Increased Apolipoprotein A-I production improves MS-like symptoms in mice

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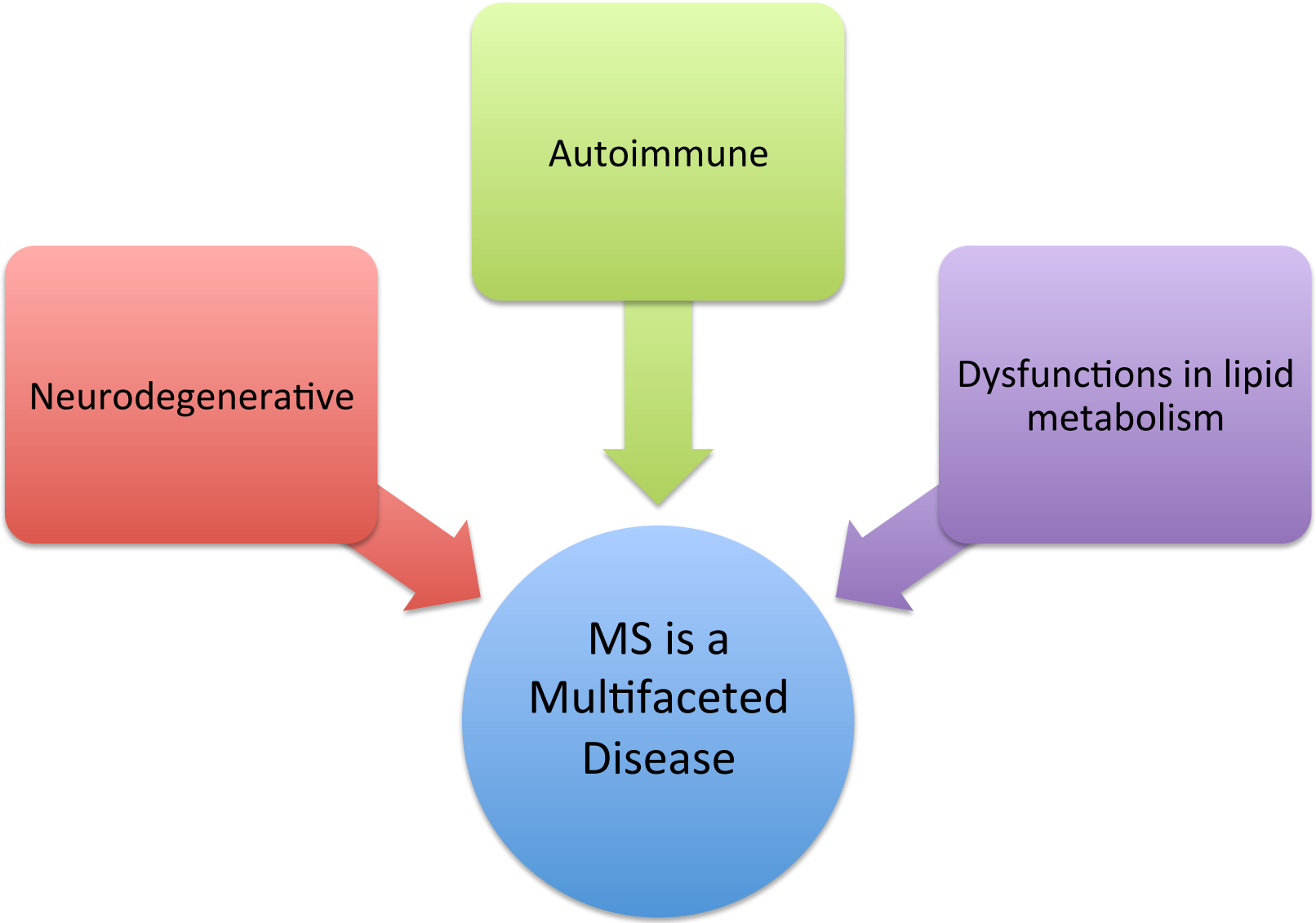
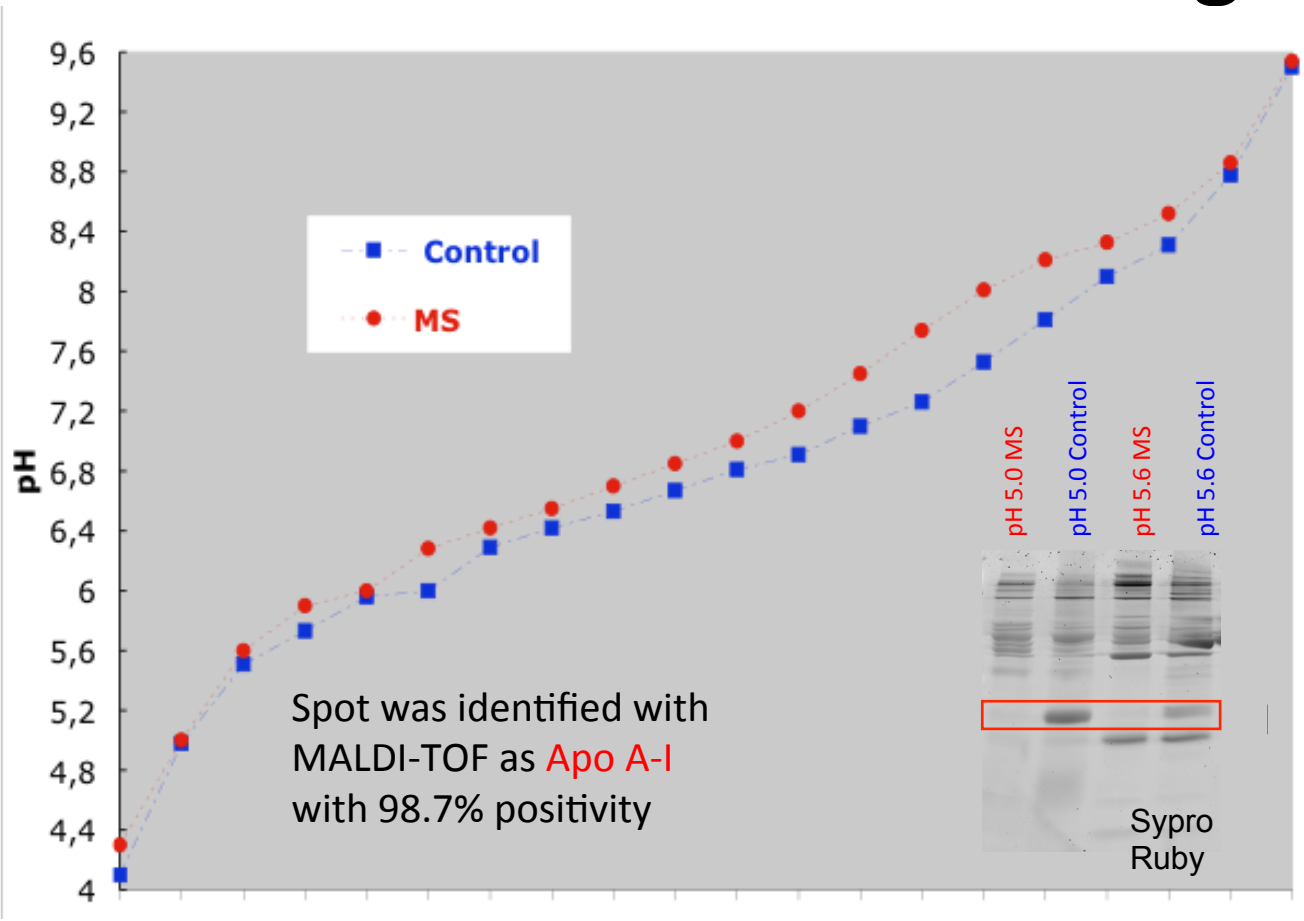
MS is a disease of the CNS



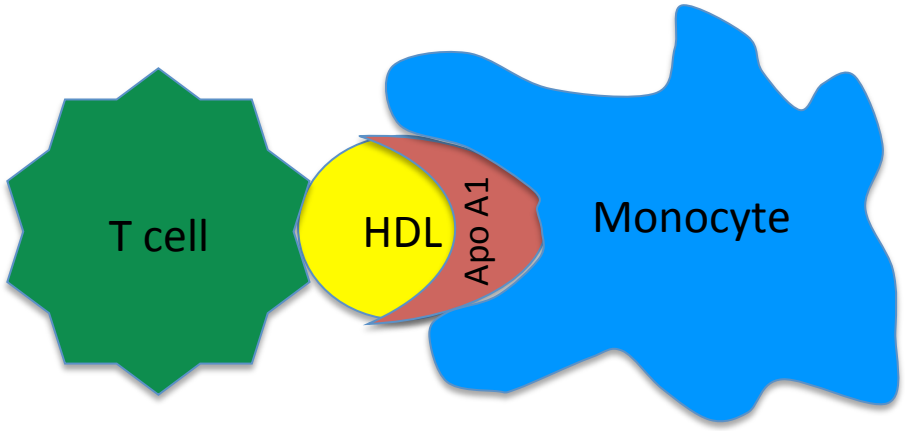
Analysis of human plasma by isoelectric focusing



What connection ApoA-I has to MS?

