

# New Pathways to CFTR Correction

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**FD1881042 AND FD2052160:  
NOVEL CORRECTORS OF CFTR  
TRAFFICKING DEFECTS**

# Presenter Disclosure

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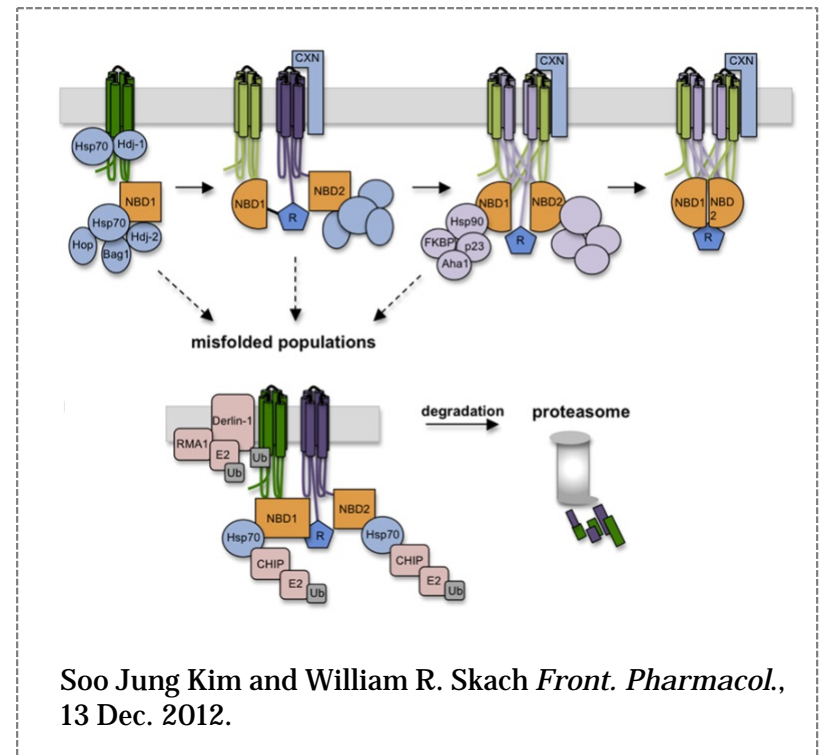
- Andrew Kolodziej, Ph.D.
- No conflicts to disclose
- Flatley Discovery Labs is a not-for-profit company wholly supported by the Flatley Foundation

# FDL Second Generation Correctors

## Allele selective therapeutics for patients with CFTR misfolding mutations

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- Efficacy ceiling reached with single correctors, e.g. VX809
  - Multiple defects in  $\Delta F508$ -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  $\Delta F508$ -CFTR correction will translate to improved efficacy for treating heterozygote population
- New correctors of  $\Delta F508$ -CFTR may also have significant efficacy against other CFTR folding mutations.

