Myelin & Multippel sklerose
MYELIN

Myel- = μψελ · gresk: marg
Myelin proteines interesserer

• Neurobiologists
  – the function of myelin in the nervous system
• Neuropathologists and neurologists
  – the many demyelinating diseases that afflict the human population
• Immunologists
  – autoimmune mechanisms because myelin proteins induce autoimmun responses in susceptible animals, and the y have been used to generate animal models of autoimmune inflammatory disease, such as multiple sclerosis

• Developmental and cellular neurobiologists
  – because the MBPs and PLPs are markers of endstage oligodendrocyte (OL) development and are critical for the terminal differentiated function of OLs
• Molecular biologists
  – because the complexity of their gene products, the role the genes may play in neurological diseases, and the multiple functions of these proteins within and without the nervous system. Mutations in the genes for these proteins also account for a number of the dysmyelinating animal mutants that serve as models of human diseases

Campagnoni & Campagnoni, 2004
MYELIN

• Omhyggelig bearbeidet, isolerende flerlaget membran (hylster/skjede) omkring nervecelleutløpere (axoner)

• Spesielle celler i nervesystemet danner svøp av egne utløpere om axoner
  - Oligodendrocytter i sentralnervesystemet (CNS)
  - Scwannske celler i det perifere nervesystemet (PNS)
MYELIN

• Myeliniserings prosessen krever et komplekst samarbeid mellom spesialiserte celler og axoner
• Detaljene i denne prosess er relativt ukjent
• Myelinets funksjon er å isolere nerveceller for mer effektiv og raskere ledning av elektriske impulser
  – viktig for at et kompleks nervesystem ikke skal bli urimelig stort
Myelin

• Myelin er en høyt spesialisert flerlaget membran essensiell for axonets velbefinnende og overlevelse og dermed hjernens funksjon

• Motoriske og kognitive prosesser er helt avhengige av korrekt myelinisering og vedlikehold av myelinskjeden i hjernens grå og hvite substans så vel som i perifere nerver.
MYELIN

• ~25-35% av hjernens tørrvekt
  - 70% lipider
  - cholesterol og fosfolipider
  - 30% proteiner
  - MBP og PLP står for >80% av proteinene i myelin i CNS
Myelin proteiner

- **I PNS**
  - *Myelin protein zero* (*P₀*)
    - 30-kDa membran glycoprotein, utgjør > 50% av myelinet i PNS

- **I CNS**
  - *Myelin proteolipid proteiner* (*PLPs*)
  - *Myelin basisk proteiner* (*MBPs*)

Andre myelin proteiner

- *Myelin-assosiert glycoprotein* (*MAG*)
- *Myelin oligodendrocyt glycoprotein* (*MOG*)
- *2’,3’cyclic nucleotide 3’-phosphodiesterase* (*CNP*)
- *PMP22* - ++++
• Hovedkomponenten i PNS myelin
  - 50 - 60% av myelinet i PNS
  - Glycolysert

• Integrert membran protein (IMP type I)
P₀ og PLP

- P₀ initialt det primære strukturprotein i CNS og PNS myelin
- Oppstod i bruskfisk for ~ 440 millioner år siden
- PLP proteinet oppstod med benfiskene for ~ 400 millioner år siden
- Både PLP og P₀ hadde høye mutasjonsrater inntil for ~ 300 millioner år siden
- Etter at PLP og P₀ ble hovedkomponenter i henholdsvis CNS og PNS myelin, sank deres mutasjonsrate dramatisk
- Begge disse myelinproteiner er høyt konservert (så godt som 100%) i alle pattedyr som er undersøkt
- Dette mer enn antyder en essensiell rolle for PLP og/eller en forstyrrende rolle for P₀ protein i høyere dyrearters CNS
P0 Protein Accelerates Axonal Degeneration, Neurological Disability and Death in PLP-Null Mice

Yin, X.1, Baek, R.2, Kirschner D.A.2, Peterson, A.3, Fujii Y.1, Nave K.-A.4, Macklin W.B.1 and Trapp, B.D.1

