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CYSTIC FIBROSIS CONFERENCE
OCTOBER 27-29, 2016 • ORANGE COUNTY CONVENTION CENTER • ORLANDO, FL

W02: CFTR: CFTR 2016

Feng Liu, Ph.D.

Presenter Disclosure

Feng Liu, Ph.D.

The following relationship(s) exists related to this presentation:

Catabasis employee

CAT-5571 AS A NOVEL AND POTENT AUTOPHAGY ACTIVATOR THAT ENHANCES THE TRAFFICKING OF F508DEL-CFTR

Catabasis Pharmaceuticals

Forward Looking Statements

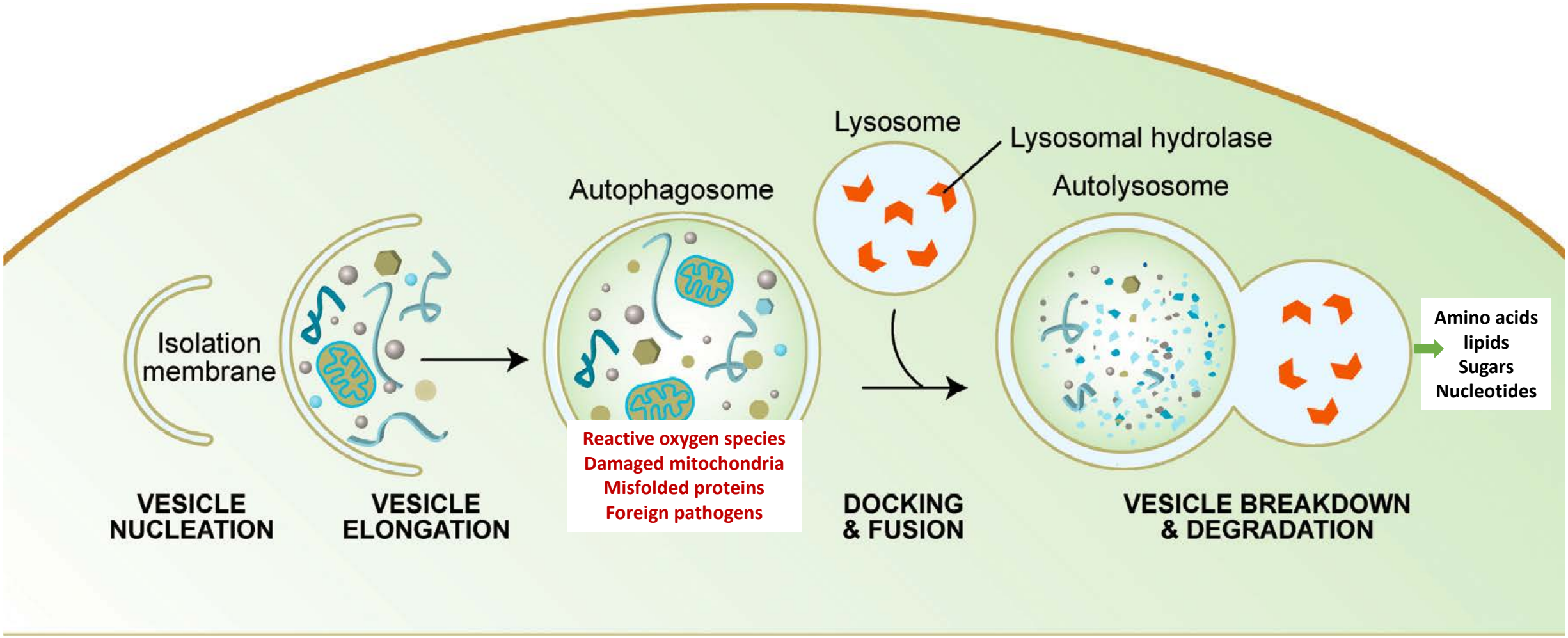
This presentation contains forward-looking statements within the meaning of The Private Securities Litigation Reform Act of 1995, including statements regarding our expectations and beliefs about our business, future financial and operating performance, clinical trial plans, product development plans and prospects. The words “believe”, “anticipate”, “plans,” “expect”, “could”, “should”, “will”, “would”, “may”, “intend” and similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words.

The forward-looking statements contained in this presentation and in remarks made during this presentation and the following Q&A session are subject to important risks and uncertainties that may cause actual events or results to differ materially from our current expectations and beliefs, including: uncertainties inherent in the initiation and completion of preclinical studies and clinical trials and clinical development of our product candidates; availability and timing of results from preclinical studies and clinical trials; whether interim results from a clinical trial will be predictive of the final results of the trial or the results of future trials; expectations for regulatory approvals to conduct trials or to market products; availability of funding sufficient for our foreseeable and unforeseeable operating expenses and capital expenditure requirements; other matters that could affect the availability or commercial potential of our product candidates; and general economic and market conditions. These and other risks are described under the caption “Risk Factors” in our Quarterly Report on Form 10-Q for the three months ended June 30, 2016, which is on file with the Securities and Exchange Commission, and in other filings that we may make with the Securities and Exchange Commission in the future.

In addition, the forward-looking statements included in this presentation represent our views as of the date of this presentation. We anticipate that subsequent events and developments will cause our views to change. However, while we may elect to update these forward-looking statements at some point in the future, we specifically disclaim any obligation to do so. These forward-looking statements should not be relied upon as representing our views as of any date subsequent to the date of this presentation.

