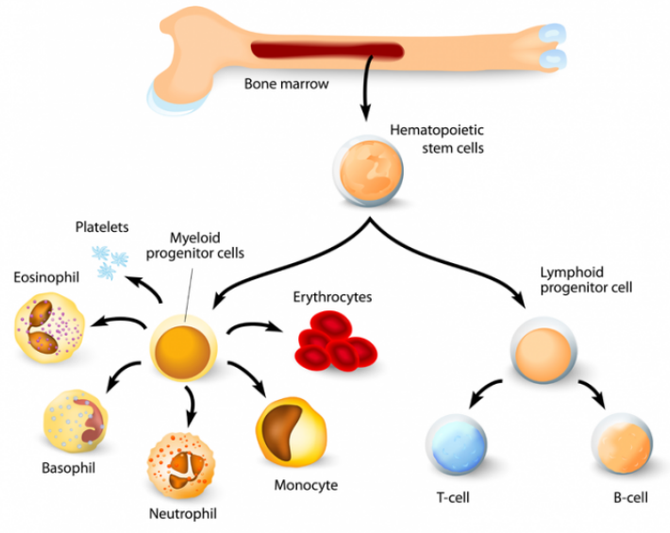
Multiple Sclerosis History and Basic Science

Esther Melamed, MD PhD



Assistant Professor
Research Director PASC Clinic
Department of Neurology
Dell Medical School
UT Austin



The University of Texas at Austin
Dell Medical School

First MS Case



14th C, Holland

A depiction of Saint Lidwina's skating accident, which triggered her MS.

"the Lord's hand had touched this woman."

-court physician of the Duke Albrecht of Holland

Second Case of MS

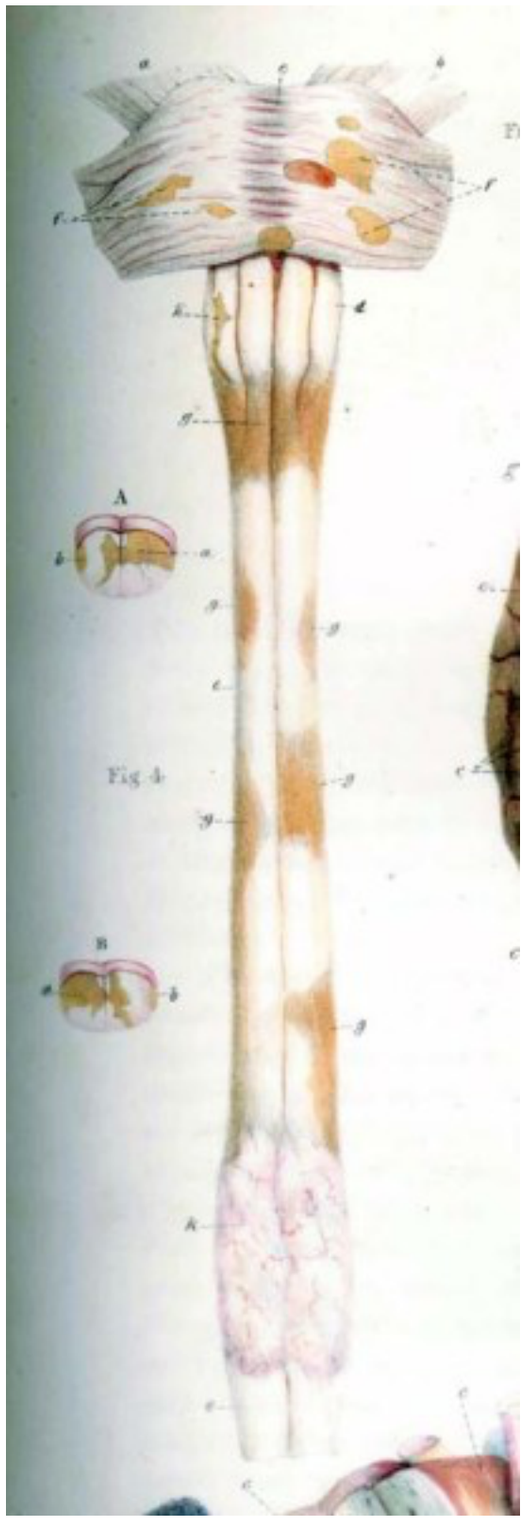
- Augustus D'Este, an illegitimate grandson of George III
- Kept a detailed diary for 26 years of a mysterious illness from which he suffered
- It all began at the age of 28 with an episode of visual impairment, followed by weakness in his legs as well as motor symptoms.



Augustus D'Este

First depiction of MS in pathological atlas of 1838

Robert Caswell
(1793-1857)
Pathologist and artist





neoplasm of the stomach



“To learn how to treat a disease, one must learn how to recognize it. The diagnosis is the best trump in the scheme of treatment.” -Charcot



neurologist at the Hôpital de Salpétrière in Paris

1868
la sclérose en plaques



Charcot demonstrating the use of hypnosis during one of his classes

Charcot's Triad

- intention tremor
- nystagmus
- scanning speech

Potential Treatments

-gold and silver
-strychnine
-arsenic
-two months' complete rest in the country

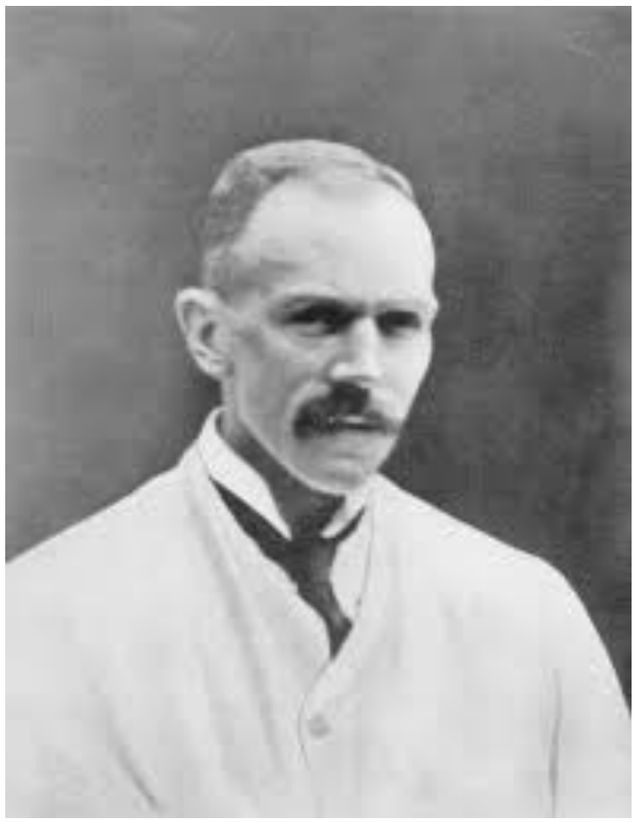
1873 Dr. Walter Moxon officially recognized MS in England
1878 Dr. Edward Seguin recognized MS in the United States

By the end of 19th Century:

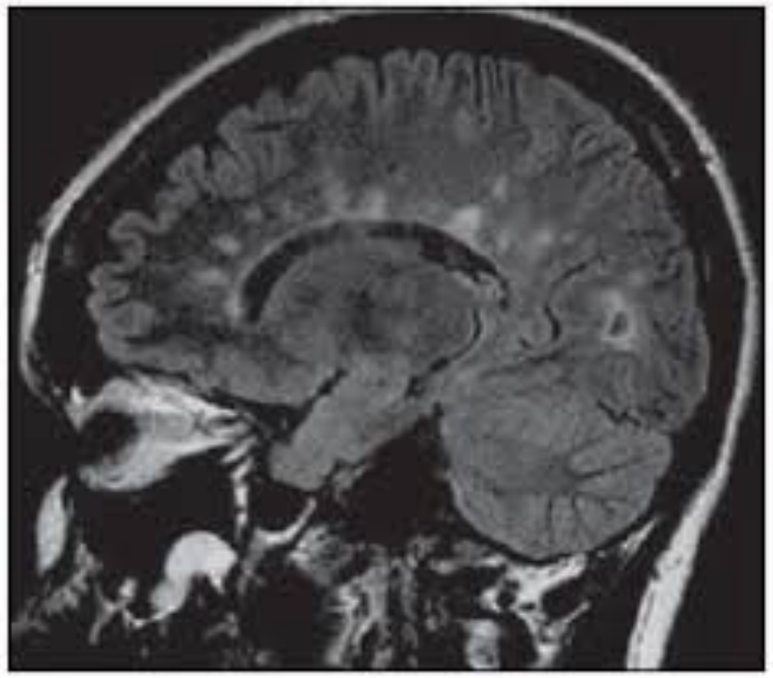
- MS is more common in women than men
- not directly inherited
- can produce many different neurological symptoms
- MS could not be considered an immune disease because the existence of the immune system was still unknown

1916 Dr. James Dawson at the University of Edinburgh

- detailed microscopic examinations of the brains of patients who had died with MS
- inflammation around blood vessels and damage to the myelin



Dr. James Dawson



1919 Abnormalities in spinal fluid noted, though significance was puzzling

1928 Oligodendrocytes discovered — Myelin making cells (myelin discovered in 1878 by Dr. Louis Ranvier)

Scientists suspect a form of toxin or poison caused MS because most MS damage occurs around blood vessels



Demyelination in the parietal lobe of a Rhesus macaque



Dr. Tomas Rivers

1935: First EAE experiment — > immune cells and not viruses directly produced the MS-like illness in laboratory animals

Overlooked by most doctors in 1930’s as toxins still a major concept in MS

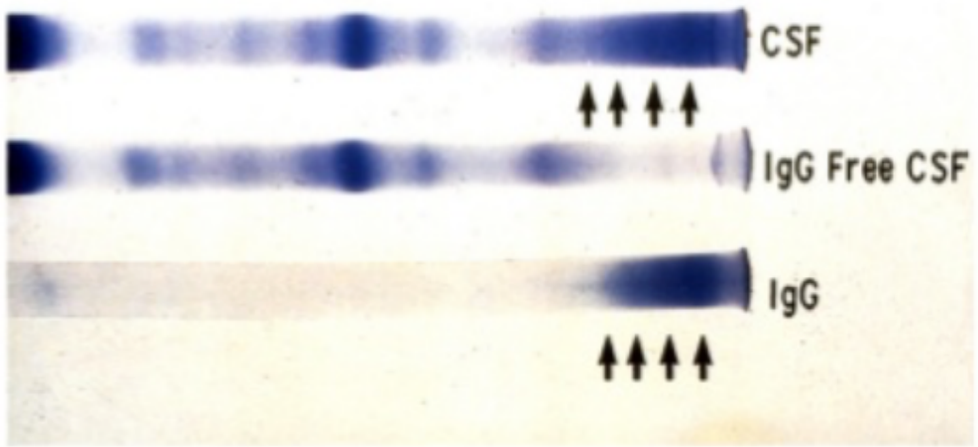
MS: a circulatory problem?



