CNS Barriers and Immune Responses in Mouse CNS TB

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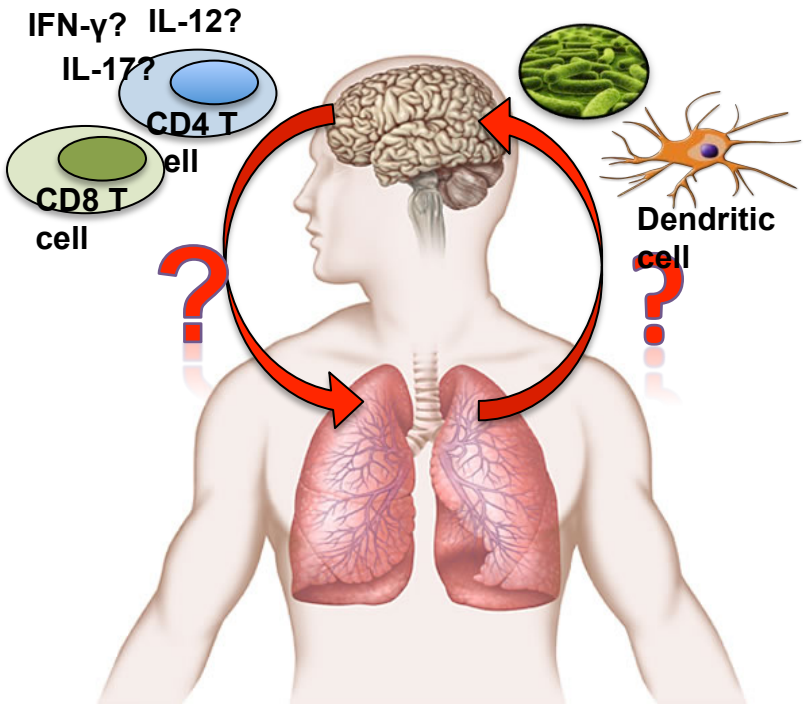
Basic Question: What are the mechanisms that govern CNS TB?

- Question 1: What is the mechanism of *Mtb* dissemination into the CNS?
- Question 2: What are the CNS and systemic host responses to CNS TB?



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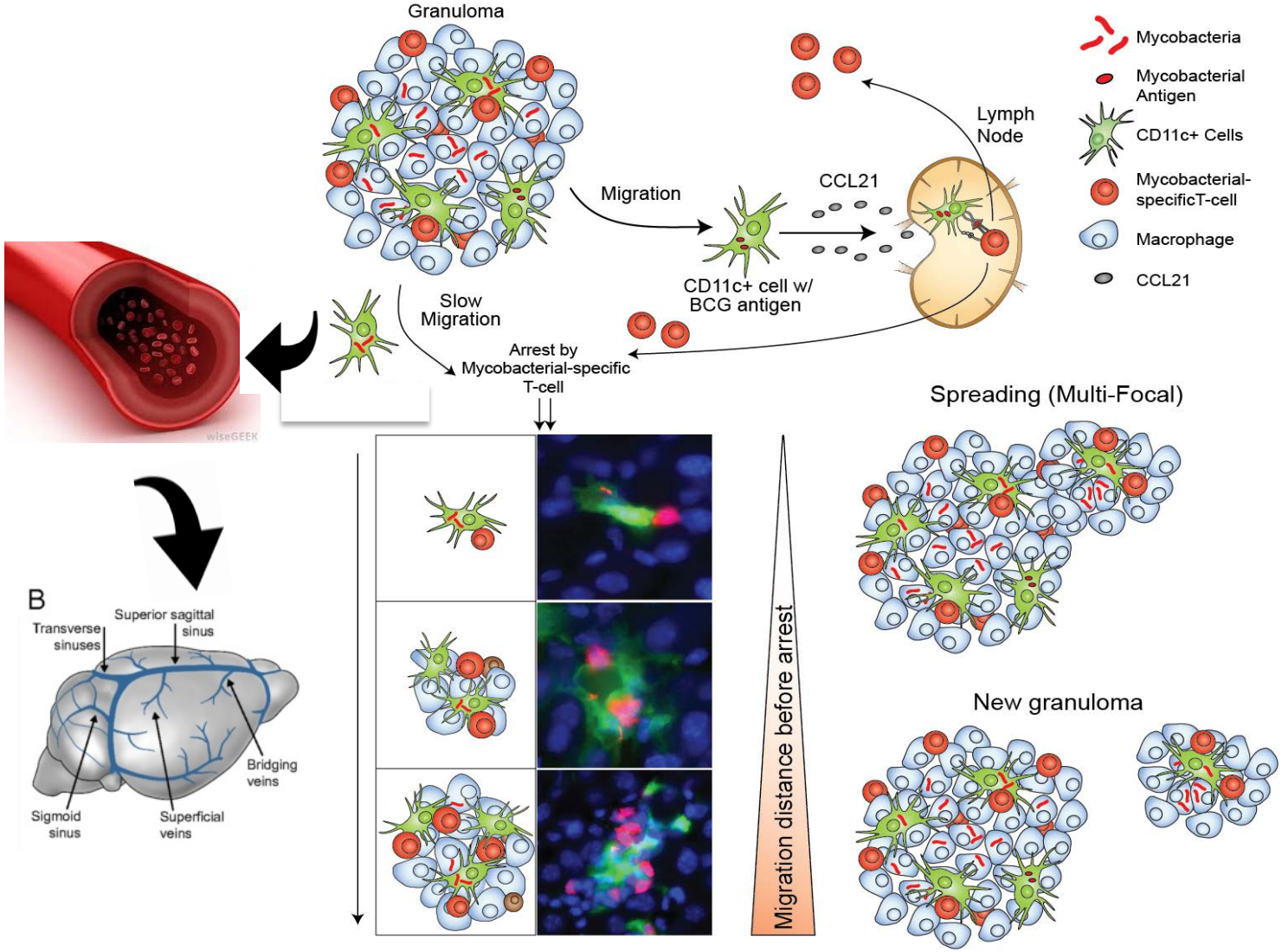
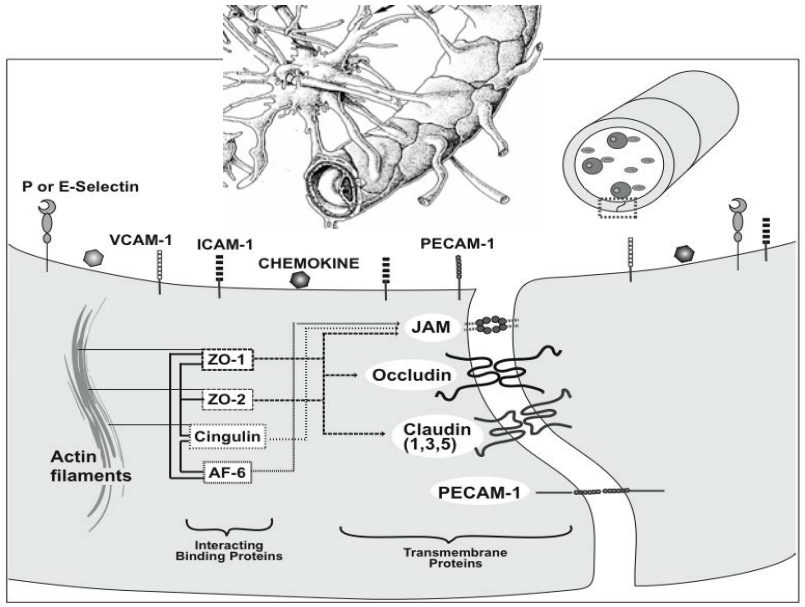
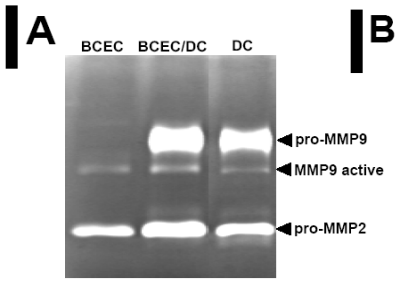
Hypothesis: Infected CD11c^{high} cells traffic from granulomas and might contribute to dissemination to the CNS

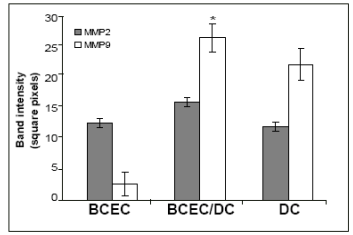


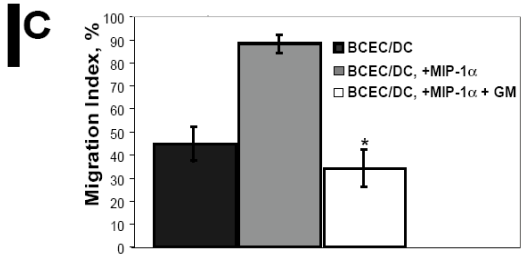
Schreiber et. al 2011 JCI, Harding et. al 2015 Sci Rep

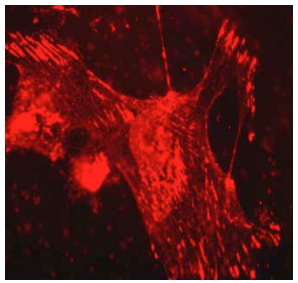
DCs produce MMP2 and 9 and DC transmigration through BBB is inhibited by MMP inhibitors (TJ proteins are substrate for MMPs)