Autophagy- maintain cellular homeostasis

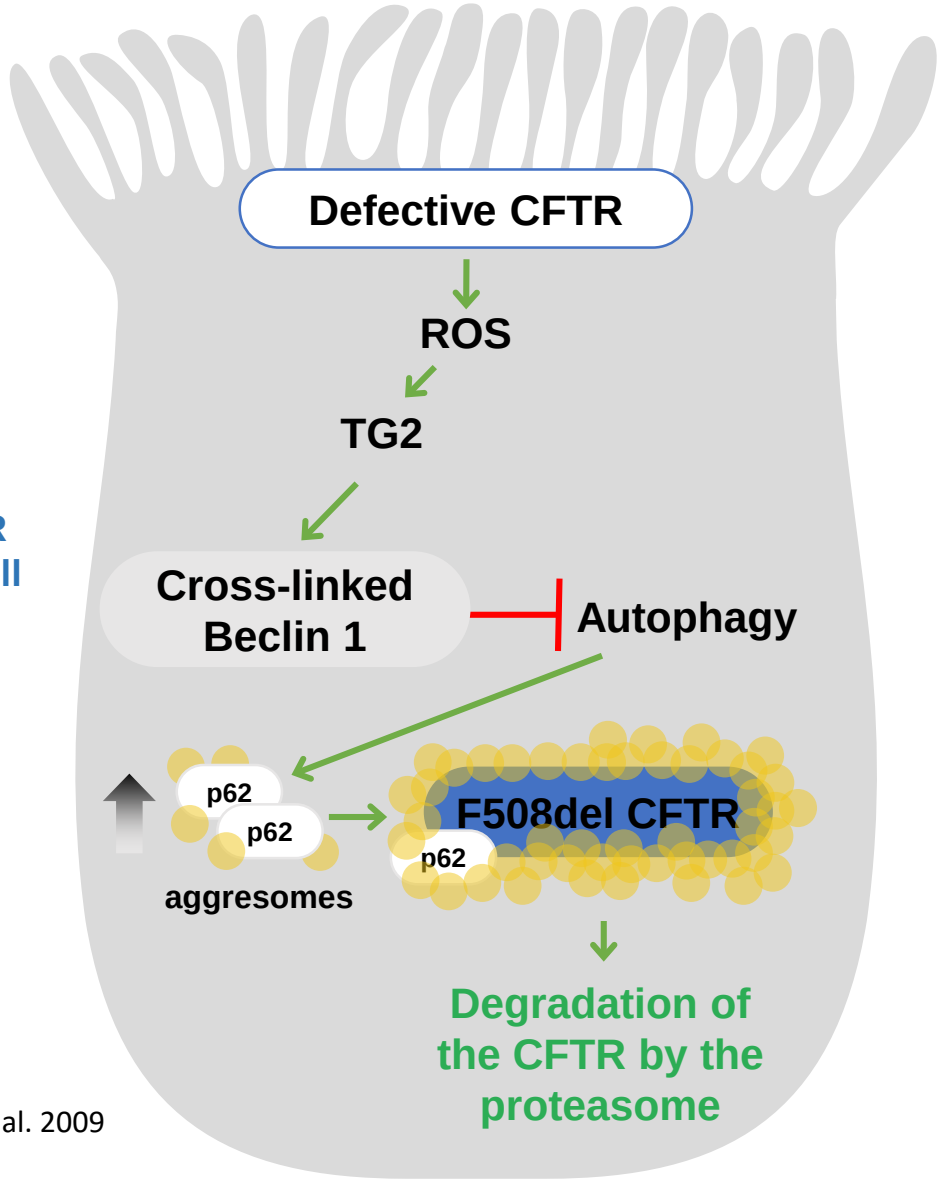
Autophagy – “auto” self “phagy” eating



Activation of Autophagy: A Therapeutic Approach to the Regulation of CFTR in Cystic Fibrosis

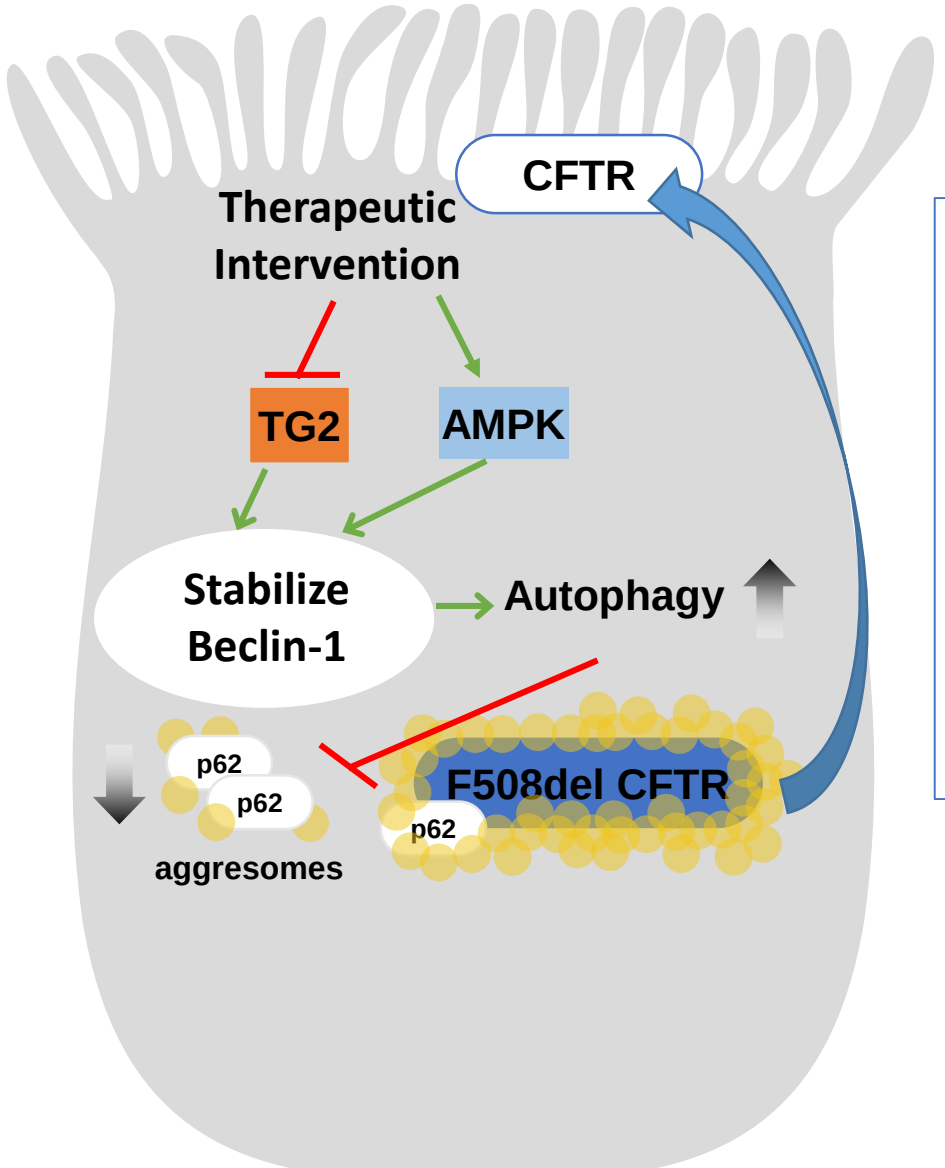
catabasis

Depressed autophagy causes an accumulation of the autophagy substrate p62, which traps the CFTR and prevents its trafficking to the cell surface