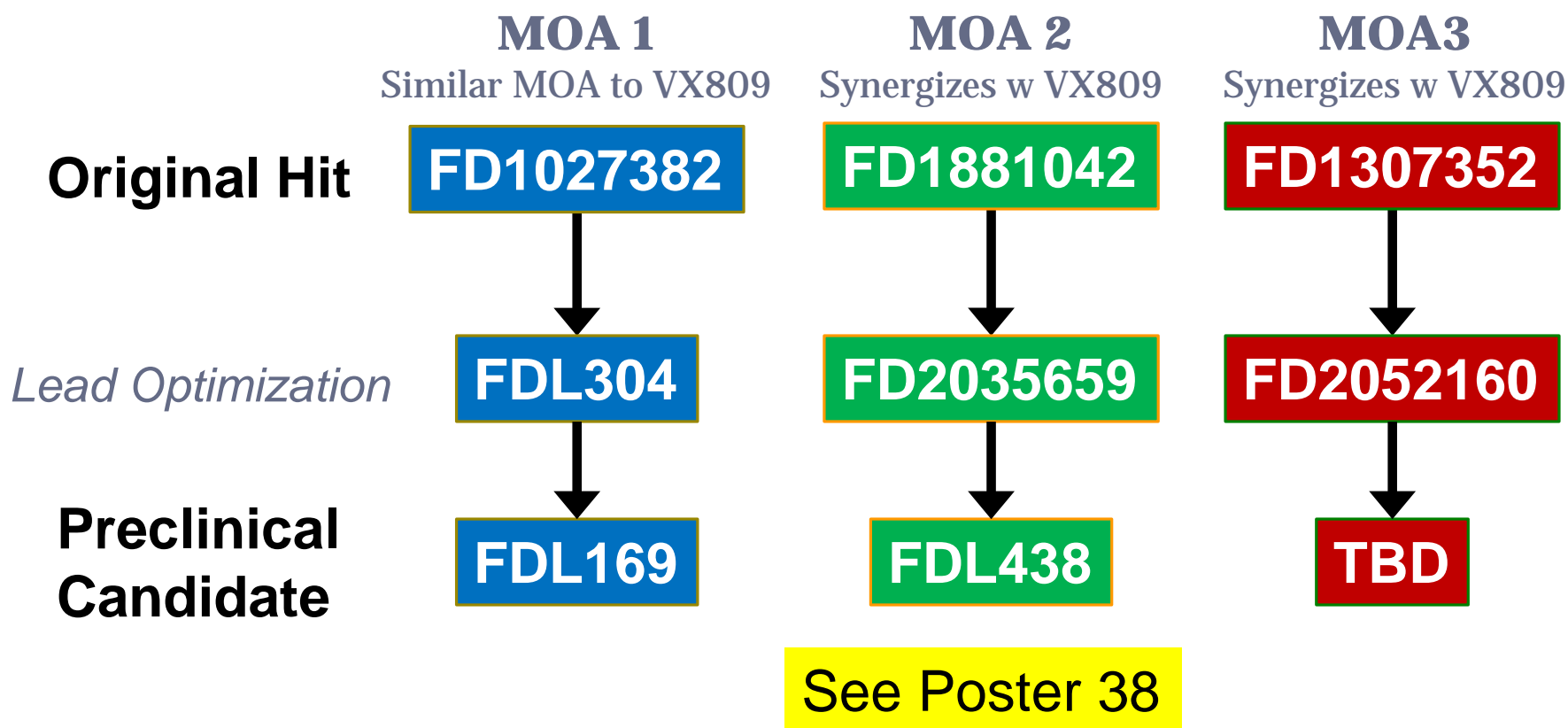


Soo Jung Kim and William R. Skach *Front. Pharmacol.*,  
13 Dec. 2012.

# Three CFTR Correctors: Multiple Combinations

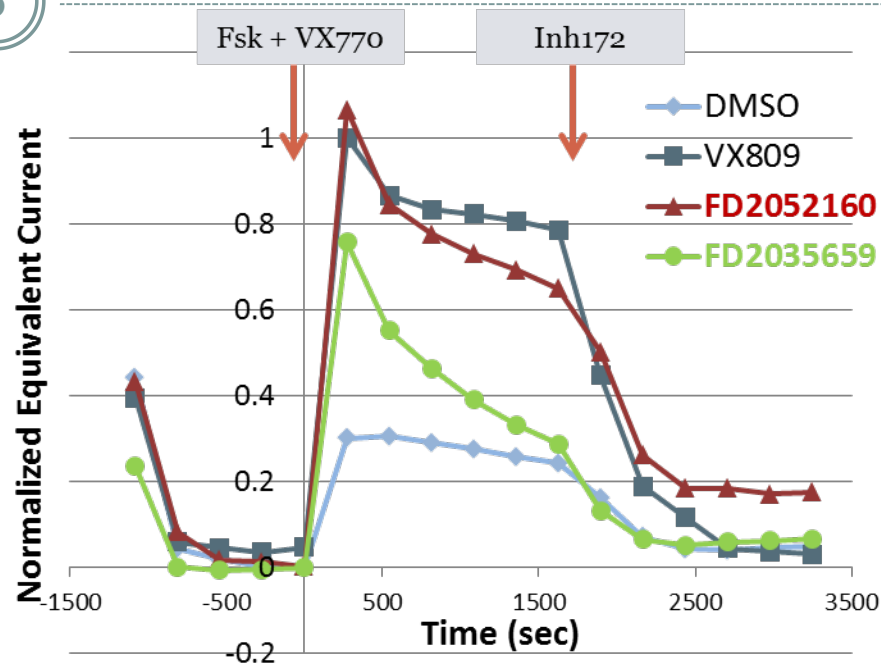
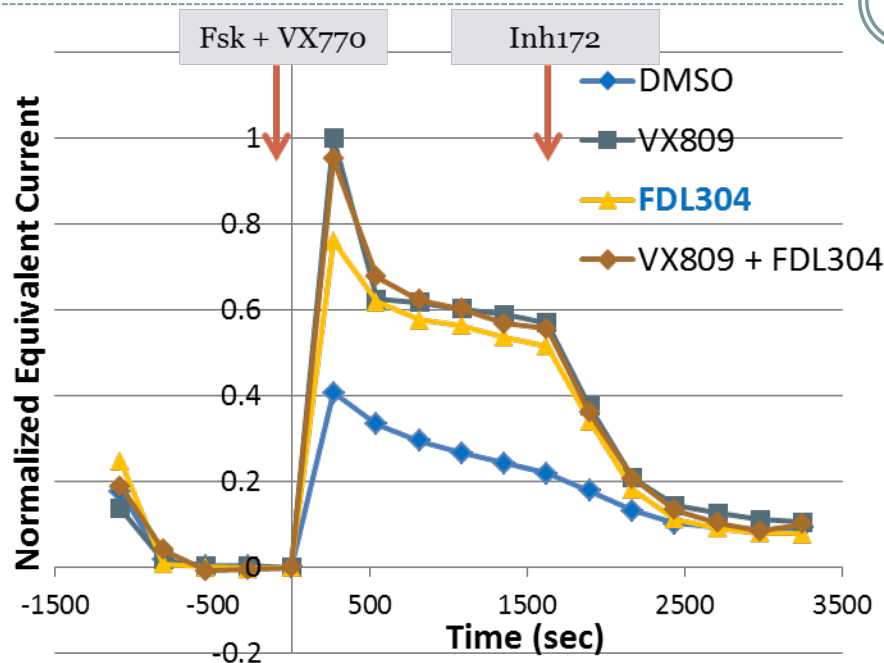
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## Chemically Distinct and Mechanistically Synergistic



