

Fenebrutinib, a Potent, Highly Selective, Noncovalent BTK Inhibitor for the Treatment of Multiple Sclerosis

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Disclosures

A Johnson is employed by Genentech, Inc., a Member of the Roche Group.

C Harp is employed by Genentech, Inc., a Member of the Roche Group.

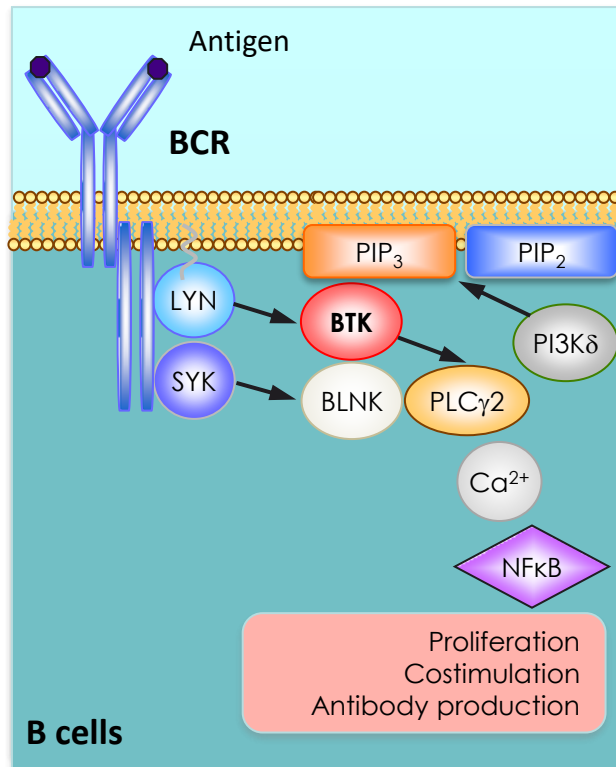
J Yu is employed by Genentech, Inc., a Member of the Roche Group.

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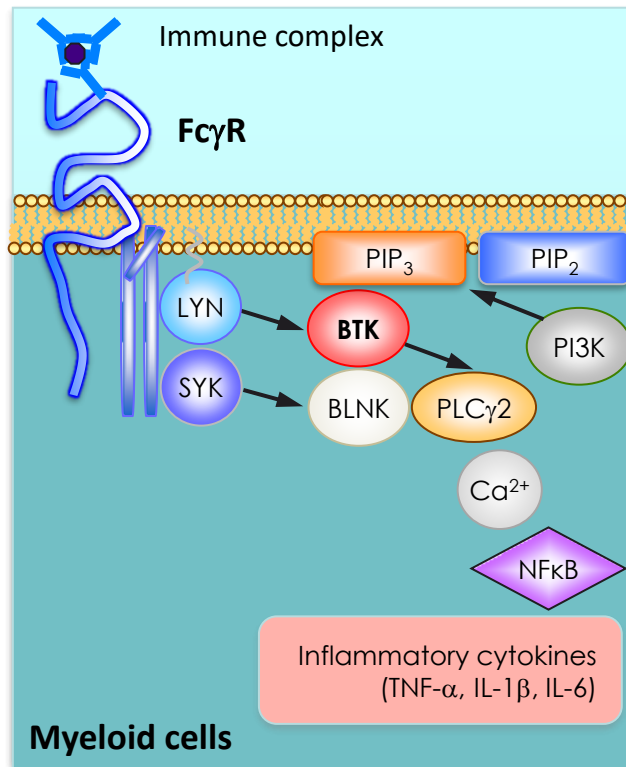
J Crawford is employed by Genentech, Inc., a Member of the Roche Group.

