

Immunology of Multiple Sclerosis: from bench to bedside

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March 4th, 2017

The Rocky Mountain MS Center
At the University of Colorado



Disclosures

- Research grants from Biogen, Rocky Mountain MS Center, Novartis, Acorda
- Consulting for Genzyme, Genentech, Teva, Novartis, and Biogen

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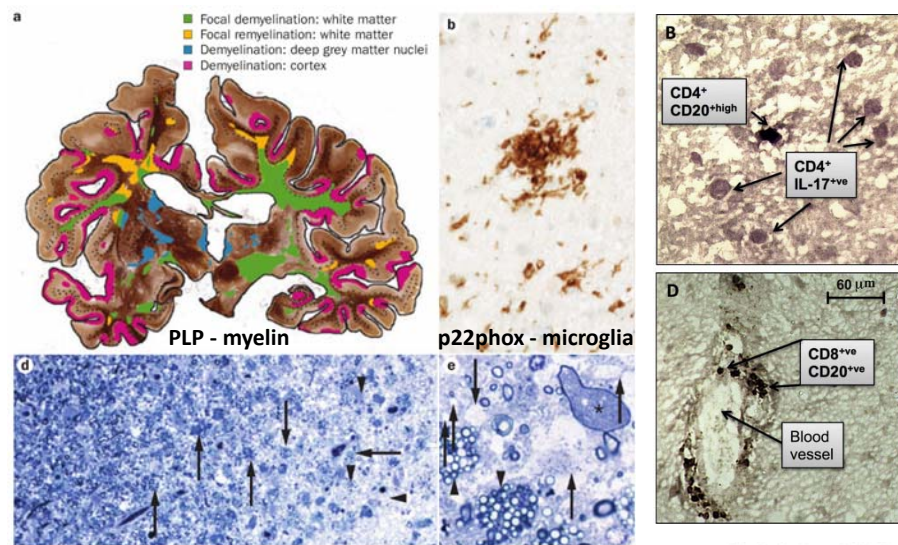


Objectives

- MS as an autoimmune disease
- Introduction of the immune system
 - Types of immunity
 - The players
- How do MS drugs affect the immune system

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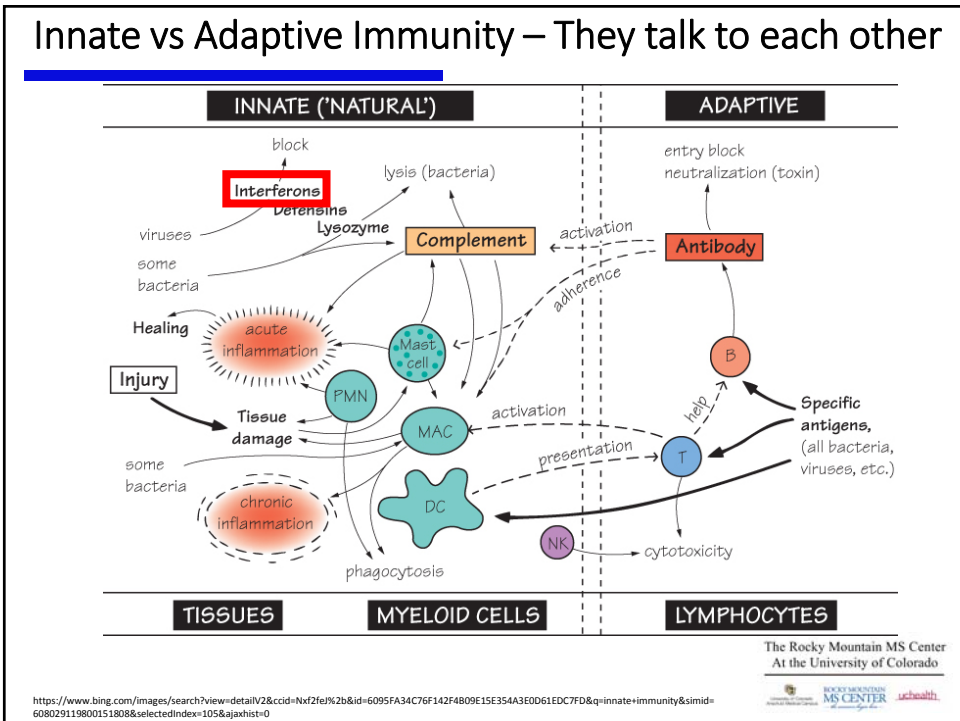
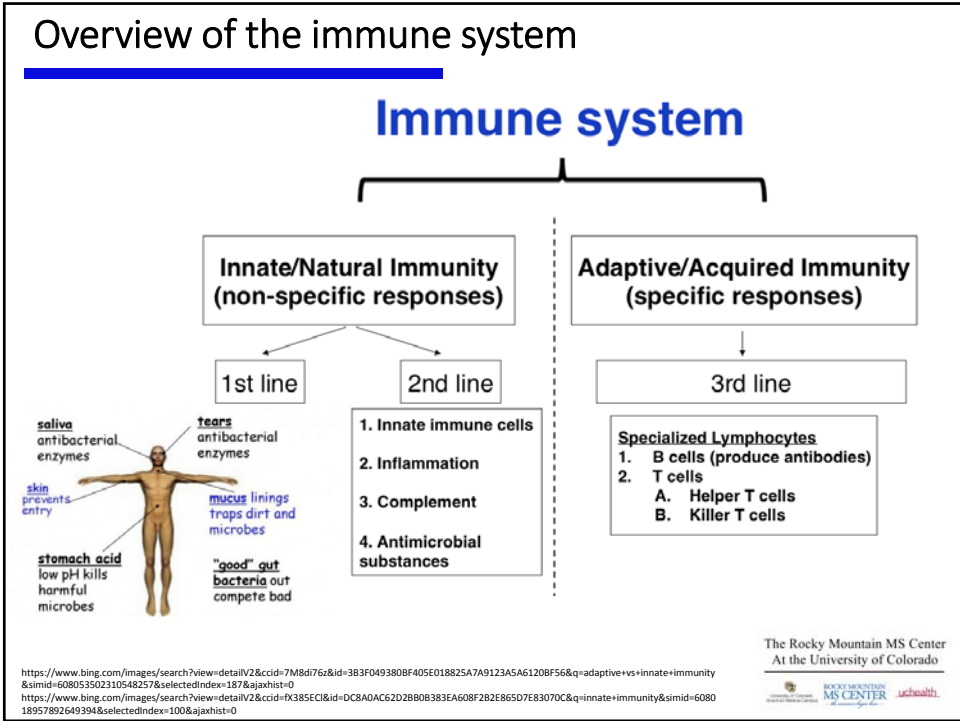
MS Pathology