# FDL Correctors: Equivalent Current Assay

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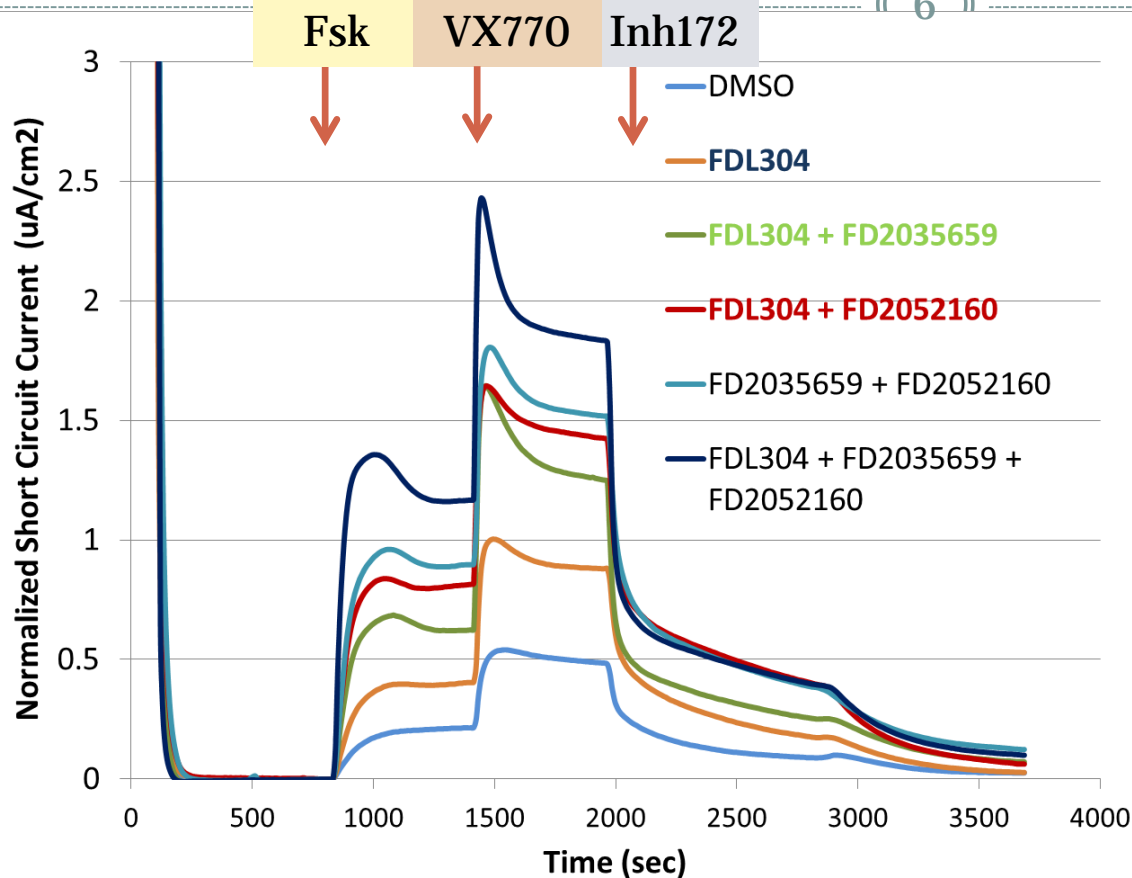
- **FDL304** efficacy is ~90% of VX809
- EC50: 32 nM
- No synergy/additivity with VX809

