Target Organ Trafficking

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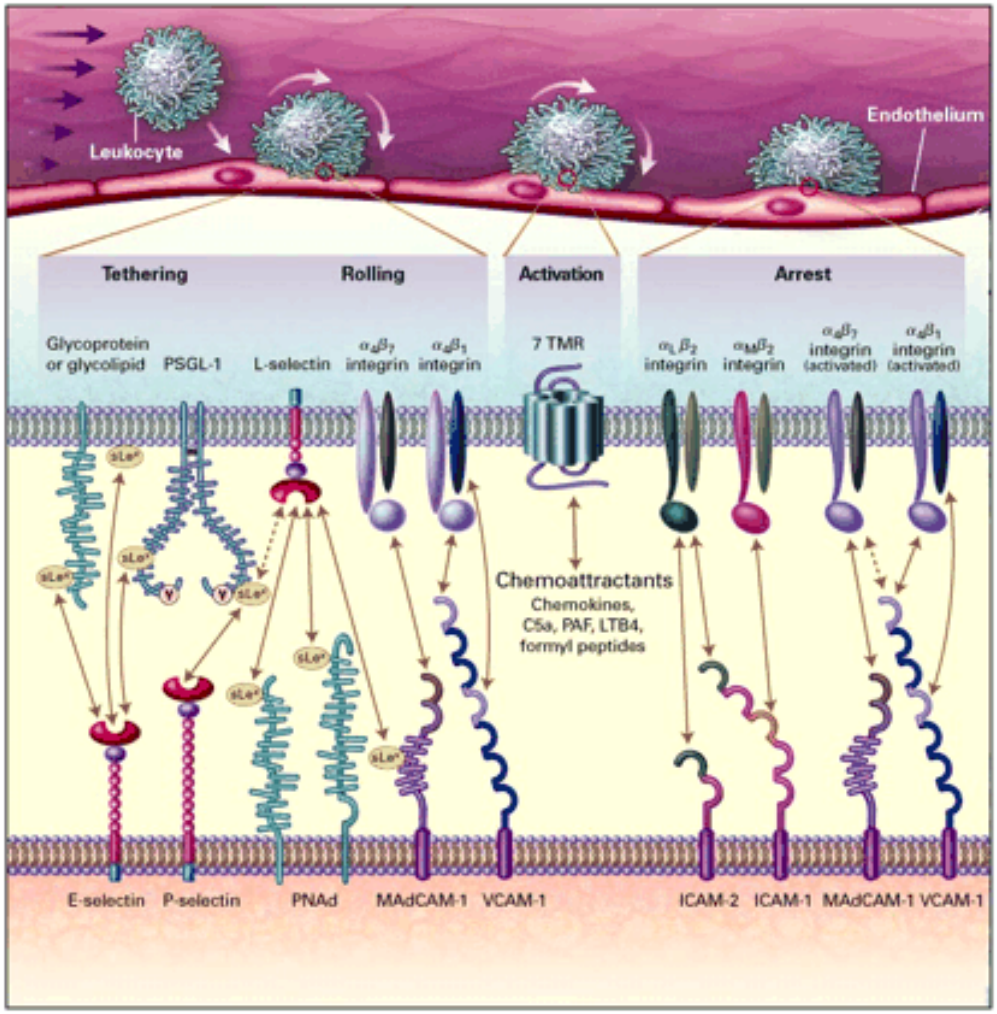
Useful References

- Butcher & Picker Science **272**,60-66 (1996)
- von Andrian & Mackay **343**, 1020-1034 (2000)
- McLachlan & Jenkins **4**, 439-442 (2007)

Overview of the presentation

- Lymphocyte recirculation is essential for normal immune function
- Cells with different functions recirculate differently
- Controlling recirculation helps optimise immune responses
- Cellular localisation influences disease pathology
- Common activating signals have cell type specific effects on trafficking

The mechanisms of cell trafficking



von Andrian & Mackay
NEJM **343**:1020 (2000)

A multi-step process:

Both common mechanisms and selective expression of specific ligands plays a role

The challenges of immunosurveillance

- To bring antigen in contact with the rare cells that can respond to it
- To expand antigen specific cells efficiently and distribute these cells to all tissues
- To do this as fast as possible

A seminal observation in cellular immunology

- Rapid small lymphocyte recirculation was essential for normal immune function
- Experiments started because of the inscrutable nature of small lymphocyte function
- Depended on being able to canulate the thoracic duct of the rat

The lymphocyte -- a disgraceful gap in medical knowledge
Immunol. Today **17**:288 (1996)

Gowans et al. Nature 196:651 (1962)

