Research advances in animal models for OCD/PANDAS

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Disclosures

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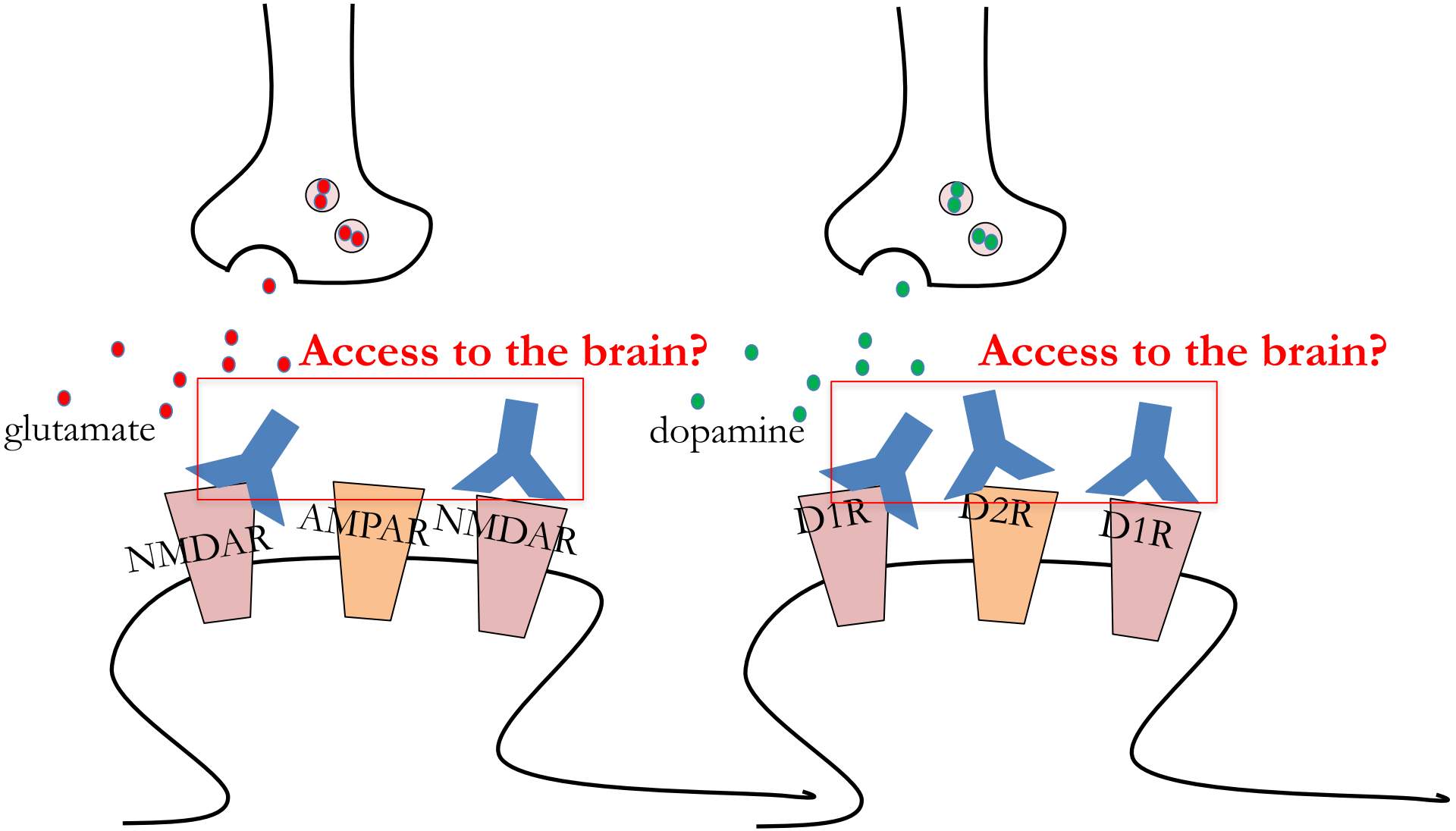
Autoantibodies in movement and psychiatric disorders

