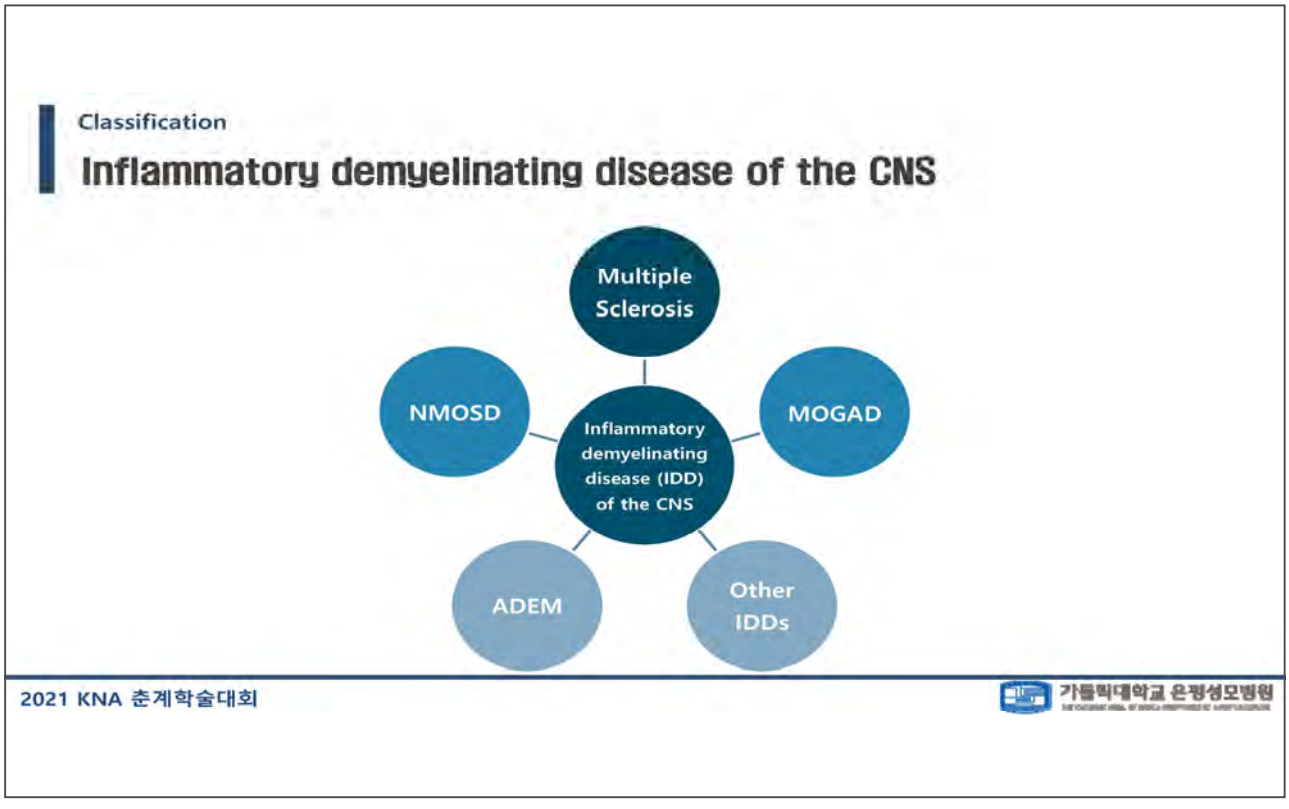
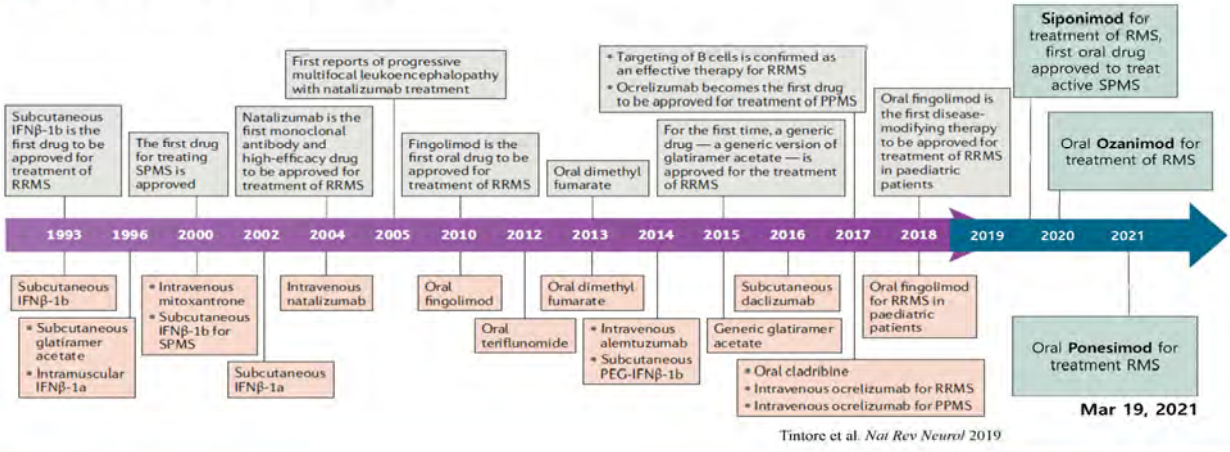
Demyelinating

권 영 남
가톨릭의대 은평성모병원



CNS Demyelinating disease
MULTIPLE SCLEROSIS

MS
FDA approved Drugs



Tintore et al. *Nat Rev Neurol* 2019

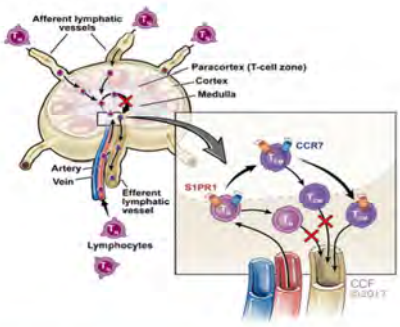
2021 KNA 춘계학술대회

가톨릭대학교 은평성모병원

MS

Ponesimod

- Selective sphingosine 1-phosphate 1 receptor (S1PR1) modulator



Receptor	Drug	Associated cell types	Function
S1PR1	Fingolimod Siponimod Ozanimod Ceralifimod GSK2018682 Ponesimod MT-1303	Lymphocytes Neurons Endothelial cells AV node and Conduction system Smooth muscle	Egress from lymph nodes Neuron migration and function Permeability barrier Heart rate slowing Permeability barrier
S1PR2	✕	CNS Endothelial cells Smooth muscle	Hearing and balance Permeability barrier Vascular tone
S1PR3	Fingolimod	Neurons AV node and Conduction system Endothelial cells Smooth muscle	Neuron migration and function Slowed heart conduction Permeability barrier
S1PR4	Fingolimod	Lymphocytes	Lymphoid tissue expression Dendritic and TH17 cell modulation
S1PR5	Fingolimod Siponimod Ozanimod Ceralifimod GSK2018682	CNS Natural killer cells	Oligodendrocyte function Natural killer cell migration