Adapted from Luciani, et al. 2009

Activation of Autophagy: A Therapeutic Approach to the Regulation of CFTR in Cystic Fibrosis

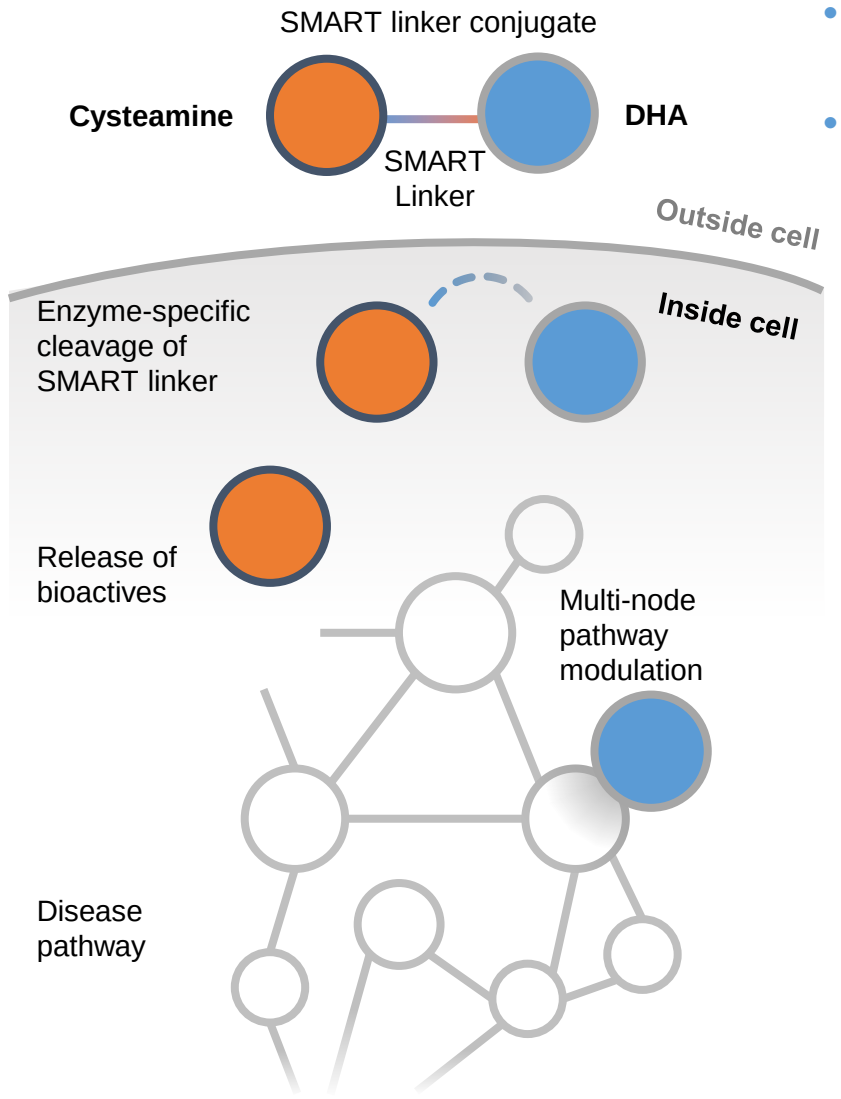


Hypothesis

Activation of autophagy by the simultaneous inhibition of TG2 and activation of AMPK.

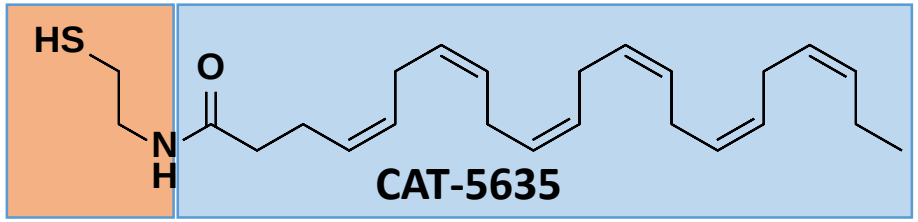
Reduces p62 and allows the trafficking of the CFTR to the cell surface

Safely Metabolized And Rationally Targeted (SMART) linker drug discovery platform

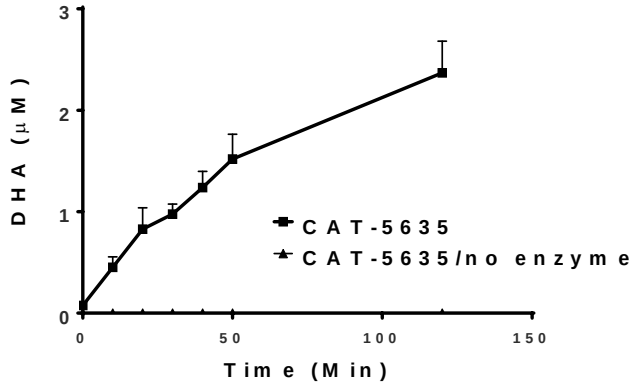


- **SMART linker conjugate allows modulation of multiple targets in a disease pathway**
- **Pharmacology of conjugate significantly different from individual bioactives, alone or in combination**

