

Double Trouble:
Consequences of Immune Cell
Mis-Recruitment following Multiple
Viral Challenges

Christine Matullo
Glenn Rall

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Overview

Question

Model

Outcomes

Significance

Opportunity

Lunch

**Can peripheral viral infections--
or the immune responses to those infections--
contribute to CNS disease?**

**CNS diseases of
unknown etiology**

- Multiple sclerosis
- Autism
- Alzheimer's
- Lou Gehrig's disease/ALS
- Parkinson's

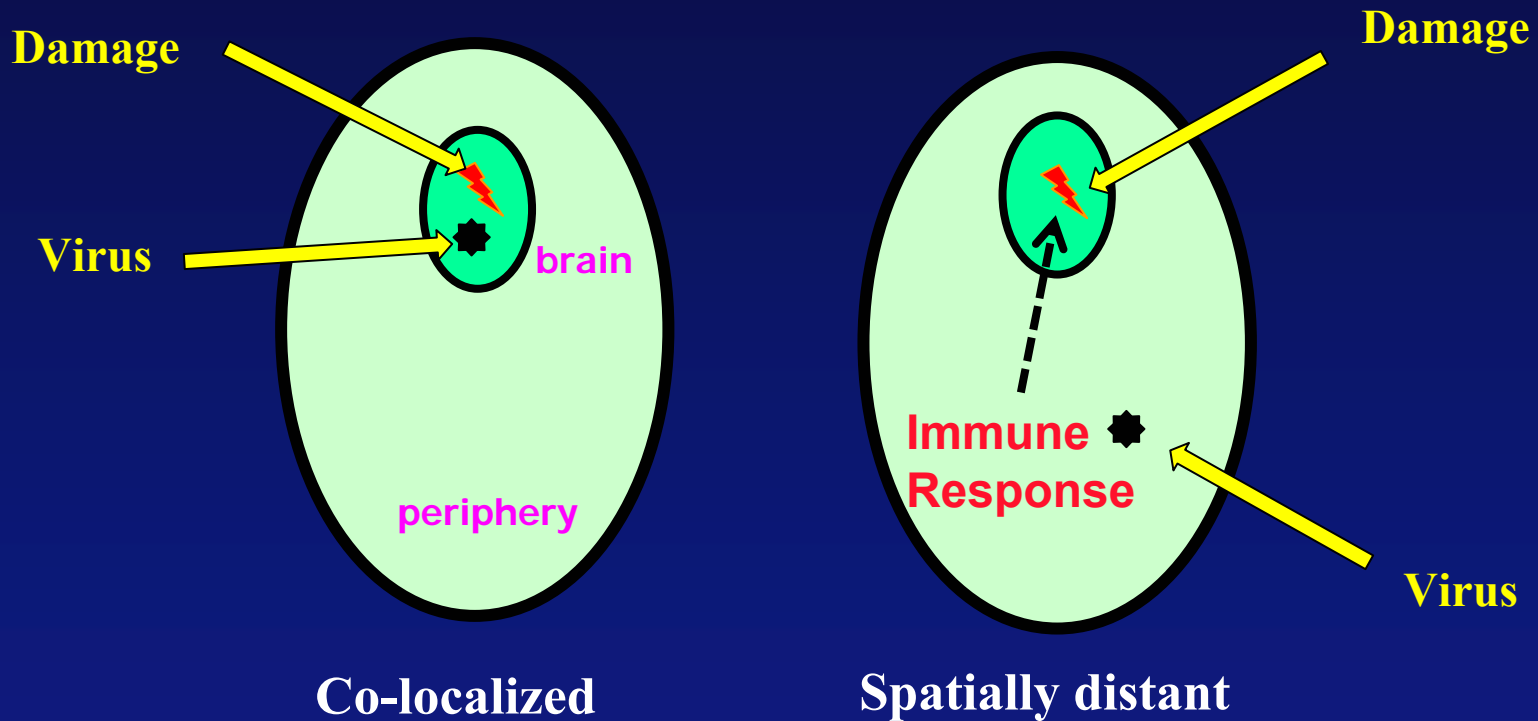


**Each possess “hallmarks” of
infection:**

- Chronic inflammation
- Relapsing/remitting
- Timing

*...but no viruses have been
detected at the sites of damage*

Putative roles for viruses in CNS disease



Outline

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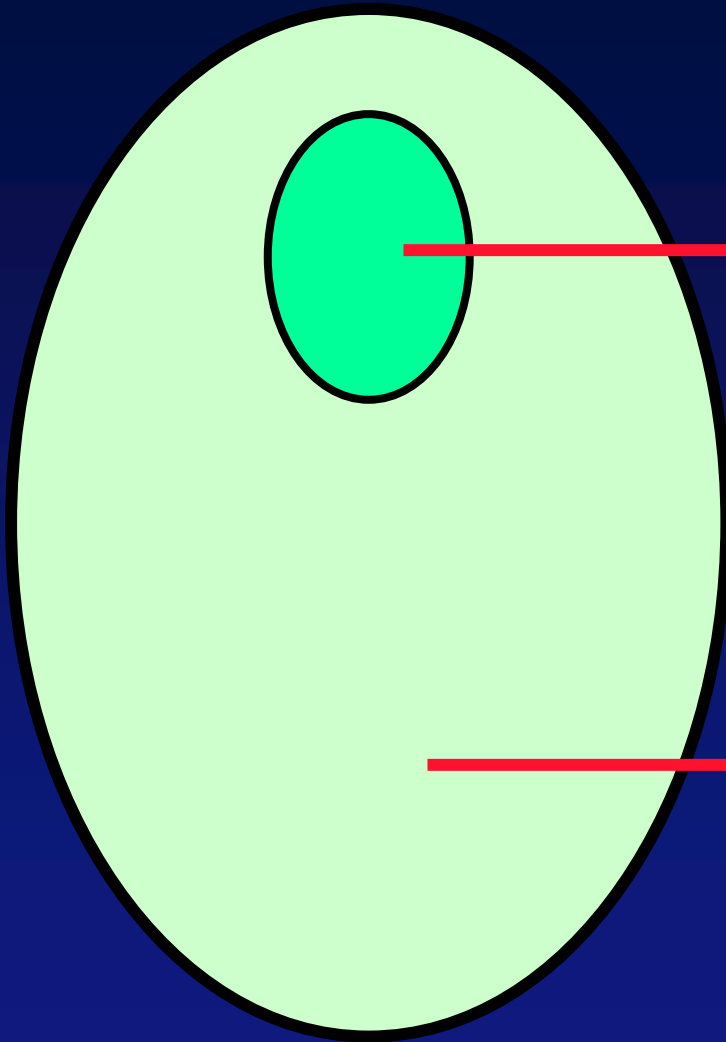
Two-Virus Model