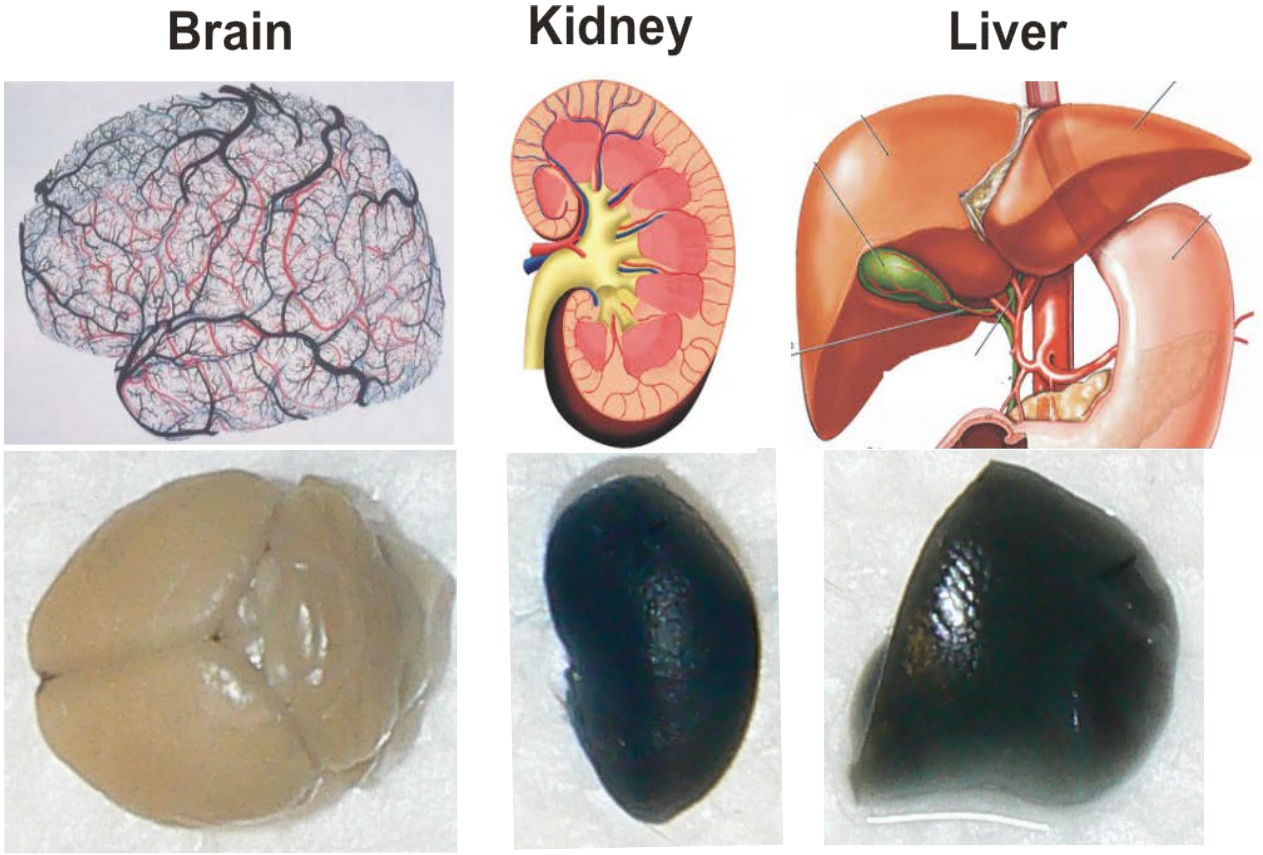
Antibody target	Disease
NMDAR	Autoimmune Encephalitis
GlyR	Progressive Encephalomyelitis with Rigidity and Myoclonus (PERM)
AMPAR	Limbic Encephalitis
VGKC complex	Limbic Encephalitis
$GABA_BR$	Paraneoplastic or immune-mediated limbic encephalitis
D2R, D1R	Basal ganglia encephalitis (Sydenham's chorea, PANDAS)
GAD65	Stiff Person Syndrome (Cerebellar Ataxia)

Sinmaz N *et al.* (2015), Ann. NY Acad. Sci 1351: 22-38

Autoantibodies disrupt communication between neurons in autoimmune encephalitides

