

Dysregulation of B cells in Clinically Isolated Syndrome and Multiple Sclerosis

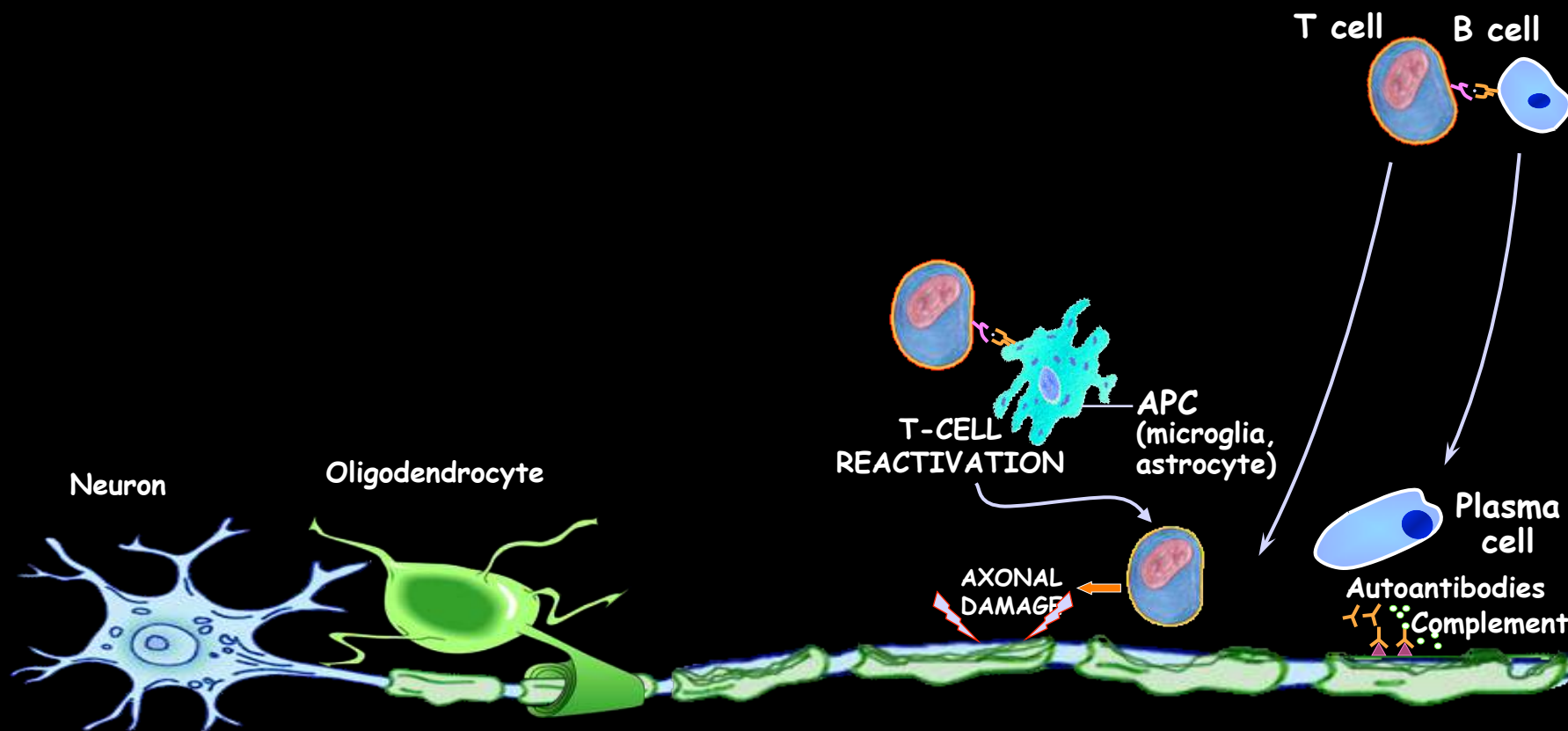
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Associate Professor of Neurology and Neurotherapeutics

Associate Professor of Immunology

University of Texas Southwestern Medical Center

Dallas Texas



DISCLOSURES:

