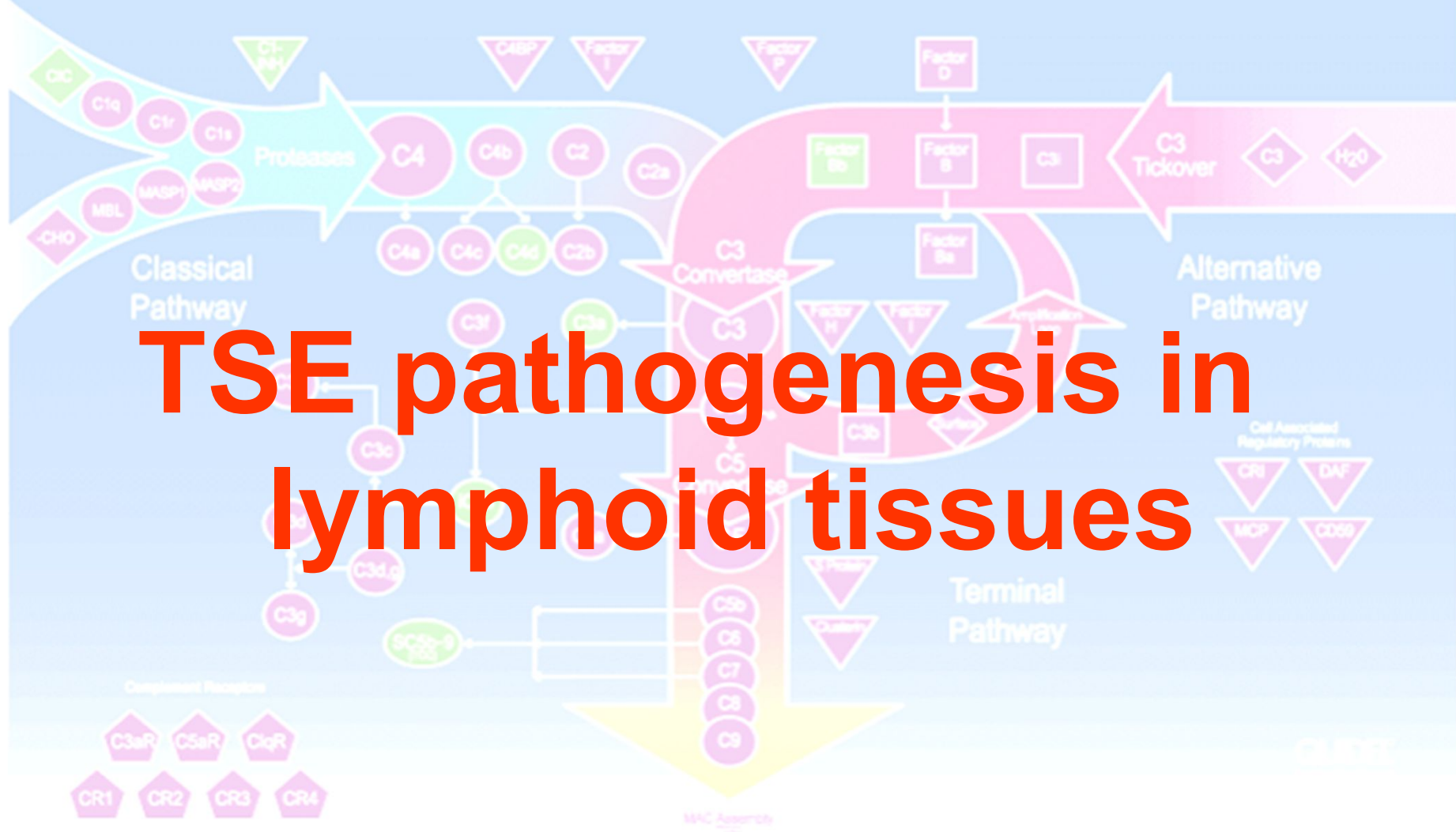


# Complement System

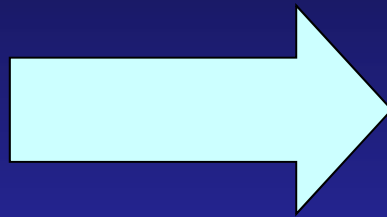


# Transmissible spongiform encephalopathies

Disease	Species
Creutzfeldt-Jakob disease	human
Kuru	human
Scrapie	sheep & goats
Bovine spongiform encephalopathy	cattle
Feline spongiform encephalopathy	cats
Chronic wasting disease	deer & elk
Transmissible mink encephalopathy	mink