Arrows – demyelinating axons; Asterix – dystrophic axon;
Arrowheads - macrophages with myelin

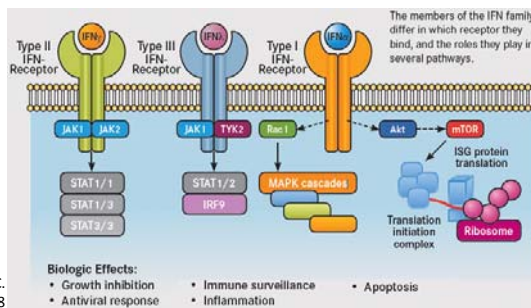
Lassmann, H. et al. Nat. Rev. Neurol. 8, 647–656 (2012);
Holley, JF et al. MS and related disorders. 3, 650-658 (2014).

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Interferons

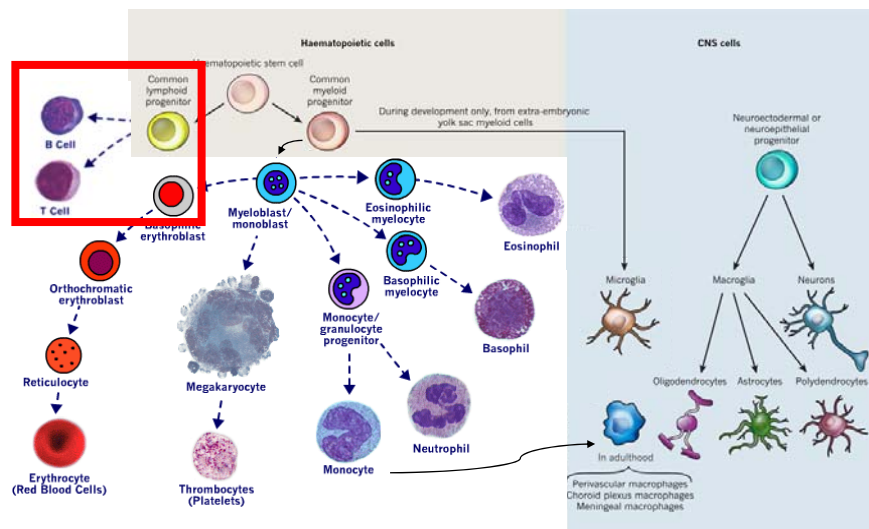
- Alpha: Produced by virus infected leukocytes
 - Used to treat Hep B and C
- Beta: Produced by virus infected fibroblasts.
 - Used to treat MS
- Gamma: Produced by activated T and NK cells
 - Make MS worse
- Lambda
 - New



Katsoulidis E, Kaur S, Plataniias LC. Pharmaceuticals. 2010;3:406-418

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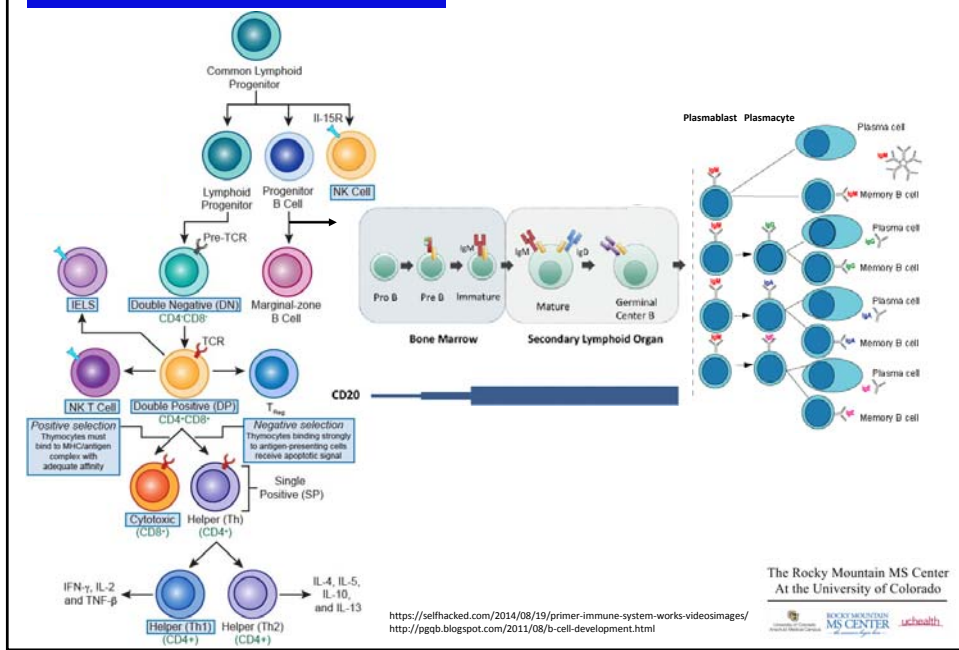
The Players