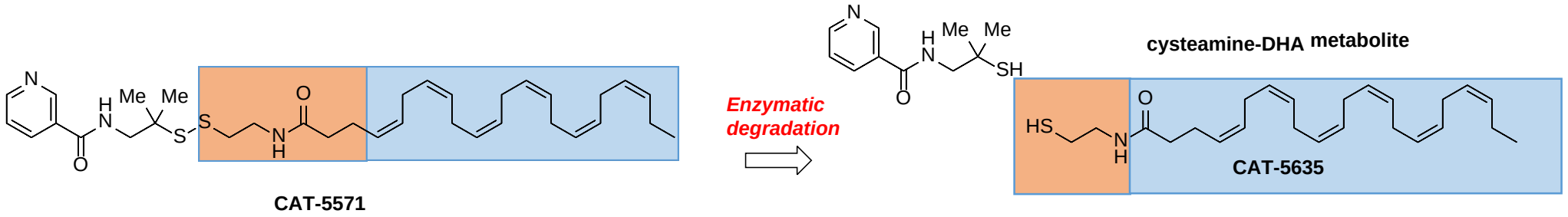
A covalent conjugate of cysteamine and docosahexaenoic acid (DHA)

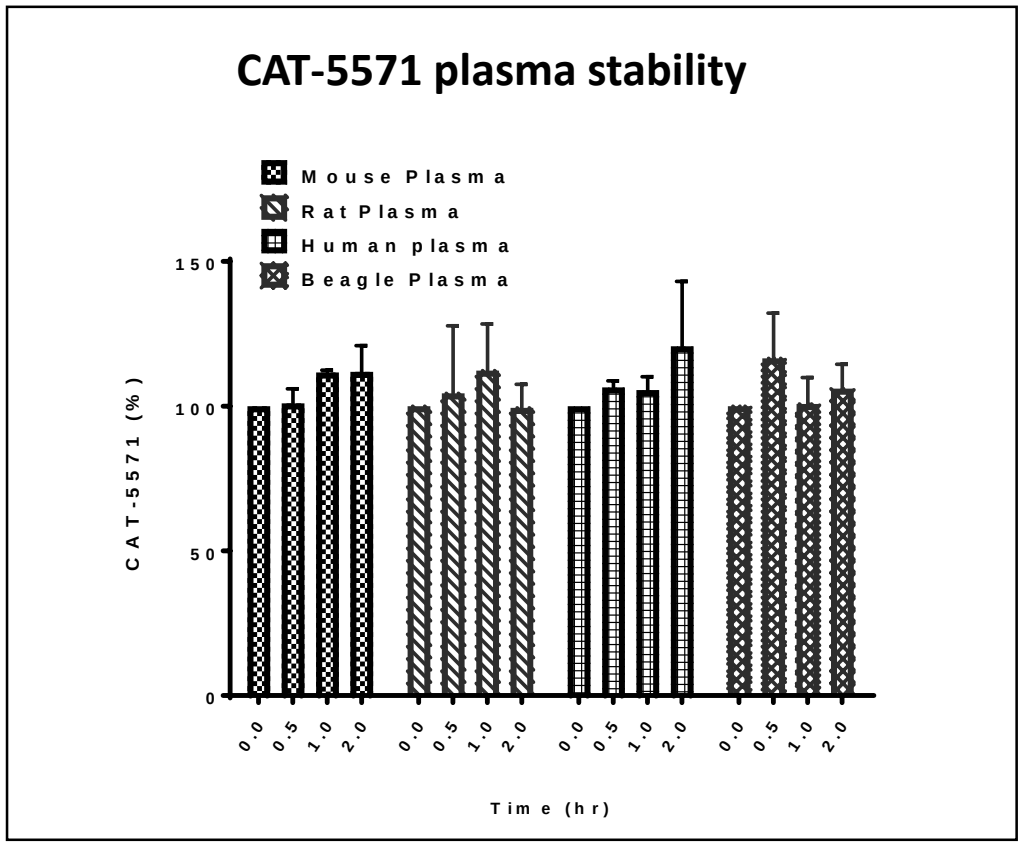


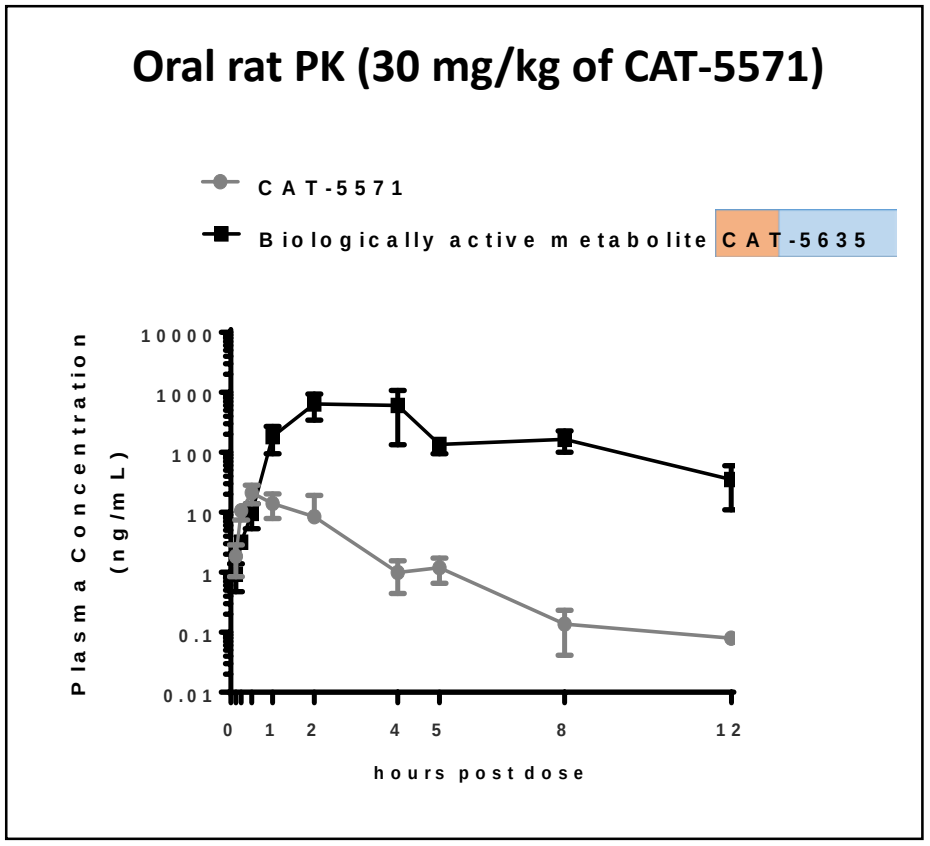
Hydrolysis of CAT-5635 using recombinant FAAH