- Inhibition of adhesion molecules ICAM-1 and VCAM-1 that assist in T-cell adhesion and penetration through BBB (Calabresi et al., 2001)
- Inhibition of cytokines IL-1B and TNF-α (Burger and Dayer, 2002)
- Improved cognitive parameters (Koutsis et al., 2009)
- Apo A-I is a serum biomarker for MS treatment (Gandhi, 2010)
- ApoA-I coordinates peripheral and CNS lipid metabolic systems (Stukas et.al., 2012)

Apo A-I is an anti-inflammatory protein



- Apo A-I is found in blood and other tissues in humans
- Apo A-I reduces inflammation and may protect neurons from the immune attack in MS

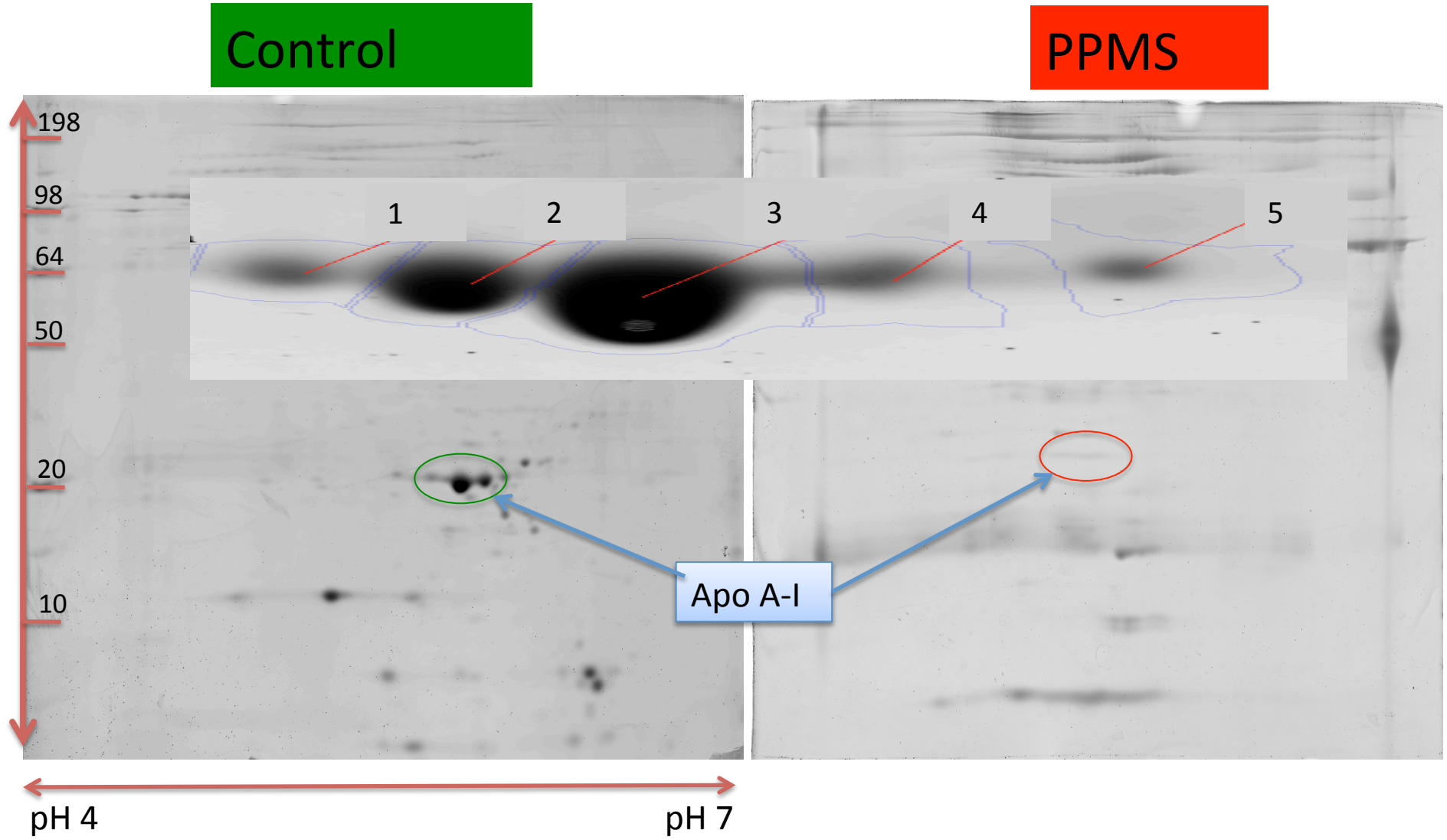
Apolipoproteins in the CNS

Name	Function	Diseases
Brain		
Apolipoprotein A-I (Apo A-I)	Anti-inflammatory, immunosuppressive, neuronal regeneration	MS, Alzheimer's, Arthritis
Apolipoprotein E (Apo E)	Regeneration of axons and myelin	MS, Alzheimer's, Huntington, PD, ALS
Apolipoprotein D (Apo D)	Up-regulated during cellular stress	Schizophrenia, bipolar
Apolipoprotein J (Apo J)	Poorly defined functions	
Cerebrospinal Fluid		
Apo A- I, Apo E, Apo J, Apo D, Apo A-II, Apo A-IV		

Apo A-I expression in plasma of MS Patients

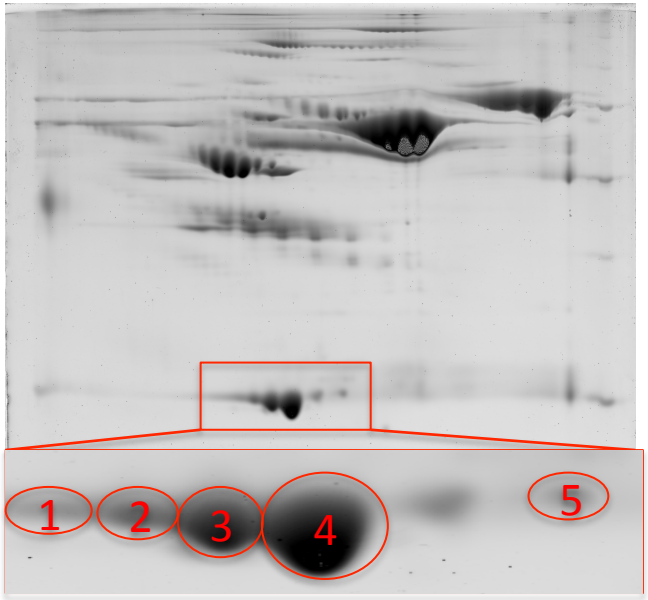
MS type	Mean age	EDSS range	Disease duration (range, yrs.)
RRMS n=5	50.3	1-5.5	5-23
SPMS n=5	50.8	6-8	8-33
PPMS n=5	49.8	6-8	3-7
CONTROL n=5	50	N/A	N/A

