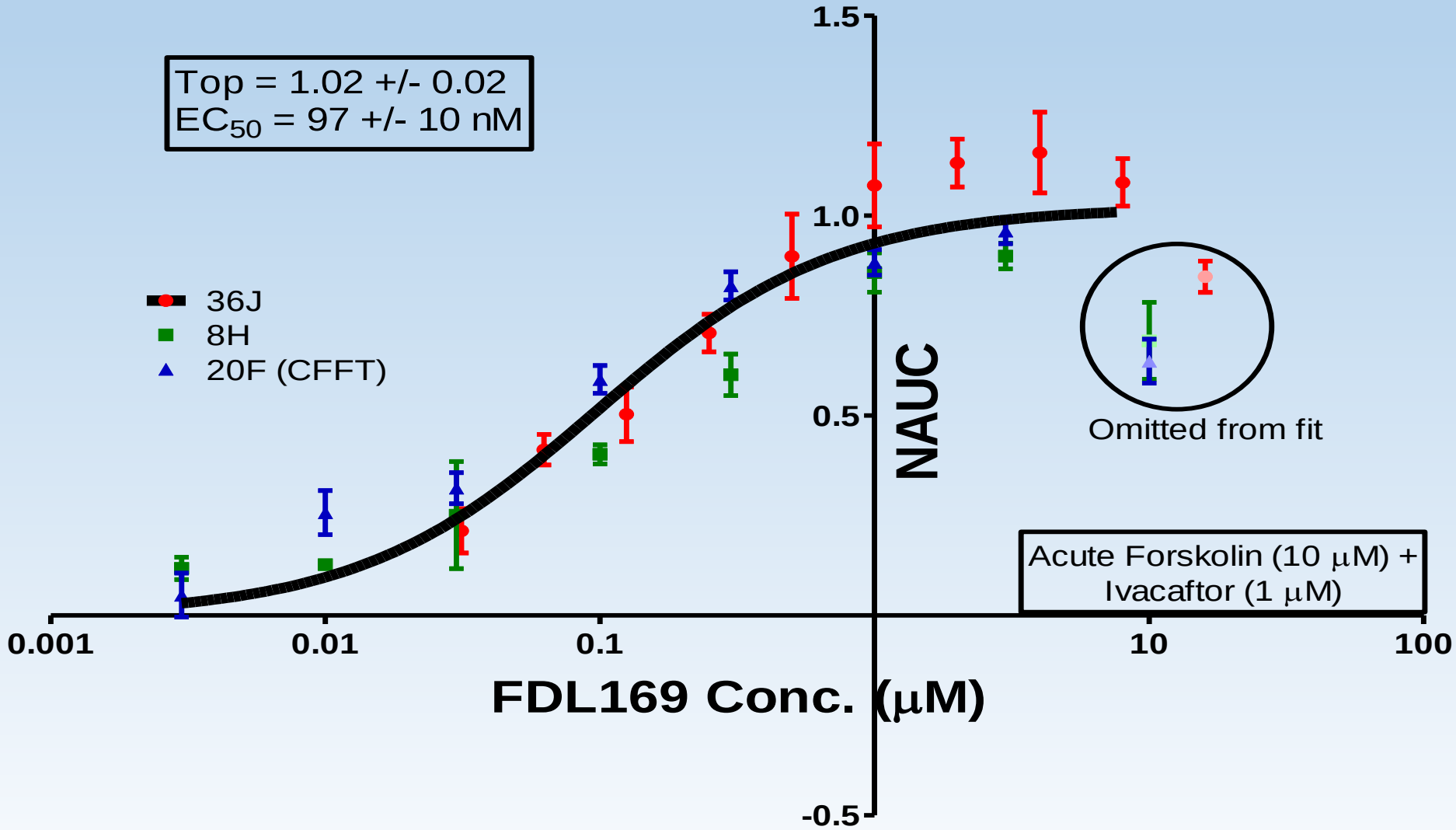
A New Combination of CFTR Modulators Corrects Processing and Reduces Chronic Inhibition of F508del-CFTR

