Disability Accumulation in Multiple Sclerosis

November 2022

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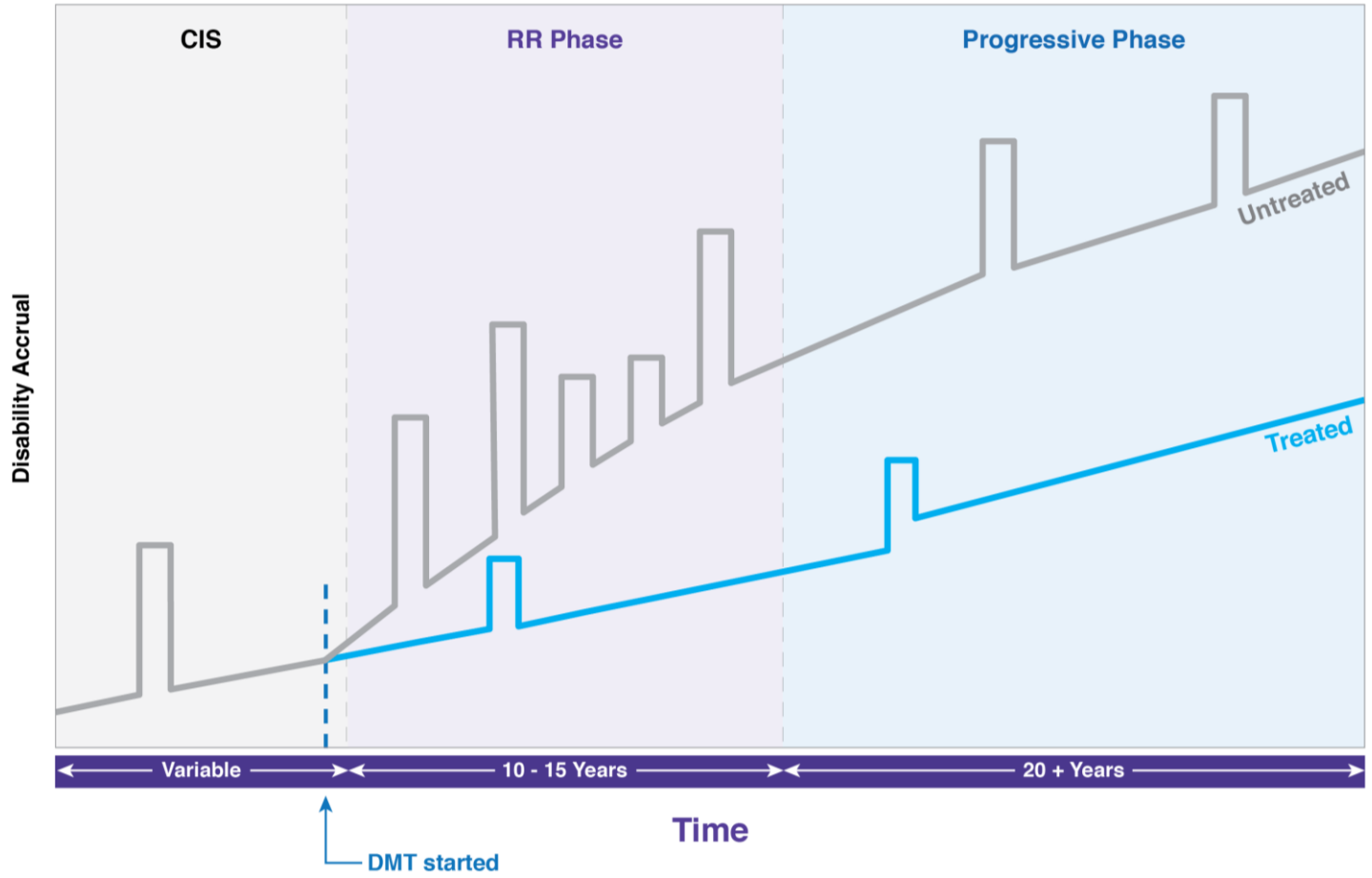
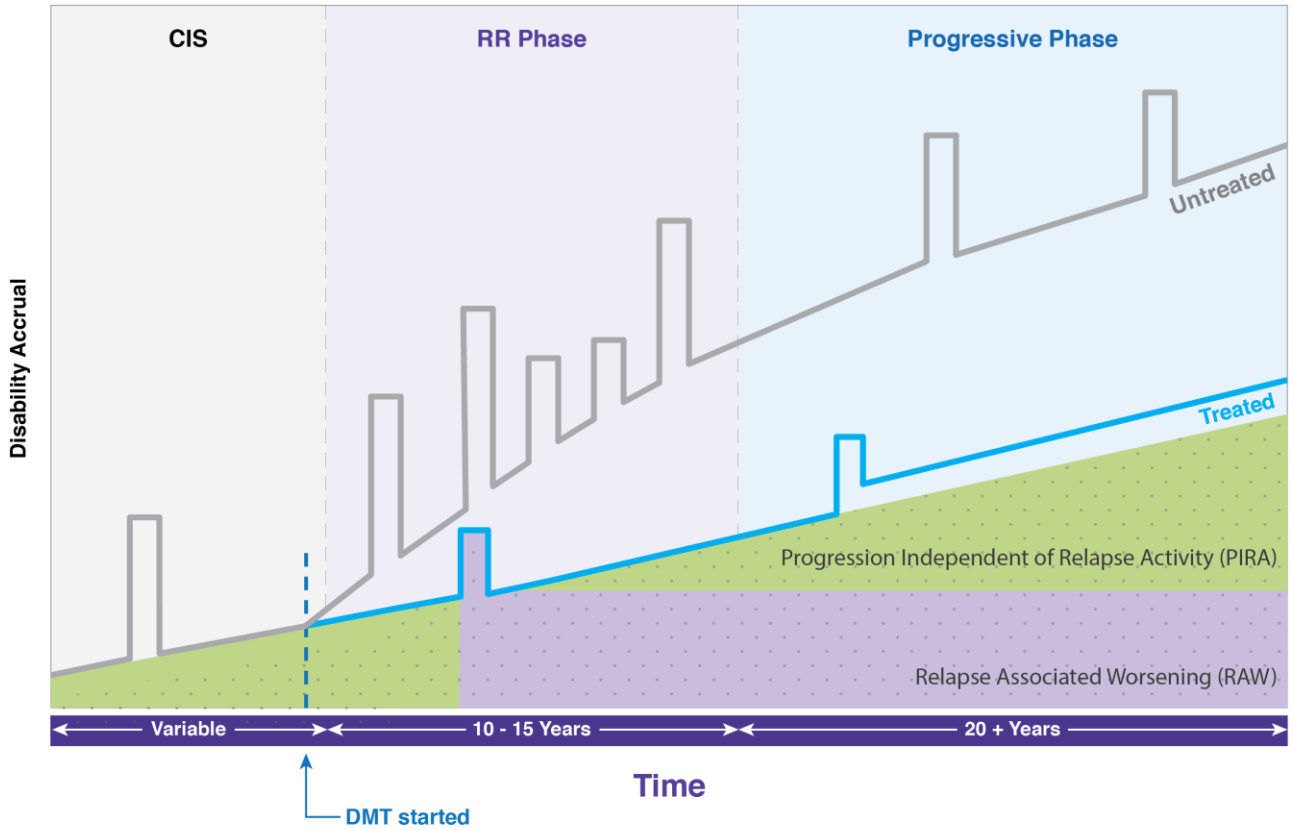
Despite effective relapse reduction with treatment, patients continue to accrue disability