1Dept. of Neurosciences, Cleveland Clinic Foundation, Cleveland, OH, 44195
2Dept. of Biology, Boston College, Chestnut Hill, MA, 02167
3Laboratory of Developmental Biology/Molecular Oncology, McGill University, Montreal, QC, Canada
4Dept. of Neurogenetics, Max Planck Institute of Experimental Medicine, Goettingen, Germany.
Figure 4. X-ray diffraction patterns demonstrate the ordered structure of the myelin sheath, and indicate that the periodicity of myelin in the P0+PLP- CNS is essentially that of PNS myelin, which has a wider period than that of CNS myelin. X-ray diffraction patterns are presented for optic nerves of WT (black), P0+PLP- (red, panel A), P0+PLP+ (purple, panel B), and PLP- (green, panel B) mice, and for sciatic nerves of WT (black) and P0+PLP- (red) mice. The inset in (A) shows the wide-angle region of the pattern at higher magnification. The diffraction pattern demonstrated that the periodicity of P0+PLP- optic nerve was 174 Å, which is the same as that of WT sciatic myelin (A). The periodicity of P0+PLP+ optic nerve was 155 Å and the same as that of WT CNS myelin (B). Consistent with this, electron micrographs of compact myelin sheaths showed that the periodicity of myelin was identical between P0+PLP- CNS (C) and WT PNS (D); it was also the same between WT CNS (E) and P0+PLP+ CNS (F). Thus, addition of P0 protein to CNS myelin in the absence of PLP appears to define the periodicity of CNS myelin, and to convert it essentially to that of PNS myelin.
$P_0$ og PLP

Evolution of a neuroprotective function of central nervous system myelin

Xinghua Yin et al.,
Journal of Cell Biology,
January 30, 2006
“This elegant study indicates that the shift from to PLP during CNS myelin evolution was associated with an important neuroprotective function of myelin-forming glia.

This finding may further our understanding of human myelin diseases, in which a spectrum of neurological disabilities is associated with null mutations, deletions and point mutations in the PLP gene.
Proteolipid Protein (PLP)

- PLP er det vesentligste membranproteinet i *CNS myelin*
- PLP består av 276 aminosyrer og fire sterkt hydrofobe transmembrane domener
- En isoform, DM20, er generert gjennom alternative RNA splicing
  - mangler 35 AAs av en intracellulær “loop region”.

![PLP/DM20 Antibodies](image)
• PLPs extracellulære “loop” definerer membran-til-membran avstanden i kompakt myelin

• PLP er assosiert med “detergent insoluble membrane fractions (lipid rafts)”, men den presise rolle ved dannelsen av myelinskjeden er uklar

• PLPs cellebiologiske funksjoner for øvrig?

• Som andre plasmamembran proteiner er syntesen lokalisert til cellens endoplasmatiske reticulum
PLP

- Korrekt folding i det endoplasmiske reticulum er essensielt for den videre transport av proteinet

- Feil foldet PLP utløser en apoptotisk respons i oligodendroglia
  - Patogenese ved mutasjoner i PLP genet (PLP)
Among the mutations in PLP1 gene that can cause PMD is a duplication of PLP in which the duplicated region may be far away from the original PLP locus in chromosome region Xq22. The PLP duplication is almost always present in the mothers of affected boys and usually can be traced to the maternal grandfather.

*Changed a bit – after Nave*
Mutasjoner i \textit{PLP} kan lede til Pelizaeus-Merzbacher sykdom, en X-bundet recessiv tilstand karakterisert ved myelin tap.

PMD gir nystagmus (rytmiske bevegelse av øyeneplet), psykomotorisk retardasjon, tremor, økt muskeltonus (spastisitet) og ataxia.

Myelin tapet fører til neurologiske problemer.