- blocking the blood supply to the brain sometimes caused myelin to die and damage looked a bit like MS

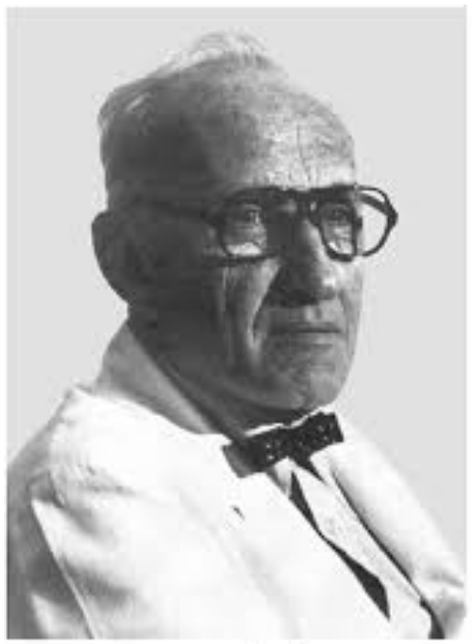
- blood thinners and drugs to dilate blood vessels

1942-1960 Discoveries by Dr. Kabar, Dr. Karcher van Sande, and Dr. Lowenthal lead to identification of oligoclonal bands



Oligoclonal bands





Elvin A Kabat

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Micro-Eletrophoresis in Agar Gel of Proteins of the Cerebrospinal Fluid and Central Nervous System 1959. D. Karcher, M. van Sande and A. Lowenthal. Institute of Tropical Medicine, Antwerp, and Institute Bunge, Berchem Antwerp, Belgium Journal of Biochemistry 1959; 4: 135-140

The Journal of Immunology

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Autoaggressive T lymphocyte lines recognizing the encephalitogenic region of myelin basic protein: in vitro selection from unprimed rat T lymphocyte populations.

H J Schluesener and H Wekerle

J Immunol November 1, 1985, 135 (5) 3128-3133;

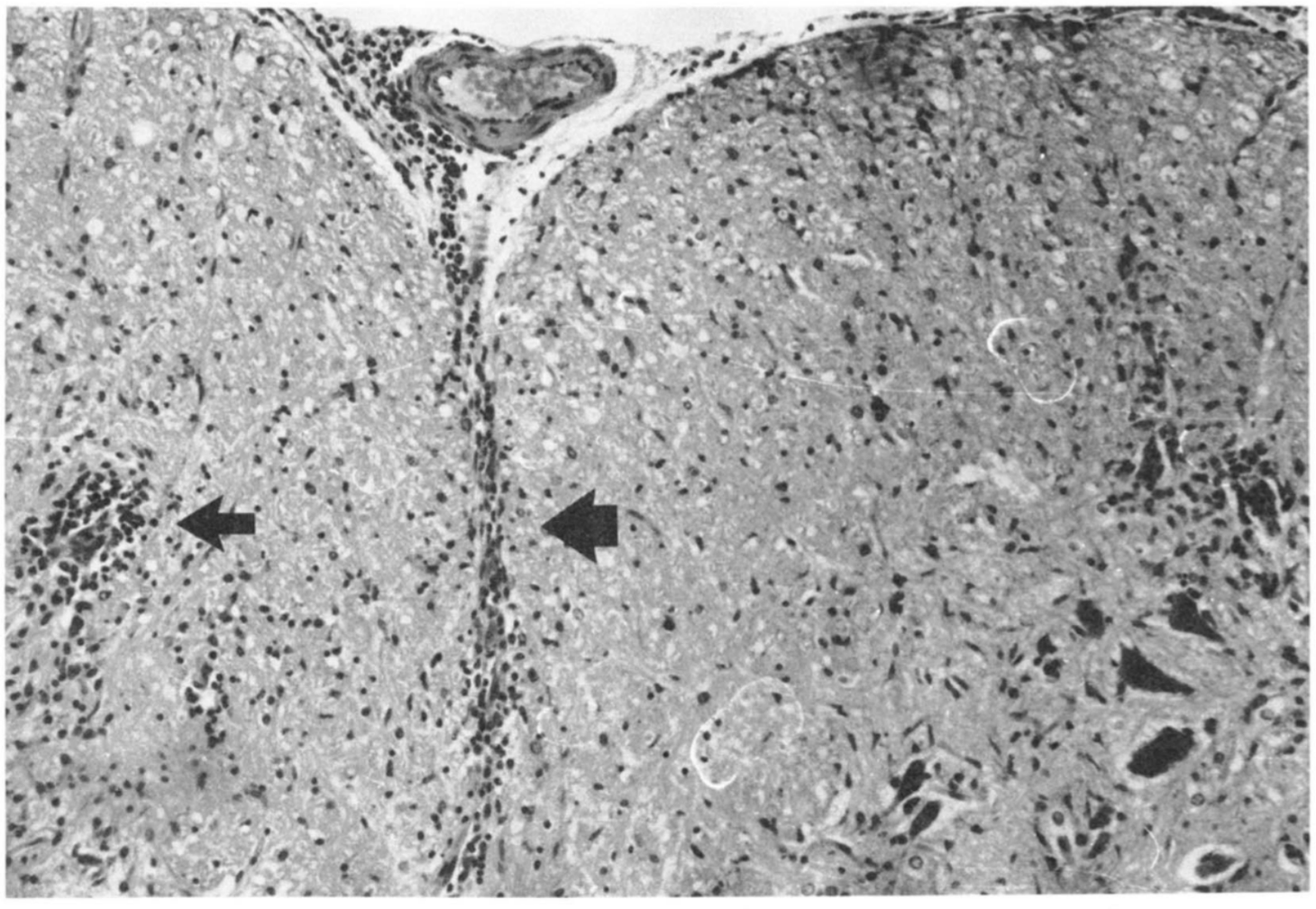


Figure 1. Meningeal and perivascular infiltrations (*arrow*) in the spinal cord of a LEW rat injected with 1×10^6 vLe line blast cells 5 days ago.

The First Valid Scientific Trial in MS: ACTH

Neurology. 1970 May;20(5):1-59.

Cooperative study in the evaluation of therapy in multiple sclerosis. ACTH vs. placebo--final report.

Rose AS, Kuzma JW, Kurtzke JF, Namerow NS, Sibley WA, Tourtellotte WW.

European Neurology

Double-Blind Randomized Trial of ACTH versus Dexamethasone versus Methylprednisolone in Multiple Sclerosis Bouts

Clinical, Cerebrospinal Fluid and Neurophysiological Results

Milanese C.[a] · La Mantia L.[a] · Salmaggi A.[a] · Campi A.[a] · Eoli M.[a] · Scaioli V.[b] · Nespolo A.[c] · Corridori F.[a]

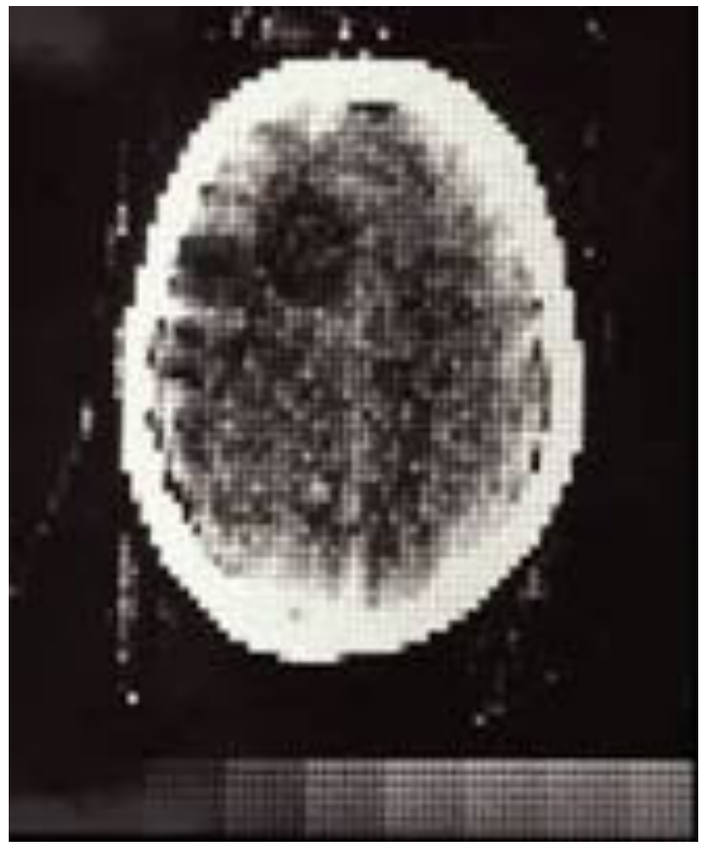
Author affiliations

Keywords: Multiple sclerosis bouts · Adrenocorticotropic hormone · Steroid treatment · Evoked potentials · Cerebrospinal fluid · CT scan

Eur Neurol 1989;29:10–14

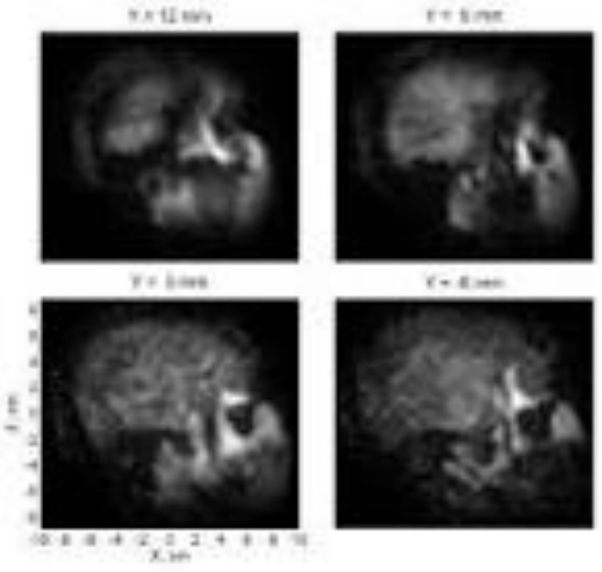
CT and MRI

In 1978, the first CAT scans performed on people with MS



The **first** MRI images were produced in the early 1970s, and the **first** live human subject was imaged in 1977





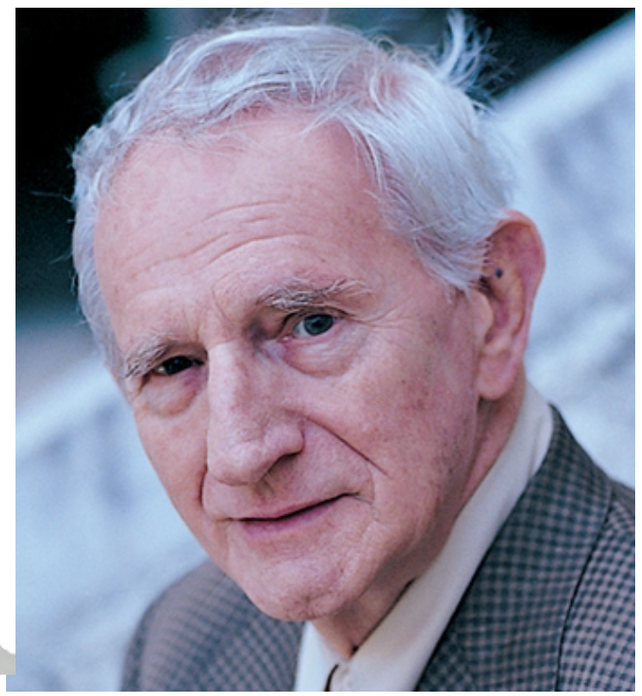
Copolymer 1: First MS drug developed in EAE 1971