CCF ©2017

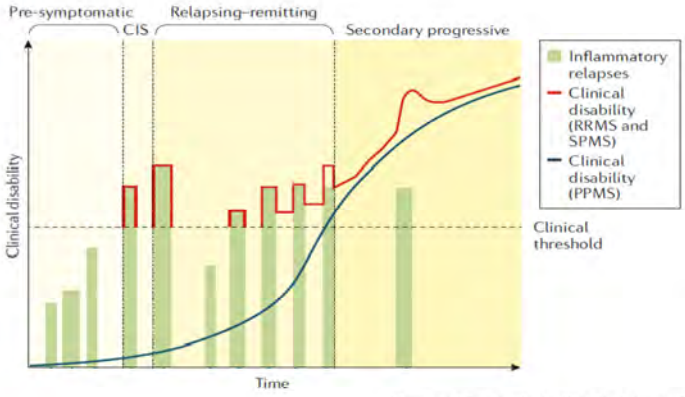
Chaudhry et al. *Neurotherapeutics* 2017

2021 KNA 춘계학술대회

가톨릭대학교 은평성모병원

MS

Progressive MS treatment



Massimo Filippi et al. *Nat Rev Dis Primers*. 2018
Thompson and Ciccarelli *Nat Rev Neurol*. 2020

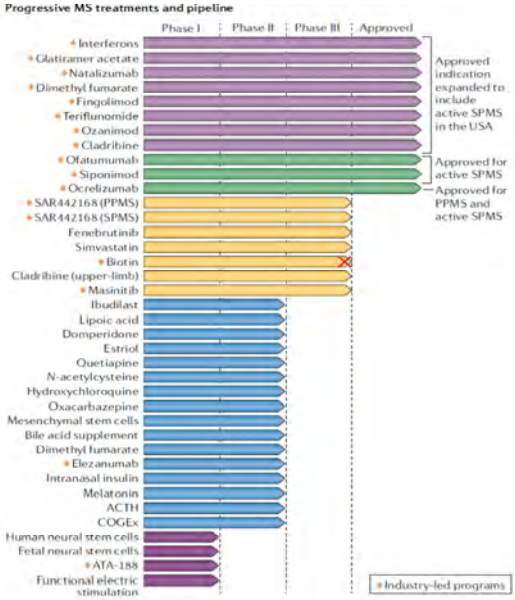
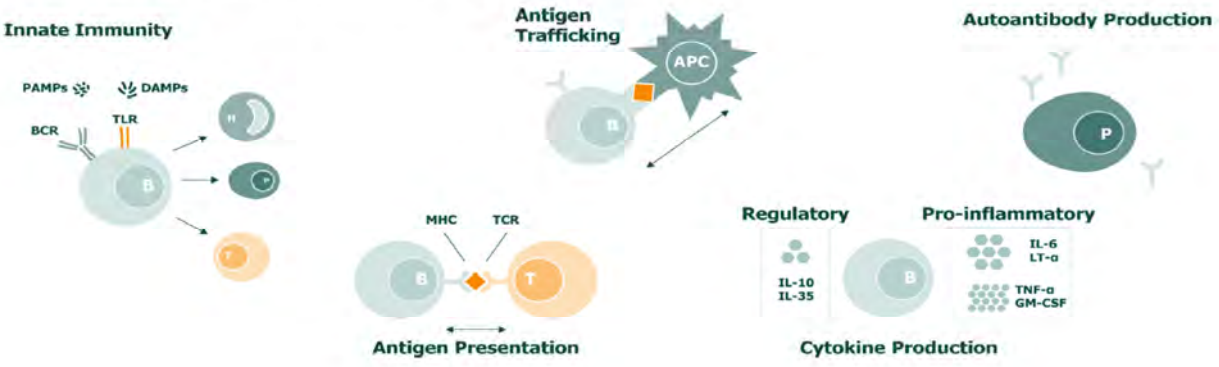


Fig. 1 | **Agents that are currently being studied for treatment of progressive MS.**

2021 KNA 춘계학술대회

MS

B-Cell Pathophysiology



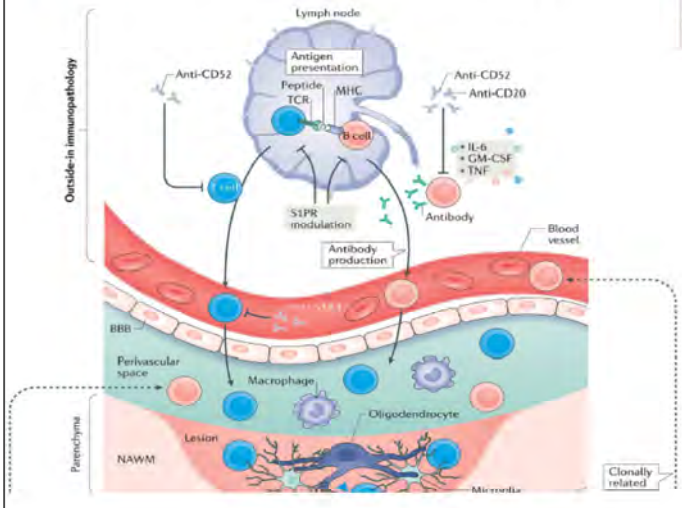
Giancarlo Comi et al, *Ann Neurol*, 2021