Bruton's tyrosine kinase (BTK) is a target in activated immune cells in MS

Adaptive immunity



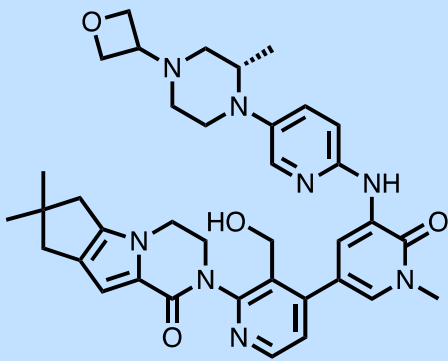
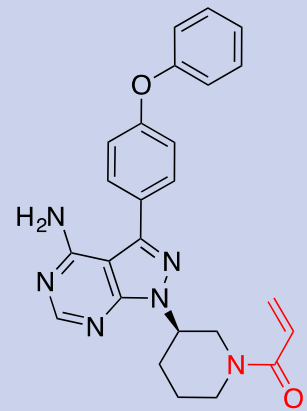
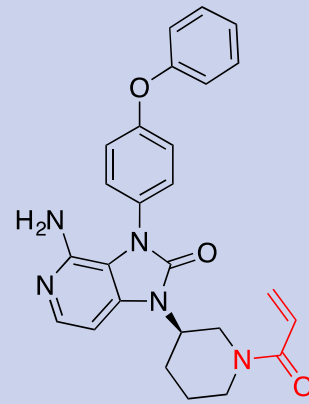
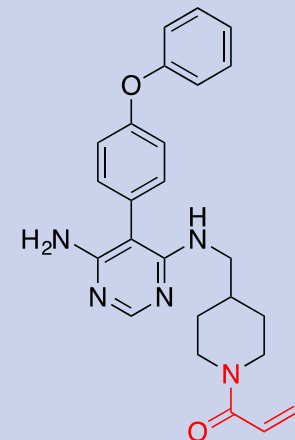
Innate immunity



BTK

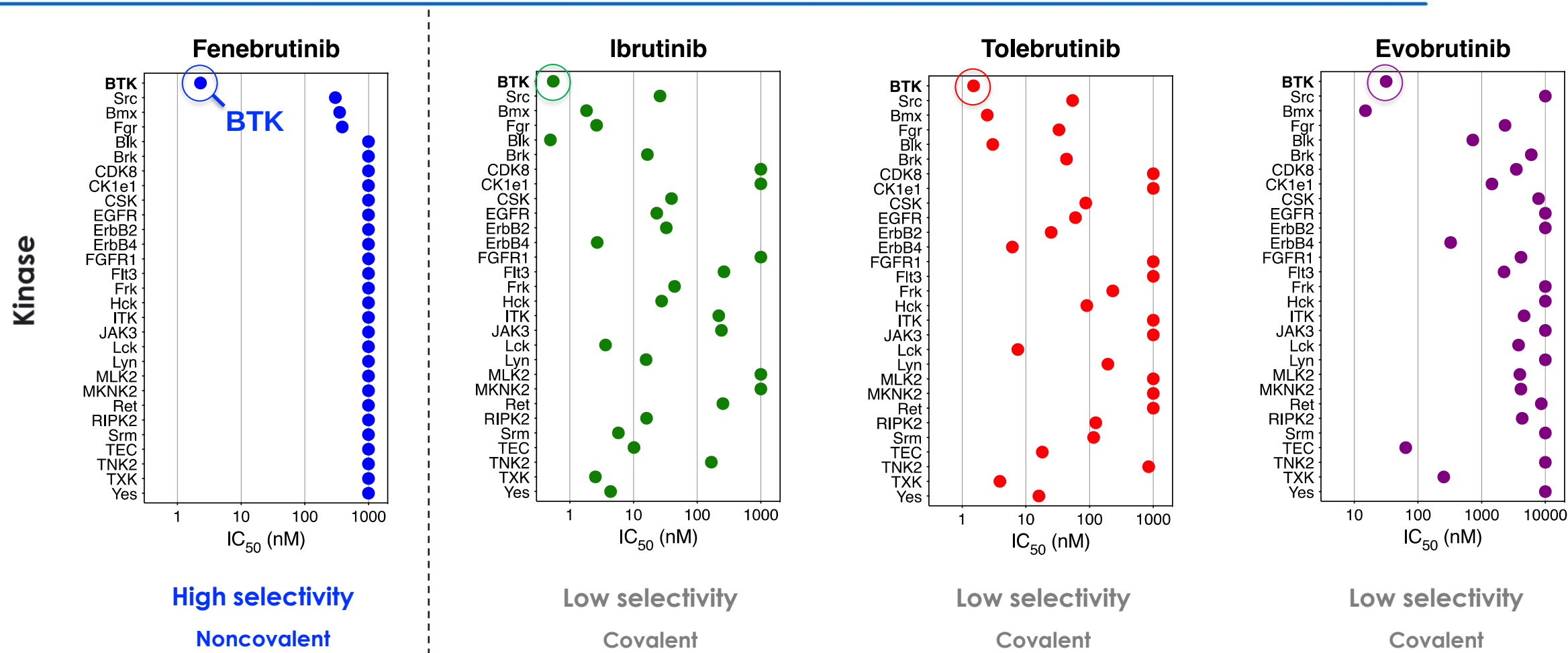
- Non-receptor tyrosine kinase¹
- In B cells and myeloid cells (macrophages, microglia)^{2,3}
- Key role in BCR and F_cR signaling¹⁻⁴
- Adaptive and innate immunity⁴
- Target in MS (activated B and myeloid cells)⁵