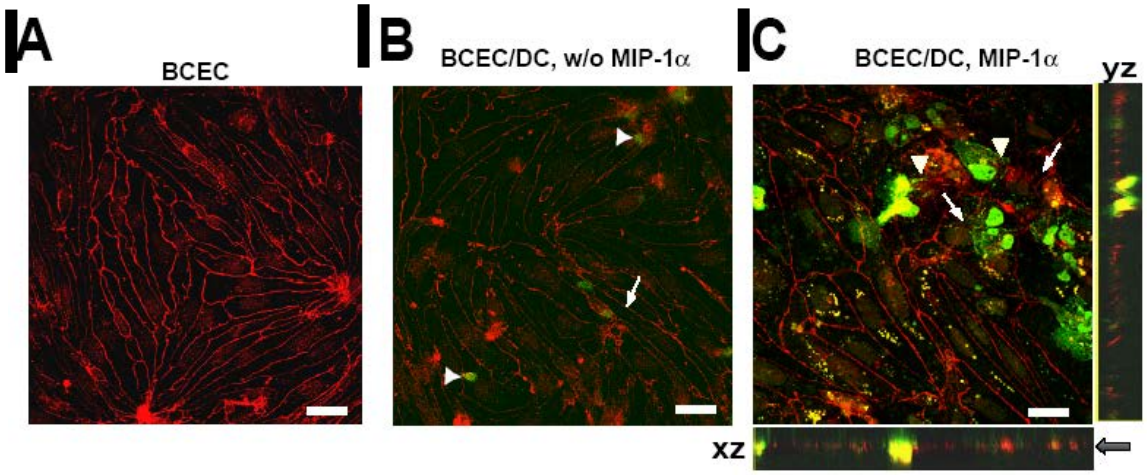






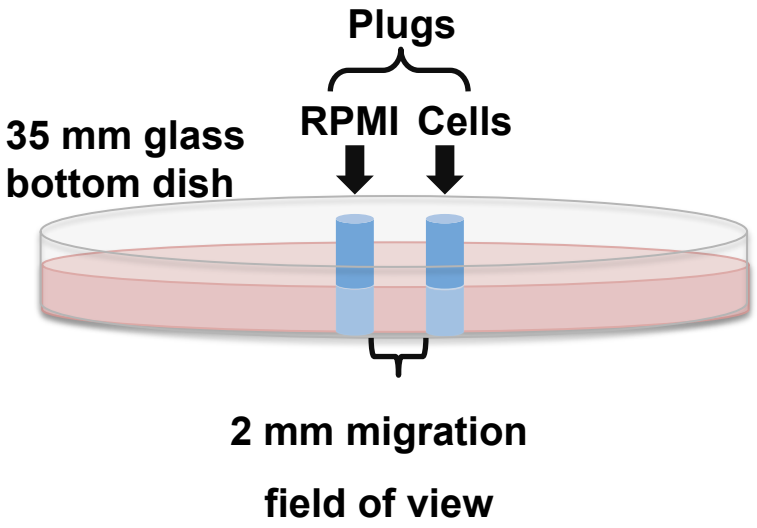


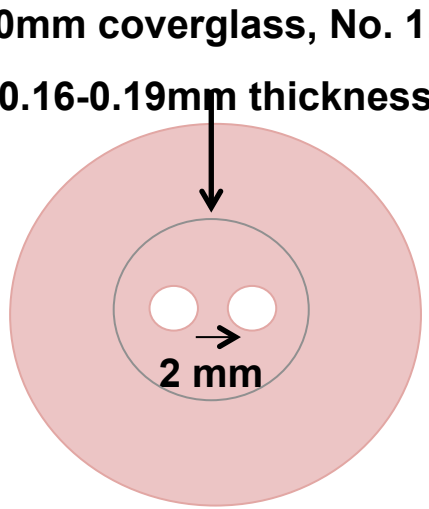


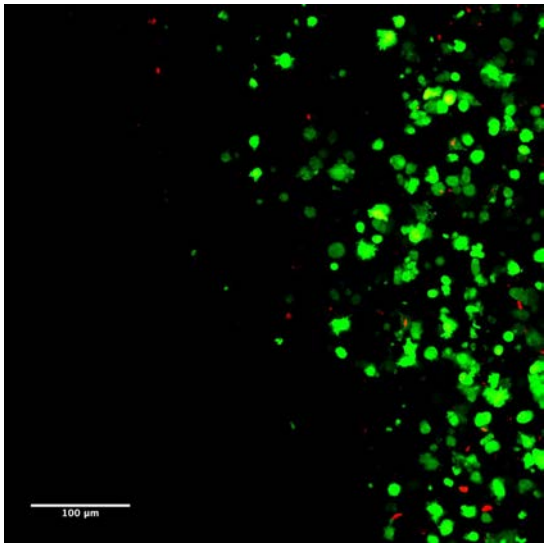


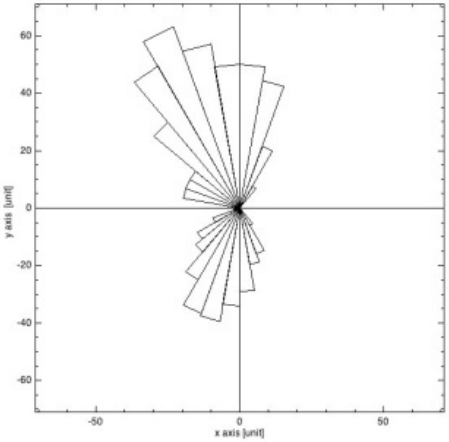
Zozulya A.

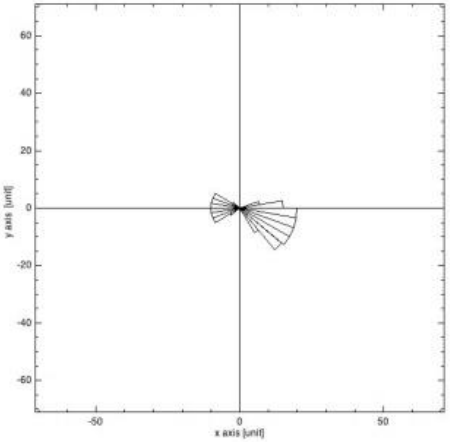
Mtb infection of CD11c^{high} cells leads to their decreased mobility (and chemokine receptor expression)

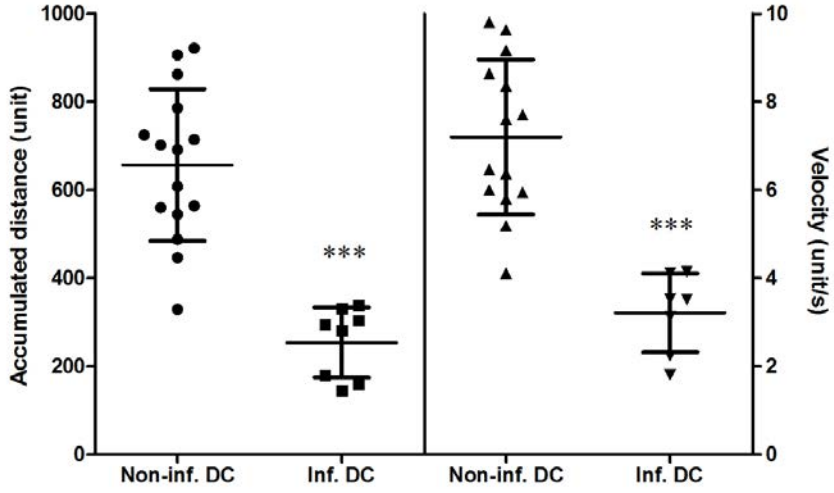








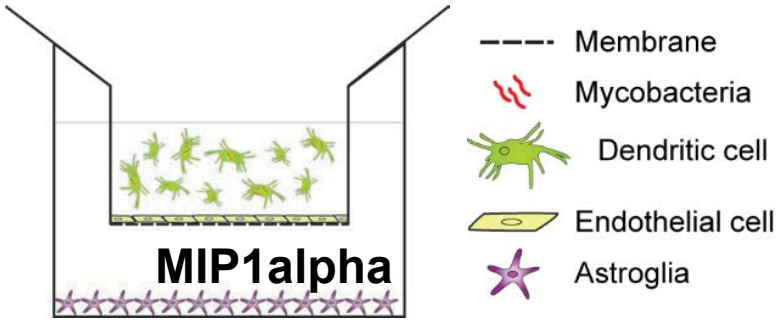


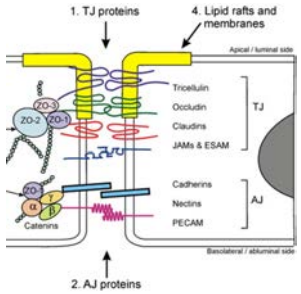


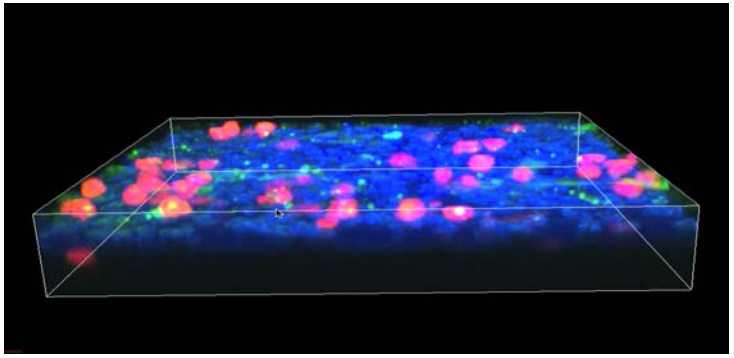
Fruzsina Walter and Trey Gilpin, AAI presented abstract 2017