- **FD2052160** efficacy is ~90% of VX809, EC50=0.5  $\mu$ M
- **FD2035659** efficacy is ~40% of VX809, EC50=2.4  $\mu$ M

Conditions:  $\Delta$ F508-CF-hBE, 24 hr treatment; 3  $\mu$ M FDL304, 10  $\mu$ M FD2052160, 10  $\mu$ M FD2035659

# Corrector Combinations TRIPLE VX809 Efficacy

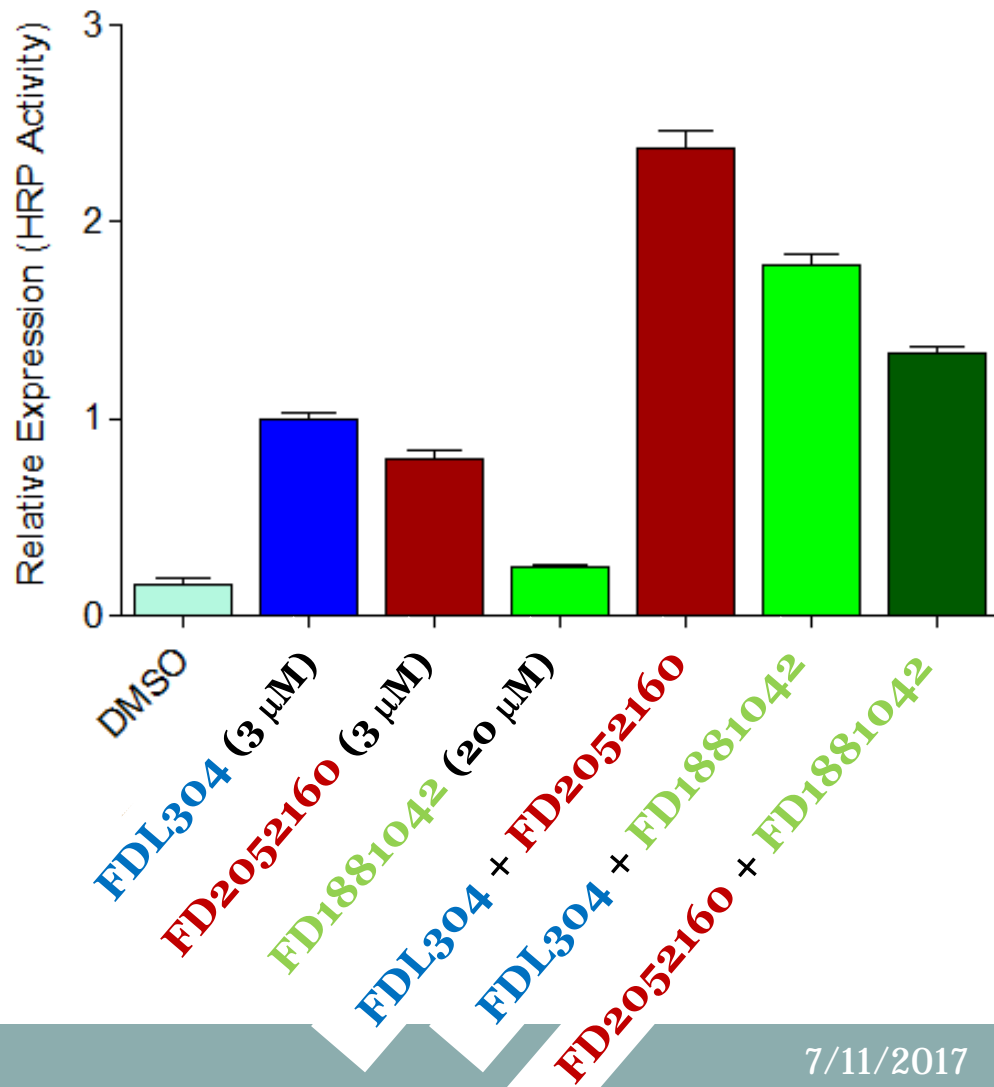
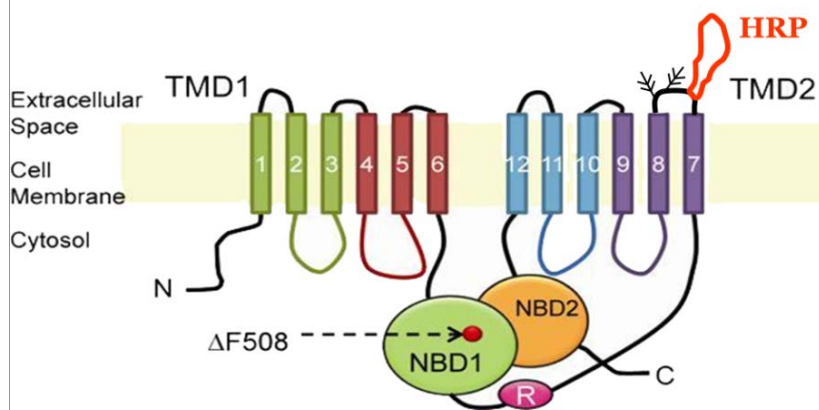
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Combination	Relative Efficacy
<b>FDL304</b>	<b>0.87</b>
<b>FD2035659</b>	<b>0.44</b>
<b>FD2052160</b>	<b>1.35</b>
<b>FDL304 + FD2035659</b>	<b>1.99</b>
<b>FDL304 + FD2052160</b>	<b>2.16</b>
<b>FDL304 + FD2035659 + FD2052160</b>	<b>3.93</b>
<b>VX809 + FD2035659</b>	<b>1.84</b>
<b>VX809 + FD2052160</b>	<b>1.90</b>
<b>VX809 + FD2035659 + FD2052160</b>	<b>3.00</b>
<b>FD2035659 + FD2052160</b>	<b>2.75</b>