Current MS treatments reduce focal inflammation, relapses, and relapse-associated progression

CIS, clinically isolated syndrome; DMT, disease modifying therapy; MS, multiple sclerosis; RR, relapsing-remitting
The graphic is for illustrative purposes only and not related to the effect of specific therapies

Progression independent of relapse activity occurs from the earliest stages of MS and is not effectively reduced with some DMTs[1]



PIRA is a sustained increase in disability that occurs independently of relapse measured after re-baselining following relapse recovery[1].

89% of 24-week confirmed disability accumulation over a 96-week period in phase 3 studies was due to PIRA despite treatment with **B-cell depleting therapy**[1].

RAW is a sustained increase in disability that begins with an incomplete relapse recovery[2].

CIS, clinically isolated syndrome; DMT, disease modifying therapy; MS, multiple sclerosis; PIRA, progression independent of relapse activity; RAW, relapse-associated worsening; RR, relapsing-remitting
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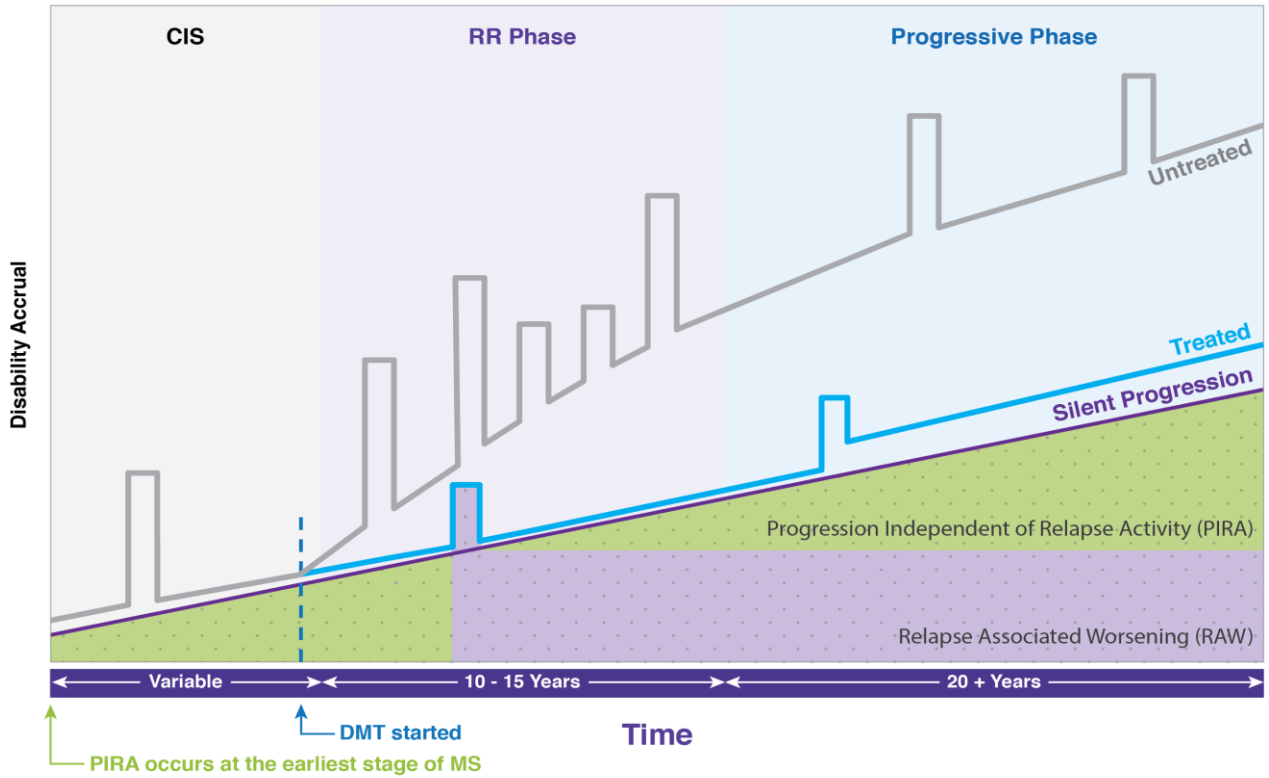
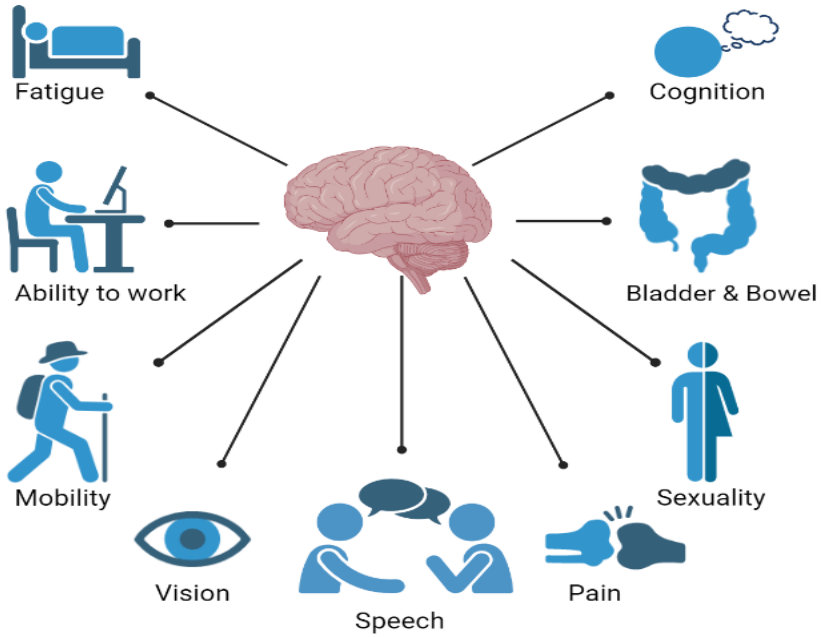
Progression in MS is more than just physical disability and includes, but is not limited to, fatigue, cognitive difficulties, and imbalance[1]



