Therapeutic developments for autoimmune demyelinating diseases: Musings from a MD (Mouse Doctor)

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Relevant Disclosures

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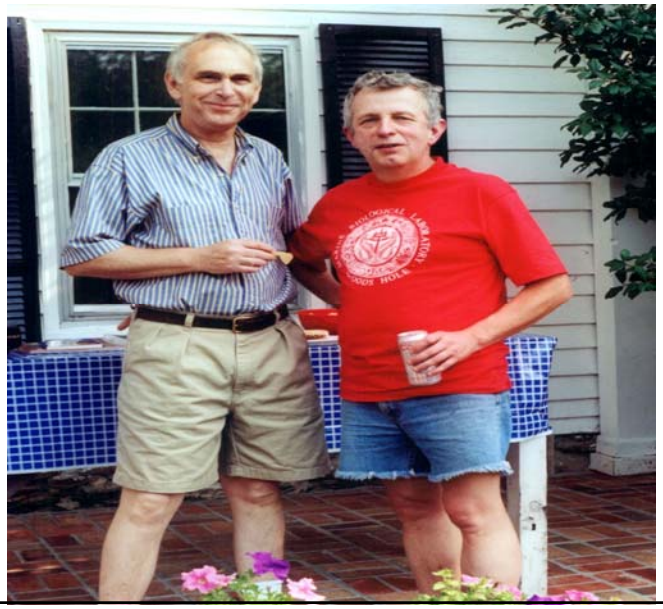
Consultant for Accorda, Biogen Idec, Diogenix, Genentech, Questcor, Revalesio, Novartis, Roche and Teva Neuroscience

Multiple Sclerosis

- Worked on the mechanism of glatiramer acetate (copolymer 1) as a resident
- Copolymer 1 first treatment derived from EAE model
- Bob Fritz's relationship with Dale results in my heading to Bethesda

McFarland and McFarlin



To understand MS, you need to work on patients!

