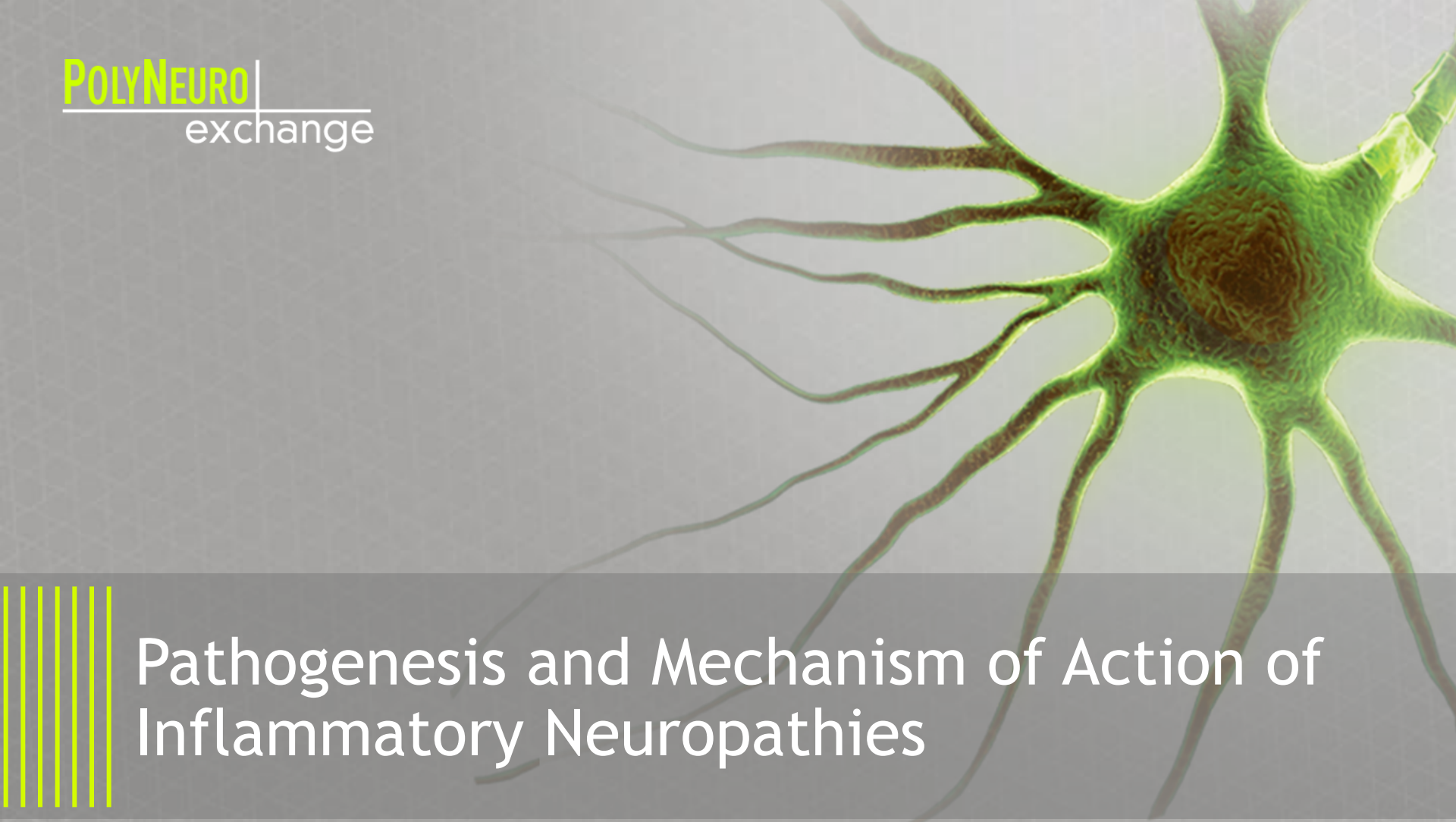
PolyNeuro exchange



Pathogenesis and Mechanism of Action of Inflammatory Neuropathies

Pathogenic processes significant to inflammatory neuropathies

- There are common pathogenic processes involved in acute and chronic inflammatory immune neuropathies:

Axonal dysfunction

- Axonal dysfunction causes alterations in impulse propagation at the Nodes of Ranvier which slows / blocks conduction
- Changes in conduction results in transient weakness which can be reversible with treatment; however, may lead to axonal degeneration

Demyelination

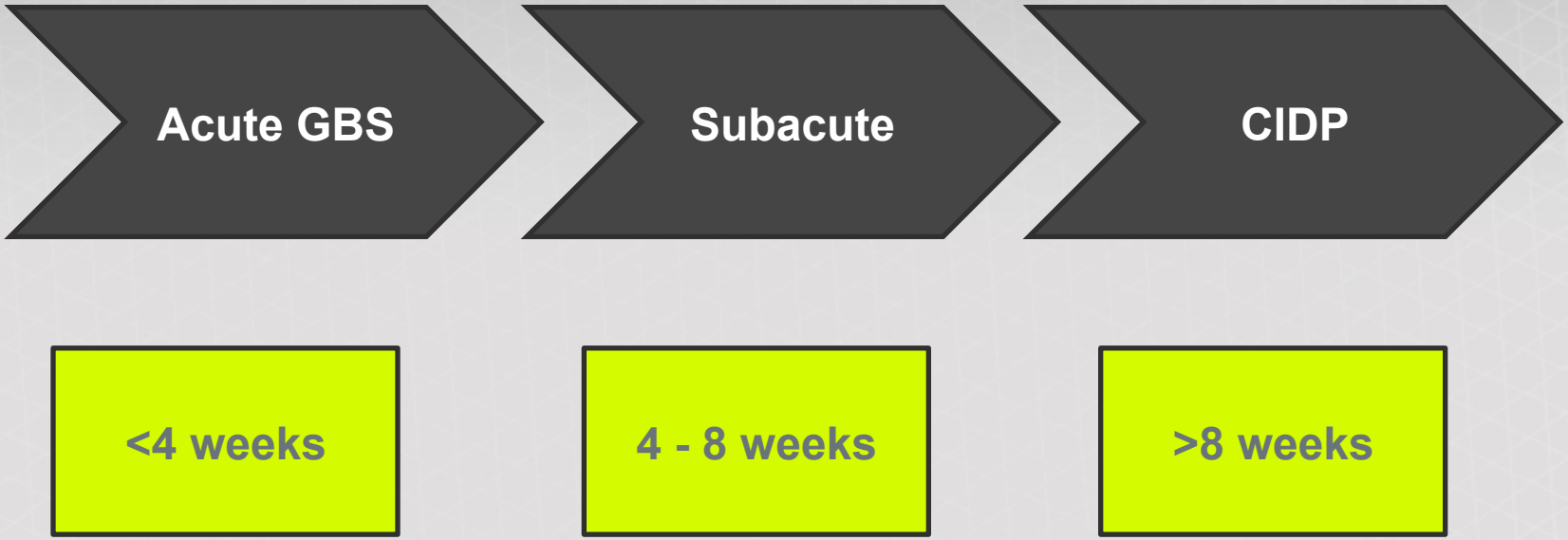
- Leads to dysfunction at inter- / para- nodes affecting conduction
- Transient weakness can be reversible with treatment; may lead to permanent axonal damage

Axonal structural damage

- If axonal degeneration occurs, it is less amenable to treatment and is more likely to cause permanent disability

CIDP: chronic inflammatory demyelinating polyneuropathy, GBS: Guillain-Barré Syndrome

Temporal evolution of disease: The GBS to CIDP continuum



- It is currently unclear what causes acute or chronic forms of disease

CIDP: chronic inflammatory demyelinating polyneuropathy, GBS: Guillain-Barré Syndrome

Current understanding of GBS pathogenesis[1]