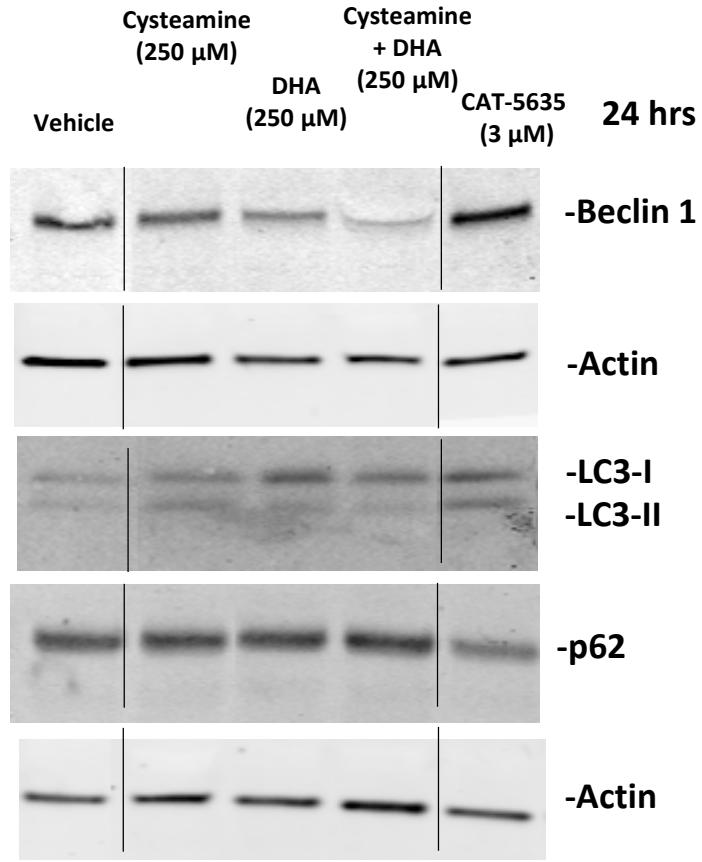
CAT-5571 delivers a sustained exposure of CAT-5635, a covalent conjugate of cysteamine and DHA



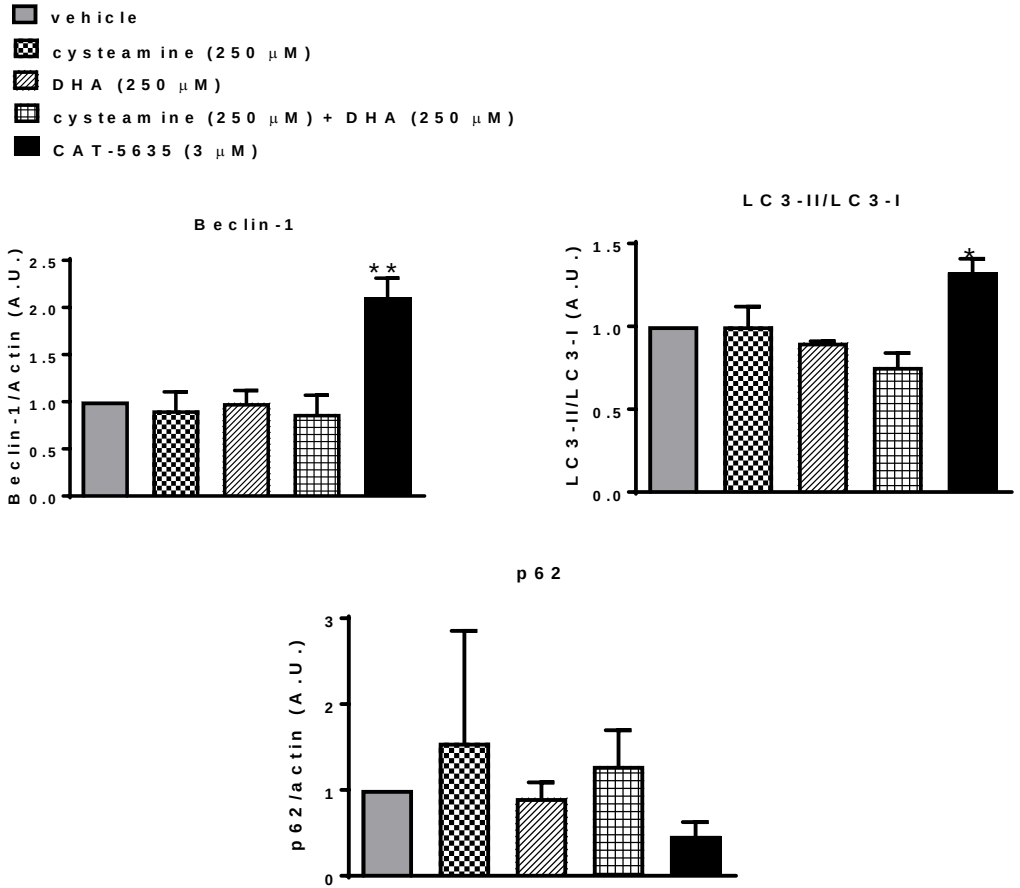




CAT-5635 activates autophagy in cultured primary homozygous F508del hBE monolayers