# TSEs and the prion protein, PrP

**PrP<sup>c</sup>**



**PrP<sup>Sc</sup>**

**Soluble**

**PK sensitive**

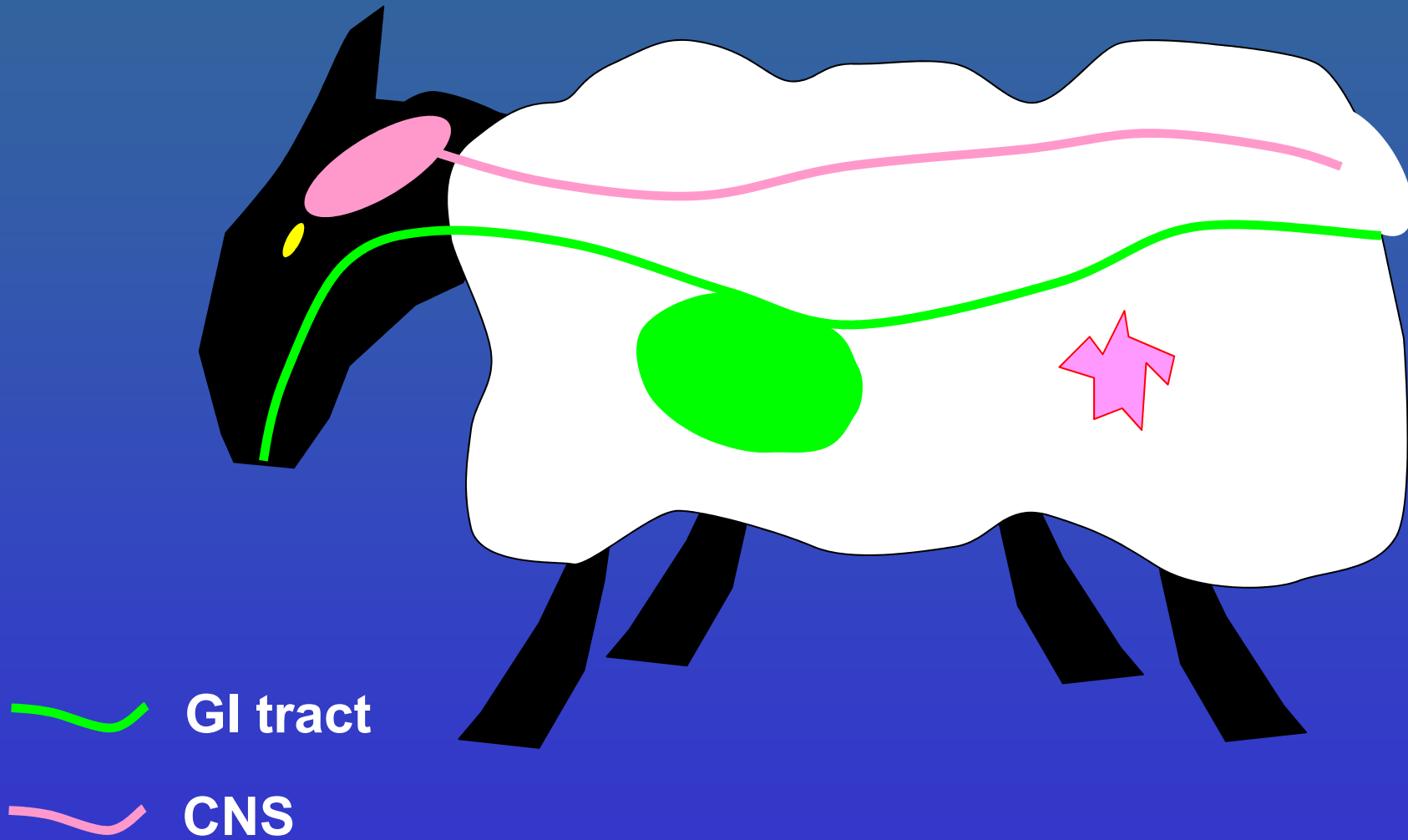
**Cell membrane**

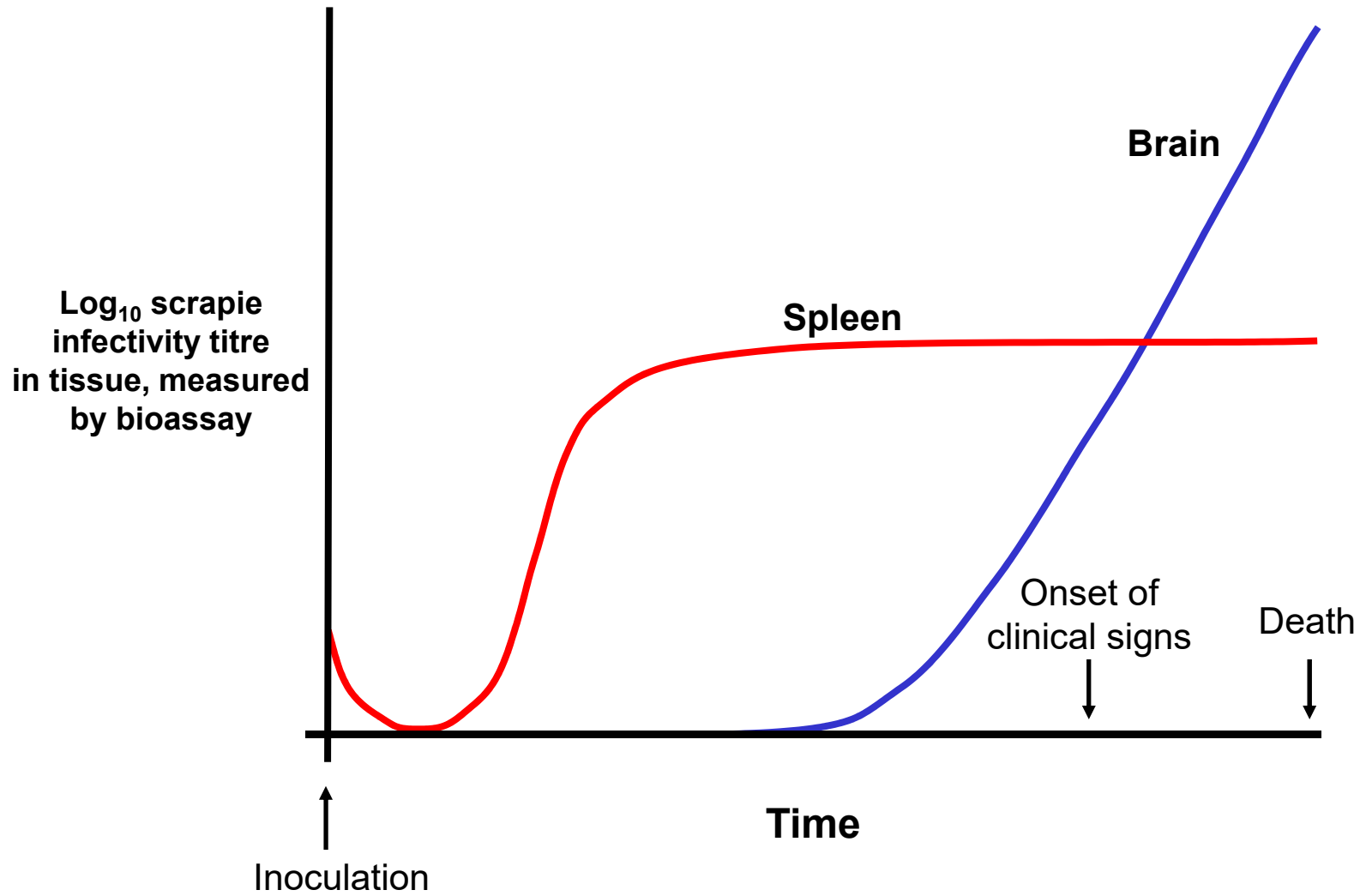
**Insoluble**

**Relatively PK resistant**

**Fibrillar**

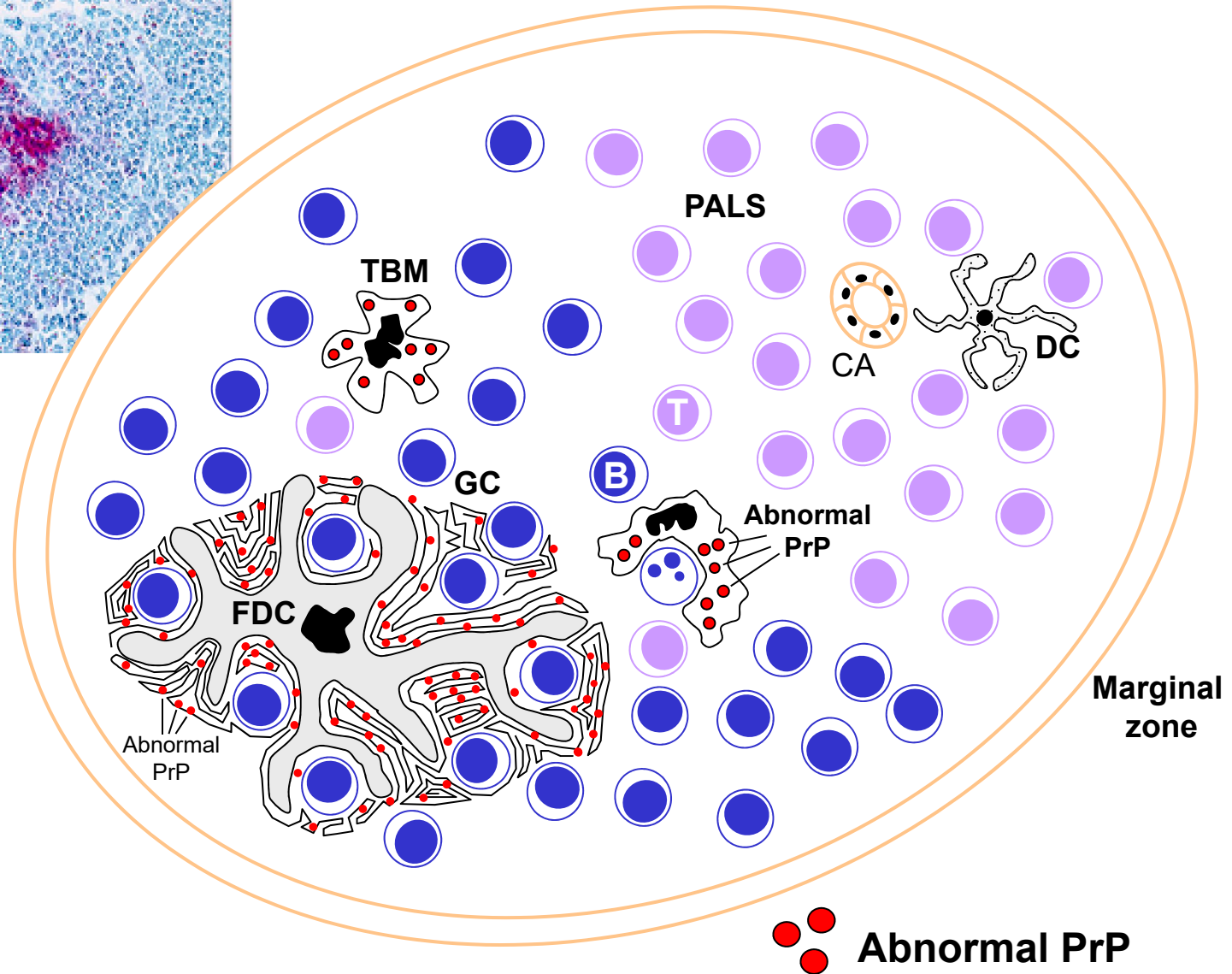
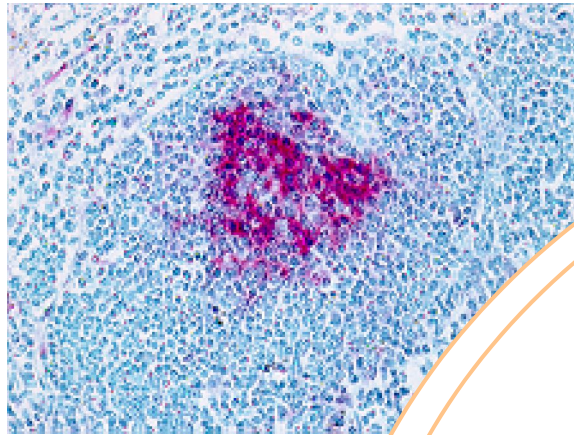
# How do TSEs reach the brain?



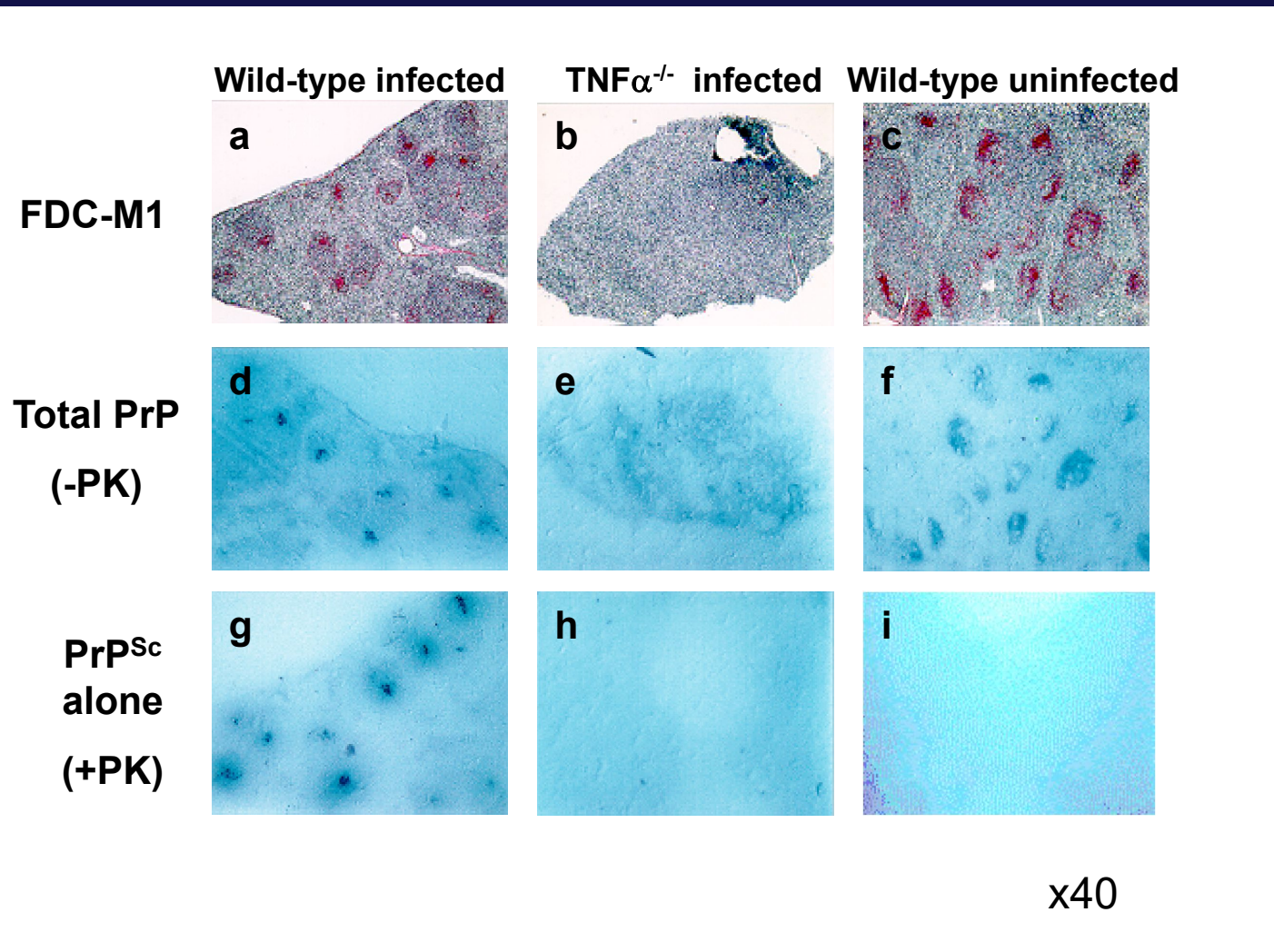


**Accumulation of infectivity in the spleen and brain following peripheral challenge of mice with scrapie**

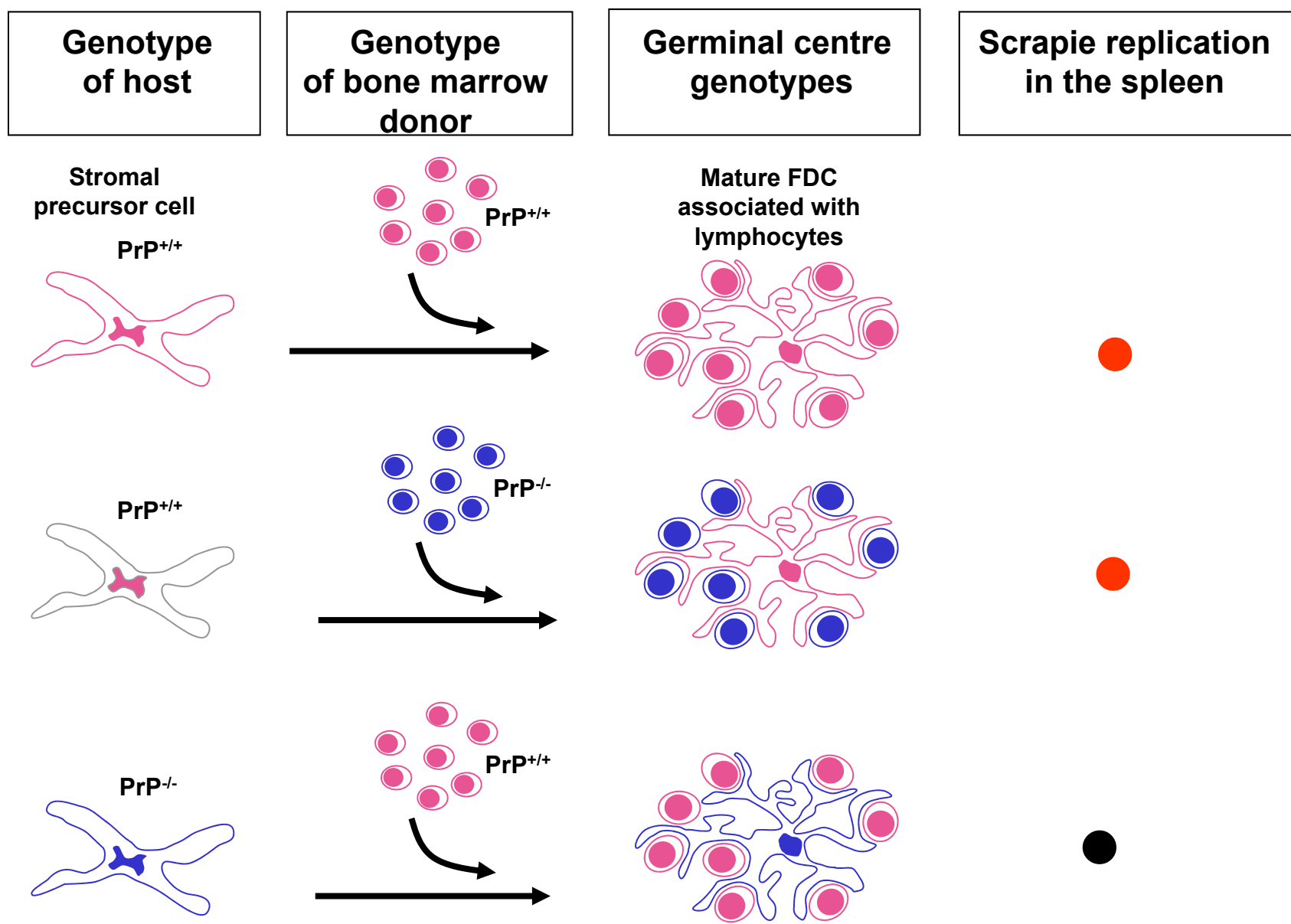
# Sites of abnormal PrP accumulation in the spleen