Recruitment Signal:

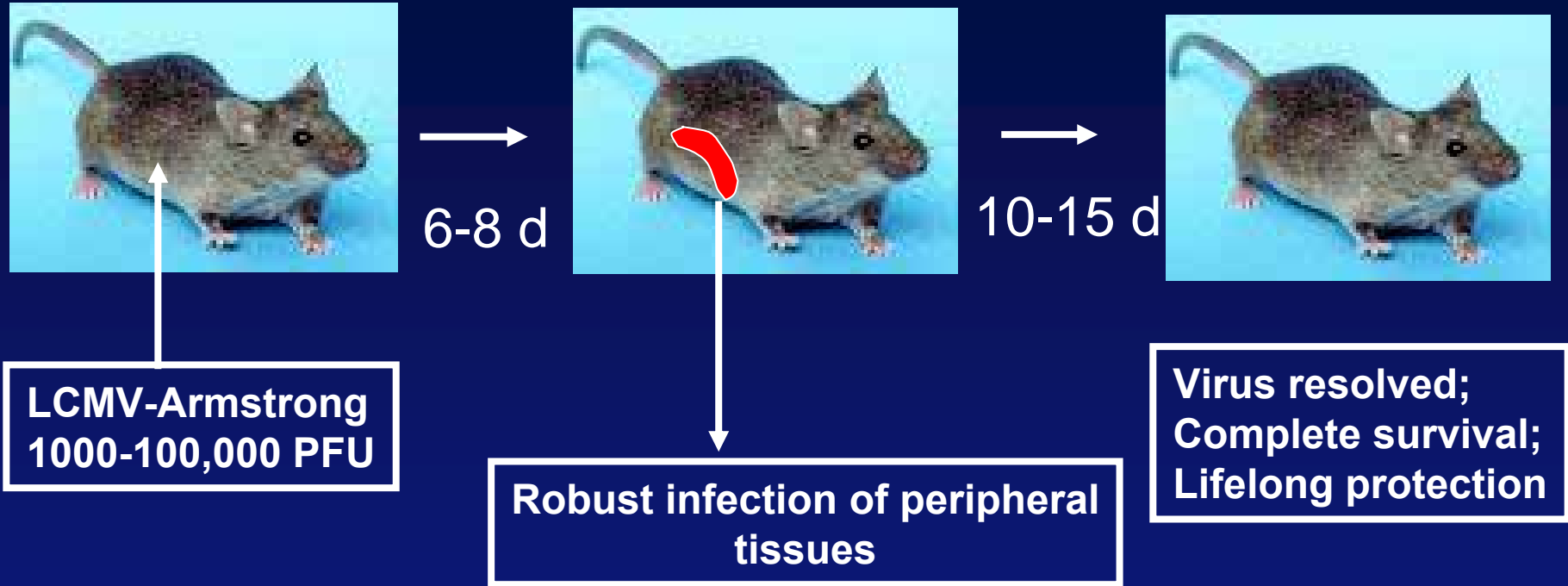
Measles Virus

Peripheral Challenge:

Lymphocytic
Choriomeningitis Virus



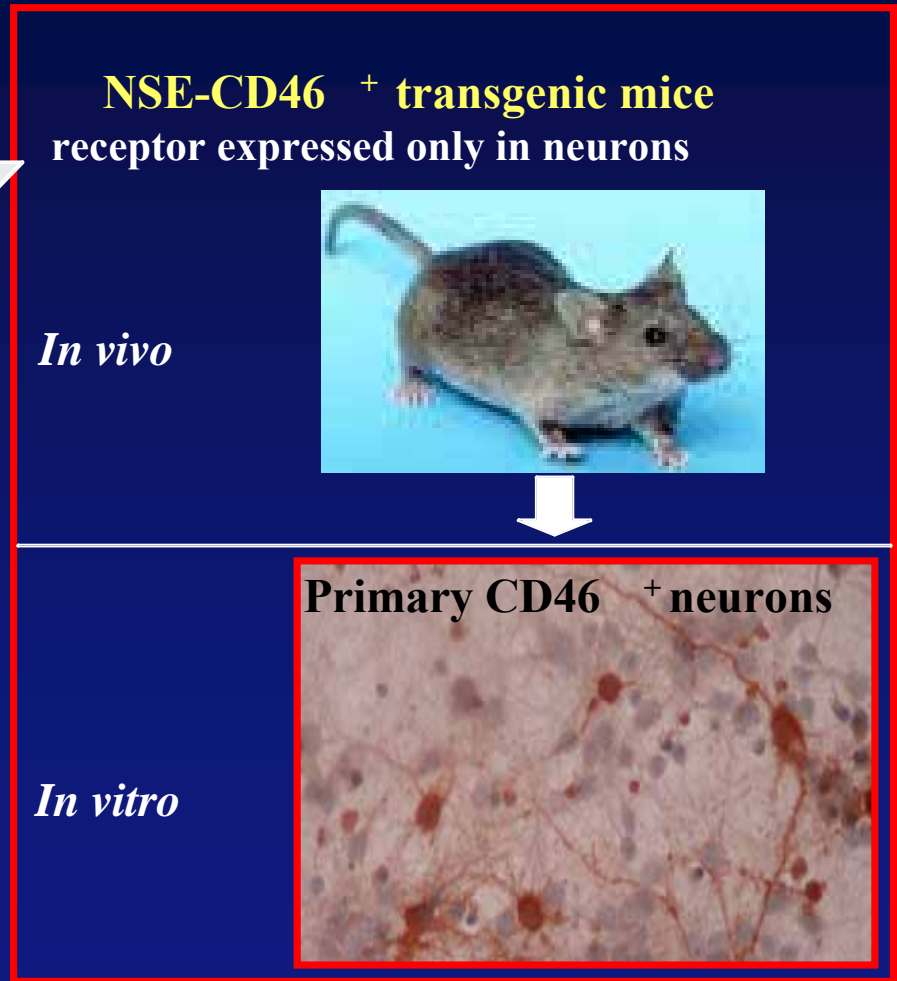
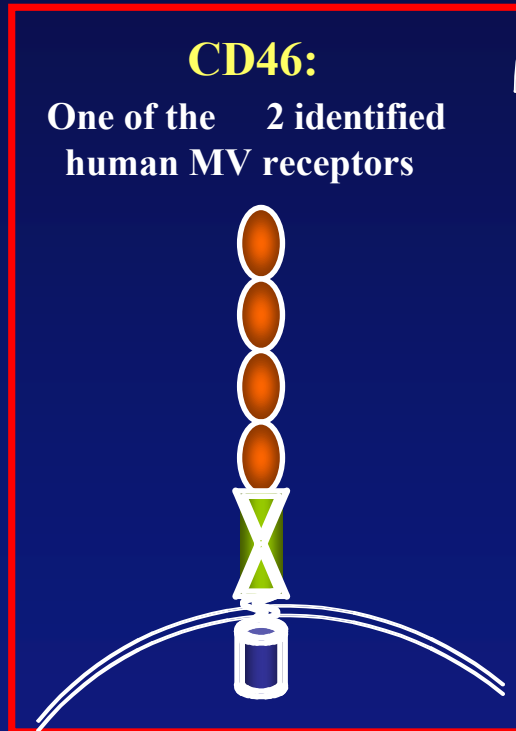
LCMV: Peripheral Challenge