2D image of the plasma proteome

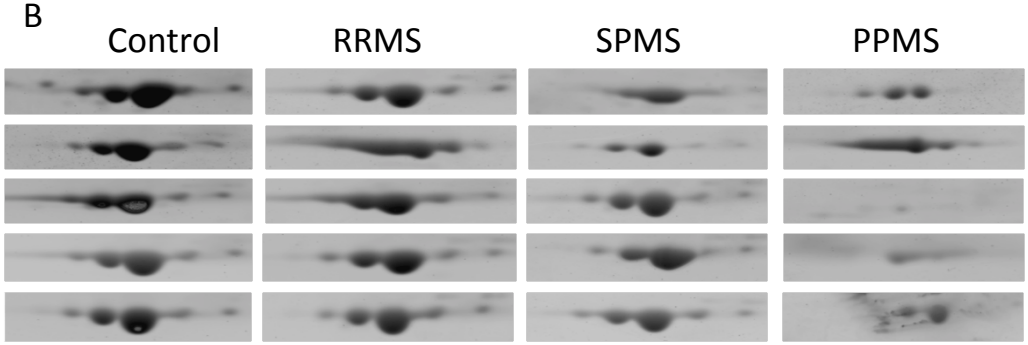


2-D quantification of Apo A-I in human plasma

A

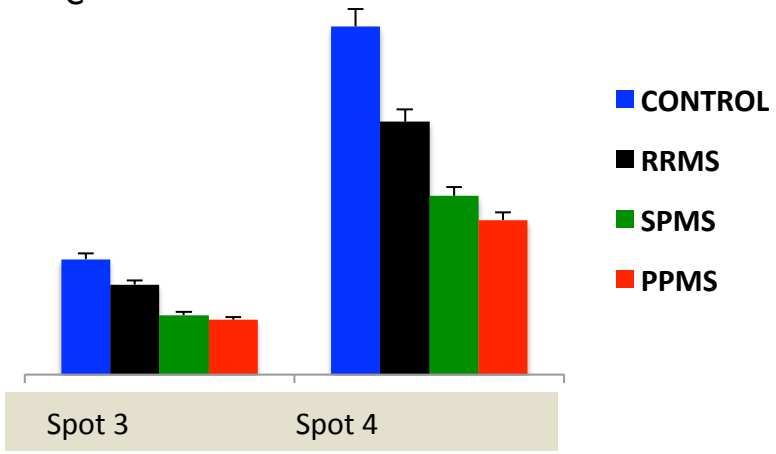


B



Spot #	ANOVA (p)	Fold change	Averaged Normalized Volumes			
			CTRL n=5 *10 8	RRMS n=5 *10 8	SPMS n=5 *10 8	PPMS n=5 *10 8
3	0.045	2.1	1.71	1.34	0.88	0.82
4	0.050	2.3	5.17	3.75	2.65	2.3

C

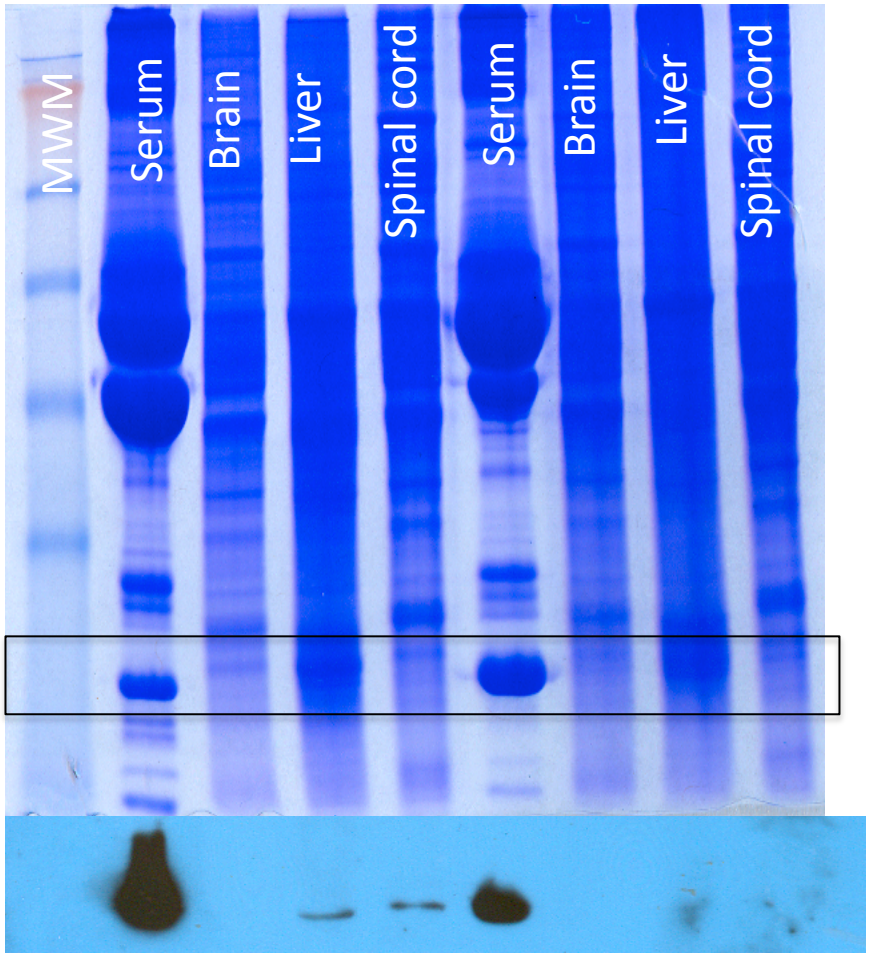


Hypothesis: will lover ApoA-I levels result in worse EAE?

C57BL/6J	C57BL/6-Tg(APOA1)1Rub/J
Control mouse Normal plasma ApoA1 and cholesterol 	Mice carrying the human apolipoprotein A1 transgene show a two fold increase in total plasma cholesterol levels and **greater than a four fold decrease** in the levels of mouse ApoA-I protein.

Experimental Autoimmune Encephalomyelitis (EAE) is induced with MOG_{35-55} and mice are scored on a scale 1-5 starting at day 14 post-injections

Serum and tissue Apo A-I expression in mice



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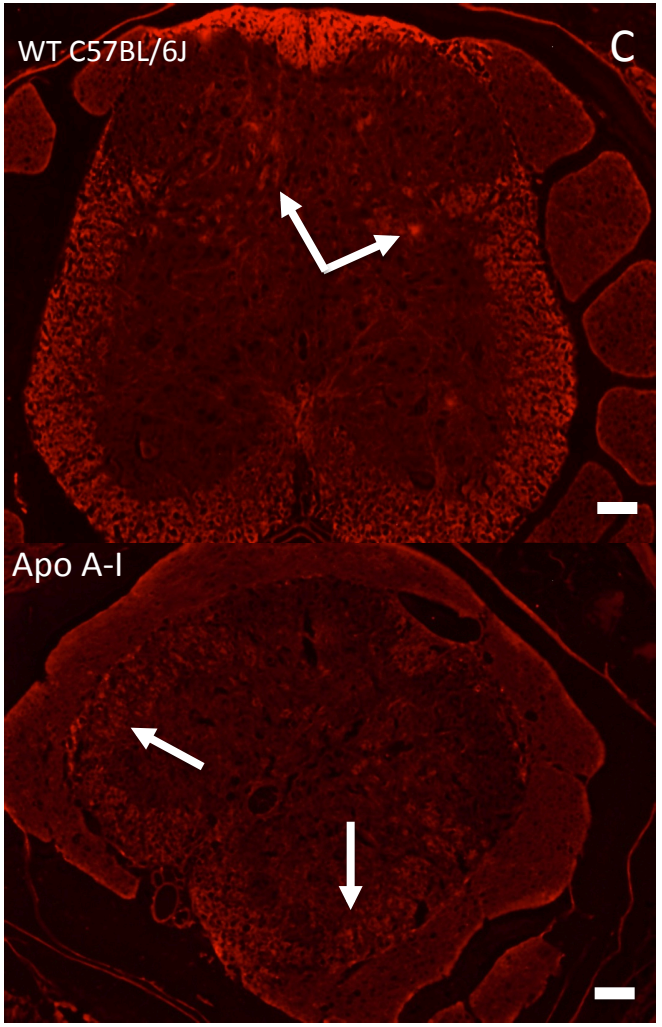
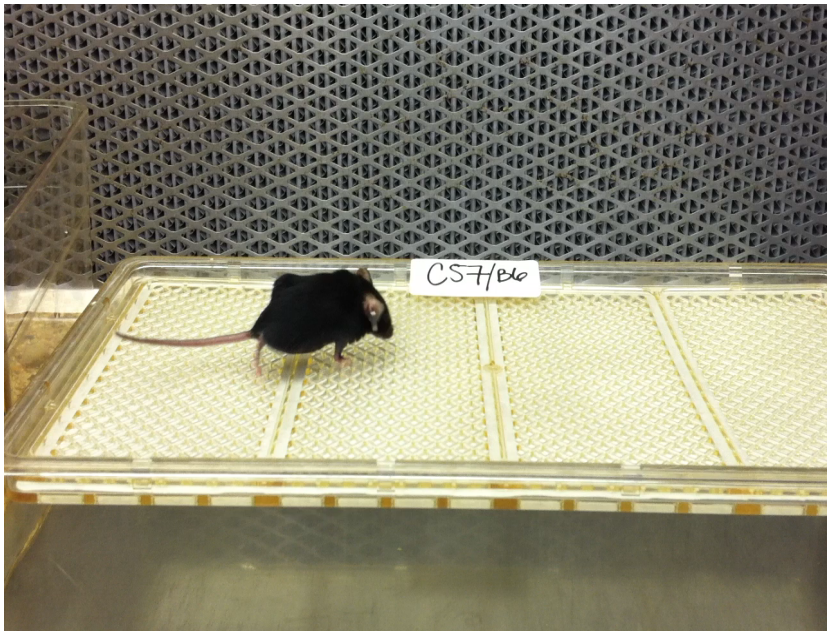
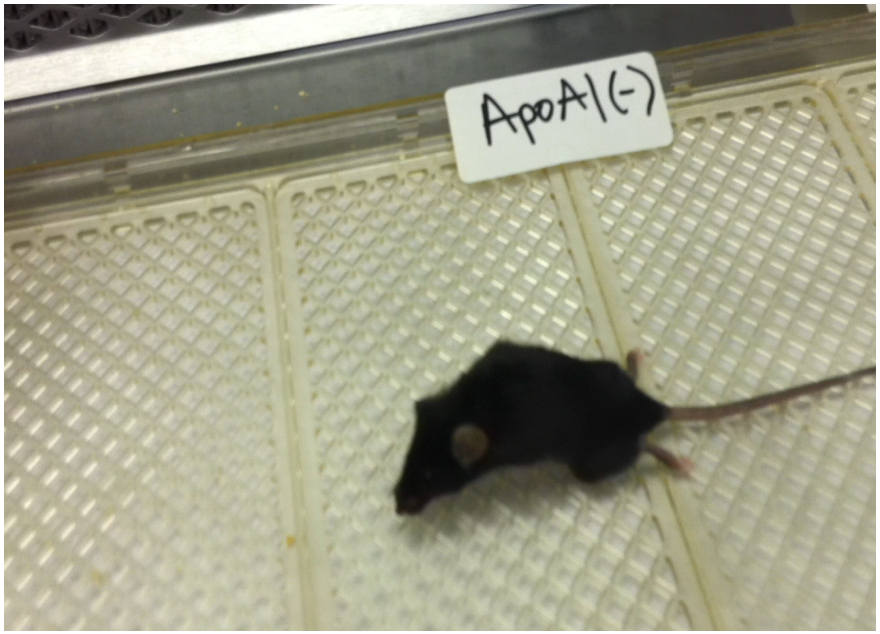


