Sphingosine Kinase Inhibitors for Multiple Sclerosis

Inventor: Kevin Lynch
Multiple Sclerosis

– Most widespread disabling neurological condition of young adults around the world
  • ~2.3 million people living with MS worldwide, >400,000 in the US

– Ranks 2nd in terms of costliness compared with other chronic conditions
  • Directly and indirectly, MS costs $8,500 - $54,000/patient/yr in the US

– Currently no cure for MS. Medications are designed to lessen frequency of relapses and slow the progression of the disease.
Vasculature – New therapeutic target in MS

- BBB disruption is an early feature of MS pathogenesis, might precede immune cell infiltration
- MS lesions are associated with vascular abnormalities
  - Acute MS lesion typically center around vessels where perivascular inflammation is an early feature
  - Tight junctional abnormalities and the egress of high molecular serum proteins from the vasculature into the brain parenchyma occur in early, relapsing-remitting and late progressive MS

Spencer et al. J Neurol Neurosurg Psychiatry 2018; 89:42-52
S1P gradient: Critical regulator of vascular integrity

S1P: an essential lipid
- Rapid turnover
  - Synthesis (SphK1/SphK2), SphK2 is additionally involved in clearance of S1P from blood by liver
  - S1P Lyase and Phosphatases (degradation in tissue)
- Highly bound to plasma proteins
  - ApoM-containing HDL particles (2/3)
  - Albumin (1/3)
- “Inside-out” signaling
  - Five S1P receptors (GPCRs), S1P1R most prominent
- Compartmentalization (S1P Gradient)
  - Blood (µM) vs tissue (nM) levels

Steep S1P gradient between vascular and extravascular compartments is essential for vascular integrity.
Novel SphK2 selective inhibitor increases S1P gradient

High levels of blood S1P cause tonic stimulation of endothelial S1P1 receptors

Damage in MS causes neurovasculature to become “leaky”

SphK2 inhibitors increase the S1P gradient and counter vascular leak

Novel SphK2 selective inhibitors increase the S1P gradient

- Pharmacologic inhibition or genetic knock-out of SphK1 \textit{in vivo} causes decreased S1P levels in tissue and circulation, whereas inhibition or knock-out of SphK2 causes increased S1P levels in circulation and decreased S1P levels in tissue.

- Novel best-in-class SphK2 selective inhibitor and the only SphK inhibitor that increases circulating S1P levels so far.

Lead compound

SphK2 selective inhibitor causes circulating S1P to rise significantly.
Lead compound has efficacy in EAE model

No lymphopenia or first dose bradycardia observed, which are commonly seen side effects of currently available S1P1R agonist or S1P lyase inhibitor drugs
Intellectual Property

• US 9,421,177, expire in Aug. 2030
• US 9,908,849, expire in Aug. 2030
• PCT/US2013/025341
  – US 9,688,668, expire in Feb. 2033
  – EP 13820704.8 pending
• PCT/US2015/053315
  – US 20170298032, pending
  – EP 15846548.4, pending
• PCT/US2017/024852 pending