

The Immunopathogenesis of Secondary Progressive MS



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Disclosures

- Benjamin Segal, MD
 - Grants/research support: NIH, VA, NMSS, TEVA Neuroscience
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 - Honoraria from Industry: Biogen, Innate Therapeutics
- CME Staff Disclosures
 - Professional Education Services Group staff have no financial interest or relationships to disclose.

Learning Objectives

At the conclusion of this activity, the participant will be able to:

- A. Discuss the immune abnormalities that characterize different stages of multiple sclerosis
- B. Discuss the role of lymphoid neogenesis in progressive MS
- C. Discuss novel MRI outcome measures in MS

Obtaining CME Credit

- If you would like to receive CME credit for this activity, please visit:

<http://www.pesgce.com/PVAsummit2011/>

- This information can also be found in the Summit 2011 Program on page 8.

Is progressive MS a neuroimmunological or a neurodegenerative disorder?

Is the accumulation of disability during progressive MS the result of the delayed degeneration of axons / death of neurons that were originally damaged by immune mediators during the relapsing remitting phase, or is ongoing neuroinflammation responsible?

Evidence that SPMS is a non-inflammatory disorder

- Loss of responsiveness to immunomodulators (IFN β , glatiramer acetate)
- Decreased frequency of enhancing lesions on MRI

Evidence that SPMS is an inflammatory disorder

- Efficacy of chemotherapeutic agents in some patients
(Mitoxantrone)
- Persistence of oligoclonal bands in the CSF
- Evidence of persistent immune dysregulation in the periphery
- Presence of diffuse T cell infiltration and microglial activation in CNS specimens from individuals with SPMS

Neuropathological Patterns in MS Subsets

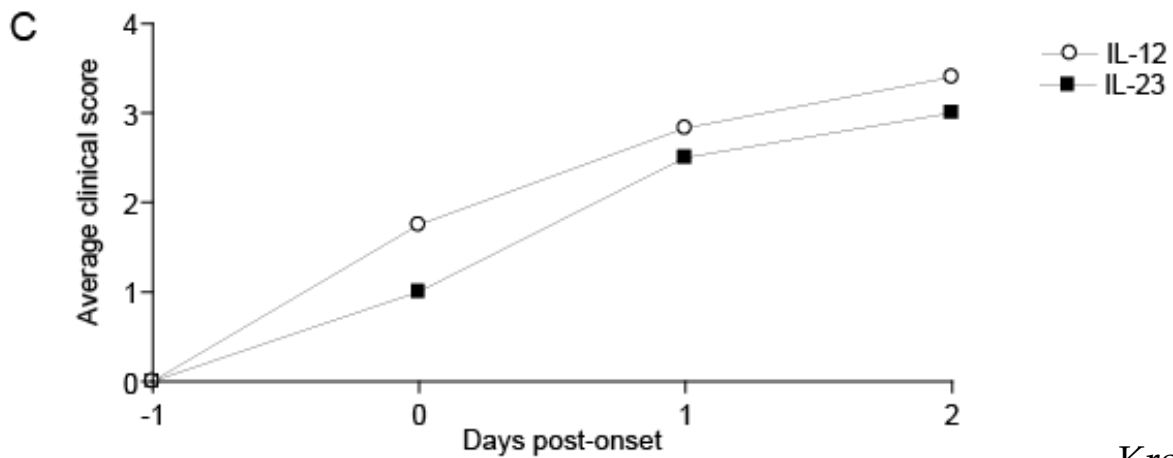
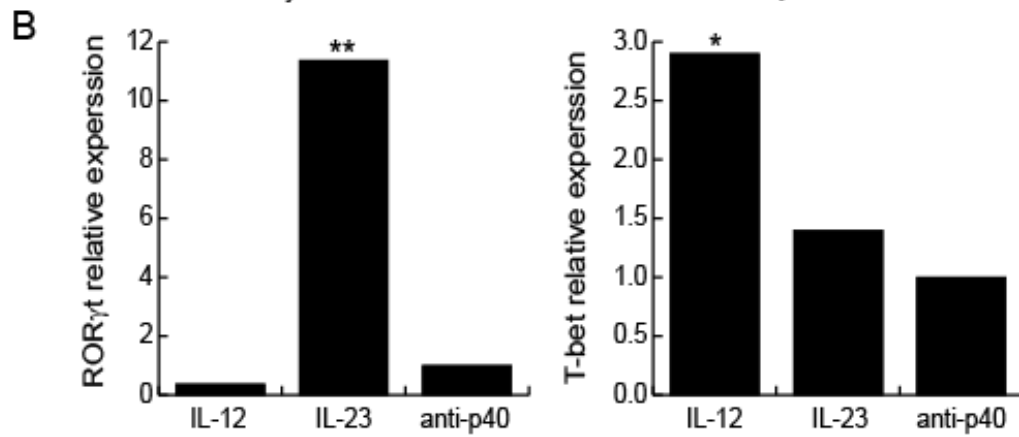
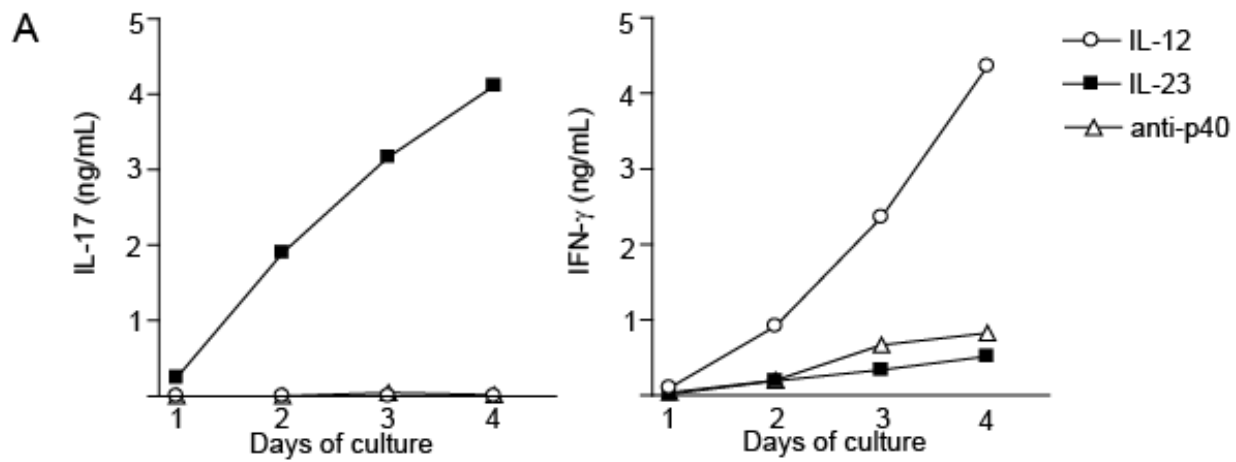
Pattern	Acute (< 1 yr)	RRMS (<1yr)	SPMS (>1 yr)	PPMS (> 1yr)	Total
I	6	1	1	1	9
II	20	9	6	4	39
III	20	1	1	0	22
IV	0	0	0	3	3
Total	46	11	8	8	73

Specimens from 88% of SPMS patients had prominent inflammatory features

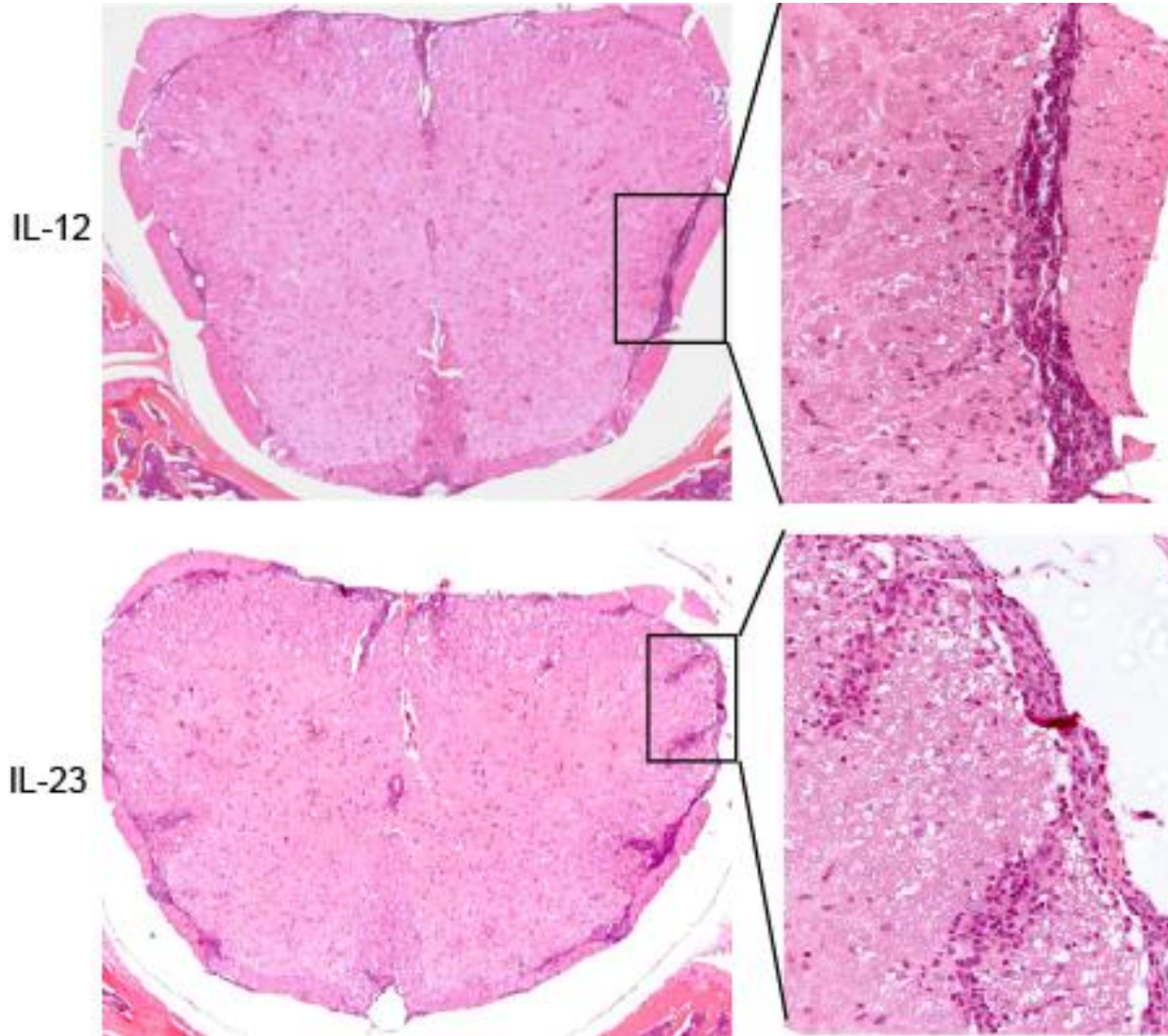
Lucchinetti, et al. *Annals of Neurology* 2000 **47**:707

Myelin specific Th1 and Th17 effector T cells have both been implicated in MS pathogenesis:

- Th1 cells are induced by IL-12 and produce IFN γ**
- Th17 cells are induced by IL-23 and produce IL-17**



IL-12 and IL-23 modulated cells induce qualitatively different types of spinal cord inflammation

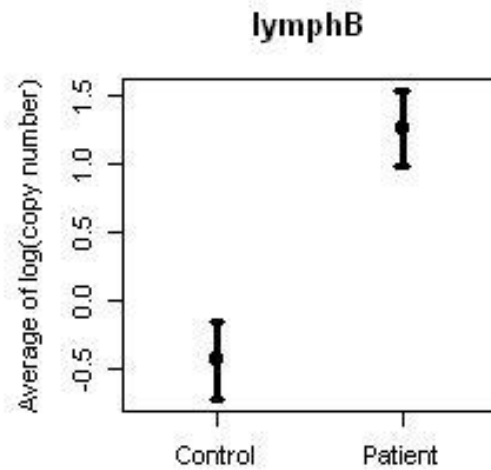
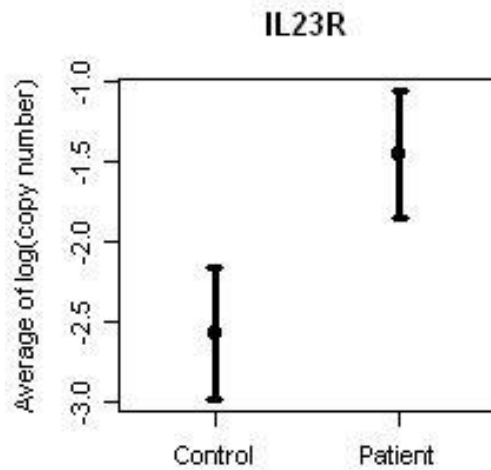
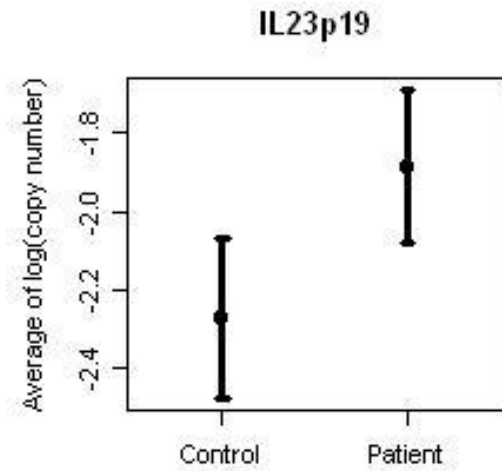
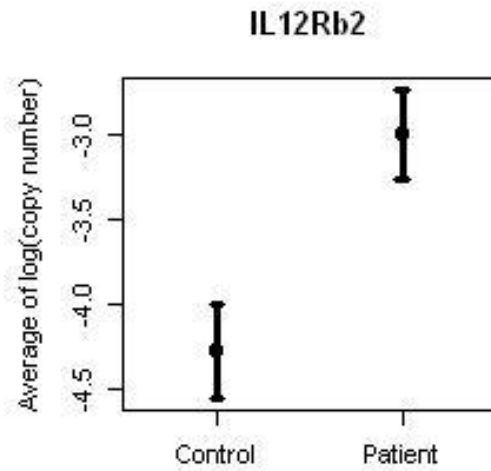
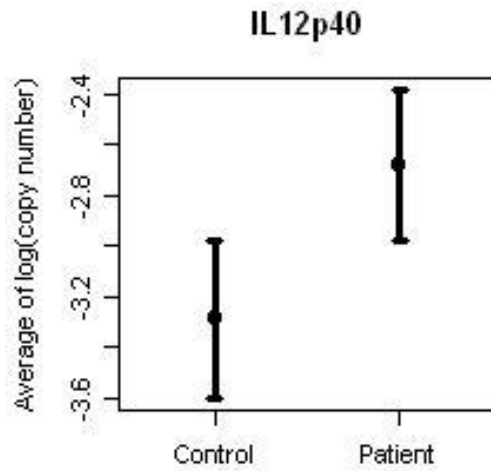


Genes upregulated in PBMCs during SPMS

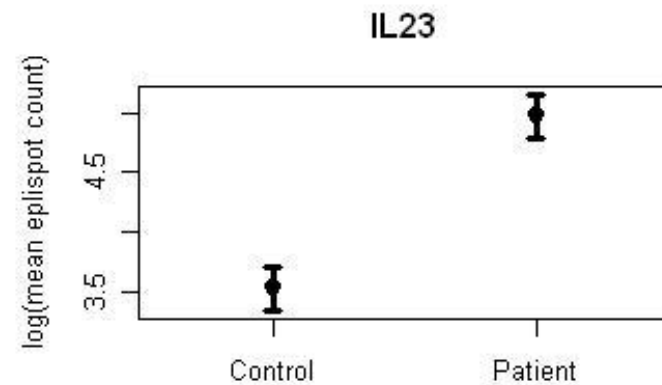
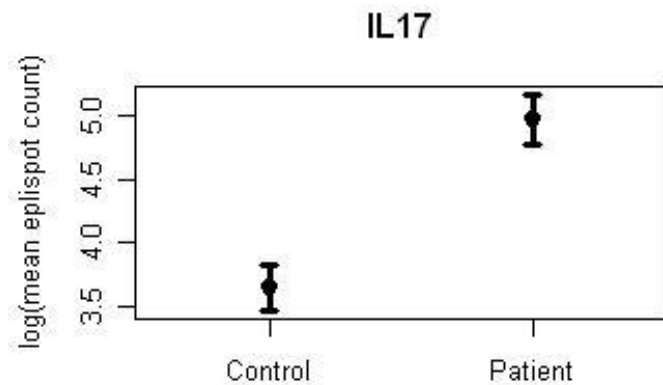
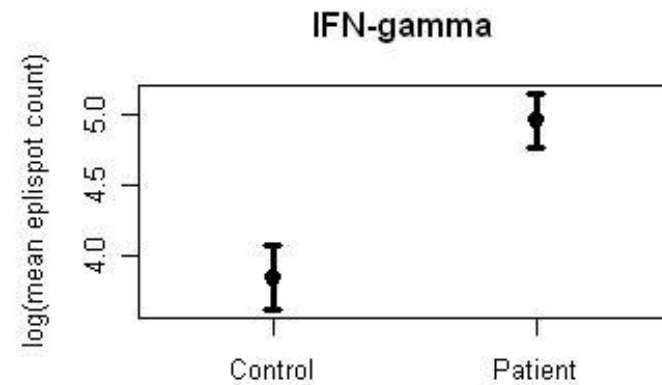
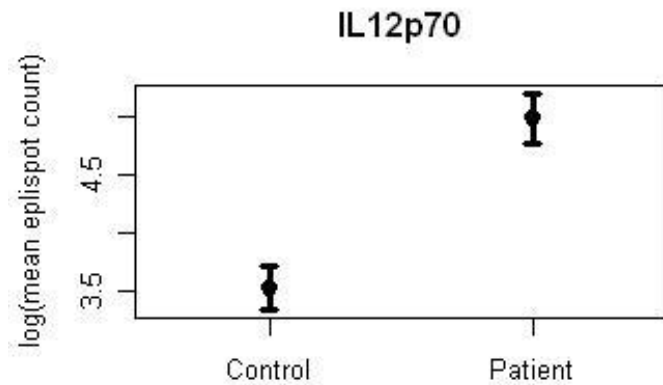
Genes	p-value
Alpha-4-integrin	0.1030
Beta-7	0.1700
FOXP3	0.2769
EBI3	0.0698
GMCSF	0.1419
IFN-gamma	0.5830
IL12p35	0.1541
IL12p40	0.0075**
IL12Rb1	0.4245
IL12Rβ2	<0.0001**
IL17	0.4240
IL23p19	0.0094**
IL23R	0.0004**
RORγT	0.0471*
Tbet	0.1855