Clinical Score Evaluation in EAE

1=limp tail

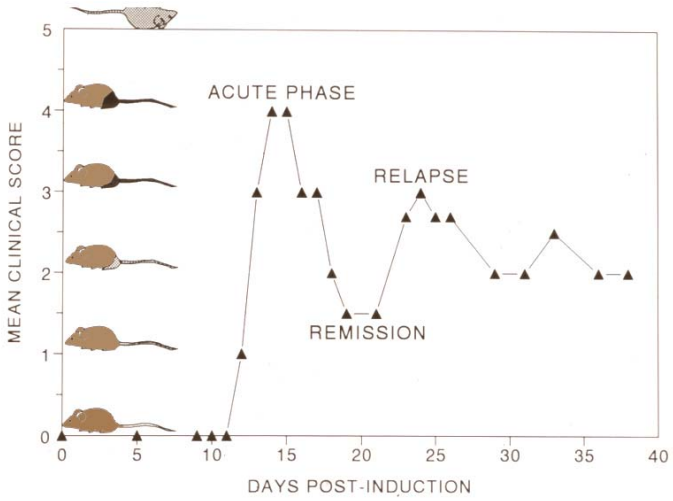
2=moderate hind limb weakness

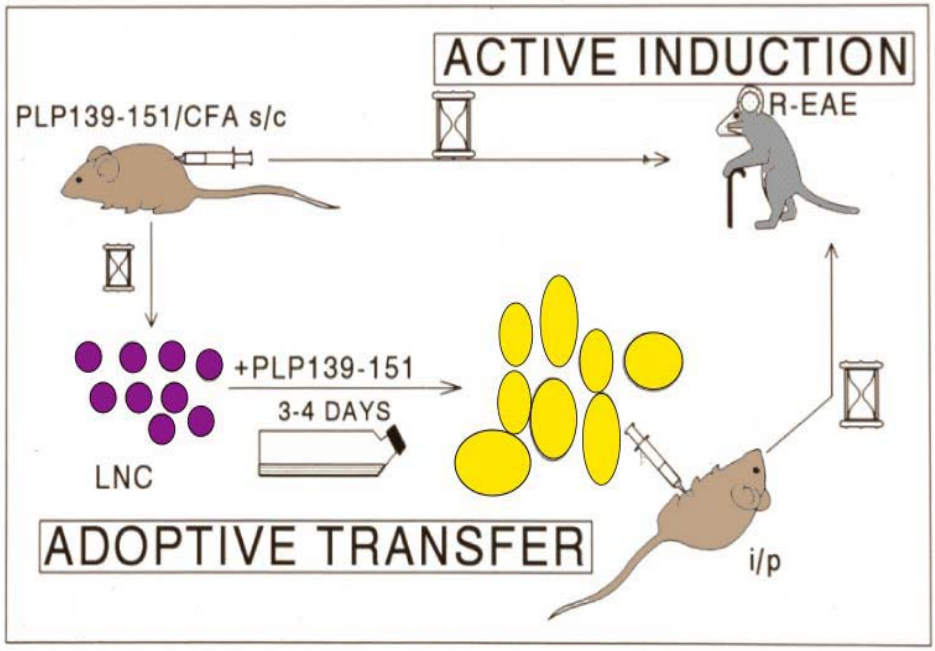
3=severe hind limb weakness

4=hind limb paralysis

5=hind and fore limb paralysis

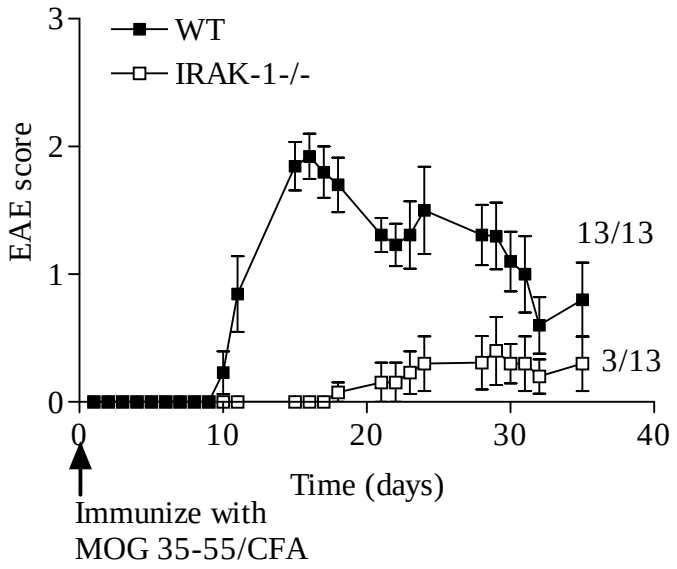
6=death due to EAE



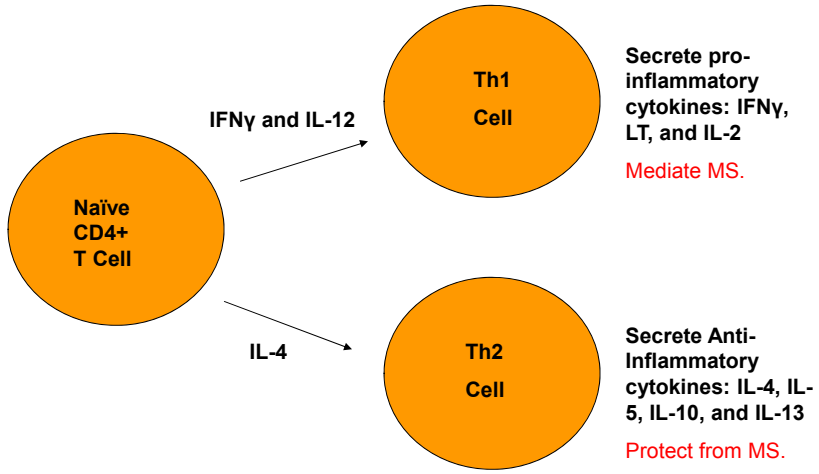


Role of adjuvants

- Component of pathogen that engages Toll-like receptors
- IRAK-1 is important molecule to deliver signal from TLR to nucleus
- Immune genes are activated as part of the innate immune response



Differentiation of Naïve T Cells is Primarily Determined by Cytokine Environment



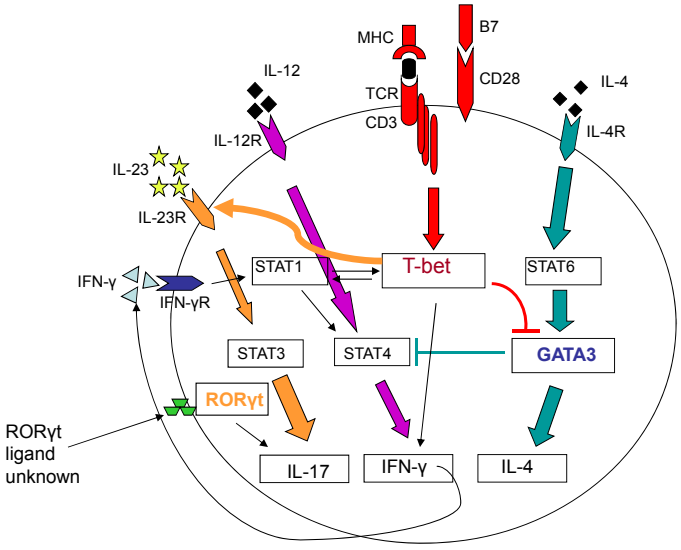
Secrete pro-inflammatory cytokines: IFNγ, LT, and IL-2

Mediate MS.

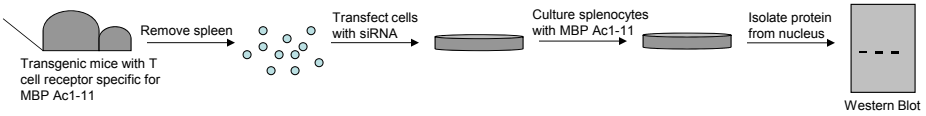
Secrete Anti-Inflammatory cytokines: IL-4, IL-5, IL-10, and IL-13

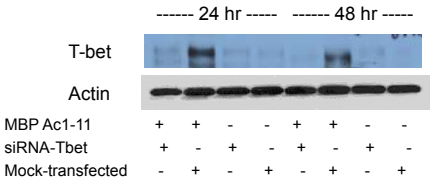
Protect from MS.

