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Original Article

Recent progress in translational cystic fibrosis research using precision medicine strategies

Deborah M. Cholon [a], Martina Gentzsch [a,b,*]

[a] Marsico Lung Institute/Cystic Fibrosis Research Center, University of North Carolina, Chapel Hill, NC, USA
[b] Department of Cell Biology and Physiology, University of North Carolina, Chapel Hill, NC, USA

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Abstract

Significant progress has been achieved in developing precision therapies for cystic fibrosis; however, highly effective treatments that target the ion channel, CFTR, are not yet available for many patients. As numerous CFTR therapeutics are currently in the clinical pipeline, reliable screening tools capable of predicting drug efficacy to support individualized treatment plans and translational research are essential. The utilization of bronchial, nasal, and rectal tissues from individual cystic fibrosis patients for drug testing using in vitro assays such as electrophysiological measurements of CFTR activity and evaluation of fluid movement in spheroid cultures, has advanced the prediction of patient-specific responses. However, for precise prediction of drug effects, in vitro models of CFTR rescue should incorporate the inflamed cystic fibrosis airway environment and mimic the complex tissue structures of airway epithelia. Furthermore, novel assays that monitor other aspects of successful CFTR rescue such as restoration of mucus characteristics, which is important for predicting mucociliary clearance, will allow for better prognoses of successful therapies in vivo. Additional cystic fibrosis treatment strategies are being intensively explored, such as development of drugs that target other ion channels, and novel technologies including pluripotent stem cells, gene therapy, and gene editing. The multiple therapeutic approaches available to treat the basic defect in cystic fibrosis combined with relevant precision medicine models provide a framework for identifying optimal and sustained treatments that will benefit all cystic fibrosis patients.

Keywords: Cystic fibrosis; Precision medicine; CFTR; Primary human airway epithelial cells; Bronchospheroids; Nasospheroids; Patient-derived models

1. Introduction

Cystic fibrosis (CF) is characterized by abnormal epithelial ion transport resulting from mutations in the CFTR gene [1]. The CFTR protein is an ion channel that mediates Cl^- and HCO_3^- transport of secretory and absorptive epithelial cells in multiple organs including lungs and intestines. The absence of CFTR also results in enhanced Na^+ uptake via the ENaC channel, leading to dehydrated airways [2–4]. The majority of morbidity and mortality associated with CF is due to airway disease caused by disturbances of airway surface liquid (ASL) homeostasis that result in viscous and sticky mucus, which leads to mucus stasis, airway obstruction, persistent infection, inflammation, and a progressive decline in lung function [5,6]. Clinical advances in comprehensive treatments of CF symptoms, including strategies to improve mucociliary clearance (MCC), and antibiotics to eradicate bacterial lung infections, result in only limited capacity to delay disease progression and increase survival of CF patients [7]. Discovery of the gene responsible for CF over 25 years ago [1] led to an understanding of how various CFTR mutations cause different CFTR biochemical or functional protein aberrations ranging from complete protein absence to defective protein activity. Approximately 2000 unique CFTR variants

* Corresponding author at: Marsico Lung Institute/Cystic Fibrosis Research Center, University of North Carolina, 1121 Marsico Hall CB 7248, 125 Mason Farm Road, Chapel Hill, NC 27599, United States.
E-mail address: gentzsch@med.unc.edu (M. Gentzsch).

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have been identified, with F508del as the most common CF-causing mutation, and a large number of rare mutations accounting for the remainder of CF cases. Notably, the severity of CF is influenced by factors beyond CFTR mutations such as modifier genes, environment, and lifestyle, such that individuals possessing the same CFTR mutation may respond differently to the same treatment [8–10]. This complexity presents an unprecedented need for relevant, predictive models for testing of CF therapies. Therapeutics are being developed that specifically target the CFTR protein, thereby alleviating CF symptoms at the molecular level. The use of small-molecular compounds that modulate CFTR (ivacaftor/VX-770 and lumacaftor/VX-809) has led to the development of two medicines for CF patients, Kalydeco (VX-770) and Orkambi (VX-770 plus VX-809). Targeted use of Kalydeco is a powerful example of how the CF community is leading the field of precision medicine. VX-770 was made available in the US in 2012 as a stand-alone therapy for individuals with CFTR gating mutations such as G551D [11,12]. Although Kalydeco has dramatically improved the lives of a small proportion of the CF population (~5%), the remaining challenge is to achieve similar success for the entire CF population. Orkambi was developed for the F508del CFTR population, but clinical gains are modest [13,14] and adverse side effects have forced some patients to stop taking this medication. Thus, despite significant progress in developing precision therapies for CF, highly effective treatments are not yet available for most CF patients. As numerous CFTR-targeting compounds and reagents are currently in the clinical pipeline (Table 1), the development of new screening tools capable of predicting drug efficacy in an individualized manner are needed and expected to have a profound impact on the well-being of CF patients.