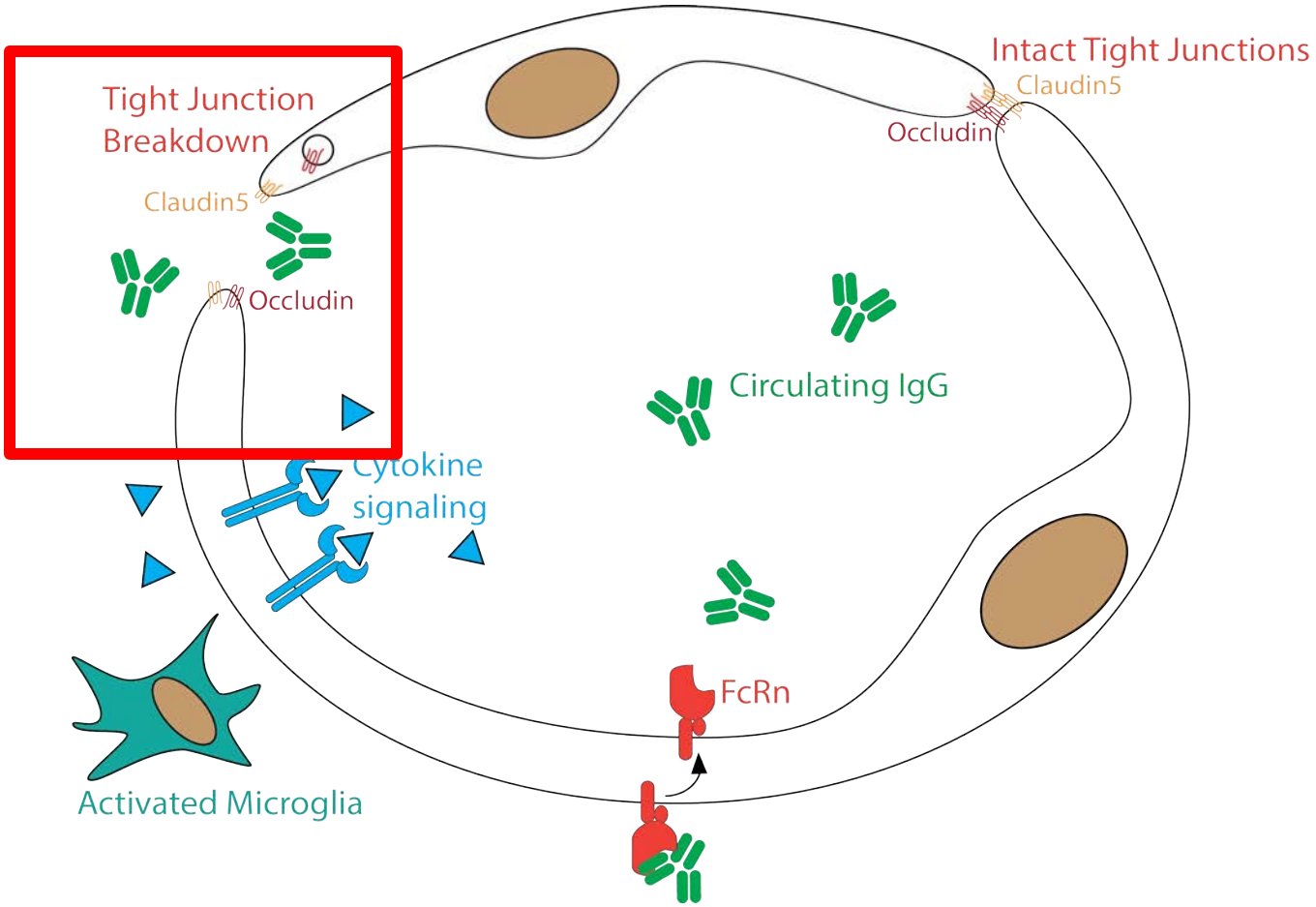


The blood-brain barrier: an important gatekeeper between the blood and central nervous system



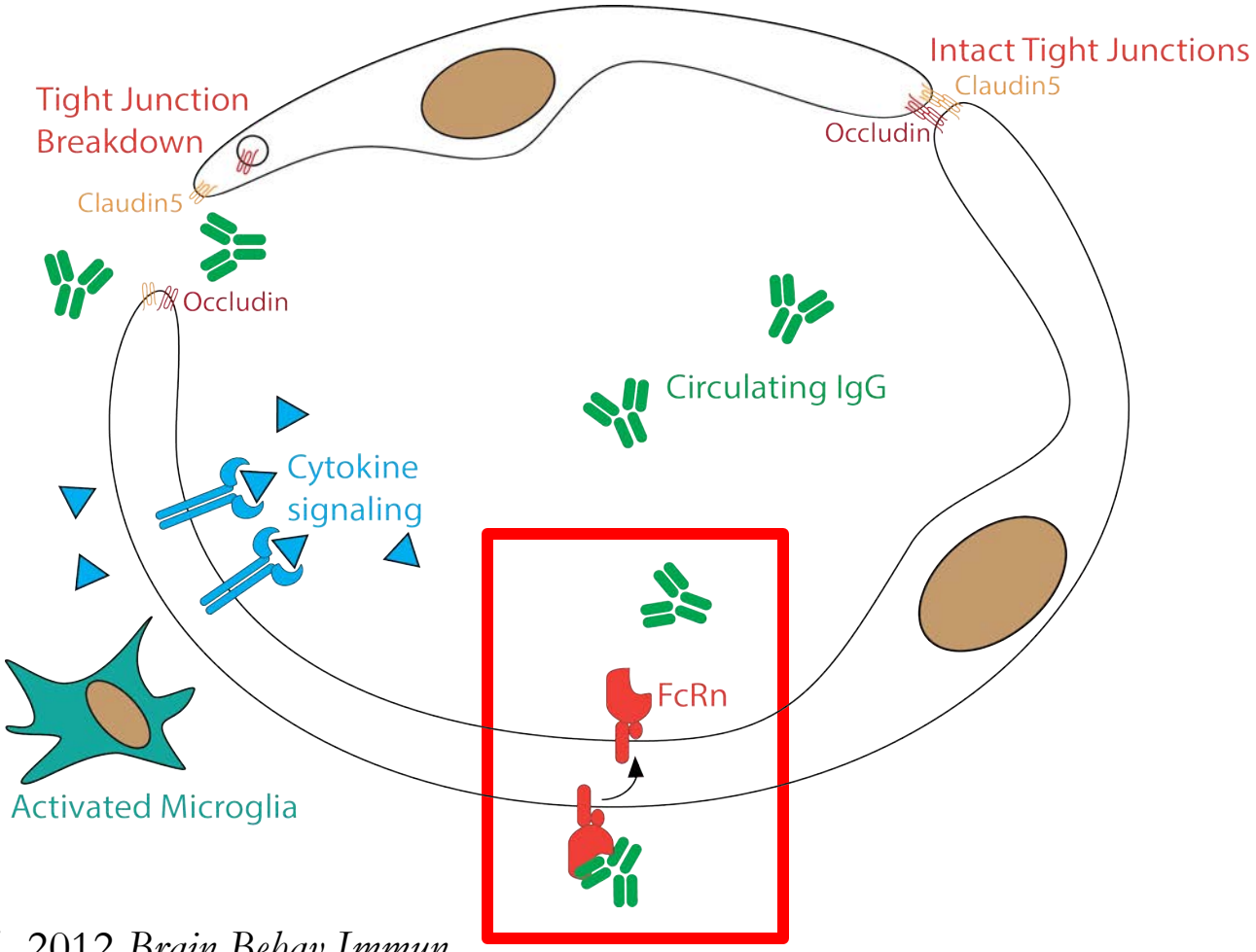
- Maintains brain homeostasis
- Limits CNS entry of
  - pathogens
  - immune cells
  - drugs