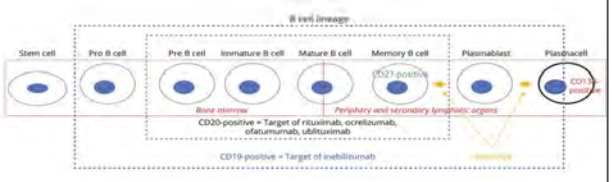
2021 KNA 춘계학술대회

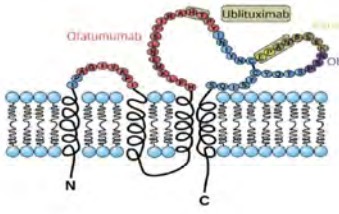
가톨릭대학교 은평성모병원

MS

B-Cell-Targeted Therapies







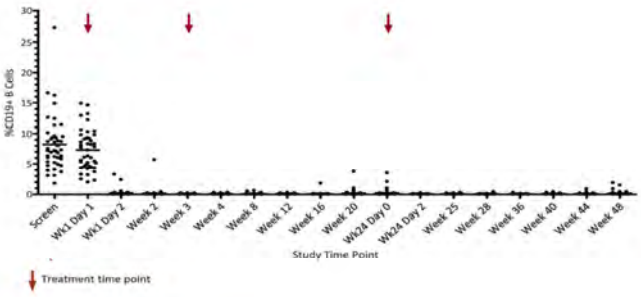
Joseph J. Sabatino Jr et al, *Nat Rev Neurosci*. 2019
Graf et al, *Neurol Neuroimmunol Neuroinflamm*. 2020

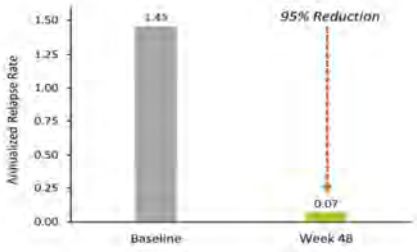
가톨릭대학교 은평성모병원

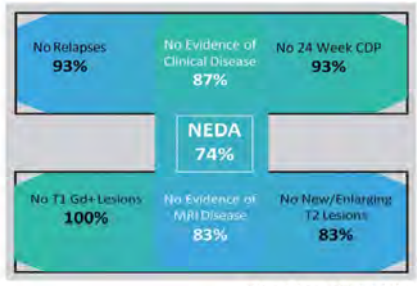
MS

Ublituximab: Phase 2

- Phase 2, placebo-controlled study
- RRMS (*N*= 48)







Edward Fox et al, *MSJ*, 2021

2021 KNA 춘계학술대회

가톨릭대학교 은평성모병원

MS

Ublituximab: Phase 3

TG Therapeutics

TG Therapeutics Announces Positive Topline Results from the ULTIMATE I & II Phase 3 Studies Evaluating Ublituximab Monotherapy for the Treatment of Patients with Multiple Sclerosis

December 10, 2020

Both studies met their primary endpoint of significantly reducing annualized relapse rate (ARR) (p<0.005 in each study) with ublituximab demonstrating an ARR of <0.10 in each of the studies

Relative reductions of approximately 60% and 50% in ARR over teriflunomide were observed in ULTIMATE I & II, respectively

Detailed data presentation targeted in 1H 2021 with a BLA submission targeted mid-year 2021

Conference call to be held today, Thursday, December 10, 2020 at 8:30 AM ET

2021 KNA 춘계학술대회

가톨릭대학교 은평성모병원

MS

Ublituximab; Phase III

- ULTIMATE I & II
  - Phase 3, randomized, double-blinded, active-controlled, global, multi-center studies
    - ① Initial infusion of UTX 150 mg over 4 hours on day 1
    - ② UTX 450-mg infusion over 1 hour on day 15
    - ③ 1-hour, UTX 450-mg infusion every 6 months
  - UTX vs. teriflunomide 14-mg oral tablets taken once per day

2021 KNA 춘계학술대회

가톨릭대학교 은평성모병원

MS

Bruton's tyrosine kinase (BTK) inhibitor

Table 1 | BTK inhibitors in clinical development for autoimmune disorders

Drug	Lead developer(s)	BTK binding mechanism	Lead indication(s)	Phase
Evobrutinib	Merck KGaA	Covalent, irreversible	MS	3
Tolebrutinib	Sanofi/Principia	Covalent, irreversible	MS	3
Fenebrutinib	Genentech	Non-covalent, reversible	MS	3
Rilzabrutinib	Sanofi/Principia	Covalent, reversible	Pemphigus vulgaris, immune thrombocytopenia	3
Remibrutinib	Novartis	Covalent, irreversible	Urticaria	2
Tirabrutinib	Gilead Sciences, Ono Pharmaceutical	Covalent, irreversible	Pemphigus vulgaris	2
Branebrutinib	Bristol Myers Squibb	Covalent, irreversible	Rheumatoid arthritis, lupus, Sjögren's syndrome	2
Orelabrutinib	InnoCare	Covalent, irreversible	MS	2
BIIB091	Biogen	Non-covalent, reversible	MS	1
AC0058	Acea Therapeutics	Covalent, irreversible	Lupus	1
PRN473	Sanofi/Principia	Covalent, reversible	Dermatology	1

