Understanding the pathophysiology of multiple sclerosis and the development of new therapies

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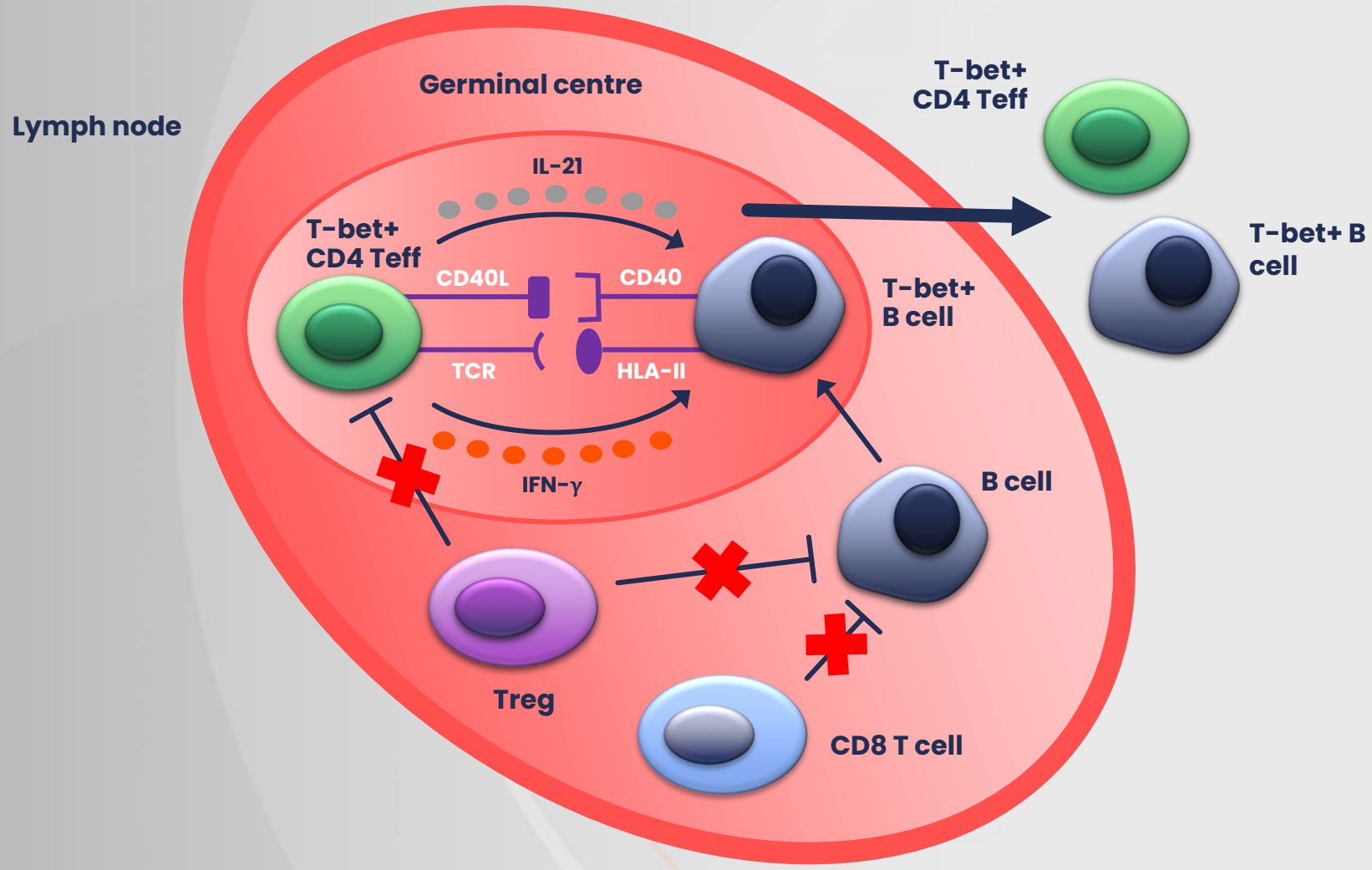
The role of immune cells in multiple sclerosis pathogenesis

Key pathogenic steps in multiple sclerosis: B and T cells



CD, cluster of differentiation; HLA, human leucocyte antigen; IFN, interferon; IL, interleukin; TCR, T-cell receptor; Teff, T effector cell; Treg, regulatory T cell.
van Langelaar J, et al. *Front Immunol*. 2020;11:760.

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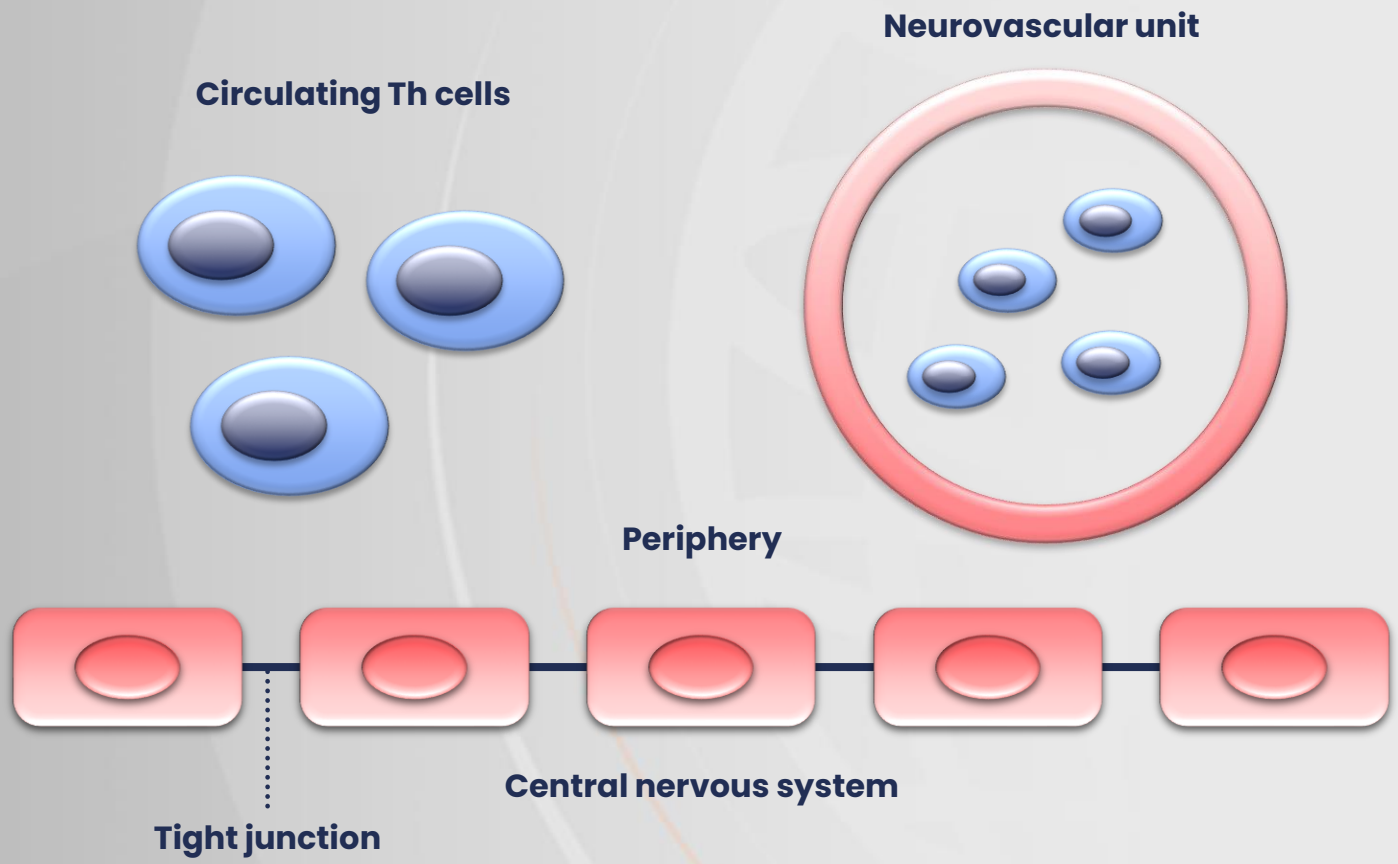
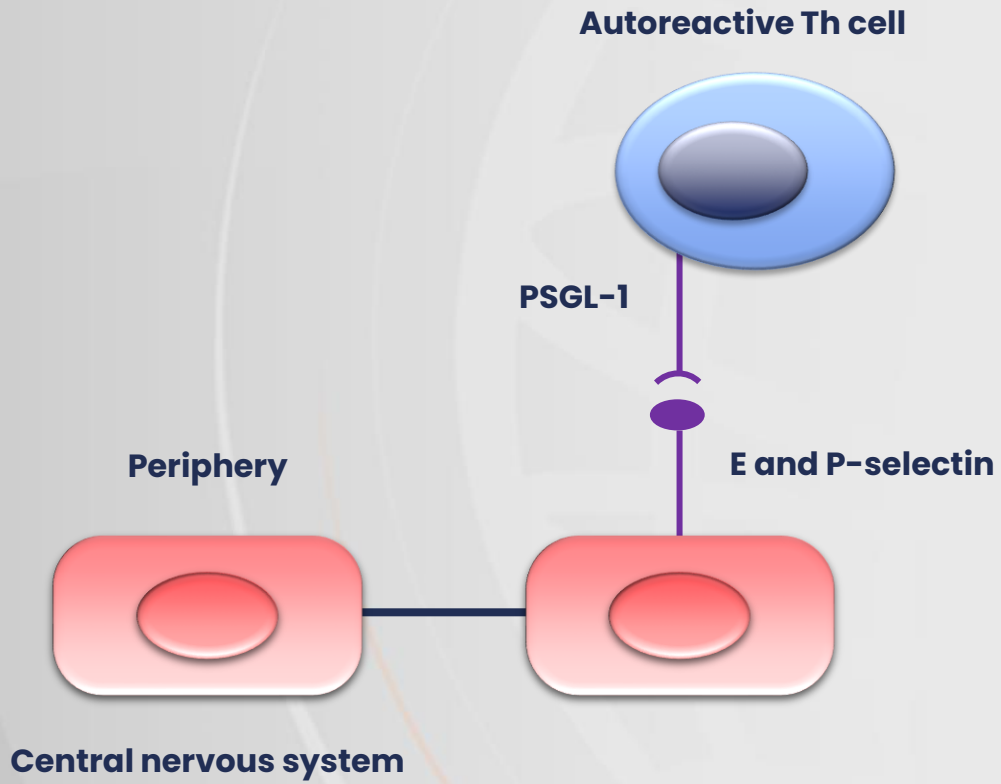
Key pathogenic steps in multiple sclerosis: Disruption of the blood–brain barrier



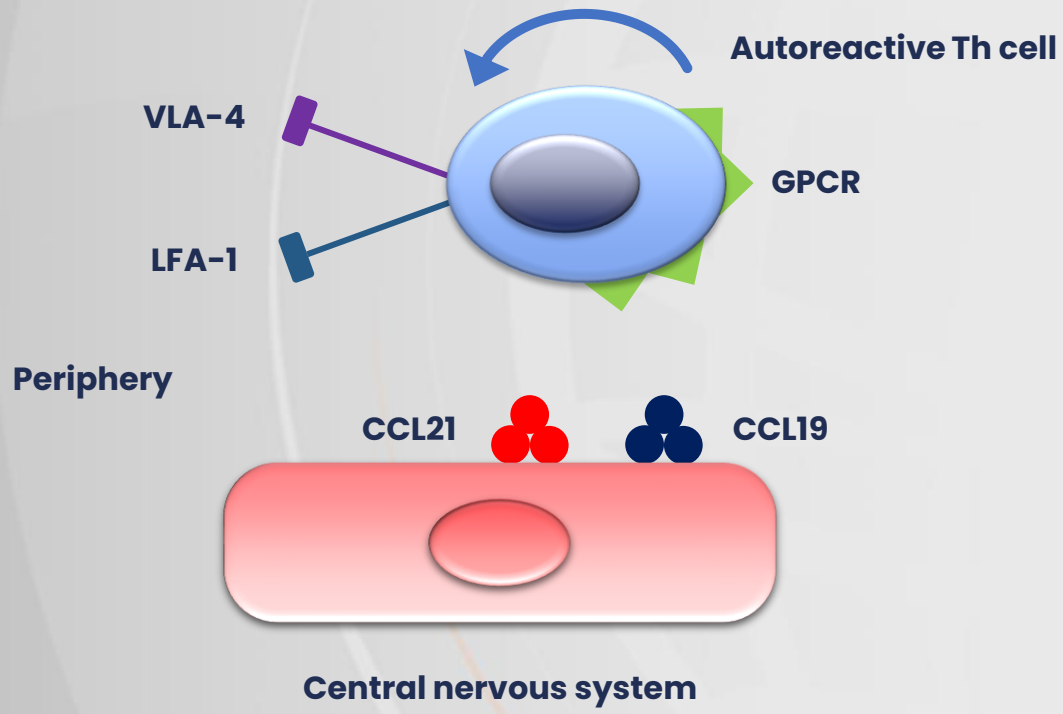
Th, T helper.
Balasa R, et al. *Int J Mol Sci*. 2021;22:8370.