Hypothesis 1: Destruction of tight junctions between endothelial cells



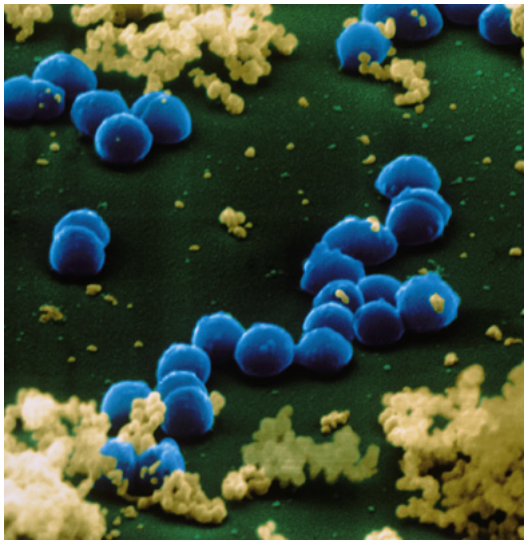
Engelhardt & Ransohoff, 2012 *Trends Immunol*
Huppert, J. *et al.*, 2010 *FASEB*
Okada & Khoury, 2012 *JCI*
Risau W. *et al.*, 1990 *JCB*

Hypothesis 2: Selective transport of antibodies from endothelial cells into the brain



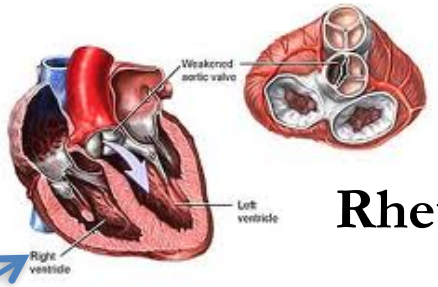
Zhang, D. *et al.*, 2012 *Brain Behav Immun*
Abuqayyas & Balthasar, 2012 *Mol Pharmaceutics*
Okun, E. *et al.*, 2010 *Neuromol Med*
Diamond, B. *et al.*, 2013 *Ann Rev Immunol*

Group A β-hemolytic *Streptococcus pyogenes* causes a plethora of autoimmune diseases



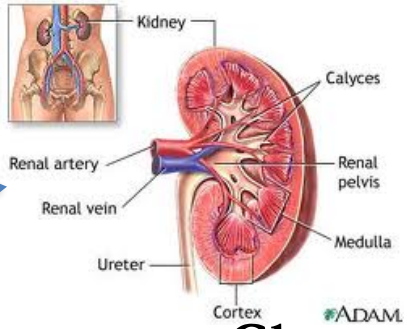
Implicated in autoimmunity

heart



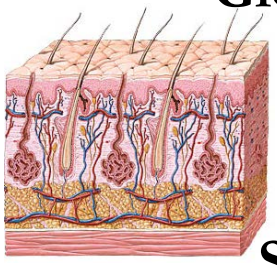
Rheumatic fever

kidney



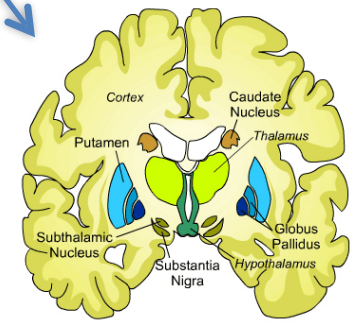
Glomerulonephritis

Skin (viral toxin)