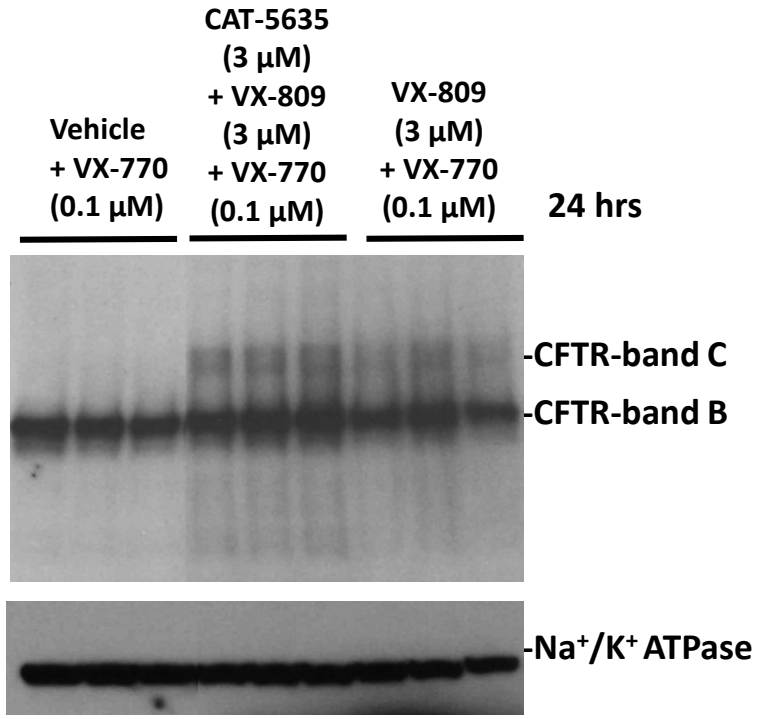


(Charles River Labs, homozygous F508del hBE, KKCFFT004I)

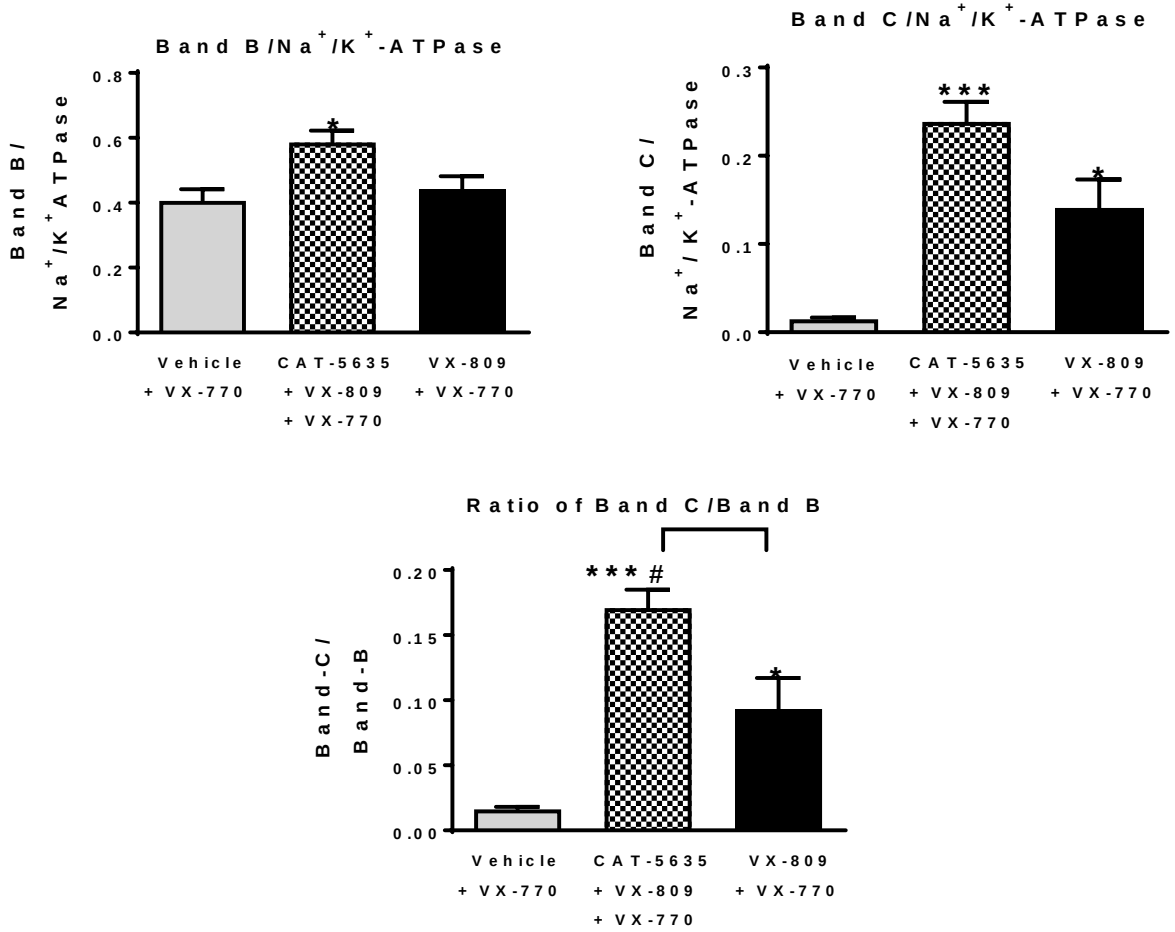


(SEM, n = 3). *$p < 0.05$, **$p < 0.01$, compare to the vehicle with Dunnett's multiple comparison test.

CAT-5635 increases trafficking of the CFTR to the cell surface at the presence of VX-809 (lumacaftor) and VX-770 (ivacaftor)



