Unravelling CIDP:

Exploring the Role of Complement in Axonal Integrity

Sanofi Medical Symposium
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Agenda
Unravelling CIDP: Exploring the Role of Complement in Axonal Integrity

01 Welcome and Introduction: Understanding heterogeneity, disease burden, and disability in CIDP
Claudia Sommer, MD

02 Axonal integrity and the role of complement
Jan Lünemann, MD, MBA

03 Demyelination and axonal damage interplay in CIDP
Claudia Sommer, MD

04 Opportunities to target the pathobiology of CIDP
Jeffrey Allen, MD

05 Panel discussion and Q&A Session
All Faculty

Chair

Claudia Sommer, MD

Speakers

Jeffrey Allen, MD

Jan Lünemann, MD, MBA

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Today’s interactive session

Polling

- Scan the QR code on the right to launch the app to participate in polling
  Note: responses are anonymous; only aggregate responses will be shown on screen

Panel discussion and Q&A

- Faculty will discuss topics in CIDP and encourage you to submit questions for the Q&A via the QR code to contribute to the discussion

Feedback survey

- Please participate in the brief feedback survey by scanning the QR code at the end of the presentation

Recording

- This symposium will be audio/video recorded

CIDP, chronic inflammatory demyelinating polyneuropathy.

Understanding Heterogeneity, Disease Burden, and Disability in CIDP

Claudia Sommer, MD

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CIDP is a common, heterogeneous, immune-mediated neuropathy[1]

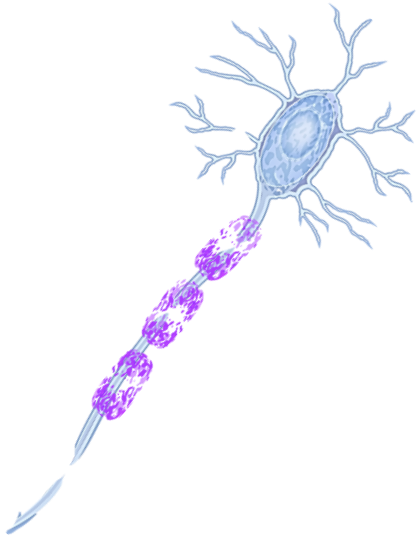
CIDP is a ***chronic immune-mediated*** disease characterized by various degrees of ***demyelination*** and ***axonal damage*** of the ***peripheral nerves*** that typically manifest as:[1-6]

Proximal and distal muscle weakness, loss of balance

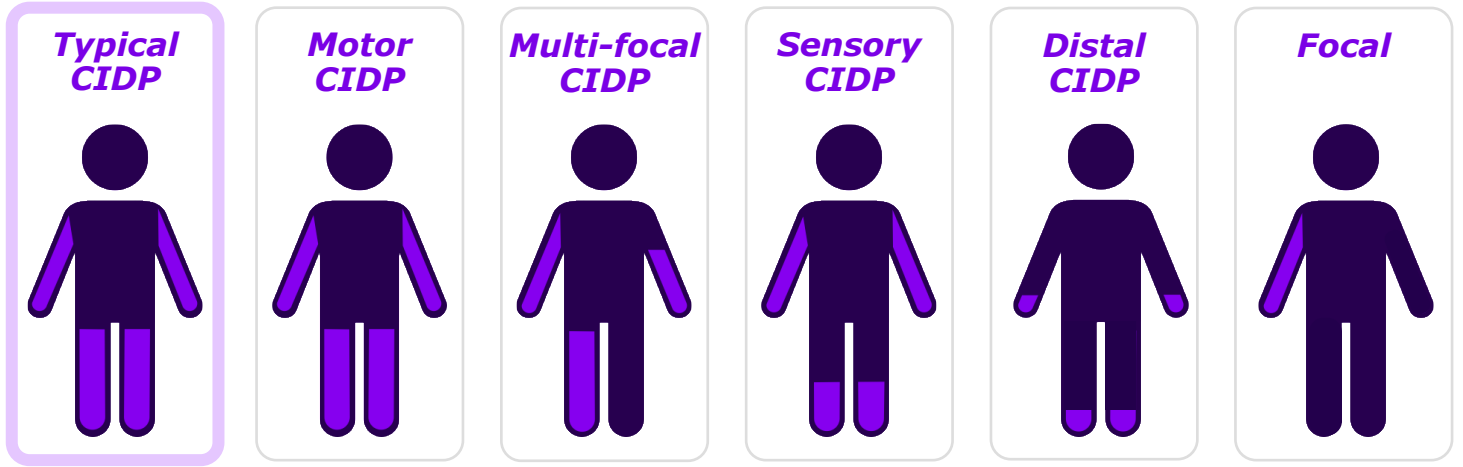
Hyporeflexia or areflexia

Sensory problems or numbness (e.g. paresthesia) mainly in limbs

Estimated prevalence of CIDP is ***0.7–10.3 cases per 100,000 people*** worldwide[1]



CIDP Is Clinically Heterogeneous With a Range of Presentations[4,7,8]



CIDP, chronic inflammatory demyelinating polyneuropathy.

1. Broers MC, et al. *Neuroepidemiology.* 2019;52(3-4):161–172. 2. Querol LA, et al. *Neurotherapeutics.* 2022;19(3):864-873. 3. Bunschoten C, et al. L*ancet Neurol.* 2019;18(8):784-794.
4. Mathey EK, et al. *J Neurol Neurosurg Psychiatry.* 2015;86(9):973-985. 5. Dalakas MC, Engel WK. Ar*ch Neurol.* 1980;37(10):637-640. 6. Johns Hopkins Medicine. Chronic Inflammatory Demyelinating Polyradiculoneuropathy. www.hopkinsmedicine.org/health/conditions-and-diseases/chronic-inflammatory-demyelinating-polyradiculoneuropathy. Accessed February 20, 2025.
7. Allen J. *Neurol Ther.* 2020;9:43-54. 8. Lewis RA, et al. *J Neurol Sci.* 2022;443:120478.

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Heterogeneity of CIDP: CIDP is a syndrome[1–5]

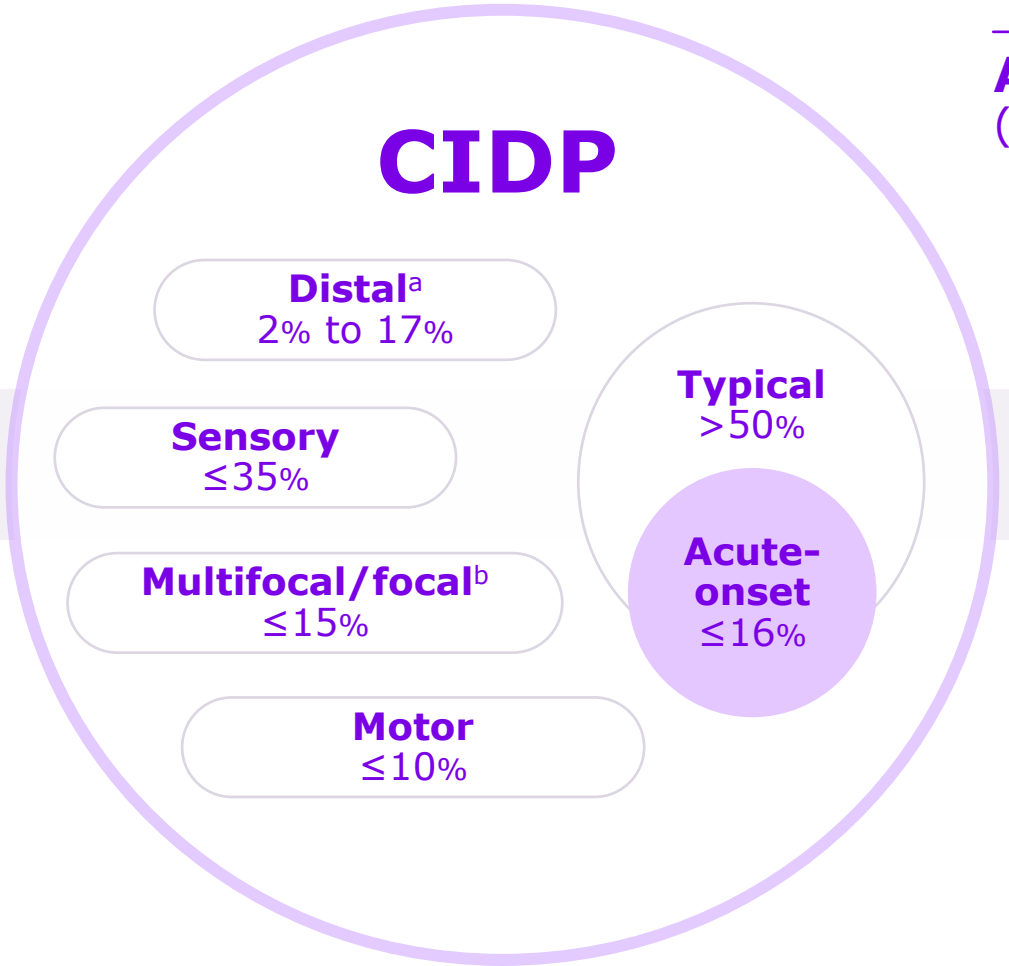
Hematological comorbidities

Monoclonal gammopathies

- IgM-MAG^{+ve}
- MGUS IgG/IgA IgM-MAG^{-ve}

Autoimmune nodopathy (nodo-paranodopathies)

- CASPr1
- CNTN1
- NF186
- NF155



Chronic immune sensory polyradiculopathy (CISP)

Guillain-Barré syndrome

[a]Additionally termed distal acquired demyelinating symmetric polyneuropathy.[1] [b]Additionally termed multifocal acquired demyelinating sensory and motor neuropathy or Lewis-Sumner syndrome.[1]

CASPr, contactin-associated protein; CIDP, chronic inflammatory demyelinating polyneuropathy; CNTN, contactin; IgA/G/M, immunoglobulin A/G/M; IgM-MAG-ve, IgM monoclonal gammopathy without MAG antibodies; IgM-MAG+ve, IgM monoclonal gammopathy with MAG antibodies; MGUS, monoclonal gammopathy of undetermined significance; NF, neurofascin.

1. Lewis RA, et al. *J Neurol Sci.* 2022;15:120478. 2. Gogia B, et al. In: StatPearls [Internet. Treasure Island (FL): StatPearls Publishing; 2025 Jan. 3. Yu Z, et al. *Eur J of Paediatric Neurol.* 2024;53:25-32. 4. Gonzalez Caldito N, et al. *Practical Neurol.* 2024;23(3):19-25. 5. Mathey EK, et al. *J Neurol Neurosurg Psychiatry.* 2015;86(9):97385.

CIDP is associated with a significant disease burden and long-term disability

Can lead to progressive disability, reduced quality of life, and time lost from work or school

"Early symptoms were difficulty climbing stairs, getting up from the floor… and frequently falling."

"I was misdiagnosed during my first neurological exam."

"Each day became a torturous struggle… relentless burning sensation and my muscles had no strength."

Highlighting the Patient Voice in CIDP

"I saw the neurologist [who did not see 'anything neurological' to explain my symptoms]… suggested [to] see a psychiatrist… I was defeated and felt helpless."

"I became trapped in a body that was failing me, isolated and consumed by chronic pain."

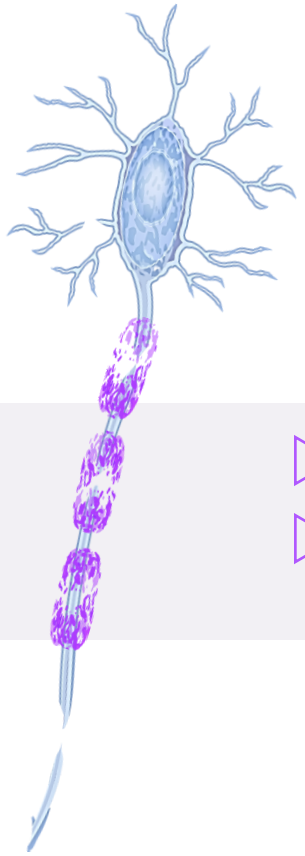
"I was getting so frustrated when I would drop things because my limbs no longer felt like mine."

Is a functional cure achievable for people with CIDP?

CIDP, chronic inflammatory demyelinating polyneuropathy.

Patient stories. The GBS | CIDP Foundation International. Available at: https://www.gbs-cidp.org/support/connect-with-gbs-cidp-community/patient-stories/. Permissions for use obtained from The GBS | CIDP Foundation International.

Axonal damage could be the primary determinant of CIDP disability



Recent studies suggest axonal damage occurs **early in the disease**[1]

- **Axonal loss at diagnosis** is **predictive** of **long-term disability** and may indicate an **aggressive disease course**[2,3]

Total disability is largely determined by extent **of axonal damage**[2]

- Implies that **destruction of axonal integrity** is an **intrinsic part** of **CIDP pathogenesis**[2]
- Although **extent of axonal damage may vary**, its **prevention** and **management** is important regardless of CIDP variants[2,4]

Figure adapted from reference 1.

CIDP, chronic inflammatory demyelinating polyneuropathy.

1. Al-Zuhairy A, et al. *Clin Neurophysiol.* 2021;132(4):1000-1007. 2. Grüter T, et al. *Eur J Neurol.* 2022;29(2):583-592. 3. Al-Zuhairy, et al. *Muscle Nerve.* 2022;66(6):715-722. 4. Ricciardi D, et al. *Brain Sci.* 2022;12(11):1510.

ACTIVE POLL

What challenges are most pressing for you in CIDP?

A. Timely accurate diagnosis

B. Suboptimal response to current treatments in patients

C. Lack of targeted treatment options

D. Prevention and reversal of long-term disability

CIDP, chronic inflammatory demyelinating polyneuropathy.

