

# Rabbit Model of TB Meningitis in Children

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# Disclosures

- No conflicts of interest or financial disclosures to report

# Background: CNS Tuberculosis

- WHO 2016: 1 million new childhood cases
- Central Nervous System (CNS) Tuberculosis (TB) is the most severe form of extrapulmonary TB
  - TB meningitis
  - Tuberculomas
- Disproportionately affects young children!
- Difficult to diagnose

# Background: CNS Tuberculosis

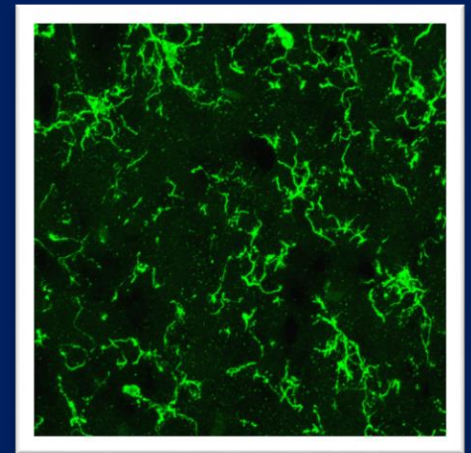
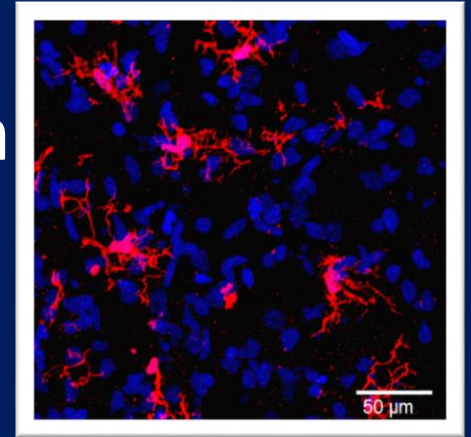
- Fatal without treatment
- Despite treatment
  - Mortality is high (13-50%)
  - Morbidity is high in survivors
- Poor neurodevelopmental outcomes unique to children
  - Hydrocephalus
  - Infarcts

# Background: Treatment

- Long duration
- Poor CNS penetration
  - Ethambutol, Rifampin
- No current tools for therapeutic monitoring
- Ideal target for non-invasive imaging modalities
- New additions:
  - High-dose Rifampin
  - Fluoroquinolones

# Background: Microglia

- Major **immune cells** of brain
- Infection causes microglial activation
- Activated microglia/macrophages highly express **TSPO**
- Important for **normal development**
  - Neurodevelopmental apoptosis
  - Neurogenesis
  - Synaptogenesis



# Objective

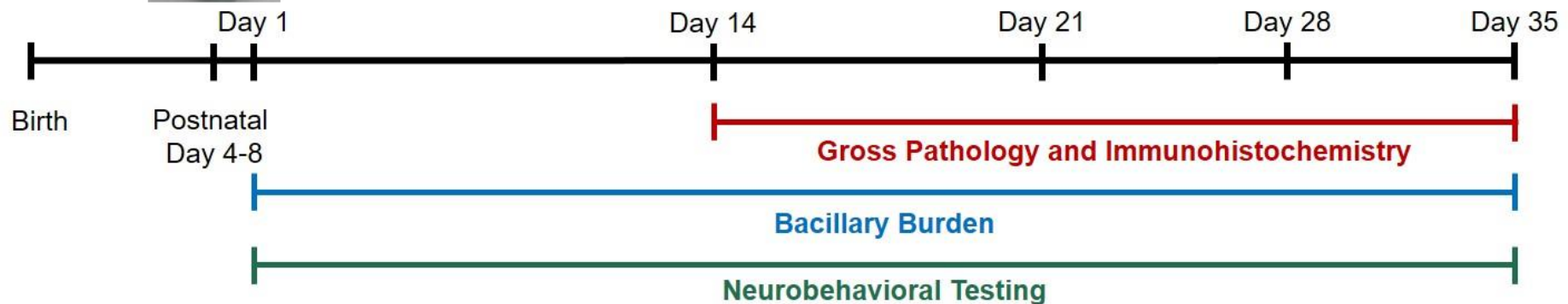
- To establish a pediatric CNS TB animal model
- To investigate microglia's unique role in CNS TB infection in the developing brain

# *In-vivo* Pediatric Rabbit Model

New Zealand White Rabbits  
In Vivo Subarachnoid Injection of  
*Mycobacterium tuberculosis* H37Rv