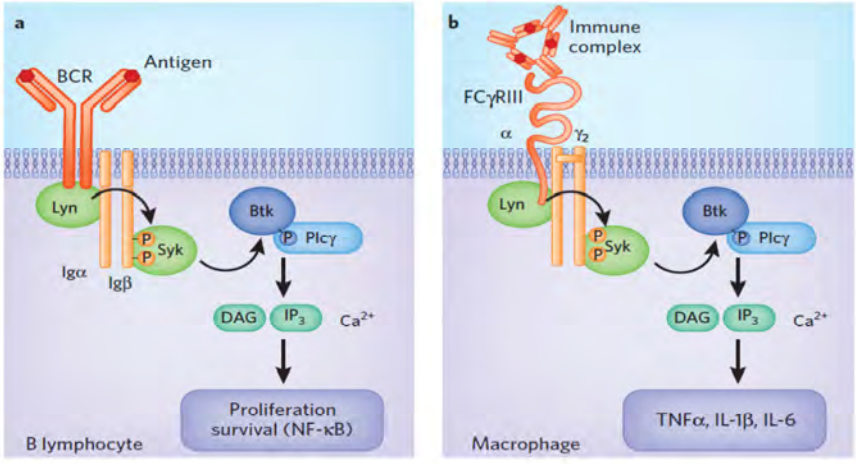
Elie Dolgin, *Nat Biotechnol*, 2021

2021 KNA 춘계학술대회

가톨릭대학교 은평성모병원

MS

Bruton's tyrosine kinase (BTK) inhibitor



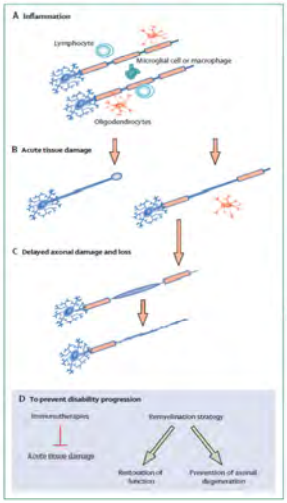
Rudi W Hendriks, *Nat Chem Biol*, 2011

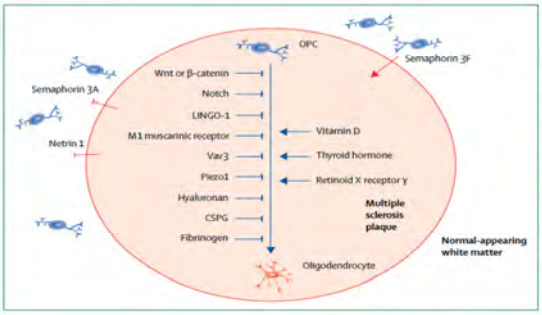
2021 KNA 춘계학술대회

가톨릭대학교 은평성모병원

MS

Remyelination theraphy in MS





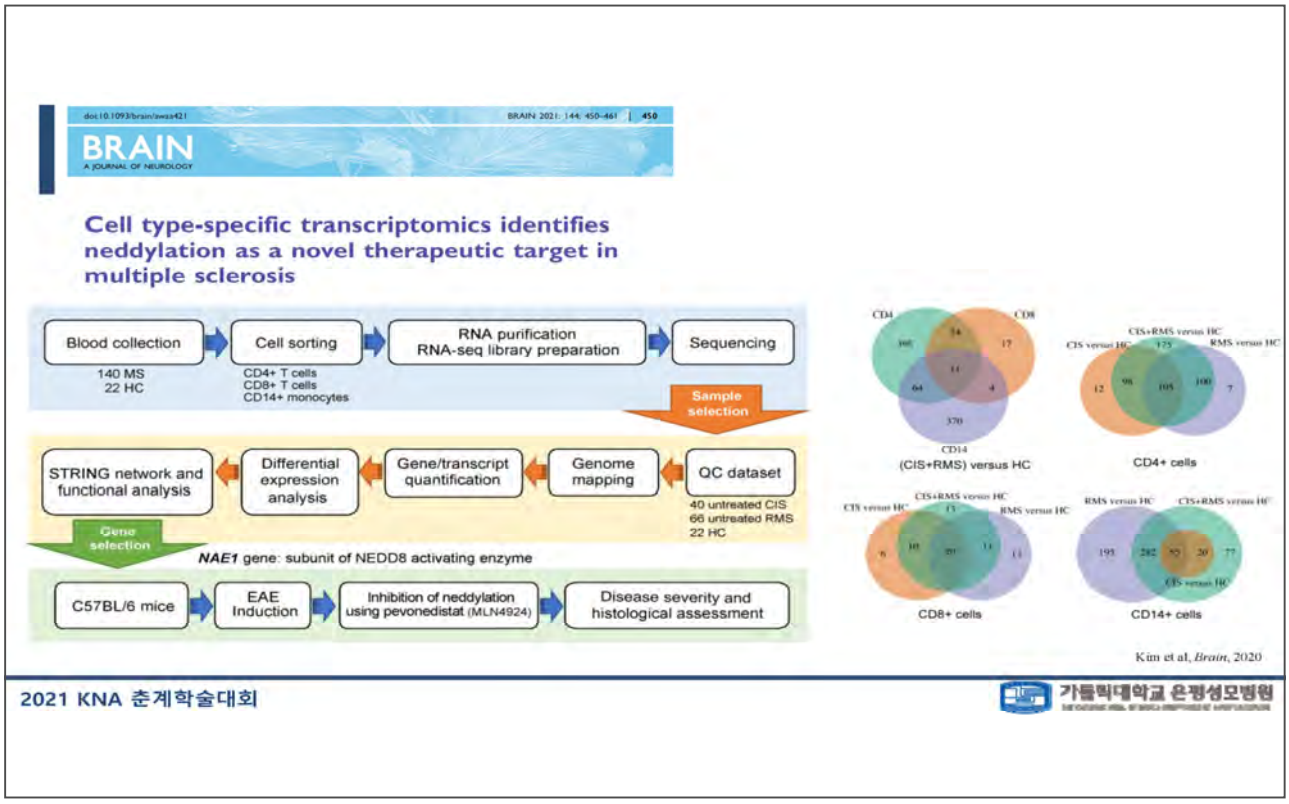
	Population	Mechanism of action	Status	Patients (ITT)	Results (or outcomes for ongoing studies)
GNbAC1[101]	RRMS	Monoclonal antibody against HERV	Completed	270	Negative for primary MRI outcome
GSK239512[102]	RRMS	Histamine H_3 receptor antagonist	Completed	131	Small effect on MTR
Opicinumab[103]	RMS	Anti-LINGO1 monoclonal antibody	Completed	419	Negative for clinical outcomes
Bexarotene (EudraCT 2014-003145-99)	RMS	Retinoid X receptor γ agonist	Completed	50	Results pending (lesion MTR changes)
Opicinumab (NCT03222973)	RMS	Anti-LINGO1 monoclonal antibody	Ongoing	—	Overall Response Score
Domperidone (NCT02493049; open-label)	RRMS	Increases serum prolactin	Completed	24	Results pending (MRI measures of lesion repair)
Opicinumab[104]	Acute optic neuritis	Anti-LINGO1 monoclonal antibody	Completed	82	Reduced VEP latency in PP population
Clemastine fumarate[105] (crossover)	Chronic optic neuritis	Anti-histaminic	Completed	50	Reduced VEP latency
Clemastine fumarate (NCT02521311)	Acute optic neuritis	Anti-histaminic	Ongoing	—	VEP latency
Transorbital electrical stimulation (NCT04042363)	Acute optic neuritis	Stimulation-induced repair	Ongoing	—	VEP latency
Transorbital electrical stimulation (NCT03862313)	Acute optic neuritis	Stimulation-induced repair	Ongoing	—	Retinal nerve fibre layer
Nanocrystalline gold (NCT03536559)	Chronic optic neuritis	Myelin gene transcription	Ongoing	—	VEP latency
Bazedoxifene (NCT04002934)	Chronic optic neuritis	Oestrogen receptor modulator	Ongoing	—	VEP latency

