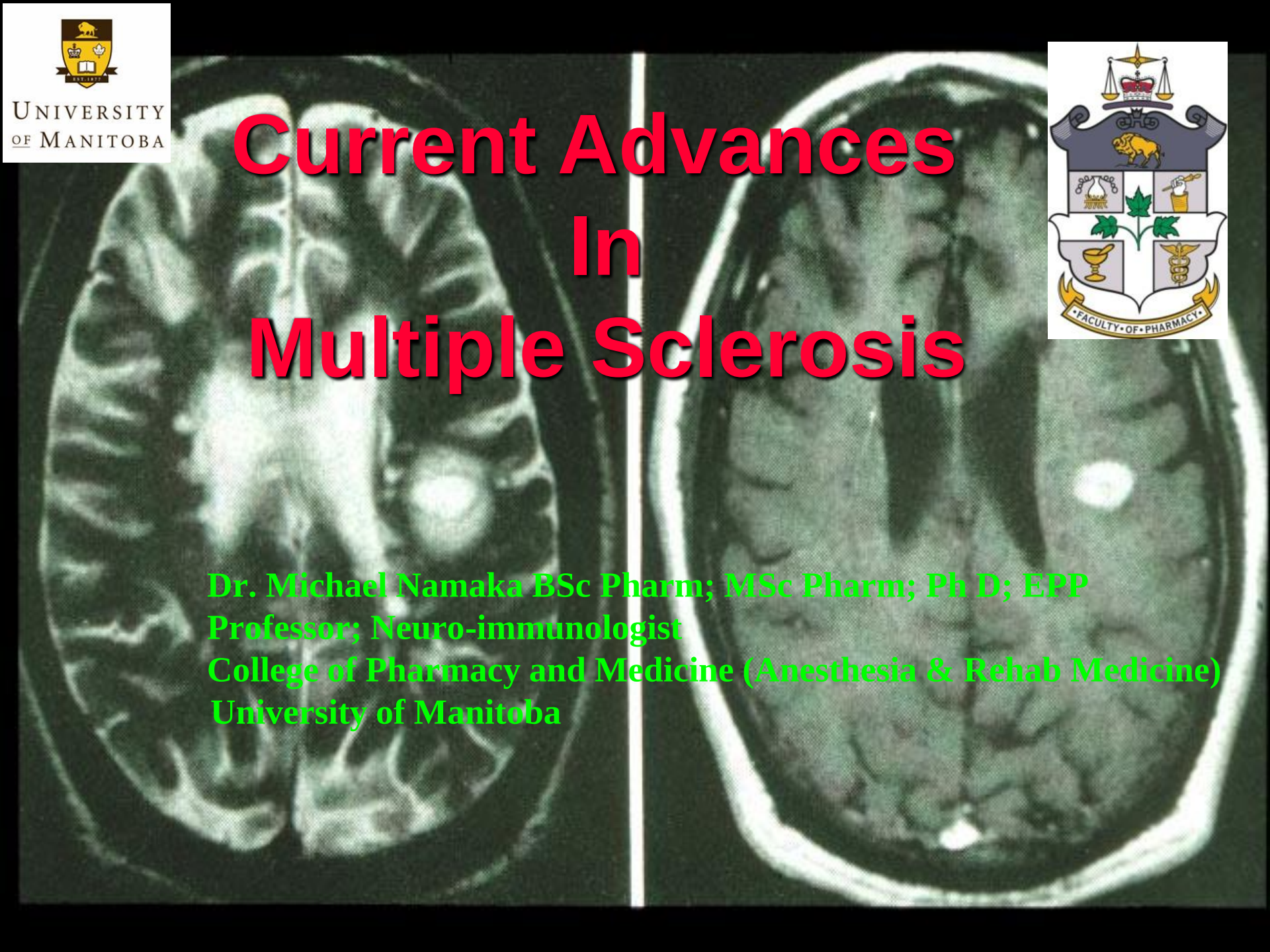


Current Advances In Multiple Sclerosis

Dr. Michael Namaka BSc Pharm; MSc Pharm; Ph D; EPP
Professor; Neuro-immunologist
College of Pharmacy and Medicine (Anesthesia & Rehab Medicine)
University of Manitoba

Educational Objectives

At the end of this section, you will be able to:

- Describe the pathophysiology involved in Multiple Sclerosis (MS).
- Understand the contributing factors associated with MS.
- Understand the diagnostic tests used in the diagnosis of MS.
- Describe the hallmark clinical presentation of MS.
- Identify the classification of the various types of MS.
- Understand the immuno-modulatory treatment of MS.
- Addressing non-conventional treatment approaches to MS
- Recognizing the realistic treatment outcomes.

Canadian Statistics of Multiple Sclerosis

- 1:500 to 1:1000 (2-3 patients diagnosed every day)
- Canadian population: ~31 Million
- 30,000 to 60,000 MS new patients/year
- Costs: 1.6 million per patient
- 2000-2001: 1 Billion per year Canadian

Contributing Factors

- Race (Caucasian)
- Age (25 and 38)
- Sex: male vs female
- Infection (Epstein-Barr, HHV6, Chlamydia pneumoniae etc)
- Injury
- Genetics
- Geography (less 15 yrs of age acquires susceptibility of the new region but >15 will not affect susceptibility)
- Diet/Sunshine

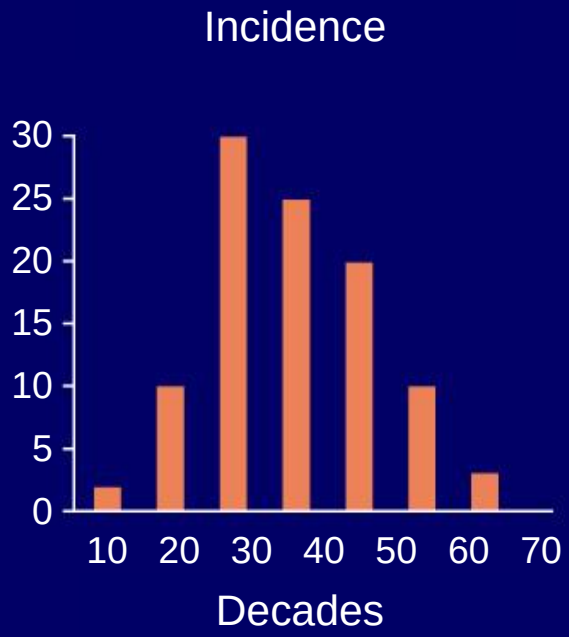
Susceptibility to MS
Sex, Age and Ethnicity

Sex

Sex ratio :
3F/1M

Age of onset

30-40yrs



Ethnicity

High Risk

Northern Europeans, US Caucasians, Canadians

Australians South African whites Southern Europeans

African blacks Orientals

Low Risk

Compston A. Genetic susceptibility to Multiple Sclerosis in Mc Alpine's Multiple Sclerosis. 3rd ed. London: Churchill Livingstone 1998.

Genetic factors

- In a first degree family relative of patient with MS, absolute risk of MS is: **< 5% which equates to 20 to 40 times** increased risk compared to the general population
- In monozygotic twins: concordance rate for MS is higher **(31%)** than in dizygotic twins **(5%). As such since not 100% concordance rates in identical twins, this is proof that genetics alone is not solely responsible for this disease.**
- Presence of **HLA-DR2 allele** increases the risk of MS

Noseworthy J.H. et al. Medical Progress: Multiple Sclerosis N Engl J Med 2000 ; 343 : 938-52.

- MS is **not a hereditary** disease BUT patients may have a **genetic predisposition** for the disease

Theories of MS

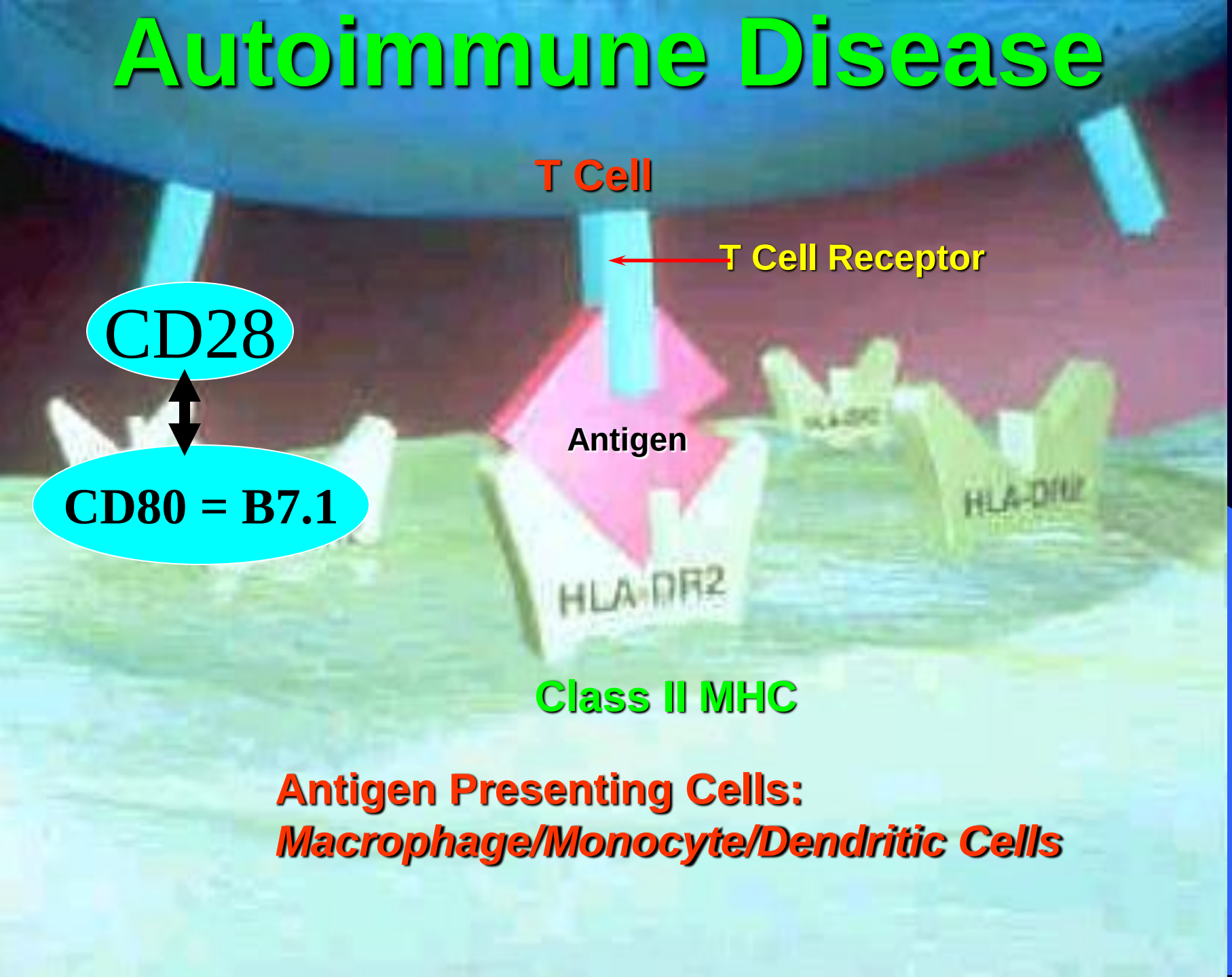
- ✓ **Infectious Theory**

  (Measles, Mumps, Rubella, EBV, HHV-6)

- ✓ **Molecular Mimicry**

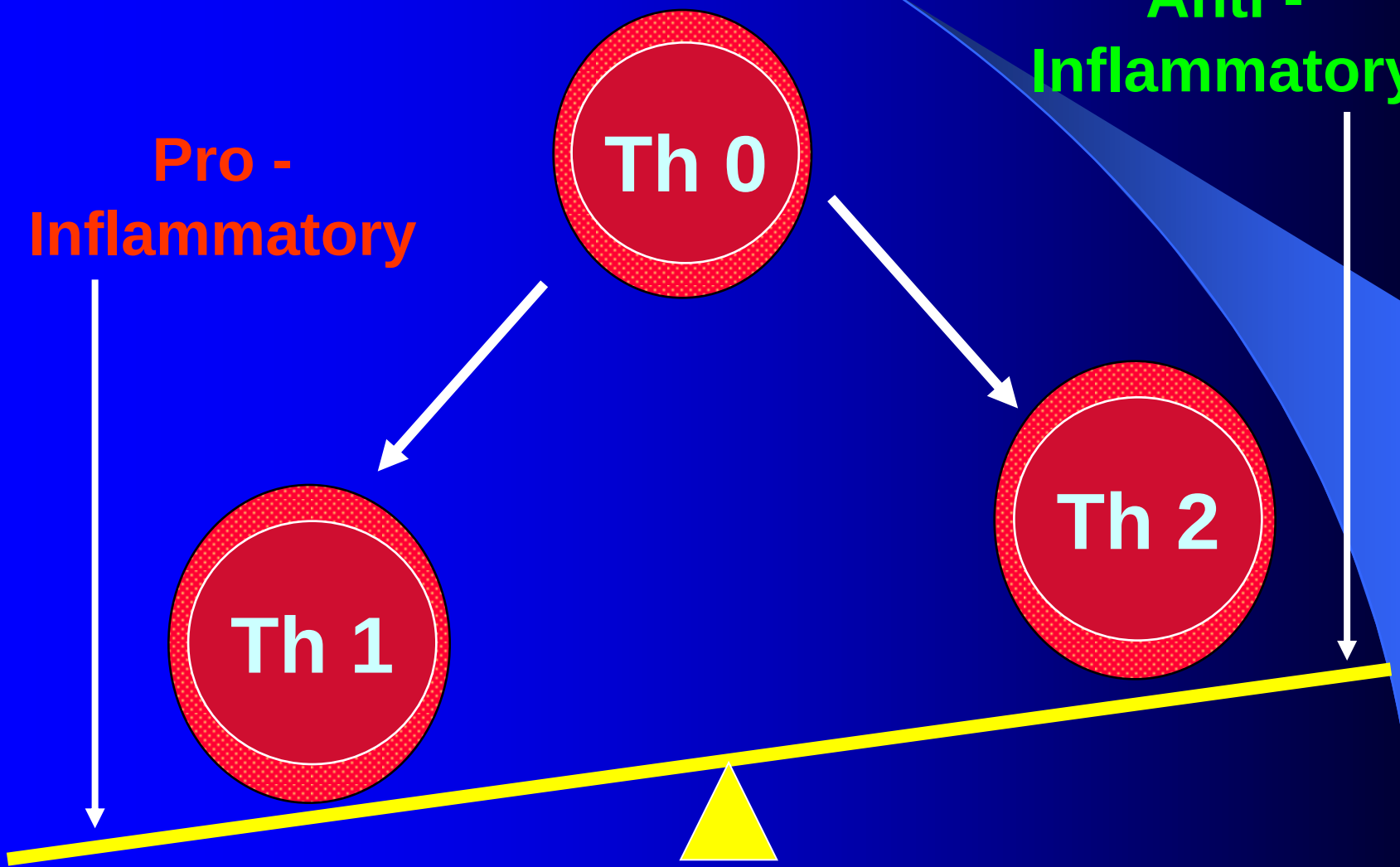
- ✓ **Autoimmune Disease**

Autoimmune Disease



Antigen Presenting Cells:
Macrophage/Monocyte/Dendritic Cells

Imbalance of the Immune System



T-CELL BALANCE

Th1
(Inflammatory)