Imaging with Biocontainment System





# Bio-Safety Level 3 Facility



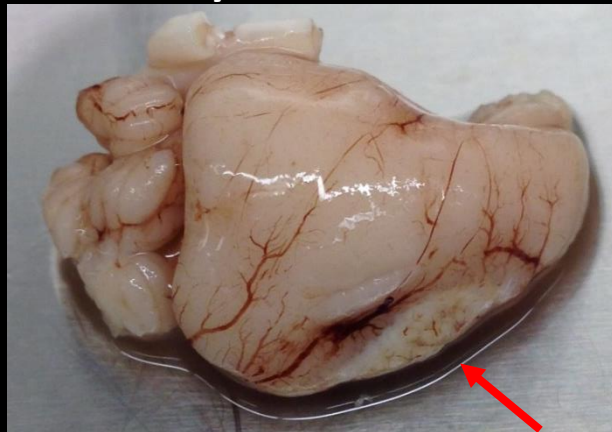
# Exudative Meningitis and Tuberculoma Formation After Subarachnoid Infection

Control



Infected

14 Days Post-Infection

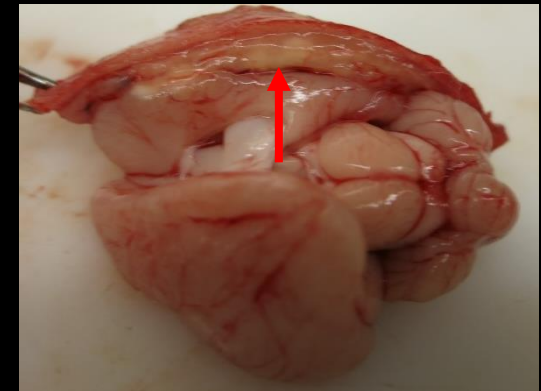


21 Days Post-Infection



Infected

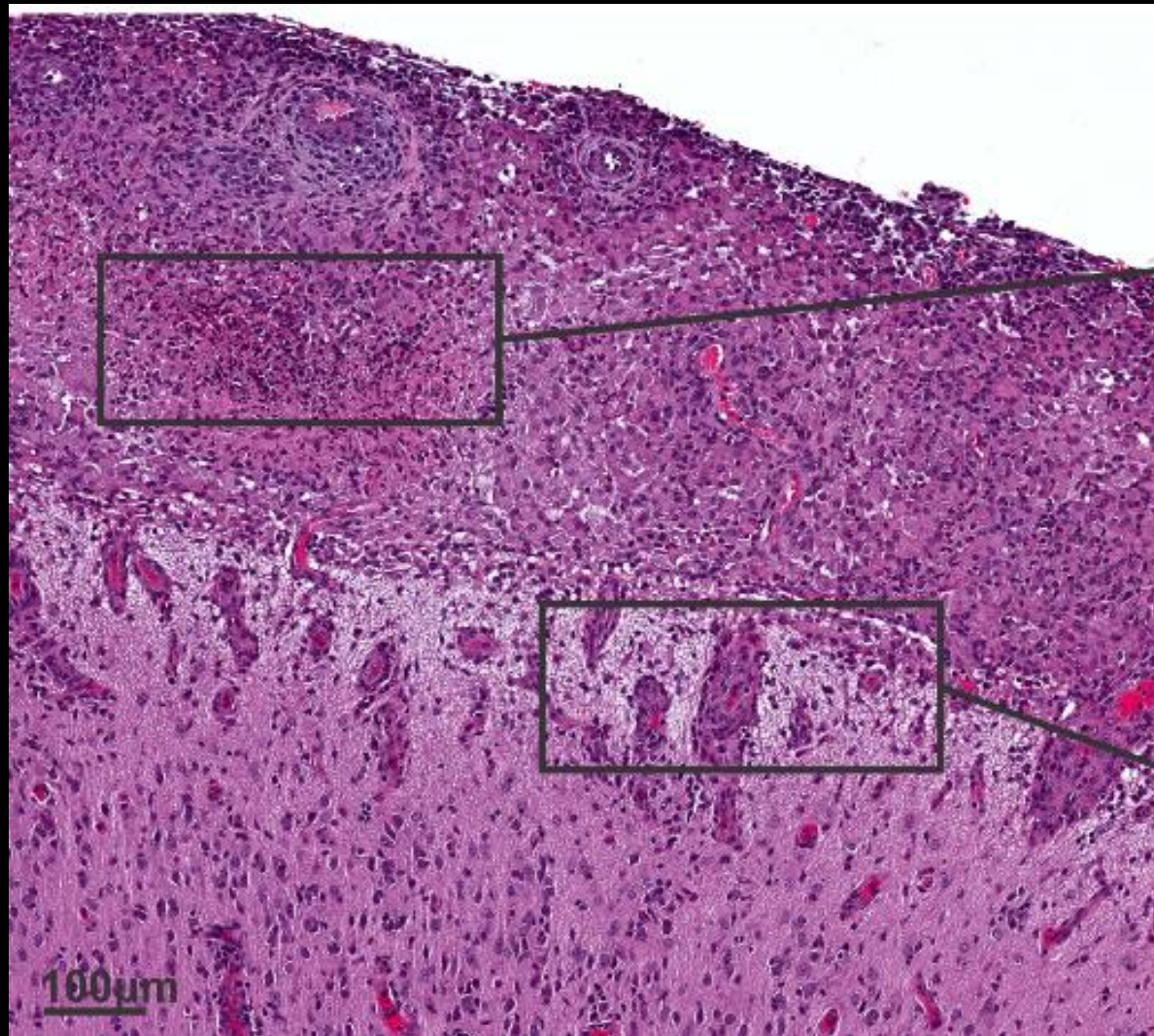