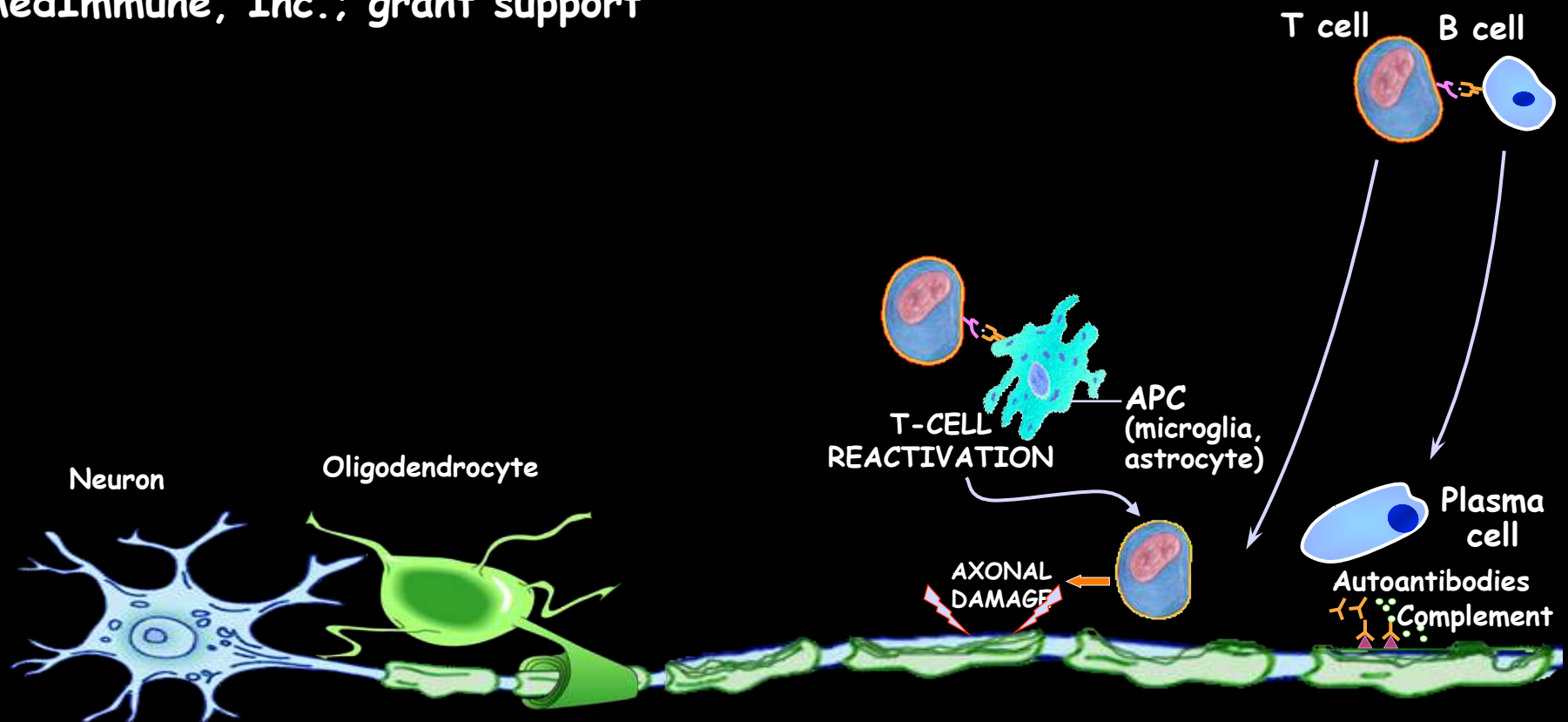
National MS Society: grant support

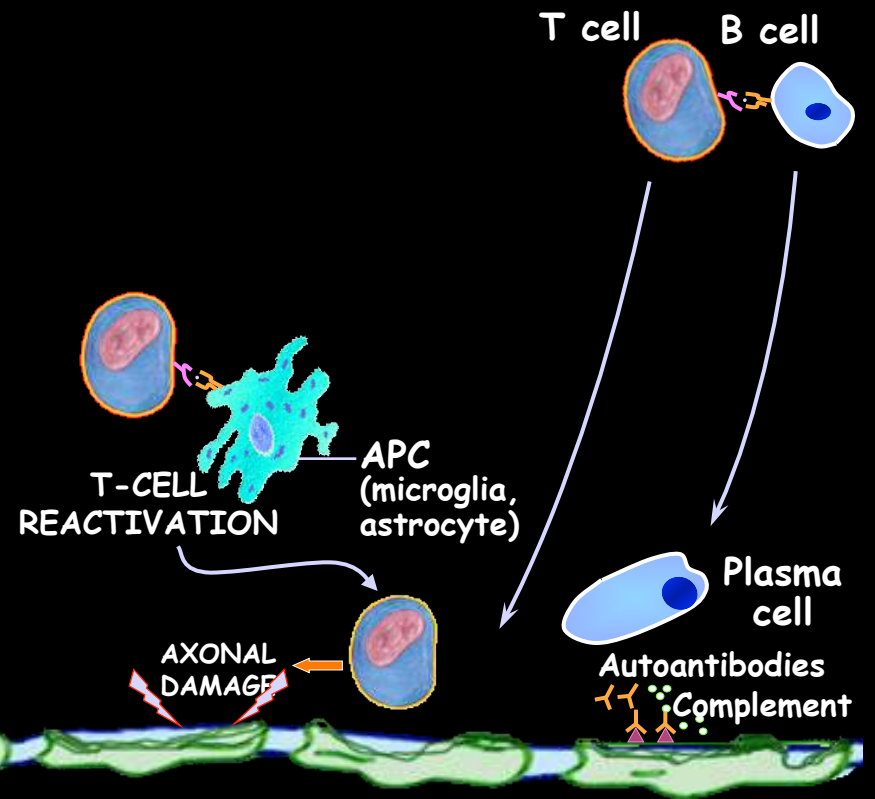
Genentech, Inc.; Advisor

TEVA Neuroscience; grant support

DioGenix, Inc.; grant support

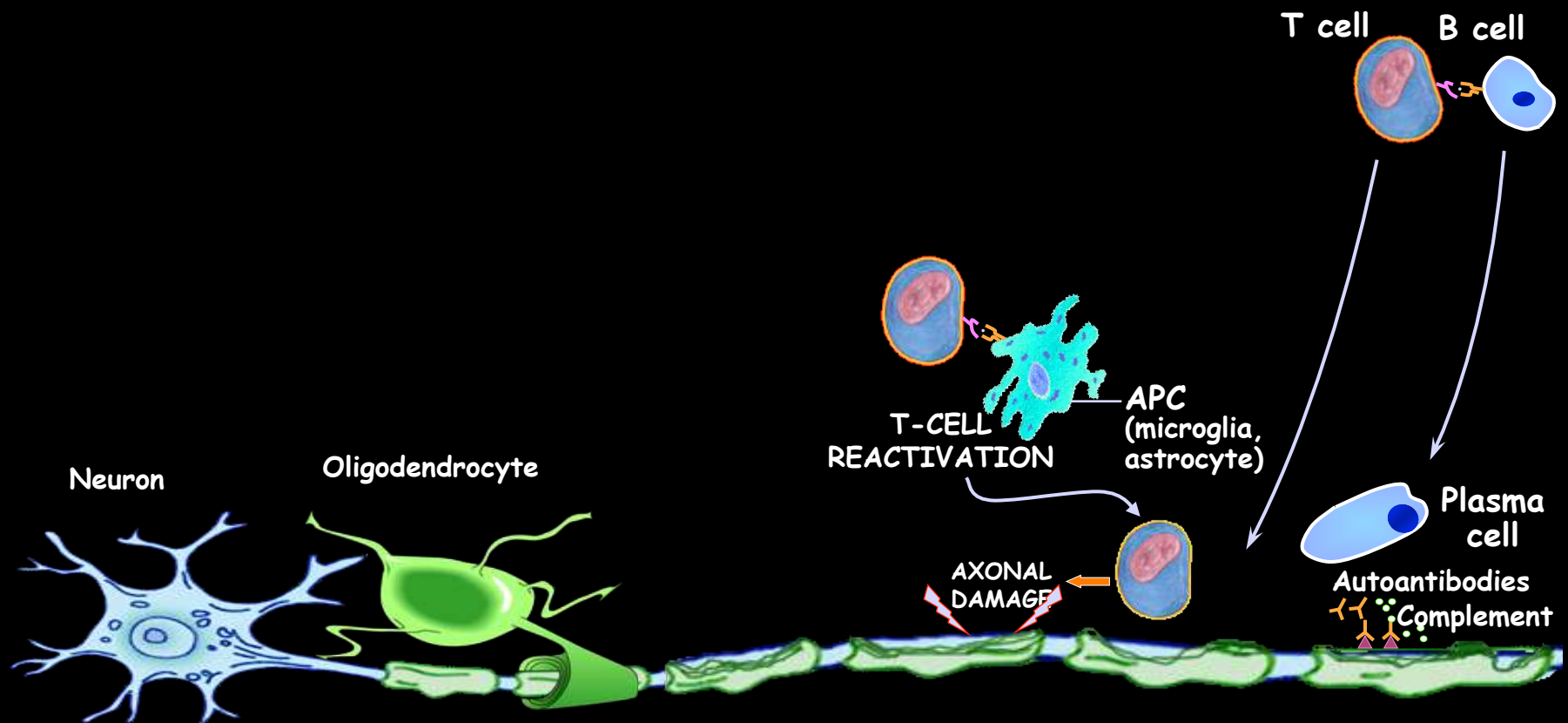
MedImmune, Inc.; grant support





Objectives:

- What are some important features of TM from an Immunologist's perspective?
- Do TM patients have a different immune profile compared to ON patients?
- Can we use this information to identify patients that will develop MS?
- Do antibodies from B cells in the CSF bind to the brain?



TRANSVERSE MYELITIS

- Symptoms involve weakening of limbs or sensations of numbness due to demyelination occurring across short segments of the spinal cord
- The presence of lesions in the brain of TM patients also increases the risk of conversion to MS
- TM patients with brain lesions typically have a faster occurrence of a second attack than patients with optic neuritis (ON)
- ON patients have better long-term prognosis than other presentations including TM

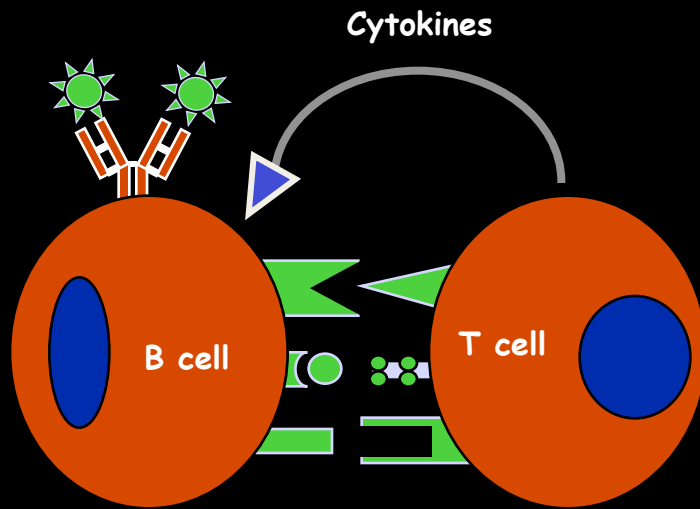
These differences in progression to clinically definite MS and location of initial lesions between ON and TM patients may suggest different underlying biology.



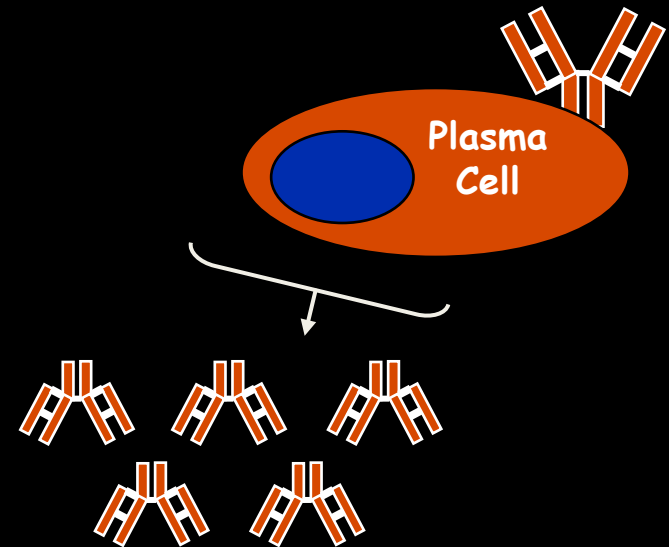
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WHAT ARE THE JOBS OF A B CELL?