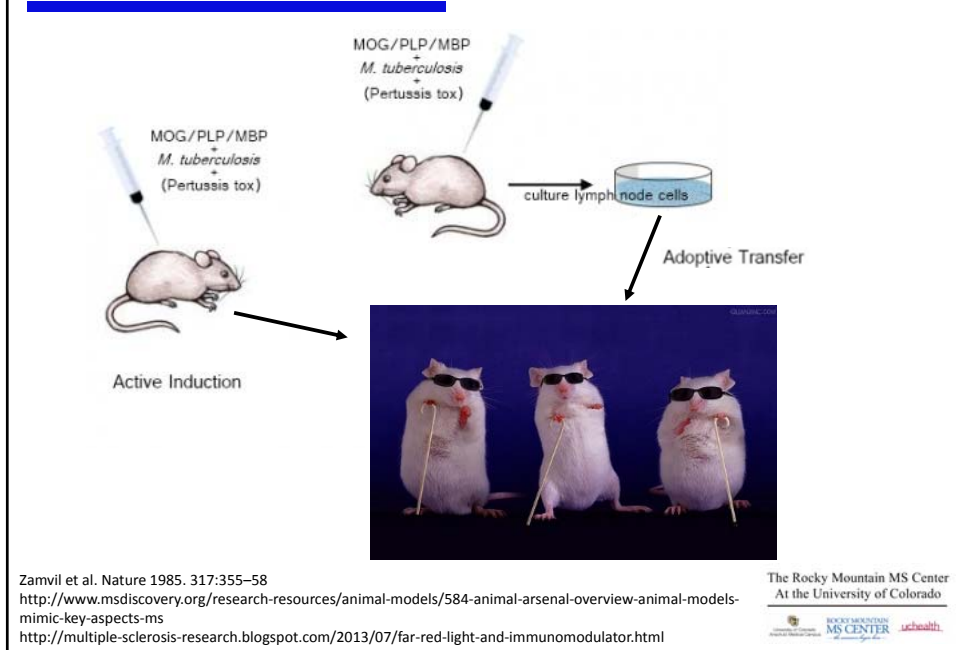
Venkat, CLL topics Updates website
Ransohoff and Cardona, Nature 486, 253-262

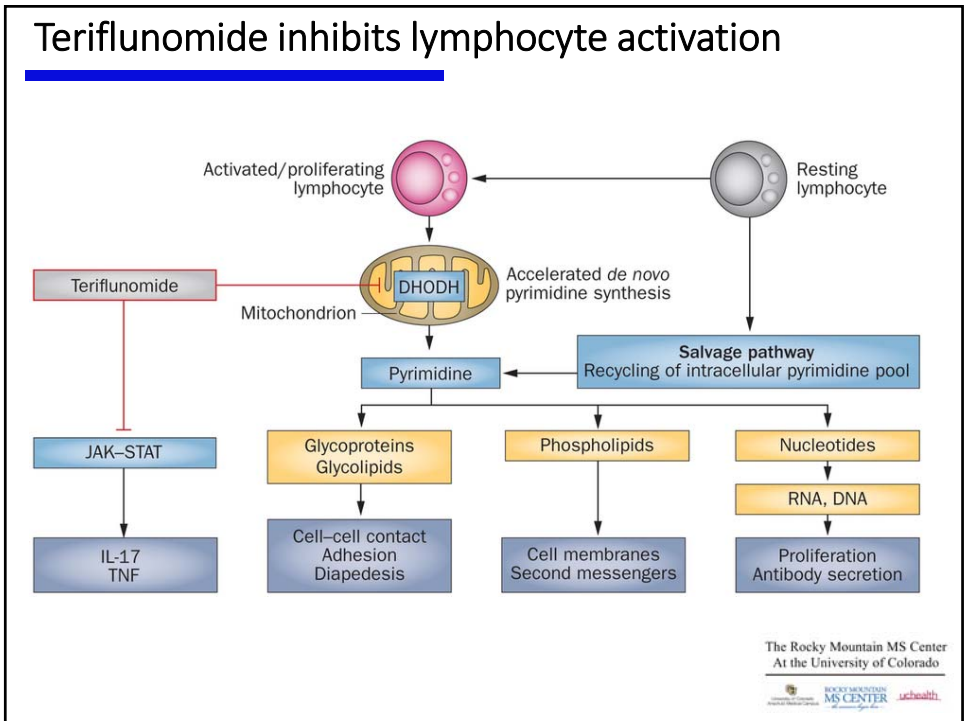
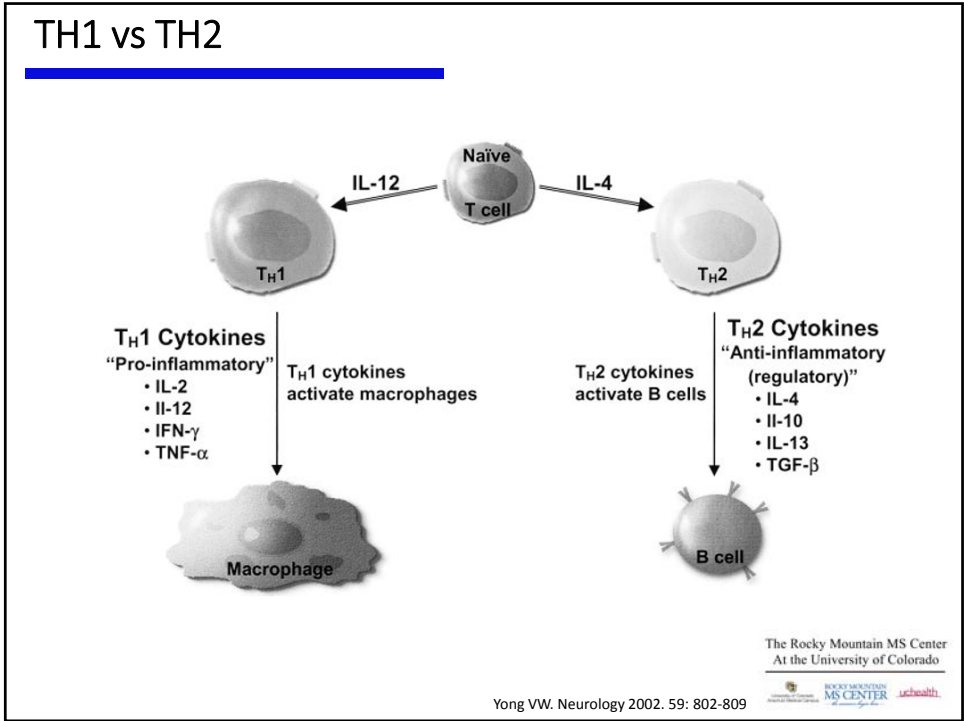
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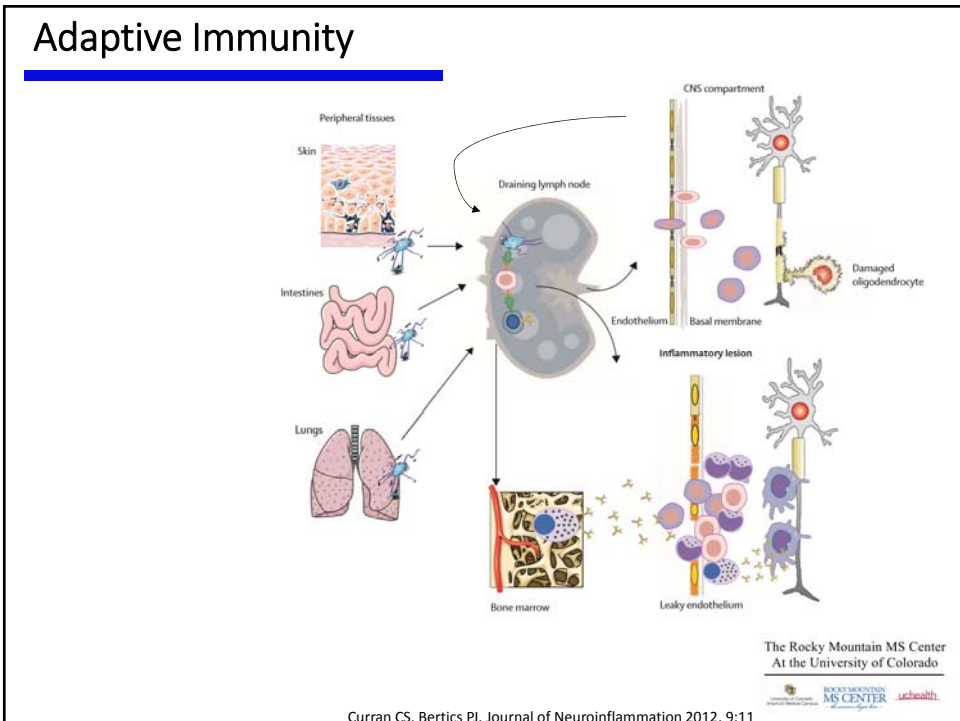
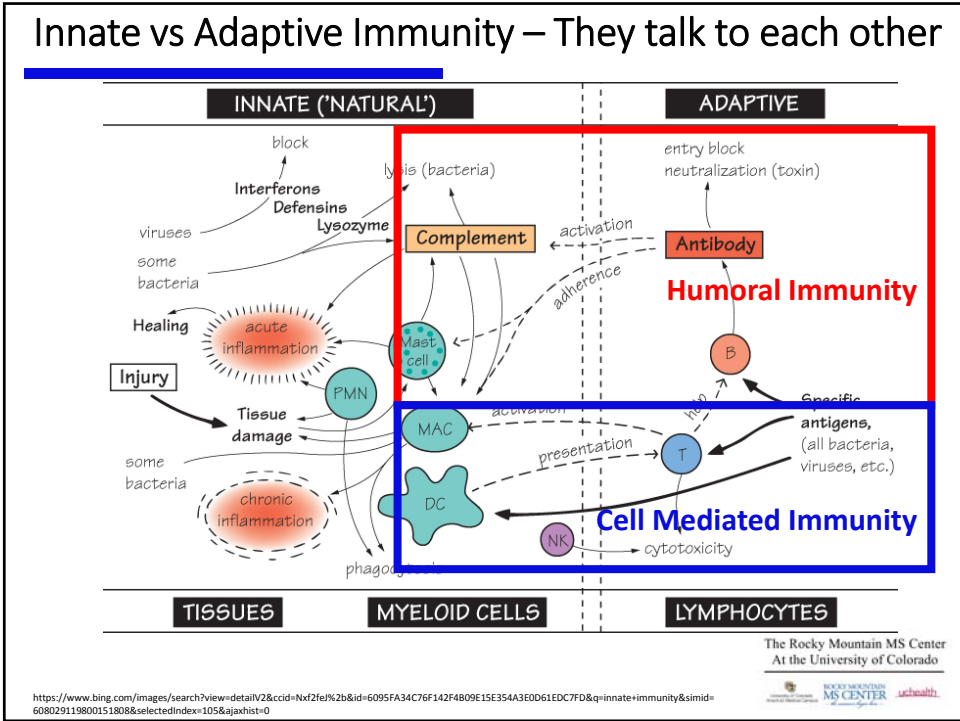
The Lymphocyte Lineage