Patient-centric view of disease progression[2,3]



In patients with an EDSS of 0, challenge tasks unmasked deficits undetected with routine clinical tests[4]

Silent progression describes the insidious disability that accrues in many patients who satisfy traditional criteria for relapsing–remitting MS

CIS, clinically isolated syndrome; DMT, disease modifying therapy; EDSS, expanded disability status scale; MS, multiple sclerosis; PIRA; progression independent of relapse activity; RAW, relapse-associated worsening; RR, relapsing-remitting
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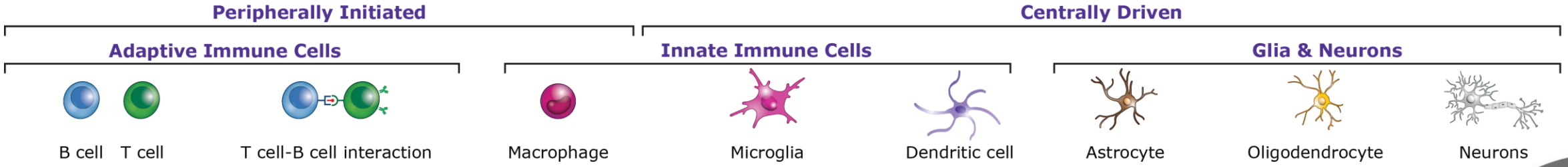
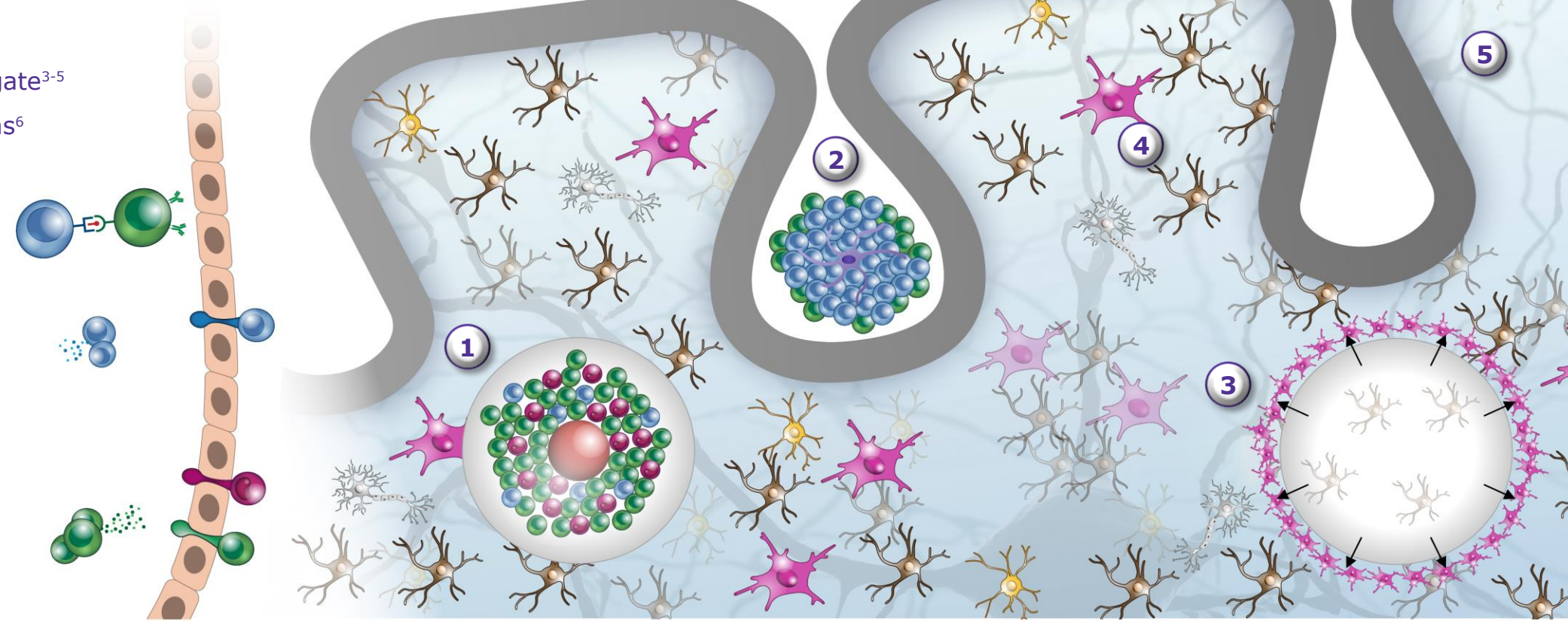
The pathologies underlying MS progression include peripherally initiated and centrally-driven processes[1,2]