Experimental Autoimmune Encephalomyelitis (EAE)

C57Blk/6J

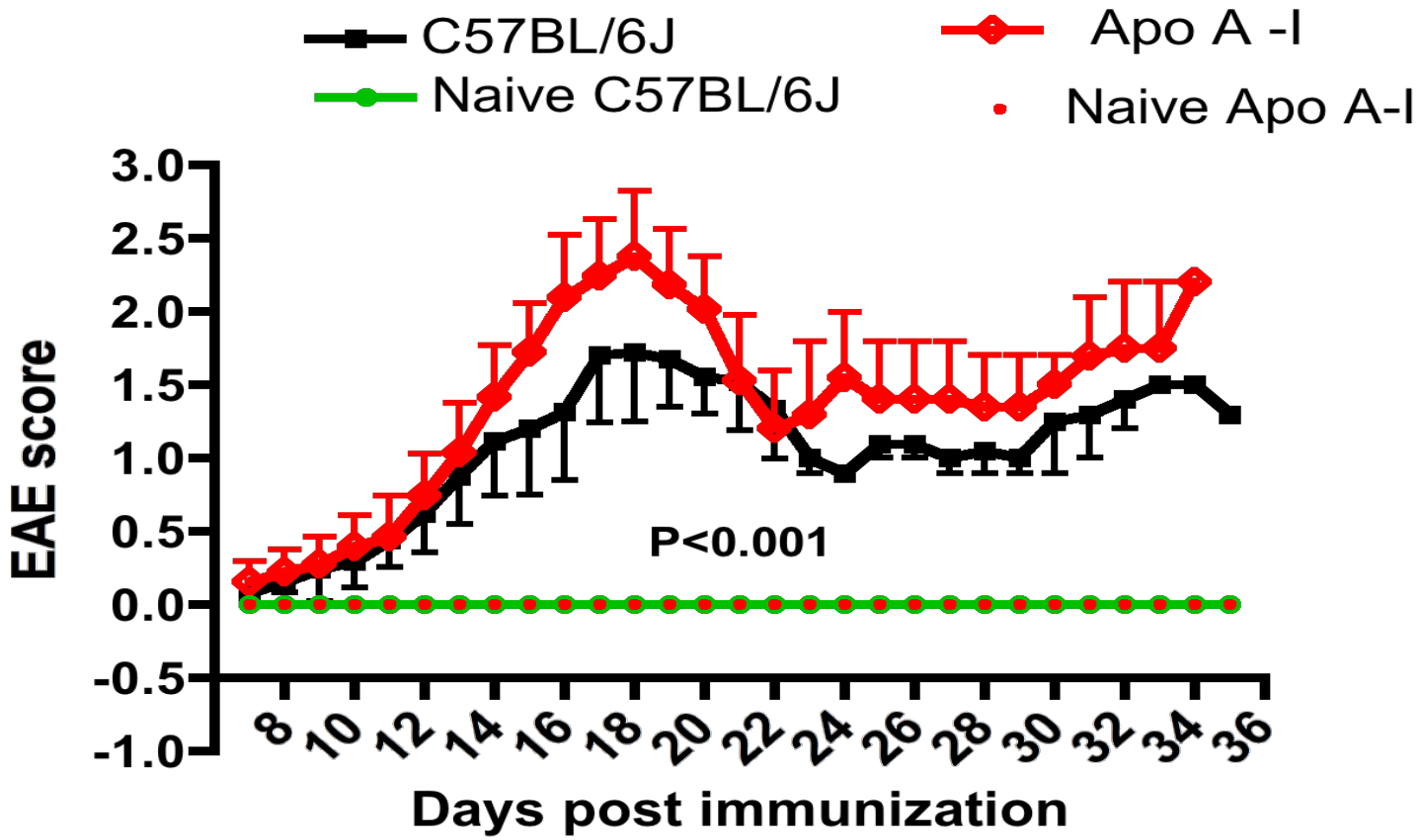


C57BL/6-Tg(APOA1)1Rub/J

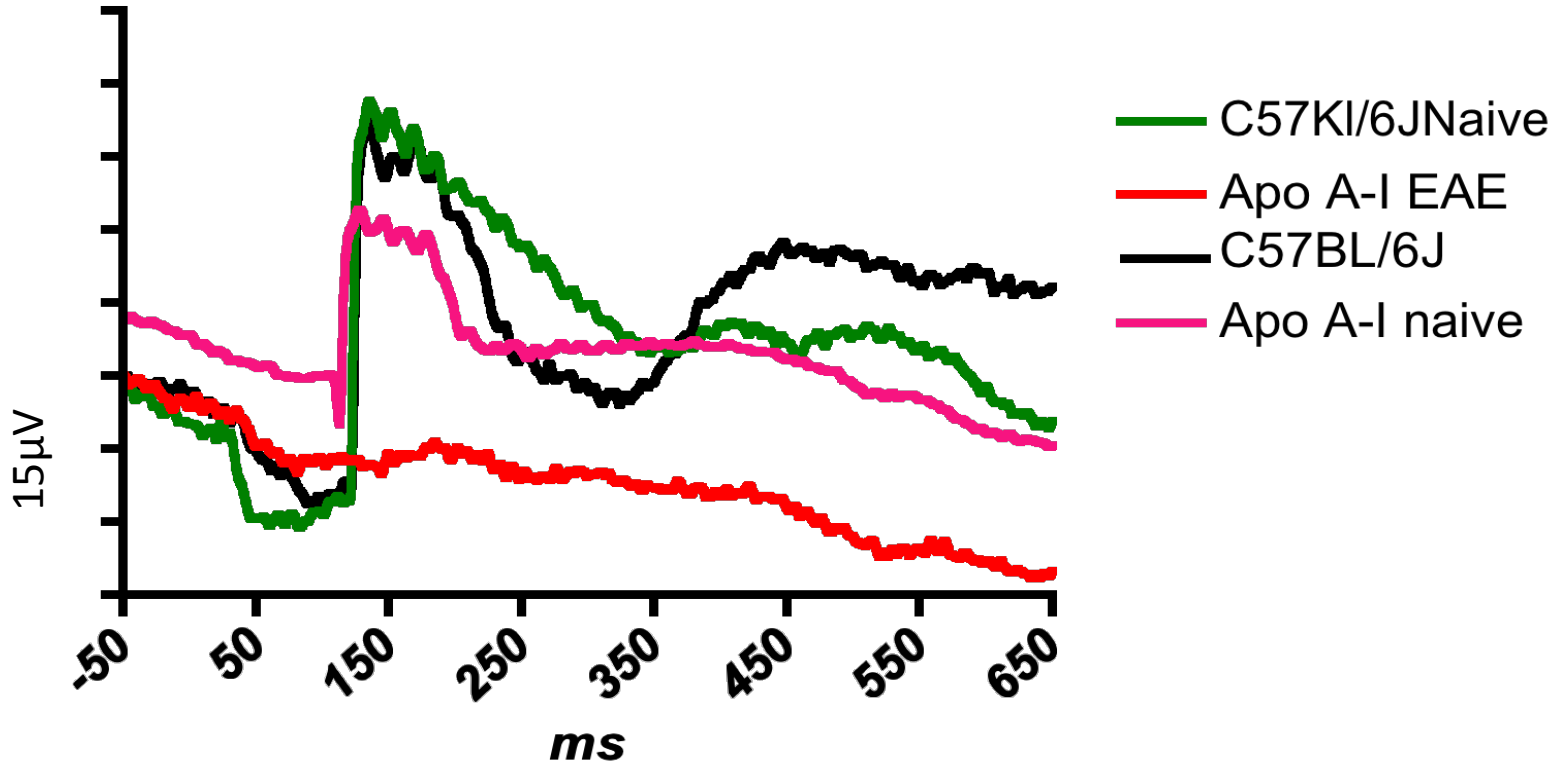


Day 17

EAE mouse model of MS

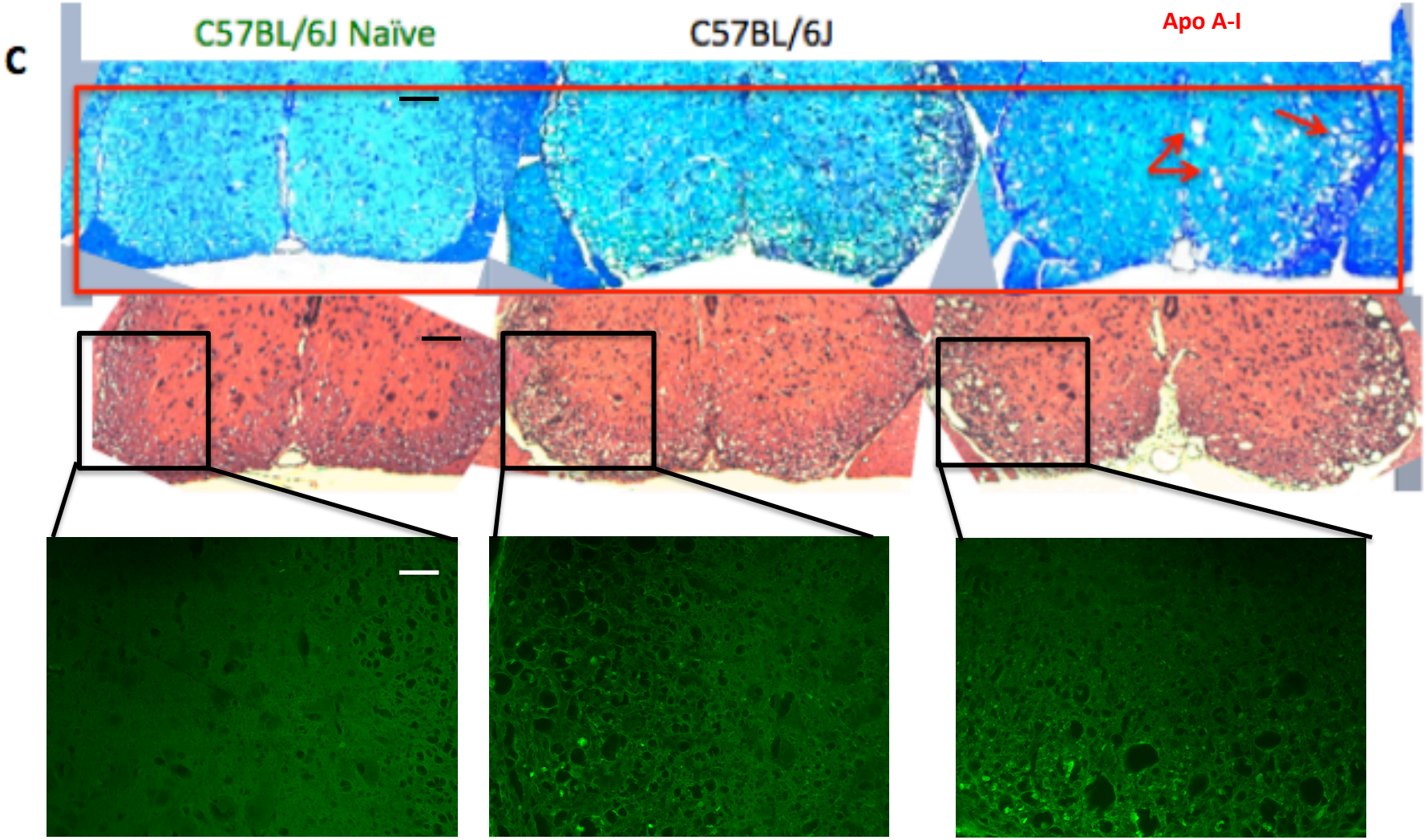


