RESEARCH UPDATE
GBS AND CIDP

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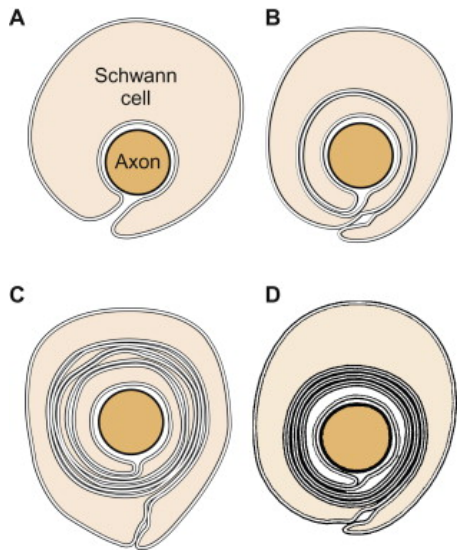
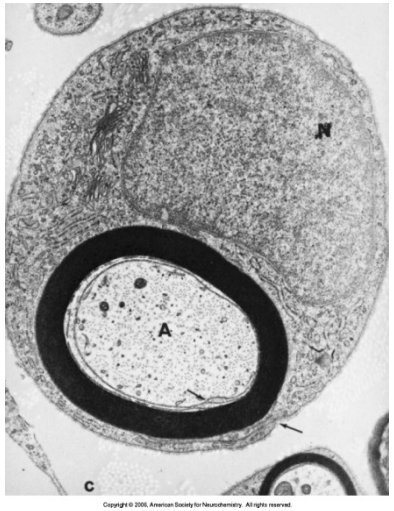
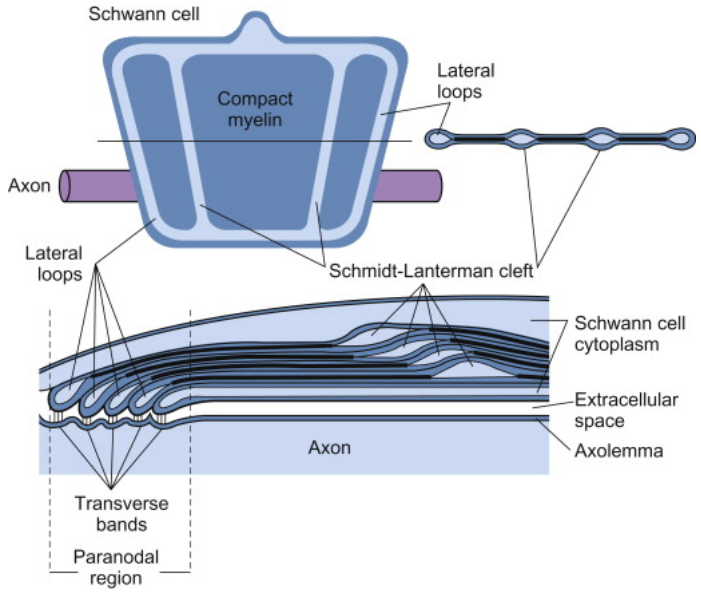
DISCLOSURES

- **Robert P Lisak over the past 2 years has been funded for research support by the National Institutes of Health, National Multiple Sclerosis Society (USA), Genentech, Teva Pharmaceuticals, Novartis, Medimmune, Ra Pharmaceuticals, Argenx and Chugai. He has served as a consultant to Argenx, Novartis, Mallinckrodt GLG, Syntimmune, Alexion, Argenx, Alpha Sites, Insights Consulting, Informa Pharma Consulting, Slingshot Consulting, Schlesinger Group Consulting, Health Choices. He has served on speakers bureau for Teva Pharmaceuticals (non-branded talks only)**







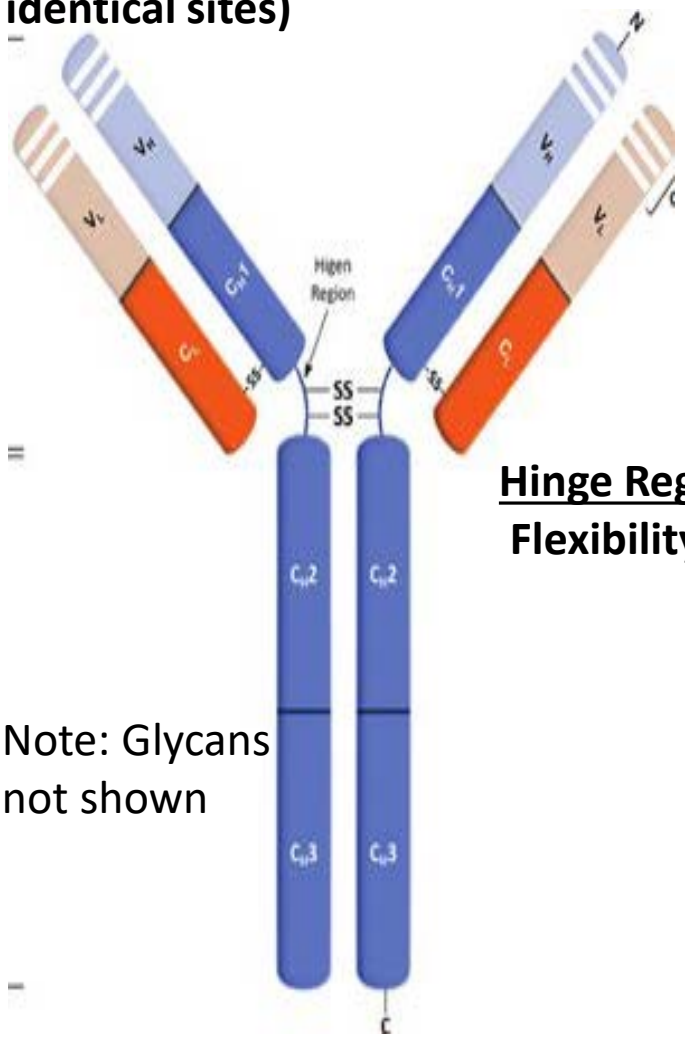
Macklin and Rasband, Chapter 31, Basic Neurochemistry 8th edition, 2011