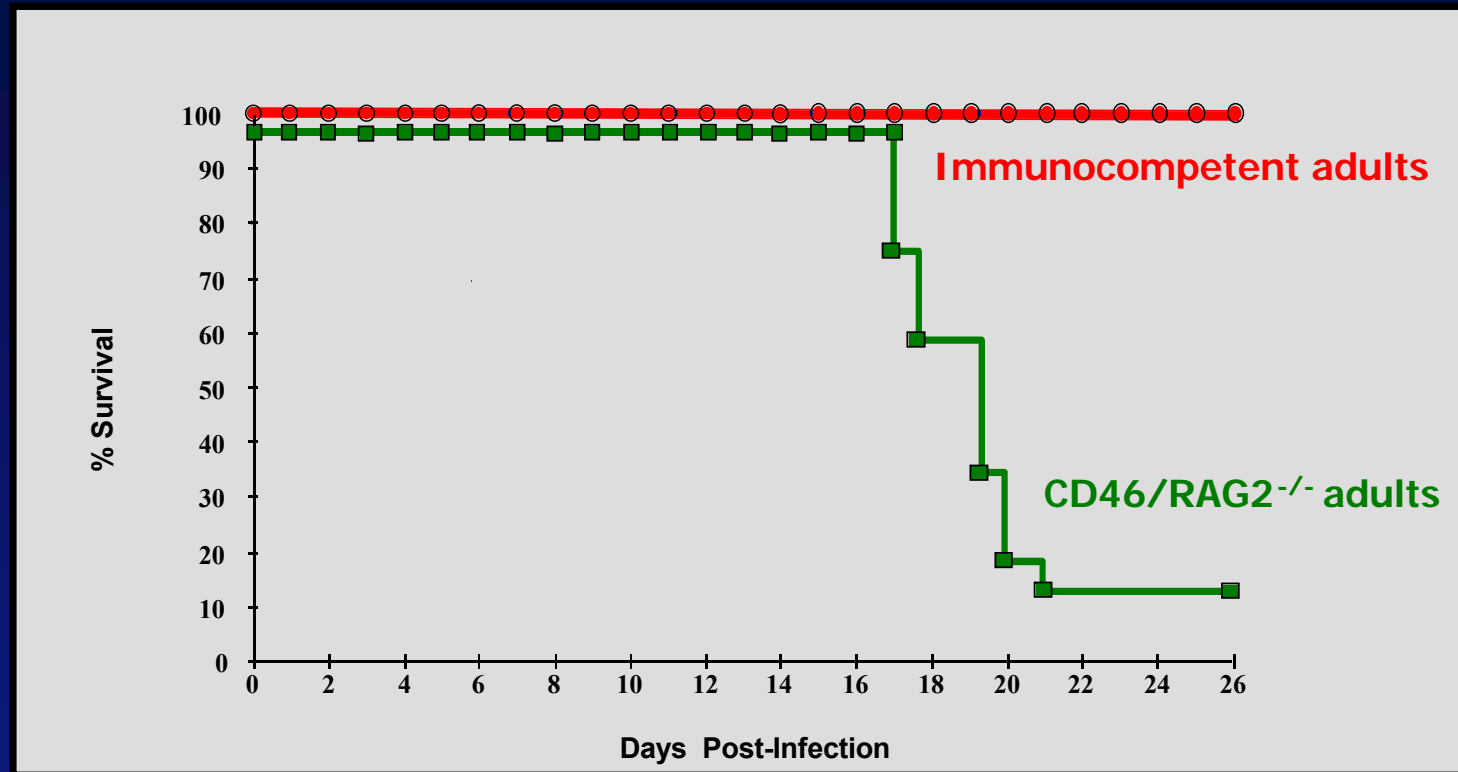
NO CNS INVOLVEMENT

Model of neuronal measles virus infection

NSE-CD46⁺ transgenic mice



Immune-Mediated Protection of MV-infected NSE-CD46 Transgenic Mice



NO PERIPHERAL INVOLVEMENT



Route

Site

Immune
Profile

Outcome

i.c./i.n.

CNS

CNS:
CD4, CD8

Periphery:
none

100%
Survival



i.p.

periphery

CNS:
none

Periphery:
CD8 > CD4

100%
Survival

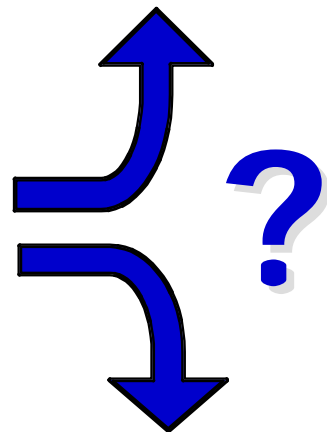
* Peak immune response for both viral infections: 6-10 dpi

Patterson et al, 2001

Khanolkar, Fuller, & Zajac, 2002



Immune response
tissue-restricted



Immune response
homogenized

Outline

Question

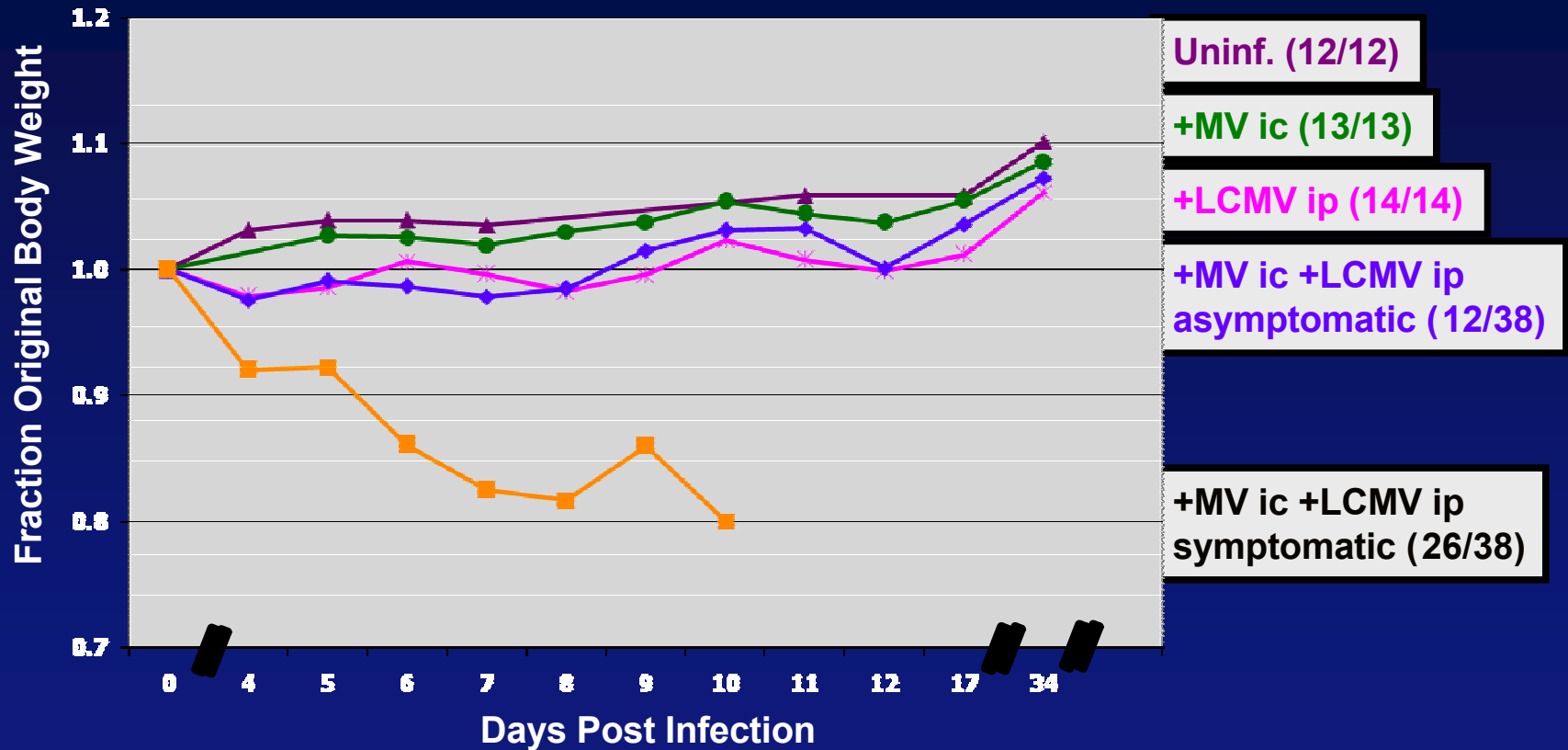
Model

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Pathogenesis in doubly infected mice associated with extensive weight loss