L-alanine, L-lysine, L-glutamic acid, and L-tyrosine)

Weizman Institute







Prof. Dvora Teitelbaum Prof. Ruth Arnon Prof. Michael Sela

European Journal of Immunology



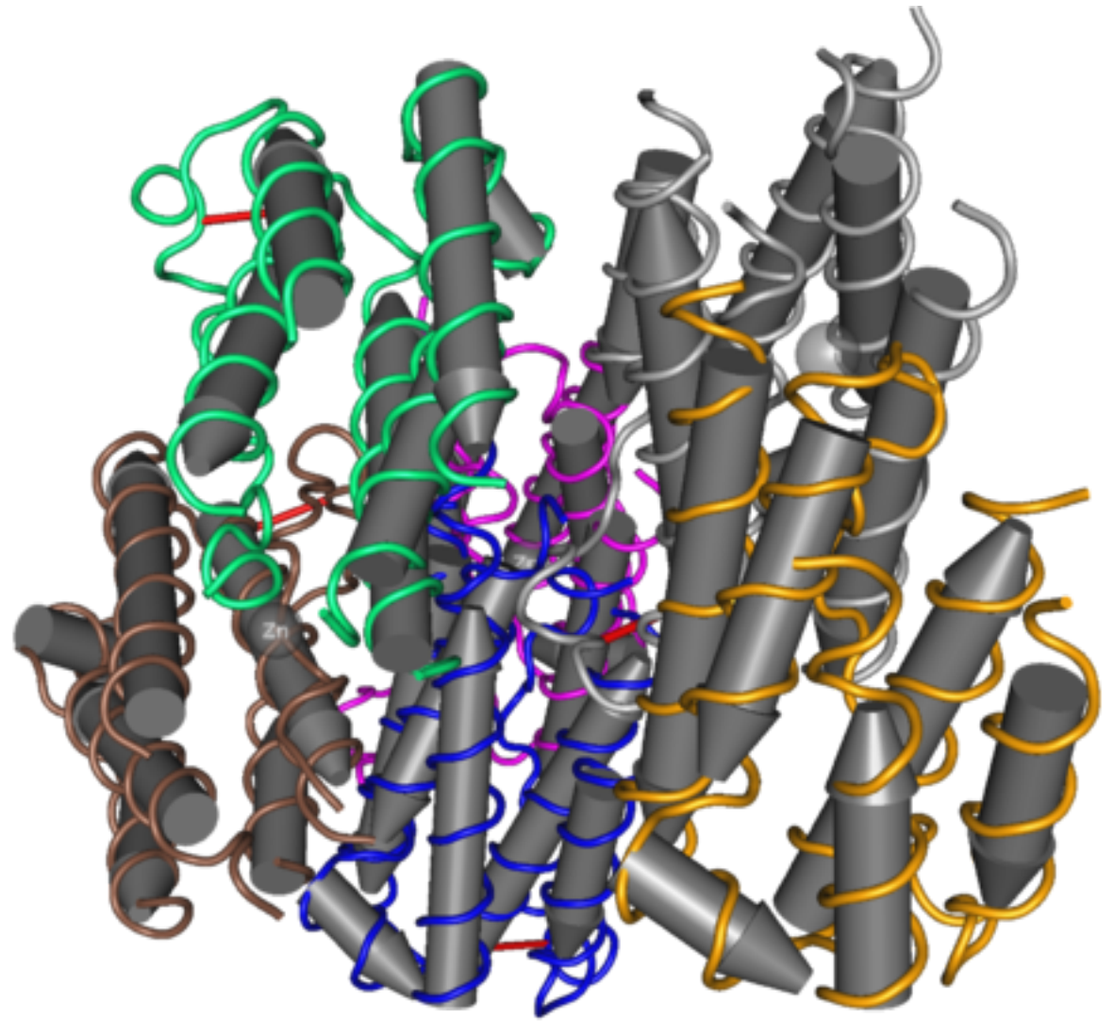
Article

Suppression of experimental allergic encephalomyelitis by a synthetic polypeptide

Dvora Teitelbaum, A. Meshorer, T. Hirshfeld, Ruth Arnon, M. Sela

Interferons: interfere with viral replication





1970’s development that led to FDA approval in 1993

Making and Breaking of Self-Tolerance

A critical function of the immune system is to discriminate self from nonself

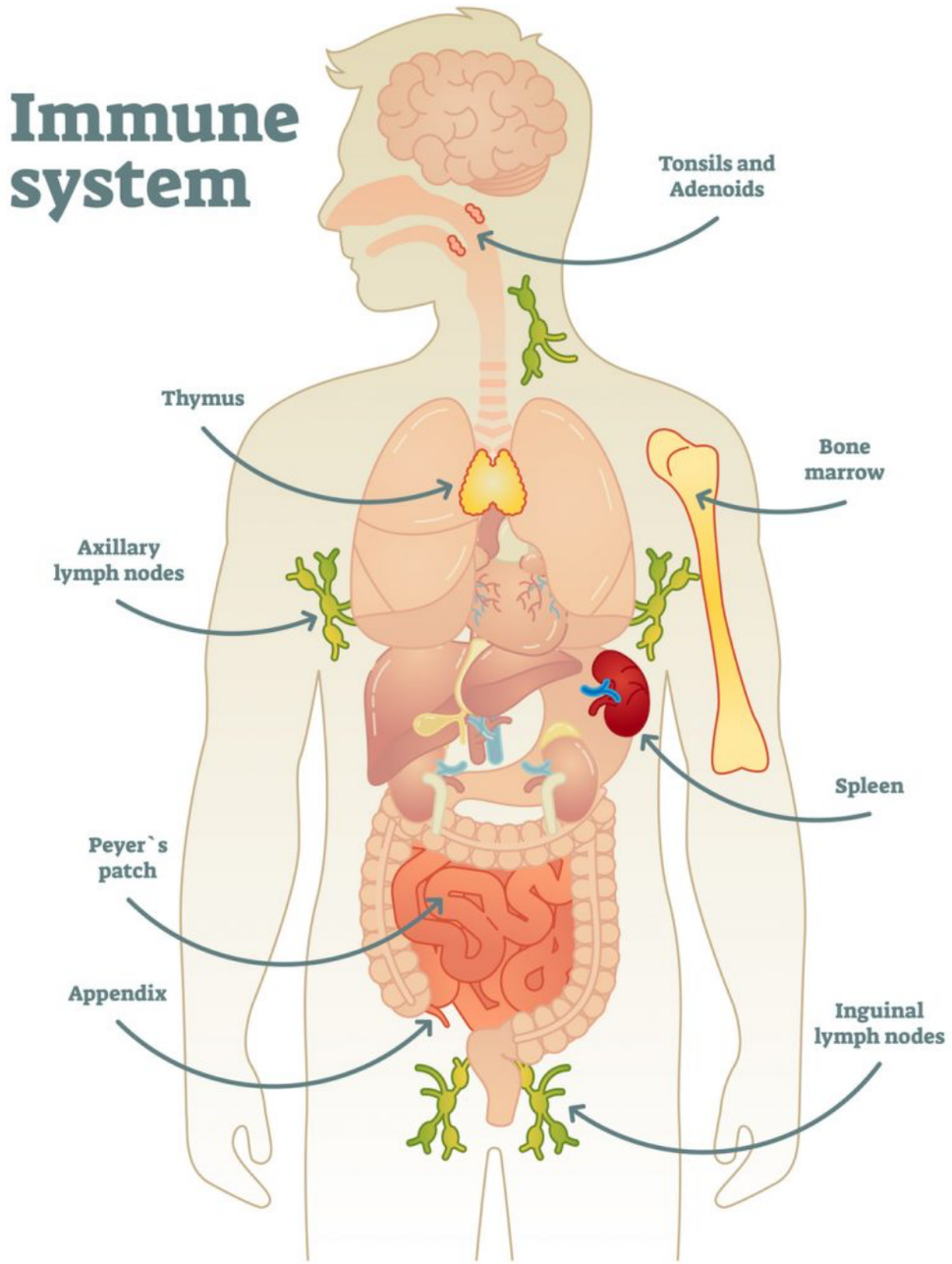
Paul Ehrlich -‘horror autotoxicus.’



Psoriasis
Rheumatoid arthritis
Graves' disease
Hashimoto's thyroiditis
Systemic lupus erythematosus
Sjögren's syndrome
Crohn's disease
Multiple sclerosis
Type 1 diabetes (insulin-dependent diabetes mellitus, IDDM)