Research Updates in GBS

- Inhibition of the complement ‘cascade’ as ‘add on’ therapy in GBS
  - Inhibition of C5-C5a to C6 inhibition the MAC 5-9 which damages cells
  - Inhibition of other steps including C1 activation to C1q
- Several studies looking at possible “biomarkers” in GBS (and CIDP)
- Several studies on GBS in poorer countries including Zika virus related
- Use of animal models to study reducing axonal damage in immune neuropathies
- Animal models looking at inflammatory mediators and stimulators of inflammatory cells

Prototypic Ig Structures

Fab: Antigen Binding Domain (2 identical sites)

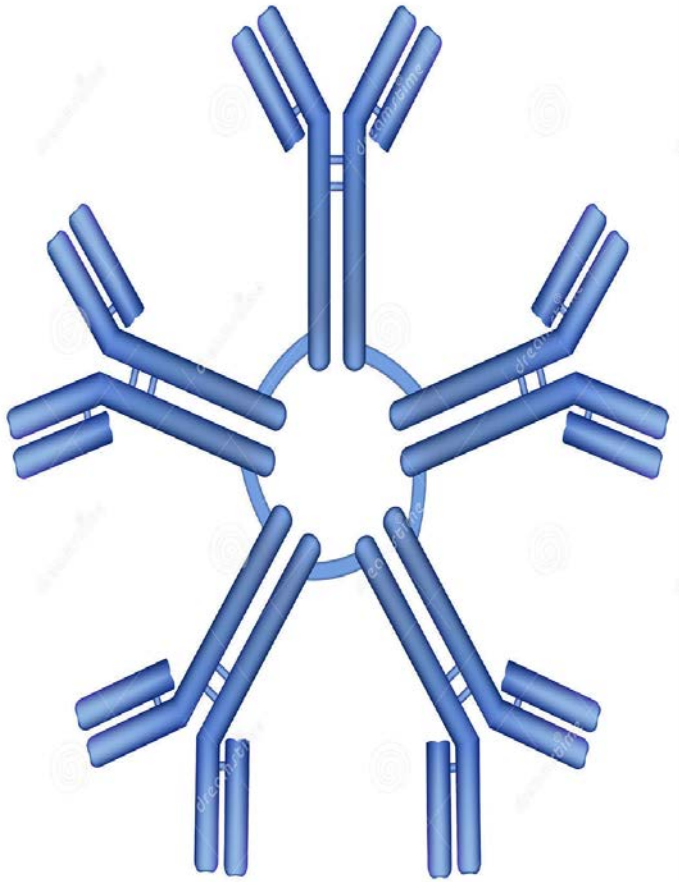


Hinge Region: Flexibility

Note: Glycans not shown

Fc: Effector/Interaction Domains

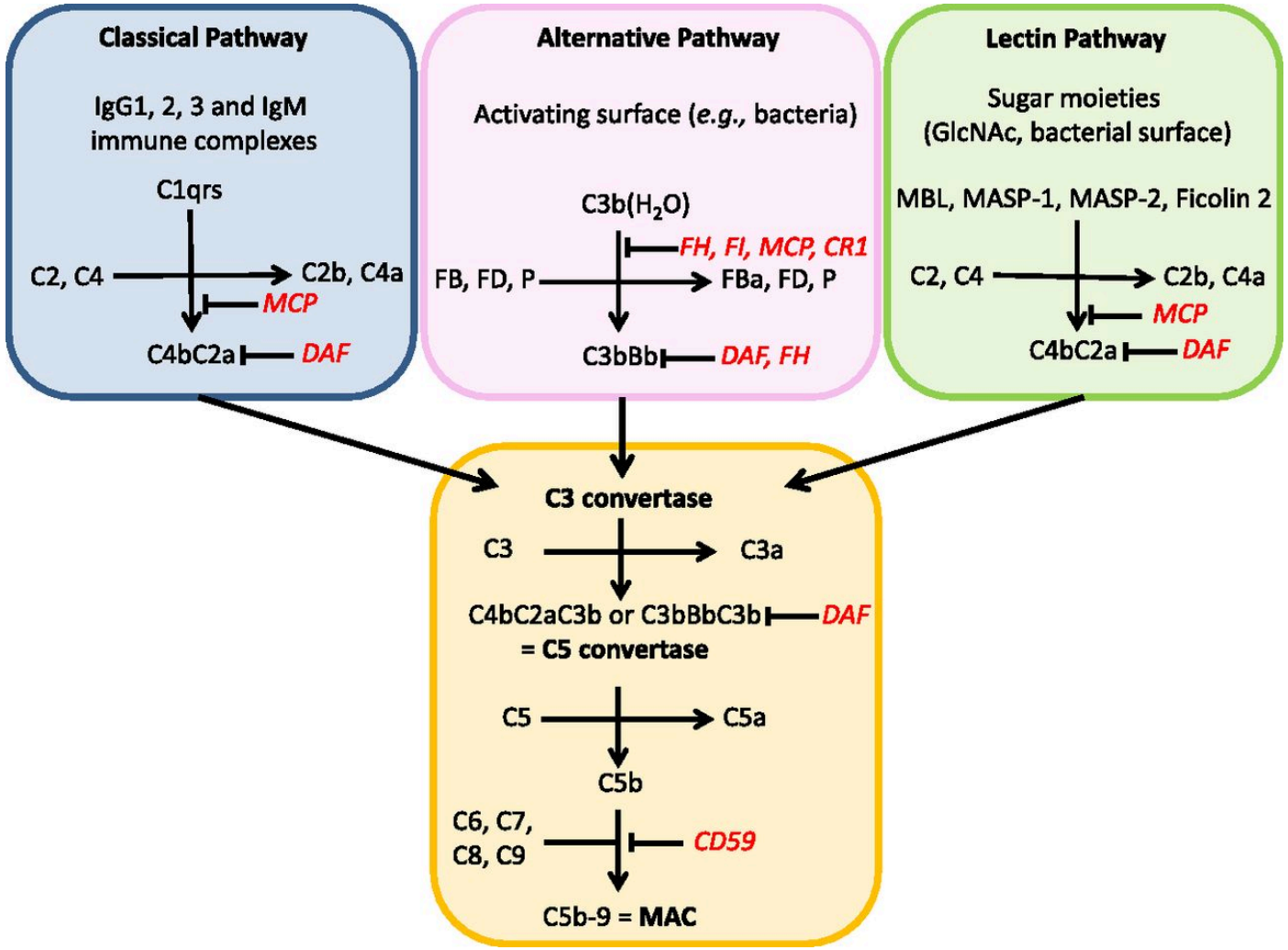
γ 1–4 Heavy Chains Determine Function



IgM: 5 x 4 chain Ig protomers with μ heavy chains 1 joining (J chain)

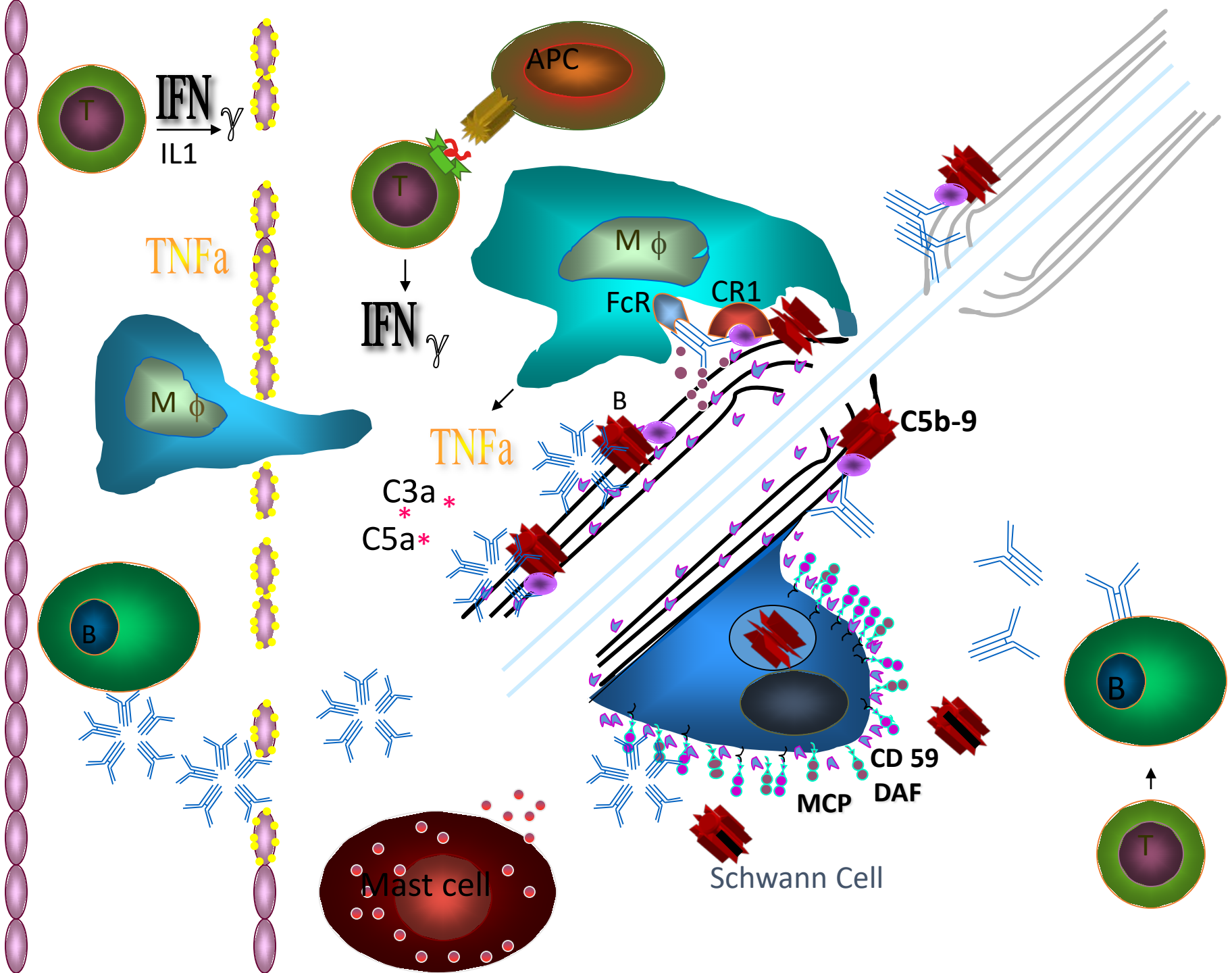
MW= 790,000- mostly intravascular or bound to Ag

Three pathways of complement activation.