Repeated measurement analysis

IL-12p40 family genes elevated in SPMS



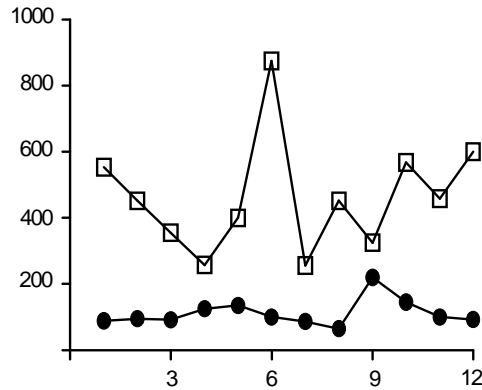
IL-12p40 related proteins are produced in excess in SPMS



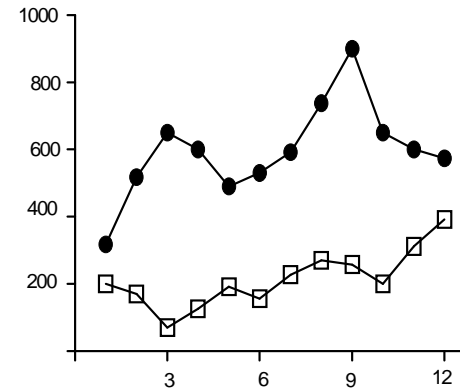
The Th1/Th17 balance
changes during the transition
to SPMS

Longitudinal patterns of MBP-specific cytokine production in SPMS

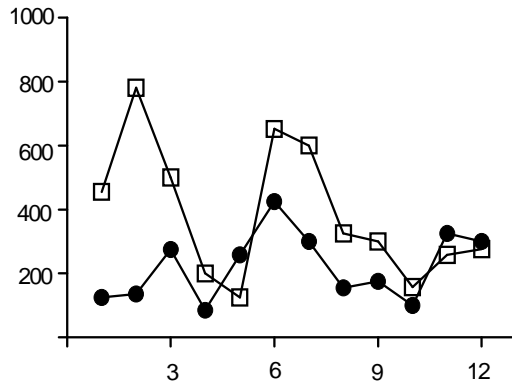
Th1 dominant
(62%)



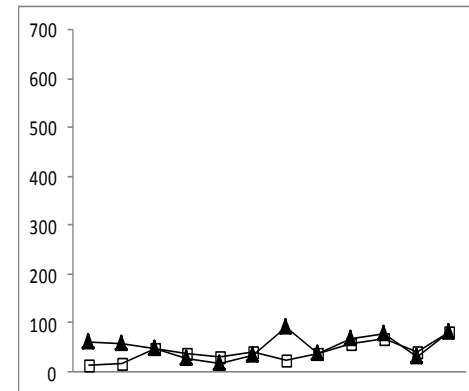
Th17 dominant
(22%)



Mixed
(22%)



Healthy control

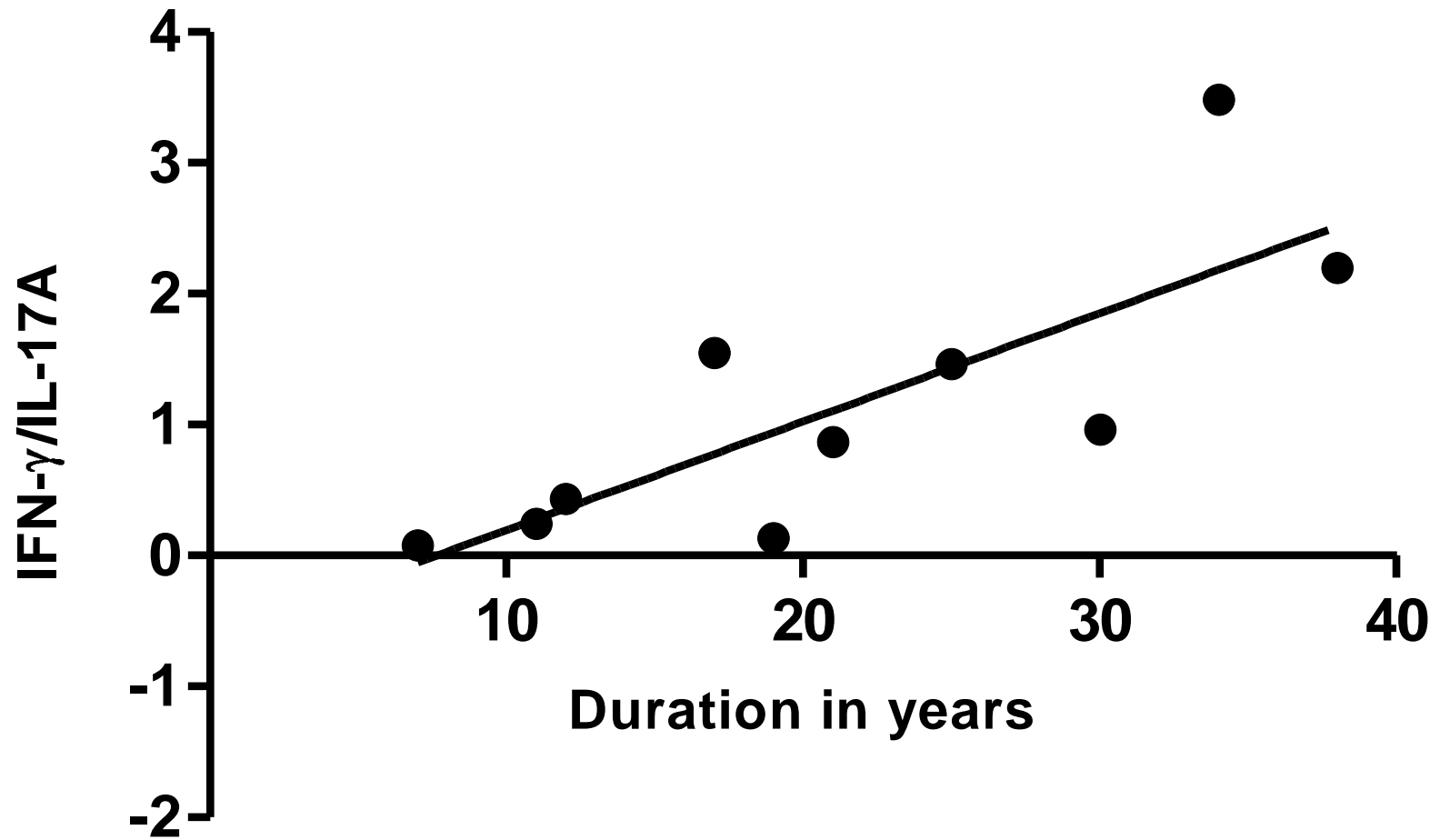


□ IFN- γ
● IL-17

MBP-specific cytokine patterns in RR and SPMS

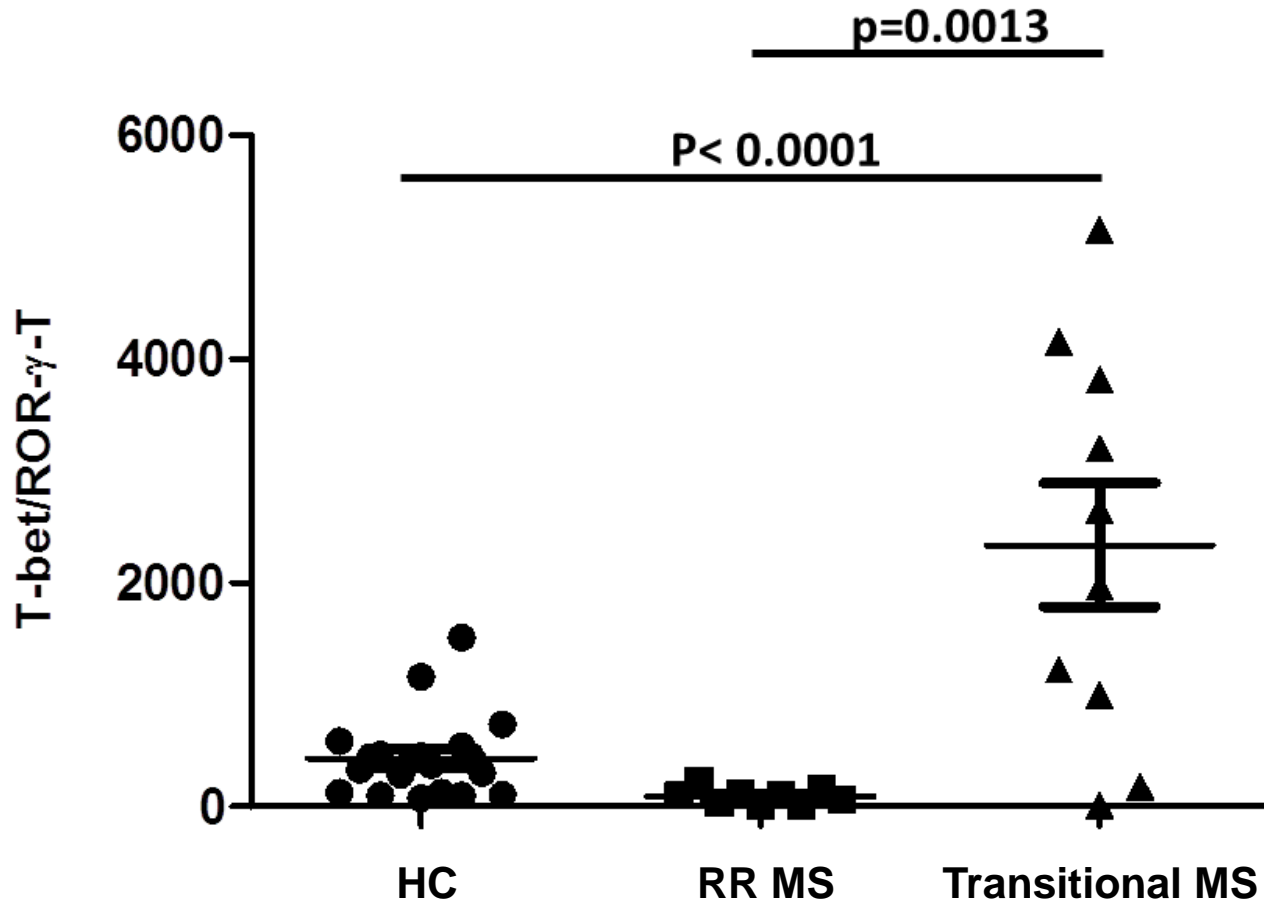
	RRMS	SPMS
Th1 dominant	44% (4/9)	62% (10/16)
Th17 dominant	22% (2/9)	19% (3/16)
Mixed	33% (3/9)	19% (3/16)

Correlation between IFN γ /IL-17 ratio and disease duration



$r^2=0.63$

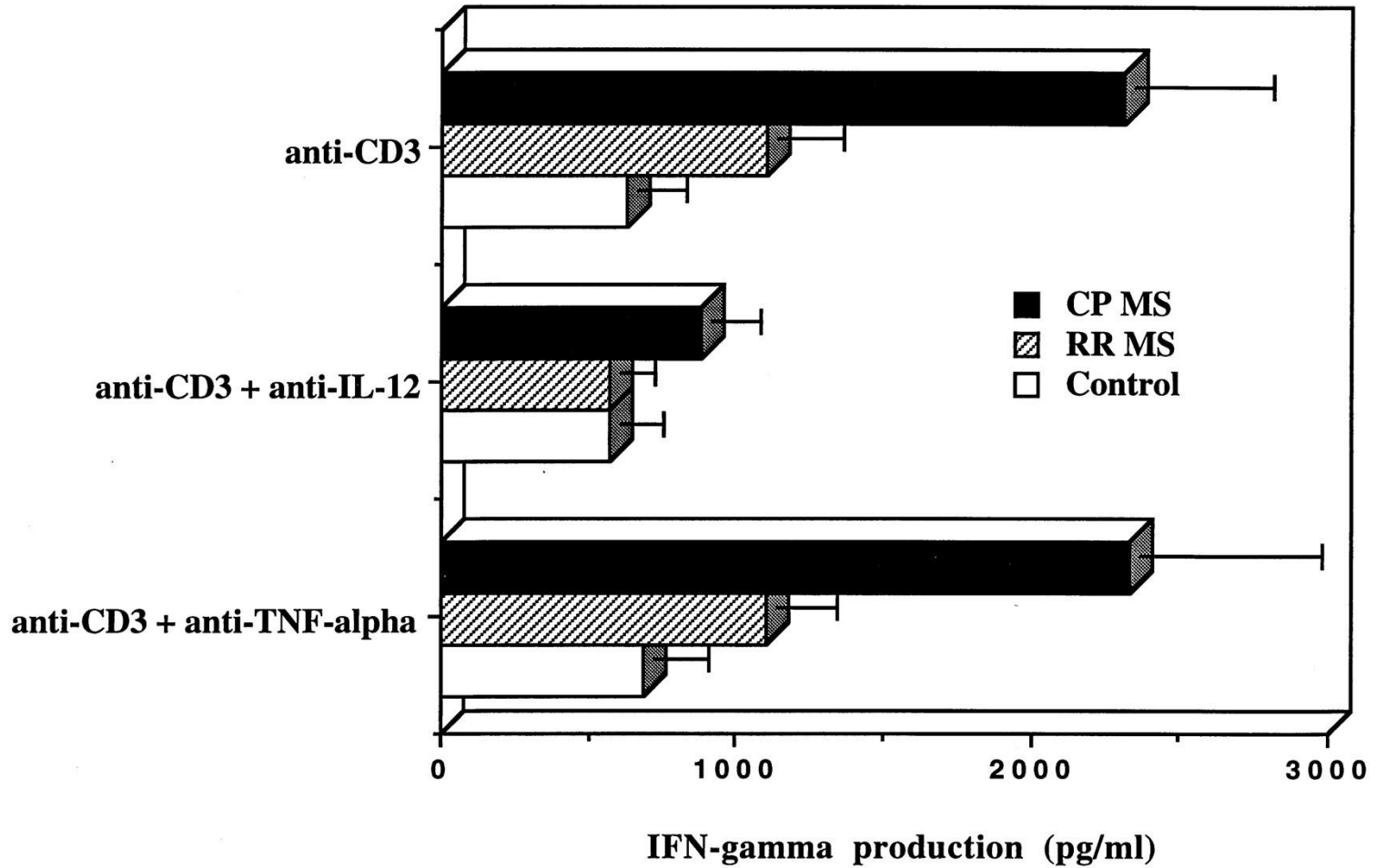
The Tbet:ROR γ T ratio is elevated in transitional MS



A higher % of patients with transitional than RR MS mount Th1 recall responses

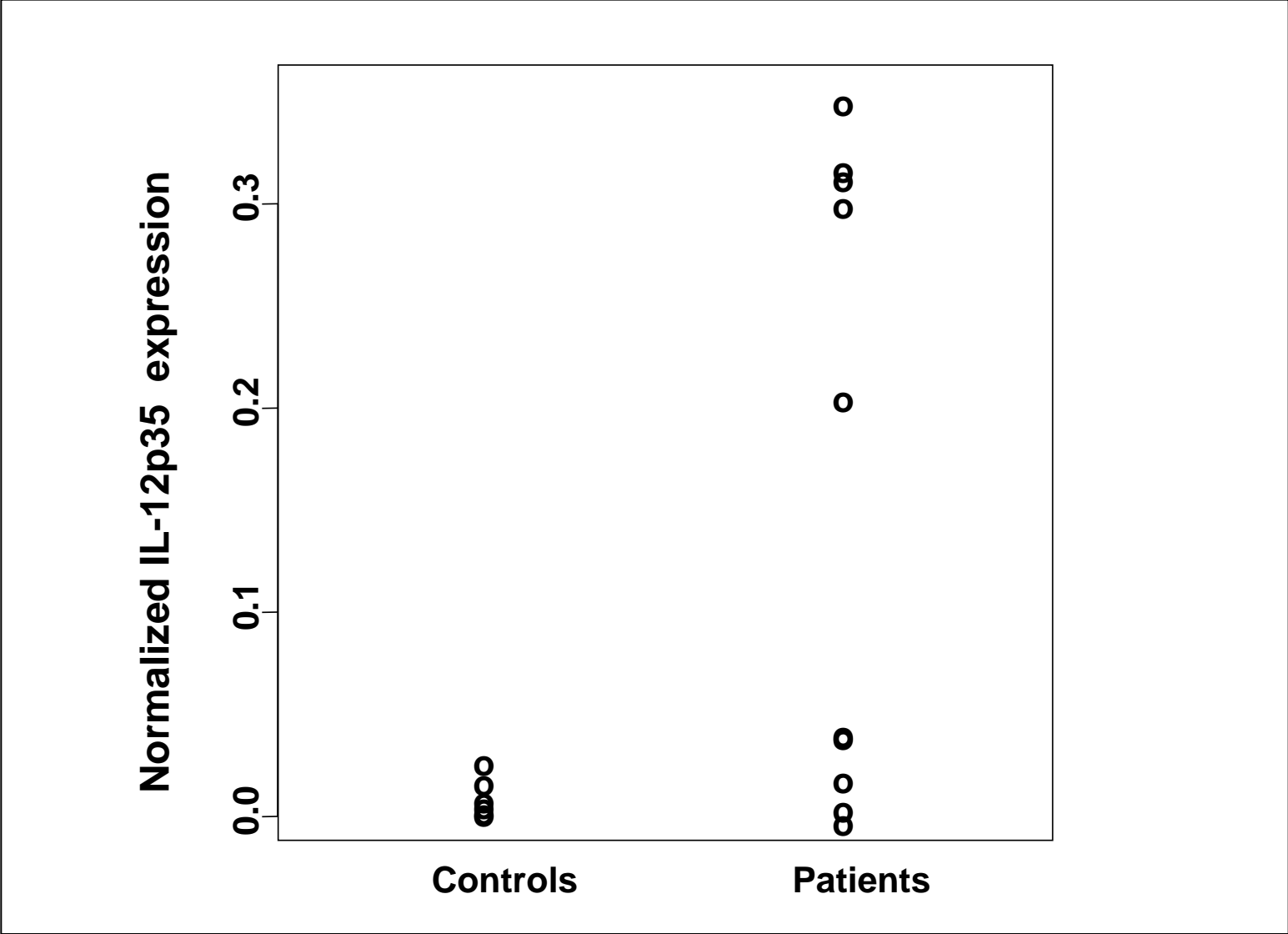
Cytokine profiles	Patients with relapsing–progressive course (<i>n</i> =10)	Patients with relapsing–remitting course (<i>n</i> =21)	<i>p</i> values
	number (%)		
Type 1	6 (60)	5 (24)	<0.05
Type 2	1 (10)	0	n.s.
Type 0	1 (10)	9 (43)	<0.05
No cytokine production	2 (20)	7 (33)	n.s.