# PrP<sup>Sc</sup> accumulates in direct association with FDCs

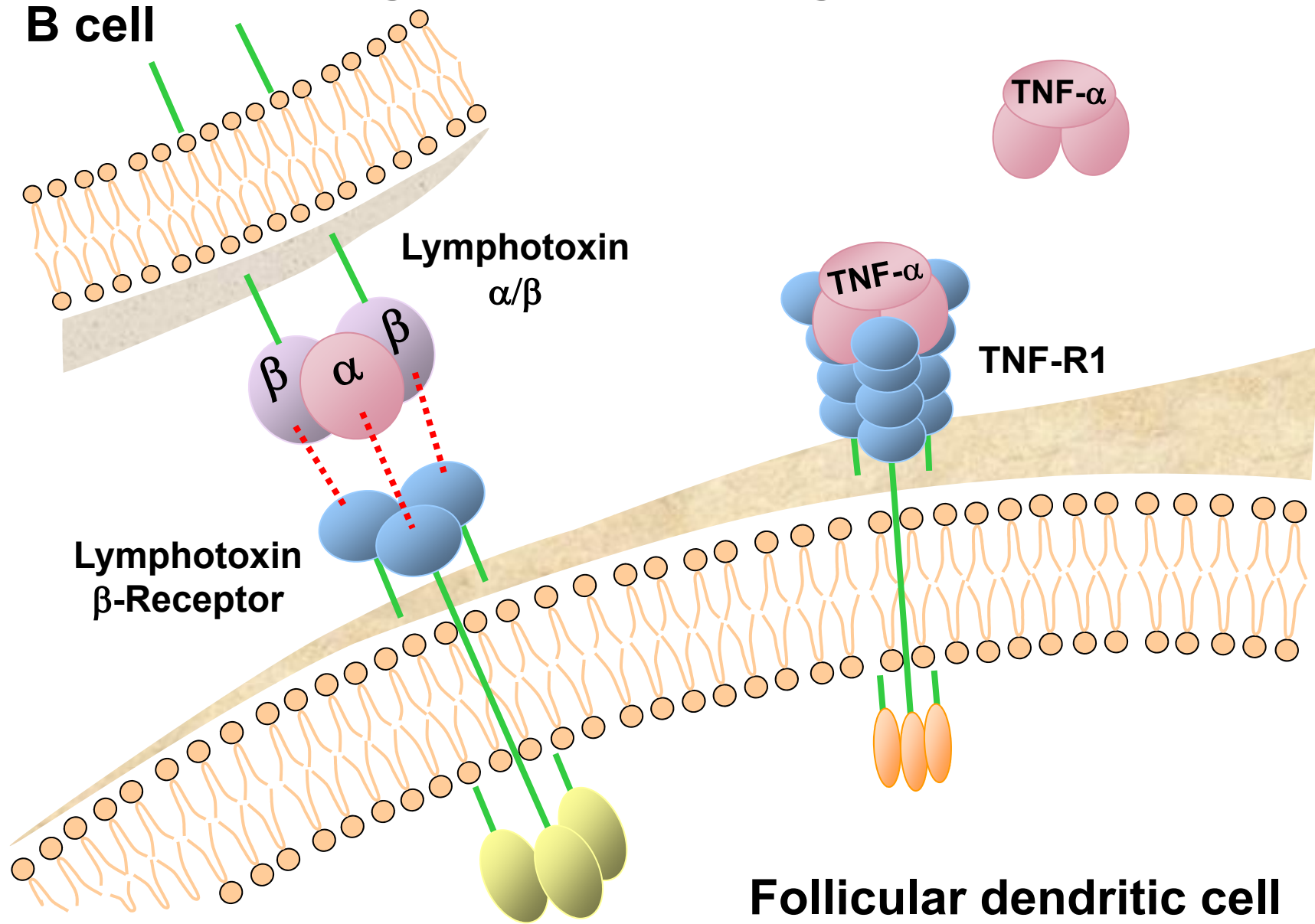


# ME7 scrapie replication in lymphoid tissues depends on PrP-expressing FDCs

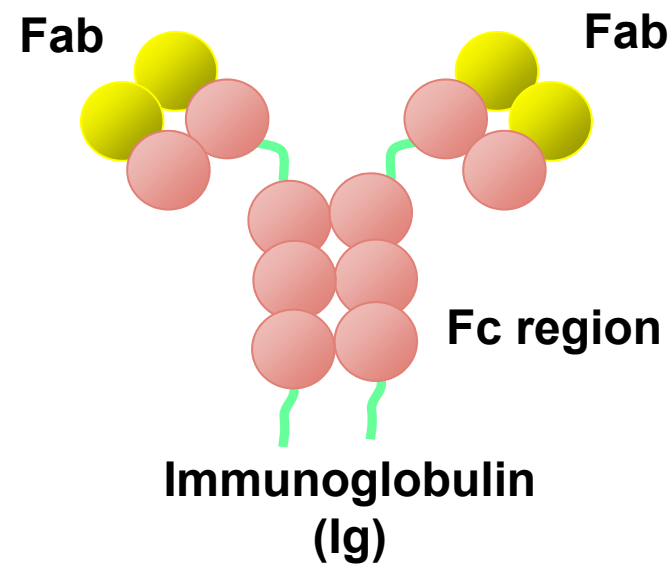
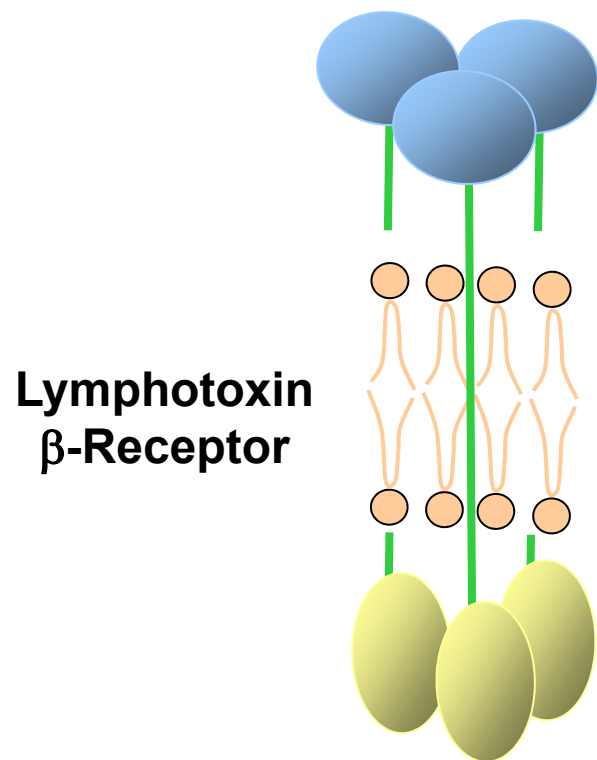
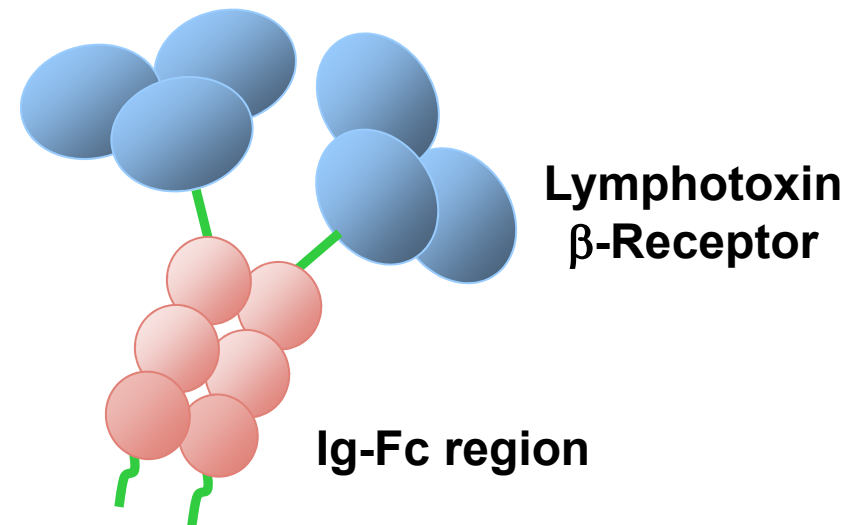




# Signals supporting FDC maintenance

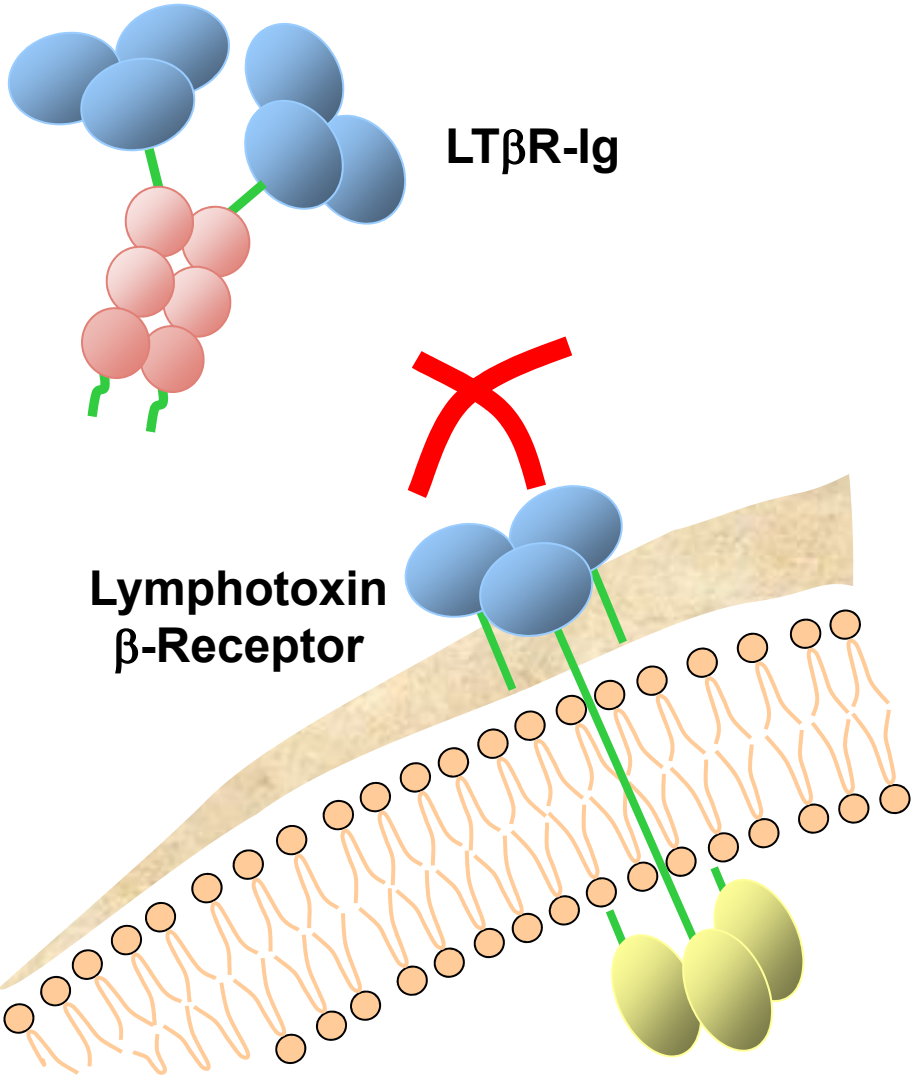
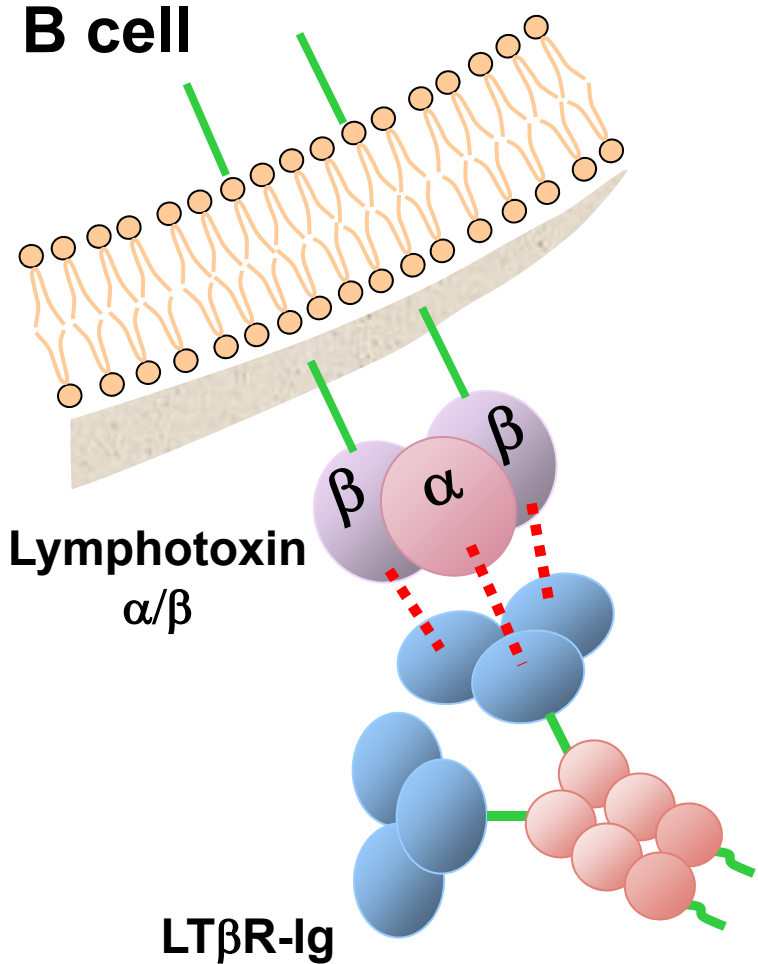


# The $LT\beta R$ -Ig fusion protein



Force et al. (1995) J. Immunol. **155**, 5280.

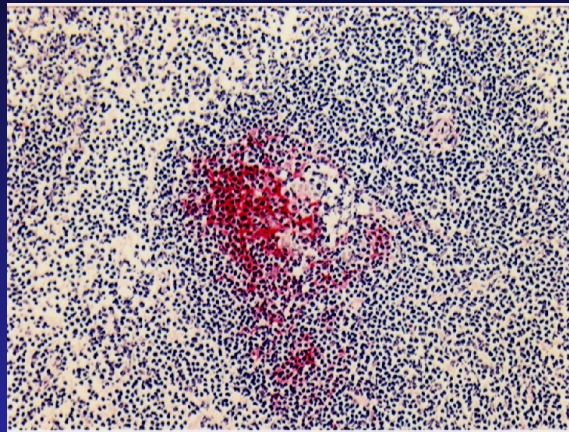
# 'Turning-off' FDCs



Mackay & Browning (1998) Nature 395, 26.

