Sphingosine Kinase Inhibitors for Acute Kidney Injury (AKI) and Chronic Kidney Disease (CKD)

Inventor: Kevin Lynch
The Problem: Acute Kidney Injury

- Affects 1.2MM people/year in US and 300,000 people die in the US annually from AKI

- Main causes:
  - Decreased blood flow and Ischemia-Reperfusion Injury: e.g. cardiac surgery, heart attack, renal transplantation
  - Direct damage to the Kidney e.g. sepsis, nephrotoxic drugs, contrast-imaging

- Costs US >$10B/year (hospital stay, dialysis)

- No FDA-approved treatments
Endothelial Dysfunction Is a Critical Driver of AKI

- Loss of barrier integrity / vascular leak
- Microvascular dropout
- Pericyte detachment

Normal Kidney

Blood vessel

Endothelium

Interstitial space

HDL

Albumin

Damaged Kidney

Blood vessel

Endothelium

Interstitial space

Damaged endothelium

Immune cells

Cytokines

Pericyte detachment
S1P Gradient: Critical Regulator of Endothelial Barrier Integrity

- **Rapid turnover**
  - Synthesis (SphK1/SphK2), **SphK2 is additionally involved in clearance of S1P from blood by liver**
  - S1P Lyase and Phosphatases (degradation in tissue)

- **“Inside-out” signaling**
  - Five S1P receptors (GPCRs), **S1P1R most prominent**

- **Compartmentalization** (**S1P Gradient**)
  - Blood (μM) vs tissue (nM) levels

**S1P gradient maintains endothelial barrier integrity in humans**
The human body maintains the integrity of endothelial barriers via a sphingosine 1-phosphate (S1P) gradient; high levels of blood S1P cause tonic stimulation of endothelial S1P1 receptors.

Acute renal injury causes the renal vasculature to become “leaky.” Subsequent inflammation causes endothelial cells to die and pericytes to detach leading to microvascular dropout and fibrosis.

“Mixed” SphK inhibitors increase the S1P gradient and counteract vascular leak and microvascular dropout, provide protection to the endothelium during acute renal injury, preventing further decline in renal function.
How Do Dual SphK Inhibitors Increase the S1P Gradient

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

- Mixed SphK inhibitors are moderately selective for SphK2 over SphK1; *in vivo* administration increases circulating S1P levels and decreases tissue S1P levels.
Lead Compound – SKX223307

- Low double digit nanomolar potency against SphK2
- Physicochemical and ADME profiles suitable for further development
- Excellent PK - long-lived in vivo
- Pro-drugs with oral bioavailability have been developed
Pharmacodynamic Response – SKX223307 Causes Circulating S1P to Rise Significantly

- **n=3 mice per arm**
- **5 mg/kg i.p.**
- **Single dose**

The diagram shows the concentration of S1P (in μM) over time (ASAP, 2 hrs, 6 hrs, 24 hrs) for two groups: Veh (gray) and SKX223307 (black). The data indicates a significant increase in S1P levels in the SKX223307 group compared to the Veh group at all time points.
Dose-dependent Protection From AKI in the 26’ Bilateral IRI Model – SKX223307

- n=4 mice per treatment arm
- Creatinine measurement 24 hours post-reperfusion
- ‘307 given 2 hrs before surgery, i.p
- Acute Tubular Necrosis (ATN) Scoring: 5-10 fields from each of cortex, medulla, and inner medulla were evaluated scored and averaged
  - 0=normal
  - 1= <10% ATN
  - 2= 10-25% ATN
  - 3= 26-75% ATN
  - 4= >75% ATN
Significant Treatment Effect of SKX223307 in the 26’ Bilateral IRI Model

- \( n = 3 \) mice per treatment arm
- Creatinine measurement 24 hours post-reperfusion
- Arm 1: 2 mg/kg ‘307 given 2 hrs before surgery, i.p
- Arm 2: 2 mg/kg ‘307 given 1 hr after reperfusion, i.p.
Pharmacokinetics – SKX223307

<table>
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<th>PK parameters</th>
<th>Unit</th>
<th>Estimated value</th>
<th>Route of administration</th>
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<td>CL</td>
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<td>Vss</td>
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### Mean plasma concentration-time profiles of SKX223307 after single IV and IP administrations in CD1 mice (N=3/time point)

![Graph showing mean plasma concentration-time profiles](image_url)
AKI & CKD as Interconnected Syndromes

Chronic Kidney Disease (CKD):
- Affects 26MM+ people in US
- Main causes: diabetes/hypertension
- Treated with anti-hypertensive medications with only modest efficacy
- Renal failure requires dialysis or transplant
- >25% of Medicare spending (dialysis, transplant)

- Rapid (AKI) vs slow (CKD) decline in kidney function
- AKI is a major risk factor for CKD and vice versa
- Shared disease biology

SKX223307 Significantly Blocks Renal Fibrosis in the 7 Day UUO Rat Model

- n=4 mice per treatment arm
- 7 day model
- Treatment initiated day of surgery (post-surgery) and continued once a day for 7 days
- Note: treatment with SphK1 inhibitor ineffective
Intellectual Property

• Long Chain Base Sphingosine Kinase Inhibitors
  – US 9,688,668, issued in June 2017
  – EP 13820704.8 pending

• Sphingosine Kinase Inhibitors
  – US 20170298032, filed in March 2017
  – EP 15846548.4, filed in September 2015

• Sphingosine Kinase Inhibitor Amidoxime Prodrugs
  – PCT/US2017/024852, filed in October, 2017