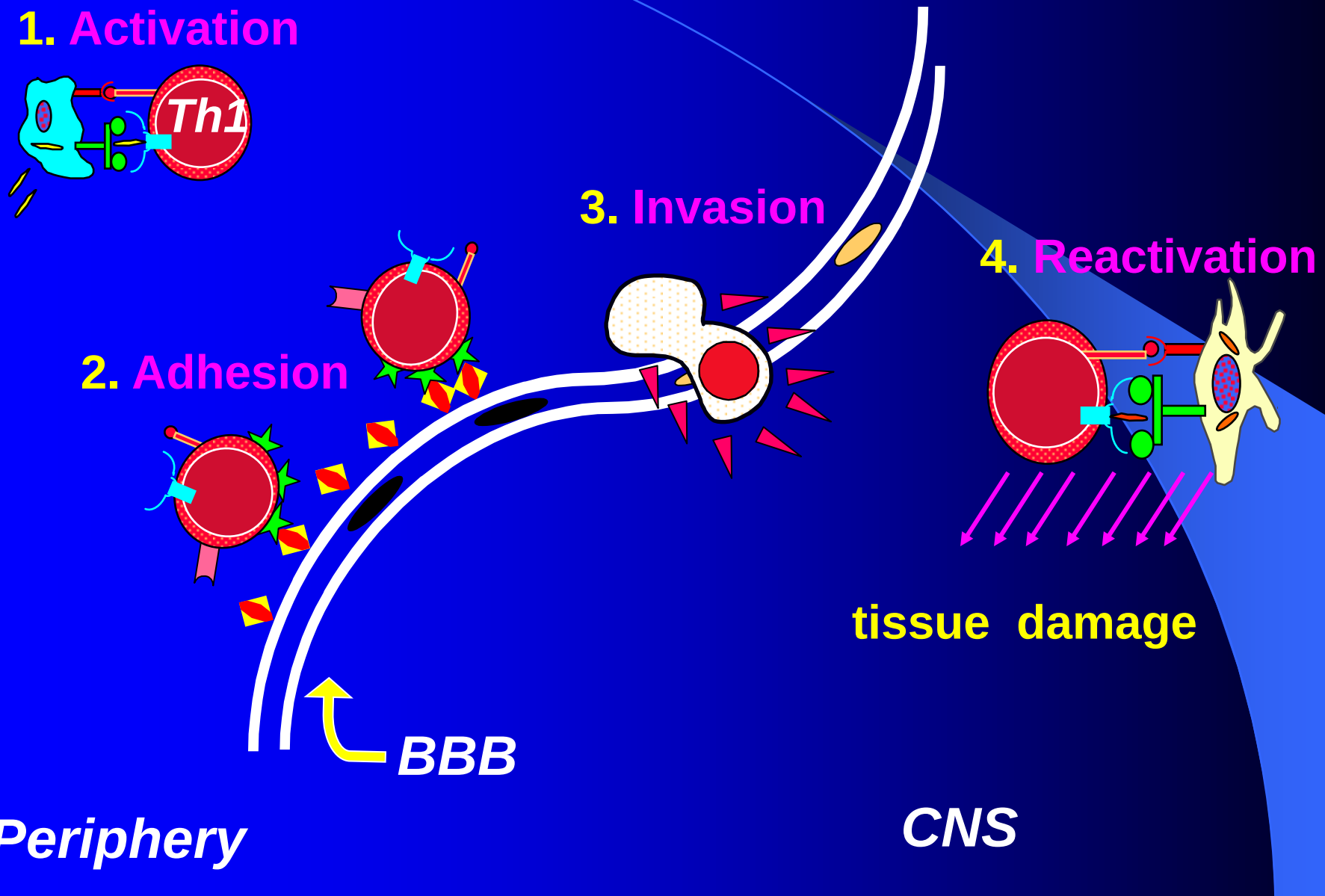
- IL-12
- IL-2
- IL-6
- IFN-γ
- TNF-α

Th2 (Th3)
(Protective)