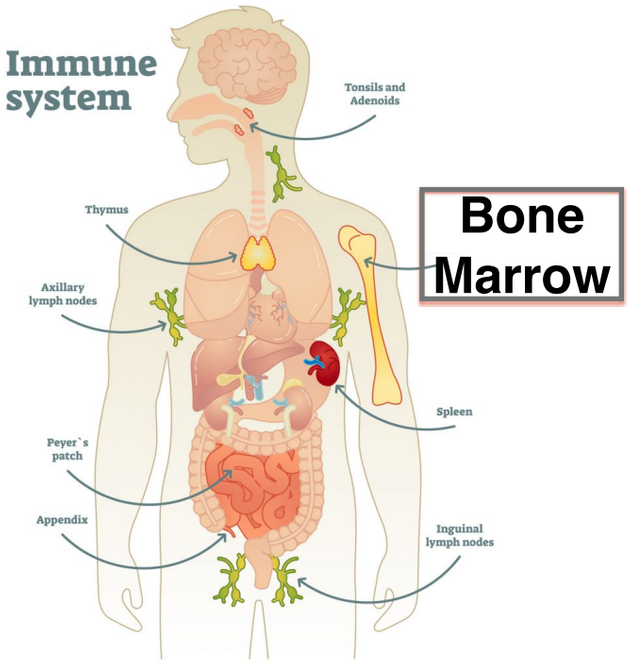
Immune organs

Crash Course NeuroImmunology

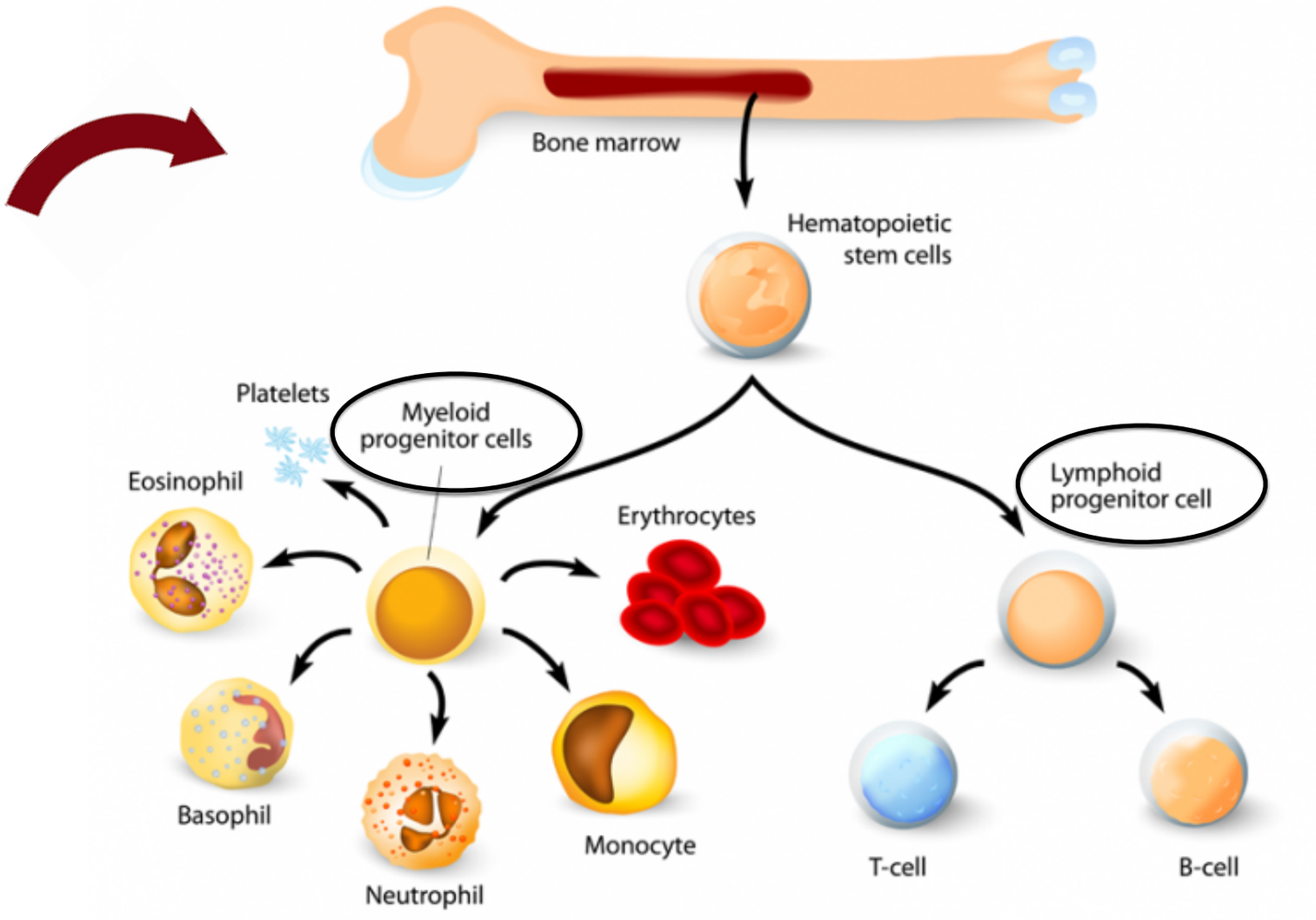


Crash Course NeuroImmunology

Birth of immune cells

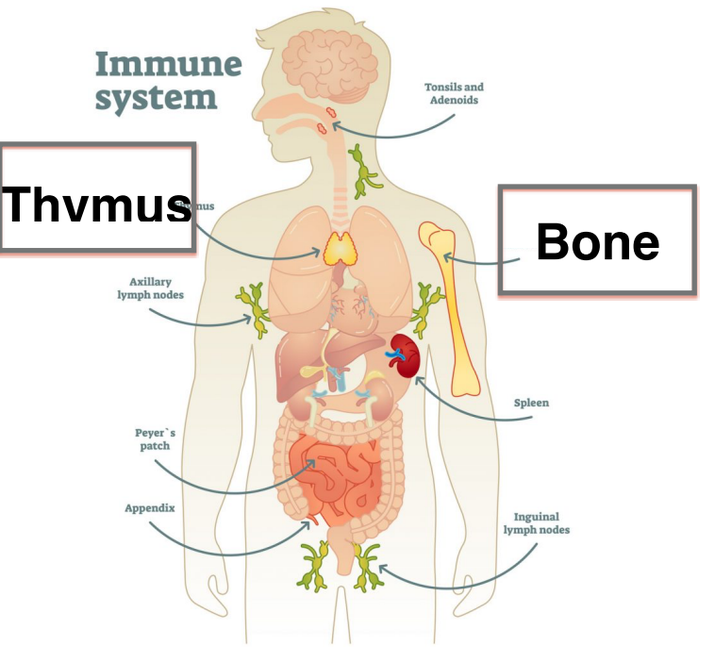


Bone Marrow

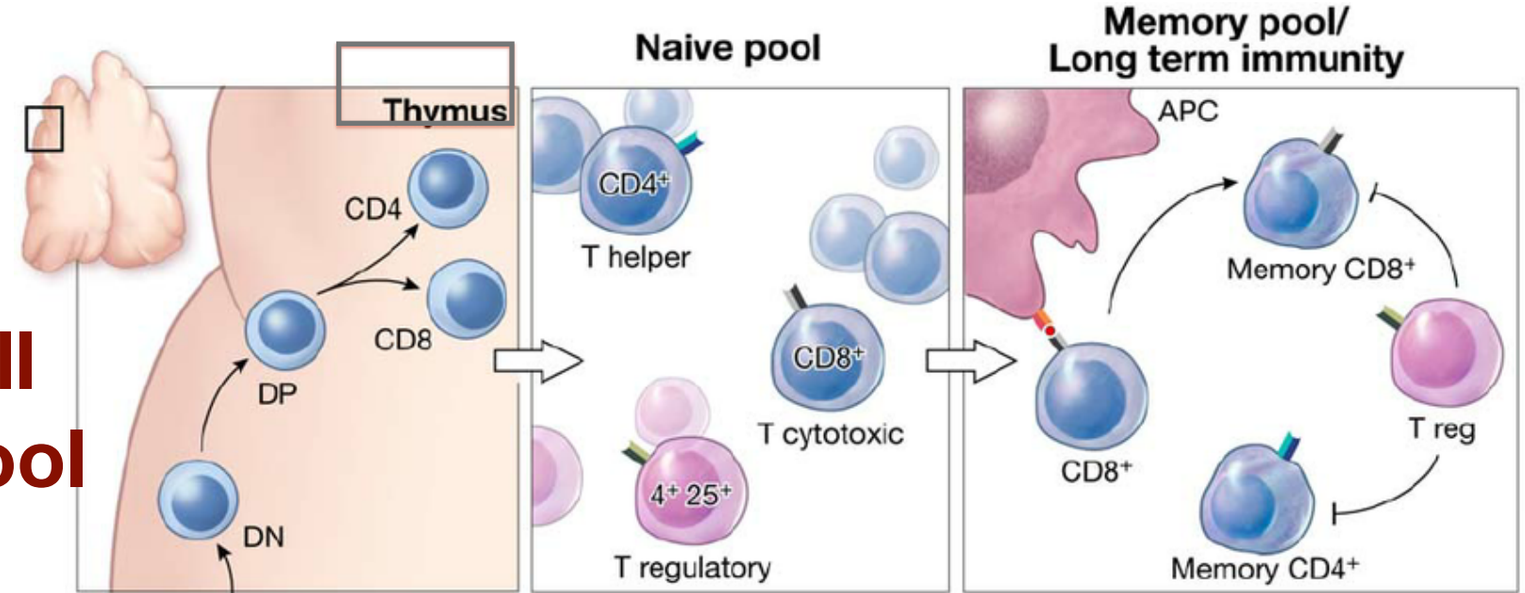


Immune cell “schooling”

