Immunological neuropathies

Anti-MAG ,antigaglioside neuropathies

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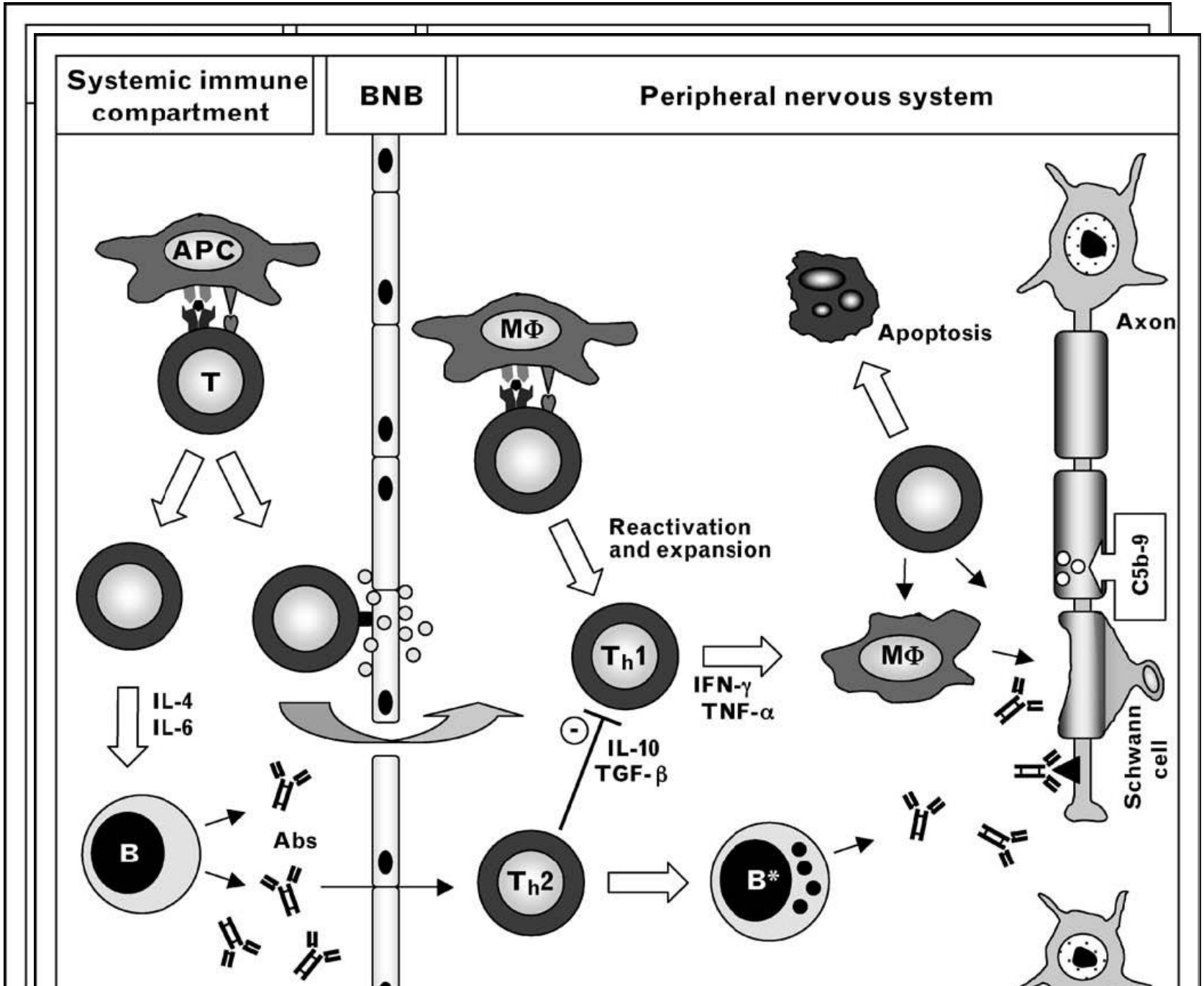

Systemic immune compartment
BNB
Peripheral nervous system
APC
T
MΦ
Reactivation and expansion
Apoptosis
Axon
C5b-9
Schwann cell
IL-4
IL-6
Th1
IFN-γ
TNF-α
MΦ
IL-10
TGF-β
B
Abs
Th2
B*

Immune mechanism in PN

- Triggering of auto reactive T- and B-cell
  - -molecular mimicry
  - -epitope spreading
- Induction phase and effector phase
  - -co-stimulatory molecules

- Entry of inflamatory cells

  adhesion molecules,chemokines ,

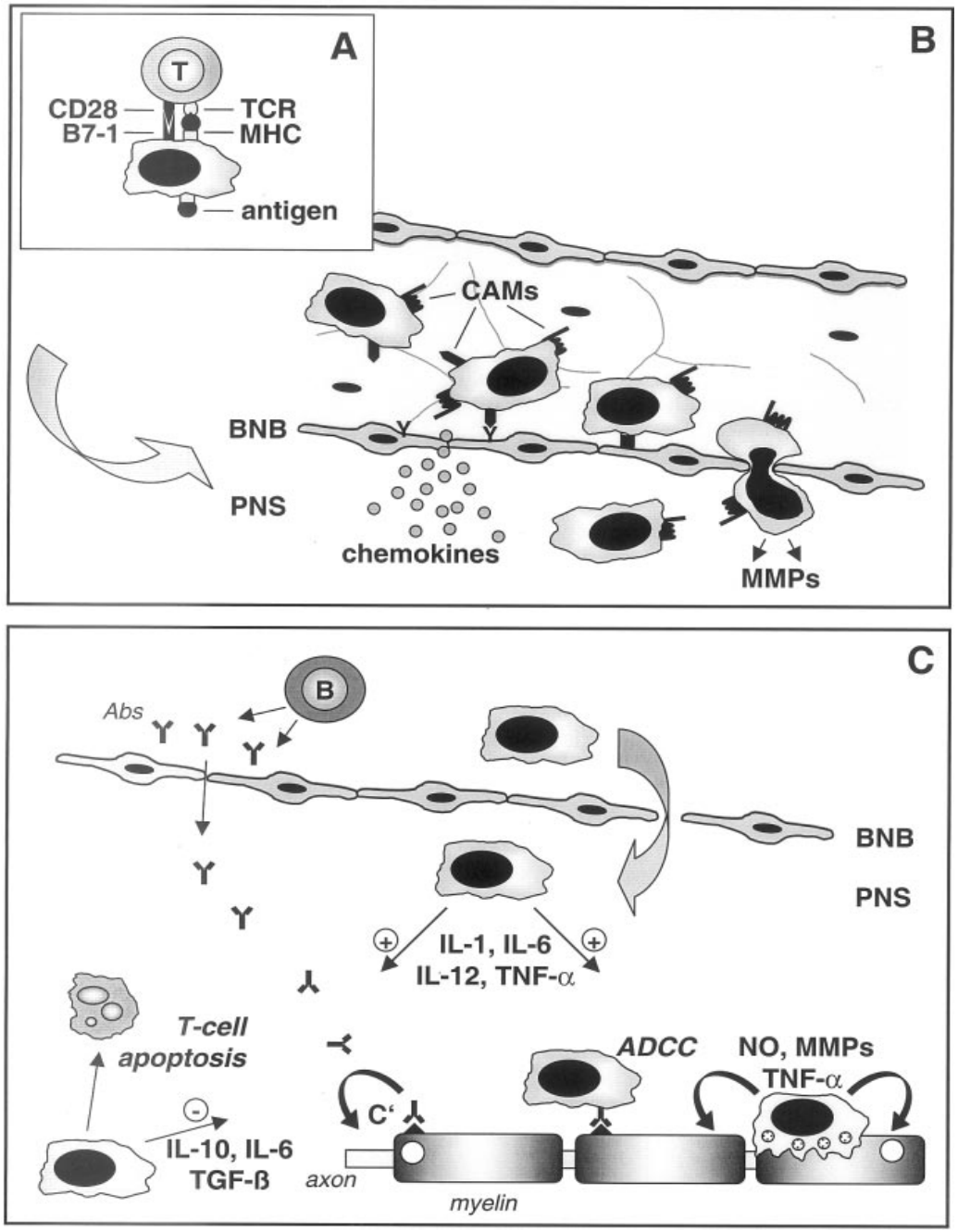
  matrix metaloproteinases
- Amplification and termination of the local immune response

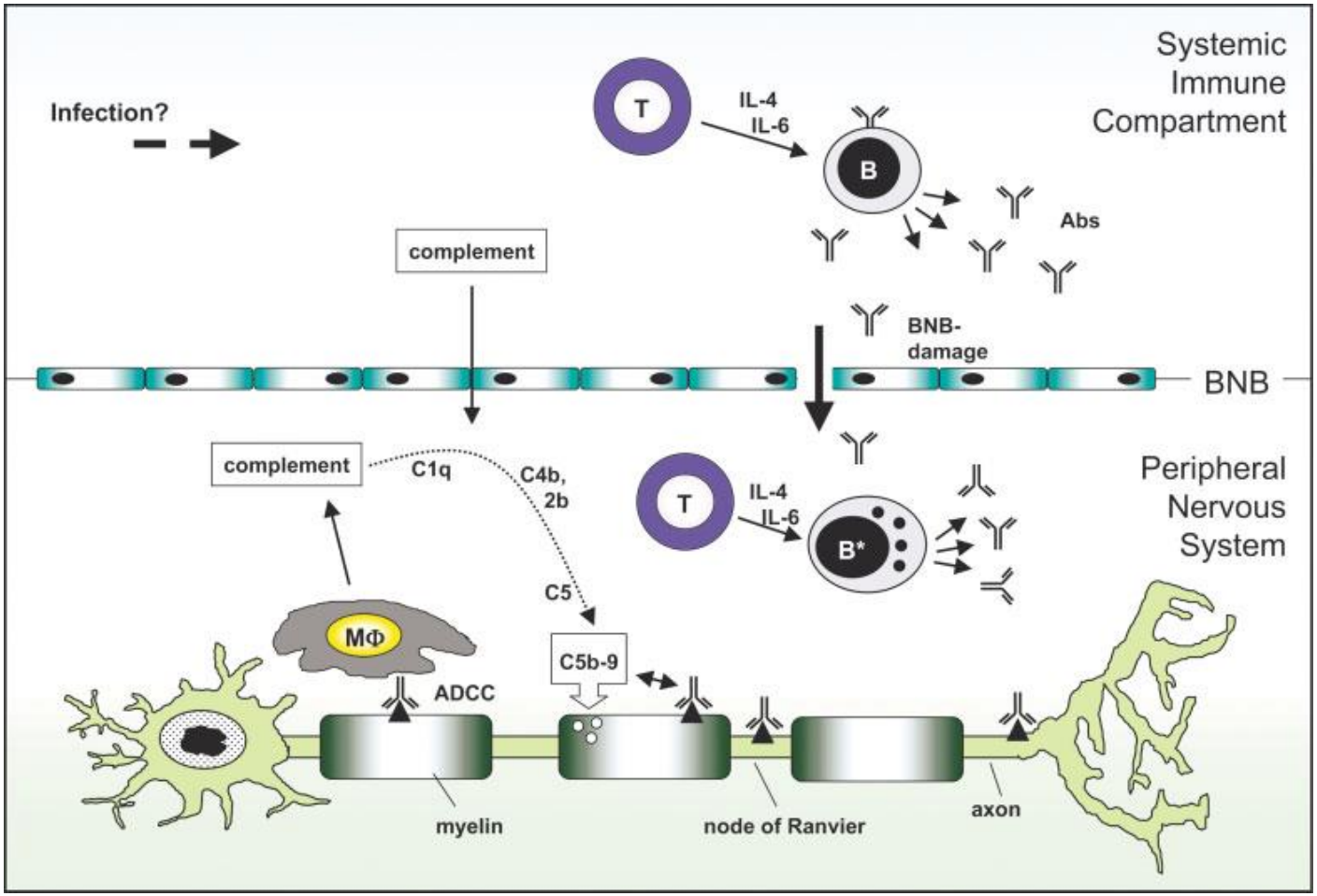
  -cytokines[IL-8, IL-2,Th1/Th2]

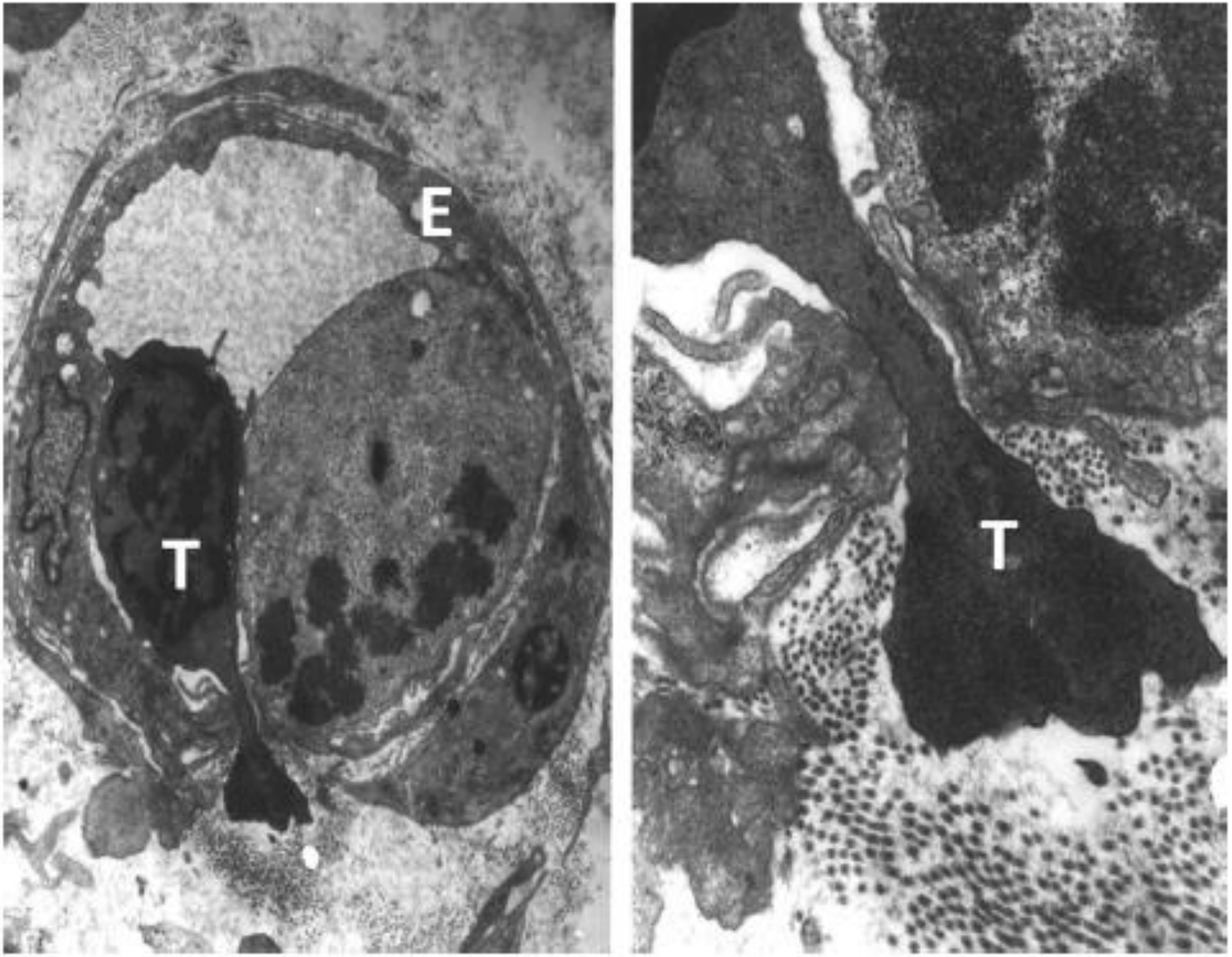
- Effector mechanisms of the myelin destruction:macrophages, antibodies ,complement

Macrophages in PN

- Endoneurian macrophages act as APC
- Hematogenous transmigrate through adhession molecules ,and MMP.once within produce pro-inflamatory cytokines
- Antibody driven,complement depented attack to the target Antigen.Cell mediated cytotoxicity.
- Anti-inflamatory cytokines production


A
T
CD28
B7-1
TCR
MHC
antigen
B
CAMs
BNB
PNS
chemokines
MMPs
C
B
Abs
BNB
PNS
IL-1, IL-6
IL-12, TNF-α
T-cell
apoptosis
IL-10, IL-6
TGF-ß
C'
ADCC
NO, MMPs
TNF-α
axon
myelin

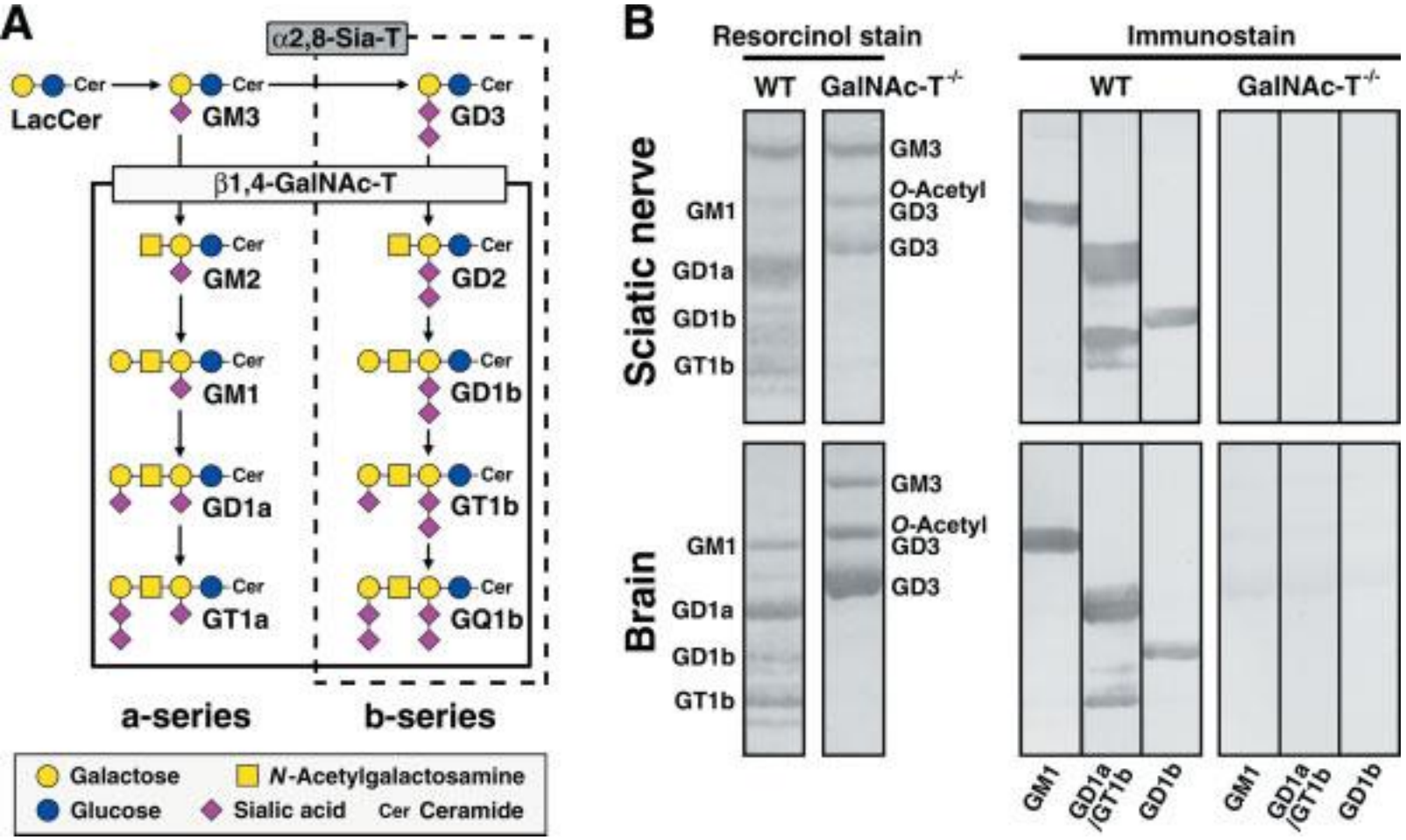

Systemic
Immune
Compartment
Infection?
T
IL-4
IL-6
B
Abs
complement
BNB-
damage
BNB
complement
C1q
C4b,
2b
T
IL-4
IL-6
B*
Peripheral
Nervous
System
C5
MΦ
C5b-9
ADCC
myelin
node of Ranvier
axon