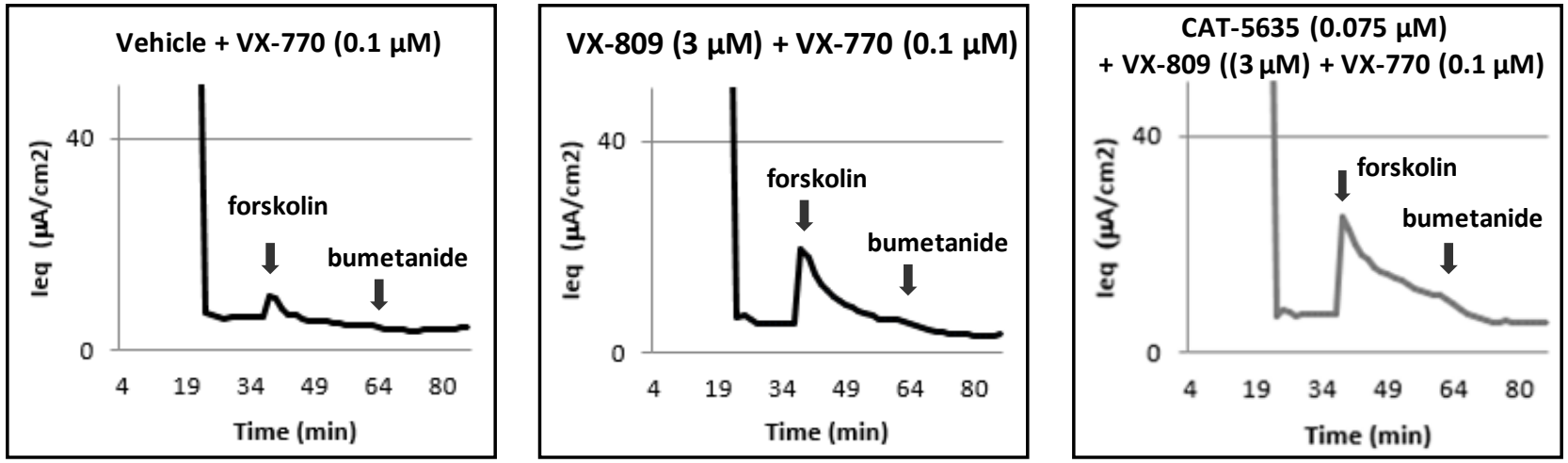
(Charles River Labs, homozygous F508del hBE, KKCFFT006F)

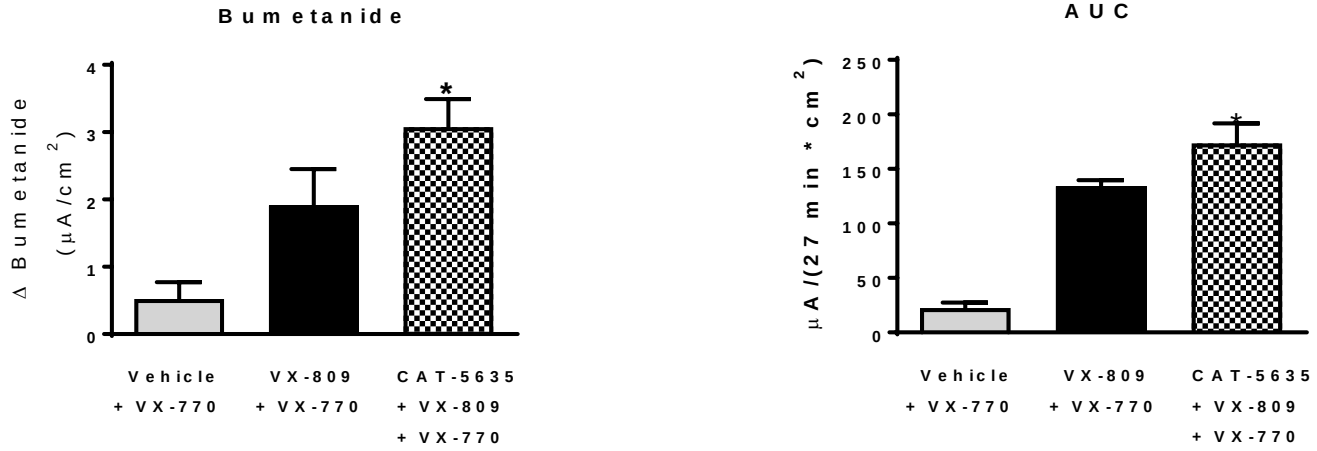


(SEM, n = 3). * $p < 0.05$, ***$p < 0.001$, compare to vehicle;
# $p < 0.05$, compared to VX-809/VX-770, with Dunnett's multiple comparison test

A triple combination consisting of CAT-5635 enhances the correction of the F508del-*CFTR* relative to the VX-809 (lumacaftor) /VX-770 (ivacaftor) combination