-Dose level independent

-Neuropathology is independent of any viral variable (e.g., tropism, clearance rate, virus level)

Increased CD8⁺ T-cell infiltration into brains of doubly infected mice

+ MV

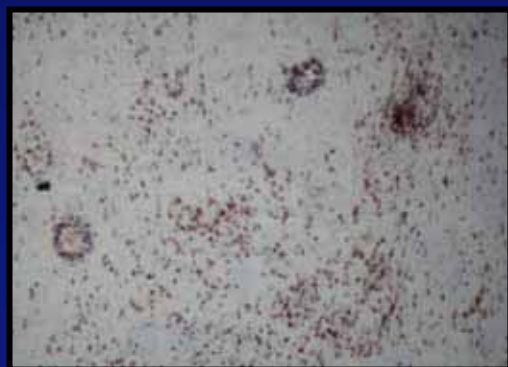
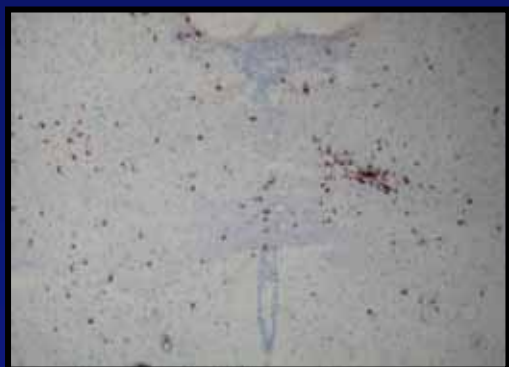
+ LCMV

+ MV + LCMV

α -CD4

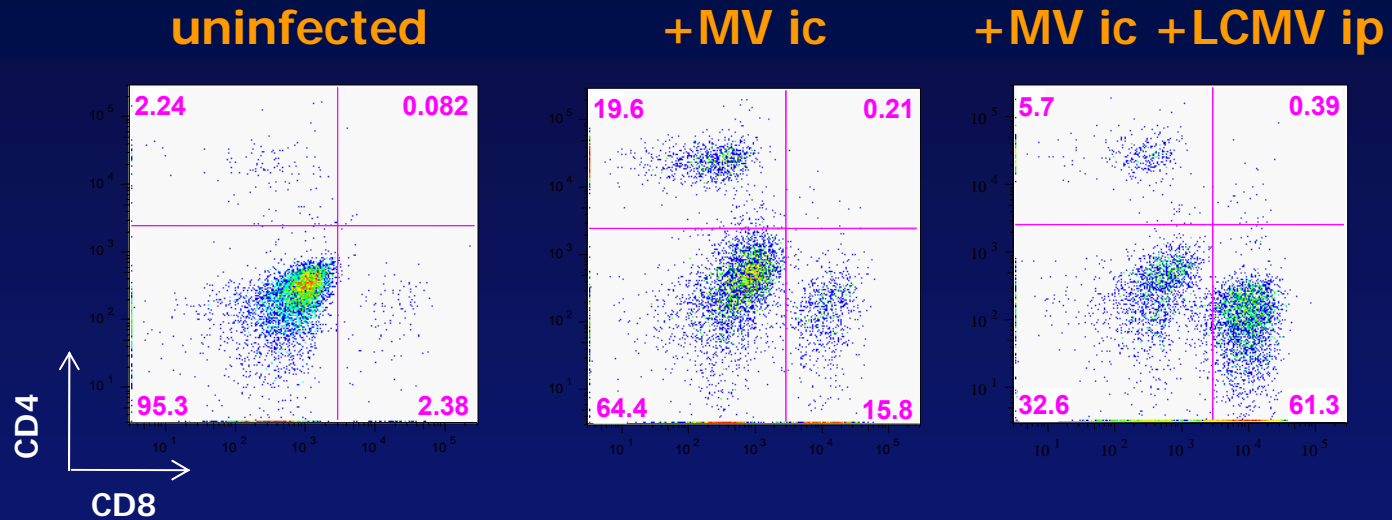


α -CD8



Quantitation?

>10-fold increase in CD8+ T-cell infiltration into brains of doubly infected mice



