Dual mode of action of siponimod in secondary progressive multiple sclerosis: A hypothesis based on the relevance of pharmacological properties

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Introduction

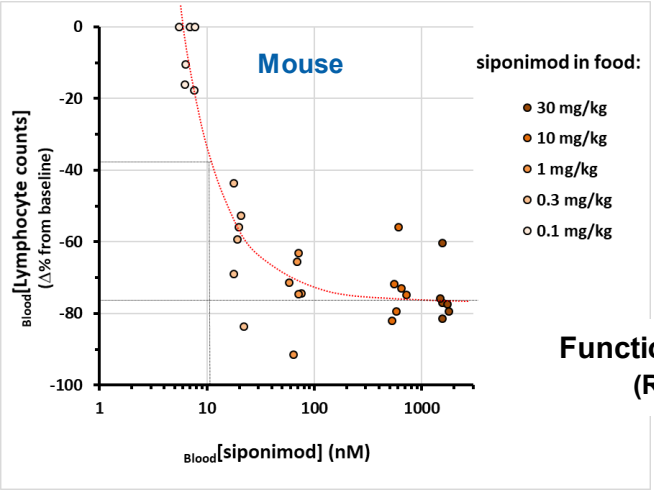
As MS evolves, peripherally driven inflammation declines while centrally driven inflammation and neurodegeneration become more prominent[1]

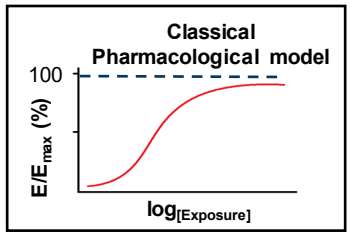
Objective

To propose a working hypothesis of a dual MoA for siponimod in SPMS, based on latest preclinical and clinical observations, and explore differences to fingolimod MoA

Siponimod MoA in the periphery and in the CNS

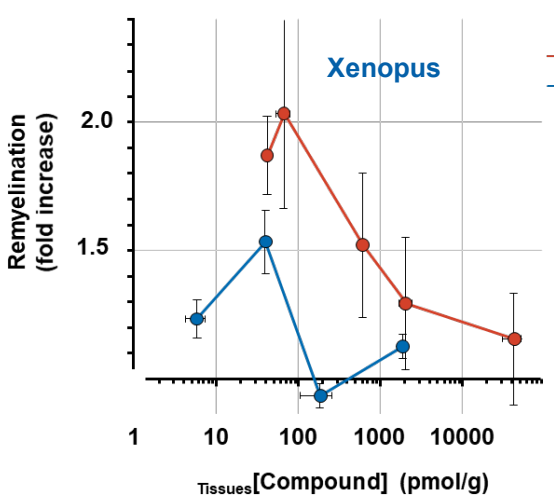
$S1P_1$-dependent effects in blood (lymphocyte count)

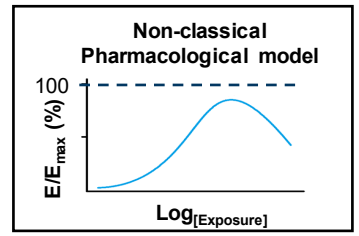




Functional antagonism = Steady E_{max} (Receptor down-modulation)

$S1P_5$-dependent effects in CNS (remyelination)