Exudate



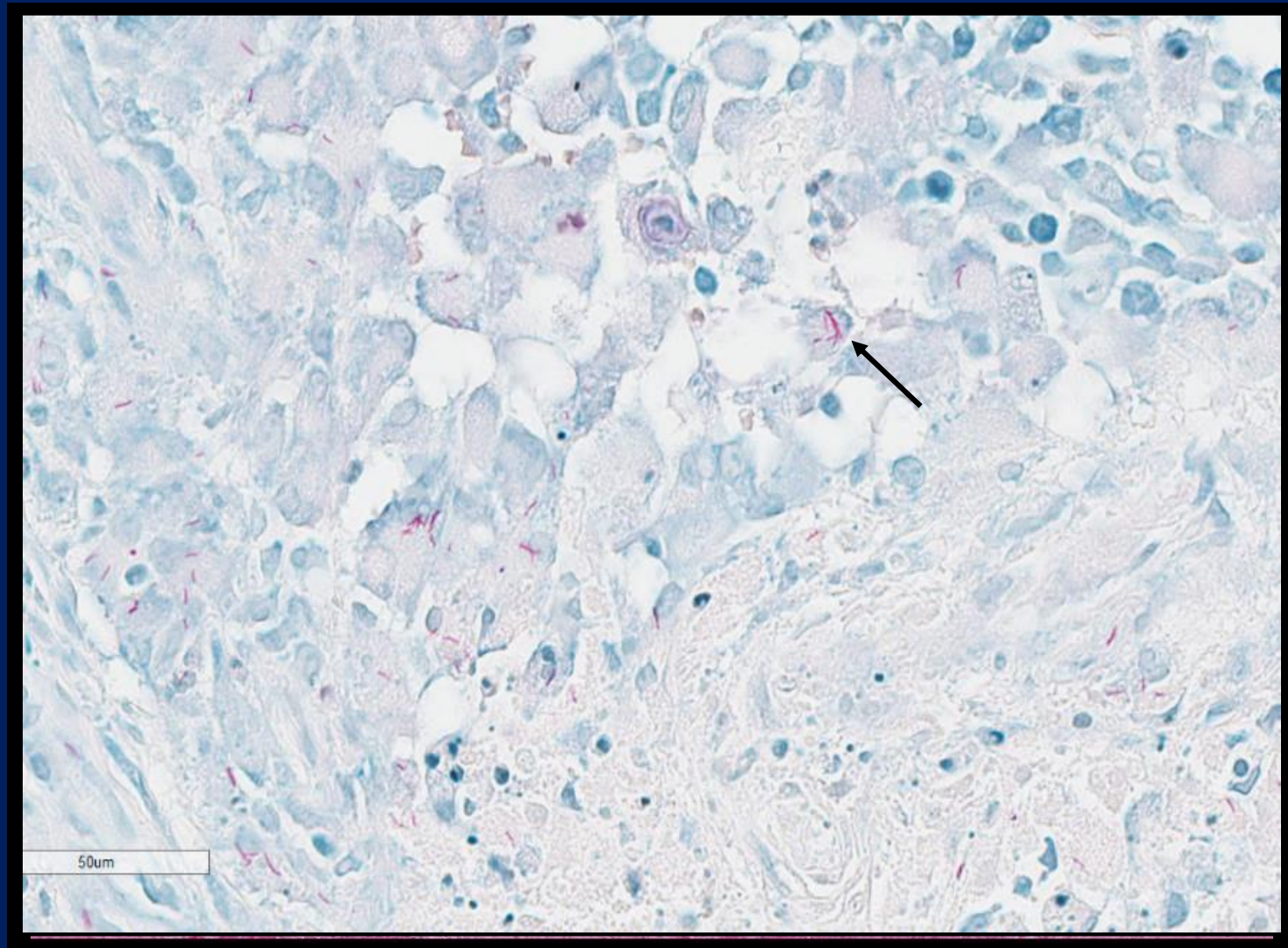
21 Days Post-Infection



# Exudative Meningitis and Perivascular Infiltrate

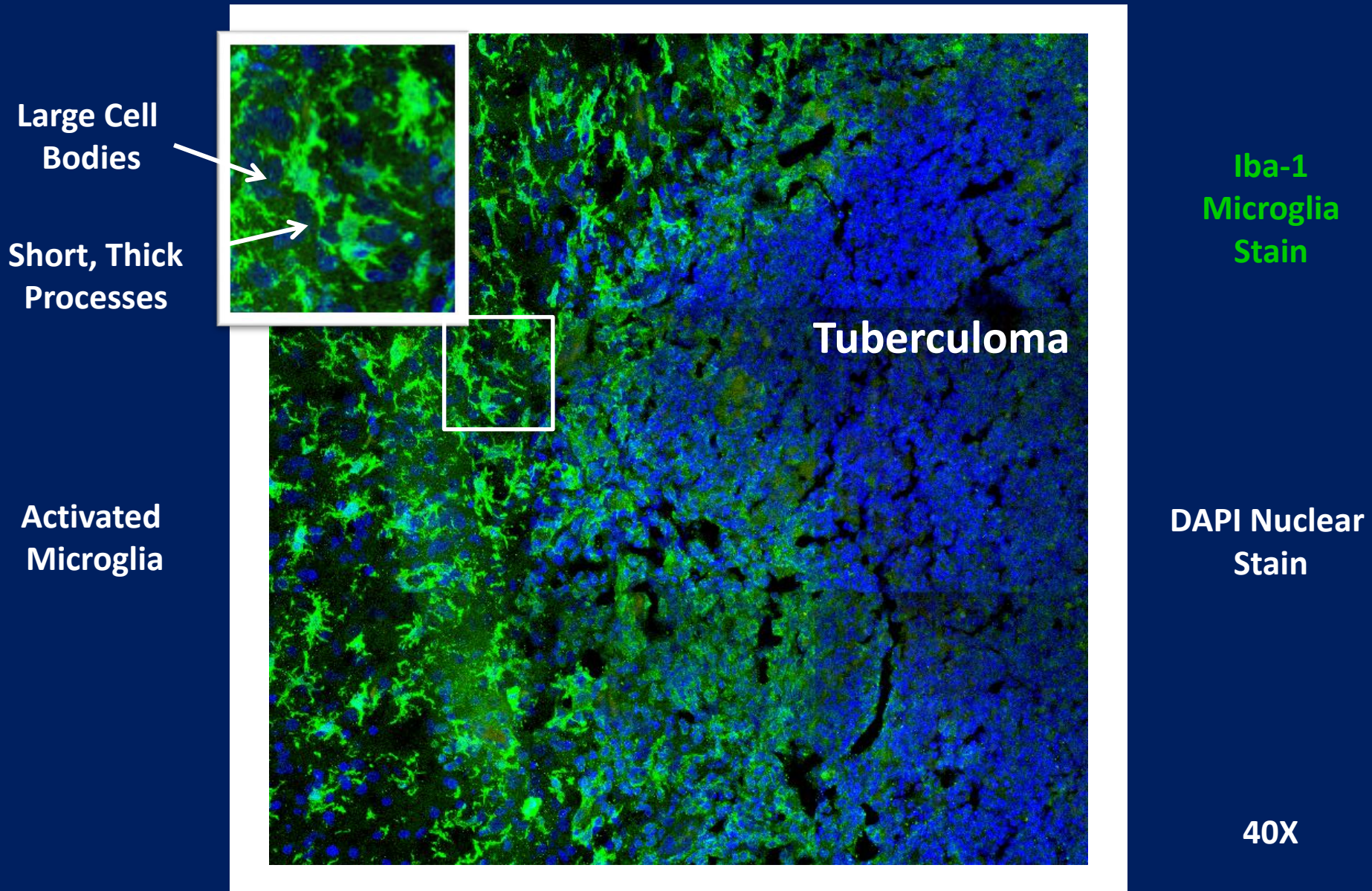