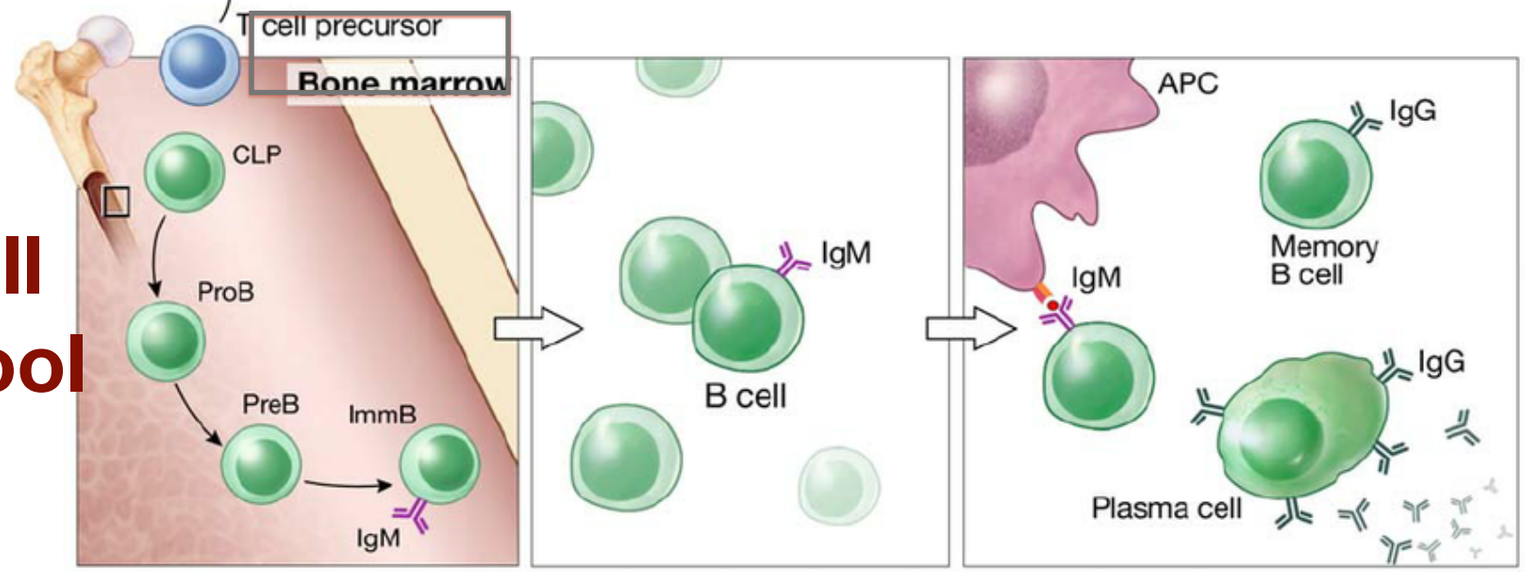
Crash Course NeuroImmunology



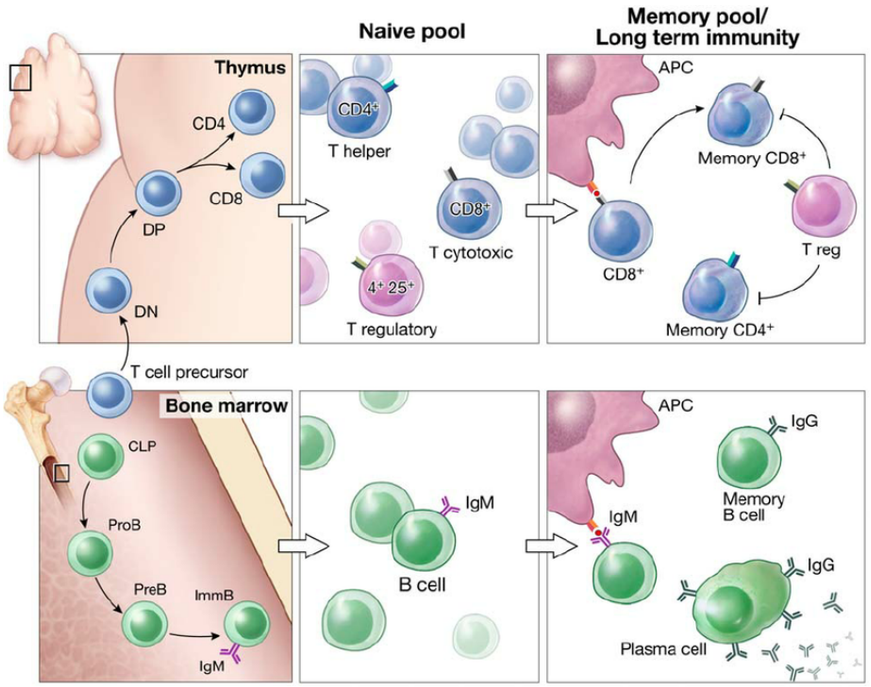
T cell school

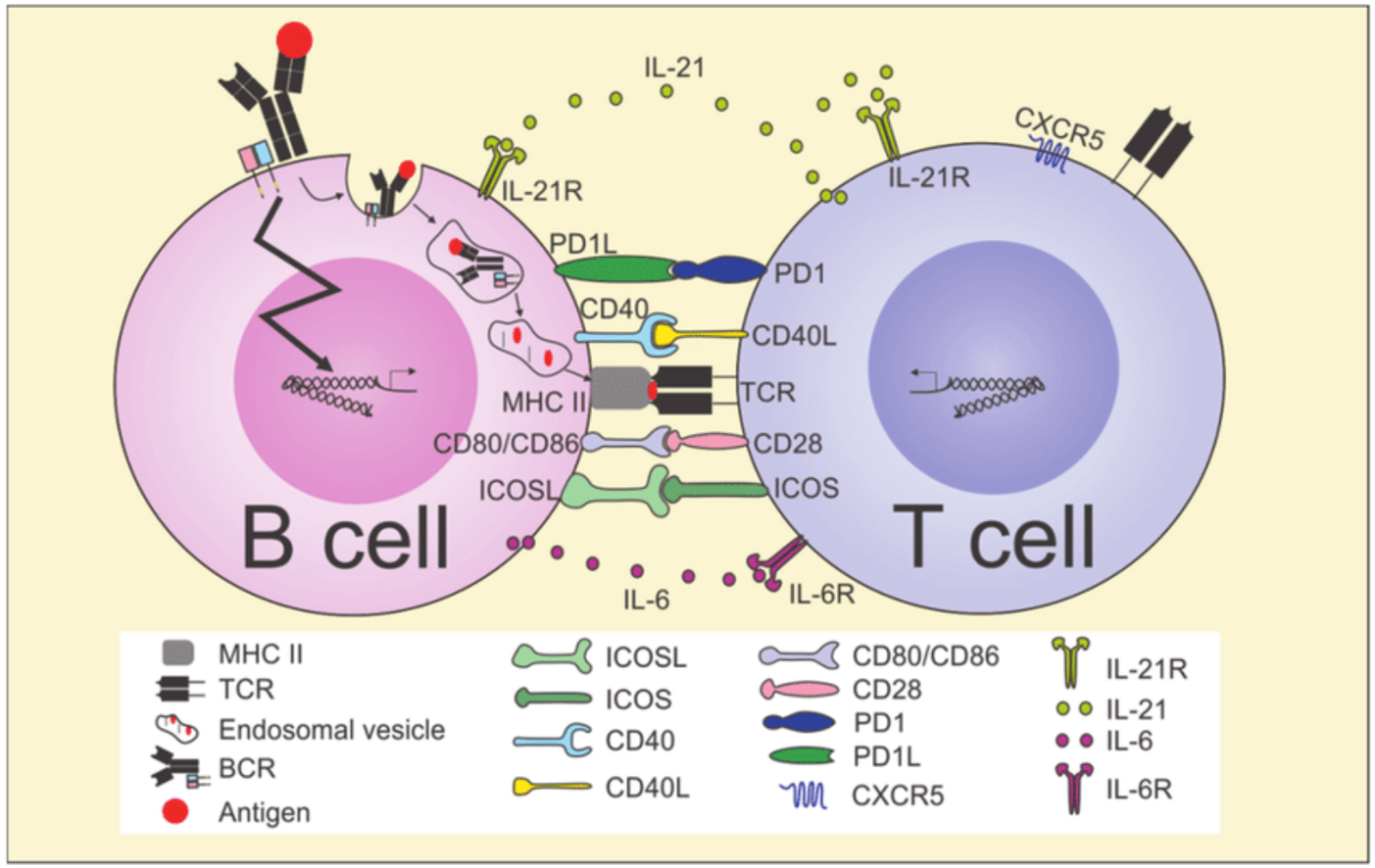


B cell school



Crash Course
NeuroImmunology
Immune cell partnerships





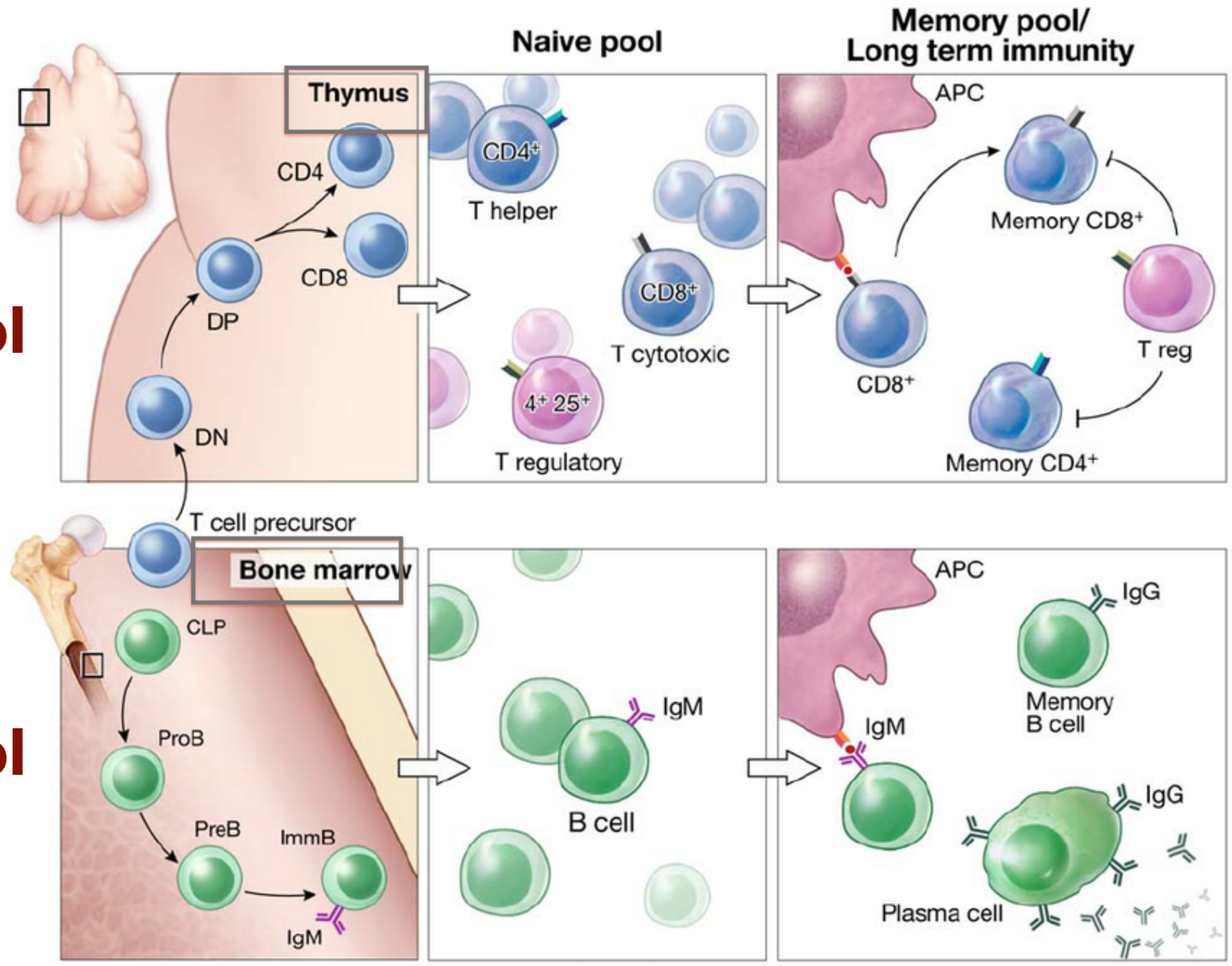
T and B cells work closely together

Rise of Autoimmunity

Crash Course NeuroImmunology:

T cell school

B cell school

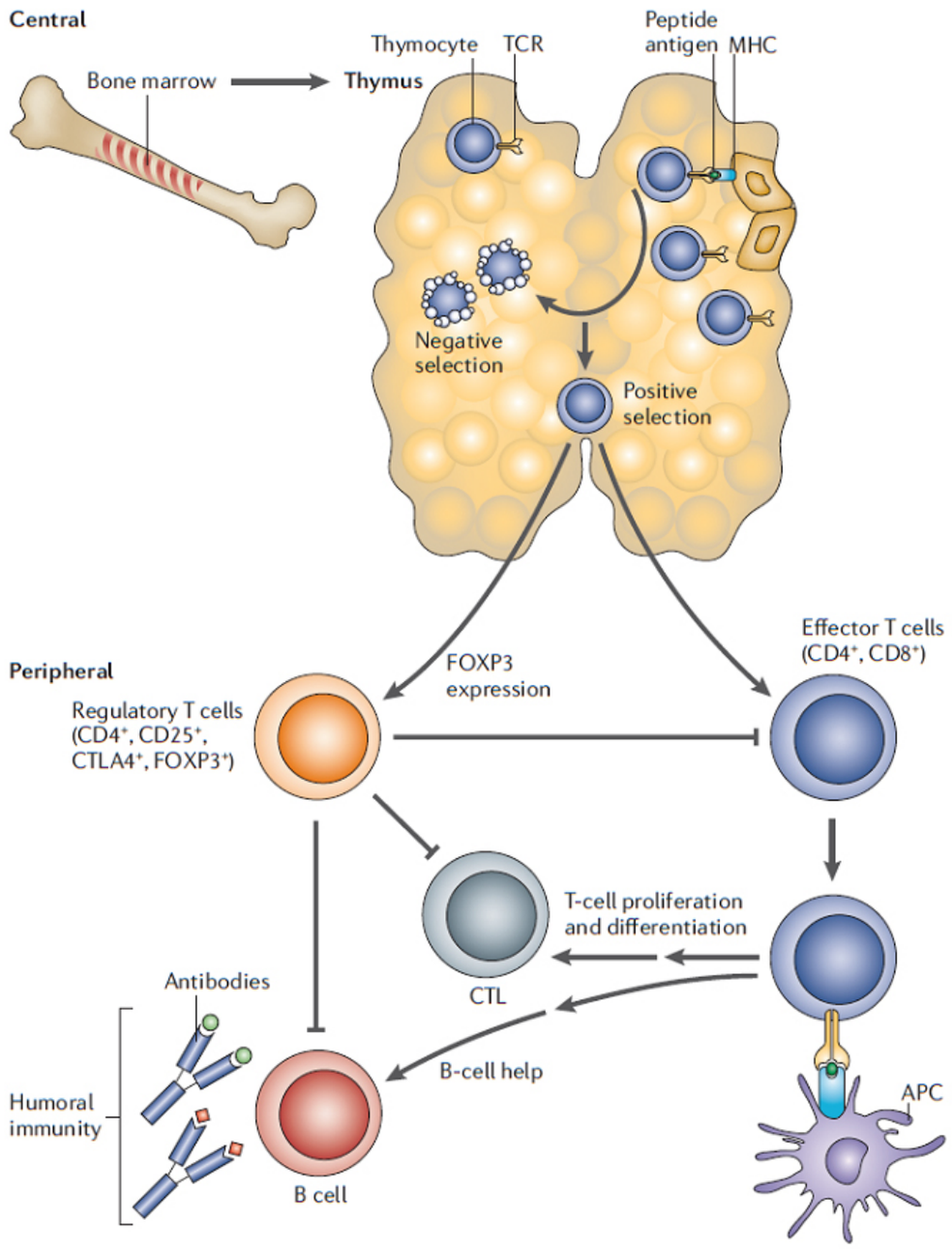


T cell students

- **Good: learn to recognize self from foreign invaders**
- **Bad: mistake self for a foreign invader**