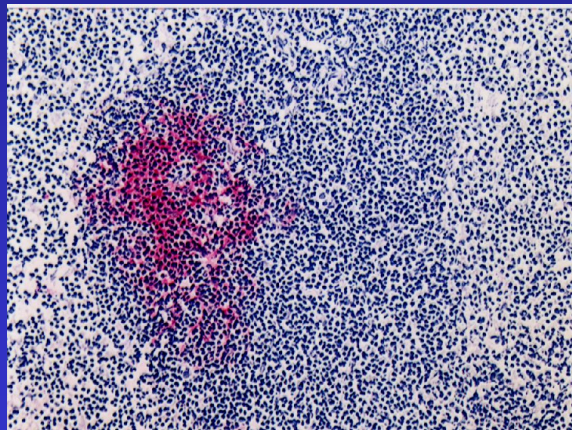
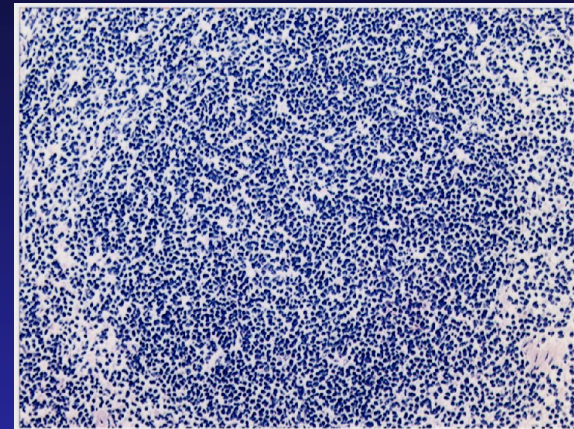
# 'Turning-off' FDCs

Control (hu-Ig)