2. Primary cells constitute a native environment for CFTR

Since the discovery of the CFTR gene, CFTR processing has been extensively studied in cell lines and some principles of quality control and cell-surface stability were later confirmed in primary human bronchial epithelial (HBE) cells. For example, in both systems, the F508del mutant is misprocessed, and when rescued has a shortened half-life at the plasma membrane [15–17]. However, CFTR displays increased cell surface stability in differentiated HBE compared to non-polarized and polarized cell lines [16]. Although BHK-21, FRT, and CFBE41o- cell lines have been commonly used to screen for CFTR modulators, it has become apparent that heterologous expression systems do not always reliably predict CFTR modulator efficacy in primary cells [18–20]. Establishing the therapeutic benefit of available compounds such as VX-809 and VX-770 to correct rare CFTR mutation defects is currently an active research area, and the field is moving toward development of personalized medicine, where the individual CF patient's tissue is used (Fig. 1), and thus, each patient's genetic makeup will be the basis for determining therapeutic options. Physiologically relevant and predictable model systems that can be utilized for screening and prediction of clinical outcomes for multiple mutations are needed. As the stringency of CFTR rescue is higher in primary airway epithelial cultures than in cell lines, to accurately assess pharmacological

Table 1
Novel CFTR therapeutics that are currently in the drug pipeline or in clinical trials.

Company	Compound
4D Molecular Therapeutics	Gene therapeutic for CF using adeno-associated virus to target lung airway cells
AbbVie/Galapagos	C1 (GLPG2222, GLPG2851) and C2 (GLPG2737) correctors and potentiators (GLPG1837, GLPG2451, GLPG3067)
Arcturus Therapeutics	LUNAR-CF, mRNA therapeutic to restore CFTR expression
Bayer	Riociguat to improve CFTR channel expression and function
Calista Therapeutics	Peptide drugs that inhibit the interaction between CAL and CFTR
Catabasis Pharmaceuticals	CAT-5571 to activate autophagy and improve CFTR function
Concert Pharmaceuticals	Potentiator CTP-656, a deuterium-modified version of ivacaftor
CRISPR Therapeutics	CRISPR-Cas9 gene editing
DiscoveryBioMed	Dual acting correcting and activating CFTR ligands
Editas Medicine	CRISPR/Cas approaches to edit CFTR DNA
Flatley Discovery Lab	Correctors (FDL169) and potentiators (FDL176)
Genzyme/Sanofi	Non-viral gene transfer agent (gene–liposome complex pGM169/GL67A), corrector compounds
Homology Medicines	CFTR gene therapy and gene editing
Ionins Pharmaceuticals	Antisense oligonucleotides to increase CFTR and reduce ENaC expression
Moderna Therapeutics	mRNA therapeutic for CFTR protein expression
Novartis	Potentiator (QBW251) and corrector compounds
Parion Sciences	Corrector compounds and ENaC inhibitor (VX-371/P-1037)
Pfizer	Correctors (PYR-41 targeting ubiquitination) and potentiators (CP-628006)
ProQR Therapeutics	QR-010, 33mer antisense oligonucleotide to restore CFTR expression
Proteostasis Therapeutics	CFTR amplifier PTI-428; corrector (PTI-801) and potentiator (PTI-808)
PTC Therapeutics	Ataluren for treatment of CFTR nonsense mutations
Reata Pharmaceuticals	Corrector compounds
Shire Rare Disease	Technology to deliver normal CFTR to the lungs
Southern Research Institutes	Drugs for translational readthrough of CFTR nonsense mutations
Talee Bio	Virus-based (TL-101, TL-102) CFTR gene therapy
Traffick Therapeutics	Correctors NU001 and NU002
Vanda Pharmaceuticals	CFTR activators discovered by Alan S. Verkman, M.D., Ph.D., (UCSF)
Vertex Pharmaceuticals	Corrector VX-661, next-generation correctors VX-152, VX-440, VX-445, VX-659

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