Although affecting only 4–5% of those with cystic fibrosis (CF), the G551D-CFTR mutation is the target of the recently approved ‘orphan drug’, ivacaftor. The promise of such genomically guided therapies heralds a new era in the management of CF. A phase 3 trial demonstrated significant improvements in forced expiratory volume in 1 s (FEV1) from baseline, average weight gain, concentration in sweat chloride and reductions in pulmonary exacerbations [Ramsey, B.W., et al. A CFTR potentiator in patients with CF and the G551D mutation. N. Engl. J. Med., 2011. 365: 1663–1672.]. Ivacaftor is among a group of recently approved, novel, mutation guided ‘orphan drug’ therapies that have established clinical benefits within their respective disease categories. They do not, however, offer a cure. Pharmaceutical and biotech companies have leveraged the incentivized benefits of the Orphan Drug Act to develop more of these drugs for orphan disorders affecting populations of <200000 patients. With marked clinical efficacy via DNA sequence guidance, these drugs have also set a precedent in terms of the substantial annual costs and if this trend continues, such expenditures may become unsustainable. This paper explores the genomic pathophysiology of CF and how therapies such as ivacaftor provide benefit to those with the disease but at a considerably elevated price point.

INTRODUCTION

The discovery of the CFTR gene in 1989 ushered in a new era of possibilities in the treatment of cystic fibrosis (CF). Several attempts at manipulating the underlying gene defect have met with varied levels of success (1–4). Ivacaftor, a recently Federal Drug Administration (FDA)-approved CFTR modulating therapy, is the first DNA-guided therapy for a subset of patients afflicted with CF. Coupling the gene defect with the therapy most likely to result in clinical benefit is an excellent demonstration of the strength of a precision therapy. However, with this level of individualized medicine comes substantial cost. Medications, which can cost upward of $400 000 per patient per year, are being approved by the FDA under the auspices of the Orphan Drug Act (5). These therapies, often tailored specifically to the underlying defect of the disease, still only result in symptomatic benefit rather than a cure. Precision medicine is certainly needed to target these devastating, often neglected diseases but if the clinical benefit is primarily symptom reduction, one has to question to what degree the extremes in cost offset the remarkable triumphs in molecular medicine. Moreover, this precedent of a small molecule pill form of therapy, rather than a biologic, which has a relatively low cost of goods to manufacture, raise the question as to what will be considered acceptable norms for DNA-guided therapies in the future.

CYSTIC FIBROSIS

With a frequency of 1 in 2000–3000 live births, CF is the most common fatal autosomal recessive disease among Caucasian populations (6). Worldwide it affects ~70 000 people (7–9). Although a multisystem disease, it is the progressive pulmonary involvement that is responsible for the majority of the morbidity and mortality associated with the condition. Currently, there is no cure for CF. The disease results from mutations in CFTR, a 250 kb gene on the long (q) arm of chromosome 7 that encodes for the CF transmembrane conductance regulator protein ‘CFTR’ (10–15). This protein is an epithelial ion channel that regulates the absorption and secretion of salt and water in a variety of tissues, including the lung, sweat glands, gastrointestinal tract and pancreas (7,16). The resultant viscous mucosal obstructions of exocrine glands with neutrophil dominated debris are among the
pathological hallmarks of the disease. This mucinous impac-
tion leads to a variety of clinical manifestations including in-
adequate airway hydration, rendering the airways vulnerable
to chronic infection and inflammation with subsequent irre-
versible lung damage (17). Chronic fibrosis of the pancreas
due to ductal obstruction causes pancreatic inflammation and
insufficiency. Meconium ileus, a presenting feature in
≏10%
of newborn CF patients, is almost pathognomonic of the
disease (18,19). Infertility occurs due to glandular obstruction
in utero in males and secondary amenorrhea as a result of malnutrition in females (16).