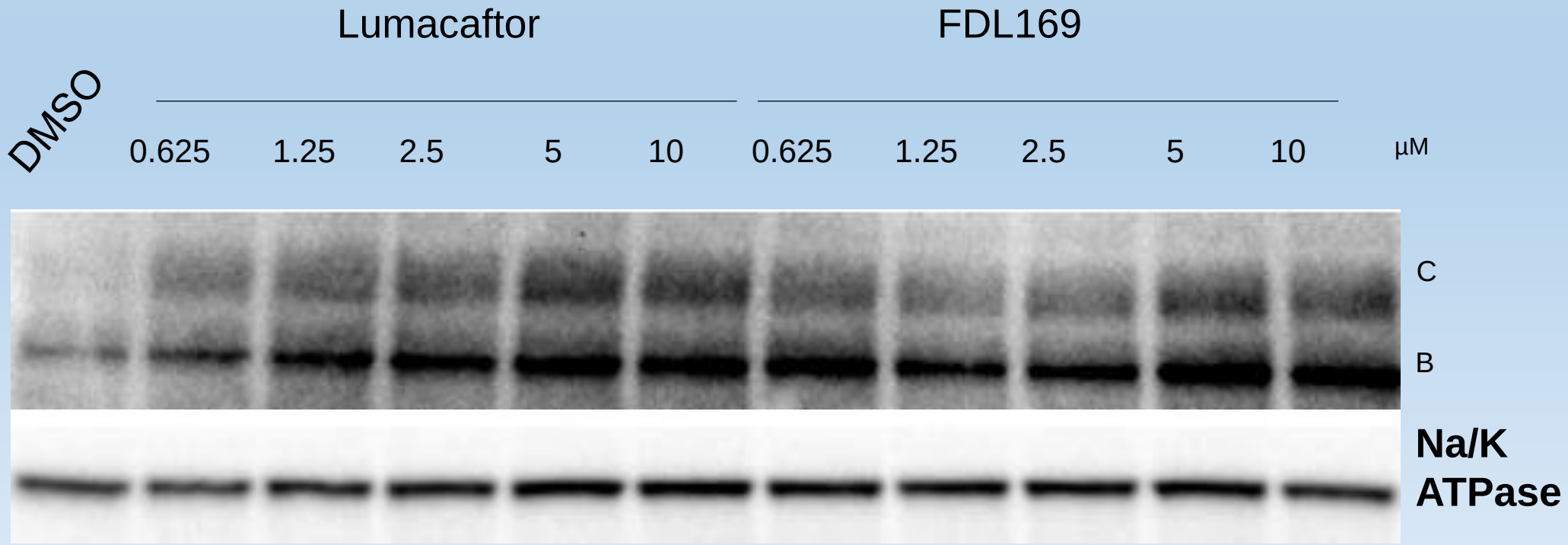
Flatley Discovery Lab is a not-for-profit drug discovery company focused exclusively on cystic fibrosis.

Flatley Discovery Lab, Charlestown, Massachusetts United States

FDL169 is a Corrector with In-Vitro Efficacy and Potency Equivalent to Lumacaftor