First dose

Second dose

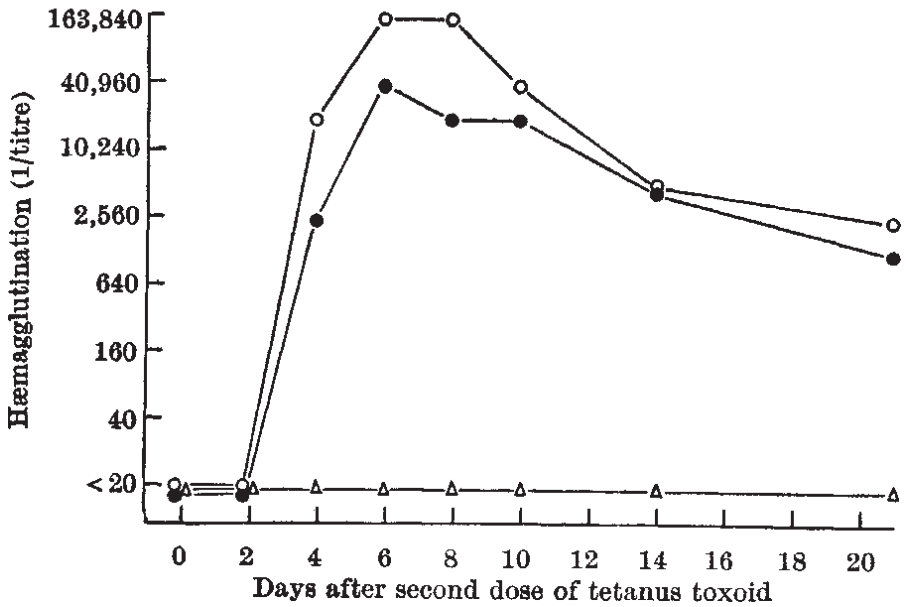
●

○

△

5 days:
$2x10^9$ small lymphocytes

5 days:
$2x10^9$ small lymphocytes



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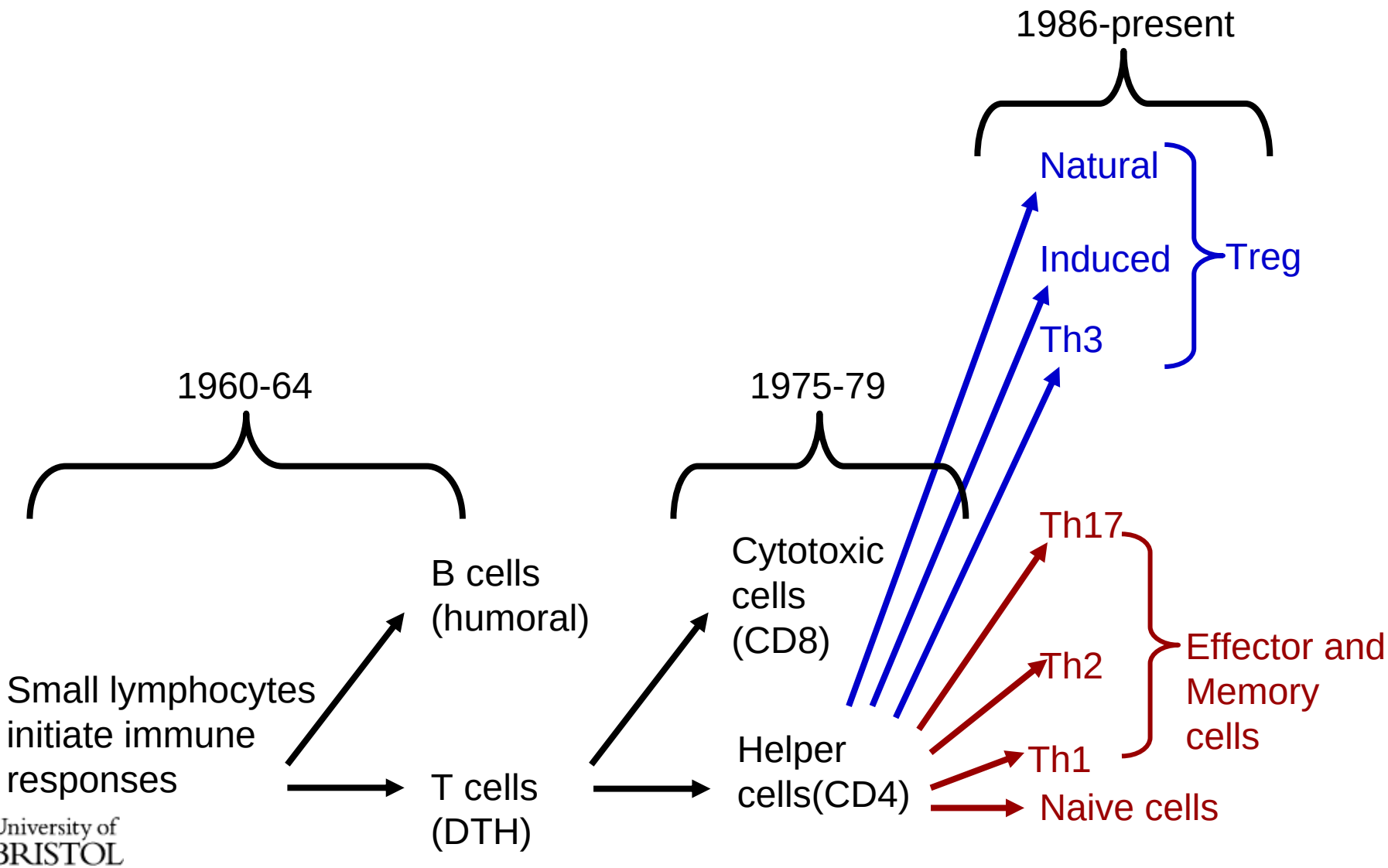
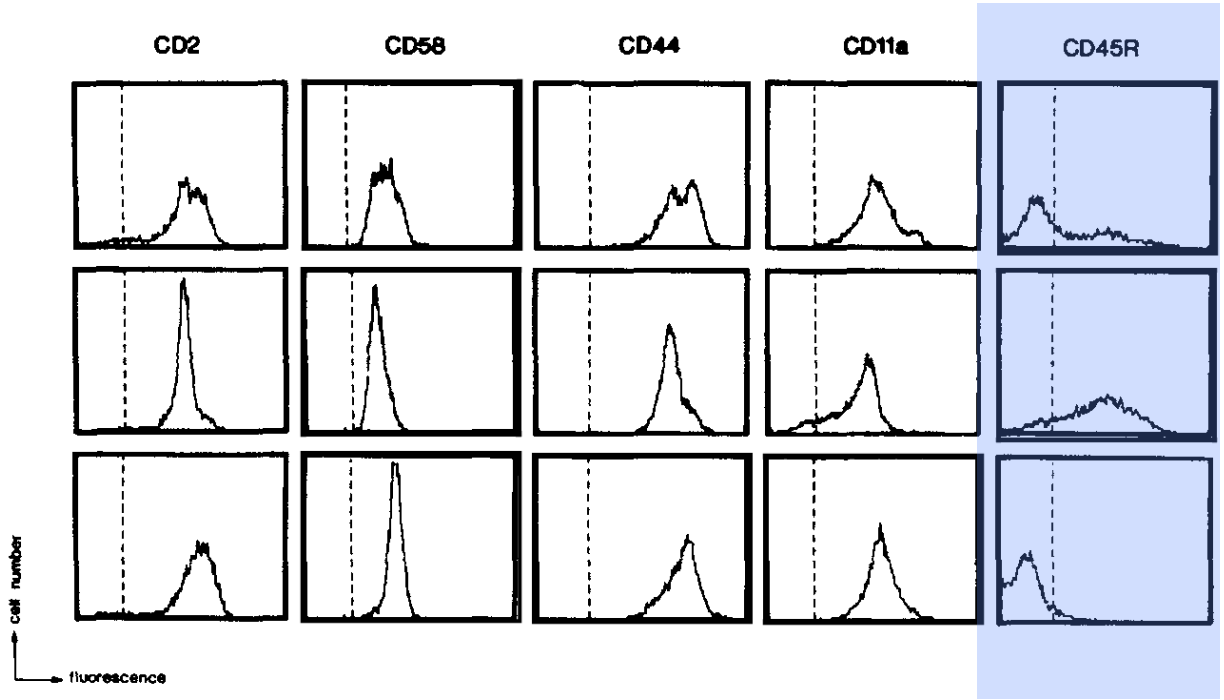
Subdividing the immune system



Optimisation of cell trafficking

- By cell type (naive vs memory)
- By target tissue (imprinting allows memory cells to return to site of antigen production)
- By effector phenotype (influence of T cell phenotype on trafficking patterns)

Tissue dependent lymphocyte phenotype



Lymphocytes from blood
Naive cells

Lymphocytes from tissue
Memory cells

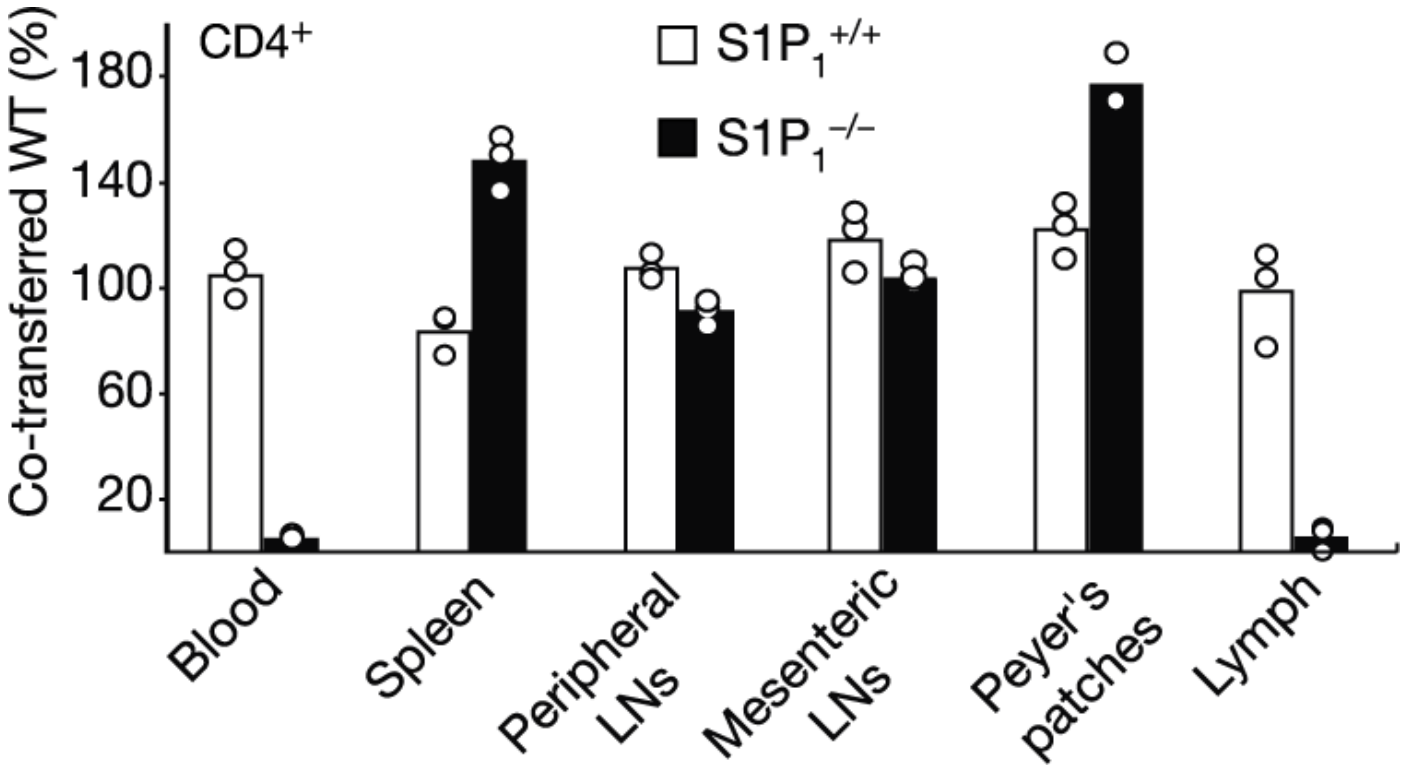
Mackay et al J . Exp. Med. **171:** 801-817 (1990)
Data from canulation of the popliteal lymph node of sheep