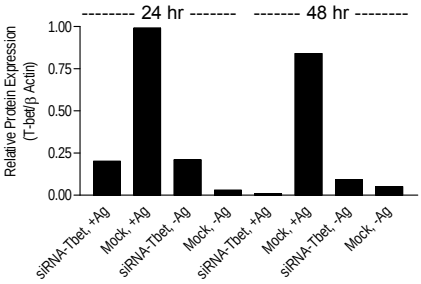
Transcriptional Regulation of T Cell Differentiation



Development of an siRNA specific for T-bet

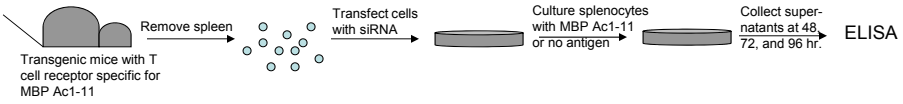


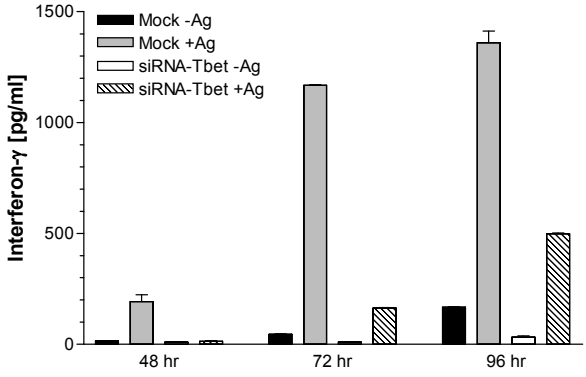




Lovett-Racke et al (2004) *Immunity 21:719-731.*

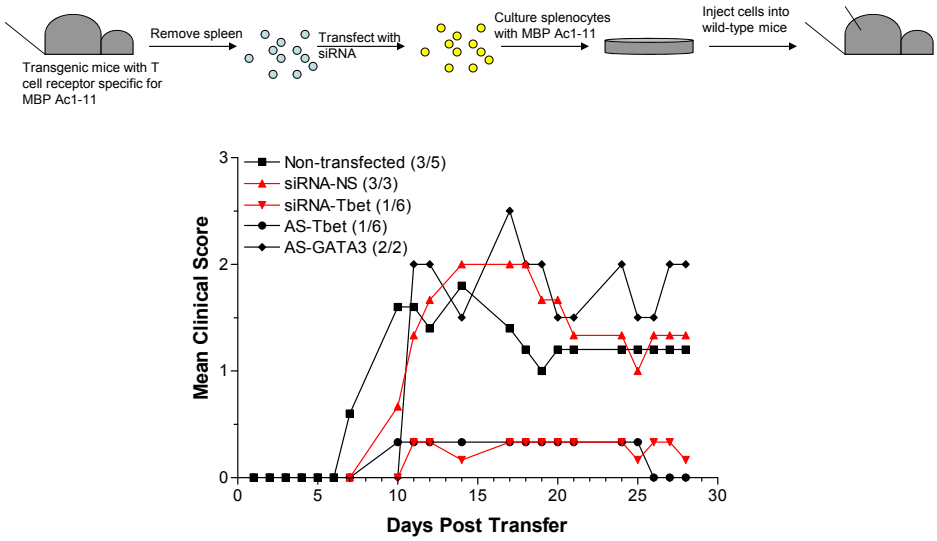
Silencing T-bet Inhibits IFNγ Production and Th1 Differentiation





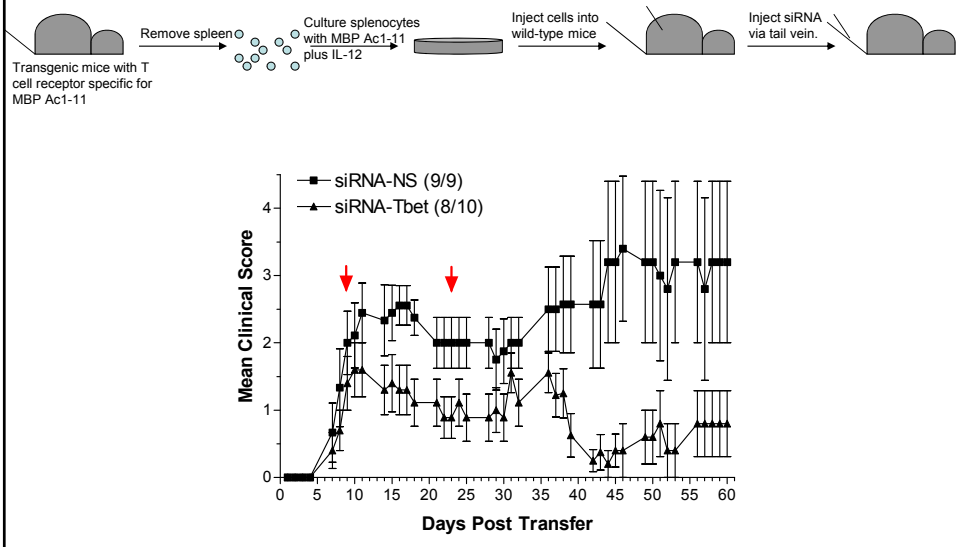
Lovett-Racke et al (2004) *Immunity 21:719-731.*