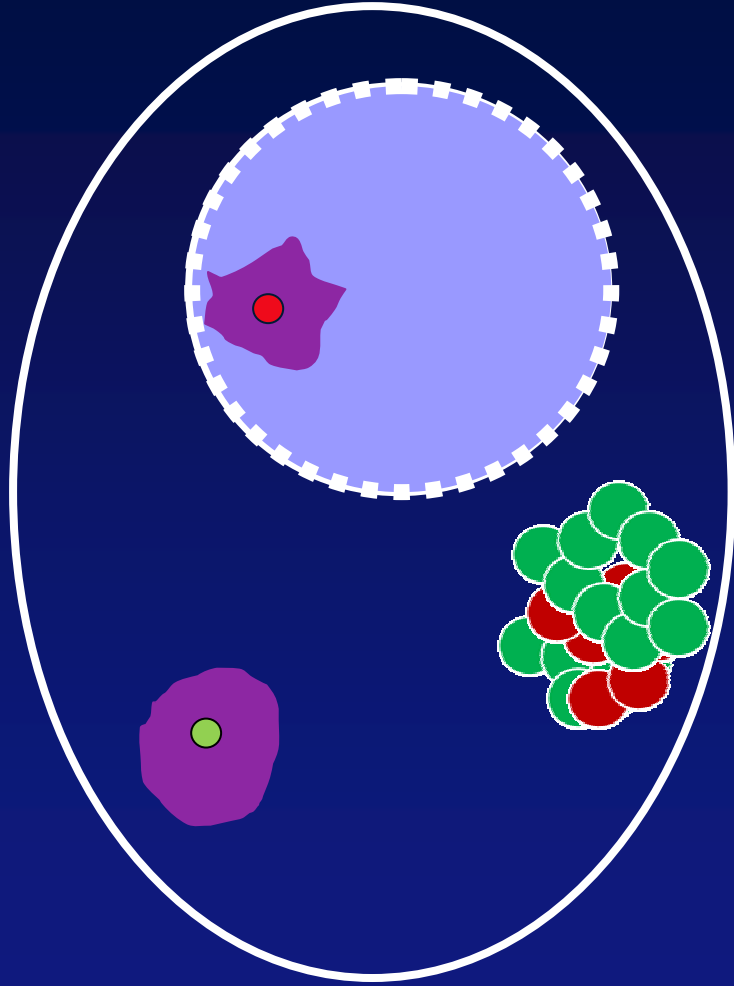
Percent CD8+

Total CD8+ count

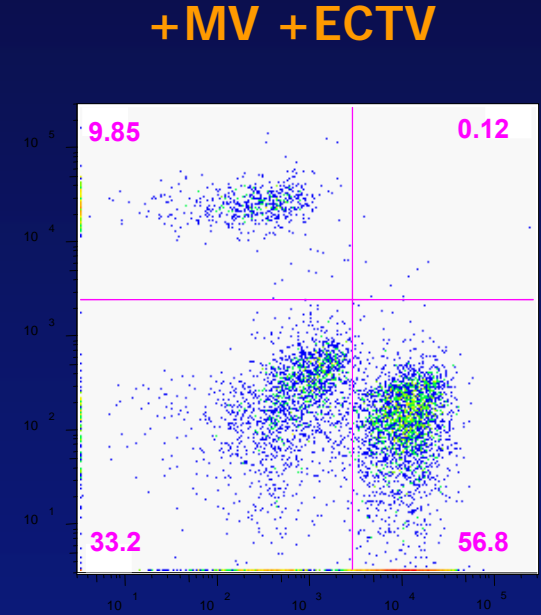
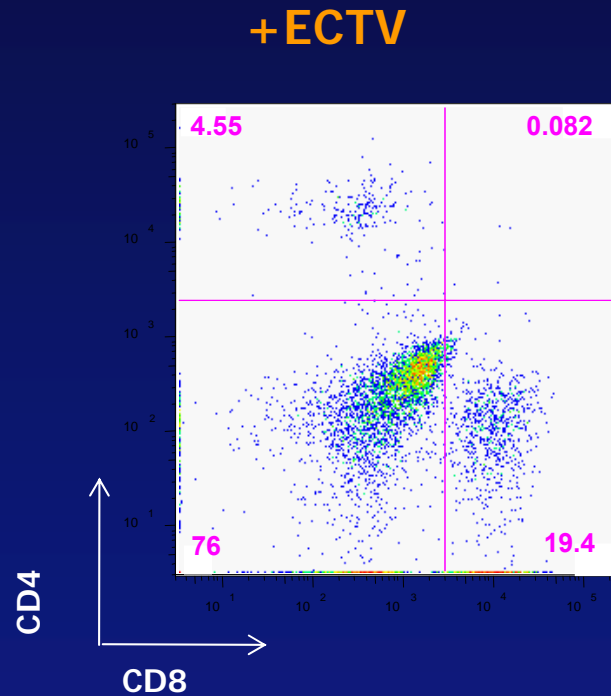
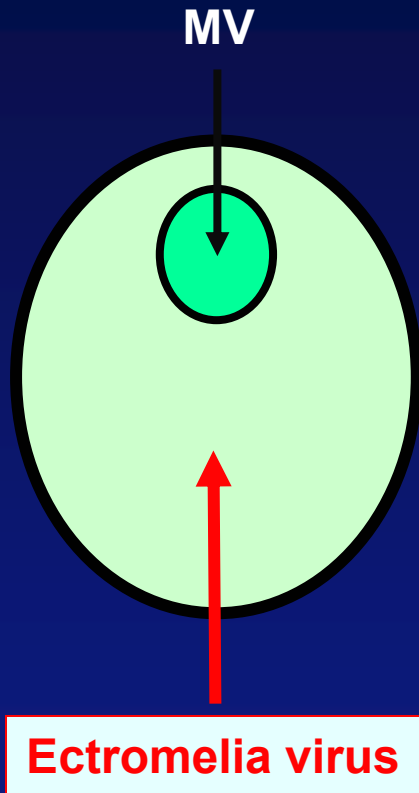
Percent CD8+	2.2 %	14.7 %	56.7 %
Total CD8+ count	469	14,050	170,518
	n=15	n=28	n=37

$p < 0.0001$

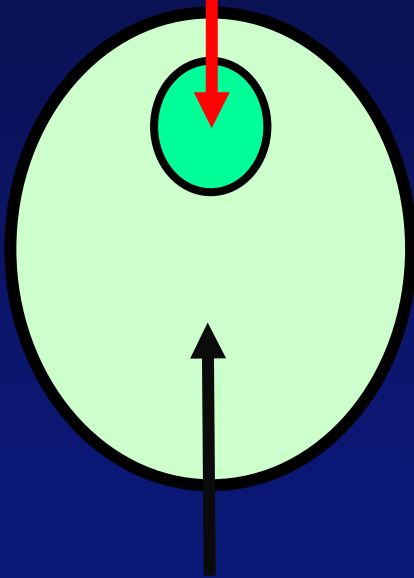
About 60% of these CNS-infiltrating T cells are of LCMV specificity!



