

A detailed medieval battle scene painting. In the foreground, a large, dense army of soldiers in chainmail and surcoats is engaged in combat, with many flags flying. In the middle ground, a fortified city with a castle on a rocky hillside is visible. The background shows a wide river or lake with a forested landscape under a cloudy sky.

# The Immune Response to TB

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# The Immune Response to TB

- Multifaceted
- Evolving topic
- Diagnostically useful
- Informs vaccine design



# A Partial View

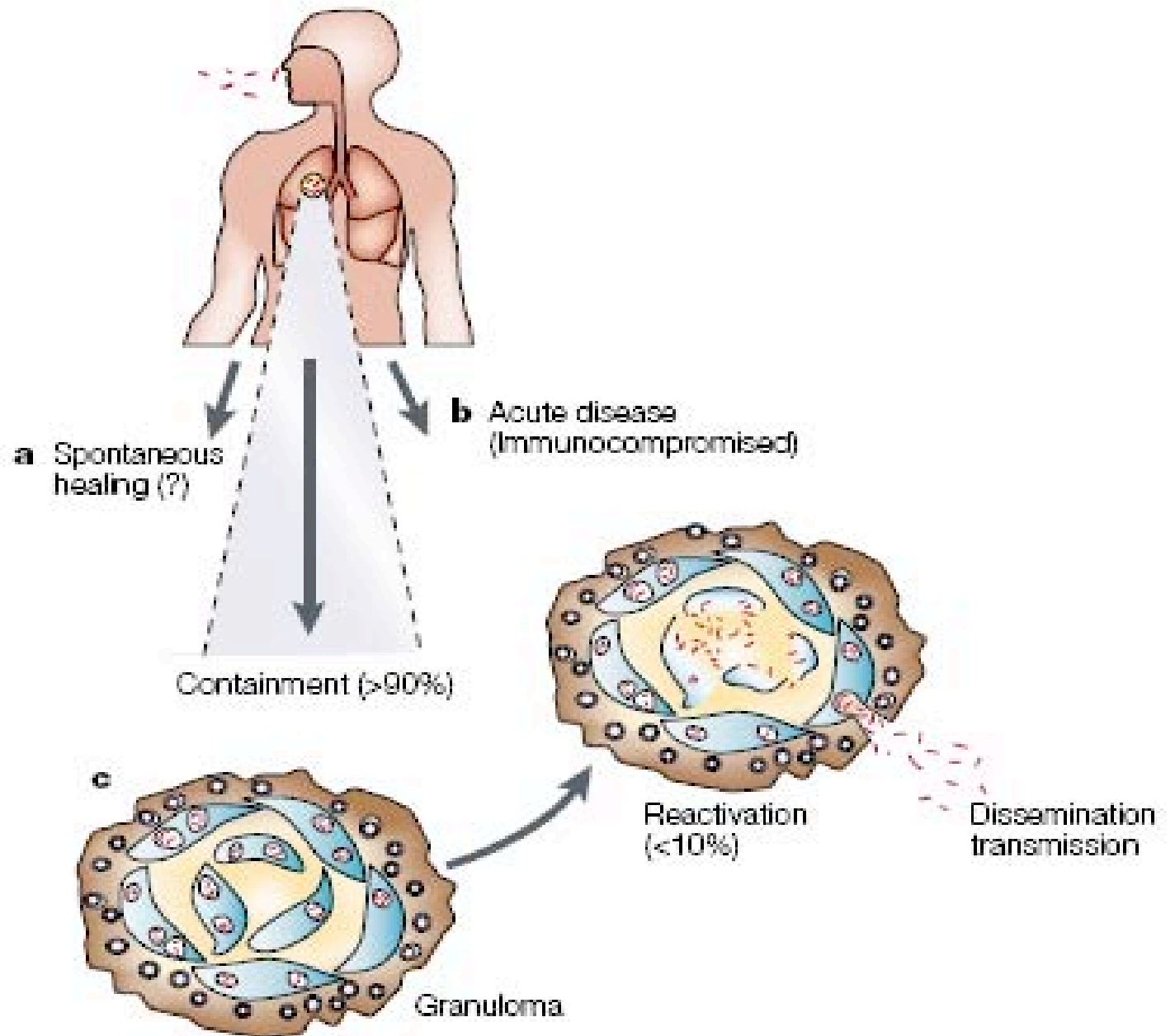
- Innate immunity
- Persistence in macrophages
- Critical cellular responses
- Cytokines
- Modulation