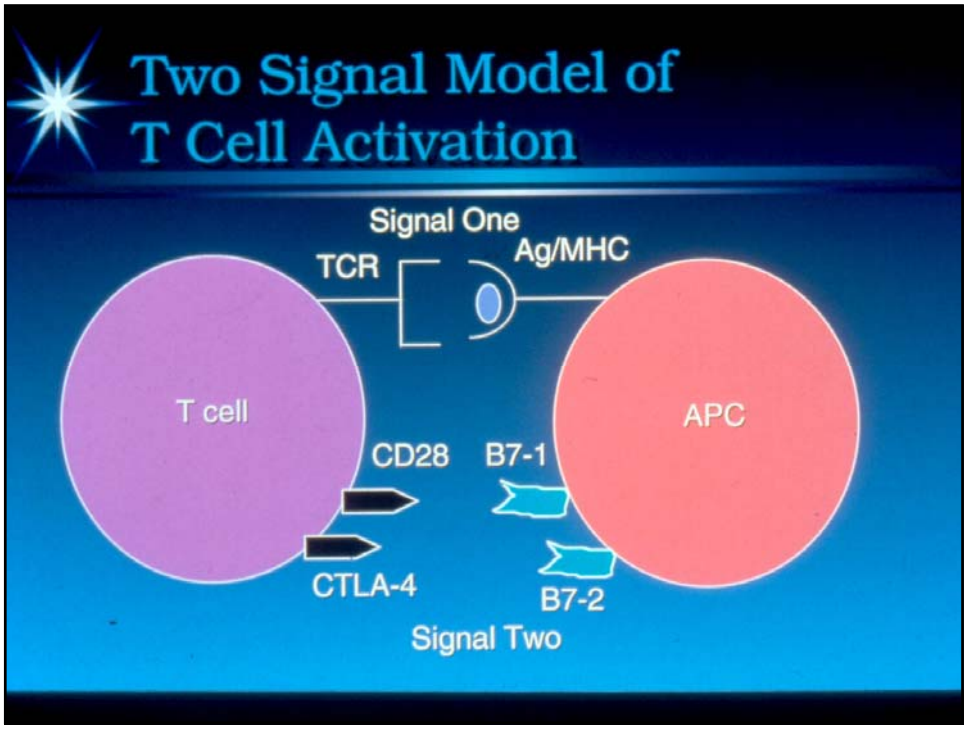
Myelin-specific T cells in which T-bet has been Silenced Fail to Transfer Experimental Autoimmune Encephalomyelitis