Maturation of F508del-CFTR is Similarly Enhanced by FDL169 and Lumacaftor

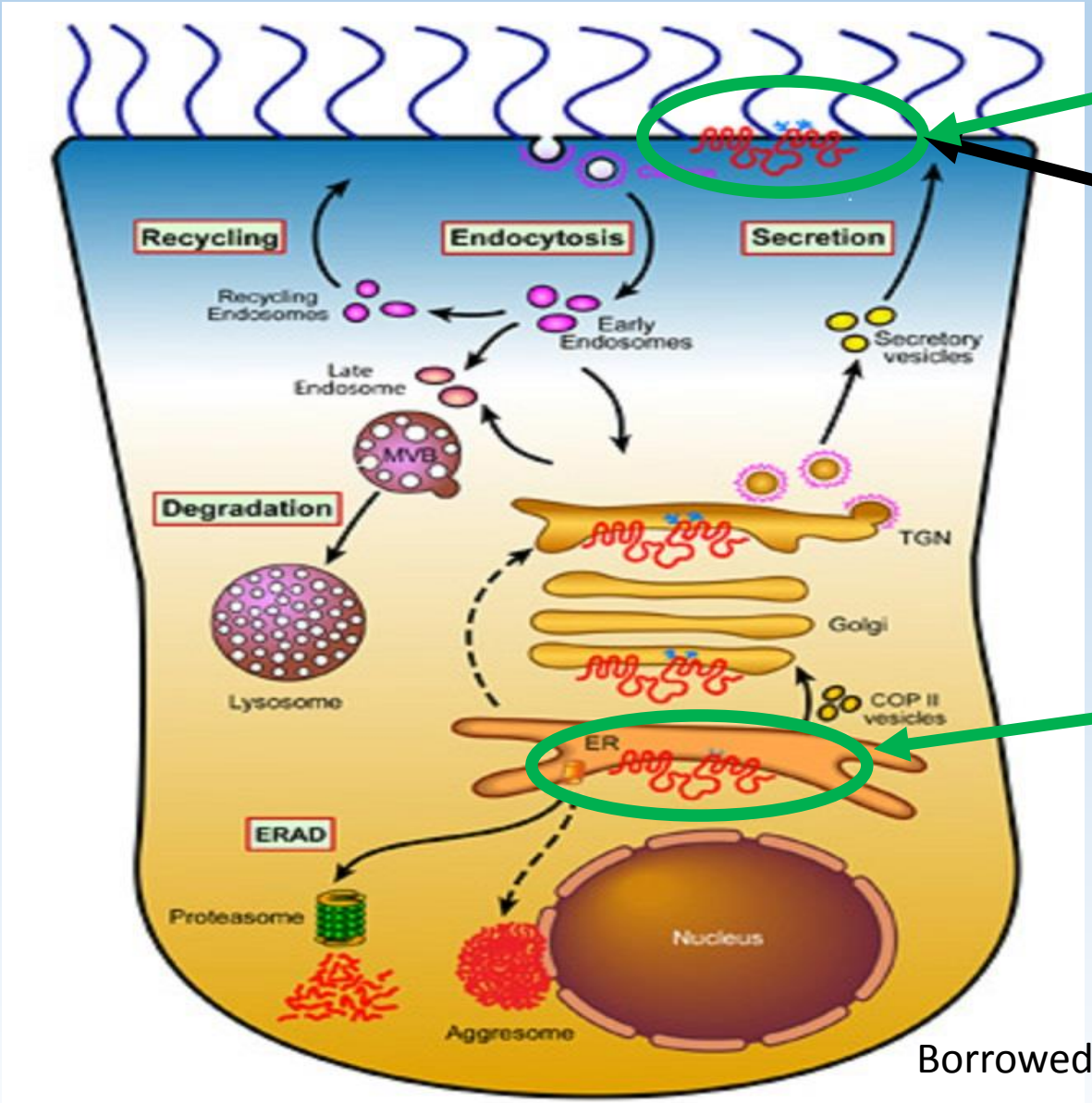


Ratio of F508del CFTR band B and C to Na/K ATPase

C	0.10	0.93	0.91	0.97	1.04	0.97	0.86	0.68	0.80	1.02	1.09
B	0.40	0.80	0.82	0.81	0.80	0.80	0.90	0.76	0.87	0.98	1.11
C/B	0.25	1.16	1.10	1.19	1.29	1.22	0.95	0.91	0.91	1.03	0.98

Band B and Band C are increased by lumacaftor and FDL169

Where do correctors work?