Fenebrutinib is a potent, highly selective, noncovalent BTK inhibitor for MS

Fenebrutinib (GDC-0853)	Ibrutinib (PCI-32765)	Tolebrutinib (PRN-2246, SAR442168)	Evobrutinib (M2951, MSC 2364447)
Phase 3	Launched	Phase 3	Phase 3
MS	Oncology	MS	MS
			
Noncovalent, reversible	Covalent, irreversible	Covalent, irreversible	Covalent, irreversible
BTK IC ₅₀ , 2 nM	BTK IC ₅₀ , 1 nM	BTK IC ₅₀ , 1 nM	BTK IC ₅₀ , 32 nM
High selectivity	Low selectivity	Low selectivity	Low selectivity

BTK IC₅₀ values determined *in vitro* using a kinase activity assay that monitors phosphorylation of a peptide substrate with ATP at its apparent K_m. BTK, Bruton's tyrosine kinase; IC₅₀, half maximal inhibitory concentration; MS, multiple sclerosis.

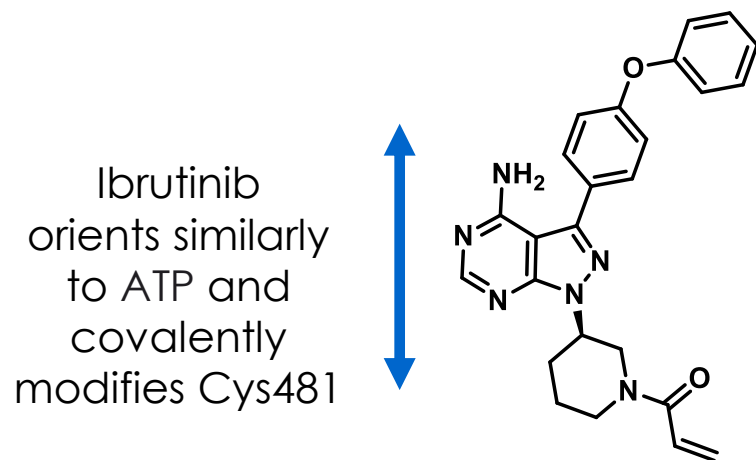
Fenebrutinib is highly selective for BTK over other kinases^{a,b}