Key pathogenic steps in multiple sclerosis: Disruption of the blood–brain barrier – tethering



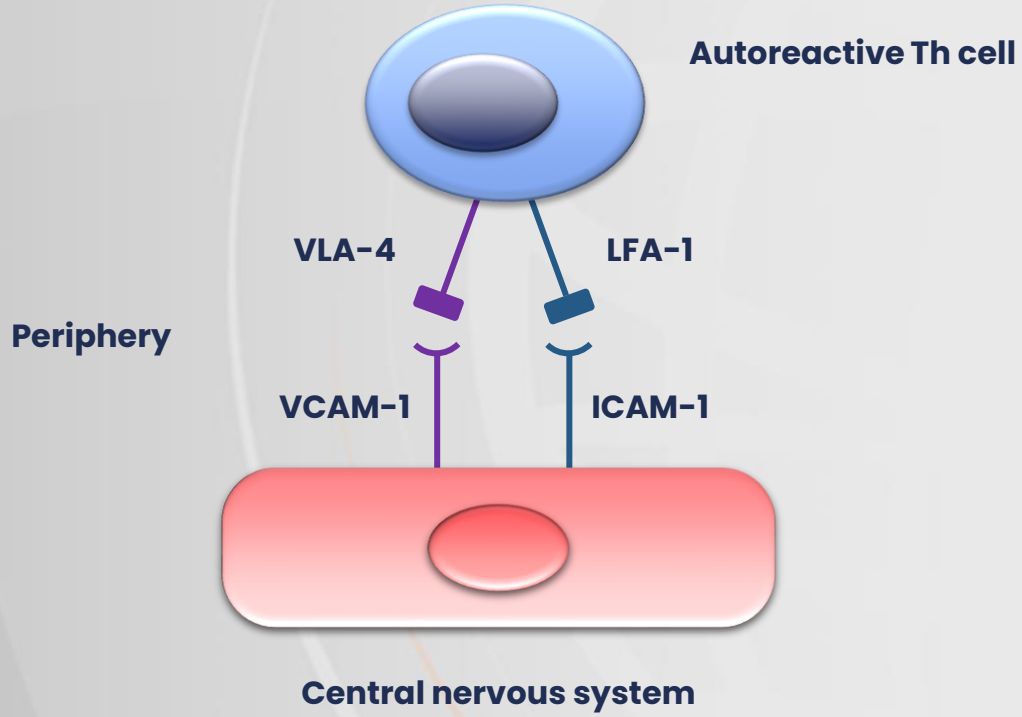
PSGL-1, P-selectin glycoprotein ligand-1; Th, T helper.
Balasa R, et al. *Int J Mol Sci*. 2021;22:8370.

Key pathogenic steps in multiple sclerosis: Disruption of the blood–brain barrier – rolling



CCL, chemokine (C-C motif) ligand; GPCR, G protein-coupled receptor; LFA-1, lymphocyte function-associated antigen 1; Th, T helper; VLA-4, very late antigen-4.
Balasa R, et al. *Int J Mol Sci*. 2021;22:8370.

Key pathogenic steps in multiple sclerosis: Disruption of the blood–brain barrier – adhesion



ICAM-1, intercellular cell adhesion molecule 1; LFA-1, lymphocyte function-associated antigen 1; Th, T helper; VCAM-1, vascular cell adhesion molecule 1; VLA-4, very late antigen-4.
Balasa R, et al. *Int J Mol Sci*. 2021;22:8370.

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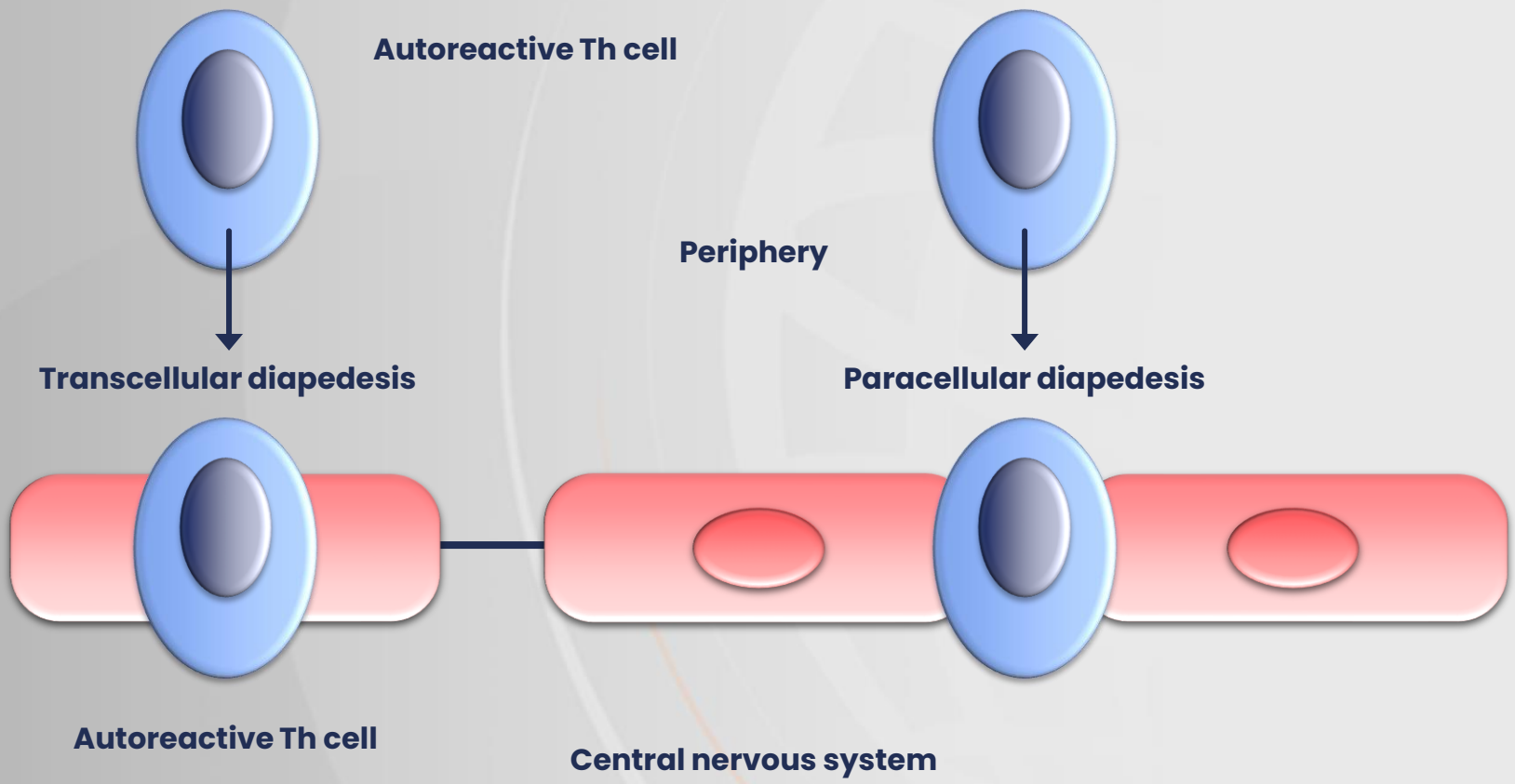
Key pathogenic steps in multiple sclerosis: Disruption of the blood–brain barrier – transversing



Th, T helper.
Balasa R, et al. *Int J Mol Sci*. 2021;22:8370.

Key pathogenic steps in multiple sclerosis: A role for brain microvascular endothelial cells?

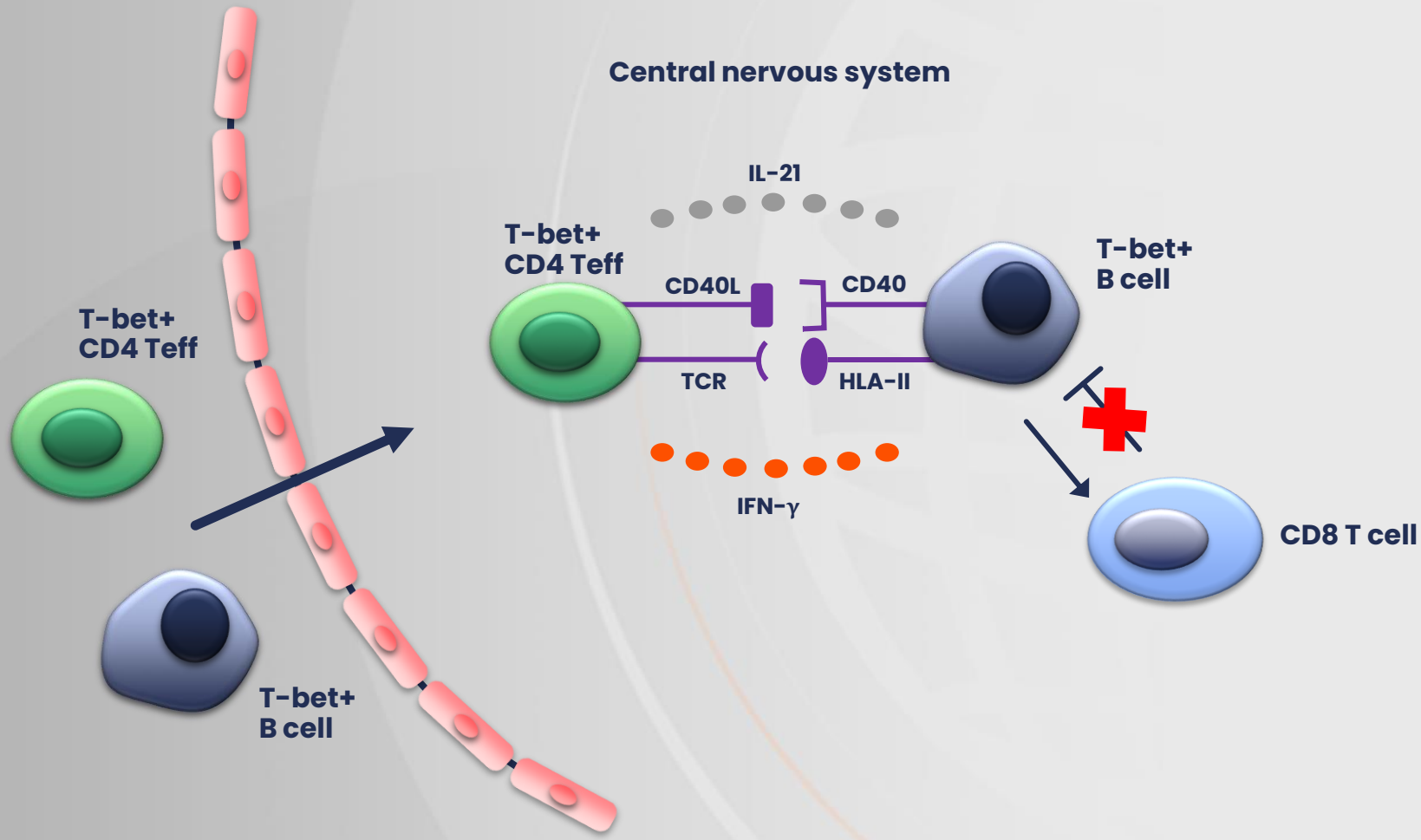
An in *vitro model* of the blood–brain barrier using cells from patients with MS showed impaired junctional integrity, barrier properties and efflux pump activity

Additionally, the cells of the model had an inflammatory phenotype with increased adhesion molecule expression and immune cell interactions

MS, multiple sclerosis.

