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Organoids to evaluate novel treatment strategies for intrahepatic cholestatic disease

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BACKGROUND:
ATP8B1 and ABCB11 deficiency (PFIC1 and PFIC2) are rare pediatric liver diseases characterized by intrahepatic cholestasis. Treatment options are limited to invasive therapies, including liver transplantation. We recently tested promising novel therapies *in vitro* to rescue specific *ATP8B1* genotypes, that might also be applicable to specific *ABCB11* genotypes. However, there is no good *in vitro* model to predict clinical effect of these mutation-specific therapies.

METHODS / CASE REPORT:
We used liver organoids to generate a functional preclinical treatment assay for the bile salt export pump (BSEP). BSEP is encoded by *ABCB11,* and functionally dependent on ATP8B1 because of its putative role in plasma membrane composition and localization of apical transmembrane proteins, such as BSEP. To allow preclinical testing in a personalized manner without the need for a liver biopsy, we also evaluated functional assessment of ATP8B1 in rectum organoids.

RESULTS:
We generated liver and rectum organoids with ATP8B1 and ABCB11 deficiency from patient tissue and through CRISPR-Cas9 gene editing. We show that BSEP function can be evaluated with fluorescent taurocholate in differentiated liver organoids, which might be used as a functional assay for both ATP8B1 and ABCB11 deficiency. We additionally show we can use the Forskolin induced swell test in rectum organoids to assess activity of the cystic fibrosis transmembrane conductance regulator (CFTR) as a functional assay for ATP8B1.

DISCUSSION:
Organoids provide a unique *in vitro* model to evaluate the clinical effect of novel therapeutic strategies for ATP8B1 and ABCB11 deficiency in patients' native cellular and genetic background. After optimization, these assays will be used to study the patient-specific effect of our novel therapeutic strategies.