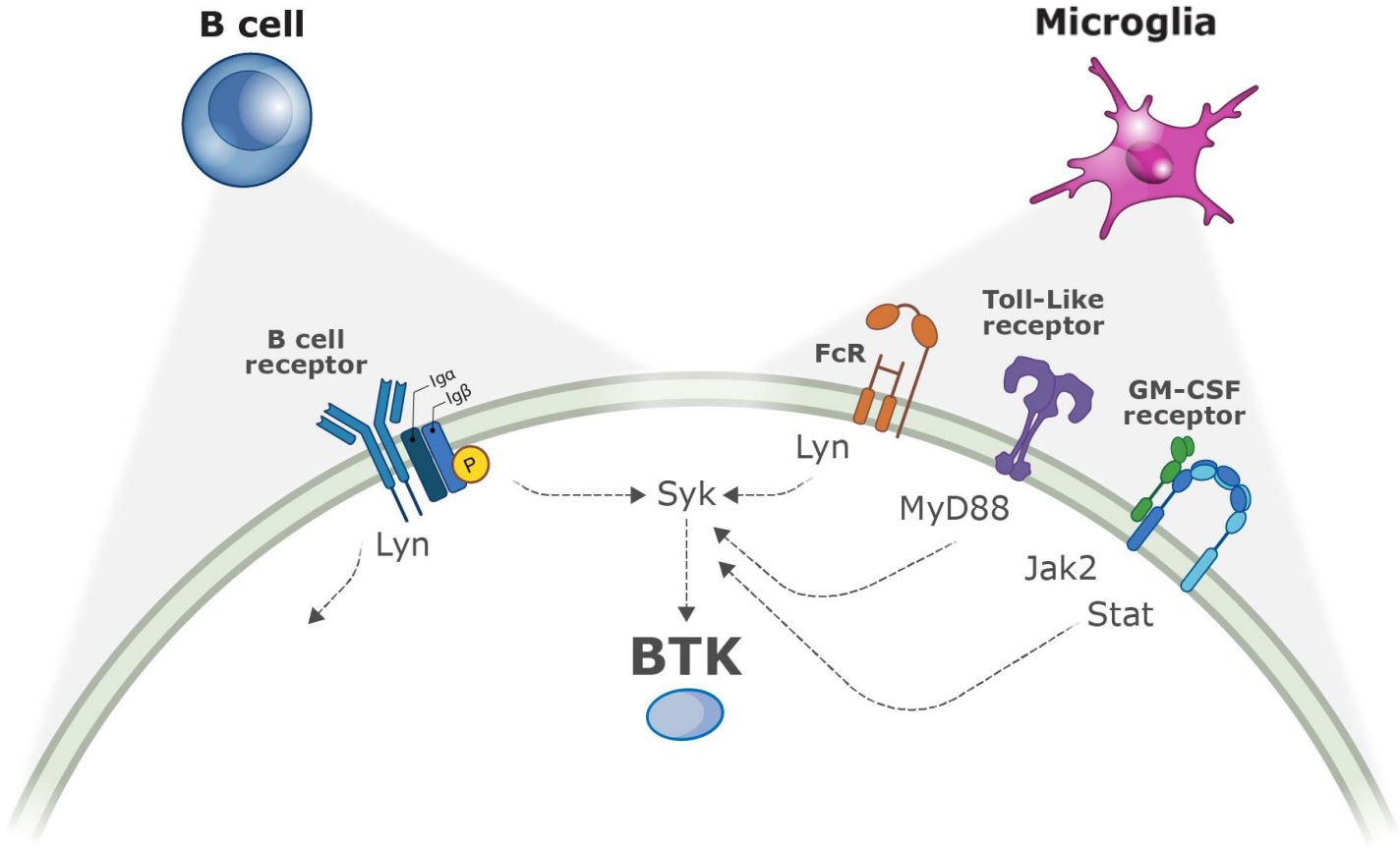
Pathologies underlying MS progression[1]

1. Focal MS lesions[1]
2. Meningeal B-cell aggregate[3-5]
3. Slowly expanding lesions[6]
4. Diffuse gliosis[7]
5. Age-related atrophy[1]



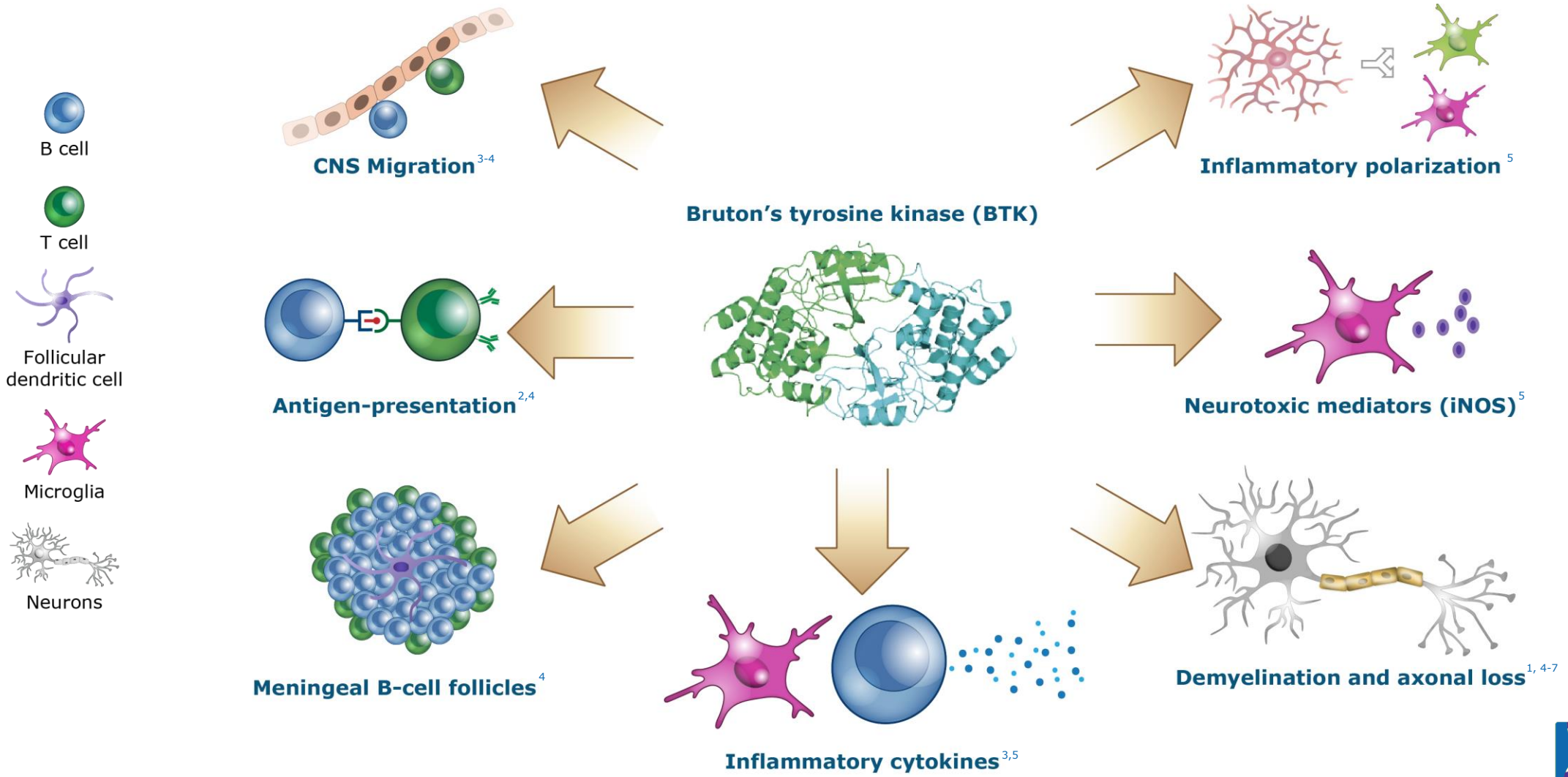
MS, multiple sclerosis

Bruton's Tyrosine Kinase is a signaling molecule in B cells and microglia[1]



BTK, Bruton's tyrosine kinase; FcR, Fragment, crystallizable; GM-CSF, granulocyte-macrophage colony-stimulating factor; JAK2, Janus kinase 2; MyD88, myeloid differentiation primary response 88; P, phosphate; STAT, signal transducer and activator of transcription

Bruton's Tyrosine Kinase mediates inflammatory processes in B-cells and microglia relevant to MS[1]



BTK, Bruton's tyrosine kinase; CNS, central nervous system; iNOS, inducible nitric oxide synthase; MS, multiple sclerosis

Thank you!

