



# Cystic Fibrosis Research News

**Title:**

Accumulation and Persistence of Ivacaftor in Airway Epithelia with Prolonged Treatment

**Authors:**

Tara N. Guhr Lee<sup>1,2</sup>, Deborah M. Cholon<sup>2</sup>, Nancy L. Quinney<sup>2</sup>, Martina Gentsch<sup>2,3</sup>, and Charles R. Esther Jr<sup>1,2</sup>

**Affiliations:**

<sup>1</sup>Division of Pediatric Pulmonology, Department of Pediatrics, University of North Carolina School of Medicine, 450-D MacNider Hall, Campus Box 7217, Chapel Hill, NC 27599-7217, USA.

<sup>2</sup>Marsico Lung Institute/Cystic Fibrosis Research Center, University of North Carolina, Chapel Hill, NC 27599, USA

<sup>3</sup>Department of Cell Biology and Physiology, University of North Carolina, Chapel Hill, NC 27599, USA.

**What was your research question?**

We wanted to know whether the CFTR modulators—the active components of the drugs Kalydeco (ivacaftor), Orkambi (ivacaftor plus lumacaftor), and Symdeko (ivacaftor plus tezacaftor)—accumulate in the lungs, and to what extent. We also wanted to see whether these drugs stay in the lung even after stopping treatment.

**Why is this important?**

CFTR modulators have to penetrate the cells of the lung to restore CFTR function, but how well they do so is unknown. Previous evidence has suggested that these drugs may accumulate in lung cells over time, and a better understanding of this process could alter how we dose these medications. This is of particular importance for ivacaftor, since accumulation of this drug has been shown to interfere with the function of other CFTR modulators.

**What did you do?**

Cultured lung cells derived from three individuals with CF who express two copies of the most common CFTR mutation (F508del) were treated with ivacaftor plus either lumacaftor or tezacaftor for two weeks. We continued to monitor these cells for an additional two weeks without any treatment. At various intervals, we measured the concentrations of each drug and how well they restored the function of CFTR.

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[cfresearchnews@gmail.com](mailto:cfresearchnews@gmail.com)



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## **What did you find?**

We found that ivacaftor continued to accumulate during the entire two-week treatment period, whereas lumacaftor or tezacaftor accumulated to a lesser extent. We also found that ivacaftor concentrations remained elevated even after two weeks without treatment, whereas lumacaftor and tezacaftor were eliminated much more quickly. The amount of CFTR and its functional activity were highest one week after starting treatment but started to decline as ivacaftor continued to accumulate. We also noticed that CFTR functional activity was still slightly affected even after treatment had been stopped for two weeks.

## **What does this mean and reasons for caution?**

The accumulation of CFTR modulators, especially ivacaftor, in lung cells was not factored into current dosing regimens for these drugs. It is possible that other dosing strategies may help these drugs work better or offer fewer side effects. The persistence of ivacaftor in lung cells for long periods of time off therapy will have to be taken into account when doing tests of CFTR function in patients who have stopped therapy.

## **What's next?**

Future studies are needed to see if the accumulation that we observed in cultured cells is also occurring in patients on CFTR modulator therapy. If so, we need to examine other dosing strategies in animal models and clinical trials to find the optimal doses. We would also want to see if we get similar results with the new CFTR modulator elxacaftor, found in Trikafta.

## **Original manuscript citation in PubMed**

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