E
T
T

Peripheral neuropathy

- Autoantibodies against
- gagliosides[GM1,GM2,GD1a,GD1b,GT1a, GQ1b cerebroside[Galc,SGPG, SGLPG Sulfatide]
- Proteins [MAG, OMgp,P0,PMP22 ,P2]
- Proteins- gagliosides cross reactivities
- T- cell indepented reactions

Gangliosides in peripheral nerve



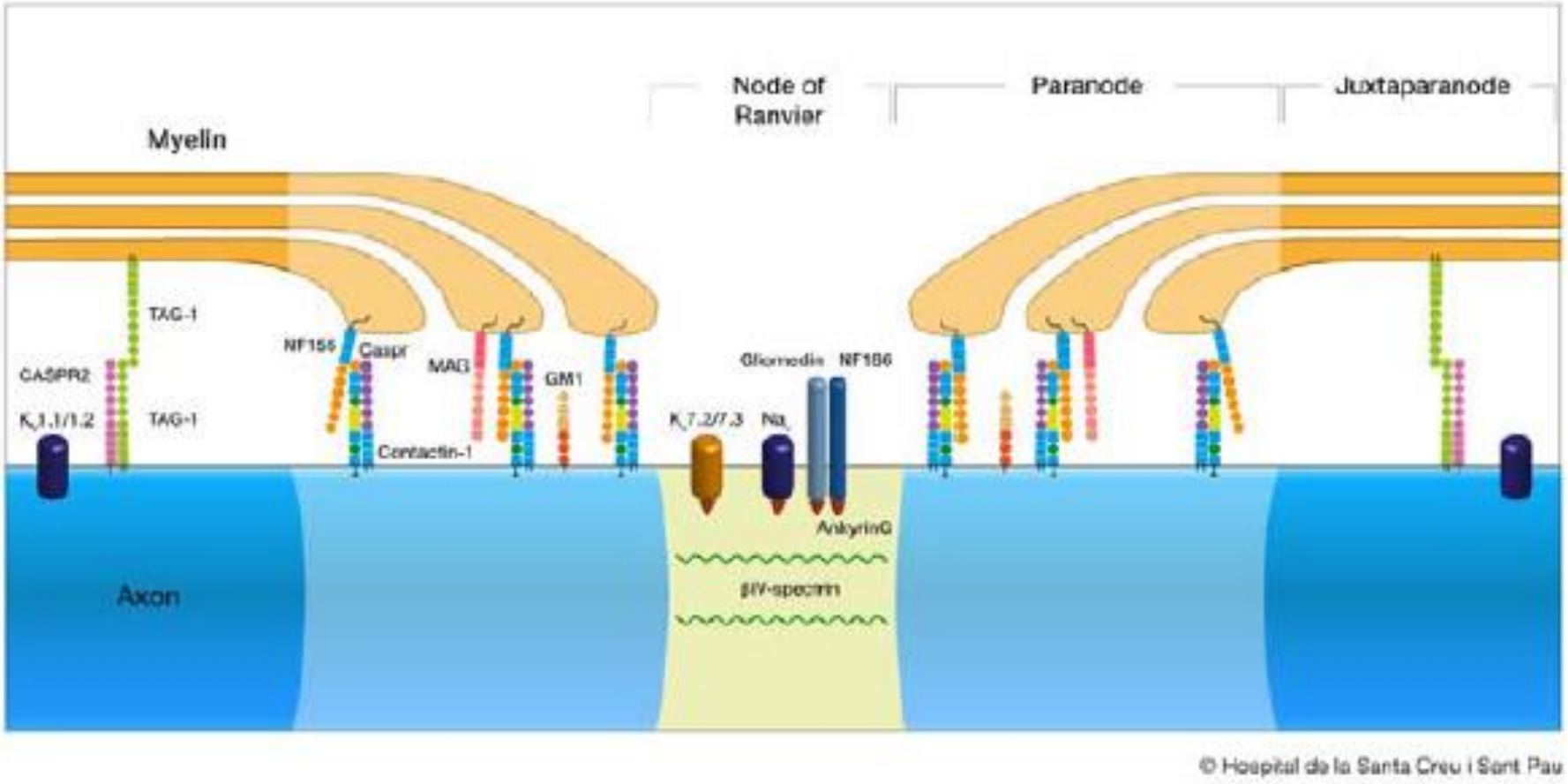


Figure 2. The main nodal and paranodal target antigens, recently described in CIDP.

Illa 2016

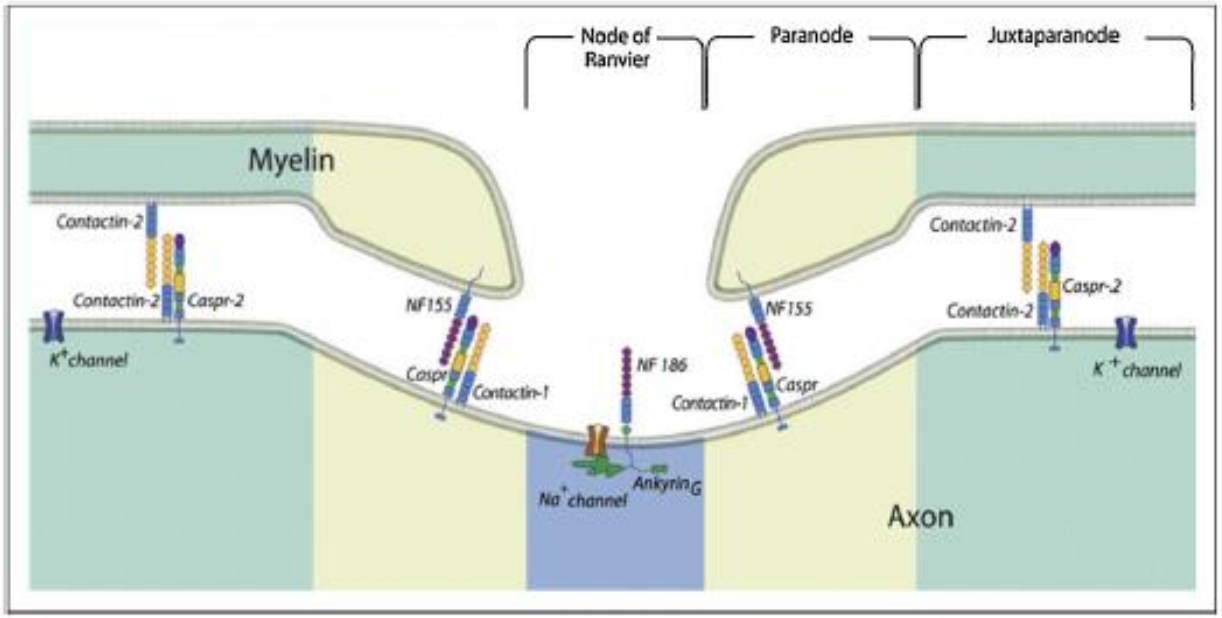


FIGURE 3

Candidate antigens in the nodal, paranodal and juxtaparanodal regions of the myelinated fiber

Conatctin 1, Na+ channel, Ankyrin G, Neurofascin 186 are the most common putative antigens in the nodal region; Neurofascin 155, Caspar 1 and contactin 1 in the paranodal; and contactin 2, Caspar 2 and K+ channel in the juxtaparanodal region. Additional ones (see text) include gliomedin, connexin, NCAM, cadherin and others.

In CIDP, KCNQ2, a K+ channel subunit, is diminished; Caspar 1, is more widespread extending to internodal regions; the nodal Na+ channel clusters are disrupted; antibodies to several proteins have been observed; polymorphisms in the Contactin 2 (TAG-1) have been associated with response to IVIg.

Dalakas 2015

Immune neuropathies

- GBS
- CIDP
- Miller-fisher syndrome and anti-GQ1b
- Anti-MAG paraproteinemic neuropathy
- MN with MMCB and anti-GM1 antibodies
- Paraproteinemic neuropathies and anti glycolipid antibodies[against GM2,GDIb, GQ1b ,GT1b ,SGPG, Sulfatide]
- AMAN and anti-GM1,anti-GD1a

Acute motor inflamatory neuropathy

- Gullain Barre syndrome
- AIDP
- AMAN
- AMSAN
- Mller- Fisher syndrome
- Sensory axonal GBS
- Acute pandysautonomia

ANTI-MAG NEUROPATHY

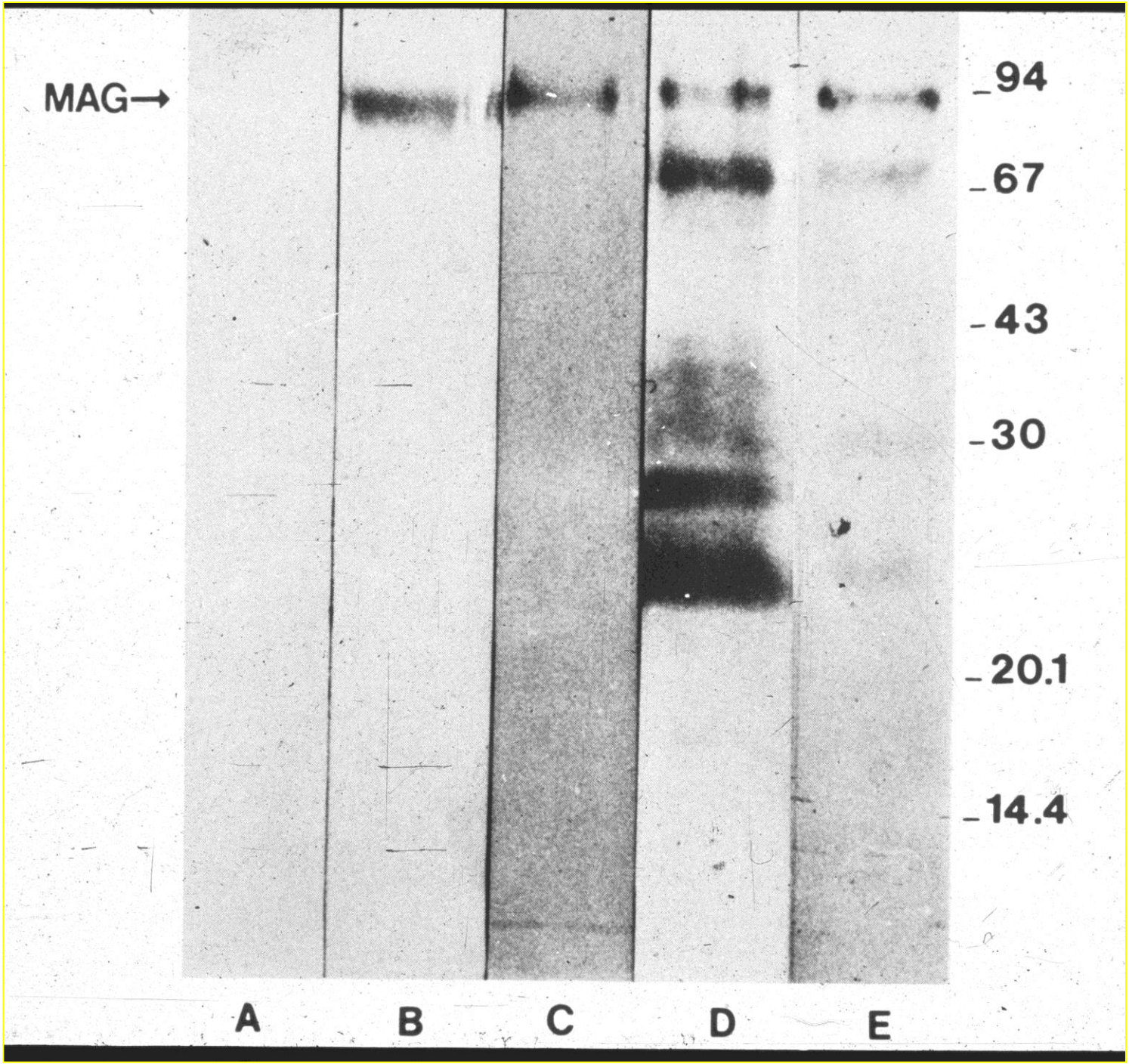
Anti-MAG neuropathy

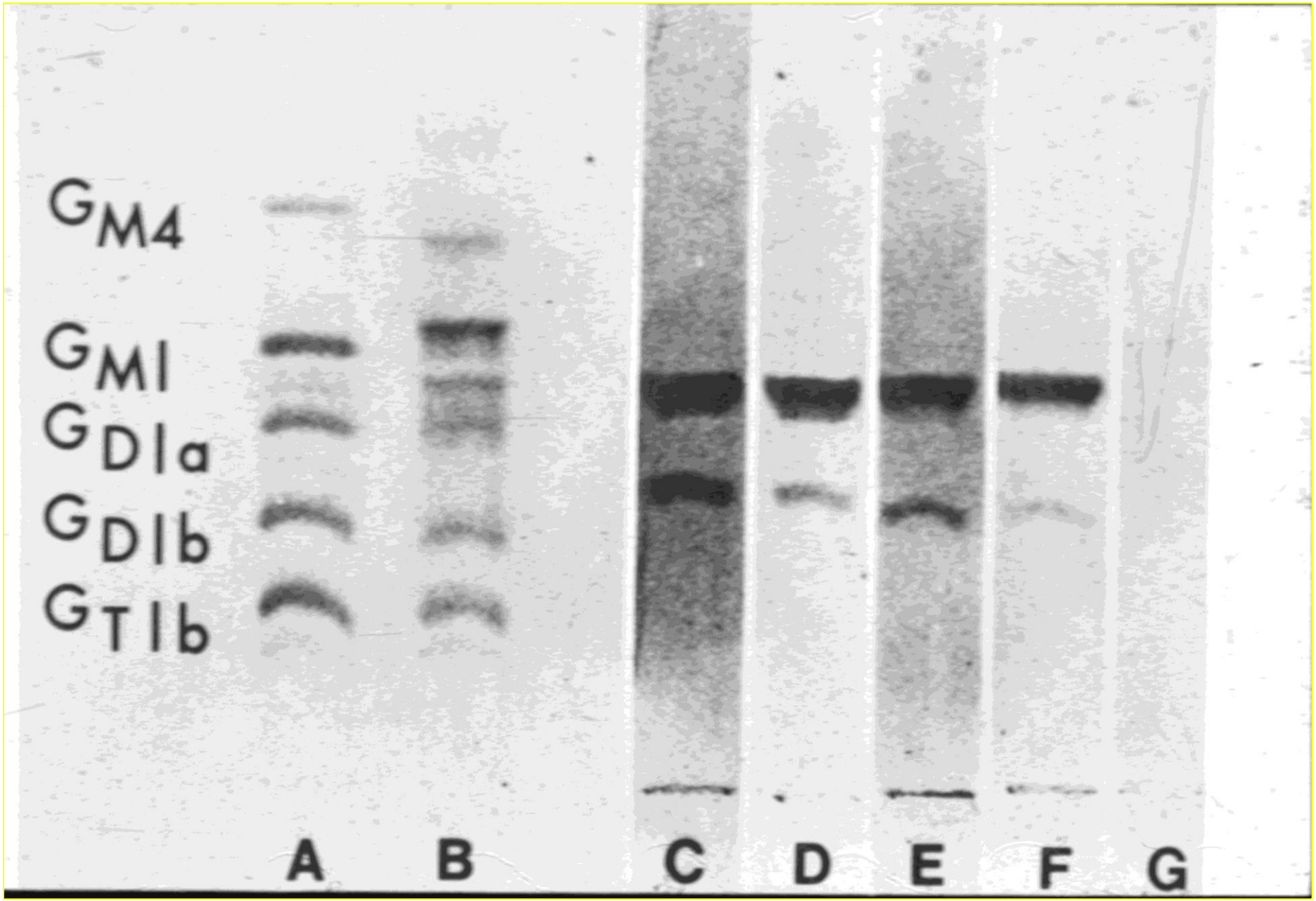
- Sensory neuropathy and later sensory motor neuropathy
- Distal ,ascending paresthesia,numbness, sensory ataxia pain uncommon , positive Romberg test
- Reflexes decreased or absent in lower extremities and deccreased in upper. distal weakness
- Monoclonal IgM anti--MAG specificity

Wide spaced myelin and demyelination

immunology

- IgM and complement deposition in peripheral myelin
- Monoclonal IgM with anti-MAG specificity
- Passive transfer of neurophysiological and pathological features of the disease to experimental models [demyelination]
- Sucesfull therapy with B-cell depletion or immunosupression