Activate T cells
that are involved in disease



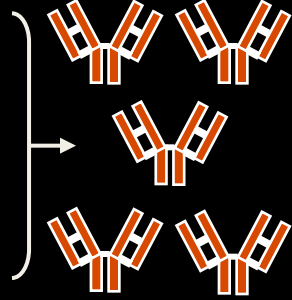
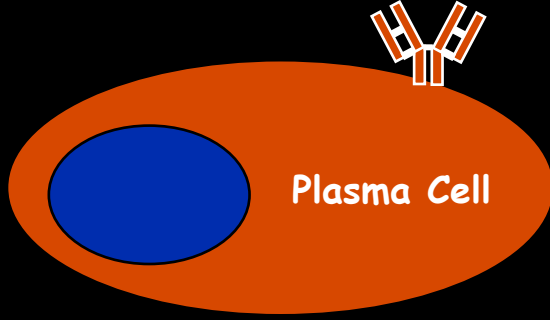
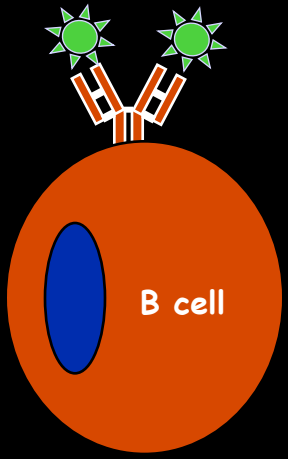
Produce antibodies
that are involved in the disease

3 QUESTIONS WE ARE ASKING:

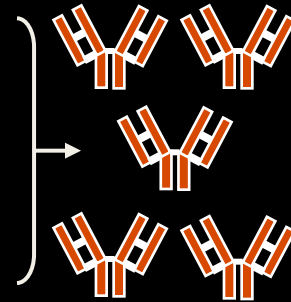
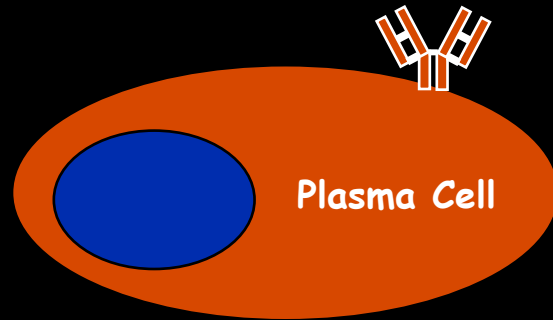
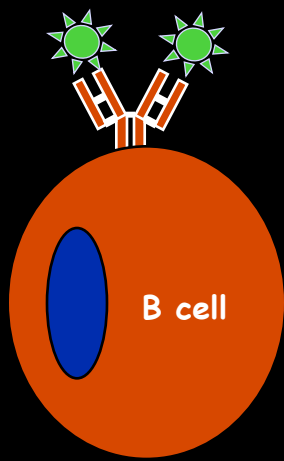
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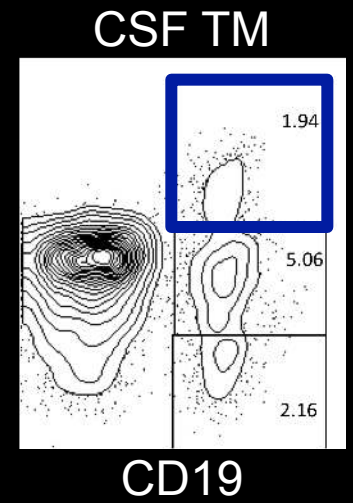
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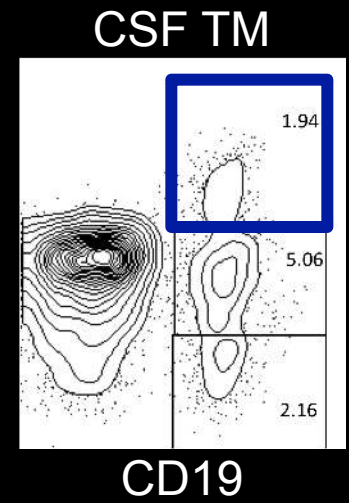
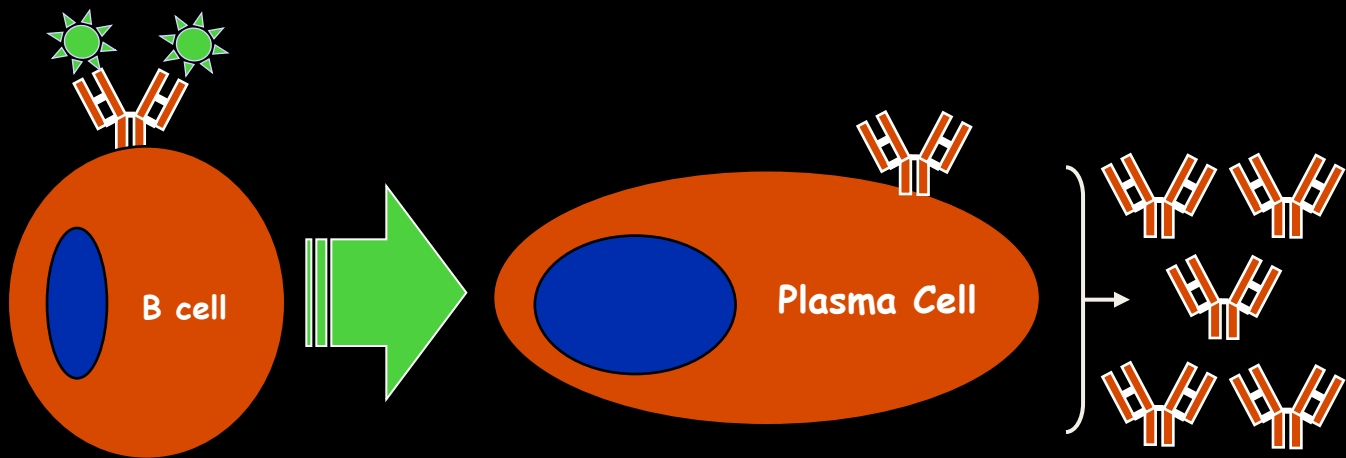


CD27

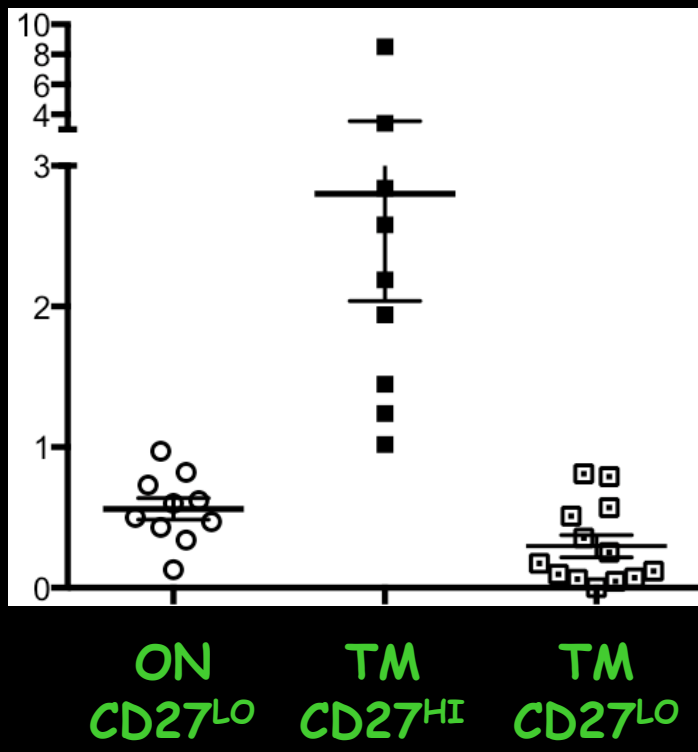


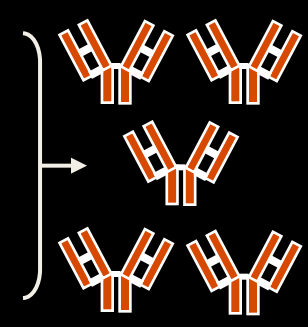
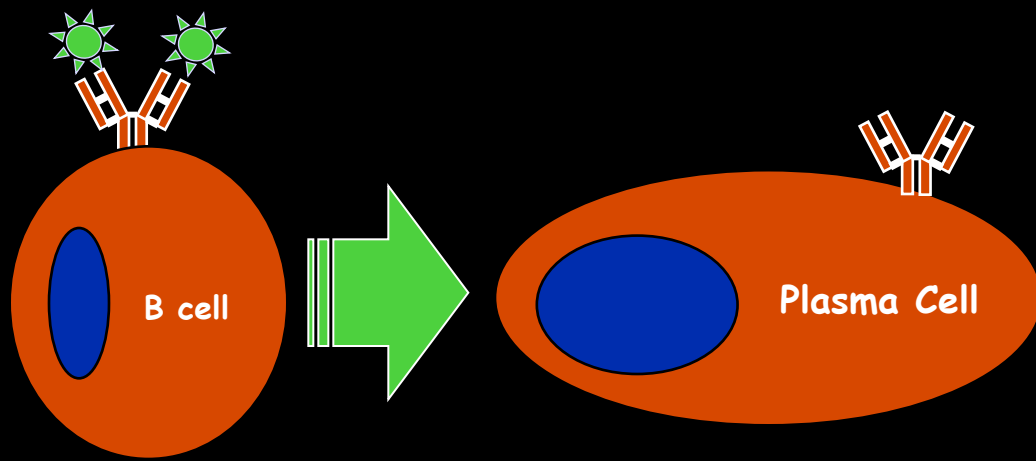
CD27