Footnotes Verdana regular 8pt

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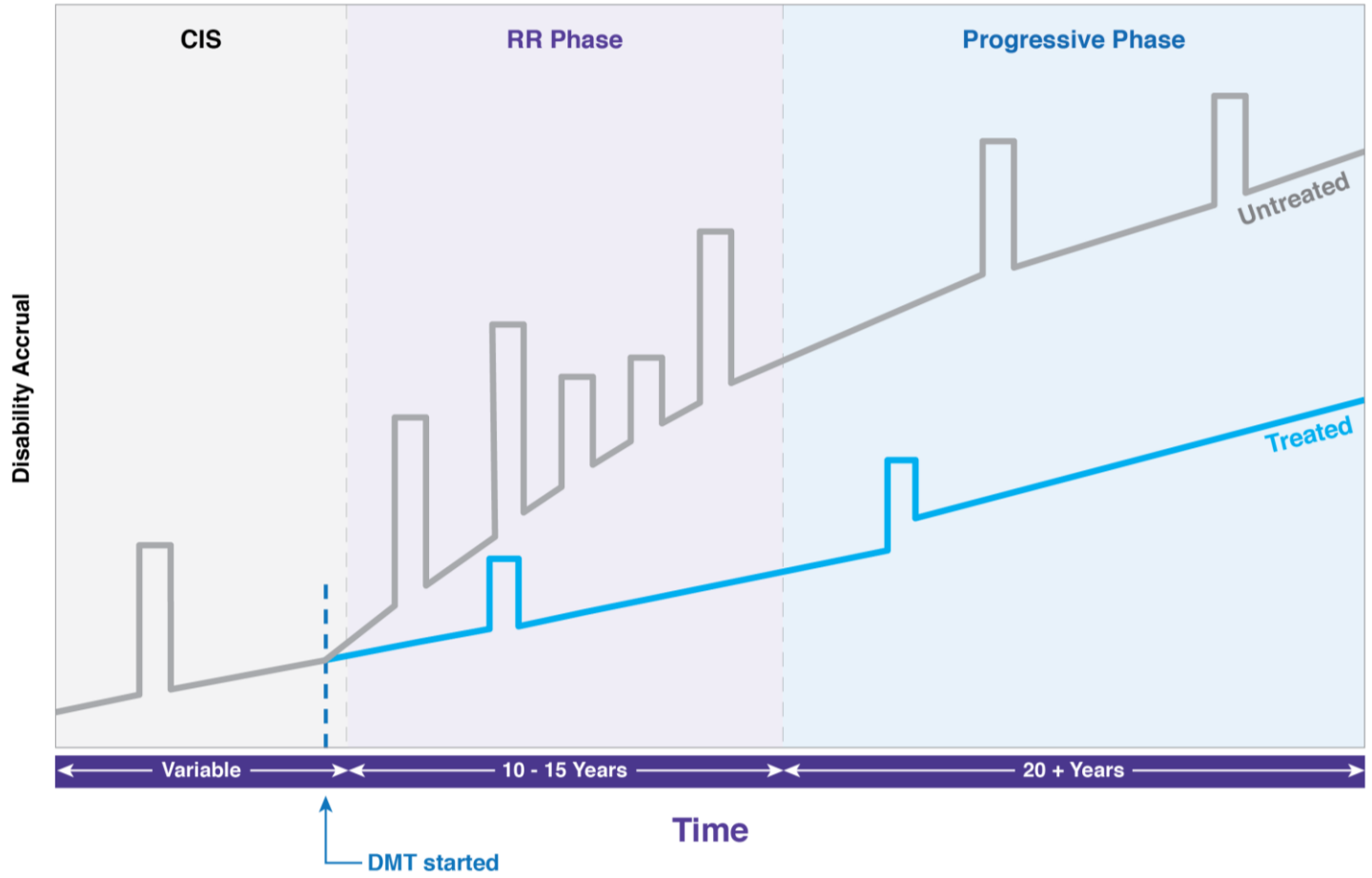

Current MS treatments reduce focal inflammation, relapses, and relapse-associated progression

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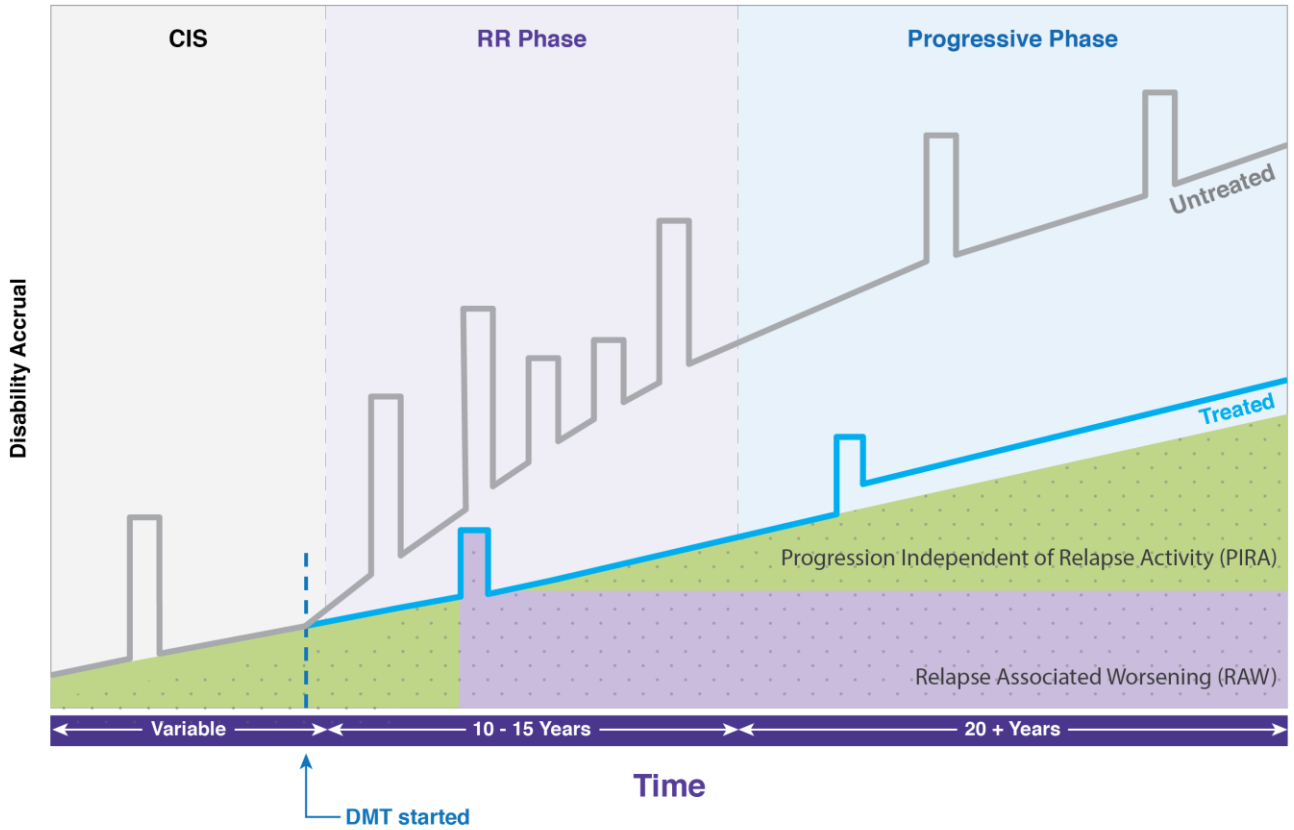