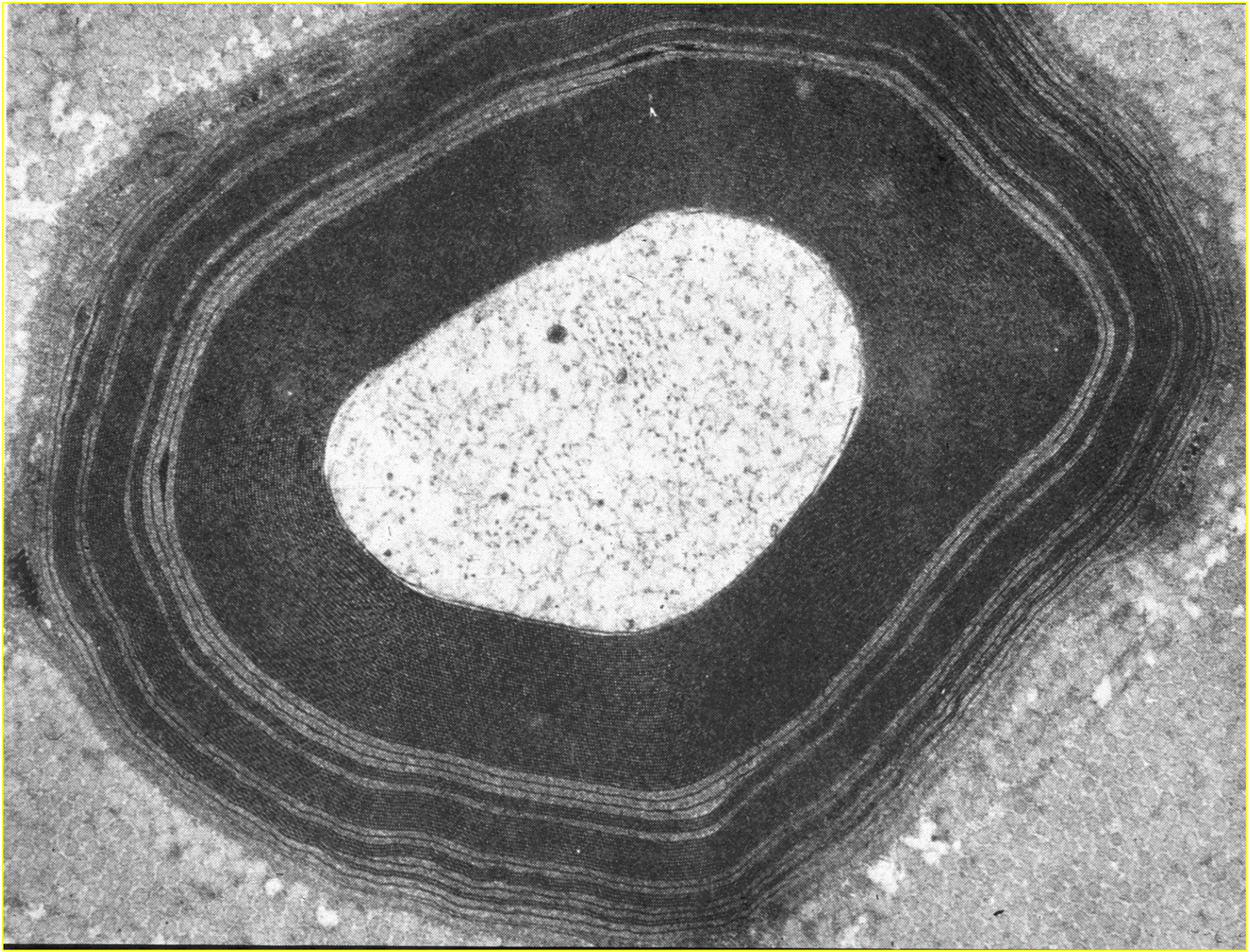

MAG→
94
67
43
30
20.1
14.4
A
B
C
D
E


GM4
GM1
GDIa
GDIb
GTIb
A
B
C
D
E
F
G

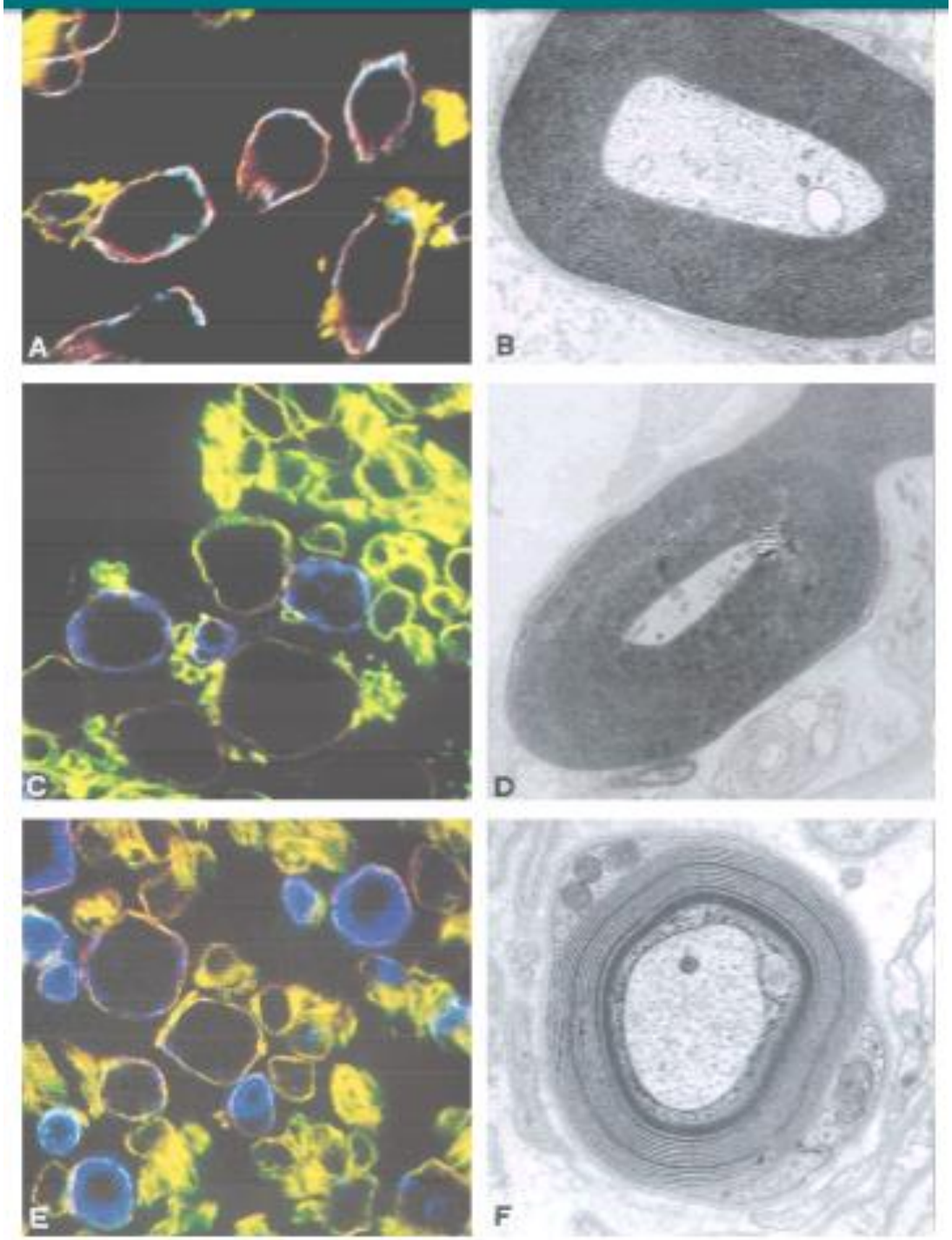
Cross-reactivities

MAG	SGPG
Po	SGLPG
Pm-22	

Common carboydrate epitope: HNK-1



RITZ …STECK
1999



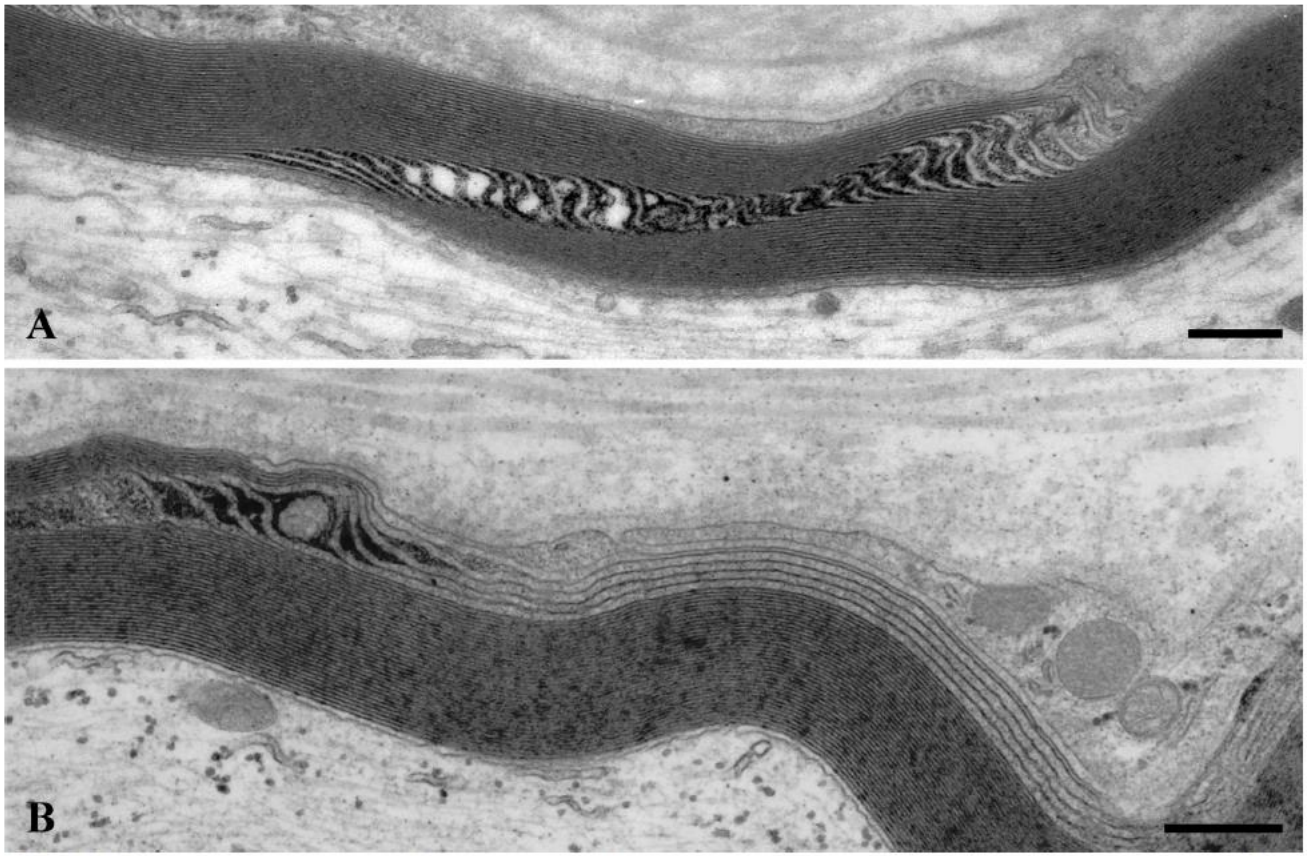


FIGURE 8. Electron micrographs of longitudinal sections of Schmidt-Lanterman incisures in specimens from a normal control **(A)** and anti–myelin-associated glycoprotein neuropathy **(B)**. Widely spaced myelin is in continuity with Schmidt-Lanterman incisures. Scale bars = 0.5 μm

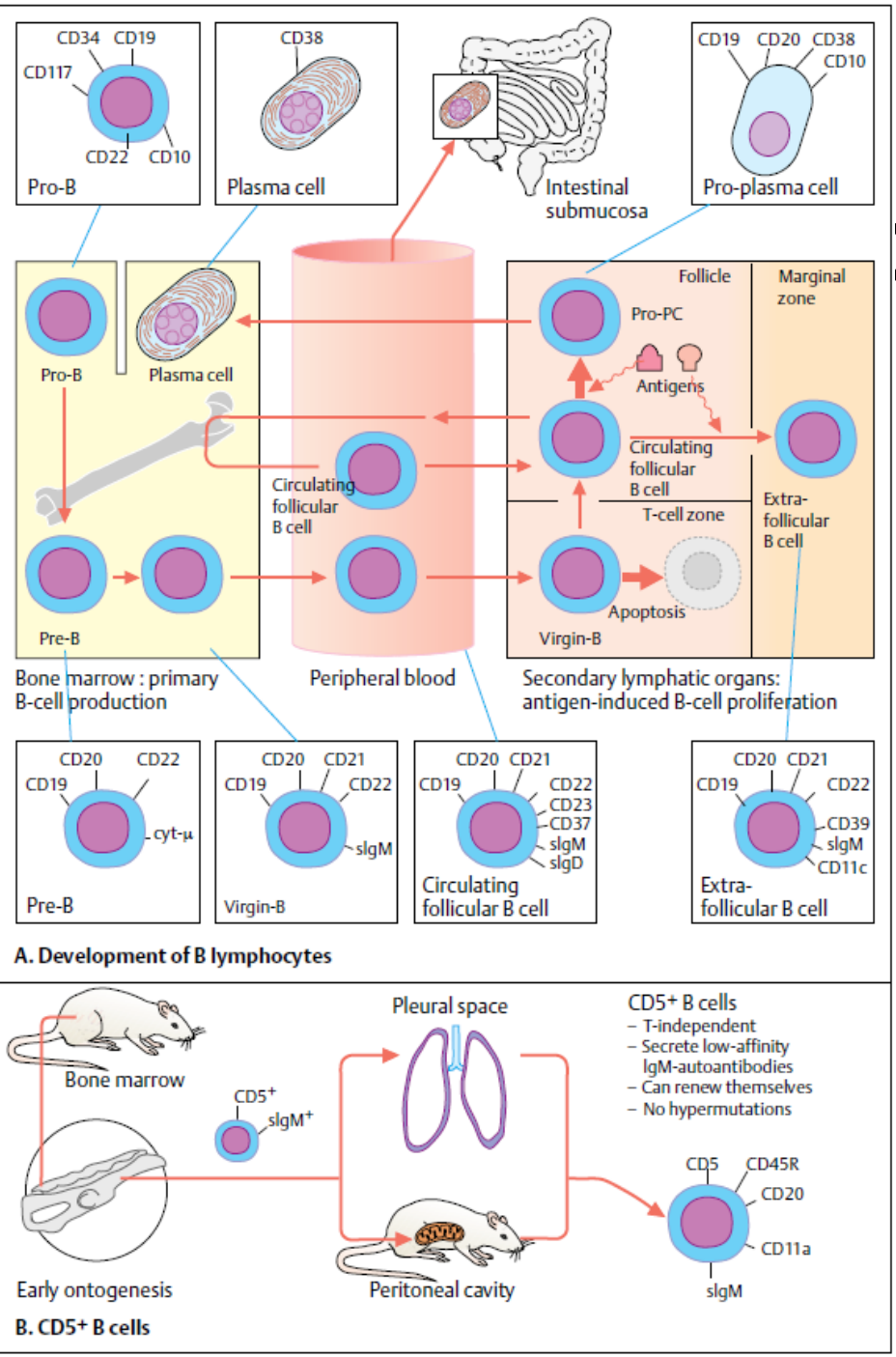
- Kawagashira et al 2010

Anti-MAG antibodies

- Monoclonal gammopathy IgM
- CD5 Bcells
- Natural immune repertoire

B cell

ogeny


CD34 CD19
CD117
CD22 CD10
Pro-B
CD38
Plasma cell
Intestinal submucosa
CD19 CD20 CD38
CD10
Pro-plasma cell
Pro-B
Plasma cell
Circulating follicular B cell
Pre-B
Bone marrow : primary B-cell production
Peripheral blood
Follicle
Marginal zone
Pro-PC
Antigens
Circulating follicular B cell
T-cell zone
Extra-follicular B cell
Apoptosis
Virgin-B
Secondary lymphatic organs: antigen-induced B-cell proliferation
CD20 CD22
CD19
cyt-μ
Pre-B
CD20 CD21
CD19
CD22
sIgM
Virgin-B
CD20 CD21
CD19
CD22
CD23
CD37
sIgM
sIgD
Circulating follicular B cell
CD20 CD21
CD19
CD22
CD39
sIgM
CD11c
Extra-follicular B cell
A. Development of B lymphocytes
Bone marrow
CD5+
sIgM+
Pleural space
CD5+ B cells
– T-independent
– Secrete low-affinity IgM-autoantibodies
– Can renew themselves
– No hypermutations
CD5
CD45R
CD20
CD11a
sIgM
Early ontogenesis
Peritoneal cavity
B. CD5+ B cells

Anti-MAG neuropathyTherapy

- Rituximab
- Cytostatics [cyclophosphamide]

Anti-MAG neuropathy

- ANTIGEN

MAG cross ractivities to

P0,PMP22,SGPG,SGLPG

IMMUNOGENIC EPITOPE

HNK-1 carboydrate

EFFECTOR

Monoclonal IgM

IMMUNE CELLS

B CD5+ , Tcell independed reaction

1. Ανίχνευση Αντισωμάτων

2. Χαρακτηρισμός Αντιγόνου στόχου

3. Πτώση των τίτλων συνδυάζεται με ύφεση της νόσου

4. Μεταφορά της νόσου σε πειραματόζωο μέσω των χαρακτηρισθέντων αντισωμάτων

5. Ανοσοποίηση με το χαρακτηρισθέν αντιγόνο προκαλεί πειραματικό μοντέλο της νόσου

- Antigen: MAG
- Antibody: monoclona;l IgM
- Passive transfer
- Immunisation experimental model