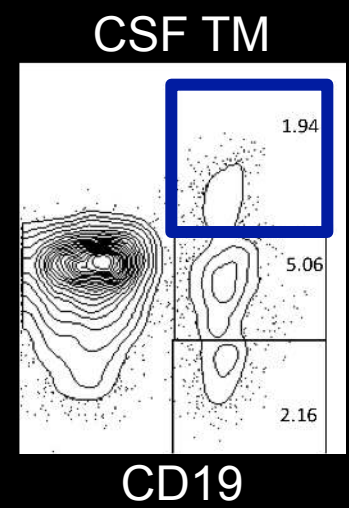


CEREBROSPINAL FLUID

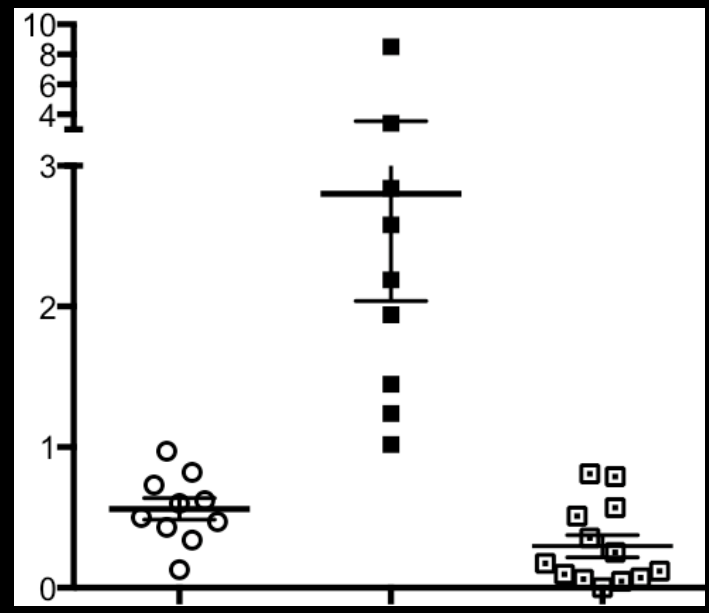




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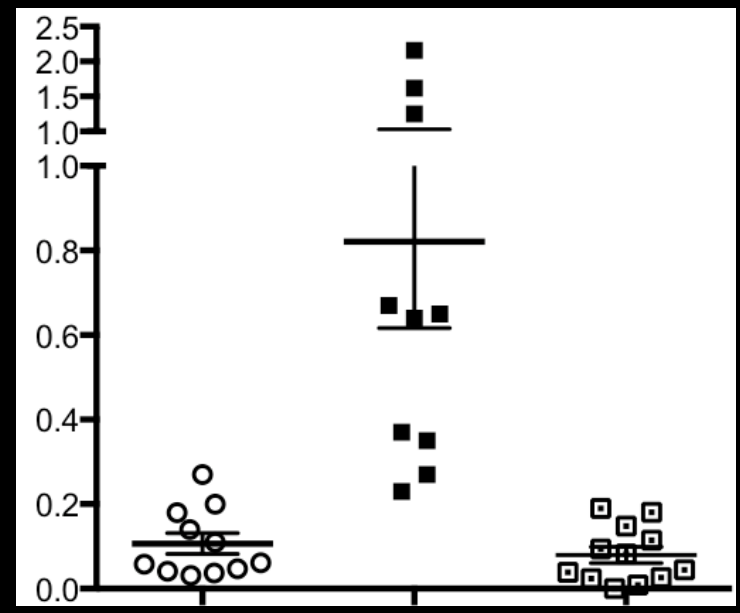


CEREBROSPINAL FLUID



ON CD27^{LO} TM CD27^{HI} TM CD27^{LO}

BLOOD



ON CD27^{LO} TM CD27^{HI} TM CD27^{LO}

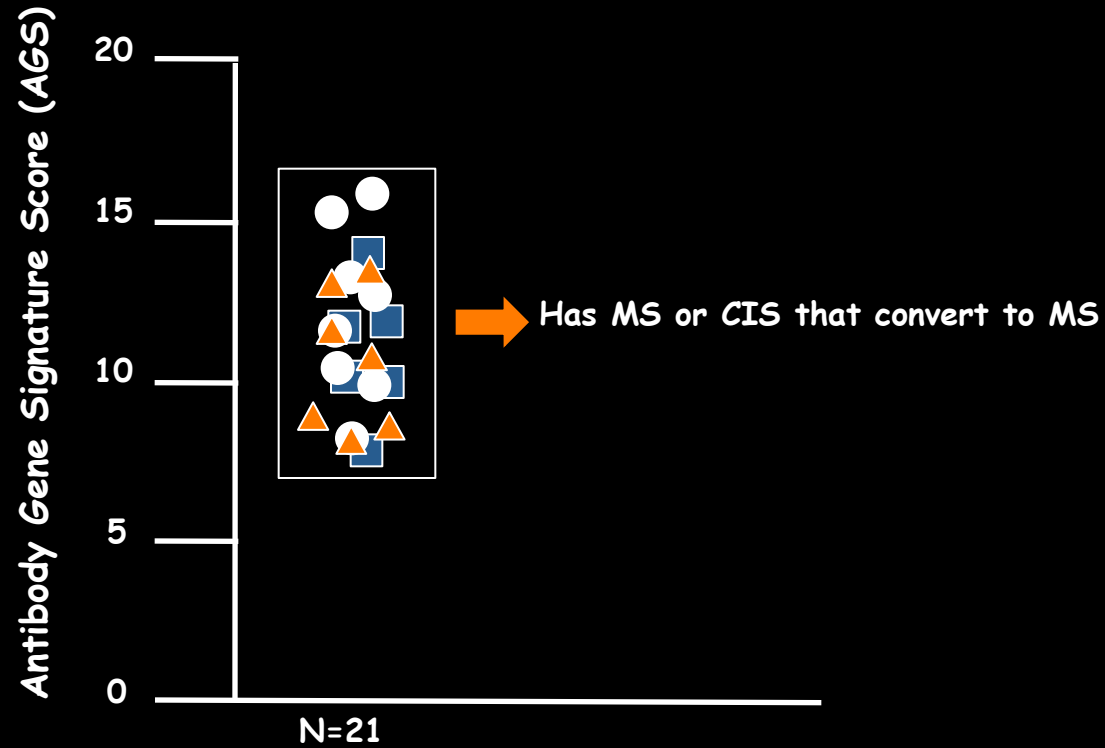
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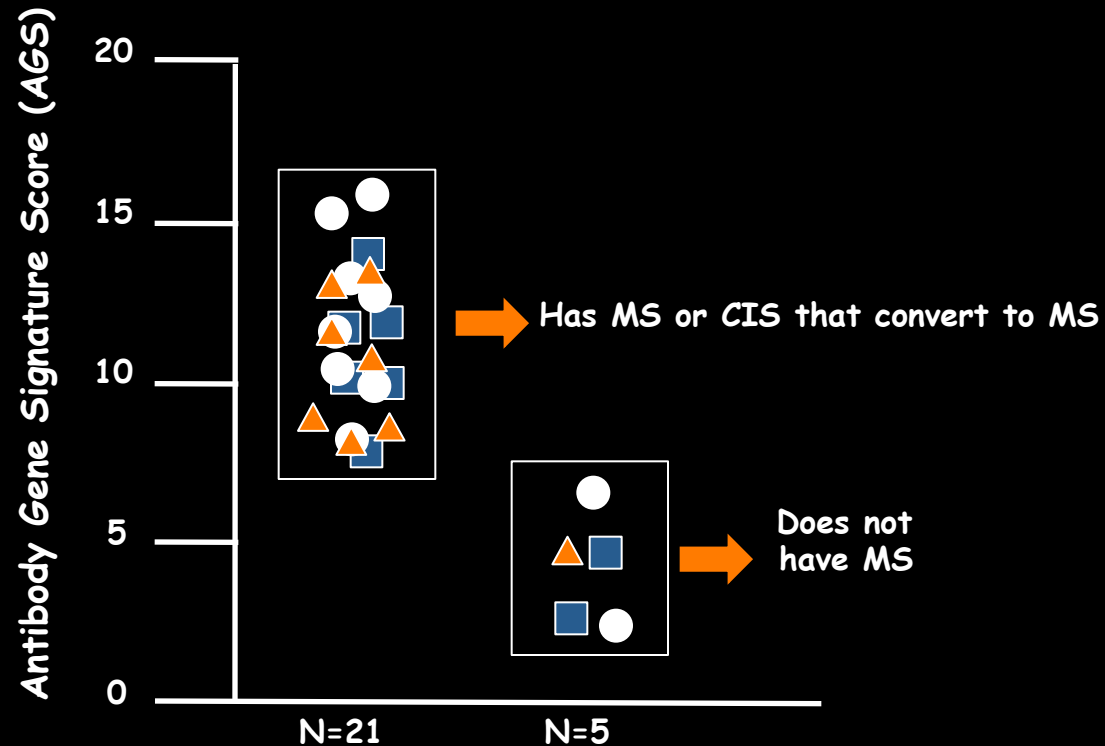
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B cell antibody genetics can be used to classify important disease groups