Increased TcR-mediated IFN- γ production in MS is linked to defective regulation by endogenous IL-12.

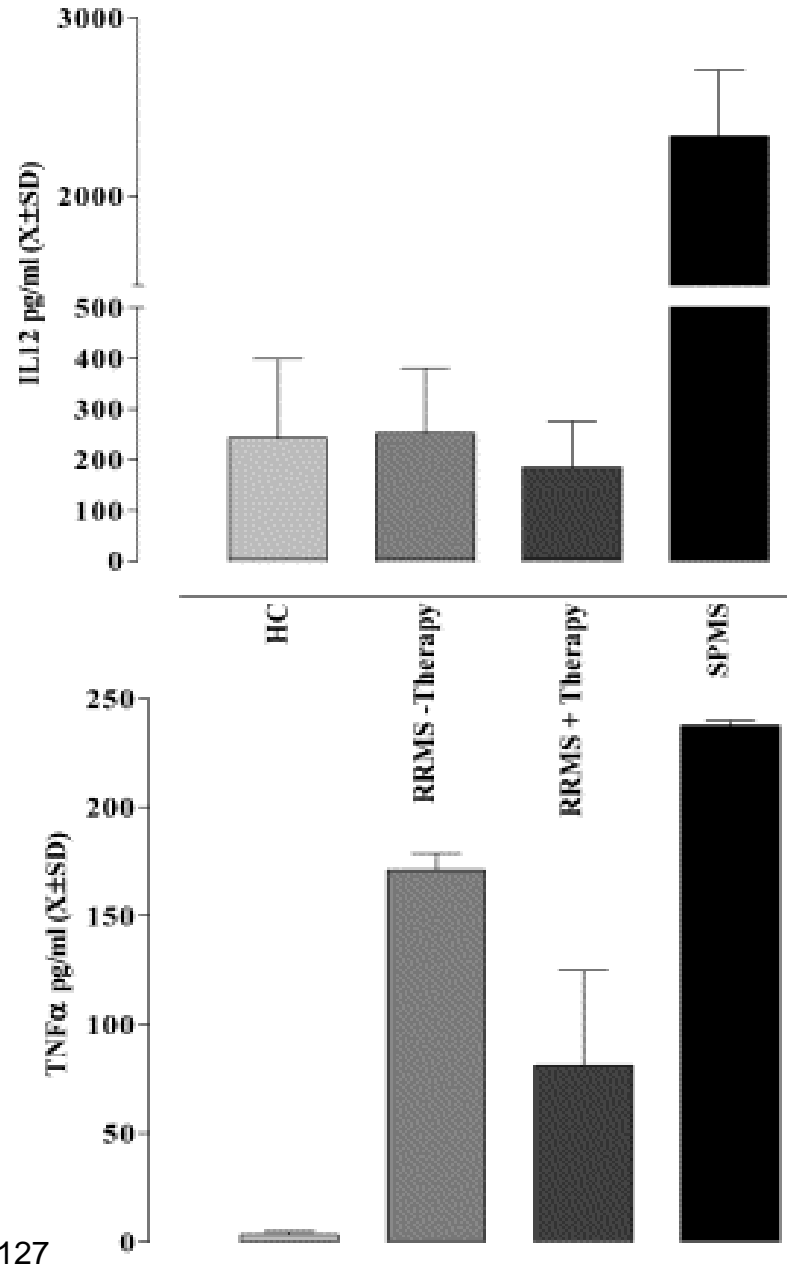


Balashov K et al. PNAS 1997;94:599-603

Normalized IL-12p35 levels in PBMCs of SPMS patients versus healthy controls

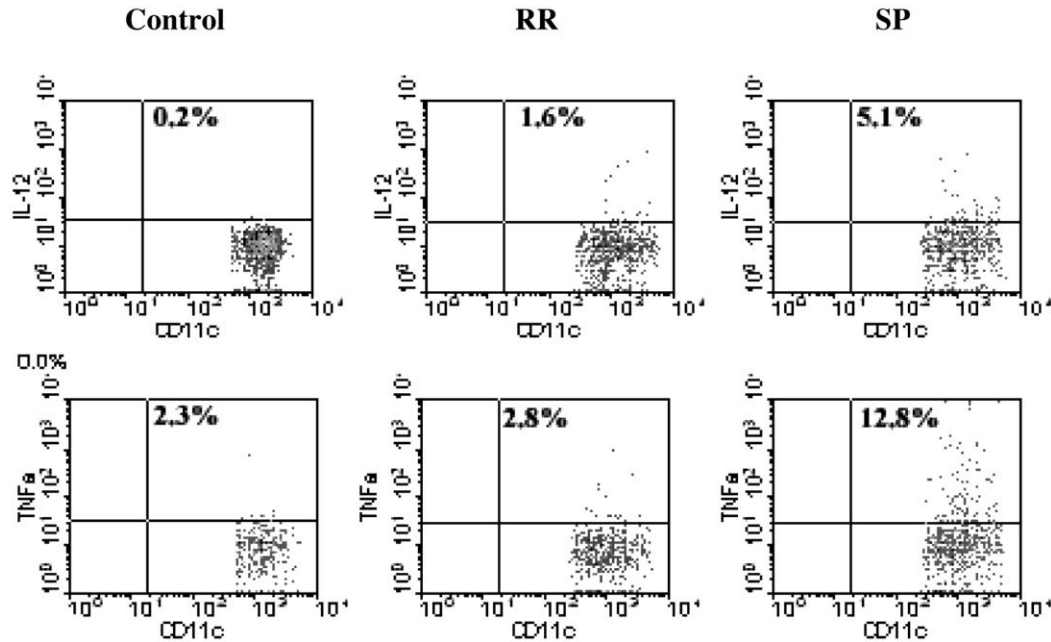


Enhanced secretion of cytokines by MO from SPMS patients

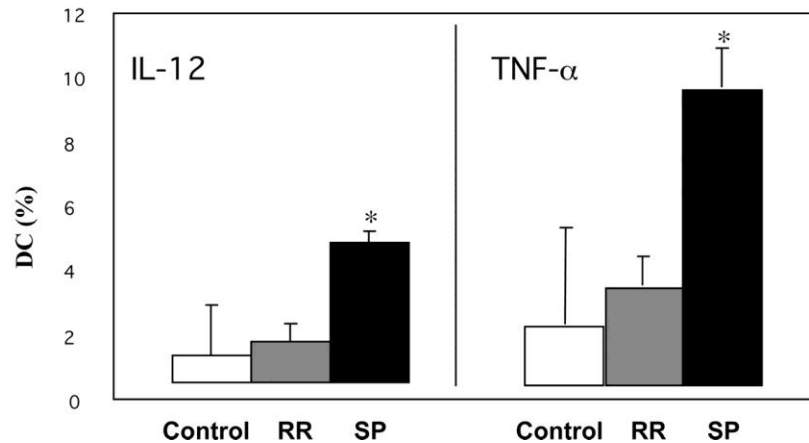


DC from SP MS donors express elevated levels of IL-12

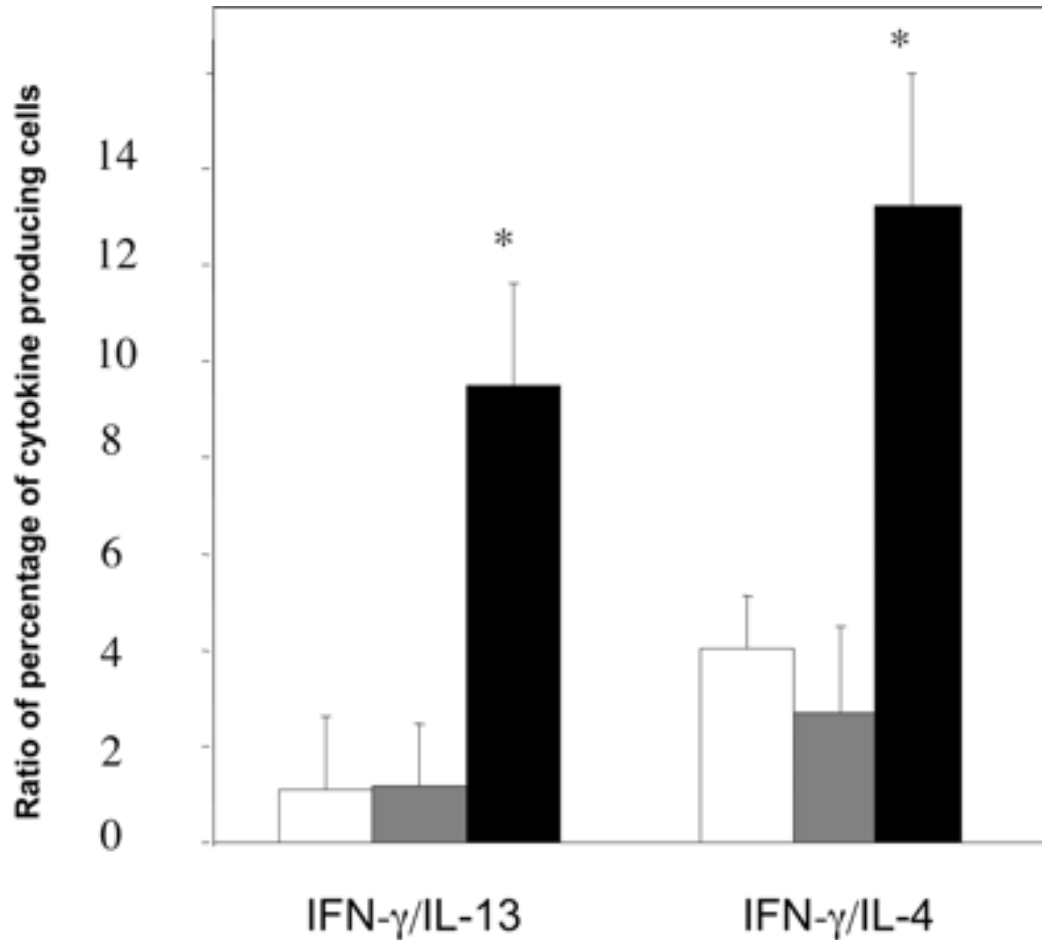
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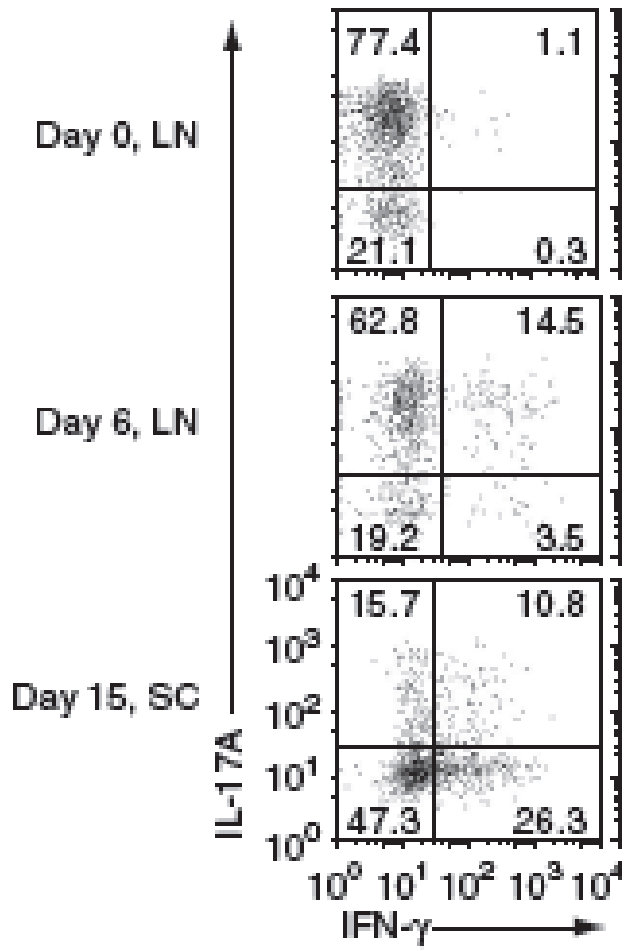
b



DC from SPMS donors stimulate T cells to produce IFN γ

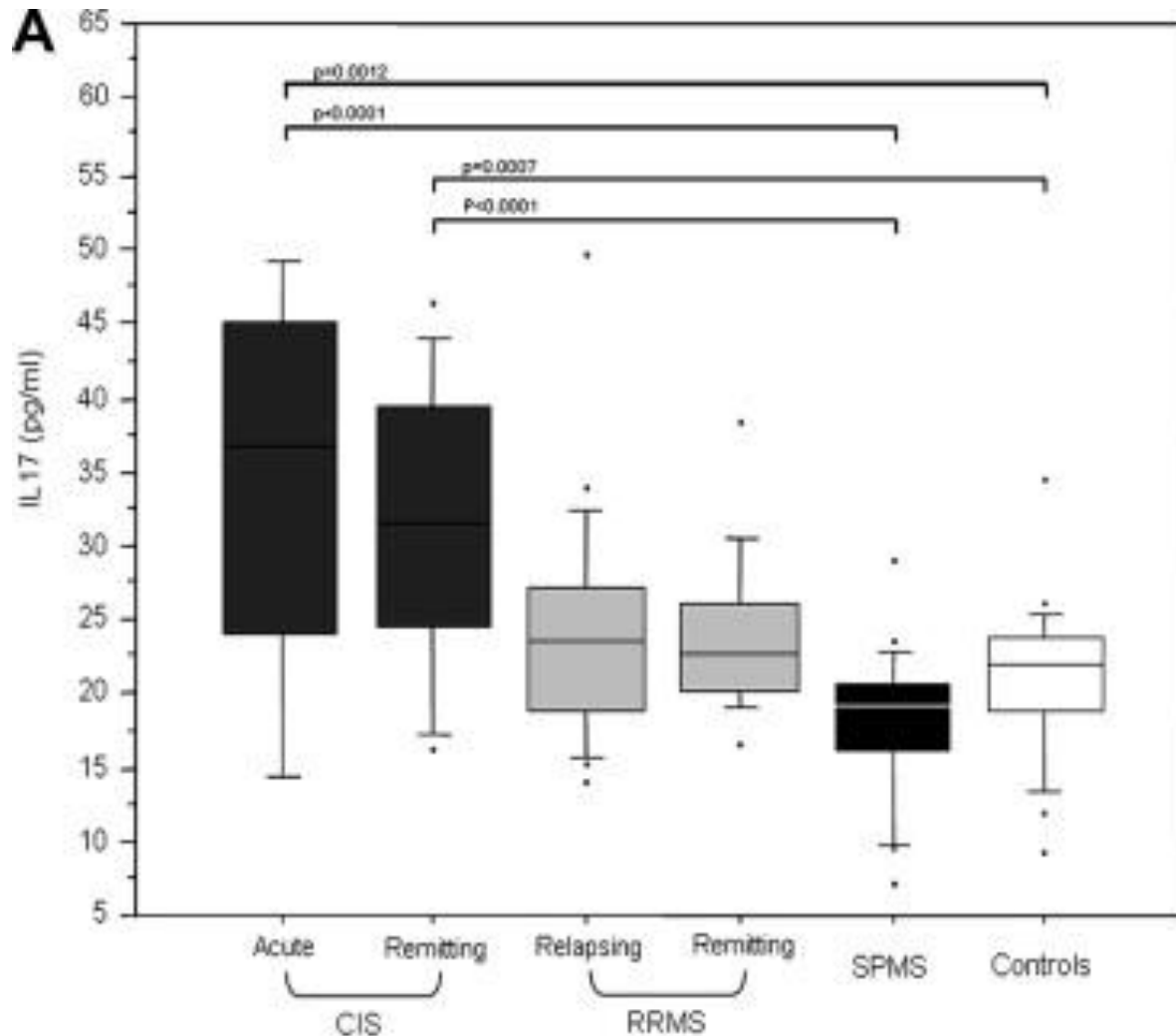


Th17 cells convert to Tbet⁺ IFN γ producers during EAE



Gated on eYFP⁺ cells

IL-17 production by PBMC is highest at the onset of MS



Summary: Evolution of the autoreactive Th repertoire during the transition from RRMS to SPMS