Band C

CFTR in the membrane

Trafficking

Processing

Band B

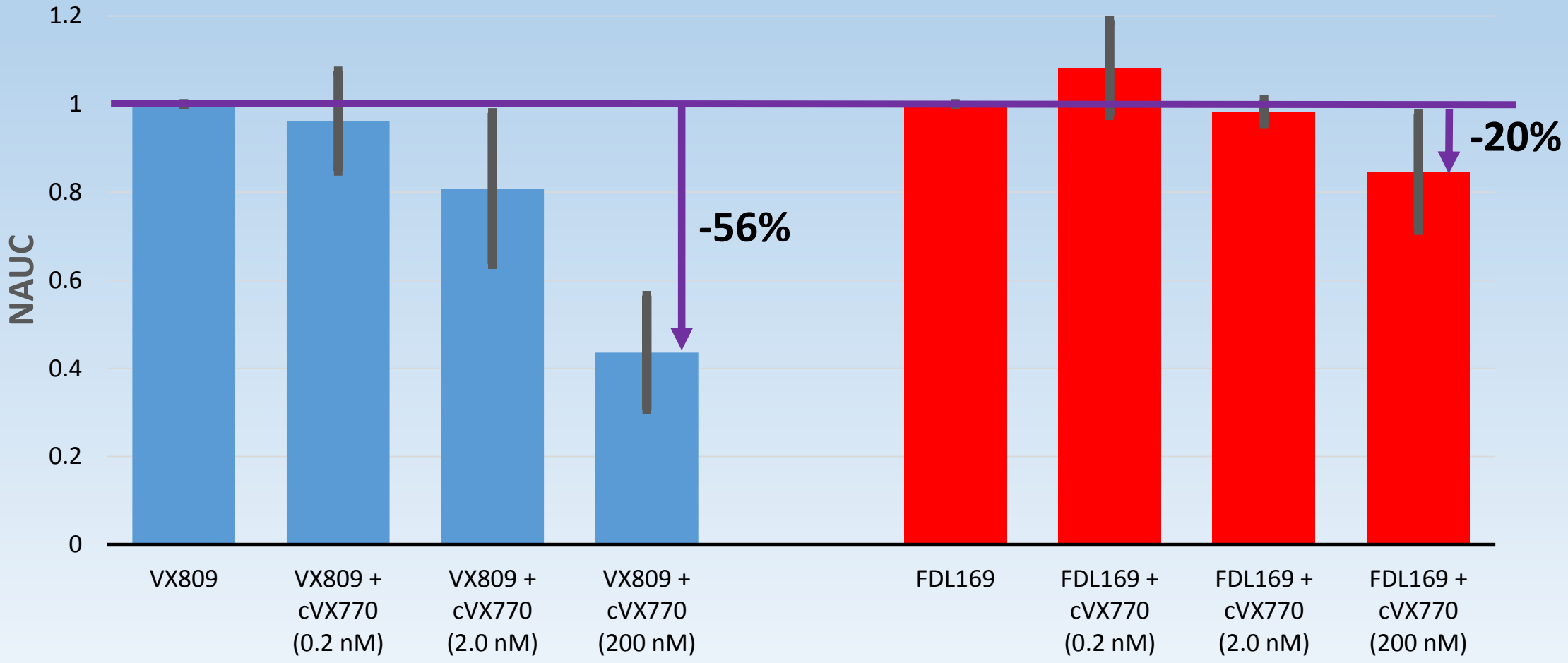
Folding

Translation

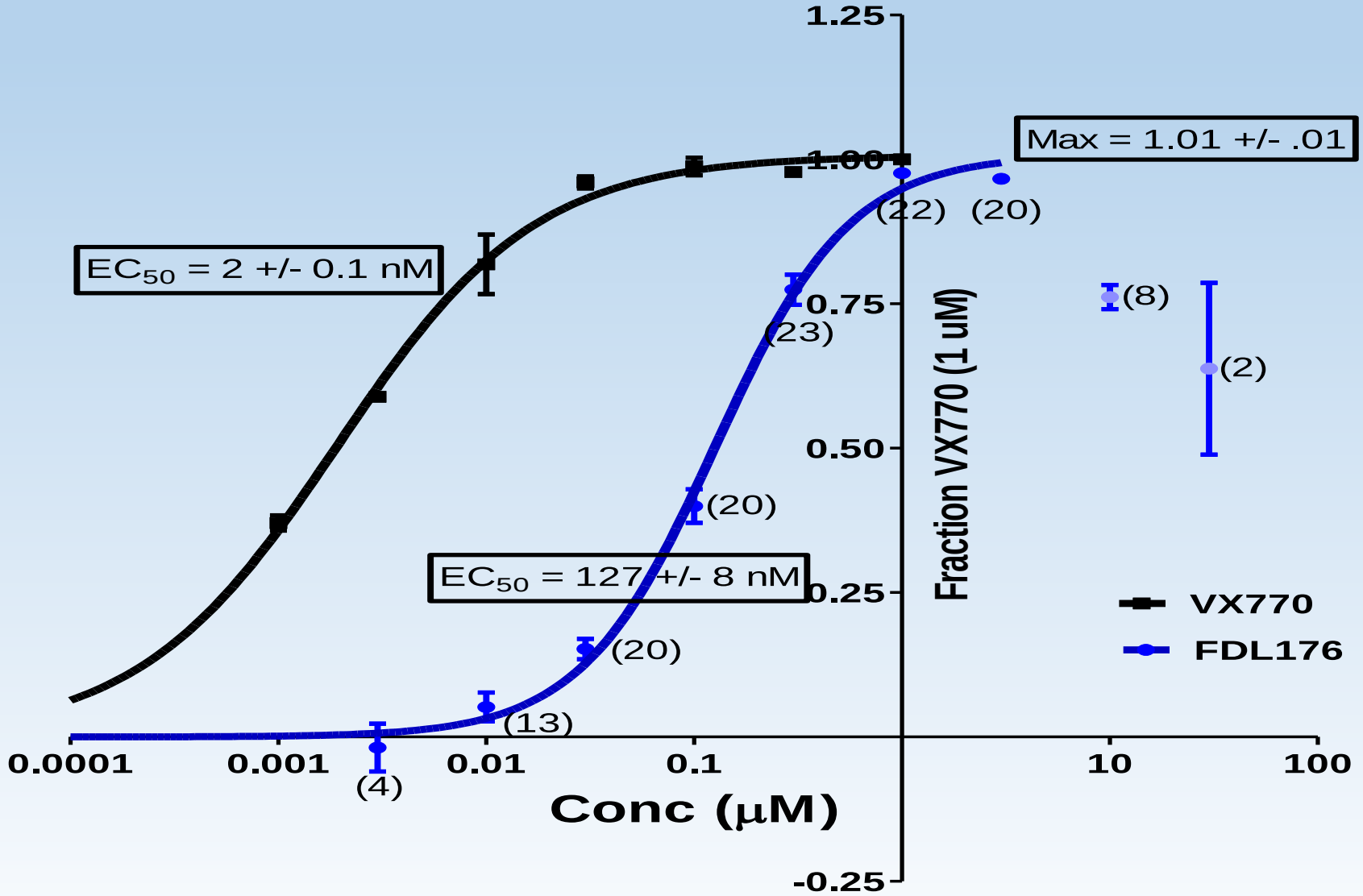
Transcription

