The alkaline mucus barrier of the duodenum plays an important role in protecting the epithelium from acidic chyme entering from the stomach. Active HCO$_3^-$ secretion involves the apical membrane activities of the cystic fibrosis transmembrane conductance regulator (CFTR) Cl$^-$ channel, the protein that is defective in cystic fibrosis (CF), and Cl$^-$ /HCO$_3^-$ exchangers. Under basal conditions, studies of CF patients and mouse models indicate that HCO$_3^-$ secretion by anion exchange predominates. In addition, basal HCO$_3^-$ secretion is reduced in the CF duodenum, but the specific pathophysiology for this deficiency has yet to be elucidated. Our studies reveal that Cl$^-$ channel activity by CFTR facilitates apical membrane Cl$_{\text{in}}$\text{/HCO$_3^-$}_{\text{out}} exchange by providing a Cl$^-$ ‘leak’ and is responsible for the reduced rate of Cl$^+$/HCO$_3^-$ exchange in the murine CF intestine. Using mice with gene-targeted deletions of the apical membrane Cl$^+$/HCO$_3^-$ exchangers PAT-1, DRA, and AE4, PAT-1 was found to be the major Cl$^+$/HCO$_3^-$ exchanger of the upper villus of the duodenum. Interestingly, these studies also revealed a novel role for PAT-1 as a base-importer (i.e., Cl$_{\text{out}}$/HCO$_3^-$$_{\text{in}}$) whereby it interacts with carbonic anhydrase II (CAII), the most widely expressed isozyme of the small intestine, during H$^+$/peptide transport to minimize intracellular acidification and sustain nutrient absorption.