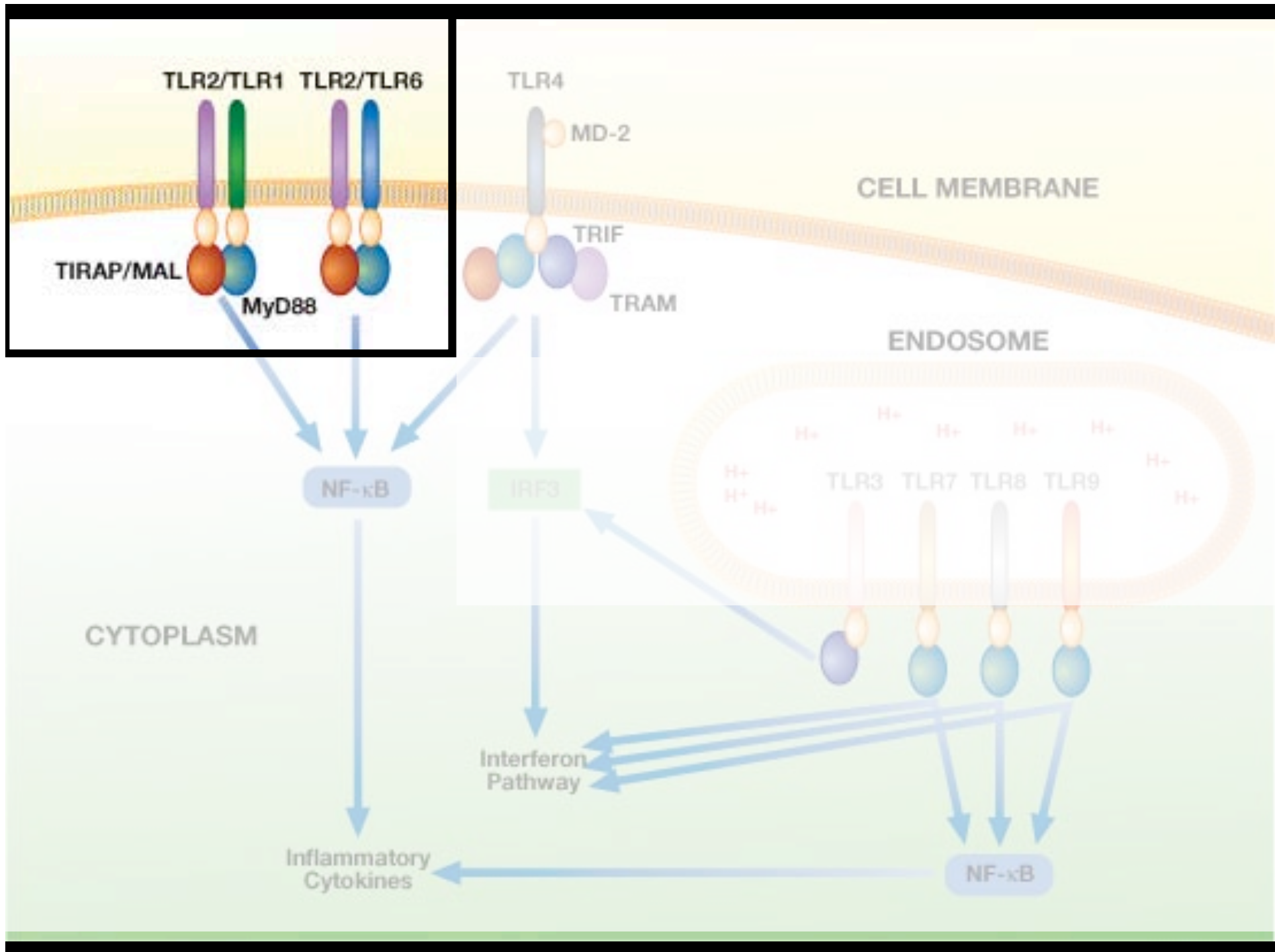


# A Partial View

- **Innate immunity**

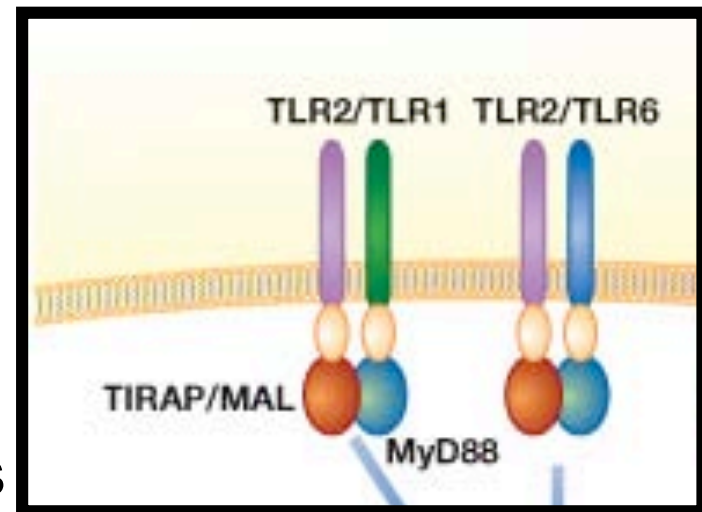




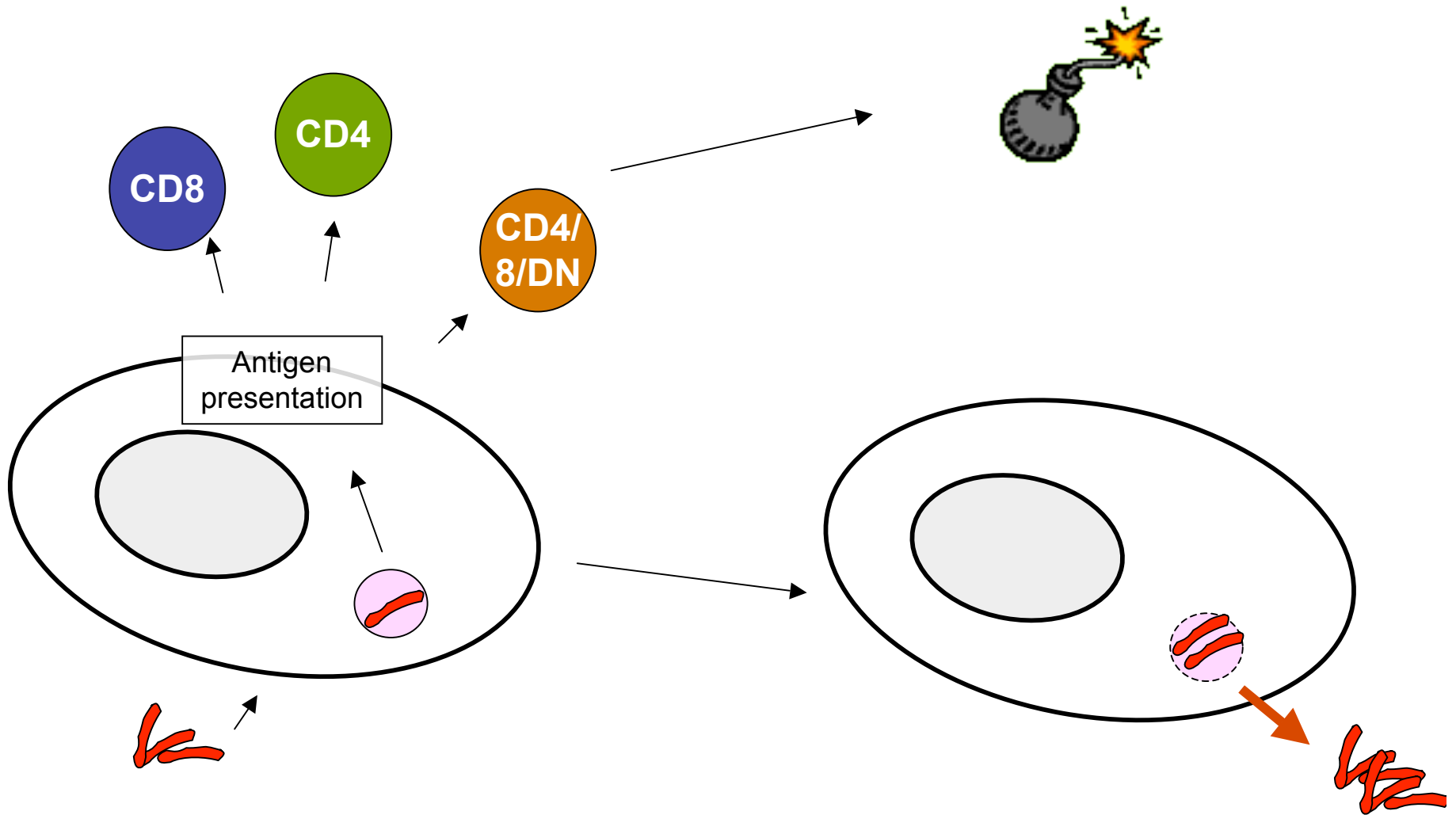


# TB and the Innate Immune System

- TB interacts with TLR2
  - **Good:** Induces macrophage IL-12 and NO production
  - **Bad:** Impedes MHC class II induction and IFN- $\gamma$  responsiveness

