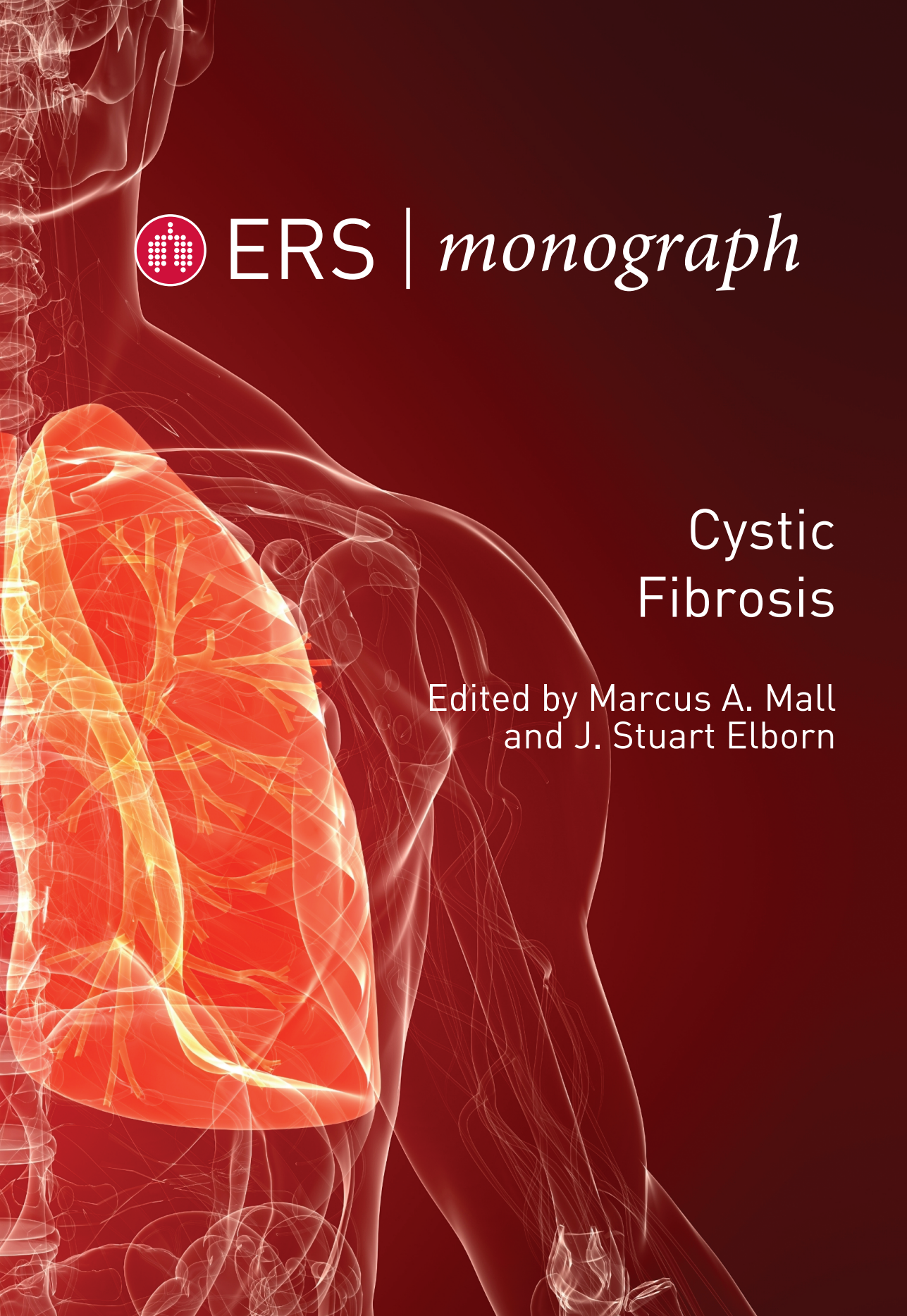
ERS | monograph
Cystic Fibrosis
Edited by Marcus A. Mall and J. Stuart Elborn

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Editor in Chief
Tobias Welte

This book is one in a series of *ERS Monographs*. Each individual issue provides a comprehensive overview of one specific clinical area of respiratory health, communicating information about the most advanced techniques and systems required for its investigation. It provides factual and useful scientific detail, drawing on specific case studies and looking into the diagnosis and management of individual patients. Previously published titles in this series are listed at the back of this *Monograph*.