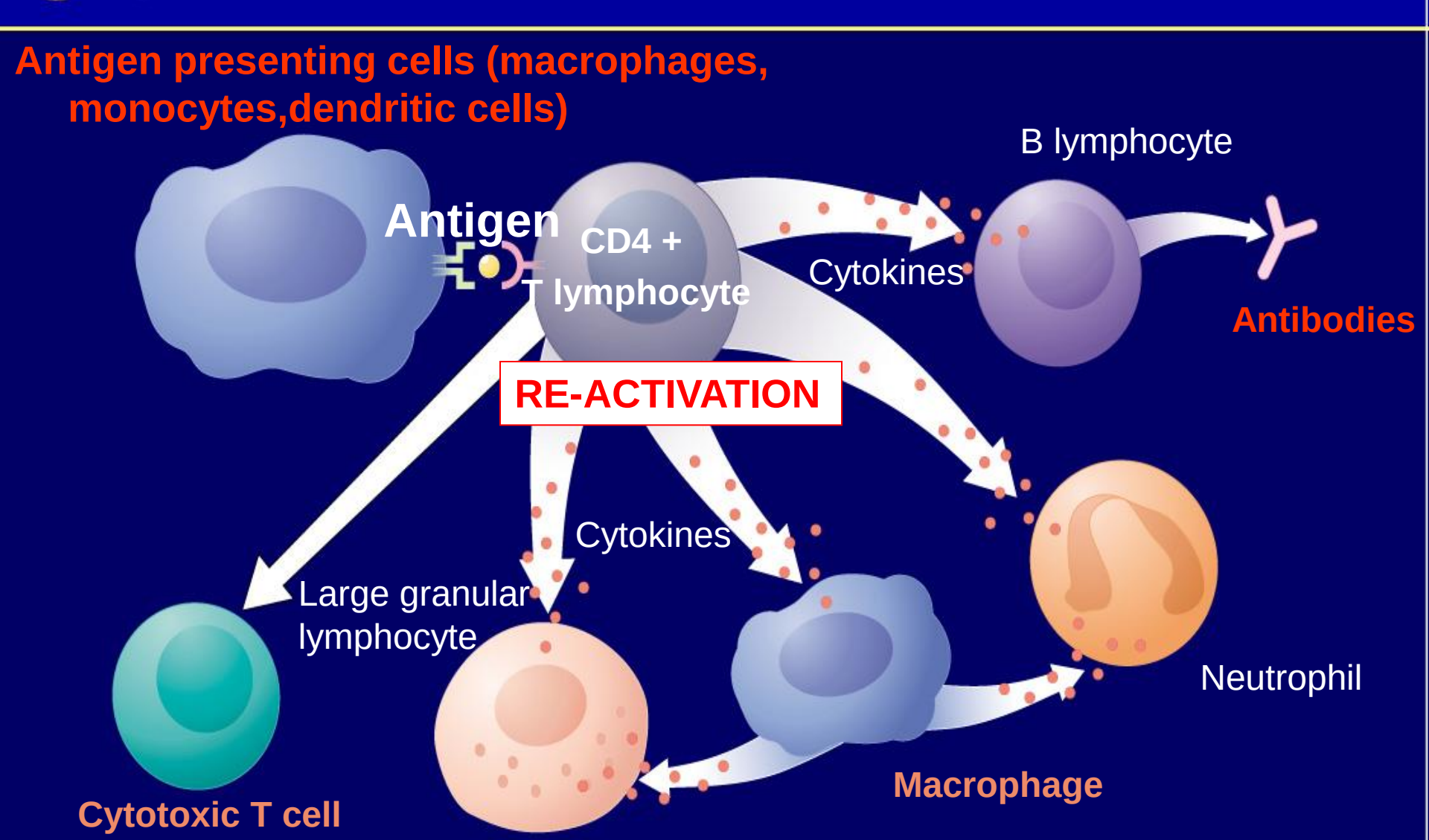
- IL-4
- IL-10
- TGF-β

IMMUNE DEVIATION

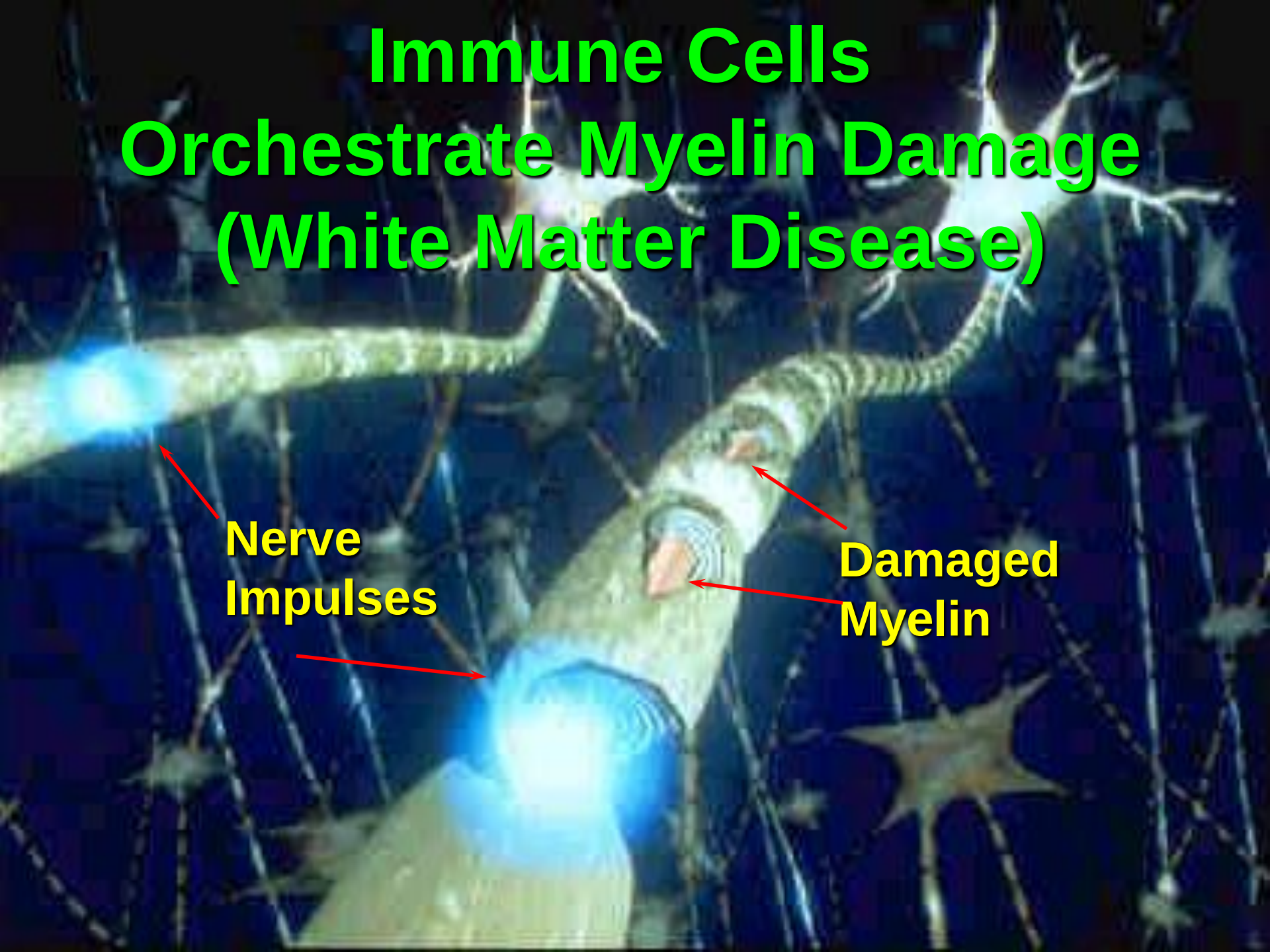
A Model of MS Immunology



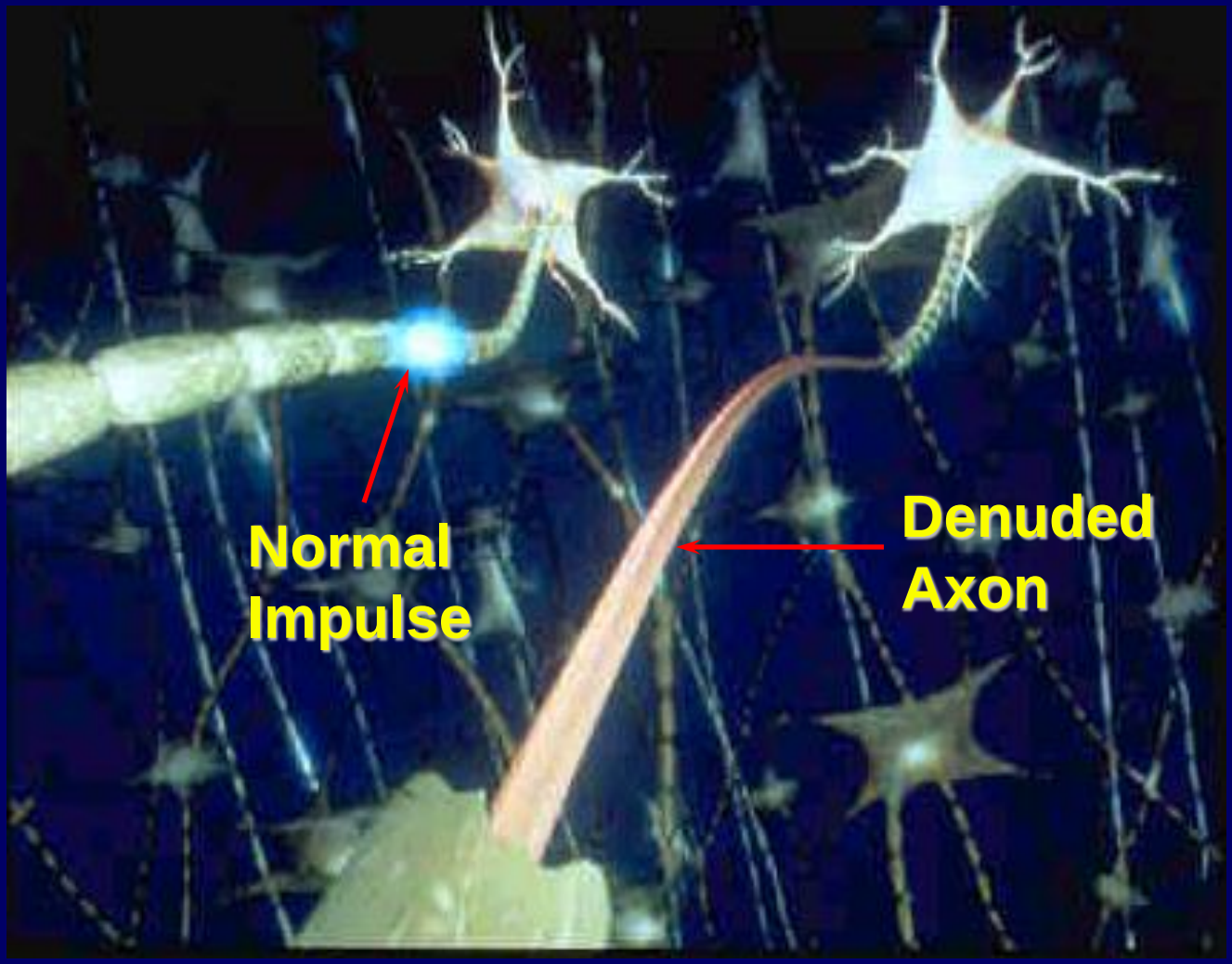
Re-Activation of Immune System



Adapted from Roitt I., Brostoff J., Male D. Introduction to the immune system in Immunology 5th edition . Edts Mosby 1998.


Immune Cells
Orchestrate Myelin Damage
(White Matter Disease)
Nerve
Impulses
Damaged
Myelin

Exposed De-myelinated Axon



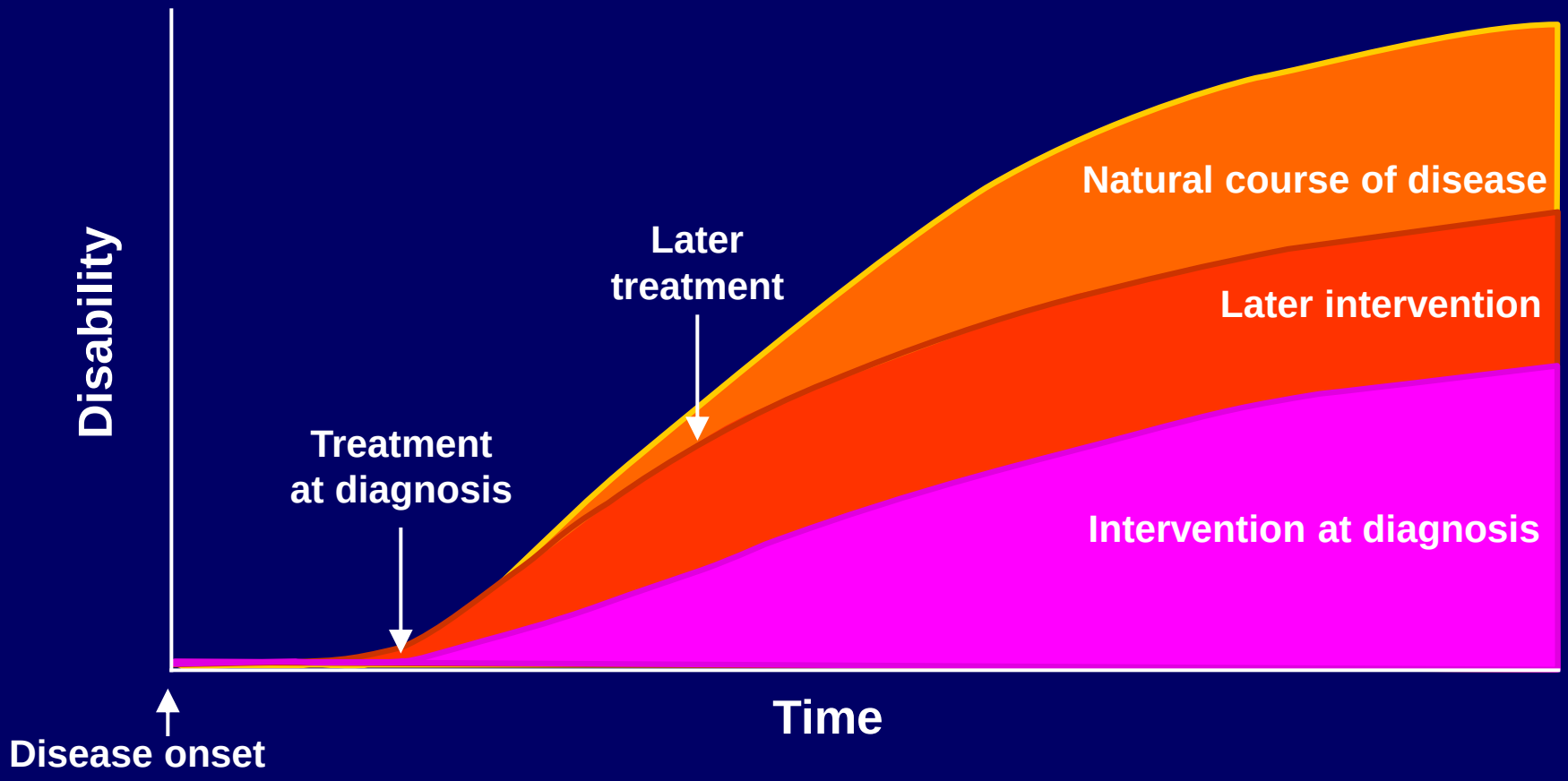
Burden of Disease

- **Physical Disability**
  - Median time to requiring cane/crutch: 15 years[1,2]
  - Median time to wheelchair confinement: 25 years[3]

1. Weinshenker BG, et al. *Brain.* 1989;112:133-146; 2. Confavreux C, et al. *Brain.* 2003;126:770-782; 3. Compston A. *McAlpine's Multiple Sclerosis.* 3rd ed. London: Churchill Livingstone; 1998.

What Are the Current Opinions Regarding Treatment Effects?

A Theoretical Model



Adapted from Trapp et al. *Curr Opin Neurol*. 1999;12:295; Trapp et al. *Neuroscientist*. 1999;5:48; Simon et al. *Neurology*. 1999;53:139.

