FD1881042 AND FD2052160:
NOVEL CORRECTORS OF CFTR TRAFFICKING DEFECTS
Presenter Disclosure

- Andrew Kolodziej, Ph.D.
- No conflicts to disclose
- Flatley Discovery Labs is a not-for-profit company wholly supported by the Flatley Foundation
FDL Second Generation Correctors
Allele selective therapeutics for patients with CFTR misfolding mutations

- Efficacy ceiling reached with single correctors, e.g. VX809
  - Multiple defects in ∆F508-CFTR folding, multiple steps to correct
- Multiple correctors required to achieve robust correction
  - Additive mechanisms sought
- Correctors acting via distinct mechanisms may be positioned to overcome distinct folding pathway barriers
- Improved ∆F508-CFTR correction will translate to improved efficacy for treating heterozygote population
- New correctors of ∆F508-CFTR may also have significant efficacy against other CFTR folding mutations.

Three CFTR Correctors: Multiple Combinations

Chemically Distinct and Mechanistically Synergistic

MOA 1
Similar MOA to VX809
- Original Hit: FD1027382
- Lead Optimization: FDL304
- Preclinical Candidate: FDL169

MOA 2
Synergizes w VX809
- Original Hit: FD1881042
- Lead Optimization: FD2035659
- Preclinical Candidate: FDL438

MOA 3
Synergizes w VX809
- Original Hit: FD1307352
- Lead Optimization: FD2052160
- Preclinical Candidate: TBD

See Poster 38
• **FDL304** efficacy is ~90% of VX809
• EC50: 32 nM
• No synergy/additivity with VX809

• **FD2052160** efficacy is ~90% of VX809, EC50=0.5 μM
• **FD2035659** efficacy is ~40% of VX809, EC50=2.4 μM

Conditions: ΔF508-CF-hBE, 24 hr treatment; 3 μM FDL304, 10 μM FD2052160, 10 μM FD2035659
Synergistic behaviors suggest three separate and independent mechanisms

Substantial correction that exceeds 30% wt current
FD1881042 and FD2052160 Enhance ΔF508-CFTR Cell Surface Expression
CFTR N-Terminal Fragment Stabilization

FDL304
FD2052160
FD1881042
VX809
DMSO
380X
653X
837X
1172X

FD1881042: stabilizes N-terminal fragment 380X and synergizes with VX809
FD2052160: no N-terminal fragment stabilization or synergy

Data courtesy Hongyu Ren and Doug Cyr, University of North Carolina
CFTR C-Terminal Fragment Stabilization

- FD1881042 stabilizes C-terminus
- FD2052160 destabilizes C-terminal terminus

Data courtesy Hongyu Ren and Doug Cyr, University of North Carolina
Stabilization of CFTR folding mutations reflects corrector mechanistic differences

- **FDL304** corrects all mutants tested: R117H, V232D, R1070W, 1172X, W1282X, and N1303K.
- **FD1881042** may increase Band B but requires FDL304 to overcome folding defects & increase trafficking
- **FD2052160** increases C/B ratio of CFTR folding mutations R117H and R1070W

Data courtesy Hongyu Ren and Doug Cyr, University of North Carolina
FD1881042 Promotes Band B Expression
Novel Synergistic Correctors

- Two new, mechanistically distinct pathways to CFTR correction identified
- Corrector combinations elicit unprecedented, synergistic correction
- New correctors and respective pathways represent potential new routes to address non-ΔF508 associated folding defects
- 50% correction is in sight!
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