

# Cystic Fibrosis Research News

**Title:**

Combination potentiator ('Co-potentiator') therapy for CF caused by CFTR mutants, including N1303K, that are poorly responsive to single potentiators

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**What was your research question?**

This study investigates the utility of combinations of two potentiators, which we call "co-potentiators", to treat selected CFTR mutations that do not respond well to one potentiator alone, such as VX-770 (ivacaftor), or one potentiator in combination with corrector(s).

**Why is this important?**

Remarkable advances have been made in the development of CFTR modulators (potentiators and correctors) to treat CF. Currently approved and investigational CFTR modulators may ultimately be effective in treating up to 90% of people with CF. Treating the "remaining 10%", i.e. those people with CF who do not respond adequately to approved or investigational CFTR modulators, is challenging. The most common CFTR mutations in these individuals include premature stop codon mutations such as G542X and W1282X, and point mutations such as N1303K, which appear to be refractory to available potentiators and correctors.

**What did you do?**

We carried out high-throughput potentiator "synergy screens" using animal cells expressing CFTR mutations including the N1303K CFTR point mutation or the W1282X CFTR premature

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stop codon mutation as well as the most common mutation in CF patients, F508del and the G551D gating mutation, which VX-770 was first approved to treat., More than 100,000 drug-like small molecules were tested, in combination with VX-770 to identify co-potentiators. The most potent co-potentiators were further studied on animal cells and human airway cells expressing F508del, G551D, N1303K and W1282X CFTR mutations.

## What did you find?

The best co-potentiator was, an arylsulfonamide-pyrrolopyridine, which we named ASP-11, in combination with ivacaftor. When ASP-11 was added with VX-770 to N1303K-CFTR expressing cell, the current increased by 7-fold more than VX-770 alone. ASP-11 together with VX-770 also increased the current by ~65 % compared to VX-770 alone in G551D-CFTR expressing cell. Furthermore, ASP-11 was additive with VX-770 on cells expressing the F508del mutation. Importantly, ASP-11 efficacy with VX-770 was shown in primary human airway cell cultures from people with CF having N1303K, W1282X and G551D CFTR mutations.

## What does this mean and reasons for caution?

These studies support combination potentiator therapy for CF caused by some CFTR mutations that are not treated effectively by single potentiators that are available to date. Additional studies of ASP-11 including mechanism of action, pharmacokinetics and toxicity profiles are needed before advancing to pre-clinical studies. Co-potentiator therapy is a logical extension of the two-corrector plus one-potentiator approach currently in clinical trials.

## What's next?

The co-potentiator approach is being tested on less common CFTR mutations that are found in ~10% of the CF population, who do not respond well to the current CFTR modulator therapies that are available.

## Original manuscript citation in PubMed

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