The predominant cystic fibrosis (CF)-associated mutation, deletion of Phe508 (ΔF508) causes defects at the level of CFTR mRNA, protein translation, and channel function. Small molecules partially rescue the distal ΔF508-associated defects in vitro. Specifically, correctors rescue the biosynthetic processing of CFTR protein while potentiators improve the function of rescued CFTR channels; however, their efficacy is marginal in vivo. Most CF patients have increased levels of TGF-β1, compared to non-CF controls. TGF-β1 inhibits CFTR mRNA and may represent a prevalent key antagonist limiting responses to the corrector/potentiatior therapy in the majority of CF patients. Mechanisms of CFTR repression by TGF-β1 will be discussed.