

"The combination of expert multidisciplinary care, the optimum application of therapies currently available and the use of powerful, potentially disease modifying new therapies will bring further significant improvements in the quantity and quality of life for people with cystic fibrosis."

In this issue of *Therapy*, cystic fibrosis (CF), one of the most devastating autosomal recessive disorders in man is discussed. This condition, which was only properly recognized in the 1940s, had a very poor prognosis at that time with most children dying in their first decade of life [1]. Since then the introduction of multidisciplinary center care, the use of effective pancreatic enzyme replacement therapy and antipseudomonal antibiotics has progressively improved outcomes. Median survival in most developed countries is now around 40 years and the anticipated median survival for children born in the current decade is into the sixth decade of life [2]. This success has been achieved by improving nutrition and controlling infection and inflammation by optimizing the clearance of infected mucus from the airway and using aggressive antibiotic therapy. However, CF remains a life-shortening condition with median age of death still stubbornly in the mid-to-late 20s. New and transformative therapies are therefore required for this condition.

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chloride and hyperabsorption of sodium ions results in a reduction in the height of airways surface liquid and subsequent dysfunctional mucociliary clearance. This defect results in chronic infection, which drives inflammation and subsequent lung destruction from proteolytic enzymes primarily from host neutrophils [5]. To significantly perturb this pathogenesis the current strategies are to optimize the clearance of infected mucus, reduce inflammation and treat acute and chronic infection [4]. However the ultimate goal is to find therapies that will correct the basic defect using strategies, such as gene therapy or small molecule correctors and potentiators [6,7]. In this edition of *Therapy* these issues are explored by a number of experts in the field.

In most developed countries CF is diagnosed in the neonatal period following newborn screening programs. This allows for early preventative interventions which, if effective, could be disease modifying by preventing early infection [8]. Wainwright and colleagues discuss the importance of developing a proper evidence base for such interventions, in spite of the difficulty of designing studies in infants and small children where surrogate measures of lung function, for example, are difficult [9,10]. Therapies that correct the basic defect are likely to be most effective in this early stage of disease development. It is critically important that clinical trial design and outcome measures are developed to determine whether the exciting new therapies, such as potentiators and correctors, are truly disease modifying.



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development and have significant and clinically important effects on some important biomarkers and clinical outcomes in this condition. VX-770 in patients with G551D significantly improves lung function and patients symptoms while significantly reducing pulmonary exacerbations [7]. This is associated with a large reduction in sweat chloride, an important biomarker of CFTR dysfunction in sweat glands. Although G551D is a relatively uncommon mutation accounting for around 5% of people with CF, this effect is very encouraging and shows that mutant CFTR, which is on the cell membrane but does not gate chloride appropriately, can be corrected [12]. The bigger challenge will be for corrector therapies that bring F508del CFTR to the cell membrane where it can be activated by potentiators. This combination may have a significant therapeutic effect for people with the most common CFTR mutations. Correction of class I mutations may also be possible through compounds that lead to 'read through' of stop codons [4,8,13].

Gene therapy is also a potential transformative therapy and has been an aspiration in the CF research community since the cloning of the gene in 1989. However, the challenges of gene therapy in terms of developing an effective plasmid construct and bringing this together with an effective delivery vector has proven to be very challenging. Alton outlines some of the challenges faced by the UK Cystic Fibrosis Gene Therapy Consortium and indicates the current approaches to optimize this form of therapy [14]. Much progress has been made and the result of a planned multidose proof-of-concept study in 2010 will be eagerly awaited by the CF community.

The current most tractable part of the CF phenotype that can influence outcome is the treatment of infection with a range of new inhaled therapies being developed. New perspectives on the range of bacteria present in the airways of people with CF has challenged our thinking about the bacterial pathophysiology of infection in this condition [15–17]. Tunney and colleagues show that airways infection is clearly polymicrobial and many of the bacteria found in the airways are either obligate or facultative anaerobes [15,18]. Molecular methods that allow the identification of nonculturable bacteria, particularly second generation sequencing, have identified a very wide range of bacterium in the airways and this may begin to challenge our approach to antimicrobial therapy [19].

Chronic infection in the airways is punctuated by pulmonary exacerbations that are associated with pulmonary symptoms, as reduction in measures of lung function and evidence of airways and often systemic inflammation [20,21]. These events, which are often clear to clinicians but difficult to define for clinical trials, are treated with oral or intravenous antibiotics depending on the background of chronic infection and the identification of any new bacteria. Bell and colleagues describe the empirical nature of this therapy and the challenges in defining and appropriately treating these episodes [22]. Pulmonary exacerbations are associated with poorer outcomes and a high priority in the treatment of people with CF is the prevention of these exacerbations, which may in turn improve long-term survival [23].

There are a number of other critically important aspects of the treatment of people with CF [8]. For example, nutrition is a strong independent predictor of outcome and it is of utmost importance that optimal nutritional status is maintained in children and adults with this condition. Other important aspects of care are ensuring that micronutrient levels are maintained, preferably through a balanced diet, although supplementation is often required [24]. General lifestyle issues are also important as there is a significant and strong relationship between socioeconomic class and long-term outcomes in CF [25,26]. Support for parents of a child with CF and for CF adults is important and requires holistic care by a multidisciplinary team that includes physicians, nurses, physiotherapists, nutritionists, psychologists, social workers, as well as pharmacists with the support of a wide range of other disciplines, such as primary care doctors, diabetologists, ENT surgeons, obstetricians and gastroenterologists. The combination of expert multidisciplinary care, the optimum application of therapies currently available and the use of powerful, potentially disease modifying new therapies will bring further significant improvements in the quantity and quality of life for people with CF.

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