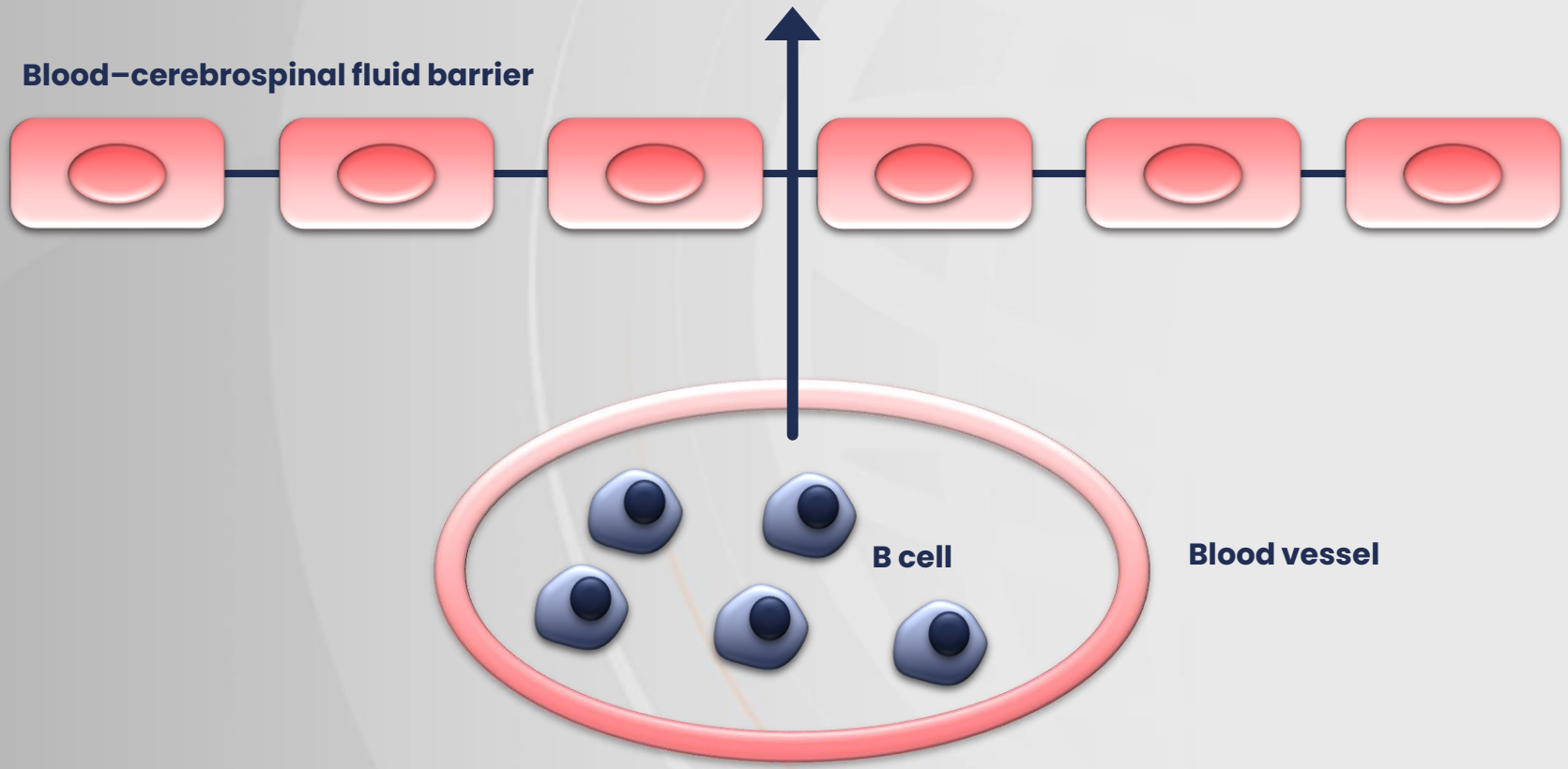
Nishihara H, et al. *Brain*. 2022;145:4334–48.

Key pathogenic steps in multiple sclerosis: Infiltration of the central nervous system



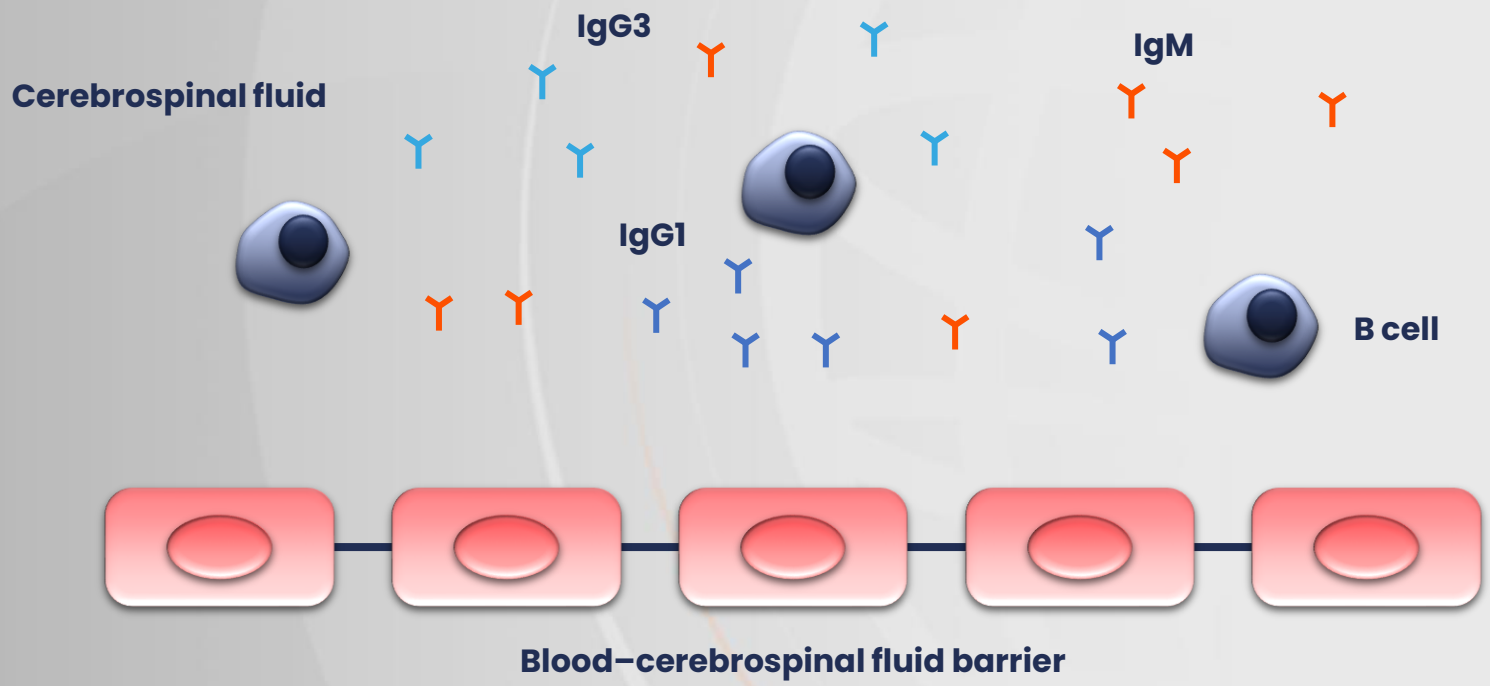
CD, cluster of differentiation; HLA, human leucocyte antigen; IFN, interferon; IL, interleukin; TCR, T-cell receptor; Teff, T effector cell.
van Langelaar J, et al. *Front Immunol*. 2020;11:760.

Antibody-mediated multiple sclerosis: Migration across the blood–brain barrier



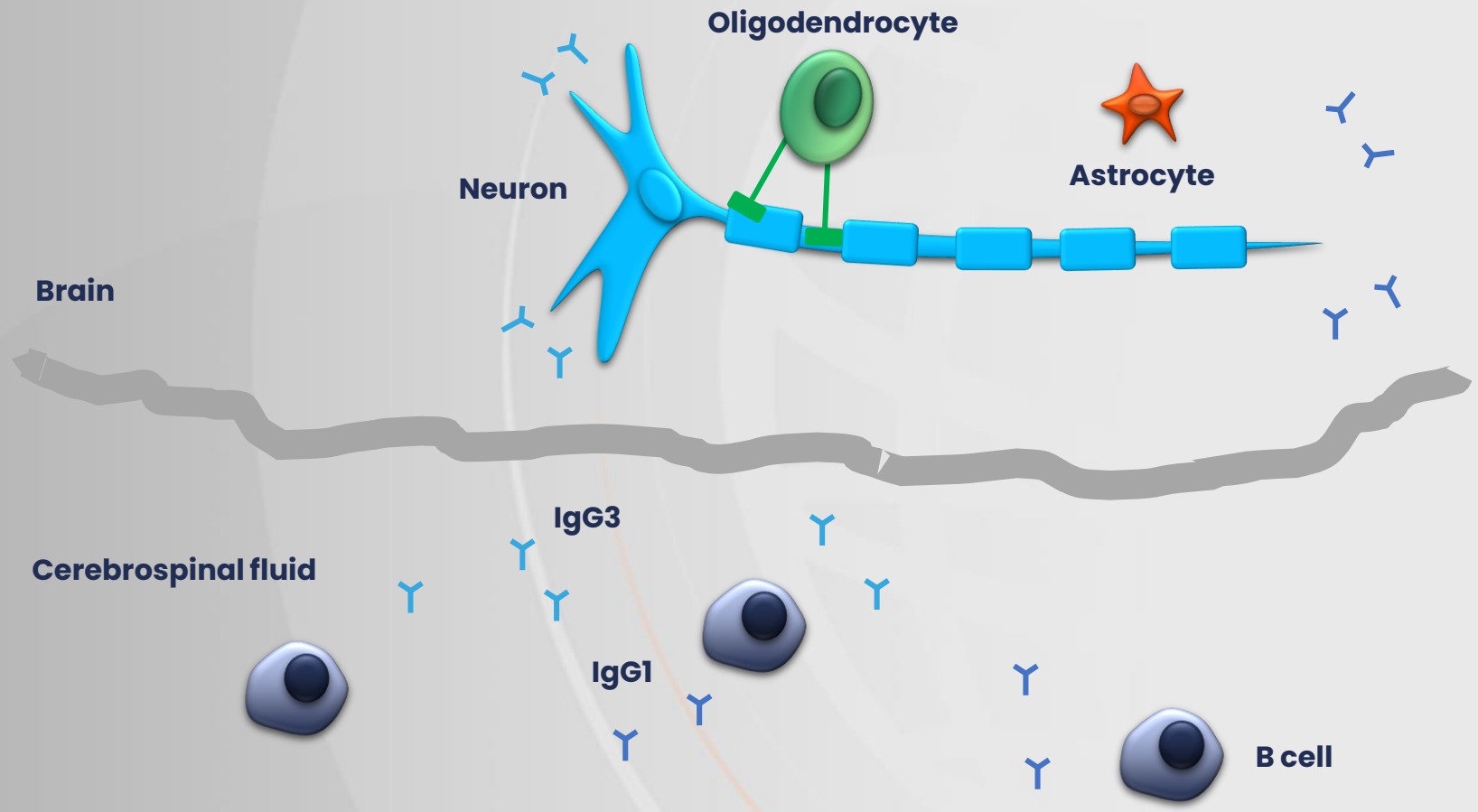
Yu X, et al. *Front Neurol*. 2020;11:533388.

Antibody-mediated multiple sclerosis: Production of antibodies



Ig, immunoglobulin.
Yu X, et al. *Front Neurol*. 2020;11:533388.

Antibody-mediated multiple sclerosis



Ig, immunoglobulin.
Yu X, et al. *Front Neurol*. 2020;11:533388.