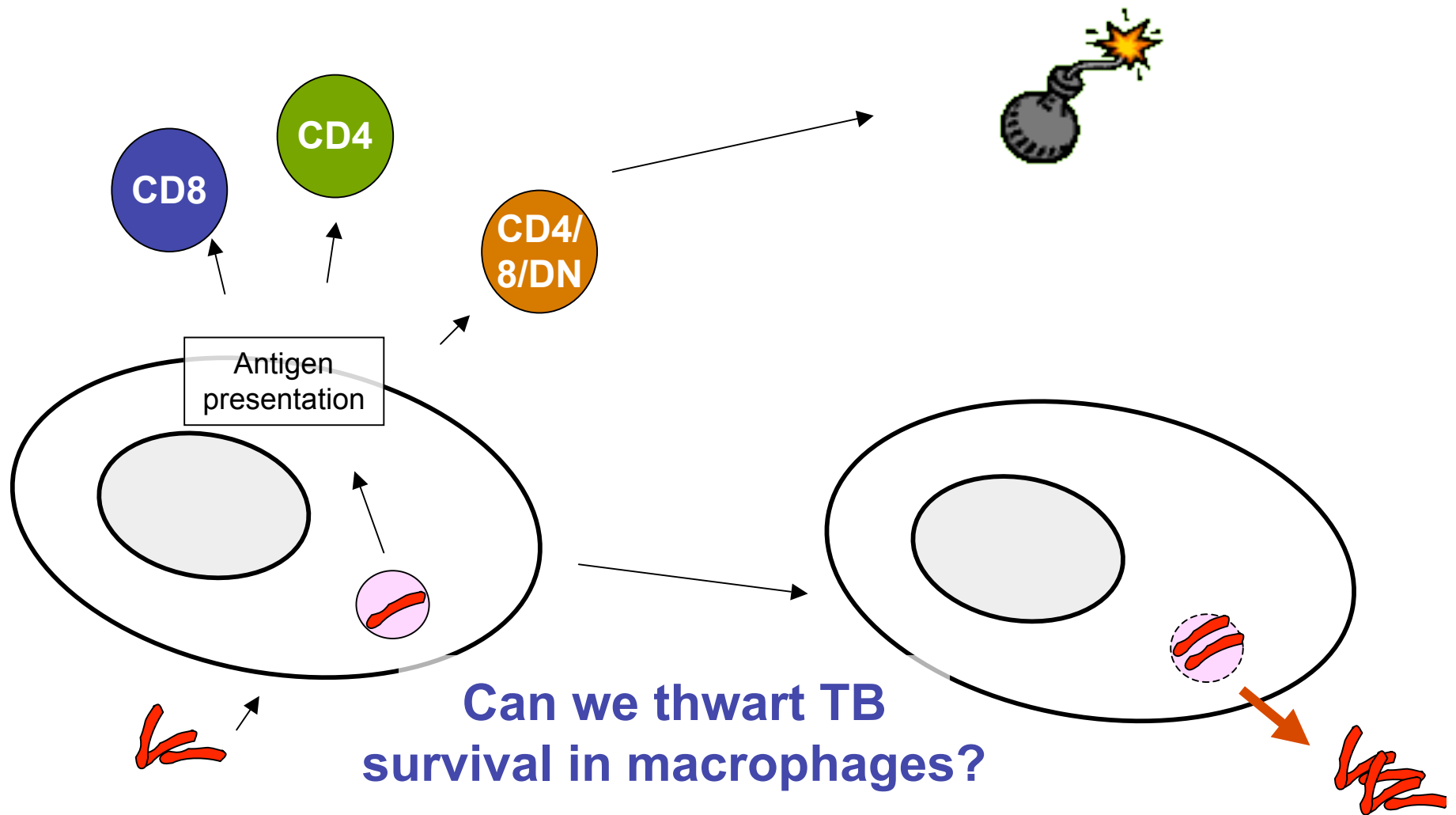


# TB in the Macrophage



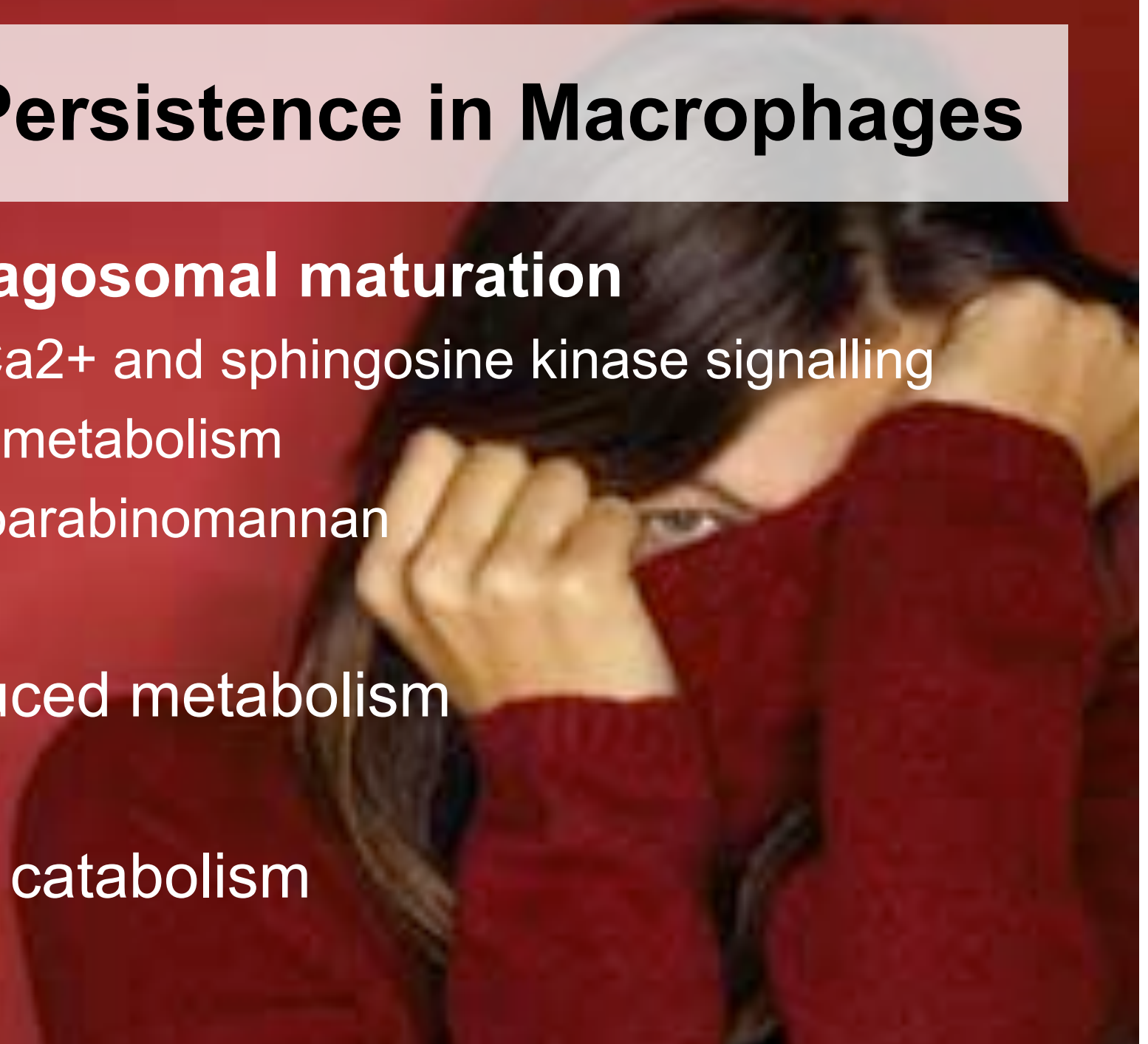


# TB in the Macrophage



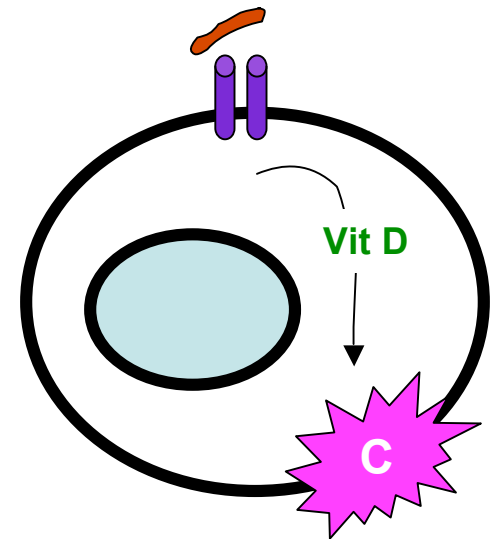
# TB Persistence in Macrophages

- **↓ phagosomal maturation**
  - ↓ Ca<sup>2+</sup> and sphingosine kinase signalling
  - Fe metabolism