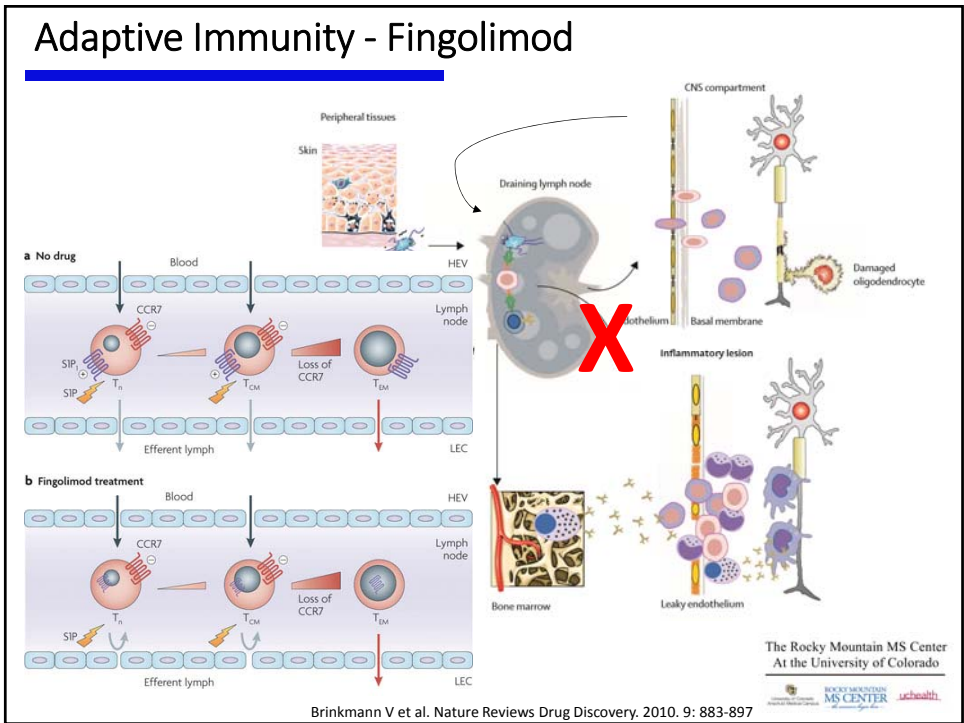
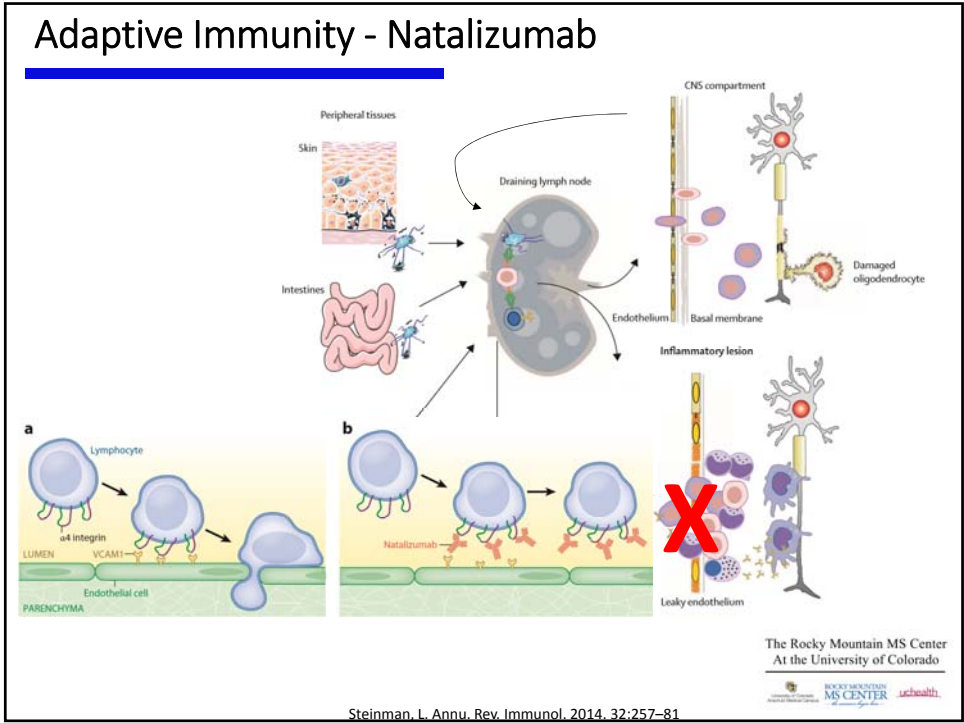


