**Transcript Details**
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Cell Death and Differentiation: A Novel Treatment of Cystic Fibrosis Acting On-Target

**Interpretation:**

Cystic fibrosis, the most common lethal recessive disease in Caucasians, affects approximately 70,000 patients worldwide and results from mutations in the cystic fibrosis transmembrane conductance regulator (CFTR). For the vast majority of cystic fibrosis patients bearing the most common *Phe508del*-CFTR mutation, an FDA-approved combined treatment with the corrector Lumacaftor (that promotes ER to plasma membrane traffic) and Ivacaftor is only marginally effective.

Tosco et al has previously reported that the combination of two safe proteostasis regulators, cysteamine and epigallocatechin gallate (EGCG), can be used to improve deficient expression of the cystic fibrosis transmembrane conductance regulator in patients homozygous for the CFTR *Phe508del* mutation.

In this new article, Tosco et al provide the proof-of-concept that this combination treatment restored CFTR function and reduced lung inflammation ($P<0.001$) in *Phe508del/Phe508del* or Phe508del/null-CFTR (but not in CFTR-null mice), provided that such mice were autophagy-competent.

Primary nasal cells from patients bearing different class II CFTR mutations, either in homozygous or compound heterozygous form, responded to the treatment in vitro. The study assessed individual responses to cysteamine plus EGCG in a single-centre, open-label phase-2 trial. The combination treatment decreased sweat chloride from baseline, increased both CFTR protein and function in nasal cells, restored autophagy in such cells, decreased CXCL8 and TNF-α in the sputum, and tended to improve respiratory function.

These positive effects were particularly strong in patients carrying *Phe508del* CFTR mutations in homozygosity or heterozygosity. However, a fraction of patients bearing other CFTR mutations failed to respond to therapy. Importantly, the same patients whose primary nasal brushed cells did not respond to cysteamine plus EGCG in vitro also exhibited deficient therapeutic responses in vivo.

Altogether, these results suggest that the combination treatment of cysteamine plus EGCG acts ‘on-target’ because it can only rescue CFTR function when autophagy is functional (in mice) and improves CFTR function when a rescuable protein is expressed (in mice and men). These results should spur the further clinical development of the combination treatment.