

## Cystic fibrosis: current treatment and future direction

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Received: 23 January 2021

Revised: 28 February 2021

Accepted: 02 March 2021

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### ABSTRACT

Cystic fibrosis is an autosomal recessive genetic disorder, characterized by mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene, leading to abnormality in the chloride channels of the mucus and sweat producing glands. Multiple organs systems are affected in this disorder, like respiratory systems and gastrointestinal tract, severely impacting the patient's quality of life, eventually leading on to several complications and death. Since the uncovering of the underlying genetic defect in cystic fibrosis (CF), our knowledge of the disease process has increased substantially, but we still lack a holistic approach to its management, which comprises of multiple facades, requiring both pharmacological and non-pharmacological or rehabilitative approaches. So far, the therapeutic options were limited to targeting the consequences and complications of the disease, such as respiratory infection, mucus retention, pancreatic insufficiency, etc., but now several promising therapies may be able to address the underlying pathology rather than its long-term effects. This review summarizes the current and upcoming pharmacological options for CF, such as those targeting the CFTR gene defect directly, including gene editing, CFTR correctors and potentiators; drugs targeting the epithelial sodium channels (ENaC inhibitors); repositioning of some existing drugs and evaluating their role in CF; and understanding the disease better by transcriptomic approaches and the role of gut microbiota in the disease process and severity.

**Keywords:** Cystic fibrosis, CFTR, Chloride ion channels, Sodium epithelial channels

### INTRODUCTION

Cystic fibrosis (CF) is a progressive, autosomal recessive disorder characterised by severe damage to the various mucus, sweat and digestive juices secreting organs, such as lungs, sweat glands and pancreas, and currently affects more than 30,000 individuals in the United States. With an incidence of 1 in 3400 live births, about 900-1000 new cases of CF are diagnosed each year in US. Although CF is common in people of all races and ethnicity, it is most commonly diagnosed in Caucasians, with one in every 29 individuals a carrier of the CF gene mutation.<sup>1-3</sup>

The gene defect in CF is in the cystic fibrosis transmembrane conductance regulator (CFTR), which functions as a chloride ion trafficker in the plasma

membrane of the epithelial cells of pancreas, liver, intestines, epididymis, sweat glands and lungs. Adequate chloride transport across ion channels helps maintain the movement of water in tissues, necessary for production of thin, free flowing mucus. Normal CFTR protein is exported from the endoplasmic reticulum (ER) to the Golgi apparatus for further processing, following which it gets transported to the cell membrane of acinar and other epithelial cells, where it regulates sodium and chloride ion transportation, thereby modulating the composition and amount of exocrine glands' secretion. It encodes an adenosine triphosphate gated chloride channel, which has different roles in different organ systems. CFTR aids in chloride secretion in the lungs and gastrointestinal tract, whereas it promotes the reabsorption of chloride in sweat glands. Failure or disruption of this mechanism causes

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Cilia, Mucus, and Mucociliary Interactions Nadav Liron,Ervin Ostfeld,Zvi Priel,Yehudah Roth,1998-02-26 Written by nearly 60 of the world's leading investigators in this rapidly expanding field this state of the art reference furnishes detailed presentations on the basic science and clinical aspects of cilia mucus and mucociliary interactions Providing stimulating coverage of the latest information in a single source Cilia Mucus and Mucociliary Interactions discusses the genetic determinants of mucociliary system structure and function explains ciliary wave activity in cell cell communication elucidates many of the key physiological processes in ciliary regulation reveals possible means of treating irregularities in mucus secretion and clearance improves understanding of clinical syndromes including abnormalities pertaining to nasal sinuses upper and lower airways and the systemic role of cilia approaches the clinical management of mucociliary dysfunction logically using currently available diagnostic and therapeutic techniques and much more Containing bibliographic citations tables equations drawings and photographs this exhaustive guide is essential reading for physiologists pulmonologists otolaryngologists pediatricians microbiologists basic scientists and graduate and medical school students in these disciplines

Gene Therapy David Cooper,Prof Nick Lemoine,2020-09-10 Gene Therapy describes the delivery systems now available to target a given tissue with specific gene or oligonucleotide sequences and explores the utility of animal modules as test systems In the context of selected disease states it summarises in vitro and in vivo studies and clinical trials performed to date

**Amiloride-Sensitive Sodium Channels: Physiology and Functional Diversity** ,1999-05-04 Sodium reabsorbing epithelia play a major role in whole body sodium homeostasis Some examples of sodium regulating tissues include kidney colon lung and sweat ducts Sodium transport across these membranes is a two step process entry through an amiloride sensitive sodium channel and exit via the ouabain sensitive sodium potassium ATPase The sodium entry channels are the rate limiting determinant for transport and are regulated by several different hormones The sodium channels also play a significant role in a number of disease states like hypertension edema drug induced hyperkalemia and cystic fibrosis Amiloride Sensitive Sodium Channels Physiology and Functional Diversity provides the first in depth exchange of ideas concerning these sodium channels their regulation and involvement in normal and pathophysiological situations Summarizes current state of amiloride sensitive sodium channel field Analyzes structure function of epithelial sodium channels Discusses immunolocalization of epithelial sodium channels Examines hormonal regulation of sodium channels Discusses sodium

channels in lymphocytes kidney and lung Considers mechanosensitivity of sodium channels Provides ideas on sodium channels and disease

**Subject Guide to Books in Print** ,1997      **Research Awards Index** ,      *Journal of the Royal Society of Medicine* ,1999      *Novinky zahraniční literatury* ,1996      **Molecular Diagnosis and Gene Therapy** H.E. Blum,C.H. Wu,G.Y. Wu,1996-06-30 Molecular diagnosis and gene therapy are of increasing interest and importance in clinical medicine The increasing understanding of the pathogenesis of human diseases at the molecular level opens new perspectives for their diagnosis prevention and therapy The first part of this book the proceedings of Falk Symposium No 88 Molecular Diagnosis and Gene Therapy held in Basel Switzerland October 22 23 1995 is aimed at an in depth understanding of the methodology of molecular diagnosis by hybridization analysis polymerase chain reaction and others Further the applications and limitations of these technologies in clinical medicine for the detection of genetic malignant and infectious diseases are reviewed In the second part of the book the basic strategies of gene therapy are presented including gene transfer and targeting Further experimental and clinical applications of gene therapy strategies for the prevention and treatment of hepatic and other diseases are presented Molecular diagnosis and gene therapy are clearly going to be key elements of clinical medicine after the year 2000 In this sense the book should allow basic scientists as well as clinicians to be informed about the state of the art of molecular diagnosis and gene therapy and should provide a perspective for future developments in molecular medicine

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maintain it the basic idea is to have one central server with all relevant information about machine configuration

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