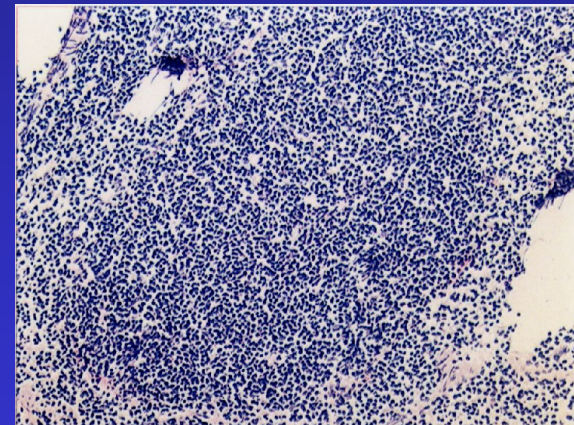


FDC-M2

Lt $\beta$ -R-Ig



CD35

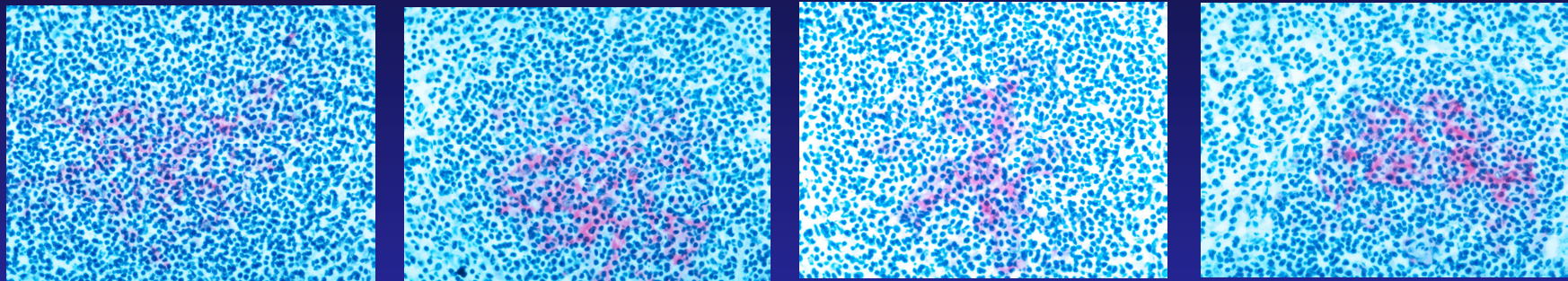


x100

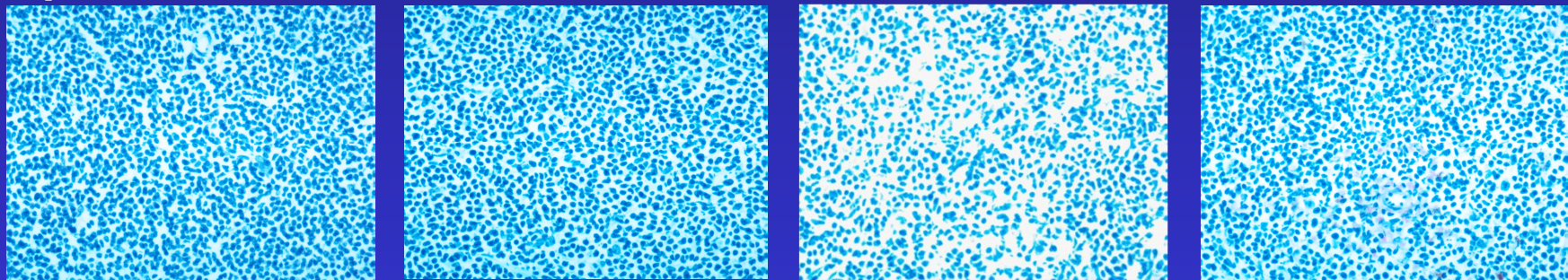
72 h-post treatment

# Temporary inactivation of follicular dendritic cells

hu-Ig control



LT $\beta$ R-Ig



T = 7d

T = 14d

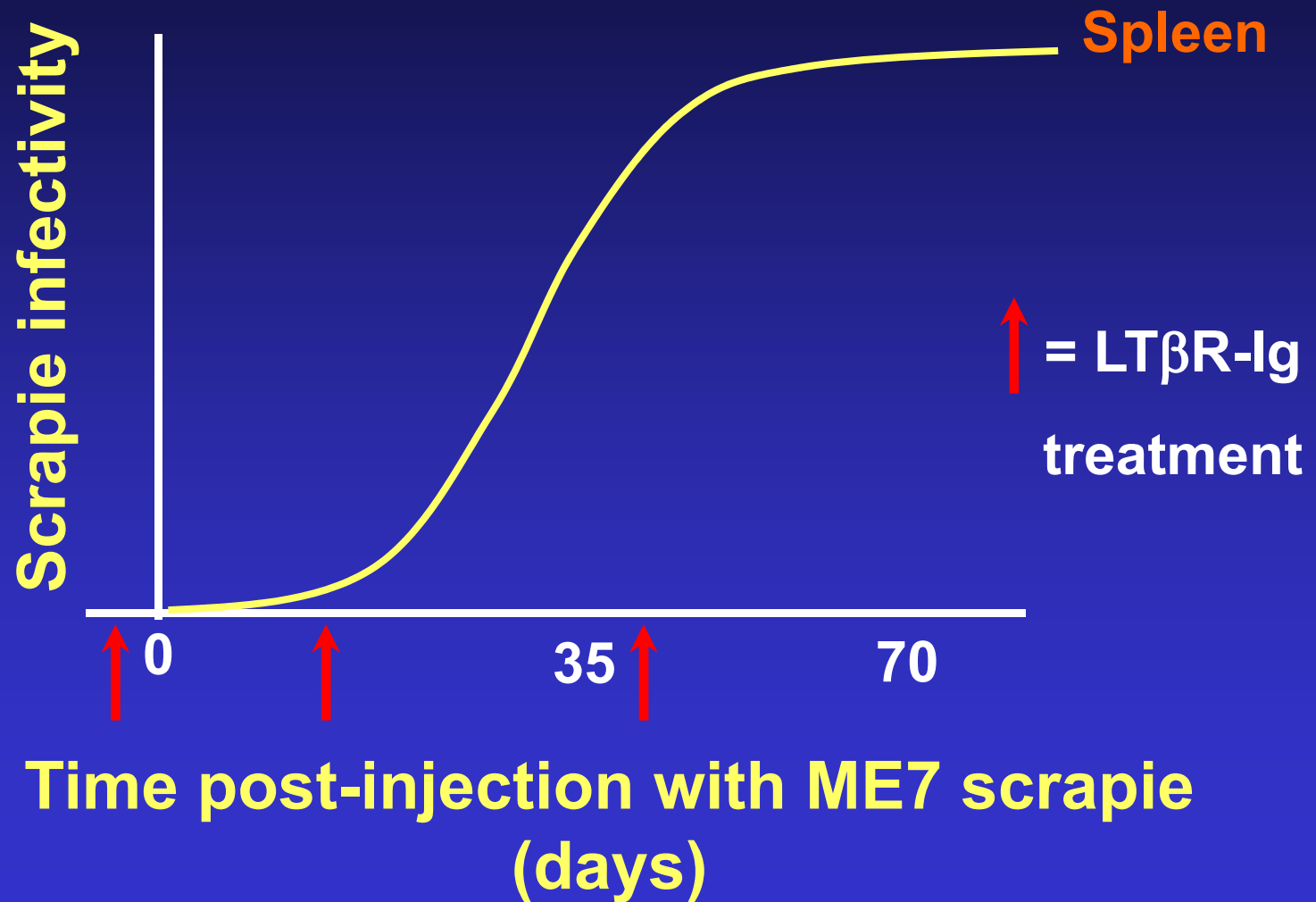
T = 21d

T = 28d

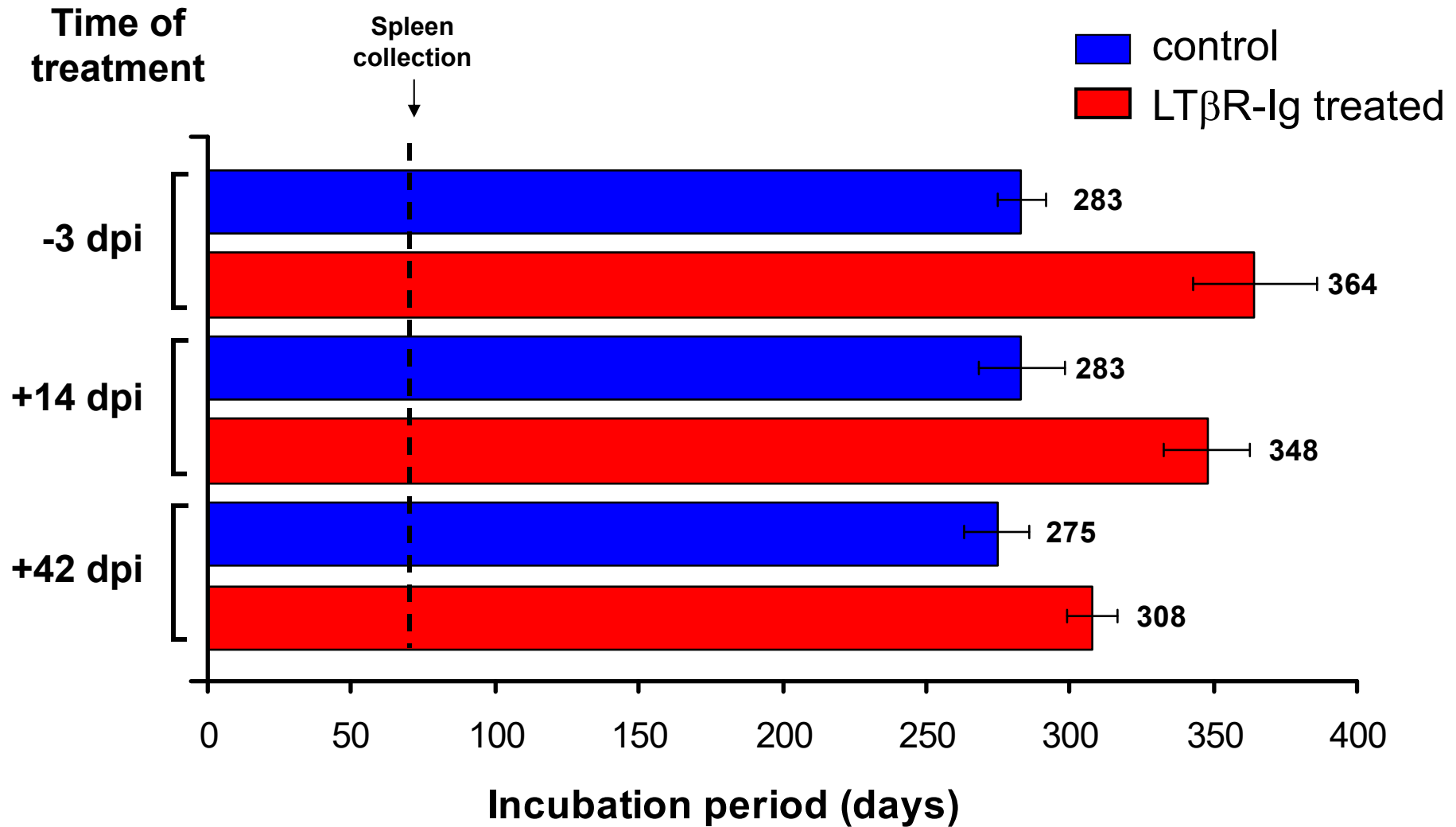
FDCM2 positive cells

x 400

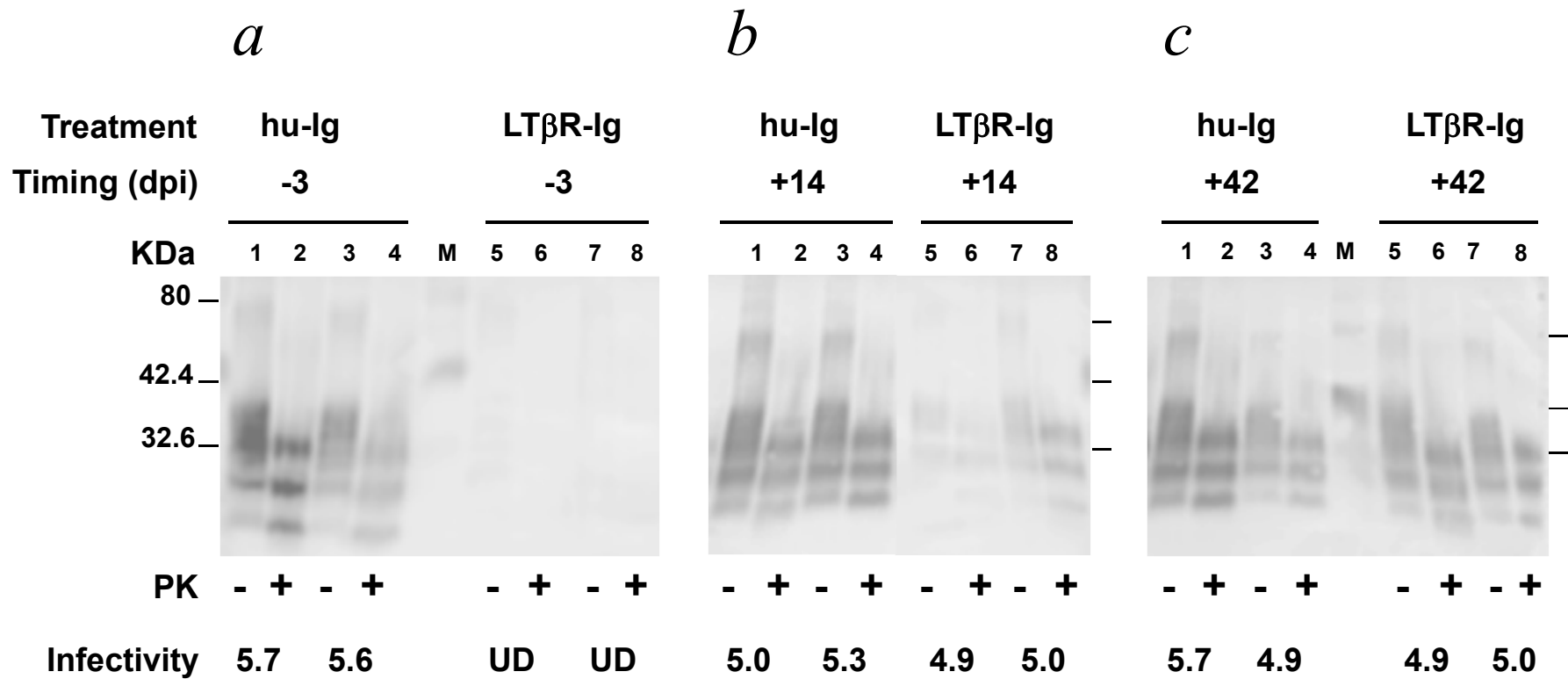
# Experiment Design



# Temporary inactivation of FDCs delays neuroinvasion of scrapie

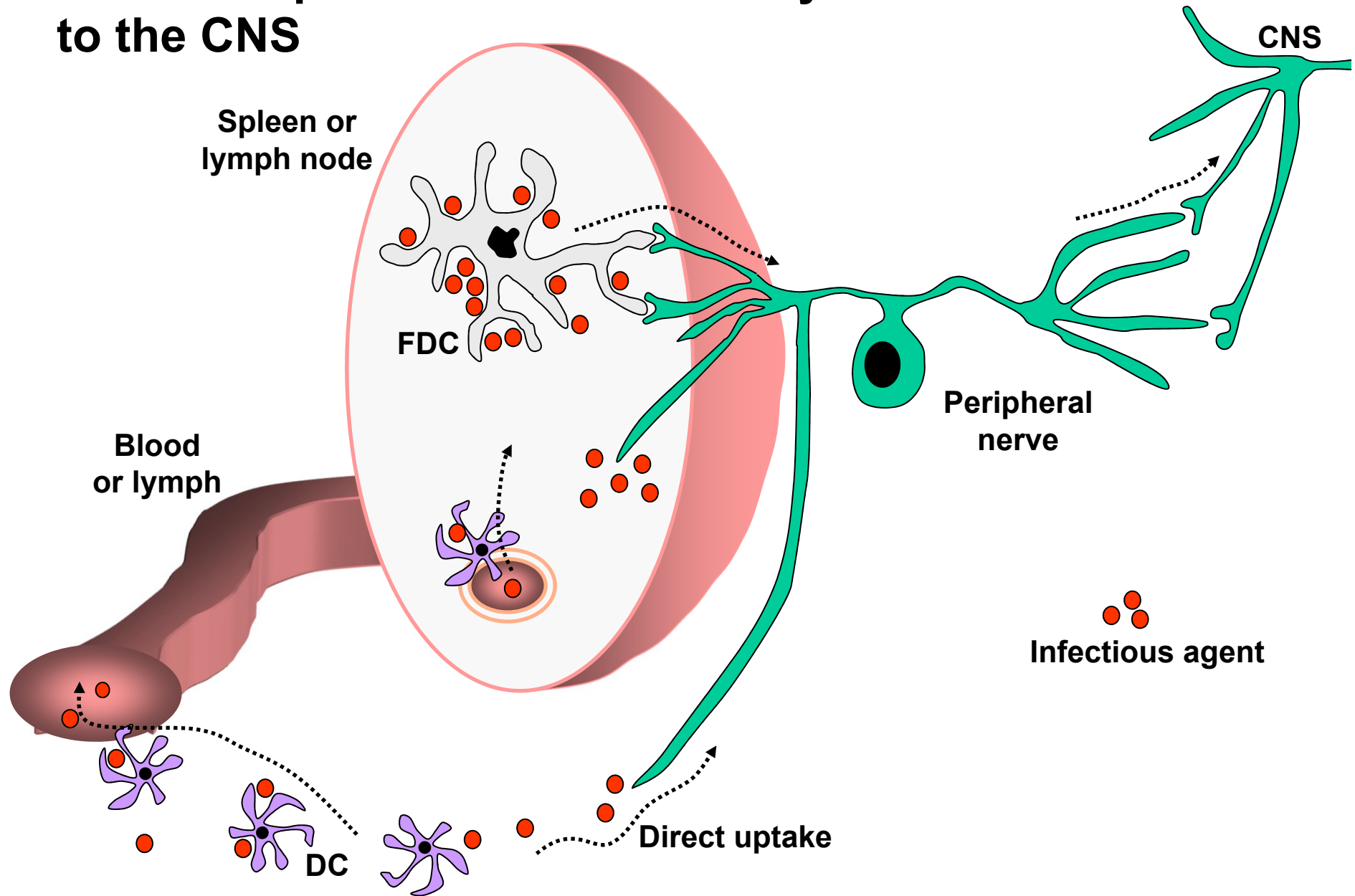