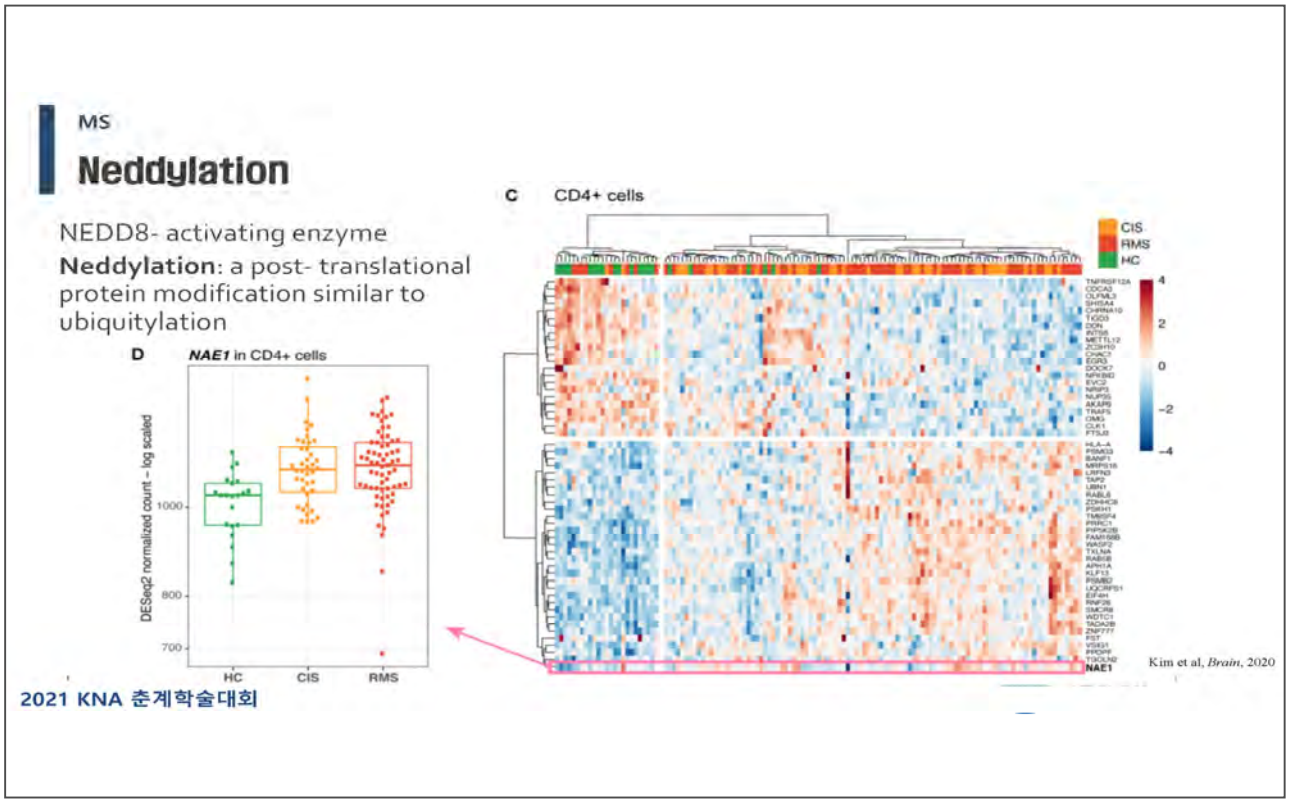
All trials are at phase 2. HERV=human endogenous retrovirus. ITT=intention-to-treat population. MTR=magnetisation transfer ratio. PP=per-protocol population. RRMS=relapsing-remitting multiple sclerosis. RMS=multiple sclerosis with relapses (either relapsing-remitting or progressive disease). VEP=visual evoked potentials.

Table: Clinical trials targeting remyelination

Catherine Lubetzki et al, *Lancet Neurol*, 2020

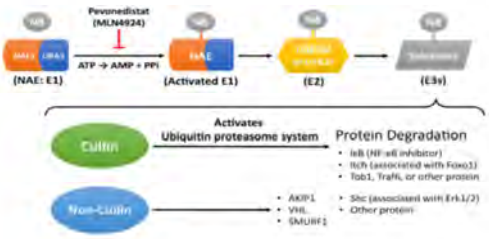
가톨릭대학교 은평성모병원

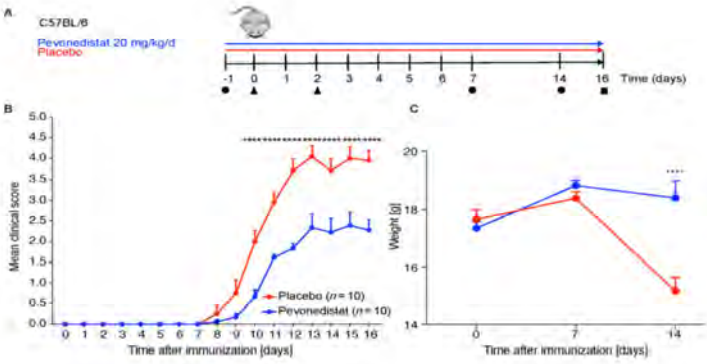

BRAIN
A JOURNAL OF NEUROLOGY
Cell type-specific transcriptomics identifies neddylation as a novel therapeutic target in multiple sclerosis
Blood collection
140 MS
22 HC
Cell sorting
CD4+ T cells
CD8+ T cells
CD14+ monocytes
RNA purification
RNA-seq library preparation
Sequencing
Sample selection
QC dataset
40 untreated CIS
66 untreated RMS
22 HC
Genome mapping
Gene/transcript quantification
Differential expression analysis
STRING network and functional analysis
Gene selection
NAE1 gene: subunit of NEDD8 activating enzyme
C57BL/6 mice
EAE Induction
Inhibition of neddylation using pevonedistat (MLN4924)
Disease severity and histological assessment
CD4
CD8
CD14
(CIS+RMS) versus HC
CIS+RMS versus HC
CIS versus HC
RMS versus HC
CD4+ cells
CD8+ cells
CD14+ cells
Kim et al, Brain, 2020
2021 KNA 춘계학술대회
가톨릭대학교 은평성모병원