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The Role of Complement in Axonal Integrity

Jan Lünemann, MD, MBA

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Axonal integrity in the healthy nervous system[1–6]

Axonal integrity is tightly regulated by multiple mechanisms

Signaling between axons and Schwann cells[1,6]

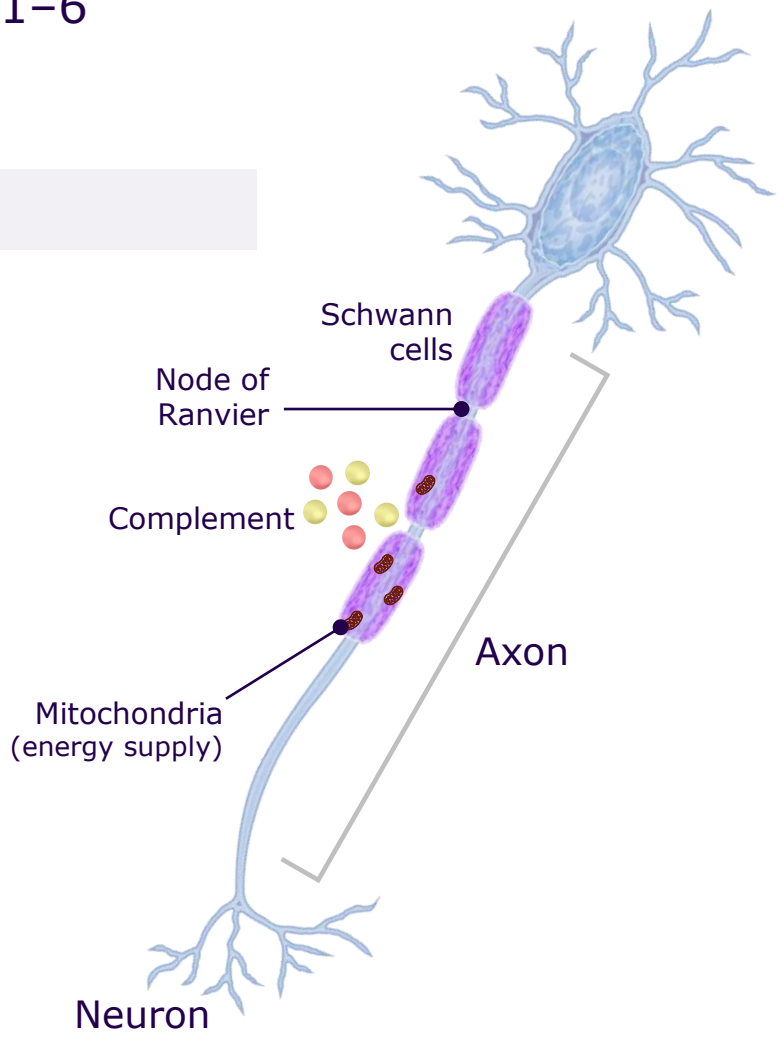
- **Schwann cells** surrounding **peripheral nerves** are essential for **nerve development**, **function, maintenance, regeneration**[2,3]
- Schwann cells form an insulating myelin layer supporting **homeostasis** and **injury repair,** as well as allowing efficient action potential transmission[1,4]

Energy supply[5]

- The high-energy demand of neurons requires specialized mechanisms to **maintain energy homeostasis** throughout the cell[5]
- Mitochondria, local glial cells (e.g., astrocytes and oligodendrocytes) are thought to play a role[5–7]

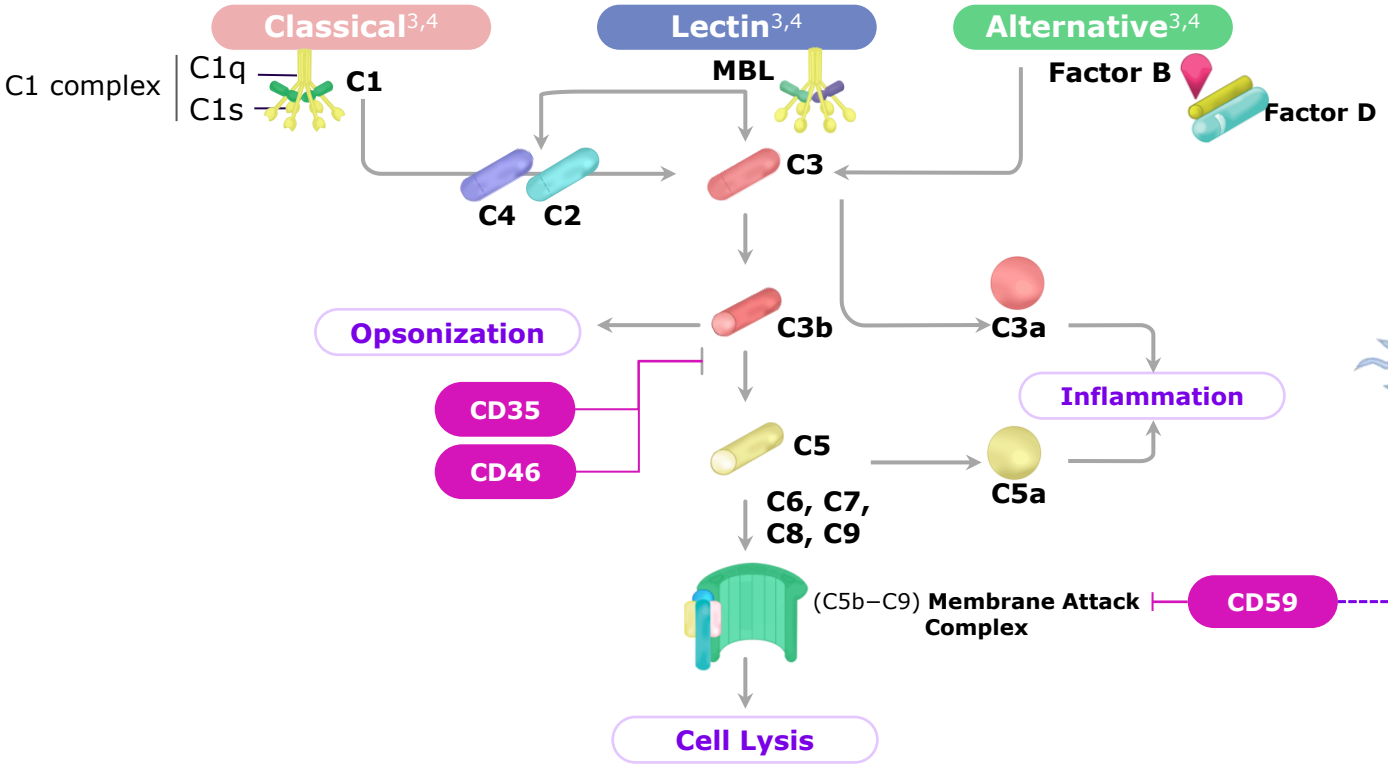
Complement[8,9]

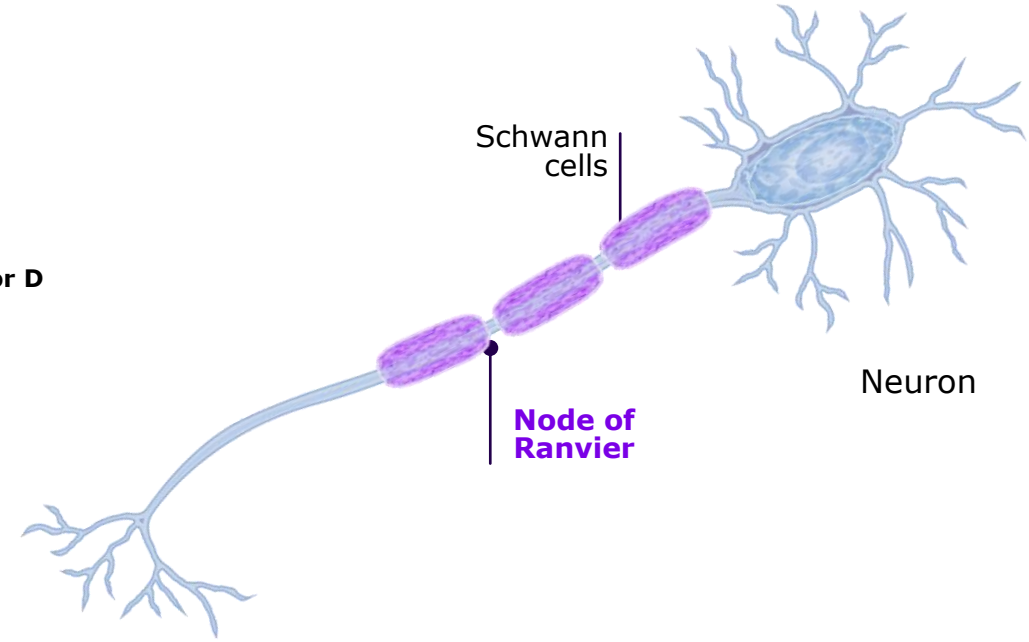
- **Protects** from **infection/ inflammation** and supports **axonal regeneration**[8]
- Plays a role in **eliminating damaged cells** (myelin and cellular debris clearance)[8,9]



1. Pereira JA, et al. *Trends Neurosci.* 2012;35(2):123-134. 2. Oliveira JT, et al. *Front Cell Neurosci.* 2023;17:1248922. 3. Previtali SC. *Neurotherapeutics.* 2021;18(4):2156-2168. 4. Schumacher N, et al. *J Neurochem.* 2025;169(1):e16268. 5. Chamberlain KA, Sheng ZH. *J Neurosci Res.* 2019;97(8):897-913. 6. Ohno N, Ikenaka K. *Neurosci Res.* 2019;139:48-57. 7. Krauss R, et al. *Trends Pharmacol Sci.* 2020;41(4):281-293. 8. Warwick CA, et al. *J Biol Chem.* 2021;297(3):101085. 9. Yuan Y, et al. *Front Neurol.* 2022;13:908148.

Complement activation pathways are tightly regulated to avoid host tissue damage[1]





- **CD59 –** last line of defense for human cells from damage during complement activation via inhibitory regulation of MAC formation[2]
- **Lack of CD59 at Nodes of Ranvier** renders the nodes and myelin in the PNS vulnerable to complement attack[5]

CD59[2], **CD46**[3], and **CD35**[3] are protective regulators of complement components that can cause damaging effects on normal tissue[3,4]

Figure adapted from Murphy K, Weaver C. Janeway's Immunobiology (9th edition), Garland Science, 2016. Copyright © 2016 by the authors. Licensed under the terms of the Creative Commons CC BY-NC license.

MAC, membrane attack complex; MBL, mannose-binding lectin; PNS, peripheral nervous system.

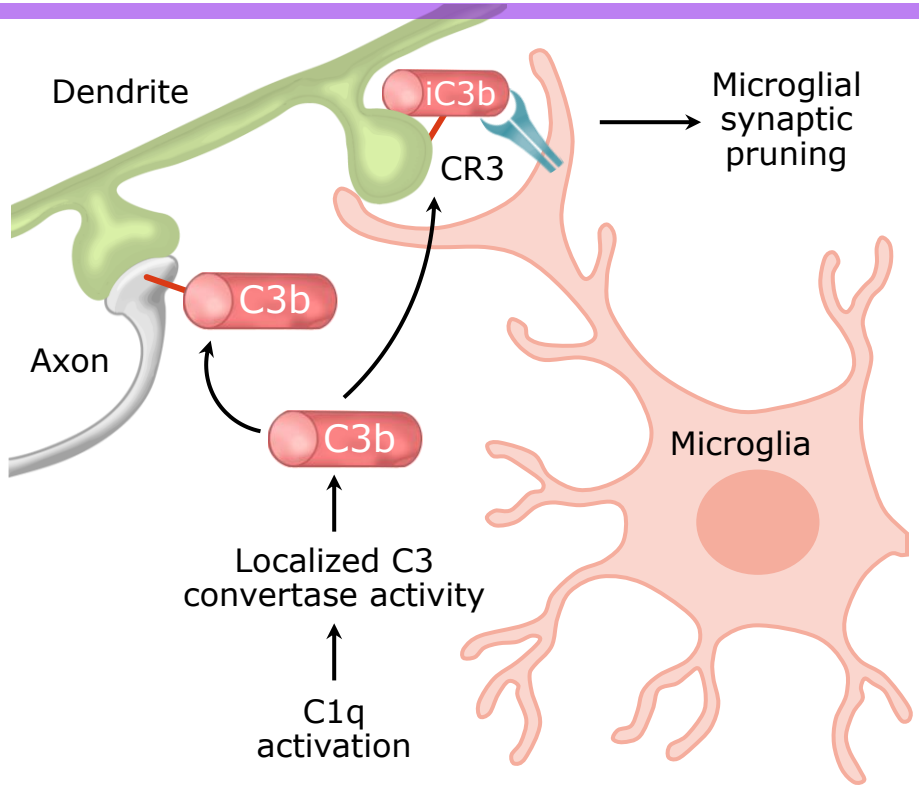
1. Giorgio C, et al. *Biomedicines.* 2021;9(4):399. 2. Couves EC, et al. *Nat Commun.* 2023;14(1):890. 3. Liszewski MK, Atkinson JP. *Hum Genomics.* 2015;10;9(1):7. 4. Schartz ND, Tenner AJ. *J Neuroinflammation.* 2020;17(1):354. 5. Karbian N, et al. *J Neuroinflammation.* 2023;20(1):245.

The complement system helps maintain a healthy nervous system

Under physiological conditions, complement-dependent changes in neuronal excitability, synaptic strength, and neurite remodeling promote nerve regeneration, tissue repair, and healing[1–3]

Prominent complement-mediated mechanisms in the nervous system[1]

1 SYNAPTIC PRUNING



Role of complement

C1q and C3 mediate:[1,2]

- synaptic refinement during development
- structural remodeling during synaptic plasticity
- memory formation in mature brain

Figure adapted from ref 1.

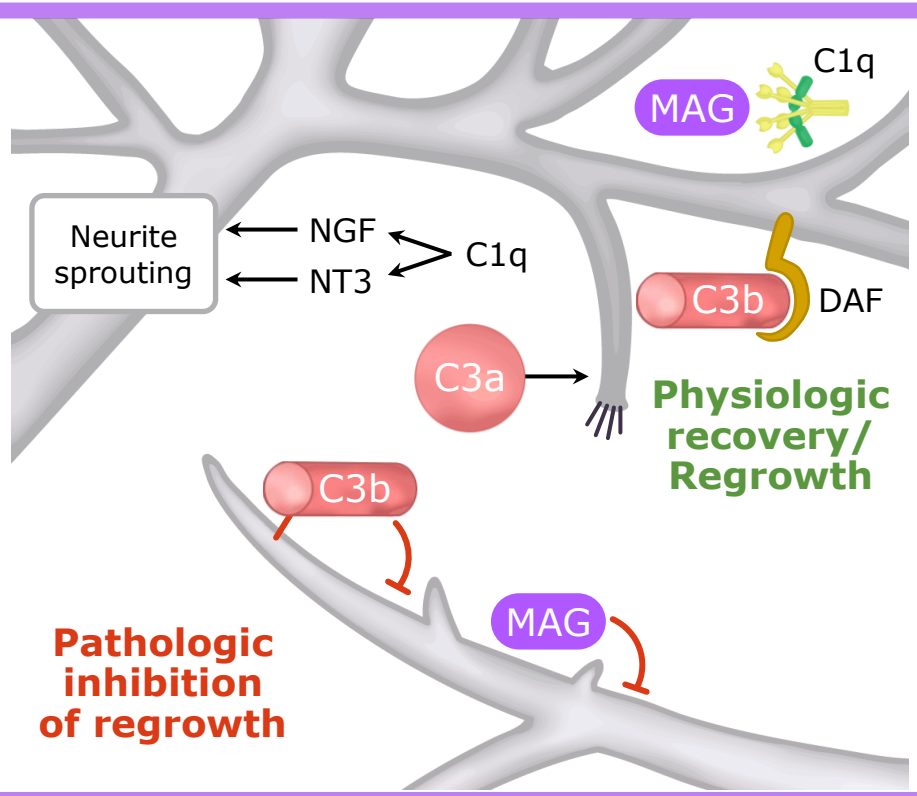
1. Warwick CA, et al. *J Biol Chem.* 2021;297(3):101085. 2. Schartz ND, Tenner AJ. J *Neuroinflammation.* 2020;17(1):354. 3. Dalakas MC, et al. *Nat Rev Neurol.* 2020;16(11):601-617.

The complement system helps maintain a healthy nervous system

Under physiological conditions, complement-dependent changes in neuronal excitability, synaptic strength, and neurite remodeling promote nerve regeneration, tissue repair, and healing[1–3]

Prominent complement-mediated mechanisms in the nervous system[1]

2 AXONAL GROWTH



Role of complement

Promotes or suppresses axonal growth, depending on specific complement involved[1,2]

- C1q may stimulate whereas C3 inhibits axonal growth
- C1q promotes axonal regeneration and recovery

Figure adapted from ref 1.

MAG, myelin-associated glycoprotein; NGF, nerve growth factor; NT3, neurotrophin 3; TPCC, terminal pathway complete complex.

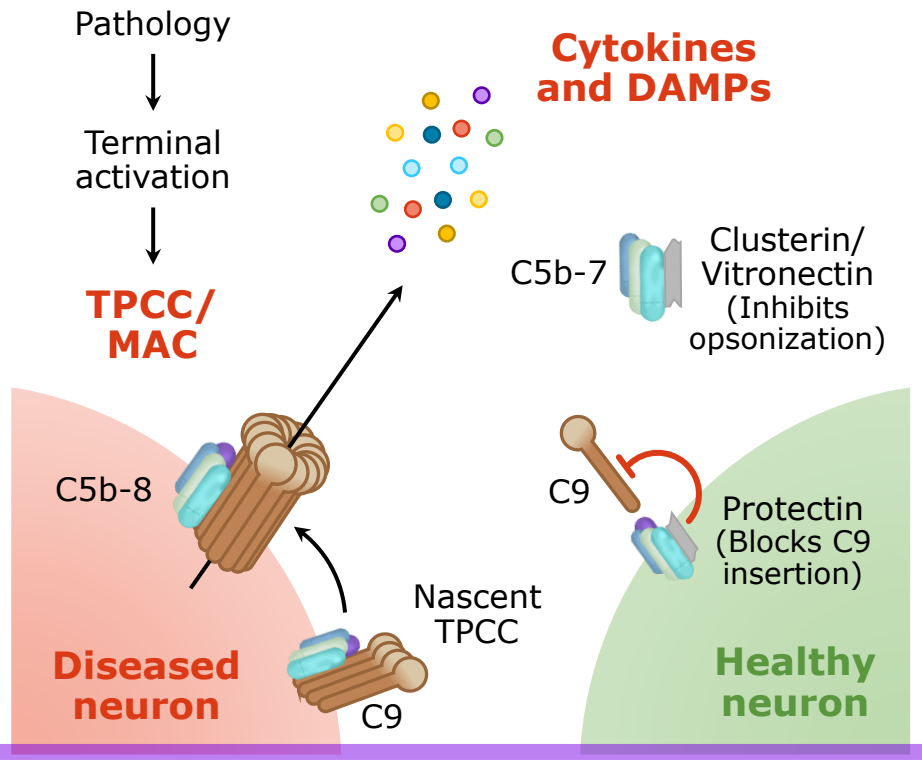
1. Warwick CA, et al. *J Biol Chem.* 2021;297(3):101085. 2. Schartz ND, Tenner AJ. J *Neuroinflammation.* 2020;17(1):354. 3. Dalakas MC, et al. *Nat Rev Neurol.* 2020;16(11):601-617.

