

Irreversible S1PR2 Antagonists for the Treatment of Inflammation and Fibrosis

Lead Inventor:

Timothy Hla, Ph.D.

Chair and Professor, Patricia K. Donohoe, Department of Surgery, Harvard Medical School



Business Development Contact:

Lukasz Kowalik

Senior Licensing and Business Development Officer

(646) 962-7052

kowalik@cornell.edu

Irreversible S1PR2 Antagonists for the Treatment of Inflammation and Fibrosis

Background & Unmet Need

- 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 Overview

- **The Technology:** Lead compounds with demonstrated efficacy in the mouse bile duct ligation model
- Irreversible S1PR2 antagonists TDI-6142 and TDI-6408 were developed based on CYM-5520 following extensive SAR studies
- TDI-6408 is a functional S1PR2 antagonist that binds irreversibly, leading to receptor endocytosis and thus overcomes the challenge of outcompeting the high concentration of circulating S1P ligand
- **PoC Data:** TDI-6408 dramatically increased survival (73% of animals) compared to vehicle control (27%) in the mouse bile duct ligation model
- TDI-6408 did not exhibit useful activity in the carbon tetrachloride (CCl₄) fibrosis model, suggesting additional fibrosis models should be explored
- **Safety:** No significant interactions in broad screen of receptors, enzymes, hormones, and ion channels

Inventors:

Timothy Hla
Irina Jilishitz

Developed in collaboration with the Tri-I TDI

Patents:

[US Application Filed](#)
[EP Application Filed](#)

Publications:

N/A

Biz Dev Contact:

Lukasz Kowalik
(646) 962-7052
kowalik@cornell.edu

Cornell Reference:

D-8089

Irreversible S1PR2 Antagonists for the Treatment of Inflammation and Fibrosis

Technology Applications

- Prevention of fibrotic disease in the lung and liver
- Treatment of highly angiogenic tumors (e.g., glioblastoma, renal cell carcinoma)
- Treatment of age-related macular degeneration (AMD)
- Treatment of cytokine release syndrome (CRS) associated with CAR-T therapy

Technology Advantages

- Irreversible antagonist, 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

Supporting Data / Figures

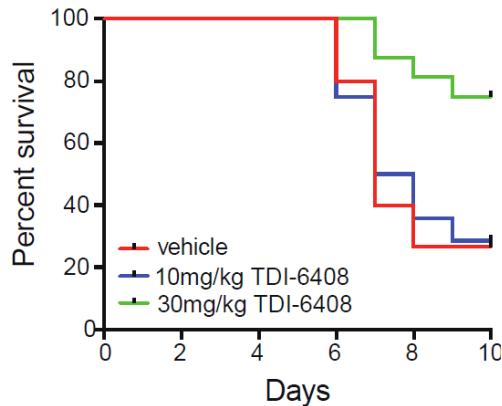


Figure 1: A high dose of TDI-6408 conferred a significant survival benefit (73%) in bile duct ligated mice compared to low dose TDI-6408 (33%) and vehicle control (27%).

The Tri-I TDI has produced an extensive preclinical data package that is available under CDA

Inventors:

Timothy Hla
Irina Jilishitz

Developed in collaboration with the Tri-I TDI

Patents:

[US Application Filed](#)
[EP Application Filed](#)

Publications:

N/A

Biz Dev Contact:

Lukasz Kowalik
(646) 962-7052
kowalik@cornell.edu

Cornell Reference:

D-8089



**Weill
Cornell
Medicine**