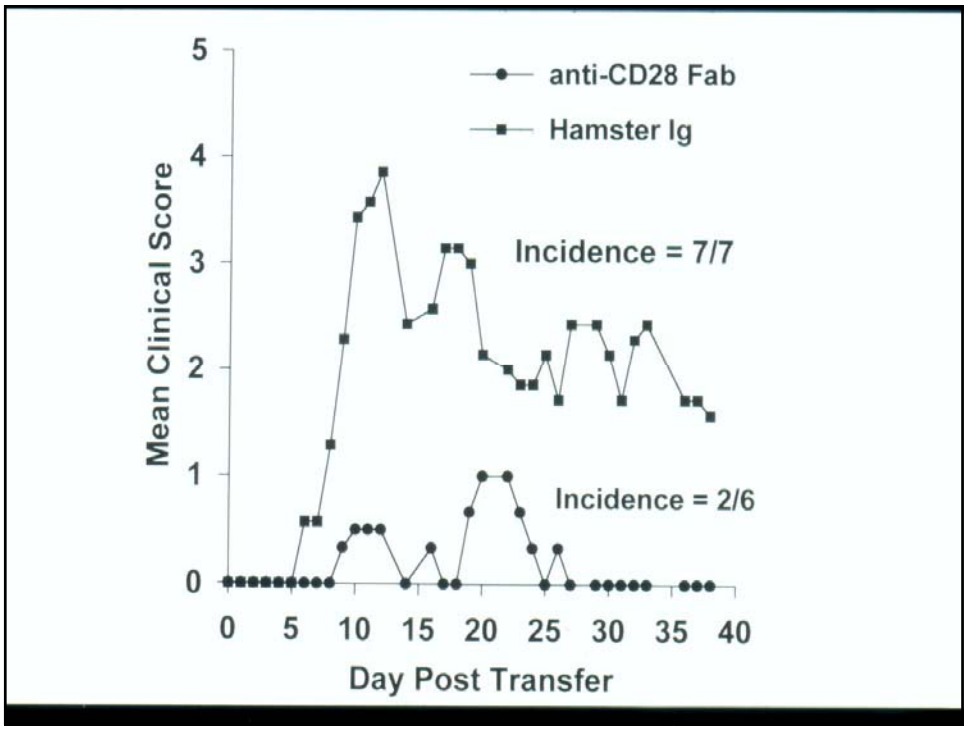


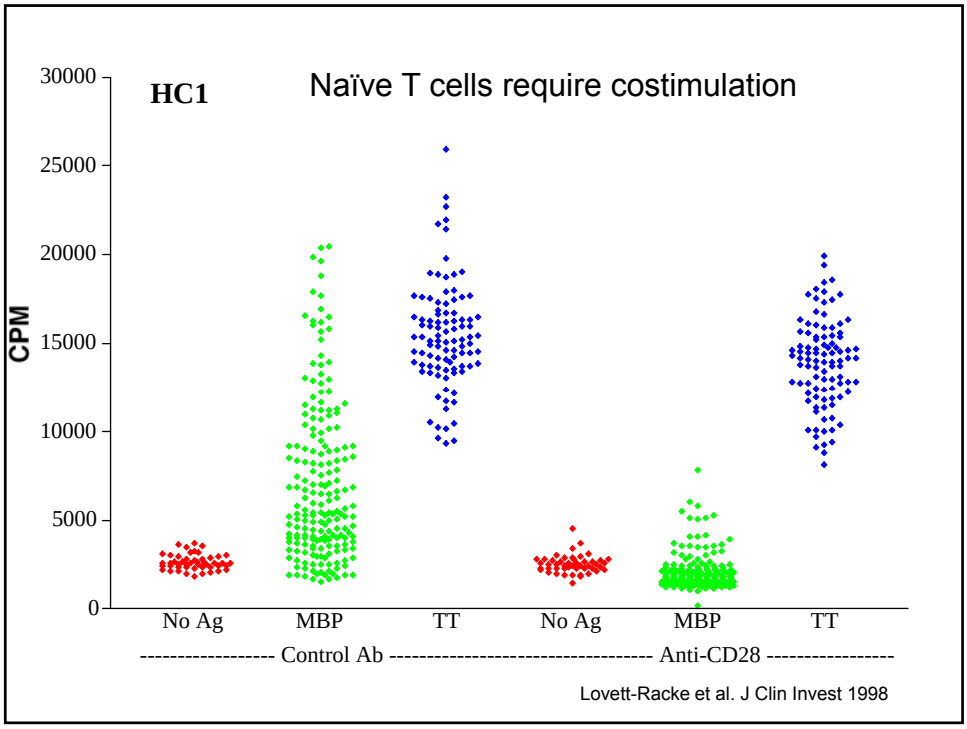
Lovett-Racke et al (2004) *Immunity 21:719-731.*

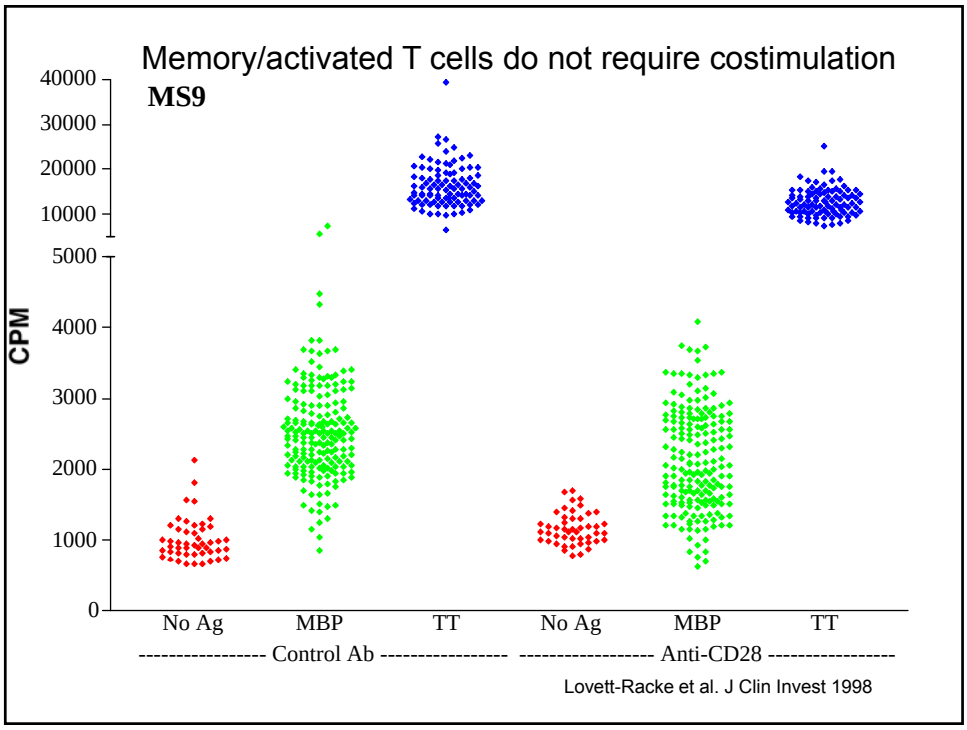
Silencing T-bet Ameliorates EAE



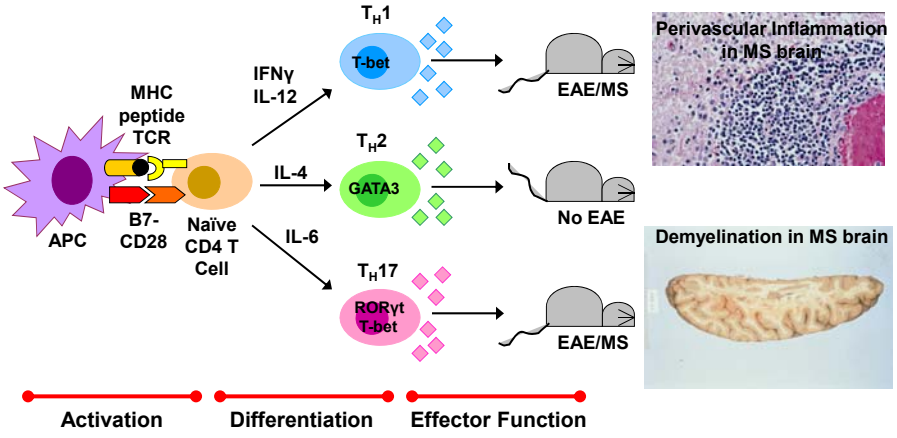

Two Signal Model of
T Cell Activation
Signal One
TCR
Ag/MHC
T cell
APC
CD28
B7-1
CTLA-4
B7-2
Signal Two


anti-CD28 Fab
Hamster Ig
Incidence = 7/7
Incidence = 2/6
Mean Clinical Score
Day Post Transfer
0
1
2
3
4
5
0
5
10
15
20
25
30
35
40