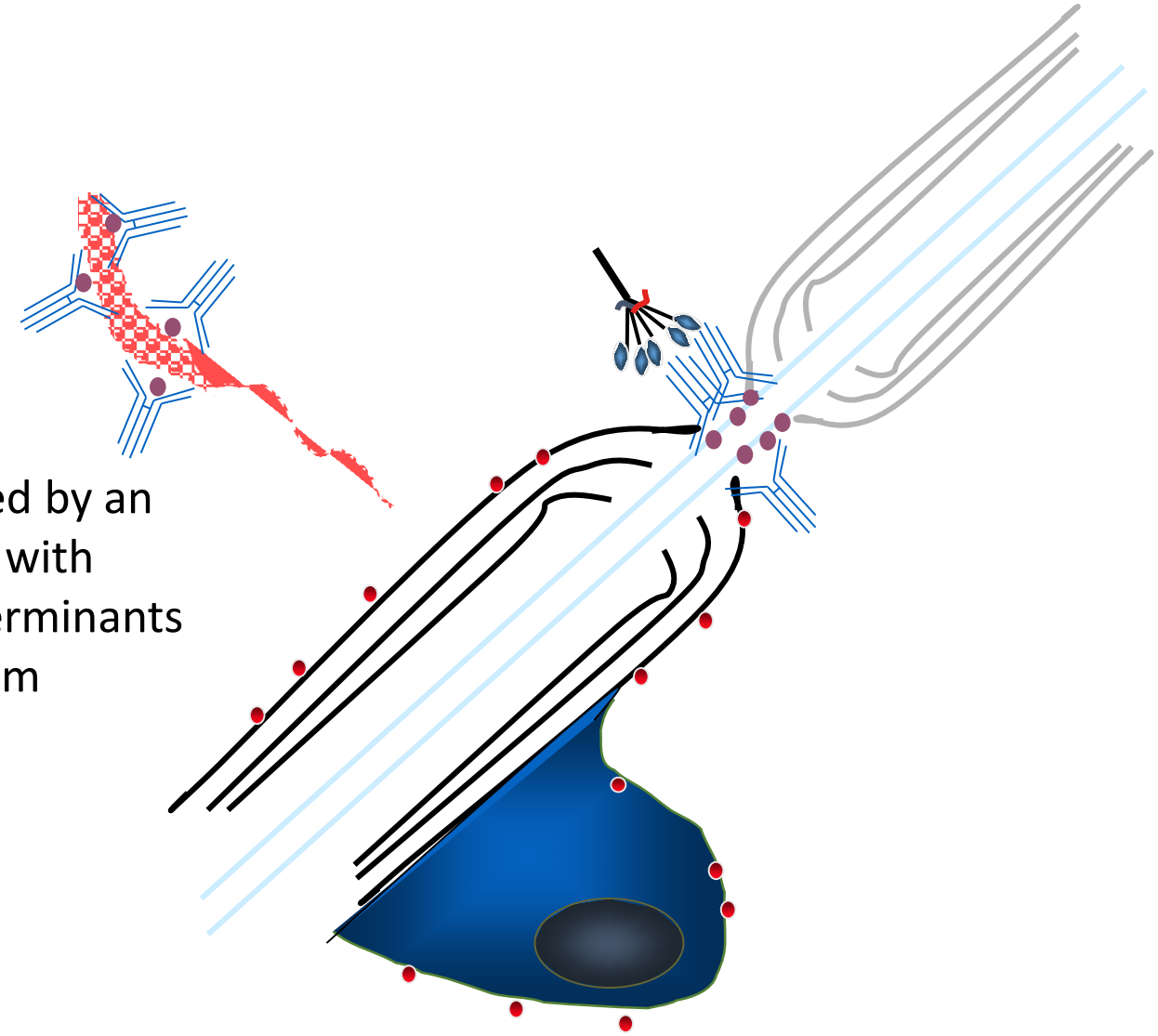
Nicolas Maillard et al. JASN 2015;26:1503-1512

JASN Journal of the American Society of Nephrology


T
IFN γ
IL1
APC
T
TNFa
M ϕ
IFN γ
M ϕ
FcR
CR1
B
C5b-9
TNFa
C3a *
*
C5a*
B
CD 59
DAF
MCP
Mast cell
Schwann Cell
B
T