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1. Kappos L et al. JAMA Neurology, 2020;77(9):1132–40; **2**. Lublin FD et al. Brain, 2022, awac016.

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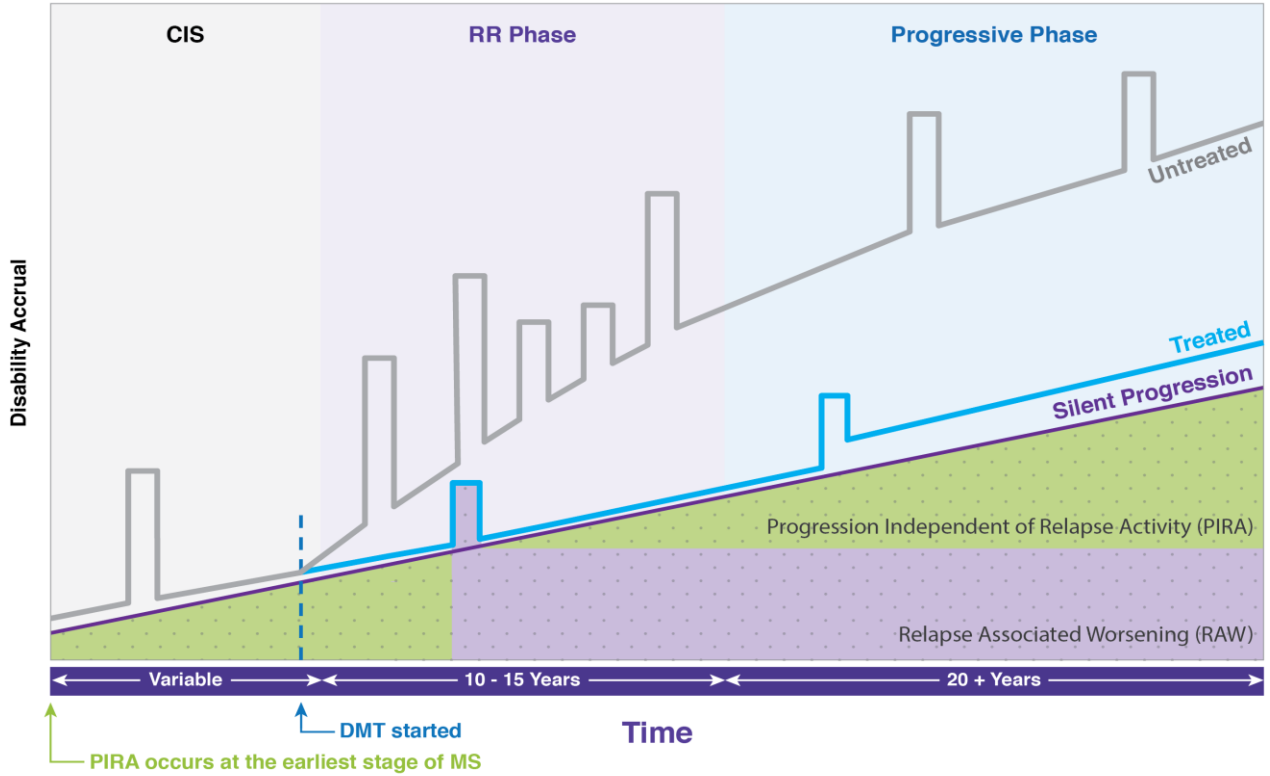

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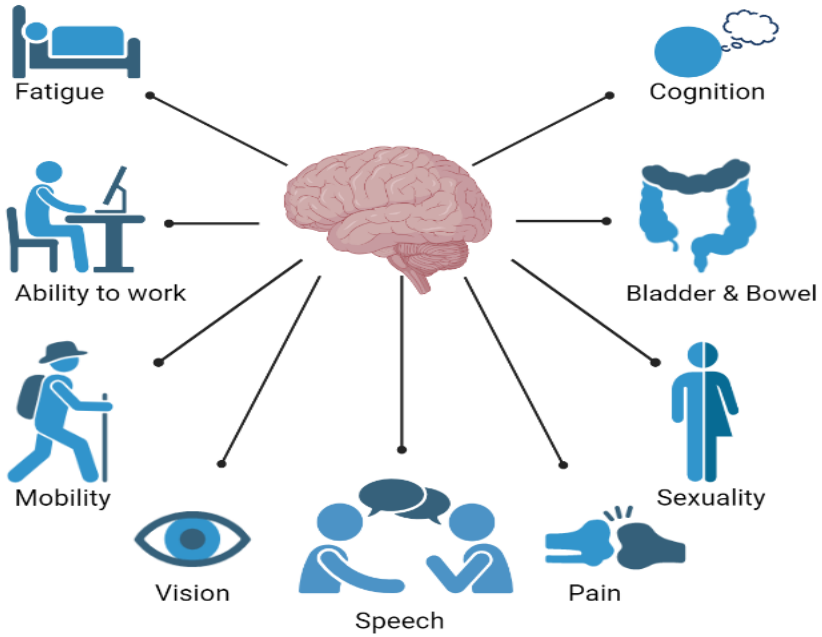

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1. University of California et al. Ann Neurol, 2019;85(5):653-666; **2**. Lublin FD et al. Brain, 2022:awac016; **3**. Marin CE et al. Mult Scler Relat Disord, 2021;50:102806; **4**. Krieger SC et al. Mult Scler, 2022 Jul 13;13524585221108297.