Controlling recirculation helps optimise immune responses

- FTY720 antagonises S1P receptors
- It's an effective immunosuppressant
- Administration leads to the retention of lymphocytes in 2^{o} lymphoid tissue
- Lymphocytes express $S1P_1$ and $S1P_4$

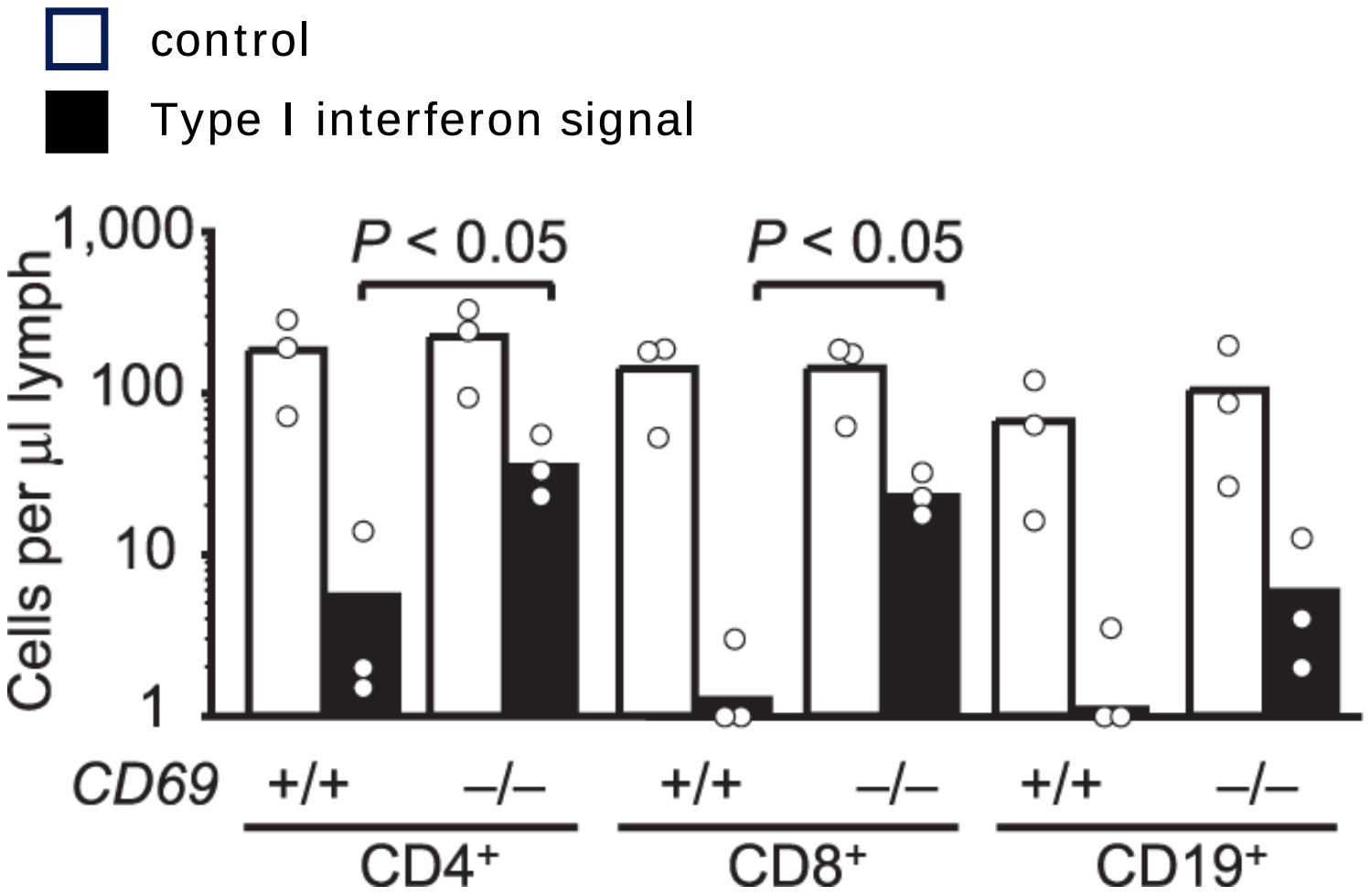
$S1P_1$ is essential for efficient lymphocyte egress from 2^o lymphoid tissue

Animals reconstituted with equal amounts of $S1P_1$ positive and $S1P_1$ negative thymocytes