  - lipoarabinomannan
- Reduced metabolism
- Lipid catabolism

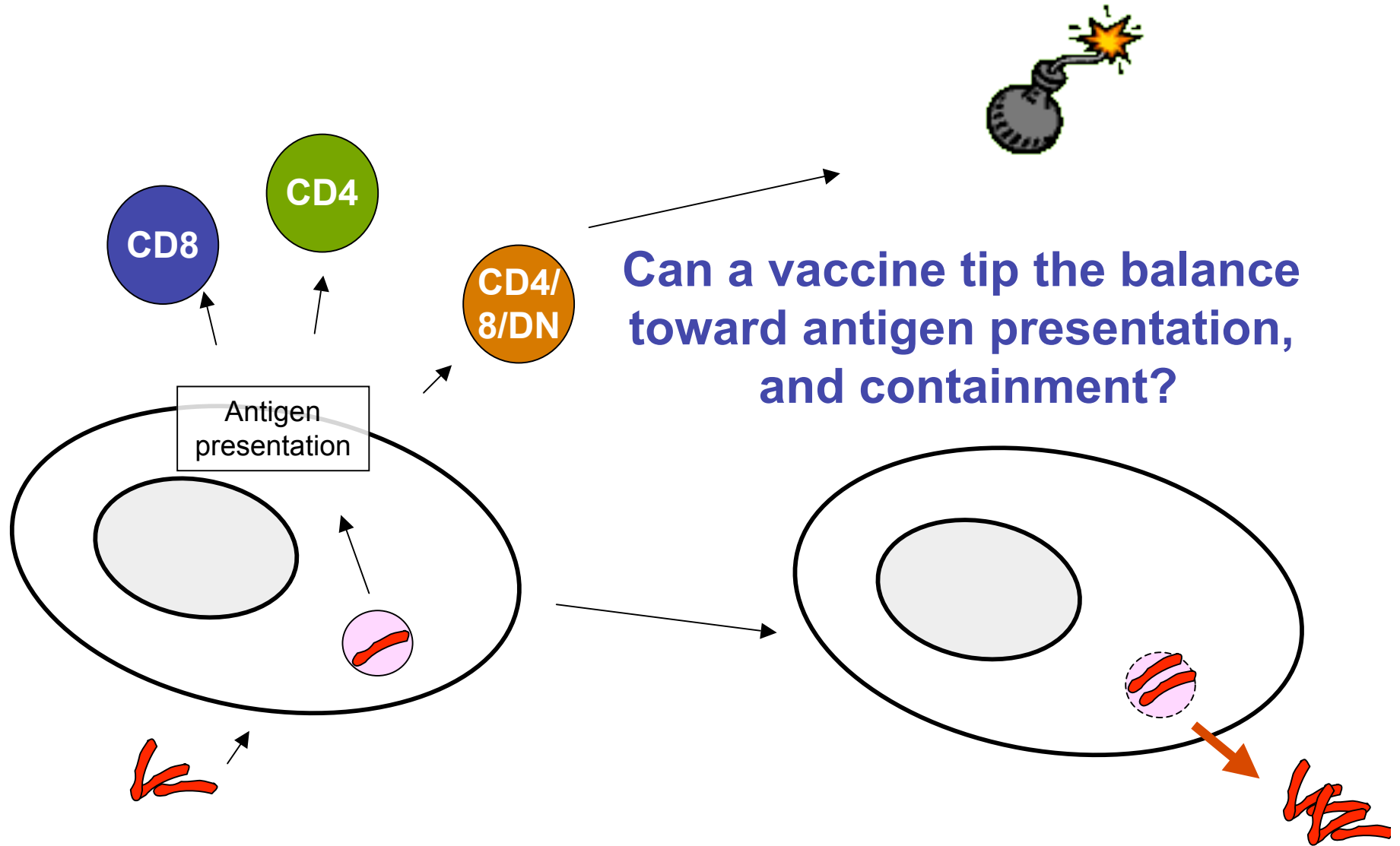


# Vitamin D & Tuberculosis

- **TLR** induction of **vitamin D receptor**
- Induction of **cathelicidin**
- Vit D required for induction
- Killing of intracellular **TB**
- **A way to kill TB in macrophages?**