# Tuberculoma with Central Necrosis & Cellular Rim

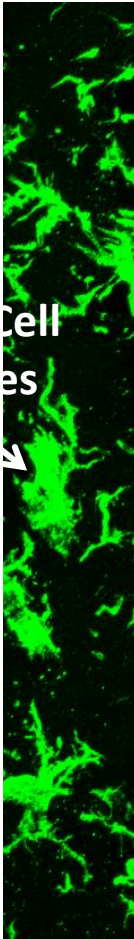
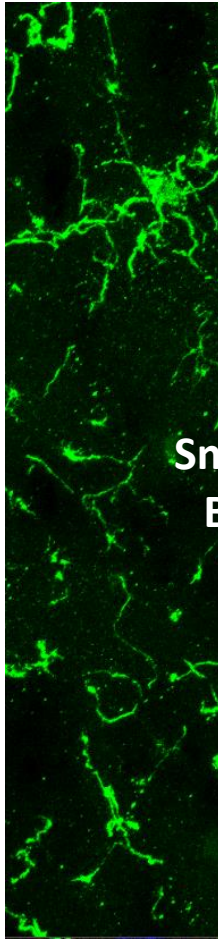
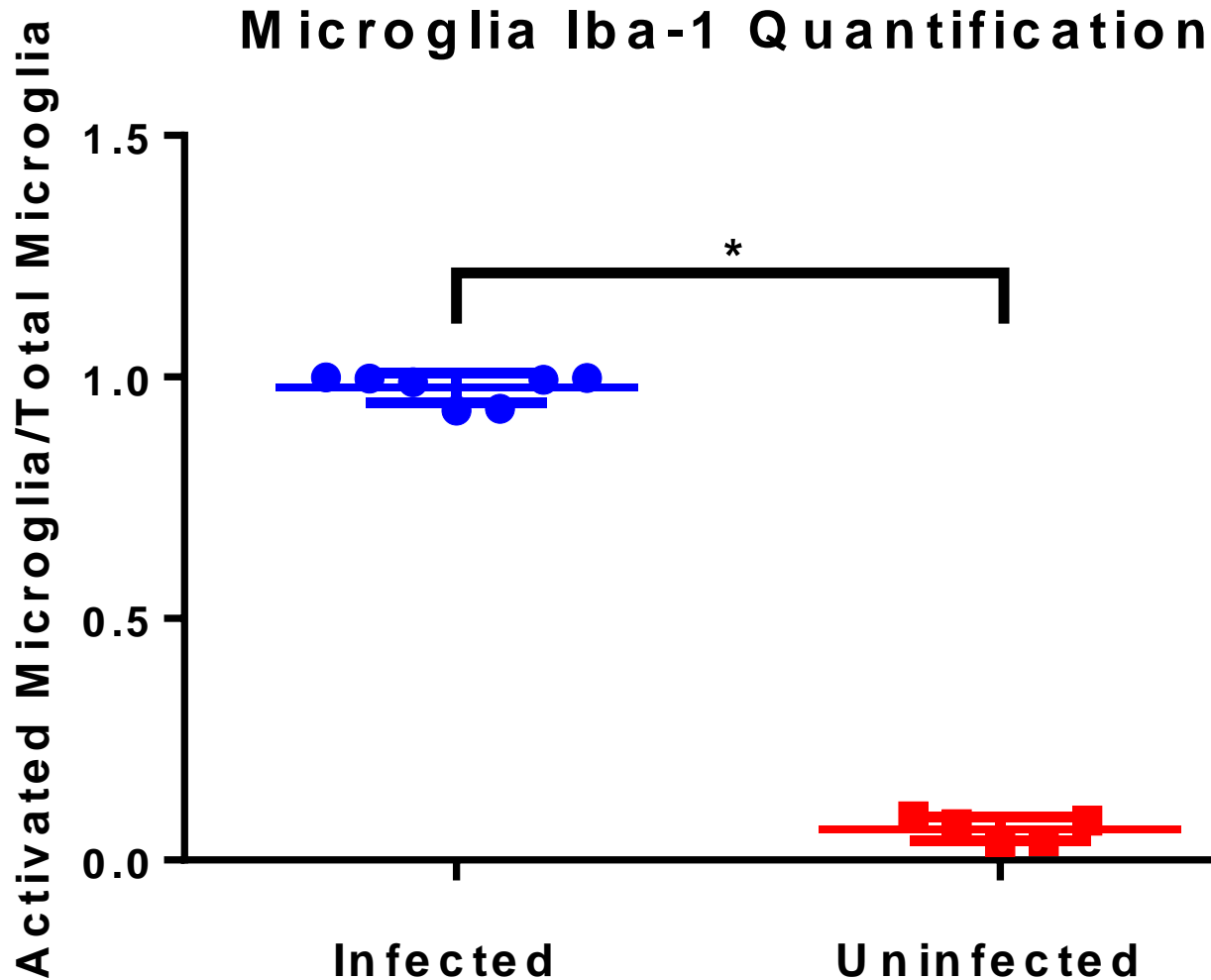