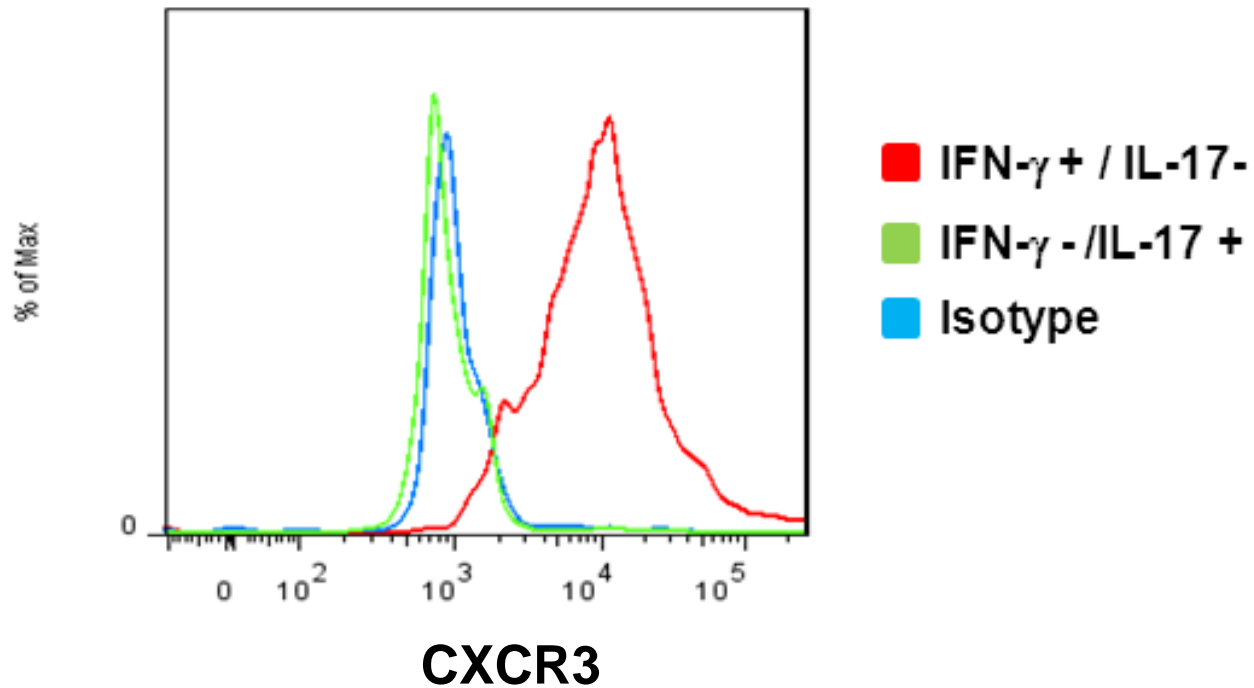
- PBMCs from MS patients over-express IL-12 and contain elevated frequencies of MBP-specific cytokine producing cells
- The majority of SPMS patients in our study exhibited Th1 dominant MBP-specific responses that were stable over time
- This Th1 “skewing” was more prominent in SPMS than in RRMS

Hypothesis: The autoreactive T cell response evolves over the course of MS to favor TH1 immunity, in part, as a consequence of Th17 plasticity

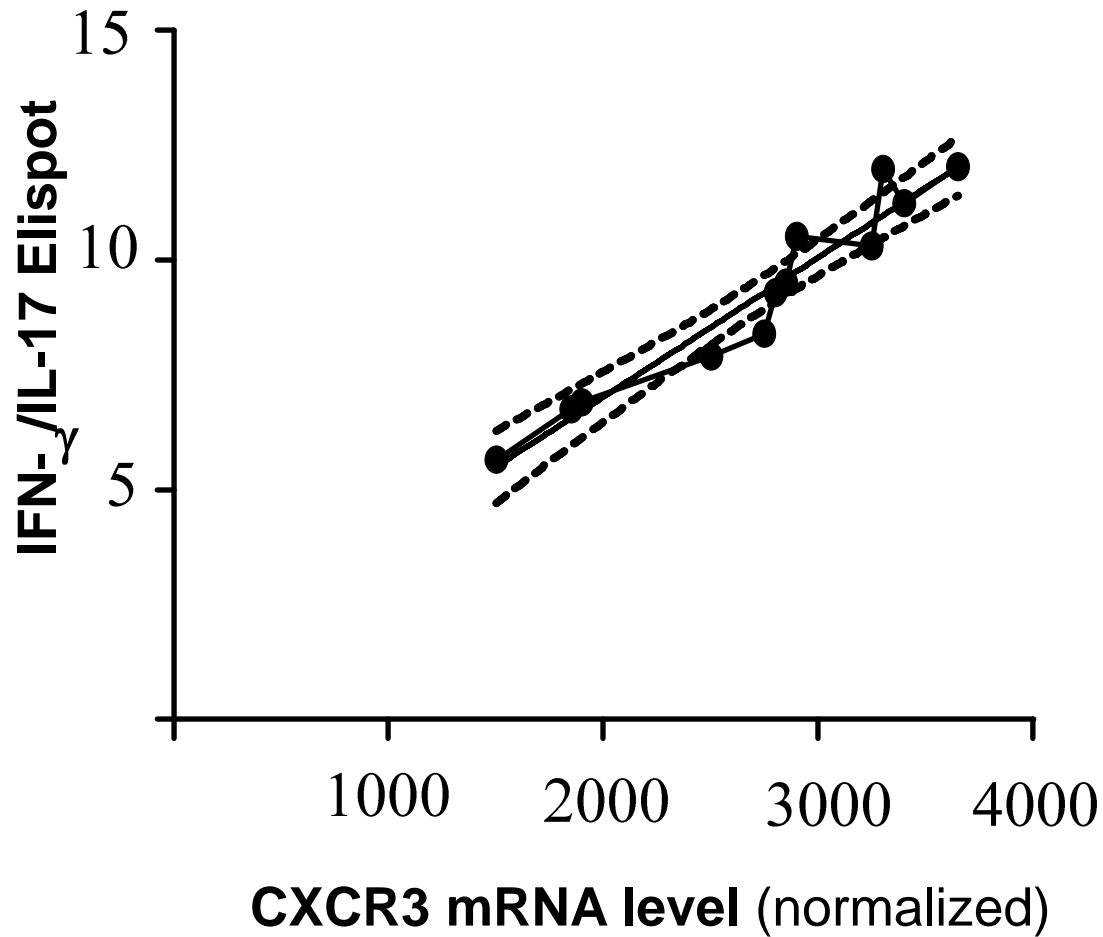
Therapeutic Implications

Targeting Th1 cells and their factors in individuals with transitional and progressive forms of MS

CXCR3 is preferentially expressed on Th1 cells from subjects with transitional MS

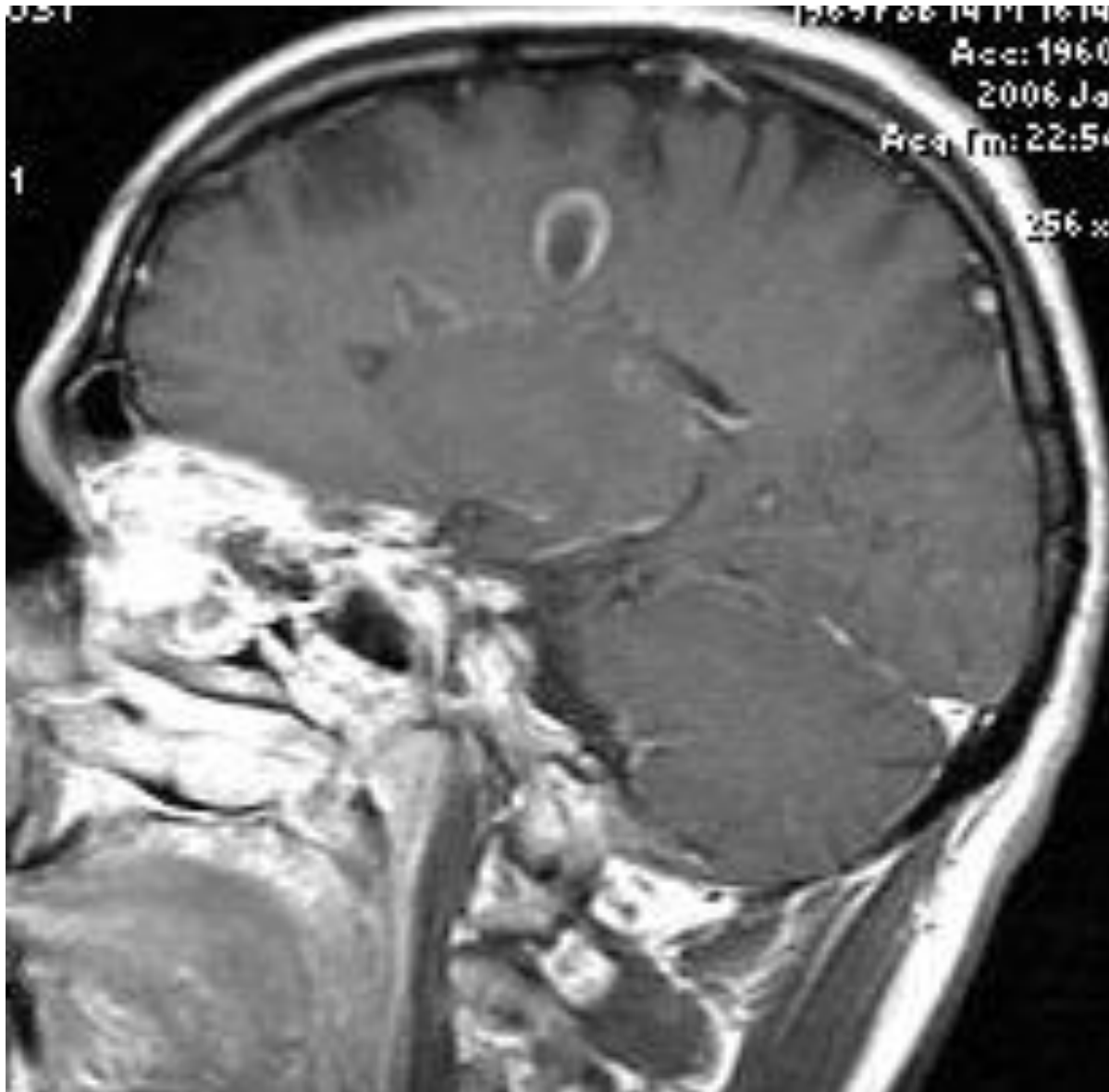


CXCR3 expression correlates with the Th1:Th17 ratio

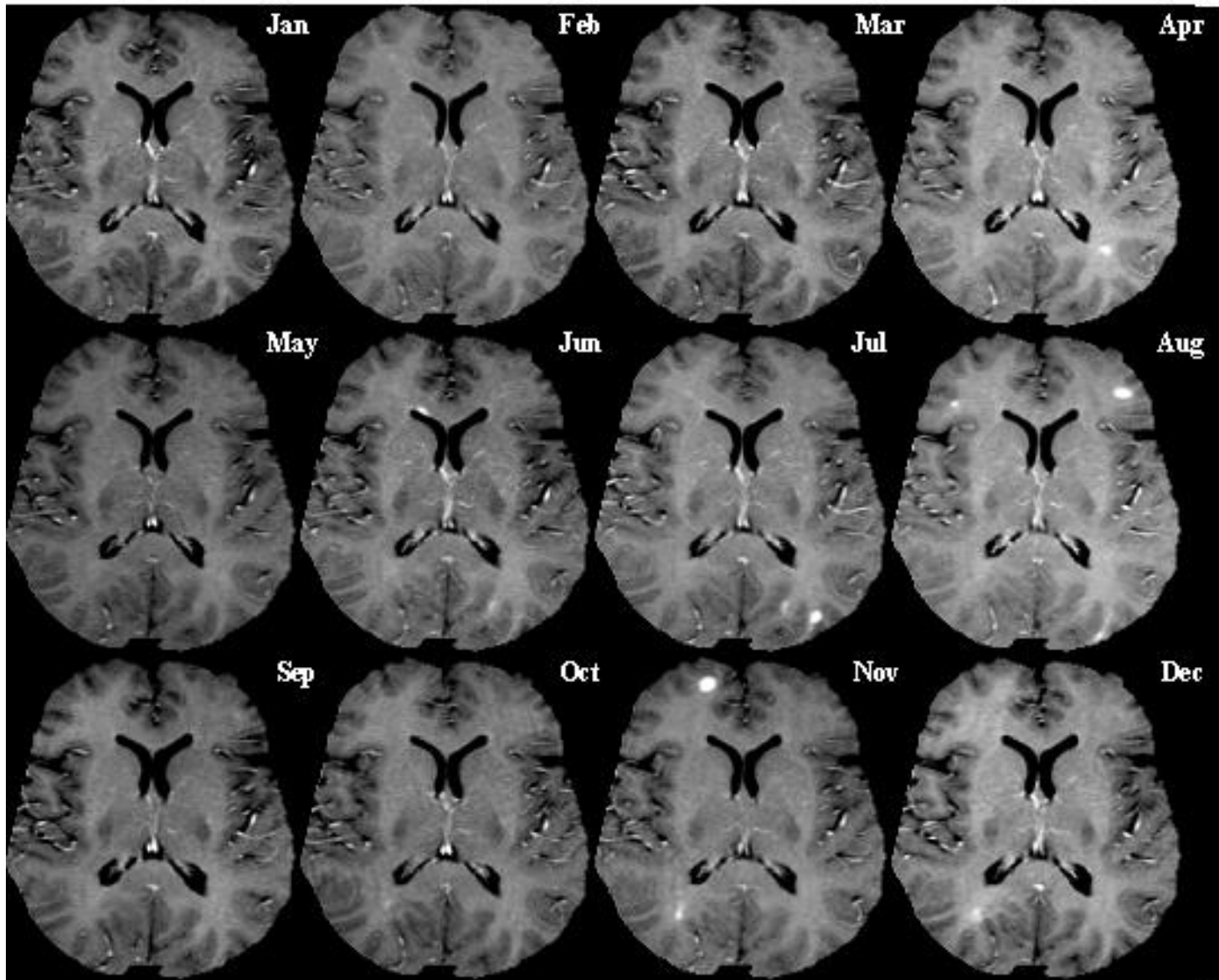


SPMS is associated with a
shift of the autoimmune
response from a peripheral to
a CNS driven process

