



Introduction

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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.