The complement system helps maintain a healthy nervous system

Under physiological conditions, complement-dependent changes in neuronal excitability, synaptic strength, and neurite remodeling promote nerve regeneration, tissue repair, and healing[1–3]

Prominent complement-mediated mechanisms in the nervous system[1]

3 NEURONAL TOXICITY



Role of complement

- Promotes cell death/ clearance through the TPCC, or clearance of myelin to promote axonal regeneration and repair[1]

Figure adapted from ref 1.

DAMP, danger-associated molecular patterns; MAC, membrane attack complex; TPCC, terminal pathway complete complex.

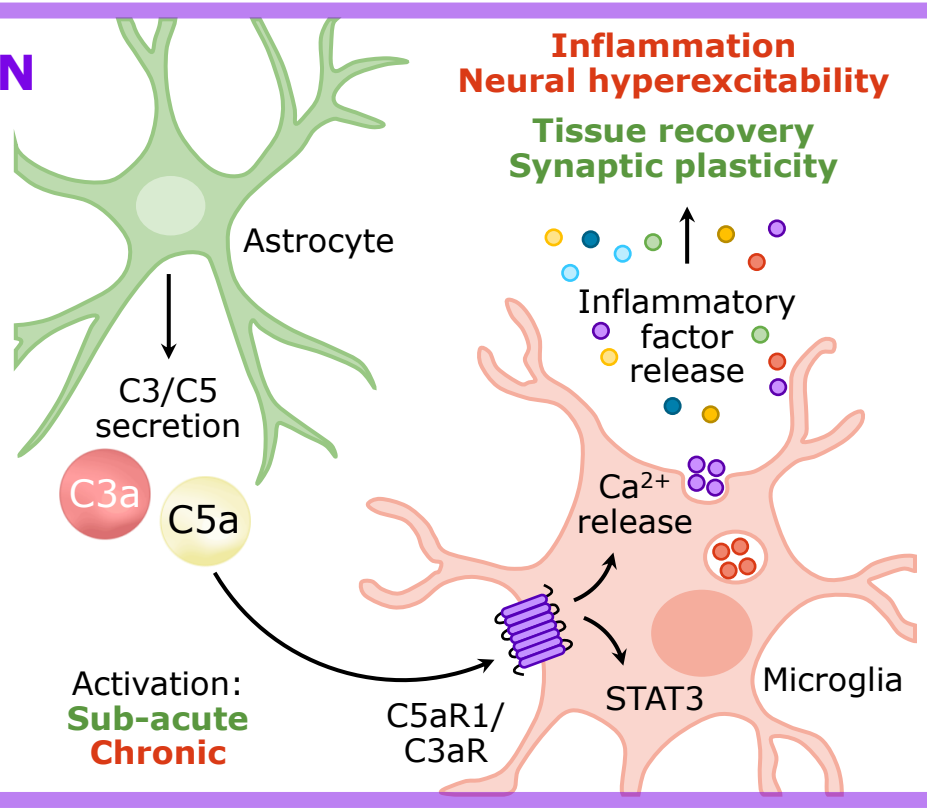
1. Warwick CA, et al. *J Biol Chem.* 2021;297(3):101085. 2. Schartz ND, Tenner AJ. J *Neuroinflammation.* 2020;17(1):354. 3. Dalakas MC, et al. *Nat Rev Neurol.* 2020;16(11):601-617.

The complement system helps maintain a healthy nervous system

Under physiological conditions, complement-dependent changes in neuronal excitability, synaptic strength, and neurite remodeling promote nerve regeneration, tissue repair, and healing[1–3]

Prominent complement-mediated mechanisms in the nervous system[1]

4 NEUROINFLAMMATION



Role of complement

C3a and C5a play roles in tissue repair and promote inflammatory responses to infection or injury[1]

- C3a–C3aR axis also has a role in neuronal migration[3]
- C5a–C5aR1 axis is critical during embryonic neurogenesis[3]

Figure adapted from ref 1.
STAT, signal transducers and activators of transcription.
1. Warwick CA, et al. *J Biol Chem.* 2021;297(3):101085. 2. Schartz ND, Tenner AJ. *J Neuroinflammation.* 2020;17(1):354. 3. Dalakas MC, et al. *Nat Rev Neurol.* 2020;16(11):601-617.

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The complement system helps maintain a healthy nervous system

Under physiological conditions, complement-dependent changes in neuronal excitability, synaptic strength, and neurite remodeling promote nerve regeneration, tissue repair, and healing[1–3]

Prominent complement-mediated mechanisms in the nervous system[1]

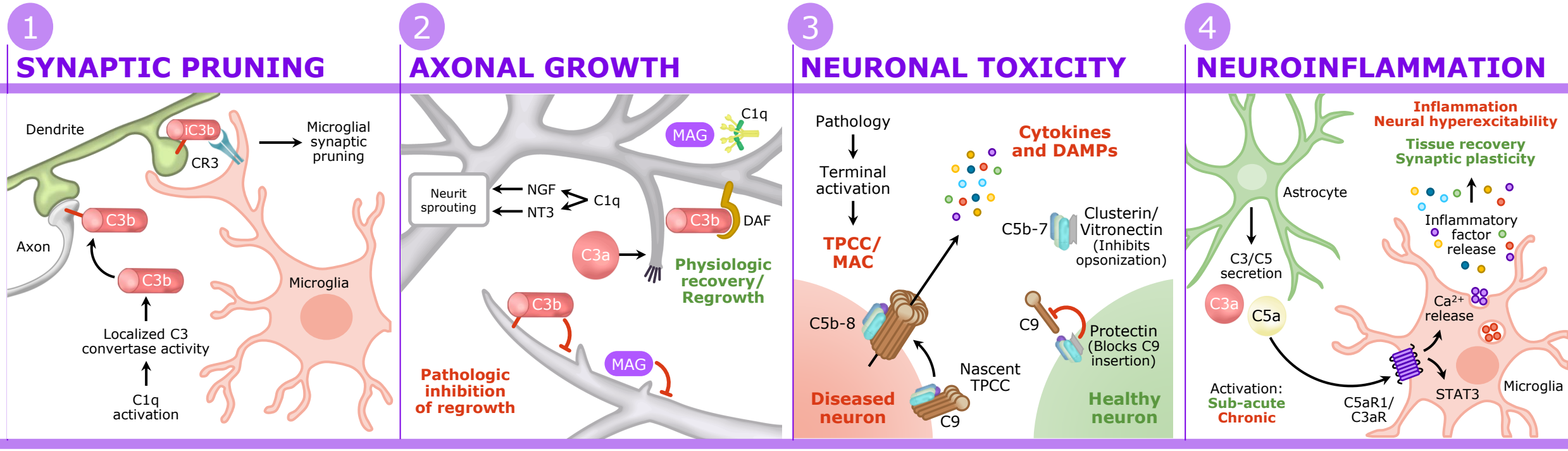

Figure adapted from ref 1.

DAMP, danger-associated molecular patterns; MAC, membrane attack complex; MAG, myelin-associated glycoprotein; NGF, nerve growth factor; NT3, neurotrophin 3; STAT, signal transducers and activators of transcription; TPCC, terminal pathway complete complex.

1. Warwick CA, et al. *J Biol Chem*. 2021;297(3):101085. 2. Schartz ND, Tenner AJ. *J Neuroinflammation*. 2020;17(1):354. 3. Dalakas MC, et al. *Nat Rev Neurol.* 2020;16(11):601-617.

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The duality of complement

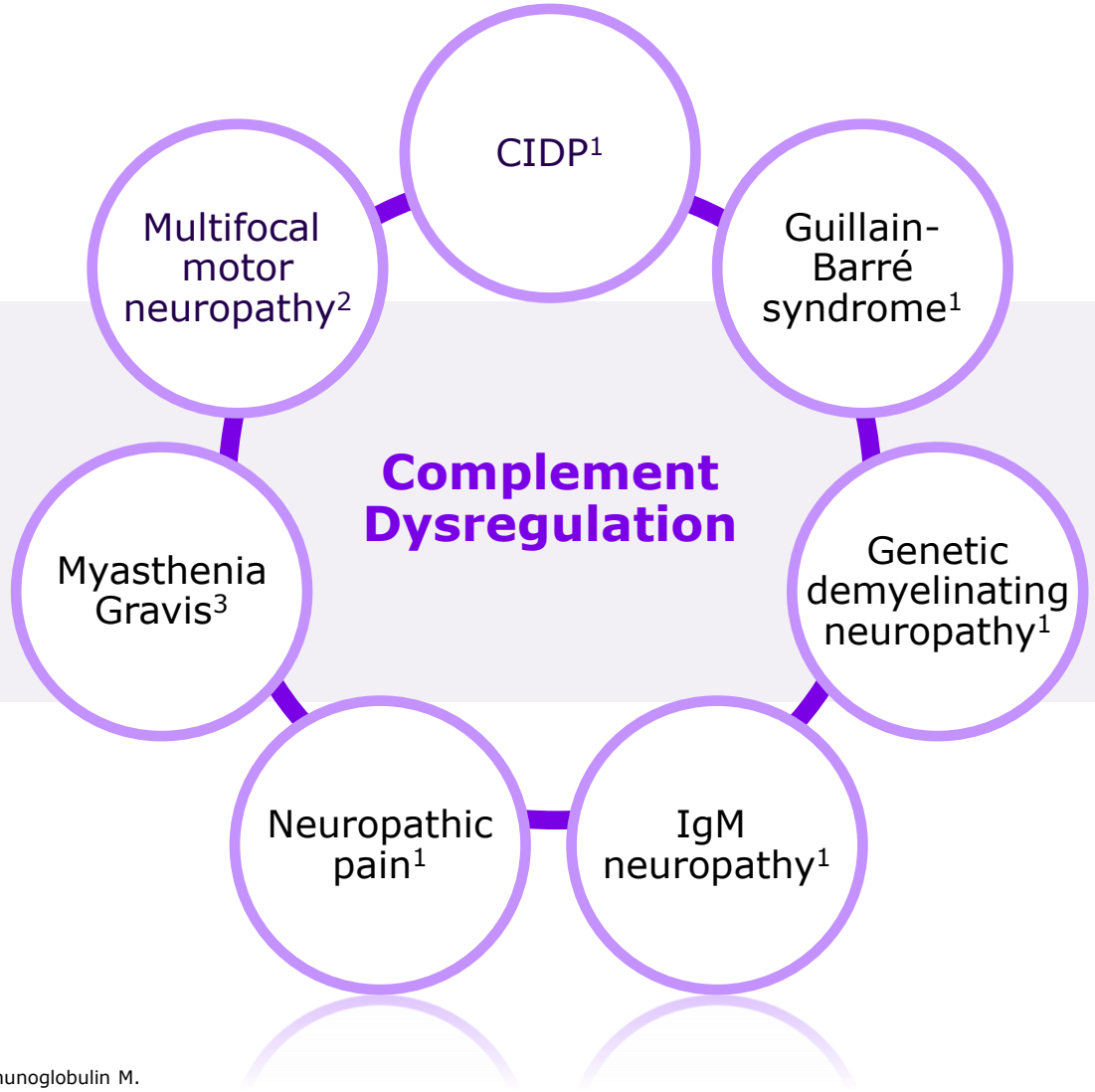
Despite promoting nerve regeneration, repair, and healing, dysregulation of the complement cascade can lead to chronic inflammation and neural dysfunction[1]

- The **complement** system is **tightly regulated**[2]
- The **PNS** may be **vulnerable** to **complement dysregulation**[3]
- Phenotype of complement-driven neuronal injury resembles neuropathy observed in GBS and CIDP[4]
- **Complement dysregulation** could be a **key** pathophysiological **mechanism** in genetically predisposed individuals[4–6]

CIDP, chronic inflammatory demyelinating polyneuropathy; GBS, Guillain-Barré syndrome; PNS, peripheral nervous system.

1. Warwick CA, et al. *J Biol Chem.* 2021;297(3):101085. 2. Giorgio C, et al. *Biomedicines.* 2021;9(4):399. 3. Karbian N, et al. *J Neuroinflammation.* 2023;20(1):245.
4. Querol LA, et al. *Neurotherapeutics.* 2022;19:864-873. 5. Nevo Y, et al. *Blood.* 2013;121:129-135. 6. Dalakas MC, et al. *Nat Rev Neurol.* 2020;16:601-617.

Complement dysregulation is implicated in several neurological disorders[1–3]



CIDP, chronic inflammatory demyelinating polyneuropathy; IgM, immunoglobulin M.

1. Dalakas MC, et al. *Nat Rev Neurol.* 2020;16(11):601-617. 2. Budding K, et al. *Neurol Neuroimmunol Neuroinflamm*. 2021;10;9(1):e1107. 3. San PP, Jacob S. *Front Neurol*. 2023;5;14:1277596.

Demyelination and Axonal Damage Interplay in CIDP

Claudia Sommer, MD

University Hospital of Würzburg,
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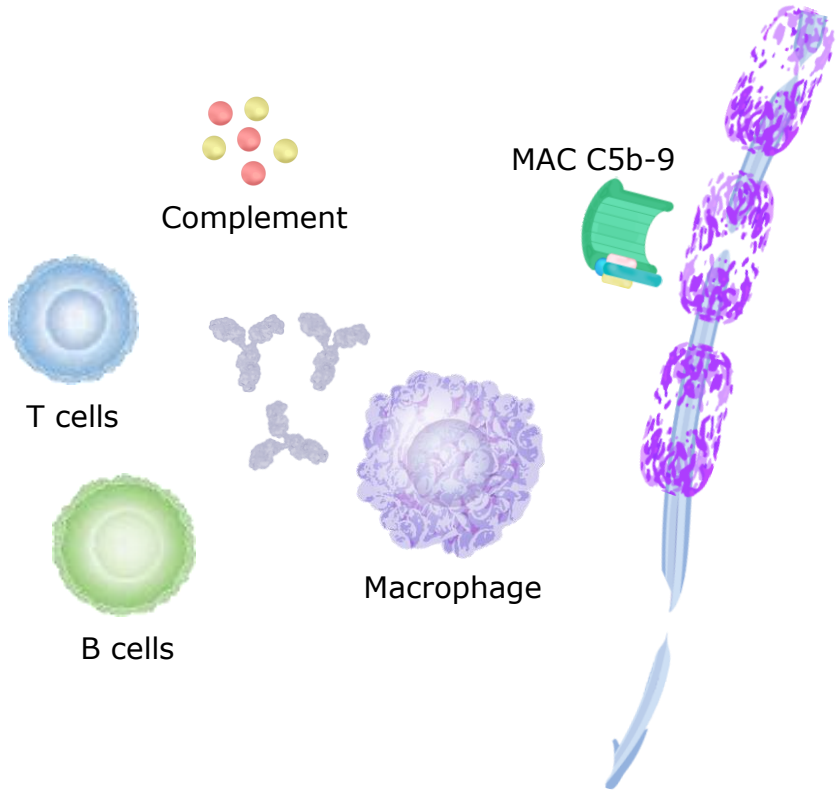
The pathogenesis of CIDP involves multiple mechanisms

Complex interplay between multiple aberrant immune responses, creating a pro-inflammatory environment, causing myelin and axonal damage[1]



- Histopathological changes in CIDP include **breakdown of the blood–nerve barrier** (BNB), **segmental demyelination** and various degrees of **axonal damage**[1]
- Both **humoral factors** and **macrophage-mediated demyelination** appear to play a crucial role in CIDP[1]
- Macrophage infiltration in myelinated fibers around the nodes of Ranvier, and in the internodal region appears to be involved[1]
- The **complement system** plays a role in **promoting demyelination** and **axonal damage**[1]
- **Complement deposition** seen in sural nerve biopsies along with **increased complement activation** in **CIDP**[1–3]

CIDP, chronic inflammatory demyelinating polyneuropathy; MAC, membrane attack complex.