**CFTR PROTEIN**

The CFTR protein contains 1480 amino acids and belongs to
the ATP-Binding Cassette family of proteins that are primarily
concerned with transmembrane transport functions. It has two
intracellular nucleotide-binding domains, two groups of six
membrane-spanning regions and an ‘R domain’ containing
multiple phosphorylation sites. Phosphorylation of the ‘R’
domain by phosphokinase A is required for activation of its
chloride channel (20,21). Channel activity is governed by
two nucleotide-binding domains, which regulate channel
gating and include the carboxyl terminal composed of threo-
nine, arginine and leucine. Six alpha helices comprise each
membrane-spanning domain (Fig. 1). The role of CFTR may
extend beyond chloride permeability and include regulation
of inflammatory response, ion transport and cell signaling
(16). A variety of protein defects result from a host of differing
gene mutations. Efforts to correct such defects have been the
focus of high throughput small molecule screening programs
(Fig. 2).

**THE CFTR GENE**

More than 1700 CFTR gene mutations have been described to
date with the potential to cause disease (4,22). The
G551D-CFTR mutation encodes for defective protein regula-
tion. The most common mutation is F508del-CFTR, which
is a deletion of three DNA bases coding for the 508th amino
acid residue, phenylalanine. In the USA, 70% of Caucasian
CF patients harbor this mutation. However, only five muta-
tions account for 97% of cases in the Ashkenazi Jewish popu-
lation (23).

**CFTR GENE CLASS MUTATIONS**

The G551D-CFTR mutation is the most common class 3 mu-
tation occurring in 4–5% of all CF patients (7). Class 3 muta-
tions cause defective protein regulation often by means of
reduced channel activity in response to ATP. Such defects
result in normal CFTR protein production but abnormal
chloride channel transport. By targeting the abnormal chloride channel activity, ivacaftor promotes more effective chloride transfer. Four other classes of mutations exist and each is a target for future CFTR modulating therapies. Class 1 mutations result in defective protein production. Such mutations account for 2–5% of mutations and are usually caused by frameshift, nonsense or splice site mutations. This results in premature termination of mRNA and complete absence of the CFTR protein. Class 2 mutations result in defective protein processing, which prevents protein transition to its intended cellular location. Although this defect results in relatively normal chloride channel function, the protein is recognized as misfolded and quickly degraded thereby never reaching the cell membrane. Importantly, the most common mutation F508del-CFTR falls into this class. Class 4 mutations involve defective conductance. As with class 3 mutations, CTFR is normally produced and localized to the cell surface; however, the rate of ion flow and duration of channel opening is reduced. Class 5 mutations result in reduced number of CFTR transcripts (16,26–29). With several classes of gene mutations, there are multiple opportunities to target the disease process, a fact that could be used to great advantage in those with non-homologous defects.

NOVEL GENOMICALLY GUIDED CFTR MODULATING THERAPIES

With the discovery of the CFTR gene in 1989, a gene-based therapy to correct the core abnormalities of the disease seemed tantalizingly close. Although there were some early successes with gene therapy, this approach has yet to yield the promised panacea for CF.

IVACAFTOR

Ivacaftor (VX-770) is a recently FDA-approved therapy for those with CF designed to act as a ‘potentiator’ of epithelial CFTR channels thereby prolonging opening and increasing chloride transport activity. As it does not correct abnormal protein folding or transcription as is seen in the more common class 2 F508del-CFTR mutation, studies of ivacaftor have focused on those with class 3 mutations, primarily G551D-CFTR (7,25,30).

By using a high throughput-screening library containing nearly 228 000 candidate compounds, Vertex Pharmaceuticals identified VX-770 (Ivacaftor) as a possible ‘potentiator’ of the CFTR function (30,31). Subsequent in vitro assays demonstrated that human bronchial epithelia expressing G551D-CFTR showed the greatest increase in chloride channel potentiation after stimulation of the cAMP/PKA-signaling pathway when compared with those cells expressing the F508del-CFTR or wild-type mutation. Further preclinical testing using open circuit recordings of nasal potential differences revealed similarly positive results, again in those with the G551D-CFTR mutation. These encouraging results prompted fast-track clinical trials beginning in 2006 directed at CF patients harboring at least one G551D-CFTR mutation (30,32,33).