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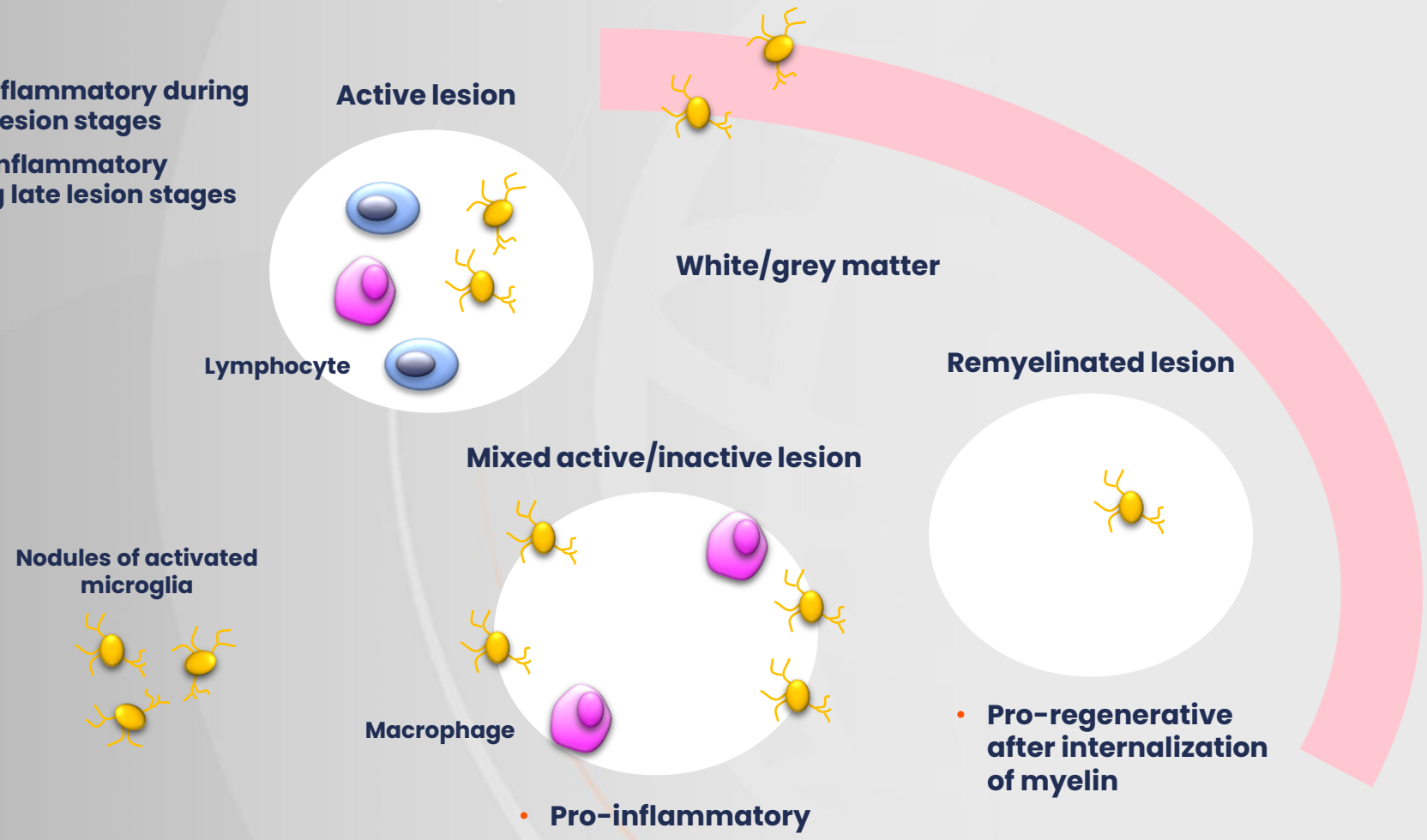
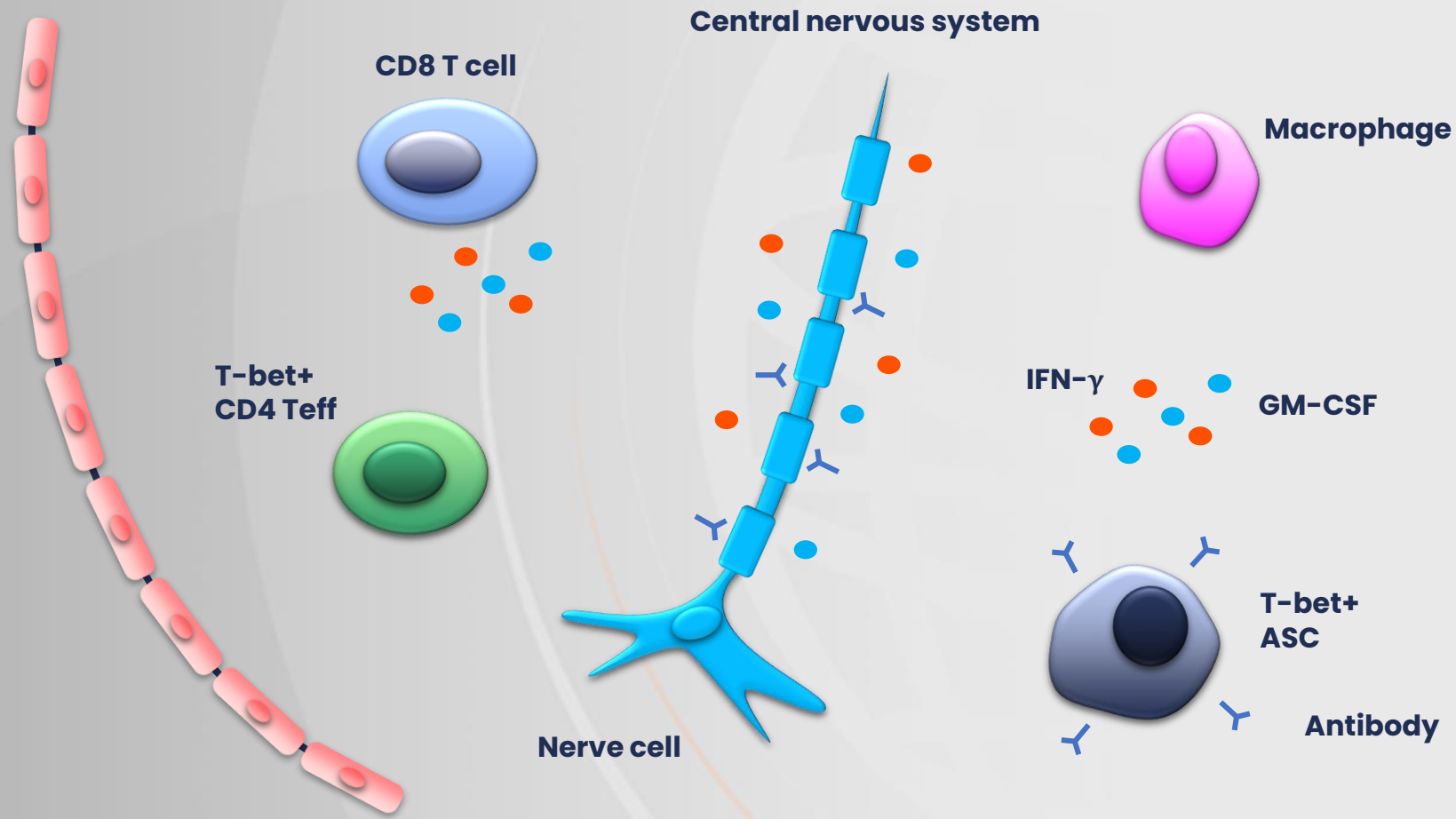
Role of microglia in multiple sclerosis pathology

- Pro-inflammatory during early lesion stages
- Anti-inflammatory during late lesion stages



Guerrero BL, Sicotte NL. *Front. Immunol.* 2020;11:374.

Key pathogenic steps in multiple sclerosis: Production of inflammatory cytokines and antibodies



ASC, antigen-secreting cell; CD, cluster of differentiation; GM-CSF, granulocyte-macrophage colony-stimulating factor; IFN, interferon; Teff, T effector cell.
van Langelaar J, et al. *Front Immunol*. 2020;11:760.

Conclusions

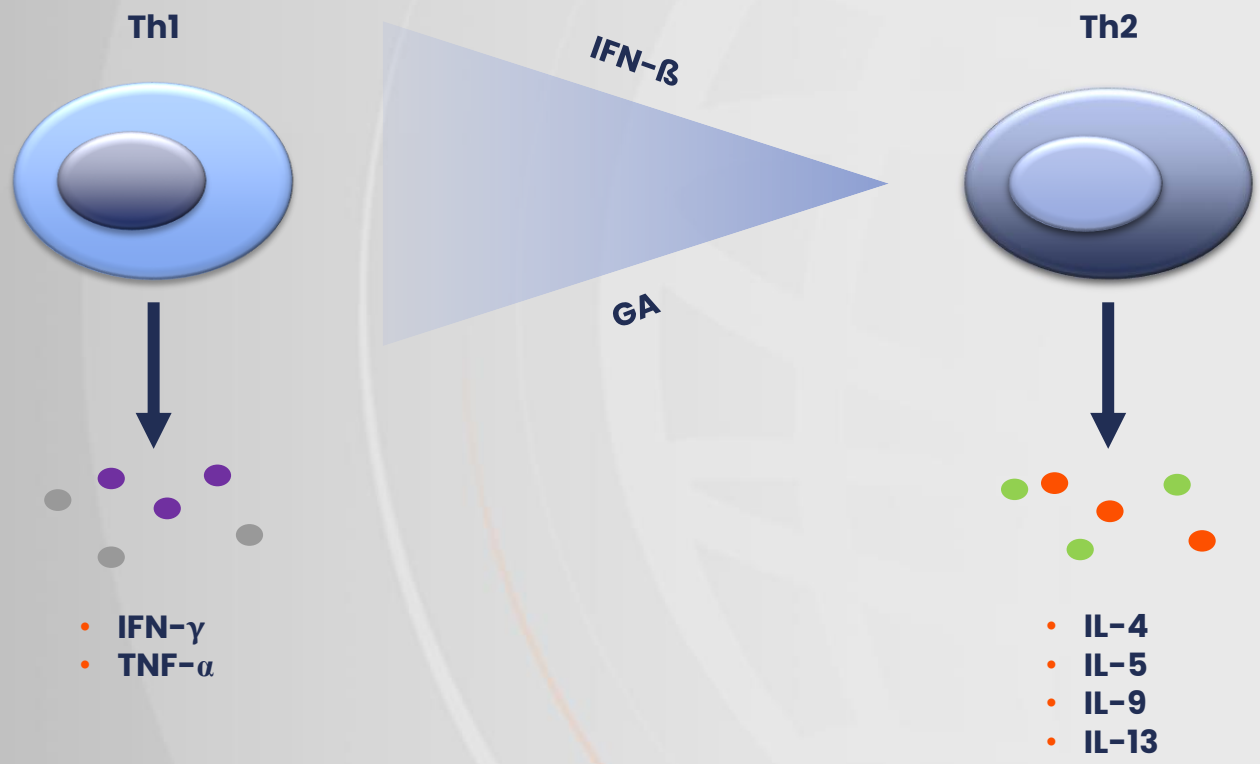
- Peripheral B cells can escape from tolerance checkpoints to activate/reactivate T cells and break through blood-CNS barriers[1]
- Dysfunction of the BBB is considered an essential step in the initiation and maintenance of the immune attack against the CNS[2]
- Microglia are present throughout all stages of lesion formation as a driver of inflammation but also play important roles in remyelination and in limiting inflammatory responses[3]
- Antibodies exert primary and pathogenic effects in multiple sclerosis development[4]

BBB, blood–brain barrier; CD, cluster of differentiation; CNS, central nervous system.

1. van Langelaar J, et al. *Front Immunol*. 2020;11:760; 2. Balasa R, et al. *Int J Mol Sci*. 2021;22:8370; 3. Guerrero BL, Sicotte NL. *Front Immunol*. 2020;11:374; 4.Yu X, et al. *Front Neurol*. 2020;11:533388.

Pathogenic mechanisms as therapeutic targets

Modulators of inflammatory mediators: IFN-ß and glatiramer acetate



GA, glatiramer acetate; IFN, interferon; IL, interleukin; Th, T helper; TNF, tumour necrosis factor.
Yang JH, et al. *Front Neurol*. 2022;13:824926.