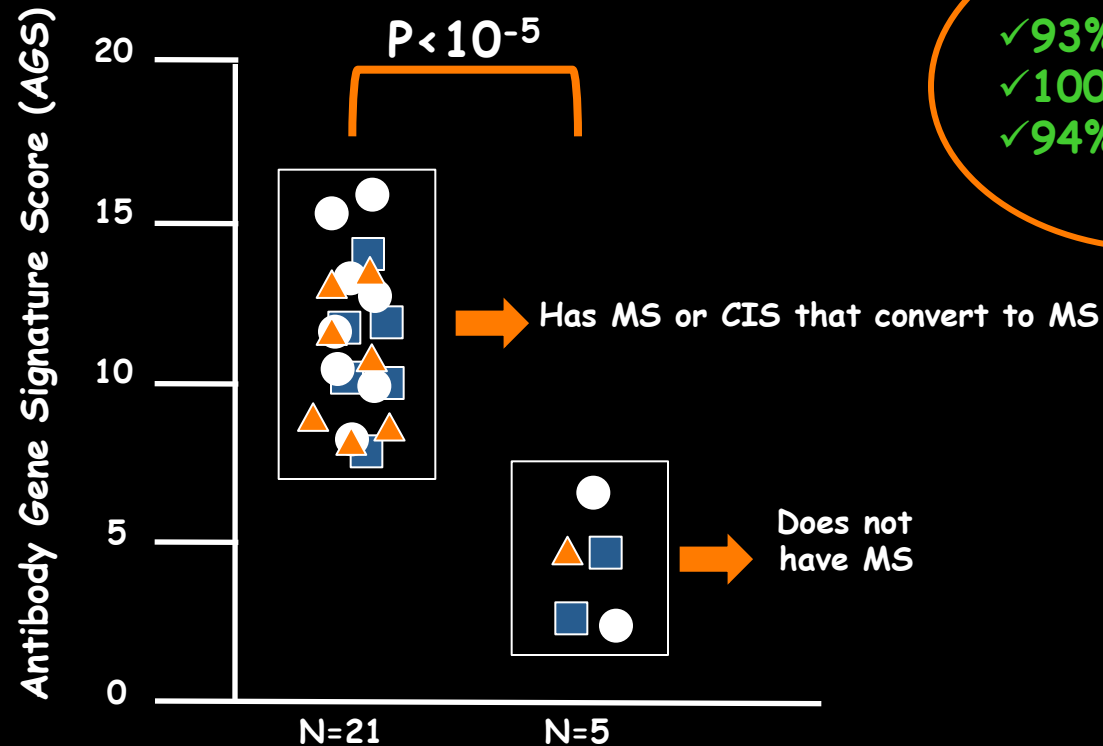
B cell antibody genetics can be used to classify important disease groups



Over 100,000
codons analyzed

Cameron et al. (2009) *Journal of Neuroimmunology*: 213, 123-130
and unpublished data

B cell antibody genetics can be used to classify important disease groups



✓93% PPV
✓100% NPV
✓94% Accuracy

Over 100,000
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MSPrecise/DioGenix