# PrP<sup>Sc</sup> accumulation in the spleen 70 d following i.p. injection with ME7 scrapie

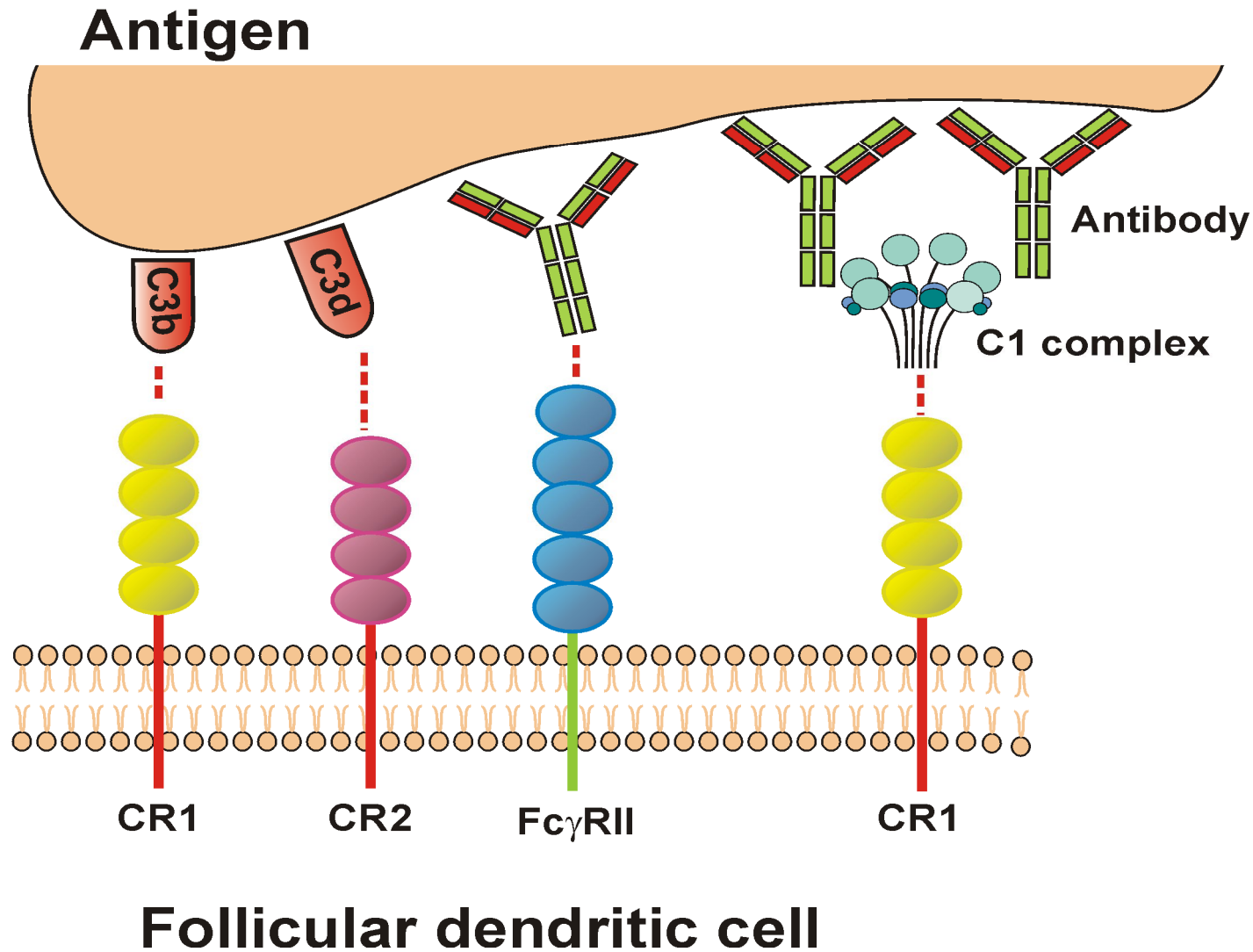




# Possible spread of TSE infectivity from site of infection to the CNS

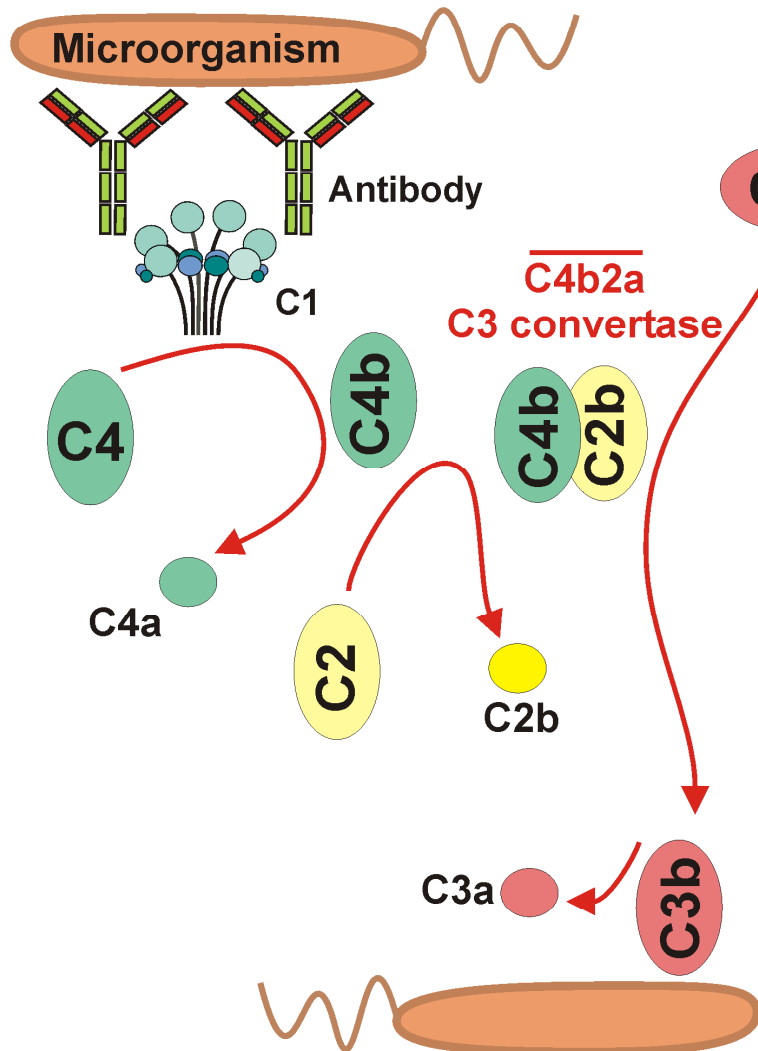


# Molecular mechanisms of immune complex-trapping by follicular dendritic cells

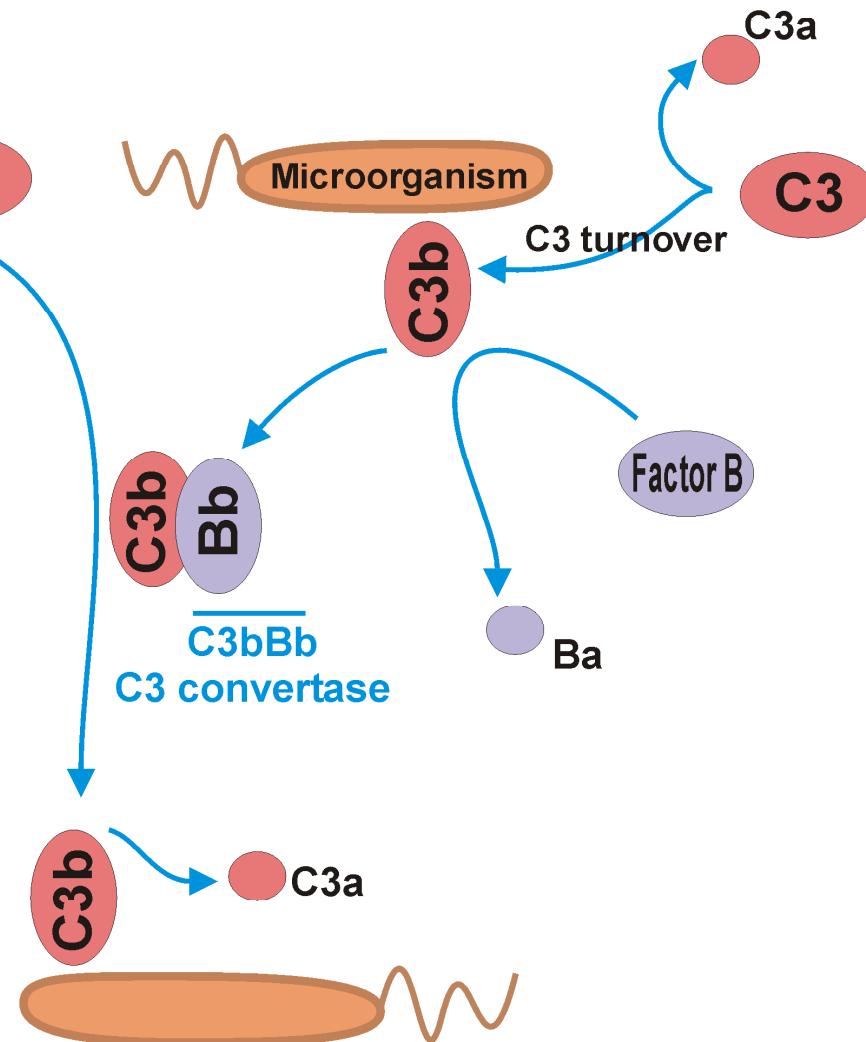


# Brief overview of complement C3 activation

## Classical pathway

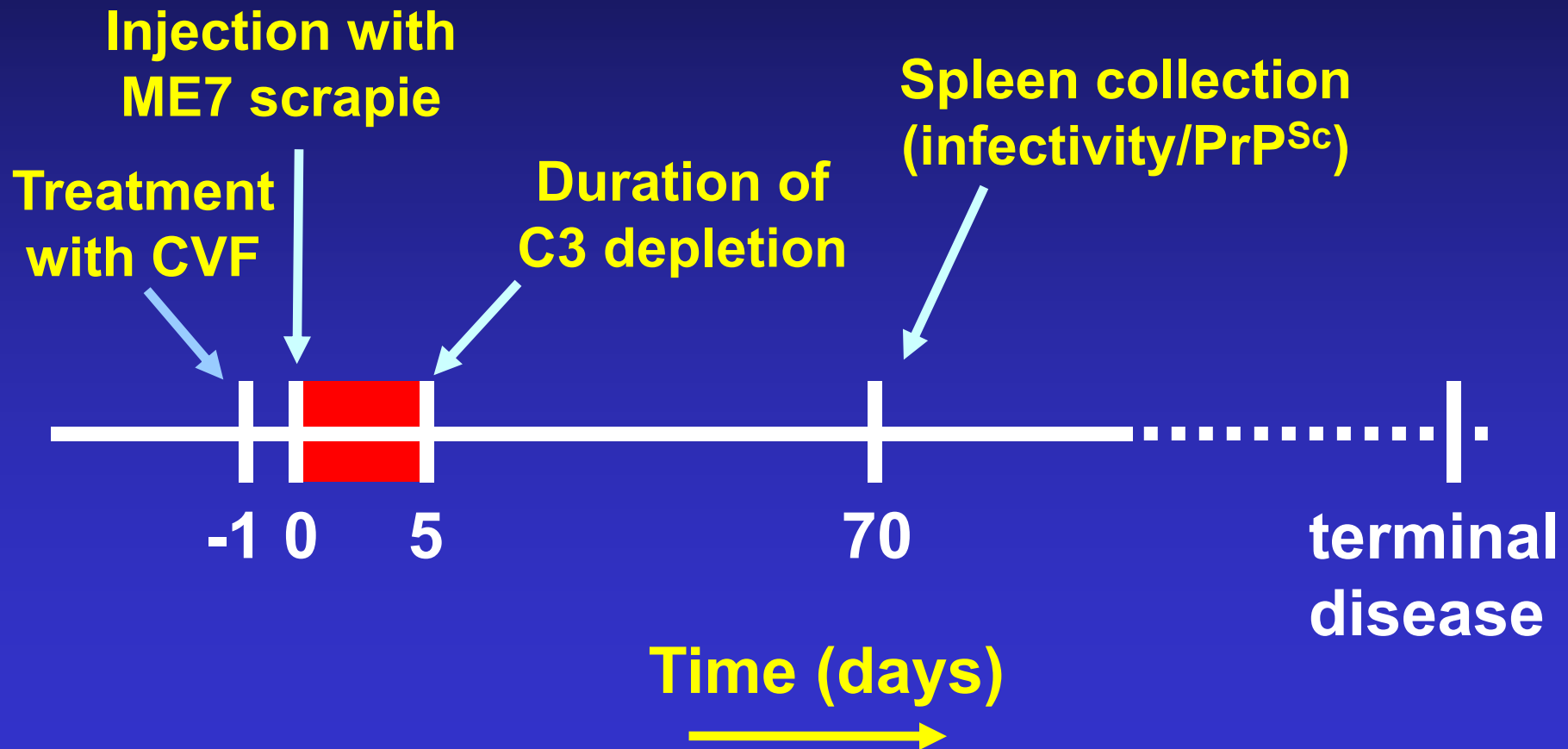


## Alternative pathway



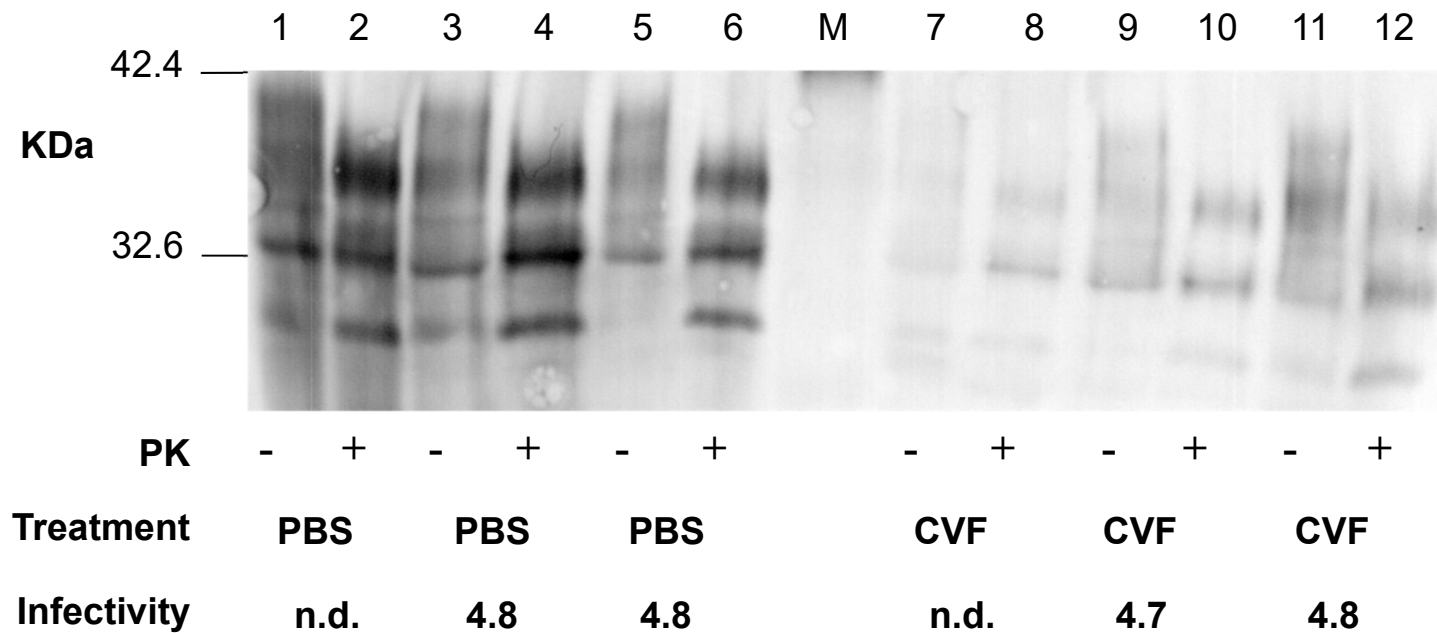
# Role of C3 in scrapie pathogenesis

## Experiment design

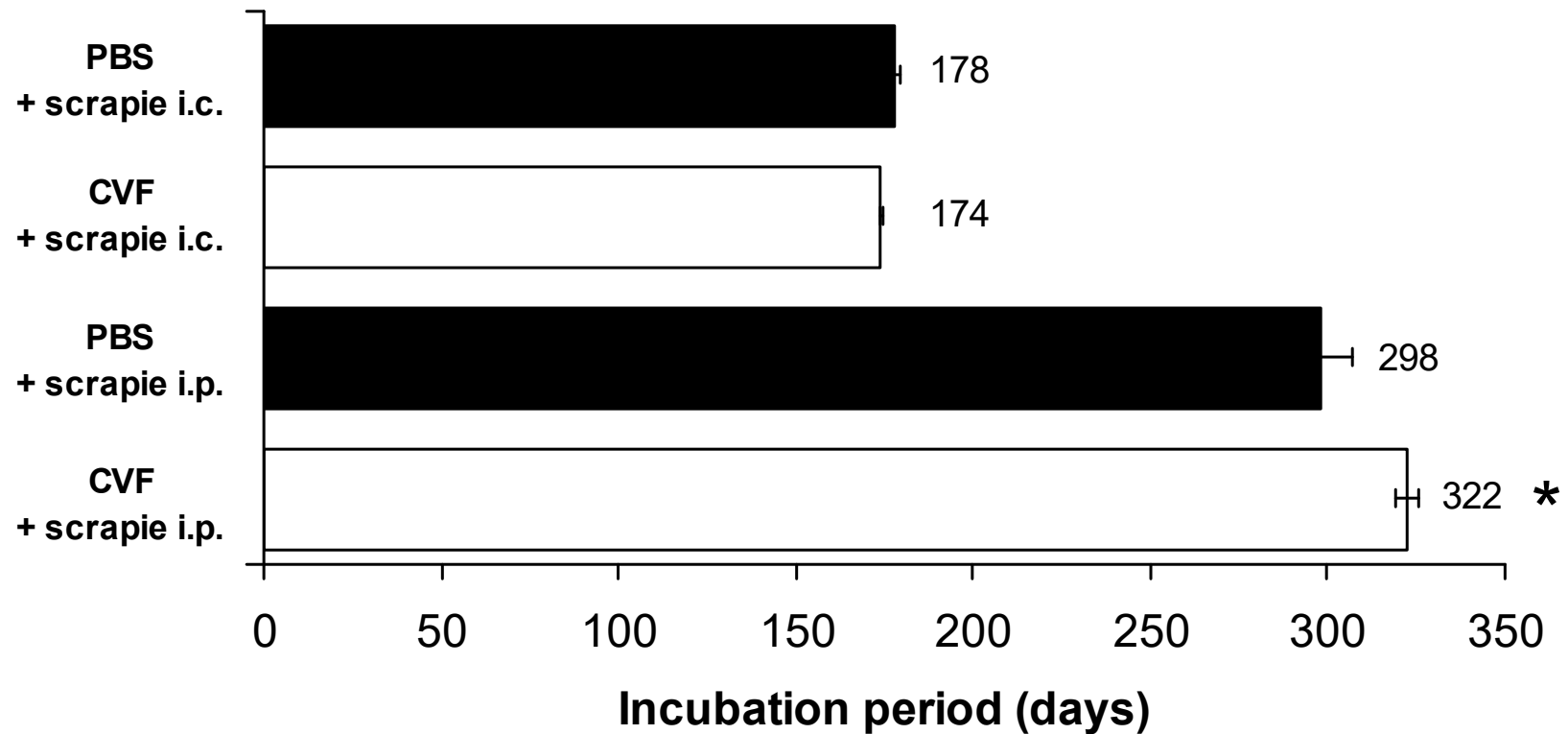


