

## Cystic fibrosis: current treatment and future direction

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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 adenine 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

# Cystic Fibrosis Current Topics

**Claudio Donner, Roger  
Goldstein, Nicolino Ambrosino**

## **Cystic Fibrosis Current Topics:**

*The Gut as a Model in Cell and Molecular Biology* F. Halter, D. Winton, N.A. Wright, 1997-12-31 There are many separate groups working in gut biology and they feel that the gut is an excellent model for investigating general problems in differentiation growth control stem cell biology and regeneration and adaptive responses There is a pressing need to define the objectives of the next 5 to 10 years and the meeting Part III of the Gastroenterology Symposia Freiburg 1996 Falk Symposium No 94 held in Freiburg Germany October 25 26 brought together some of these groups with a view to identifying areas which are not being utilized and need to be exploited such as transgenic and knockout approaches retrovirus delivery systems and model cell tissue systems The main themes of the book are gastrointestinal development and differentiation gut stem cell biology and the control of gut growth in normal and abnormal situations Basic research findings are related to clinical situations and the book will appeal not only to gut cell and molecular biologists but also to gastroenterologists interested in the potential applications of these subject areas

**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

**Current Serials Received** British Library. Document Supply Centre, 1995

*Journal of the Royal Society of Medicine*, 1999

**Pulmonary Rehabilitation** Claudio Donner, Roger Goldstein, Nicolino Ambrosino, 2005-05-27 Pulmonary rehabilitation programmes are now a fundamental part of the clinical management of patients with chronic respiratory diseases This comprehensive reference book places pulmonary rehabilitation within the wider framework of respiratory disease and the health burden that this now poses worldwide Part one of the book examines the evidence

*Journal of the Royal Society of Medicine* Royal Society of Medicine (Great Britain), 2009 Includes selected papers from meetings of the Society and of its sections

*Diseases of the Sinuses* David W. Kennedy, William E. Bolger, S. James Zinreich, 2001 This book provides a complete and authoritative text that comprehensively covers all medical and surgical aspects of the paranasal sinuses and the diseases that affect them Kennedy Bolger and Zinreich have recruited the best basic scientists clinicians and surgeons to contribute their expertise to this new work the first on the subject in decades

*Structure-function Analysis of the Chloride Conduction Pathway of the Cystic Fibrosis Transmembrane Conductance Regulator (CFTR)*. Monique Kristine Mansoura, 1996

**Catalogue of Periodicals and Continuations**, 1995

*Diagnosis and Management of Paediatric Respiratory Disease* Robert Dinwiddie, 1997 Respiratory diseases are the most commonly encountered medical problems in children and many need long term management This book provides a clear overview of an increasingly complex subject and helps them to grasp the myriad of tests and procedures available This new edition deals with the increasing impact of HIV and AIDS and the latest development in the management of cystic fibrosis

**Cystic Fibrosis—Current Topics** J. A. Dodge, D. J. H. Brock, J. H.

Widdicombe,1996-08-06 This volume contains an authoritative collection of review articles by leading researchers Each topic has been chosen for its current interest and helps to identify areas of consensus disagreement or lack of information thereby providing a stimulus for further research     *Physiotherapy for Respiratory and Cardiac Problems* Jennifer A. Pryor,Ammani

S Prasad,2008-03-06 Now in it s fourth edition *Physiotherapy for Respiratory and Cardiac Problems* continues to be an essential textbook and reference source for undergraduate and postgraduate students and for the clinician working with patients with cardiac and respiratory problems It strengths lie in integrating the evidence with clinical practice and in covering the whole patient lifespan infants children adolescents and adults new chapters on critical care surgery and psychological aspects of care expanded evidence for clinical practice case studies multi contributed chapters written by internationally recognised experts extensively revised text with new illustrations and photographs comprehensive reference lists which directs the reader to further sources of information Part of the *Physiotherapy Essentials* series core textbooks for both students and lecturers Online image bank now available Log on to <http://evolve.elsevier.com> Pryor physiotherapy and type in your unique pincode for access to over 300 downloadable images     *The Lancet* ,1995-03     **The European**

**Respiratory Journal** ,1993-06     **Cystic Fibrosis** ,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

**Annual Scientific Report** Howard Hughes Medical Institute,1994     *Advances in Second Messenger and Phosphoprotein Research* ,1999     **Walker's Pediatric Gastrointestinal Disease** Ronald E. Kleinman,2008 This new edition is dedicated to the maintenance of a comprehensive approach to the practice of pediatric gastroenterology The size and content of various sections have been modified and new chapters have been added Specific sections deal with Physiology and Pathophysiology Clinical Presentation of Disease Clinical Manifestations and Management discussing the Mouth and Esophagus The Stomach and Duodenum The Intestine and The Pancreas Diagnosis of Gastrointestinal Diseases and

Principles of Therapy Each author selected because of their particular expertise in the field has provided an authoritative and comprehensive account of their topic This volume s need to know information is supported by a varied selection of tables illustrations and photographs      **Nutrition in Child Health** D. P. Davies,1995

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