SPECIFIC CHARACTERISTICS OF IMMUNE NEUROPATIES

Γλυκολιπιδικά αντιγόνα

GM_1
GM_2
GD_{1a}
GD_{1b}
GT_{1a}
GQ_{1b}

Μέθοδοι ανιχνεύσεως και ποσοτικοποίησης αντισωμάτων
TCL, ELISA

Πρωτεϊνικά αντιγόνα

M.A.G
P_0
PMP-22
OMgP
Versican
NF
Hu

Μέθοδοι ανιχνεύσεως και ποσοτικοποίησης αντισωμάτων
ELISA, Western Blot

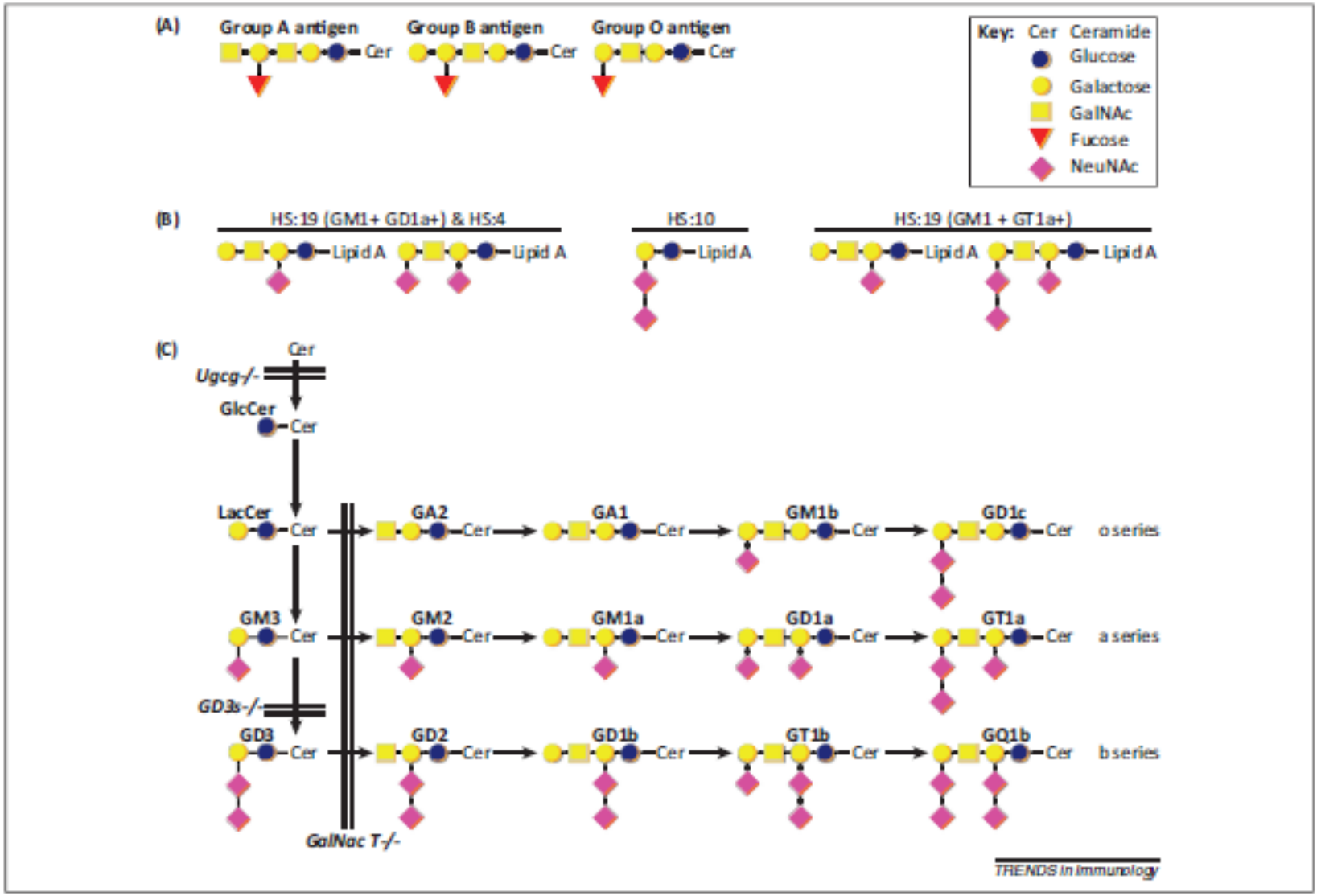


Figure 1. Glycan structures associated with red blood cells, *Campylobacter* lipo-oligosaccharides (LOSs) and membrane gangliosides. **(A)** The ABO blood group antigens are differentiated based on the expression of terminal N-acetylgalactosamine (GalNAc) (Group A), galactose (Group B), or neither (Group O). **(B)** Guillain–Barré syndrome (GBS) associated *Campylobacter jejuni* LOS structures, although linked to lipid A rather than ceramide, are structural mimics of gangliosides. Strains of *C. jejuni* can express multiple structural variants of LOS. **(C)** The biosynthetic pathway of gangliosides is controlled by several glycotransferase enzymes [UDP-glucose ceramide glucosyltransferase (Ugcg), GD3-synthase (GD3s) and GalNAc transferase (GalNAcT)]. Knockout mice for these enzymes (indicated by double lines through the arrows) will not express the subsequent gangliosides.

WILLISON 2013

Complex antigenic targets

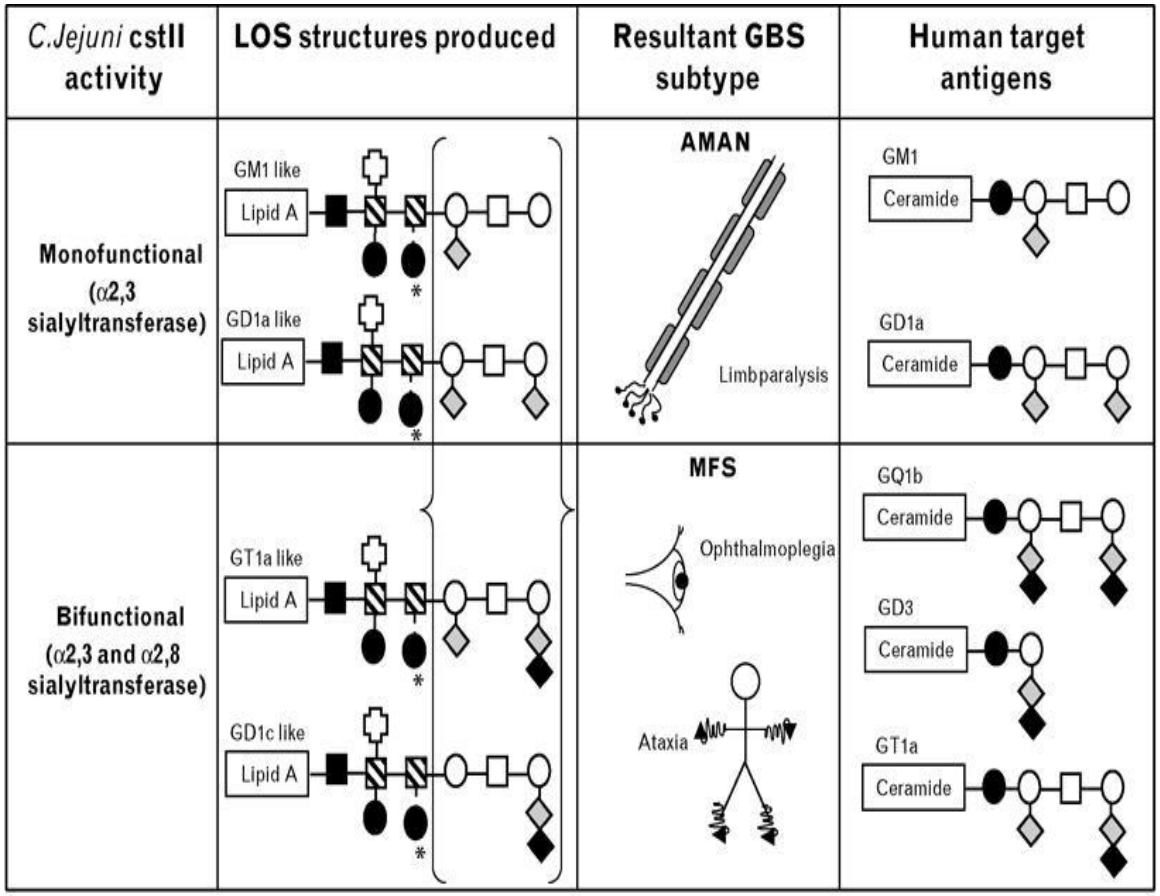
- Potential antigenic targets may have been overlooked because of focusing in single molecules
- -complex gangliosides
- -antibodies to specific gangliosides

may not recognise clusters of gangliosides,cholesterol,GPI-anchored proteins .

Triggering factors of molecular mimicry

- Camp jejuni [IgG anti-GM1 , anti-GD1a,anti-GQ1b]
- Mycoplasma pneumonia [anti-Galc]
- Haemophilus influenza [anti-GM1,anti-GQ1b]
- CMV [IgM antI- GM2]

Molecular mimicry and neuropathy



Camplylobacter jejuni with the cstII allele Thr51 have α2,3-activity alone and produce GM1 and GD1a-like LOS, resulting in AMAN via the induction of anti-GM1 and anti-GD1a antibodies. Those possessing the Asn51 allele have bifunctional enzyme activity. GT1a and GD1c LOS with terminal disialosyl groups induce anti-GQ1b, GD3 and GT1a antibodies. AMAN, acute motor axonal neuropathy; *C. jejuni*, *Camplylobacter jejuni*; GBS, Guillain–Barré syndrome; LOS, lipo-oligosaccharide; MFS, Miller–Fisher syndrome. {} = ganglioside mimicking structure of LOS. *Presence of second glucose on core LOS structure is serotype-dependent. ○, Galactose; □, *N*-acetyl-galactosamine; ▨, heptose; ⬡, phosphorylethanolamine; ●, glucose; ■, *N*-acetyl-glucosamine; ◇, α2,3 *N*-acetyl-neuraminic acid; ◆, α2,8 *N*-acetyl-neuraminic acid.

Specific features of immune response in PN

- Topografy of antigenic epitopes and clinical phaenotype .
- Cross reactive epitopes in lipids and proteins.
- Epitope spreading .
- Immunoglobulin class,isotype, and disease .

- Neuropathy pathogenesis
- 1.specificity of immunoglobulin
- 2.immunoglobulin class
- 3.other coexisting factors asVEGF in POEMS

Target AG	Immunoglobulin Class	Clinical Syndrome
GM1	lgM	M.N withMMCB
GM1	lgG	axonal GBS

- Topographical distribution of antigen determines the clinical syndrome
- GM1 mainly localised in Ranvier nodes
- Clinical syndrome Motor neuropathy

with multifocal conduction block

Anti-GM1 titers increased more than 1 6400

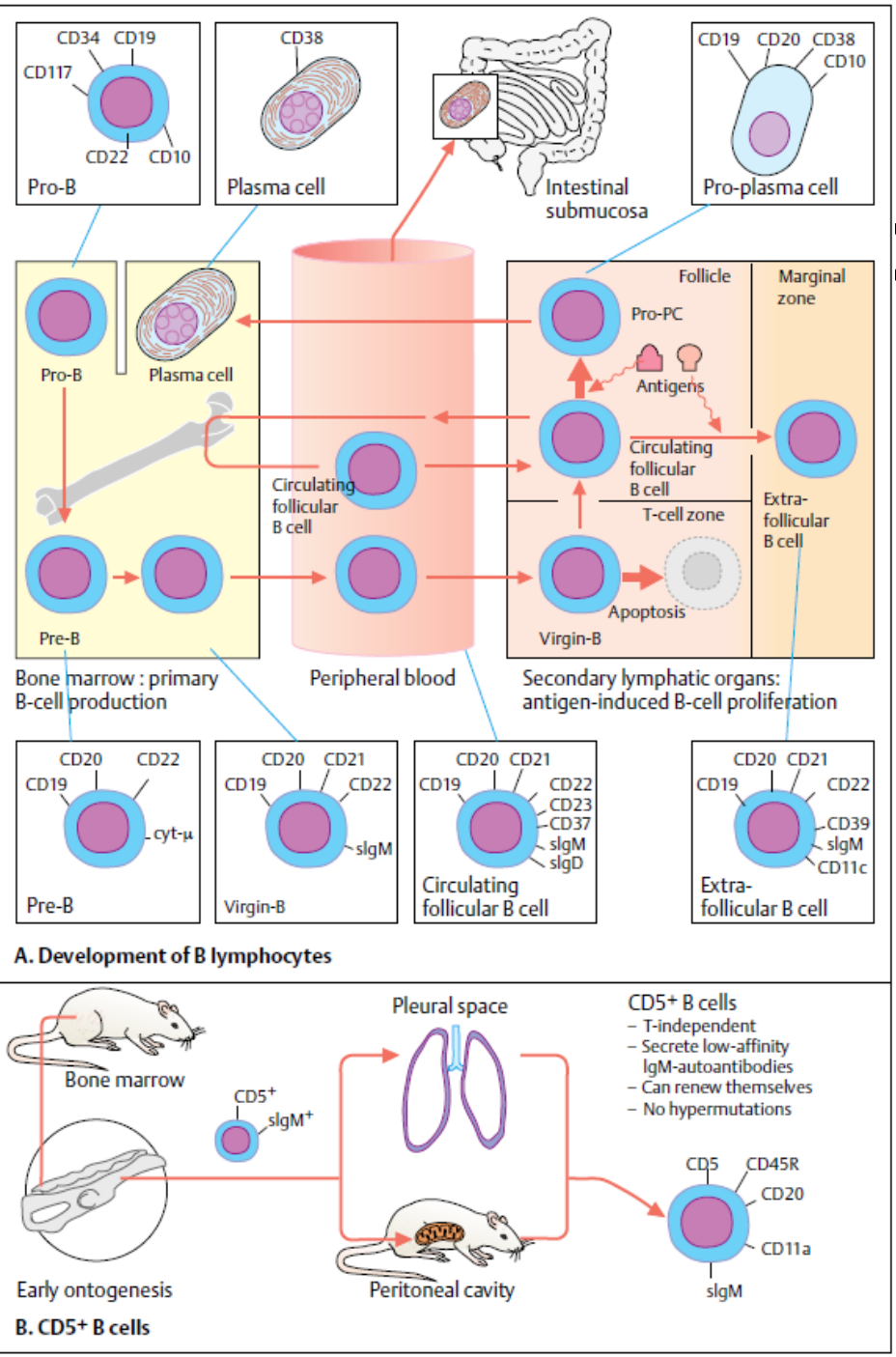
- Molecular mimicry and complex specificities
- During B-cell maturatrion the antibody specificity is altered : restricted to one ganglioside to an affinity of complex ganglioside

- Determination of target antigen gives information about the characteristcs of immune response[e.g anti-GM1 and T-cell independend reactions]

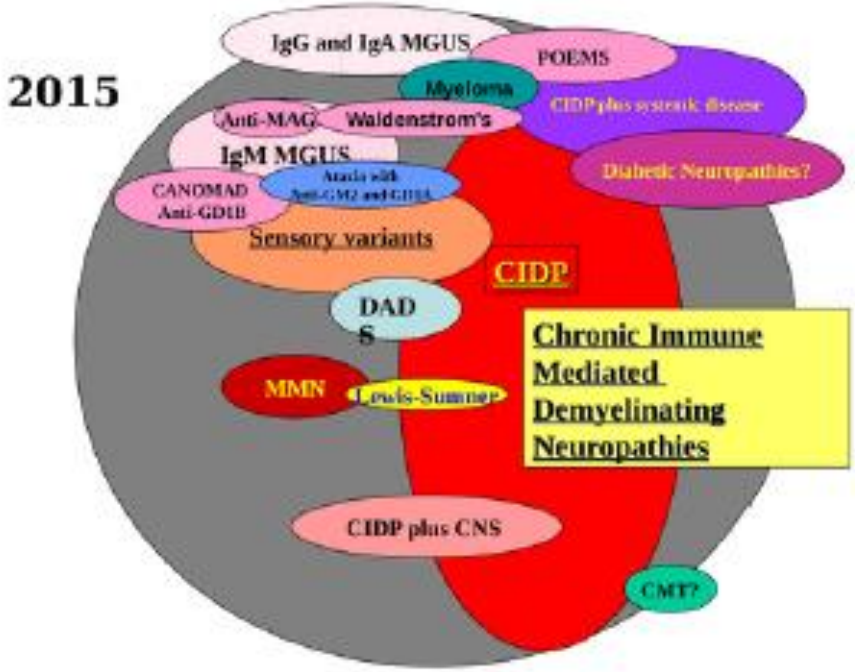
- Natural autoantibodies are range products of innate like B cells that include B1 and marginal B cells
- The example of ABO blood group

B cell

ogeny


CD34 CD19
CD117
CD22 CD10
Pro-B
CD38
Plasma cell
Intestinal submucosa
CD19 CD20 CD38
CD10
Pro-plasma cell
Pro-B
Plasma cell
Circulating follicular B cell
Pre-B
Bone marrow : primary B-cell production
Peripheral blood
Follicle
Marginal zone
Pro-PC
Antigens
Circulating follicular B cell
T-cell zone
Extra-follicular B cell
Apoptosis
Virgin-B
Secondary lymphatic organs: antigen-induced B-cell proliferation
CD20 CD22
CD19
cyt-μ
Pre-B
CD20 CD21
CD19
CD22
sIgM
Virgin-B
CD20 CD21
CD19
CD22
CD23
CD37
sIgM
sIgD
Circulating follicular B cell
CD20 CD21
CD19
CD22
CD39
sIgM
CD11c
Extra-follicular B cell
A. Development of B lymphocytes
Bone marrow
CD5+
sIgM+
Pleural space
CD5+ B cells
– T-independent
– Secrete low-affinity IgM-autoantibodies
– Can renew themselves
– No hypermutations
CD5
CD45R
CD20
CD11a
sIgM
Early ontogenesis
Peritoneal cavity
B. CD5+ B cells

