A New Combination of CFTR Modulators Corrects Processing and Reduces Chronic Inhibition of F508del-CFTR

Flatley Discovery Lab is a not-for-profit drug discovery company focused exclusively on cystic fibrosis.

Flatley Discovery Lab, Charlestown, Massachusetts United States
FDL169 is a Corrector with In-Vitro Efficacy and Potency Equivalent to Lumacaftor

Top = 1.02 +/- 0.02
EC$_{50}$ = 97 +/- 10 nM

Acute Forskolin (10 μM) + Ivacaftor (1 μM)
Maturation of F508del-CFTR is Similarly Enhanced by FDL169 and Lumacaftor

Lumacaftor

FDL169

<table>
<thead>
<tr>
<th>DMSO</th>
<th>0.625</th>
<th>1.25</th>
<th>2.5</th>
<th>5</th>
<th>10</th>
<th>0.625</th>
<th>1.25</th>
<th>2.5</th>
<th>5</th>
<th>10</th>
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</tbody>
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**Na/K ATPase**

Ratio of F508del CFTR band B and C to Na/K ATPase

<table>
<thead>
<tr>
<th></th>
<th>0.10</th>
<th>0.93</th>
<th>0.91</th>
<th>0.97</th>
<th>1.04</th>
<th>0.97</th>
<th>0.86</th>
<th>0.68</th>
<th>0.80</th>
<th>1.02</th>
<th>1.09</th>
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<tbody>
<tr>
<td>C</td>
<td>0.40</td>
<td>0.80</td>
<td>0.82</td>
<td>0.81</td>
<td>0.80</td>
<td>0.80</td>
<td>0.90</td>
<td>0.76</td>
<td>0.87</td>
<td>0.98</td>
<td>1.11</td>
</tr>
<tr>
<td>B</td>
<td>0.25</td>
<td>1.16</td>
<td>1.10</td>
<td>1.19</td>
<td>1.29</td>
<td>1.22</td>
<td>0.95</td>
<td>0.91</td>
<td>0.91</td>
<td>1.03</td>
<td>0.98</td>
</tr>
<tr>
<td>C/B</td>
<td></td>
<td></td>
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</tbody>
</table>

Band B and Band C are increased by lumacaftor and FDL169.
Where do correctors work?

- Band B
- Folding
- Translation
- Band C
- Trafficking
- Processing
- Transcription

Borrowed from Martina Gentzsch
FDL169 Protects F508del CFTR from Inhibition by Prolonged Exposure to Ivacaftor in CFhBE Cells

<table>
<thead>
<tr>
<th>Condition</th>
<th>NAUC Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>VX809</td>
<td>1.0</td>
</tr>
<tr>
<td>VX809 + cVX770 (0.2 nM)</td>
<td>-56%</td>
</tr>
<tr>
<td>VX809 + cVX770 (2.0 nM)</td>
<td>-56%</td>
</tr>
<tr>
<td>VX809 + cVX770 (200 nM)</td>
<td>-56%</td>
</tr>
<tr>
<td>FDL169</td>
<td>-20%</td>
</tr>
<tr>
<td>FDL169 + cVX770 (0.2 nM)</td>
<td>-20%</td>
</tr>
<tr>
<td>FDL169 + cVX770 (2.0 nM)</td>
<td>-20%</td>
</tr>
<tr>
<td>FDL169 + cVX770 (200 nM)</td>
<td>-20%</td>
</tr>
</tbody>
</table>
Potentiator Effect of FDL176 on Chloride Current in F508del CFhBEs is Similar to Ivacaftor

EC₅₀ = 2 +/- 0.1 nM
EC₅₀ = 127 +/- 8 nM
Max = 1.01 +/- .01
EC₅₀ = 2 +/- 0.1 nM

Conc (µM)  Fraction VX770 (1 uM)

0.0001 0.001 0.01 0.1 10 100
-0.25 0.25 0.50 0.75 1.00 1.25

FDL176
VX770

Max = 1.01 +/- .01
EC₅₀ = 127 +/- 8 nM
EC₅₀ = 2 +/- 0.1 nM
FDL176 induces less inhibition than Ivacaftor.

Concentration (μM)

<table>
<thead>
<tr>
<th>NAUC</th>
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<tbody>
<tr>
<td>0.00001</td>
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<tr>
<td>0.25</td>
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</table>

VX770

FDL176

25% Reduction

65% Reduction
Maximum Chloride Current of FDL169 + FDL176 Combination

Peak Current

Peak

FDL169

FDL176

2-3
3-4
4-5
5-6
6-7
7-8
8-9
9-10
Co-treatment Under Chronic Conditions with FDL169 + FDL176 Yields Higher Chloride Current than Lumacaftor + Ivacaftor
Summary of this talk + poster #32

• FDL169 similar *in vitro* efficacy and potency to lumacaftor
• FDL169 protects F508del CFTR from inhibition by ivacaftor
• FDL169 less protein bound in human serum
• FDL169 distributes better to the rat lung
• FDL176 has *in vitro* efficacy similar to ivacaftor
• FDL176 has less chronic inhibition than ivacaftor
• FDL176 + FDL169 combine advantages of both drugs: further reducing chronic inhibition of F508del CFTR
• FDL169 in phase 1 clinical trial
• FDL176 in preclinical development
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Jingwen Chai

**DMR**
Karen Handley

**CEO**
Richard Fitzpatrick
Figure 5: Cell surface expression of F508del CFTR at low (A) and high (B) potentiator concentrations. CFBE41o- cells were electroporated with the plasmid for HRP tagged F508del CFTR, and treated for 24 hours with either lumacaftor + ivacaftor or FDL169 + FDL176. In agreement with the electrophysiological studies, lumacaftor in combination with chronic ivacaftor treatment resulted in a lower CFTR protein at the plasma membrane than FDL169 in combination with chronic FDL176 treatment. Average 2 experiments Y axis: HRP cell surface activity, Relative Light Units