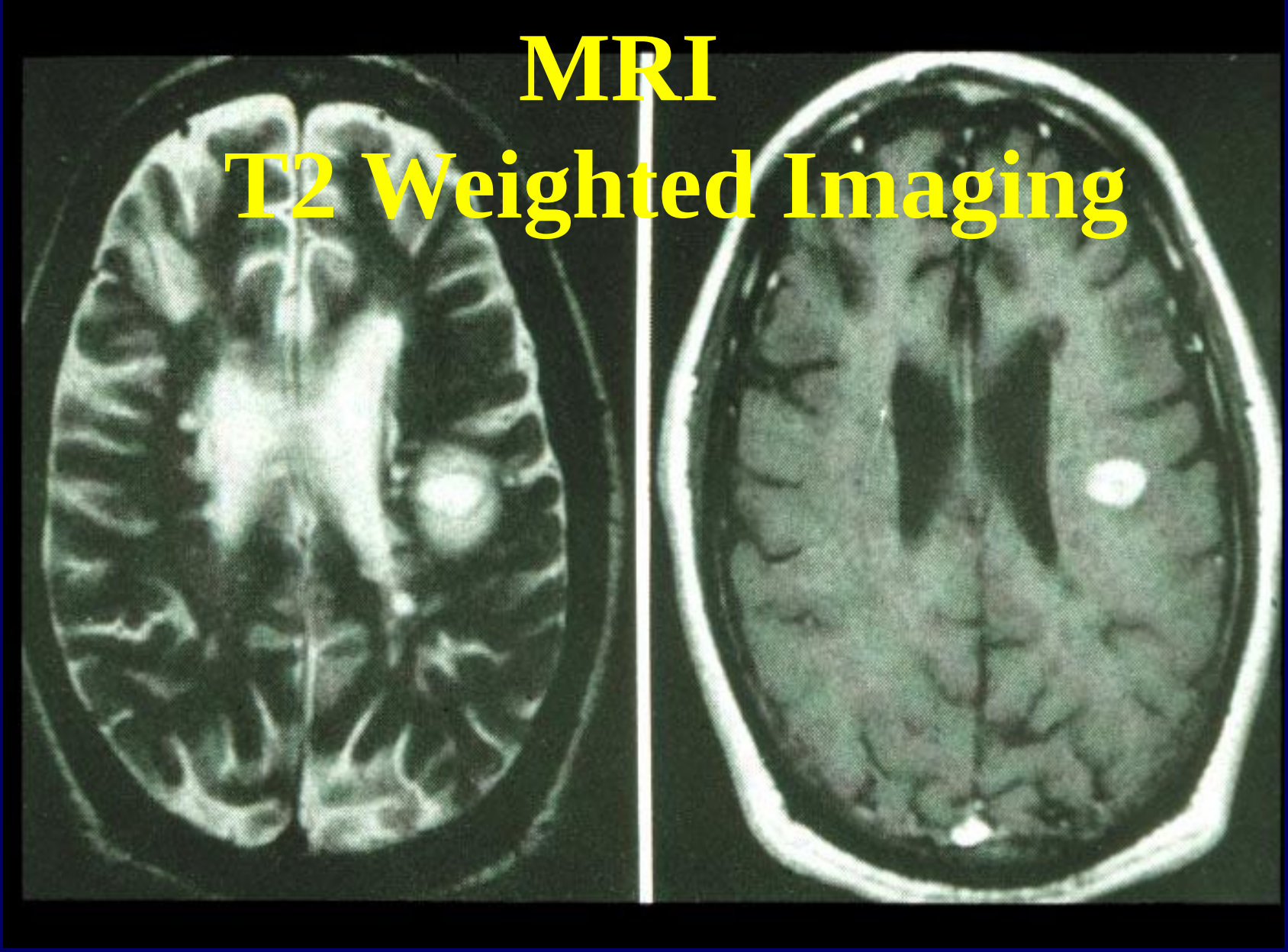
Clinical Diagnostic Tools

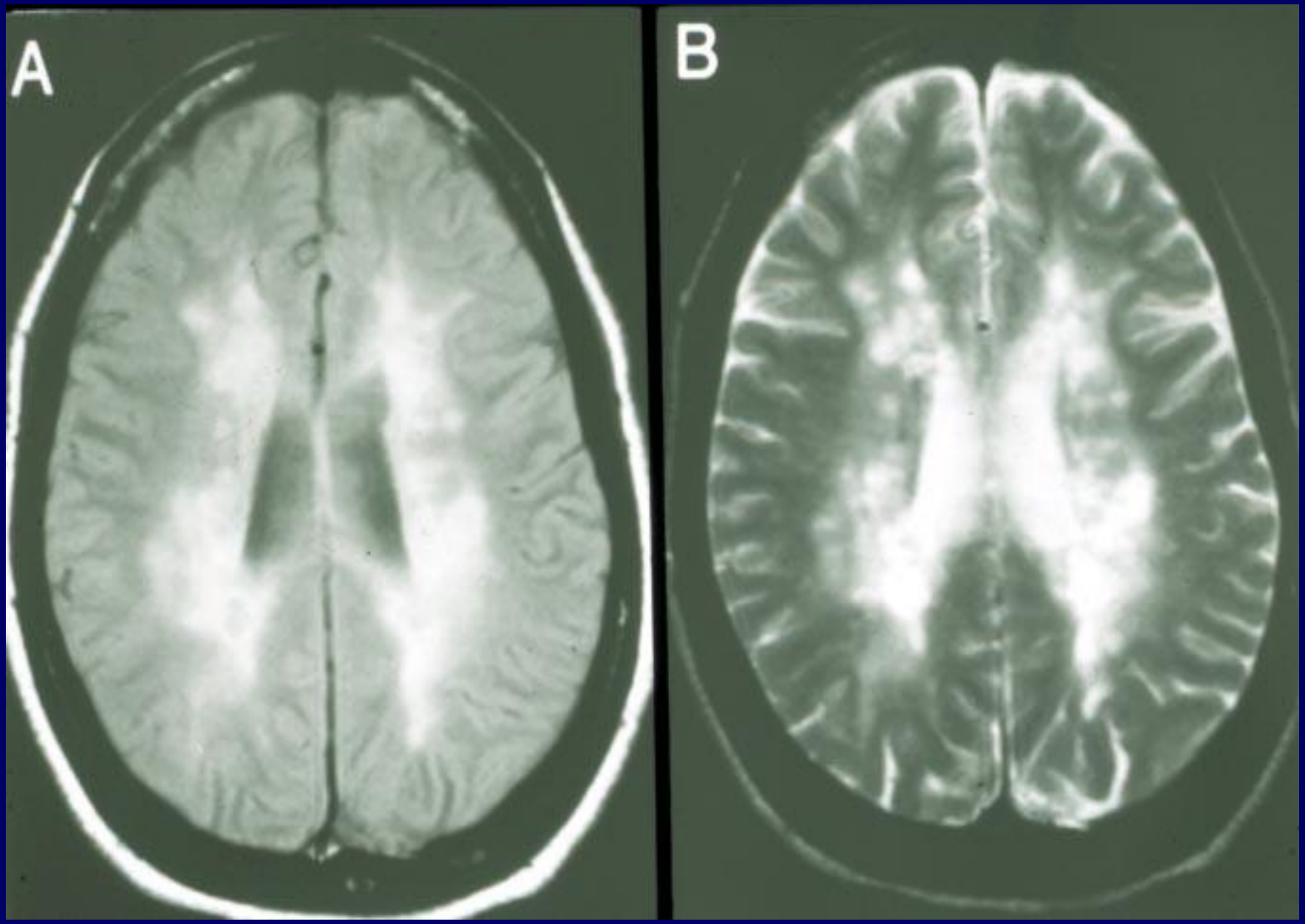
Examination of the Cerebro-spinal Fluid

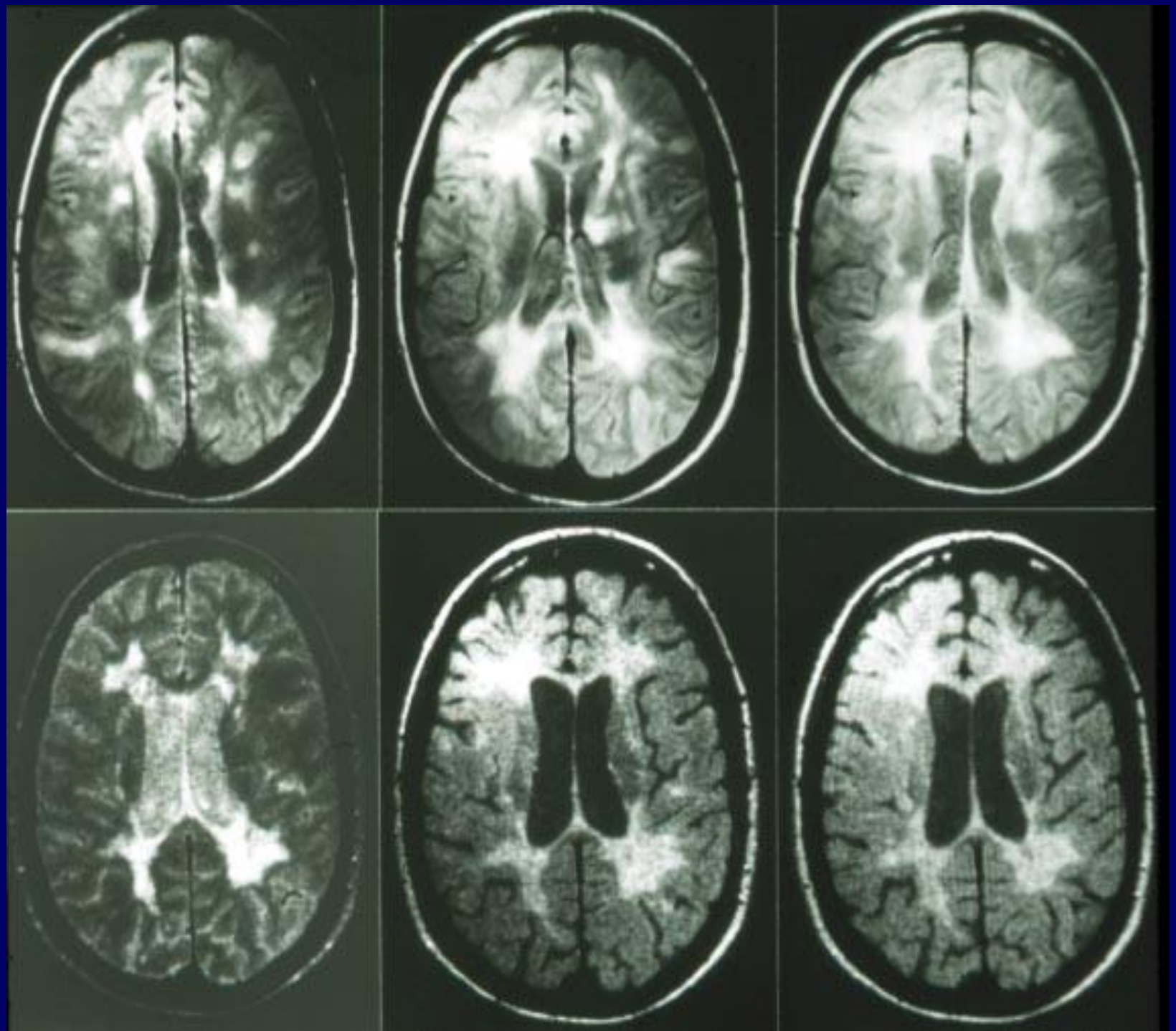
- **Oligoclonal IgG bands**
  [*in > 95% patients with Clinically Definite MS (CDMS)*]
- **Severe Headaches post-CSF Sample**

Mc Donald I. Diagnostic methods and investigation in Multiple Sclerosis in Mc Alpine's Multiple Sclerosis. 3rd ed London: Churchill Livingstone 1998.