- THE IMPORTAND DISCOVERY OF PATTERN RECOGNITION ANTIBODIES INSTEAD OF SPECIFIC CARBOHYDRATES OR GLYCOLIPIDS

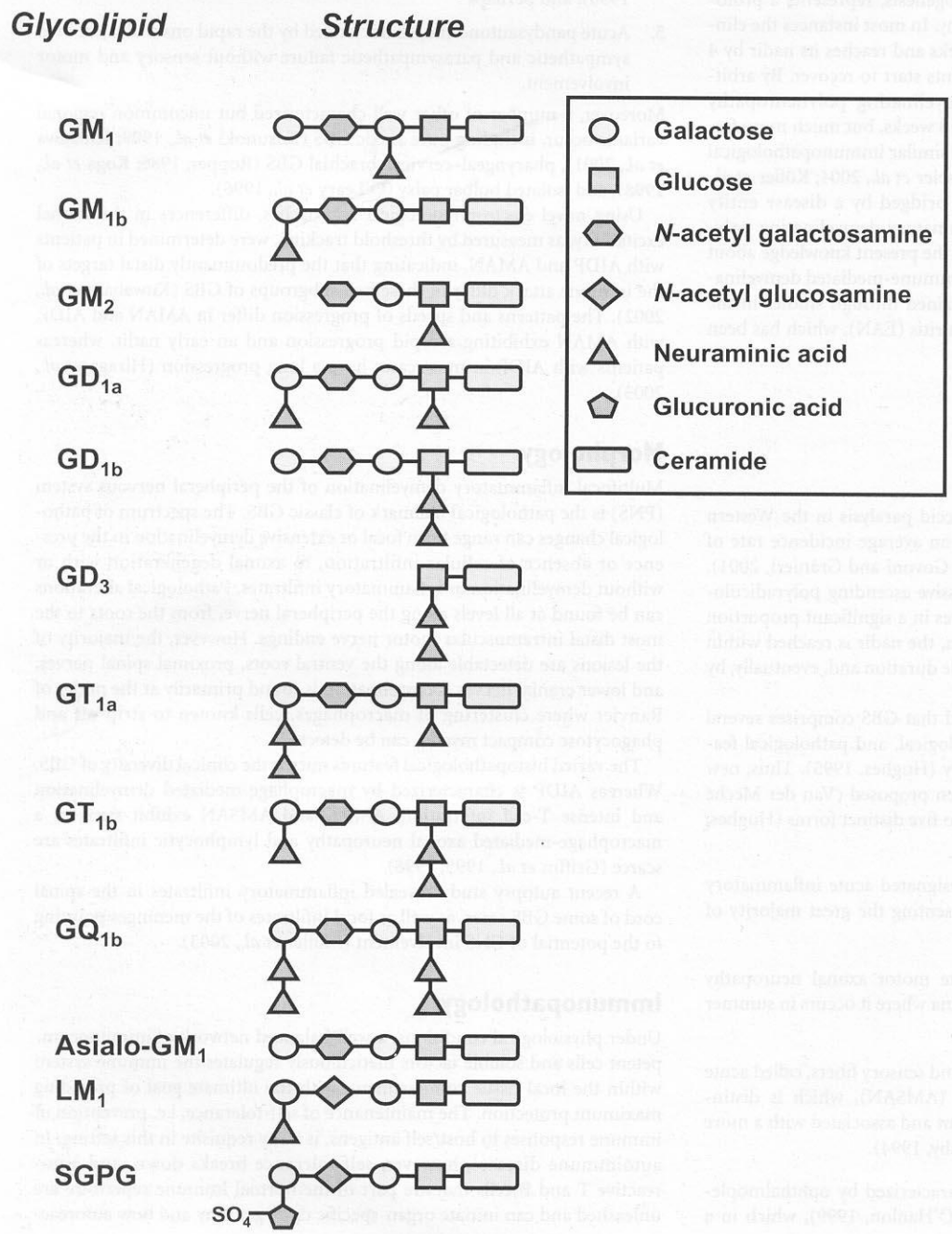


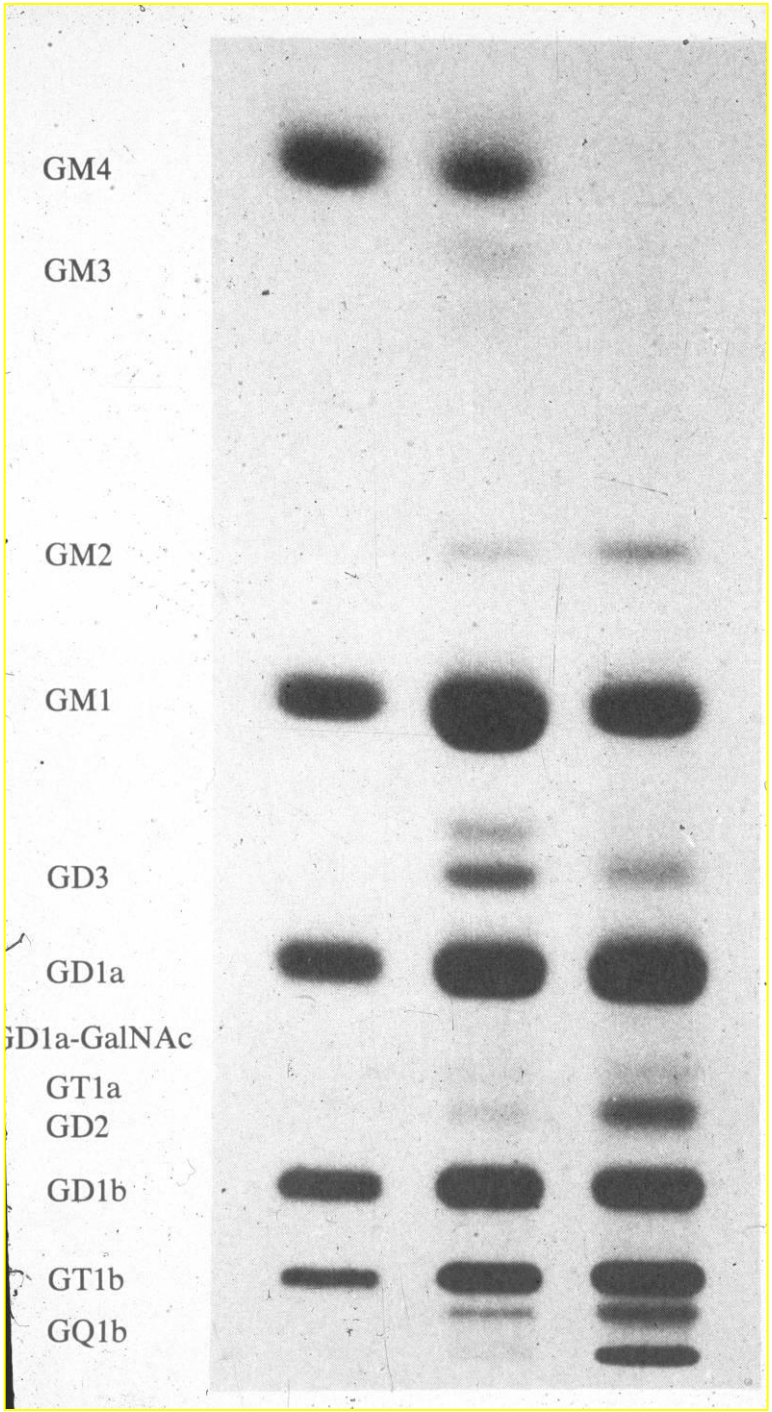
Chronic Immune Mediated Demyelinating Neuropathy (CIMDP)

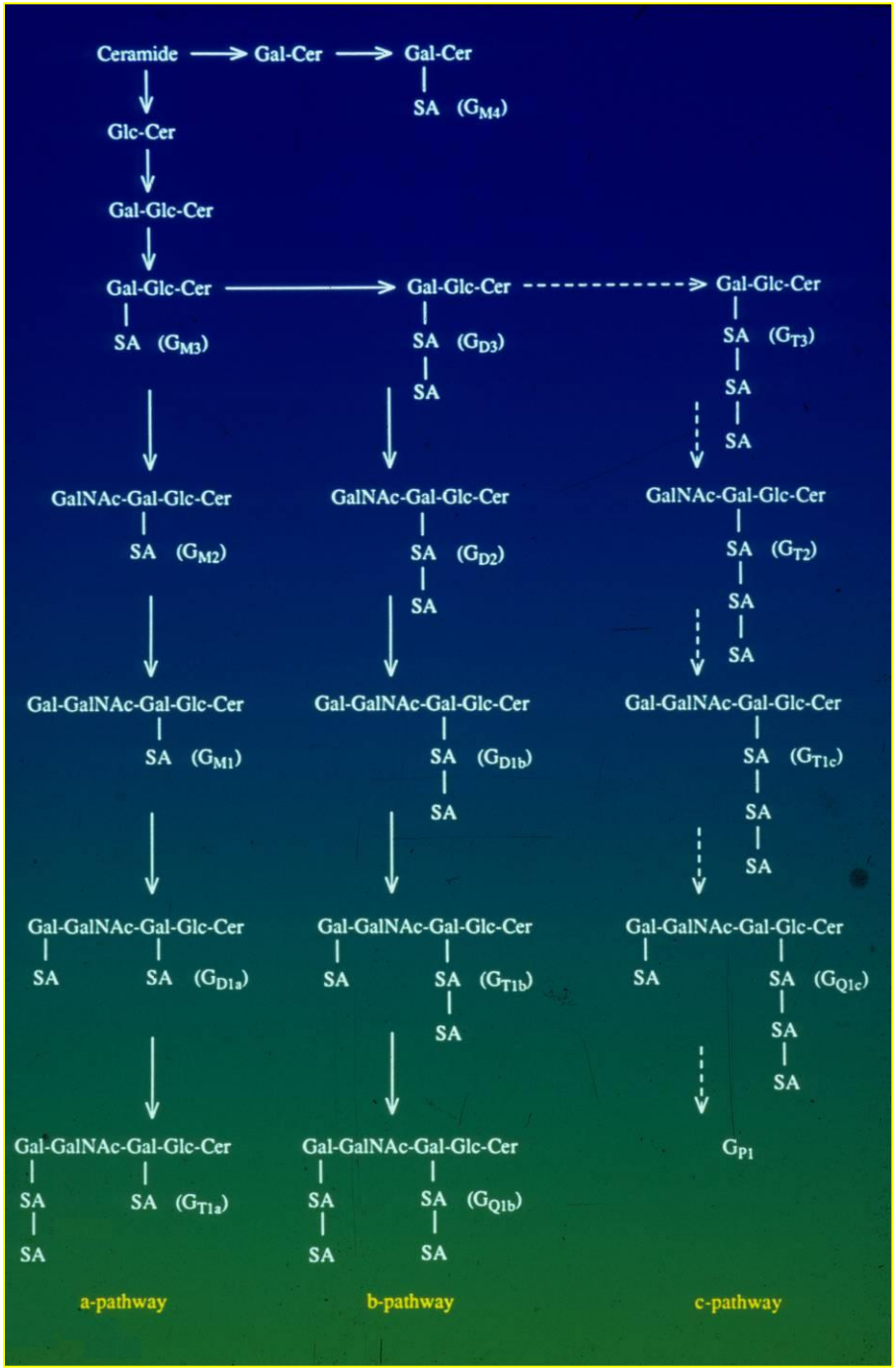
- **CIDP**
  - Classic
  - Variants
- **PARAPROTEIN**
  - Strong Association
    - IgM
    - POEMS
  - Weak Association
    - IgG
    - IgA

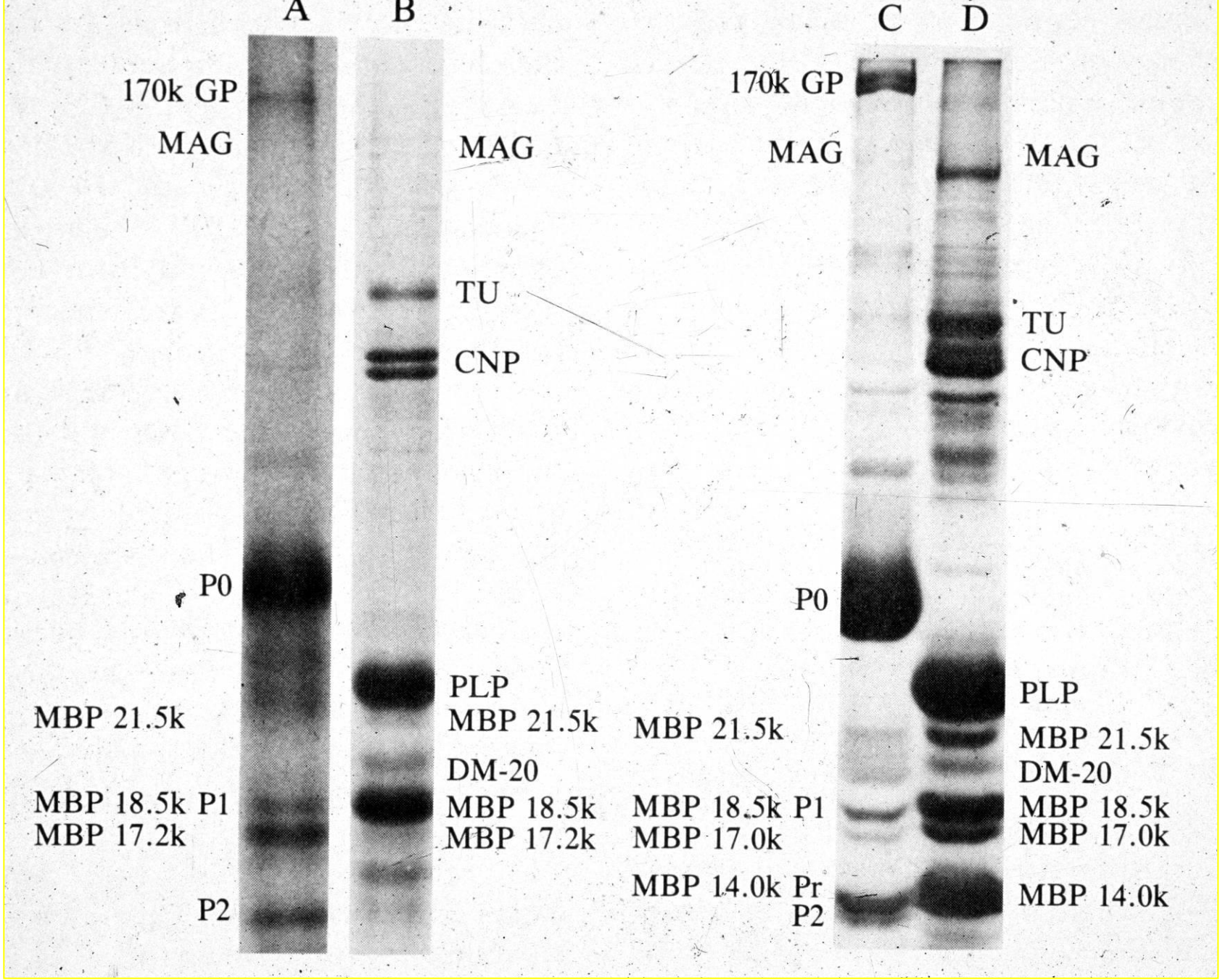
- **CIDP Variants**
  - Sensory Predominant
  - Multifocal
    - Lewis-Sumner
  - With CNS
  - With Diabetes
  - With Autoimmune
  - With Other Disorders

LIPID AND PROTEIN ANTIGENS IN PERIPHERAL NERVE


Glycolipid
Structure
GM1
GM1b
GM2
GD1a
GD1b
GD3
GT1a
GT1b
GQ1b
Asialo-GM1
LM1
SGPG
SO4
Galactose
Glucose
N-acetyl galactosamine
N-acetyl glucosamine
Neuraminic acid
Glucuronic acid
Ceramide


GM4
GM3
GM2
GM1
GD3
GD1a
GD1a-GalNAc
GT1a
GD2
GD1b
GT1b
GQ1b


Ceramide
Gal-Cer
Gal-Cer
SA (G_{M4})
Glc-Cer
Gal-Glc-Cer
Gal-Glc-Cer
Gal-Glc-Cer
Gal-Glc-Cer
SA (G_{M3})
SA (G_{D3})
SA
SA (G_{T3})
SA
SA
GalNAc-Gal-Glc-Cer
GalNAc-Gal-Glc-Cer
GalNAc-Gal-Glc-Cer
SA (G_{M2})
SA (G_{D2})
SA
SA (G_{T2})
SA
SA
Gal-GalNAc-Gal-Glc-Cer
Gal-GalNAc-Gal-Glc-Cer
Gal-GalNAc-Gal-Glc-Cer
SA (G_{M1})
SA (G_{D1b})
SA
SA (G_{T1c})
SA
SA
Gal-GalNAc-Gal-Glc-Cer
Gal-GalNAc-Gal-Glc-Cer
Gal-GalNAc-Gal-Glc-Cer
SA
SA (G_{D1a})
SA
SA (G_{T1b})
SA
SA
SA (G_{Q1c})
SA
SA
Gal-GalNAc-Gal-Glc-Cer
Gal-GalNAc-Gal-Glc-Cer
G_{P1}
SA
SA (G_{T1a})
SA
SA (G_{Q1b})
SA
SA
SA
a-pathway
b-pathway
c-pathway

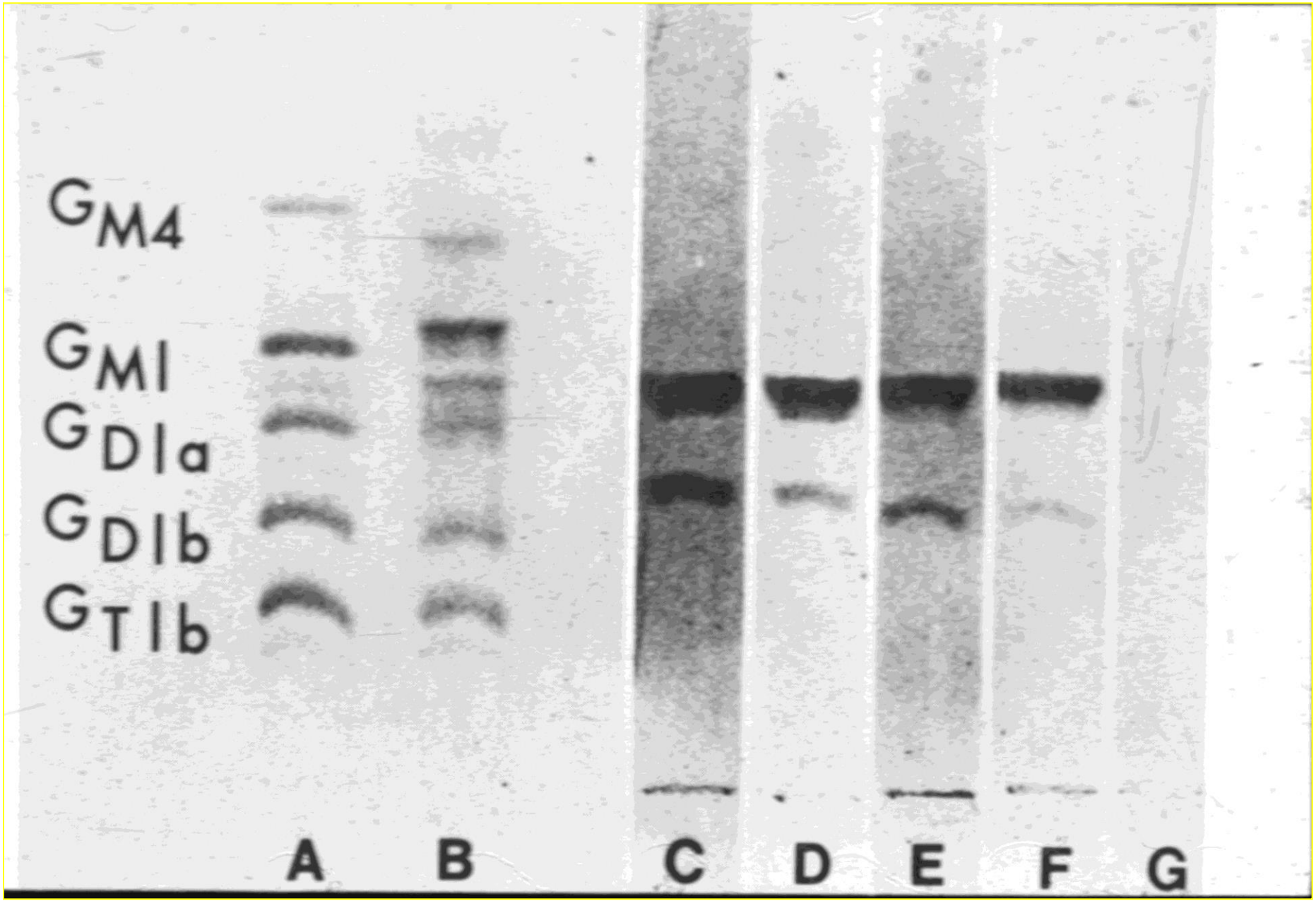

A
B
C
D
170k GP
MAG
P0
MBP 21.5k
MBP 18.5k P1
MBP 17.2k
P2
MAG
TU
CNP
PLP
MBP 21.5k
DM-20
MBP 18.5k
MBP 17.2k
170k GP
MAG
P0
MBP 21.5k
MBP 18.5k P1
MBP 17.0k
MBP 14.0k Pr
P2
MAG
TU
CNP
PLP
MBP 21.5k
DM-20
MBP 18.5k
MBP 17.0k
MBP 14.0k

Specific features of immune response in PN

- Topografy of antigenic epitopes and clinical phaenotype .
- Cross reactive epitopes in lipids and proteins.
- Epitope spreading .
- Immunoglobulin class,isotype, and disease .