Graden av myelin tap og klinisk fenotype avhenger av den spesifikke mutasjon

- varierer fra letale former til lettere spastisk paraplegi
MBP

- Klassisk MBP
- Primærfunksjon er å vedlikeholde strukturen i myelinskjeden
- \( MBP \) ligger på kromosom 18
- Flere isoformer
- Uklart hvilken funksjon disse har
- MBP finnes også i PNS (5-15%)
Øvrige

- **Myelin-Assosiert Glycoprotein (MAG)**
  - transmembran glycoprotein MW 100 kDa, ~30% er karbohydrat
- **Myelin Oligodendrocyt Glycoprotein (MOG)**
- **Perifert Myelin Protein (PMP) 22**
  - kvantitativt mindre komponent i PNS kompakt myelin, deltari adhesjons prosesser via glycosylert extracellular domene
- **2',3'-Cyclic Nucleotid 3'-Phosphodiesterase (CNP)**
  - myelin-relatert protein som uttrykkes tidlig i differensierende oligodendrocyter og Schwann celler
PMP 22

- Forskjellige mutatsjoner i dette genet forårsaker CMT Type IA, Dejerine-Sottas syndrom, og Hereditary neuropathy with liability to pressure palsies (HNPP)
- PMP 22 interagerer med Pzero
Charcot-Marie-Tooth (CMT)

- Axon damage in CMT due to mutation in myelin protein P0
- A novel mutation of myelin protein zero associated with an axonal form of CMT disease
- Mutations of Peripheral Myelin Protein 22 Result in Defective Trafficking through Mechanisms Which May Be Common to Diseases Involving Tetraspan Membrane Proteins
- Mutations of myelin and myel in-related protein genes in Charcot-Marie-Tooth disease
- Myelin Proteolipid Protein: Function in Myelin Structure Is Distinct from Its Role in Oligodendrocyte Development
- Proteolipid protein 1 gene mutation in nine patients with Pelizaeus-Merzbacher disease
- A point mutation in the proteolipid protein gene of the 'shaking pup' interrupts oligodendrocyte development
MULTIPLE SCLEROSIS

Harald Nyland
1977
Multippel sklerose (MS)

• Kronisk CNS sykdom
• Histopatologiske trekk
  - Fokalt myelintap
  - partielt axon tap (ikke leger 'axonal sparing')
  - Predilesjonsteder
  - n. opticus, periventrikulær hvit substans, subpial cerebral cortex, hjerrnestamme, rygmgmarg cervicalt
MS

- Heterogen sykdom med et bredt spektrum av interindividuelle forskjeller i klinisk presentasjon, lokalisering og hyppighet av lesjoner, abnorm serologi, og varierende respons på immunosuppressiv behandling
MS LESION

• **ACTIVE (ACUTE, FRESH) LESIONS**
  
  – edema
  
  – myelin swelling
  
  – activation of endothelial cells
  
  – preservation of axons
    • variable degree of axonal damage
  
  – perivascular infiltration of inflammatory cells
    (T-lymphocytes and microglia
    (monocytes/macrophages)
MS LESION

• CHRONIC ACTIVE LESIONS
  – Areas of demyelination and active inflammation, typically at their interface with normal tissue
    • Myelin breakdown
    • Myelin phagocytosis (foamy macrophages)
    • Reduction in the number of oligodendrocytes
    • Reactive astrocytosis
    • Sparing of axons
      – variable degrees of axonal damage may be present
MS LESION

• CHRONIC LESIONS
  – Demyelinated areas sharply delimited from adjoining normal myelinated tissue
    • Astrocytic gliosis
    • Loss of oligodendrocytes
    • Variable axonal loss
    • Scant perivascular lymphocytes (cuffs)
    • Monocytes (Plasmacells may be focally present)
    • Blood vessels may be sclerotic
MS LESION

• SHADOW PLAQUES

- Partially demyelinated or incompletely remyelinated less sharply delimited
- Occasionally “overshadowing” the principal plaque
- Unpredictable occurrence
  • Absent - infrequent - (frequent)
MULTIPPEL SCLEROSIS

Harald Nyland
1977
• Nyland fra 1980
• Bø & Nyland fra 1990
• Trapp & Bø fra 1994
• Trapp & Bjartmar fra 2000
Klassifisering av MS lesjoner