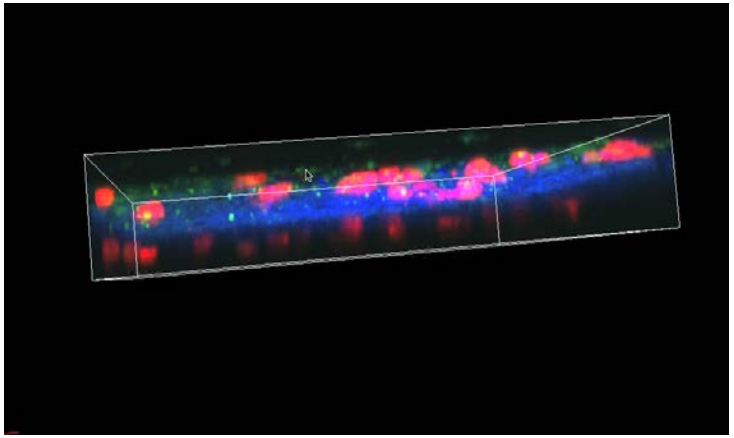
BMDC transmigrate through brain microvessel endothelium by a MIP1a and MMP dependent manner . DC produced MMP 2 and 9 reorganize occludin and decrease electrical resistance. MMP blockers decrease DC migration (Zozulya A et al 2007 JI)

In an in vitro blood brain barrier model infected BMDC has limited capacity to migrate through



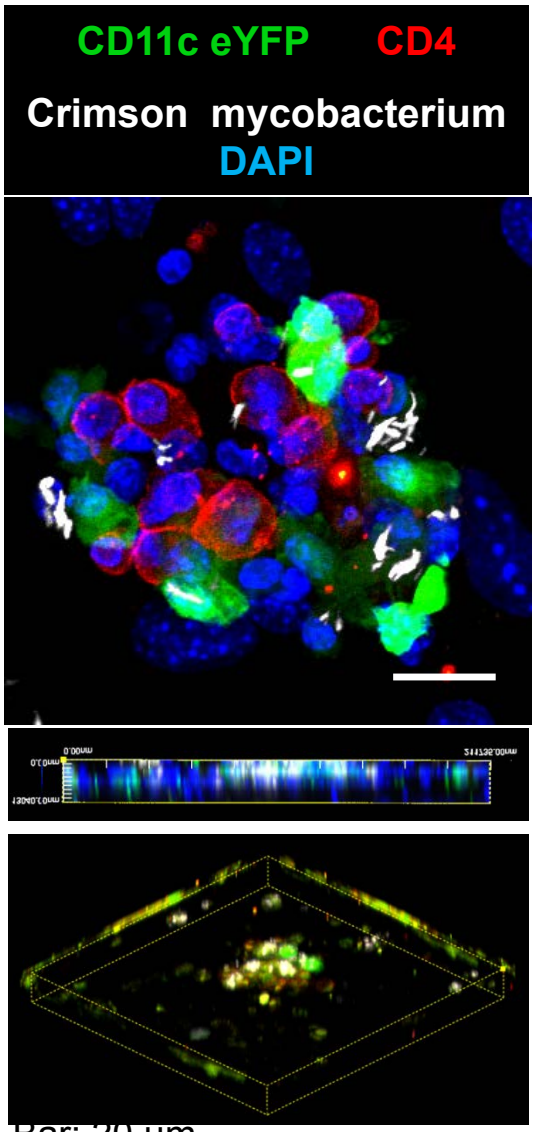


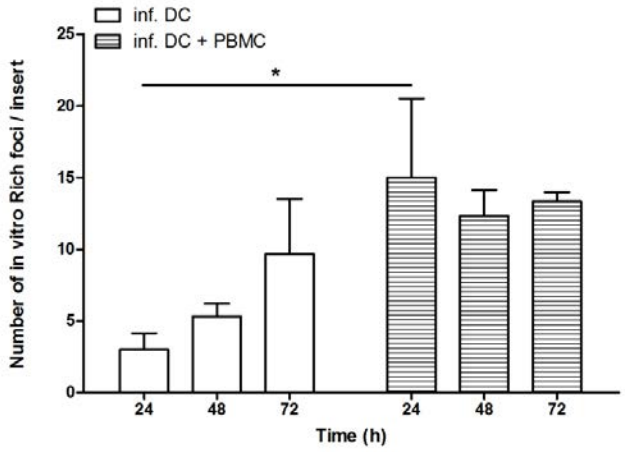


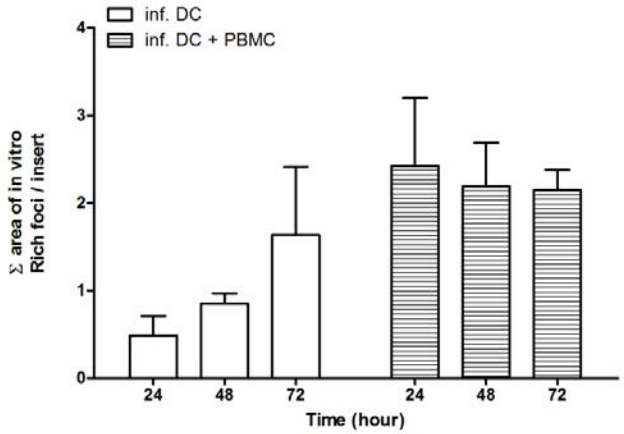


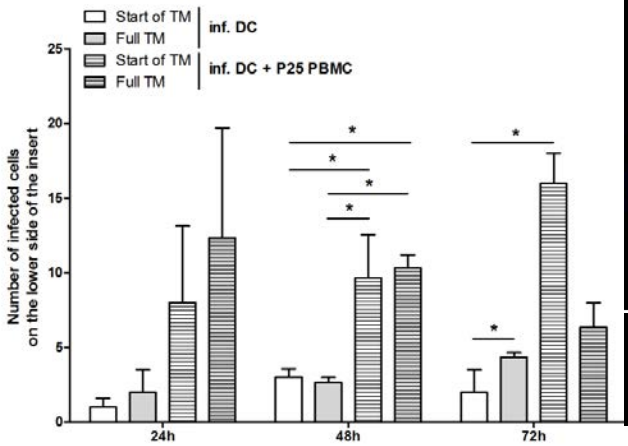
Joe Bednarek

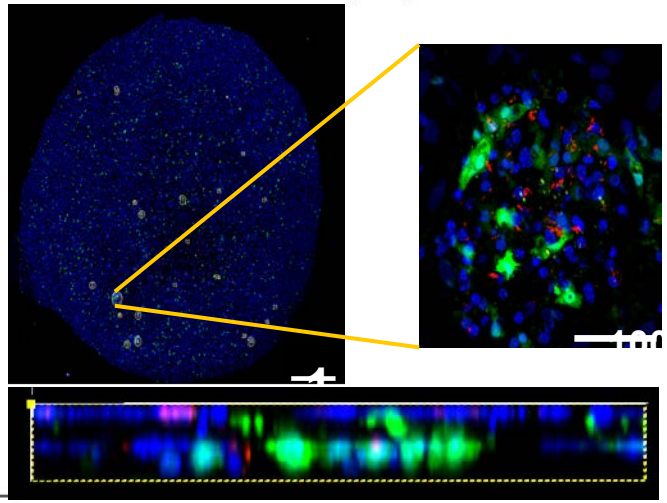
Infected CD11c^{high} cells cross the Blood Brain Barrier (BBB) at sites of cellular aggregates formed with P25 PBMCs