# TB in the Macrophage



# Critical T<sub>H</sub>1 CD4+ T cells

- Phagosome → MHC class II → CD4+ T cells

**IL-12** → **IFN- $\gamma$**

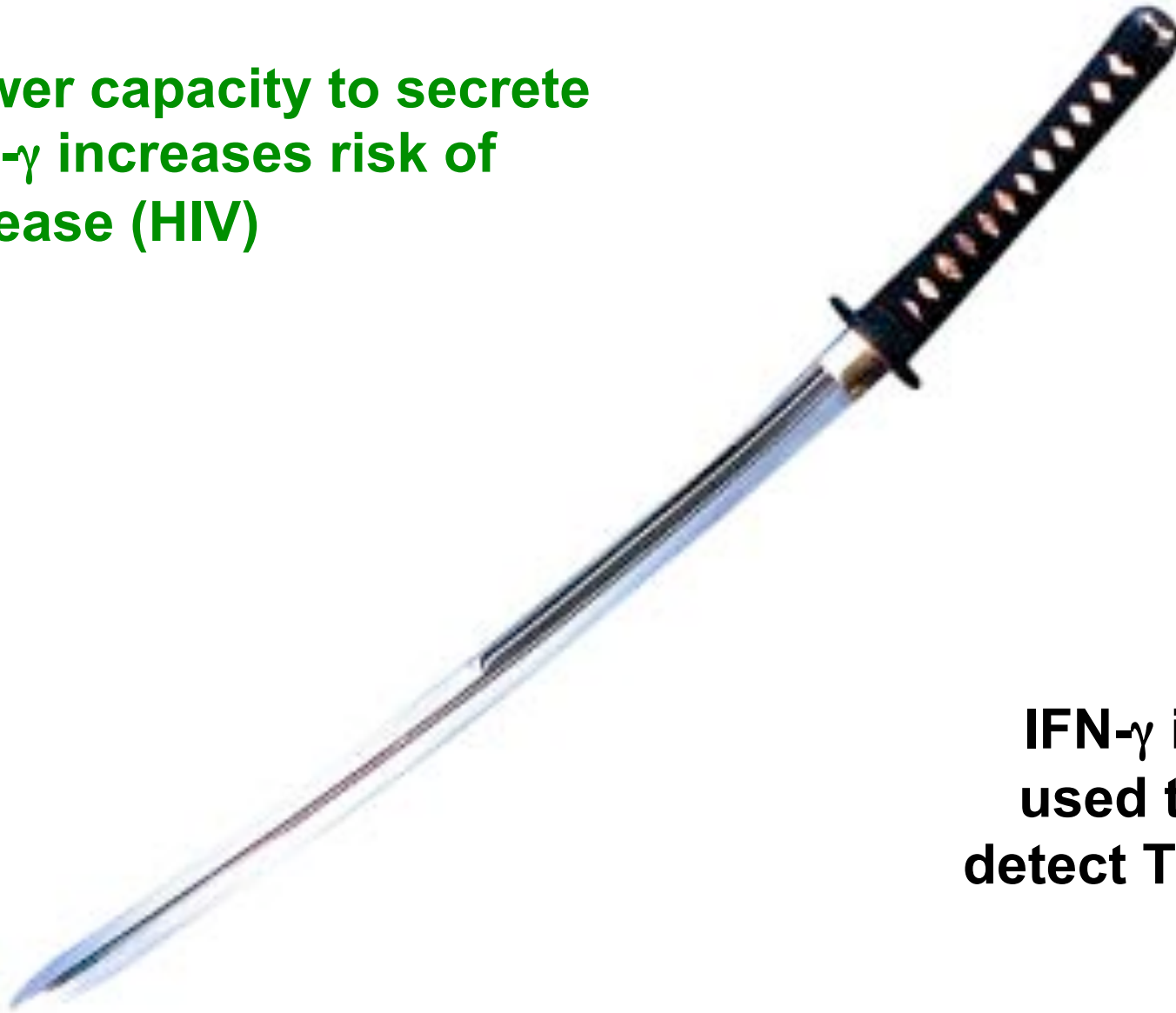
- CD4+ T cell IFN- $\gamma$  vital to containment
- IL-12 promotes CD4+ T cell IFN- $\gamma$
- HIV ..



# Is More IFN- $\gamma$ Better?

- Boosting IFN- $\gamma$  via vaccines in mice did not enhance protection – seems to depend on vaccine
- Patients with active disease have more IFN- $\gamma$

**Lower capacity to secrete  
IFN- $\gamma$  increases risk of  
disease (HIV)**



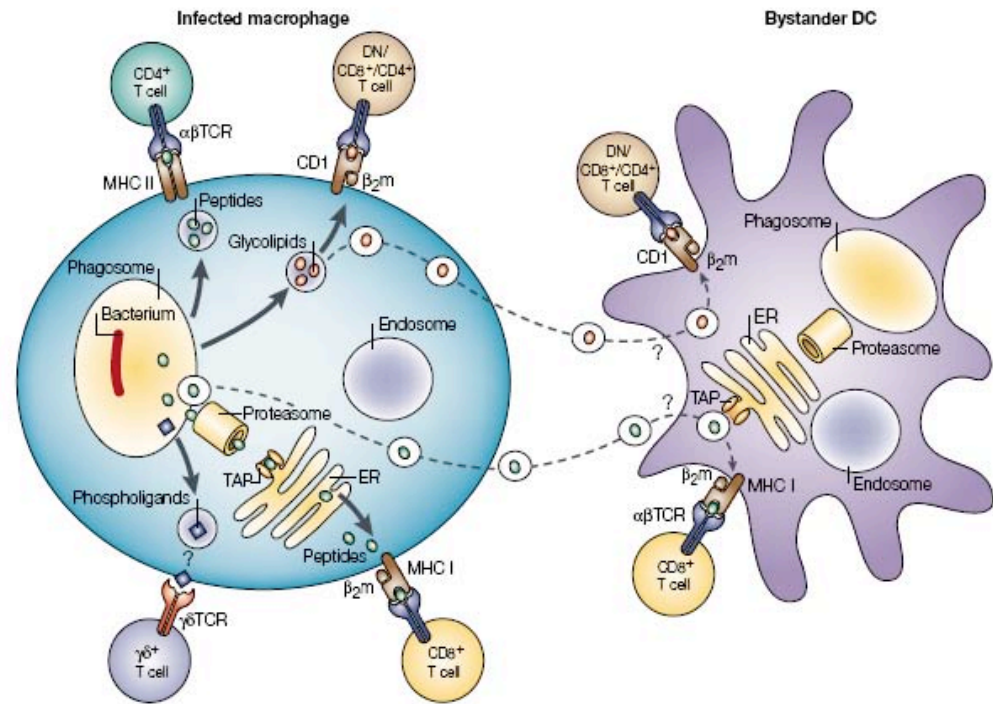
**IFN- $\gamma$  is  
used to  
detect TB**