Pathogenesis of tissue injury in MS lesions
Bruce D. Trapp, Lars Bö, Sverre Mörk, Ansi Chang
Department of Neurosciences,
Lerner Research Institute, The Cleland Clinic Foundation,
9500 Euclid Avenue, Cleland, OH 44195, USA

Journal of Neuroimmunology 98 1999. 49–56

Detection of MHC class II-antigens on macrophages and microglia, but not on astrocytes and endothelia in active multiple sclerosis lesions.
Bö L, Mörk S, Kong PA, Nyland H, Pardo CA, Trapp BD.
J Neuroimmunol. 1994 May;51(2):135-46
ACTIVE (A,D), CHRONIC ACTIVE (B,E), CHRONIC (C,F) MS LESIONS

Activated Microglia, increased in lesion edge, core, and adjacent tissue.

Microglia increased at lesion edge, normal or decreased in core.

Microglia display similar density as in normal appearing cortex.
Design/Methods

- Only specimens where strict sampling of brain tissue from the predetermined areas could be achieved were included in this series.
- Paraffin-embedded sections were immunostained for myelin basic protein.
- Areas of gray and white matter, and areas of demyelination were analyzed by morphometry.
CORTICAL MS LESIONS

Type 1 lesions involve both subcortical white matter (WM) and cortex (Ctx)

Type 2 lesions are confined to the cortex

Type 3 lesions extend from the pial surface into the cortex. (Sub-pial demyelination).
In 1998, i January 29 nummeret av *The New England Journal of Medicine*

- viste vi at tap av nerve fibre var en vanlig forekomst i MS lesjoner (områder med myelin tap). Vi framsatte den hypotese at dette kunne henge sammen med den progressive neurologiske utvikling i MS. Dette har vist seg å være en 'såkorn' artikkel som minnet andre i MS-sfæren om at ødelggelse av nervefibre er en viktig og tidlig del av patologien ved MS. Noe som har ført til revurdering av behandlingsstrategier med fokus på tidligst mulig behandling for å forebygge permanent funksjonstap.
### Transections in White Matter and Cortex

<table>
<thead>
<tr>
<th></th>
<th>Cortex</th>
<th>WM</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Active</strong></td>
<td>4119±540</td>
<td>11,236±2775</td>
</tr>
<tr>
<td><strong>Chronic</strong></td>
<td>1107±148</td>
<td>4,013±688</td>
</tr>
<tr>
<td><strong>Active</strong></td>
<td>25±6</td>
<td>789±16</td>
</tr>
<tr>
<td><strong>Inactive</strong></td>
<td>8±8</td>
<td>1±1</td>
</tr>
</tbody>
</table>

Peterson et al., (2001), Ann Neurol 50:389-400
"Losen" (The Pilot), Christian Krogh, 1852-1925
Leading Neuroscientist Awarded 2003 Dystel Prize

• Bruce D. Trapp, PhD, Professor and Chair of the Department of Neurosciences in the Lerner Research Institute at the Cleveland Clinic Foundation, has been chosen by a committee of his peers to receive the National MS Society/American Academy of Neurology's 2003 John Dystel Prize for Multiple Sclerosis Research. Dr. Trapp has made major contributions to understanding the brain tissue destruction and repair in MS, and these findings have significant implications for the development of new therapies.
Vi har karakterisert forskjellige molekyler med sannsynlig relevans for MS lesjoners utvikling.

- **MHC class II**
  - aktiverer immun celler

- **iNOS**
  - NO – signalmolekyl; økt mengde i lesjoner

- **ICAM**
  - adhesjon og rekrutering av betennelsesceller til hjerneparenkym
• Med Carl Bjartmar, Trapp og Mørk dokumenterte relasjon mellom 'hjernemolekylet' "n-acetyl aspartate" (NAA) og tap av nervefibre I ryggmargen. Noe av viktighet for oppfølging og behandling av MS siden NAA kan monitoreres via non-invasiv billedframstilling.
TABLE 1
Clinical Data and Mean Percentage of Demyelinated Area in the Cerebral Cortex and in White Matter in the MS Patients Studied