Central vs Peripheral Tolerance

- Central auto reactive T cell elimination
- Peripheral Anergy
- T regs



Antigens in immunologically privileged sites do not induce immune attack but can serve as targets.

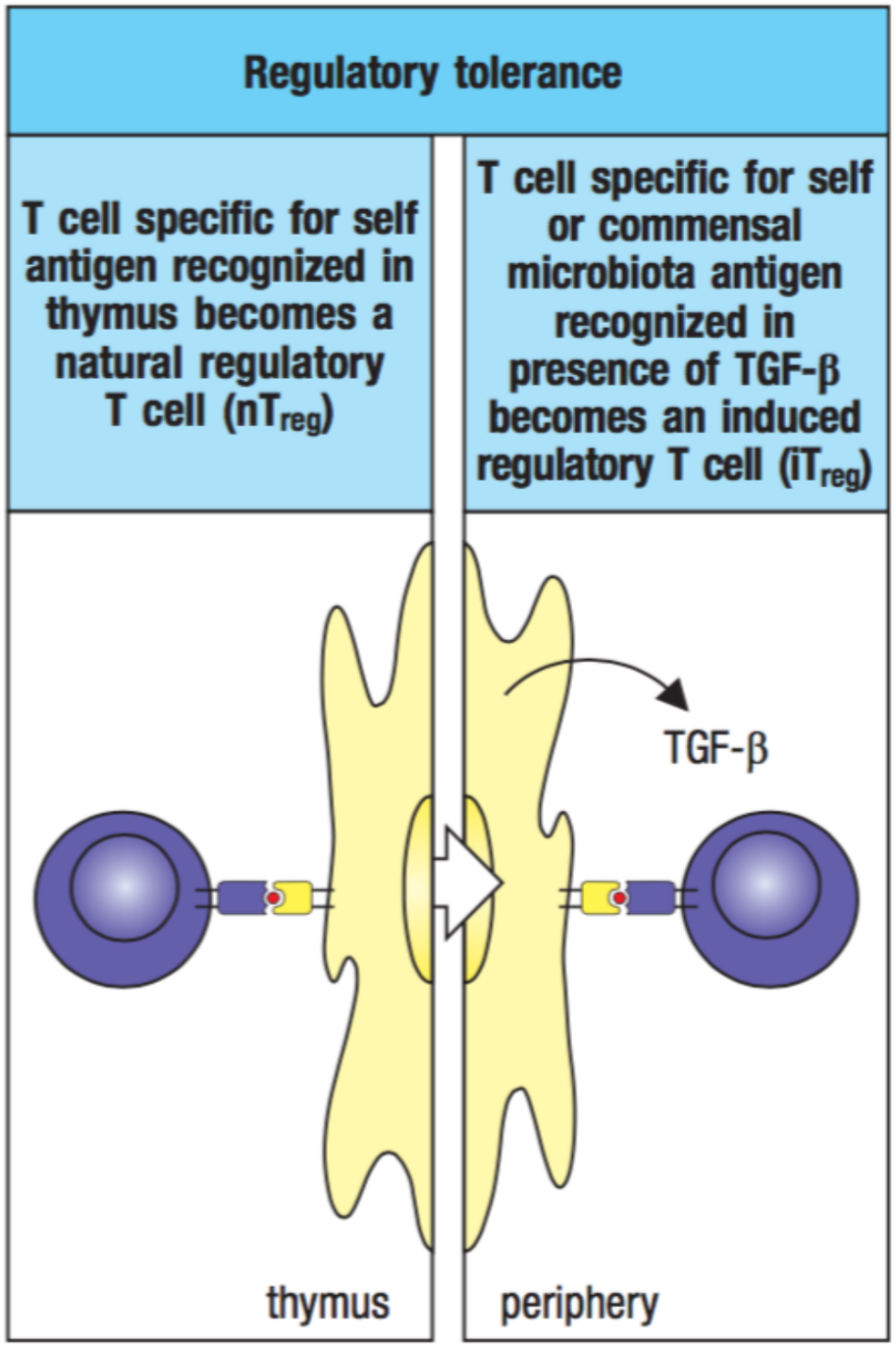
Immunologically privileged sites
Brain
Eye
Testis
Uterus (fetus)