1. Querol LA, et al. *Neurotherapeutics.* 2022;19:864-873. 2. Hays AP, et al. *J Neuroimmunol.* 1988;18:231-244. 3. Dalakas MC, et al. *Neurology.* 1980;30:864-867.

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The fundamental role of humoral factors in CIDP

- Speed of response to plasmapheresis suggests that a circulating factor is responsible for demyelination and conduction block in CIDP[1]
- Evidence of humoral involvement in CIDP:
  - Presence of **complement-fixing IgG and IgM deposits** on myelin sheath and sural nerve biopsy samples[1,2]
  - Induction of conduction block and demyelination after passive transfer of serum or purified IgG from people with CIDP into rats[3]

Putative pathologic changes in the node of Ranvier in CIDP[4]

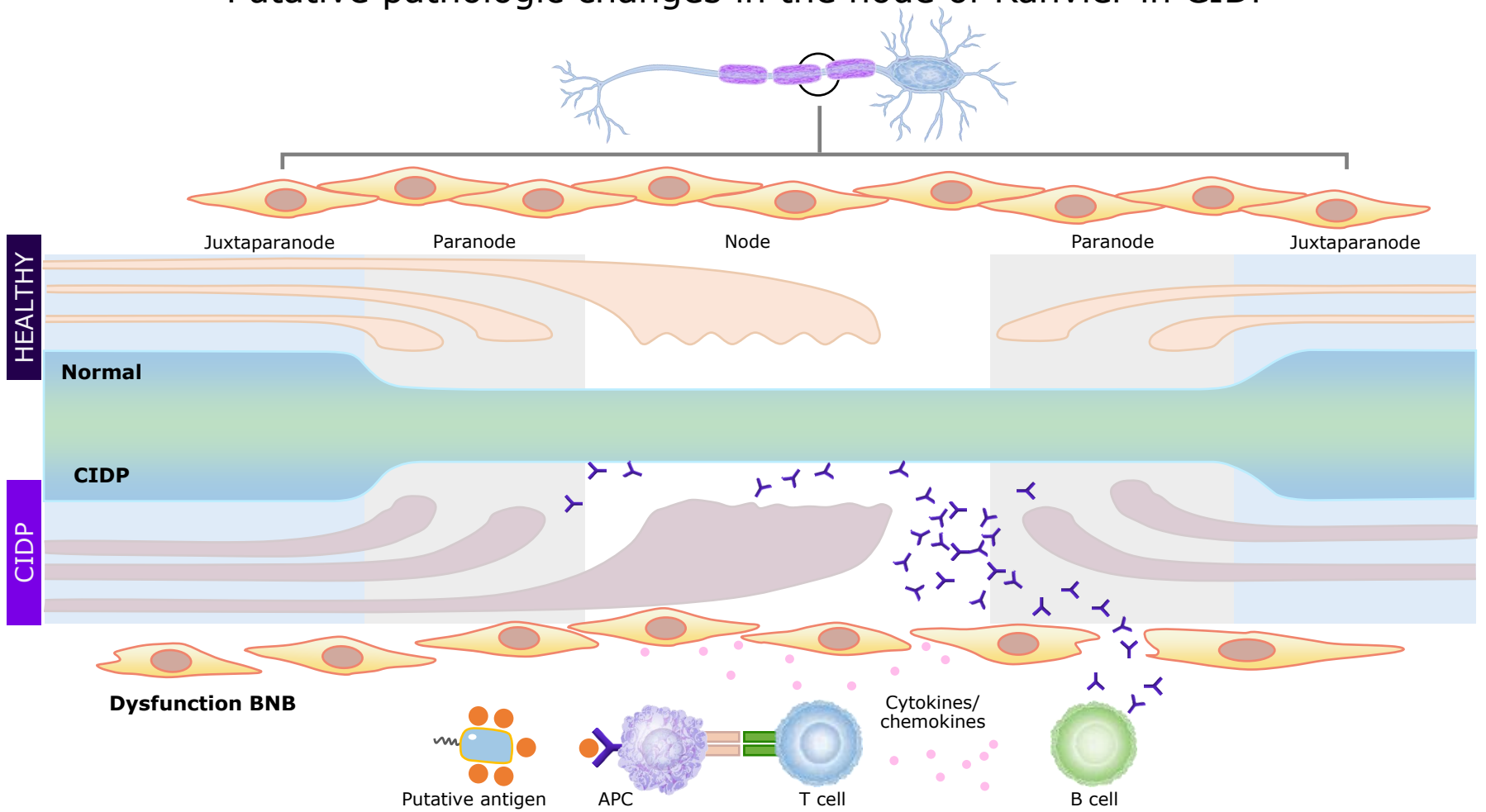


Figure adapted from reference 4. Copyright © 2021 by the authors. Licensed under https://creativecommons.org/licenses/by/4.0/

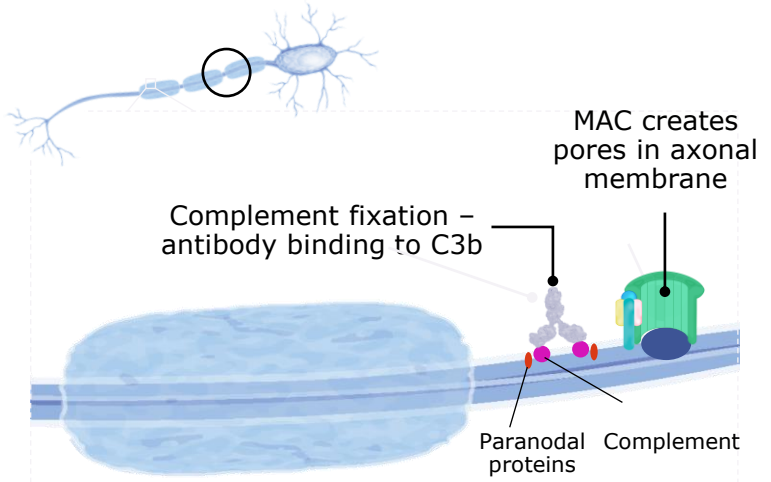
APC, antigen-presenting cell; BNB, blood nerve barrier; CIDP, chronic inflammatory demyelinating polyneuropathy.

1. Dalakas MC. *Biochimica et Biophysica Acta.* 2015;1852:658-666. 2. Querol LA, et al. *Nat Rev Neurol.* 2017;13:533-547. 3. Lewis RA. Chronic inflammatory demyelinating polyneuropathy: Etiology, clinical features, and diagnosis. In UpToDate, Pos TW (ed), Waltham MA, 2020. 4. Gao Y, et al. *Front Mol Neurosci.* 2021;14:779385.

Potential role of complement in demyelination and axonal damage in CIDP[1–4]

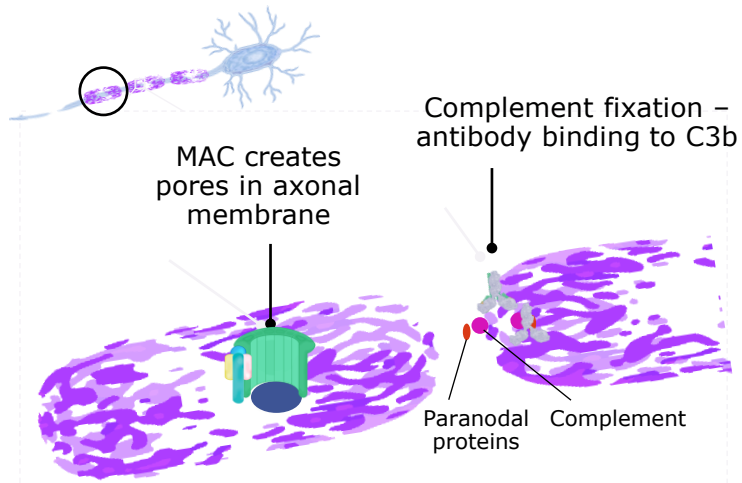
Activated complement may contribute to axonal damage in CIDP directly, or secondary to demyelination

PRIMARY AXONAL DAMAGE



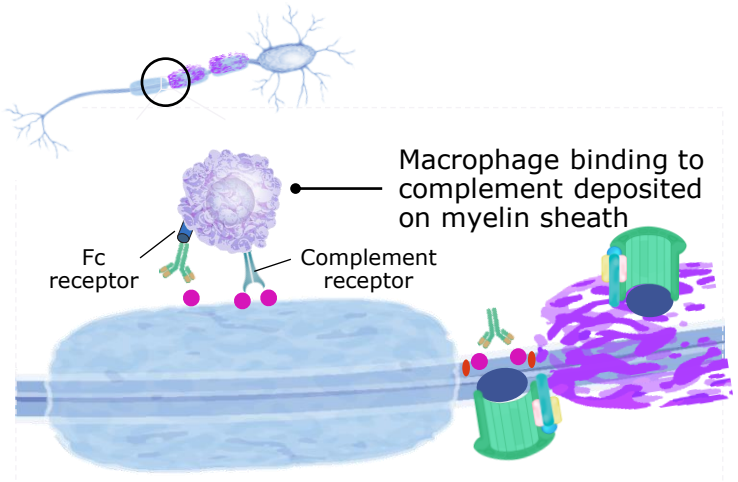
Complement (e.g., C3) deposition and MAC formation around the nodes of Ranvier and paranodes may lead to axonal damage[1–3]

AXONAL DAMAGE SECONDARY TO DEMYELINATION



Complement deposition and MAC formation on the node and surrounding areas of demyelination may lead to axonal damage[3]

AXONAL DAMAGE IN PARALLEL WITH DEMYELINATION



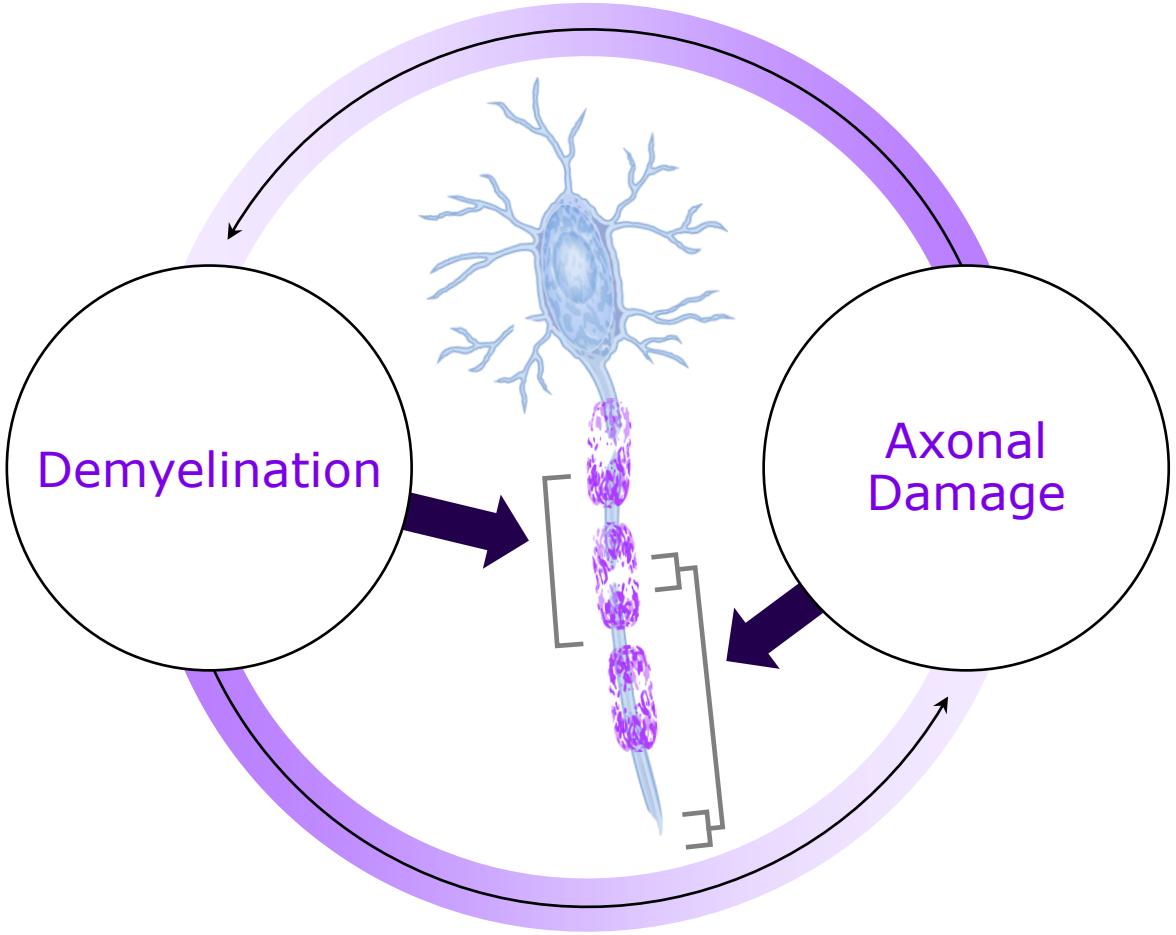
Complement deposition (e.g., C3 and C4) may trigger macrophage-induced demyelination and axonal damage particularly around nodes of Ranvier[1,4–6]

CIDP, chronic inflammatory demyelinating polyneuropathy; MAC, membrane attack complex.

1. Querol LA, et al. *Neurotherapeutics.* 2022;19:864-873. 2. Al-Zuhairy A, et al. *Muscle Nerve.* 2022;66(6):715-722. 3. Mathey EK, et al. *J Neurol Neurosurg Psychiatry.* 2015;86(9):973-985. 4. Schartz ND, et al. *J Neuroinflammation.* 2020;17(1):354. 5. Köller H, et al. *N Engl J Med.* 2005;352(13):1343-1356. 6. Dalakas MC, et al. *Nat Rev Neurol.* 2011;7(9):507-517.

