KDDF
Korea Drug Development Fund

Asset #16
Weill Cornell Medicine

# Irreversible S1PR2 Antagonists for the Treatment of Inflammation and Fibrosis

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| **Therapeutic Area** | Immunology, Oncology, Ophthalmology | **Indications** | Fibrosis in Lung and Liver, Angiogenic Tumors, Age-Related Macular Degeneration, Cytokine Release Syndrome |
| **Modality** | Small Molecule | **Development Stage** | Hit to Lead/Lead Optimization |

## Overview

### Background

- Sphingosine-1-phosphate (S1P) is a bioactive lipid that regulates many physiological (and pathophysiological) processes
- The S1PR2 receptor is an abundant GPCR widely expressed in the endothelium, in addition to fibrogenic and immune cells, and is upregulated by inflammation
- S1PR2 modulates several metabolic pathways in the liver, including regeneration after hepatic injury
- S1PR2 is believed to be one of the key drivers of tissue injury and fibrosis, and is thus a promising therapeutic target
- Unmet Need: Novel anti-fibrotic agents that prevent disease progression by targeting pro-fibrotic factors such as S1PR2

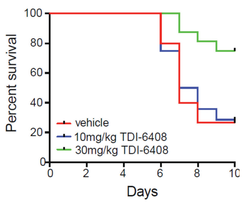
### Technology Advantages

- Irreversible antagonist (TDI-6408), resulting in S1PR2 internalization and degradation
- Demonstrated efficacy in mouse bile duct ligation model
- No significant interactions in a broad array of receptor, enzyme, hormone, and ion channel screens

## Key Data

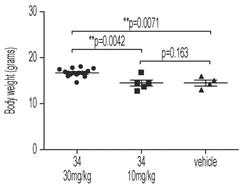
### Irreversible S1PR2 antagonists (TDI-6408) dramatically increased survival compared to vehicle control in the mouse bile duct ligation model

**A**



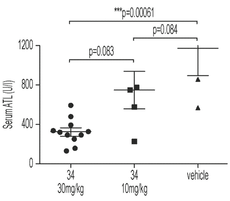

(A) A high dose of TDI-6408 conferred a significant survival benefit (73%) in bile duct ligated mice compared to low dose TDI6408 (33%) and vehicle control (27%).

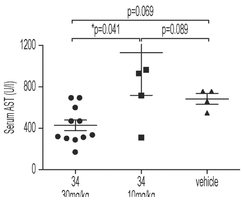
**B**




(B) Weight loss for mice treated with TDI-6408 (10 mg / kg and 30 mg / kg ) or vehicle control in bile duct ligated mice.

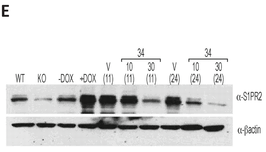
**C**




(C) Serum ALT levels and (D) serum AST levels for mice treated with TDI-6408 (10 mg / kg and 30 mg / kg) or vehicle control in bile duct ligated mice.

**E**




(E) An immunoblot analysis of liver samples of S1PR2, levels in liver tissue from a mouse BDL study.

## IP Status & Publication(s)

### Intellectual Property

**Patent Number**
PCT-US2019-021482 (2019.03.08))

**Patent Family**
PCT, US, EP

### Publication(s)

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