Borrowed from Martina Gentzsch

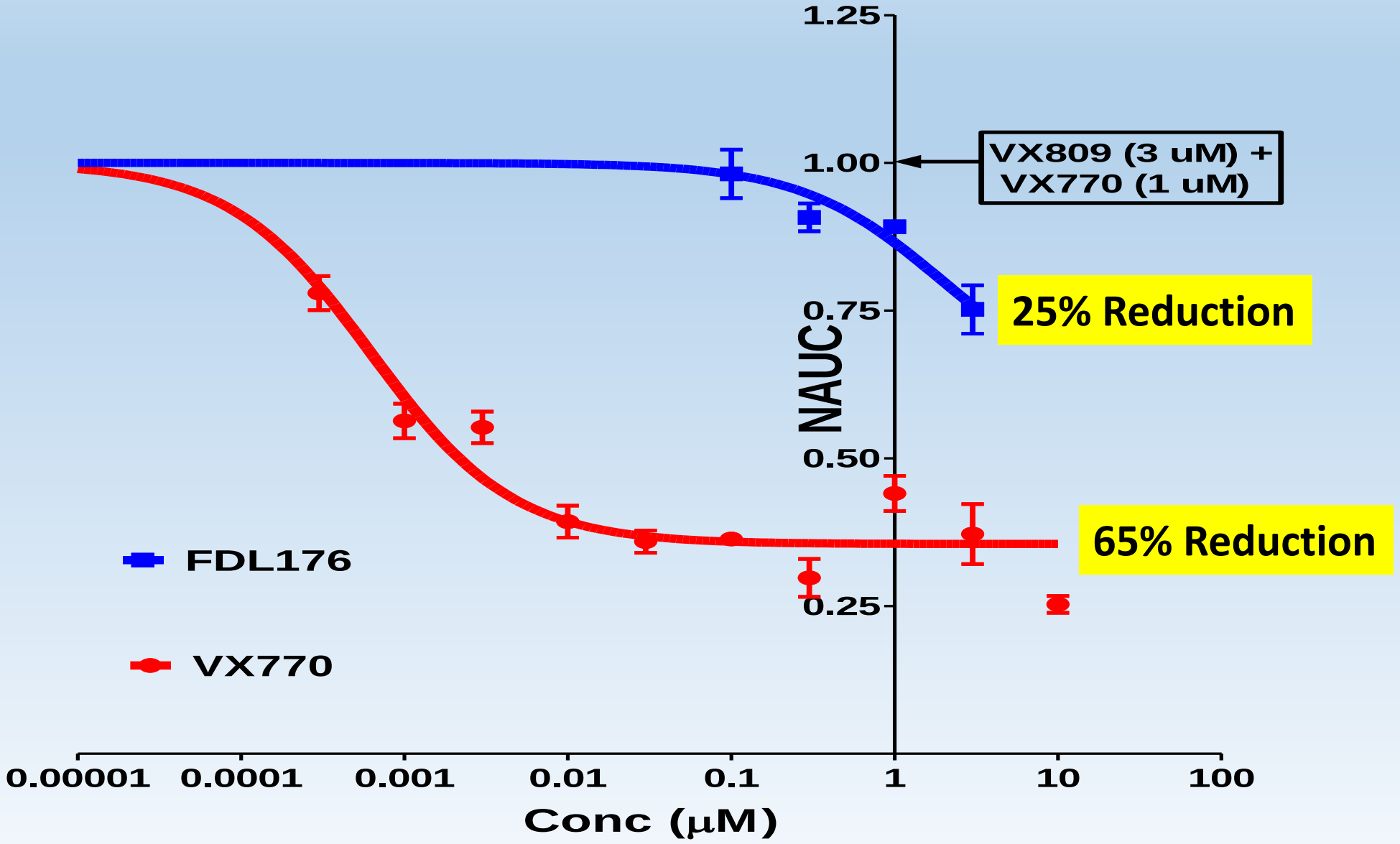
FDL169 Protects F508del CFTR from Inhibition by Prolonged Exposure to Ivacaftor in CFhBE Cells



