In vitro rescue of the bile acid transport function of some ABCB11 variants by CFTR potentiators: a targeted pharmacotherapy in progressive familial intrahepatic cholestasis type 2

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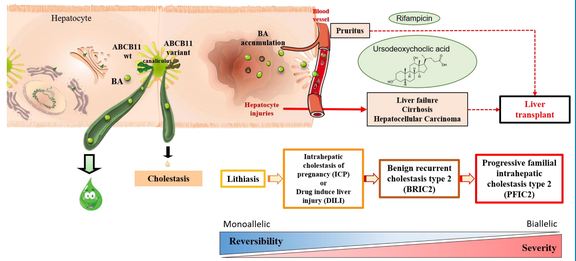
INTRODUCTION

ABCB11 is expressed at the canalicular membrane of hepatocytes and is responsible for biliary bile acid secretion. Variations in the *ABCB11* gene cause a spectrum of rare liver diseases. The most severe form is progressive familial intrahepatic cholestasis type 2 (PFIC2).[1] Current medical treatments of these conditions have limited efficacy.[2] Hence, the identification of new targeted pharmacotherapies as an alternative to liver transplantation for patients with severe forms of ABCB11-related diseases is a major challenge.



AIM

To correct the defective function of three *ABCB11* variations (i.e. A257V, T463I and G562D) identified in PFIC2 patients. To do so, in a repositioning strategy, we evaluated the effect of Ivacaftor (VX-770, Kalydeco®)[3], GLPG1837[4], SBC040 and SBC219[5], known as potentiators of Cystic Fibrosis Transmembrane Conductance Regulator (CFTR).

METHOD

The three *ABCB11* disease-causing variations have been studied by 3D structure modelling. These variations were reproduced in a plasmid encoding a rat Abcb11-green fluorescent protein (GFP). After transfection, the expression and the localization of the variants were studied in HepG2 and Can 10 cells. The taurocholate (TC) transport activity of the variants and the drug effects were studied in Madin-Darby canine kidney (MDCK) clones co-expressing Abcb11 and the rat sodium taurocholate co-transporting polypeptide (Ntcp/Slc10A1).

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RESULTS

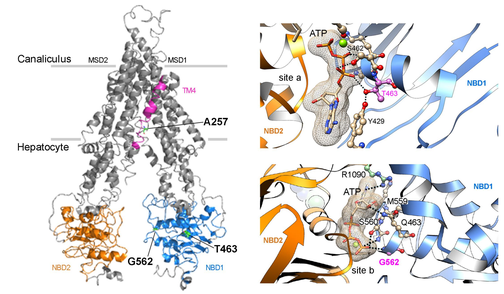

Figure 1 ***: Three dimensional molecular modelling of ABCB11.*** A257V-, T463I- and G562D-*ABCB11 variations might directly or indirectly impact ABCB11 transport function by disrupting ATP binding or ABCB11 local conformational change between the inward- and outward-facing states.*