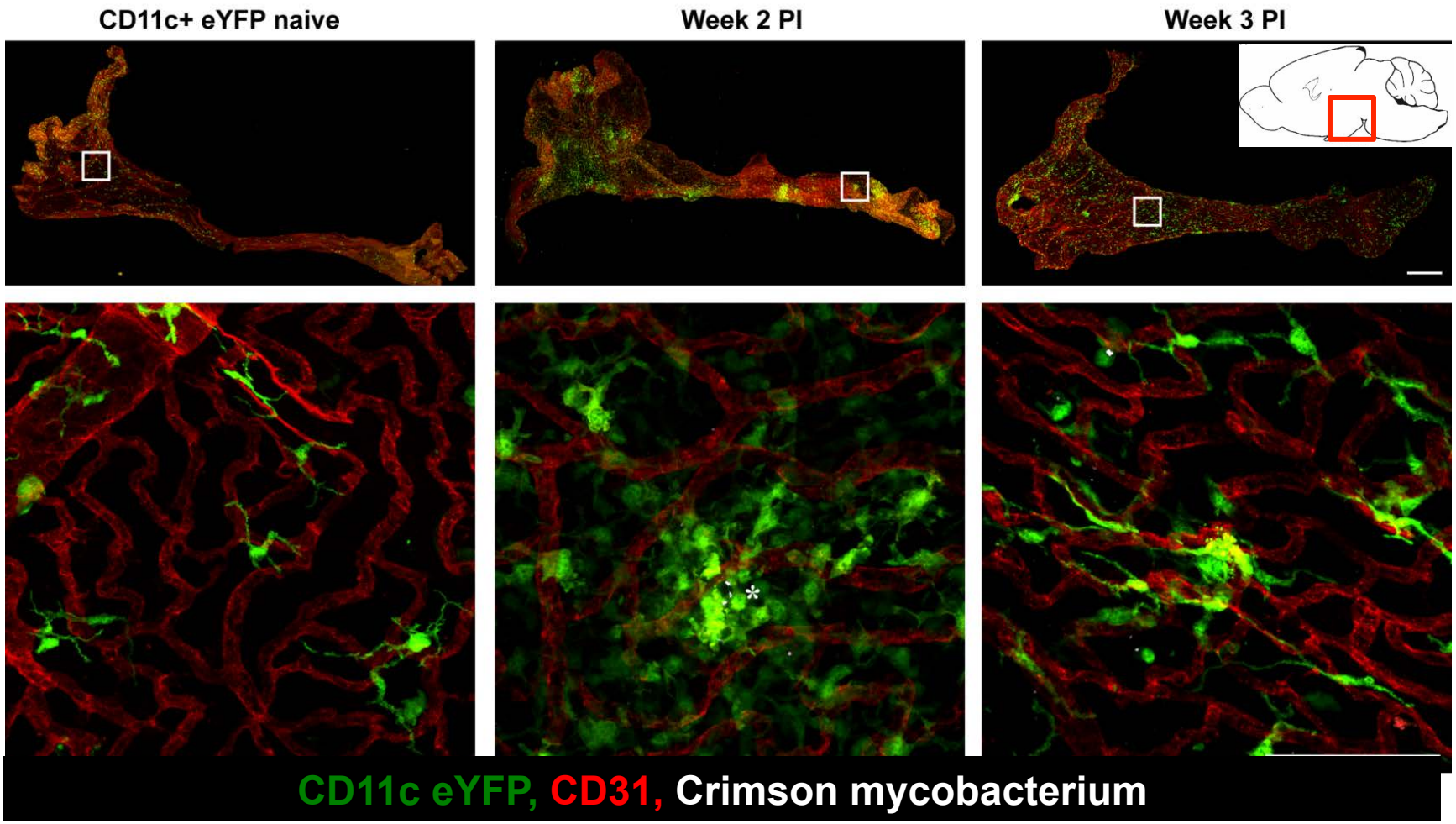






Bar: 20 µm

CD11c^{high} cell invasion and foci formation in the choroid plexus

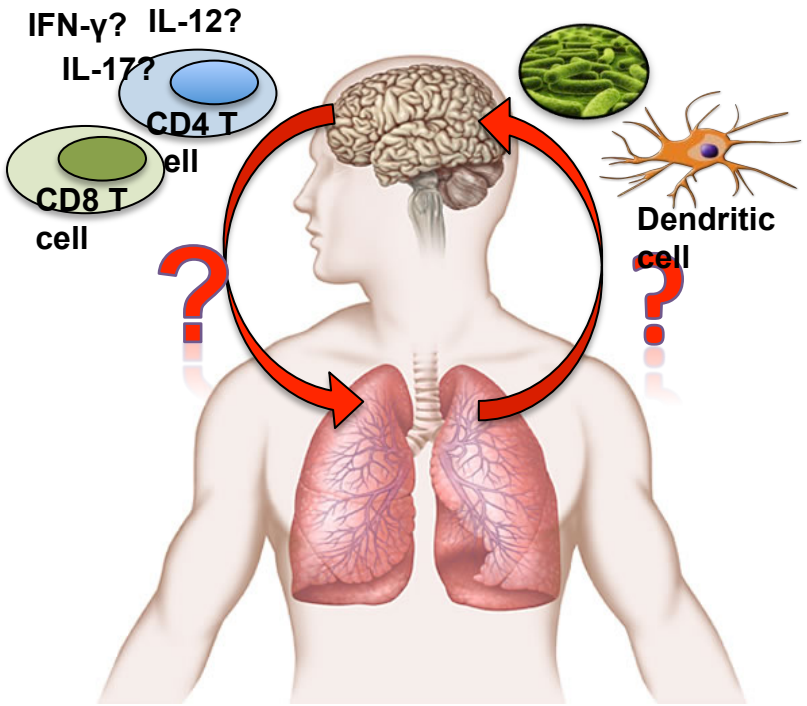


Bar: top row: 0.5 mm, bottom row: 100 µm.

Fruzsina Walter and Trey Gilpin, AAI presented abstract May 2017

Basic Question: What are the mechanisms that govern CNS TB?

- **Question 1: What is the mechanism of *Mtb* dissemination into the CNS?**
- CD11c expressing dendritic cells might contribute to *Mtb* entry into the CNS
- Infected DCs induce inflammatory foci formation that correlates with dissemination
- Meninges and choroid plexus are potential portals



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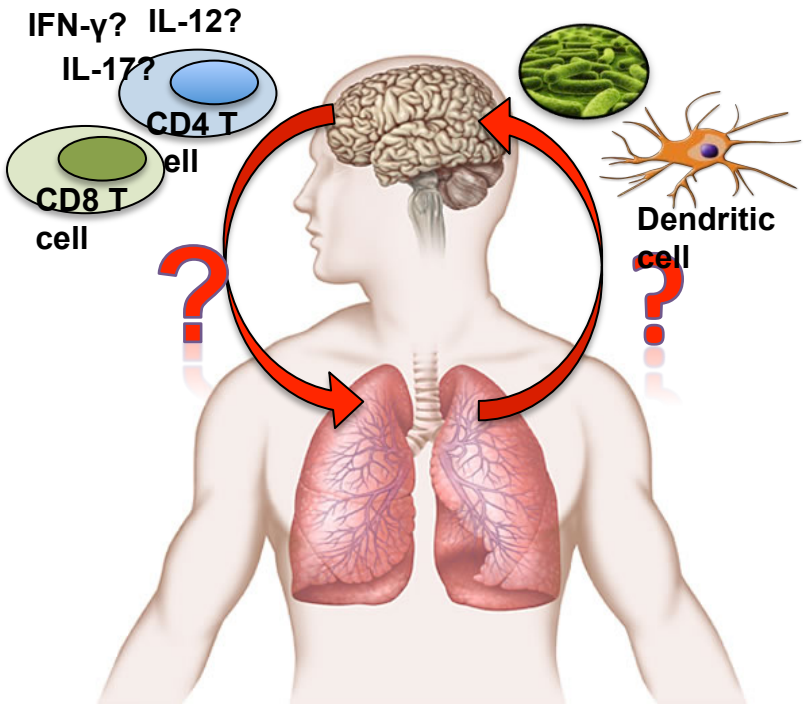

