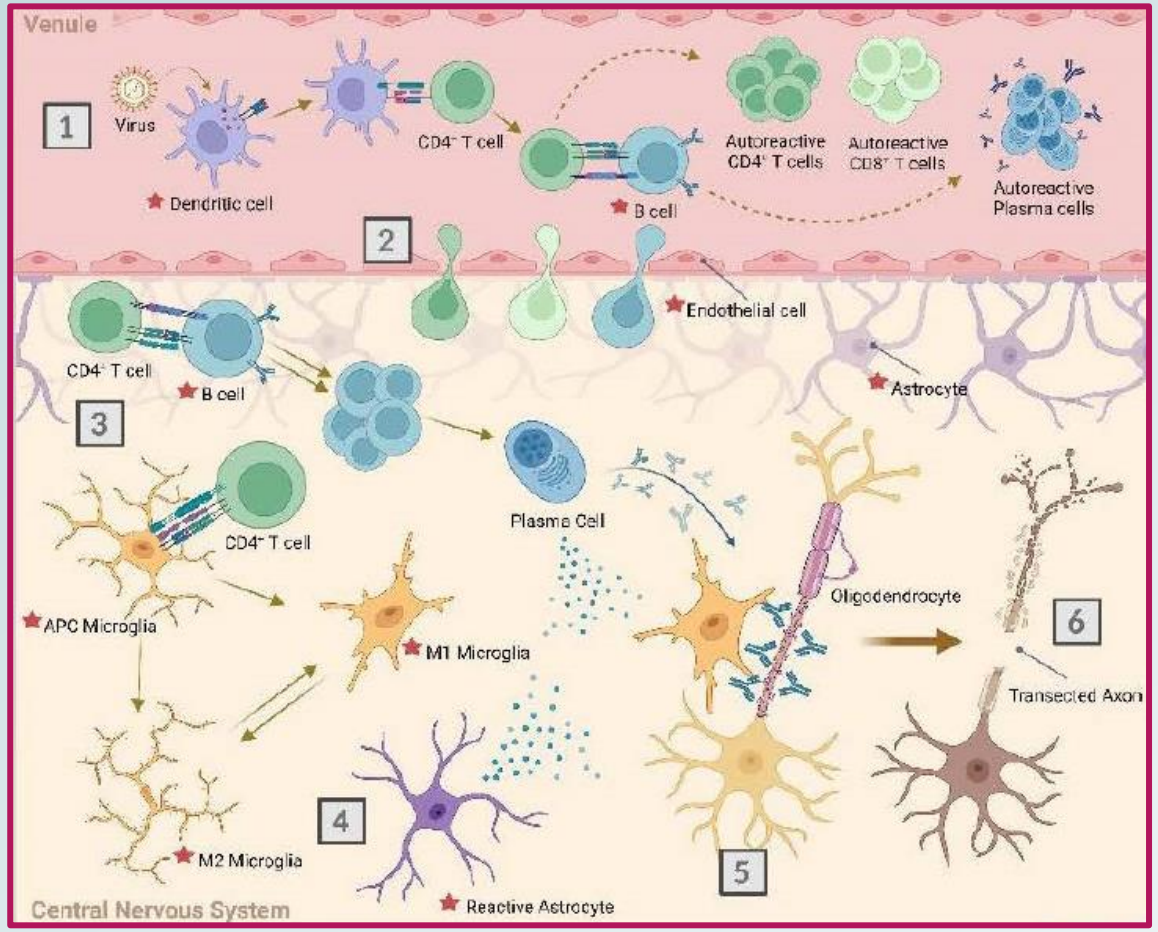
BTK Inhibitors Disrupt Multiple Steps in MS Pathology

★ expresses BTK



BTK Inhibitors

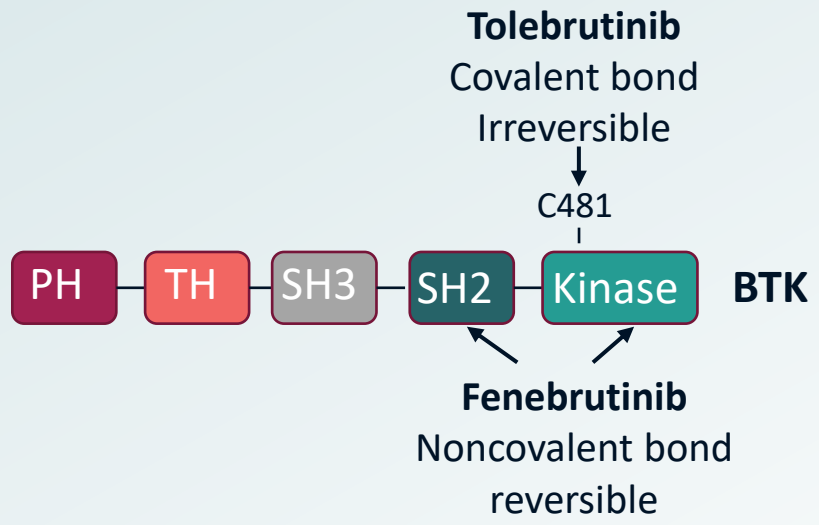
- Act selectively on BTK expressing pathologic autoreactive cells
- Cross the blood brain barrier
- Multiple mechanisms of actions
  - Anti-inflammatory effects
    - Selective modulation of B cells and B-T cell interaction (Steps 1-2 in Figure)
    - Suppression of proinflammatory microglia (Steps 3-4)
  - Structural repair
    - Remyelination (Step 5)
    - Repair of axonal injury (Step 6)

APC, antigen-presenting cell; BTK, Bruton's tyrosine kinase.

BTK Inhibitors Studied in Progressive MS

Two BTK inhibitors currently in clinical trials for non-active progressive MS

- Tolebrutinib binds to kinase domain (C481)
  - Bond is irreversible and covalent
- Fenebrutinib binds to alternate sites on the SH2 and kinase domains
  - Reversible, noncovalent bond



BTK, Bruton tyrosine kinase; PH, pleckstrin homology; SH2, Src homology 2; SH3, Src homology 3; TH, Tec homology.
Garcia-Moreno A. *Cells*. 2021;10:2560; Ringheim GE et al. *Front Immunol* 2021;12:662223.
Illustration adapted from Jayagopal LA et al. *Pract Neurol*. February 2022;29-32,48.

Ongoing Trials of BTK inhibitors

The BTK inhibitors fenebrutinib and tolebrutinib are currently in phase 3 trials to determine efficacy and safety in patients with progressive MS

Bruton's Tyrosine Kinase Inhibitor	Trial Name	Patient Population	Control Group	Primary Endpoint
Fenebrutinib	FENtrepid	PPMS	Ocrelizumab	Time to onset of composite 12-week confirmed disability progression
Tolebrutinib	HERCULES	nSPMS	Placebo	Time to onset of 6-month confirmed disability progression
Tolebrutinib	PERSEUS	PPMS	Placebo	Time to onset of 6-month confirmed disability progression

BTK, Bruton's tyrosine kinase; nSPMS, nonactive secondary progressive multiple sclerosis; PPMS, primary progressive multiple sclerosis.
ClinicalTrials.gov. Accessed January 6, 2023.