New Therapeutic Approaches to Modulate and Correct Cystic Fibrosis Transmembrane Conductance Regulator

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KEYWORDS

• CFTR modulator • Personalized medicine • Therapeutics • Potentiator • Corrector

KEY POINTS

- Cystic fibrosis transmembrane conductance regulator (CFTR) mutations can be classified into defects that lead to reduced quantity or reduced function of CFTR protein, impairing critical salt and fluid homeostasis in multiple organs.
- Classification of mutations is a framework for therapeutic approaches to identify compounds that improve CFTR presence at the cell surface (corrector therapy) or augment channel function of the nascent protein (potentiator therapy).
- Ivacaftor (Kalydeco), the first approved CFTR potentiator for individuals with class III (gating) mutations, and Arg117H have demonstrated significant and sustained multisystem improvement.
- The combination of ivacaftor and lumacaftor (Orkambi) was approved in 2015 for individuals homozygous for the Phe508del mutation. Its long-term clinical impact is not yet known.
- Novel systems and disease markers that address and monitor individualized response to therapies are being developed and will serve as important tools to explore current and future CFTR modulators.

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INTRODUCTION

The science of personalized medicine is taking shape in the cystic fibrosis (CF) community with genotype-directed therapies available for more than half of the CF population. Personalized or precision medicines approach the treatment of disease by accounting for an individual's variability in genes, environment, and lifestyle.[1]

This momentum in precision medicine launched with the basic understanding of CF as a result of mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene.[2–4] In the decades since CFTR gene identification, knowledge of CFTR mutations and their pathophysiologic consequences has rapidly expanded, leading to the development of small-molecule therapies that target specific CFTR variants that have some level of CFTR protein produced.[5] These small-molecule therapies are defined as CFTR modulators, a novel class of precision medicines directed to improve CFTR function and/or presence at the cell surface level.

In this review, we focus on therapeutic approaches, known as "potentiators" and "correctors" that explore our understanding of specific CFTR variants and aim to augment or repair function of the CFTR protein.

APPROACHING CYSTIC FIBROSIS TRANSMEMBRANE CONDUCTANCE REGULATOR: REVIEW OF STRUCTURE AND FUNCTION

CFTR, located in the apical membranes of epithelial cells in multiple exocrine organs, is a chloride and bicarbonate ion channel that regulates salt and fluid homeostasis.[6] The CFTR glycoprotein has multiple membrane-integrated subunits that form 2 membrane-spanning domains (MSDs), 2 intracellular nucleotide-binding domains (NBDs), and a regulatory (R) domain, which acts as a phosphorylation site.[7,8] MSD1 and MSD2 form the channel pore walls. Opening and closing of the pore is through ATP interactions with cytoplasmic NBD domains, leading to conformational changes of MSD1 and MSD2.[9] Gating and conductance is regulated through R domain phosphorylation with protein kinase A (PKA).[7]

The intricate regions of CFTR require processing and maturation to allow precise folding. CFTR structure must satisfy rigorous quality standards to be exported from the endoplasmic reticulum and subsequently transported to the cell surface. CFTR that fails to meet these standards is destined to endoplasmic reticulum–associated protein degradation (ERAD).[7] Such a complex quality-control system operates at the detriment of efficiency, decreasing export production of even wild-type CFTR to 33% of similar family cell transporters.[10]

CF is a result of mutations that alter CFTR in these domains or the way these domains interact with each other. Ultimately, these defects affect the function or quantity of the channel at the cell surface.[5] With nearly 2000 disease-causing mutations identified in CFTR, variants have historically been categorized in 5 or 6 functional classifications (**Fig. 1**).[8,11] Class I mutations lead to a lack of protein synthesis, such as those with a premature termination codon present. Class II mutations are unable to mature, leading to early degradation through the mechanism of ERAD and resulting in CFTR rarely reaching the cell surface. Class III mutations are considered gating defects with abnormal regulation that make the pore nonfunctioning. Class IV defects have inefficient CFTR function with defective chloride conductance. Class V and VI mutations are those that lead to decreased quantity of CFTR at the cell surface as a result of promoter or splicing defects (V) or increased turnover from the cell surface (VI).

These categories of molecular mechanisms provide a useful framework to consider personalized therapeutic approaches (**Table 1**), but present an oversimplification in that a single variant can disrupt multiple functional classes. Phe508del, the most