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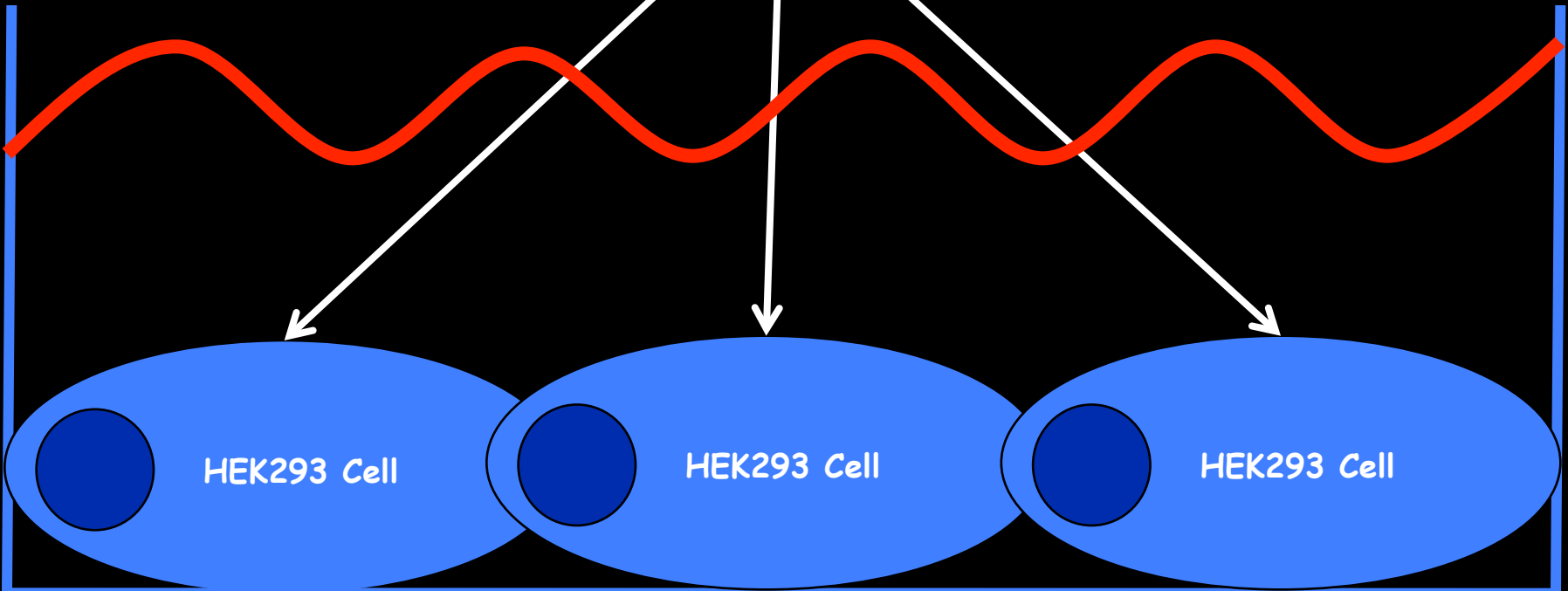
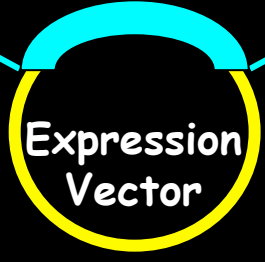
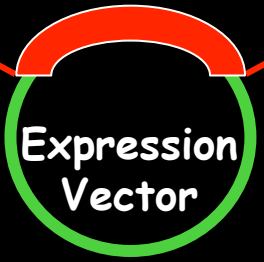
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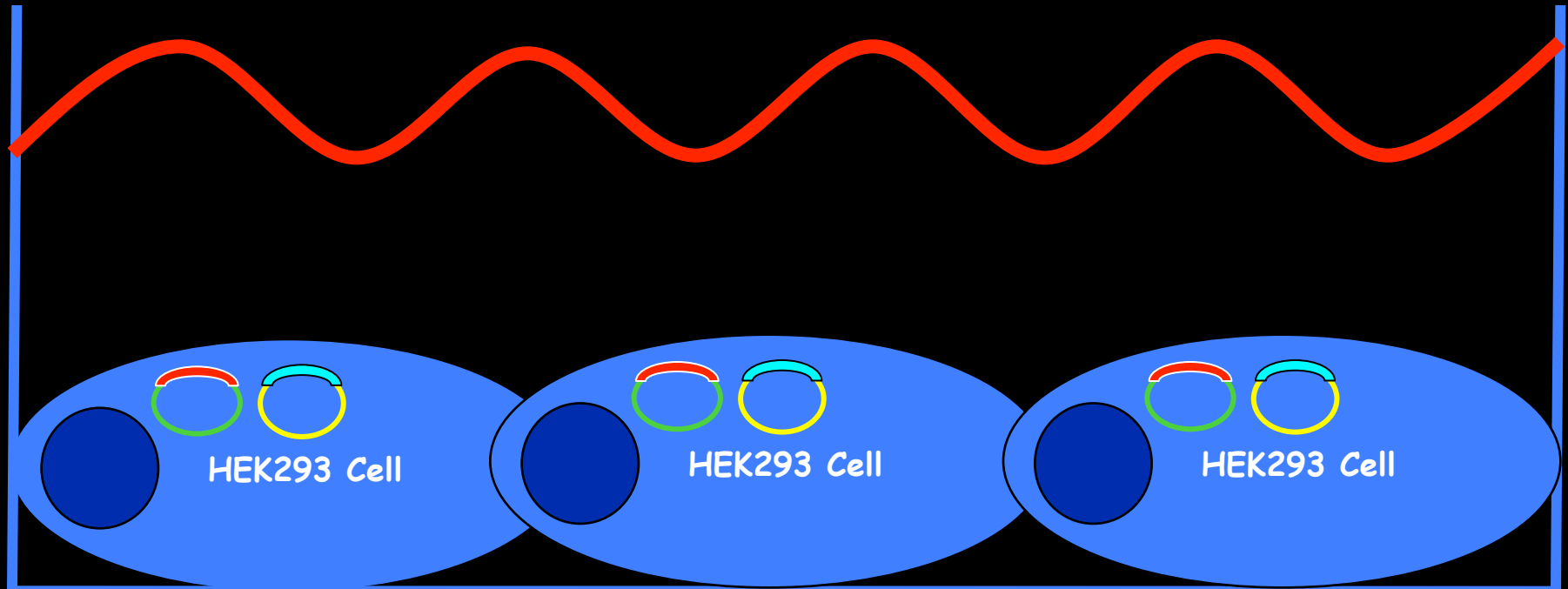
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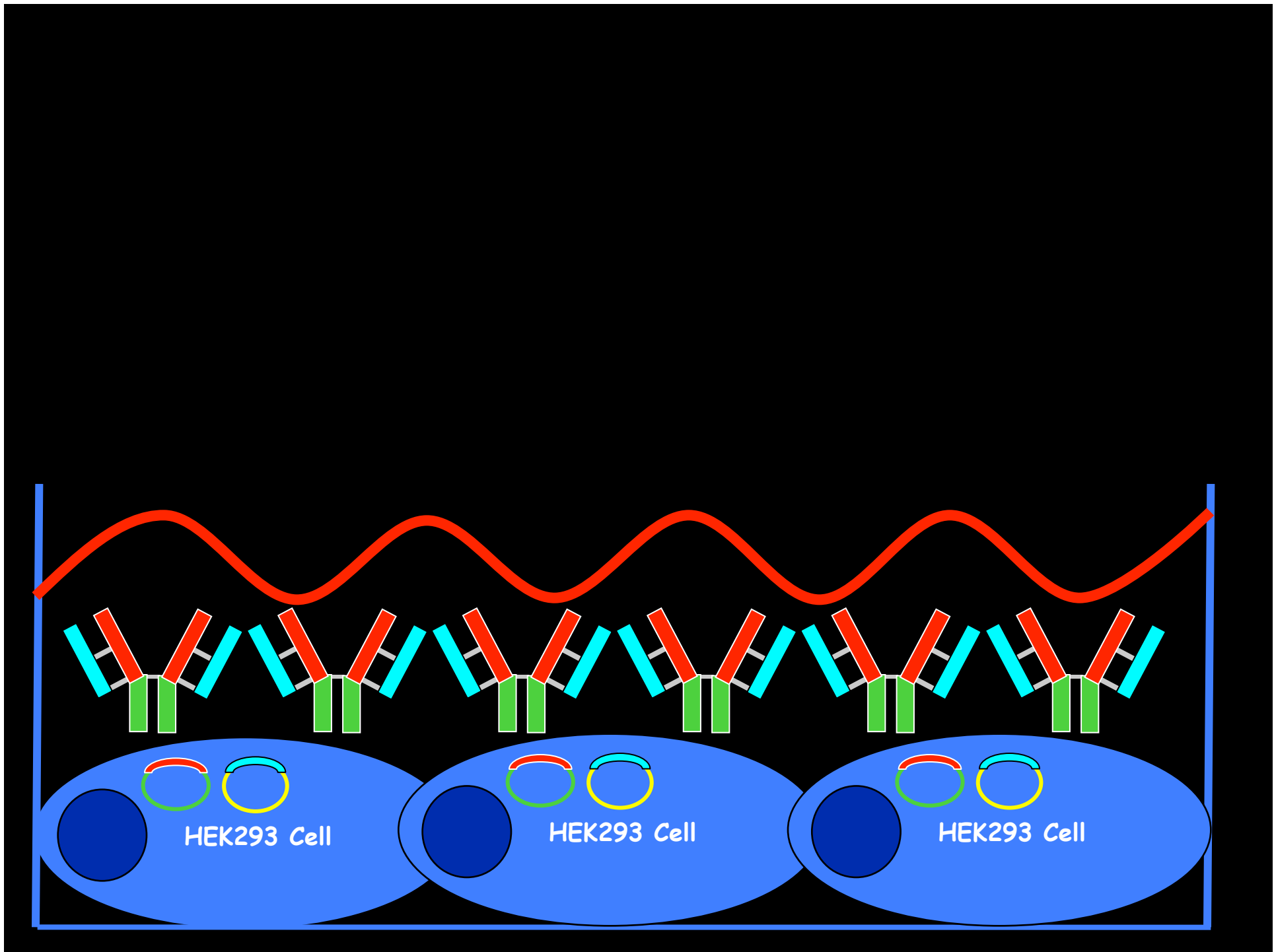
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Antibody Heavy Chain

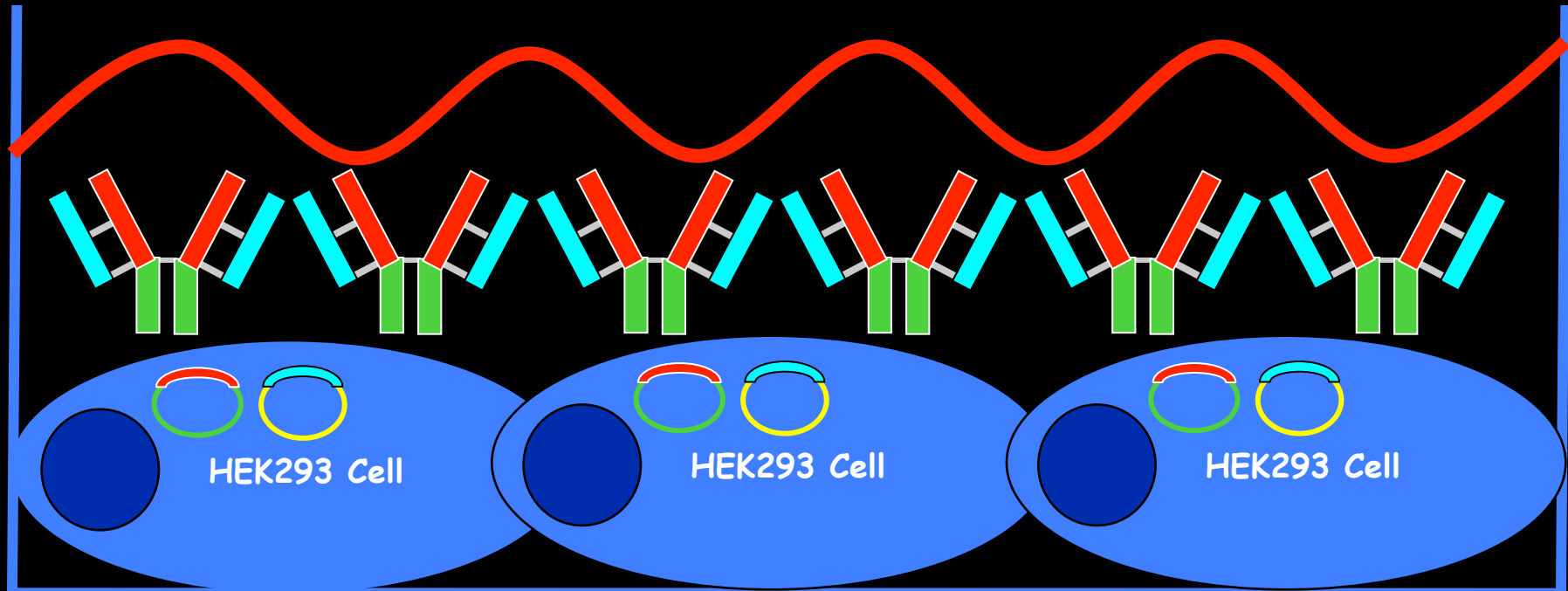
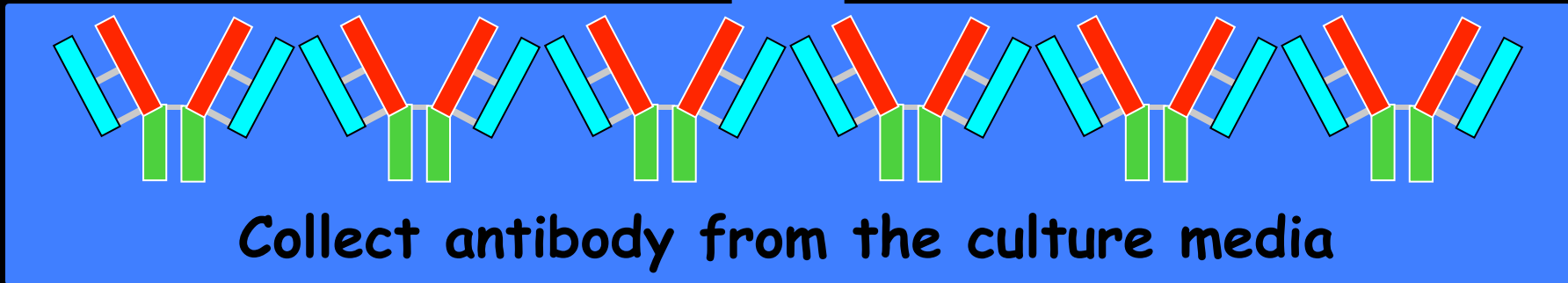
Antibody Light Chain