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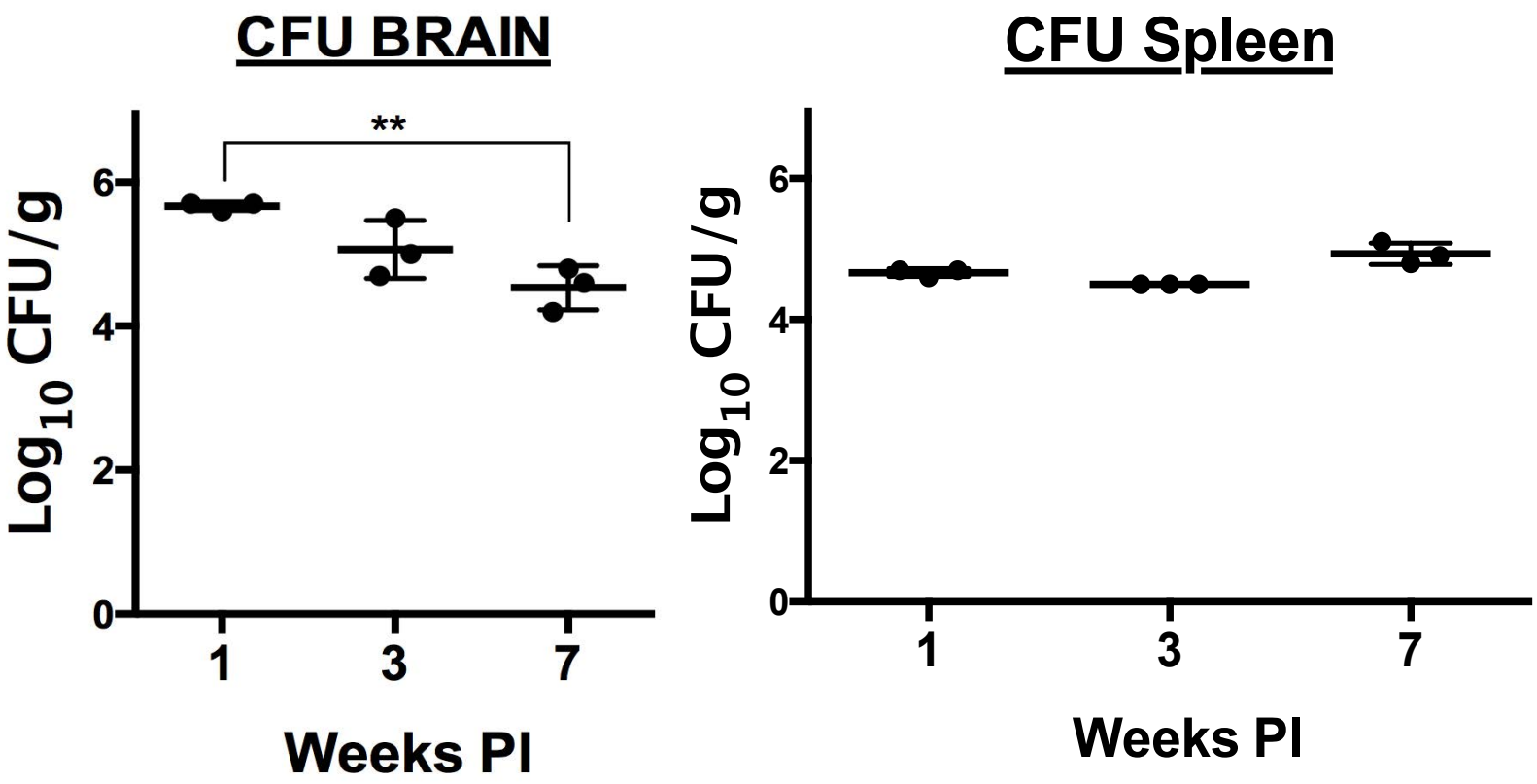
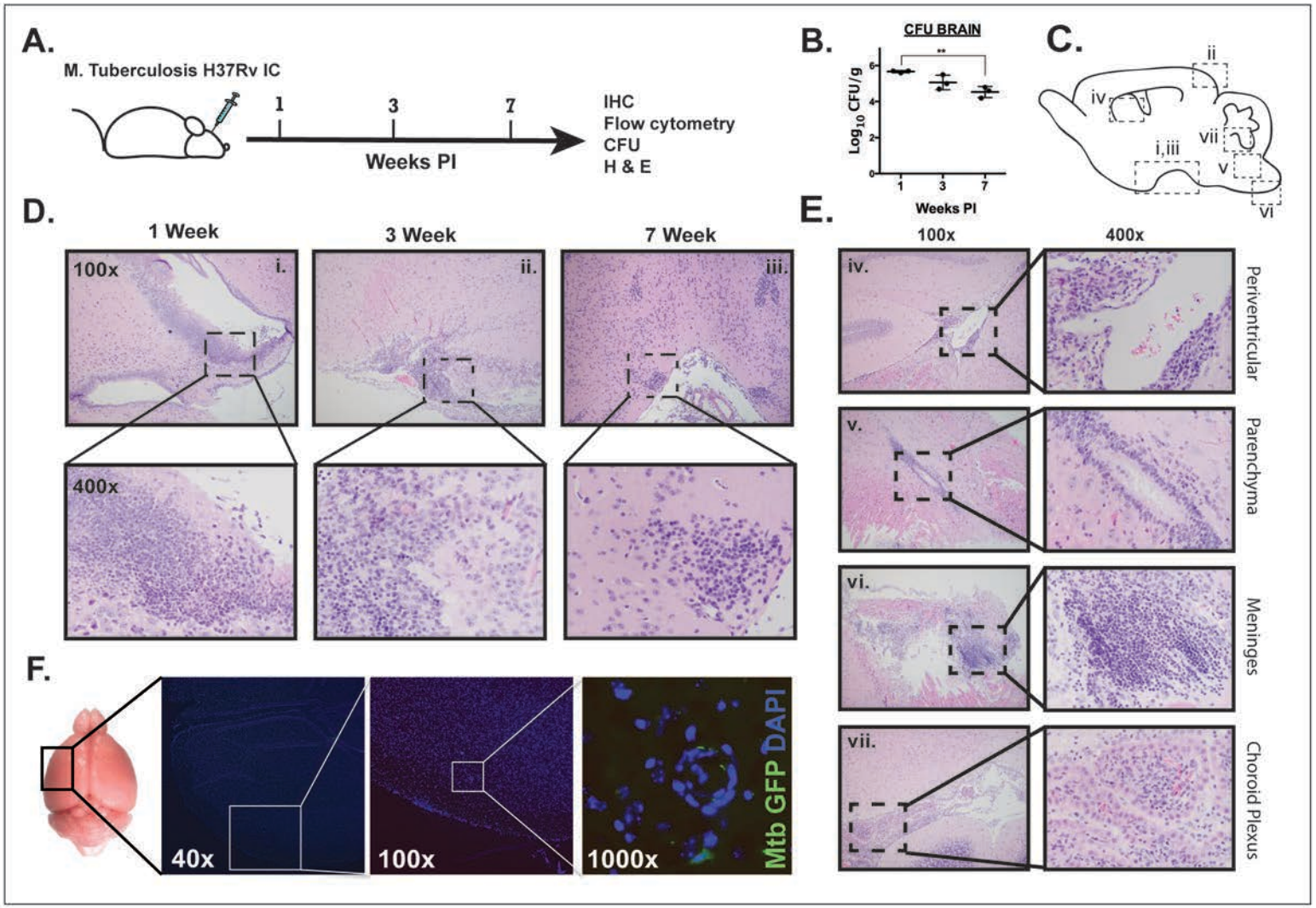
Mtb Infection is Controlled in the CNS



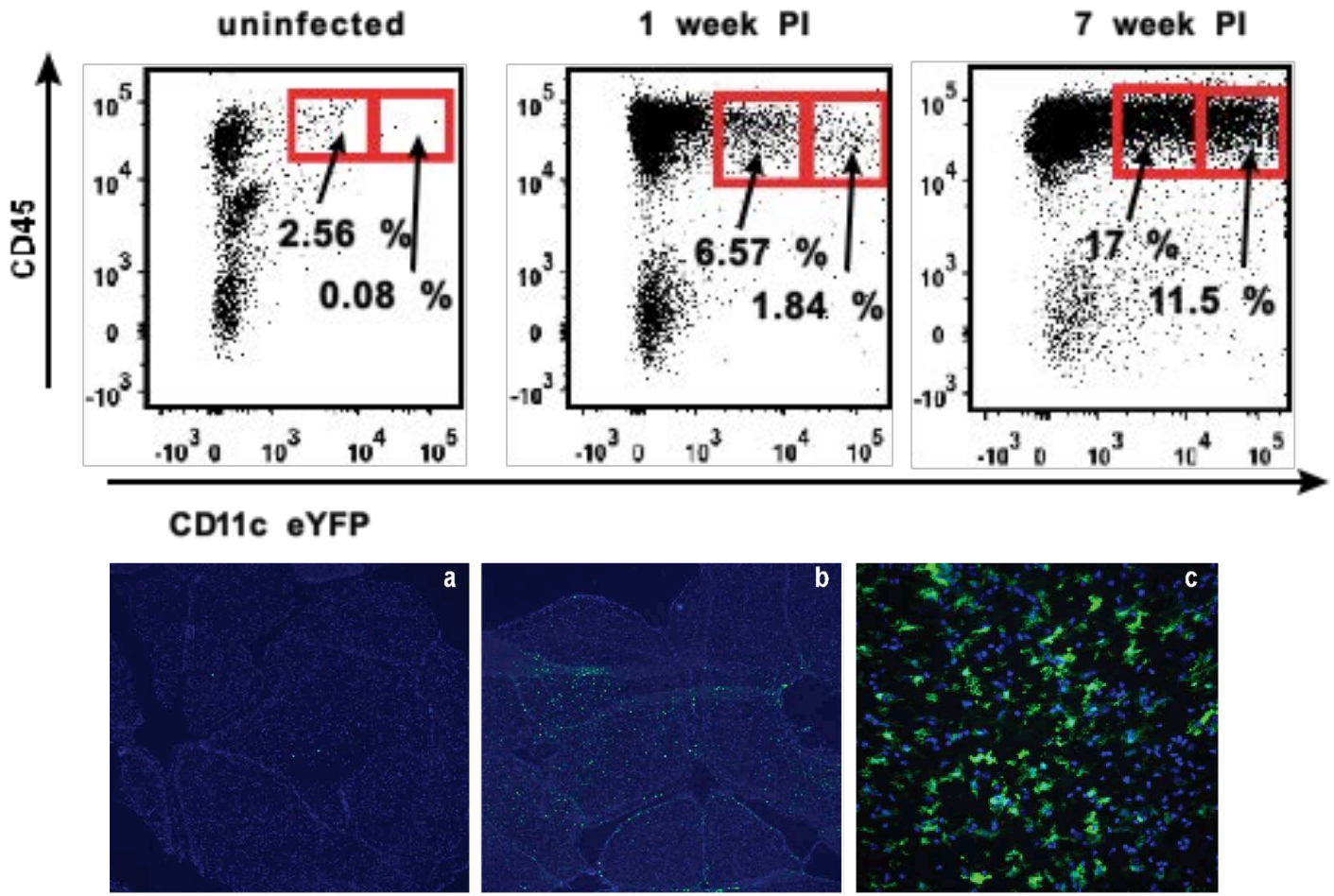
Hernandez, G. Manuscript in submission AJP 2017