MS
Neddylation
NEDD8- activating enzyme
Neddylation: a post- translational protein modification similar to ubiquitylation
D
NAE1 in CD4+ cells
DESeq2 normalized count – log scaled
1000
800
700
HC
CIS
RMS
C
CD4+ cells
CIS
RMS
HC
4
2
0
−2
−4
NAE1
Kim et al, Brain, 2020
2021 KNA 춘계학술대회

MS

Blocking neddylation reduced disease severity in a mouse model of MS





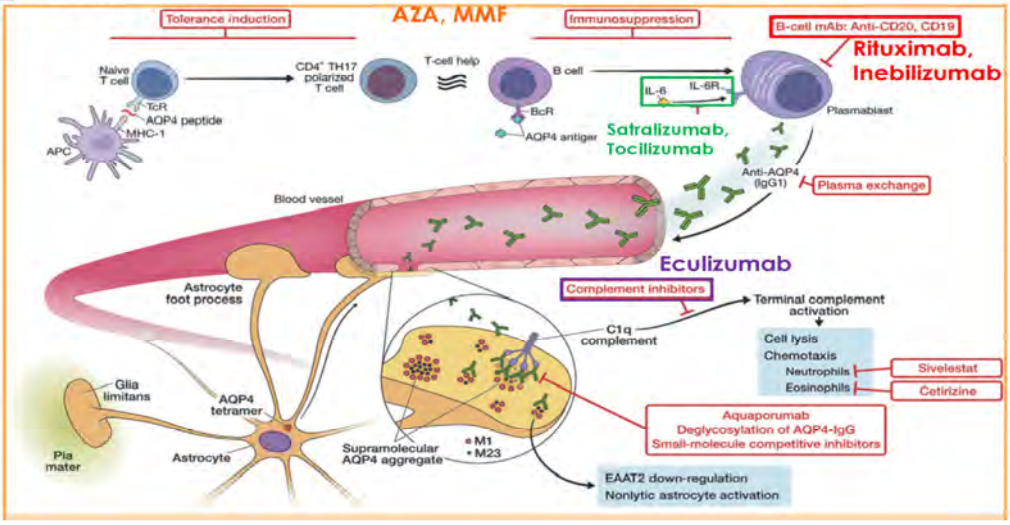
Kim et al, *Brain*, 2020

CNS Demyelinating disease

NEUROMYELITIS OPTICA SPECTRUM DISORDER (NMOSD)

NMOSD

Drug action



Weinshenker and Wingerchuk *Mayo Clin Proc.* 2017

NMOSD

Major randomized clinical trials

	RIN-1	N-MOmentum	TANGO phase 2 trial	SAkuraStar	SAkuraSky	Prevent
Target	CD20	CD19	IL6R	IL6R	IL6R	C5
Arms	Rituximab vs placebo	Inebilizumab vs placebo	Tocilizumab vs azathioprine	Satralizumab vs placebo	Satralizumab vs placebo	Eculizumab vs placebo
Design	Double-blind	Double-blind	Open	Double-blind	Double-blind	Double-blind

Holmoy et al, *J Neurol.* 2020

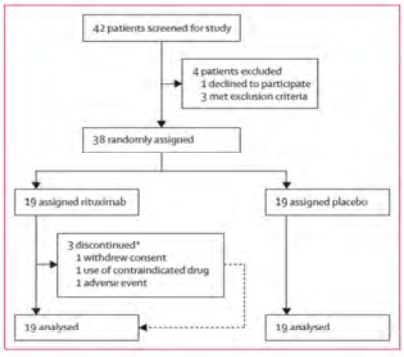
NMOSD

RIN-1

Safety and efficacy of rituximab in neuromyelitis optica spectrum disorders (RIN-1 study): a multicentre, randomised, double-blind, placebo-controlled trial

Masayuki Tahara, Tomoko Oeda, Kazumasa Okada, Takao Kiriyama, Kazuhide Ochi, Hirofumi Maruyama, Hikoaki Fukaura, Kyoichi Nomura, Yuko Shimizu, Masahiro Mori, Ichiro Nakashima, Tatsuro Misu, Atsushi Umemura, Kenji Yamamoto, Hideyuki Sawada

Lancet Neurol 2020; 19: 298–306



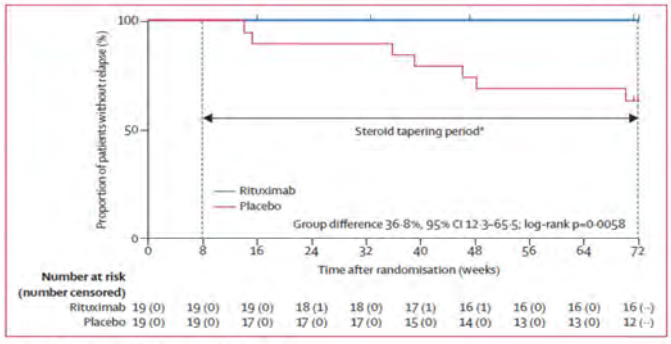


Figure 2: Proportion of patients without relapse

2021 KNA 춘계학술대회

가톨릭대학교 은평성모병원

NMOSD: Treatment

Proposed long-term management

Diagnosis established

As soon as possible[n]

First choice[a]
- RTX[b,c] or, only if AQP4-IgG positive, ECZ[d,e,f] or IBZ[d,e,h] or STZ[e,g]

Alternatives[a]
- AZA plus overlapping maintenance treatment with OS during first (3–)6 months (then slow tapering) *or* MMF[i] plus overlapping maintenance treatment with OS[k] during first (3–)6 months (then slow tapering) *or*, only if AQP4-IgG positive, TCZ[l]

In case of further significant attacks[p]

Pre-treatment with RTX or IBZ[q]
First choice
- If AQP4-IgG positive, switch to ECZ[d,e,h] or STZ[e,g]