# CD8+ T cells Also Participate

- Macrophage breakdown
- Dendritic cell presentation

- CD4 >> CD8

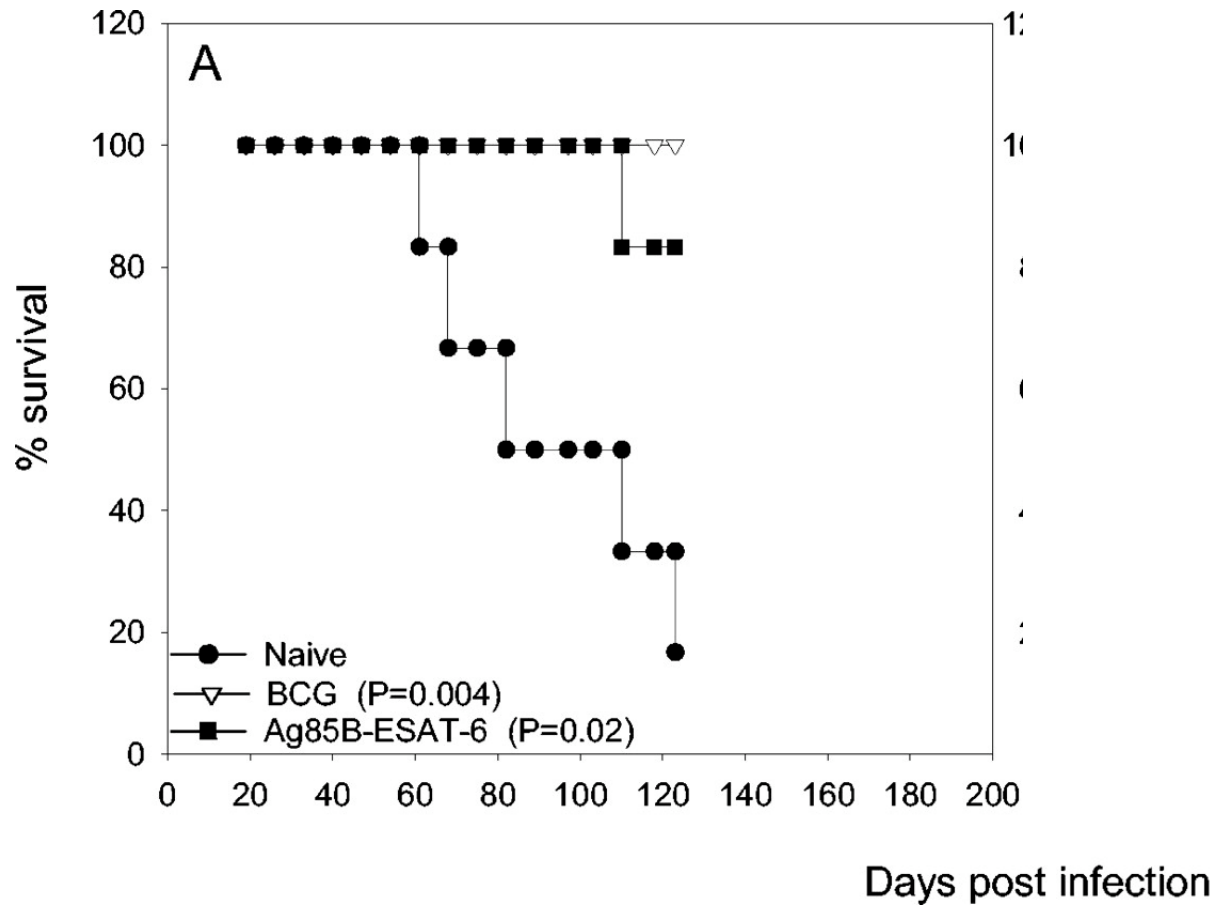
- ↓ latency?



# Other Responders

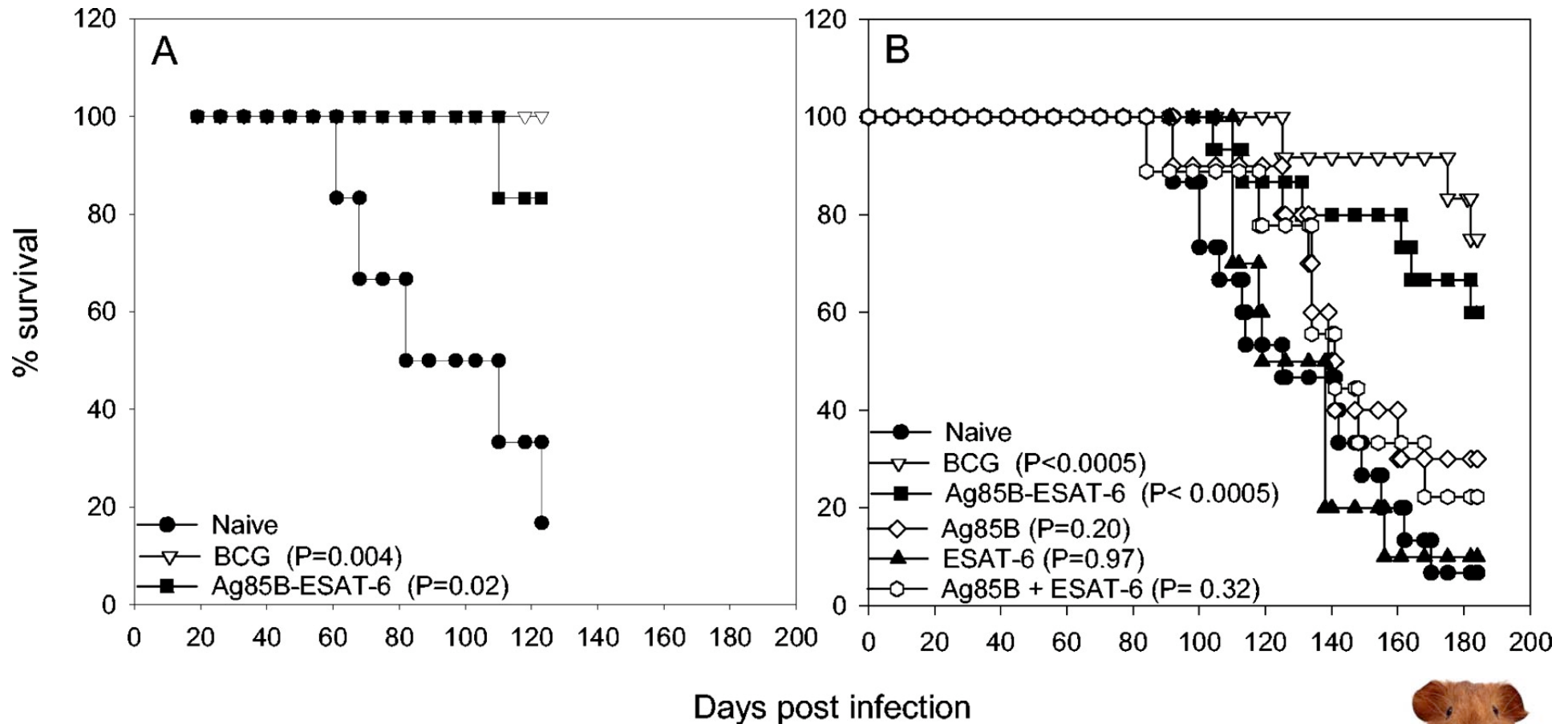
- $\gamma\delta$  T cells
  - Early responders
  - Modulate later conventional T cell responses
- NK and CD1-restricted NKT cells