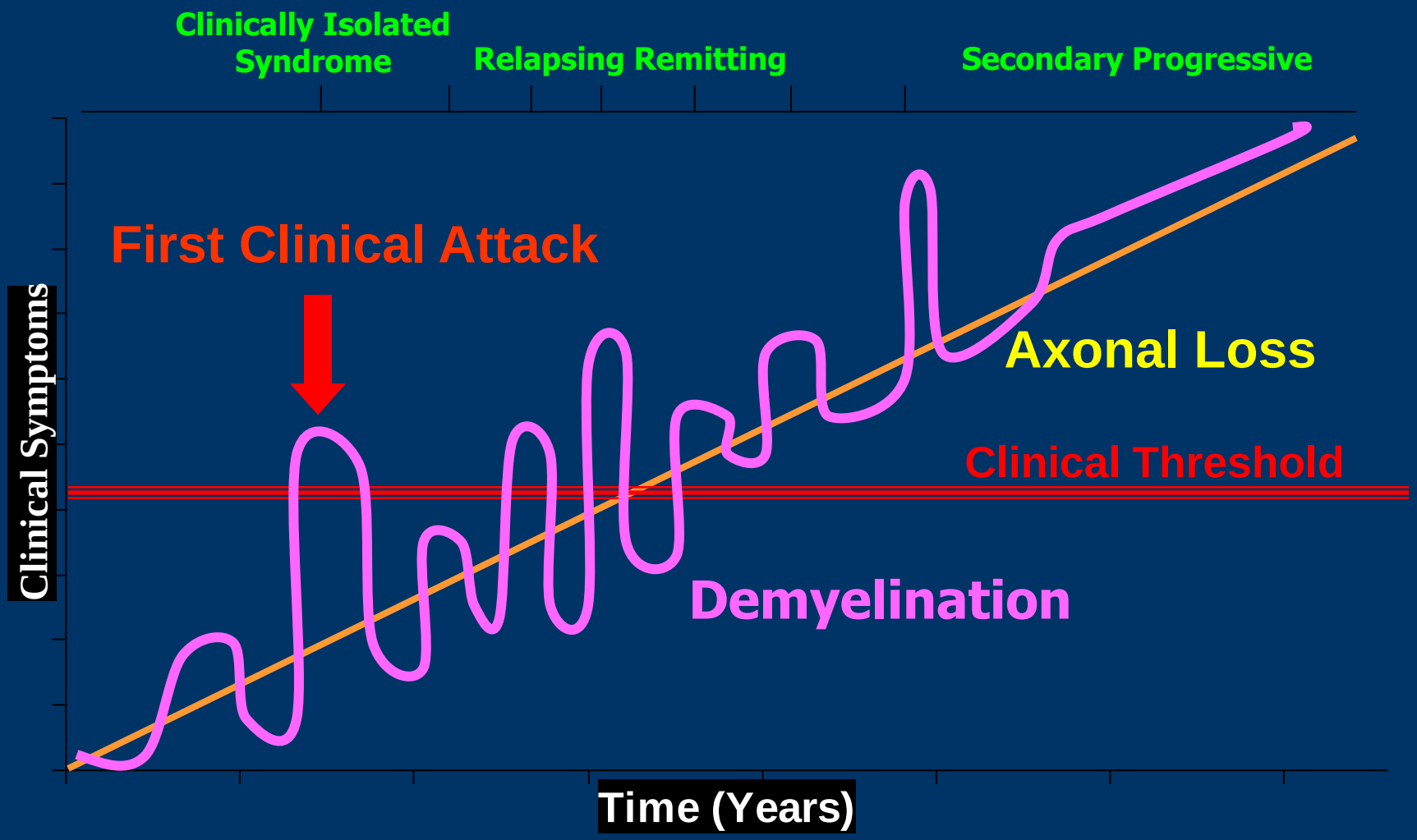
MRI
T2 Weighted Imaging



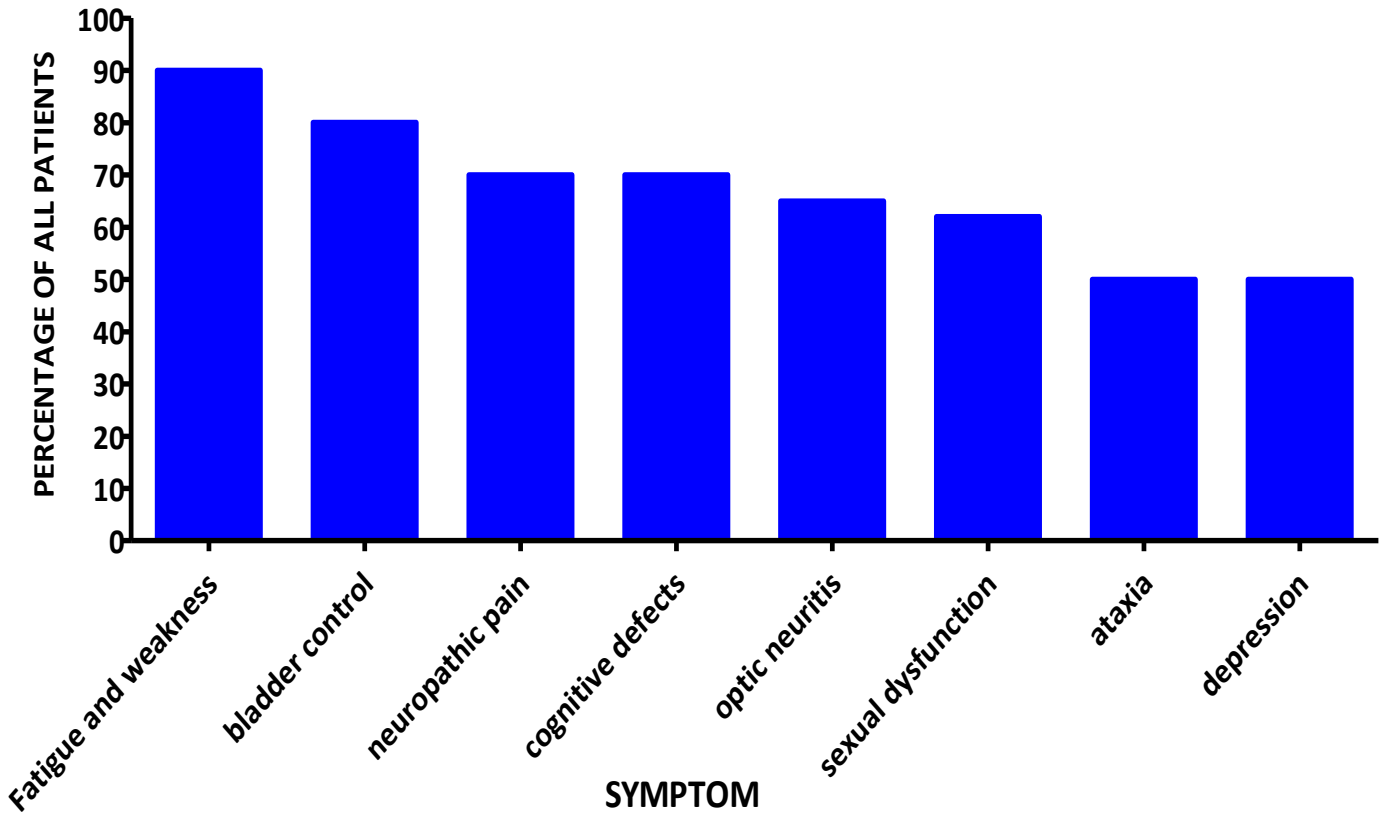

A
B



MS: Pathological vs. Clinical Course of Disease



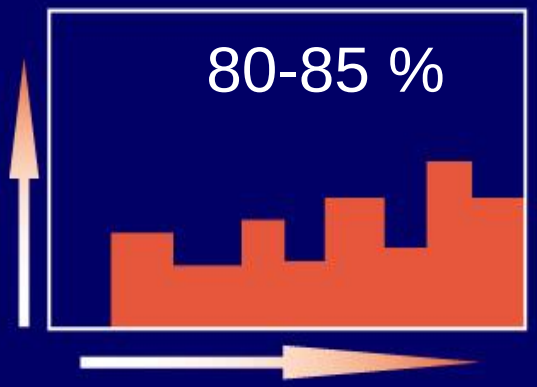
MS-Induced Symptoms



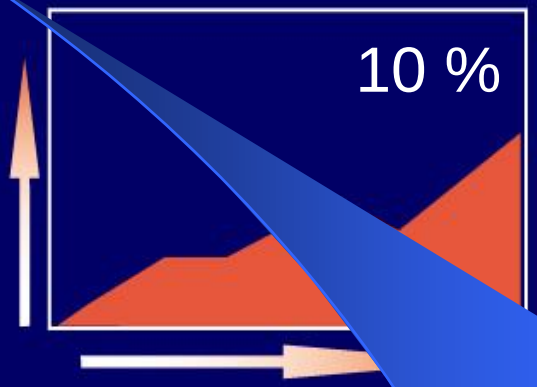
Paty, DW (1997) J Neural Transm Suppl. ***49:211-7*** *Lublin, FD and Reingold, SC (1996) Neurology* ***46:907-11***
Melanson, M, et al. (2009) Mult Scler ***15:1135-1145*** *McDonald, WI, et al. (2001) Ann Neurol* ***50:121-7***
O'Connor, P and Group, CMSW (2002) Neurology ***59:S1-33*** *O'Connor, P (2002) Toronto: Key Porter* ***N/A:N/A***
Namaka, M, et al. (2008) Consult Pharm ***23:886-96***

Various Clinical Types of MS

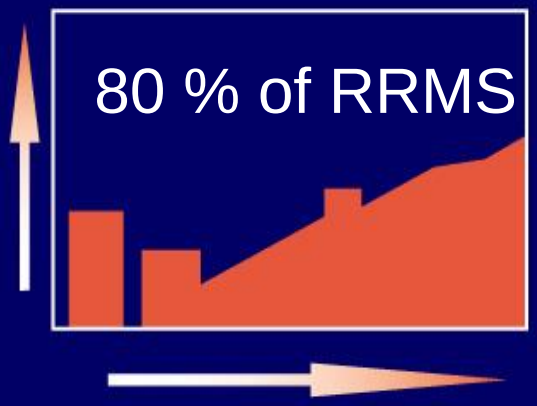
Relapsing-remitting MS



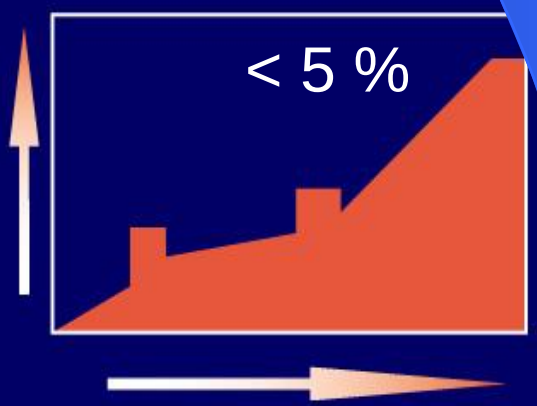
Primary progressive MS



Secondary progressive MS



Progressive relapsing MS



Adapted from Waubant L.E. et al. Pathophysiology of Multiple Scerosis Lesions. Science and Medicine 1997 ; 4 (6): 32-41.
Noseworthy J.H. et al. Medical Progress: Multiple Sclerosis N Engl J Med 2000; 343: 938-52.

Clinical Types of MS

Type of MS[a]	Incidence	Characteristics	Comments
Relapsing-remitting (RRMS)	85-90% of cases at onset	Relapses with stable neurological disability between episodes	DMT should be initiated upon diagnosis
Primary progressive (PPMS)	10-15% of cases at onset	Steadily increasing objectively documented neurologic disability independent on relapses from disease onset	DMT has no effect, except if relapses occur
Secondary progressive (SPMS)	65% of patients with RRMS after 15-20 yrs[19]	Progressive course following an initial relapsing-remitting course	DMT has no effect, except if relapses occur

Clinical Investigations

Investigations are guided by clinical presentation and may be more extensive or limited depending on how clearly the history, physical examination and MRI indicate MS.

- Complete blood count (CBC) with differential
- Liver function tests (ALT, AST)
- Antinuclear antibody (ANA), rheumatoid factor (RF) and C-reactive protein (CRP)
- Thyroid-stimulating hormone (TSH)
- Vitamin D levels
- Vitamin B12 (deficiency can mimic MS symptoms)
- MRI ± gadolinium to identify and quantify lesions in brain and/or spinal cord
- Cerebrospinal fluid exam for oligoclonal banding and visual evoked potential, to support the diagnosis
- Complete neurologic exam

McDonald Clinical Criteria: RRMS-Definitive Diagnosis

- ✓ *Clinical attack(s) +/- MRI must show dissemination in time and space.*
- ✓ *2 clinical attacks where each attack lasted greater than 24 hours.*

  Dissemination in time (at least 30 days apart).
- ✓ *Does not require a + MRI*

MRI Criteria: RRMS Definitive Diagnosis

- ✓ ≥ 1 Gad+ or 9 Peri-ventricular lesions
- ✓ ≥ 1 Infratentorial (contains cerebellum that controls motor functon) lesion
- ✓ ≥ 1 Juxtacortical (spans between grey and white matter) lesion
- ✓ ≥ 1 Spinal Cord lesion

Pt must have 3 out of 4 criteria for MRI to fulfill dissemination in space criteria

OR

MRI criteria depicting dissemination in time + 1 clinical attack.

Clinically Isolated Syndrome (CIS)

- ✓ **1 attack that lasted greater than 24 hours EVEN with a +/- ve MRI that doesn't fulfill McDonald criteria in regard to dissemination in time and/or space**

- ✓ **NO Definitive Diagnosis of MS**

RRMS: Manitoba/Alberta

IMA DRUG COVERAGE

(Interferon- Beta 1a & 1b and glatiramer acetate)

- ✓ **2 attacks where each attack lasts greater than 24 hours and is separated in space by at least 30 days with a positive MRI that meets McDonald criteria within the past 2 years.**

SECTION II: Immunomodulatory Treatment of RRMS

Immunomodulatory (IMA) Therapy for RRMS (20K/YR)

- Interferon beta 1a 30 µg IM once weekly
- Interferon beta 1b 8 M.U. sc EOD
- Interferon beta 1a 44µg sc tiw
- Glatiramer acetate 20 mg sc qd

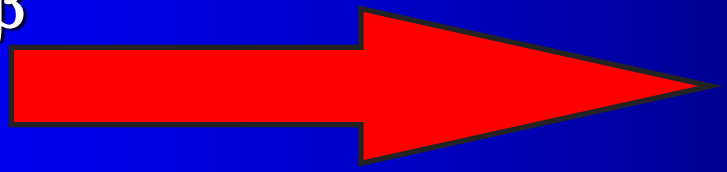
T-CELL BALANCE SHIFT

Th1
(Inflammatory)

- IL-12
- IL-2
- IL-6
- IFN-γ
- TNF-β

Th2 (Th3)
(Protective)

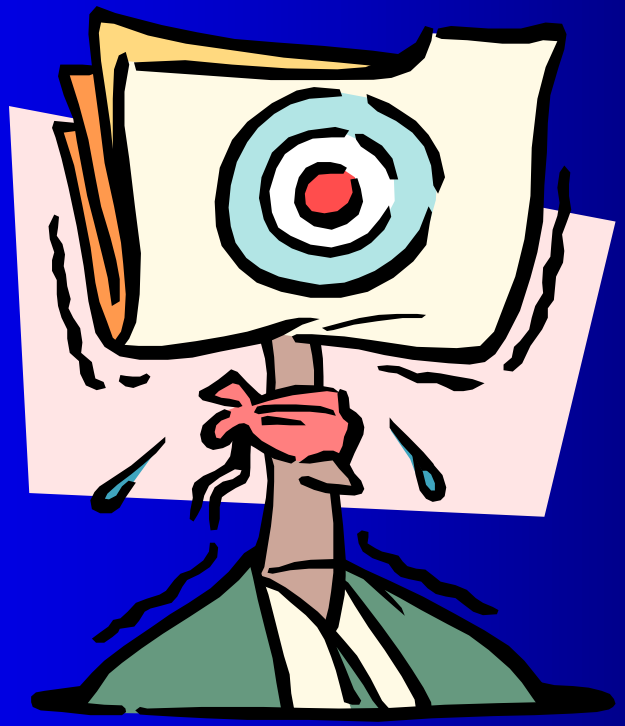
- IL-4
- IL-10
- TGF-β



IMMUNOMODULATORY AGENTS SUPPRESS THE IMMUNE SYSTEM INFLAMMATORY RESPONSE

TREATMENT SELECTION

?



Interferon beta 1a

- ✓ 30mcg intramuscular (IM) once weekly
- ✓ No dosage titration
- ✓ Flu-like symptoms (muscle aches, headache, malaise, fever and chills)
- ✓ LFT's (ALT,AST >3 x ULN)
- ✓ Injection site reactions
- ✓ Lowest incidence of neutralizing antibodies (NABs) …..2 - 5%
- ✓ ~30% reduction in annualized relapse rate (ARR)-Biogen

Plegridy™: Long Acting Avonex

- ✓ Peginterferon beta-1a derived from interferon beta-1a (125mcg/0.5 ml)
- ✓ Dosed once every 2 weeks *via* subcutaneous injection for RRMS
- ✓ Pegylation process is designed to extend the protein's half-life and prolong its exposure in the body
- ✓ Results of Phase 3 trial announced March 21st, 2013 – ARR 36% -- Approval in EU (July 2014) and USA (Aug 2014) – Biogen
- ✓ AE's: Joint pain; muscle pain; injection site itching; injection site pain

Interferon beta 1a

- ✓ 44mcg SC TIW
- ✓ dosage titration over 3-6 weeks
- ✓ Flu-like symptoms
- ✓ Depression
- ✓ LFT's (ALT,AST >3 x ULN)
- ✓ Injection site reactions
- ✓ Alopecia
- ✓ NAB's ~20-30%
- ✓ ~30% reduction in relapse rate - Serono

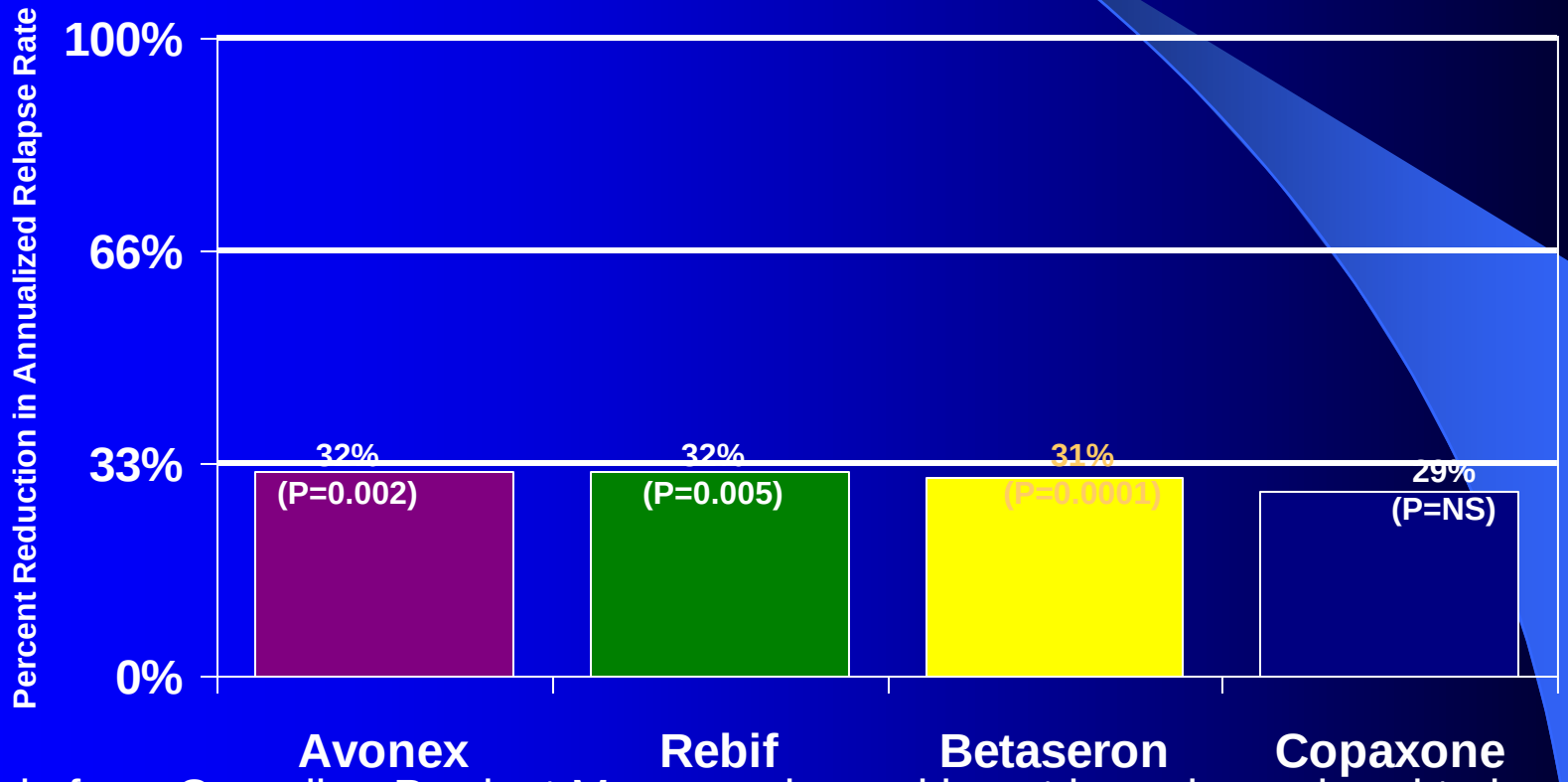
Interferon beta 1b

- ✓ **8 MIU SC EOD**
- ✓ **dosage titration over 2-3 weeks**
- ✓ **Flu-like symptoms**
- ✓ **Depression**
- ✓ **LFT's (ALT,AST > 3 x ULN)**
- ✓ **Injection site reactions**
- ✓ **Indicated for RRMS and SPMS still experiencing relapses**
- ✓ **NAB's ~20-30 %**
- ✓ **~30% reduction in ARR -** Bayer Schering & Novartis