Granuloma formation in the brain following IC *Mtb* innoculation



Hernandez, G. Manuscript in submission AJP 2017

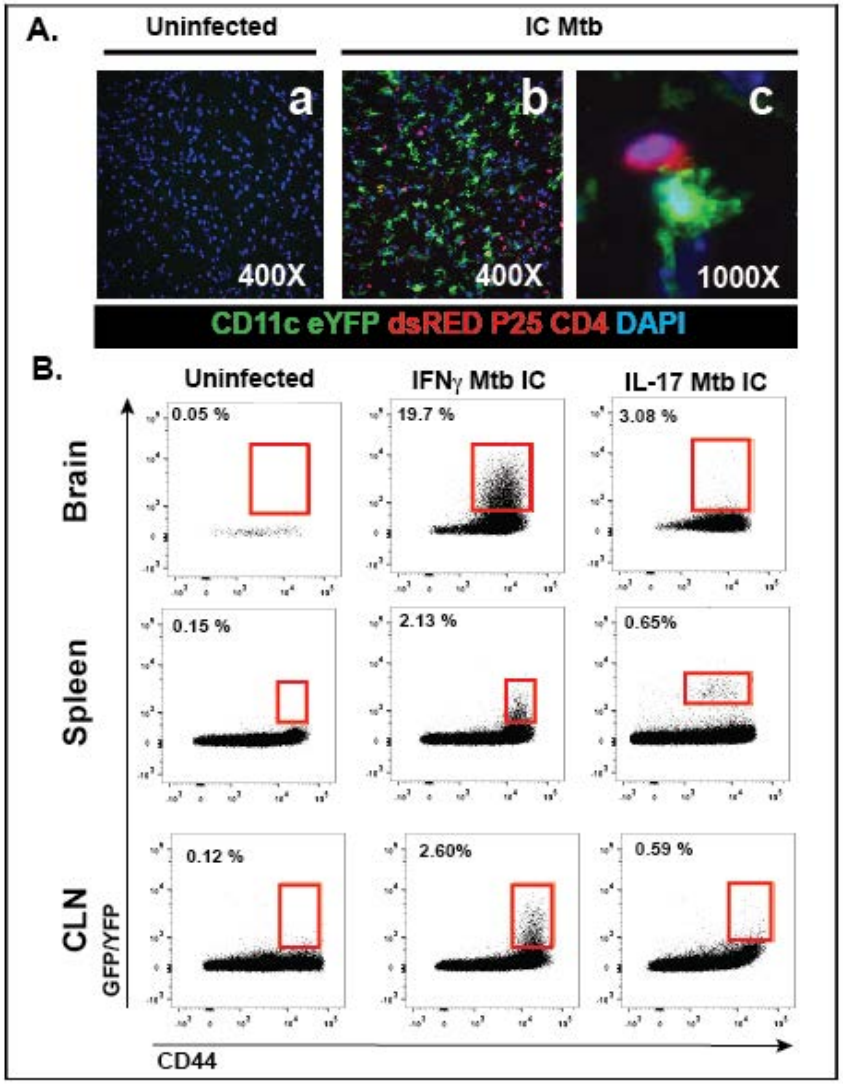
CD11c^{high} Dendritic Cells Infiltrate into the CNS Following IC *Mtb* Infection

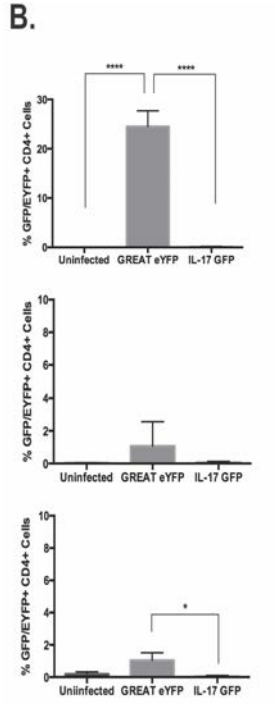


Uninfected **1 Week Post Infection**

Hernandez, G. Manuscript in submission AJP 2017

IC *Mtb* leads to robust infiltration of IFNγ-producing T lymphocytes

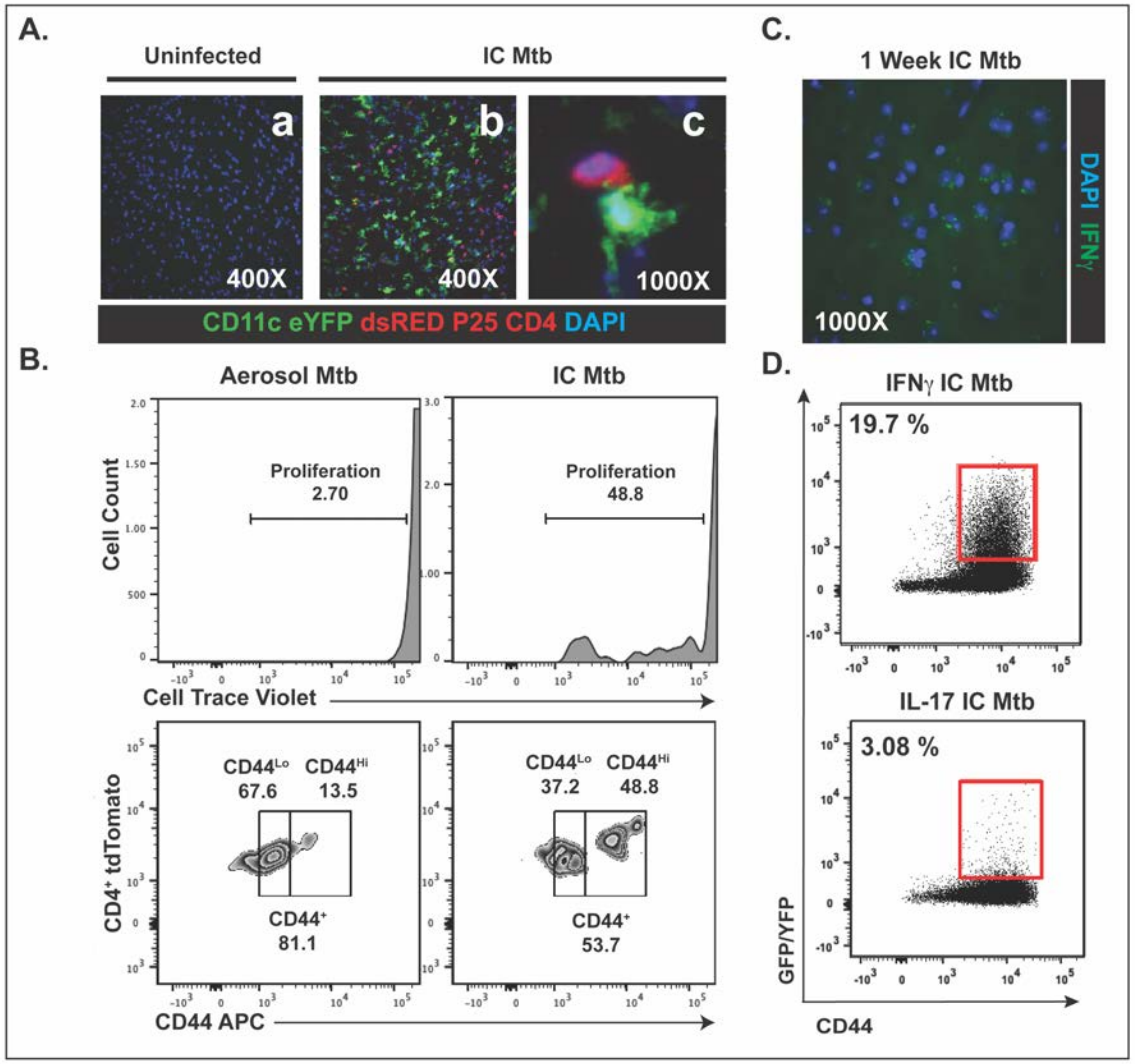




- **Post IC infection there is an IFNγ dominant T cell response in the CNS**
- **Most are in granulomatous lesions**
- **P25 transgenic T cells are seen directly interacting with eYFP+ cells in the CNS**

Hernandez, G. Manuscript in submission AJP 2017

Specific anti-bacterial T cell expansion is induced earlier by IC *Mtb* compared to lung infection