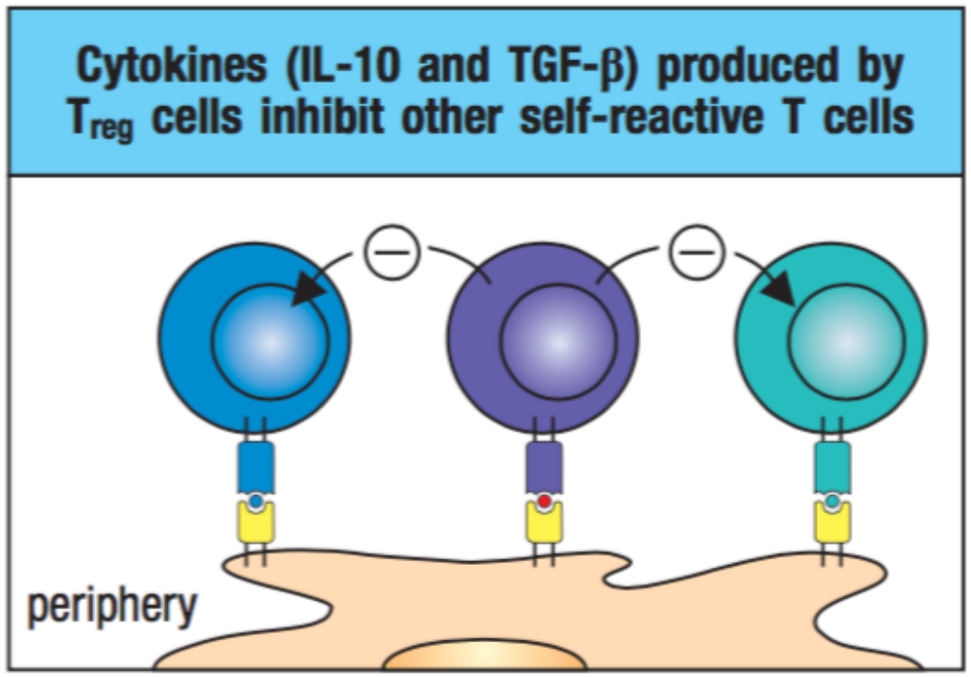




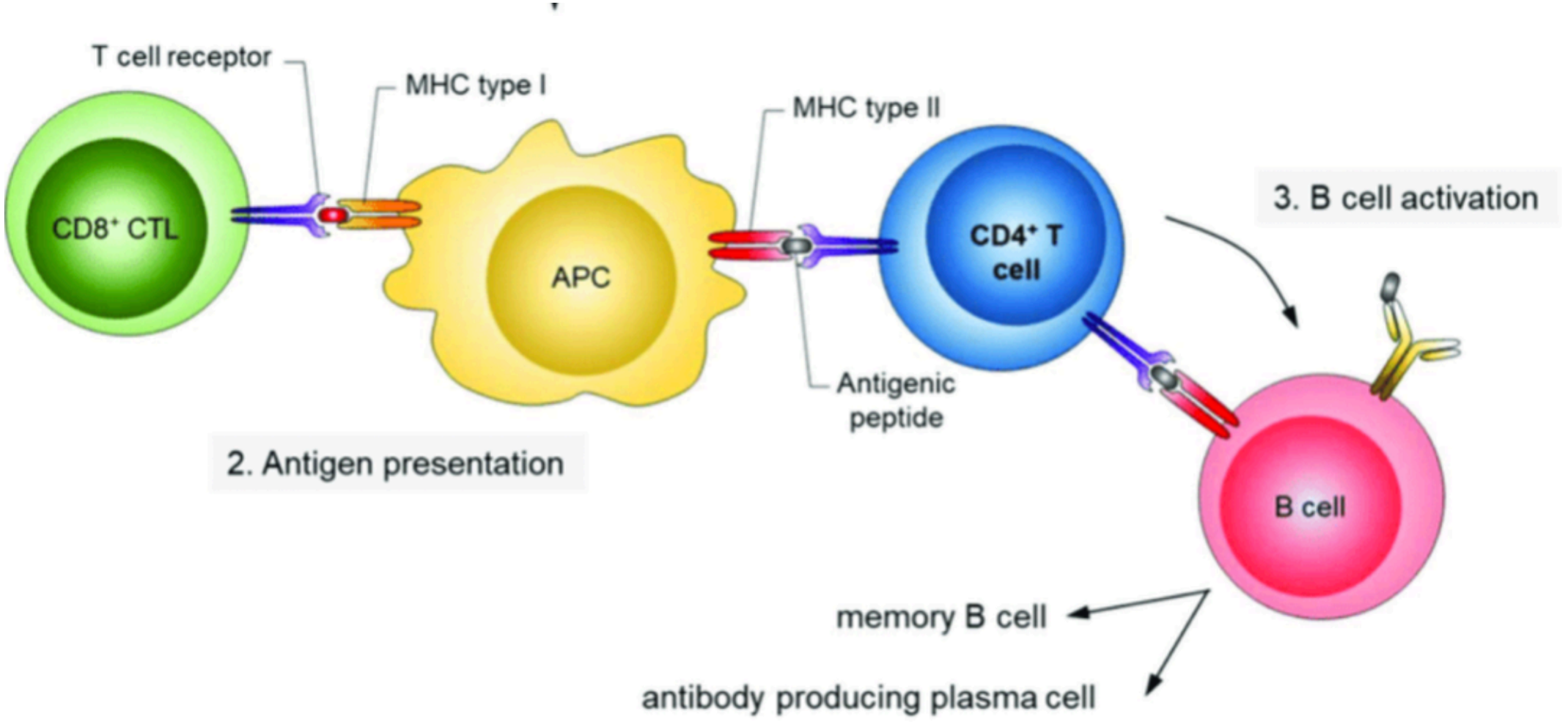
2D2 and optic neuritis

Regulatory Tolerance





The Main Immune Players

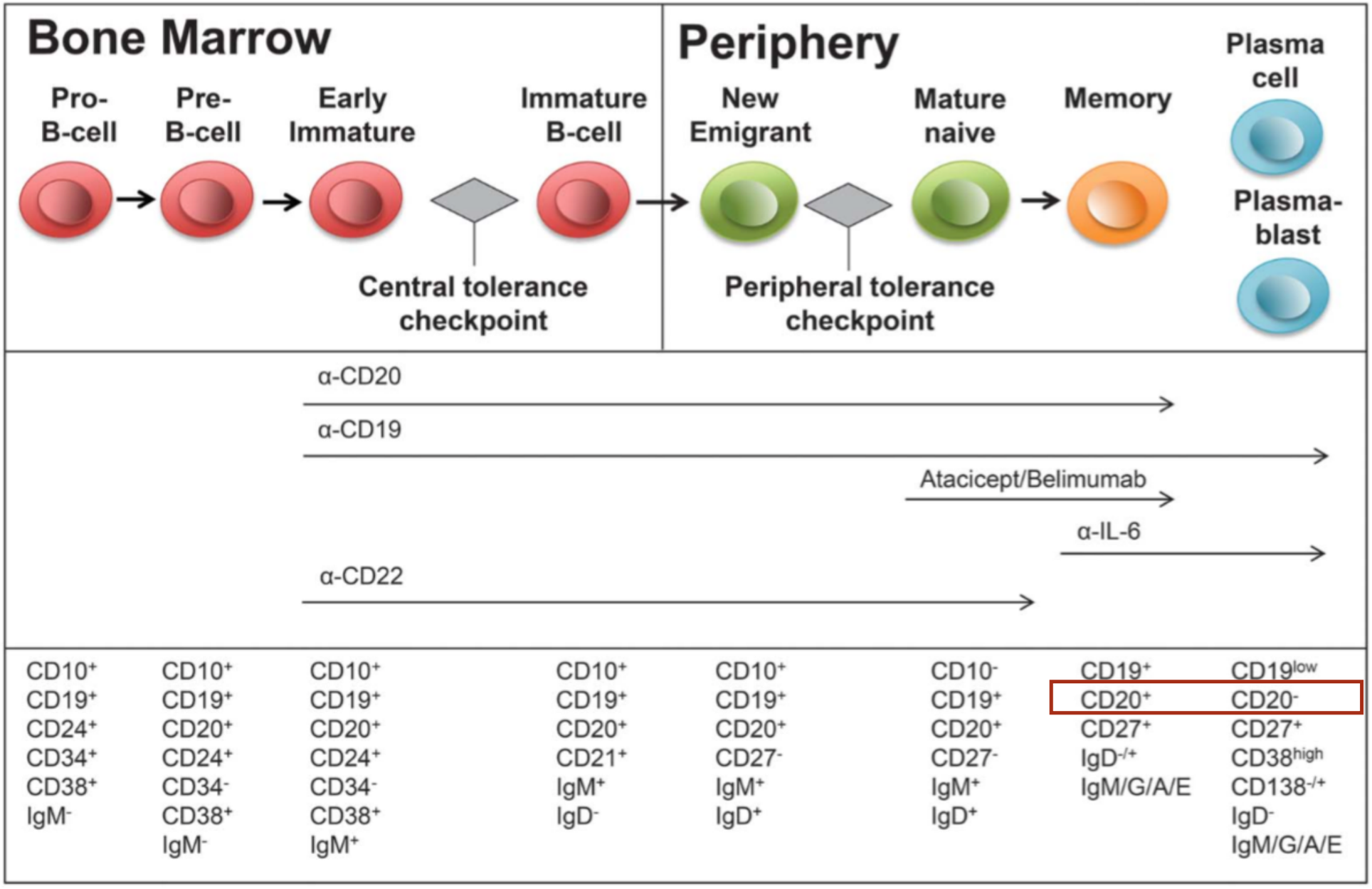


Brief report

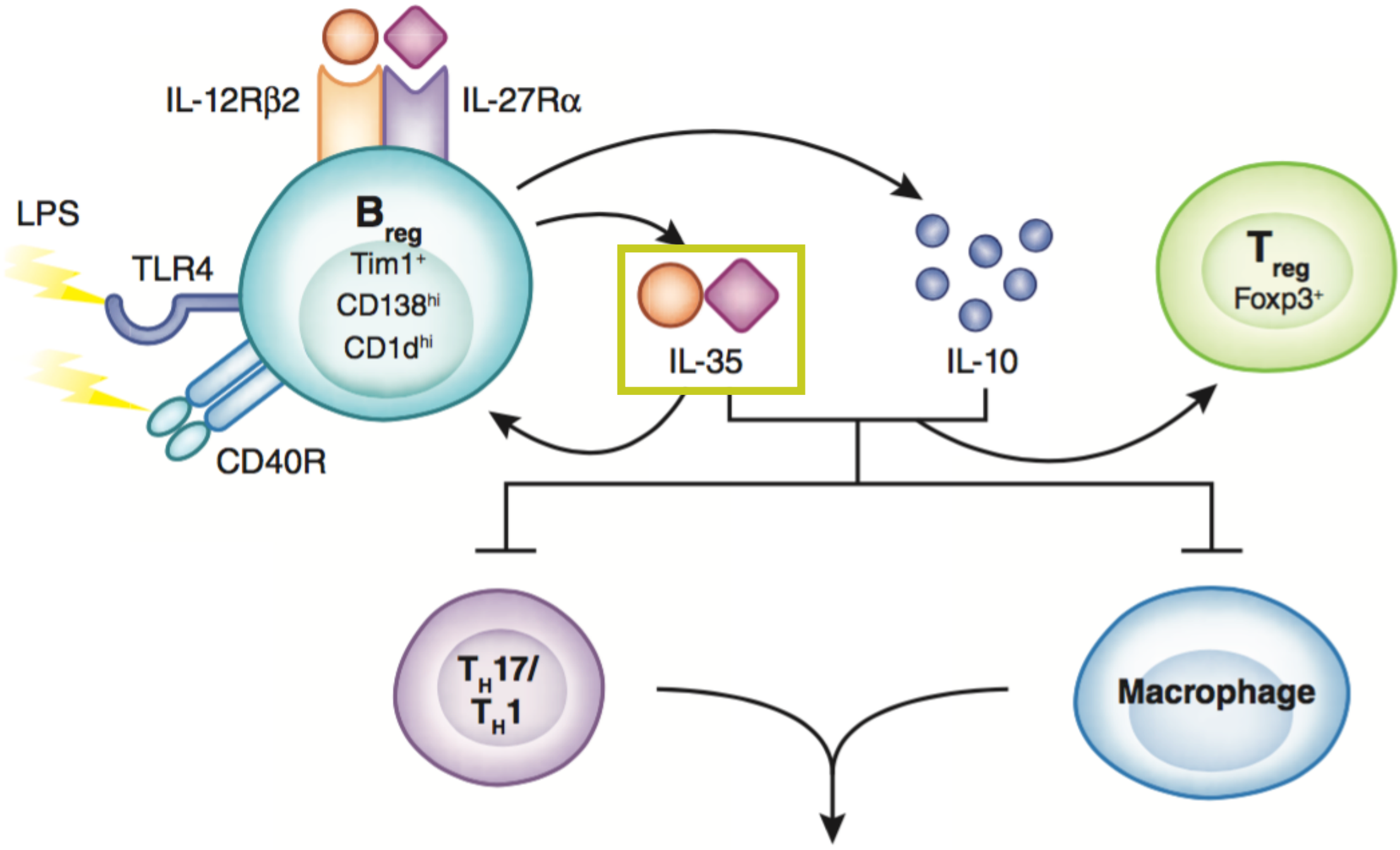
Specific peripheral B cell tolerance defects in patients with multiple sclerosis

Tuure Kinnunen,[1] Nicolas Chamberlain,[2] Henner Morbach,[2] Tineke Cantaert,[2] Megan Lynch,[2] Paula Preston-Hurlburt,[2] Kevan C. Herold,[2,3] David A. Hafler,[1] Kevin C. O'Connor,[1] and Eric Meffre[2]

[1]Department of Neurology, [2]Department of Immunobiology, and [3]Department of Internal Medicine, Section of Endocrinology and Metabolism, Yale University School of Medicine, New Haven, Connecticut, USA.


Bone Marrow
Periphery
Pro-
B-cell
Pre-
B-cell
Early
Immature
Immature
B-cell
New
Emigrant
Mature
naive
Memory
Plasma
cell
Plasma-
blast
Central tolerance
checkpoint
Peripheral tolerance
checkpoint
α-CD20
α-CD19
Atacicept/Belimumab
α-IL-6
α-CD22
CD10+ CD19+ CD24+ CD34+ CD38+ IgM-
CD10+ CD19+ CD20+ CD24+ CD34- CD38+ IgM-
CD10+ CD19+ CD20+ CD24+ CD34- CD38+ IgM+
CD10+ CD19+ CD20+ CD21+ IgM+ IgD-
CD10+ CD19+ CD20+ CD27- IgM+ IgD+
CD10- CD19+ CD20+ CD27- IgM+ IgD+
CD19+ CD20+ CD27+ IgD-/+ IgM/G/A/E
CD19low CD20- CD27+ CD38high CD138-/+ IgD- IgM/G/A/E

B CELLS

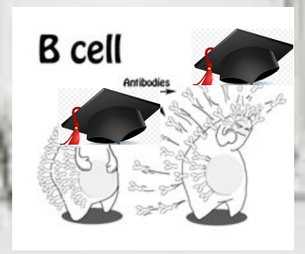


Mauri and Nistala Nature Medicine 2014

B CELL TOLERANCE AND MS PATHOGENESIS

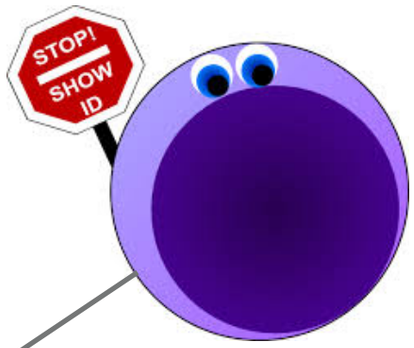
Bone Marrow

B Cell University

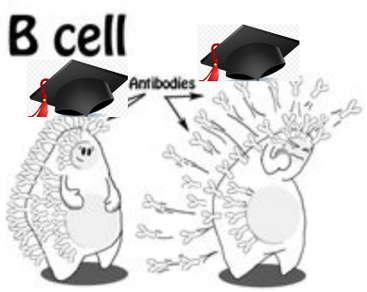


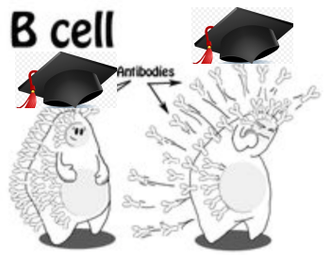


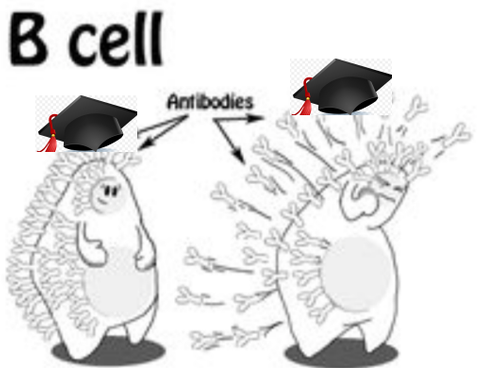
Don't Cross if you are REACTIVE!