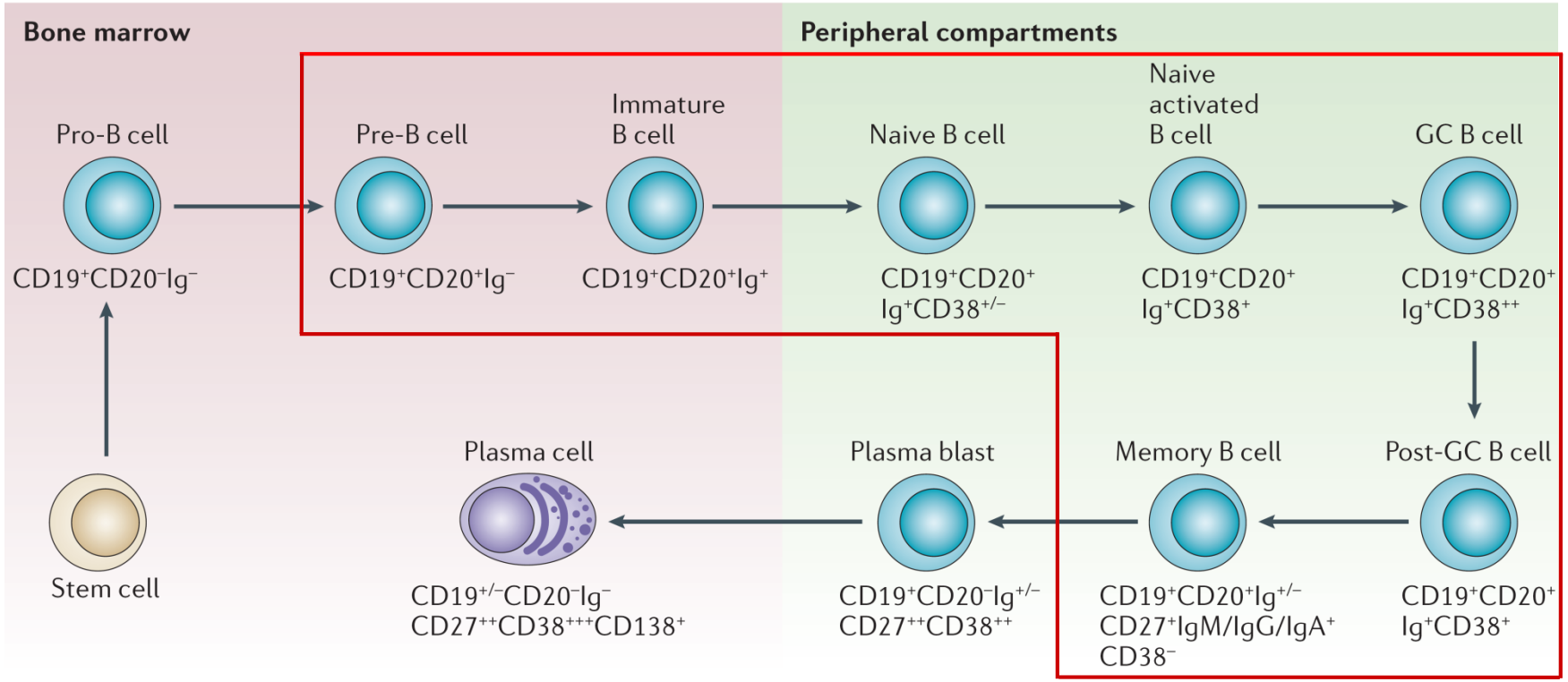
AMAN

Immune responses stimulated by an an infectious organism react with shared foreign and host determinants expressed in the endoneurium



Schwann Cell

CD20 expression



Edwards *et al. Nature Reviews Immunology* (2006) 6, 394–403

Research Updates in CIDP

- **Does rituximab work in CIDP?**
  - **Large multicenter study in Italy in ‘all’ CIDP patients?**
  - **Are the CIDP patients with antibodies to ‘nodal’ and ’paranodal’ proteins different in their clinical responses to Rx- IVIG vs PLEX, CS and/or rituximab?**
- **Are T cells important in CIDP or just antibody mediated disease with cells being secondary?**
- **Inhibition of the neonatal Fc receptor in the treatment of CIDP**
  - **Increasing interest in this as a strategy in chronic autoimmune diseases in which IgG antibodies cause the disease.**
  - **In development of CIDP how much is antibody to PNS components of IgG types as opposed to IgM type and how much is T lymphocyte (T-cell mediated)?**

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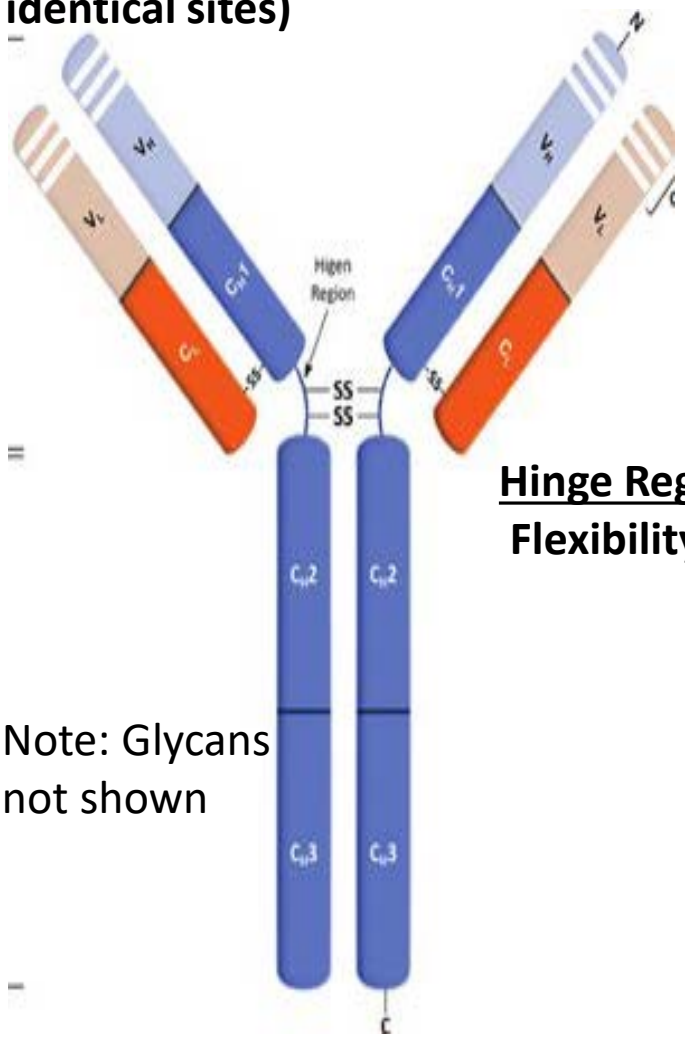