A recent phase 3, randomized, double-blind, placebo-controlled study demonstrated that ivacaftor significantly improved predicted forced expiratory volume in 1 s (FEV1) by 10.6 percentage points (P < 0.001) over a 48-week period (7). Subjects also were 55% less likely to have a pulmonary exacerbation (P < 0.001) and gained more weight (P < 0.001) than those receiving placebo alone (Fig. 3). Importantly, there was no difference in adverse events between the two groups. Although each subject had at least one G551D-CFTR mutation thereby limiting the potential broader applicability of the study, it is indeed a leap forward in treatment of CF. For the first time, a therapy that targets the protein defect itself may become part of the armamentarium of the treating physician. A separate compound also discovered by Vertex Pharmaceuticals, VX-809 would appear more suitable for the treatment of those harboring the more frequent F508del-CFTR mutation. Although it has proven safe in phase 2a trials assessing its use in isolation and in combination with ivacaftor, its effect on pulmonary function have been mixed (17,34,35).

FUTURE DIRECTIONS

Ivacaftor has demonstrated the considerable benefits achievable with the development of precision therapies that target
the very defect underlying the disease itself. Although this is a major step forward in the treatment for one molecular form of CF, it must be remembered that it remains a symptomatic therapy rather than a cure. For the applicable 4–5% of the CF population with the G551D-CFTR mutation, this clinical benefit will come with a large price tag. The yearly cost per patient receiving ivacaftor is approximately $294 000 (36).

A combination pill including VX-809, which could be prescribed to a much broader population of CF patients would likely be similarly priced. With patients likely to receive such therapies for 30 years or more, the cumulative lifetime cost for a symptomatic therapy would be substantial. The possibility of such treatments being initiated at even earlier time points in the course of the disease could see this figure continue to grow.

Ivacaftor and other such novel, high cost therapeutics have appeared mainly because many pharmaceutical companies have shied away from development of drugs targeting common conditions due to increasing development costs and decreasing likelihood of approval. Instead, many pharmaceutical companies have focused their efforts on orphan drug therapies, costs and prevalence: From phase 2 trials onwards, orphan drugs also have a much higher chance of approval, with an 82% success rate as opposed to 35% for traditional drugs (40).

In opposition to the falloff in approval of drugs for common conditions by the FDA, there has been an acceleration in the rate of orphan drug approvals. 2008 was a record year, with the FDA’s Office of Orphan Drug Development designating 165 products for orphan diseases. As of May 2009, the FDA had designated 2002 drugs for orphan indications, 338 of which have been granted marketing approval (41). Ivacaftor is among a group of orphan drug therapies with similar price points. Eculizumab, a treatment for paroxysmal nocturnal hemoglobinuria, a condition affecting ~8000 people in the USA, costs ~$409 500 per patient per year. Gal-sulfase, a treatment for Maroteaux–Lamy syndrome (Mucopolysaccharidosis VI), which affects an estimated 50–300 people in the USA, costs ~$365 000 per patient per year (5). As opposed to ivacaftor, these drugs are biological therapies and account for ~60% of the orphan drug market (41). Although targeted at small populations, biologics carry with them a potential incremental cost structure. Many of these therapies target pediatric populations and the drug cost is weight based. As these children live longer, the annual cost of therapy would be expected to increase concordantly. The figure of $365 000 per year for gal-sulfase is calculated based on an average weight and accordingly, treatment of a child of <5 years of age would be far less expensive. However, if this same child were to reach 20 years of age, the annual cost could possibly be in the range of $1 million per year (42).