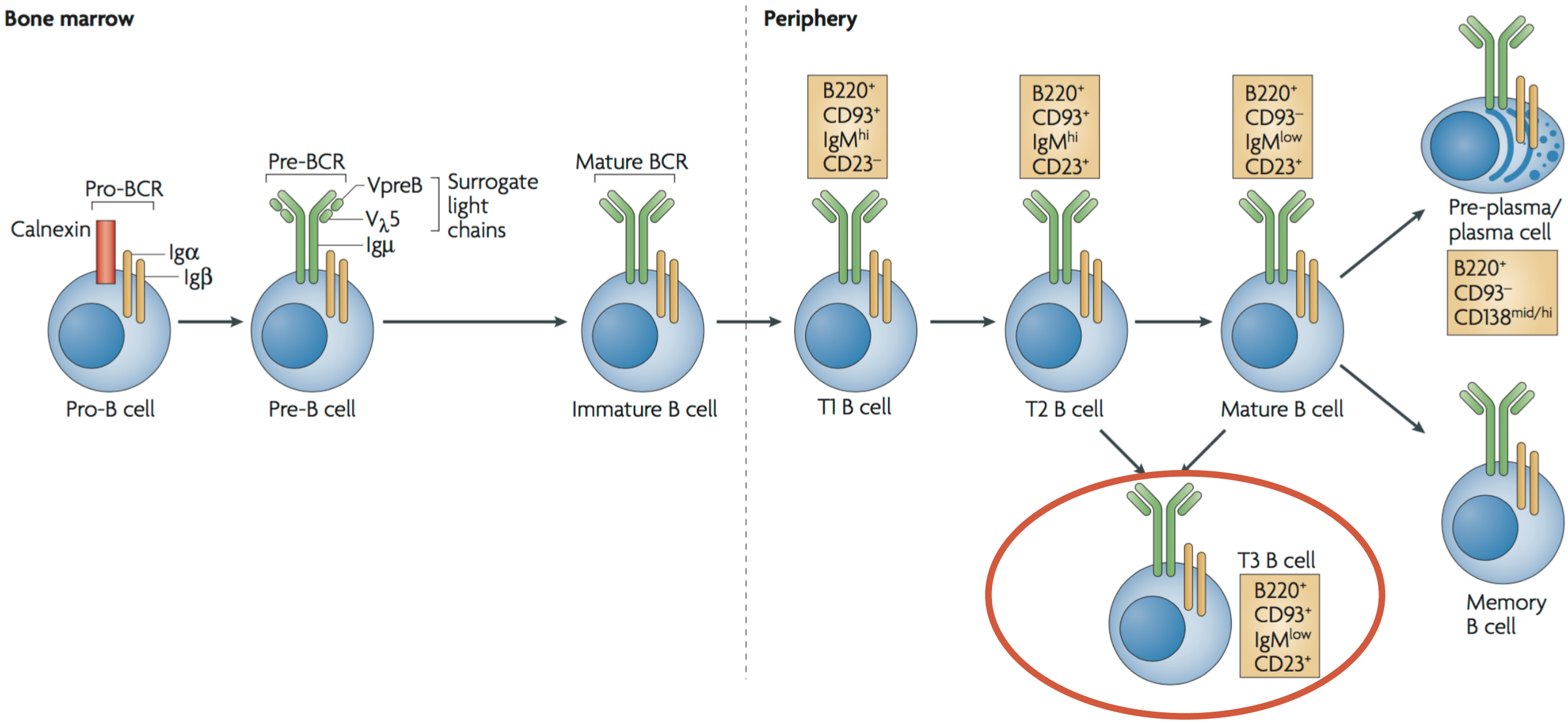
Periphery







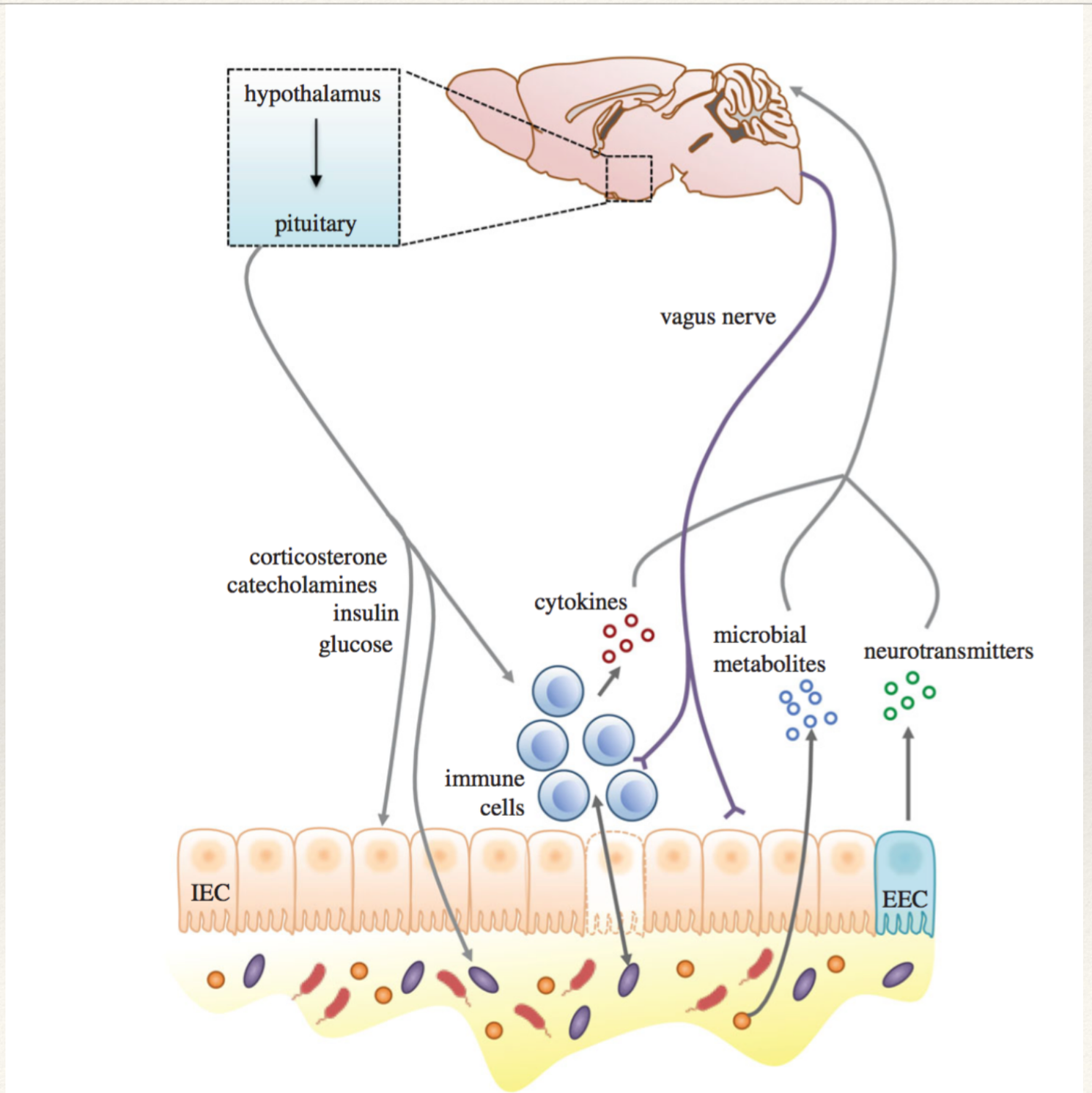
B CELL ANERGIC ESCAPE IN MS AND NMO



Anergic B cell

Camber et al Nature Reviews 2007

Gut-Brain Axis



Jasarevic et al 2016

Sex Differences in the Gut Microbiome Drive Hormone-Dependent Regulation of Autoimmunity

Janet G. M. Markle,[1,2] Daniel N. Frank,[3] Steven Mortin-Toth,[1] Charles E. Robertson,[4] Leah M. Feazel,[3] Ulrike Rolle-Kampczyk,[5] Martin von Bergen,[5,6,7] Kathy D. McCoy,[8] Andrew J. Macpherson,[8] Jayne S. Danska[1,2,9]*

MULTIPLE SCLEROSIS JOURNAL | MSJ

Topical Review

Digesting the emerging role for the gut microbiome in central nervous system demyelination

Jennifer Joscelyn and Lloyd H Kasper

Curr Treat Options Neurol (2015) 17: 18
DOI 10.1007/s11940-015-0344-7

Multiple Sclerosis and Related Disorders (P Villosla

The Gut Microbiome in Multiple Sclerosis

*Daniel W. Mielcarz, PhD**
Lloyd H. Kasper, MD

Annals of NEUROLOGY
An Official Journal of the American Neurological Association and the Child Neurology Society
ANA American Neurological Association

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Brief Communication

Gut microbiome analysis in neuromyelitis optica reveals overabundance of *Clostridium perfringens*

Bruce A. C. Cree MD, PhD, MAS, Collin M. Spencer BS, Michel Varrin-Doyer PhD, Sergio E. Baranzini PhD, Scott S. Zamvil MD, PhD

nature COMMUNICATIONS

ARTICLE

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DOI: 10.1038/ncomms12015 OPEN

Alterations of the human gut microbiome in multiple sclerosis

Sushrut Jangi[1,*], Roopali Gandhi[1,*], Laura M. Cox[1], Ning Li[2], Felipe von Glehn[1], Raymond Yan[1], Bonny Patel[1], Maria Antonietta Mazzola[1], Shirong Liu[1], Bonnie L. Glanz[1], Sandra Cook[1], Stephanie Tankou[1], Fiona Stuart[1], Kirsy Melo[1], Parham Nejad[1], Kathleen Smith[1], Begüm D. Topçuolu[3], James Holden[3], Pia Kivisäkk[1], Tanuja Chitnis[1], Philip L. De Jager[1], Francisco J. Quintana[1], Georg K. Gerber[2], Lynn Bry[2] & Howard L. Weiner[1]

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The latest buzz in innate immunity
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InvivoGen

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ion is current as
16.

TNFR2 Deficiency Acts in Concert with Gut Microbiota To Precipitate Spontaneous Sex-Biased Central Nervous System Demyelinating Autoimmune Disease

Patrick G. Miller, Michael B. Bonn, Craig L. Franklin, Aaron C. Ericsson and Susan C. McKarns

J Immunol 2015; 195:4668-4684; Prepublished online 16 October 2015;
doi: 10.4049/jimmunol.1501664
http://www.jimmunol.org/content/195/10/4668