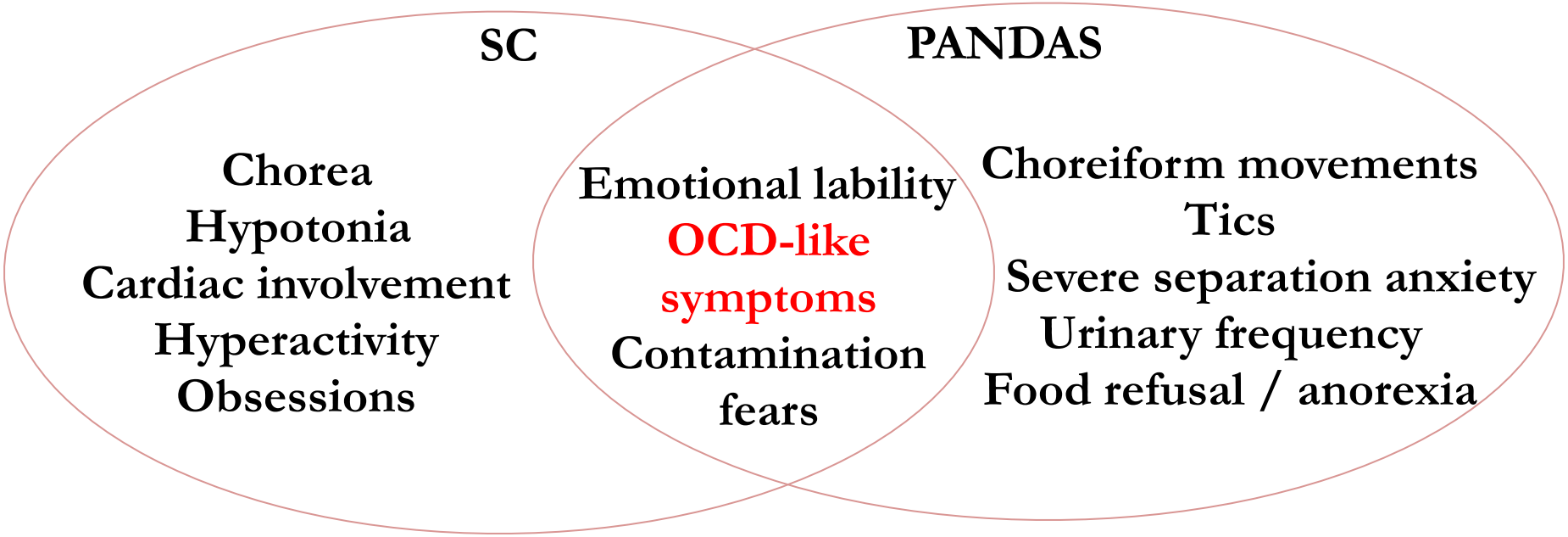
Scarlet fever

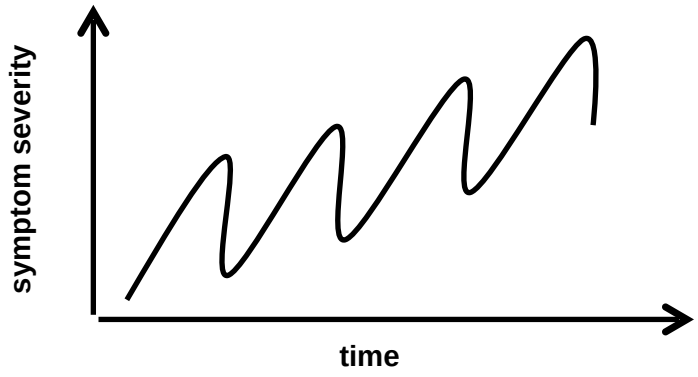
brain



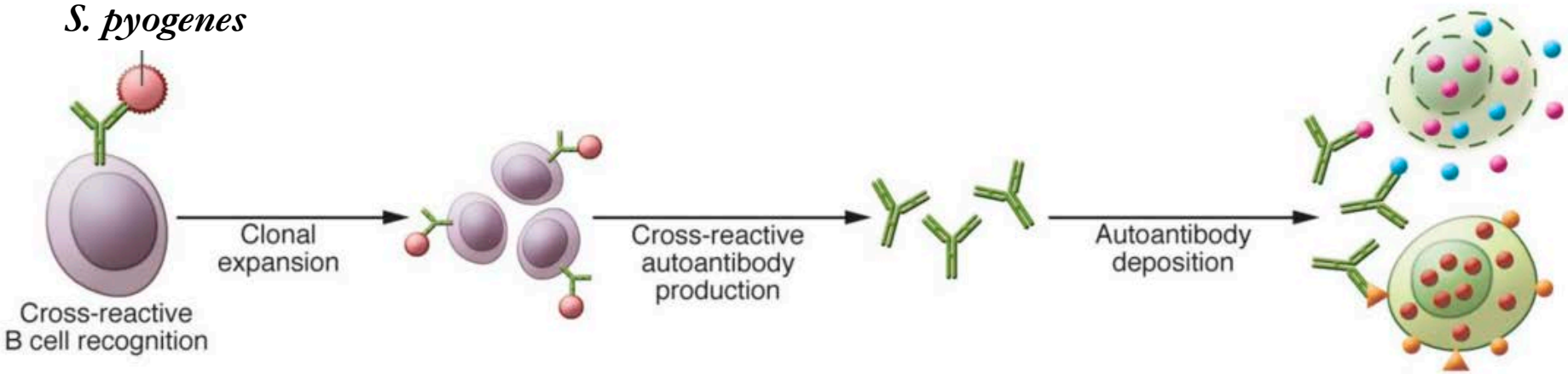
Sydenham's chorea
PANDAS

Neurological symptoms in SC and PANDAS

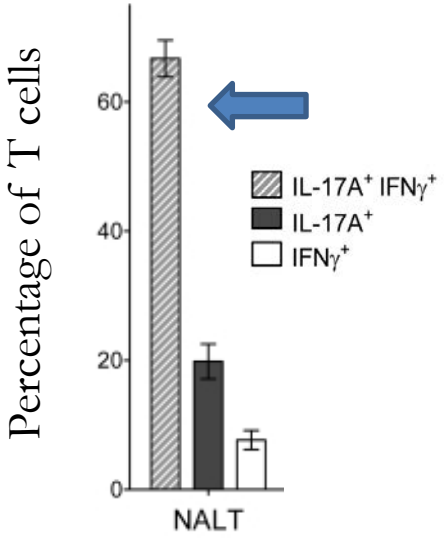


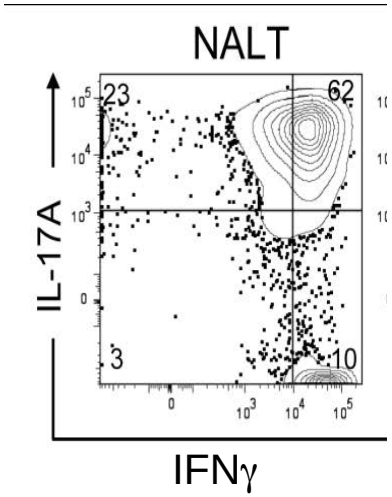


S. pyogenes activates both the humoral (antibodies) and cellular (Th17 cells) immune system



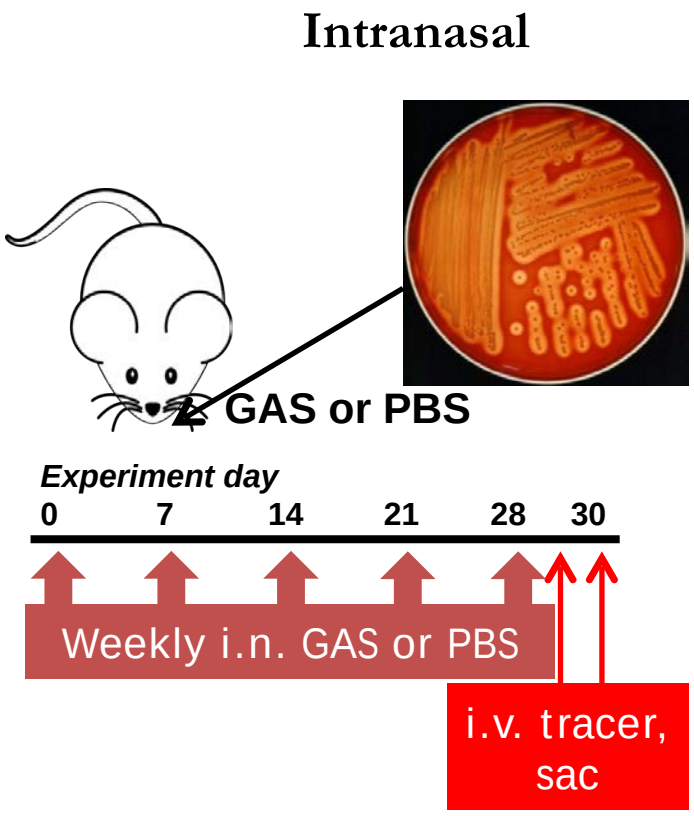