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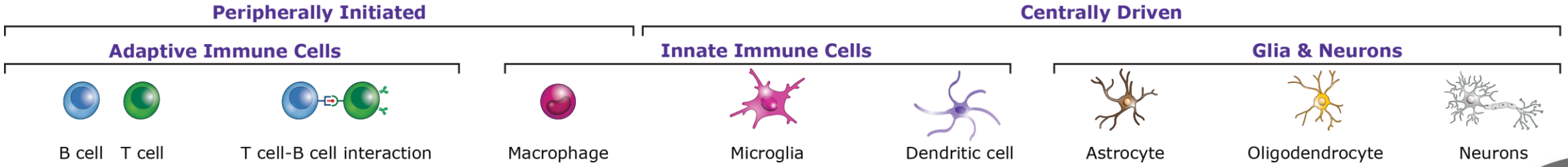

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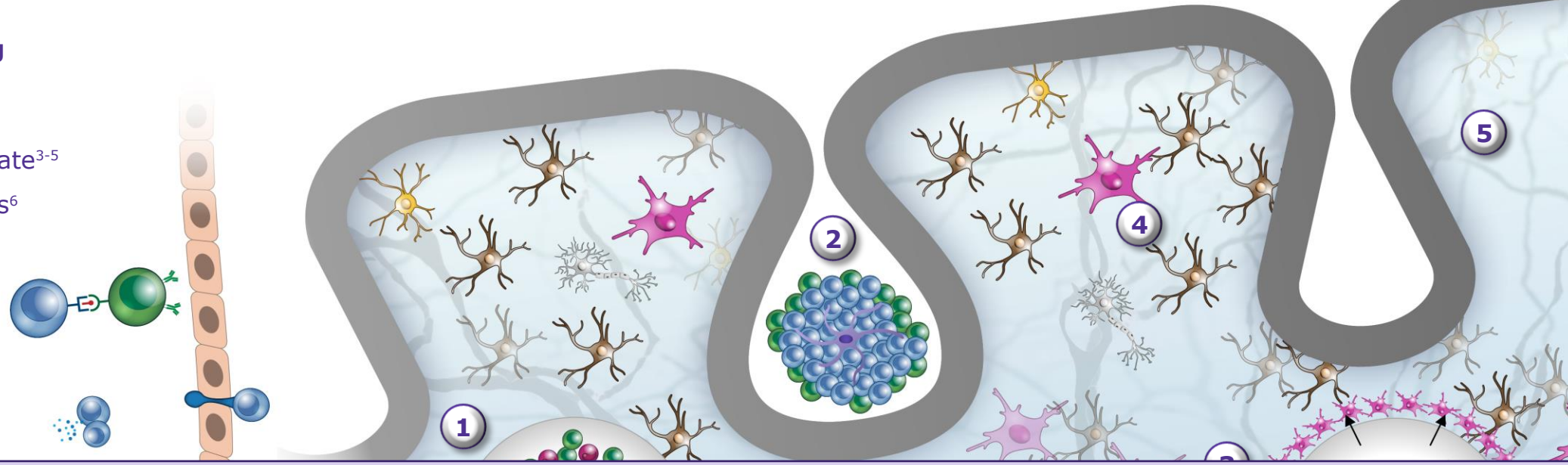

Peripherally initiated refers to the influx of cells from outside the CNS and Centrally-driven refers to disease processes that are compartmentalized within the CNS

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1. Hauser SL, Cree BAC. Am J Med 2020;133:1380–90; **2**. Dendrou CA et al. Nat Rev Immunol, 2015;15:545–58; **3**.Michel L et al. Front Immunol, 2015;6:636; **4**. Serafini B et al. Brain Pathol, 2004;14:164–74; **5**. Howell OW et al. Brain, 2011;134:2755-71; **6**. Elliott C et al. Brain, 2019;142:2787–99; **7**. Cavaliere C et al. Front Cell Neurosci, April 2020;14;75.