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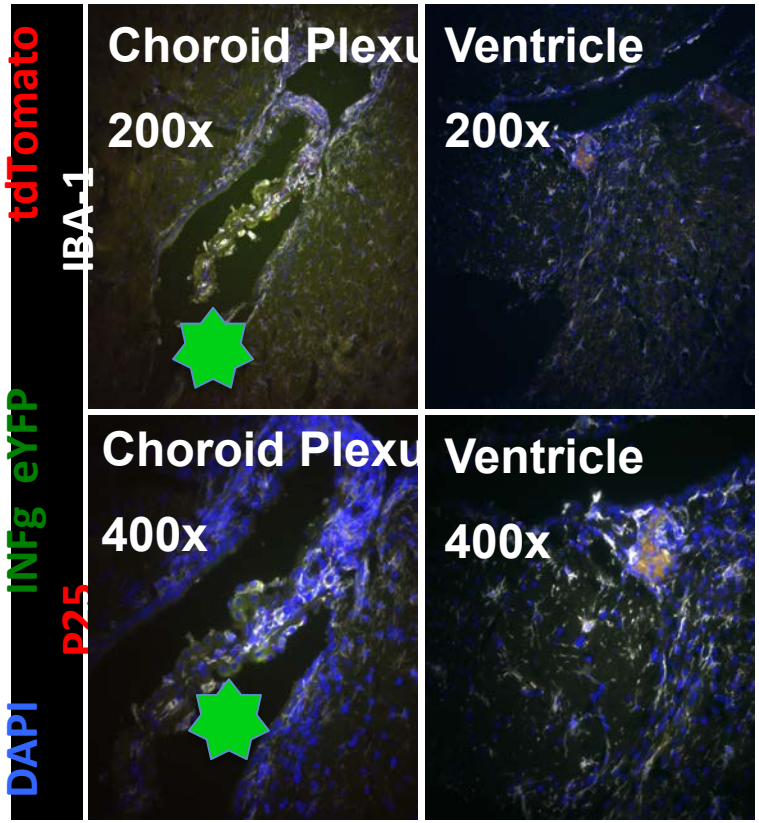
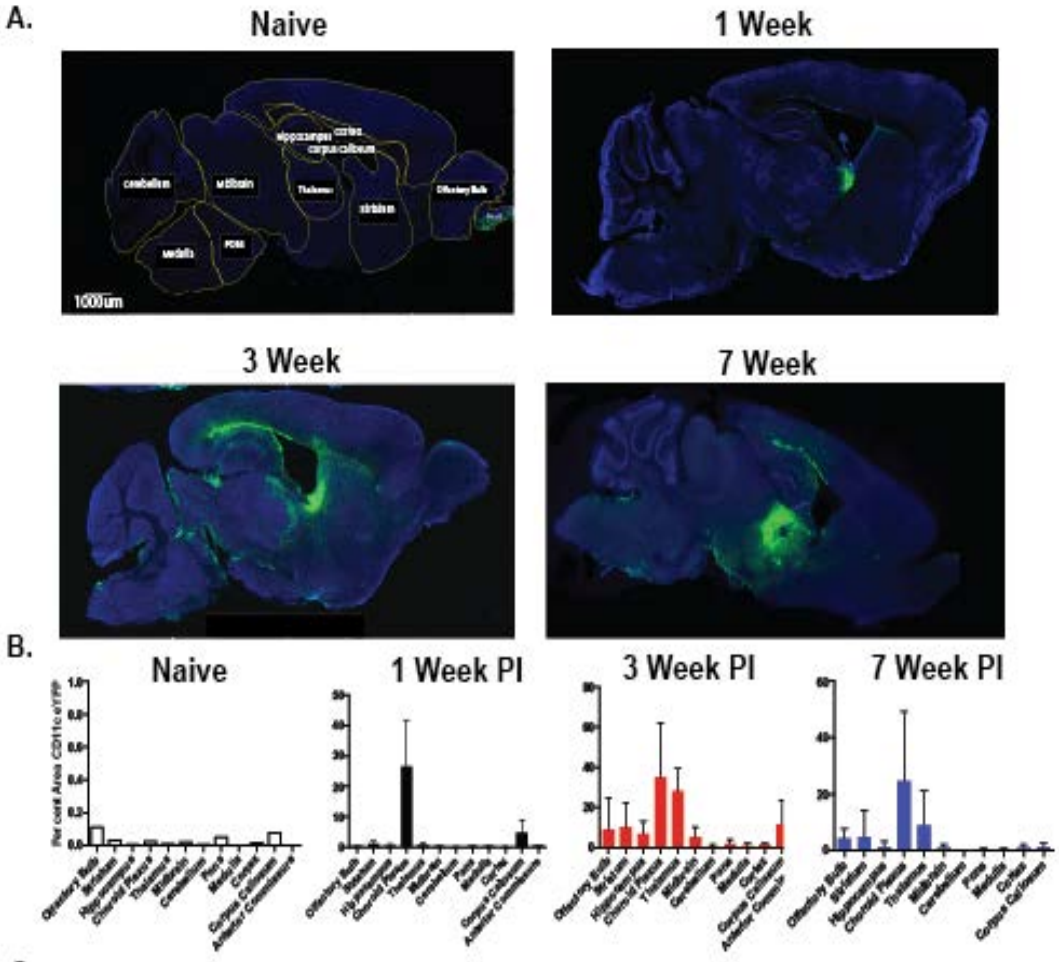
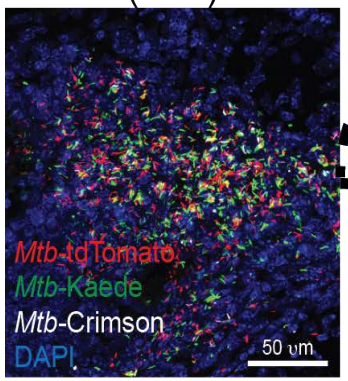
IFNγ-producing T lymphocytes and CD11c cells most likely access the CNS via the choroid plexus





CNS *Mtb* infection induces microglia and astrocyte activation in the brain

Myobacterium Tuberculosis (*Mtb*)



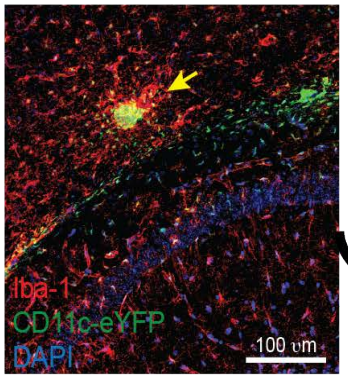
?

Neuronal Death

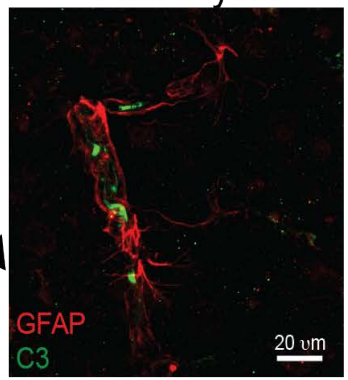
?

"Neurotoxin"?

Migroglia Activation



Reactive Astrocytes



C1q?

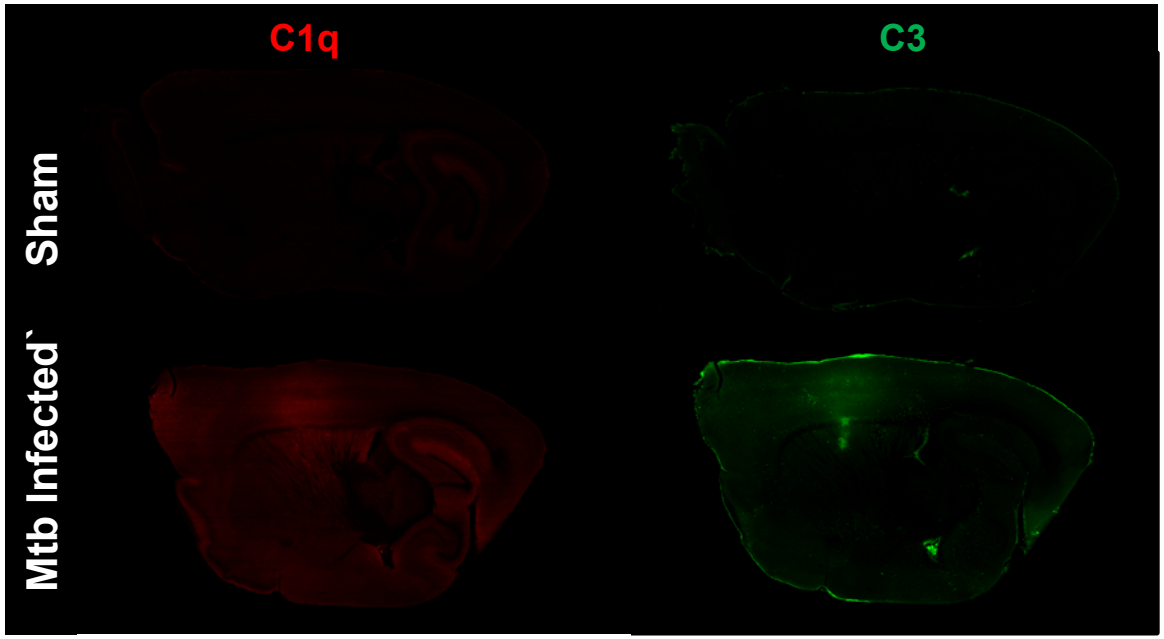
TNF∝?

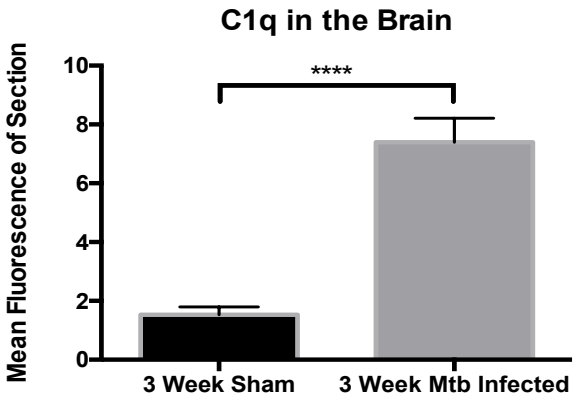
IL1 ∝?

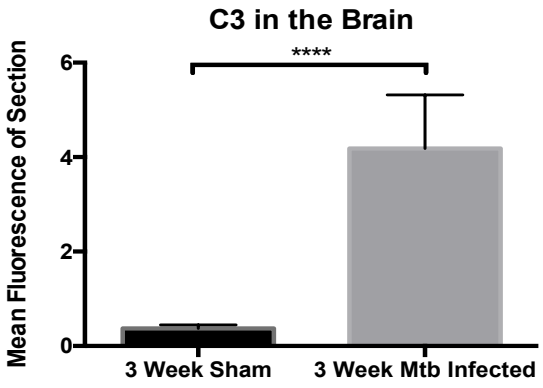
A1?

Factor B?

