TO THE EDITOR: We appreciate the interest that Dr. Kaunitz and colleagues (1) have expressed regarding our recent article. One aspect of the manuscript was our conjecture that sustained alkalinity in the crypt epithelium would support intestinal hyperproliferation, a statement based on numerous previous reports in a variety of cells/tissues for which we cite only a few examples. We strongly agree with Kaunitz and colleagues that resistance to cellular acidification resulting from CFTR deficiency in villus cells would be protective against an increased luminal acid load in the cystic fibrosis (CF) intestine. It was not made clear in their letter, though, how resistance to cellular damage might increase the proliferative status of the epithelium. We apologize to Dr. Kaunitz and colleagues for unintentionally omitting citation of their article that, indeed, provides another example of intestinal cell alkalinity in the CF condition. However, our investigation dealt specifically with intracellular pH (pHi) dysregulation in the proliferative compartment of the Cftr knockout (KO) crypt epithelium and not with terminally differentiated cells of the villi that were the focus of Dr. Kaunitz’s study.

The emphasis of our study was to understand the lack of pH i regulation in Cftr KO crypt epithelium, an apparently epithelial-autonomous effect of Cftr loss because it was observed in organoids in the absence of microbial, neuroendocrine or immune factors of the CF intestinal environment. Since cell alkalinity facilitates proliferation, it is reasonable to suggest that pHi dysregulation may contribute to the intestinal hyperproliferation of unknown etiology that occurs in the Cftr KO mouse intestine (2). As shown recently by the Vogelstein laboratory, the rate of stem cell proliferation in various tissues explains cancer risk (4); therefore it is also reasonable to surmise from this and cited information in the article that “hyperproliferation provides a platform for neoplasia.” Although loss of CFTR function in CF patients has not been associated with reproductive tract or lung cancer, these tissues differ in pH i regulation and stem cell turnover. Downregulation of CFTR, however, has been recognized in primary human breast cancer and is associated with poor prognosis (5), much as was recently shown for human gastrointestinal (GI) cancer (3). CF mice recapitulate this aspect of CF by showing a 61% intestinal tumor penetrance at 12 mo of age as well as a corresponding dysregulation of Wnt/β-catenin signaling. Thus, the designation of CFTR as an intestinal tumor suppressor is consonant with hyperproliferation in its absence. Given the increasing life expectancy of CF patients (40.7 yr, CF Registry) and the numbers of CF patients receiving lung transplantation, it is appropriate that the present discussion focuses attention on the seriousness of GI cancer risk in the CF population. There is a growing need to investigate the underlying causes for increased GI cancer risk in CF which are ultimately a consequence of dysfunction by CFTR, an epithelial Cl− and HCO3− channel.

DISCLOSURES
No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS
N.M.W. and L.L.C. edited and revised manuscript; N.M.W., J.L., S.R.S., A.M.S., and L.L.C. approved final version of manuscript; L.L.C. drafted manuscript.

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