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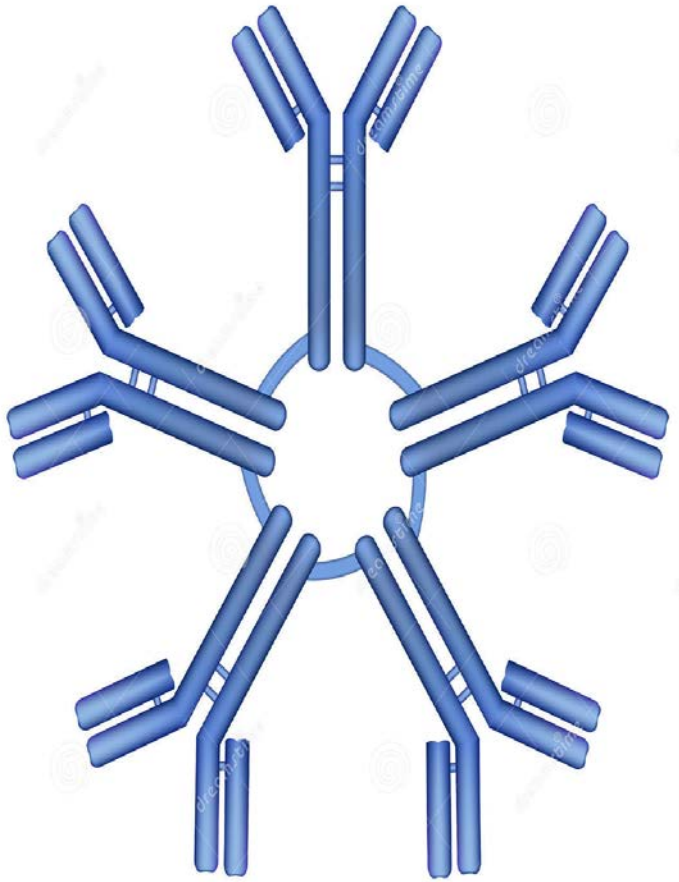

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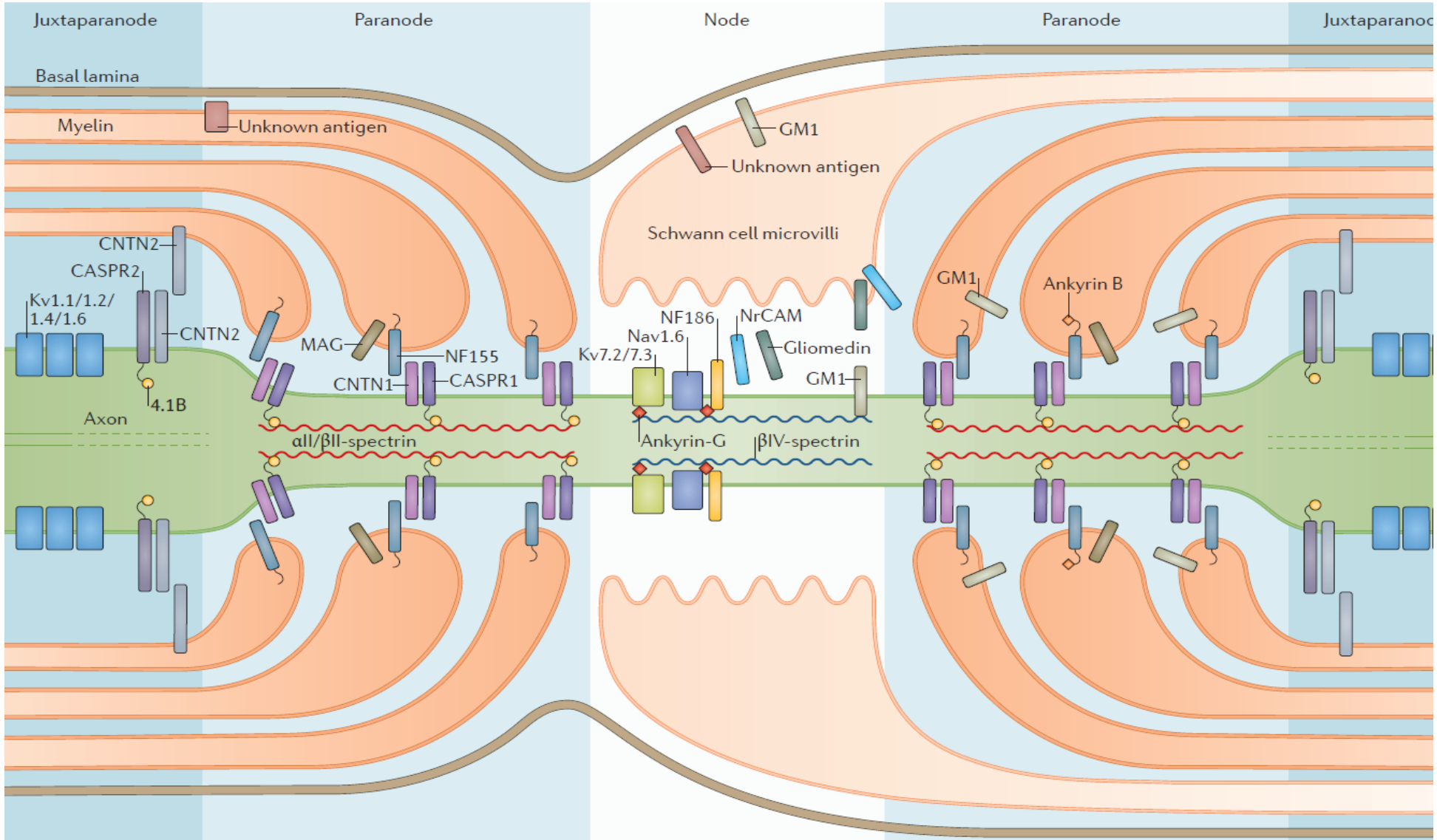
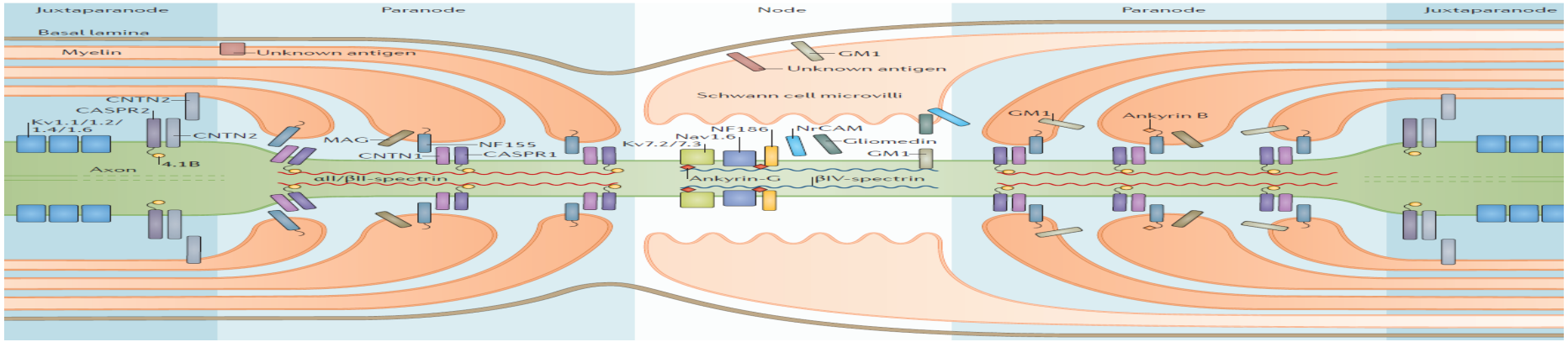
ANATOMY OF THE NODE AND INTERNODE