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Preface

Tobias Welte, Editor in Chief

Although it is the most common genetic disease in Europe, cystic fibrosis (CF) is a rare disease. Nevertheless, it provides a good example of how a powerful patient organisation and dedicated researchers and doctors can help to arouse the interest of the public and the pharmaceutical industry in a disease. This was the key factor in maintaining continuous financial support to make translation from basic research into clinical practice possible.

The success in the treatment of CF patients has contributed to significant improvements in the care of other patient groups. Essential elements of CF therapy have been transferred into the management of non-CF bronchiectasis patients and have recently been approved in randomised controlled trials. The best examples are three major macrolide antibiotic trials that demonstrate impressive effects on exacerbations in non-CF bronchiectasis patients. The concept of inhaled antibiotic therapy to reduce microbiological burden, which was established in CF, has now been used in studies in long-term ventilated patients with Gram-negative pneumonia and could provide a new treatment option for these patients, who still suffer from high morbidity and mortality.

Along with pulmonary hypertension, CF is one of the few diseases where basic scientific findings have been translated into therapeutic concepts. The modification of the cystic fibrosis transmembrane conductance regulator (CFTR), even if it is possible only for particular mutations, represents a breakthrough in the development of new drugs. Through this, we have hopefully learned how dynamic basic research could be transferred into advanced therapies for other diseases, for example usual interstitial pneumonia, for which we do not have a convincing treatment option yet. Overall, CF research could be an excellent role model to stimulate research in respiratory medicine.

This issue of the *ERS Monograph* summarises the most important developments in CF diagnosis and treatment since the publication of the previous CF issue in 2006. I want to congratulate the Guest Editors, Marcus Mall and Stuart Elborn, for the tremendous work they have done in setting up this excellent

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Monograph, which should be of interest to paediatric and adult CF physicians, basic researchers and people working in drug development. I hope this *Monograph* will stimulate joint research, leading to better understanding of and more successful therapy for respiratory diseases.

Guest Editors

Marcus A. Mall

Marcus A. Mall is Professor of Paediatrics and director of the Dept of Translational Pulmonology at the Heidelberg University Medical School, and head of the Division of Paediatric Pulmonology and Allergy and the Cystic Fibrosis Center at the Dept of Paediatrics, University Hospital Heidelberg, Heidelberg, Germany. In 2011, he was appointed director of the Translational Lung Research Center Heidelberg (TLRC) and member of the board of directors of the German Center for Lung Research (DZL). He is an active member of several professional societies, including the European Cystic Fibrosis Society (ECFS), the European Respiratory Society (ERS) and the American Thoracic Society (ATS). He serves on journal editorial boards and on the scientific committee of the ECFS.

Marcus Mall qualified in medicine at the University of Freiburg, Freiburg, Germany, and received his clinical training at the Universities of Freiburg and Heidelberg, and his postdoctoral training at the University of North Carolina at Chapel Hill, NC, USA, where he was appointed Assistant Professor of Medicine. In 2005, he received a grant from the European Commission to establish a Marie Curie Excellence Team at the University of Heidelberg, and in 2009 he was awarded the prestigious Heisenberg Professorship by the German Research Foundation. He is board certified in paediatrics, paediatric pulmonology and infectious diseases.

Marcus Mall's research is focused on the cellular and molecular pathogenesis of CF and other airway diseases, and the development of novel diagnostic approaches and therapeutic strategies. His research programme has been funded by the German Research Foundation (DFG), the German Ministry for Education and Research (BMBF), the European Commission, and others, and he has received several research awards. He developed a mouse that overexpresses the epithelial sodium channel (βENaC), the first animal model with CF-like lung disease. He coordinates interdisciplinary translational research projects, integrating basic research with cohort studies and early phase clinical trials, to improve our understanding of CF lung disease and the translation of research results into the clinic.

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J. Stuart Elborn

J. Stuart Elborn is Dean of the School of Medicine, Dentistry and Biomedical Sciences (SMDBS), Queen's University Belfast, Belfast, UK. He was previously director of the Centre for Infection and Immunity in SMDBS and Professor of Respiratory Medicine. He is a consultant physician in Belfast City Hospital (Belfast, UK), where he started an adult CF programme that now has 300 patients, and he collaborates closely with his paediatric colleagues who provide care for 180 patients. Additionally, he is president of the ECFS and is a trustee of the UK CF Trust.