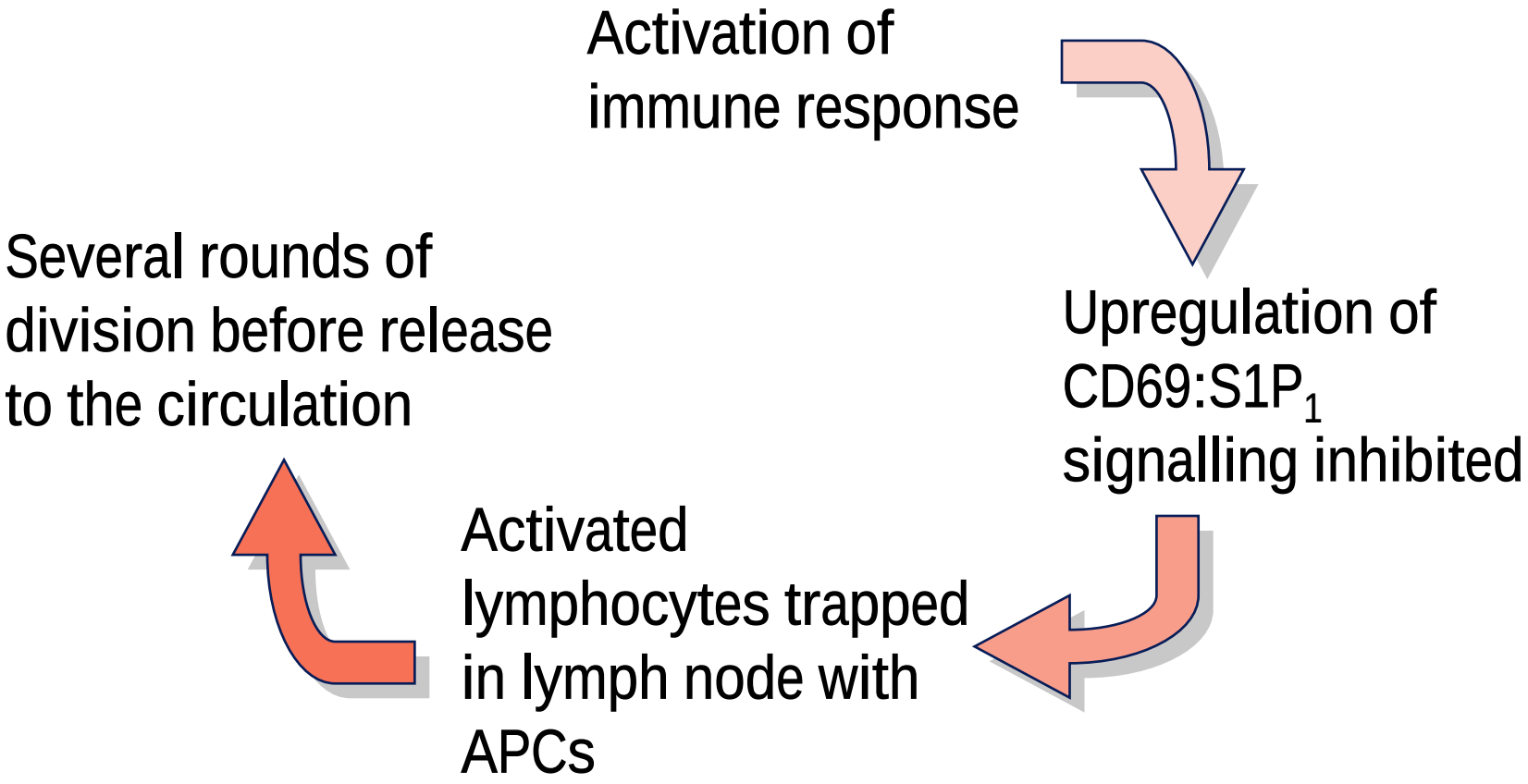
Matloubian et al. Nature **427**:355 (2004)

CD69 contributes to lymphocyte retention in 2º lymphoid tissue

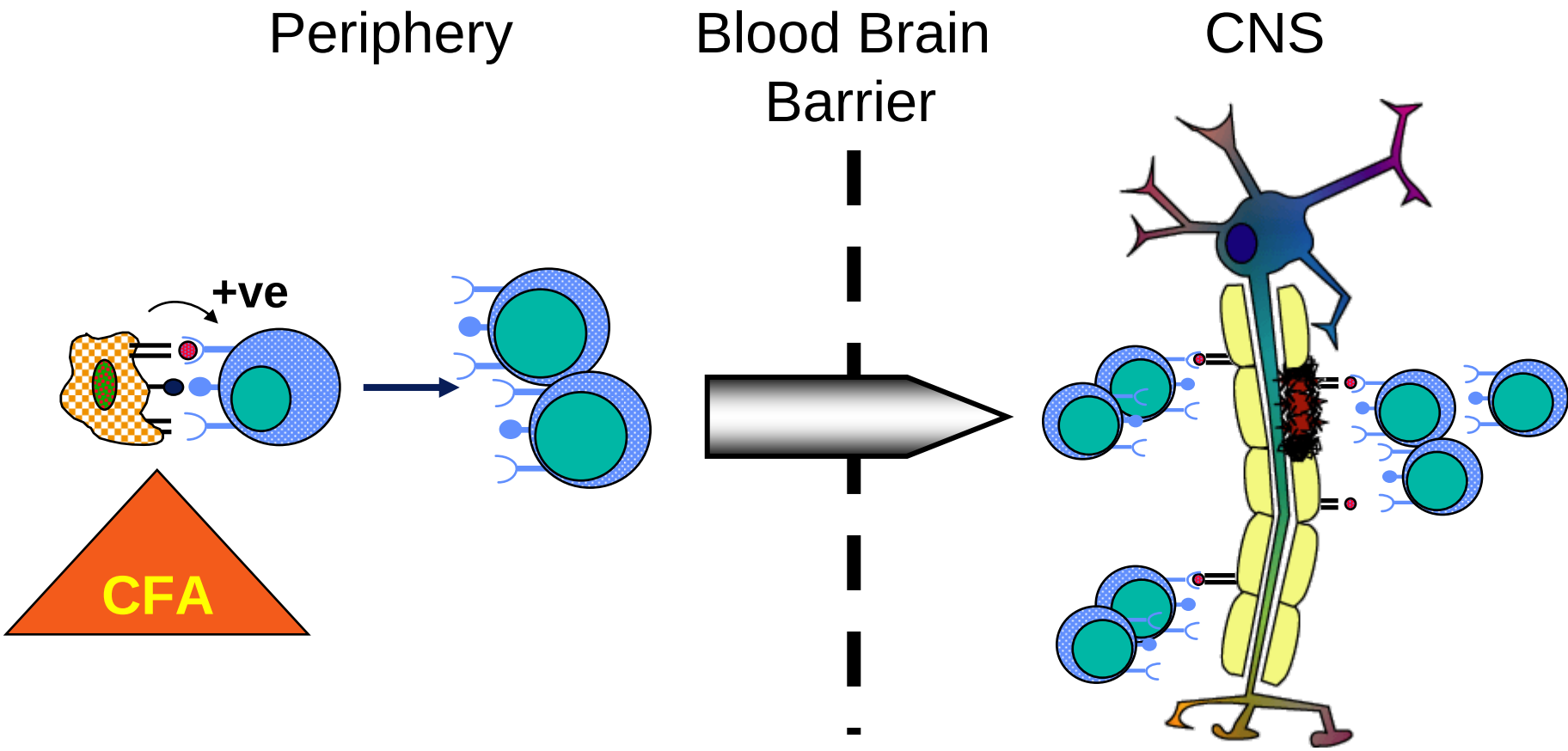


Shiow et al Nature **440**:540 (2006)

Local concentration of antigen specific and antigen presenting cells



Cellular localisation influences disease pathology



Experimental autoimmune encephalomyelitis (EAE)

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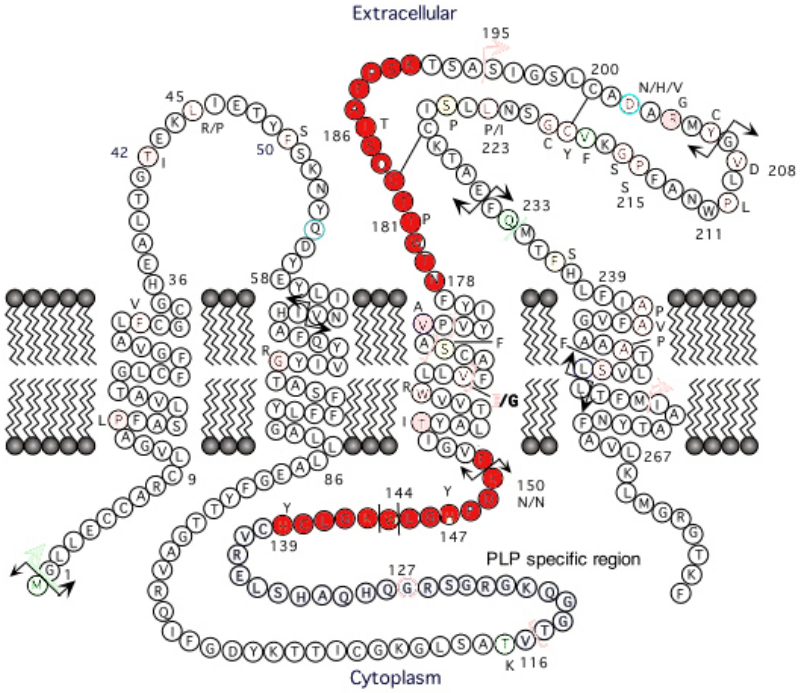