Alternatives
- Switch to AZA plus overlapping OS or MMF[i] plus overlapping OS or, only if AQP4-IgG positive, TCZ[l]

Pre-treatment with ECZ
First choice
- Switch to RTX[c] or, if AQP4-IgG positive, IBZ[d,e,h] or STZ[e,g]

Alternatives
- Switch to AZA plus overlapping OS or MMF[i] plus overlapping OS or, only if AQP4-IgG positive, TCZ[l]

Pre-treatment with STZ or TCZ
First choice
- Switch to RTX[c] or, if AQP4-IgG positive, ECZ[d,e] or IBZ[d,e,h]

Alternatives
- Switch to AZA plus overlapping OS or MMF[i] plus overlapping OS

Pre-treatment with AZA or MMF
First choice
- Switch to RTX[c] or, if AQP4-IgG positive, ECZ[d,e], IBZ[d,e,h] or STZ[e,g]

Alternatives
- Switch from AZA to MMF[i] or vice versa, plus overlapping OS, or, only if AQP4-IgG-positive, from AZA or MMF[i] to TCZ[l]

Further treatments reported in the literature[j]
- Other immunosuppressants
- Combination therapies[m] (e.g. addition of long-term OS)
- Intermittent PEX/IA (in particular, but not exclusively, if AQP4-IgG positive; alone or in addition to other treatments[o])
- IVIG (especially in children, in mild cases or in case of contraindications against other treatments)

Jarius et al. *Nat Rev Dis Primers.* 2020

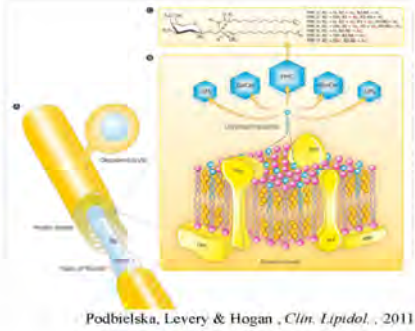
CNS Demyelinating disease

MYELIN OLIGODENDROCYTE GLYCOPROTEIN ANTIBODY–ASSOCIATED DISEASE (MOGAD)

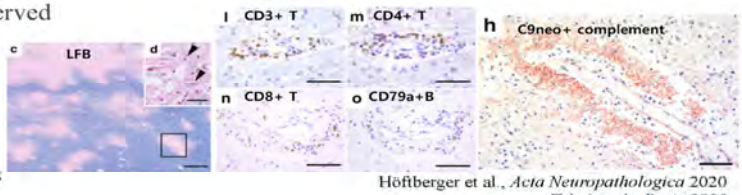
MOGAD

Histopathology

- Myelin Oligodendrocyte Glycoprotein
  - Oligodendrocyte surface membranes
- Histopathological findings
  - Coexistence of both perivenous and confluent white matter demyelination
  - MOG-dominant myelin loss with preserved oligodendrocytes
  - CD4+T-cells outnumber CD8+T-cells
  - Complement deposition or not
  - Preserved AQP4 expression
  - Perivascular MOG-laden macrophages



Podbielska, Levery & Hogan , *Clin. Lipidol.*, 2011



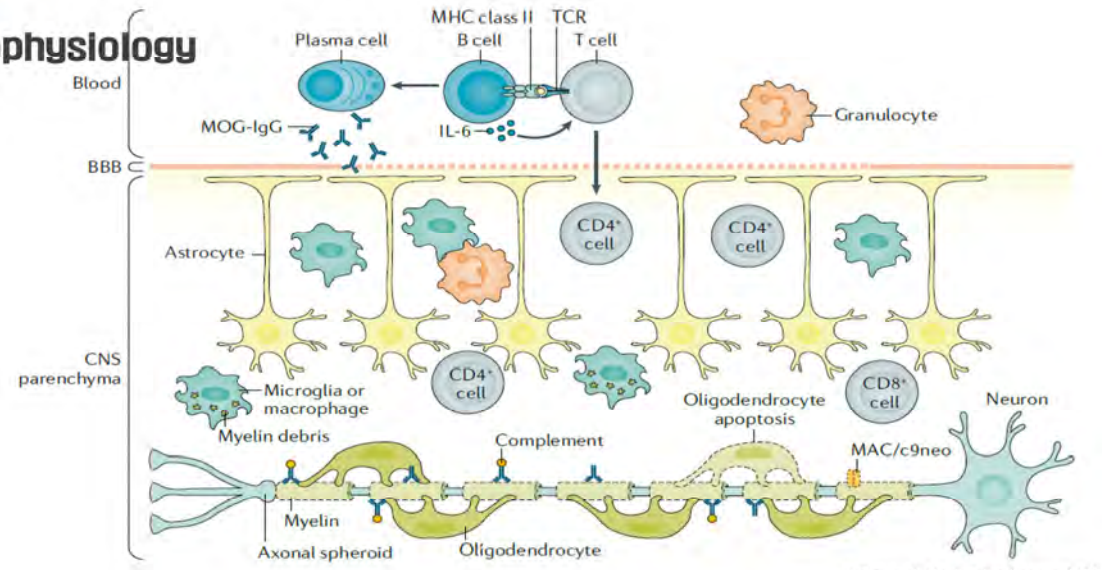
Höftberger et al., *Acta Neuropathologica* 2020
Takai et al., *Brain* 2020

