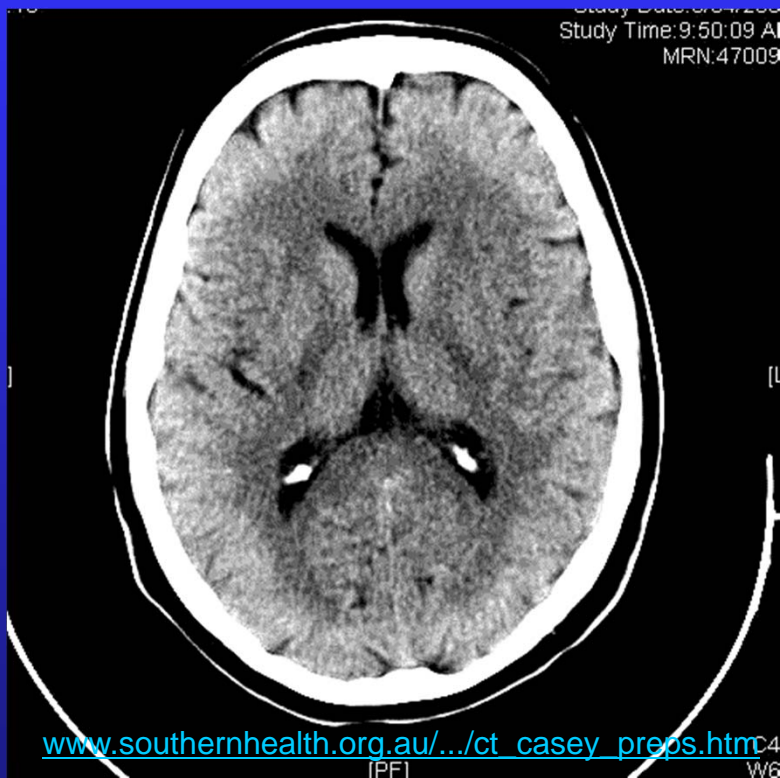
Toxoplasma predominantly interacts with neurons



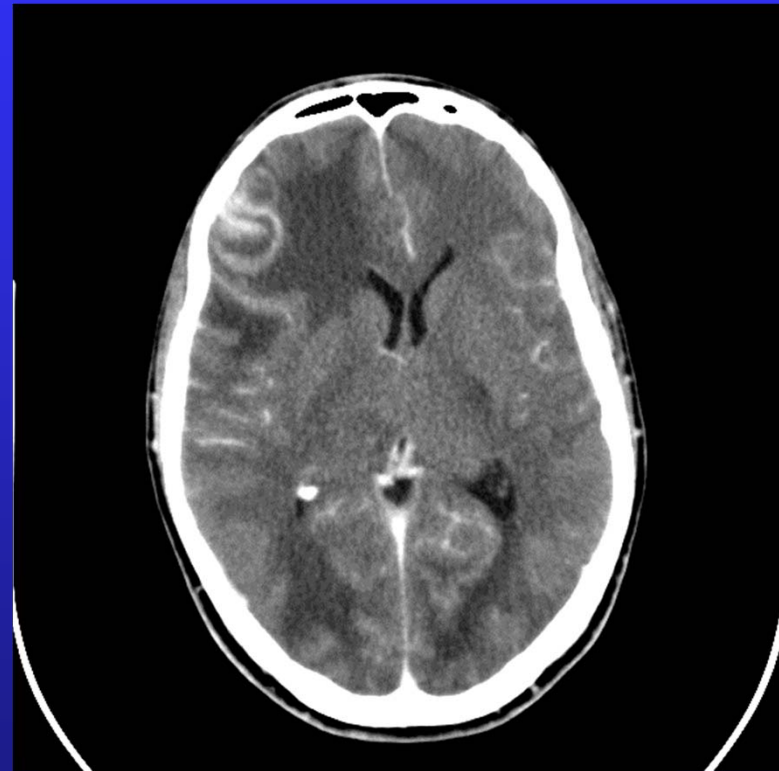
dpi	Identified	Astrocytes	Neurons
10	42	8	34
20	252	10	242
40	81	2	79
80	90	0	90

Clinical Implications of CNS toxoplasmosis

Normal



Congenital AIDS toxoplasmosis



Red Book Online Visual Library, 2006. Image 139_03. Available at: <http://aapredbook.aappublications.org/visual>. Accessed February 21, 2007