Visual Evoked Potential (VEP) test in EAE mice



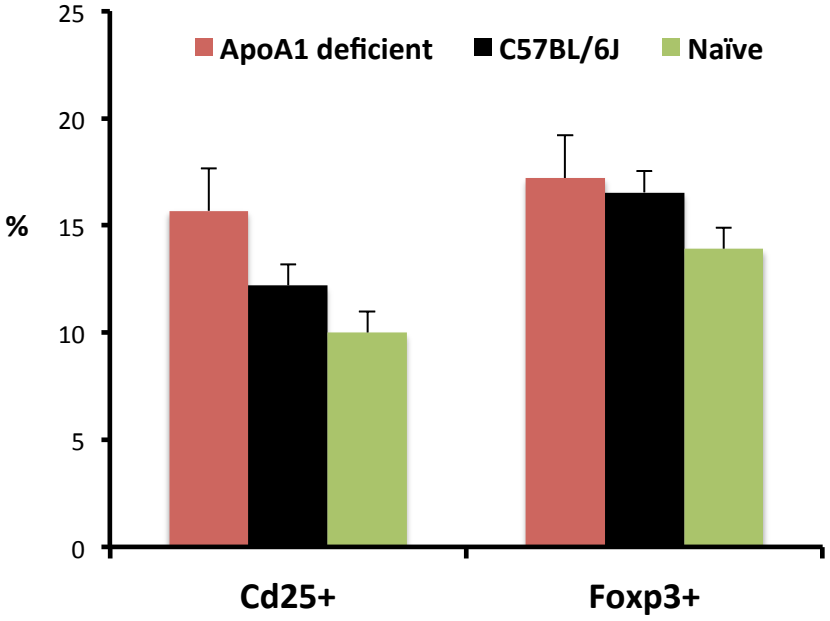
Myerers et al., A role fro Apolipoprotein A-I in the pathogenesis of Multiple Sclerosis. 2014 *Journal of Neuroimmunology.*