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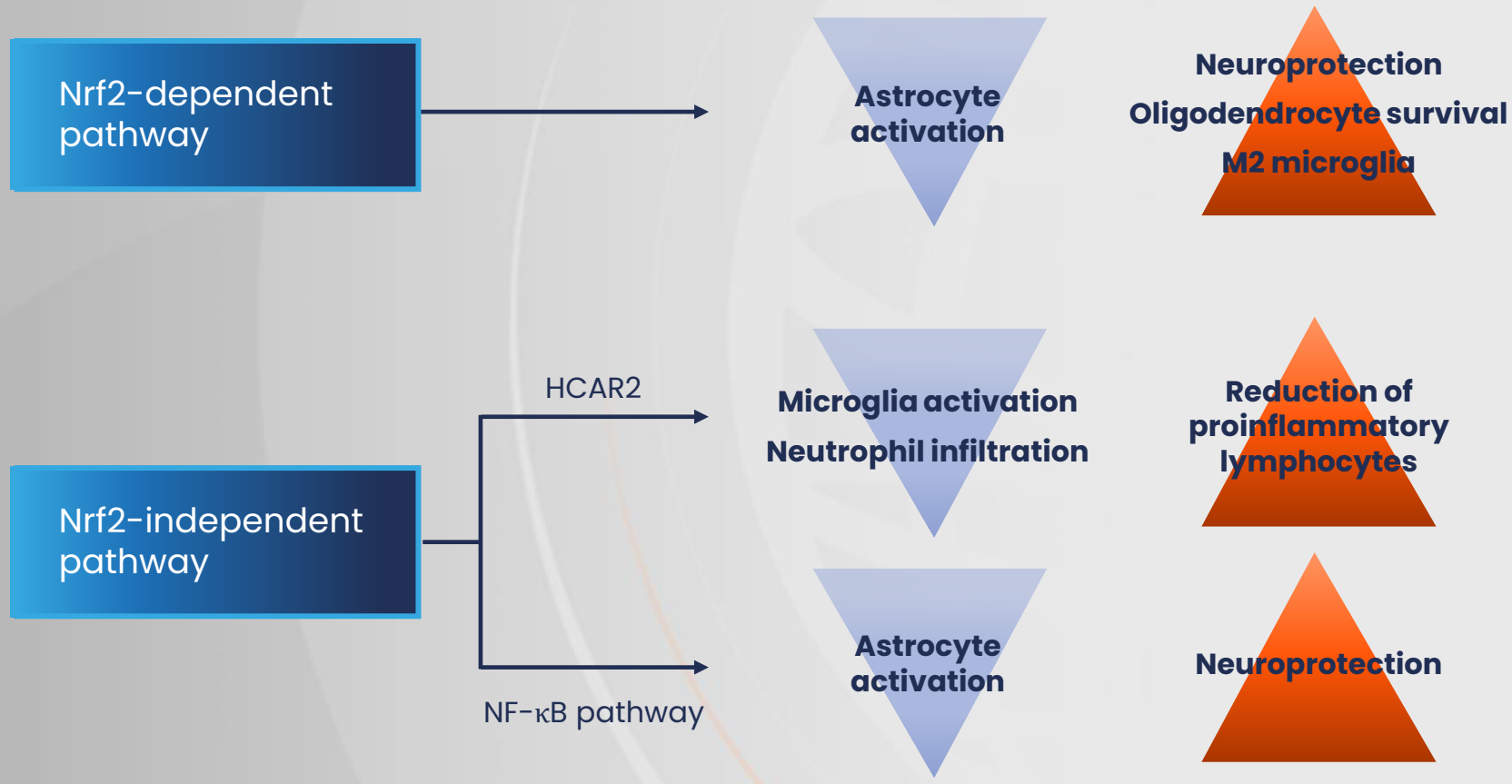
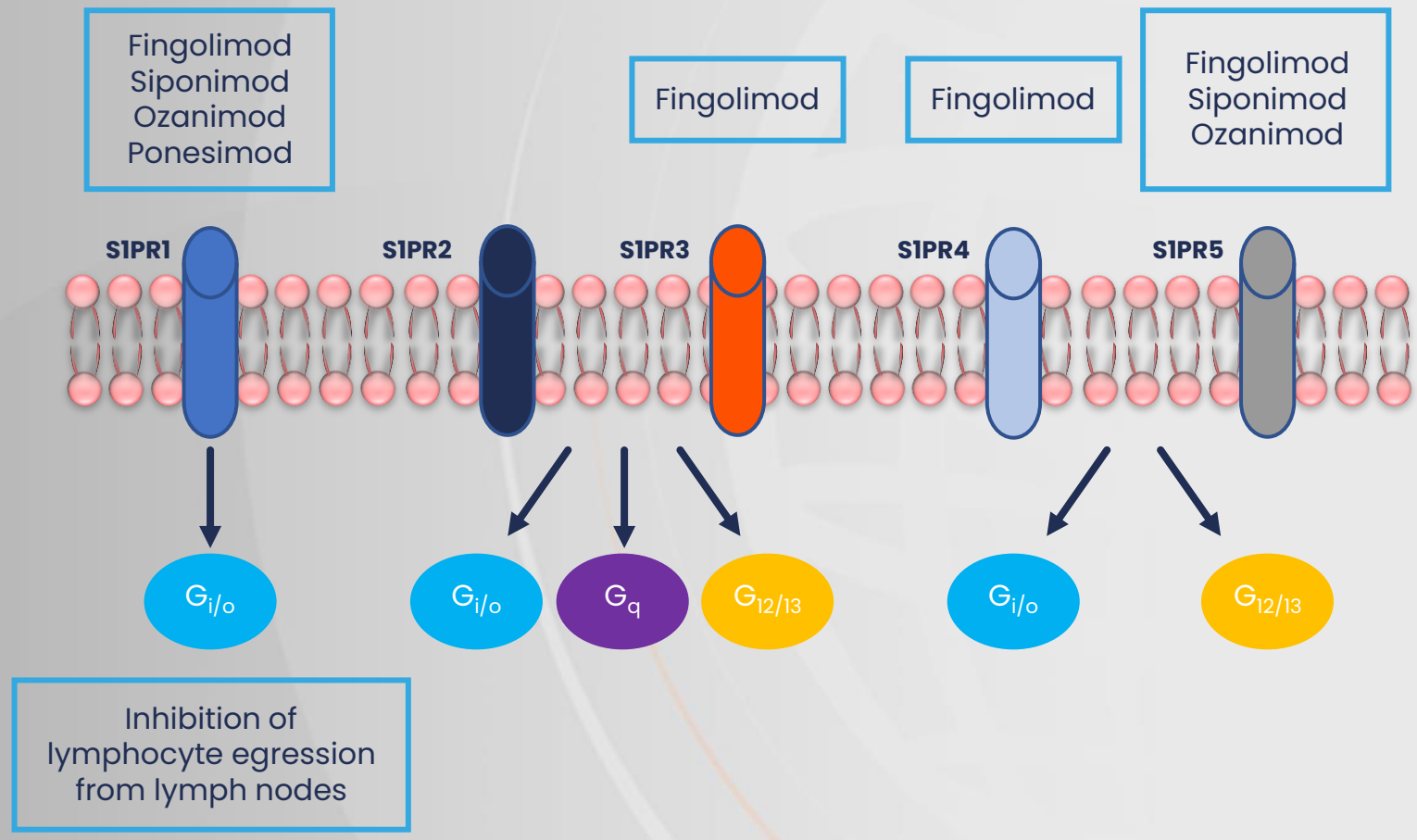
Modulators of inflammatory mediators: Dimethyl fumarate



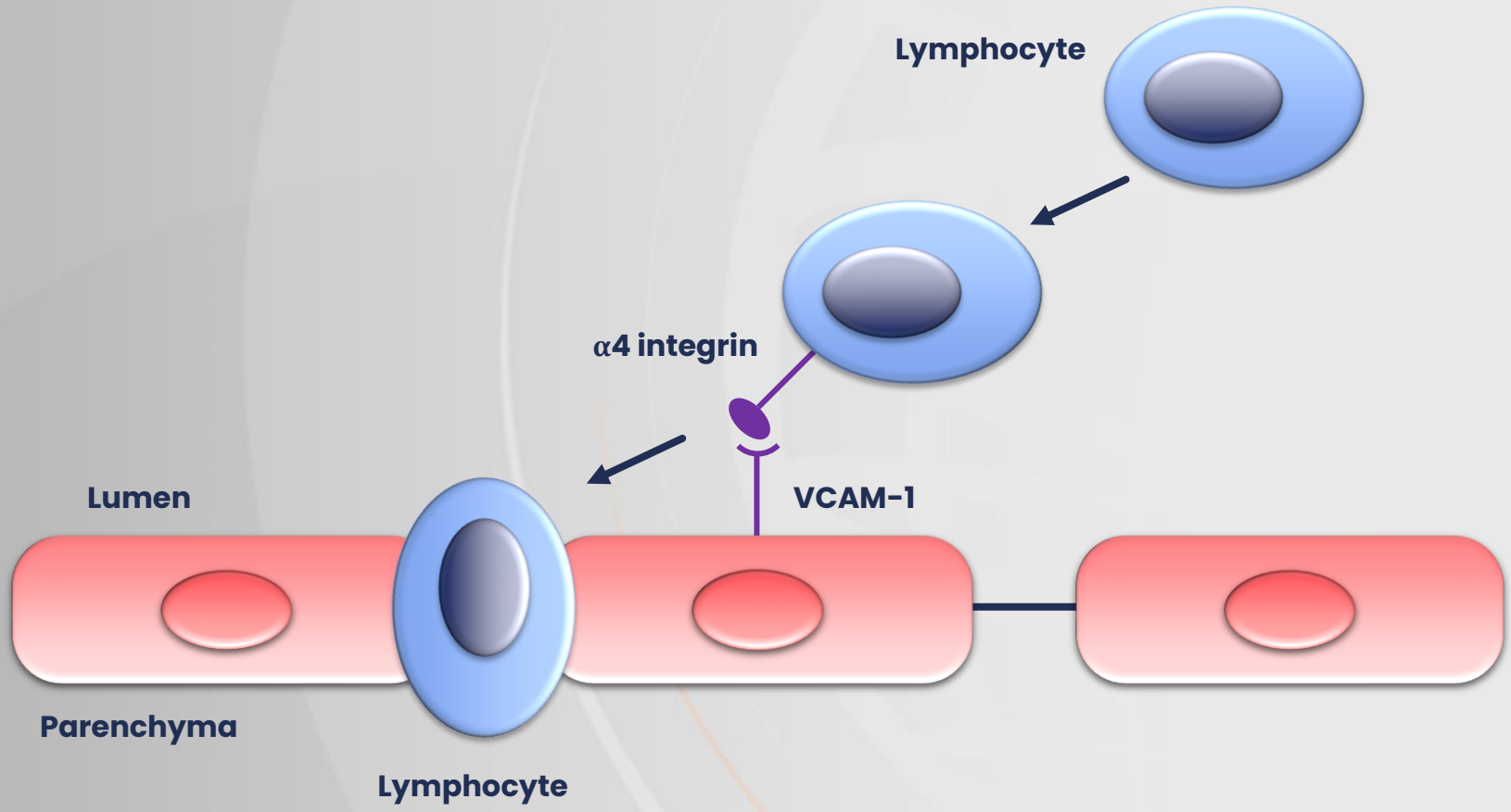
HCAR2, hydroxy-carboxylic acid receptor 2; NF-κB, nuclear factor kappa B; Nrf2, nuclear factor erythroid 2-related factor.
Yadav SK, et al. *J Mol Med (Berl).* 2019;97:463–72.

Immune cell migration inhibitors: S1P receptor modulators



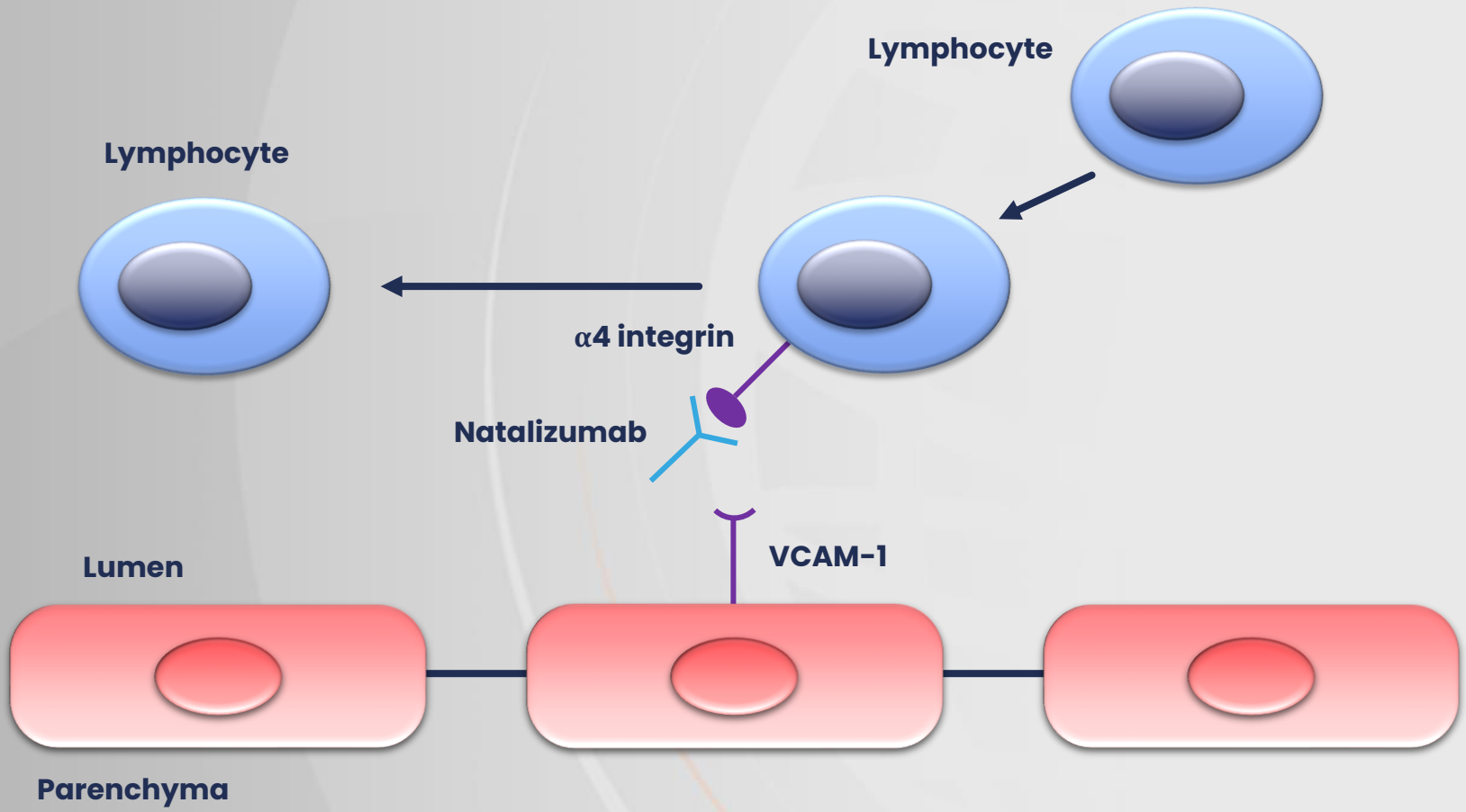
S1PR, sphingosine-1-phosphate receptor.
Bravo GÁ, et al. *Cells*.2022;11:2058.