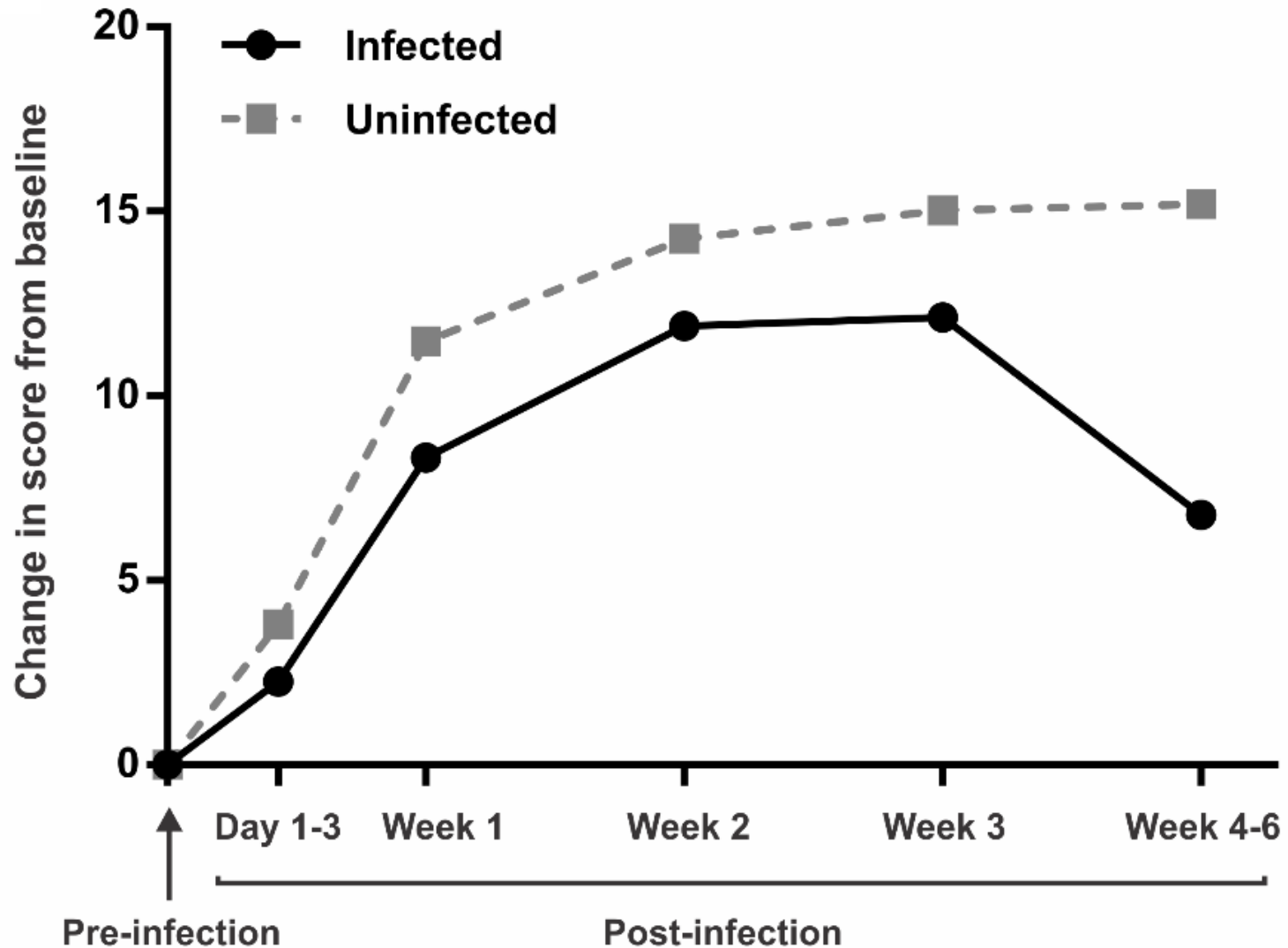
# Activated Microglia Surrounding Tuberculoma Formation