Cross-Reactivities : Glycoproteins and Glycolipids

- Anti-MAG antibodies and peripheral nerve
- Anti-GM1 and peripheral nerve
- The concept of intermolecular spreading


GM4
GM1
GDIa
GDIb
GTIb
A
B
C
D
E
F
G

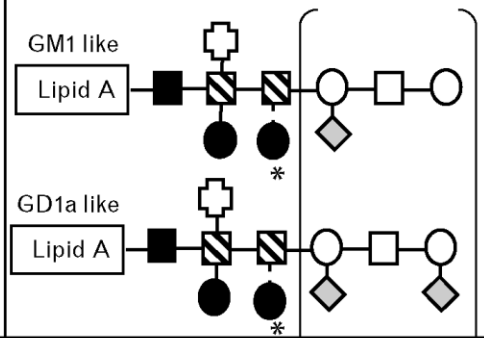
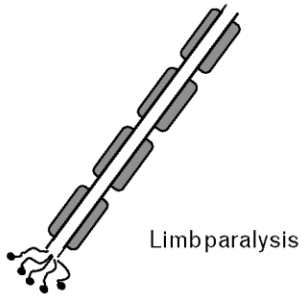
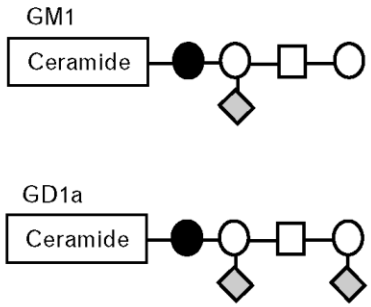
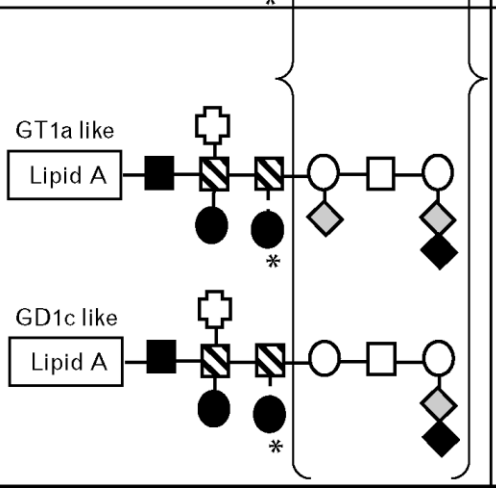
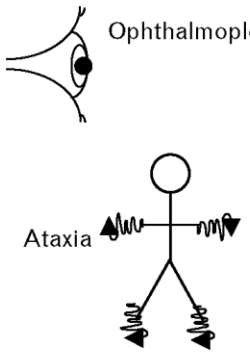
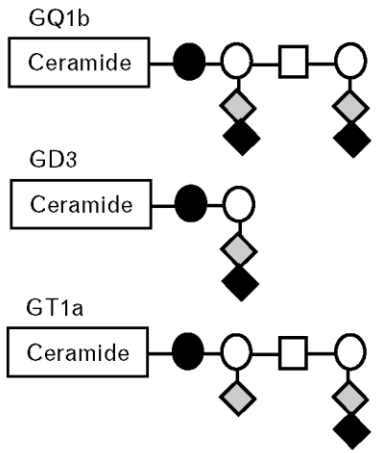
Antigens and molecular mimicry

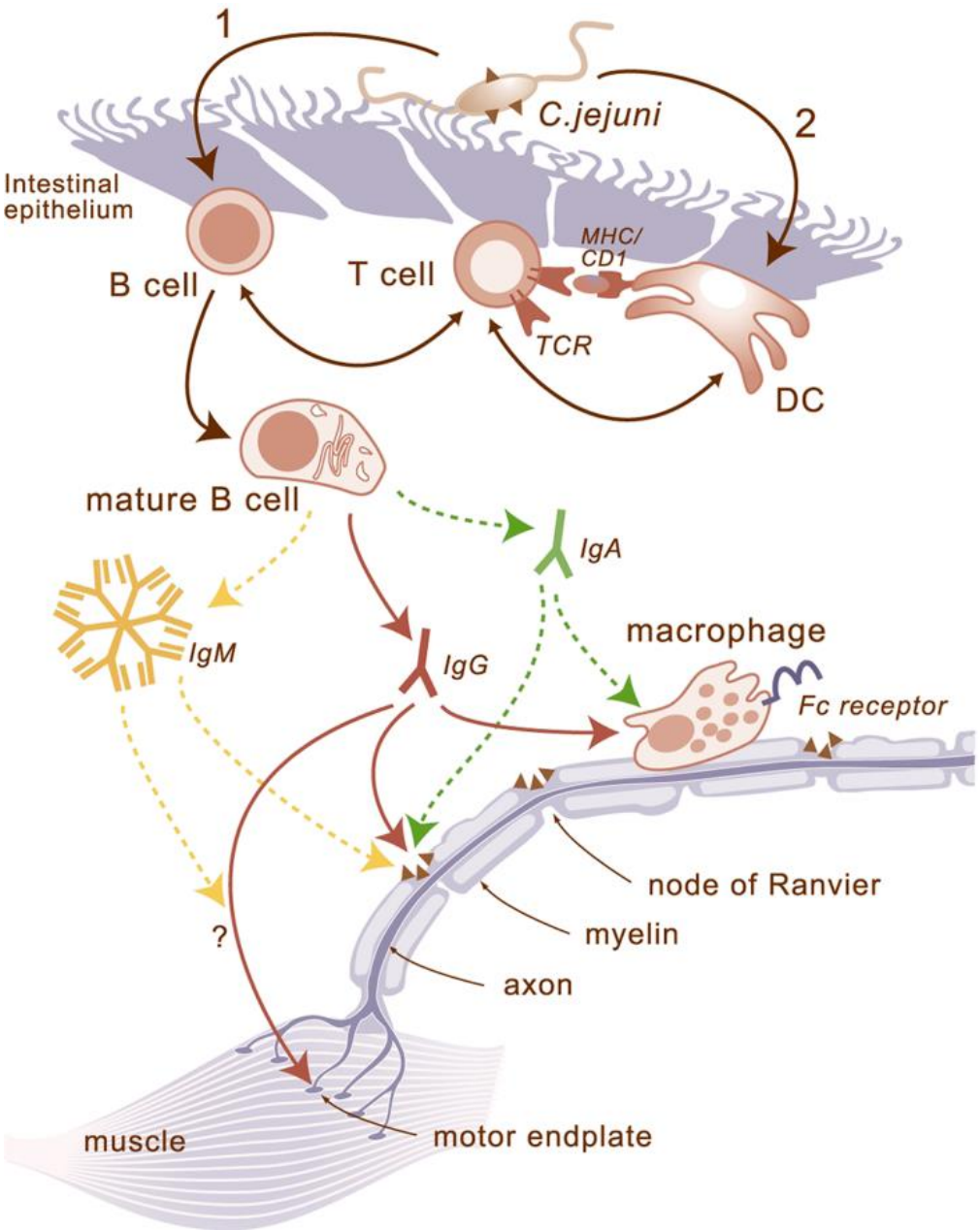
- GM1[MN with MMCB,AMAN]
- GD1a [AMAN]
- GQ1b [MFS]

Microbial infection and autoimmune neuropathy

- Camp jejuni [serotype PennerD19]
- Mycoplasma pneumoniae
- Haemophilus influenza
- Borelia Burgdorfi

Camp.Jejuni and molecular mimicry

C.Jejuni cstII activity	LOS structures produced	Resultant GBS subtype	Human target antigens
Monofunctional (α2,3 sialyltransferase)		**AMAN**  Limb paralysis	
Bifunctional (α2,3 and α2,8 sialyltransferase)		**MFS** 	

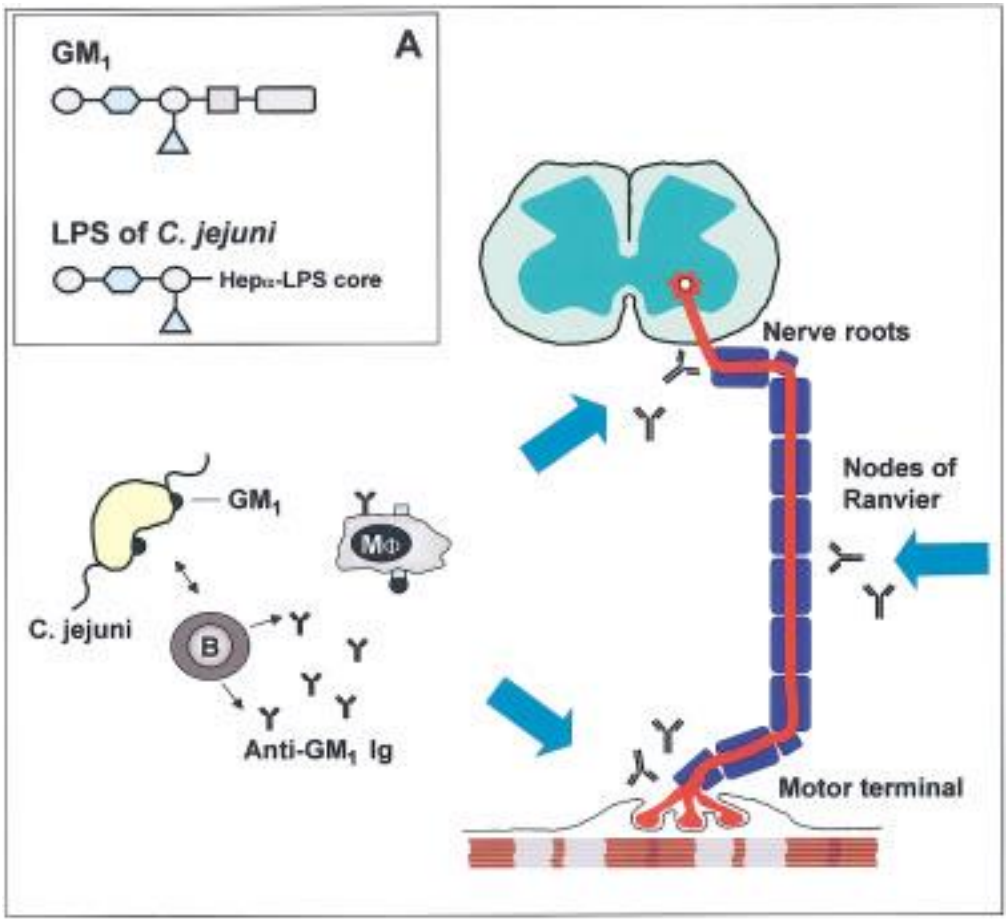

1
C.jejuni
2
Intestinal epithelium
B cell
T cell
MHC/ CD1
TCR
DC
mature B cell
IgA
IgM
IgG
macrophage
Fc receptor
node of Ranvier
myelin
axon
?
muscle
motor endplate

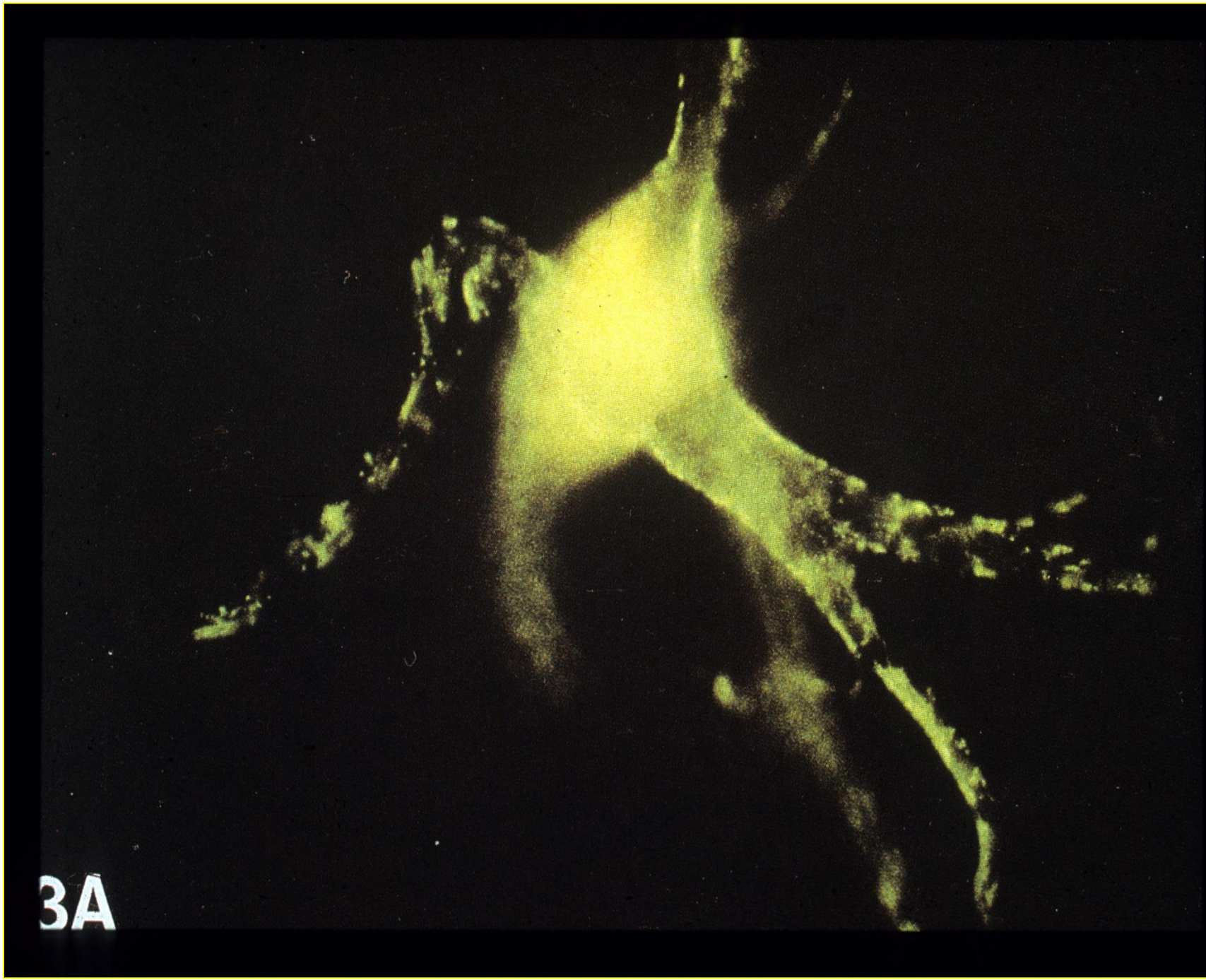
- C.jejuni siasltransferase enzyme cstII

  cstII with a2,3 activity : LOS GM1, mimics[AMAN]

  cstII bifunctional a2,3 and a2,8-csII: disialosylmimics [MFS]

Host factors: CD1 polymorphisms


A
GM1
LPS of C. jejuni
Hep2-LPS core
Nerve roots
Nodes of Ranvier
Motor terminal
GM1
MΦ
C. jejuni
B
Anti-GM1 Ig

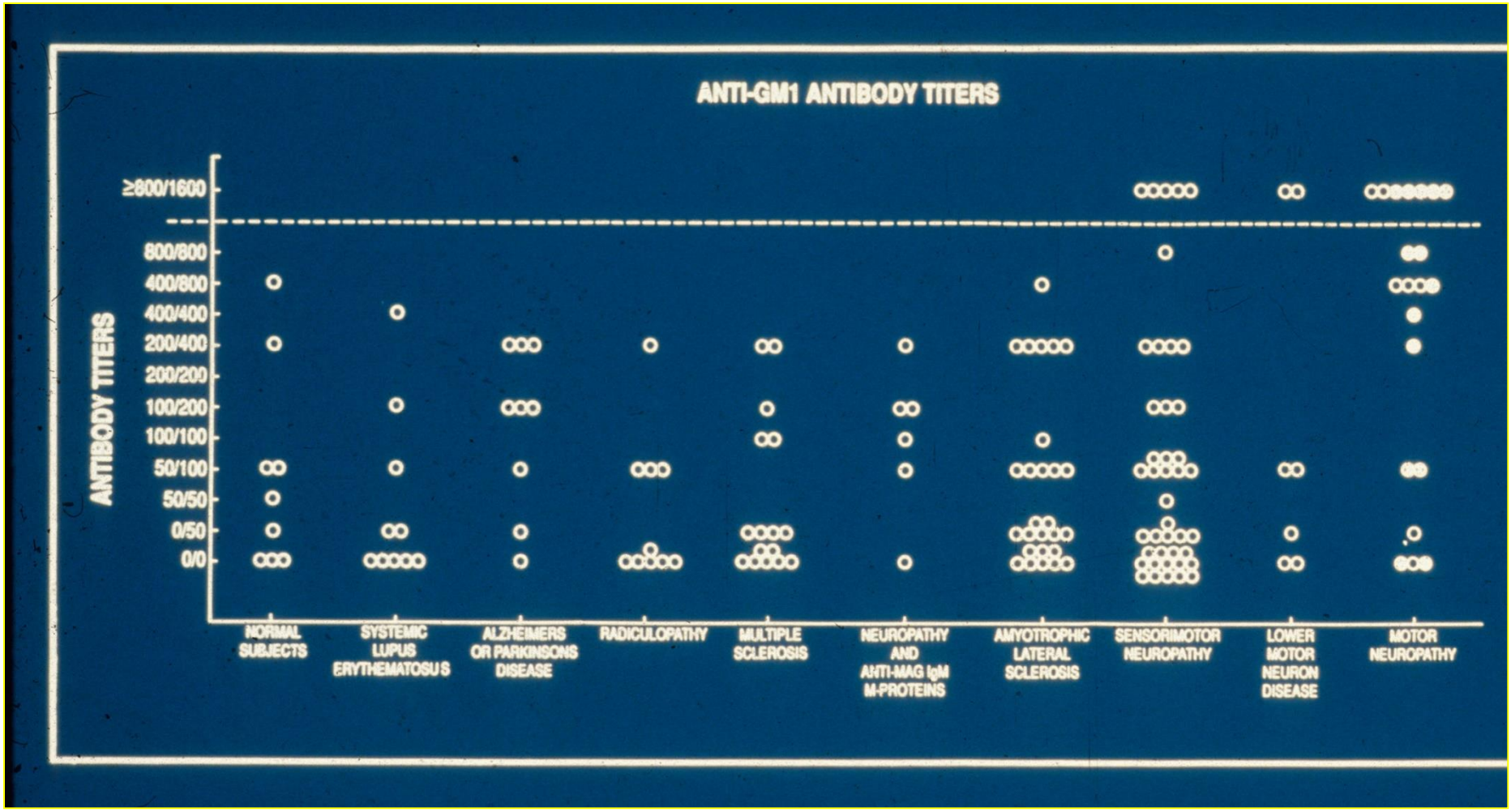

3A

The spectrum of anti-GM1 associated neurologic disorder

1. MN with MMCB [IgM class]
   - -T-cell indepented reaction,natural immune repertoire]
2. AMAN [IgG class igG1 andIgG3 isotypes]