Immune cell migration inhibitors: Natalizumab



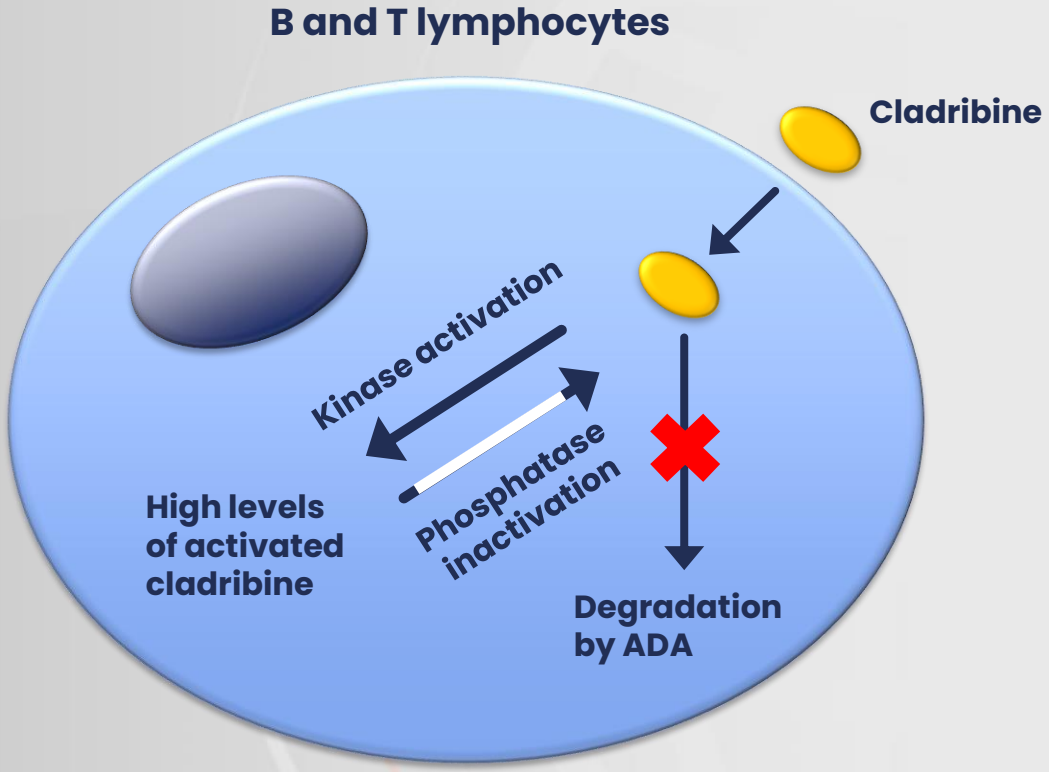
VCAM-1, vascular cell adhesion protein 1.
Steinman L. *J Cell Biol*. 2012;199:413–6.

Immune cell migration inhibitors: Natalizumab



VCAM-1, vascular cell adhesion protein 1.
Steinman L. *J Cell Biol*. 2012;199:413–6.

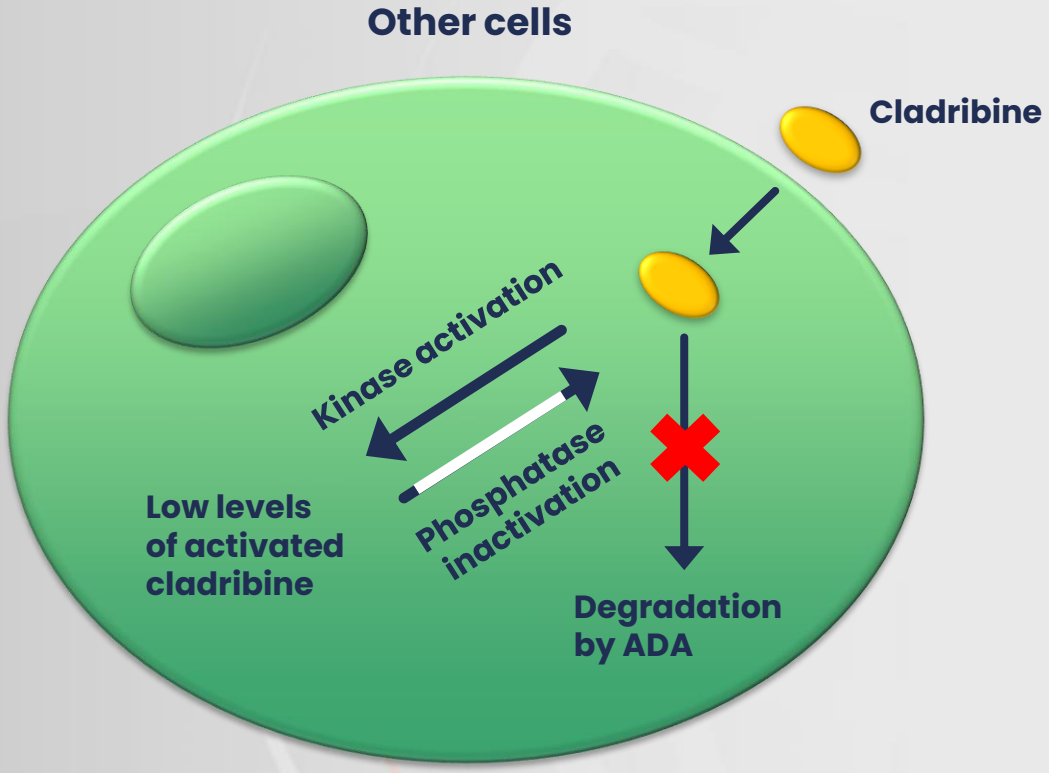
Cell depleting/induction therapies: Cladribine



High kinase to phosphatase ratio

ADA, adenosine deaminase.
Giovannoni G. *Neurotherapeutics*. 2017;14:874–87.

Cell depleting/induction therapies: Cladribine

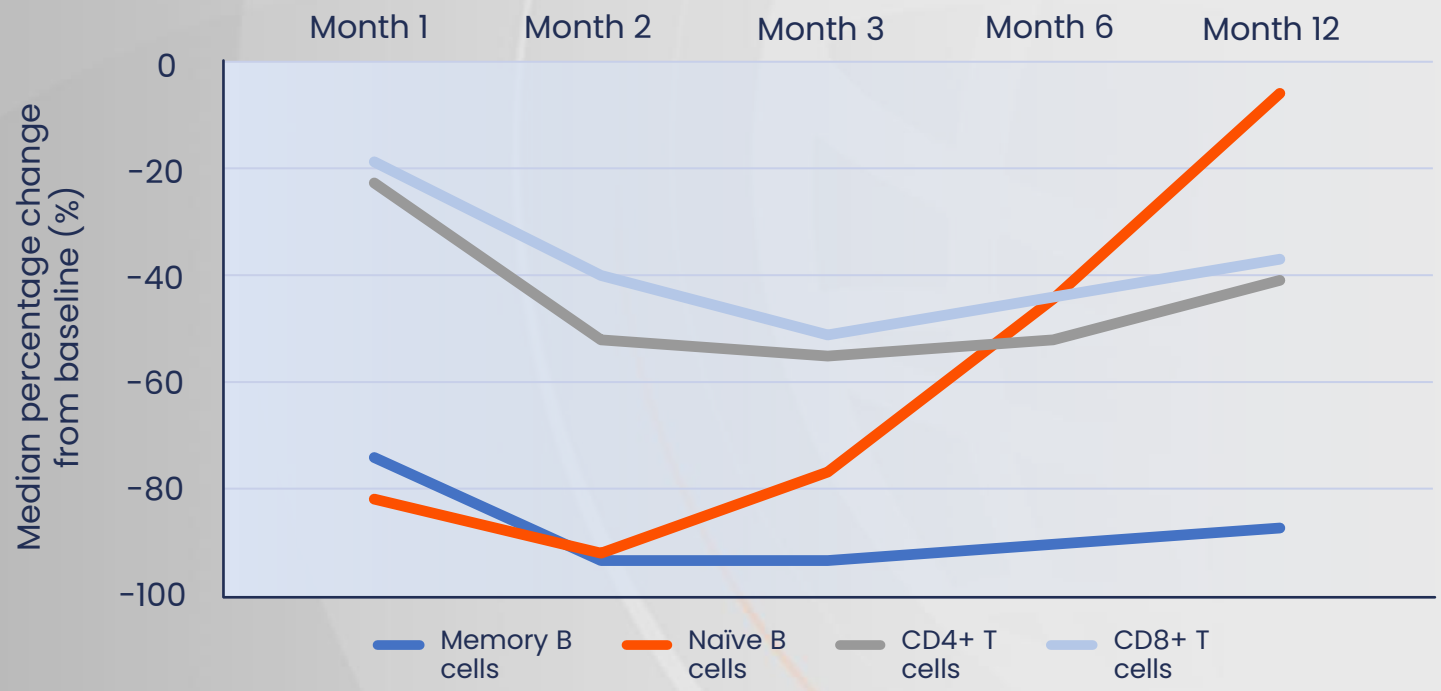


Low kinase to phosphatase ratio

ADA, adenosine deaminase.
Giovannoni G. *Neurotherapeutics*. 2017;14:874–87.

Cell depleting/induction therapies: Cladribine

MAGNIFY-MS substudy investigated cell subtypes and immunoglobulin levels in patients with highly active relapsing multiple sclerosis



CD, cluster of differentiation.

Wiendl H, et al. *Neurol Neuroimmunol Neuroinflamm.* 2023;10:e200048.

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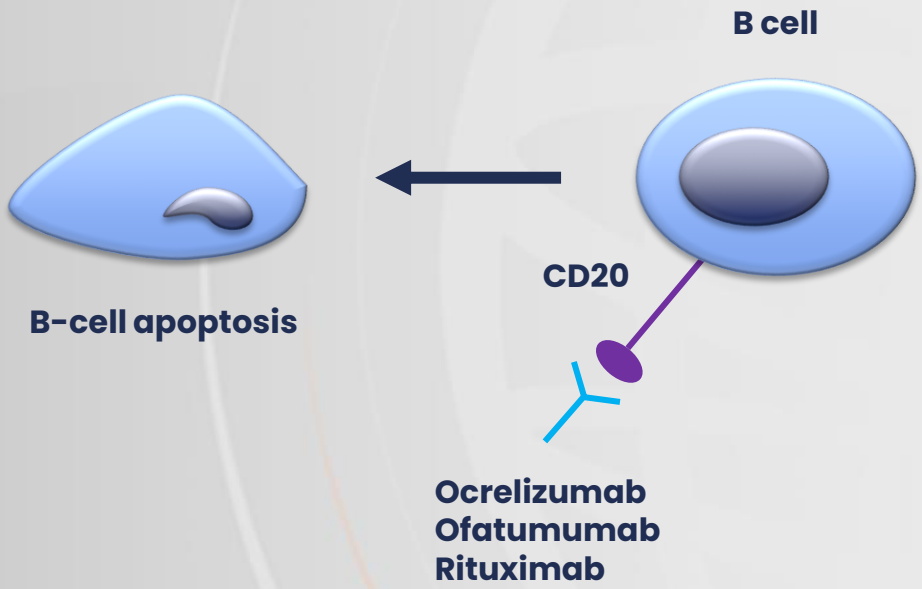
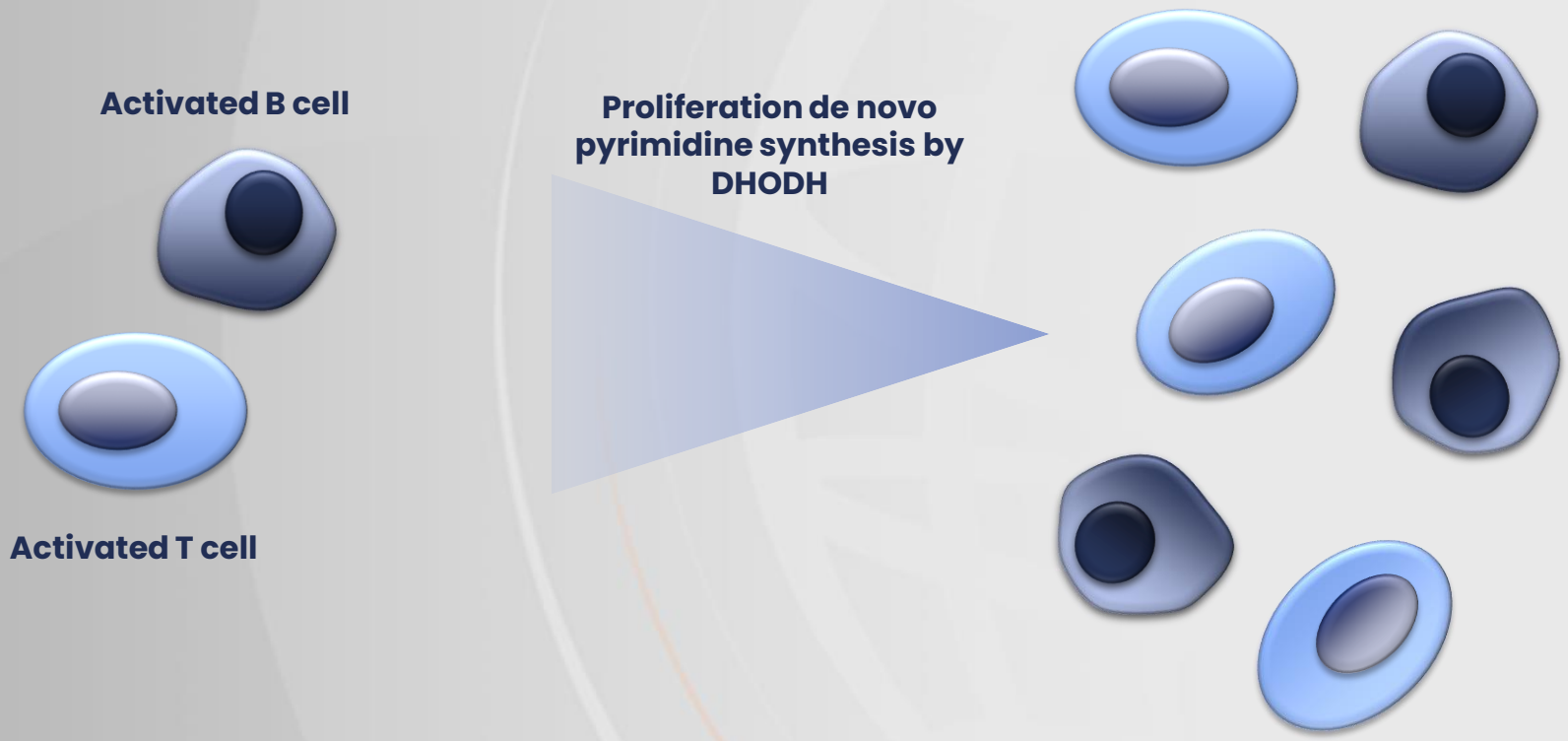
Cell depleting/induction therapies: Anti-CD20 monoclonal antibodies