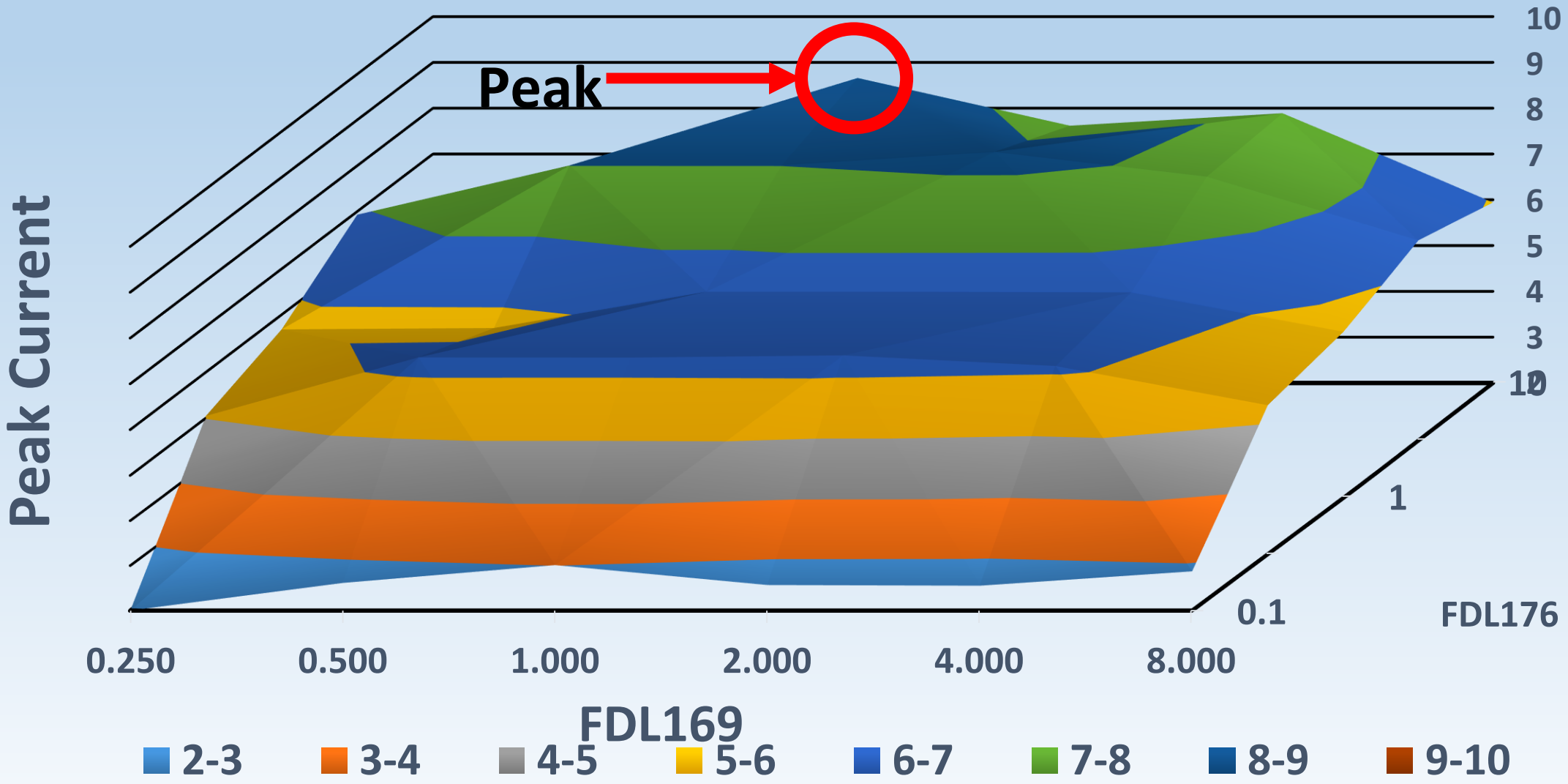
Potentiator Effect of FDL176 on Chloride Current in F508del CFhBEs is Similar to Ivacaftor