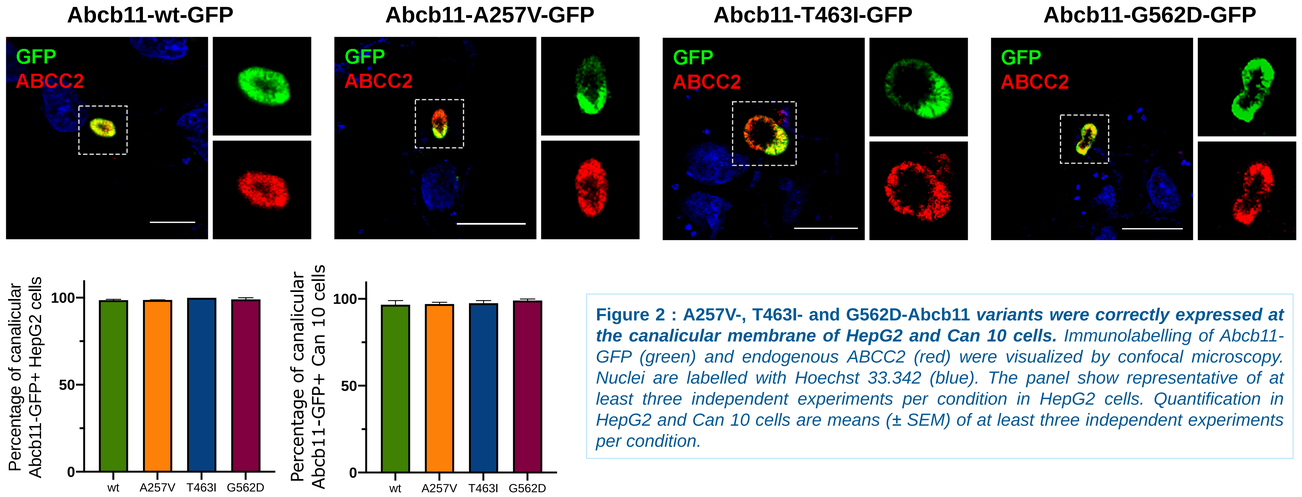

Figure 2 : A257V-, T463I- and G562D-Abcb11 ***variants were correctly expressed at the canalicular membrane of HepG2 and Can 10 cells.*** *Immunolabelling of Abcb11-GFP (green) and endogenous ABCC2 (red) were visualized by confocal microscopy. Nuclei are labelled with Hoechst 33.342 (blue). The panel show representative of at least three independent experiments per condition in HepG2 cells. Quantification in HepG2 and Can 10 cells are means (± SEM) of at least three independent experiments per condition.*

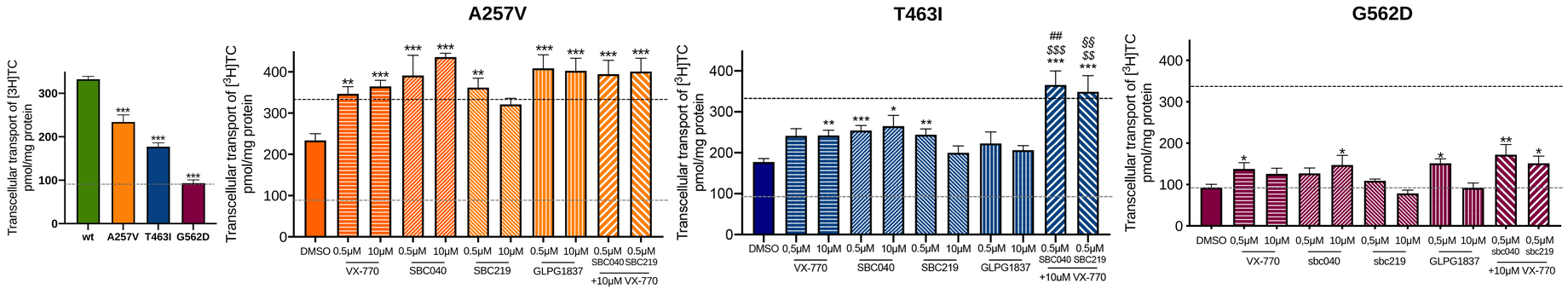

Figure 3 : CFTR potentiators totally or partially rescue the functional defect of Abcb11 variants. A257V-, T463I- and G562D-Abcb11 *variants had a defective function when studied in MDCK cells with a TC transport activity ranging from 28 to 70 % of the one observed in MDCK cells expressing the wt Abcb11. VX-770, SBC040, SBC219 and GLPG1837 potentiators increased by 1.3 to 1.9-fold the TC transport activity of A257V, T463I and G562D variants of Abcb11, allowing the TC transport activity of the A257V variant to reach the one of the wt-Abcb11. Furthermore, an additive effect was observed for the T463I variant of Abcb11 when VX-770 was combined with SBC040 or SBC219. The upper and lower dashed lines indicate [³H]TC transport measured in MDCK cells expressing both wt and Ntcp and Ntcp alone, respectively. DMSO was used as control vehicle at the same dilution (0.1 % DMSO for all conditions). Means (± SEM) of at least six independent experiments for each tested condition are shown. *p < .05; **p < .01; ***p < .005 vs non-treated Abcb11-wt expressing cells; $$p < .01; $$$p <.005 vs VX 770-treated cells; ##p <.01 vs SBC040 treated cells; §§p < .01 vs SBC219-treated cells.*

CONCLUSIONS

This proof of concept suggests that such CFTR potentiators may constitute an efficient targeted pharmacotherapy approach for some selected PFIC2 patients carrying *ABCB11* variations affecting the transport function. Such potentiator drugs could increase the pharmacopoeia available for patients with ABCB11 deficiency and thus delay or even suppress the need for liver transplantation.

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