   -molecular mimicry,the role of Camp jejuni
3. LMND

   -controvercial


ANTI-GM1 ANTIBODY TITERS
ANTIBODY TITERS
≥800/1600
800/800
400/800
400/400
200/400
200/200
100/200
100/100
50/100
50/50
0/50
0/0
NORMAL SUBJECTS
SYSTEMIC LUPUS ERYTHEMATOSUS
ALZHEIMERS OR PARKINSONS DISEASE
RADICULOPATHY
MULTIPLE SCLEROSIS
NEUROPATHY AND ANTI-MAG IgM M-PROTEINS
AMYOTROPHIC LATERAL SCLEROSIS
SENSORIMOTOR NEUROPATHY
LOWER MOTOR NEURON DISEASE
MOTOR NEUROPATHY

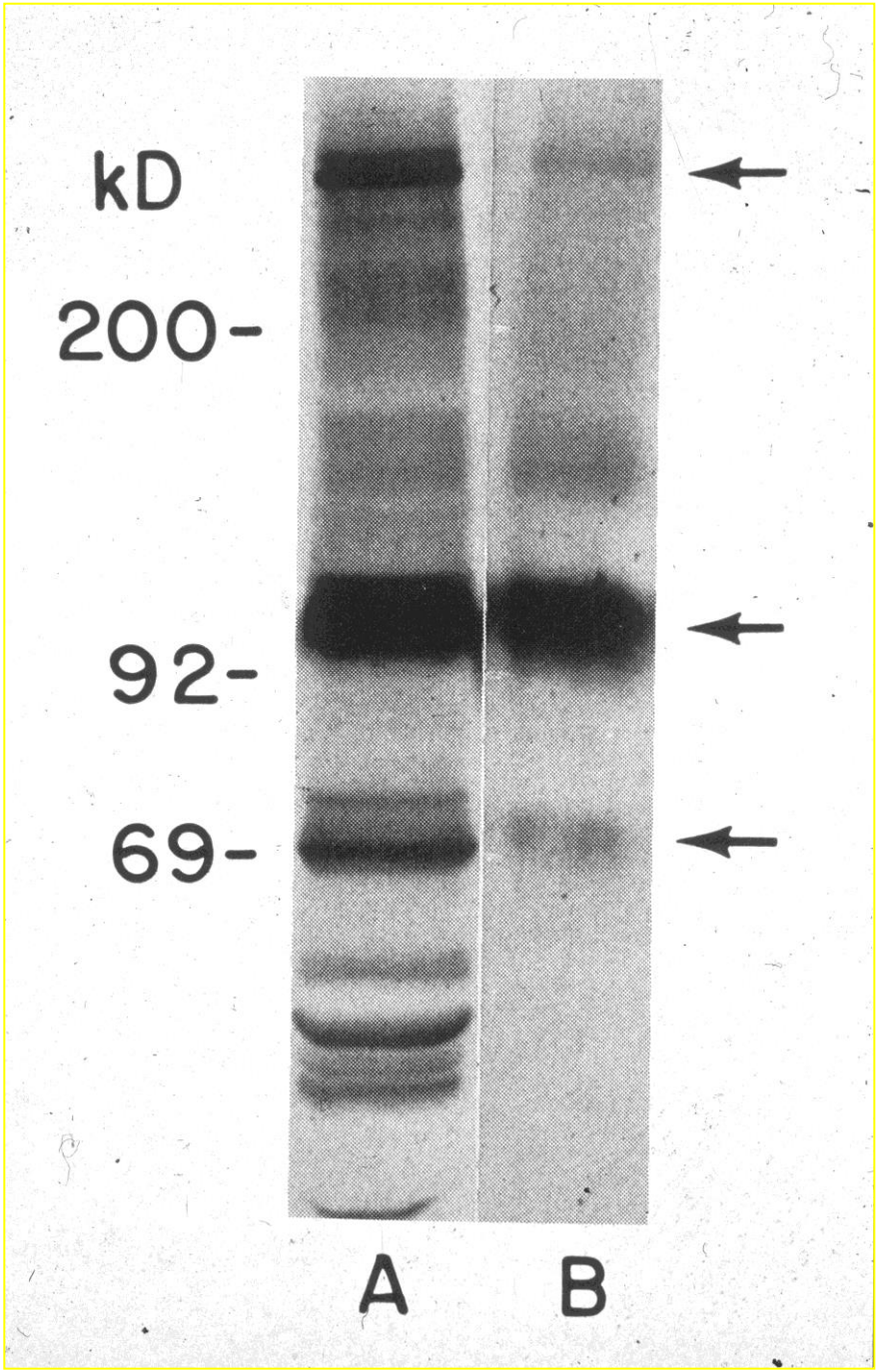
MN withMMCB

- Motor neuropathy
  asymetral neuropathy,upper extremities
  more involved,muscles atrophies
- Motor conduction block in neurophysiology studies
- Anti-GM1 IgM antibodies
- T-cell independent reaction
- Anti-GM1 gathered in Ranvier nodes

Therapy: MN with MMCB

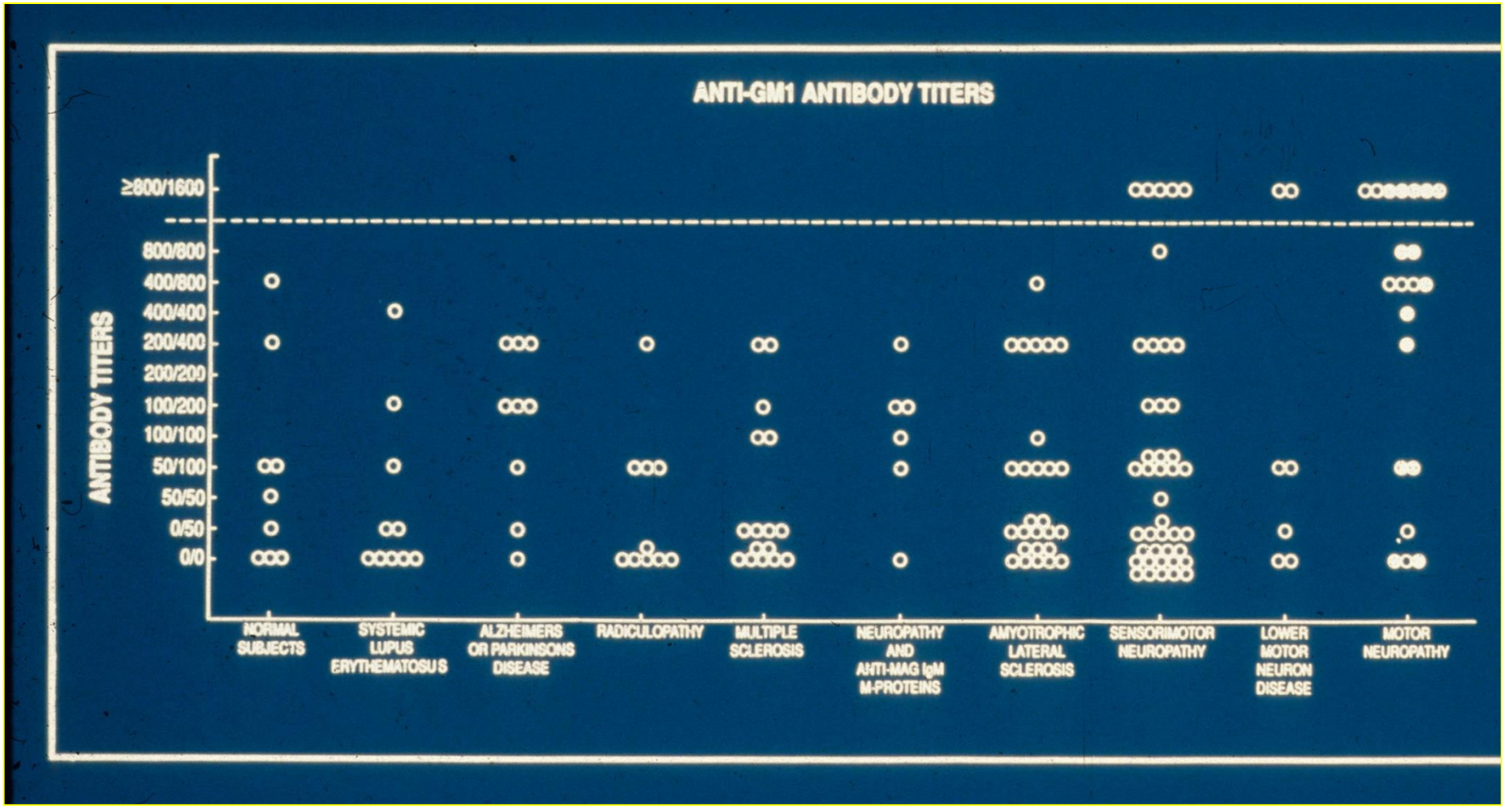
- IVIg
- Cyclocophosphamide
- Corticosteroids worsen the neuropathy

Target AG	Immunoglobulin Class	Clinical Syndrome
GM1	lgM	M.N withMMCB
GM1	lgG	axonal GBS


kD
200-
92-
69-
A
B

GM1 and cross reactivities

- GalGalNack carbohydrate epitope
- GM1,AsGM1
- versican


ANTI-GM1 ANTIBODY TITERS
ANTIBODY TITERS
≥800/1600
800/800
400/800
400/400
200/400
200/200
100/200
100/100
50/100
50/50
0/50
0/0
NORMAL SUBJECTS
SYSTEMIC LUPUS ERYTHEMATOSUS
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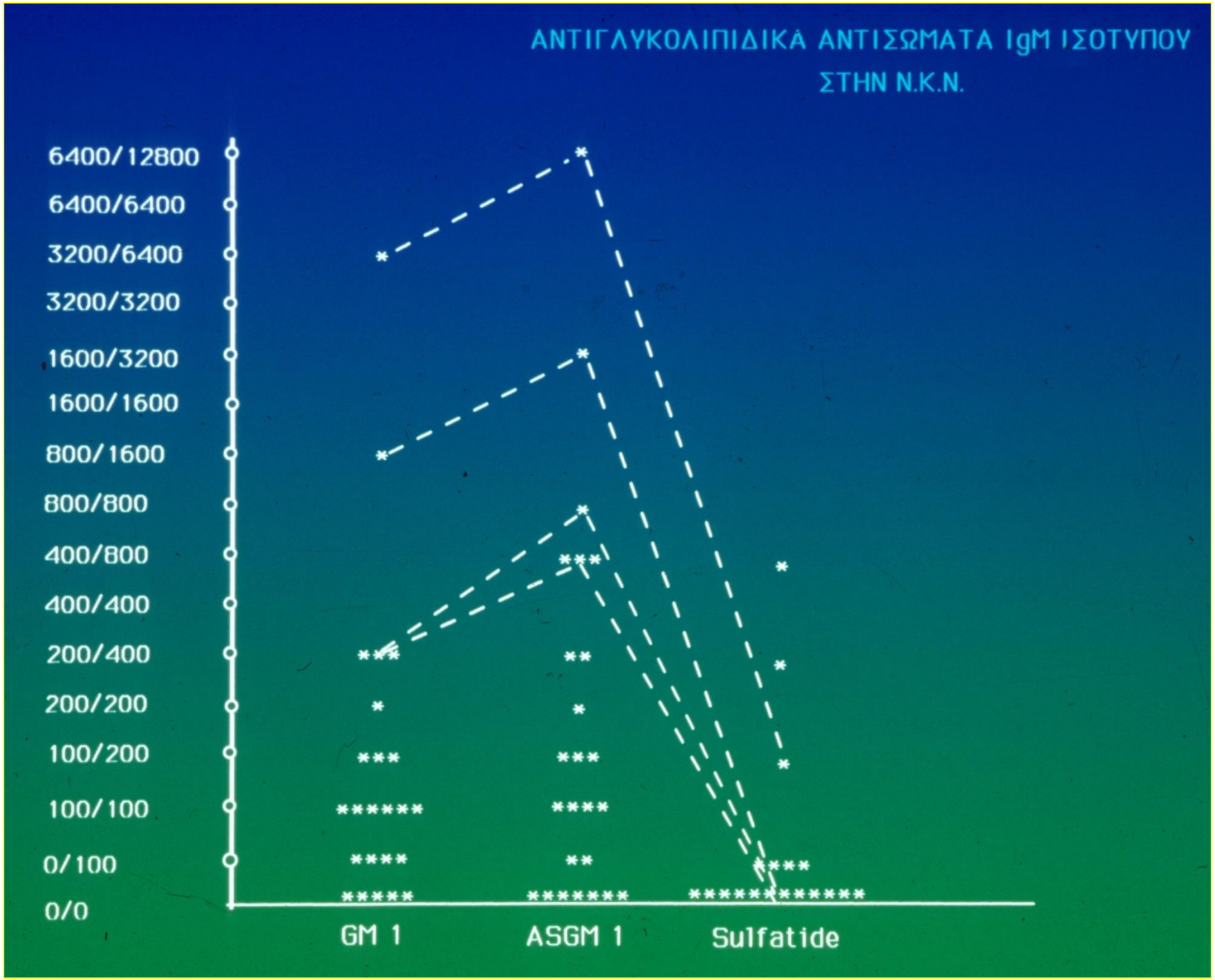
SENSORIMOTOR NEUROPATHY
LOWER MOTOR NEURON DISEASE
MOTOR NEUROPATHY

Binding of serum antibodies to GM_1 and other glycoconjugates

No./Pt	Antigen					
	GM_1	AGM_1	GD_{1b}	GM_2	Gal(β1-3)GalNAc	Gal(β1-3)GlcNAc
1/A.G.	409,600 819,200	13,107,200 13,107,200	3,276,800 3,276,800	50 50	2,048,000 2,048,000	4,096,000 8,192,000
2/H.U.	409,600 819,200	819,200 819,200	409,600 409,600	0 50	512,000 1,024,000	512,000 1,024,000
3/E.K.	25,600 51,200	400 300	0 50	50 50	1,000 2,000	0 0
4/R.M.	25,600 25,600	12,800 12,800	3,200 3,200	200 200	16,000 16,000	500 1,000
5/A.B.	12,800 25,600	204,800 204,800	102,400 204,800	0 50	64,000 64,000	64,000 128,000
6/R.J.	12,800 12,800	1,600 3,200	1,600 3,200	0 50	8,000 8,000	8,000 8,000
7/V.U.	3,200 6,400	51,200 102,400	3,800 3,800	400 800	32,000 64,000	16,000 16,000
8/J.S.	3,200 6,400	6,400 12,800	6,400 12,800	100 100	32,000 32,000	32,000 32,000
9/A.W.	3,200 3,200	6,400 6,400	0 0	800 1,600	32,000 64,000	16,000 16,000
10/L.T.	1,600 3,200	25,600 25,600	400 400	100 100	32,000 32,000	8,000 16,000
11/R.D.	1,600 3,200	51,200 51,200	0 50	1,600 3,200	32,000 32,000	8,000 16,000
12/P.W.	1,600 3,200	800 800	0 0	800 1,600	4,000 8,000	2,000 4,000
13/I.H.	1,600 1,600	6,400 12,800	800 800	0 50	8,000 16,000	16,000 16,000
14/S.P.	800 1,600	6,400 12,800	400 400	0 50	8,000 16,000	8,000 16,000

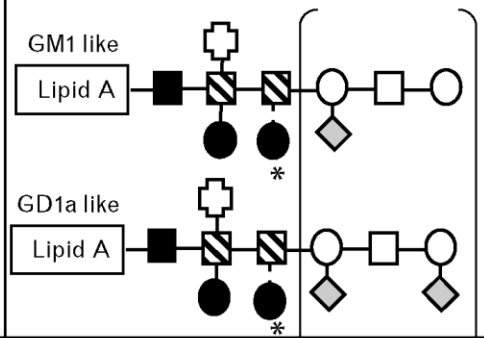
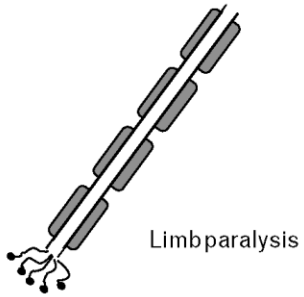
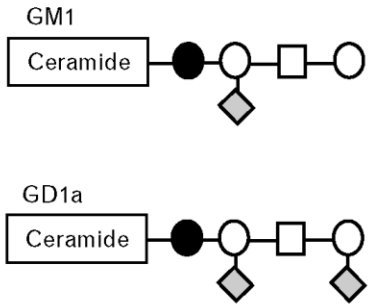
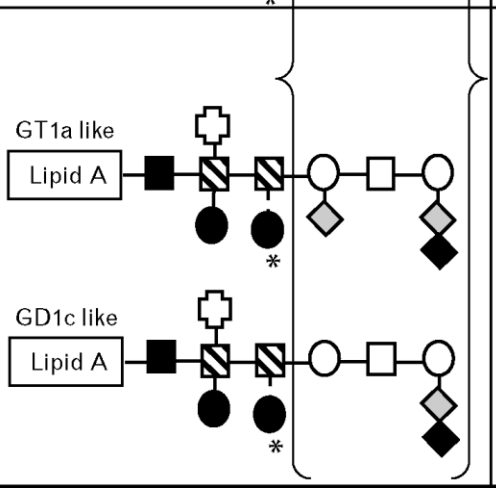
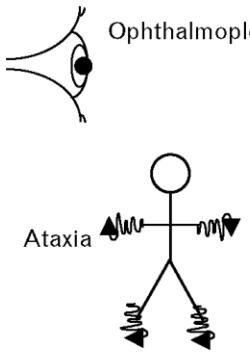
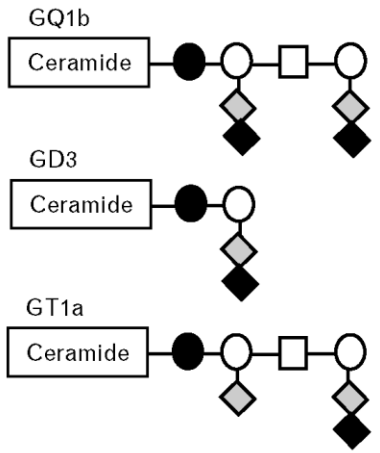
Binding of patients' IgM antibodies to GM_1 and other glycoconjugates. The antigens tested were the gangliosides GM_1, asialo GM_1 (AGM_1), GD_{1b}, and GM_2, and the BSA glycoconjugates Gal(β1-3)GalNAc and Gal(β1-3)GlcNAc.

