TO THE EDITOR:

This is regarding the editorial “Aquaporin gene therapy for disorders of cholestasis?” by Tradtrantip and Verkman. We thank the authors for their comments in our recent studies. Nevertheless, we believe that an analysis of the role of aquaporins (AQP) in hepatocyte canalicular water transport and bile secretion should take into account several published contributions that were not cited in the editorial.

Two independent studies using the polarized rat hepatocyte couplet as in vitro model for bile secretion indicate that the osmotically driven transepithelial transport of water is largely transcellular by AQP with a minor paracellular contribution. In line with this is the assessment of the osmotic water permeability of hepatocyte basolateral and canalicular plasma membranes. Studies in bile-canaliculi-forming, human-hepatocyte-derived HepG2 cells provide key additional support by demonstrating that the gene silencing of canalicular AQP8 markedly reduced osmotically driven and bile-agonist-induced canalicular water secretion. Altogether, these experimental evidences support the notion that canalicular AQP8 is implicated in bile formation and that a defective expression of this AQP contributes to bile secretory dysfunction. In this context, it is conceivable that AQP gene transfer may help to improve certain cholestatic disorders.

According to the editorial, studies in AQP8 knock-out mice provide evidence against a role of canalicular AQP8 in bile secretion. In that study, bile was not collected, and the conclusion was based on the fact that AQP8 knockout mice show only mild dietary fat misprocessing. Although this finding may suggest a preserved excretion of bile salts for lipid digestion, direct studies on bile secretion must be done in order to conclude whether AQP8 knockout mice have any alteration in the flow of bile.

In the editorial, it is questioned that only a subset of AQP1-expressing hepatocytes was able to increase bile flow. The transduction efficiency of 20% was estimated considering the total number of hepatocytes within the lobule (i.e., periportal, central, and perivenous). Nevertheless, the retrograde biliary vector administration allowed that most of the periportal hepatocytes were transduced with AQP1. This is relevant because periportal hepatocytes are exposed to the highest blood concentrations of bile salts and thus are the primary cells involved in bile-salt-dependent bile secretion.

We think it may be premature to judge whether the hepatic gene transfer of AQP is a credible approach for treatment of cholestasis. We anticipate that further studies will clarify its impact as a novel therapeutic strategy.

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REFERENCES


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