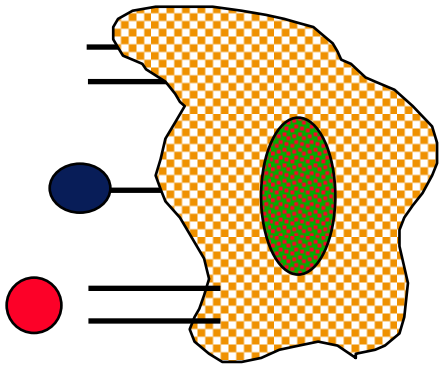

Antigen presenting cell

MOG35-55 typical EAE
MOG79-90 typical EAE
MOG97-114 atypical EAE

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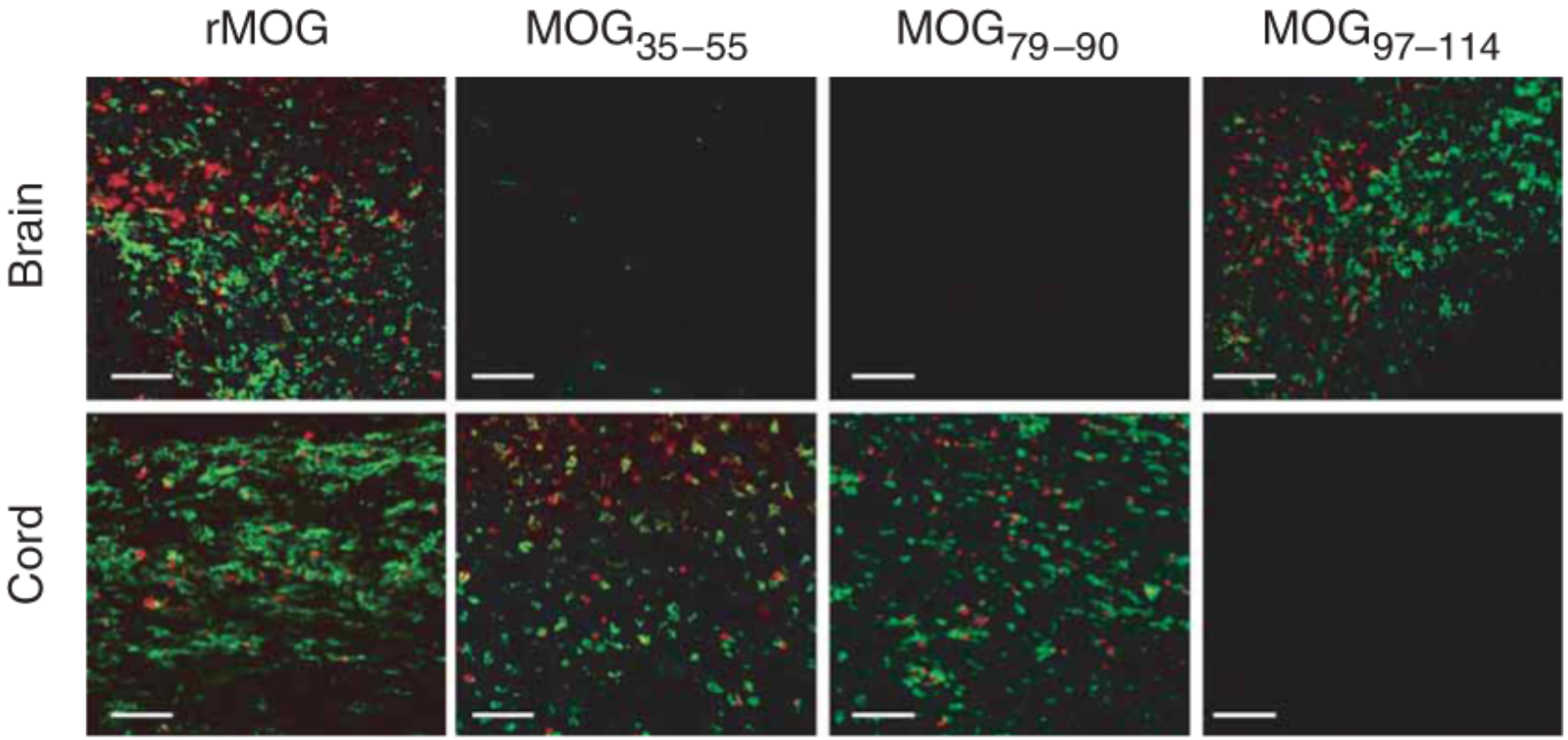
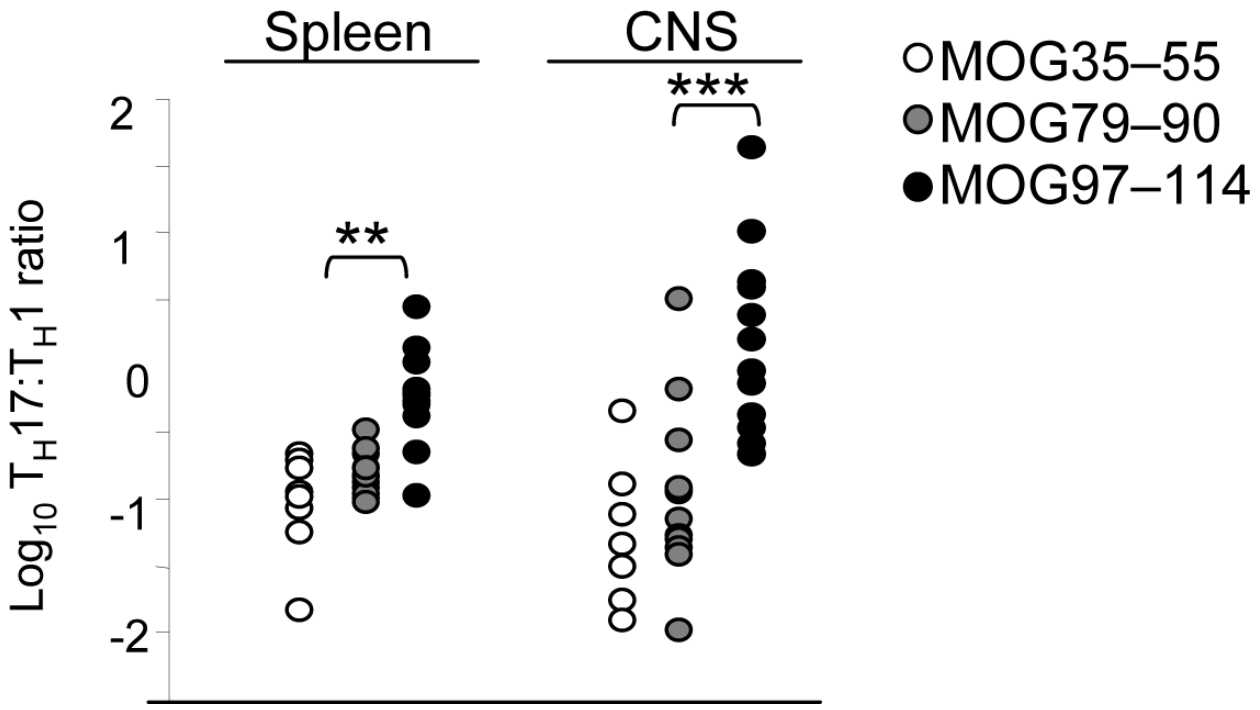
Clinical disease correlates with pattern of target organ localisation