- At least 2 GBS variants have a complement-mediated stage where a membrane-attack complex (MAC) is formed
- Acute motor axonal neuropathy (AMAN)

IgG anti-GM1 / GD1a auto-antibodies bind to membrane antigens leading to MAC formation

  - Sodium channel clusters are disrupted or disappear at lengthened nodes in addition to the disruption of paranodal junctions[2]
  - This disruption may result in myelin detachment[2] leading to nerve-conduction failure, muscle weakness, and possibly axonal degeneration. Macrophages subsequently invade and scavenge injured axons

- Acute inflammatory demyelinating polyneuropathy (AIDP)

Auto-antibodies bind to unidentified myelin antigens and activate complement. MAC forms on outer surface of Schwann cells and initiates vesicular degeneration. Macrophages later scavenge myelin debris

GBS: Guillain-Barré Syndrome, GD: ganglioside GD1, GM: ganglioside GM1, IgG: immunoglobulin G, MAC: membrane-attack complex, MoA: mechanism of action

1. Yuki N, Hartung H-P. NEJM 2012;366:2294-304
2. Susuki K *et al.* J Neurosci 2007;27:3956-3967

Current understanding of CIDP pathogenesis[1]

- May be caused by abnormal immune response mediated by lymphocytes and macrophages, in addition to auto-antibodies and complement
- In CIDP patients:
  - Pro-inflammatory and regulatory cytokines – elevated in the CSF
  - Serum TNF-α levels are raised – correlate with disease activity
  - Activated T-cells, mainly $CD4^+$ – increased in the circulation
  - Antigen-driven, major histocompatibility complex class I restricted, $CD8^+$ T-cell-mediated attack[2]
- T-cells may activate residing macrophages, leading to:
  - Enhanced phagocytosis
  - Production of pro-inflammatory molecules, e.g.:
    - Reactive oxygen species
    - Proteases
    - Pro-inflammatory cytokines
- Auto-antibodies may contribute to disease process by complement activation or antibody-dependent cellular toxicity

CIDP: chronic inflammatory demyelinating polyneuropathy, CSF: cerebral spinal fluid, MoA: mechanism of action, TNF: tumor necrosis factor

1. Lehmann HC, Hartung H-P. J Neuroimmunol 2011;231:61-69
2. Schneider-Hohendorf T, *et al*. Neurology 2012;78:402-408

Current understanding of MMN pathogenesis

- In up to 60% of MMN patients, antibodies against gangliosides including GM1 are present[1]
- Antibodies may bind to GM1 and cause disruption of ion channel clusters, which leads to conduction block;[2] a defining physiologic feature of this disease
- The resultant progressive axonal damage may lead to progressive axonal loss and permanent disability[2]

CIDP: chronic inflammatory demyelinating polyneuropathy, GBS: Guillain-Barré syndrome, GD1a/b: ganglioside GD1a/GD-1b, GM1: ganglioside GM1, MoA: mechanism of action, MMN: multifocal motor neuropathy

1. Lehmann HC, Hartung H-P. J Neuroimmunol 2011;231:61-69
2. Vlam L *et al.* Nat Rev 2012:8:48-58

Acute and chronic immune-mediated neuropathies

Acute

- AIDP
- AMAN
  - IgG anti-GM1
- Fisher Syndrome
  - IgG anti-GQ 1B

Vs.

Chronic

- CIDP
- MMN
  - IgM anti-GM1
- CANOMAD
  - IgM anti-GQ 1B
- Anti-MAG neuropathy

AIDP: acute inflammatory demyelinating polyneuropathy, CANOMAD: chronic ataxic neuropathy, CIDP: chronic inflammatory demyelinating polyneuropathy, GM1: ganglioside GM1, GQ1b: ganglioside GQ1b, MMN: multifocal motor neuropathy, SAN: sensory ataxic neuropathy

Gangliosides and disease pathogenesis

- Gangliosides are a group of glycosphingolipids widely distributed in membrane components of the nervous system[1]
- Auto-antibodies targeting gangliosides can be associated with clinical symptoms that imply selective nerve damage[2]