Generation of Th17 cells after multiple intranasal infections

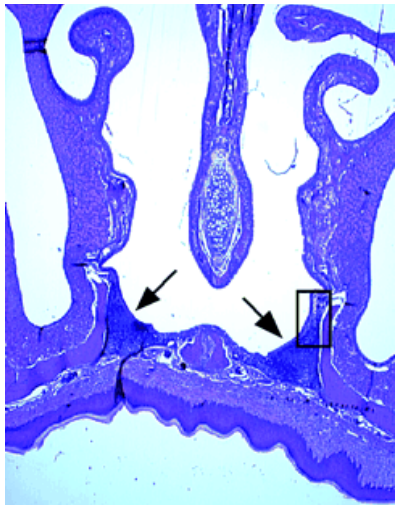


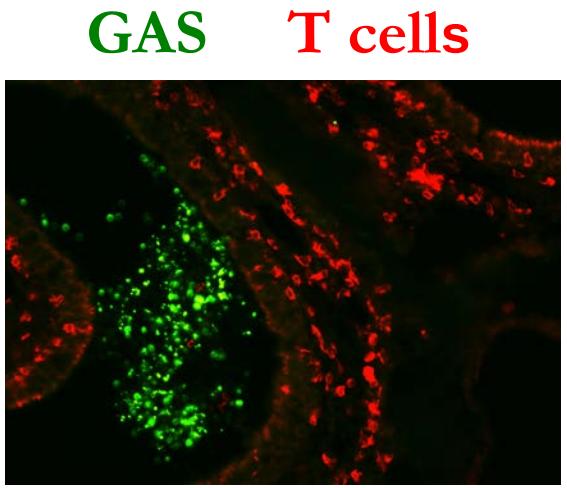


Dileepan et al., (2011). *PLoS Pathogens*

A novel intranasal rodent model to understand cell-mediated immunity after *S. pyogenes* infections





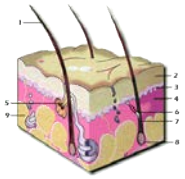


Dileepan T *et al.*, (2011) *PLoS Pathogens;*
Dileepan T., Smith E. *et al.*, 2016 *J Clin Invest*