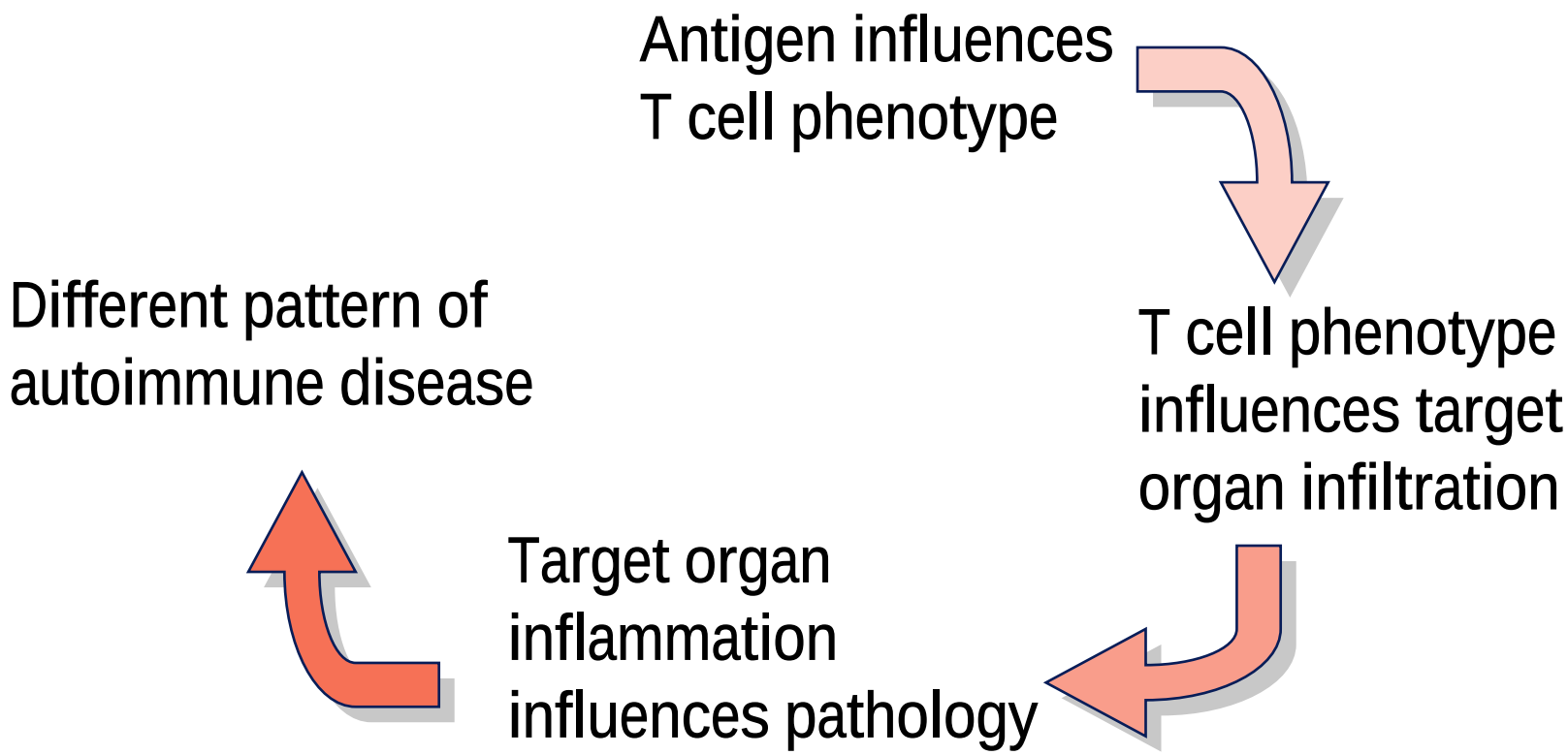
Stromnes et al. Nature Med. **14**:337 (2008)

Clinical disease correlates with pattern of target organ localisation



Stromnes et al. Nature Med. **14**:337 (2008)

Pathology reflects T cell phenotype

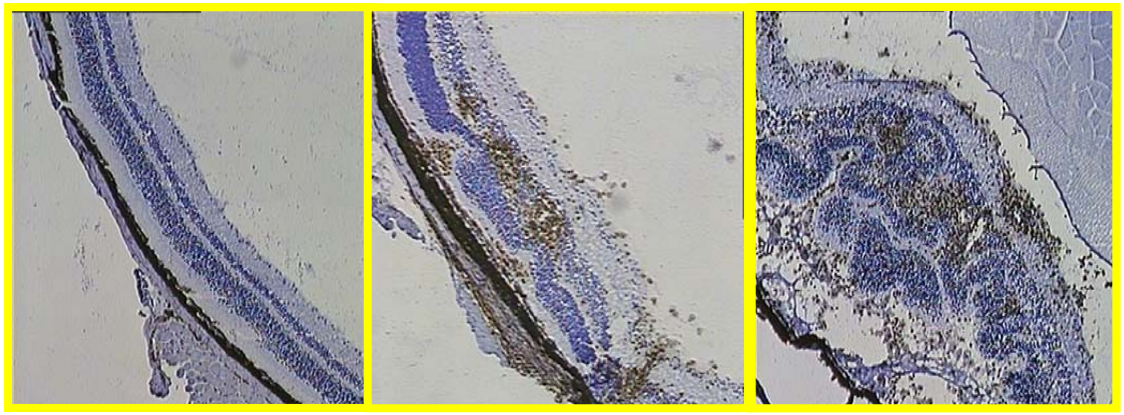


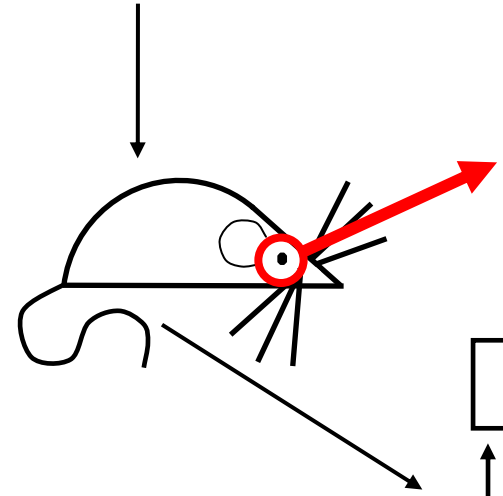
Common activating signals have cell type specific effects on trafficking

- Target organ inflammation encompasses a mixture of different leukocytes
- The composition of this mixture may have an effect on disease

EAU analysis protocol

Peptide with complete
Freund's adjuvant (CFA) s.c.