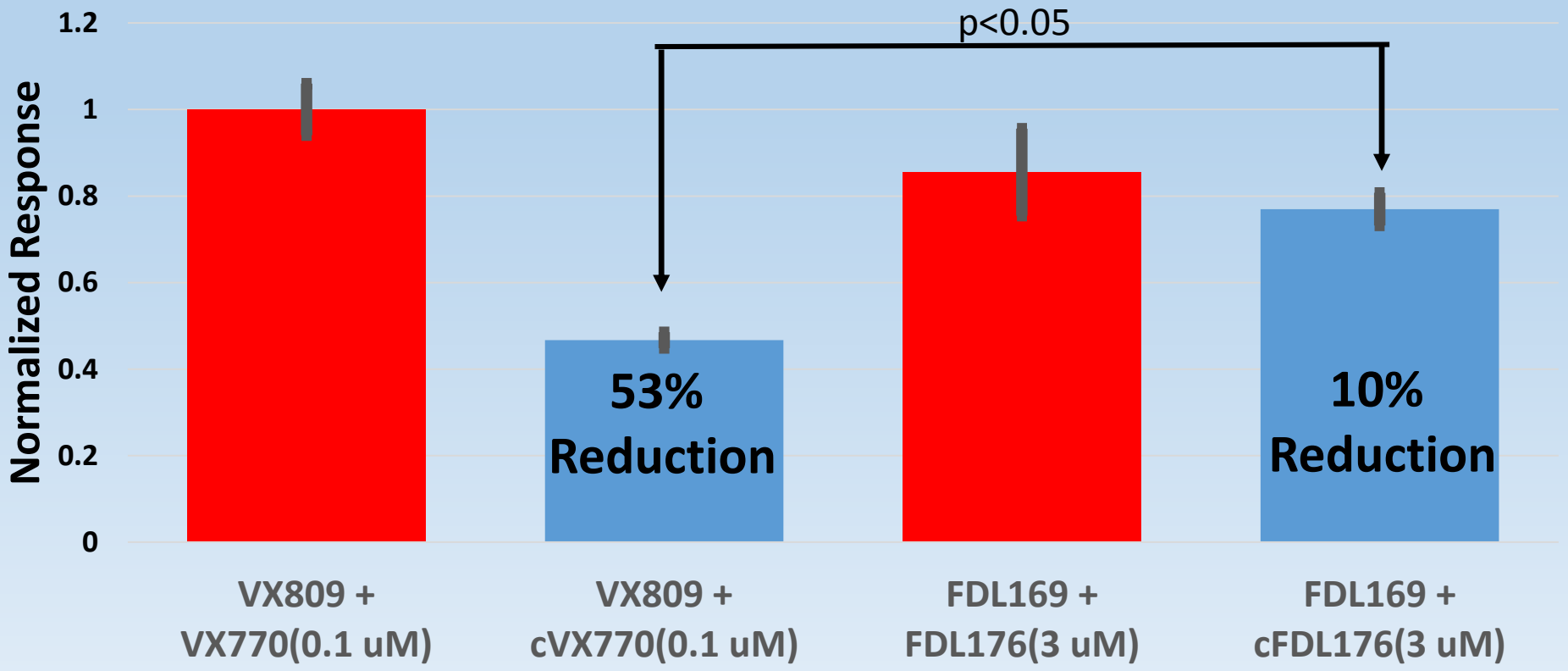
FDL176 Induces Less Inhibition Than Ivacaftor