Interdependent nature of demyelination and axonal damage in CIDP

- Biopsied nerves from people with CIDP show **axonal loss**, and **active axonal degeneration**[1]
- The activated complement system, via the MAC, is thought to contribute to axonal damage in CIDP directly, or secondary to demyelination[2]
- Though evidence of demyelination supports CIDP diagnosis, recent studies show axonal damage occurs **early in the disease**[3]
- It is debated whether the **axonal loss occurs secondary** to **demyelination** or is a **primary manifestation** due to separate nodal or paranodal disease processes[3]



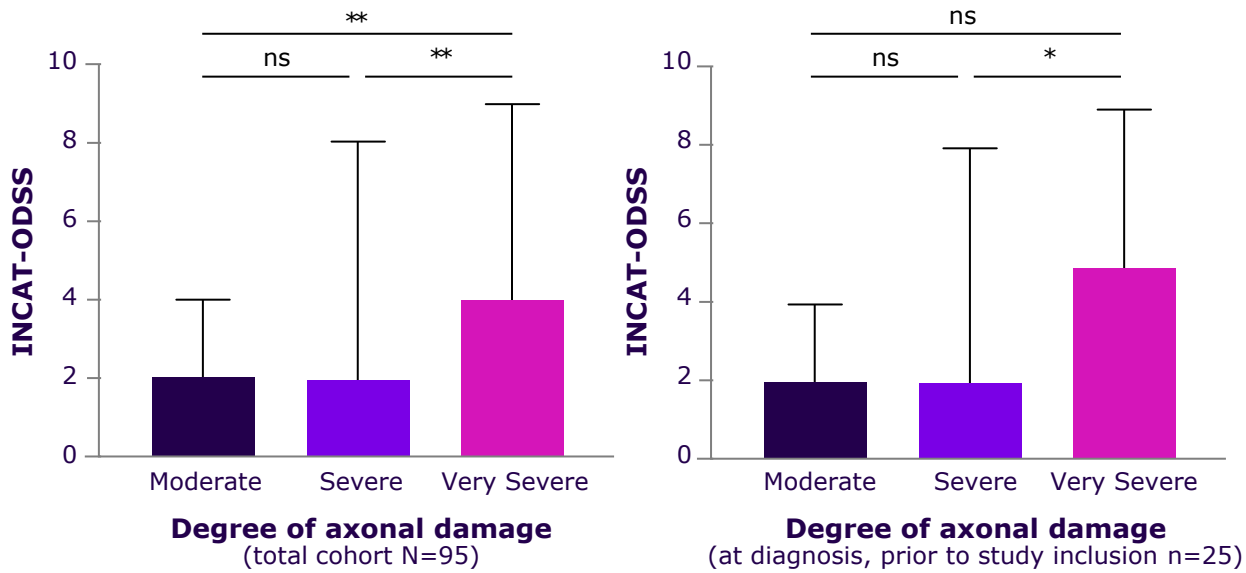
CIDP, chronic inflammatory demyelinating polyneuropathy; MAC, membrane attack complex.

1. Moss KR, et al. *Neurosci Lett.* 2021;744:135595. 2.Querol LA, et al. *Neurotherapeutics.* 2022;19:864-873. 3. Al-Zuhairy A, et al. *Muscle Nerve.* 2022;66(6):715-722.

Axonal damage occurs early in disease

- Significant presence of axonal lesions even in the first descriptions[1]
- Potential predictor of long-term disability,[2] as ***disability is largely determined by axonal damage***[3]
- Electrophysiological criteria based on demyelination[3]
  - People with severe axonal damage may not fulfill the diagnostic criteria
- Early treatment may be important to prevent axonal damage[3]

Degree of Axonal Damage versus INCAT-ODSS[3]



Axonal damage may be a possible marker of clinical disability and outcome measure in CIDP[3]

If axonal damage is a determinant of long-term disability, can prevention or mediation of axonal damage be our path to functional cure?

*p≤0.05; **p≤0.001.

Figures modified from reference 3. © 2021 The Authors. European Journal of Neurology; with permission from John Wiley and Sons Ltd; Licensed under https://creativecommons.org/licenses/by/4.0/.

CIDP, chronic inflammatory demyelinating polyneuropathy; INCAT, inflammatory neuropathy cause and treatment; ns, not significant; ODSS, overall disability sum score.

1. Dyck PJ, et al. *Mayo Clin Proc.* 1975;50(11):621-637. 2. Al-Zuhairy A, et al. *Clinical Neurophys.* 2021;132(4):1000-1007. 3. Grüter T, et al. *Eur J Neurol.* 2022;29(2):583-592.

ACTIVE POLL

What biomarkers do you think could be useful in the diagnosis and management of CIDP?

A. Peripherin

B. Neurofilament

C. Cytokines (e.g., IL-8)

D. I do not think biomarkers would be useful

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ACTIVE POLL (alternative)

How useful is neurofilament (NfL) as a biomarker in CIDP? [Select all that apply]

- A: Useful for monitoring axonal damage
- B: Useful for monitoring treatment response
- C: Useful in diagnosis and monitoring disease progression
- D: Not useful

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Biomarkers in CIDP could aid in diagnosis and treatment decisions

Emerging biomarkers in CIDP

1

MRI imaging/nerve ultrasound[1,2]

- MRI: cross-sectional area, signal changes, functional MRI (diffusion tensor imaging)
- Ultrasound: cross-sectional area, echogenicity, nerve vascularization

2

Cytokines/interleukins/complement[3–5]

- Cytokine profiles
- Terminal complement components

3

Fluid biomarkers of axonal/myelin damage[6,7]

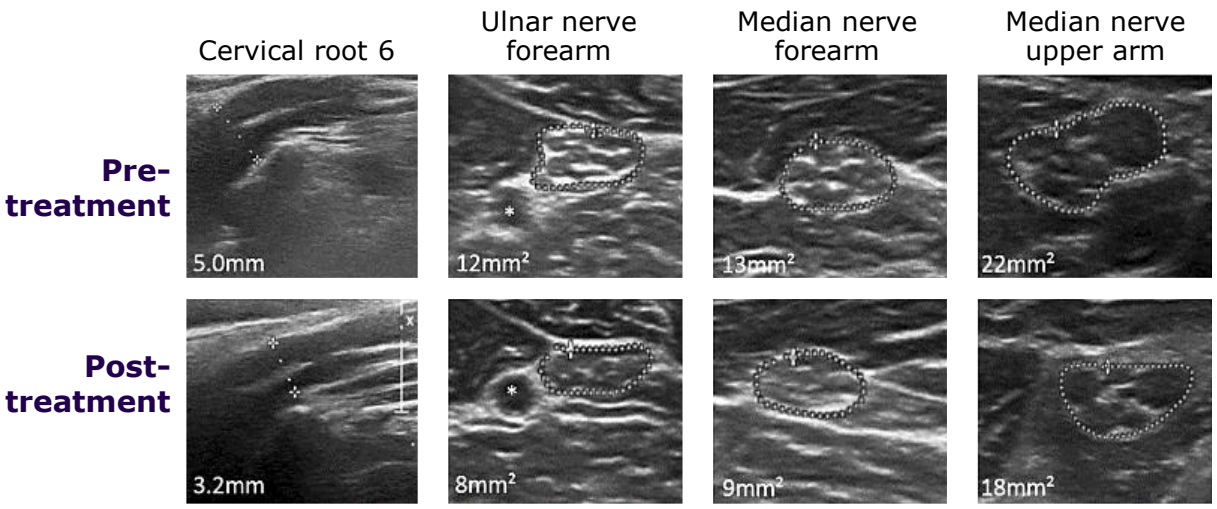
- Neurofilament (NfL)
- Peripherin
  - intermediate filament protein expressed on neurons in the PNS
- Sphingomyelin (SM)
  - sphingolipid found in the myelin sheath

CIDP, chronic inflammatory demyelinating polyneuropathy; MRI, magnetic resonance imaging.

1. Härtig F, et al. *Neurother*. 2018;15(2):439-451. 2. Priesner F, et al. *Ann Clin Transl Neurol.* 2024;11(3):593-606. 3. Quast I, et al. *Ann Clin Transl Neurol.* 2016;3(9):730-735. 4. Kmezic I, et al. *Front Immunol*. 2023;14:1241199. 5. Stascheit F, et al. *Front Neurol.* 2021;12:723009. 6. Capodivento G, et al. *J Neurol Neurosurg Psychiatry*. 2021;92(3):303-310. 7. Keddie S, et al. *Brain.* 2023;146(11):4562-4573.

Utilizing ultrasound and MRI in assessing CIDP

Ultrasound Results of a Person With CIDP Pre- and 12 Months Post-Treatment[1]



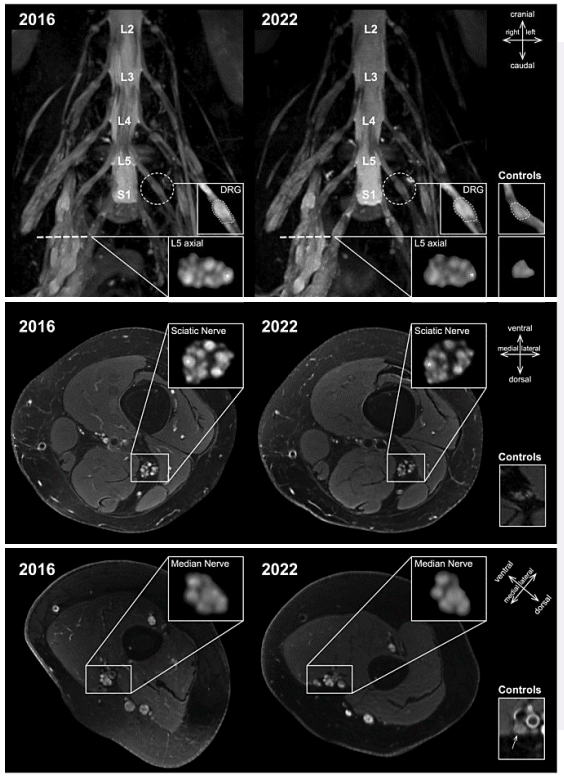
Significant reduction of the cross-section areas in the ulnar and median nerve and of the diameter of the cervical root 6

Exemplary T2-Weighted Images Showing Typical Imaging Hallmarks of CIDP Over the Longitudinal Course[2]

Enlargement of the plexus and dorsal root ganglia

Enlargement and fascicular hyperintensities in the sciatic nerve

Upper-arm level: nerve hypertrophy and T2 signal increase remained nearly unchanged



Ultrasound and MRI may be useful markers to assess nerve thickening and inflammation in CIDP[1,2]

Figure from reference 1. © 2018 The American Society for Experimental NeuroTherapeutics, Inc., published by Elsevier. Figure from reference 2. ©2023 The Authors. Annals of Clinical and Translational Neurology. Published by Wiley Periodicals LLC.

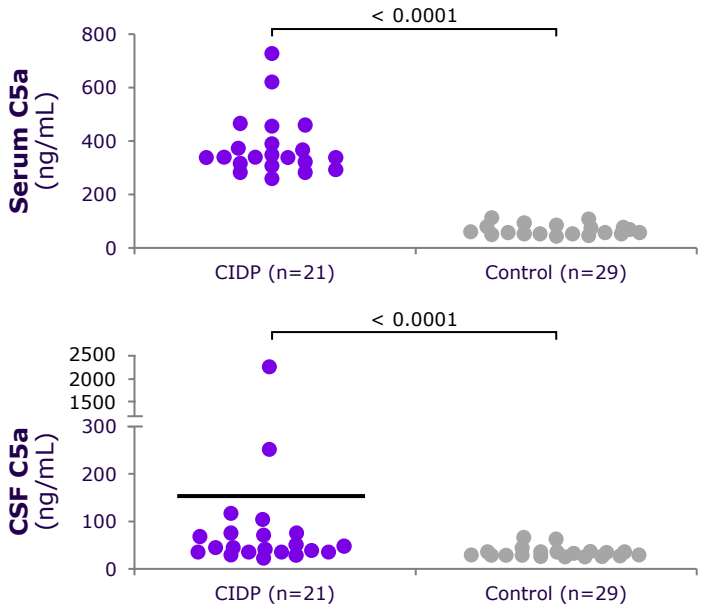
CIDP, chronic inflammatory demyelinating polyneuropathy; MRI, magnetic resonance imaging.

1. Härtig F, et al. *Neurother.* 2018;15(2):439-451. 2. Priesner F, et al. *Ann Clin Transl Neurol*. 2024;11(3):593-606.

Multiple biomarkers are being investigated in CIDP

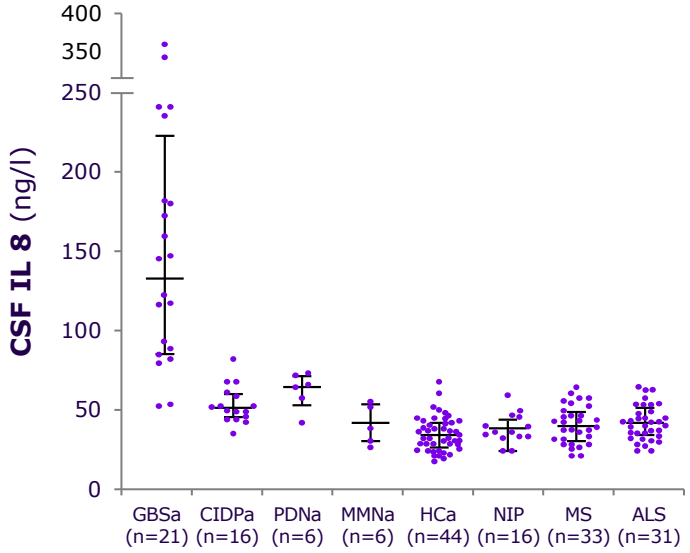
Terminal Complement

Increased Terminal Complement Activation in Serum and CSF of People With CIDP[1]



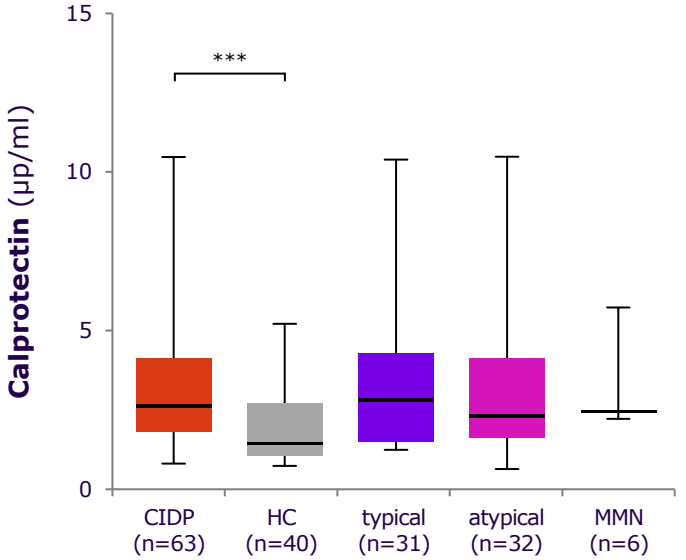
IL-8

Absolute Concentrations of Pre-Treatment Levels of IL-8[2]



Calprotectin

Comparison of Calprotectin Levels in CIDP and HC[3]



Cytokines are elevated in CIDP patients but overlap with healthy individuals and other conditions, whereas terminal complement is substantially higher in patients with CIDP compared to controls

***p<0.001.

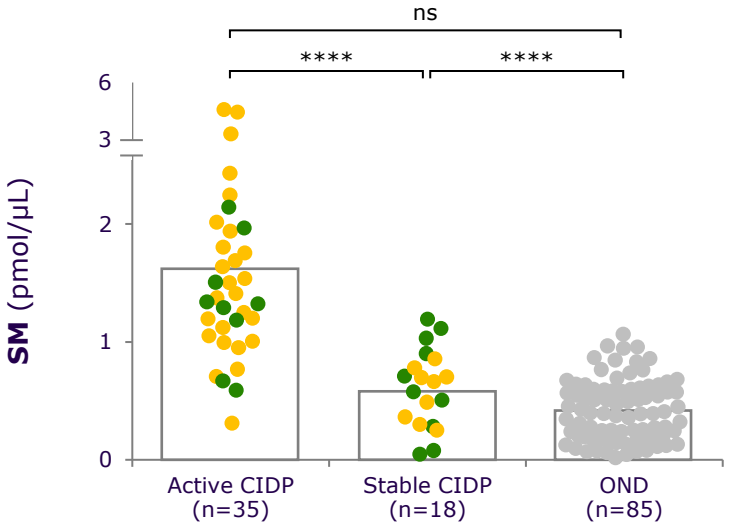
ALS, amyotrophic lateral sclerosis; C5a, complement component 5a; CIDP, chronic inflammatory demyelinating polyneuropathy; CIDPa, pre-treatment chronic inflammatory demyelinating polyneuropathy; CSF, cerebrospinal fluid; GBSa, pre-treatment Guillain-Barré syndrome; HC, healthy control; IL, interleukin; MMN, multifocal motor neuropathy; MMNa, pre-treatment multifocal motor neuropathy; MS, multiple sclerosis; NIP, non-inflammatory polyneuropathy; PDNa, pre-treatment paraproteinemia-related demyelinating polyneuropathy.