HC1
Naïve T cells require costimulation
CPM
30000
25000
20000
15000
10000
5000
0
No Ag
MBP
TT
No Ag
MBP
TT
Control Ab
Anti-CD28
Lovett-Racke et al. J Clin Invest 1998


Memory/activated T cells do not require costimulation
MS9
CPM
40000
30000
20000
10000
5000
4000
3000
2000
1000
0
No Ag
MBP
TT
No Ag
MBP
TT
Control Ab
Anti-CD28
Lovett-Racke et al. J Clin Invest 1998

T Cells in Multiple Sclerosis



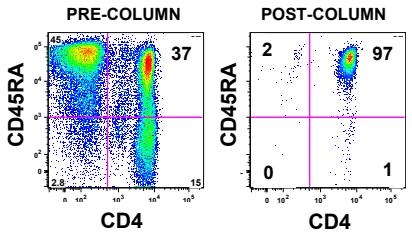
- Intrinsic defects in MS patients CD4 T cells make them more susceptible to develop into actively pathogenic cells
- Can these defects translate into clinically useful biomarkers?

Isolation of Naïve CD4 T Cells

Peripheral Blood Mononuclear Cells

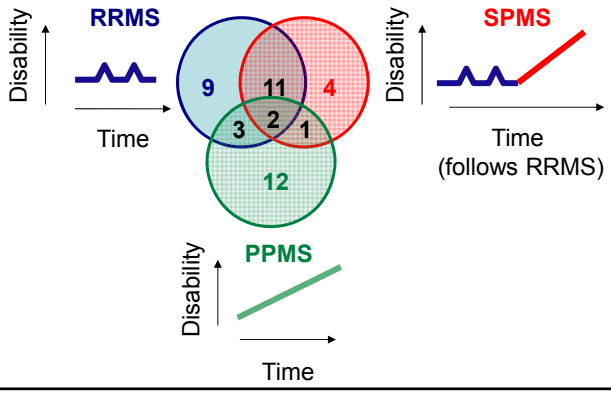
Healthy (n=16) RRMS (n=12) SPMS (n=5) PPMS (n=5)

Naïve CD4 T cells (CD4+CD45RA+)

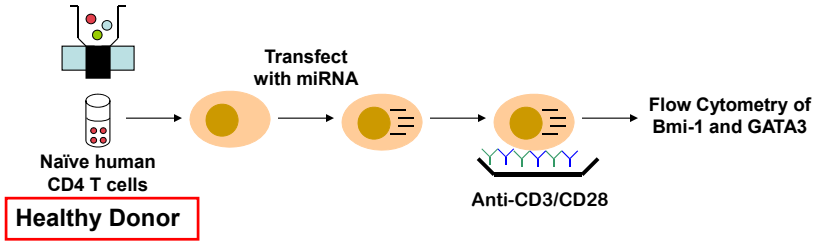


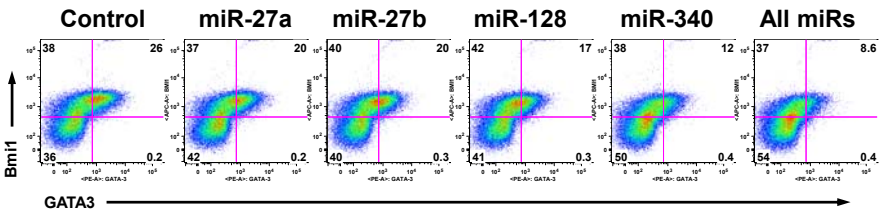
Differential Expression of miRNA in MS

- 55 significantly different miRNAS (P<0.05, StatMiner, parametric Limma test) in one or more type of MS
- 23 up-regulated
- 32 down-regulated