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Age/Sex</th>
<th>Disease course</th>
<th>Disease duration (y)</th>
<th>Cognitive impairment</th>
<th>Epilepsy</th>
<th>% Demyelinated Area</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>White matter</td>
</tr>
<tr>
<td>1</td>
<td>64/F</td>
<td>SP</td>
<td>34</td>
<td>+</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>2</td>
<td>45/F</td>
<td>SP</td>
<td>25</td>
<td>+</td>
<td>+</td>
<td>32.0</td>
</tr>
<tr>
<td>3</td>
<td>55/F</td>
<td>PP</td>
<td>22</td>
<td>0</td>
<td>0</td>
<td>0.5</td>
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<tr>
<td>4</td>
<td>54/M</td>
<td>PP</td>
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<td>0</td>
<td>0</td>
<td>0.1</td>
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<tr>
<td>5</td>
<td>57/F</td>
<td>SP</td>
<td>31</td>
<td>+</td>
<td>0</td>
<td>2.3</td>
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<tr>
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<td>+</td>
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<td>40/F</td>
<td>SP</td>
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<td>+</td>
<td>+</td>
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</tr>
<tr>
<td>12</td>
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<td>0</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>14</td>
<td>62/F</td>
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<td>27</td>
<td>+</td>
<td>0</td>
<td>11.9</td>
</tr>
<tr>
<td>15</td>
<td>58/F</td>
<td>PP</td>
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<td>11.9</td>
</tr>
<tr>
<td>16</td>
<td>51/M</td>
<td>SP</td>
<td>23</td>
<td>+</td>
<td>0</td>
<td>1.9</td>
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<tr>
<td>17</td>
<td>43/F</td>
<td>RR</td>
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<td>6.6</td>
</tr>
<tr>
<td>18</td>
<td>42/F</td>
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<tr>
<td>19</td>
<td>65/F</td>
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<tr>
<td>20</td>
<td>43/M</td>
<td>RR</td>
<td>14</td>
<td>+</td>
<td>0</td>
<td>16.2</td>
</tr>
</tbody>
</table>

Patients MS3, MS9, MS10, MS15, and MS16 had a general cortical subpial demyelination (GSD), with extensive subpial demyelination in all 4 areas studied.

Abbreviations: RR: relapsing-remitting MS; SP: secondary progressive MS; PP: Primary progressive MS.
+ = present; 0 = not present.

MATERIALS AND METHODS
Tissue
The brains of 20 MS patients and 7 patients without neurologic disease were studied. The control brains were selected because anatomical landmarks made sampling of nearly identical areas possible in the autopsy material (Fig. 1). The same areas were sampled in all brains, regardless of the presence of an active inflammatory activity.
CEREBRAL CORTEX IN MULTIPLE SCLEROSIS

- Frontal lobe mean: 25.7%
- Parietal lobe mean: 11.5%
- Temporal lobe mean: 27.4%
- Gyrus cinguli mean: 43.0%

Cerebral cortex taken from predetermined areas (unbiased for grossly visible lesions in gray or white matter).
Fig. 1. Paraffin sections immunohistochemically stained with anti-MBP antibody and lightly counterstained with hematoxylin from an MS patient (A–D, H) and a control patient (E–G). The figure illustrates the 4 areas studied in each patient: the frontal lobe (A), the temporal lobe (B, E), the parietal lobe (C), and the cingulate gyrus (D, F). The MS patient has extensive subpial demyelination in the 4 tissue specimens (A–D). The MS patient is thus considered to have a general cortical subpial demyelination (GSD). In panels (A) and (C) the lesion is subpial, but does not span the full width of the cerebral cortex (Type 3 lesion). In panels (B) and (D) the lesion spans the full width of the cortex without reaching into subcortical white matter (Type 4 lesion). The cingulate gyrus specimens include periventricular white matter and white matter of the corpus callosum (D, F). Higher magnification images from panels (B) and (E) (boxes) show myelin staining throughout the width of control cerebral cortex (G), and subpial demyelination in the MS cortex (H). Open arrows indicate the lesion border, closed arrows delineate the white matter/cerebral cortex border.
Fig. 2. Paraffin sections from MS brain (A–D) and control brain (E, F) stained with anti-myelin basic protein (MBP) antibody (A, C, E) and Luxol fast blue (LFB) (B, D, F). The border between white matter and cerebral cortex is indicated by closed arrows. The border of a white matter MS lesion is delineated by both LFB and MBP staining (A, B, open arrows). Cortical demyelination is clearly delineated by MBP immunohistochemistry (C), but not by LFB staining (D, open arrows). Abundant myelin staining is detected in the control brain cerebral cortex by MBP immunohistochemistry (E). In the same area in an adjacent section, myelin is heavily stained in the white matter, but difficult to discern from background staining in the cerebral cortex by LFB staining (F).