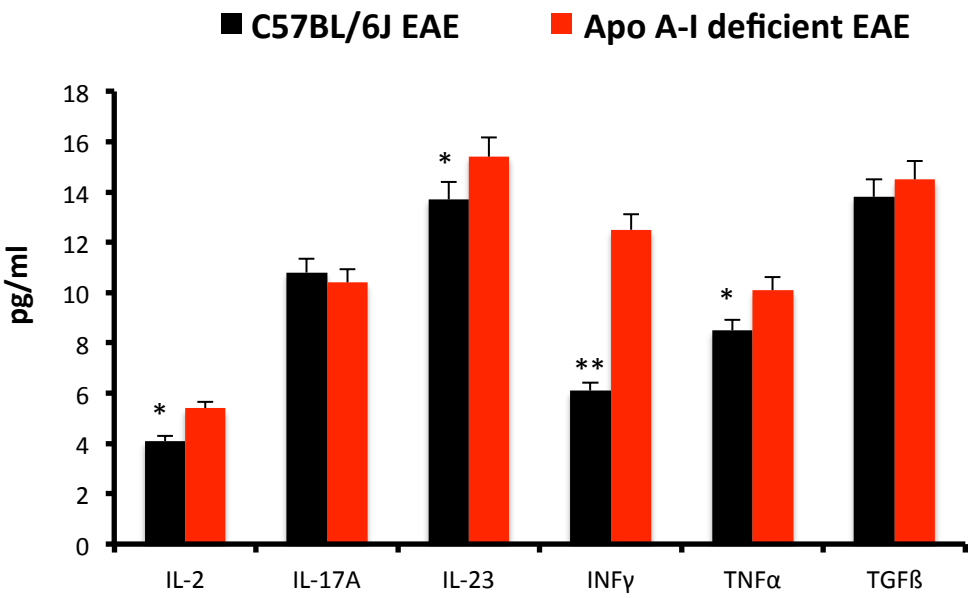
Histological analysis of spinal cord



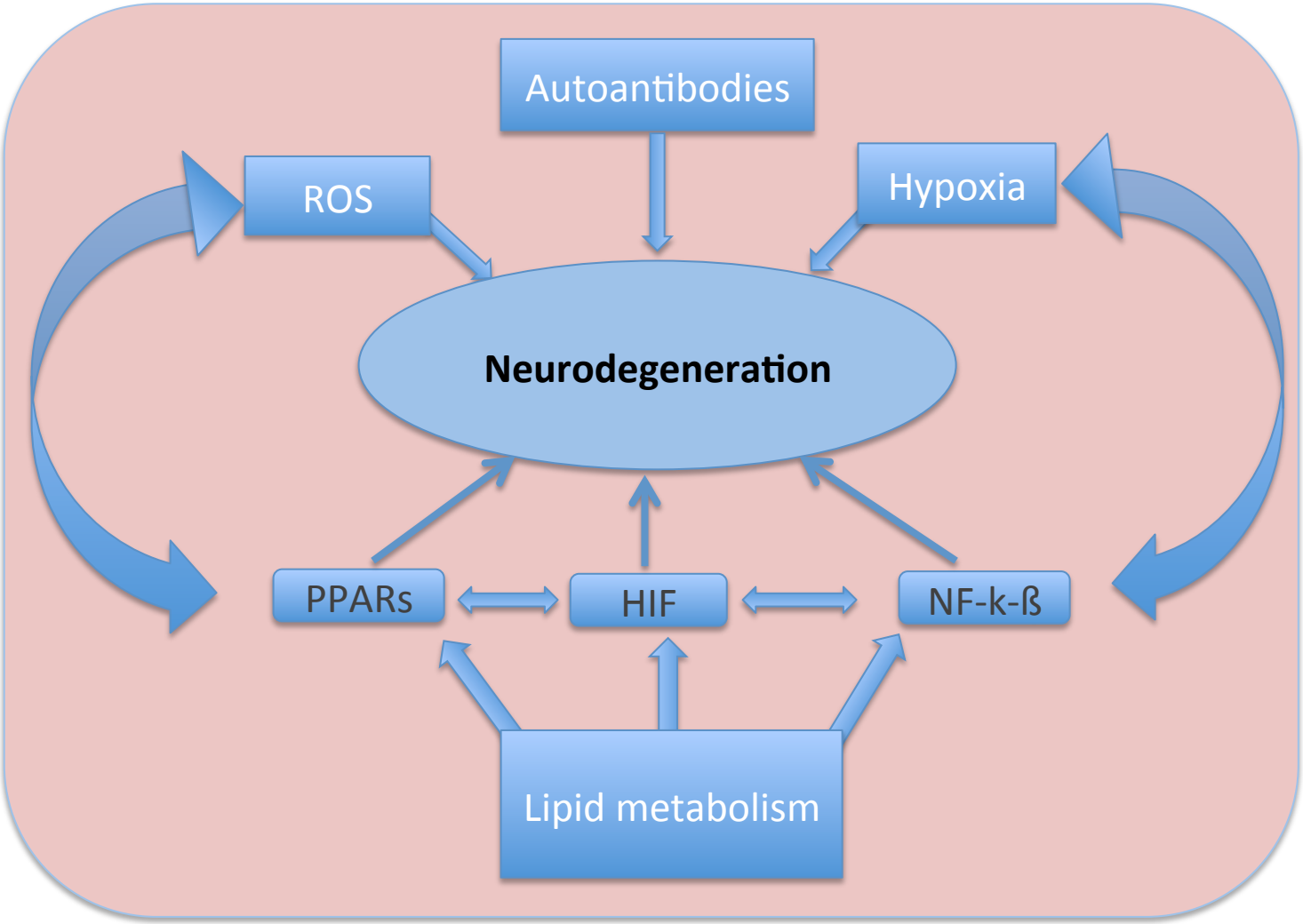
Fluoro Jade C- marker of neuronal degeneration