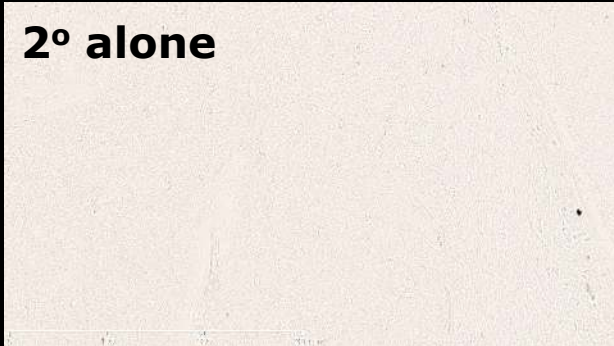


Test for binding to brain tissue

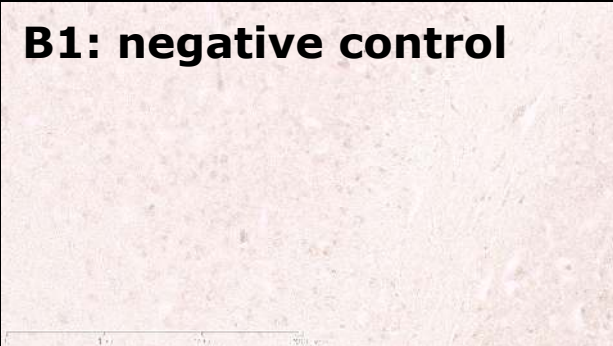


Monoclonal antibodies made by B cells in the CSF of MS patients and patients at high risk to develop MS bind to neurons and astrocytes

2° alone



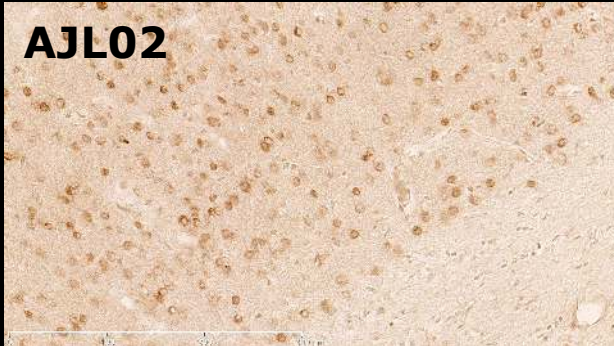
B1: negative control



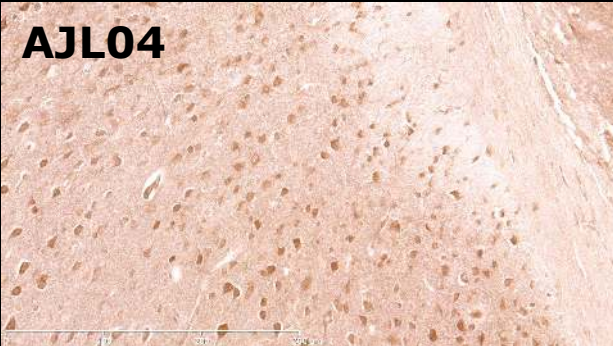
G11: positive control



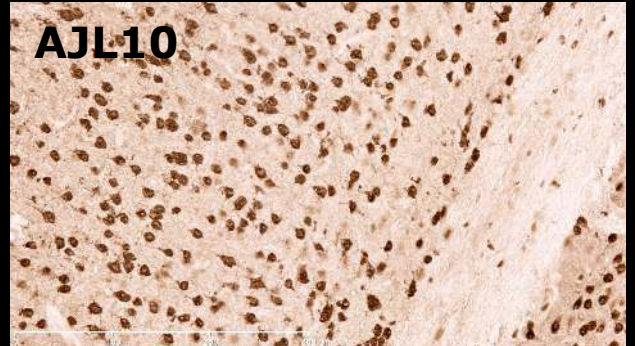
AJL02



AJL04



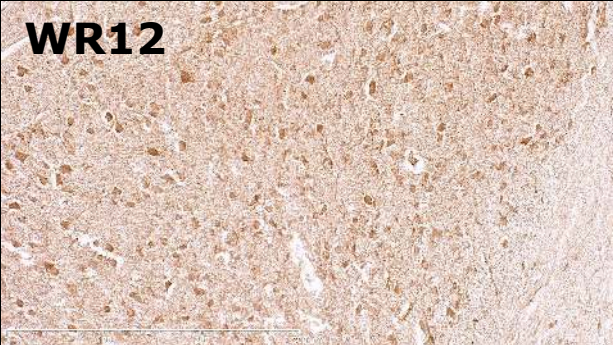
AJL10



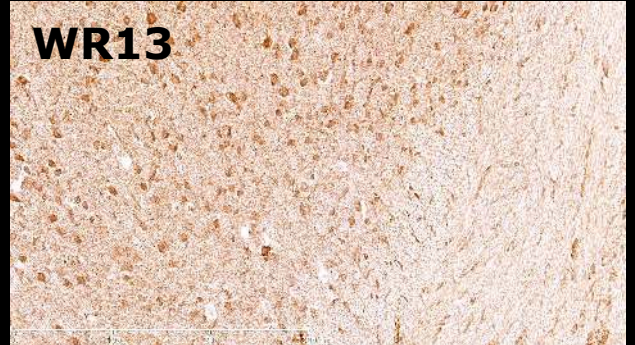
WR03



WR12



WR13

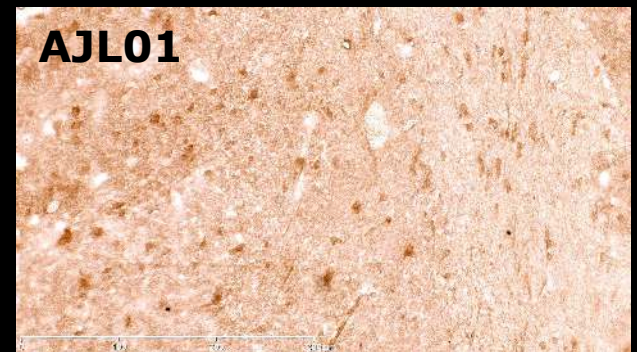
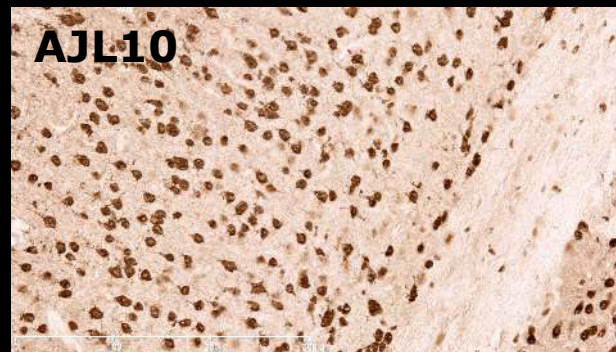
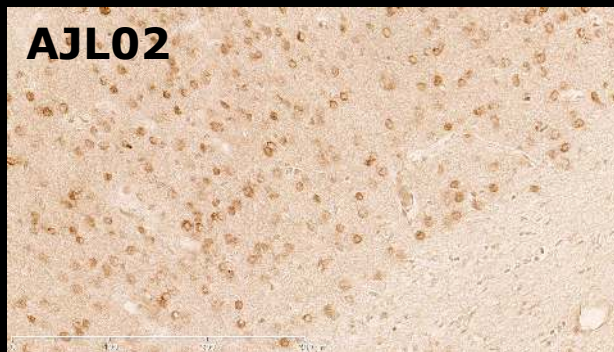