Stuart Elborn has led a number of clinical trials involving antibiotics, anti-inflammatory agents and cystic fibrosis transmembrane conductance regulator (CFTR)-modulating drugs. He also leads a clinical trials programme in bronchiectasis. His team of pulmonary researchers has recently been selected as part of a Translational Research Partnership in the UK, which focuses on academics working with the pharmaceutical industry in pre-clinical and early clinical trials. His group is also part of the ECFS Clinical Trials Network. He is principal investigator on a number of early stage anti-inflammatory and potentially disease-modifying therapies in CF and other lung diseases.

Stuart Elborn has a major clinical and laboratory research programme in airways infection, funded jointly by the National Institutes of Health (Bethesda, MD, USA), the Research and Development Office in Northern Ireland, the UK Medical Research Council, the Science Foundation Ireland and the European Union Framework 7, investigating the clinical implications of bacterial diversity and, in particular, anaerobes in the CF airway. This involves clinical research and also a range of projects investigating the interaction between bacteria and the host innate immunity.

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Introduction

Marcus A. Mall[1,2] and J. Stuart Elborn[3]

Twenty-five years ago, the sequencing of the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene set the stage for unravelling the pathogenesis of cystic fibrosis (CF) and for development of therapies that target the basic defect of this common life-limiting hereditary disease. This scientific breakthrough brought hope that therapy of CF targeted at the dysfunction of the CFTR protein may be possible and has stimulated enormous multi-disciplinary research efforts towards this goal. In early studies, expression of wild-type and mutant CFTR in cell lines shed important light on normal CFTR function and the molecular defects that can cause CF. Further genetic studies predicted that CF may be caused by a large spectrum of *CFTR* mutations with different molecular consequences, indicating a need for mutation-specific therapies.

However, for many years, the drug discovery process for CF was slow and mostly limited to pre-clinical testing of individual compounds by academic investigators. These studies provided an important proof-of-concept that pharmacological rescue of mutant CFTR function is possible. However, therapeutic development was hampered by the limited efficacy and toxicity of candidate compounds that were identified by this cumbersome and inefficient approach. Nevertheless, the prospect of a therapy to treat the basic defect provided an important rationale for the optimisation of symptomatic therapies and establishment of specialised care centres for patients with CF, a development that has led to an improvement of survival and quality of life unprecedented for a fatal genetic disease.

In recent years, this landscape has been changed dramatically following a high-throughput screening programme for the discovery of CFTR "potentiator" and "corrector" drugs. In fewer than 10 years, this approach led to the development of the first mutation-specific therapy for CF, which has now become available for a subgroup of patients. With this important breakthrough, the CF field has clearly entered a new era of personalised/stratified medicine targeting the underlying genetic defect that may well serve as a model for other rare genetic lung diseases. Furthermore, widespread implementation of newborn screening has opened a window of opportunity for early or even preventive treatment with disease-modifying therapies of future generations of people with CF. Other examples of important progress include the generation of animal models for deciphering the complex *in vivo* pathogenesis of CF lung disease and pre-clinical testing of novel mucolytic, anti-inflammatory and antibacterial

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therapies, as well as progress in basic research on regenerative therapies that are needed to improve outcome of patients with irreversible lung damage.

Despite this enormous progress, important challenges remain that have to be solved in order to deliver disease-modifying treatment, ideally in all patients. These challenges range from the development of drugs that rescue a broader spectrum of CFTR mutations in the laboratory, including the most common mutation Phe508del, all the way to the training of a larger number of CF specialists, who are urgently needed in clinics for competent care of the rapidly growing population of patients with CF as they grow older.

This issue of the *ERS Monograph* provides an update on all aspects of CF lung disease, from infancy to adulthood, including current pathogenetic concepts of mucus plugging, chronic airway inflammation and polymicrobial infection, improvements in early diagnosis and monitoring, mutation-specific and other therapeutic approaches, and important issues related to further improvement of patient care. In state-of-the-art chapters, international experts in the field highlight important recent developments and discuss the next steps that will be required for further improvement of life expectancy and quality of life of patients with CF. As editors, it was a great pleasure to assemble this *Monograph* in the year of the 25th anniversary of the discovery of CFTR, and we trust that it will be a useful reference for basic and clinical scientists, and all members of the CF team.