

# Cystic Fibrosis Research News

**Title:**

**Potentiator synergy in rectal organoids carrying S1251N, G551D or F508del *CFTR* mutations**

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**What was your research question?**

In this study we exploited intestinal organoids ("mini-guts") cultured from biopsies from people with cystic fibrosis (CF) to compare the ability of three different so called "potentiators" of the CFTR chloride channel function (the Vertex drug VX-770/Kalydeco and the food supplements genistein and curcumin), alone or in combination, to improve the opening ("gating") of the CFTR chloride channel.

**Why is this important?**

Treatment of people, who are carrying CFTR gating mutations (S1251N; G551D), with the potentiator Kalydeco dramatically improves, but does not normalize lung function and is very costly. In contrast, both genistein and curcumin are widely available on the Internet and used by millions of people worldwide. Among many beneficial health effects reported, CFTR channel gating through a mechanism that is similar (curcumin) or different (genistein) from VX-770 is well-documented but requires concentrations that are difficult to reach in individuals. However, a combination of potentiators may work together for increased effect and lower the dosage required, thereby expanding the choice of clinically effective CFTR potentiators.

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## What did you do?

We tested the ability of genistein, curcumin and VX-770, at different concentrations and alone or in various combinations, to enhance CFTR activity in “mini-guts” generated from people with CF carrying S1251N, G551D and (homozygous) F508del mutations. The latter were pre-treated with the corrector VX-809 (Lumacaftor) to recruit sufficient CFTR channels to the cell surface. To mimic conditions that may predominate in people with CF during treatment, we examined CFTR activity not only at adequate (saturating) levels of a hormone-like stimulus (forskolin), but also at sub-optimal levels, and compared acute effects of the CFTR potentiators with those of chronic exposure (2 to 3 days of treatment).

## What did you find?

All three potentiators dose-dependently increased CFTR-mediated swelling of all three groups of organoids (S1251N, G551D and F508del), with the same order of effect (potency): VX-770 had the largest effect, followed by genistein and subsequently curcumin. CFTR activation by a combination of 2 to 3 potentiators was higher than the sum of single potentiator treatment under most test conditions. Due to this increased effect of potentiators working together, the effective concentrations of genistein and curcumin were shifted to a more feasible range for use in patients. Moreover we could not confirm the severe loss of F508del-CFTR function reported for other cell models after chronic, not acute treatment with VX-770 (Kalydeco).

## What does this mean and reasons for caution?

The results of our pre-clinical study suggest that combination therapy with several potentiators, for example the food supplements genistein plus curcumin, or VX-770 (Kalydeco) plus genistein, may be more effective than monotherapy with each potentiator separately, and may help to lower the clinically effective dosage and reduce therapy costs. However, a thorough testing of this prediction in clinical trials is needed to learn whether the levels of genistein and curcumin reachable upon oral supplementation in patients are high enough to exert a synergistic action and whether the intestinal organoid model is also predictive for CF lungs.

## What's next?

Three Dutch multi-center clinical trials are underway to test the therapeutic potential of (multi)potentiator therapy in people with the S1251N mutation, named TICTAC1 (genistein-curcumin), TICTAC2 (VX-770 alone) and TRIO (VX-770-genistein). If positive, these studies



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may allow upgrading of the food supplements to the status of “evidence based” medicine in CF.

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