- Synergistic behaviors suggest three separate and independent mechanisms
- Substantial correction that exceeds 30% wt current

# FD1881042 and FD2052160 Enhance $\Delta$ F508-CFTR Cell Surface Expression



# CFTR N-Terminal Fragment Stabilization

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**FD1881042:**  
stabilizes N-terminal fragment 380X and synergizes with VX809

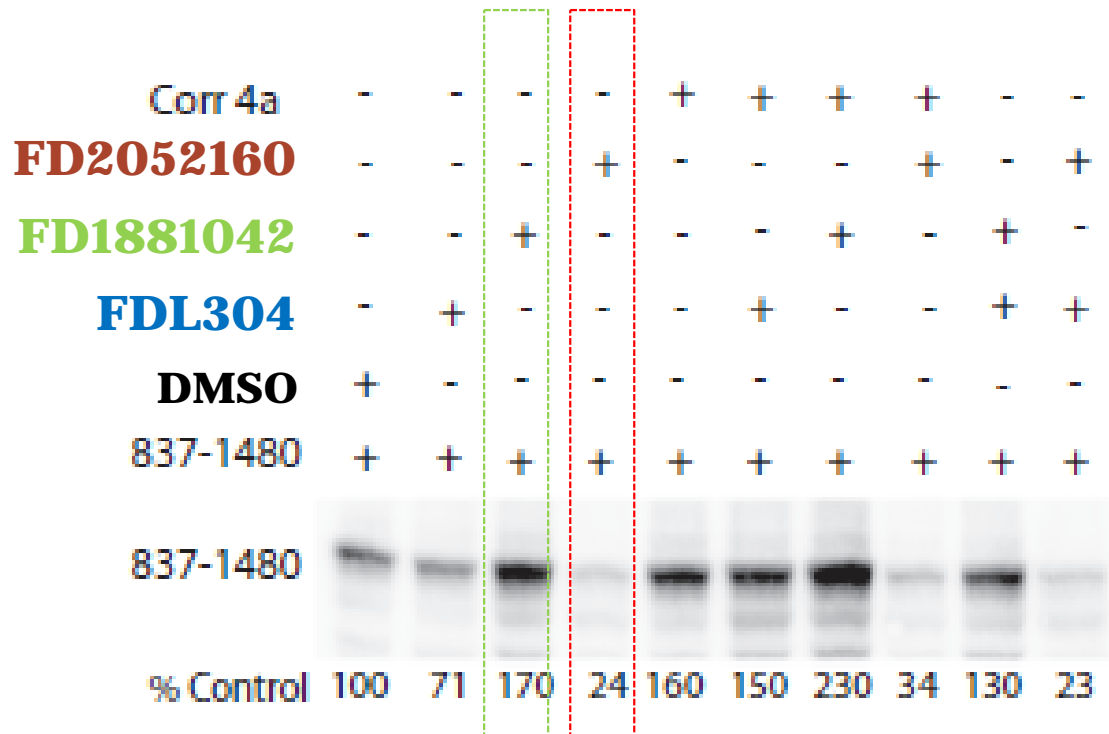
**FD2052160:** no N-terminal fragment stabilization or synergy