Abbreviations: WM, white matter; CTX, cerebral cortex.
Fig. 4. The classification of cortical MS lesions. Paraffin sections from MS brain immunostained with anti-MBP antibody. The cerebral cortex/white matter borders are delineated by closed arrows. The lesion borders are delineated by open arrows. Type 1 lesions (A) extend through both white and gray matter. Type 2 lesions (B) are intracortical, having no contact with white matter or with the surface of the brain. Type 3 lesions (C) extend inward from the surface of the brain. Type 4 lesions (D) extend through the whole width of the cortex without reaching into white matter. A small area of probable remyelination is observed (arrowhead). Abbreviations: WM = white matter; CTX = cerebral cortex.
Cortical Lesion Subtypes in MS

- **Type 1 lesion**: lesion with a continuous area of demyelination extending through both gray and white matter.
- **Type 2 lesion**: intracortical lesion without contact with white matter or pia mater.
- **Type 3 lesion**: subpial lesion.
- **Type 4 lesion**: lesion extending throughout the full width of the cerebral cortex, but not extending into white matter.
- **Intracortical lesion**: type 2–4.
Cerebral Cortex
Two Areas form same MS Patient
Activated Microglia

- Release of pro-inflammatory mediators
- Cytotoxic
- Neurotoxic
- Phagocytic

- Destroy invading micro-organisms
- Remove potentially deleterious debris
- Promote tissue repair by secreting growth factors
- Facilitate return to local homeostasis
In conclusion, we have demonstrated that purely cortical demyelination in MS is extensive, and that general cortical subpial demyelination occurs in a significant subpopulation of chronic MS patients. Although cortical lesions reaching across several gyri have been described in previous studies (Dawson, 1916; Peterson et al., 2001), the occurrence and extent of this as a general pattern has not, to our knowledge, been previously demonstrated. Demyelination and neuronal/axonal injury in these extensive cortical lesions may mediate clinically significant cognitive, motor, and sensory deficit in MS.
• I 2000 beskrev Lucchinette et al. heterogen neuropatologi i lesjoner i pasienter med tidlig MS
• Aktivt demyeliniserende MS lesjoner, karakterisert av makrofager med myelinproteiner intracellulært, kunne inndeles i 4 typer basert på funn av immunoglobulin og komplement eller påvisning av primær oligodendrocyt patolog med eller uten selektivt tap av myelin proteiner
Lucchinetti & Lassmann
Pathogenetic heterogeneity

• Critical remarks to original article
  – Highly selected material
    • 50% of the 32 autopsied MS-patients died within 3-three months of clinical onset of disease
  – Results
    • No mention of T cells as “active demyelination .. lesions were infiltrated by macrophages and activated microglia”
    • Text states: “Pattern III…composed mainly of T lymphocytes,..” and “Pattern IV...dominated by T lymphocytes..” But neither are shown in the 22 microphotographs of the article:
    • “Heterogeneity of Multiple Sclerosis Lesions: Implications for the Pathogenesis of Demyelination”
      Ann Neurol
      2000 47:707-717
• Consistent presence of complement, antibodies, and Fcgamma receptors in phagocytic macrophages suggests that antibody- and complement-mediated myelin phagocytosis is the dominant mechanism of demyelination in established MS.
Nøkkelen til å knekke MS koden finnes kun via bedre forståelse av MYELINETS biologi