Is this unique to this model system, or can other pathogenic combinations result in a similar outcome?



**Poliovirus, IC
(using PVR transgenic mice)**

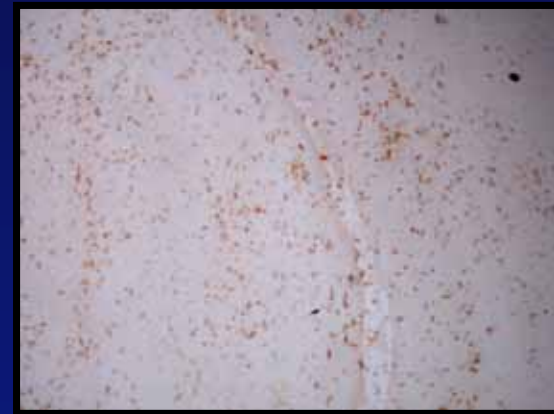


α -CD8

+PV ic



+PV ic +LCMV ip



LCMV

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I. Direct link to human disease: midbrain herniation

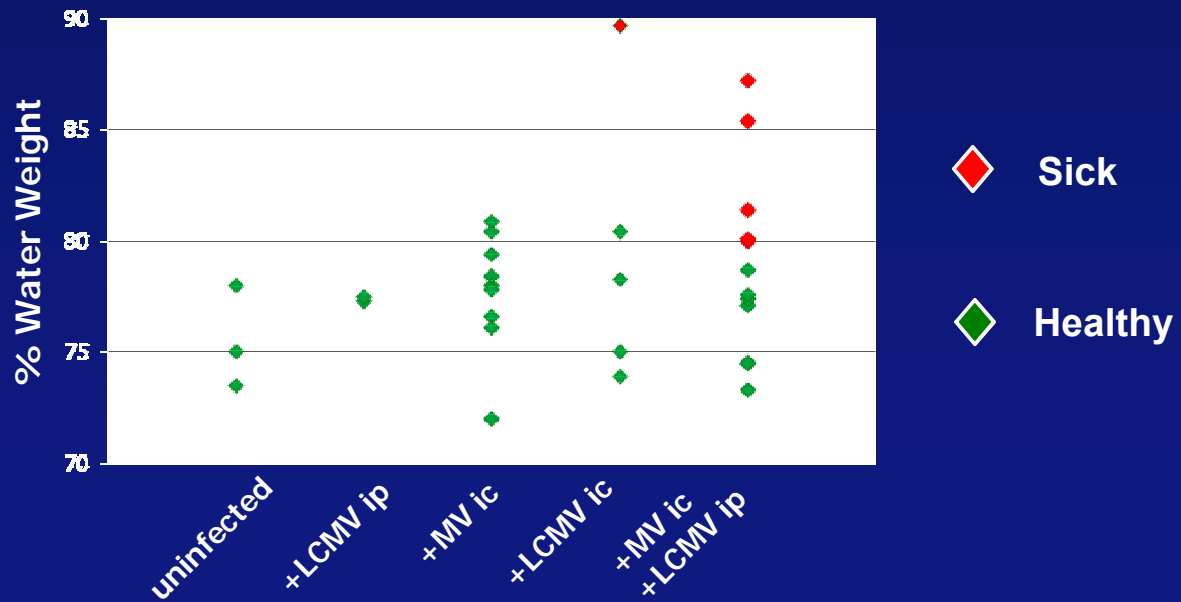
- Occurs in humans following meningitis/encephalitis, brain tumor, trauma (that is: increased intracranial pressure)--very precipitous death, often of unknown cause**
- As a result of edema, midbrain pushed through foramen into spinal cord**
- Because the origin of the optic nerves connects to the basal midbrain, sudden, unilateral pupillary dilation is the key clinical indicator of this condition**

Pupillary Dilation and Edema

MV alone



MV and LCMV



I. Direct link to human disease: midbrain herniation

--Occurs in humans following meningitis/encephalitis, brain tumor, trauma (that is: increased intracranial pressure)--very precipitous death, often of unknown cause

--As a result of edema, midbrain pushed through foramen into spinal cord

--Because the origin of the optic nerves connects to the basal midbrain, sudden, unilateral pupillary dilation is the key clinical indicator of this condition

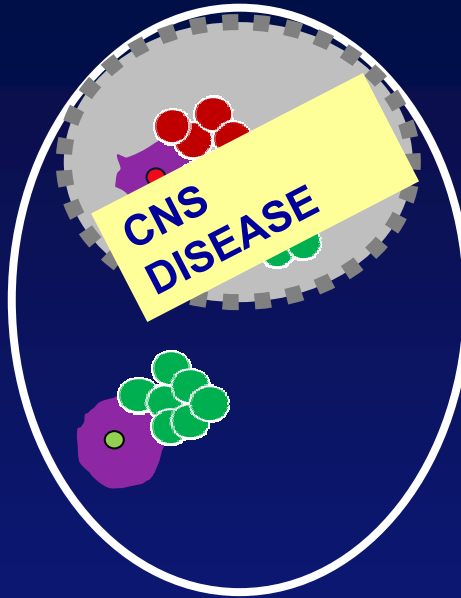
--A sense of the frequency:

Cerebral malaria: 300-500 million cases annually worldwide

>1 million deaths

50-75% of these (mostly children) show signs of midbrain herniation

II. Broadening how we think about human CNS disease



Potential role for peripherally triggered immune responses in CNS diseases with inflammatory component:

Brain tumors, MS, ALS, Parkinson's, Alzheimer's, stroke

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I. In theory, ANY immune stimulus could contribute to immune cell mis-recruitment