Monoclonal antibodies made by B cells in the CSF of MS patients and patients at high risk to develop MS bind to neurons and astrocytes

**Patient 1:
CDMS**

**Patient 2:
CIS-ON**

**Patient 3:
CIS-TM**



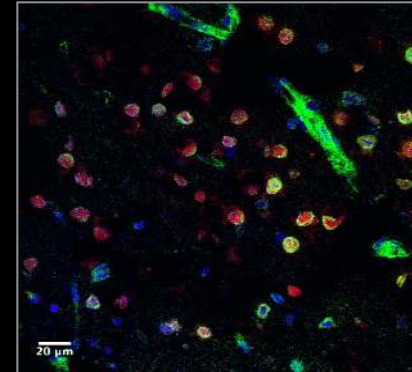
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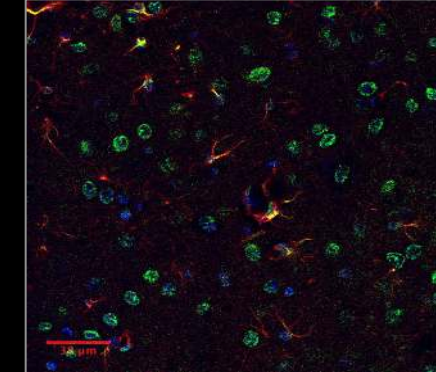
AJL02: neurons
AJL02: astrocytes



neurons **AJL02 rAb**

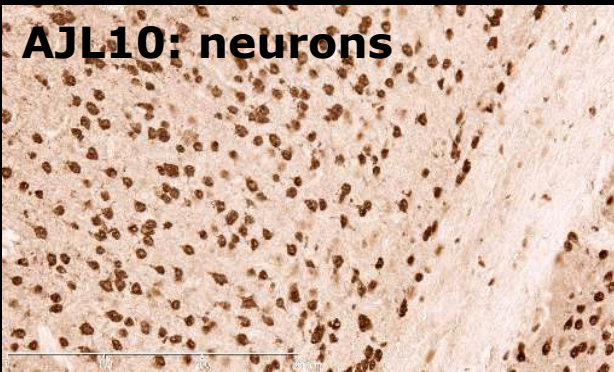


astrocytes **AJL02 rAb**

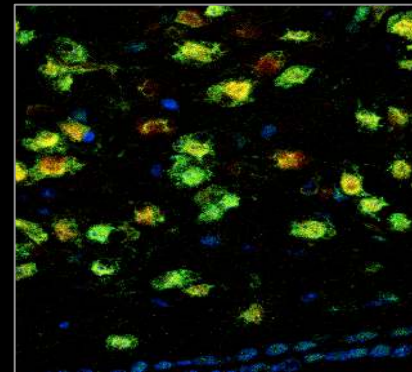


**Patient 2:
CIS-ON**

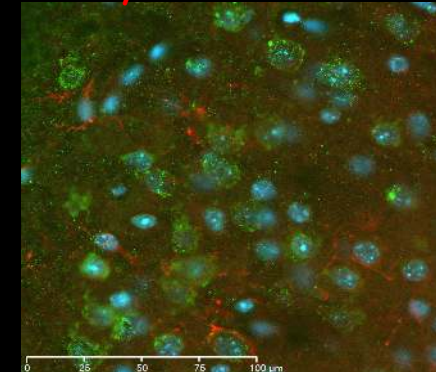
AJL10: neurons



neurons **AJL10 rAb**



astrocytes **AJL10 rAb**

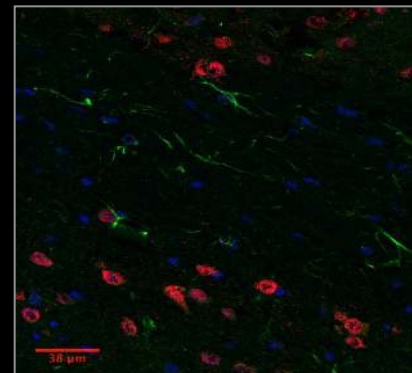


**Patient 2:
CIS-ON**

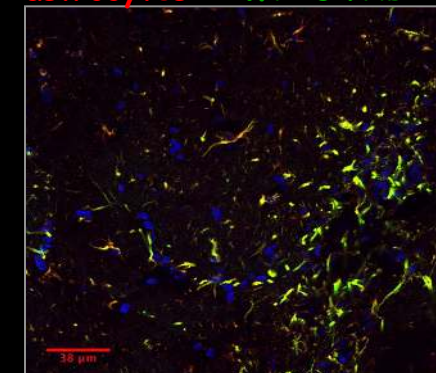
WR13: astrocytes



neurons **WR13 rAb**



astrocytes **WR13 rAb**



Monoclonal antibodies made by B cells in the CSF of MS patients and patients at high risk to develop MS bind to neurons and astrocytes

**Patient 1:
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**Patient 3:
CIS-TM**

AJL02: neurons
AJL02: astrocytes

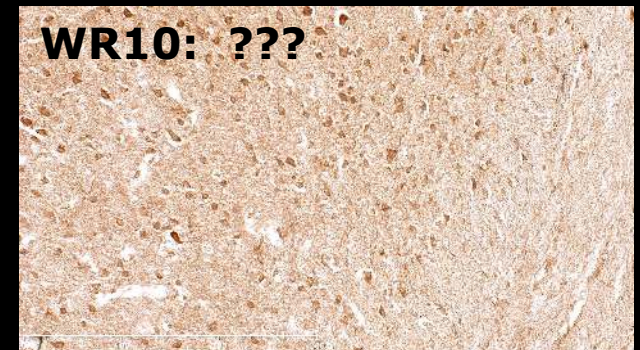
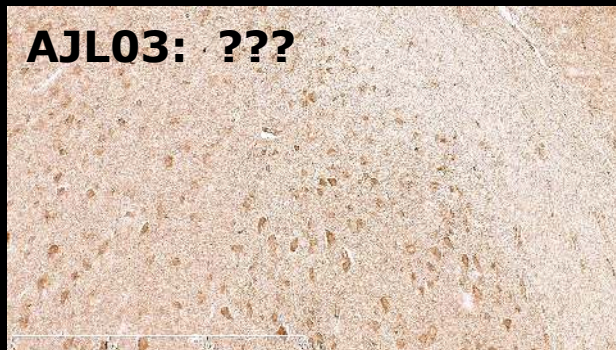
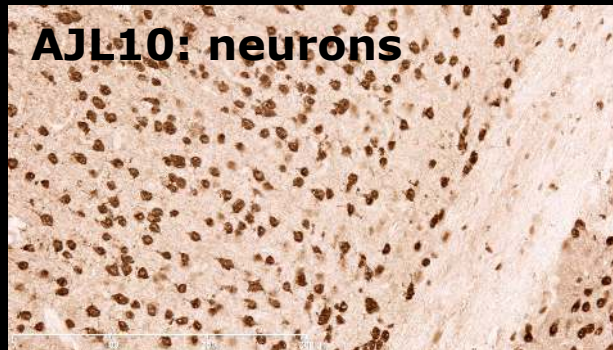
AJL10: neurons

AJL01: ???

AJL03: ???

WR13: astrocytes

WR10: ???



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Monson Lab

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William Rounds
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Ding Chen
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PJ Henson

Repository Team

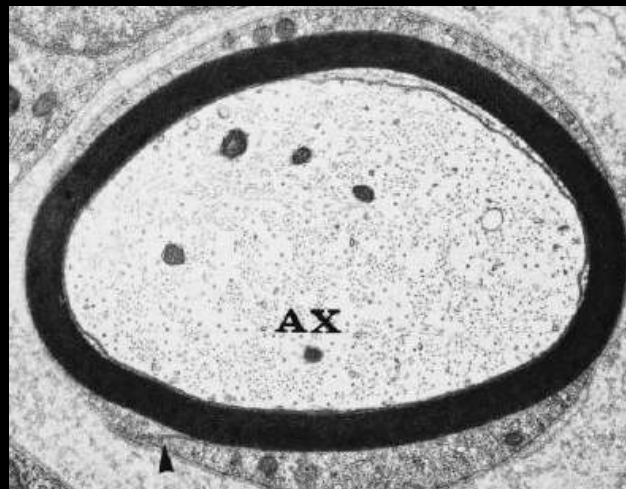
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Sally Ward
Ann Stowe
Min Li

Antibody Genetics Support

Richard Scheuermann
Lindsay Cowell
Andy Fire
Scott Boyd



Basic Neurochemistry, 6th ed., GJ Siegel et al, photo by C. Raine