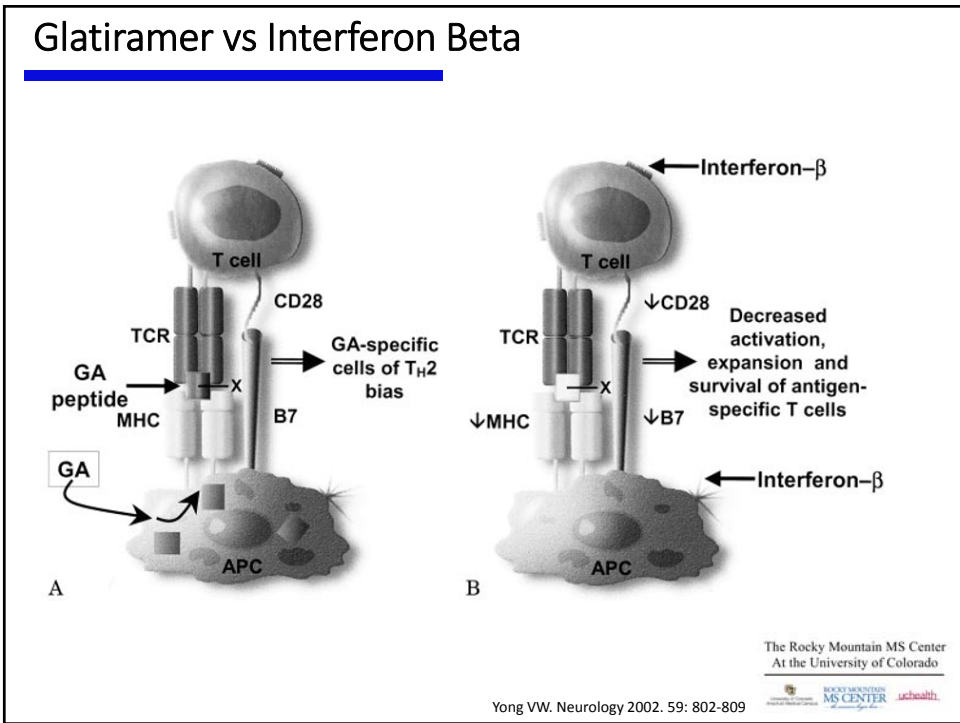
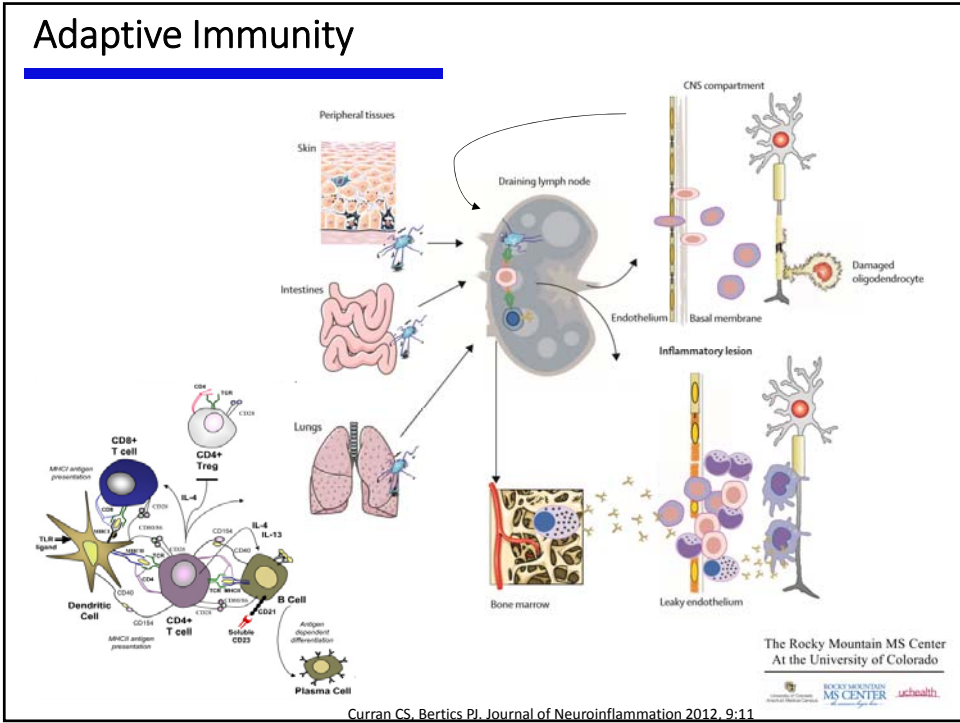
MS as a T cell mediated disease