CAT-5635 pre-incubated with VX-809 + VX-770 for 24 hrs at 37 °C



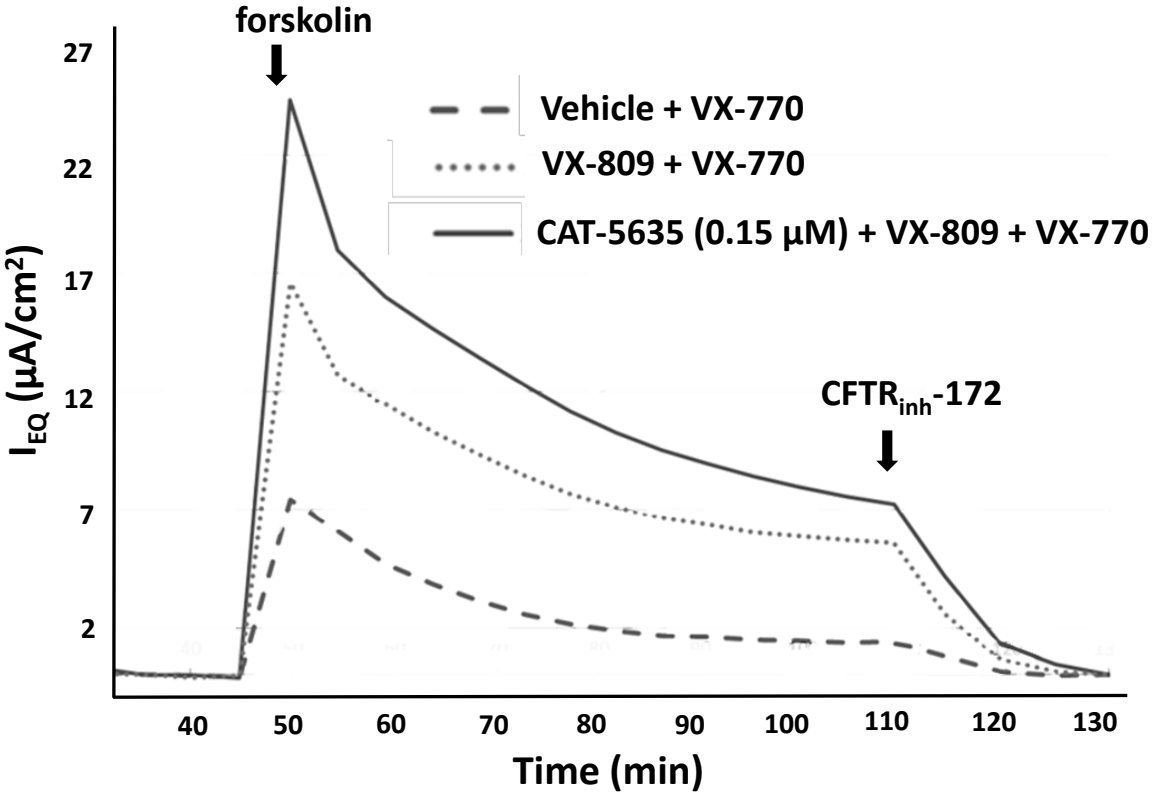


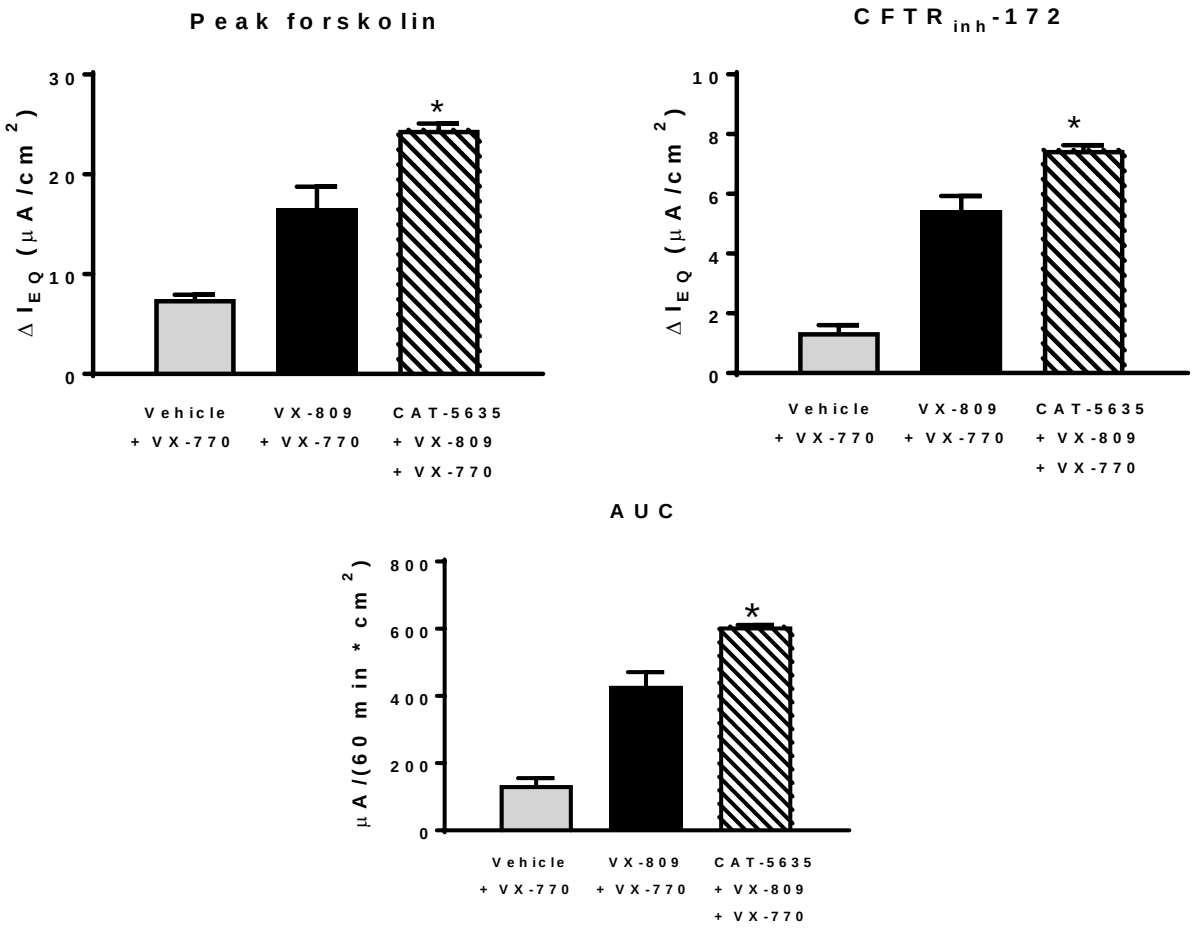
Robert J. Bridges, homozygous F508del hBE, CFFT0018I

(SEM, n = 3). * $p < 0.05$, compared to VX-809/VX-770 with Dunnett's multiple comparison test.

Additional confirmation of functional activity in a TECC-24 assay format

CAT-5635 pre-incubated with VX-809 + VX-770 for 24 hrs at 37 °C





Charles River Labs, homozygous F508del hBE, KKCFFT006F

(SEM, n = 4). * $p <$ 0.05, compare to VX-809/VX-770 with Dunnett's multiple comparison test.

Summary

Autophagy activation can enhance the correction of F508del CFTR

- CAT-5571 delivers a sustained exposure of CAT-5635, a covalent conjugate of cysteamine and DHA
- CAT-5635 potently activates autophagy in primary homozygous F508del hBE cells at ≤ 3 µM.
  - Neither Cysteamine nor DHA (alone or in combination) activates autophagy at the higher concentration (250 µM).
- CAT-5635 enhances the correction of the F508del-*CFTR* relative to the VX-809/VX-770 combination
  - Expression of CFTR Band B/C
  - CFTR chloride channel current

CAT-5571 represents a potential novel therapeutic approach for the treatment of cystic fibrosis with the F508del mutation

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  - Allison Wensley
  - Maisy Yeager

- **Rosalind Franklin University of Medicine and Science (Chicago):**
  - Robert J. Bridges
  - Cecilia Pena-Rasgado

- **Charles River Labs:**
  - Antonio E. Lacerda
  - Curtis Bordwell

CAT-5571 AS A NOVEL AND POTENT AUTOPHAGY ACTIVATOR THAT ENHANCES THE TRAFFICKING OF F508DEL-CFTR
(poster #3)

Case Western Reserve University
Tracey Bonfield
CAT-5571 as a novel autophagy activator that enhances the clearance of *Pseudomonas Aeruginosa*
(poster #223)