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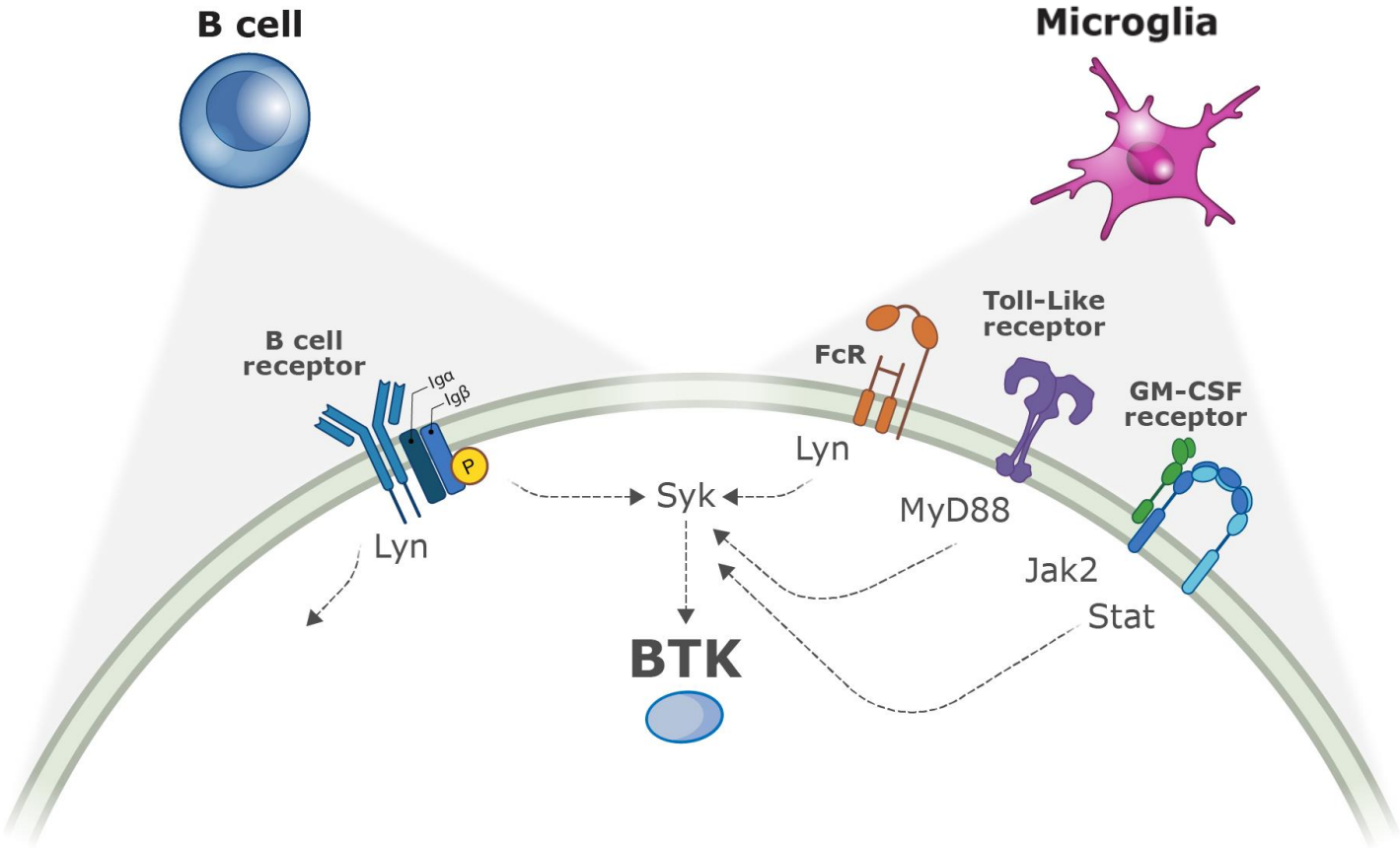
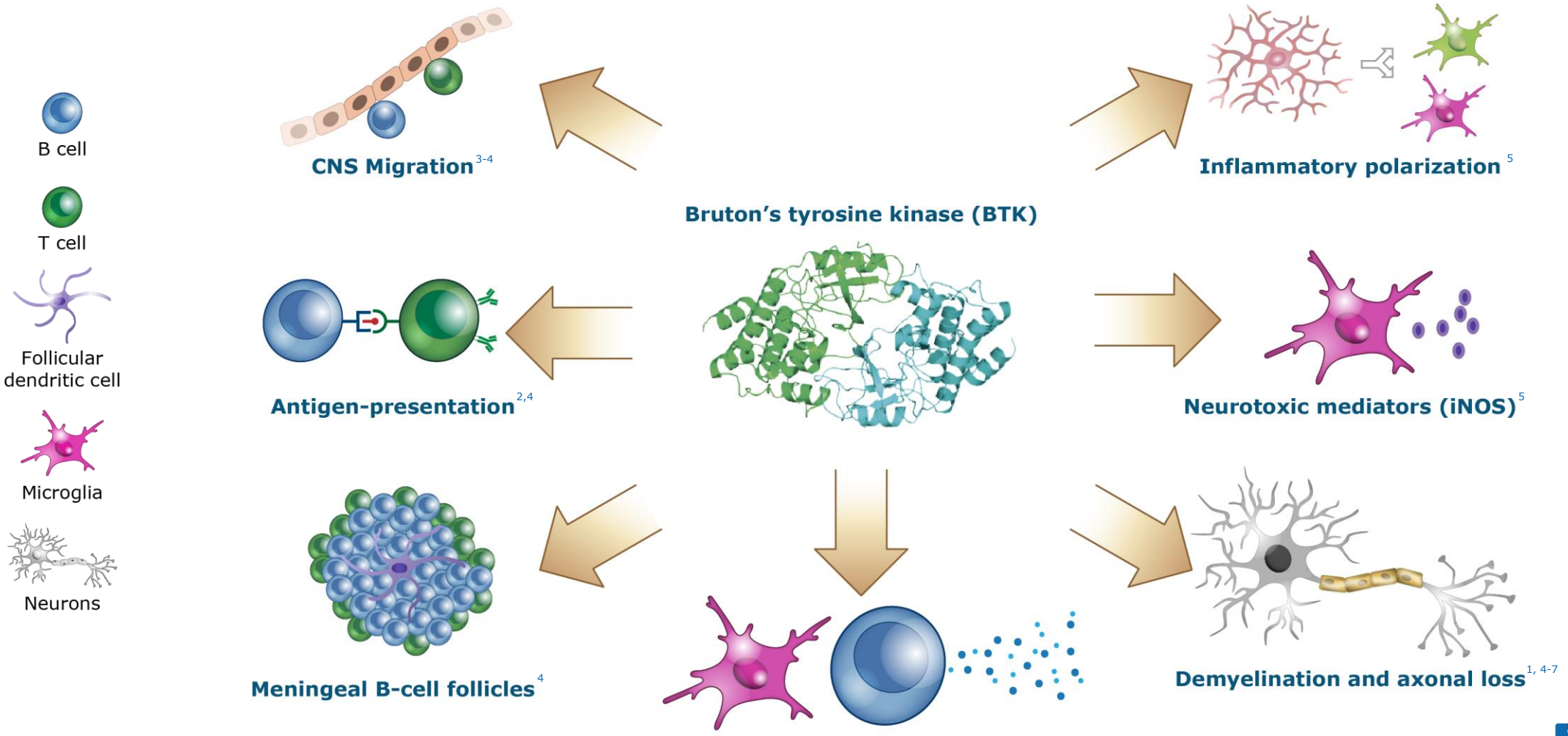


1. Becker, A et al. Clin Transl Sci, 2020;13:325.336; **2**. Hendriks RW, et al. Nat Rev Cancer, 2014;14(4):219-32; **3**. McDonald C, et al. Immunology, 2021;164(4):722-736; **4**. Zhang D, et al. Molecules (Basel, Switzerland), 2021;26(16); **5**. Neys SFH et al. Drugs, 2021;81:1605–1626.

Bruton's Tyrosine Kinase mediates inflammatory processes in B-cells and microglia relevant to MS[1]



1. Piehl F. J Intern Med, 2021;289(6):771-791; **2**. Häusser-Kinzel S, Weber MS. Front Immunol, 2019;10:Article 201:8; **3**. Jain RW, Yong VW. Nat Rev Immunol, 2021; **4**. Cree BAC et al. Lancet Neurol, 2022;21(3):211-214; **5**. Kamma E et al. J Neuroinflammation, 2022;19(1):45; **6**. Martin E et al. Brain Plast, 2020;5(2):123-133; **7**. Dhaiban S et al. Sci 2021;3:12.