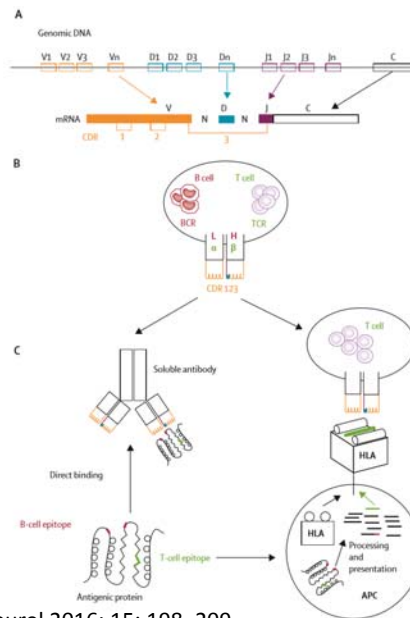








Immunogenetics of MS

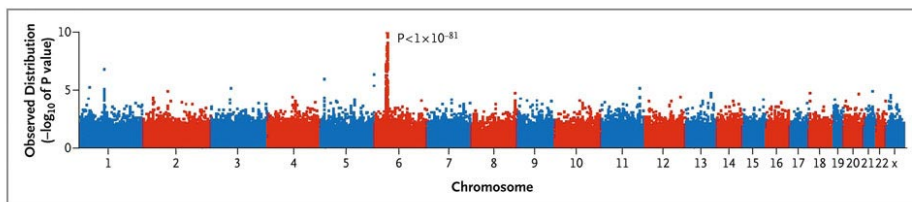


Hohlfeld et al. Lancet Neurol 2016; 15: 198–209

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Immunogenetics of MS

- Genome-wide analysis of SNPs (GWAS) studies in ≈ 1000 subjects identified alleles of HLA-DRA region on chromosome 6, IL-2RA gene, and IL-7RA gene associated with MS susceptibility risk.

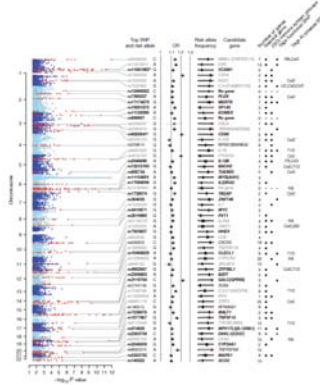


IL = interleukin; RA = receptor α ; SNP = single-nucleotide polymorphism.
International Multiple Sclerosis Genetics Consortium. *New Engl J Med.* 2007;357:851-862.

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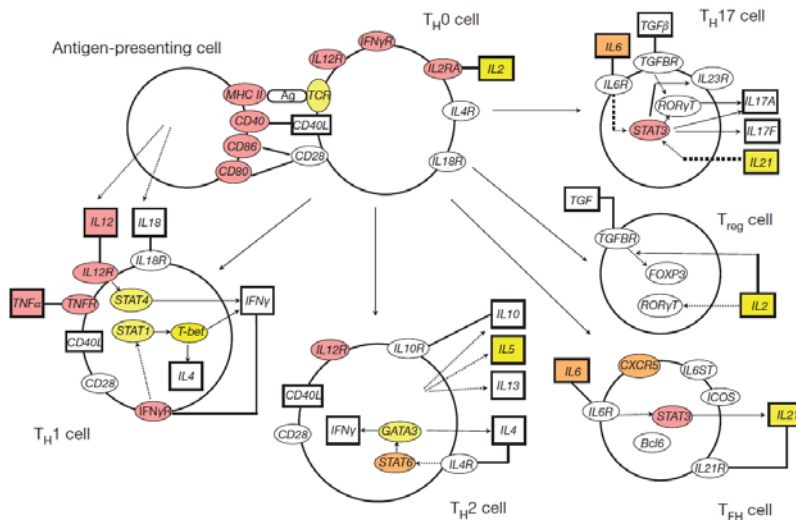


IL = interleukin; RA = receptor α ; SNP = single-nucleotide polymorphism.
 International Multiple Sclerosis Genetics Consortium. Nature. 2011 Aug 10;476(7359):214-9

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Immunogenetic of MS



International Multiple Sclerosis Genetics Consortium; Nature. 2011 Aug 10;476(7359):214-9.