Data courtesy Hongyu Ren and Doug Cyr, University of North Carolina



# CFTR C-Terminal Fragment Stabilization

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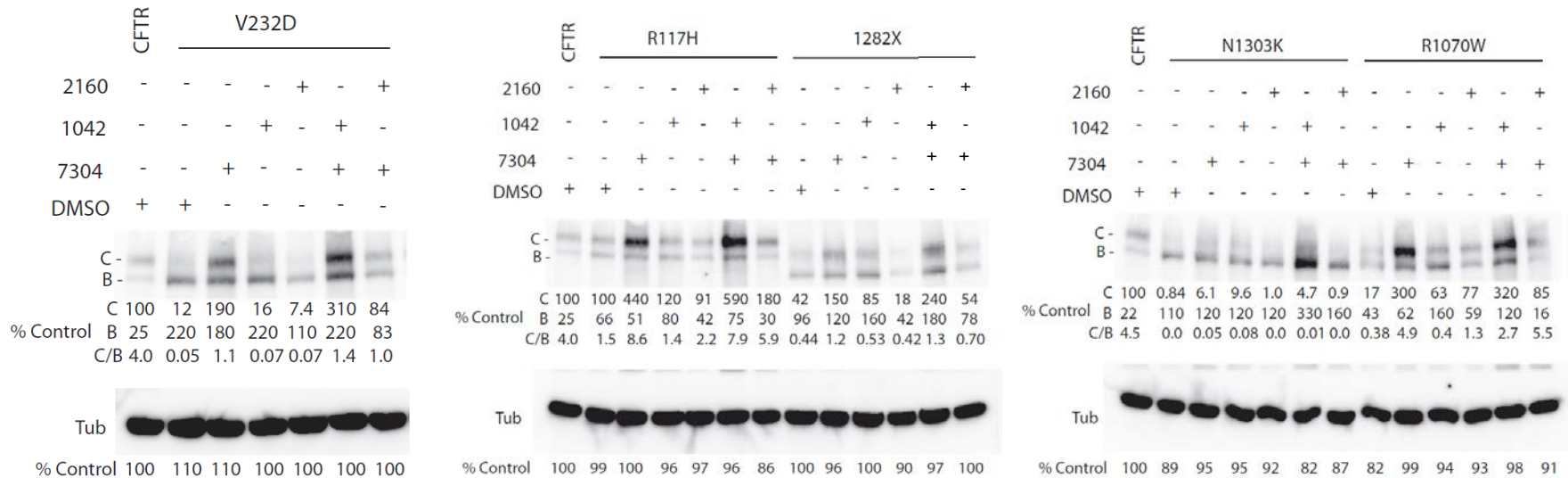


- **FD1881042** stabilizes C-terminus
- **FD2052160** destabilizes C-terminal terminus