Th17 cellular immune response: a balance between protection and disease

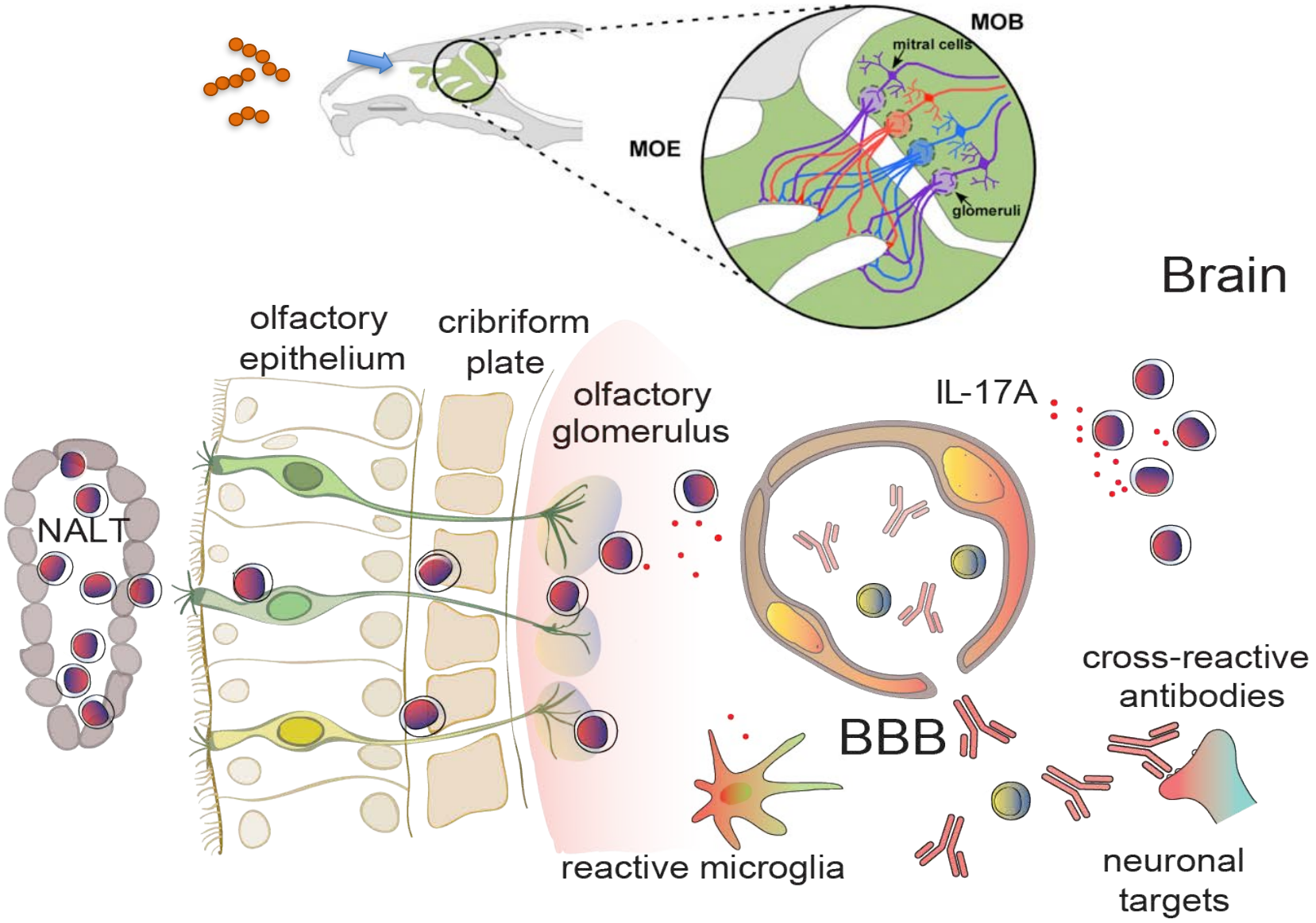
Normal immune response

Immune pathology



Hypothesis: Dysregulated Th17 immune response to *S. pyogenes* infections is key to understanding "autoimmune" complications associated with this pathogen.

Novel pathway for T cell entry into the CNS



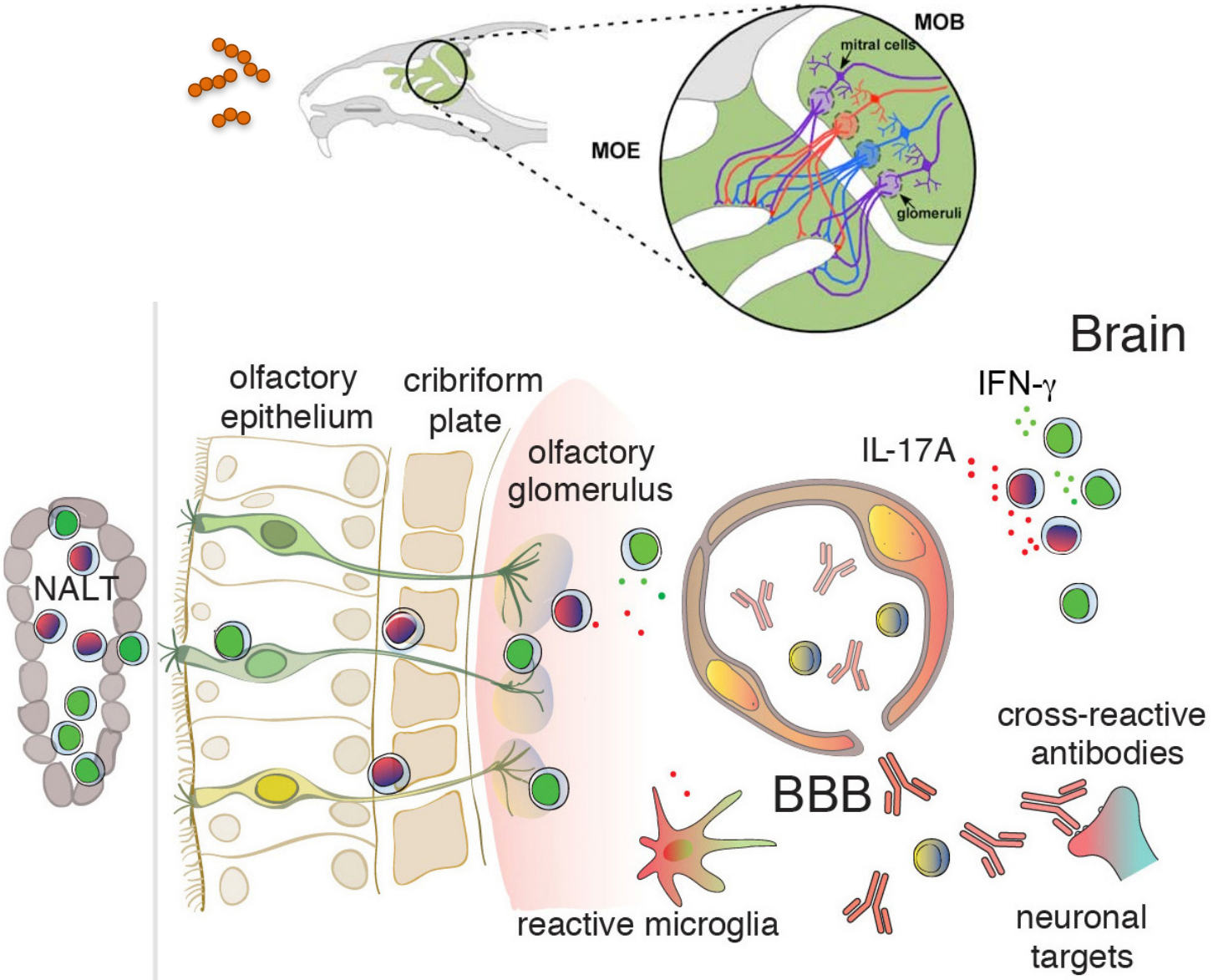
Dileepan T., Smith E. *et al.*, 2016 *J Clin Invest*