# PrP<sup>Sc</sup> and infectivity accumulation in the spleen

70 days following i.p. injection with ME7 scrapie



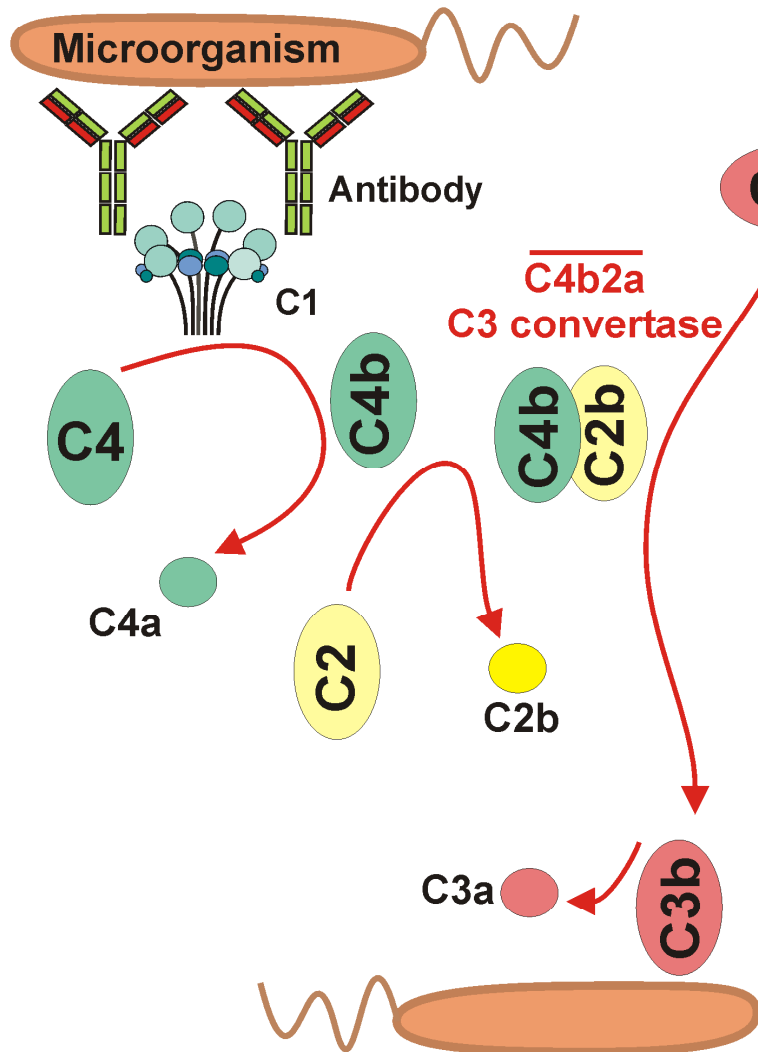
# Transient C3 depletion significantly delays onset of scrapie



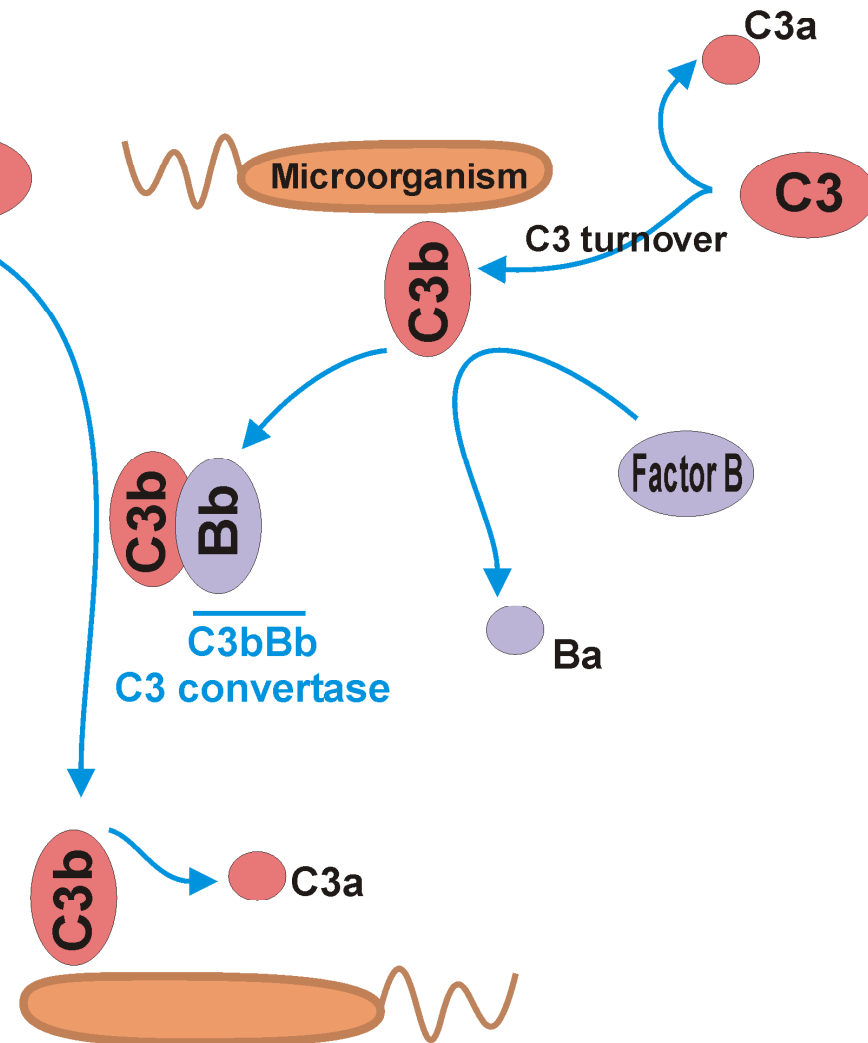
\*;  $p < 0.016$

# Which complement activation pathway?

## Classical pathway

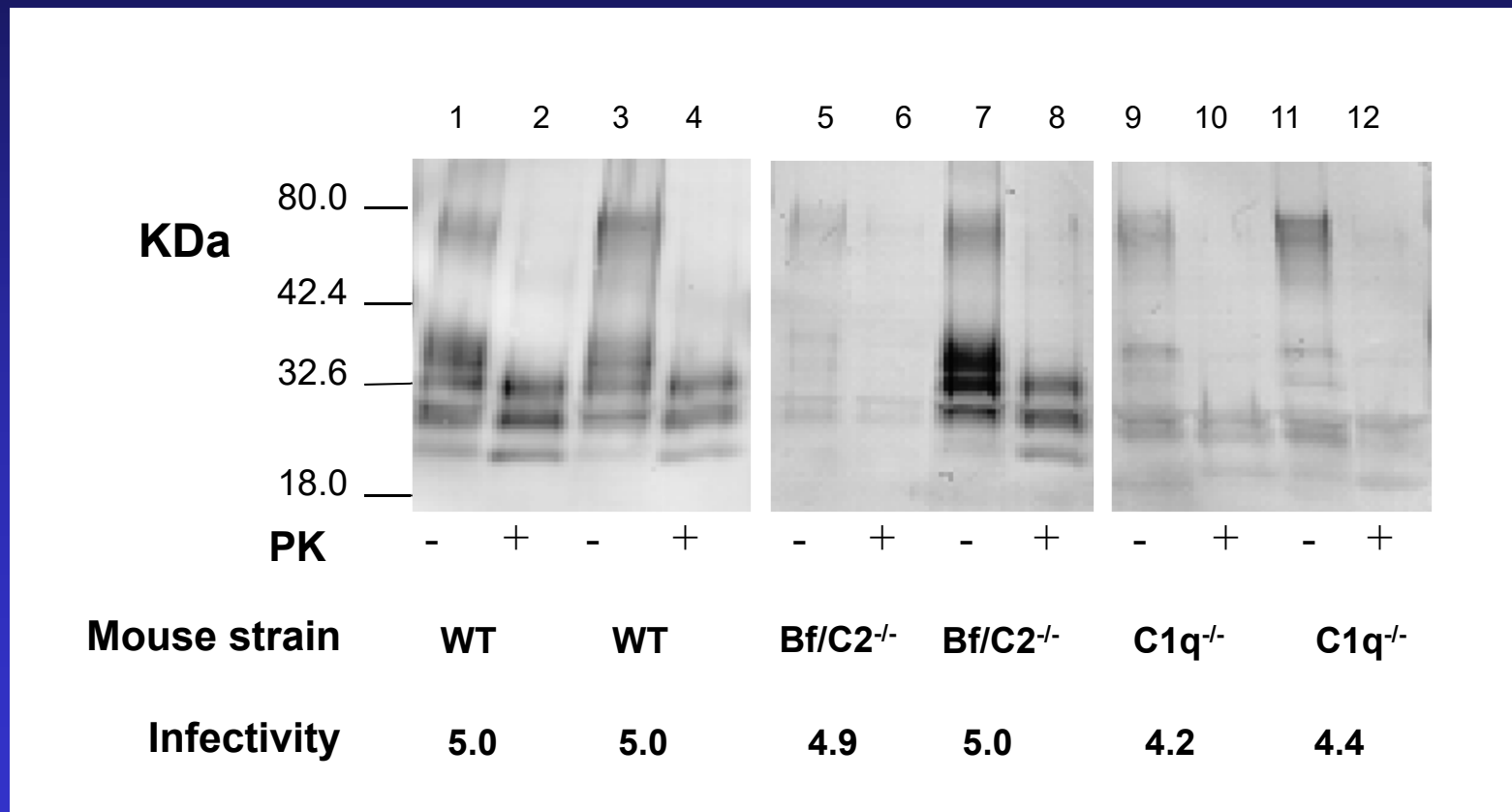


## Alternative pathway



# PrP<sup>Sc</sup> and infectivity accumulation in the spleen

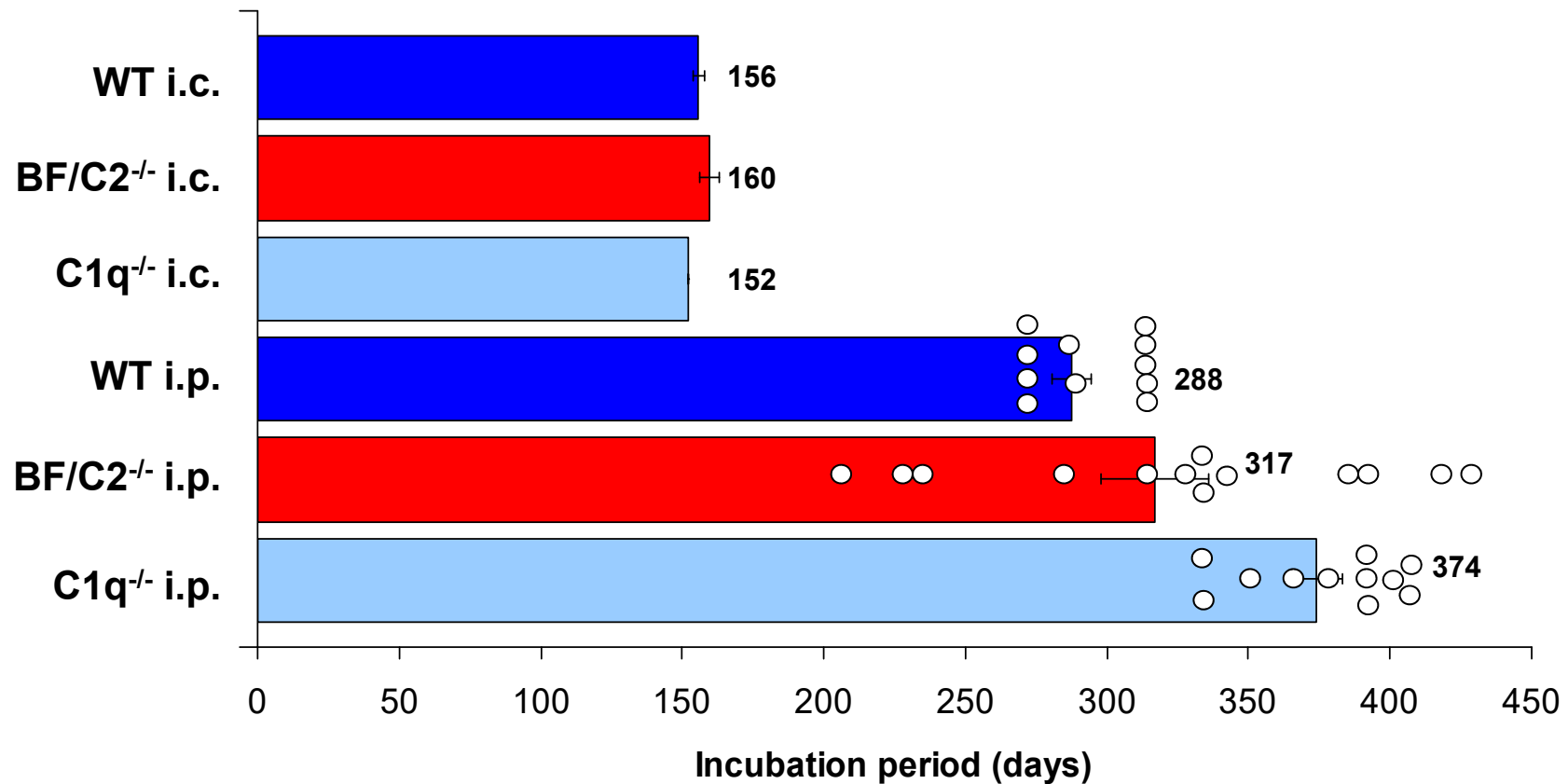
70 days following i.p. injection with ME7 scrapie