# Subarachnoid Infection Causes Microglia Activation



# Neurologic Manifestations



# Objective

- To use noninvasive imaging modalities to:
  - Demonstrate tuberculosis-associated neuroinflammation
- AND**
- Elucidate pharmacokinetic parameters



# Non-Invasive Neuroinflammation Imaging

- Tool to monitor current or novel treatments
- **Radioiodinated DPA-713**

# $^{124}\text{I}$ -DPA-713 PET/CT Imaging of Neuroinflammation

- 2nd Generation synthetic ligand of TSPO
- Highly expressed on activated microglia & macrophages
- Imaged 1 & 24 hours post-injection



Biocontainment for Bio-safety Level 3



# 3-D $^{124}\text{I}$ -DPA-713 PET/CT

*M. tuberculosis*  
Infected



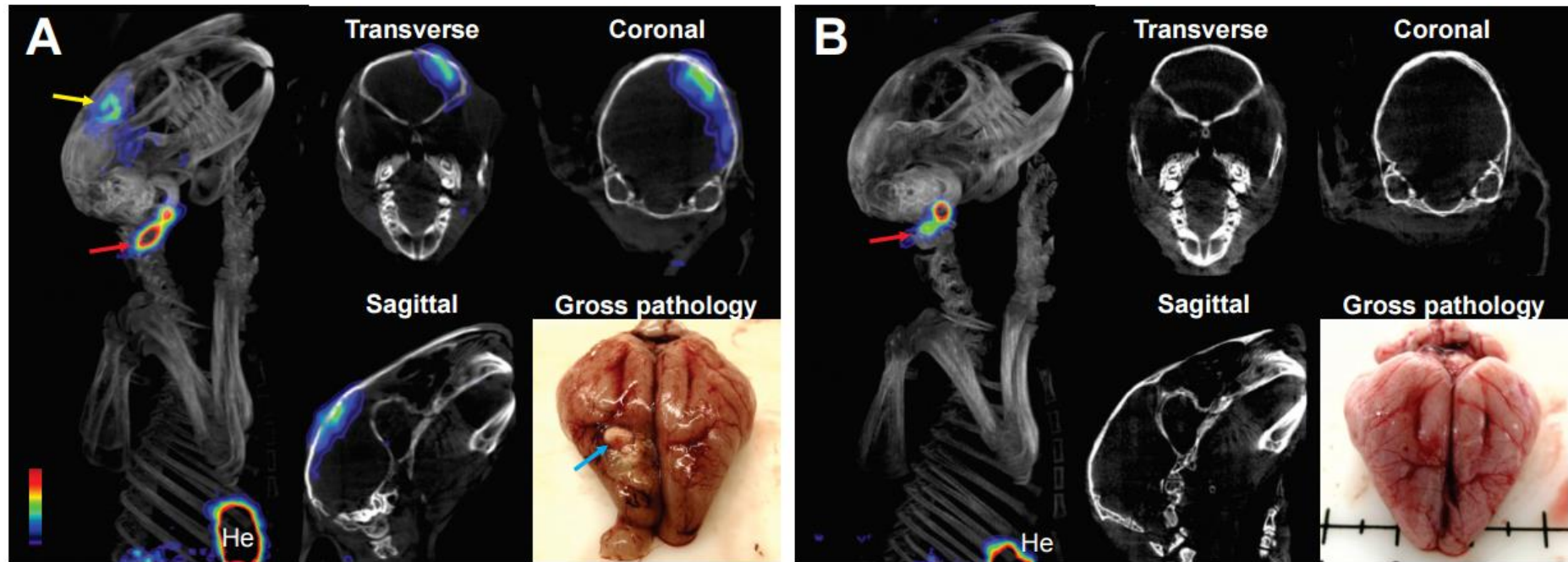