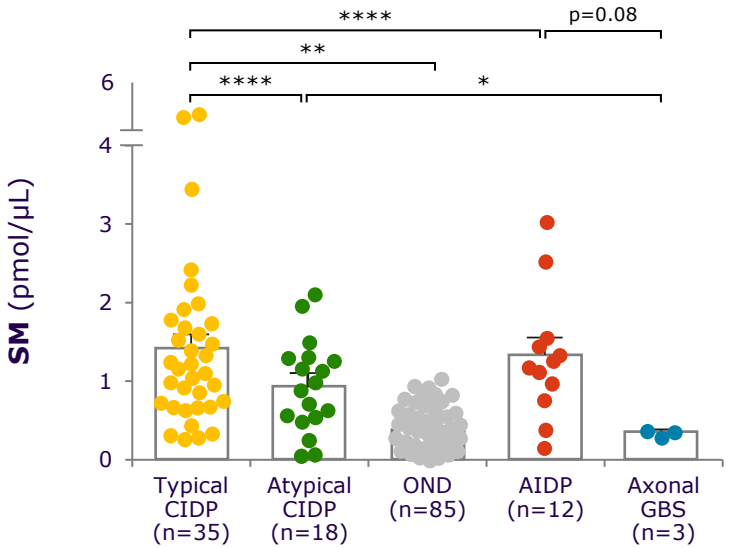
1. Quast I, et al. *Ann Clin Transl Neurol.* 2016;3(9):730-735; Figure modified from reference 1. ©2016 The Authors. Annals of Clinical and Translational Neurology published by Wiley Periodicals. Licensed under https://creativecommons.org/licenses/by-nc-nd/4.0/. 2. Kmezic I, et al. *Front Immunol.* 2023;14:1241199; Figure modified from reference 2. Available at: https://www.frontiersin.org/journals/immunology/articles/10.3389/fimmu.2023.1241199/full. Copyright ©2023 Kmezic, Gustafsson, Fink, Svenningsson, Samuelsson, Ingre, Olsson, Hansson, Kockum, Adzemovic and Press. Licensed under CC BY 4.0 - https://creativecommons.org/licenses/by/4.0/. 3. Stascheit F, et al. *Front Neurol.* 2021;12:723009. Figure modified from reference 3. Available at: https://www.frontiersin.org/articles/10.3389/fneur.2021.723009/pdf. Copyright © 2021 Stascheit, Hotter, Klose, Meisel, Meisel and Klehmet. Licensed under CC BY 4.0 - https://creativecommons.org/licenses/by/4.0/.

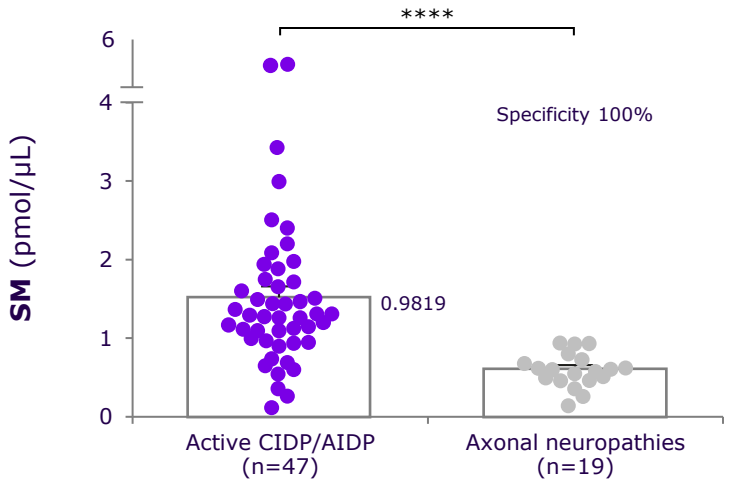
Sphingomyelin as a biomarker could identify and monitor myelin damage in CIDP

Cerebrospinal fluid sphingomyelin levels were significantly increased in people with CIDP compared with controls, with the potential to distinguish active versus stable CIDP

Cerebrospinal Fluid Sphingomyelin Levels in Participants Affected by CIDP and GBS







Participants with CIDP displayed increased levels of CSF SM when in the **active stage of the disease compared with controls and stable CIDP**

Participants with both typical and atypical CIDP **showed increased levels of CSF SM compared with controls**

SM testing displayed **a 100% specificity in the identification of participants with CIDP in the active stage of the disease** and participants with AIDP from a cohort of participants with axonal neuropathies

*p<0.05; **p<0.01; ****p<0.0001.

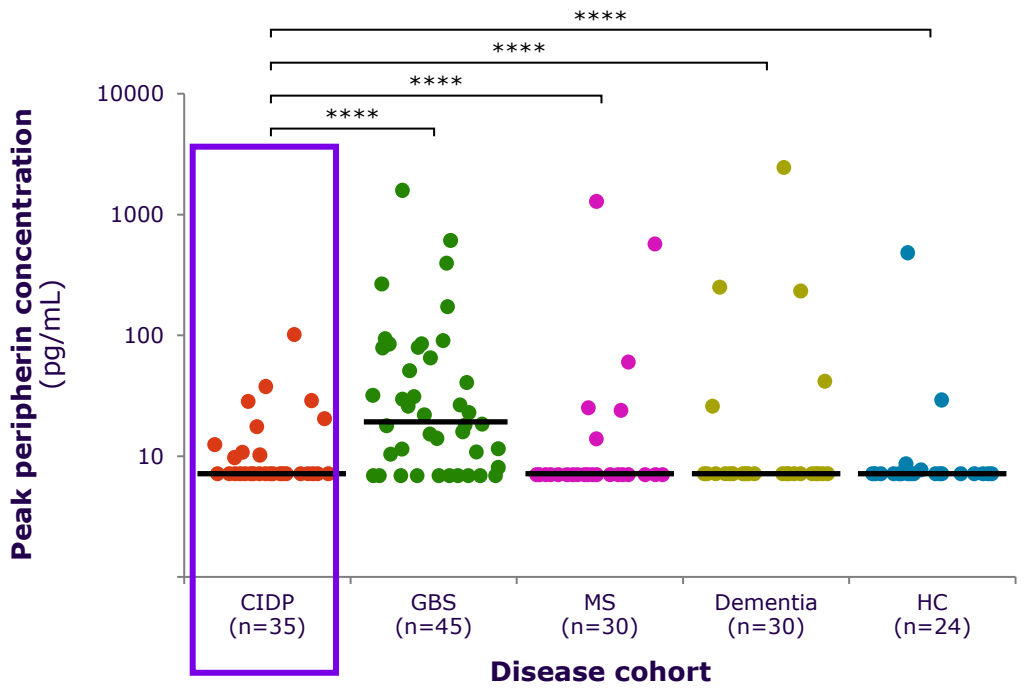
AIDP, acute inflammatory demyelinating polyneuropathy; CIDP, chronic inflammatory demyelinating polyneuropathy; CSF, cerebrospinal fluid; GBS, Guillain-Barré syndrome; ns, not significant; OND, other neurological disease; SM, sphingomyelin.

Capodivento G, et al. *J Neurol Neurosurg Psychiatry*. 2021;92(3):303-310.

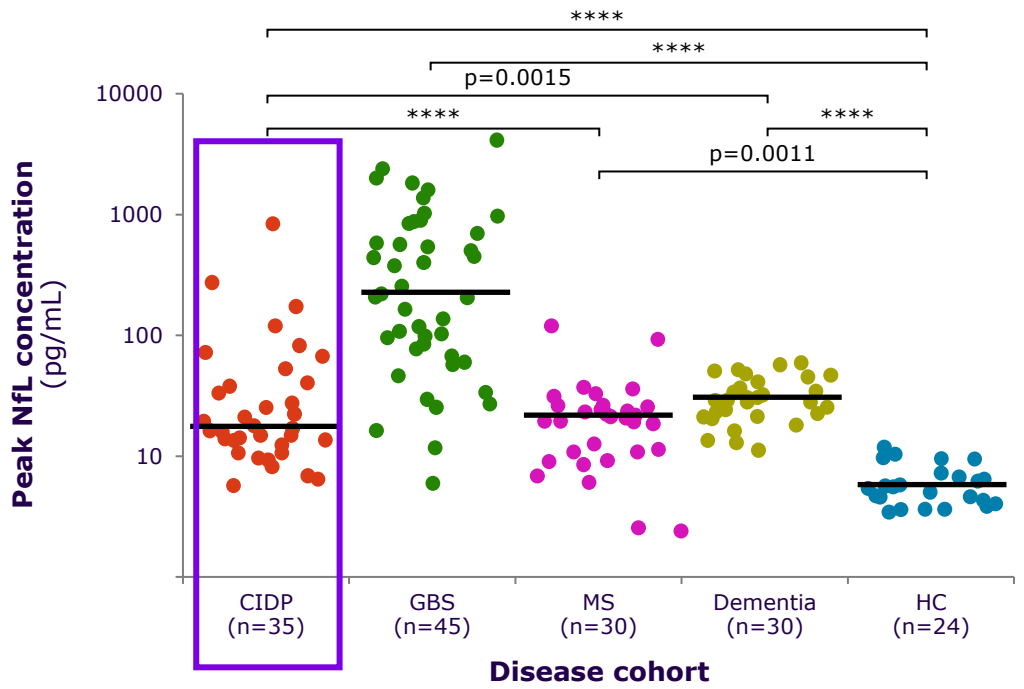
Biomarkers for axonal damage differ between PNS diseases

NfL was elevated in both CIDP and GBS, whereas peripherin was only elevated in GBS

Peripherin*[a]



NfL*[a]



Peak serum peripherin and NfL are potential markers of axonal damage in CIDP and GBS versus other PNS diseases

*Assessed using a single molecule array immunoassay. [a]For GBS and CIDP patients, the highest measured serum peripherin or NfL concentration was taken as the peak value. MS, dementia patients, and HC provided single time point samples. ****p<0.0001.

CIDP, chronic inflammatory demyelinating polyneuropathy; GBS, Guillain-Barré syndrome; HC, healthy control; MS, multiple sclerosis; NfL, neurofilament light chain.

Future directions for biomarkers in assessing disease

Biomarkers are essential to improve informed decision-making[1]

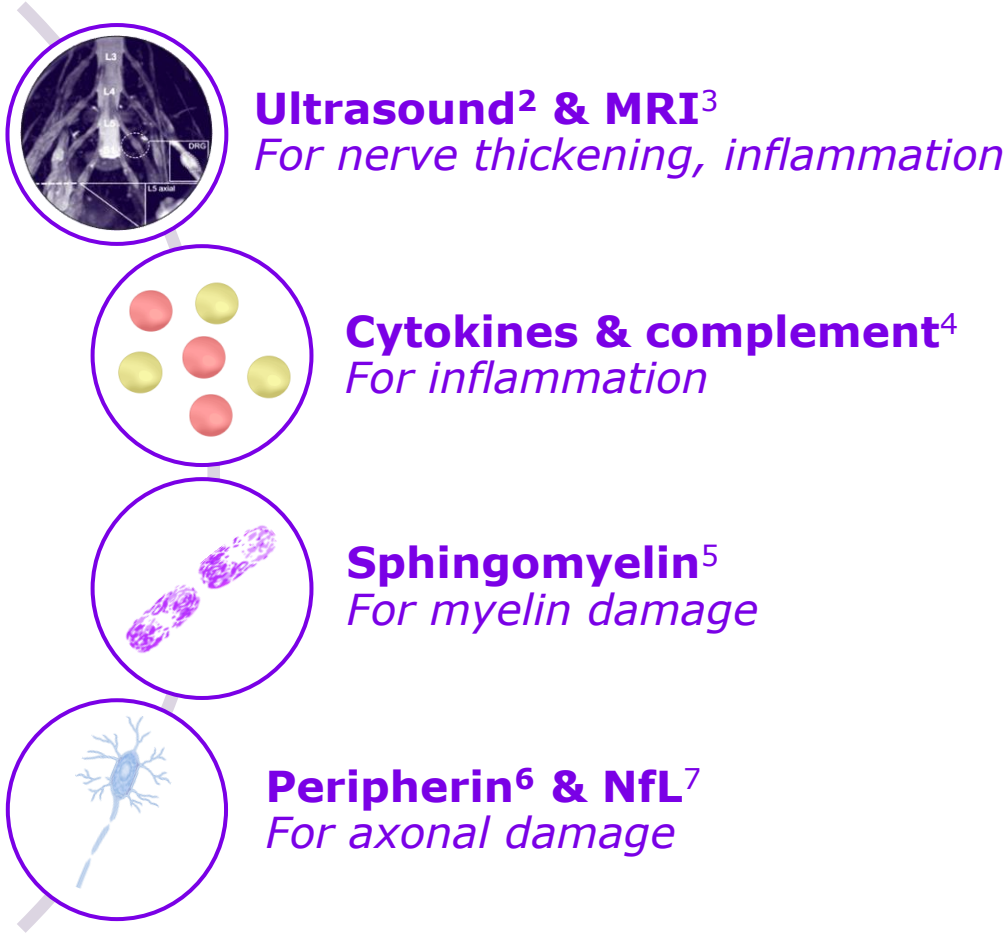
- **CIDP heterogeneity** requires **individualized** disease monitoring and treatment approaches
- People with CIDP are **commonly misdiagnosed** and often show **suboptimal response** to treatment
- **Biomarkers** could improve **diagnostic accuracy** and **guide treatment decisions**
  - E.g. those that capture nerve integrity, nerve function, drug effect and effector mechanisms

Diagnostic biomarkers

- Autoantibodies
- Electrophysiology
- Imaging

Biomarkers for treatment response

- NfL
- Cytokines/B cell counts



Ultrasound[2] & MRI[3]
For nerve thickening, inflammation

Cytokines & complement[4]
For inflammation

Sphingomyelin[5]
For myelin damage

Peripherin[6] & NfL[7]
For axonal damage

CIDP, chronic inflammatory demyelinating polyneuropathy; MRI, magnetic resonance imaging; NfL, neurofilament light chain.

1. Allen JA, et al. *Expert Rev Neurother.* 2021;21(7):805-816. 2. Härtig F, et al. *Neurother.* 2018;15(2):439-451. 3. Priesner F, et al. *Ann Clin Transl Neurol.* 2024;11(3):593-606. 4. Quast I, et al. *Ann Clin Transl Neurol.* 2016;3(9):730-735. 5. Capodivento G, et al. *J Neurol Neurosurg Psychiatry*. 2021;92(3):303-310. 6. Keddie S, et al. *Brain.* 2023;146(11):4562-4573. 7. Luigetti M, et al. *Int J Mol Sci.* 2024;25(2):1254.

ACTIVE POLL

What would you use biomarkers for?