WT = C57BL/6

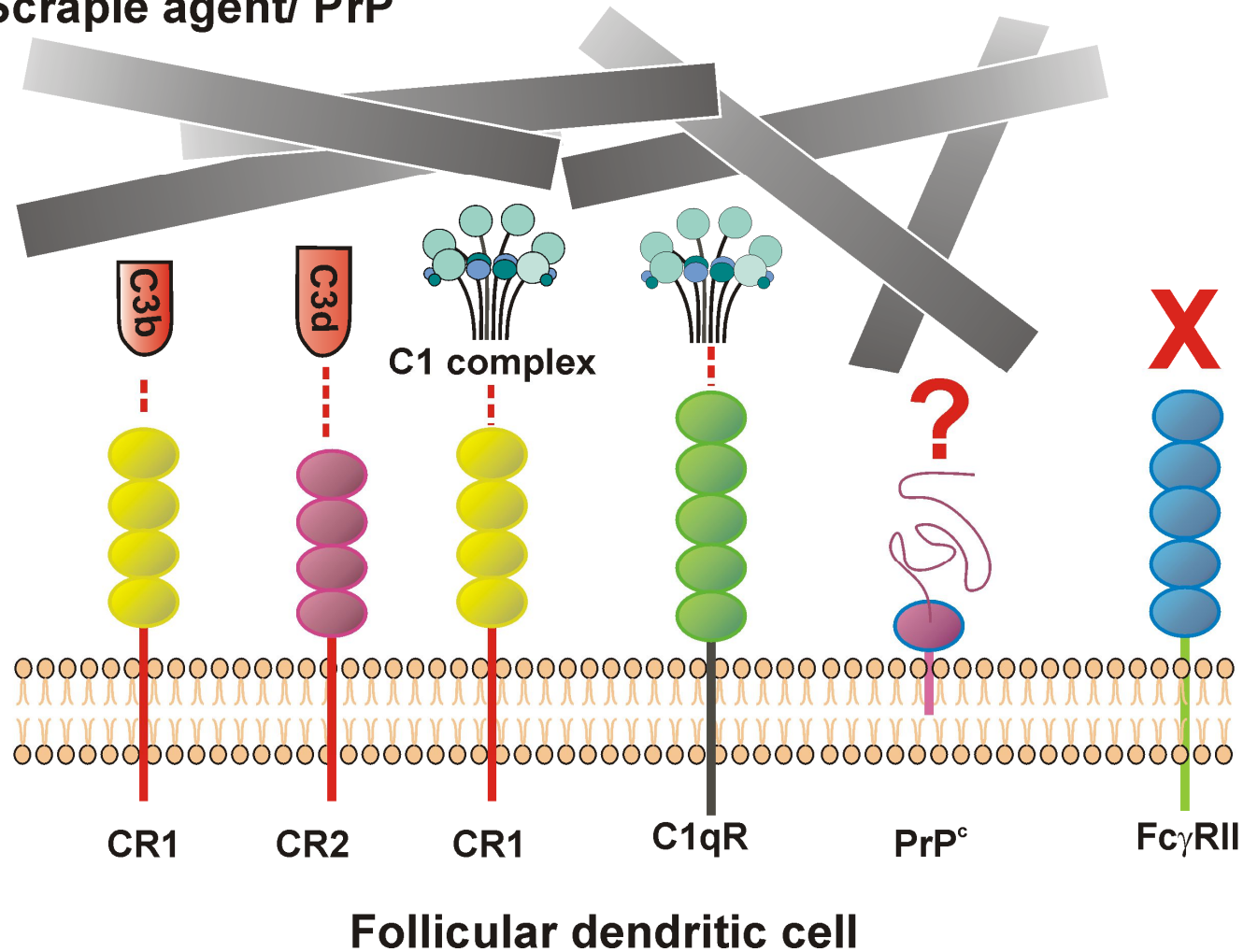


# Scrapie pathogenesis in C1q<sup>-/-</sup> and Bf/C2<sup>-/-</sup> mice

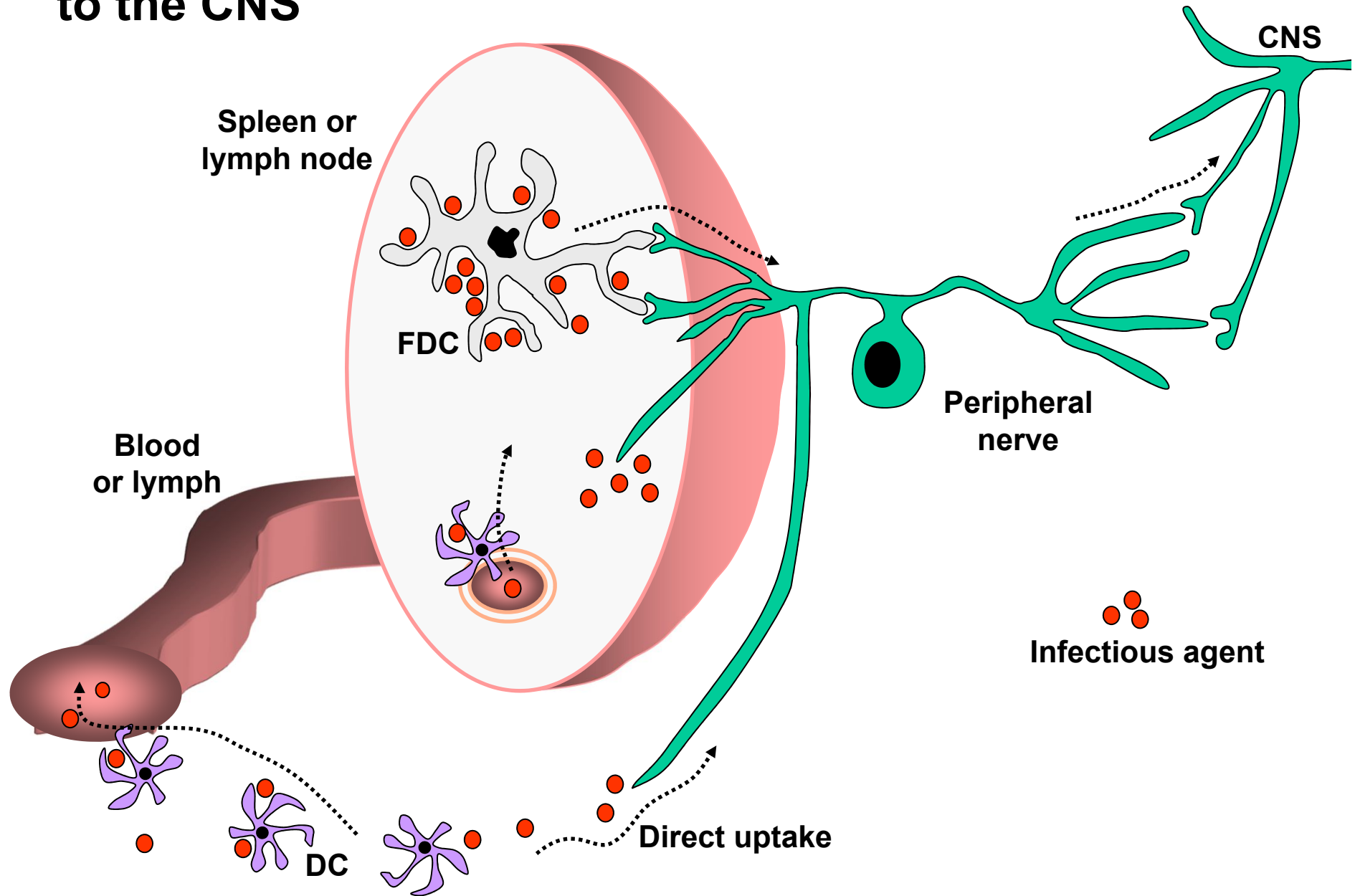


# Potential molecular interactions between scrapie and follicular dendritic cells

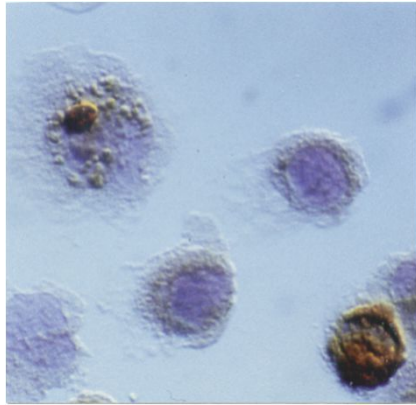
Scrapie agent/ PrP<sup>Sc</sup>



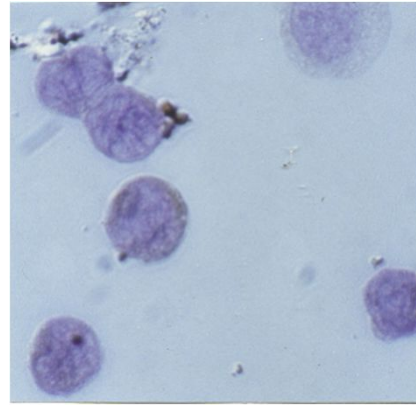
# Possible spread of TSE infectivity from site of infection to the CNS



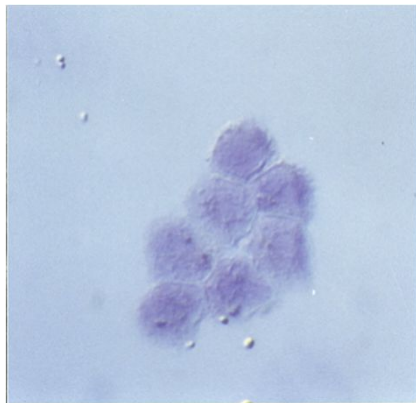
# Migrating intestinal dendritic cells transport PrP<sup>Sc</sup> from the gut



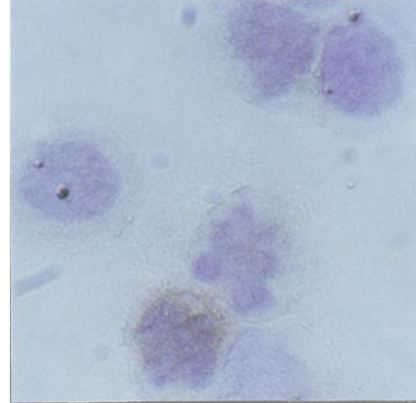
**DCs**



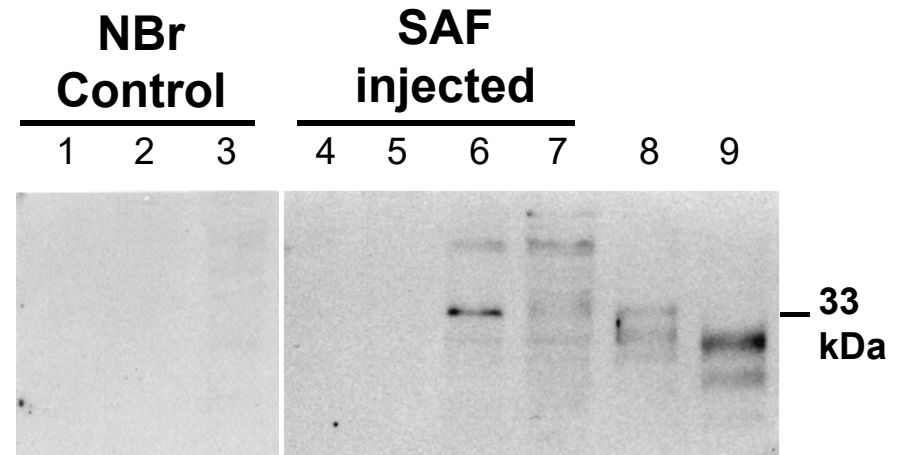
**B cells**



**T cells**



**DCs control**



Cells	T	B	DC	T	B	DC	DC	SAF	SAF
PK	-	-	-	-	-	-	+	-	+

# Possible spread of scrapie from the gut lumen to the CNS