Uninfected  
Control



24 hr

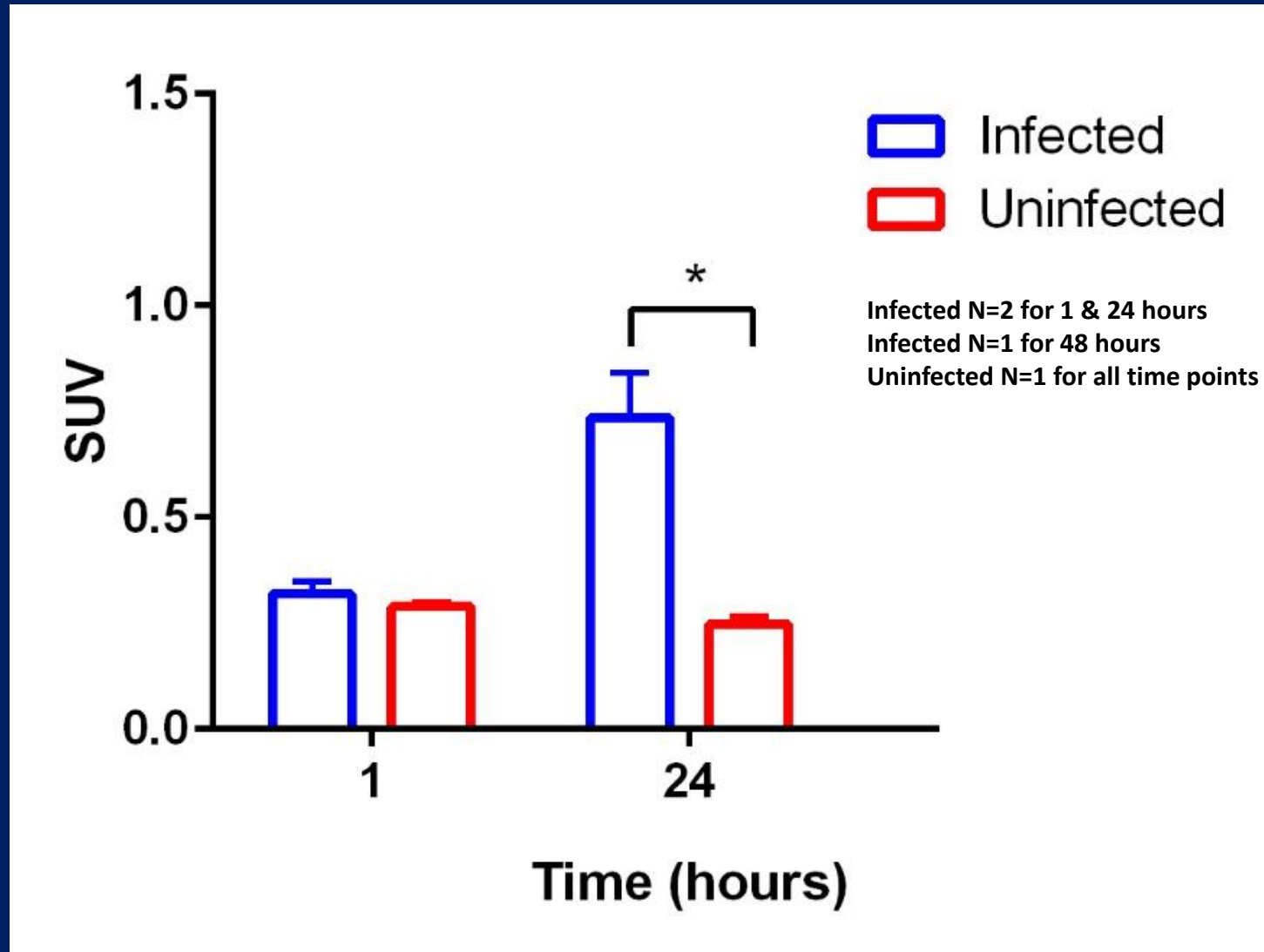
Tucker et al, DMM 2016

# Localization of $^{124}\text{I}$ -DPA-713 Correlates with CNS TB Lesion on Gross Pathology



3 Weeks Post-Subarachnoid *M. tuberculosis* Infection in Rabbit Kits

# $^{124}\text{I}$ -DPA-713 Accumulation in CNS TB Lesion



# Conclusions

- Established the 1<sup>st</sup> pediatric CNS TB animal model
  - Microglia activation
  - Neurologic abnormalities
  - Exudative meningitis and brain tuberculoma formation on gross pathology
  - Radioiodinated DPA-713 accumulates in tuberculomas & correlates with neuroinflammation on gross pathology & histology

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## Rabbits