# What are the protective antigens?

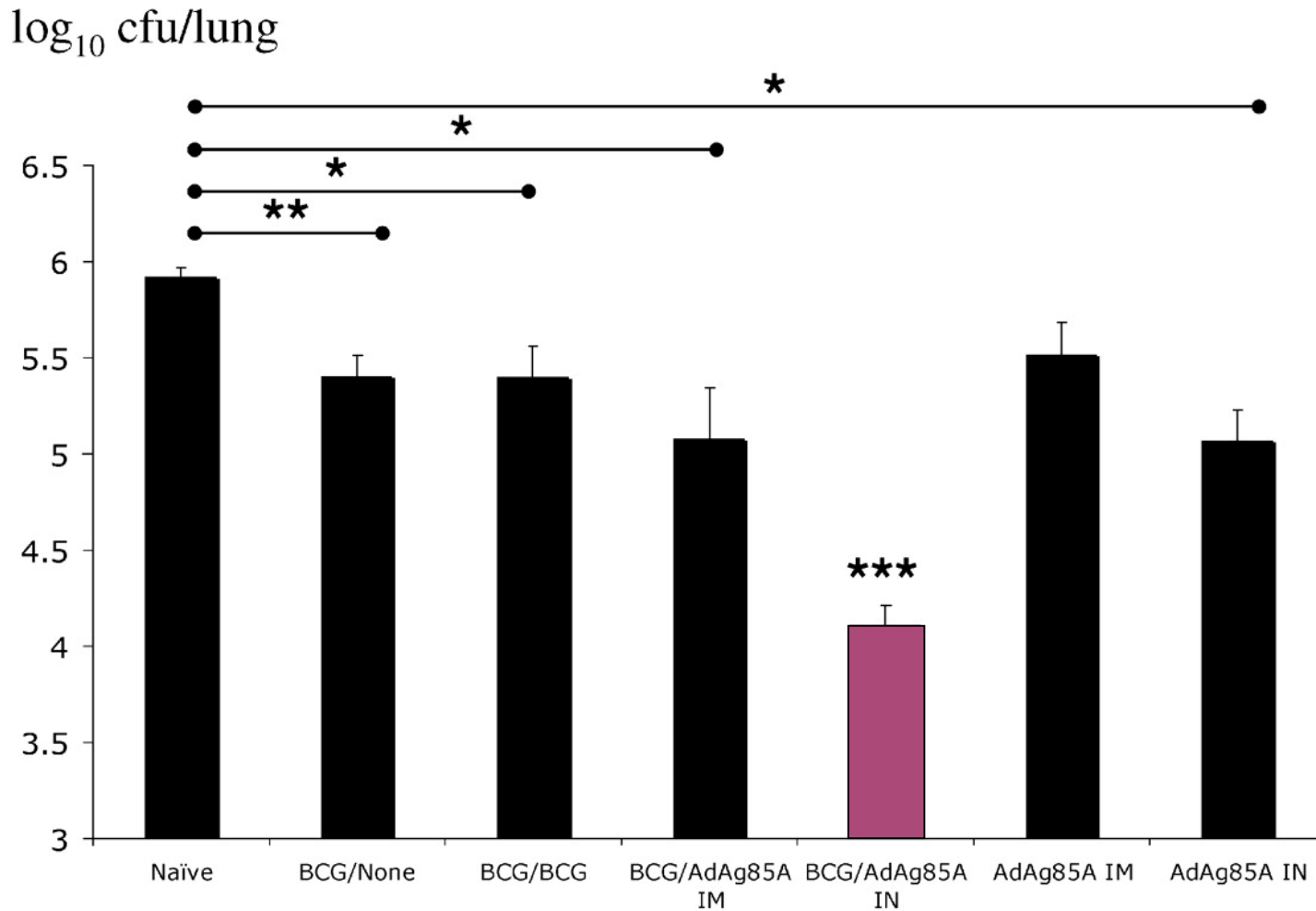




# What are the protective antigens?



# Exposure Impacts Responses

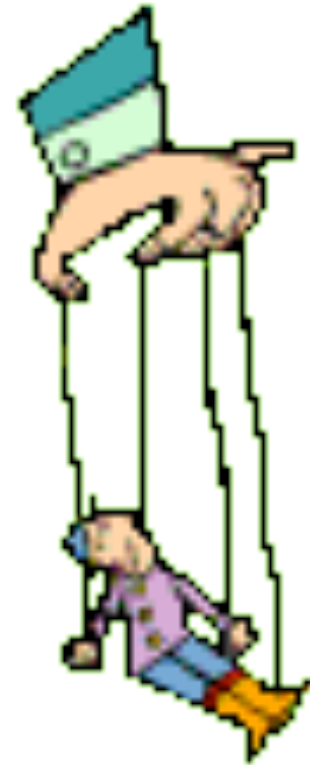


Intranasal vaccination against Ag85 induced more potent protection

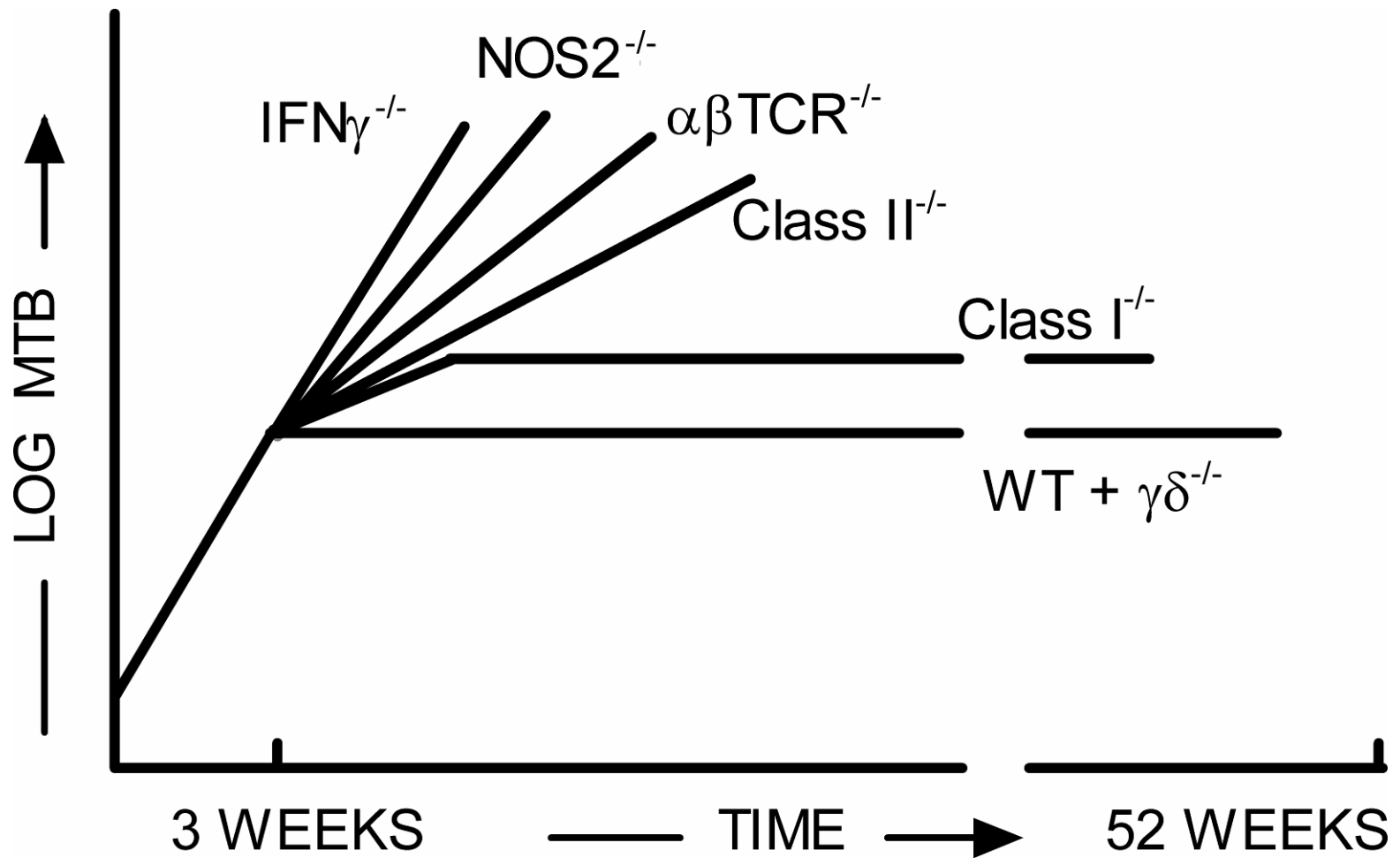


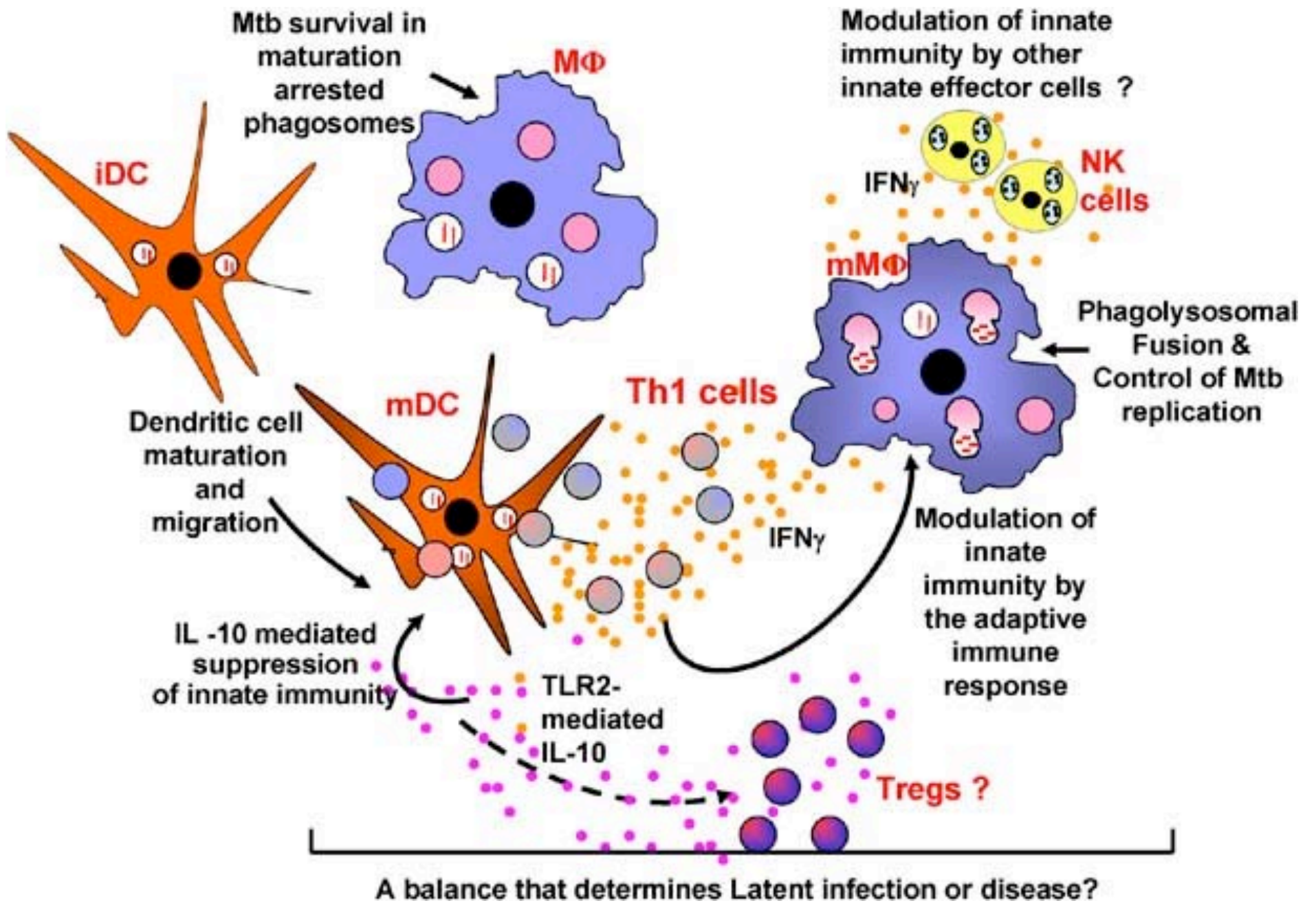
# Regulatory Influences

- Regulatory T cells
  - Suppression of inflammation
- T<sub>H</sub>17 populations
  - Recruitment of IFN- $\gamma$ + CD4+
- IL-10, IL-4, IL-23
  - Modulation of IFN- $\gamma$  responses