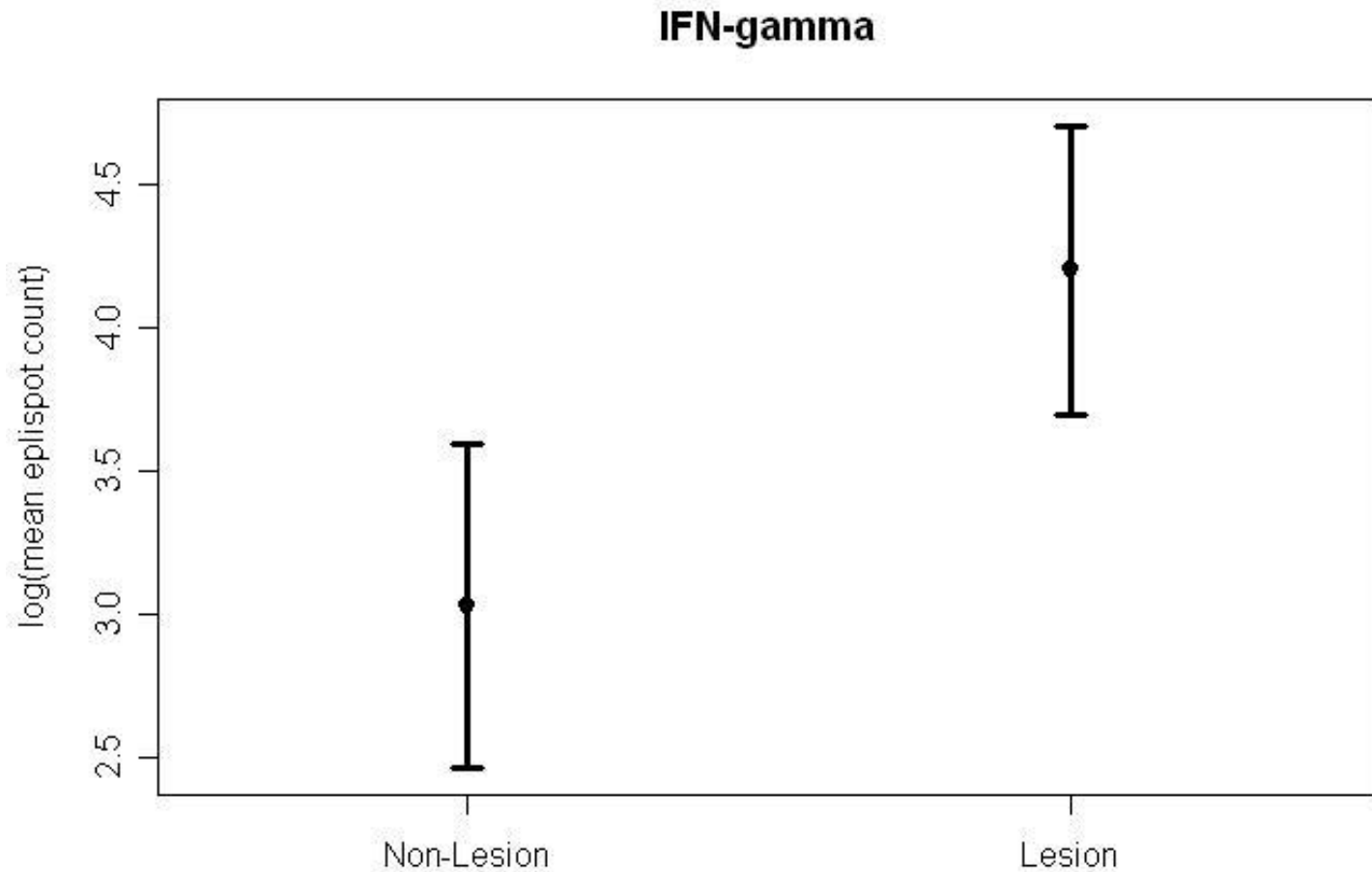
Enhancing lesions in SPMS



Enhancing lesions in a subset of SPMS



IFN γ production in SPMS patients with or without enhancing lesions

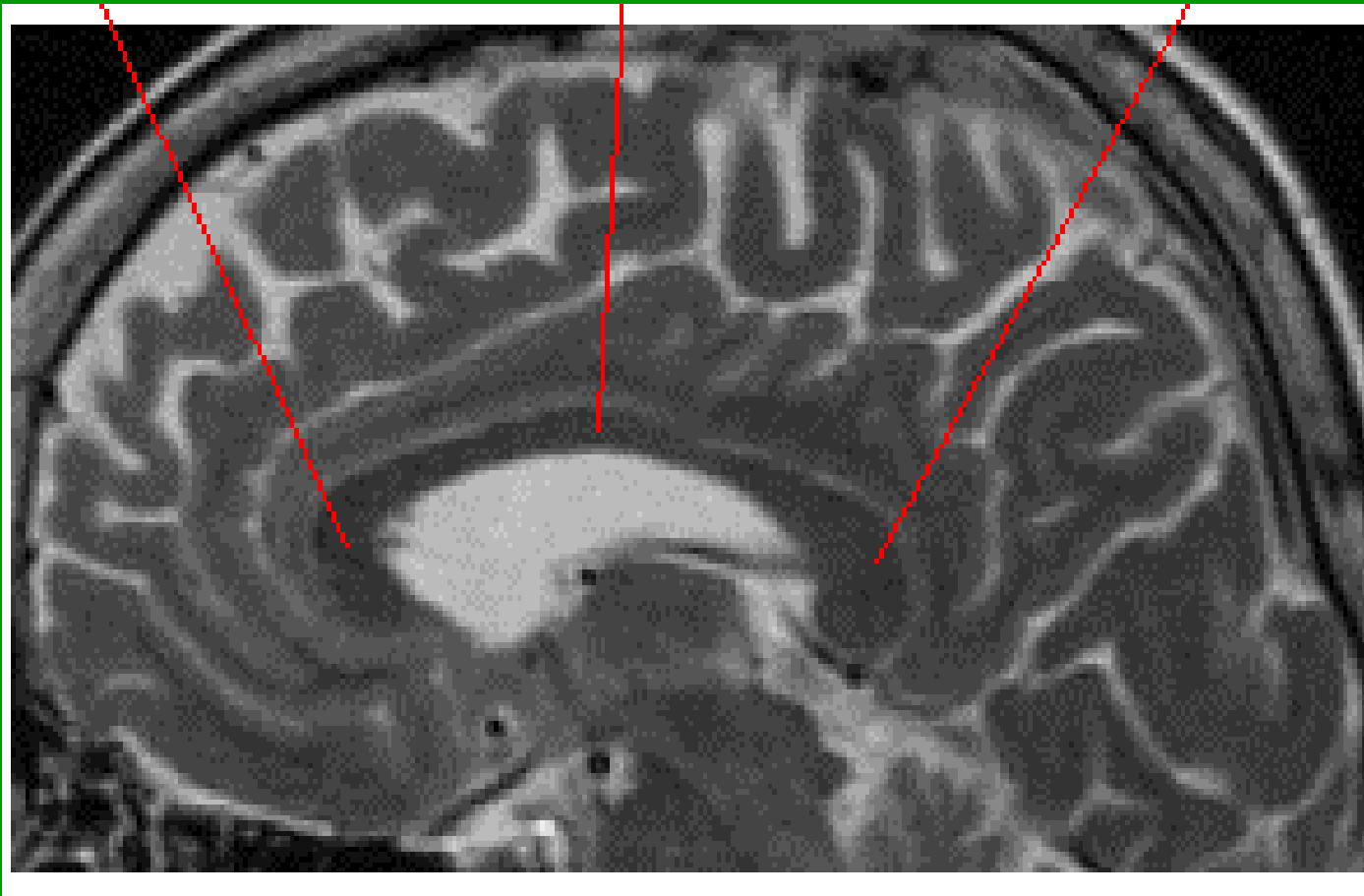


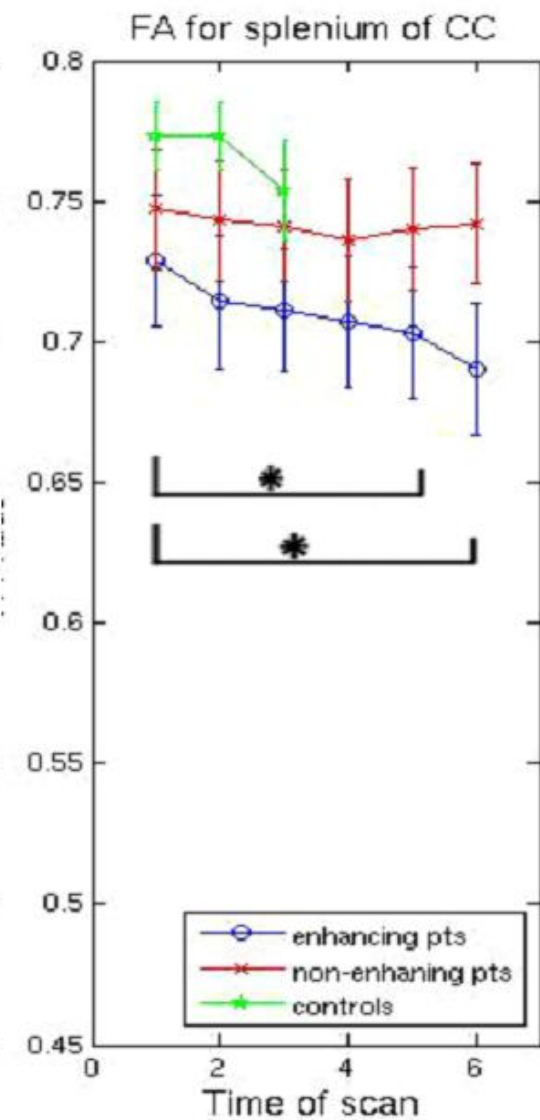
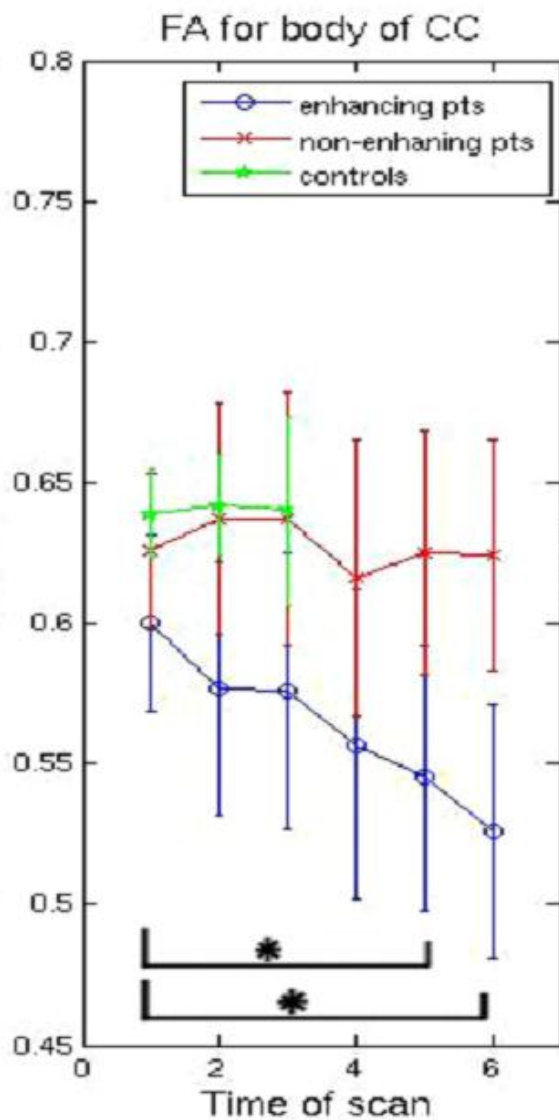
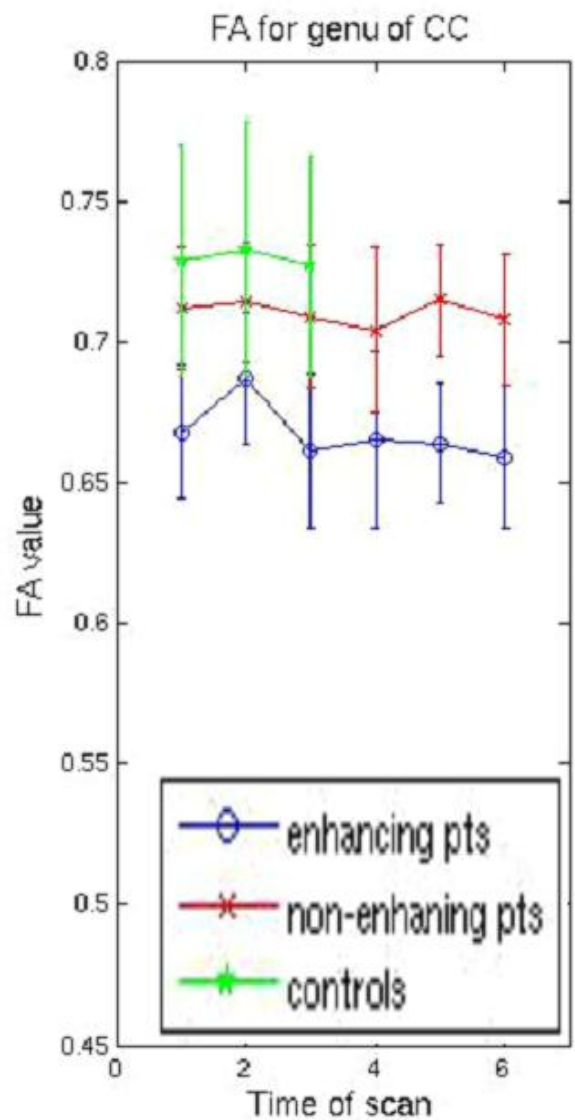
ROI Selection in Corpus Callosum

Genu

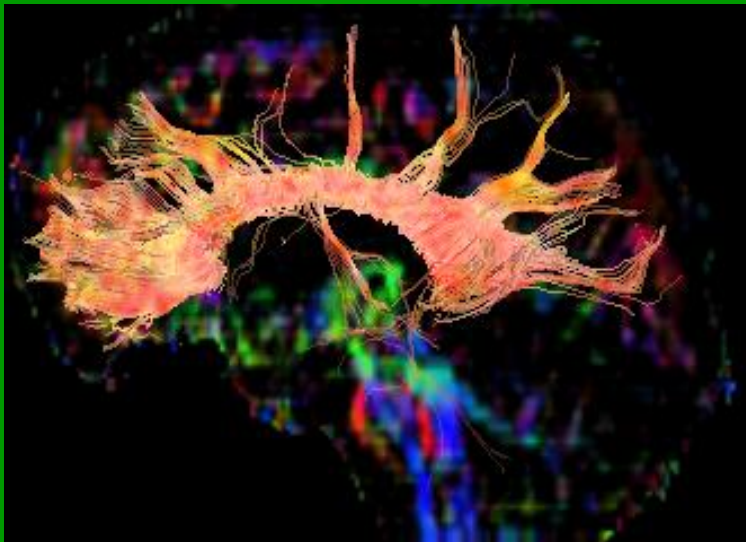
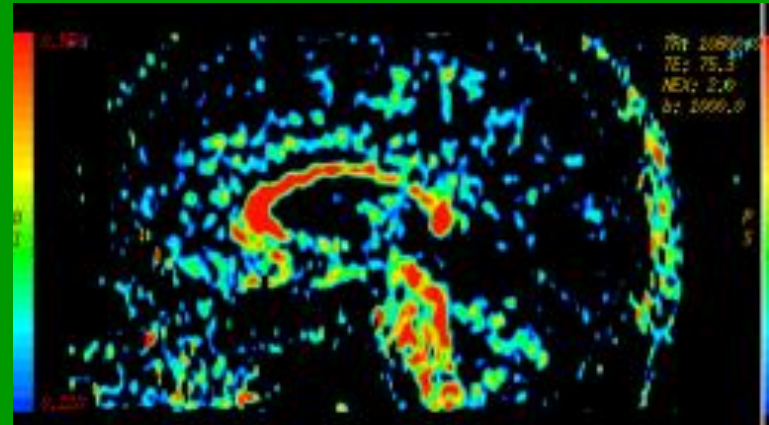
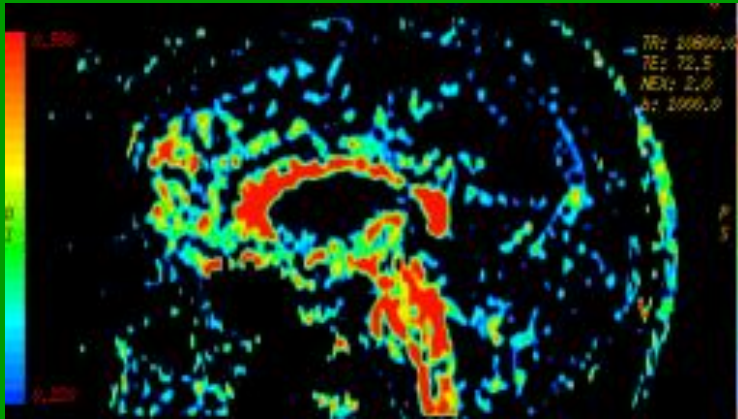
Body