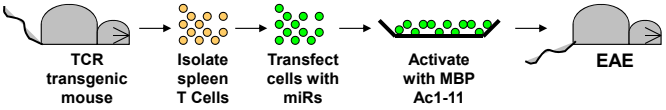
miRs Target Bmi-1 and GATA3

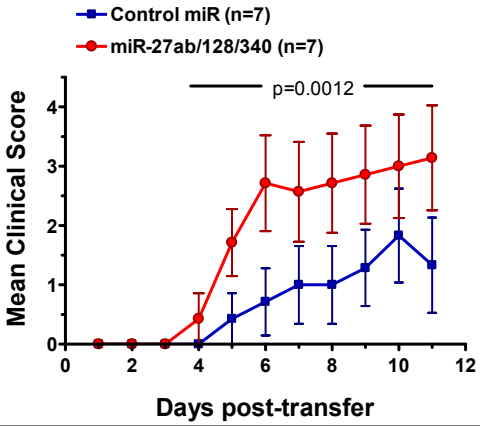




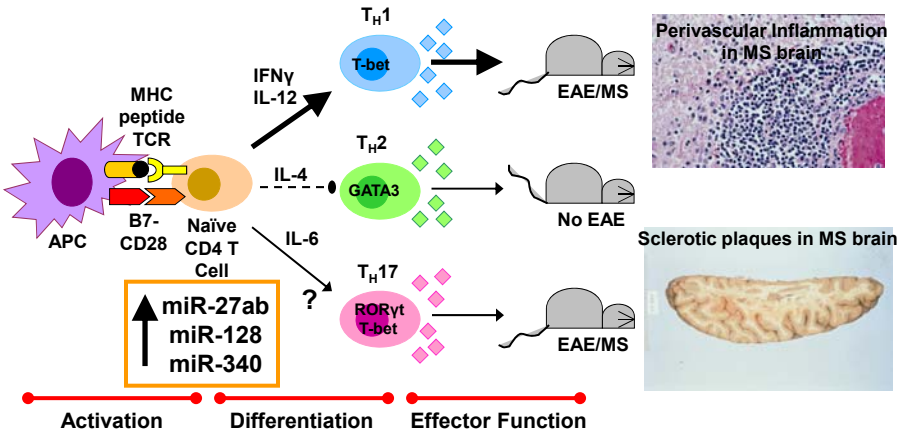
Guerau-de-Arellano et al. Brain 2011

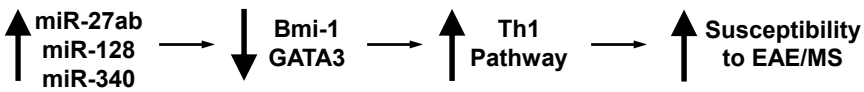
miRs Enhance Encephalitogenicity



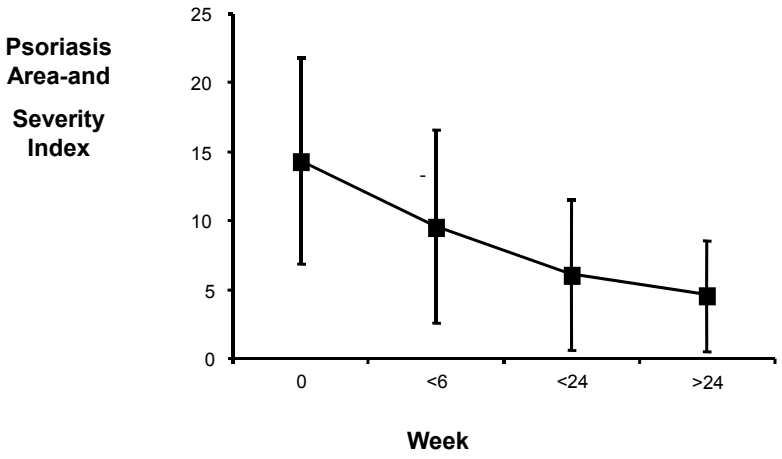


T Cells in Multiple Sclerosis

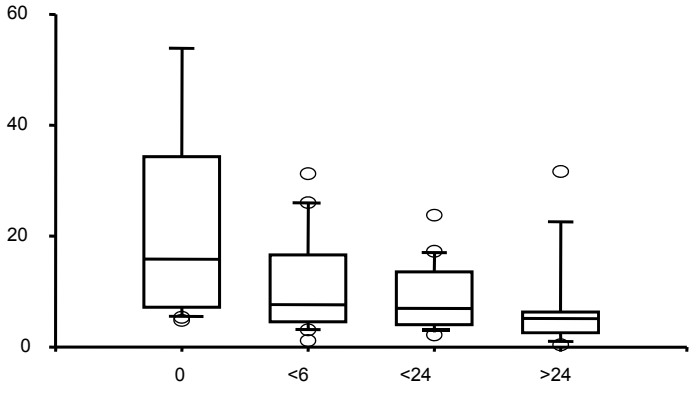




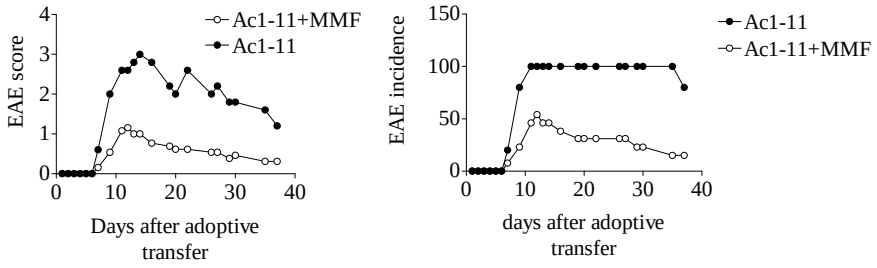
Fumarate Effect on Psoriasis



IFN-γ to IL-4 ratio in CD4+ T cells

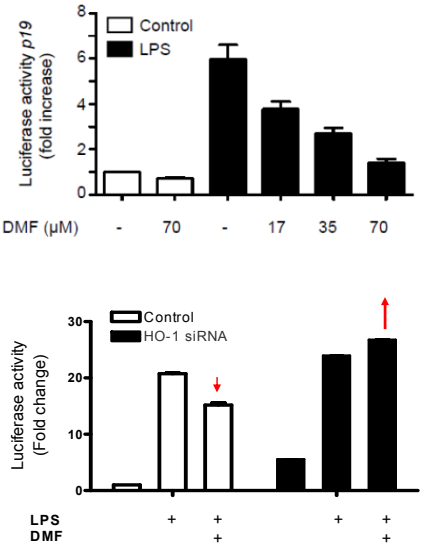


Ghoreschi et al. J Exp Med 2011

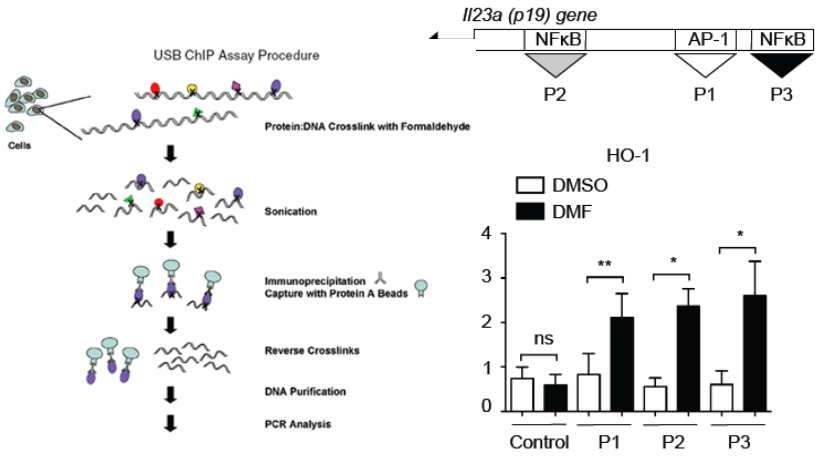


MMF treated TCR αβ Tg lymphocytes adoptively transfer a milder course of EAE.

Knocking down HO-1 successfully restored p19 activity

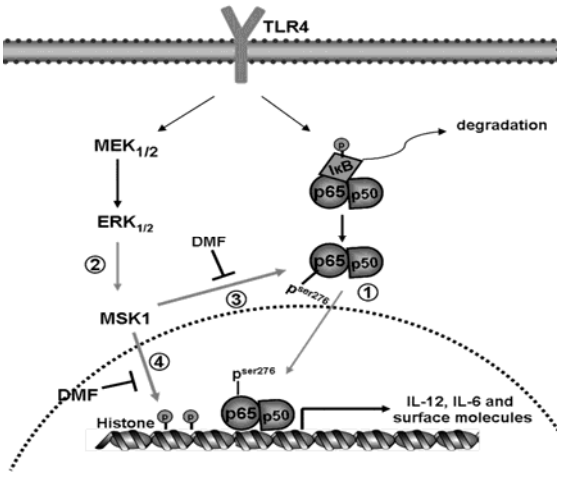


HO-1 interacts with *p*19 promoter



Journal of Experimental Medicine, Racke and Rocken lab. 2011

Effect of DMF on APCs



Peng et al. JBC 2012

My first paper in 1991

PREVENTION AND TREATMENT OF CHRONIC RELAPSING EXPERIMENTAL ALLERGIC ENCEPHALOMYELITIS BY TRANSFORMING GROWTH FACTOR-β_1[1]

MICHAEL K. RACKE,[2]* SUHAYL DHIB-JALBUT,[3]* BARBARA CANNELLA,† PAUL S. ALBERT,‡ CEDRIC S. RAINE,† AND DALE E. MCFARLIN*

*From the *Neuroimmunology Branch, National Institute of Neurological Diseases and Stroke, ‡Biometry and Field Studies Branch, National Institute of Neurological Diseases and Stroke, National Institutes of Health, Bethesda, MD 30892 and †Division of Neuropathology, Albert Einstein College of Medicine, Bronx, NY 10461*

Transforming growth factor-beta