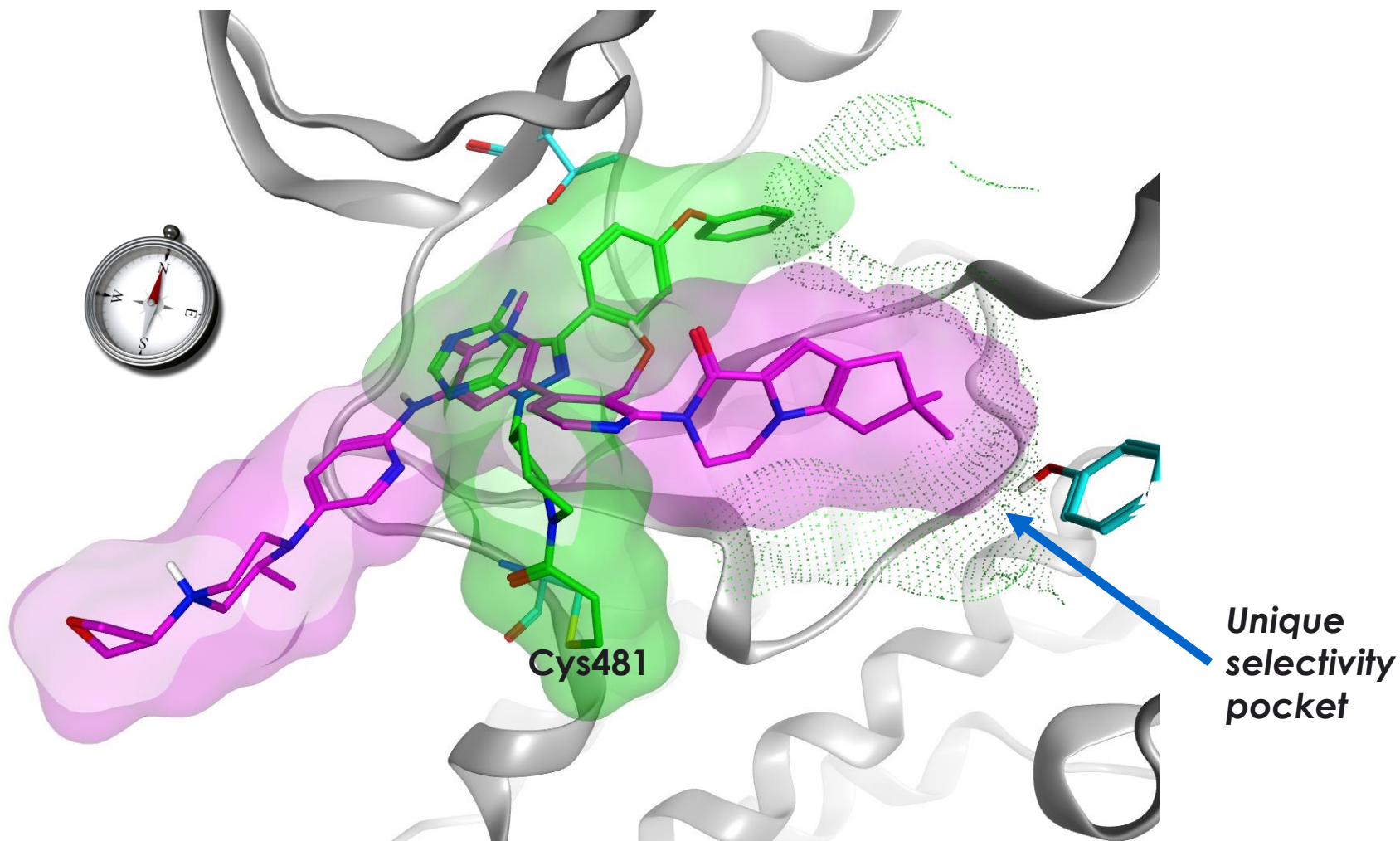
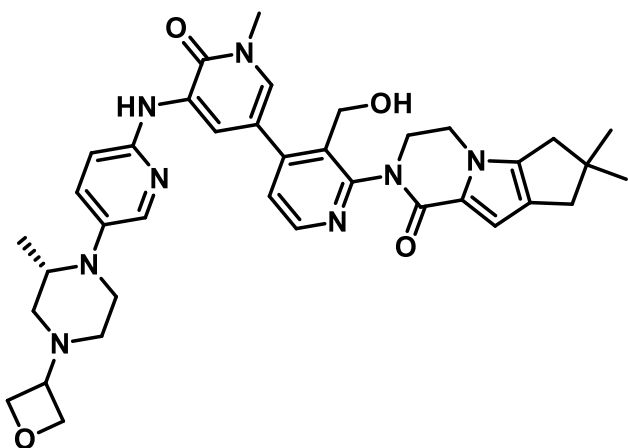
Fenebrutinib clinical safety data thus far, relative to other BTKi, appear to confirm the importance of high selectivity.