A. Help with diagnosis of CIDP

B. Help with treatment choice

C. Treatment monitoring

D. I don’t need biomarkers

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Opportunities to Target the Pathobiology of CIDP

Jeffrey Allen, MD

University of Minnesota, Minneapolis, Minnesota, USA

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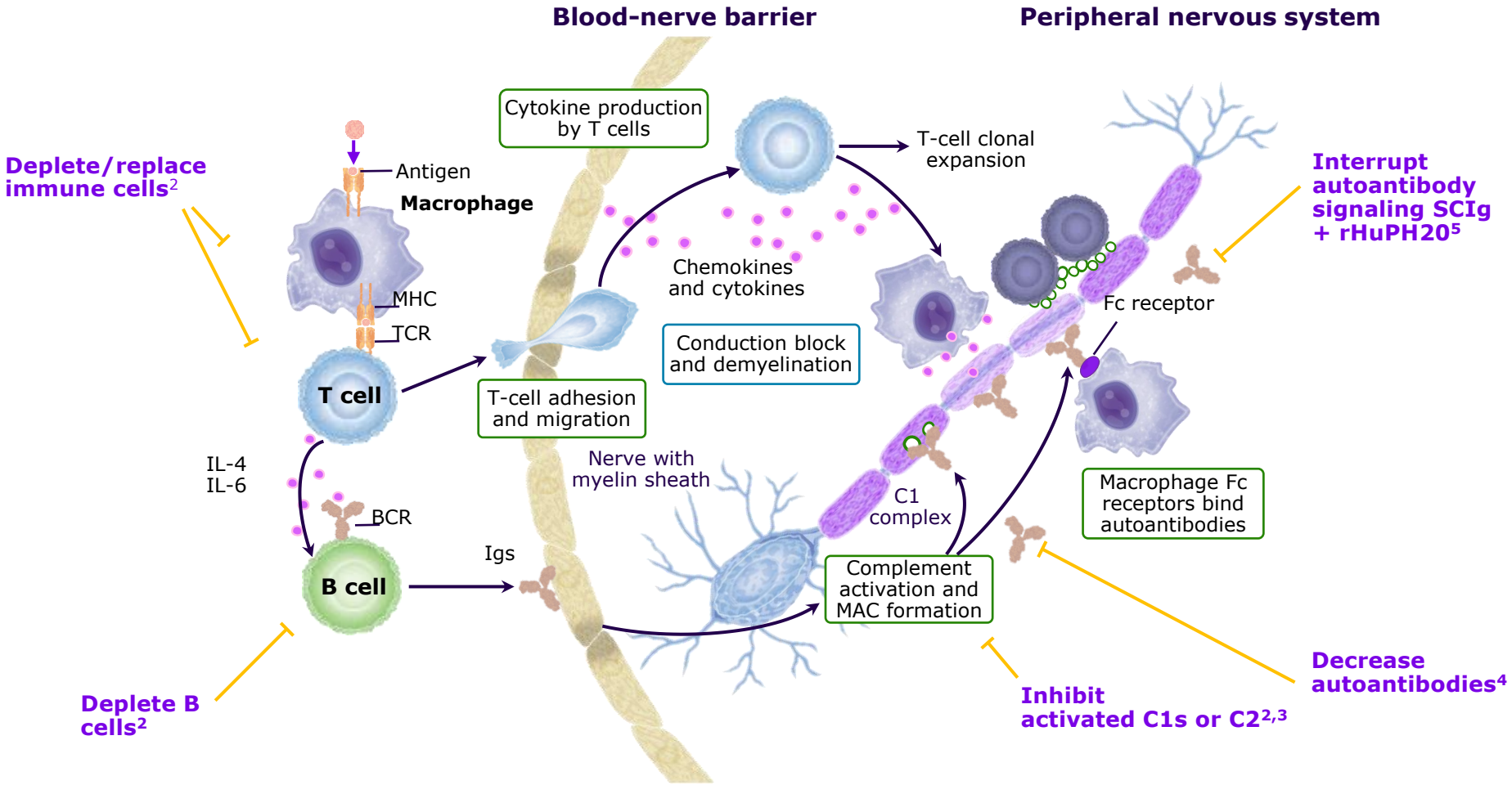
Approved treatments for people living with CIDP

	Immunoglobulin (IVIg/SCIg)	**Corticosteroids**	**Plasma Exchange** (PLEX)	**FcRn Antagonists**
Administration[1,5]	IVIG: Intravenous, at home, hospital SCIg: Subcutaneous, at home	Oral, intravenous, at home, hospital	Intravenous, hospital	Subcutaneous, office, infusion center, at home
Response[1,5]	IVIg: 1–2 weeks SCIg: 1–2 weeks	Several weeks or months	1–2 weeks	Within 4 weeks
Mechanism of Action[2–5]	Neutralization of pathogenic autoantibodies, anaphylatoxins, and cytokines	Inhibition of inflammatory mediator release		
	Scavenging complement and activation fragments Inhibition of B-cell functions	Increase of anti-inflammatory molecules	Removal of pathogenic autoantibodies, and immune complexes	Reduction of circulating IgG through IgG1 fragment binding to FcRn
	Saturation of FcRn receptors	Reduction of circulating T cells		
	Modulation of Fcγ receptors			

CIDP, chronic inflammatory demyelinating polyneuropathy; Fc, fragment crystallizable; FcRn, neonatal Fc receptor; Ig, immunoglobulin; IVIg, intravenous immunoglobulin; SCIg, subcutaneous immunoglobulin.

1. Bunschoten C, et al. *Lancet Neurol.* 2019;18(8):784-794. 2. Hoffman JHO, Enk AH. *Front Immunol.* 2019;10:1090. 3. Hughes RA, et al. *Cochrane Database Syst Rev.* 2017;11(11):CD002062. 4. Mina-Osorio P, et al. *Transfus Med Rev.* 2024;38(1):150767. 5. Allen JA, et al. *Lancet Neurol.* 2024;23(10):1013-1024. Erratum in: *Lancet Neurol*. 2025;24(5):e8.

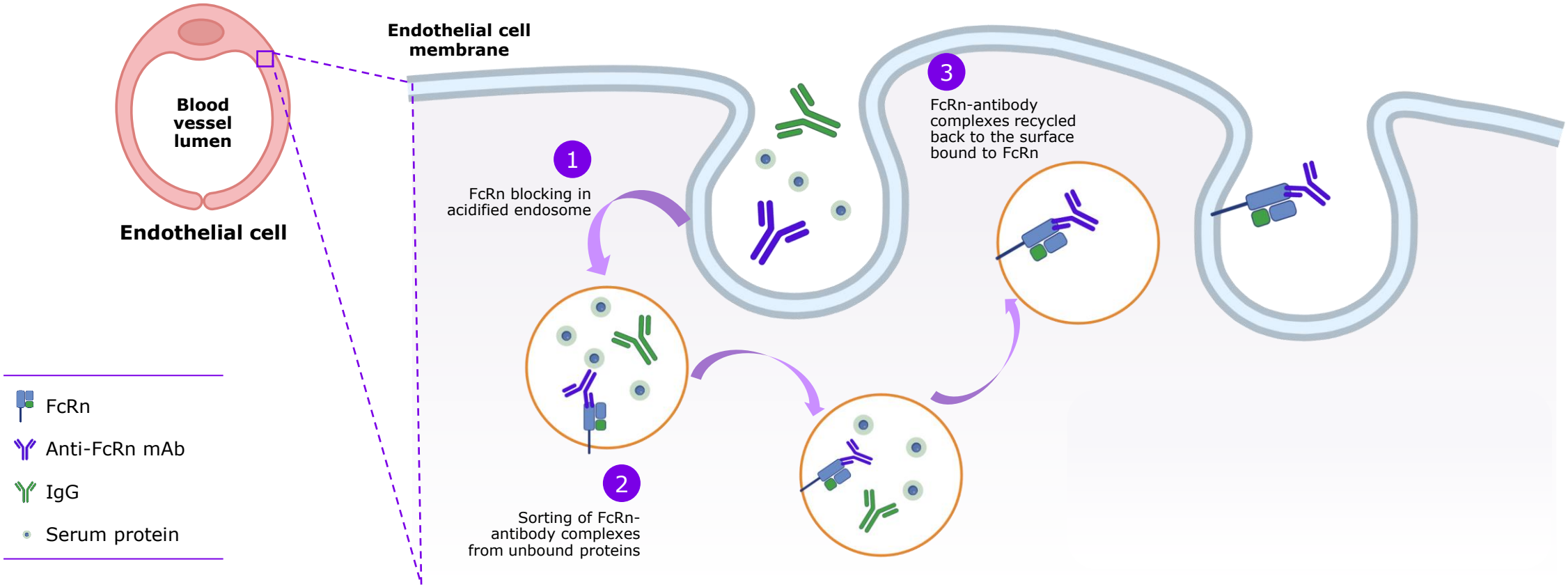
Key mechanisms in CIDP pathophysiology[1]



BCR, B-cell receptor; C1, complement component 1; Fc, fragment crystallizable; Ig, immunoglobulin; IL, interleukin; MHC, major histocompatibility complex; rHuPH20, recombinant human hyaluronidase PH20; SCIg, subcutaneous immunoglobulin; TCR, T-cell receptor.

1. Dalakas MC, et al. *Nat Rev Neurology.* 2011;7:507-511. 2. Mair D, et al. J Neurol Neurosurg Psychiatry. 2025;96:38-46. 3. Briani C, Visentin A. *Neurotherapeutics.* 2022;19:874-884. 4. Dorst J, et al. *J Neurol.* 2018;265:2906-2915. 5. Bril V, et al. *J Peripher Nerv Syst.* 2023 Sep;28(3):436-449.

Key mechanisms in CIDP pathophysiology: Proposed mechanism of action of FcRn antagonists[1]



FcRn inhibition may reduce myelin damage on peripheral nerves by reducing the levels of pathogenic IgG and IgG-immune complexes in circulation[2]

Figure adapted from reference 1. Copyright © 2020 by the authors. Licensed under https://creativecommons.org/licenses/by/4.0/.
CIDP, chronic inflammatory demyelinating polyneuropathy; FcRn, neonatal fragment crystallizable receptor; IgG, immunoglobulin G; mAb, monoclonal antibody.
1. Gable KL, Guptill JT. *Front Immunol.* 2020;10:3052. 2. Mina-Osorio P, et al. *Transfus Med Rev.* 2024;38(1):150767.

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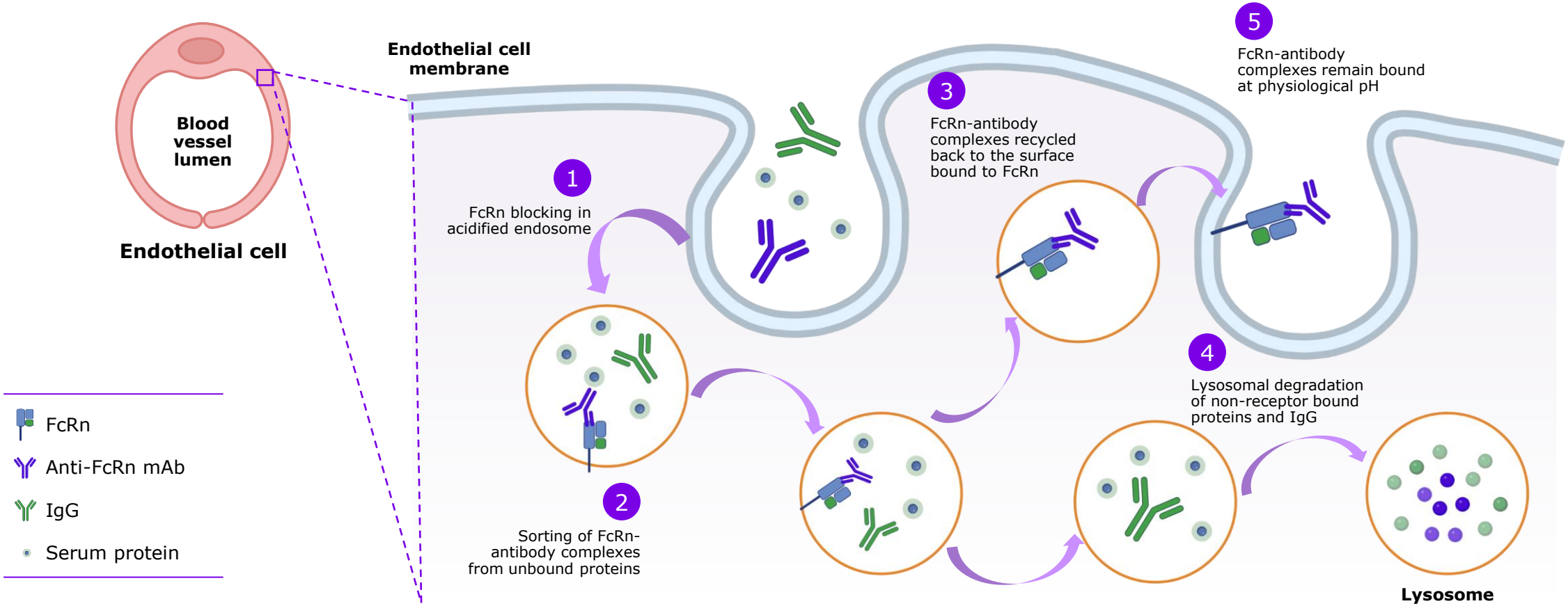

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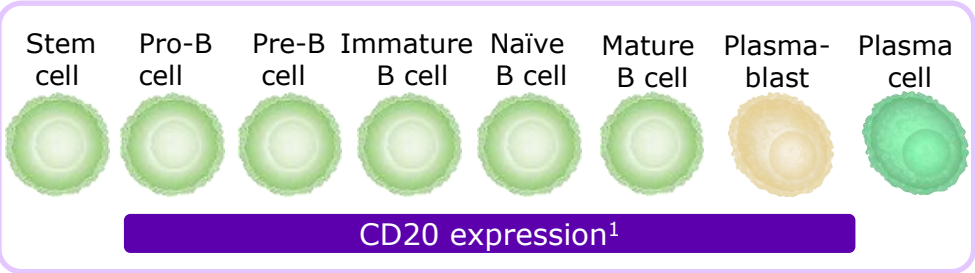
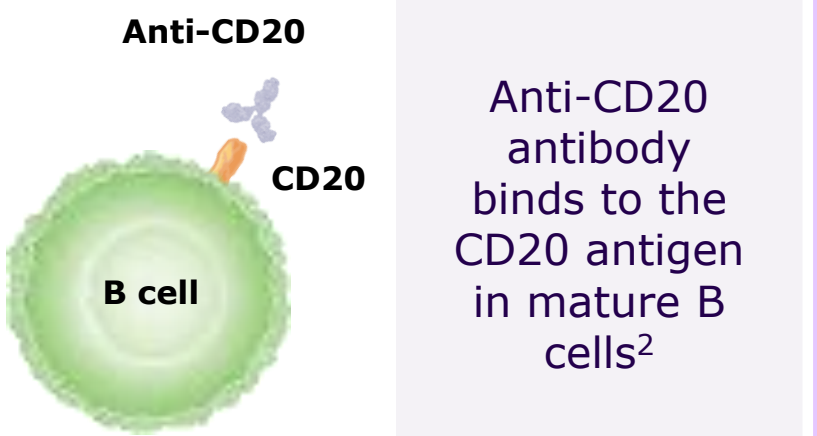
Key mechanisms in CIDP pathophysiology: B-cell targets

Proposed Mechanism of Action of Anti-CD20





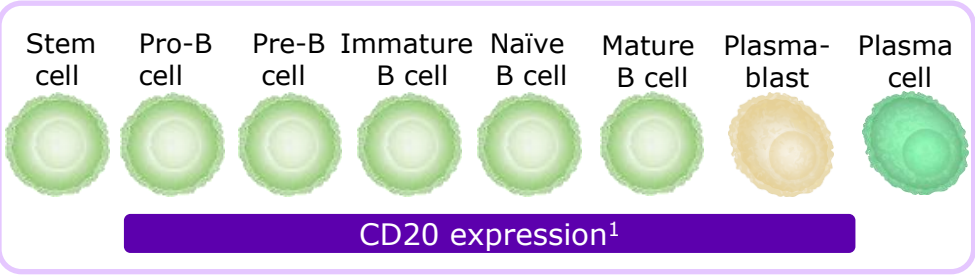
Anti-CD20 antibody binds to the CD20 antigen in mature B cells[2]

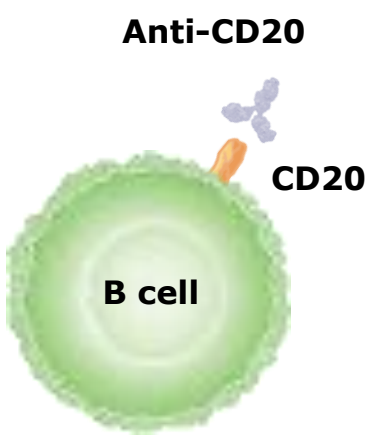
CD, cluster of differentiation; CIDP, chronic inflammatory demyelinating polyneuropathy.

1. Forsthuber TG, et al. *Ther Adv Neurol Disord.* 2018;11:1756286418761697. 2. Guo X, et al. *Front Neurosci.* 2021;15:637336. 3. Briani C, Visentin A. *Neurotherapeutics.* 2022;19:874-884.

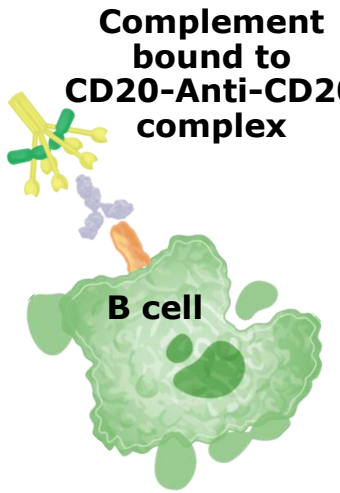
Key mechanisms in CIDP pathophysiology: B-cell targets

Proposed Mechanism of Action of Anti-CD20





Anti-CD20 antibody binds to the CD20 antigen in mature B cells[2]



Anti-CD20 leads to lysis of B cells[3]

B-cell depletion may interfere with the production of antibodies in CIDP[2]

CD, cluster of differentiation; CIDP, chronic inflammatory demyelinating polyneuropathy.