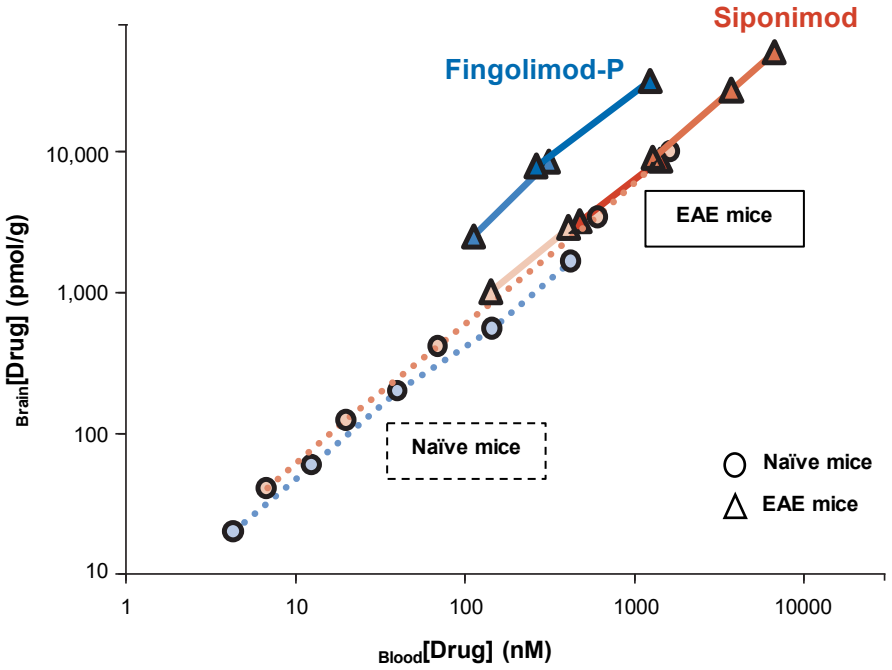
Bell-shaped dose-response curve = Receptor signaling (with desensitization at supra-maximal doses)

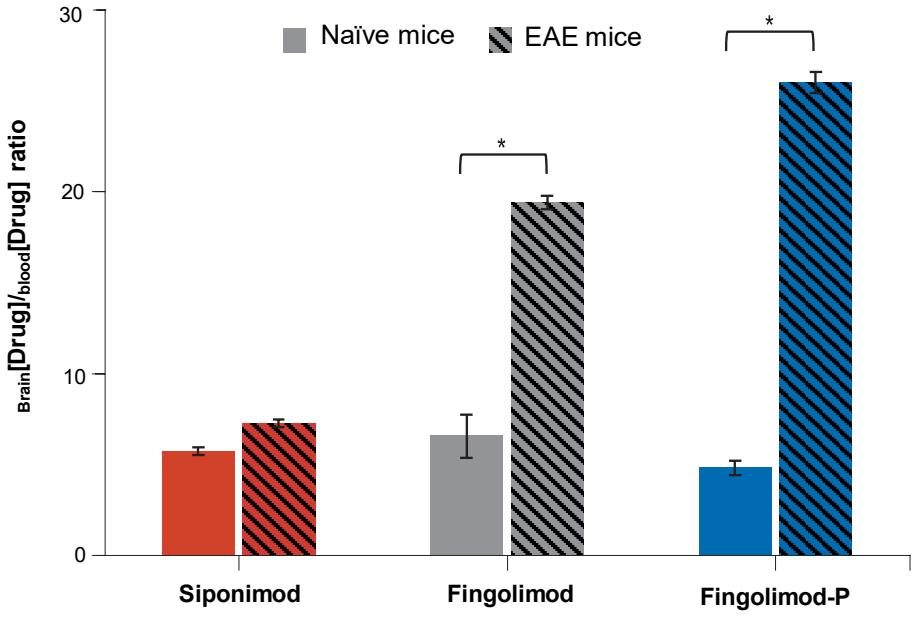
CNS, central nervous system; MoA, mechanism of action; MS, multiple sclerosis; S1P, sphingosine 1-phosphate; MS, multiple sclerosis; SPMS, secondary progressive MS.

1. Larochelle C, et al. *Trends Neurosci*. 2016;39:325–339.

$_{CNS/blood}$DER: Siponimod versus fingolimod

$_{CNS/blood}$DER of siponimod, fingolimod and fingolimod-P in naïve versus EAE mice[1,2]