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MS as a T cell mediated disease

Table 2. Change in EDSS and MRI over 1-year follow-up

Pt	Before treatment	Day 10	6 Mos	9 Mos	12 Mos	Change in EDSS*	Change in MRI
1	9.0	9.0	8.5	8.5	8.5	-0.5	ND
2	6.5	7.5	7.5	7.5	7.5	+1.0	Unchanged
3†							
4	6.5	7.5	6.0	6.5	6.5	0	Unchanged
5	7.5	8.0	7.5	7.5	7.5	0	Unchanged
6	6.0	6.5	6.5	6.5	6.5	+0.5	Worse
7	6.5	6.5	6.0	6.5	6.0	-0.5	Worse
8	7.5	8.5	8.0	8.0	8.0	0	Unchanged
9	7.0	7.0	7.0	8.5	10	+3.0	ND
10	7.0	8.0	8.0	ND	10	+3.0	Worse
11	8.0	8.5	8.0	8.5	8.0	0	ND
12	8.0	8.0	8.0	8.0	8.0	0	Unchanged
13	6.5	7.5	6.5	6.5	6.5	+0.5	Unchanged
14	7.5	8.0	6.5	ND	5.5	-2.0	ND
15	6.5	6.5	6.5	ND	7.5	+1.0	Unchanged
16	6.0	8.0	5.5	5.0	5.0	-1.0	ND

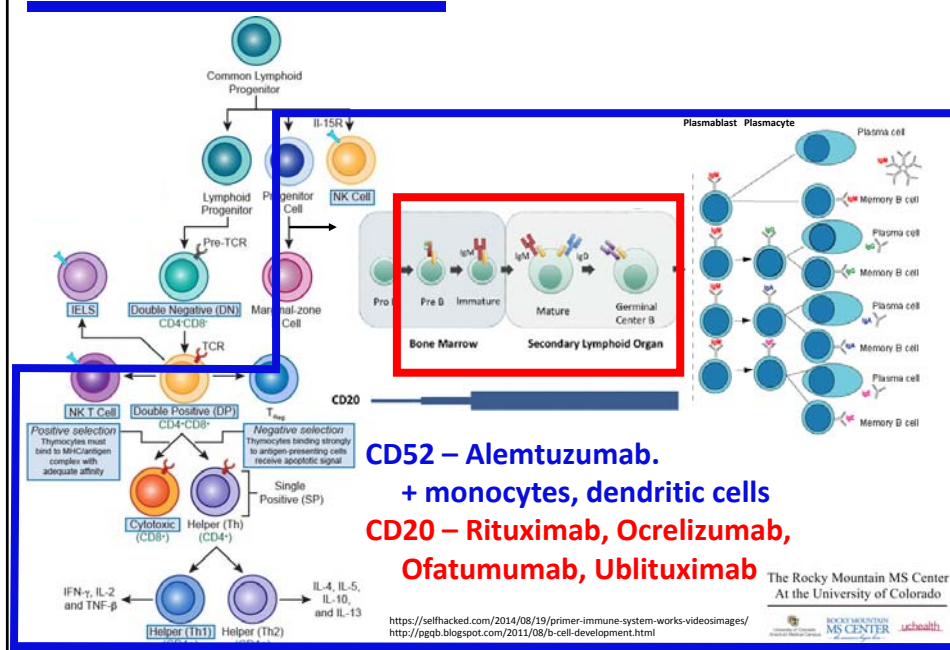
* EDSS at 1-year follow-up—EDSS pretreatment.
 † Premature termination.

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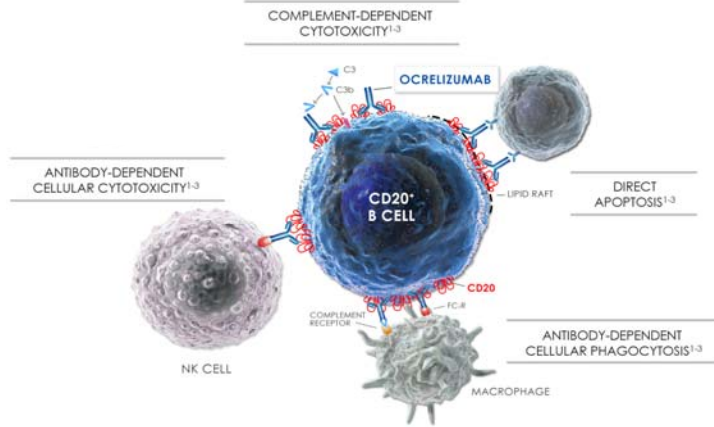
Weinshenker, et al. Neurology. 1991 41:1047-1052



The Lymphocyte Lineage



Cell Death from monoclonal Antibodies



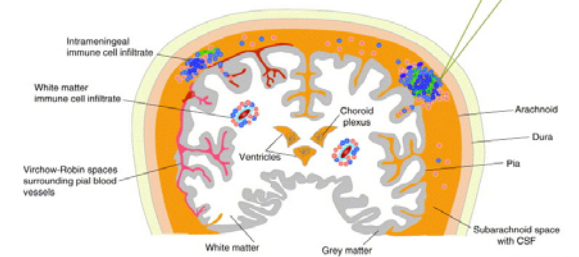
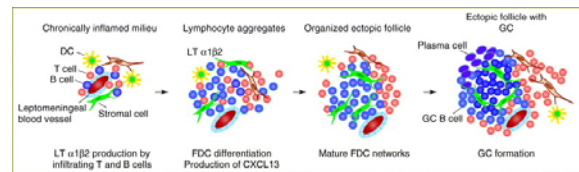
mAb, monoclonal antibody.
 1. Jagłowski SM, et al. *Blood* 2010;116:3705-14. 2. Winiarska M, et al. *Front Biosci* 2011;16:277-306. 3. Klein C, et al. *MAbs* 2013;5:22-33.

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Evidence supporting a role for B cells