Regulatory T cell and Cytokine expression in EAE mice



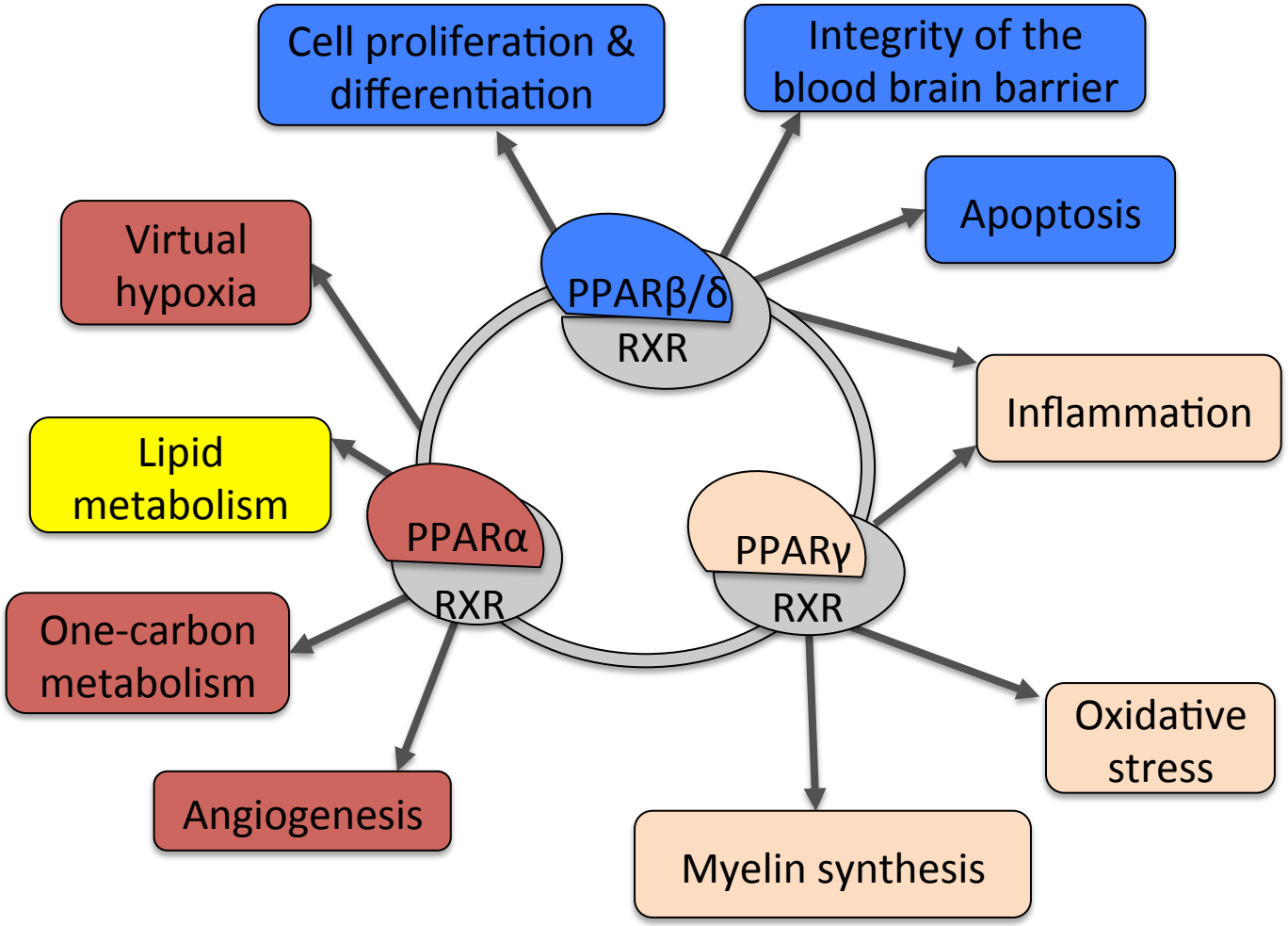


Common Pathways of Neuronal degeneration

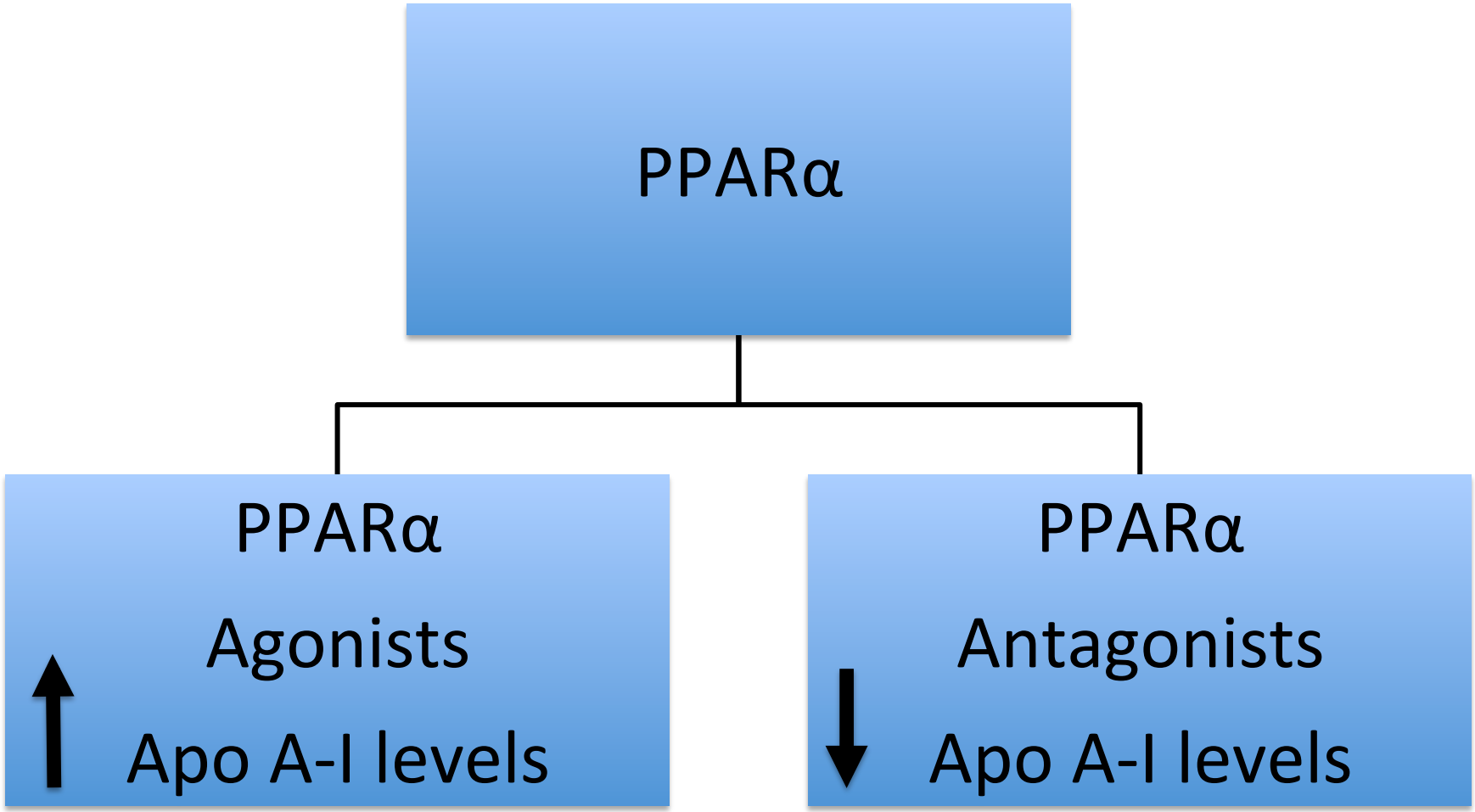


Levin et al. Degenerative Neurological and Neuromuscular Disease. 2014 Dove Press.

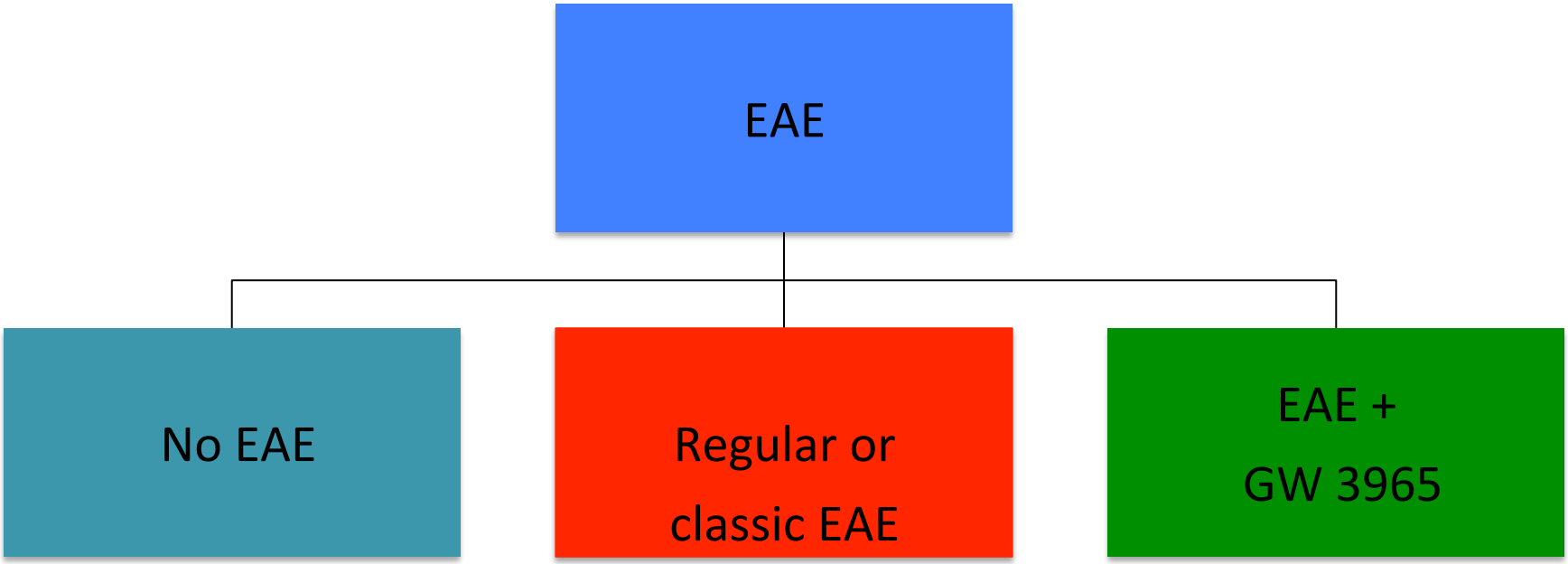
PPARs regulation of cellular processes



PPARs act as transcription factors

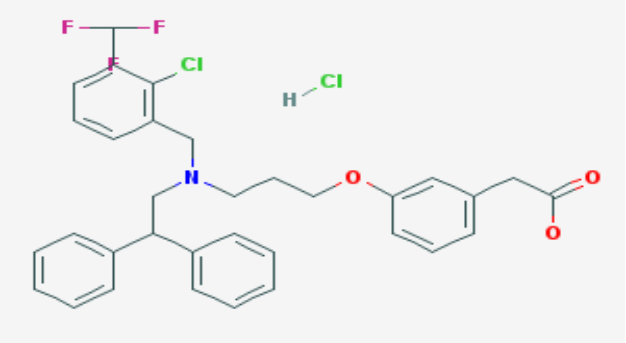


Importance of Apo A-I in MS mouse model



PPARα agonist

3-[3-[N-(2-Chloro-3-trifluoromethylbenzyl)-(2,2-diphenylethyl)amino]propyloxy]phenylacetic acid hydrochloride