Viruses

Bacteria

Parasites

Allergens

Autoimmune diseases

Vaccinations

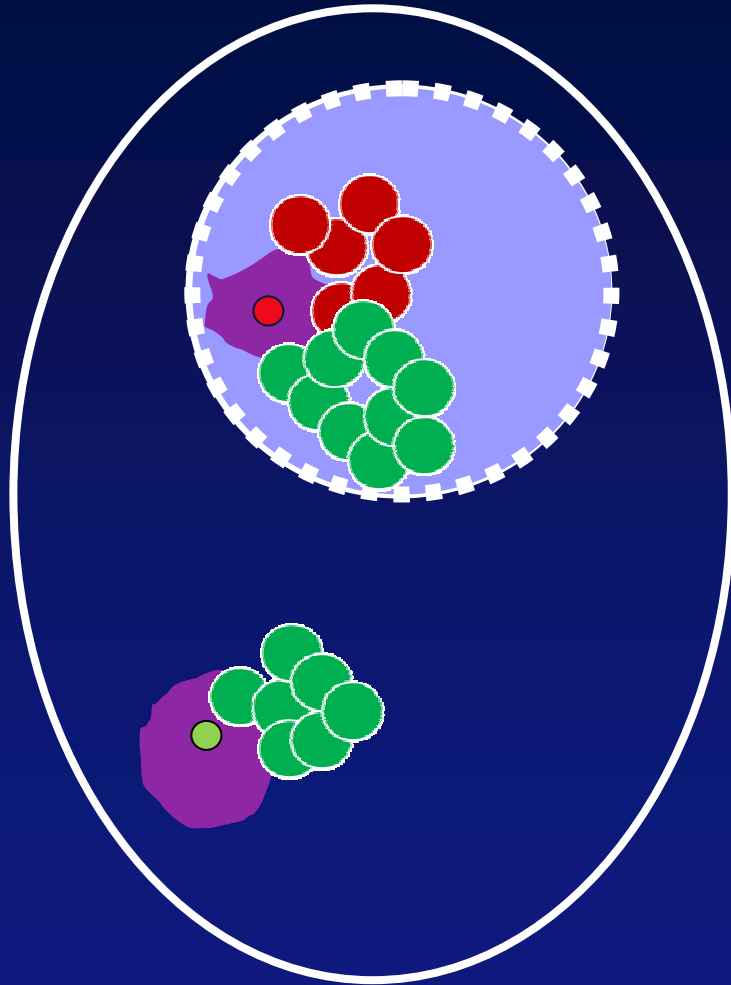
Graft rejection

Tumor

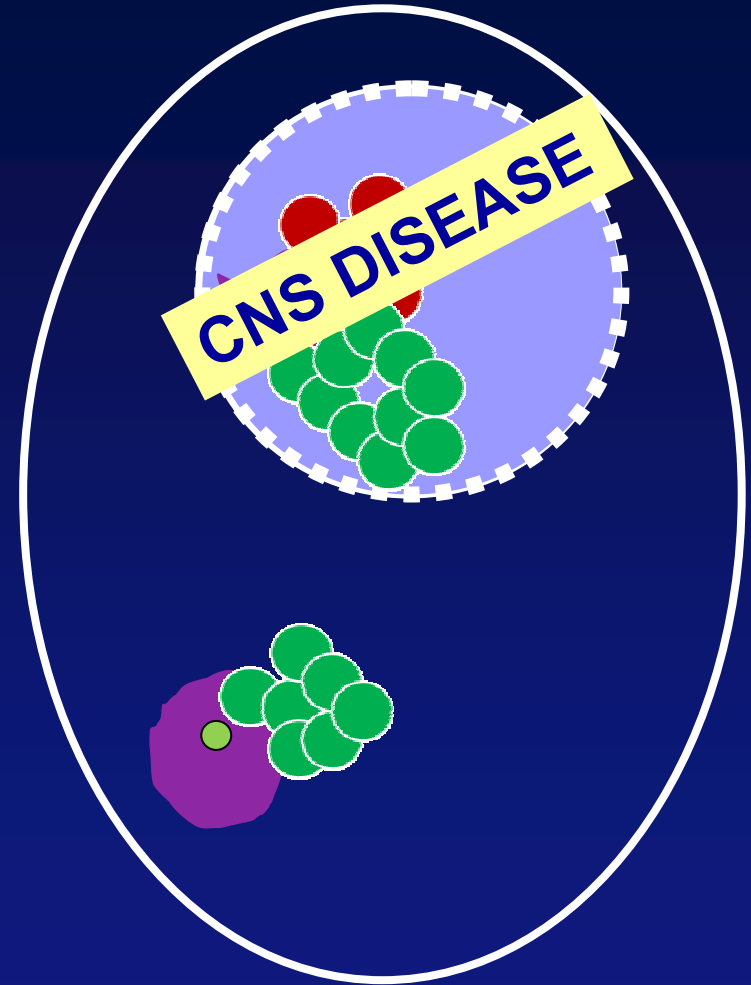
Is there a protective/ameliorative role for anti-inflammatory drugs in CNS diseases?

Development of complex animal models to understand complex human diseases

II. Patient to patient variability



~50%



~50%

Thanks...

Former:

Diane Lawrence
Catherine Patterson
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Mindy Vaughn
Alec Belman
Eric Callahan
Michael Birnbaum
Jaimy Joy
Nina Makhortova
Lisa Gechman

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Lauren O'Donnell
Jazz Skipworth
Anna Vorobyeva
Kevin O'Regan
Steve Conway

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John Wherry, Wistar
Mark Curtis, TJU

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- FACS facility
- qRT-PCR facility
- MRI facility

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