CIDP: Nodal / Paranodal Abs

- Abs against nodal / paranodal proteins in up to 15% of CIDP

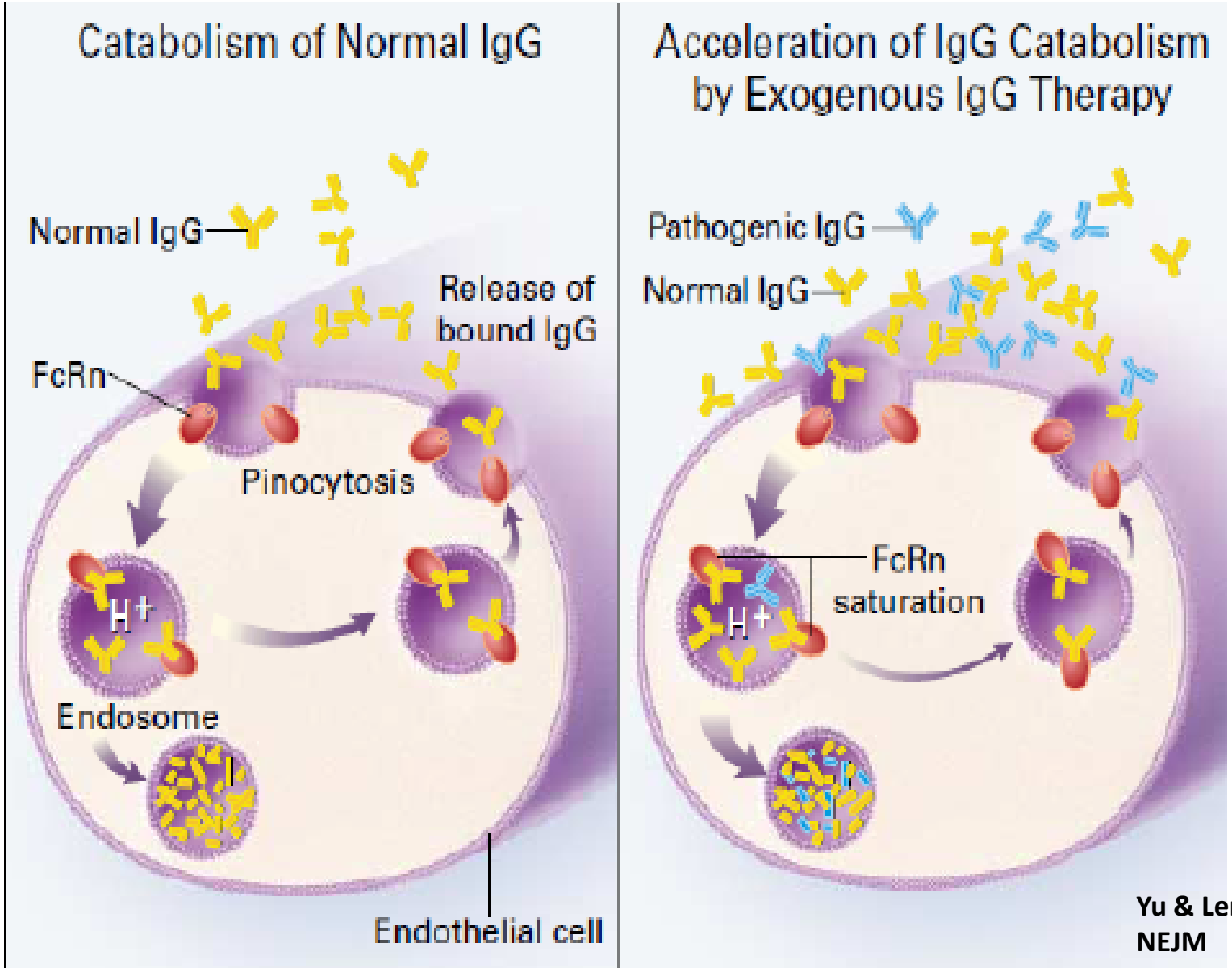


Querol, L et al. Nat Rev Neurol. 2017 Sep;13(9):533-547. doi: 10.1038/nrneurol.2017.84