1. Forsthuber TG, et al. *Ther Adv Neurol Disord.* 2018;11:1756286418761697. 2. Guo X, et al. *Front Neurosci.* 2021;15:637336. 3. Briani C, Visentin A. *Neurotherapeutics.* 2022;19:874-884.

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Key mechanisms in CIDP pathophysiology: Classical complement inhibition

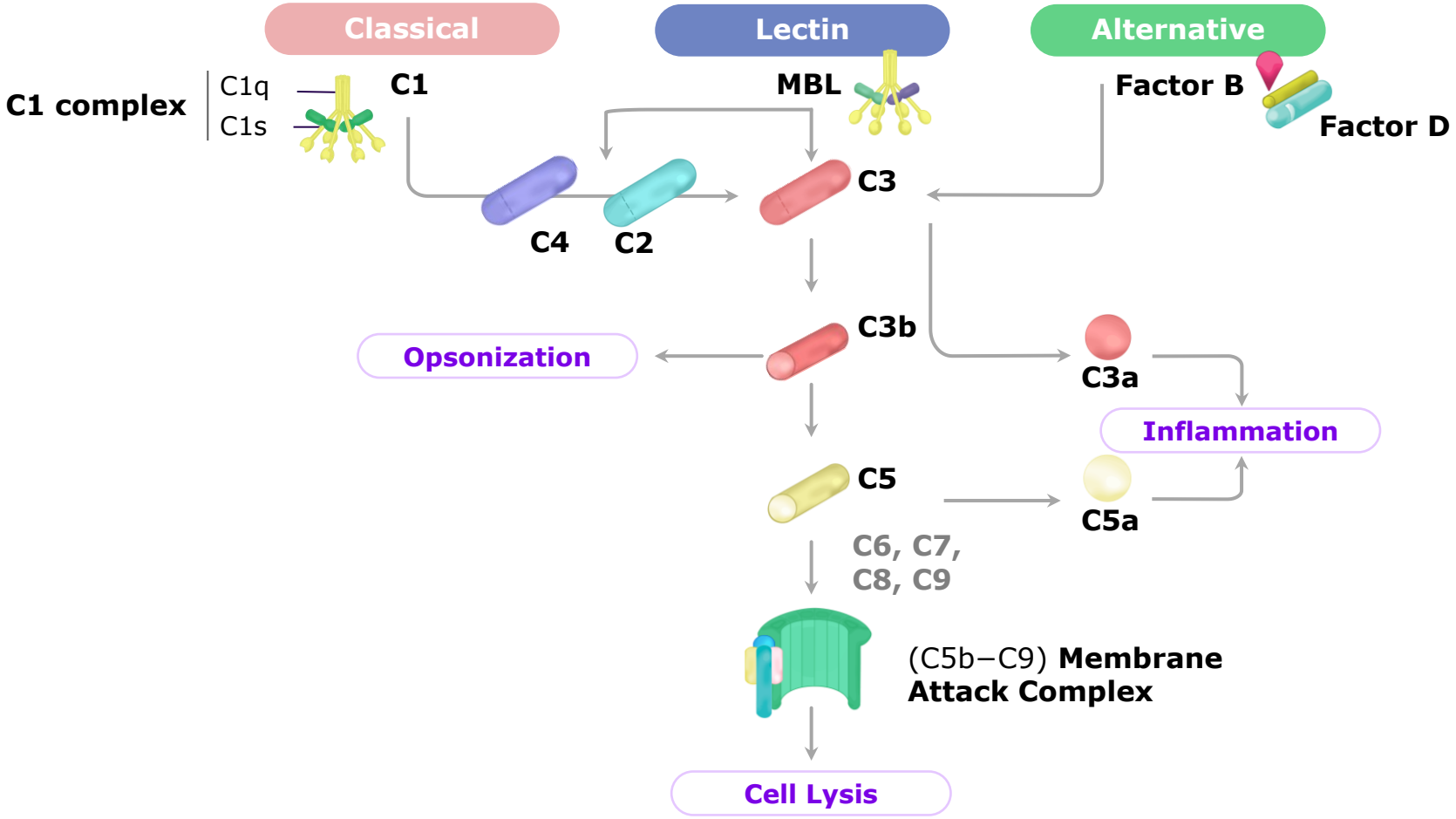

Figure adapted from Murphy K, Weaver C. Janeway's Immunobiology (9th edition), Garland Science, 2016. Copyright © 2016 by the authors. Licensed under the terms of the Creative Commons CC BY-NC license.
C, complement; CIDP, chronic inflammatory demyelinating polyneuropathy; MBL, mannose-binding lectin.
Querol L, et al. J *Peripher Nerv Syst.* 2023;28(2):276-285.

Key mechanisms in CIDP pathophysiology: Classical complement inhibition

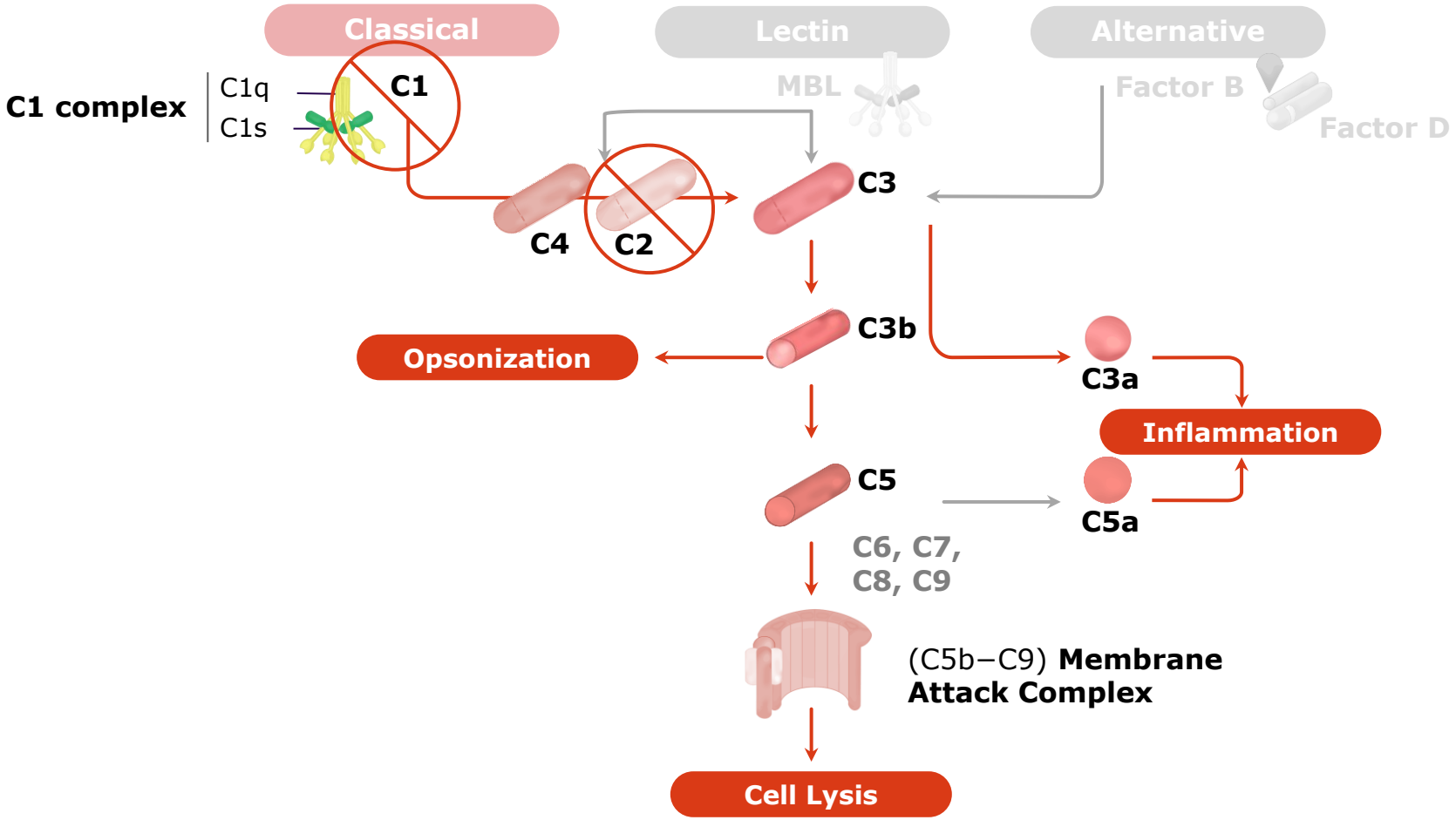

Figure adapted from Murphy K, Weaver C. Janeway's Immunobiology (9° edition), Garland Science, 2016. Copyright © 2016 by the authors. Licensed under the terms of the Creative Commons CC BY-NC license.
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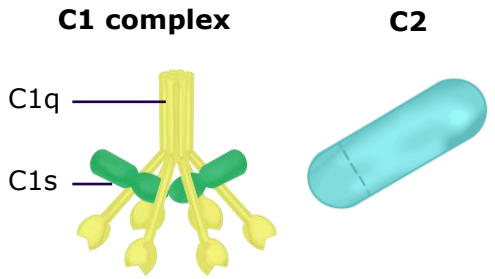
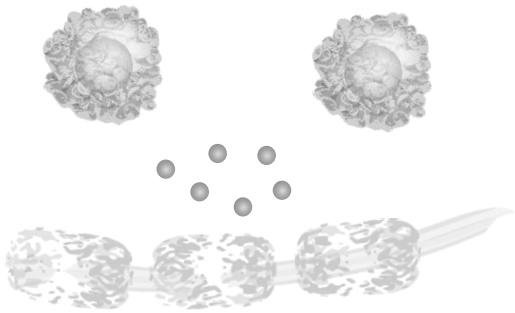
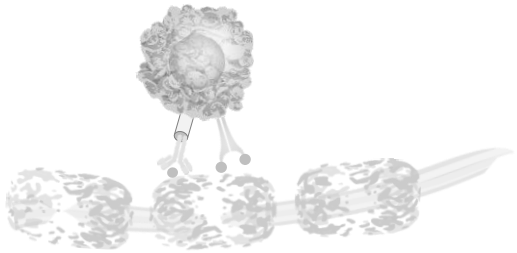
Key mechanisms in CIDP pathophysiology: Classical complement inhibition



Binding to complement proteins high in the cascade prevents activation of downstream elements



Reduced inflammation from anaphylatoxin production



Reduced phagocytosis through complement deposition/fixation on peripheral nerves

Reduced myelin sheath and axonal damage through cell lysis from MAC action

Complement inhibition may reduce demyelination and axonal damage on peripheral nerves by preventing activation of the downstream enzymatic cascade in CIDP

C, complement; CIDP, chronic inflammatory demyelinating polyneuropathy; MAC, membrane attack complex.

Querol L, et al. *J Peripher Nerv Syst.* 2023;28(2):276-285.

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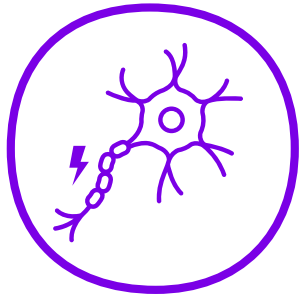
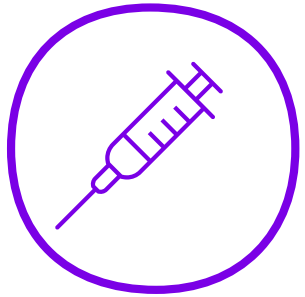
Tackling axonal damage in CIDP could help improve outcomes

The potential for new therapies to address current unmet needs is multifactorial



Prevention of **subclinical axonal degeneration** that could lead to **permanent damage**[1–3]



Potential to **impact side effects** and **burden** from **long-term SoC treatment**[4,5]

Potential to **decrease delays in treatment, severe morbidity/long-term or residual disability**[6,7]

Potential to impact **wearing-off effects** and **rates of relapse** in incomplete responders[5]

Addressing axonal damage in CIDP may be important in halting progression and restoring function

CIDP, chronic inflammatory demyelinating polyneuropathy; SoC, Standard of Care.

1. Dalakas MC. Autoimmune peripheral peuropathies. In: Rich R, et al., eds. Clinical Immunology: Principles and Practice. 6th ed. Elsevier; 2019:903-915.e1. 2. Said G, Krarup C. Chronic inflammatory demyelinative polyneuropathy. In: Handbook of Clinical Neurology. Elsevier; 2013;115:403-413. 3. Ryan M, et al. *AJMC.* 2018;24(17):S371–S379. 4. Querol LA, et al. *Neurotherapeutics.* 2022;19(3):864-873. 5. Dalakas MC. i. 2011;7(9):507-517. 6. Al-Zuhairy A, et al. *Muscle Nerve.* 2020;61(3):316-324. 7. Chiò A, et al. *J Neurol Neurosurg Psychiatry.* 2007;78(12):1349-1353.

Future directions and goals for CIDP management

01 Identify subtypes/variants of CIDP based on dominant pathophysiological mechanisms[1–3]

02 Expand CIDP management options to address axonal damage and improve efficacy and durability[3,4]

03 Optimize CIDP management to have fewer side effects, better long-term safety profiles, and reduce patient burden[2–4]

04 Consensus on definitions of treatment response in people living with CIDP (e.g., complete or partial remission, refractory, relapse)

05 Define biomarkers of myelin/axonal damage for diagnosis, clinical assessment, and monitoring[2,3,6]

CIDP, chronic inflammatory demyelinating polyneuropathy.

1. Oaklander AL, et al. Cochrane Database Syst Rev. 2017:13;1(1):CD010369. 2. Mair D, et al. J Neurol Neurosurg Psychiatry. 2025;96:38-46. 3. van Doorn IN, et al. Ther Clin Risk Manag. 2024:14;20:111-126. 4. Guptill JT, et al. Am Health Drug Benefits. 2019;12(3):127-135. 5. Menon D, Katzberg HD, Bril V. Front Neurol. 2021;15;12:653734. 6. Querol L, et al. PNS 2024, Montréal, June 22–25, 2024. Oral presentation 429. Additional information is presented at PNS 2024, Montréal, June 22–25, 2024. Poster 269.

ACTIVE POLL

What is the most important area for future CIDP research?

A. Specific biomarkers for disease diagnosis and progression

B. Novel immunotherapies aiming to prevent/minimize nerve damage

C. Personalized treatment approaches aiming to improve efficacy and minimize side effects

D. Further investigation into CIDP variants (immunopathological and clinical)

CIDP, chronic inflammatory demyelinating polyneuropathy.

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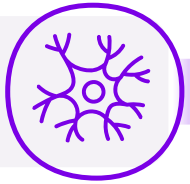
Summary

01 

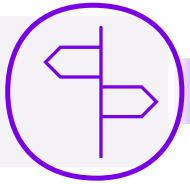
CIDP is a heterogeneous disease associated with significant patient burden and long-term disability[1]

02 

Complement plays a role in the healthy nervous system but when dysregulated can trigger demyelination and axonal damage seen in CIDP[1]

03 

Definition of biomarkers, such as NfL or sphingomyelin, for axonal damage is important for monitoring CIDP[2,3]

04 

The understanding of different pathways in CIDP is evolving, along with its management, which could help improve patient lives[2]

Could prevention or mediation of axonal damage be our path to functional cure in CIDP?

CIDP, chronic inflammatory demyelinating polyneuropathy; NfL, neurofilament light chain.

1. Querol LA, et al. *Neurotherapeutics*. 2022;19(3):864-873. 2. Mair D, et al. *J Neurol Neurosurg Psychiatry.* 2025;96:38-46. 3. Keddie S, et al. *Brain.* 2023;146(11):4562-4573.

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