Data courtesy Hongyu Ren and Doug Cyr, University of North Carolina

# Stabilization of CFTR folding mutations reflects corrector mechanistic differences

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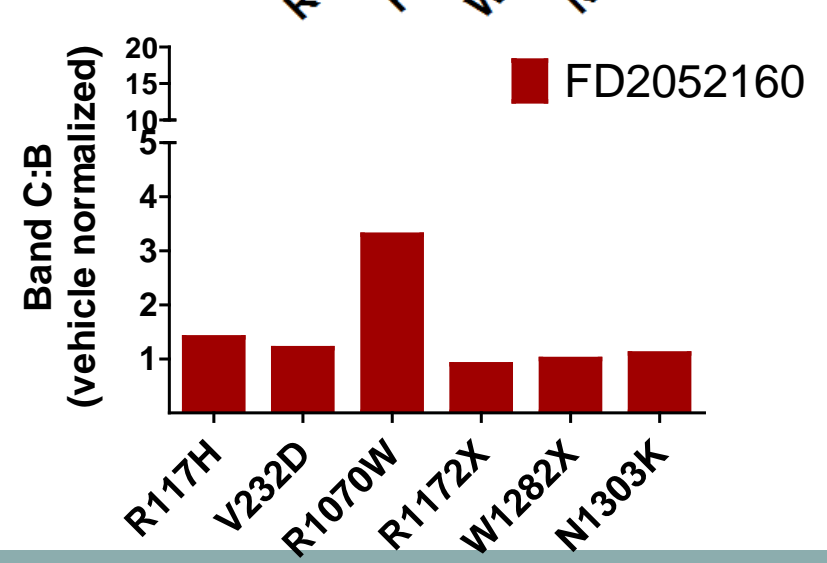
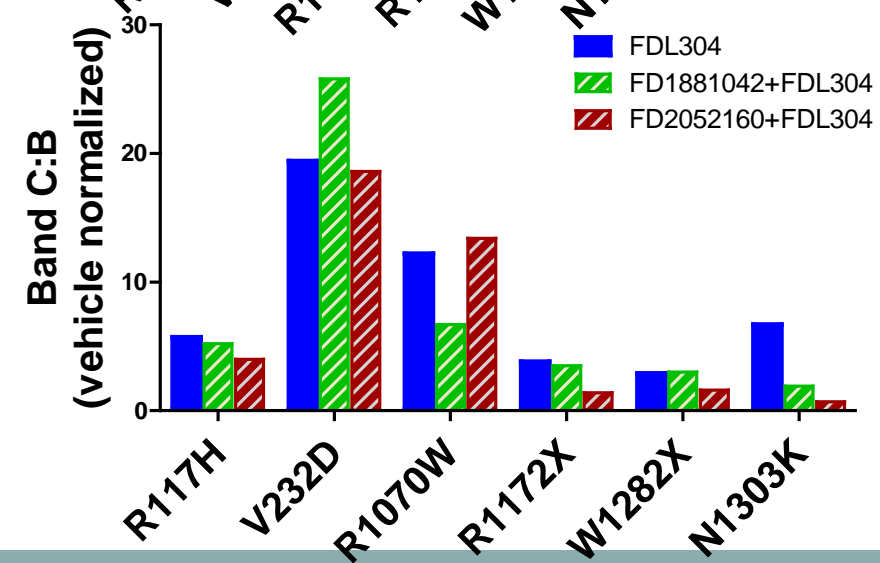
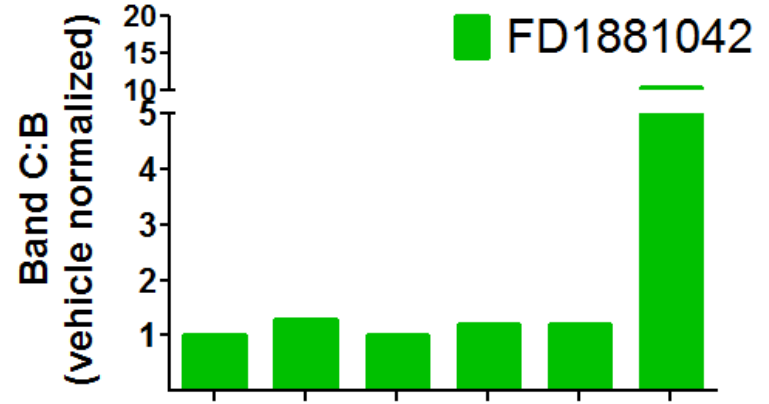
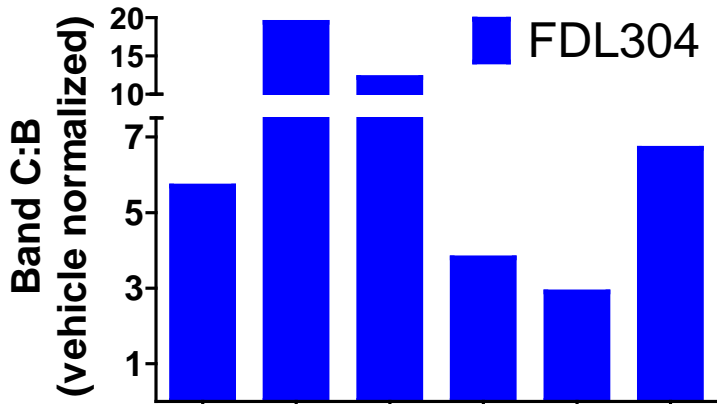


- **FDL304** corrects all mutants tested: R117H, V232D, R1070W, 1172X, W1282X, and N1303K.
- **FD1881042** may increase Band B but requires FDL304 to overcome folding defects & increase trafficking
- **FD2052160** increases C/B ratio of CFTR folding mutations R117H and R1070W