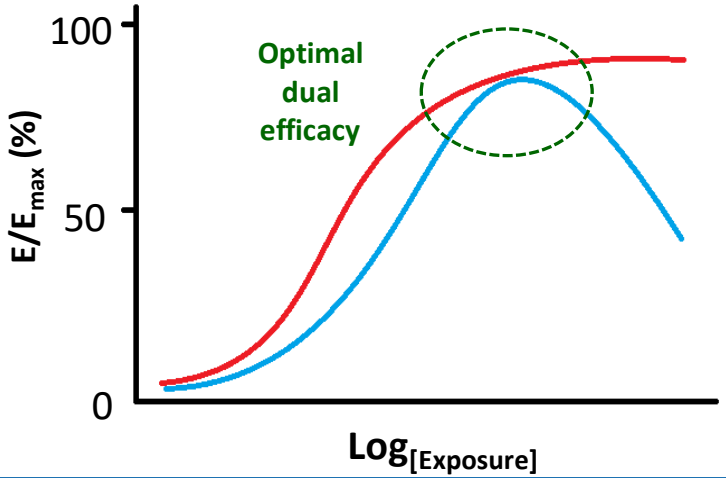
- Siponimod shows similar CNS penetration in naïve *vs* EAE mice ($_{CNS/blood}$DER: ~ 4-6)
- Fingolimod shows CNS uptake similar to siponimod in naïve mice but 3-4 fold higher CNS penetration in EAE mice ($_{CNS/blood}$DER: >20)

*p<0.05. CNS, central nervous system; DER, drug exposure ratio; EAE, experimental autoimmune encephalomyelitis; fingolimod-P, fingolimod-phosphate; PK, pharmacokinetic, S1P, sphingosine 1-phosphate.

1. Bigaud M, et al. Poster presentation at ECTRIMS. 2019. P622; 2. Bigaud M, et al. Presented at AAN. 2020; P12.1-006.

Working hypothesis about the dual MoA of siponimod

Concomitant efficacy of siponimod in blood and CNS compartments[1]



Immunomodulatory/anti-inflammatory
Blood - S1P$_1$ functional antagonism
Dose-dependent signaling and down-modulation

Pro-remyelination CNS effects
CNS - S1P$_5$ agonism
Dose-dependent signaling with desensitization

	S1P$_1$-dependent anti-inflammatory effects	S1P$_5$-dependent Pro-remyelination effects
Siponimod CNS/blood ratio: ~ 4–6	+++	+++
Fingolimod CNS/blood ratio: >20	+++	+

- **Dual MoA requires optimal (+++) exposure in both CNS and blood compartments to achieve efficacy through:**
  - S1P$_1$-dependent anti-inflammatory effects on blood lymphocytes
  - S1P$_5$-dependent pro-repair effects
- **Any treatments achieving adequate drug exposure in blood but too low/high drug exposure in CNS would show good anti-inflammatory efficacy but no or reduced pro-repair effects in the CNS**
- **CNS/blood drug exposure ratio ($_{CNS/Blood}$DER) seen as key for expression of dual MoA**

CNS, central nervous system; DER, drug exposure ratio; MoA, mechanism of action; S1P, sphingosine 1-phosphate.

1. Bigaud M, et al. Presented at AAN. 2020; P12.1-006.

Conclusions

Understanding MoA helps in differentiating siponimod from fingolimod

- **Preclinical findings show that siponimod may have the specific target selectivity ($S1P_{1,5}$) and $_{CNS/blood}$DER for a favorable expression of its dual MoA (peripheral/central anti-inflammatory and central pro-repair)**
- **In SPMS population from the EXPAND study, beneficial effects of siponimod in reducing risks for confirmed disability progression and decline in cognitive processing speed, reducing gray matter atrophy and MTR changes in normal appearing brain tissues are compatible with preclinical observations on pro-remyelination effects[1-3]**
- **PET/MRI studies including PK/PD readouts would further contribute to corroborate this hypothesis**

Disclosures

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The final responsibility for the content lies with the authors.

1. Scott J L, et al. *CNS Drugs*. 2021;35:133; 2. Arnold DL. et al. Presented at EAN. 2020; EPR1147; 3. Kappos L, et al. Presented at EAN. 2019; EPR2075.
CNS, central nervous system; DER, drug exposure ration; MoA, mechanism of action; MRI, magnetic resonance imaging; MTR, magnetization transfer ratio; PD, pharmacodynamic; PET, positron emission tomography; PK, pharmacokinetic; S1P, sphingosine 1-phosphate.