

University of Groningen

Reply to Letter to the Editor HEP-20-0593

Roscam Abbing, Reinout L P; Kuipers, Folkert; Paulusma, Coen C; Verkade, Henkjan J; Groen, Albert K; Oude Elferink, Ronald P J; van, Stan F J; de Graaf, Irene M.

Published in:
Hepatology

DOI:
[10.1002/hep.31291](https://doi.org/10.1002/hep.31291)

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2020

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Roscam Abbing, R. L. P., Kuipers, F., Paulusma, C. C., Verkade, H. J., Groen, A. K., Oude Elferink, R. P. J., van, S. F. J., & de Graaf, I. M. (2020). Reply to Letter to the Editor HEP-20-0593. *Hepatology*. <https://doi.org/10.1002/hep.31291>

Copyright

Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license. More information can be found on the University of Groningen website: <https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment>.

Take-down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): <http://www.rug.nl/research/portal>. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.

REPLY:

We sincerely thank Dr. Javitt for his interest in and perspective on our article.⁽¹⁾ He indicates that specific effects of Myrcludex B should be considered an explanation for increased biliary cholesterol and phospholipid secretion after Myrcludex B treatment as partial hepatectomy (PH) also leads to an increased contribution of pericentral hepatocytes to bile salt uptake and secretion, but biliary cholesterol and phospholipid secretion are not affected. In our opinion, nonspecific Myrcludex B–induced activation of canalicular or sinusoidal transporters seems unlikely given the absence of Na⁺-taurocholate cotransporting polypeptide (NTCP) homology with these transporters and our data from experiments with scavenger receptor class B member 1 or adenosine triphosphate binding cassette subfamily G member 8 null mice. Myrcludex B is an NTCP-specific peptide showing minimal uptake by hepatocytes.

In contrast to the situation of Myrcludex B–mediated NTCP inhibition, PH acutely leads to a higher flow per gram liver; and periportal hepatocytes thus face a large influx of bile salts, close to their maximal transport capacity. As the bile salt to cholesterol/lecithin curve tends to plateau at higher bile salt concentrations, this explains a relatively low biliary cholesterol/lecithin secretion despite increased bile salt transport.^(1,2) Another major adaptation upon PH is that the liver is reprogrammed toward rapid restoration of liver mass. This includes reduced cholesterol synthesis in periportal hepatocytes. Cholesterol and phospholipids are also pivotal for membrane formation in newly generated hepatocytes. The pool of hepatic cholesterol/lecithin available for biliary secretion is thus likely decreased after PH. Finally, PH leads to activation of the nuclear bile salt receptor farnesoid X receptor (FXR), stimulating hepatic regeneration. This is in contrast to Myrcludex B–treated mice, in which hepatic FXR activation is unaffected or even reduced and expression of FXR–regulated proliferative genes is repressed.

Dr. Javitt concludes his letter by stating that the canalicular concentration of bile salts is a major determinant of biliary cholesterol and phospholipid secretion. We partially agree with this notion but note that

the amount of lipid secreted per bile acid molecule is variable⁽²⁾ and that the location matters. Not hampered by adaptations occurring during liver regeneration, we have directly investigated zonation-related differences in bile formation using a very specific NTCP inhibitor combined with monitoring the distribution of a fluorescent bile salt.⁽¹⁾ The results are in line with a shift of hepatic bile salt uptake from predominantly periportal toward more pericentral hepatocytes, leading to increased canalicular exposure and more cholesterol and phospholipid excretion in bile while total biliary bile salts are not increased or are even decreased. It is not known to what extent such a shift occurs in the regenerating liver after PH, and given the complex adaptive changes after PH, this is difficult to predict without experimental data.

Reinout L.P. Roscam Abbing¹

Folkert Kuipers²

Coen C. Paulusma¹

Henkjan J. Verkade²

Albert K. Groen^{2,3}

Ronald P.J. Oude Elferink^{1,4}

Stan F.J. van de Graaf ^{1,4}

¹Tytgat Institute for Liver and Intestinal Research
 Amsterdam Gastroenterology and Metabolism
 Amsterdam UMC, University of Amsterdam
 Amsterdam, the Netherlands

²Departments of Pediatrics & Laboratory Medicine
 University of Groningen
 University Medical Center Groningen
 Groningen, the Netherlands

³Department of Internal and Vascular Medicine
 Amsterdam Cardiovascular Sciences
 Amsterdam UMC, University of Amsterdam
 Amsterdam, the Netherlands

⁴Department of Gastroenterology & Hepatology
 Amsterdam Gastroenterology and Metabolism
 Amsterdam UMC, University of Amsterdam
 Amsterdam, the Netherlands

REFERENCES

- 1) Roscam Abbing RLP, Slijepcevic D, Donkers JM, Havinga R, Duijst S, Paulusma CC, et al. Blocking sodium-taurocholate cotransporting polypeptide stimulates biliary cholesterol and phospholipid secretion in mice. *HEPATOLOGY* 2020;71:247–258.

- 2) Verkade HJ, Wolters H, Gerding A, Havinga R, Fidler V, Vonk RJ, et al. Mechanism of biliary lipid secretion in the rat: a role for bile acid-independent bile flow? *HEPATOLOGY* 1993;17:1074-1080.

Author names in bold designate shared co-first authorship.

© 2020 The Authors. *HEPATOLOGY* published by Wiley Periodicals LLC on behalf of American Association for the Study of Liver Diseases. This is an open access article under the terms of the Creative Commons Attribution-

NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

View this article online at wileyonlinelibrary.com.

DOI 10.1002/hep.31291

Potential conflict of interest: Nothing to report.