Splenium





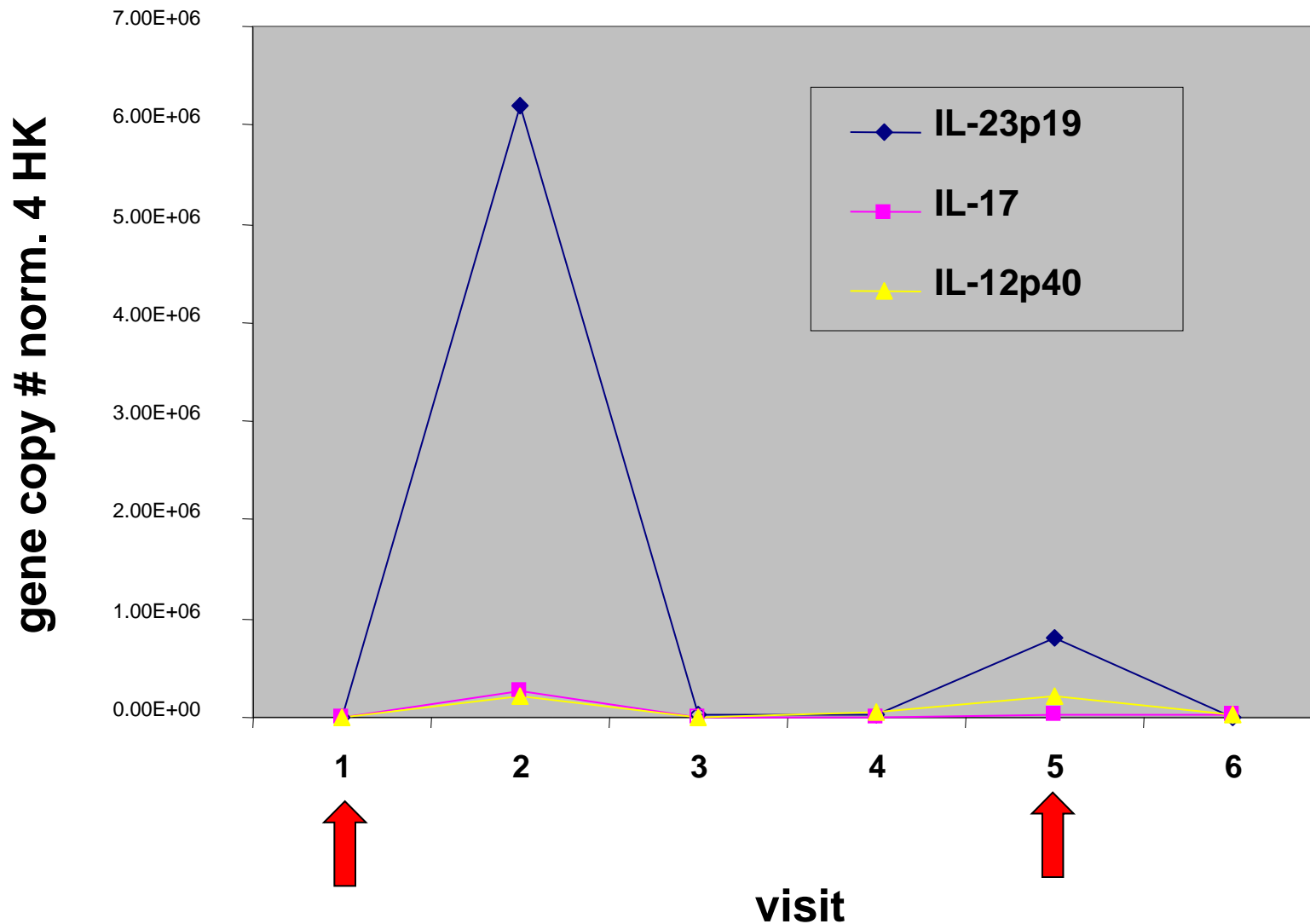
MS enhancing group P04



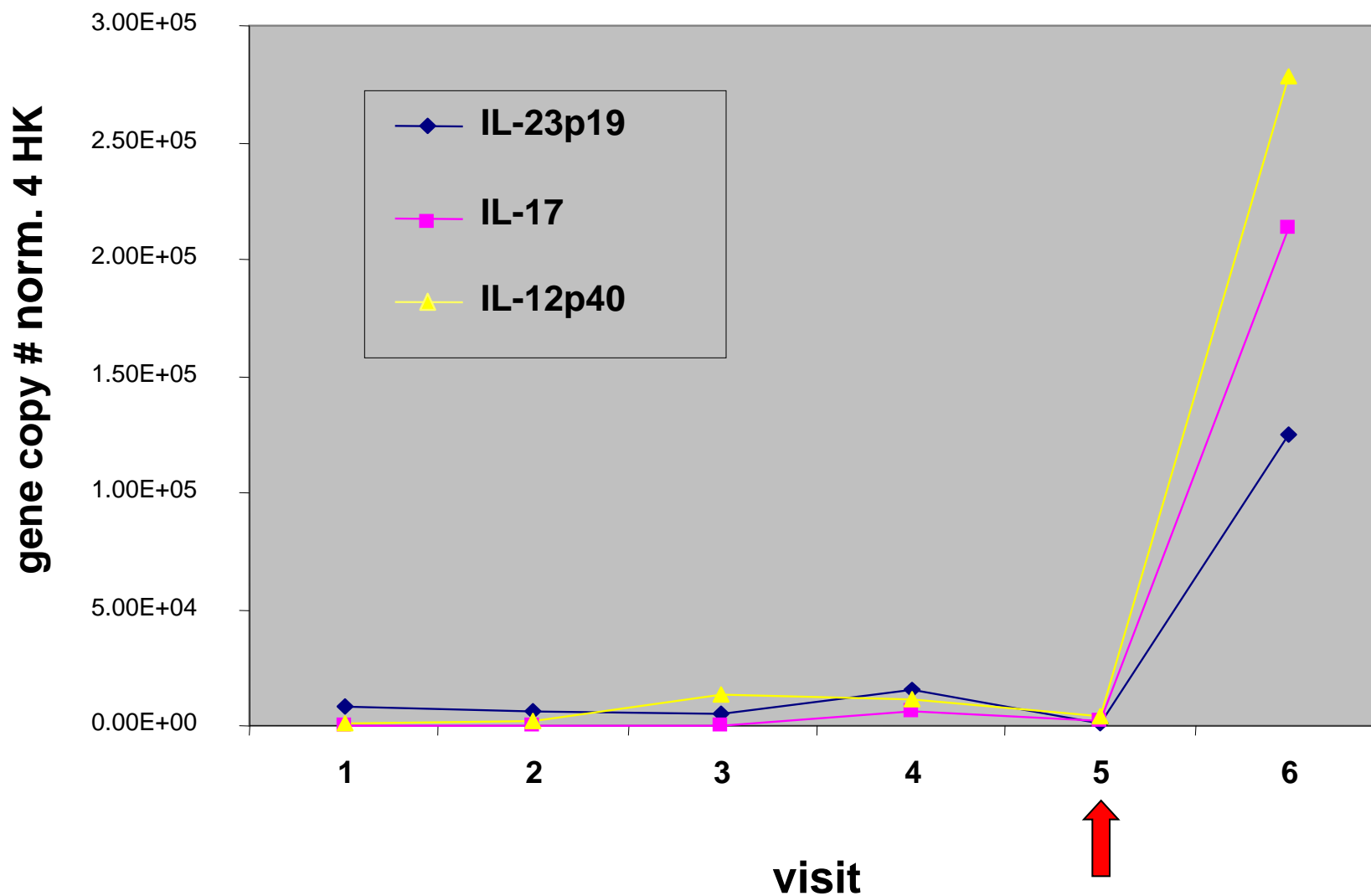
1st scan

6th(last) scan

Longitudinal patterns: IL-12p40 monokine subunits and downstream cytokines



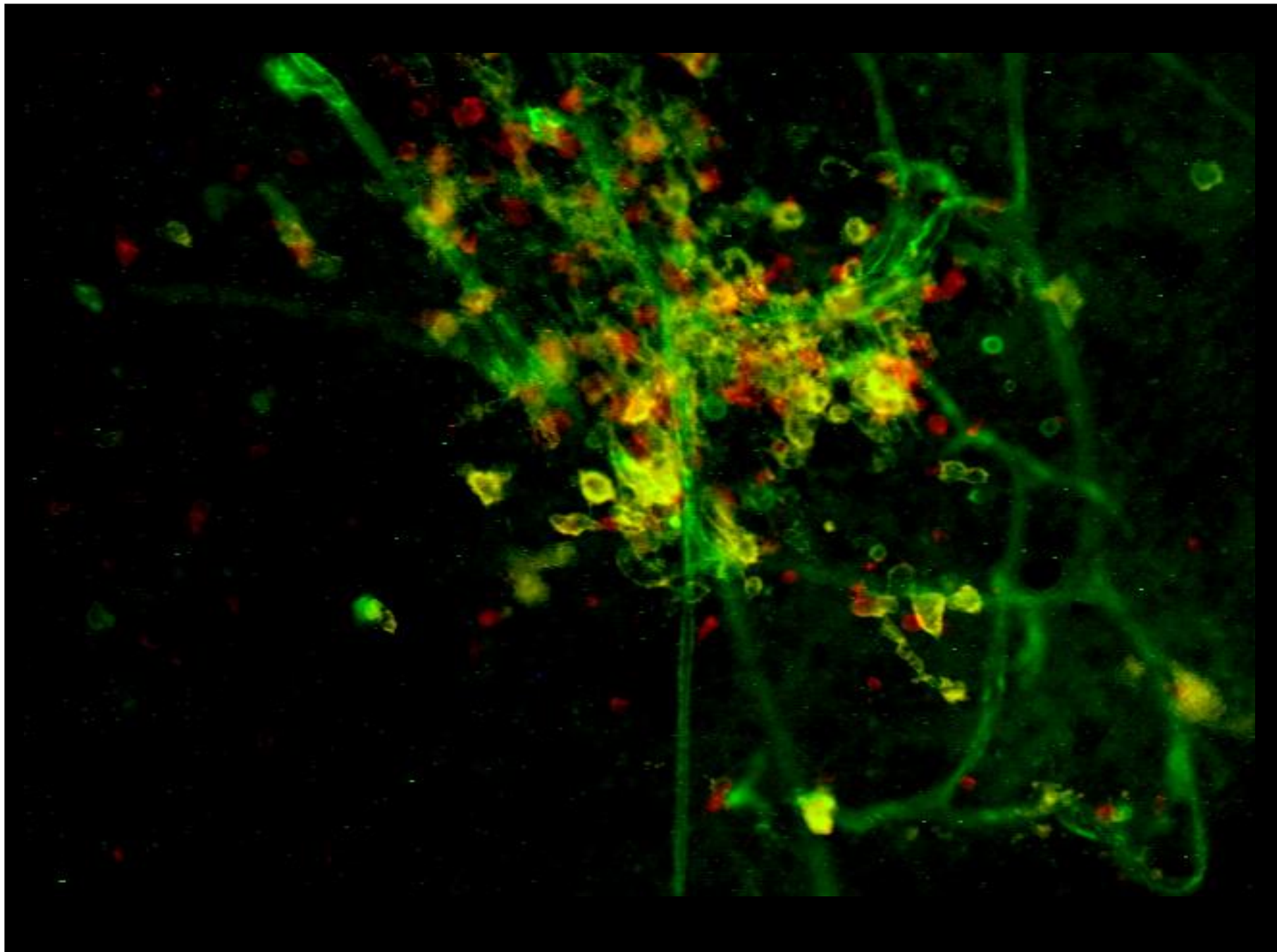
Longitudinal patterns: IL-12p40 monokine subunits and downstream cytokines

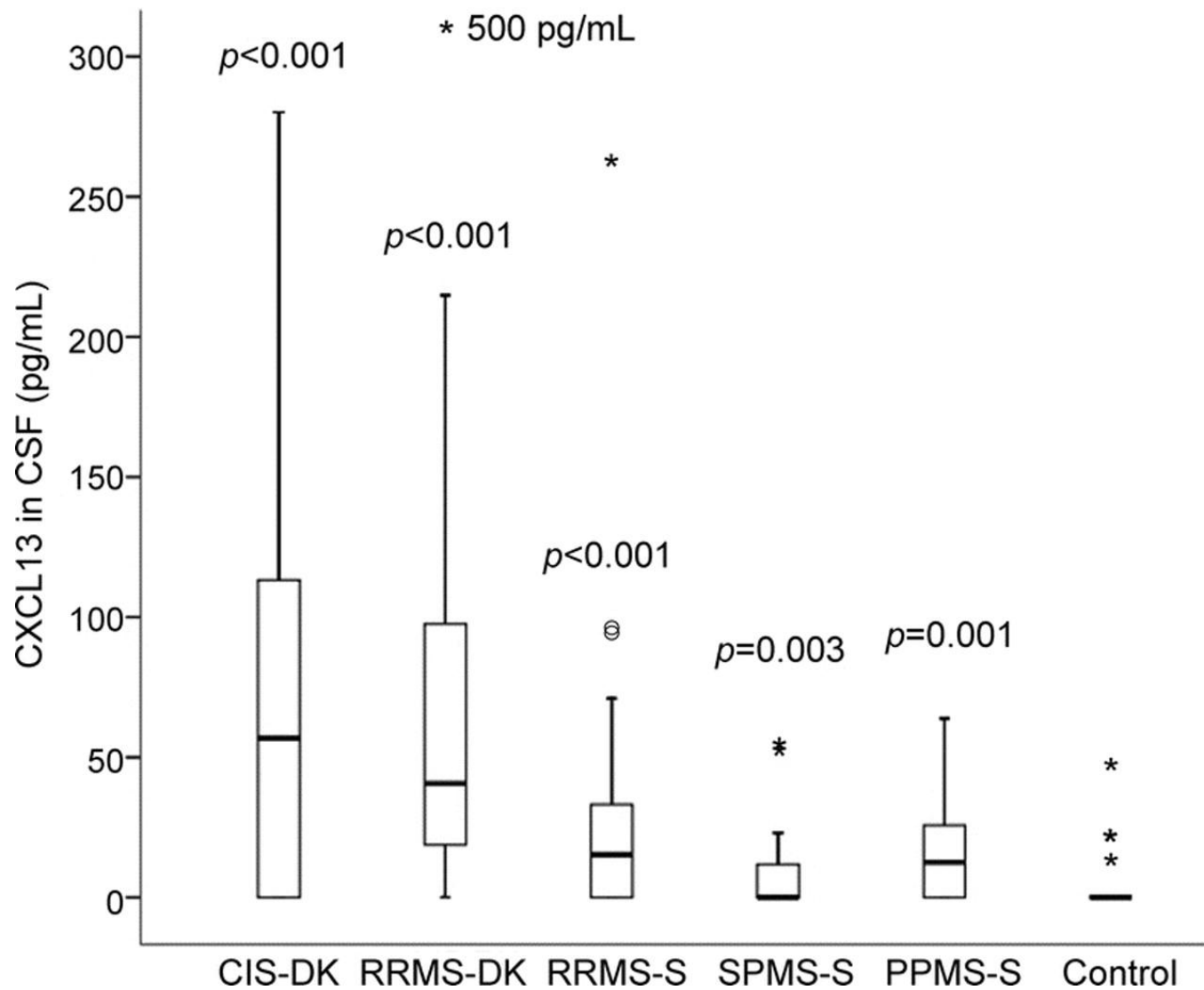


The CNS as a Lymphoid Organ

Prineas described “clusters of plasma cells together with...reticular cells surrounding collagen-free channels containing lymphocytes and macrophages” and “lymphatic-like capillaries” in plaques in brain specimens from patients with MS.

Science 203:1123-1125

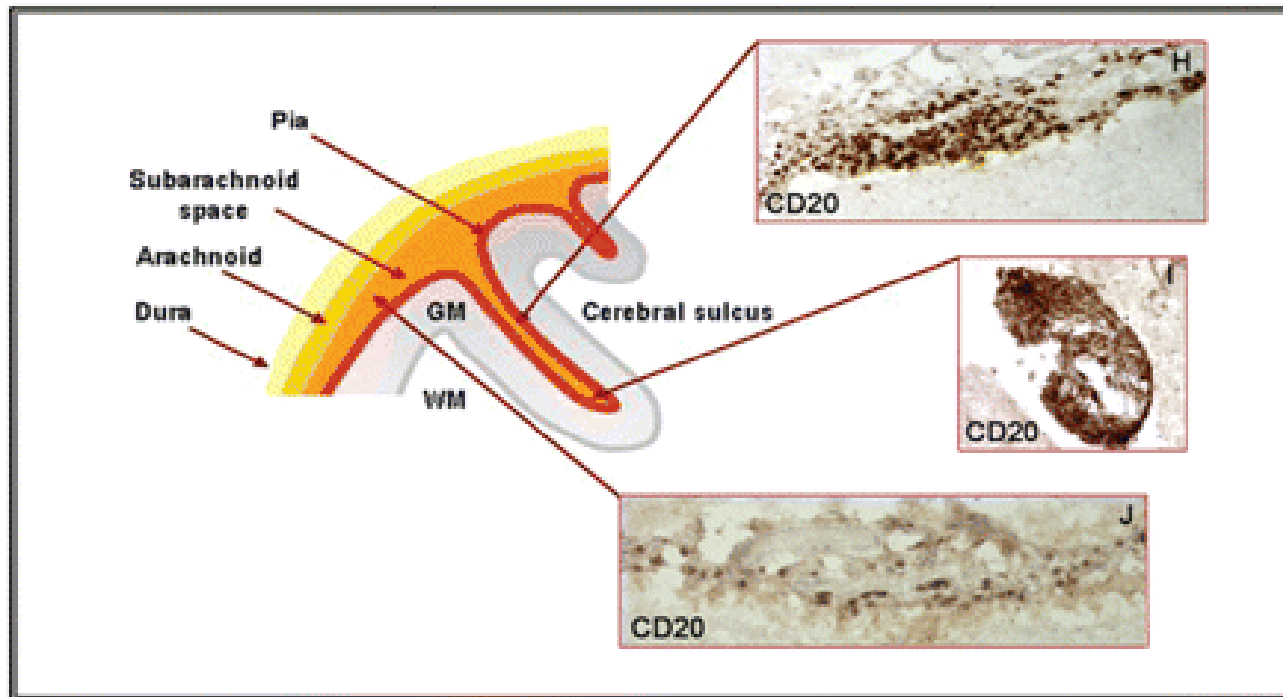
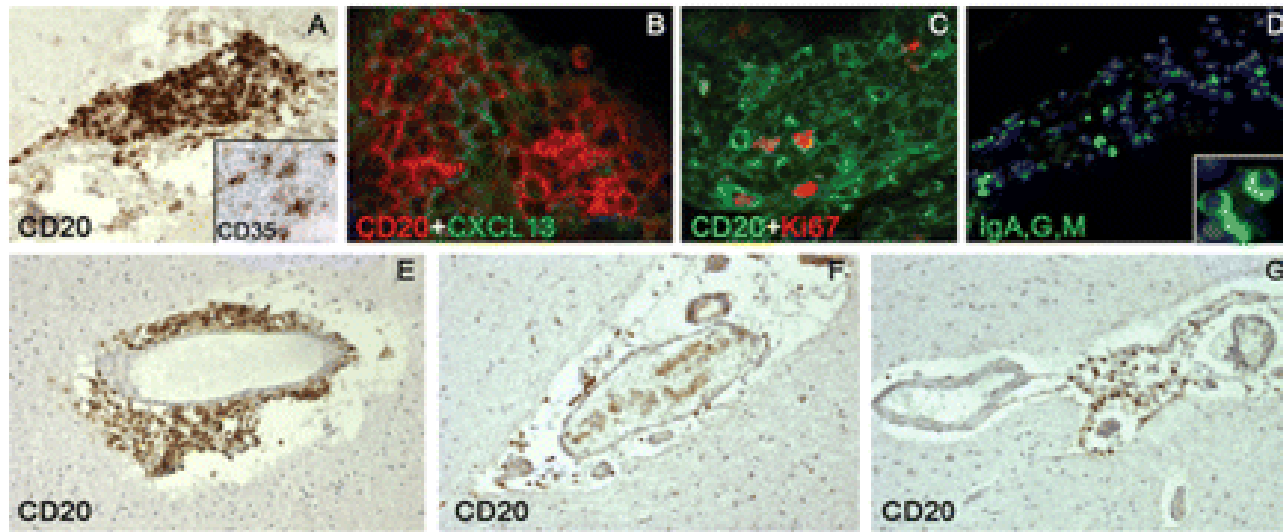