CNS *Mtb* infection induces complement production in the brain

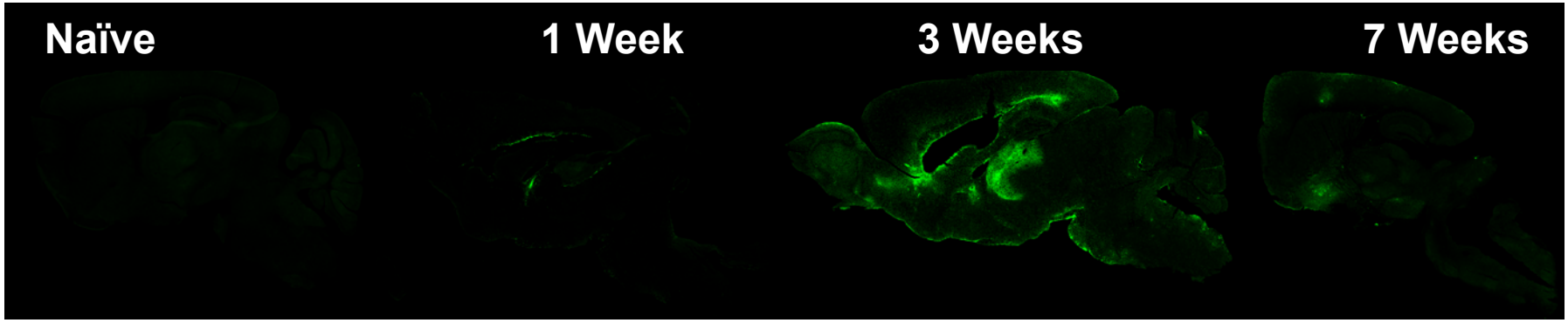


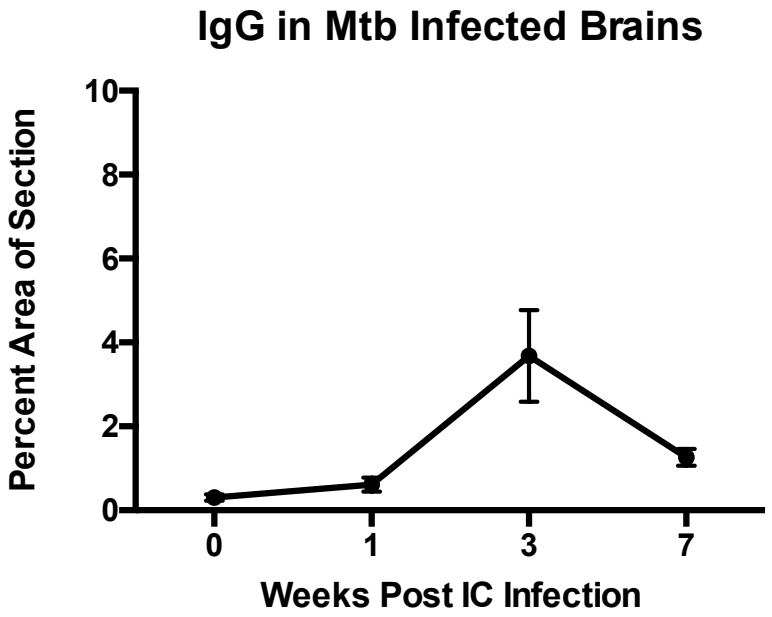




Aisha Mergaert, unpublished data

CNS *Mtb* infection increases Blood Brain Barrier (BBB) "leakage" in the brain

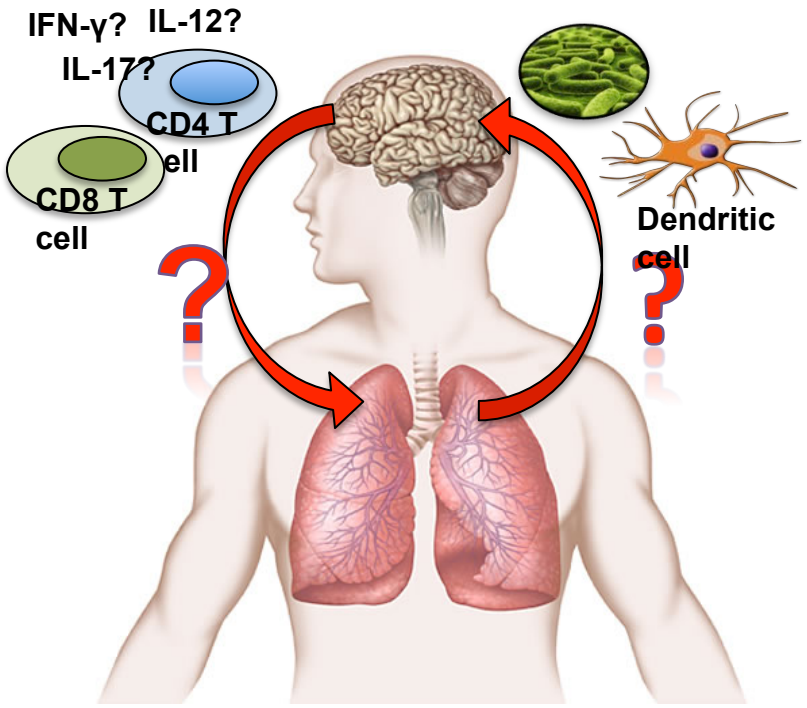




Aisha Mergaert, unpublished data

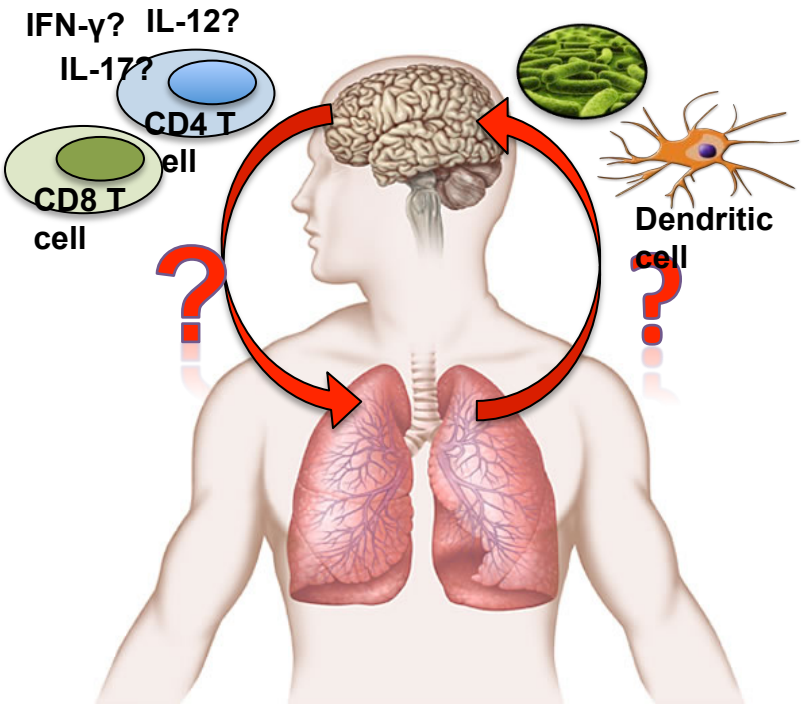
Basic Question: What are the mechanisms that govern CNS TB?

- Question 2: What are the CNS and peripheral host responses to CNS TB?
  - Gliosis (astrocytes and microglia)
  - Complement activation
  - Vascular leakage (IgG staining)
  - Robust T cell priming and infiltration via choroid plexus (mostly)
  - Inflammatory myeloid cell accumulation
  - Strong and early protection



Conclusions: What are the mechanisms that govern CNS TB?

- Infected dendritic cell-induced cellular aggregation promotes bacterial dissemination into the brain.
- Protective immunity against CNS TB is dominated by IFNγ producing Th1 cells – entry though choroid plexus.
- Bacteria-specific T cell responses are earlier compared to the lung.



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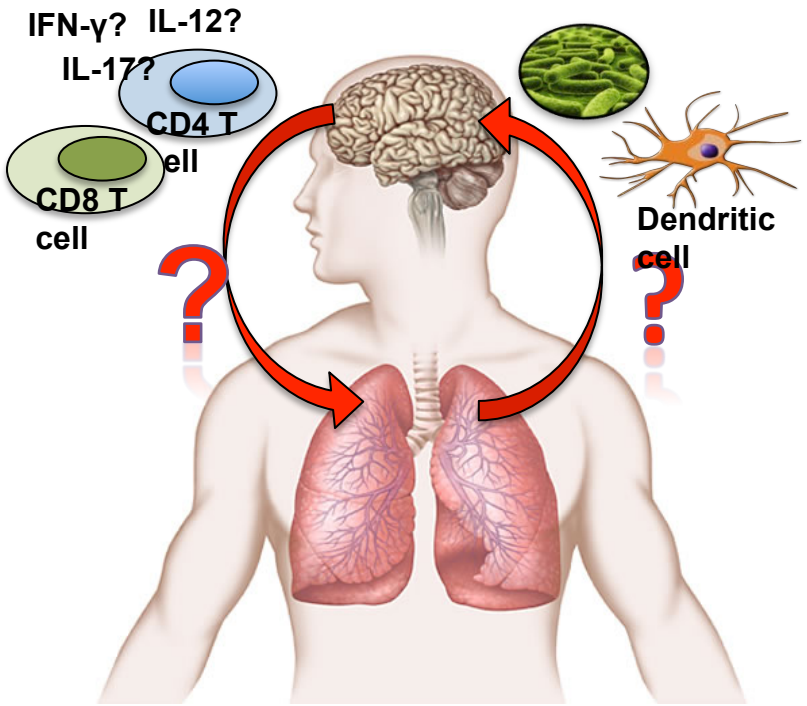
What can we learn from murine CNS TB models that could contribute to clinical CNS TB treatment?

- Inhibition of infected DC migration across the BBB might contribute to therapies: MMP blockers? Others pathways for interrupting migration?



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