- Worked on transforming growth factor (TGF)-beta as treatment for EAE and MS patients as a fellow
- This is how it is supposed to work, treatment works in EAE and then you try it in people with MS

TGF-beta for SPMS failed

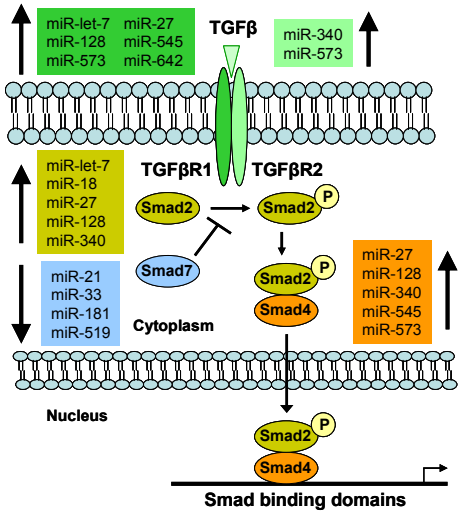
Phase 1 trial of transforming growth factor beta 2 in chronic progressive MS

Article abstract—Transforming growth factor (TGF)-β2 is a pleiotropic cytokine associated with remissions in multiple sclerosis (MS) and amelioration of allergic encephalomyelitis. We assessed the safety of TGF-β2 in an open-label trial of 11 patients with secondary progressive (SP) MS. Five patients had a reversible decline in the glomerular filtration rate. There was no change in expanded disability status scale or MRI lesions during treatment. Systemic TGF-β2 may be associated with reversible nephrotoxicity, and further investigation of its therapeutic potential in MS should be performed with caution.

NEUROLOGY 1998;51:289–292

P.A. Calabresi, MD; N.S. Fields, BS; H.W. Maloni, RN; A. Hanham, PhD; J. Carlino, PhD; J. Moore, MS; M.C. Levin, MD; S. Dhib-Jalbut, MD; L.R. Tranquill, MS; H. Austin, MD; H.F. McFarland, MD; and M.K. Racke, MD

miRNAs in MS target TGF-β signaling



Conclusions

Differences in immune response in MS patients and healthy controls will define therapeutic targets

Micro RNA may help define susceptibility and provide new therapeutic targets for a number of diseases, including MS

EAE can provide insights into pathogenesis and help test new therapies

What a crew!