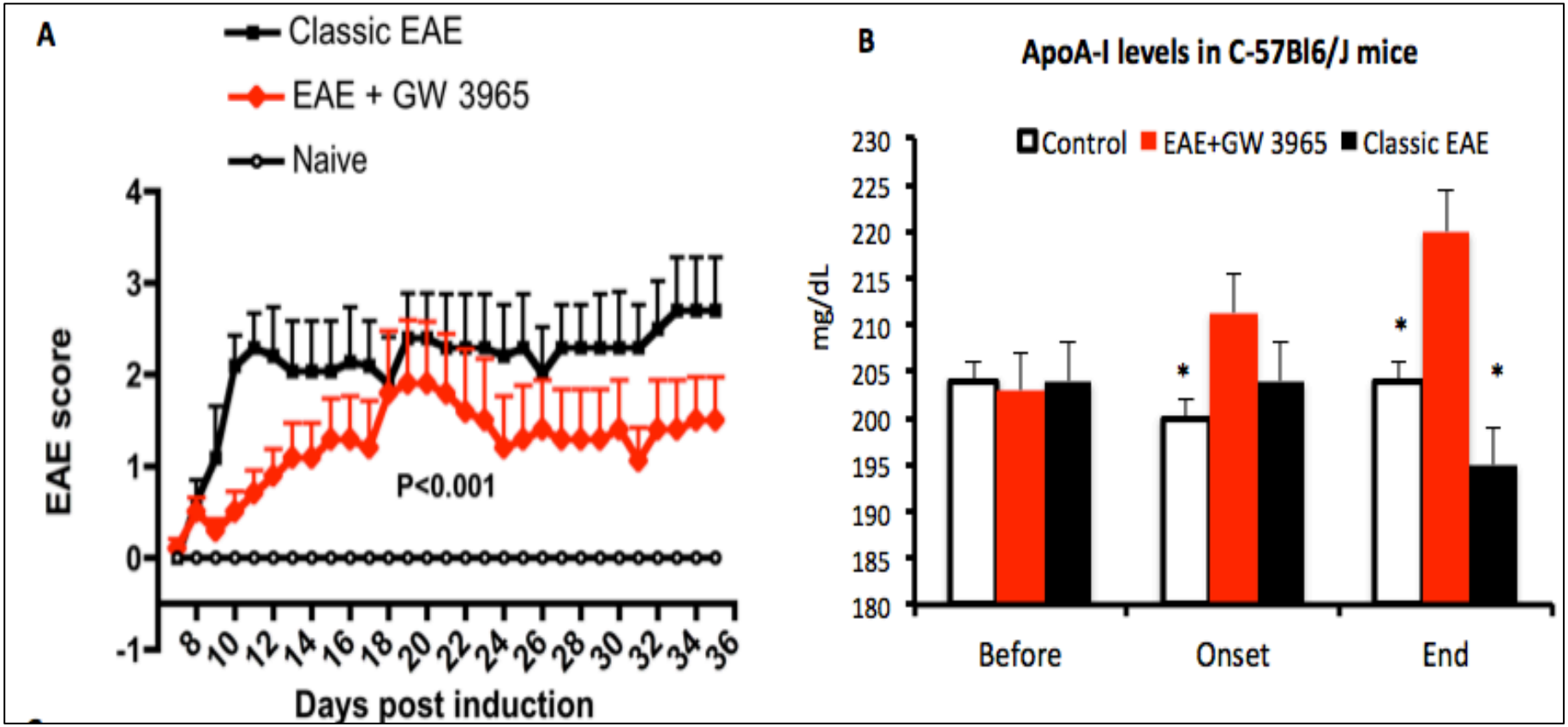
Preliminary results of the pilot study

Day 24 post-induction

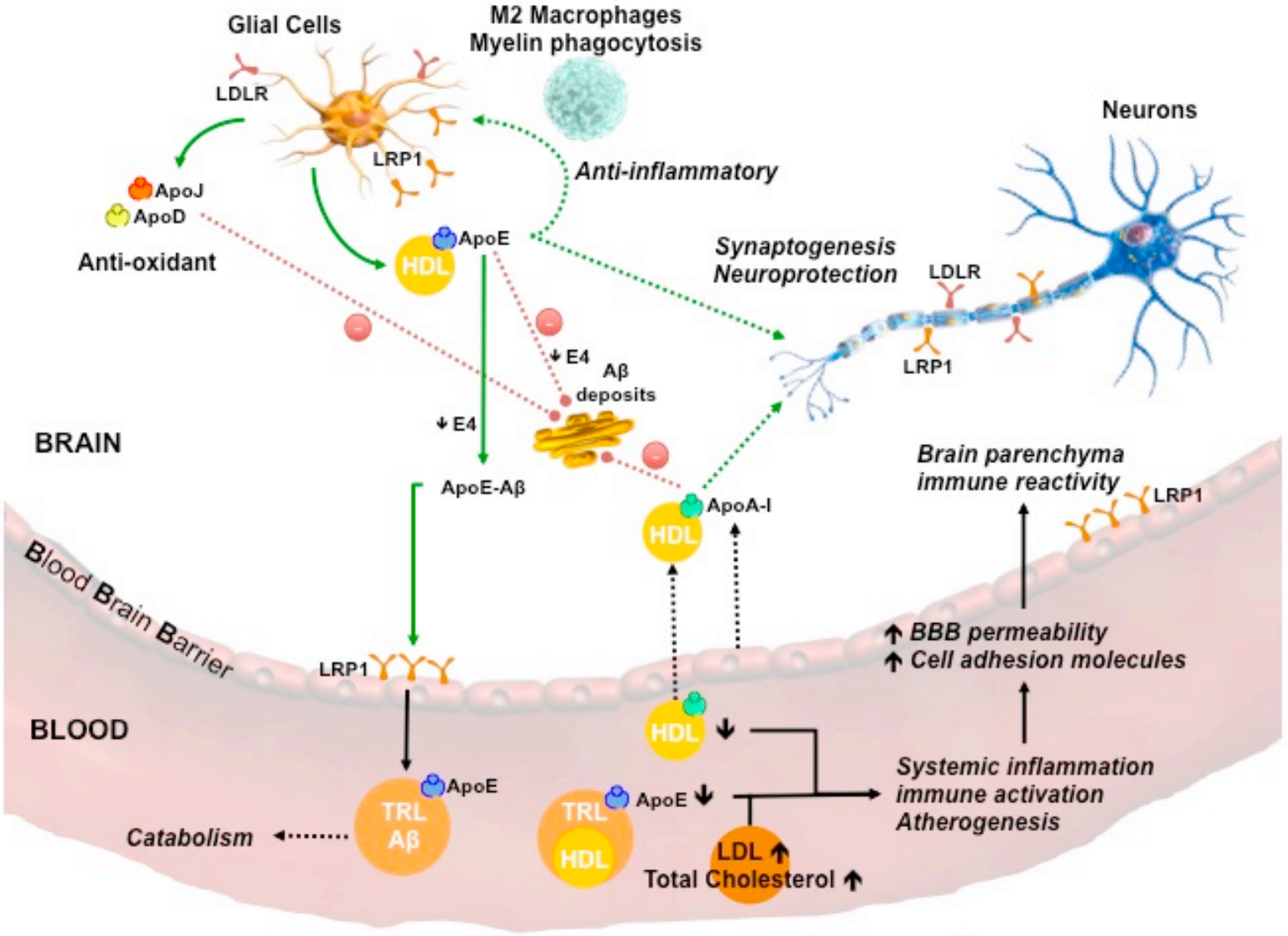
Control	Classical EAE	EAE+ GW3965
		

Average EAE Score	0	2.5	1.5
Disease incidence	0/5	4/5	2/5

Increased A-I levels in sera resulted in lower EAE scores



Lipoproteins in health and disease



Lipoproteins: Role in health and disease. 2012 Sena et al., Book Chapter 23. Intech.

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