Sellebjerg F et al. Neurology 2009;73:2003-2010

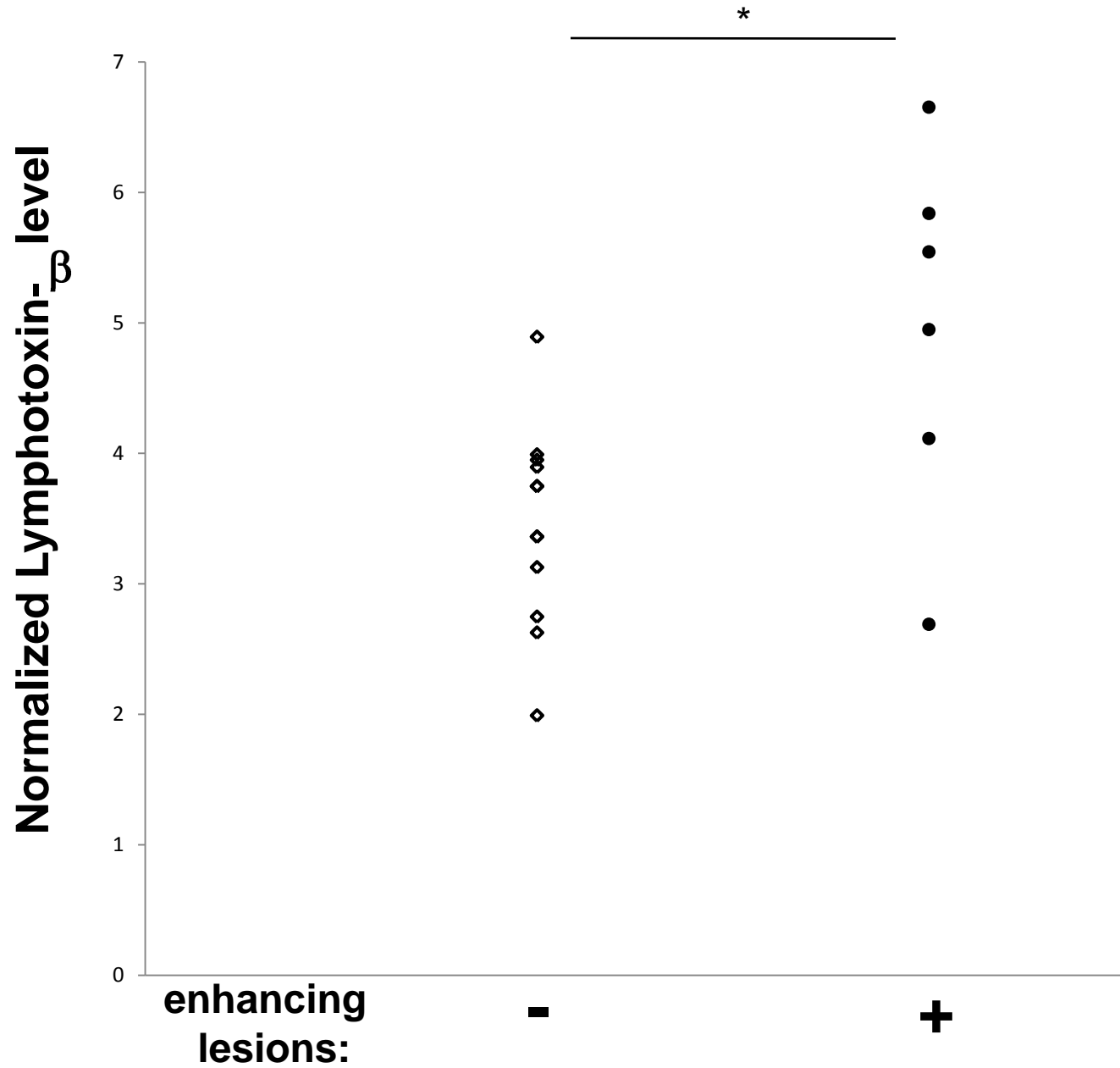


Lymphoid Follicles in Progressive MS



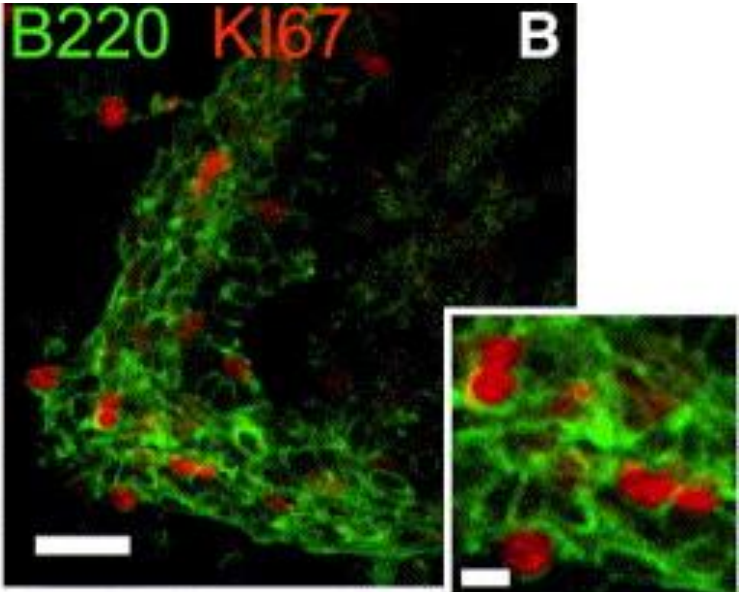
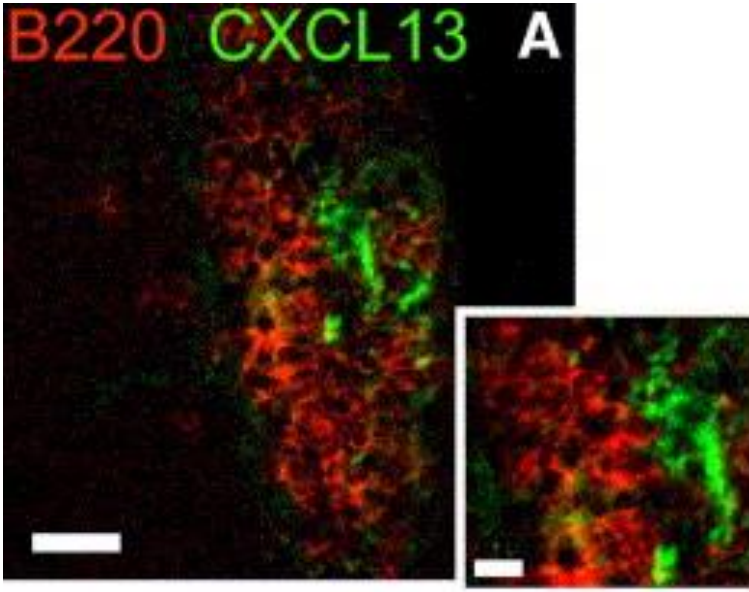
Characteristics of SPMS patients with meningeal follicles

- **Younger age of onset**
- **Frequent relapses in first three years from diagnosis**
- **Relatively high level of disability based on age**
- **Shorter lifespan**

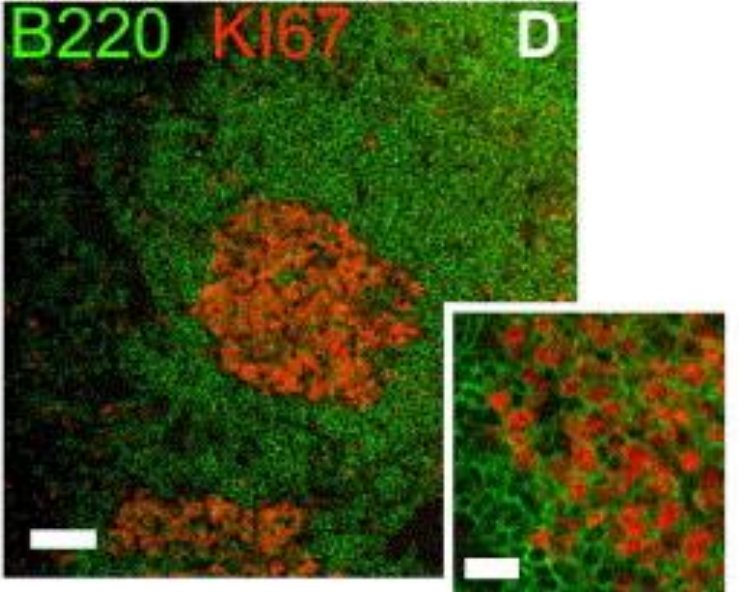
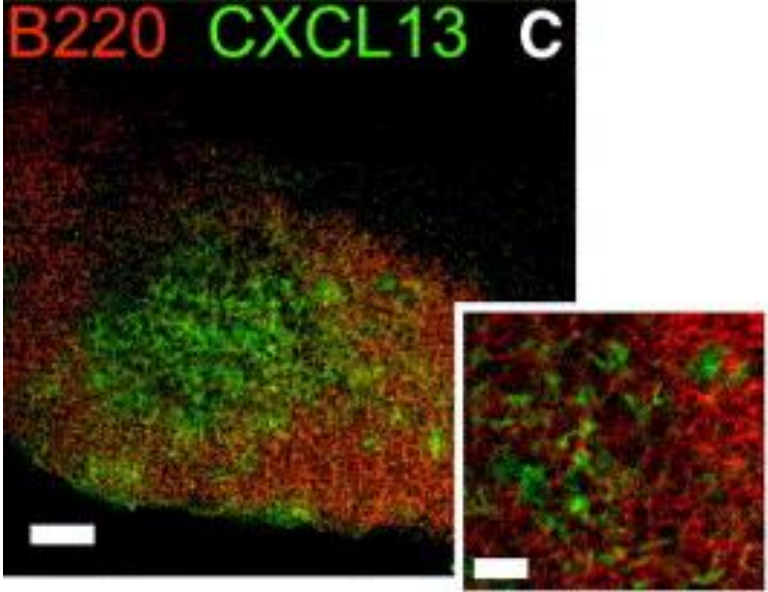


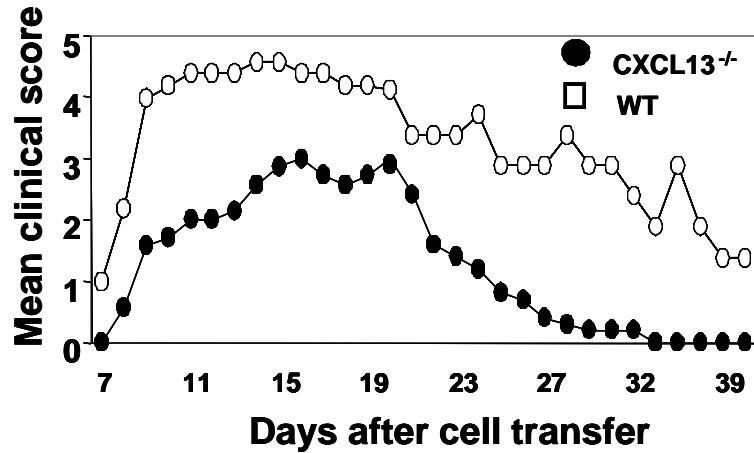
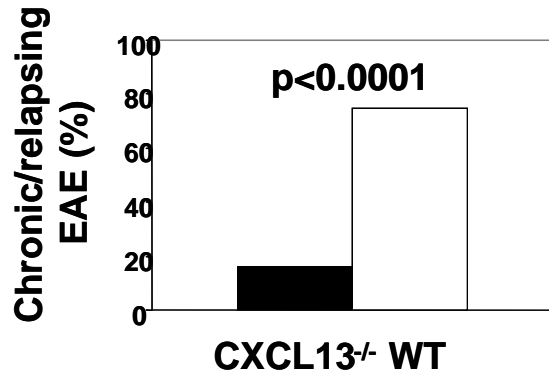
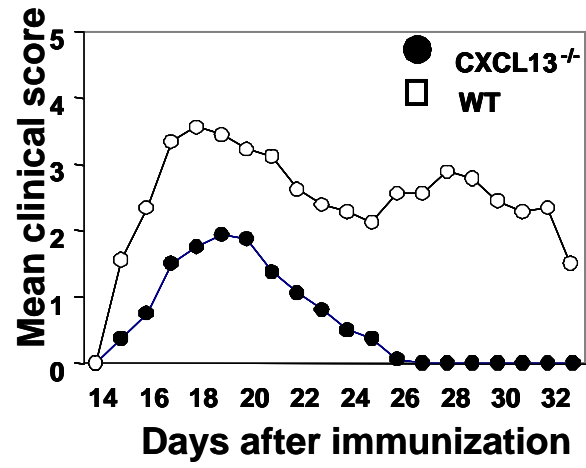
CXCL13+ Lymphoid like follicles in meninges of mice with EAE

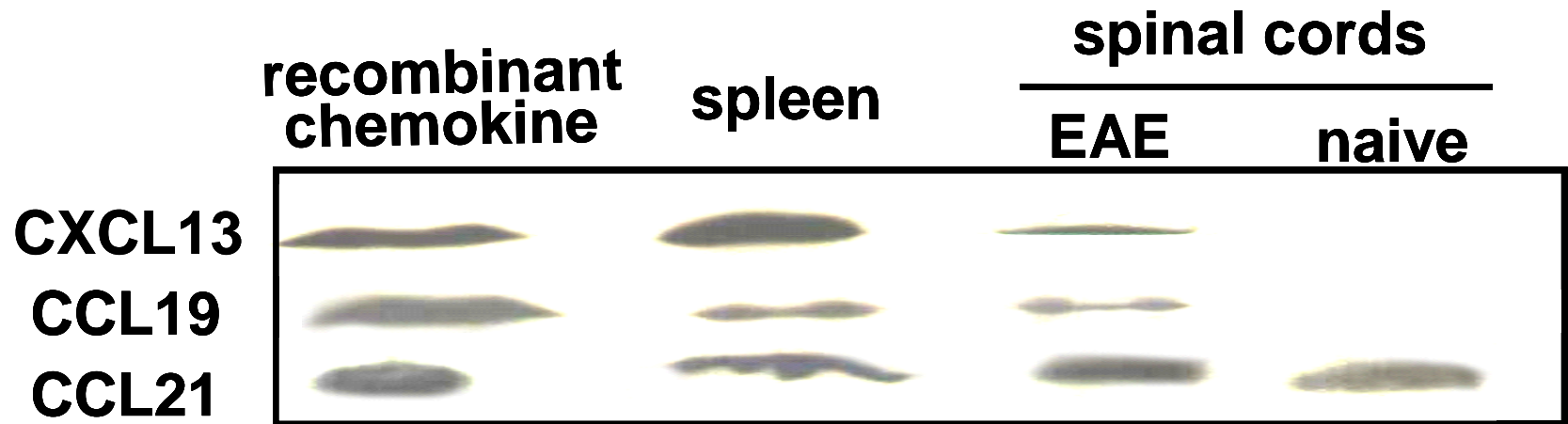
CNS



LN





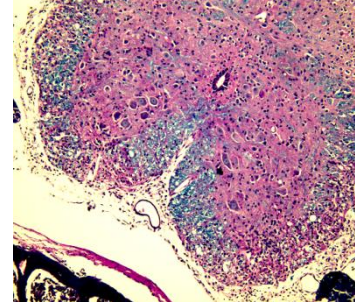
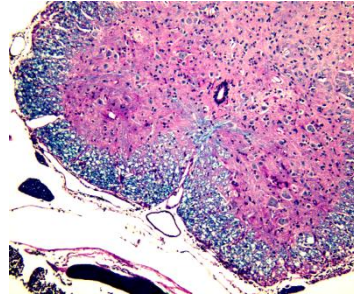


Chronic

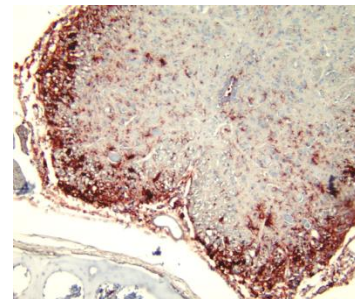
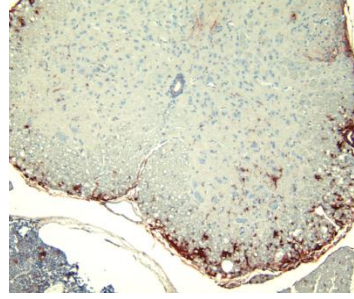
CXCL13 $-/-$

WT

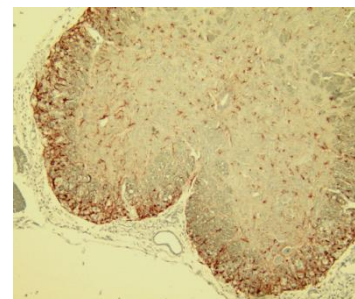
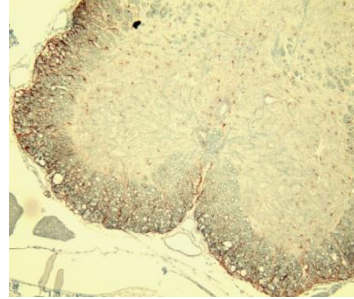
LFB-PAS



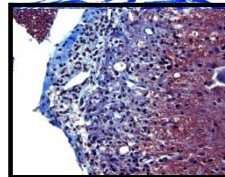
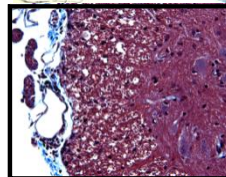
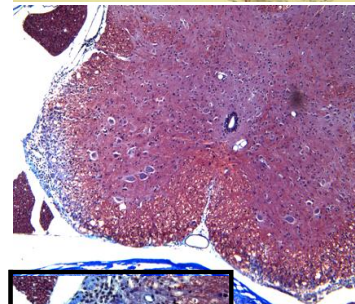
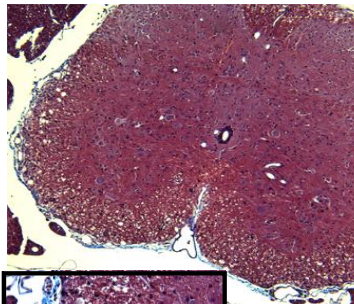
RCA



GFAP



Trichrome



Summary II: The role of CXCL13 driven lymphoid neogenesis in the CNS during SPMS

- **A subset of SPMS patients (approximately 40%) experience progressive axonal loss/ demyelination in the corpus callosum association with episodic cytokine dysregulation and CNS inflammatory activity.**
- **CNS inflammation tends to precede peripheral spikes in cytokine expression, suggesting that the autoimmune attack is mounted within the CNS**
- **Meningeal B cell follicles expressing the chemokine CXCL13 are present in SPMS patients with a more aggressive clinical course**

Summary II (cont'd)

- **Meningeal B cell follicles are most frequently located in deep sulci, in direct apposition to cortical plaques**
- **CXCL13 deficiency or $LT\beta$ receptor antagonism abrogates relapses and chronic progression of EAE**
- **Drugs designed to dissociate meningeal lymphoid follicles (such as anti-CXCL13, CXCR5-Fc fusion proteins, or Lymphotoxin β receptor fusion proteins) might be therapeutic in some patients with SPMS (?intrathecal administration?)**

HUMAN B CELL-ATTRACTING CHEMOKINE 1 (BCA-1; CXCL13) IS AN AGONIST FOR THE HUMAN CXCR3 RECEPTOR

**Chung-Her Jenh^{f1}, Mary Ann Cox, William Hipkin, Tianhong Lu,
Catherine Pugliese-Sivo, Waldemar Gonsiorek, Chuan-Chu Chou,
Satwant K. Narula and Paul J. Zavodny**

Cytokine

Volume 15, Issue 3, August 2001, Pages 113-121

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Julie Rumble, PhD

Karthik Ventakesh, Ph.D.