Glatiramer Acetate

- ✓ synthetic polypeptides containing 4 naturally occuring aminio acids: L-glutamic acid; L-alanine; L-tyrosine; L-Lysine
- ✓ 20 mg SC OD
- ✓ No dosage titration required
- ✓ Injection site reactions
- ✓ ~10% of patients experience a reversible pseudo-heart attack (chest tightness, SOB, palpitations, sweating)
- ✓ <30% ARR – slightly less ARR than interferon products
- ✓ NAB's not present

Current Unmet Need for Efficacy



Data is from Canadian Product Monographs and is not based on a head to head trial

Avonex is a registered trademark of Biogen Idec MA. Inc.
Betaseron is a registered trademark of Berlex Canada Inc.
Rebif is a registered trademark of Serono Canada In.
Copaxone is a registered trademark of Teva Neuroscience

Original IMA Treatment Goals & Limitations

- ✓ Treatments are not a cure
- ✓ At best, they slow progression of disease (~30% ARR)
- ✓ Decrease the number, severity and duration of relapses
- ✓ Increase quality of life
- ✓ NAB's vs Clinical Efficacy

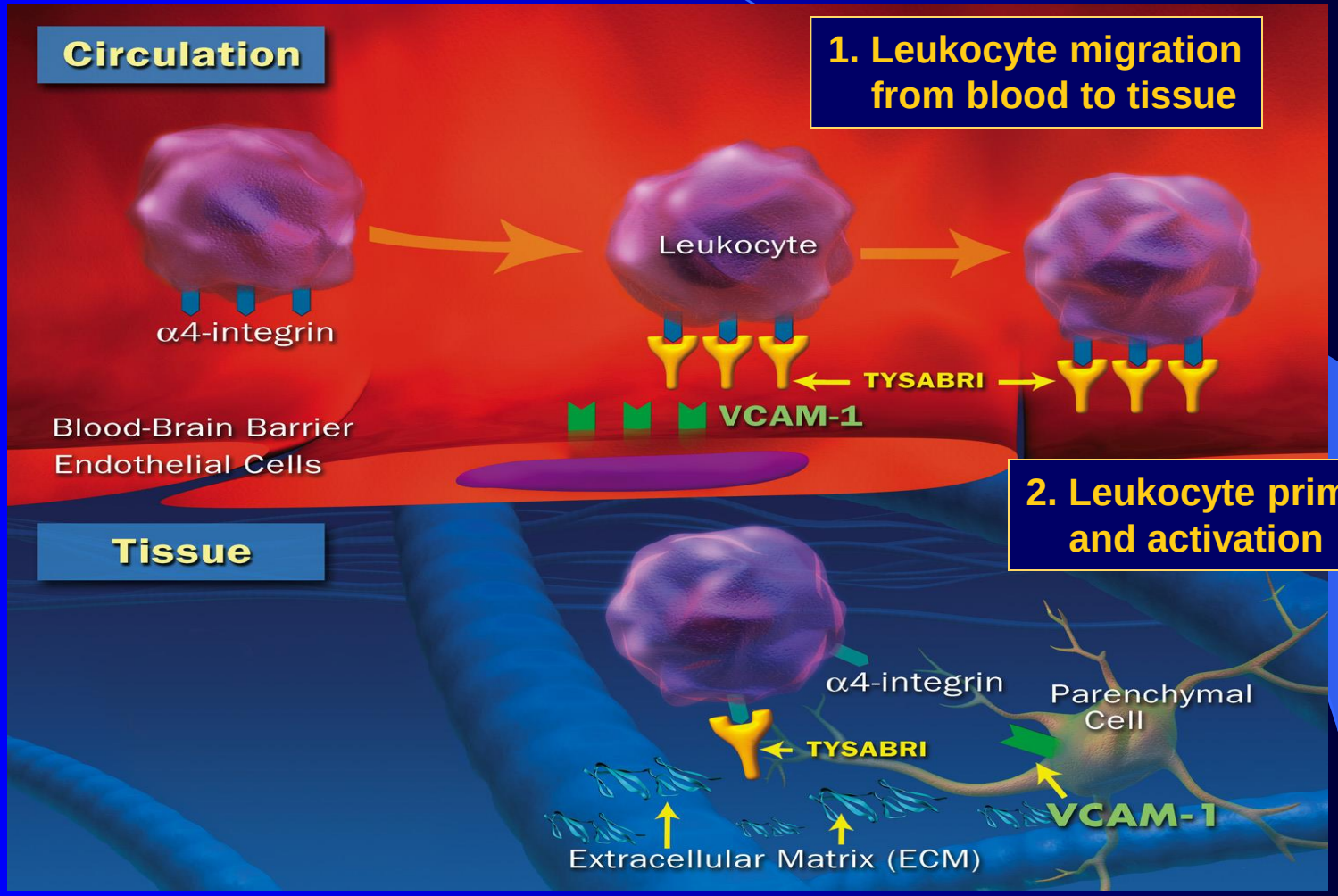
New Advances in Immunomodulatory Therapy 30-40 K/YR

Next Generation Treatments: Natalizumab

✓Natalizumab is a recombinant humanized monoclonal antibody selective for the α4β1 subunit of human integrin, blocking its ability to interact with its receptor, Vascular Cell Adhesion Molecule (VCAM-1).

✓It is administered by IV infusion, 300 mg once every 4 weeks. In the phase I and II trials, natalizumab was dosed by weight, then moved to a fixed dose of 300mg in the Phase III trials. - Biogen

Proposed Mechanism of Action



VCAM-1=vascular cell adhesion molecule-1.

Cannella B, Raine CS. *Ann Neurol.* 1995;37:424-435; 2. TYSABRI® (natalizumab) US Prescribing Information, 2004; 3. Yednock TA et al. *Nature*. 1992;356:63-66.

Indications

- ***Natalizumab is indicated as monotherapy*** (i.e. single disease-modifying agent) for the treatment of patients with RRMS:
  - to reduce the frequency of clinical exacerbations,
  - to decrease the number and volume of active brain lesions identified on magnetic resonance imaging (MRI) scans and
  - to delay the progression of physical disability.
- Generally recommended as 2nd, 3rd or 4th line treatment for RRMS patients who have had an inadequate response to, or are unable to tolerate, other therapies.

Natalizumab: Clinical Trials Summary

- TYSABRI exposure in clinical trial programs
  - 4,611 patient-years in MS and Crohn's disease trials
  - 2,910 patient-years in MS trials
- ***Three Key RRMS clinical trials***
  - 942 patients enrolled in the ***AFFIRM monotherapy*** trial
  - 1,171 patients enrolled in the ***SENTINEL add-on therapy trial (TYSABRI + AVONEX)***
  - ***TYSABRI 300 mg or placebo intravenously (IV)*** every 4 weeks
  - Duration of both phase 3 studies was 116 weeks

AFFIRM:Summary of Clinical Efficacy

- Natalizumab has significant effects on clinical end points
  - Impact on relapses
    - **68% relative reduction in annualized relapse rate (ARR)**
    - Impact seen early and maintained over time
  - Impact on disability progression
    - 42% reduction in risk of sustained change in EDSS (12 weeks)
    - 54% reduction in risk of sustained change in EDSS (24 weeks)
  - Significant slowing of brain atrophy in the second year
  - Significant improvement in cognitive function (PASAT-3)

Polman CH, et al. *N Engl J Med*. 2006;354:899-910. TYSABRI Product Monograph, 2006.

Summary of Efficacy on MRI Measures

- Natalizumab significantly reduces inflammation and lesion load
  - Significant reductions in number of:
    - Gd+ lesions: **92% ↓**
    - T2-hyperintense lesions: 83% ↓
    - T1-hypointense lesions: 76% ↓
  - Significant reduction in burden of disease as measured by T2 and T1 lesion volume
  - Significantly fewer lesions in the TYSABRI group compared to the placebo group

Polman CH, et al. *N Engl J Med*. 2006;354:899-910; TYSABRI Product Monograph, 2006.

Immunogenicity

- In the monotherapy trial, **6% of patients** developed persistent neutralizing antibodies (NABs) to Natalizumab
  - This occurred within the first 6 months in the majority of patients
  - Usually occurred in the presence of infusion reactions

- Persistent neutralizing antibody positivity was associated with:
  - Reduced efficacy
  - Increased incidence of infusion-related reactions and hypersensitivity reactions

Polman CH, et al. *N Engl J Med*. 2006;354:899-910; Rudick RA, et al. *N Engl J Med*. 2006;354:911-923.

Pre-Market Safety Surveillance

Common AEs ≥5% in Placebo or Natalizumab Groups

AE, n (%)	Placebo (n=312)	Natalizumab (n=627)
Patients with Any Event	298 (95.5)	583 (93.0)
Headache	89 (28.5)	201 (32.1)
Nasopharyngitis	97 (31.1)	182 (29.0)
MS Relapse	162 (51.9)	173 (27.6)
Fatigue	55 (17.6)	147 (23.4)
Back Pain	55 (17.6)	107 (17.1)
Influenza	49 (15.7)	99 (15.8)
Arthralgia	34 (10.9)	97 (15.5)
Pain in Extremity	39 (12.5)	84 (13.4)
Depression	38 (12.2)	83 (13.2)
Nausea	38 (12.2)	81 (12.9)
Paraesthesia	42 (13.5)	78 (12.4)
Insomnia	33 (10.6)	76 (12.1)
Urinary tract infection	32 (10.3)	75 (12.0)

Indicates ≥2.0% higher in natalizumab group.

Special Safety Considerations Post-Market Surveillance

- Progressive Multifocal Leukoencephalopathy (PML)
- Sentinel Study (Avonex + Tysabri) D/C

PML cont'd

- ✓ Attacks oligodendrocytes of CNS white matter, leading to myelin loss in cerebral hemispheres, cerebellum (motor), or brain stem (breathing), causing severe disability or death
- ✓ 3 cases identified (MS n=2 or Crohn's n=1)
- ✓ MS cases Avonex + Tysabri
- ✓ **Voluntary withdrawal Feb 2005**
- ✓ **Reintroduced to Market Jan/Feb 2007**

Overview of PML

- PML is an acquired demyelinating disease of the central nervous system (CNS)
- Past Estimated Risk: 1:1000 – 2006/2007
- Present Estimated Risk 5.05:1000 as of Feb 2013 *(JAMA Neurology Aug 5th, 2013)*
- Caused by JC virus, a human polyomavirus
  - Lytic infection of oligodendrocytes
- Primarily affects immunocompromised individuals

Padgett BL, Walker DL. In *Polyomaviruses and Human Neurological Diseases.* 1983;107-117; Sabath BF, Major GO. *J Infect Dis.* 2002;186(Suppl 2):S180-186.

Natalizumab Coverage in MB

- Confirmed diagnosis of RRMS. Not indicated for SPMS or PPMS
- >18 years of age
- EDSS < or = 5
- Failed treatment with adequate trial (6 months or longer) of both classes of IMA's (interferon beta and glatiramir acetate) or contraindications/intolerance to their treatment

New Oral MS Therapy

Fingolimod is a sphingosine-1-phosphate receptor agonist that blocks the egress of activated, presumably autoimmune lymphocytes into the circulating bloodstream from lymphoid tissues- Novartis

Fingolimod: Dosage and Administration

- One 0.5 mg capsule taken orally once daily, with or without food
- No dose adjustments necessary based on gender or ethnicity or in patients with mild to moderate hepatic impairment
- Should be used with caution in patients with:
  - ✧ Severe renal impairment
  - ✧ Mild to moderate hepatic impairment
  - ✧ Age ≥65 years
  - ✧ Diabetes

Novartis Pharmaceuticals Canada Inc. *Gilenya (Fingolimod) Product Monograph.* March 21, 2011.