^aTo identify off targets, inhibitors were screened at 1 μ M against 219 kinases in the SelectScreen panel (ThermoFisher); evobrutinib was also tested at 10 μ M due to its weaker BTK IC₅₀. Of 218 off-target kinases tested, the following number of kinases were inhibited by >50%: fenebrutinib, 3; ibrutinib, 31; tolebrutinib, 19; evobrutinib, 18 (10 μ M), 3 (1 μ M); ^bTo determine potencies, IC₅₀ values were compared against those of kinases that were inhibited by >50% in the initial large panel screen. BTK, Bruton's tyrosine kinase; BTKi, Bruton's tyrosine kinase inhibitor; IC₅₀, half maximal inhibitory concentration.

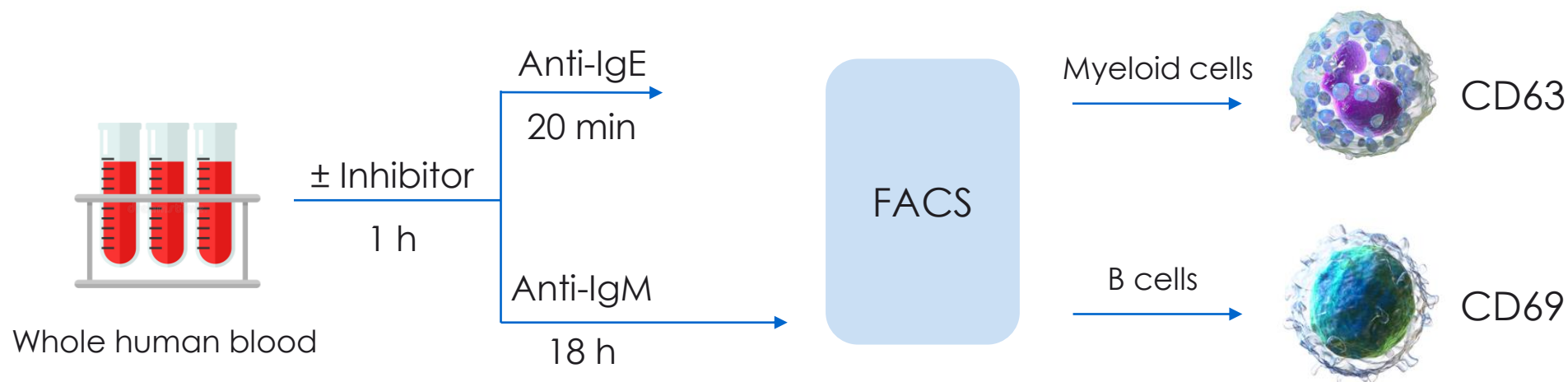
Fenebrutinib's high selectivity for BTK is due to its unique binding mode



**Fenebrutinib binds
orthogonally**



Fenebrutinib potently inhibits myeloid and B-cell activation in whole blood



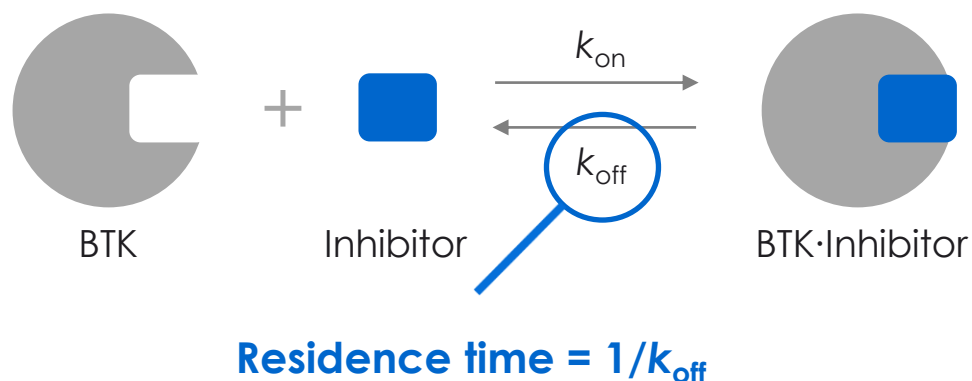
Whole human blood assay	Fenebrutinib ¹	Ibrutinib ¹	Tolebrutinib ²	Evobrutinib ³
Myeloid cell CD63 IC ₅₀ , nM	31	171	166	1660
B cell CD69 IC ₅₀ , nM	8	12	10	84

FACS, fluorescence-activated cell sorting; IC₅₀, half maximal inhibitory concentration; Ig, immunoglobulin.

