DISCOVERY AND DEVELOPMENT OF NOVEL ΔF508-CFTR CORRECTORS

Patron, Tyler; Valdez, Rachel; Bhatt, Priyanka; Deshpande, Asmita; Krouse, Mauri; Barsukov, Gene; Handley, Karen; Finnegan, David; Bag, Seema; Nugent, Richard; Zawistowski, Michael; Shang, Haibo; Kanawade, Abhijeet; Li, Taihao; Sui, Jinning; Kwok, Iris; Mai, Vy; Miranda, Luis; Lesser, Adam; Smith, Paul; Layer, Erin; Kaczmarek, Stefan; Kolodziej, Andrew; Fitzpatrick, Richard; Cole, Bridget

Flatley Discovery Lab, LLC. 529 Main Street, Suite 115, Charlestown, MA 02129

Abstract:
Cystic fibrosis is a devastating genetic disease that is caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. Until recently, most CF drugs focused on treating symptoms of the disease but not the underlying cause of non-functioning CFTR protein. Small molecule modulators that correct the most prevalent mutation, ΔF508-CFTR, have shown some clinical efficacy and present an exciting opportunity to deliver new breakthrough therapies to CF patients. Flatley Discovery Lab (FDL) is dedicated to the discovery and development of small molecule modulators that correct ΔF508-CFTR misfolding to enhance protein trafficking and restore CFTR-mediated chloride ion transport.

The FDL high throughput screening campaign identified FD1027382, which is a novel ΔF508-CFTR corrector that demonstrates modest activity in promoting iodide influx in CFBE cells transfected with ΔF508-CFTR. Subsequent screening in primary cultures of ΔF508-CFTR human bronchial epithelial cells (hBECs) confirmed the ability of FD1027382 (20 μM) to restore approximately 20% of the chloride ion flux response as compared to controls, Vx-809 and CF-C18. Hit to lead optimization of this FDL HTS HTS hit has delivered multiple compounds with maximum efficacy equivalent to positive controls at test concentrations ≤ 1 μM. The efficacy of FDL lead compounds in primary ΔF508-CFTR hBECs and their preclinical evaluation for safety, selectivity and oral bioavailability will be presented. (Supported by the Flatley Foundation)

Flatley Discovery Lab: Our Mission

FDL is a non-profit research organization dedicated to finding a cure for cystic fibrosis.

Our goal is to identify small molecule modulators of ΔF508-CFTR that restore CFTR-mediated chloride ion transport.

The FDL pipeline is strong with compounds being developed in multiple synergistic modalities:

- FDL Core Capabilities:
  - HTS facility operating whole-cell screening
  - Molecular biology lab to conduct mechanism of action studies and develop novel corrector assays
  - Electrophysiology lab to determine ion channel activity in human primary ΔF508-CFTR homozygous bronchial epithelial cells
  - Medicinal chemistry expertise to develop HTS hits into clinical candidates
  - Computational and in-silico modeling capabilities

Identification of ΔF508-CFTR Corrector FD1027382

Activity of FD1027382: FDL Starting Point

HTS hit FD1027382 elicits ~20% maximum response in primary ΔF508-CFTR human bronchial epithelial cells (hBEC) compared to positive control Vx-809 (AUC normalized to Vx-809 response, NAUC = 0.2)

Lead Optimization: Improved Potency & Efficacy

- The FDL lead optimization effort developed multiple analogs that achieve efficacy equivalent to Vx-809 with good potency (EC50<1 μM)
- FDL169 & FDL304 are the most promising compounds developed
- Compounds in this series are not synergistic with Vx-809

Pharmacokinetic Profile of FDL169

FDL169 was selected for preclinical development based on its superior potency, efficacy, safety, and pharmacokinetic profile

FDL Progression Strategy & Timeline

Summary

- Developed ΔF508-CFTR correctors with efficacy similar to Vx-809 and EC50<1 μM
- FDL169 was selected for preclinical development
- Excellent efficacy and potency in CF-hBE cells
- Very good safety pharmacology profile
- Pharmacokinetics that support bid or tid dosing in man
- FDL169 is not synergistic with Vx-809

Future Research at FDL

- FDL is pursuing leads that work in synergy with FDL169
- Promising compounds such as FDL1881042 work in combination with FDL169 and FDL304 to restore chloride ion transport ~2-fold that of positive control (3 μM Vx-809) in primary CF-ΔF508-CFTR human bronchial epithelial cells