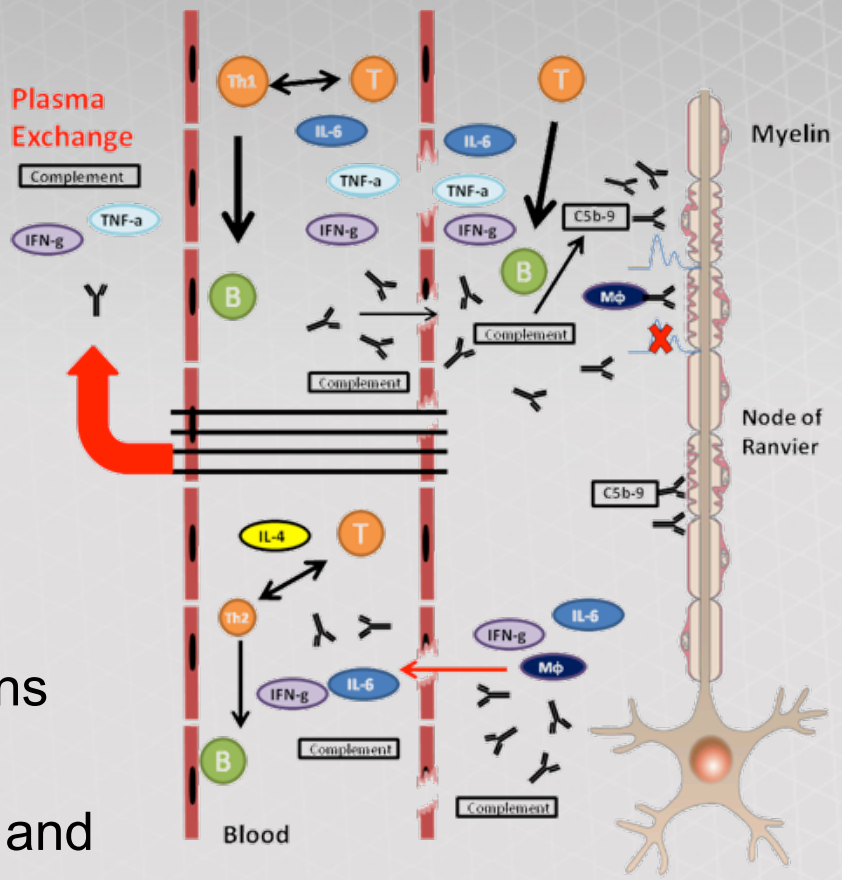
Auto-antibody	Neuropathy	Syndrome
GM1	Multifocal or lower motor	MMN, AMAN, AIDP, CIDP
Asialo-GM1	Motor and sensorimotor	AIDP
GD1a	Motor and sensorimotor	AIDP, AMAN
GD1b	Sensory w/ or w/o ataxia	SAN, ASAN, CANOMAD
GQ1b	Motor and sensorimotor	Fisher, ASAN, CANOMAD

AIDP: acute inflammatory demyelinating polyneuropathy, AMAN: acute motor axonal neuropathy, ASAN: acute sensory ataxic neuropathy, CANOMAD: chronic ataxic neuropathy, CIDP: chronic inflammatory demyelinating polyneuropathy, GD1: ganglioside GD1, GM1: ganglioside GM1, GQ1b: ganglioside GQ1b, MMN: multifocal motor neuropathy, SAN: sensory ataxic neuropathy

1. Neuropathy associated antibodies: http://www.clinlabnavigator.com/neuropathy-associated-antibodies.html Accessed May 2013
2. Gong Y, *et al.* Brain 2002;125:2491-2506

Current understanding of Plasma exchange MoA[1]

- Plasma exchange (PE) removes:
  - Auto-antibodies
  - Cytokines
  - Complement
  - Unknown humoral factors that alter lymphocyte function
- The result is:
  - Improvement of axonal functions
  - Reduced nerve injury through decreased complement attack and axonal damage
  - Clinical improvement compared to no treatment