1. Crawford JJ, et al. *J Med Chem* 2018;61:2227–2245; 2. Francesco MR, et al. *ACTRIMS-ECTRIMS* 2017; Abstract 200644; 3. Haselmayer P, et al. *J Immunol* 2019;202:2888–2906.

Fenebrutinib dissociates slowly from BTK, which may positively influence efficacy

Inhibitor dissociation and residence time

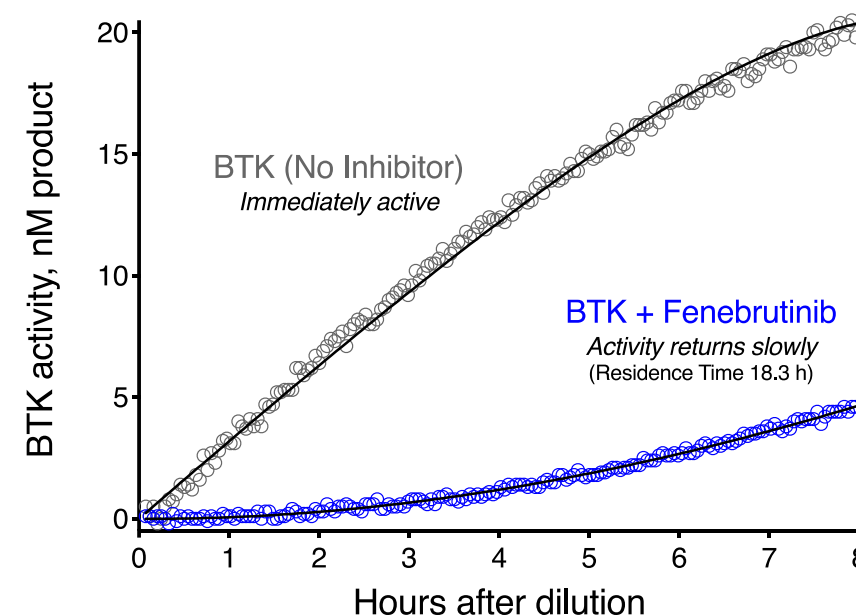


Fast dissociation $\rightarrow$ large k_{off} $\rightarrow$ short residence time

Slow dissociation $\rightarrow$ small k_{off} $\rightarrow$ long residence time

Measuring fenebrutinib dissociation *in vitro*

Activity recovery experiment¹
(room temperature, ATP 45 μ M)



Fenebrutinib's residence time *in vivo* may be <18 h (since cells have higher ATP levels than used here), but its slow dissociation from BTK may positively influence efficacy.

A noncovalent BTK inhibitor may be safer than a covalent BTK inhibitor

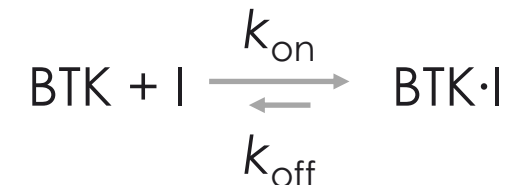
- Covalent BTK inhibitor

- Irreversible binding to BTK and off targets
- Irreversible binding to off targets **may impact safety**¹



- Noncovalent BTK inhibitor

- Reversible binding to BTK
- Slow dissociation kinetics **may positively influence efficacy**
- No irreversible binding to compromise safety



Fenebrutinib has best-in-class potential in MS

- *Fenebrutinib is a highly selective, noncovalent BTK inhibitor*
- *Fenebrutinib may be safer than less-selective, covalent BTK inhibitors*
- ***Fenebrutinib has best-in-class potential in MS***

