Reviewer's report

**Title:** State of Progress in Treating Cystic Fibrosis Respiratory Disease

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**Reviewer:** Bruce Rubin

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This is a well written and comprehensive manuscript by two great authors. Because the manuscript has neither page nor line numbers associated, it is difficult to link these comments directly to passages in the manuscript.

The most important correction to be made is that when discussing the underlying pathophysiology of cystic fibrosis (CF) airway disease it is incorrect to state that the airway surface liquid (ASL) is dehydrated. Data from animal models and cell culture demonstrates that there is isoosmolar hypovolemia of ASL. Dehydration suggests an increased concentration of ions due to water loss. Because volume is depleted but hydration remains the same; it is incorrect to call this dehydration. This is important both semantically and physiologically. If the airway was dehydrated, we might correct his by adding hypoosmolar water to the airway when in fact, benefit has only been seen using hyperosmolar aerosols. It is thought that these aerosols transiently increase the volume of ASL, unbinding secretions from the airway surface and inducing cough. Medications known to increase water content of the ASL do not provide benefit so amiloride, either by itself or in combination with hypertonic saline, appears to lead to less favorable outcomes; denufosol which increases water transport has not been demonstrated to be beneficial. Furthermore there is no evidence that there is dehydration of expectorated mucus or sputum and placing sputum in saline does not cause it to swell or change hydration.

Associated with this misconception, is the statement that dehydration “creates ciliary dysfunction effectively halting the mucociliary escalator” as a cause of airway disease. This is untrue. Airway mucociliary clearance is preserved in infants and young children with CF and in the CF nose. Furthermore, even in older patients with established disease there is some preservation of mucociliary clearance despite airway inflammation. This is in contradistinction to primary ciliary dyskinesia where there is no effective mucociliary clearance from birth but a far more benign pulmonary course. It can be stated with confidence that mucociliary dysfunction is not the primary cause of CF airway disease.

Phlegm in the CF airway is neither dehydrated nor viscous when compared with sputum from persons with asthma or chronic bronchitis. CF secretions are tenacious (adhesivity and cohesivity) so drugs that change the surface of secretions and release them from the airway epithelium are effective. These include hyperosmolar solutions and surfactant. Also for this reason, airway clearance techniques to promote effective cough are effective. Phlegm in the CF
airway contains almost no intact mucin and is predominantly polymeric DNA and F-actin with characteristics more similar to pus than mucus. This may explain why dornase alfa is effective in improving mucus clearance in CF while aerosolized N-acetyl cysteine has no benefit or even worsen lung function.

In the section on CFTR modulation, the authors accurately state that more than 1,800 CF gene mutations have been described in the SickKids database, however they also suggest that these can all be categorized as disease causing abnormalities of synthesis, processing, regulation, or channel conductance. Many, if not most of these, abnormalities have not been shown to be disease causing which has led to the unfortunate circumstance of patients with minimal or no symptoms being classified as having CF on the basis of having a non disease causing mutation identified through screening.

In the discussion on the macrolide antibiotics, please note that macrolide antibiotics have been developed that have no antimicrobial properties but that have strong immunomodulatory properties (eg EM703 and Z18010) and that the 16-member macrolides have antimicrobial properties but are not effective immunomodulators. It is now believed that the mechanism of action for the macrolides is modulation of the extracellular regulated kinase (ERK1/2) and not antimicrobial effects.

Declaration of competing interests:

Yes, I have competing interests.

I hold research grants from the Cystic Fibrosis Foundation and the Denny Hamlin Foundation to study CF. I hold patents on two novel mediations to potentially treat CF (but neither are mentioned in this review), I have been a scientific consultant to Pharmaxis and Gilead Sciences, and I hold strong scientific opinions regarding the subject of the manuscript.