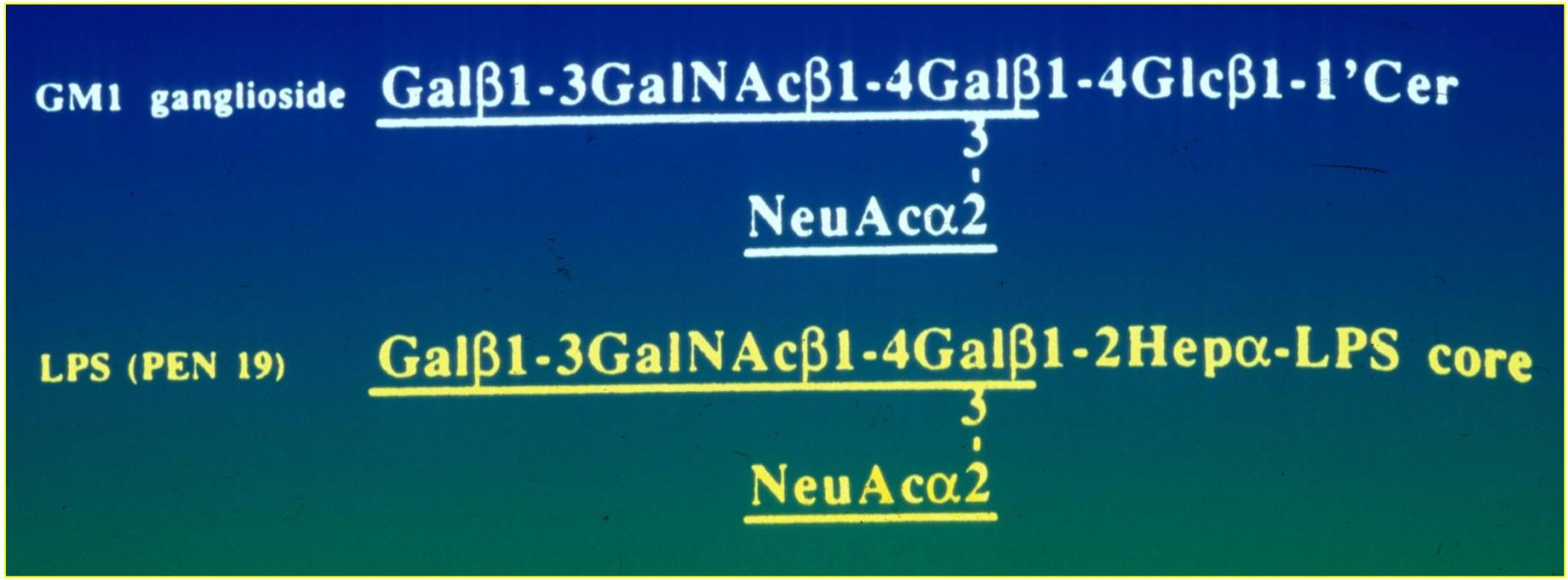

ΑΝΤΙΓΑΛΥΚΟΛΙΠΙΔΙΚΑ ΑΝΤΙΣΩΜΑΤΑ IgM ΙΣΟΤΥΠΟΥ
ΣΤΗΝ Ν.Κ.Ν.
6400/12800
6400/6400
3200/6400
3200/3200
1600/3200
1600/1600
800/1600
800/800
400/800
400/400
200/400
200/200
100/200
100/100
0/100
0/0
GM 1
ASGM 1
Sulfatide

AMAN

- Acute motor axonal neuropathy
- Infection
- China epidemics

Camp.Jejuni and molecular mimicry

C.Jejuni cstII activity	LOS structures produced	Resultant GBS subtype	Human target antigens
Monofunctional (α2,3 sialyltransferase)		**AMAN**  Limb paralysis	
Bifunctional (α2,3 and α2,8 sialyltransferase)		**MFS** 	


GM1 ganglioside
Galβ1-3GalNAcβ1-4Galβ1-4Glcβ1-1'Cer
3
NeuAcα2
LPS (PEN 19)
Galβ1-3GalNAcβ1-4Galβ1-2Hepα-LPS core
3
NeuAcα2

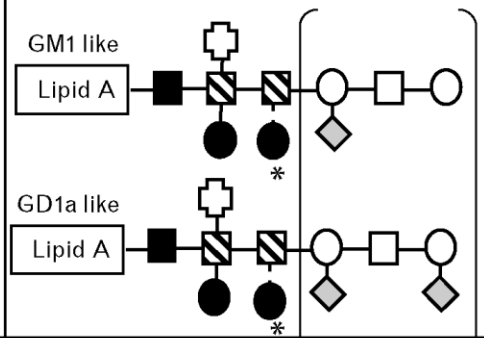
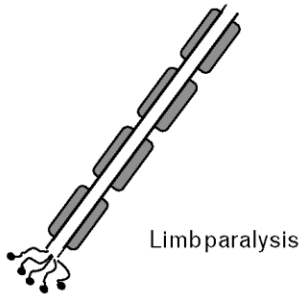
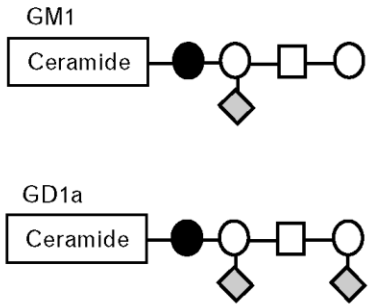
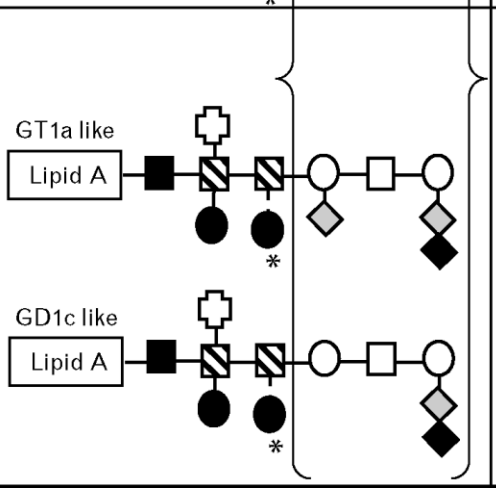
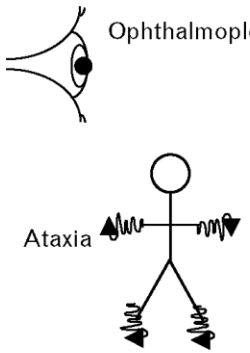
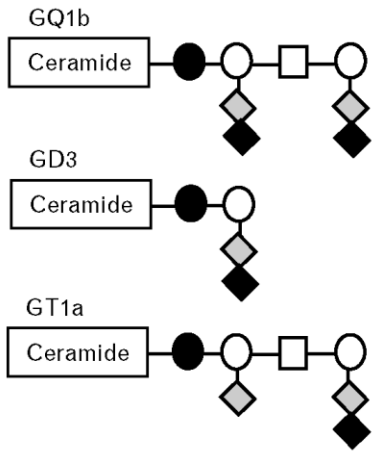
Anti-GD1a spectrum

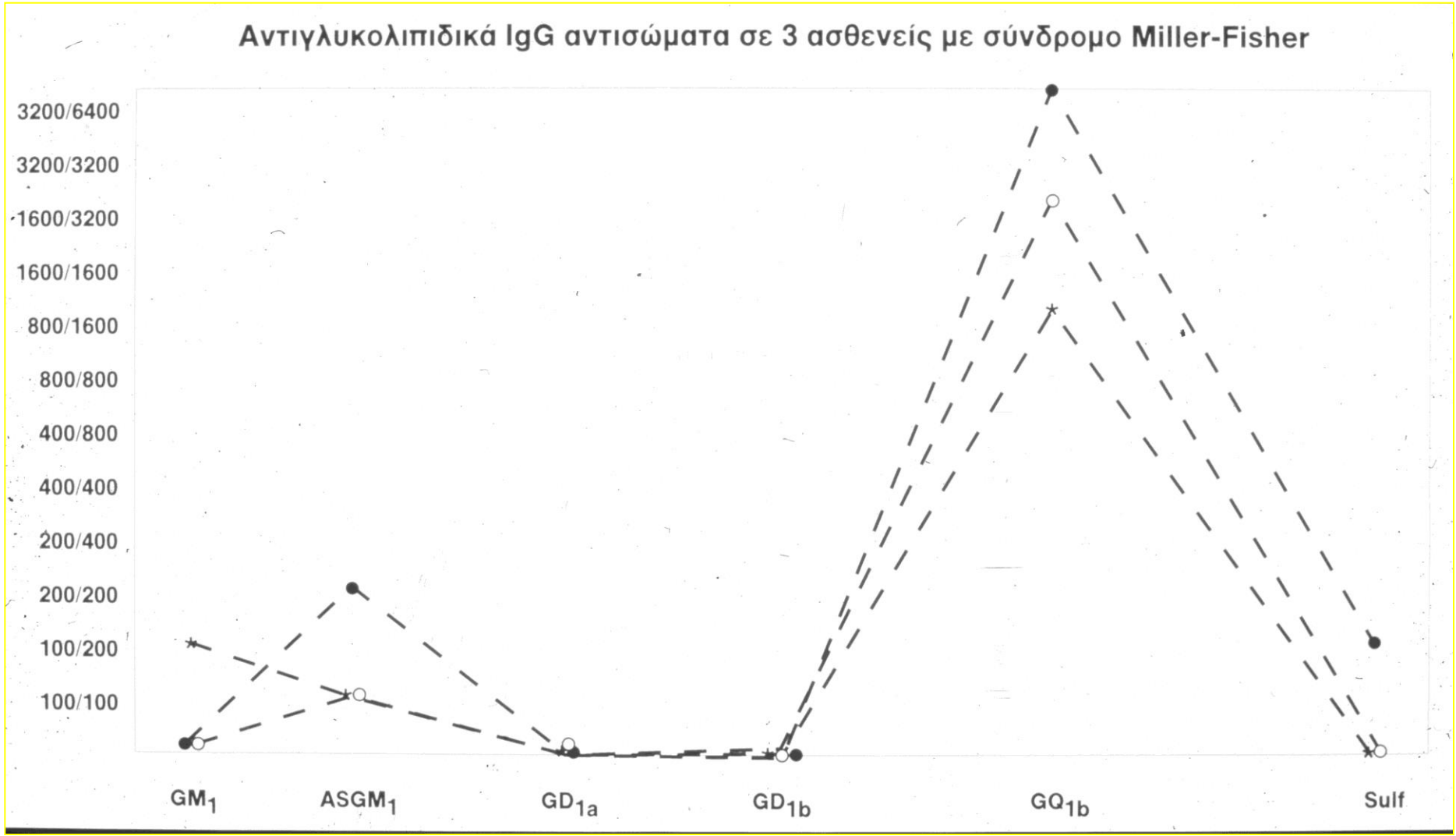
1. IgM in a few neuropathy patients
   - 2% inwhole series
     - MMN[1]
     - CIDP
2. IgG severe axonal GBS withpredecented Camp jejuni infection
   - titers reduced with therapy

s.Miller Fisher

- Clasical triad:ataxia,areflexia,ophthalmoplegia
- Anti-GQ1b IgG antibodies[IgG1,IgG3]
- Anti-GT1a and pharygo-brachial-cervical variant
- Therapy:IVIg,Plasma exchange,
- eculizumab [anti C5b9 mab] under study

Camp.Jejuni and molecular mimicry

C.Jejuni cstII activity	LOS structures produced	Resultant GBS subtype	Human target antigens
Monofunctional (α2,3 sialyltransferase)		**AMAN**  Limb paralysis	
Bifunctional (α2,3 and α2,8 sialyltransferase)		**MFS** 	


Αντιγλυκολιπιδικά IgG αντισώματα σε 3 ασθενείς με σύνδρομο Miller-Fisher
3200/6400
3200/3200
1600/3200
1600/1600
800/1600
800/800
400/800
400/400
200/400
200/200
100/200
100/100
GM1
ASGM1
GD1a
GD1b
GQ1b
Sulf

Στηλη 1 : anti GM1

Στηλη 2 : anti GQ1b

Στηλη 3 : anti GQ1b

Anti-GQ1b

- GQ1b as receptor of botulin toxin
- occulomotor nerves highly enriched
- Complement mediated damage so

eculizumab [anti-MAC mab] effective in therapy.

Ability to interfere toNeuromuscular Junction

Anti-GQ1b spectrum

1. IgM anti-GQ1b :minor percentage in Ganglioside series
   - -a few CIDP cases
   - -in CANOMAD cases [with GD3,GT1b
   - GD1b reactivity]
2. IgGanti-GQ1b :MFS,GBS with opthalmoplegia

Specific features of immune response in PN

- Topografy of antigenic epitopes and clinical phaenotype .
- Cross reactive epitopes in lipids and proteins.
- Epitope spreading .
- Immunoglobulin class,isotype, and disease .

Mycoplasma infection and neuropathy

- Anti-GM1 and anti-GalC antibodies generation [Suzuki etal2004,]
- The role of anti-GalC uncertain for AIDP,AMAN
- Cholera toxin B-subunit and rabidanti-GM1 IgG stained band in lipid extracts of mycoplasma

Lyme neuropathy

1.Infection

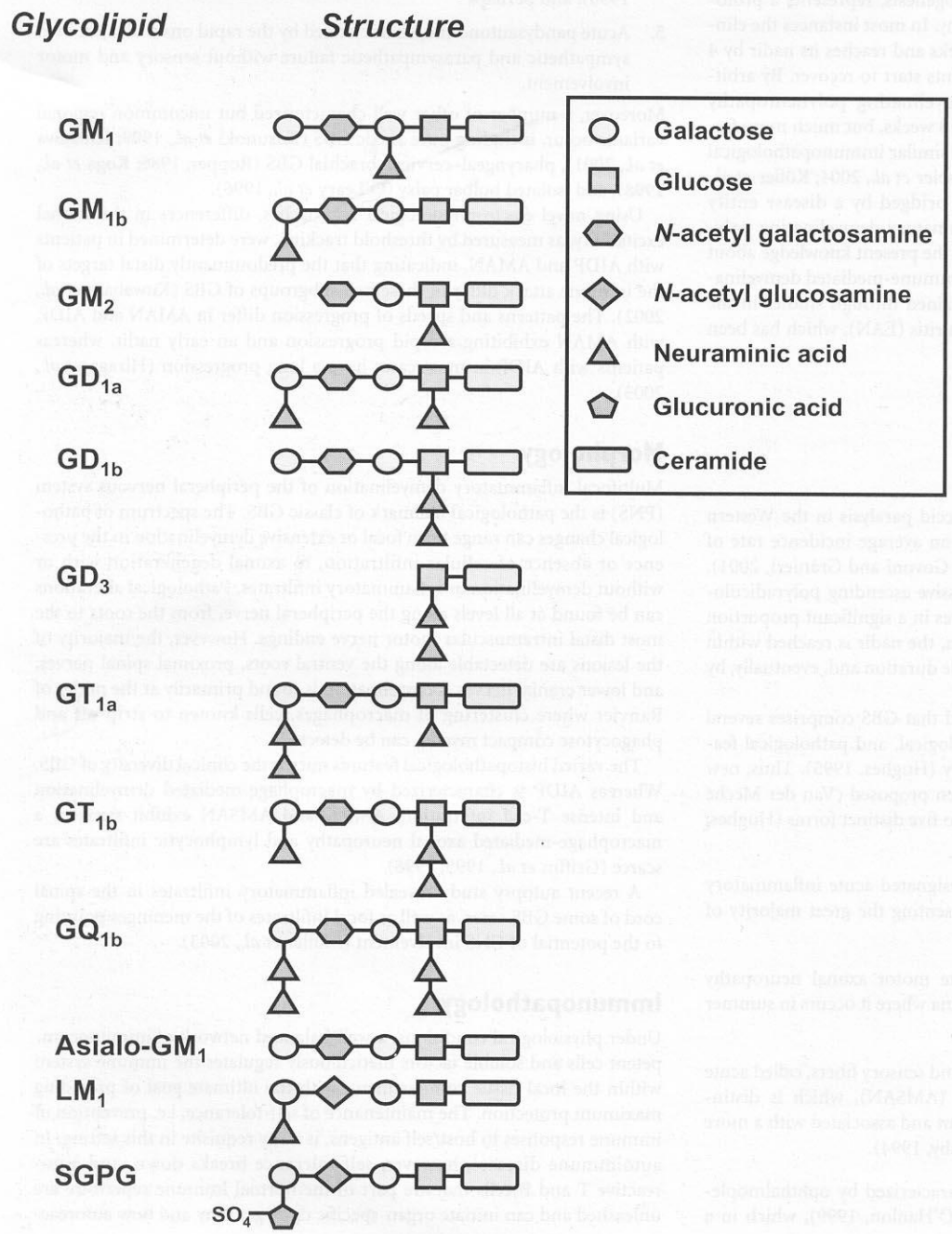
2.Molecular mimicry

- - generation anti-ganglioside ab [Garcia et al1995] etal
- - anti-flagelin ab cross react to neural antigens[Sigal etal1997
- -Anti-OspA peptides[identical cDNA sequence from brain
- Tissue[Alaedini 2005]

-

Haemophilus infl and neuropathy

- strain isolation frm MFS patient reveal bifunctional sialyltransferase activity producing disialosyl group structures linked toterminal Gal


Glycolipid
Structure
GM1
GM1b
GM2
GD1a
GD1b
GD3
GT1a
GT1b
GQ1b
Asialo-GM1
LM1
SGPG
SO4
Galactose
Glucose
N-acetyl galactosamine
N-acetyl glucosamine
Neuraminic acid
Glucuronic acid
Ceramide

Σχολια-1

- Σε ασθενεις με καθαρο συνδρομο κατωτερου κινητικου νευρωνος υποστηριζομενο από νευροφυσιολογικα ευρηματα [με η χωρις διαταραχες αγωγιμοτητος] η παρουσια ηυξημενων τιτλων IgM αντ-GM1 η GD1α βοηθα στην αποκαλυψη ανοσολογικου συνδρομου

Σχολια-2

- Σεκυριως αισθητικη αξονικη νευροπαθεια μεγαλων ινων και μονομλονικη IgM ηανιχνευσις αντι-GD1b καθοριζει ανοσολογικομ συνδρομο
- Σε οξεια γενικευμενη αδυναμια ο καθορισμος αντ-GM1 η αντι-GD1a [IgG class]μπορει να διαφοροδιαγνωση AMAN η και GBS η άλλες αιτιες αδυναμιας όπως μυασθενεια΄,βοτουλινισμο και αλλα

Σχολια -3

- Σε οξεια οφθαλμοπαρεση με η χωρις αλλη προσβολη κρανιακων νευρων ,αταξια η γενικευμενη νευροπαθεια ο καθορισμος των αντι-GQ1b IgG αντισωματων υποστηριζει την διαγνωση συνδρομου Miller Fisher και διαφοροδιαγιγνωσκει τους ασθενεις αυτους από εκεινους της νοσου των νοσου Lyme σαρκοειδοσεως και νεοπλαστικης μηνιγγιτιδος

In conclusion

- Motor neuropathy:anti-GM1-ASGM1,-GM2 IgM
- Sensory demyelinative neuropathy:anti-MAG/SGPG,
- Sensory axonal: anti-Sulfatide,-GD1b,-Hu -SGPG,ANA SS-A,SS-B [Sjogren],ANCA – DNA RF[vasculitis] ,dual MAG
- AMAN :anti-GM1 IgG,-GD1a IgG
- Acute opthalmoplegia :anti-GQ1b