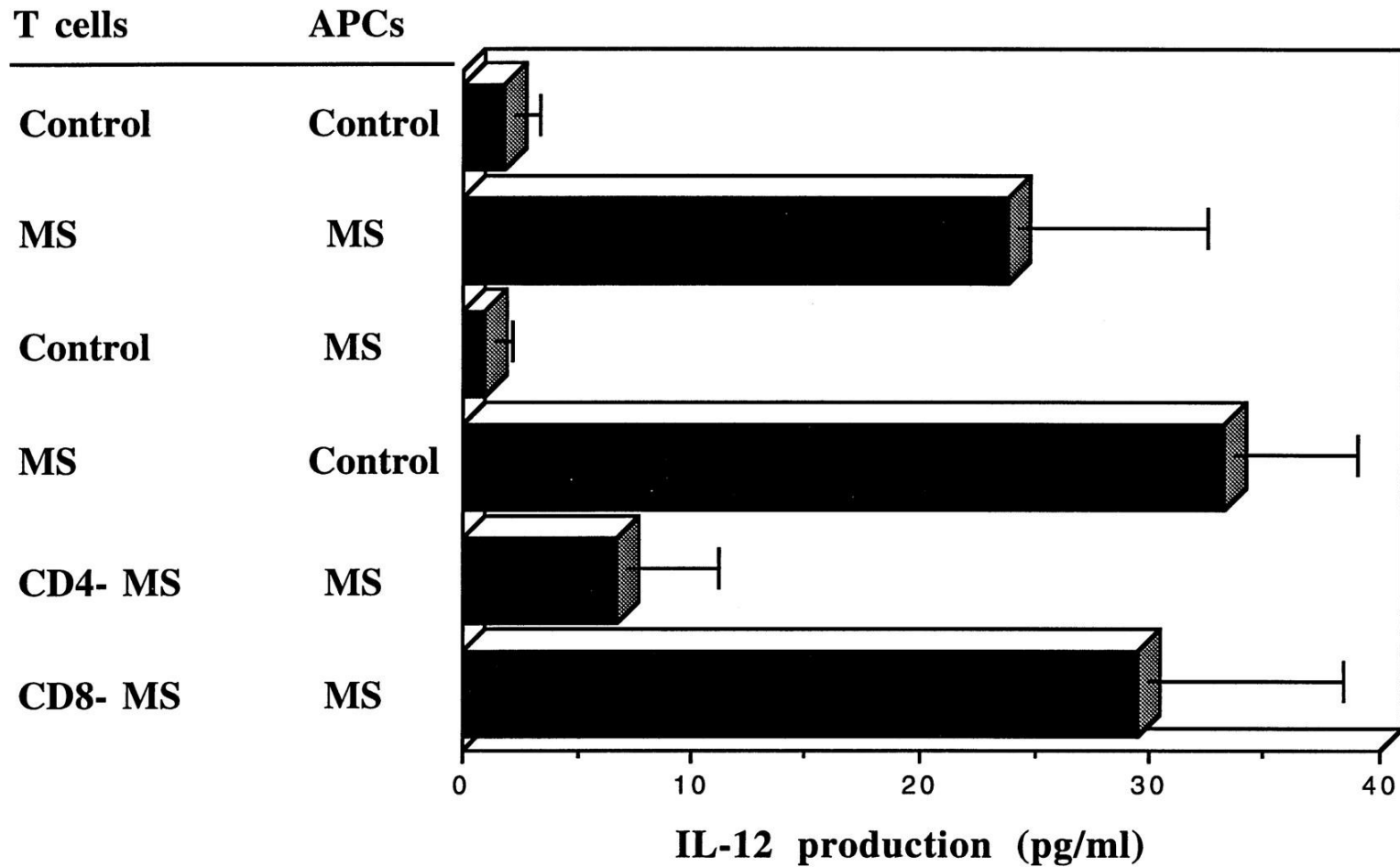
Sven Ekholm, M.D.

Ashok Srinivasan, M.D.

Lymphoid Chemokines and Chronic Inflammation

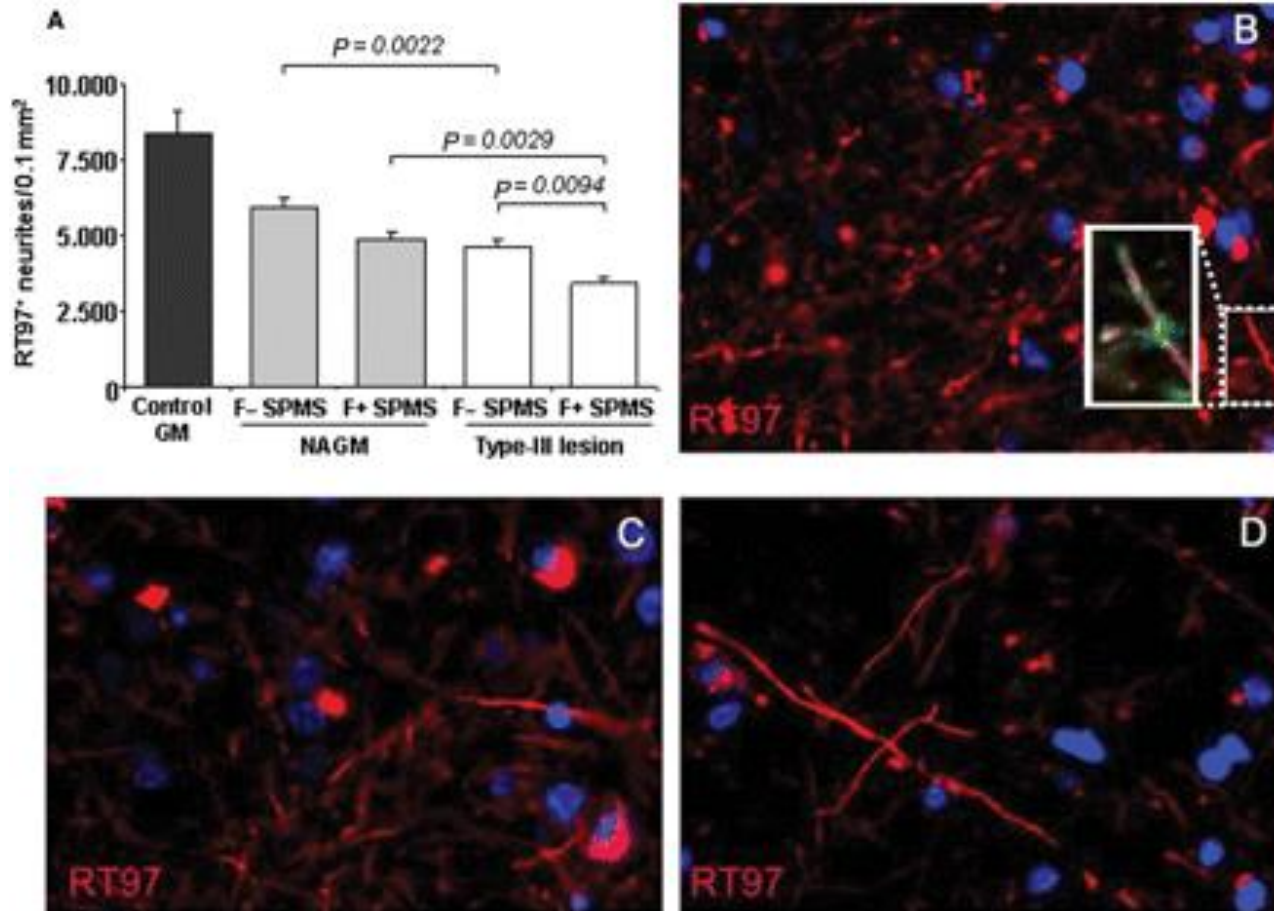
- Ectopic expression of CXCL13 in non-lymphoid organs leads to chronic inflammation and the formation of lymph node-cell like structures (“lymphoid neogenesis”)
- TNF family molecules (TNF α , LT- α and LT- β , that have been implicated in the pathogenesis of EAE and MS, stimulate production of CXCL13

Activated T cells but not APCs from progressive MS patients are responsible for increased IL-12 production.

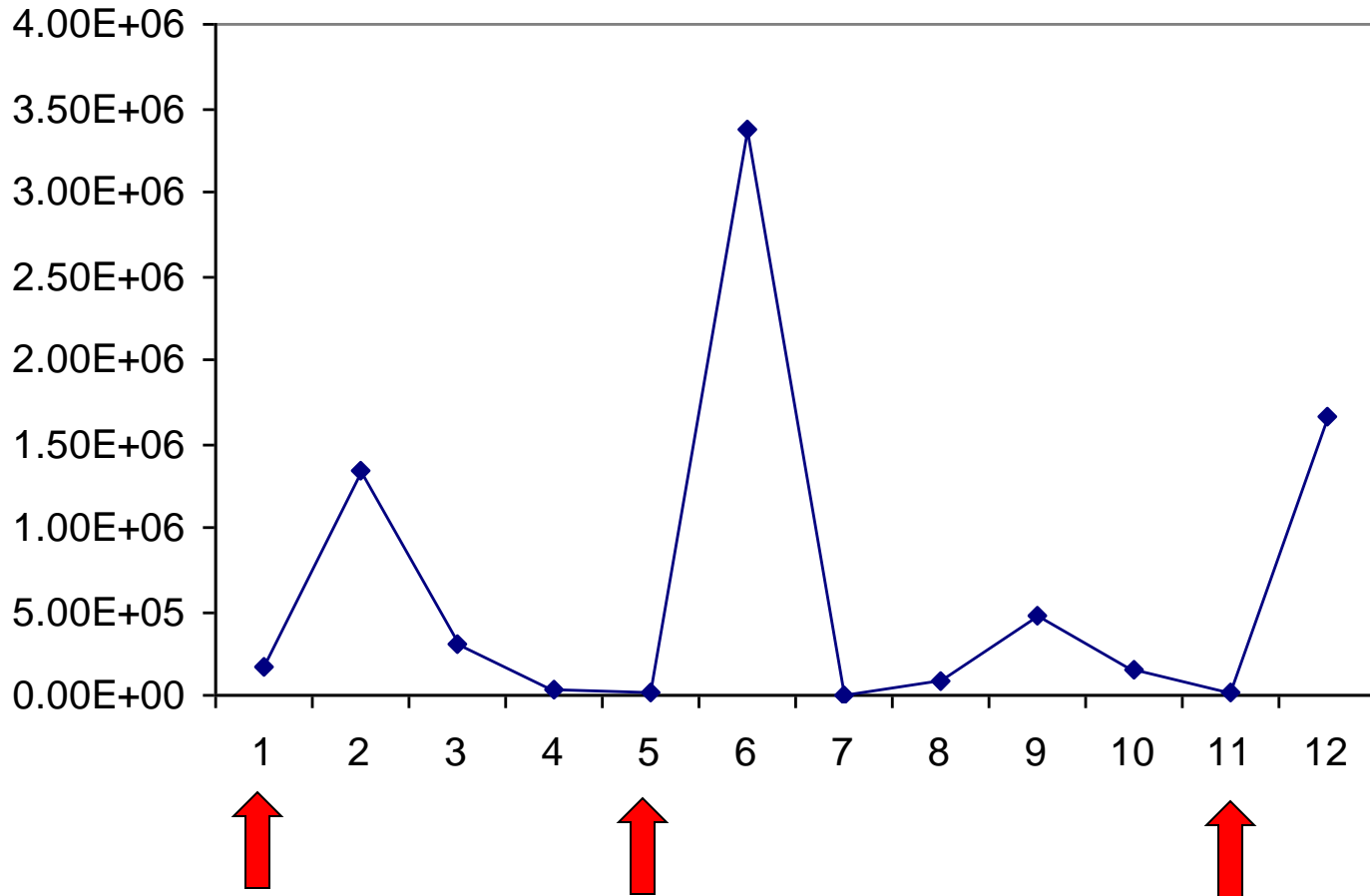


Balashov K et al. PNAS 1997;94:599-603

Neurite density is diminished in SPMS cords with follicles

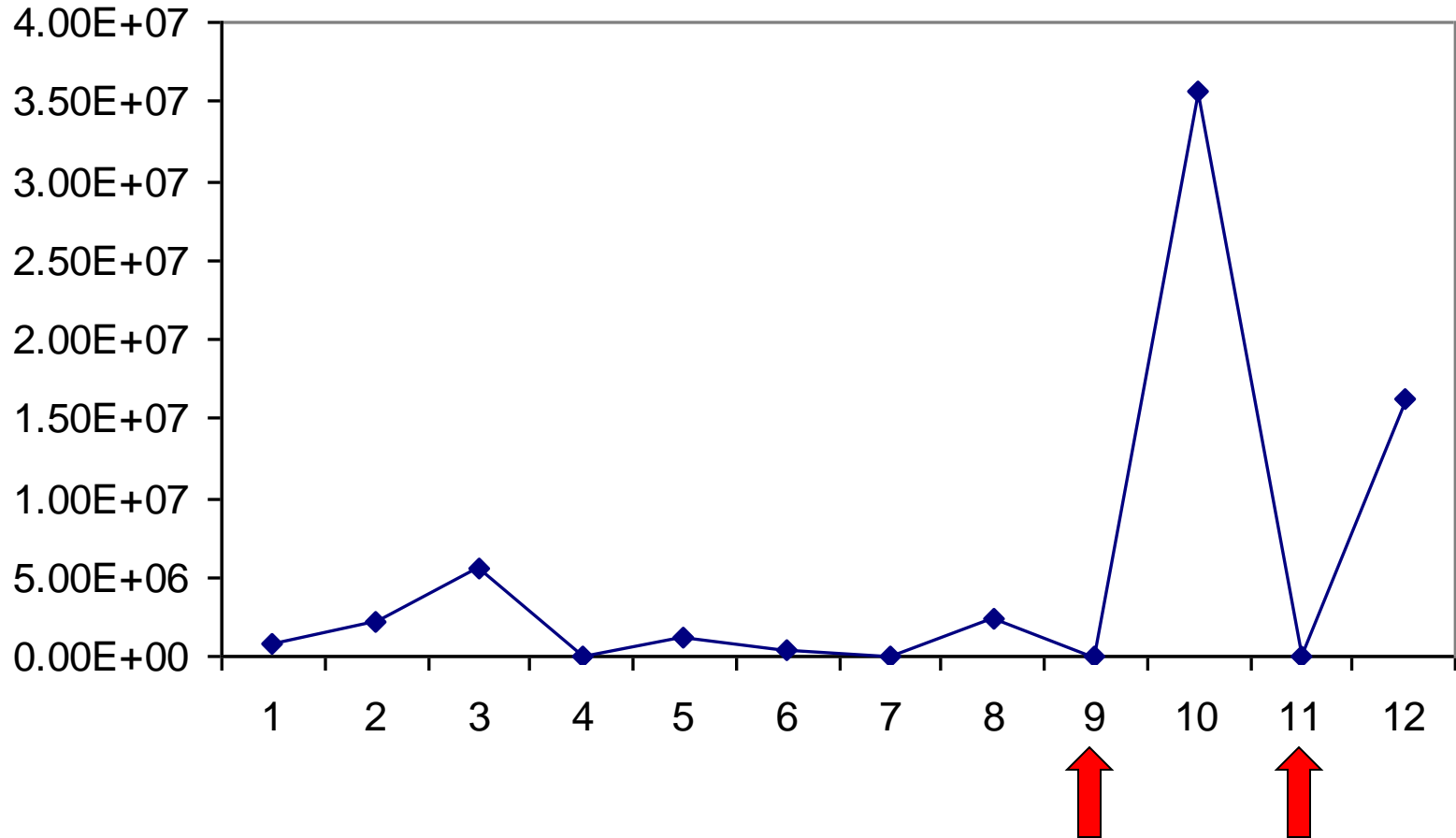


Longitudinal time course for Lymphotoxin B expression for Patient 9



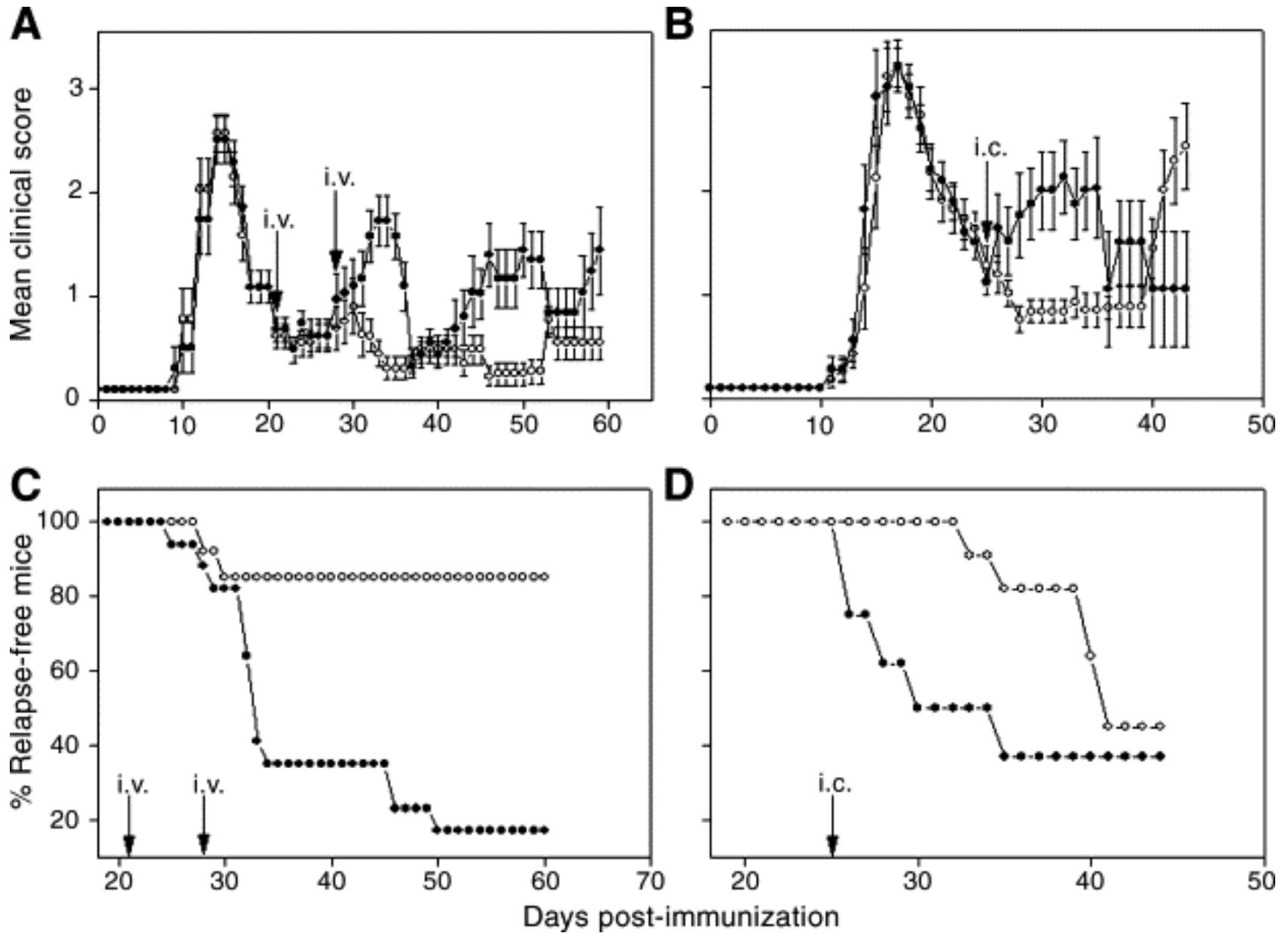
Data is normalized to 4 Housekeeping genes

Longitudinal time course for Lymphotoxin B expression for Patient 12



Data is normalized to 4 Housekeeping genes

LT β R-Ig Tx inhibits clinical EAE



RunX3 normalized to GAPDH