FREEDOMS
FTY720 Research Evaluating Effects of Daily Oral therapy in Multiple Sclerosis

The NEW ENGLAND JOURNAL of MEDICINE

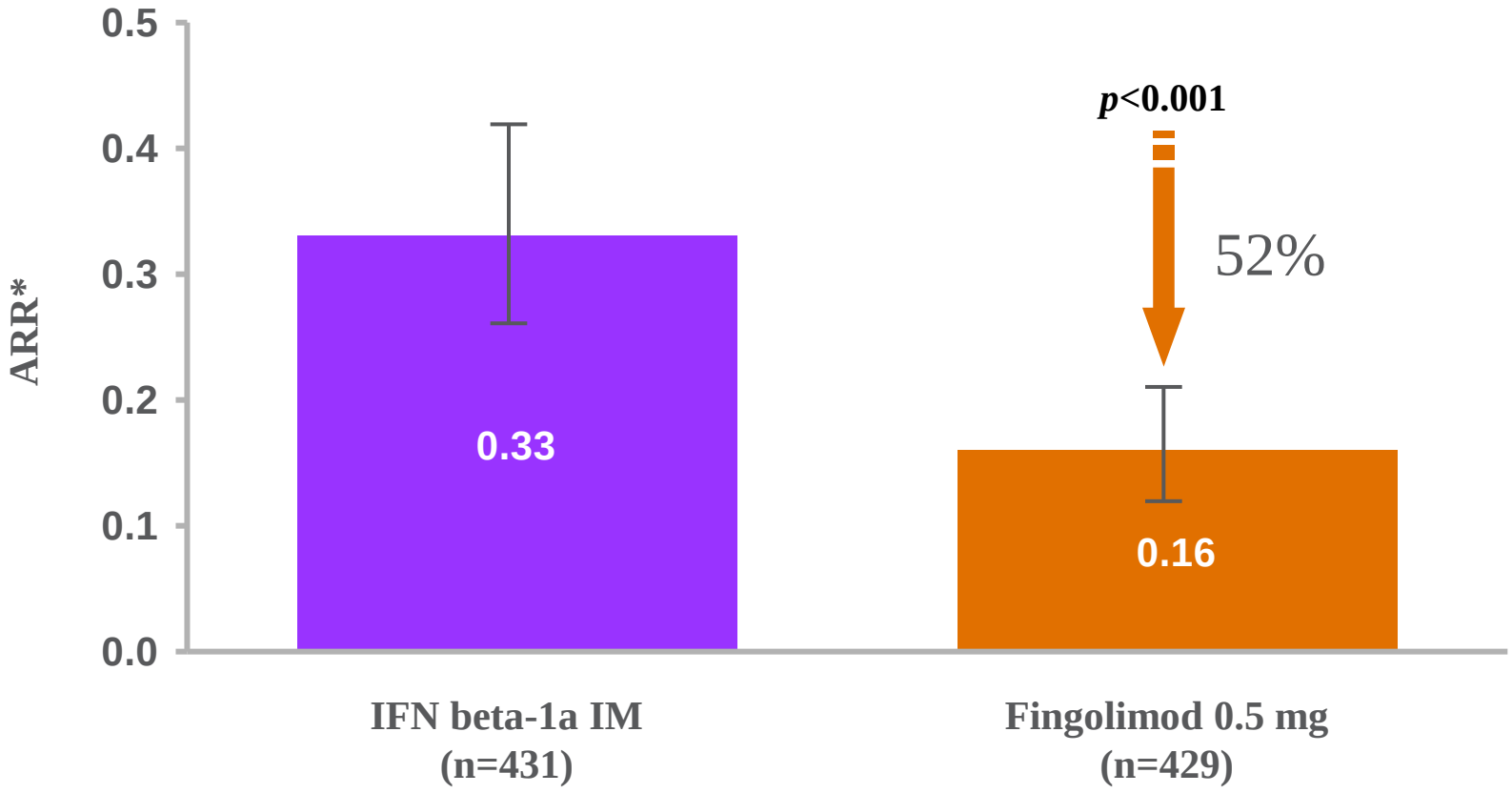
ESTABLISHED IN 1812 FEBRUARY 4, 2010 VOL. 362 NO. 5

A Placebo-Controlled Trial of Oral Fingolimod in Relapsing Multiple Sclerosis

Ludwig Kappos, M.D., Ernst-Wilhelm Radue, M.D., Paul O'Connor, M.D., Chris Polman, M.D., Reinhard Hohlfeld, M.D., Peter Calabresi, M.D., Krzysztof Selmaj, M.D., Catherine Agoropoulou, Ph.D., Malgorzata Leyk, Ph.D., Lixin Zhang-Auberson, M.D., Ph.D., and Pascale Burtin, M.D., Ph.D., for the FREEDOMS Study Group*

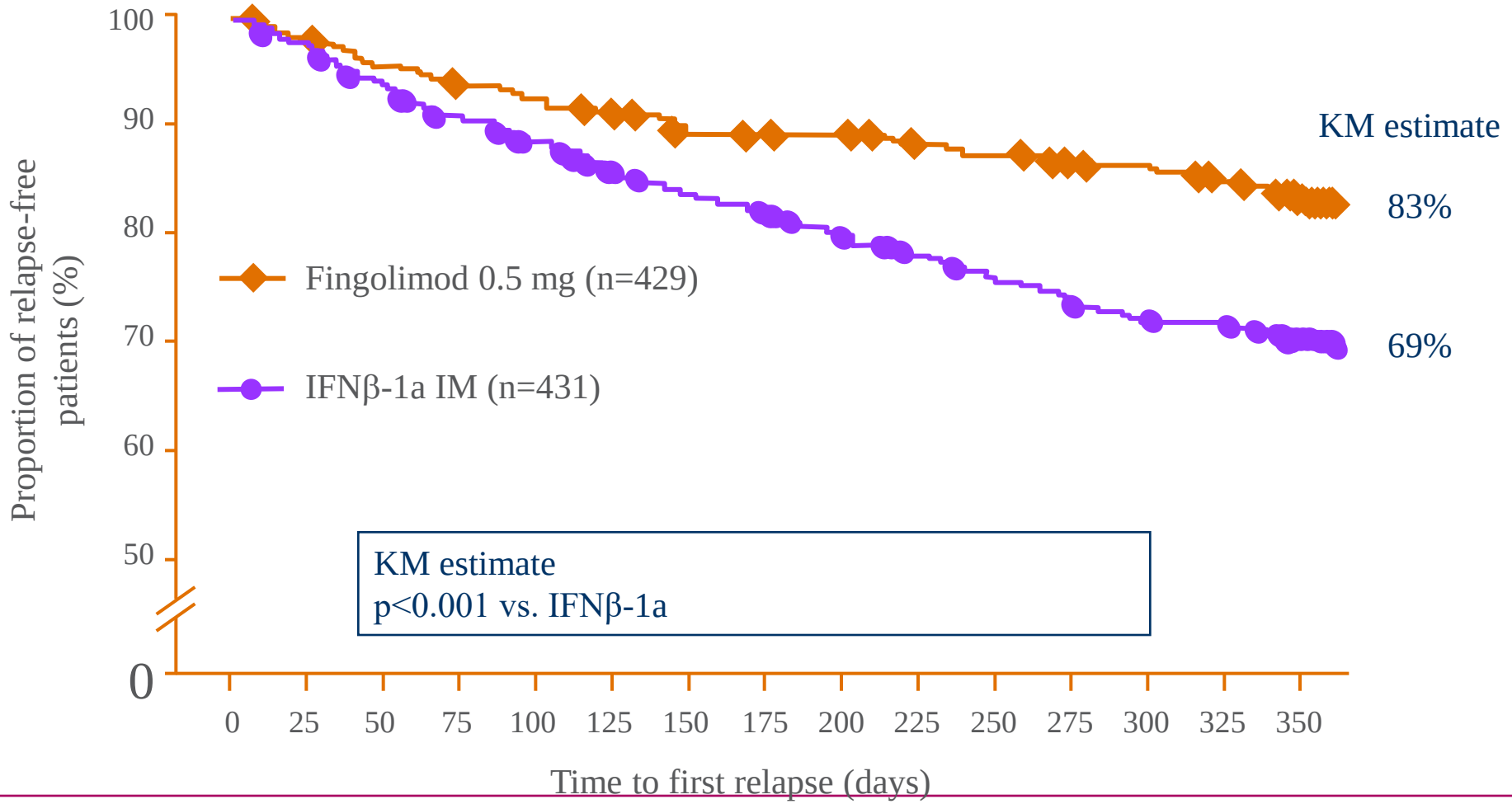
TRANSFORMS – Primary Endpoint: ARR~ 50% overall reduction

ARR ratio 0.5 mg vs. IFN β-1a IM = 0.48, $p<0.001$



Modified ITT population: all patients who underwent randomization and received one dose of a study drug
Negative binomial regression model adjusted for treatment group, country, baseline number of relapses in previous 2 years and baseline disability score; bars represent the 95% CI

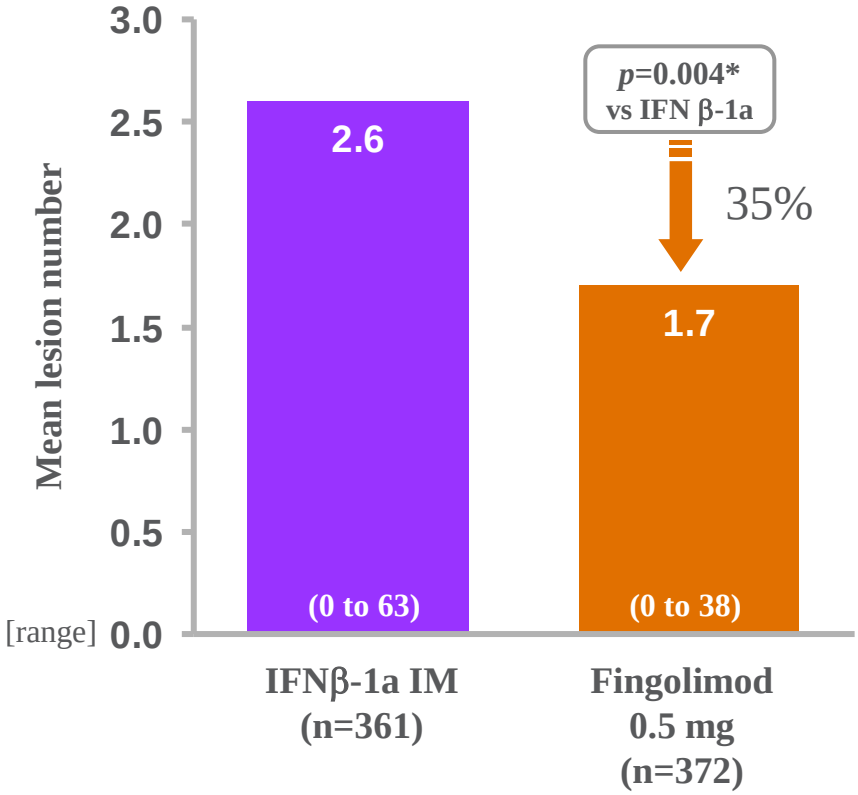
TRANSFORMS – Percentage of Relapse-Free Patients and Time to First Relapse



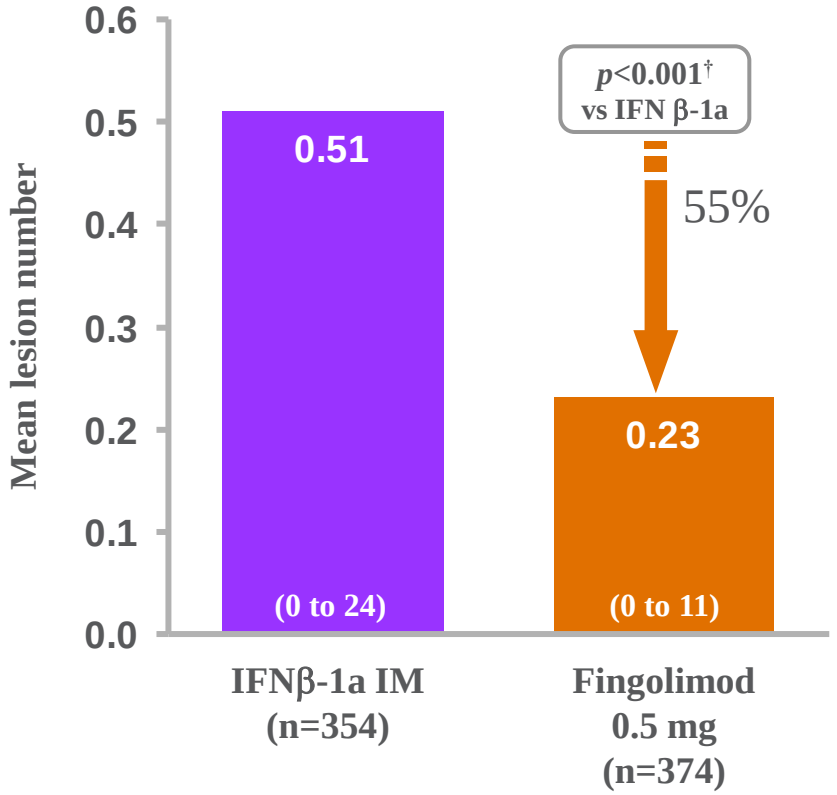
Modified ITT population: all patients who underwent randomization and received one dose of a study drug

TRANSFORMS – MRI Lesion Activity

Number of new and enlarged T2 lesions over 12 months*



Number of Gd+ T1 lesions at 12 months**



*Analysis performed using a negative binomial regression model adjusted for treatment group, country, baseline number of relapses and baseline EDSS;
**analysis performed using rank ANCOVA adjusted for treatment group, country and number of lesions at baseline; ITT population with available MRI scans

Fingolimod AE Experience

	Phase III placebo-controlled			All studies+	
	Placebo	Fingolimod		Fingolimod	
		0.5 mg	1.25 mg	0.5 mg	1.25 mg
Number of patients	418	425	429	1176	1302
Exposure (pt-years)	703.2	750.2	682.8	1878.0	2218.3
Event, N (%)					
At least 1 AE	387 (92.6)	414 (94.4)	404 (94.2)	1054 (89.6)	1203 (92.4)
AE leading to study drug discontinuation*	32 (7.7)	32 (7.5)	**61 (14.2)**	92 (7.8)	**186 (14.3)**
Any serious AE	56 (13.4)	43 (10.1)	51(11.9)	111 (9.4)	170 (13.1)
Deaths	2 (0.5)	0	1 (0.2)	0	5 (0.3)

AE = adverse event

+Includes all available data from Phase II and Phase III core and extension studies (2201, 2201E1, 2301, 2301E1, 2302 and 2302E1) with treatment durations varying between 1 to 6 years – data cut-off from 120-day safety update; *includes events occurring in patients whose primary or secondary reason for discontinuing the study drug was an adverse event (including abnormal laboratory findings)

Precautions Related to Hepatic Effects of Fingolimod

- Fingolimod may increase liver transaminases

- Obtain transaminase and bilirubin levels prior to initiating treatment, then **once per month x 3 months** then **every 3 months during the first year of** treatment and **annual or bi-annually** thereafter in the absence of symptoms or when symptoms suggestive of hepatic injury develop

Novartis Pharmaceuticals Canada Inc. *Gilenya (Fingolimod) Product Monograph.* March 21, 2011.