Data courtesy Hongyu Ren and Doug Cyr, University of North Carolina

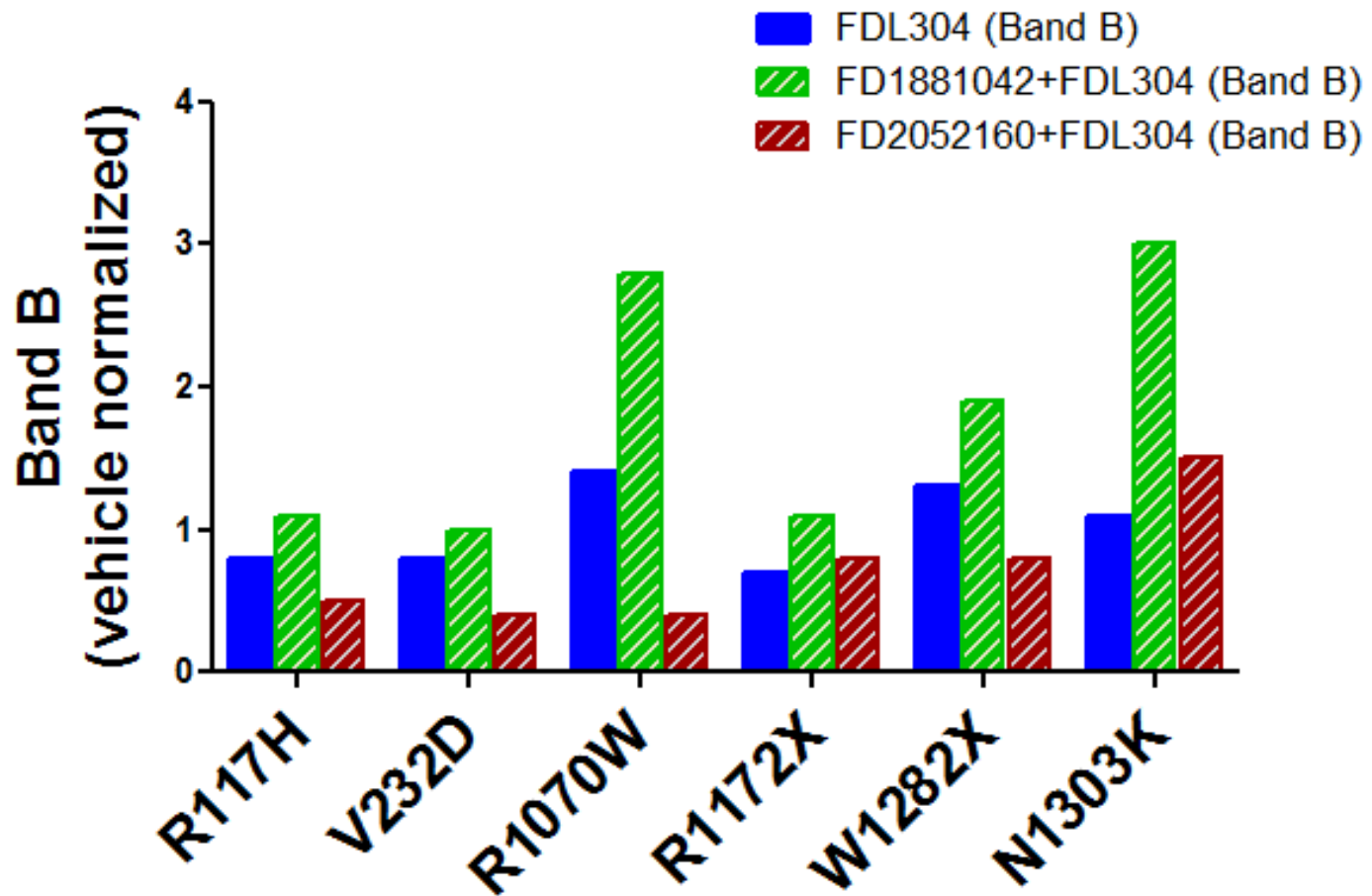
# Mutant CFTR Correction: C/B

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# FD1881042 Promotes Band B Expression

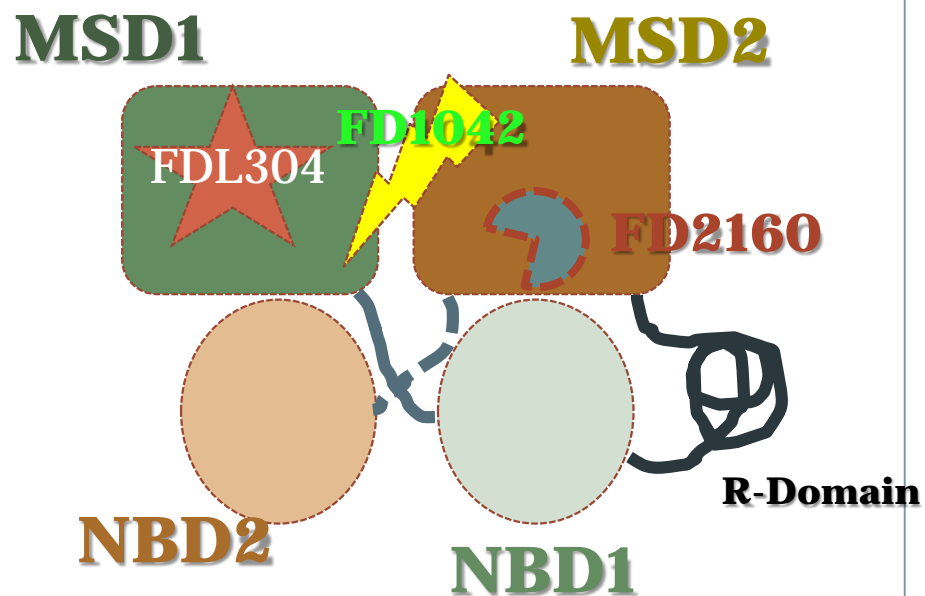
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# Novel Synergistic Correctors

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- 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- $\Delta F508$  associated folding defects
- 50% correction is in sight!



# Acknowledgements

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