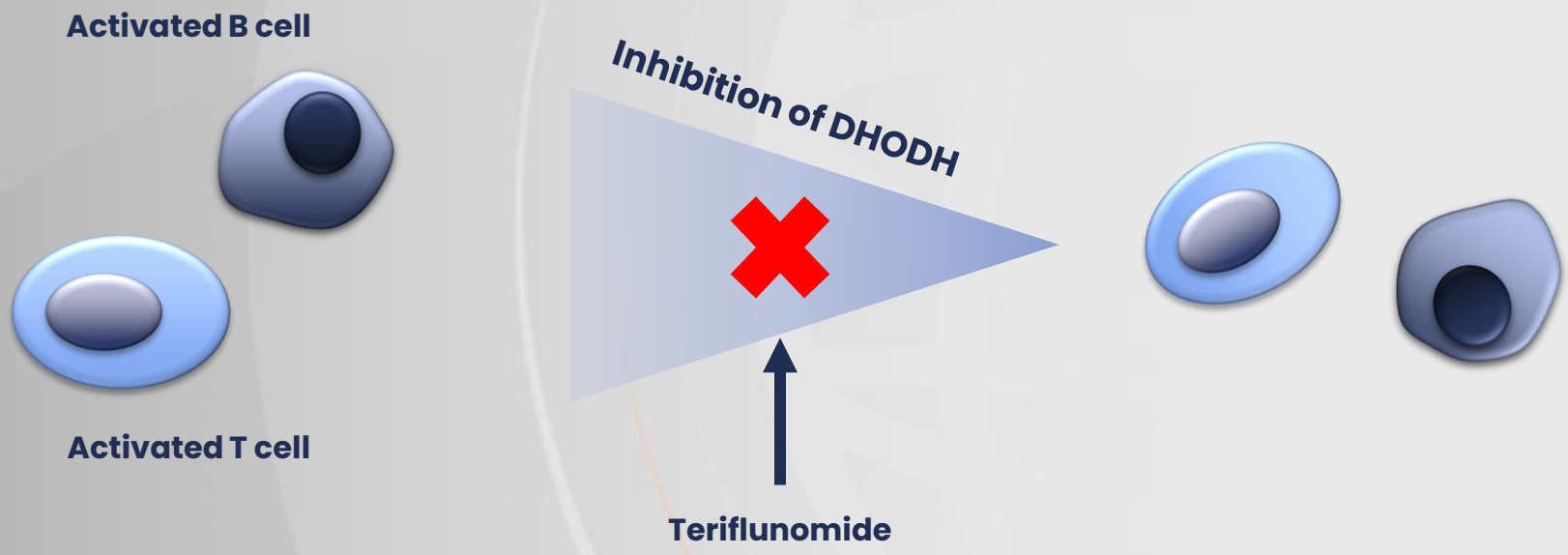
Florou D, et al. *Brain Sci*. 2020;10:758.

Anti-proliferative drug: Teriflunomide



DHODH, dihydroorotate dehydrogenase.
Miller AE. *Neurodegener Dis Manag*. 2017;7:9–29.

Cell depleting/induction therapies: Teriflunomide



DHODH, dihydroorotate dehydrogenase.
Miller AE. *Neurodegener Dis Manag*. 2017;7:9–29.

Conclusions

Modulators of Th1/2 cells[1]
- IFN-ß
- Glatiramer acetate
- Dimethyl fumarate

Immune cell migration inhibitors[2]
- Fingolimod
- Siponimod
- Ozanimod
- Ponesimod
- Natalizumab

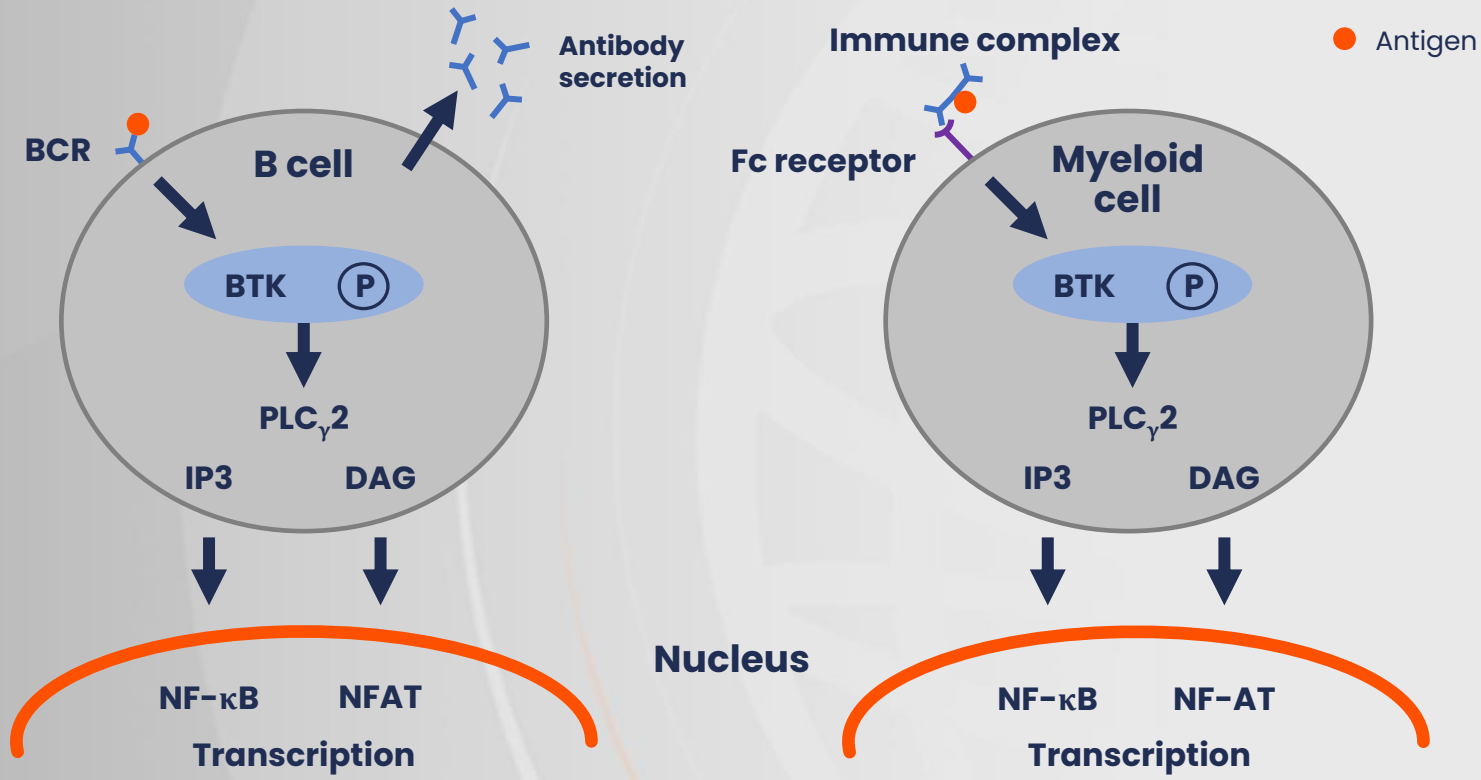
Cell depleting/induction therapies[3,4]
- Cladribine
- Ocrelizumab
- Ofatumumab
- Rituximab
- Teriflunomide

IFN, interferon; Th, T helper.

1. Yang JH, et al. *Front Neurol*. 2022;13:824926; 2. Bravo GÁ, et al. *Cells*.2022;11:2058; 3. Florou D, et al. *Brain Sci*. 2020;10:758; 4. Gallo P, et al. *Mult Scler Demyelinating Disord*. 2017;2:1–11.

A new therapeutic target: Bruton's tyrosine kinase

Mechanism of action of BTKs



- Regulation of cellular proliferation, survival and maturation
- Antigen presentation
- Cytokine production

- Transcription
- Phagocytosis
- Cytokine release

BCR, B-cell receptor; BTK, Bruton's tyrosine kinase; DAG, diacylglycerol; IP3, inositol 1,4,5-trisphosphate; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; NFAT, nuclear factor of activated T-cells; PLCγ2, phosphoinositide-specific phospholipase Cγ2.

Jayagopal JA, et al. *Pract Neurol*. 2022:29–33.

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Comparison of BTK inhibitors

BTKi	IC50[1]	Chemical bond[1]	Selectivity[1]
Evobrutininb	37.97	Covalent, irreversible	Targets BTK selectively
Tolebrutinib	0.4–0.79	Covalent, irreversible	Binds 12 of 250 tyrosine kinases at 1 mcMol
Orelabrutinib	1.6	Covalent, irreversible	BTK only (>90% inhibition)
Fenebrutinib	2.37	Noncovalent, reversible	Targets 2 of 286 kinases

CNS penetration is thought to vary between BTK inhibitors but this is yet to be confirmed in humans[2]

BTK, Bruton's tyrosine kinase; BTKi, BTK inhibitor; CNS, central nervous system; IC50, half maximal inhibitory concentration.

1. Jayagopal JA, et al. *Practical Neurol*. 2022:29–33; 2. Turner TJ, et al. Presented at: ACTRIMS Forum, West Palm Beach, FL, USA. 24–26 February 2022. Abstr P162.

NCT02975349: Evobrutinib

- Randomized phase II trial
- Relapsing multiple sclerosis
- Primary endpoint:
  - Total number of gadolinium-enhancing lesions
- Key secondary endpoints:
  - Annualized relapse rate
  - EDSS change from baseline

1:1:1:1:1

- Evobrutinib 25 mg once daily
- Evobrutinib 75 mg once daily
- Evobrutinib 75 mg twice daily
- Placebo
  - Evobrutinib 25 mg once daily
- DMF 120 mg twice daily
  - DMF 240 mg twice daily

DMF, dimethyl fumerate; EDSS, Expanded Disability Status Scale.
Montalban X, et al. *N Engl J Med*. 2019;380:2406–17.

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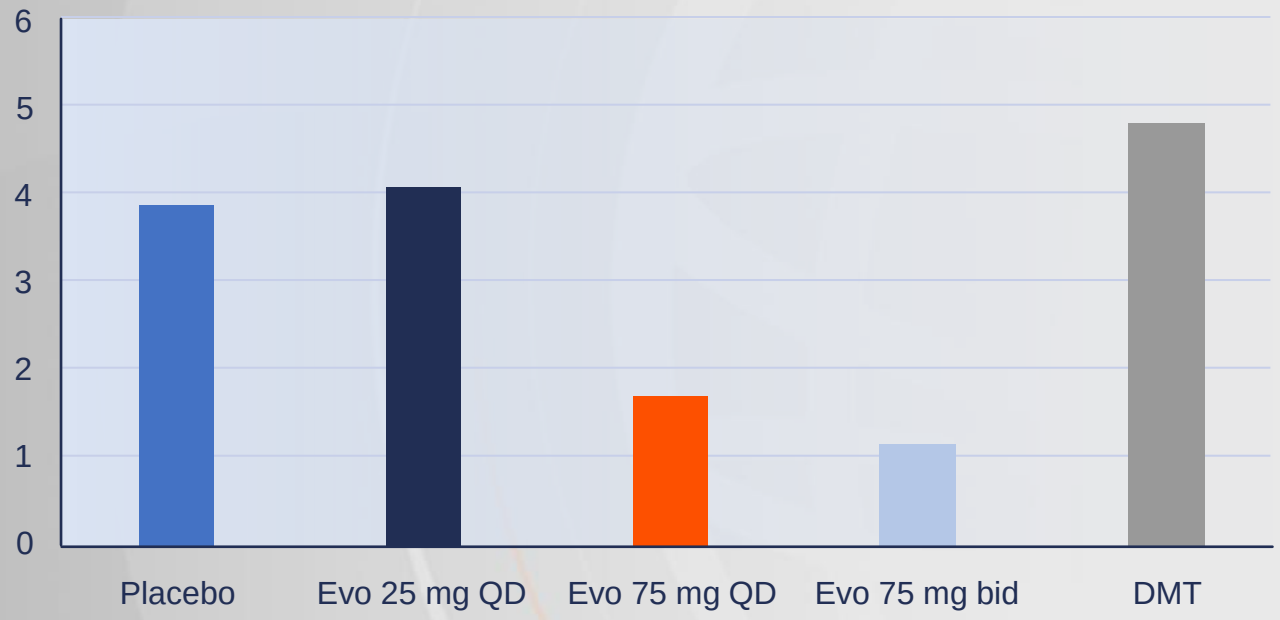
NCT02975349: Evobrutinib

Mean total number of gadolinium-enhancing lesions at Weeks 12 through 24



No significant change in evobrutinib groups from placebo for change in EDSS and annualized relapse rate

bid, twice daily; DMF, dimethyl fumerate; EDSS, Expanded Disability Status Scale; Evo, evobrutinib; QD, once daily.