Outline

1. What is the role of GAS-specific Th17 cells in post-infectious basal ganglia encephalitis?

2. How do $CD4^+$ T cells gain access to the brain?

Th17 and Th1 cells are present in the CNS after multiple GAS infections

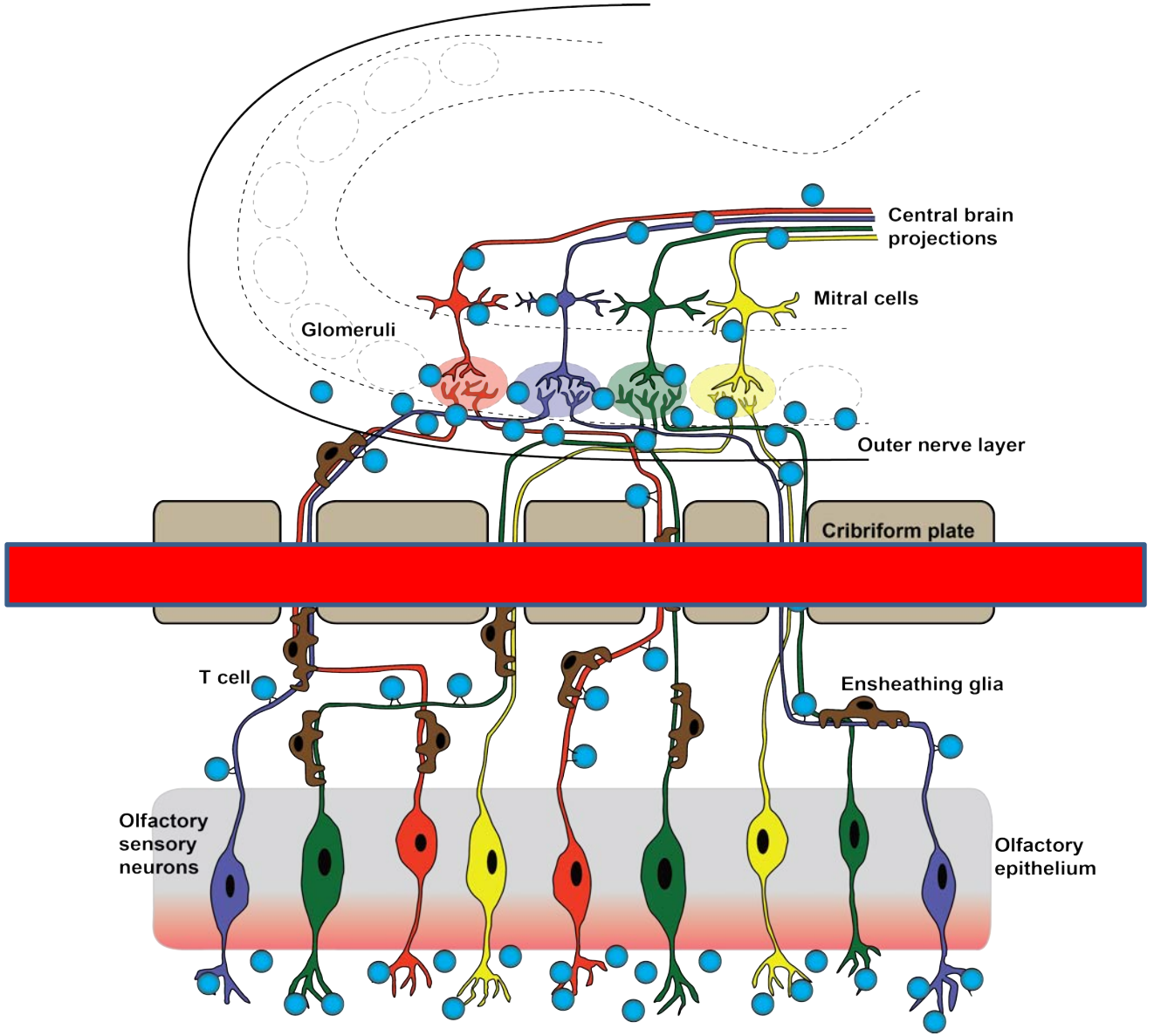


Outline

1. What is the role of GAS-specific Th17 cells in post-infectious basal ganglia encephalitis?

2. How do $CD4^+$ T cells gain access to the brain?

Blocking the recruitment of T cells into the CNS may be beneficial for the disease



Acknowledgements

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