The cost of biologics is usually a weight-based calculation; the cost of production of a pill, however, is not. Several non-biologic therapies have been approved for use by the FDA, but in terms of cost, ivacaftor is by far and away the most costly to date. Being an ‘orphan drug’ one expects an elevated price point, but this particular compound is almost twice the cost of other non-biologic ‘orphan drugs’ (Table 1). Although the price point of such non-biologic therapies is estimated based on the cost of development coupled with the smaller market potential, two main points remain. First, many of these begin as orphan drugs but are developed for more expanded indications or off label use thereby increasing their potential

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Table 1. Orphan drug therapies, costs and prevalence

<table>
<thead>
<tr>
<th>Drug</th>
<th>Estimated annual cost, $</th>
<th>Disease</th>
<th>Estimated prevalence in the USA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Small molecules</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kalydeco™ (ivacaftor)</td>
<td>294 000</td>
<td>Cystic fibrosis, G551D-CFTR</td>
<td>1200</td>
</tr>
<tr>
<td>Zavesca® (miglustat)</td>
<td>128 000</td>
<td>Gaucher disease type I</td>
<td>4000</td>
</tr>
<tr>
<td>Remodulin® (treprostinil)</td>
<td>120 000</td>
<td>Pulmonary arterial hypertension</td>
<td>175 000</td>
</tr>
<tr>
<td>Flolan® (propofenol)</td>
<td>100 000</td>
<td>Pulmonary arterial hypertension</td>
<td>175 000</td>
</tr>
<tr>
<td><strong>Biologics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Soliris® (eculizumab)</td>
<td>409 500</td>
<td>Paroxysmal nocturnal hemoglobinuria</td>
<td>8000</td>
</tr>
<tr>
<td>Elaprase® (idursulfase)</td>
<td>375 000</td>
<td>Hunter syndrome</td>
<td>500</td>
</tr>
<tr>
<td>Naglazyme® (galsulfase)</td>
<td>365 000</td>
<td>Maroteaux–Lamy syndrome (Mucopolysaccharidosis VI)</td>
<td>50–300</td>
</tr>
<tr>
<td>Cinryze®</td>
<td>350 000</td>
<td>Hereditary angioedema</td>
<td>6200</td>
</tr>
</tbody>
</table>

*(44); *(45); *(46); *(47); *(5); *(48).*

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market size considerably. Secondly, one of the original barriers to entering the orphan drug market was the potentially small return on such products, but with global orphan drug sales reaching $84.9 billion in 2009; they are certainly beginning to generate ‘blockbuster’ size revenue streams (40).

EFFORTS TO REDUCE COSTS
A significant advantage of precision therapy trials is that clinically significant and statistical differences can be demonstrated using much smaller populations of subjects over shorter periods; the phase 3 trial of ivacaftor included 161 subjects over only 48 weeks (7). It would appear that significant drug development costs savings could be accrued from the advantages of such scaled down trials. If current pricing of orphan drugs was felt to be unsustainable, the prices of such drugs might be controlled, as is the case in countries outside of the USA. The addition of a ‘clawback’ provision that exists in the EU version of the Orphan Drug Act may be included in the US law; this provision permits a reduction in the statutory exclusivity period if the orphan drug becomes sufficiently profitable within the protected time (38). The adoption of such strategies, however, may lead to pharmaceutical and biotech companies developing fewer therapies for such devastating and, to date, often neglected diseases.

CONCLUSION
The approval of ivacaftor has signaled a new chapter in the treatment of the underlying protein defect in CF. Although it represents a major step forward in terms of disease management, it must be realized that it remains a symptomatic treatment option rather than a cure. Furthermore, this progress in a DNA-guided treatment has been coupled with a heavy economic burden. This is representative of several other orphan drugs in terms of the yearly costs. This trend begs the question of what portends for new DNA-guided treatments, while on the other the potential of profoundly exacerbating an already stressed health care economic landscape. Traditional therapies have generally been associated with an acceptable threshold of cost of ~$35 000–$50 000 per quality-adjusted life year (43). Clearly, the new CF treatment and other orphan drugs cited here are at a cost well beyond the previously accepted thresholds. Much more effort in formal assessment of cost and benefit, along with health care policy, will be necessary. Furthermore, the potential for the life science industry for doing everything possible to contain costs has certainly not been apparent to date. Perhaps, a new model will ultimately surface, but until that time the benefit and cost realities seem to date leave us with a sobering impression of an unacceptably expensive, yet precise form of medicine.

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