Maximum Chloride Current of FDL169 + FDL176 Combination



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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Chronic Ivacaftor Treatment Reduces Surface CFTR Protein

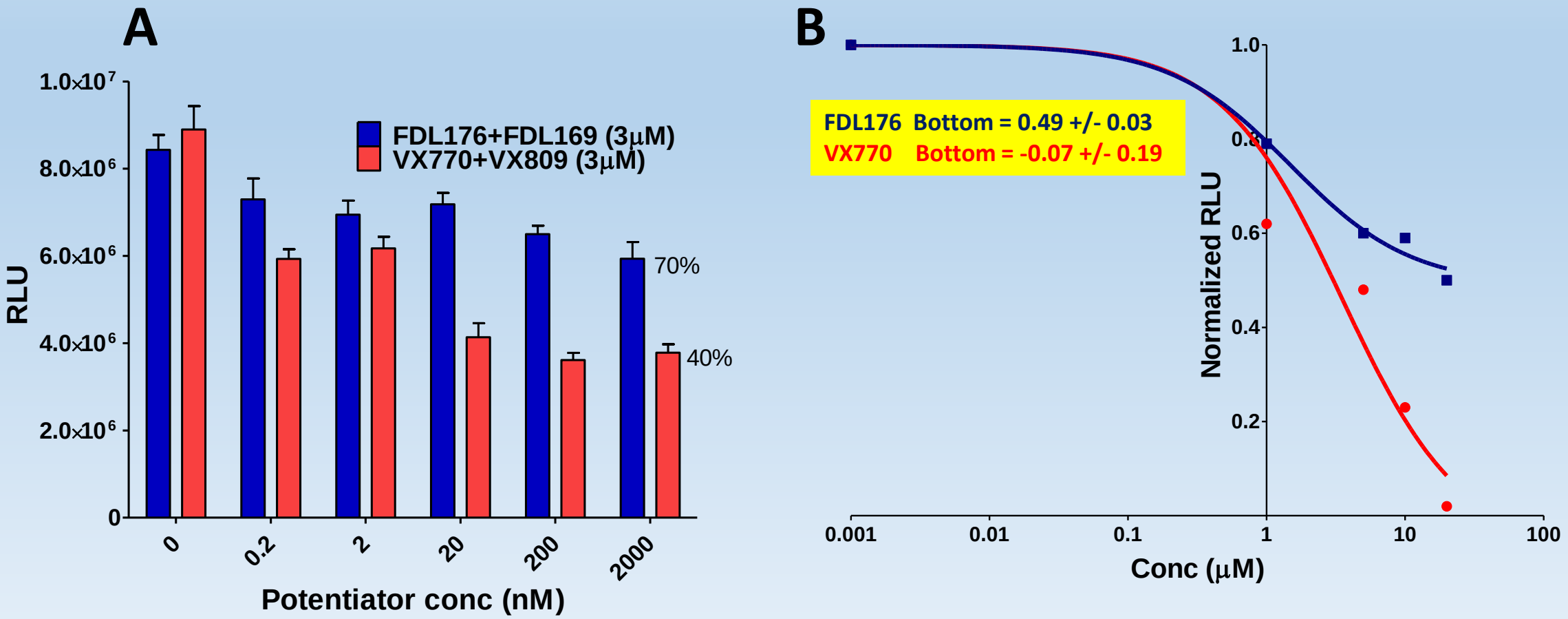

Figure 5: Cell surface expression of F508del CFTR at low (A) and high (B) potentiator concentrations. CFBE41o- cells were electroporated with the plasmid for HRP tagged F508del CFTR, and treated for 24 hours with either lumacaftor + ivacaftor or FDL169 + FDL176. In agreement with the electrophysiological 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