2021 KNA 춘계학술대회

가톨릭대학교 은평성모병원

MOGAD

Pathophysiology



Jarius et al. *Nat Rev Dis Primers.* 2020

MOGAD

Treatment

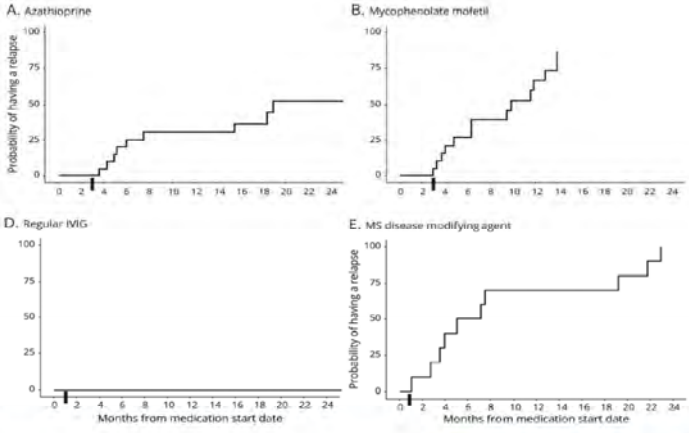
ARTICLE

Steroid-sparing maintenance immunotherapy for MOG-IgG associated disorder

John J. Chen, MD, PhD, Eoin P. Flanagan, MB, BCh, M. Tariq Bhatti, MD, Jiraporn Jitprapaikulsan, MD, Divyanshu Dubey, MBBS, Alfonso (Sebastian) S. Lopez Chiriboga, MD, James P. Fryer, MS, Brian G. Weinshenker, MD, Andrew McKeon, MB, BCh, MD, Jan-Mendelt Tillema, MD, Vanida A. Lennon, MD, PhD, Claudia F. Lucchinetti, MD, Amy Kunchok, MBBS, MMED, Colin M. McClelland, MD, Michael S. Lee, MD, Jeffrey L. Bennett, MD, PhD, Victoria S. Pelak, MD, Gregory Van Stavern, MD, Ore-Ofe O. Adesina, MD, Eric R. Eggenberger, DO, Marie D. Acierno, MD, Dean M. Wingerchuk, MD, Byron L. Lam, MD, Heather Moss, MD, PhD, Shannon Benes, MD, Aubrey L. Gilbert, MD, Veeral Shah, MD, PhD, Grayson Armstrong, MD, MPH, Gina Heithary, MD, PhD, Dean M. Cestari, MD, Hadas Dvokin-Kalish, MD, and Sean J. Pittock, MD

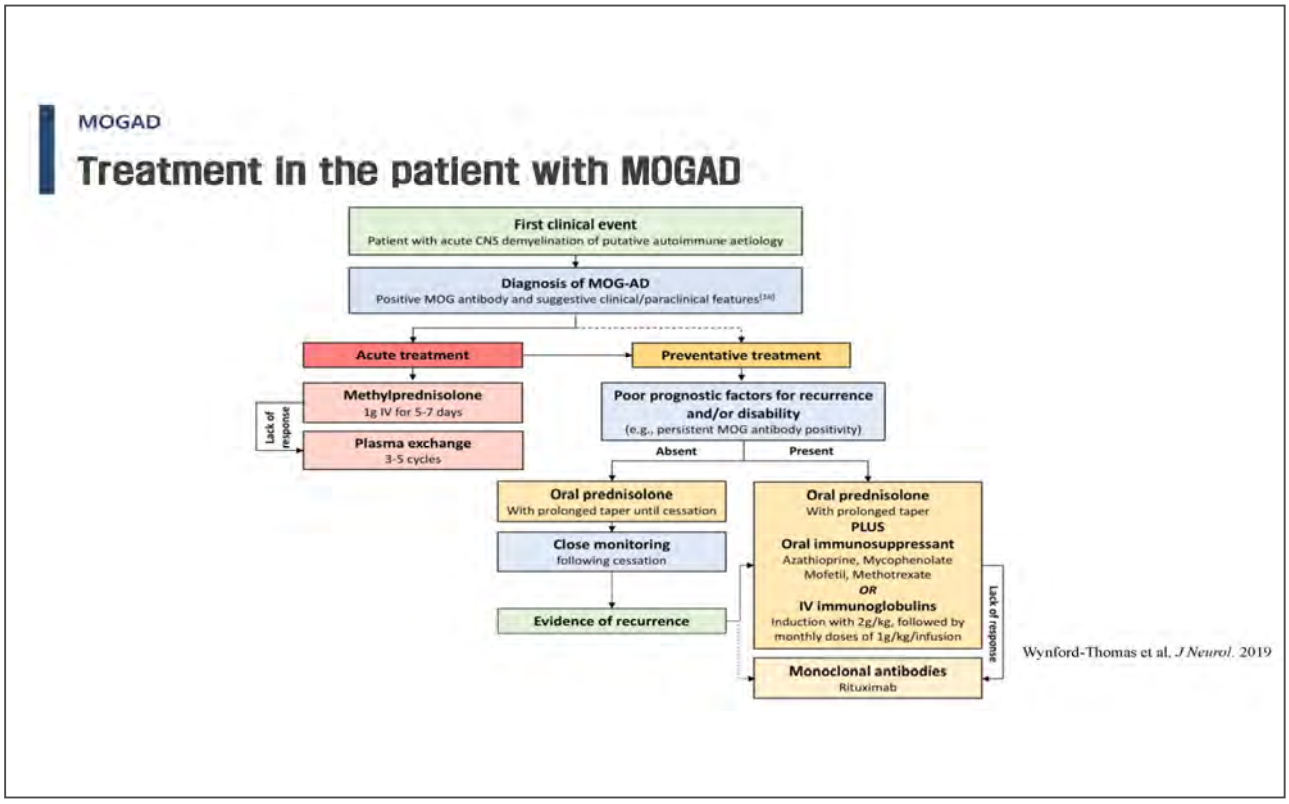
Correspondence
Dr. Chen
Chen.john@mayo.edu

Neurology® 2020;95:e11-e120. doi:10.1212/WNL.0000000000009758



2021 KNA 춘계학술대회

가톨릭대학교 은평성모병원


MOGAD
Treatment in the patient with MOGAD
First clinical event
Patient with acute CNS demyelination of putative autoimmune aetiology
Diagnosis of MOG-AD
Positive MOG antibody and suggestive clinical/paraclinical features[16]
Acute treatment
Preventative treatment
Methylprednisolone
1g IV for 5-7 days
Lack of response
Plasma exchange
3-5 cycles
Poor prognostic factors for recurrence and/or disability
(e.g., persistent MOG antibody positivity)
Absent
Present
Oral prednisolone
With prolonged taper until cessation
Close monitoring
following cessation
Evidence of recurrence
Oral prednisolone
With prolonged taper
PLUS
Oral immunosuppressant
Azathioprine, Mycophenolate
Mofetil, Methotrexate
OR
IV immunoglobulins
Induction with 2g/kg, followed by monthly doses of 1g/kg/infusion
Lack of response
Monoclonal antibodies
Rituximab
Wynford-Thomas et al, J Neurol. 2019