HISTOLOGY, TEFI and FLOW CYTOMETRY

d0 d5 d13 d18 d21 d25 d32

Clinical disease

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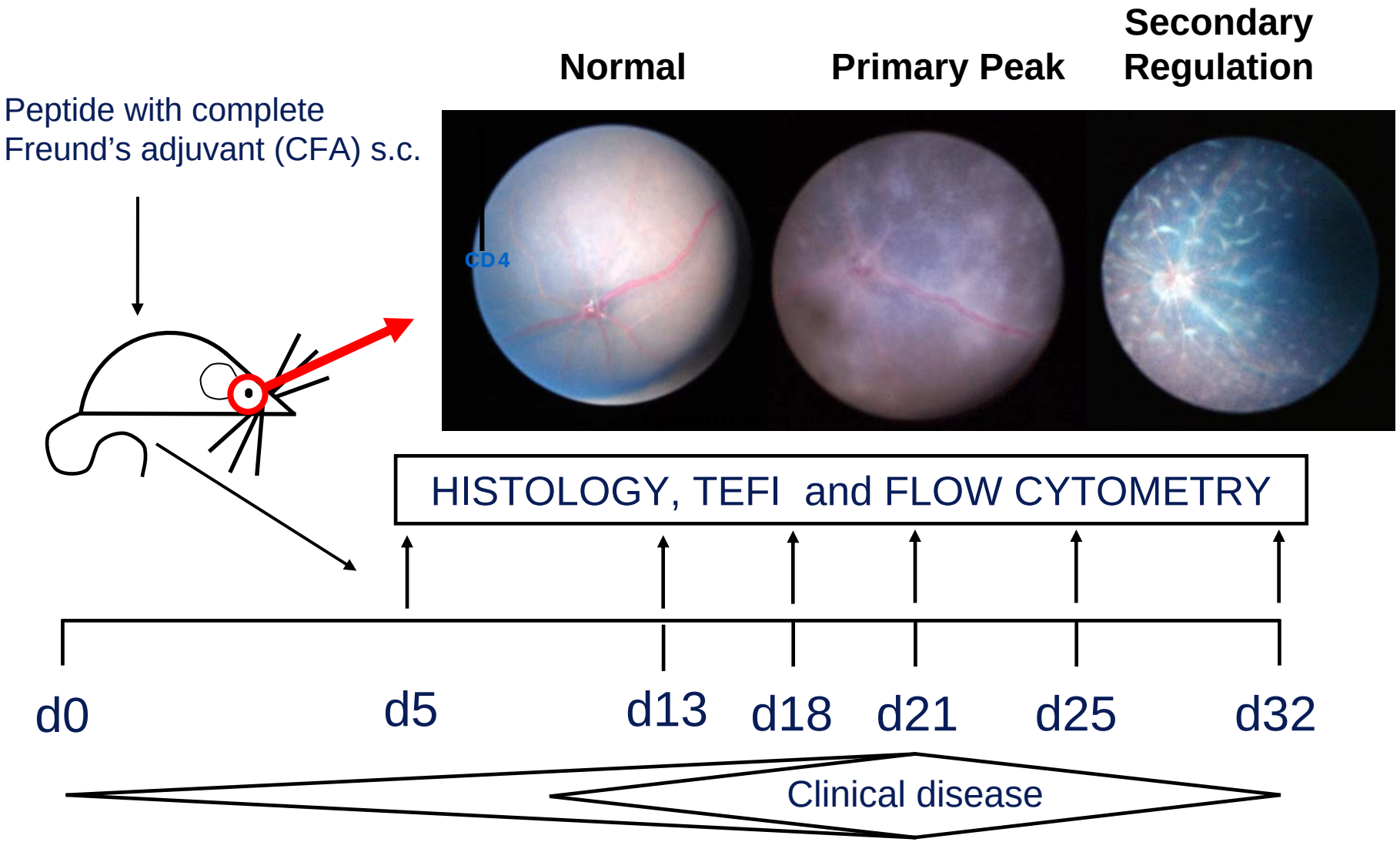
Copland et al. IOVS **49**, 5458 (2008)

EAU analysis protocol



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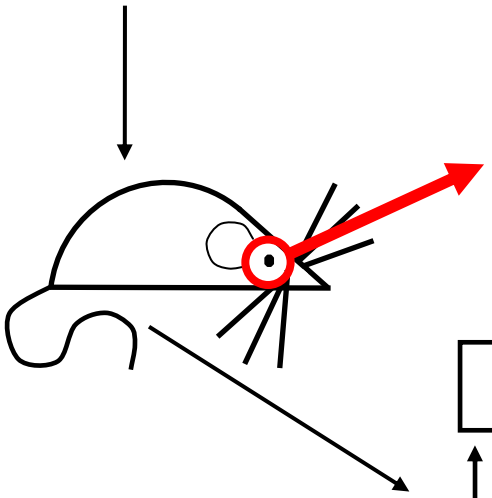