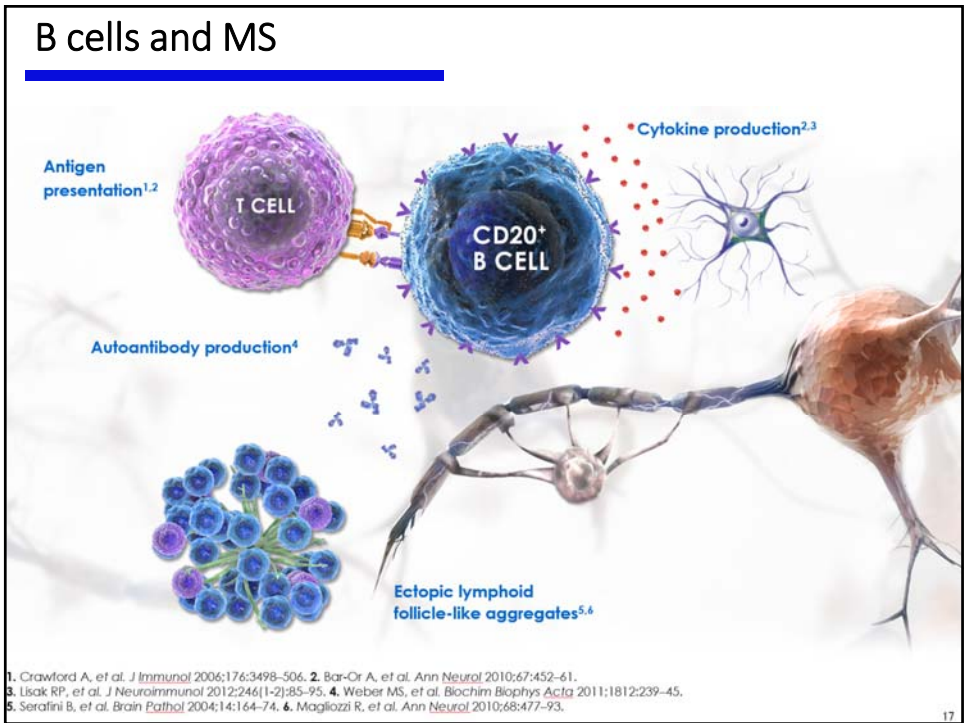
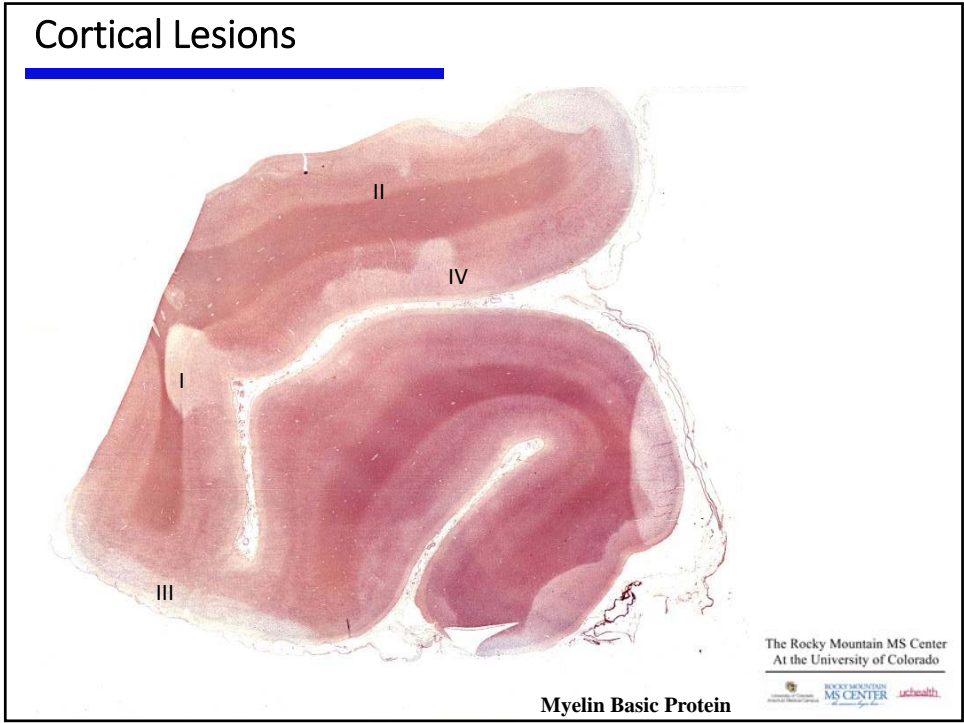
- Antibodies and complement in active MS plaques.
- Clonally expanded plasma cells intrathecally
- Ectopic lymphoid follicles with B cells and B-cell related chemokines.

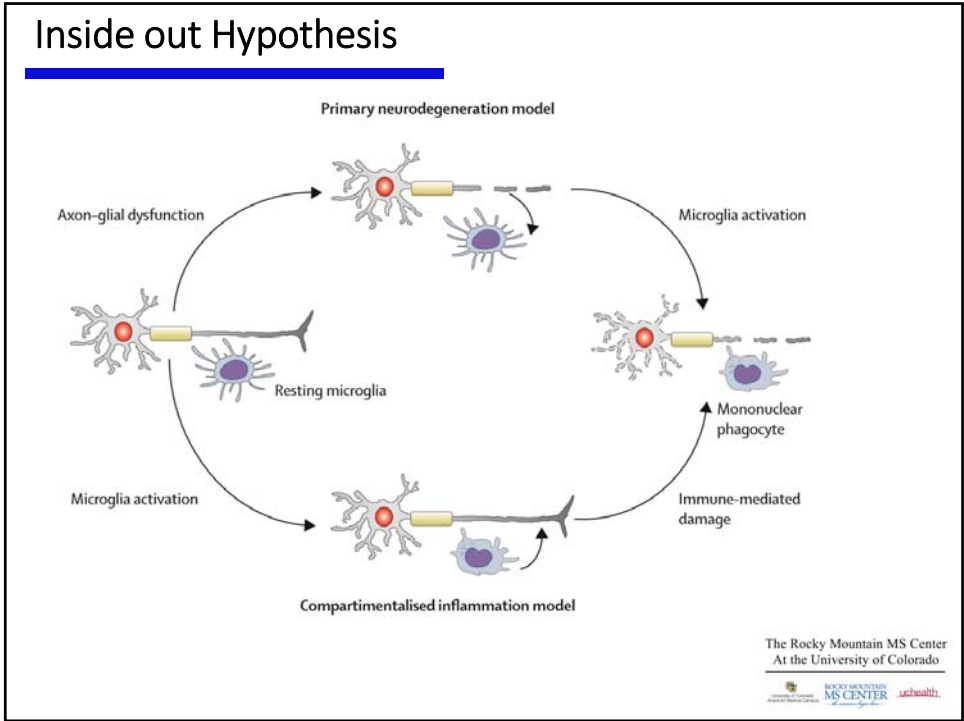


Uccelli A, et al. *Trends in immunology*. 2005. 26(5): 254-259.

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Conclusions

- Multiple pathways of the immune system are affected in MS
- Multiple sclerosis disease modifying therapies affect the immune system in many ways.

Hopefully, it this not sound like this...

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Thank You!!
Any questions???

The Rocky Mountain MS Center
at Anschutz Medical Campus

Did anybody call for a dogtor?