- Chronic demyelinating neuropathy with acute/subacute onset of weakness & sensory ataxia with high CSF protein
- In 65 CIDP, IgG Abs were detectable against: Neurofascin 155 (NF155) in 3 (4.6%); Contactin-1 (CNTN1): in 4 (6.2%) & Contactin-associated protein-1 (CASPR) in 1 (1.5%)
- 25% had IgG reactivity to DRG neurons, 12% against Schwann cells & 5% to motor neurons

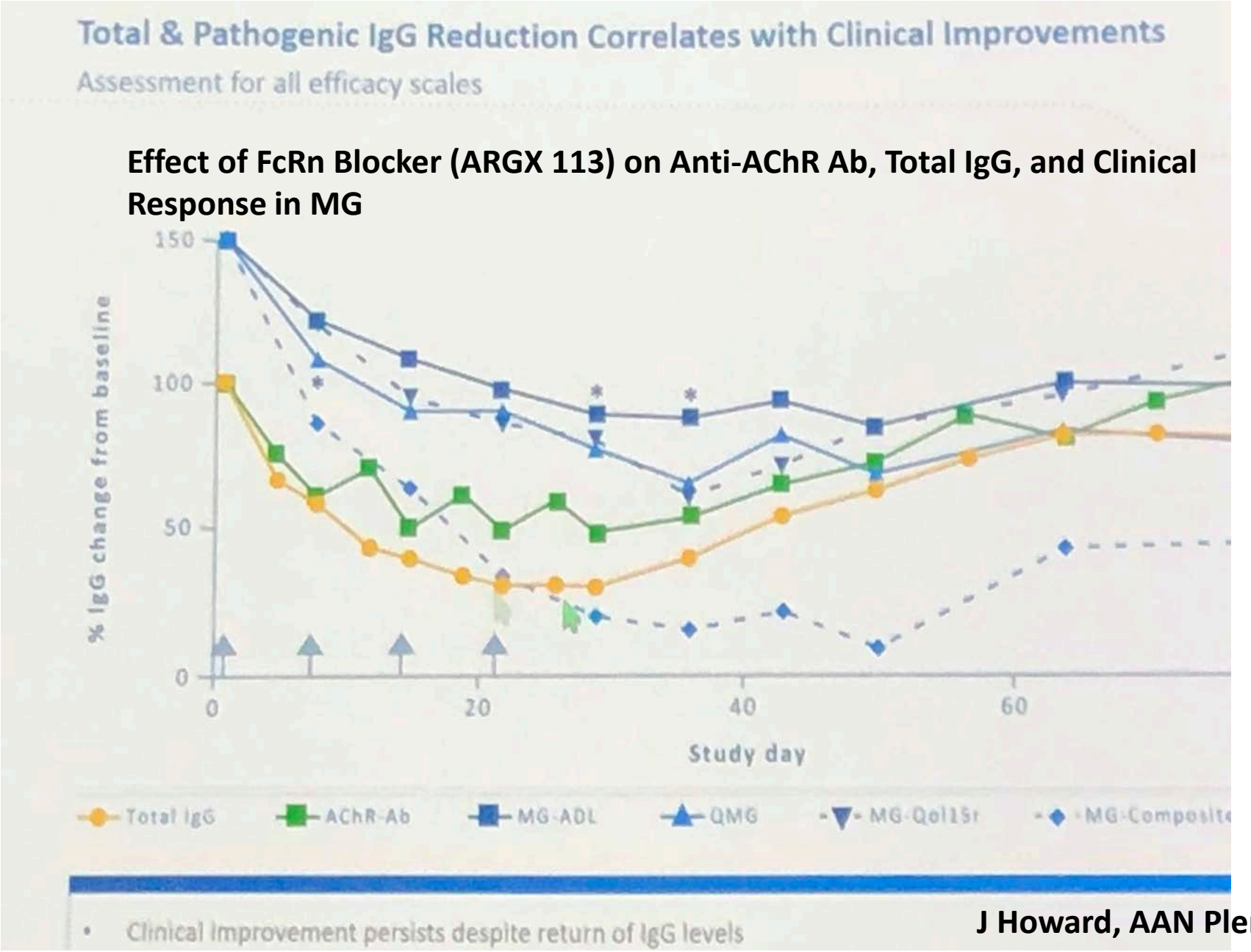
http://www.nature.com/articles/s41598-017-14853-4

FcRn on endothelial cells recycles IgG to maintain its long serum half life.
If FcRn is saturated by excess normal IgG, remaining pathologic IgG will fail to be recycled and be degraded



Yu & Lennon
NEJM

Effect of FcRn Blockade with ARGX 113 in Myasthenia Gravis



J Howard, AAN Plenary 4/24/18

Research Update in GBS and CIDP: Going Forward

- **Exciting time in GBS/CIDP research**
- **Learning more about the steps in the pathogenesis/development of each of these will allow for more refined, specific and effective treatments and should also reduce side effects**
- **Avoid ineffective treatments**
- **Better diagnostic techniques (ultrasound and MRI of nerves)**
- **Better prognostic markers with development of ways to demonstrate pathogenic biomarkers in laboratory and with imaging**