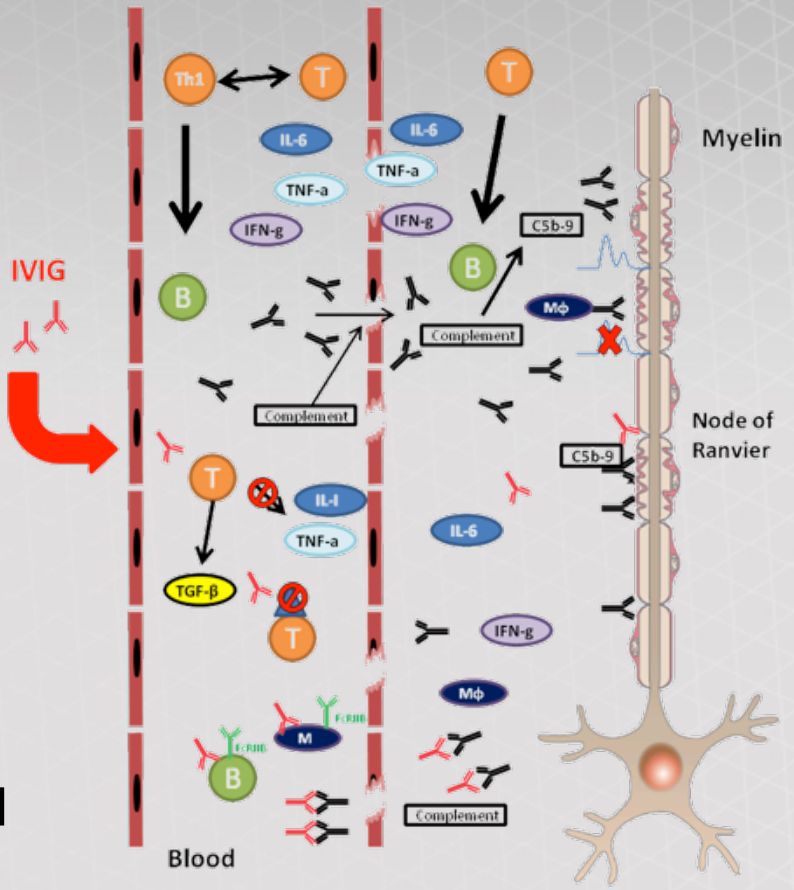
Adapted from ref[1]

PE: plasma exchange, MoA: mechanism of action

1. Lehmann HC, Hartung H-P. J Neuroimmunol 2011;231:61-69

Current understanding of IgG MoA

- IgG is thought to act by:[1,2]
  - Neutralizing pathogenic auto-antibodies
  - Inhibiting auto-antibody-mediated complement activation
  - Altering FcR expression and redressing altered cytokine patterns
- The result is:[1]
  - Improvement of axonal functions
  - Reduced nerve injury through decreased complement attack and axonal damage
  - Faster clinical improvement compared with no treatment



Adapted from ref[2]

FcR: fragment crystallizable receptor, IgG: immunoglobulin G, MoA: mechanism of action

1. Yuki N, Hartung H-P. NEJM 2012;366:2294-304
2. Lehmann HC, Hartung H-P. J Neuroimmunol 2011;231:61-69

Additional thoughts

- MMN must be distinguished from other degenerative motor neuron diseases and CIDP due to differences in prognosis and therapy
  - Certain therapies may exacerbate weakness in MMN patients
- Increasing evidence suggests that IgM antibodies to GM1 are biomarkers for MMN
- As GM1 is only found in up to 80% of patients, there may be antibodies of other specificities that perform a similar function
  - Sensitivity of current assays may affect antibody detection

CIDP: chronic inflammatory demyelinating polyneuropathy, GM1: ganglioside GM1, IgM: immunoglobulin M, MMN: multifocal motor neuropathy