# A Mouse's Perspective

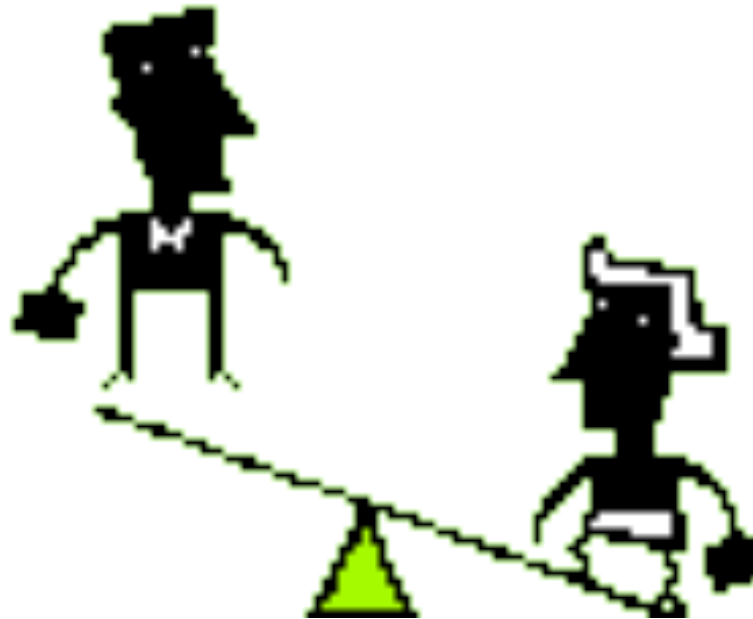






# Ways of Tipping the Scales?

**TB killing**



**TB growth**

# New Ways of Detecting TB?



# Summary

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- Innate immune responses set the tone (TLR2)
- Mycobacterial persistence in macrophages (D)
- Th1 and IFN- $\gamma$  needed for long term control
- Route is important
- Potential therapeutic role for modulating regulatory cell populations and cytokines



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