Precautions Related to Pregnancy/Reproduction

- Based on animal data, fingolimod is potentially teratogenic
- Women of childbearing potential should be counselled on the potential for serious risk to the fetus and the need for effective contraception during, and for **2 months** after treatment with fingolimod
- Available data do not suggest that fingolimod would be associated with an increased risk of male-mediated fetal toxicity or reduced fertility

Novartis Pharmaceuticals Canada Inc. *Gilenya (Fingolimod) Product Monograph.* March 21, 2011.

Safety Conclusions

- **Extensively studied: >9600 patient-years in >2600 MS patients with comprehensive multi-organ safety assessments in all studies**
- **Fingolimod 0.5 mg selected as the proposed dose**
  - **Better overall safety/tolerability than 1.25 mg dose with no differences in efficacy**
  - Overall incidence of serious AEs and AEs leading to drug discontinuation similar between 0.5 mg dose and comparator (placebo and IFNβ-1a IM)
- Dose-dependent effects include transient heart rate reduction on treatment initiation, small **increase in blood pressu**re, **liver enzyme elevations**,**pneumonia,macular edema** (fluid and protein deposits in retina of the eye)
- Data in pregnancy are limited – contraception recommended in females of child-bearing potential
- Comprehensive risk management strategy proposed to continue to further understand and manage safety profile

Risk/Benefit for Every 1000 MS Patients Treated with 0.5 mg Fingolimod Compared to Placebo over 2 Years

	Type of event	Number
Benefit	**Relapses avoided (44%)**	**440**
	Increase in patients free of relapse	233
	Increase in patients without disability progression	56
Risk	Macular edema	3*
	5-fold elevation of hepatic transaminases	9
	Hypertension	23
	Pneumonia	3

*No cases in Phase III (FREEDOMS) placebo-controlled study, data from overall program

Summary

- Fingolimod 0.5 mg is highly effective in RRMS
  - In a comparative 1-year study vs. a standard of care (IFN beta-1a IM), significant **reductions in relapse rate (44-52%)** and new MRI lesions **(55%) w**ere observed
  - In a placebo-controlled 2-year study, significant reductions in relapse rate, disability progression and new MRI lesions were observed
- There is over 9600 patient-years' experience with fingolimod
- Fingolimod was generally well tolerated over short and long term
  - Most frequent AEs are headache and influenza viral infection
- Known pharmacodynamic effects include:
  - Asymptomatic heart rate reduction upon initiation
  - Reversible redistribution of lymphocytes
- As with other DMTs, careful initial selection of patients and monitoring following treatment is required: **Medication Adherence is Key**
- **However: 49 year old male patient with RRMS treated for 4 years with 0.5mg per day developed PML Feb 17th, 2015 and tested positive for the JC virus. Detected by routine MRI. Pt did not die.**

DMT = disease-modifying treatment

Laquinimod: Phase 3 Trials

- Quinolone-3-Carboxamide
- Oral agent induces brain derived neurotrophic factor (BDNF) [0.6mg and 1.2 mg doses being evaluated)
- Induces anti-inflammatory antigen presenting cells that down regulate inflammatory Th1 and Th17 immune cells
- Down regulates nitric oxide production in astrocytes.
- Transient Transaminase Elevation (LF) monitoring required.
- Failed to get EU approval Jan 2014 due to inability to show significant decrease in ARR (23% compared to placebo) - NERVENTRA® (laquinimod) - Teva

Teriflunomide: AUBAGIO®

- Inhibits mitochondrial dihydroorotate dehydrogenase and enzyme used for the de novo synthesis of pyrimidine nucleotides in proliferating cells (T cell proliferation inhibitor)
- Oral: Approved Nov 20th, 2013 in Canada for RRMS [7 mg or 14 mg once daily]
- 35% ARR compared to placebo on 14mg/day + 59% Reduction in Gd enhancing T1 lesions
- Alopecia, diarrhea, increased LFTs, headache
- Approved in US, EU, Argentina, Chile, South Korea and Mexico
- Risk of Tuberculosis – pre-test before starting with purified protein derivative
- 10 day extended half-life----Genzyme
- Leflunomide RA /Psoriasis drug absolute contraindication

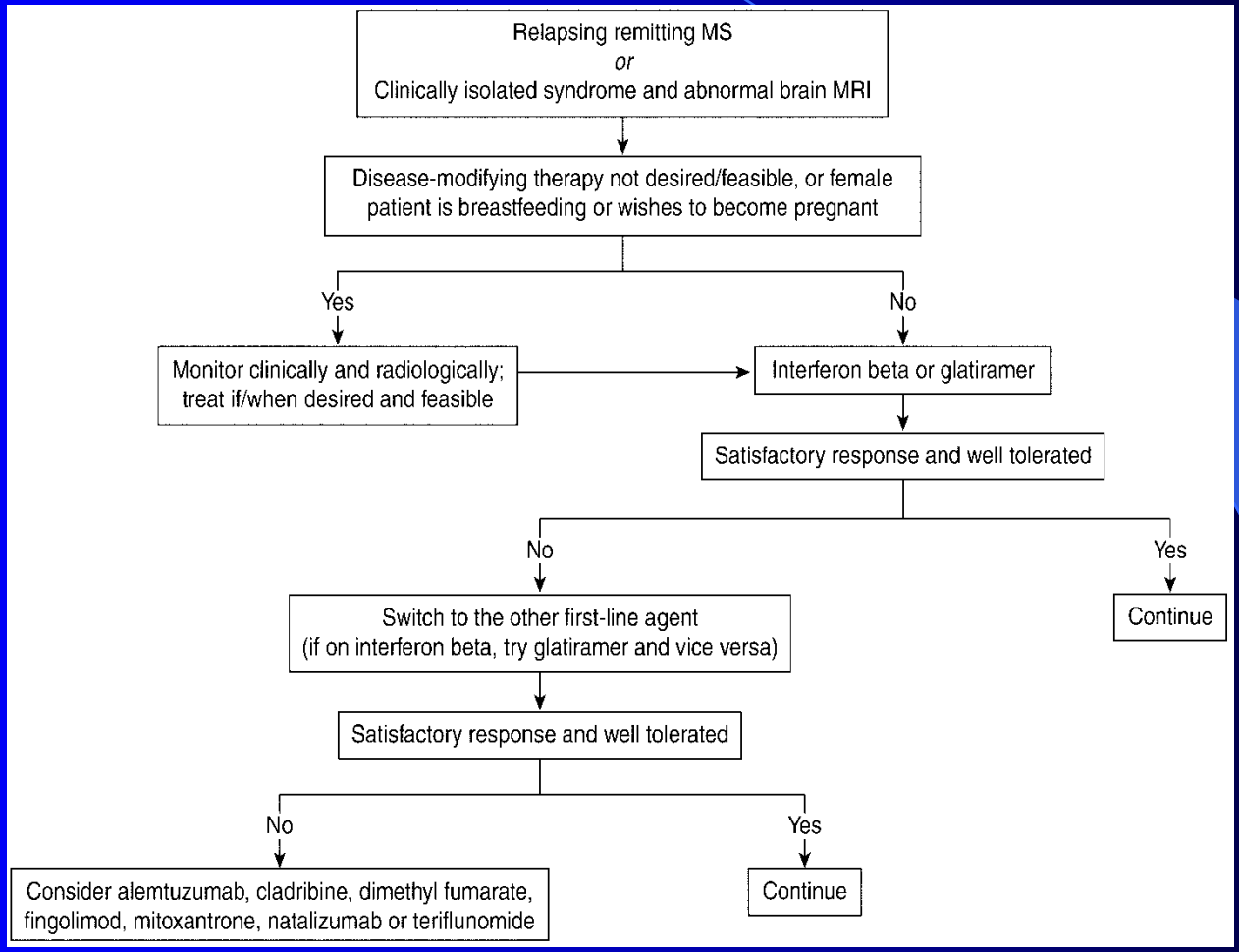
Tecfidera®
Dimethyl Fumarate (BG12)

- **Oral: Approved in Canada April 9th, 2013 (Phase 3- DEFINE and CONFIRM studies). Also approved in EU, Australia**
- **Inhibits immune cells and molecules with anti-oxidant properties – inhibits Nrf2 pathway (neuroprotective)**
- **2x120mg capsules twice daily with or without food.**
- **Flushing, diarrhea, nausea and upper abdominal pain**
- **Used in RRMS patient s with a contraindication to, or who have failed to respond adequately to at least one interferon formulation and glatiramer acetate**
- **53% ARR; 90 % decrease in Gd+ lesions, 38% reduction in EDSS**
- **Alternative for those who can't take Fingolimod , Teriflunomide or Injections - Biogen**

Alemtuzumab - Lemtrada®/Campath®

- **Monoclonal Antibody binds to CD52 on lymphocytes targeting them for distruction**
- **Indicated for RRMS patients who have an inadequate response to interferons or other disease modifying therapies.**
- **Lemtrada 12 mg has a dosing and administration schedule of two annual treatment courses. The first treatment course of Lemtrada is administered *via* intravenous infusion on five consecutive days, and the second course is administered on three consecutive days, 12 months later. Lemtrada patients require monitoring at regular intervals between treatment courses and for 48 months following the final infusion. Potential Cure as no further treatments needed**
- **Approved in Canada, EU, Australia but FDA *declined* Dec. 2013**
- **AAR 49.4%**
- **Used to treat chronic lymphocytic leukemia (CLL); cutaneous T cell lymphoma (CTCL); T cell lymphoma**
- **Main pre-caution: Risk of opportunistic infections (cytomegalovirus) -Genzyme**

Management of RRMS



Dacetuzumab – Ongoing Investigation

- Targets CD40
- Expressed on Antigen presenting cells
- The binding of CD154 (CD40L) on T_H cells to CD40 activates antigen presenting cells and induces a variety of downstream effects (Blocks Th1 activation via APC CD40 blockade)
- Because dacetuzumab is still under study, no optimal (IV) dosages have been established yet. Clinical trials have tested different dosages.

DACLIZUMAB (Zinbryta)

- Anti-CD25 monoclonal antibody for the treatment of RRMS approved in December 2016
- Voluntary withdrawal March 2nd, 2018 by Biogen and AbbVie

Rituximab – Ongoing Investigation

- Monoclonal antibody
- **Targets** against the protein **CD20**, which is primarily found **on** the surface of immune system **B cells**. Rituximab **destroys B cells** and is therefore used to treat diseases which are characterized by excessive numbers of B cells, overactive B cells, or dysfunctional B cells.
- PML Risk with this **IV drug infusion**

Hormonal Therapy

- Clinical trial
  - 12 female patients (6 RRMS, 6 SPMS)
  - Estriol 8 mg/day x 6 months
  - RRMS: improved MRI
  - SPMS: no changes
  - Side effects:
    - Menstrual cycle irregularities
    - Risk of breast cancer, heart attack, and stroke

Stem Cell Transplants

- Intensive ("extreme") immunosuppression
- "Reboot" a damaged system
  - Reconstitution with healthy stem cells will avoid redevelopment of immune response
  - Ablation of bone marrow may limit damage; stem cells may improve repair (can differentiate into new support cells)

Stem Cell Transplants

- **Collect stem cells from patient from blood or bone marrow. Then use chemo and radiation used to destroy diseased cells in bone marrow. Your stored stem cells collected prior to chemo/radiation go back into your body to reboot.Whether stem cells come from your own blood or bone marrow it is called an autologous transplant.**
- Phase II, 3-year trial
  - Ottawa, Toronto, Montreal
  - 24 transplants, 8 controls
  - Severe active MS:
    - > 5 relapses in 2 – 3 years
    - Failure of interferons, copaxone, mitoxantrone
  - Mortality rate of 3 – 8%

Vitamin D

- 2000 IU /day

Chronic Cerebrospinal Venous Insufficiency

- Zamboni P et al J Neurol Neurosurg Psychiatry 2009;80:392-399.
- 65 MS patient (35 RRMS; 20 SPMS; 10 PPMS)
- Cause or Effect

Conclusions

- ✓ MS is an autoimmune disease
- ✓ RRMS is the most prevalent form of the disease
- ✓ No cure for the disease
- ✓ Clinical efficacy is ~30% for interferons and ~70% for Tysabri ***(Caution PML)***
- ✓ NAB's compromise clinical efficacy
- ✓ New Oral Medications ~65% reduction in MRI and ~50% ARR reduction
- ✓ Increase quality of life


Questions ?