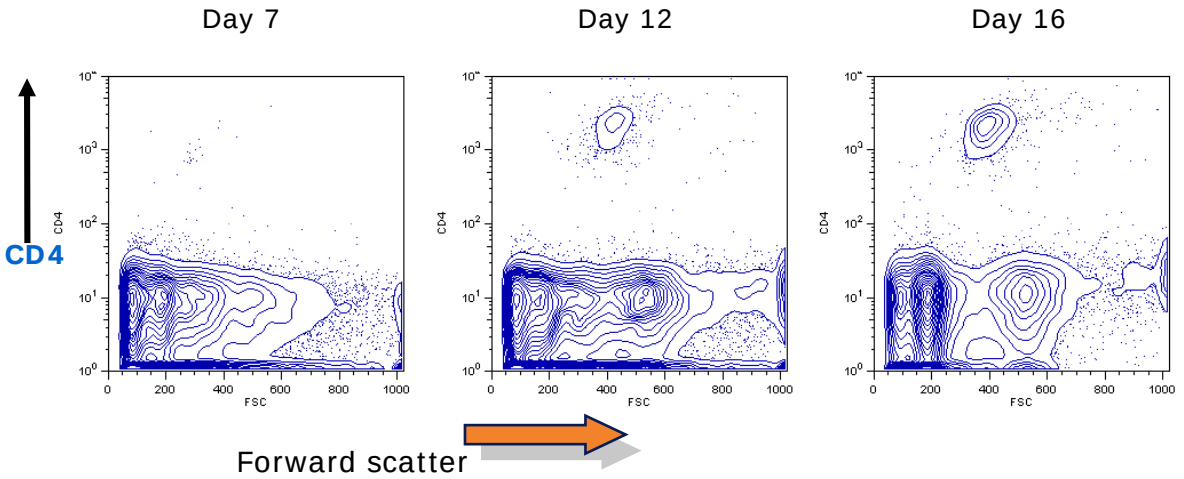

HISTOLOGY, TEFI and FLOW CYTOMETRY

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Clinical disease

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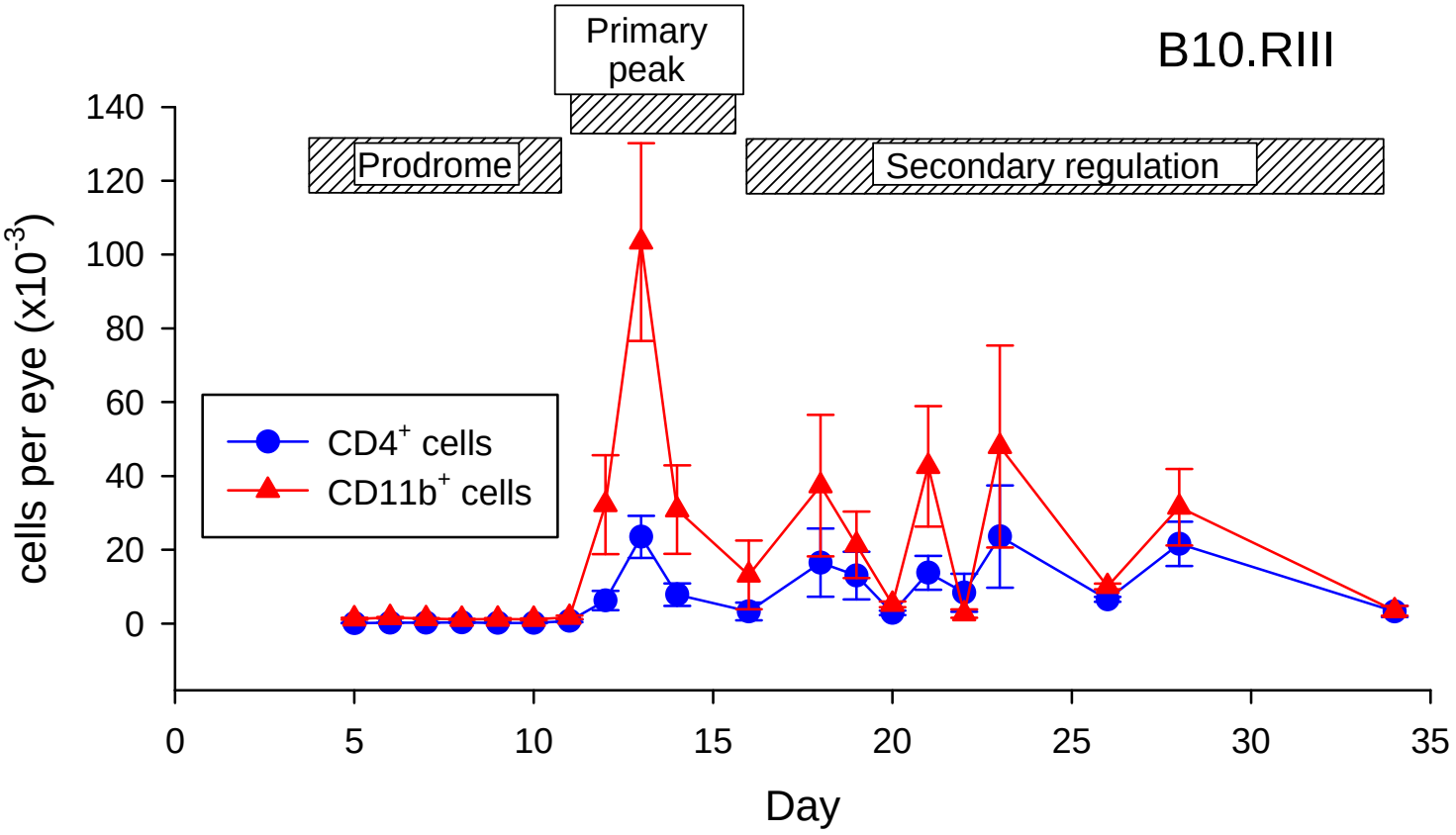
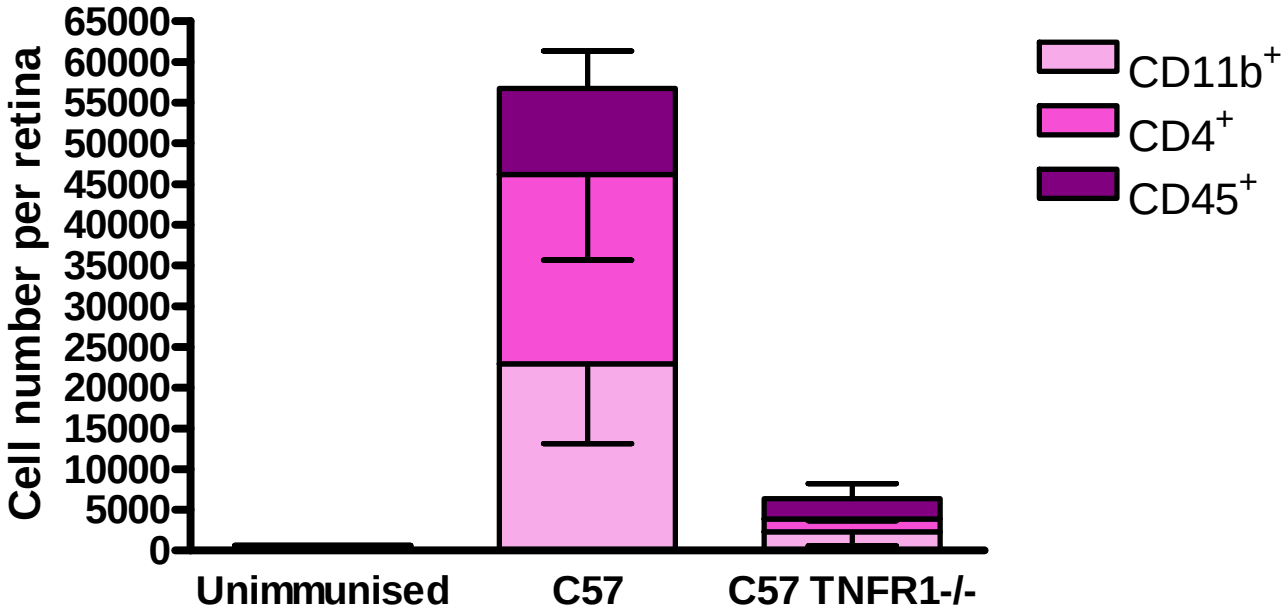
Copland et al. IOVS **49**, 5458 (2008)

Counting cells in EAU



Kerr et al. J.Autoimm **31**, 354-361

TNFR1 knockout mice are resistant to EAU



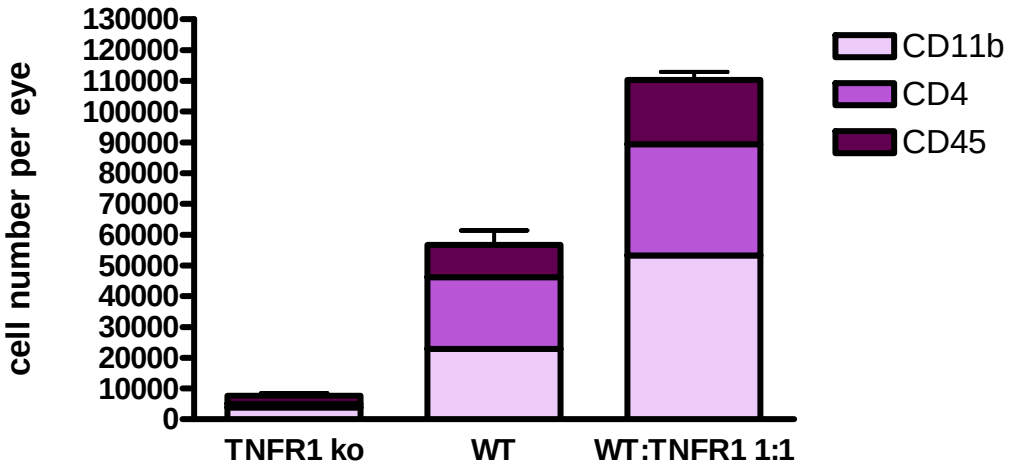
Raveney et al. J.Immunol (in press)

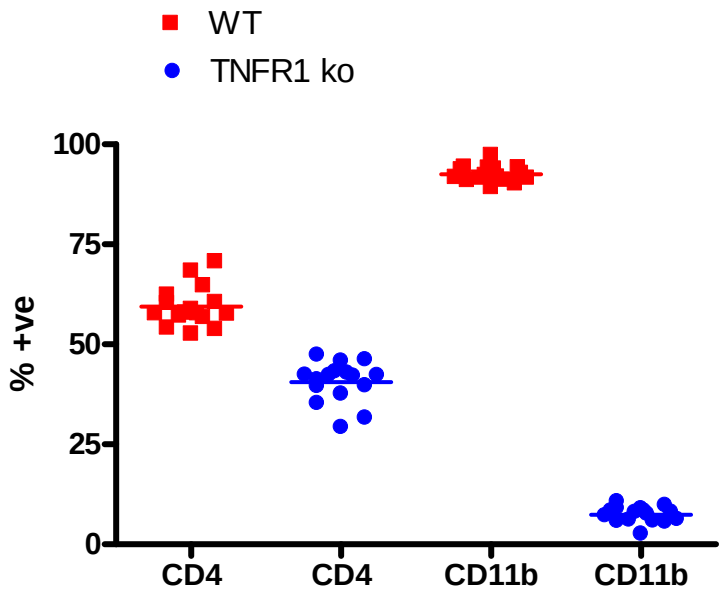
Macrophages but not T cells depend on TNFR1 for recruitment

TNFR1 ko → TNFR1 ko

WT → WT

TNFR1:WT → WT





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