Montalban X, et al. *N Engl J Med*. 2019;380:2406–17.

NCT02975349: Evobrutinib

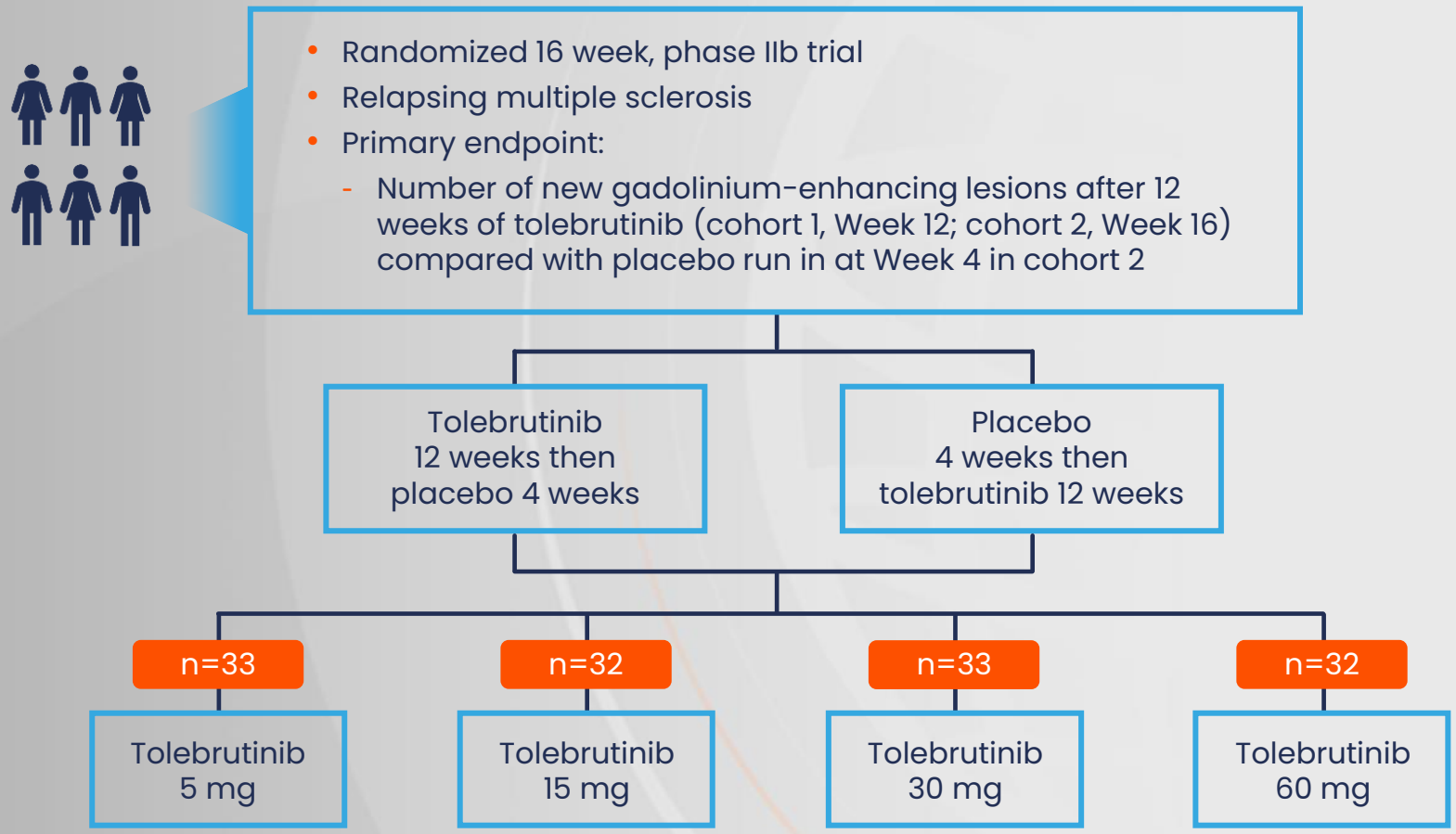
Adverse event	Evo 25 mg QD	Evo 75 mg QD	Evo 75 mg bid	DMF
Grade 3/4	2%	13%	15%	13%
Discontinuation	6%	11%	13%	4%
Most common	Nasopharyngitis	Increase in alanine aminotransferase	Nasopharyngitis	Flushing

Two identically designed phase III trials, evolutionRMS 1 and 2 (NCT04338022[2] and NCT04338061[3]) are under way to further test evobrutinib in people with relapsing forms of MS

bid, twice daily; DMF, dimethyl fumerate; Evo, evobrutinib; MS, multiple sclerosis; QD, once daily.

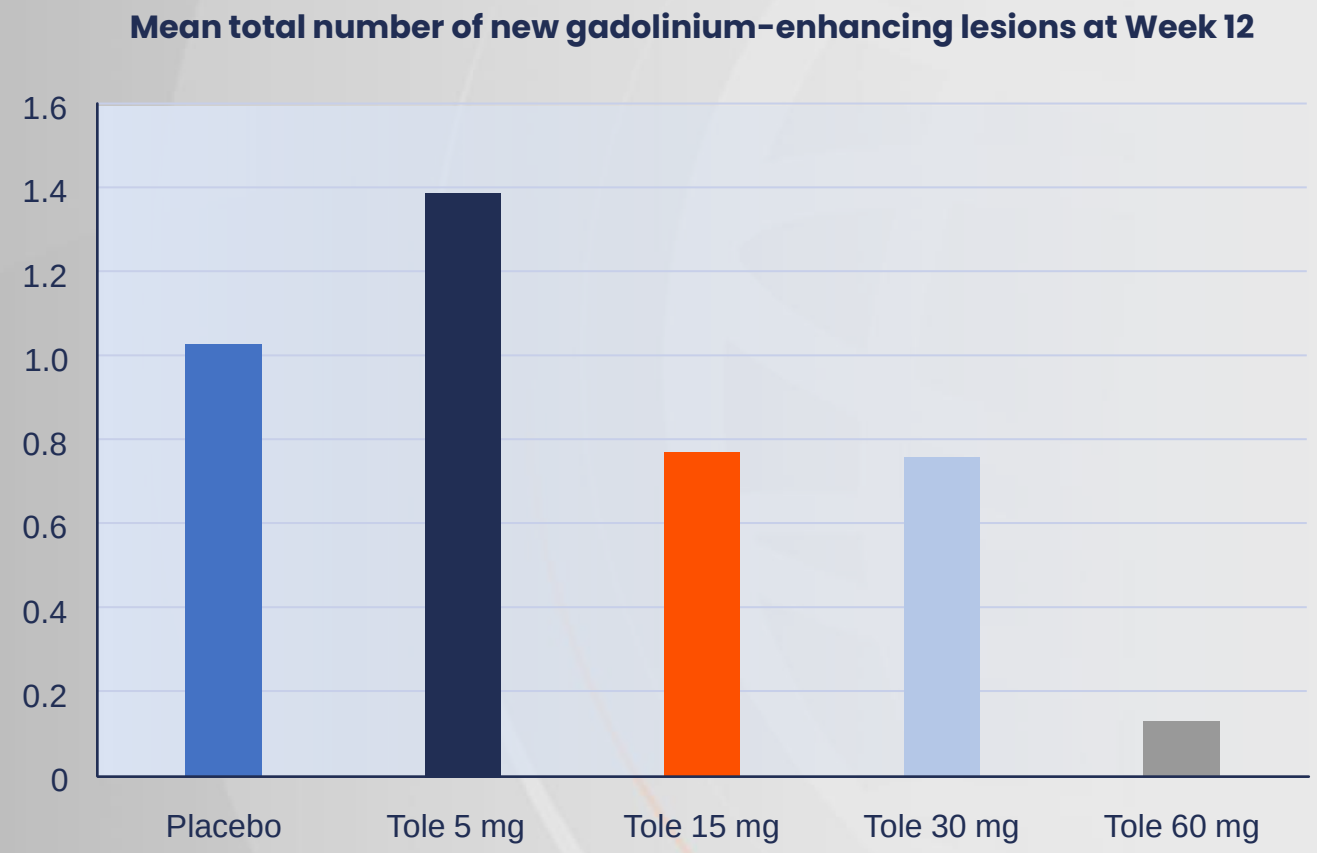
1. Montalban X, et al. *N Engl J Med*. 2019;380:2406–17; 2. NCT04338022. Available at: https://clinicaltrials.gov/ct2/show/NCT04338022 (accessed 16 December 2022);
3. NCT04338061. Available at: https://clinicaltrials.gov/ct2/show/NCT04338061 (accessed 16 December 2022).

NCT03889639: Tolebrutinib



Reich DS, et al. *Lancet Neurol.* 2021;20:729–38.

NCT03889639: Tolebrutinib



Tole, tolebrutinib.
Reich DS, et al. *Lancet Neurol.* 2021;20:729–38.

NCT03889639: Tolebrutinib

Adverse event	Tole 5 mg	Tole 15 mg	Tole 30 mg	Tole 60 mg
Severe	0%	0%	0%	3%
Discontinuation	0%	0%	0%	0%
Most common	Upper respiratory tract infection and peripheral oedema	Headache	Back pain	Headache

Two phase III trials, GEMINI 1 and 2 (NCT04410978[2] and NCT04410991[3]) are under way to test tolebrutinib against teriflunomide in people with relapsing forms of multiple sclerosis

Tole, tolebrutinib.

1. Reich DS, et al. *Lancet Neurol.* 2021;20:729–38; 2. NCT 04410978. Available at: https://clinicaltrials.gov/ct2/show/NCT04410978 (accessed 16 December 2022);
3. NCT 04410991. Available at: https://clinicaltrials.gov/ct2/show/NCT04410991 (accessed 16 December 2022).

Fenebrutinib

ClinicalTrials.gov identifier	Phase	Indication	Agents	Estimated completion
NCT04586023[1]	III	Relapsing multiple sclerosis	Fenebrutinib vs teriflunomide vs placebo	October 2025
NCT04586010[2]	III	Relapsing multiple sclerosis	Fenebrutinib vs teriflunomide vs placebo	December 2025
NCT04544449[3]	III	Primary progressive multiple sclerosis	Fenebrutinib vs ocrelizumab vs placebo	January 2026

1. NCT04586023. Available at: https://clinicaltrials.gov/ct2/show/record/NCT04586023 (accessed 16 December 2022);
2. NCT04586010. Available at: https://clinicaltrials.gov/ct2/show/NCT04586010 (accessed 16 December 2022);
3. NCT04544449. Available at: https://clinicaltrials.gov/ct2/show/NCT04544449 (accessed 16 December 2022).

Other BTK inhibitors

ClinicalTrials.gov identifier	Phase	Indication	Agents	Estimated completion
NCT05147220[1]	III	Relapsing multiple sclerosis	Remibrutinib vs teriflunomide	October 2025
NCT05156281[2]	III	Relapsing multiple sclerosis	Remibrutinib vs teriflunomide	October 2025
NCT04711148[3]	II	Relapsing-remitting multiple sclerosis	Orelabrutinib vs placebo	July 2023

BTK, Bruton's tyrosine kinase.

1. NCT05147220. Available at: https://clinicaltrials.gov/ct2/show/record/NCT05147220 (accessed 5 January 2022);
2. NCT05156281. Available at: https://clinicaltrials.gov/ct2/show/record/NCT05156281 (accessed 5 January 2022);
3. NCT04711148. Available at: https://clinicaltrials.gov/ct2/show/record/NCT04711148 (accessed 5 January 2022).

Conclusions

Via downstream signalling, BTK regulates the expression of several genes that are crucial for B cell survival and proliferation, and chemokine and cytokine expression[1]

Evobrutinib and tolebrutinib:

- Phase II results[2,3] and phase III studies are ongoing[4–7]

Fenebrutinib, relabrutinib, remibrutinib and orelabrutinib:

- Phase II and III studies are ongoing[8–13]

Possible advantages of small molecule BTK inhibitors over existing therapies includes the potential to cross the blood–brain barrier to target both the adaptive and innate (microglia) immune systems

BTK, Bruton's tyrosine kinase.

1. García-Merino A. *Cells*. 2021;10:2560; 2. Montalban X, et al. *N Engl J Med*. 2019;380:2406–17; 3. Reich DS, et al. *Lancet Neurol.* 2021;20:729–38; 4. ClinicalTrials.gov. NCT04338022; 5. ClinicalTrials.gov. NCT04338061; 6. ClinicalTrials.gov. NCT04410978; 7. ClinicalTrials.gov. NCT04410991; 8. ClinicalTrials.gov. NCT04586023; 9. ClinicalTrials.gov. NCT04586010; 10. ClinicalTrials.gov. NCT04544449; 11. ClinicalTrials.gov. NCT05147220; 12. ClincalTrials.gov. NCT05156281; 13. ClinicalTrials.gov. NCT04711148.

All clinical trials are searchable by NCT number at www.clinicaltrials.gov.

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