Intestinal tissue organoids to study drug transport and metabolism from infants to adults

Eva J. Streekstra[1,2], M. Keuper-Navis[2,3], R. Greupink[1], F.G.M. Russel[1], Kazuhiro Ariga[4] ,E. van de Steeg[2], S.N. de Wildt[1,5]

[1] Division of Pharmacology and Toxicology, Department of Pharmacy, Radboud University Medical Center, Nijmegen, The Netherlands
[2] Human Cell Biology, Department of Metabolic Health Research, TNO, Leiden, The Netherlands
[3] Experimental Pharmacology, Department of Pharmaceutical Sciences, Utrecht University, Utrecht, The Netherlands
[4] TNO, Pharma, Japan
[5] Intensive Care and Department of Pediatric Surgery, Erasmus MC Sophia Children Hospital, Rotterdam, The Netherlands

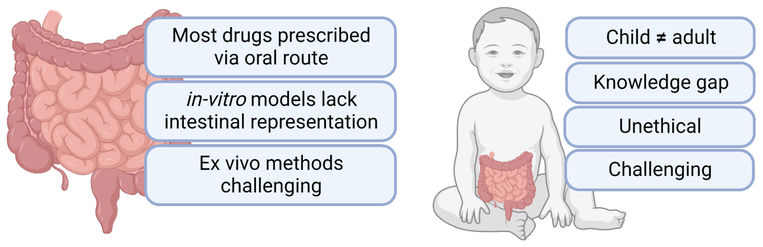
#1P-154

Background

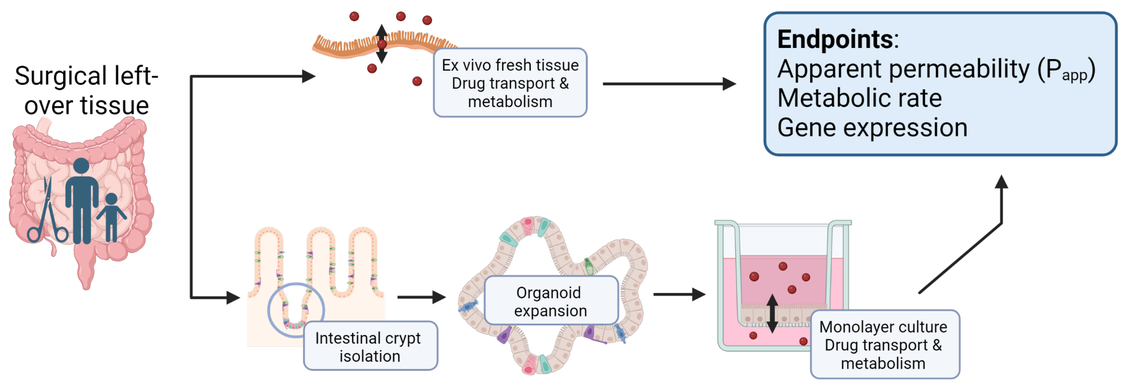
The **small intestine** plays a very important role in the oral bioavailability of drugs. Therefore, it is **important** to understand intestinal absorption, potential regional differences, and age-related effects during drug development. **Existing *in vitro* models lack** the ability to recapitulate the *in vivo* intestinal physiology, neither mimic population variation. Moreover, GI toxicity studies are profoundly dependent on animal studies[1]. Patient derived small intestinal organoids may overcome these limitations**. Differentiated organoids** show most types of intestinal cells present in epithelial barrier, and express drug transporters and metabolizing enzymes thereby being a **promising tool for pharma- and toxicokinetic research in special populations**.

Objective
To study the applicability of patient derived intestinal organoids for predicting region and population differences in drug transport and metabolism

Why an intestinal model?



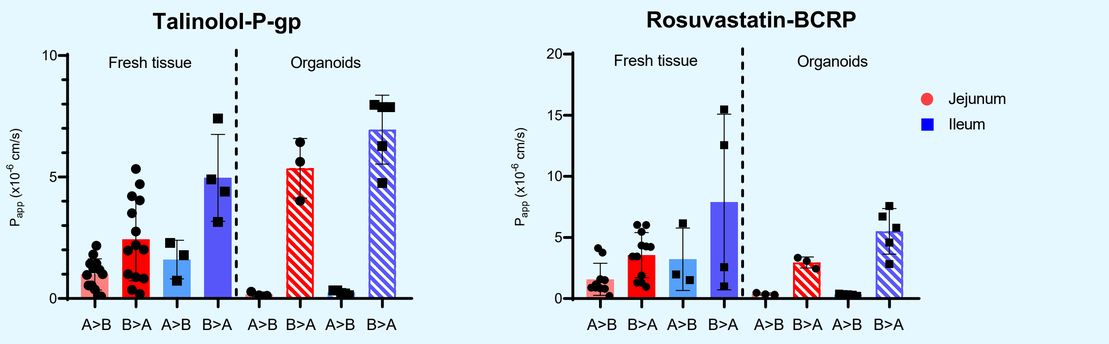
Organoid monolayer methodology



Results in fresh tissue vs patient derived organoids

Adult regional specificity fresh tissue vs organoid monolayers

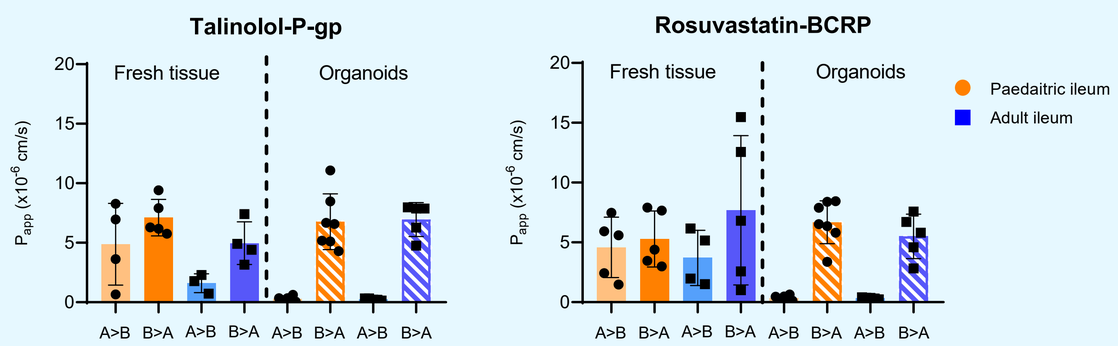
Regional specific efflux transport



A>B = apical to basolateral transport; B>A = basolateral to apical transport

Pediatric ≤1 year & adult in fresh tissue vs organoid monolayers

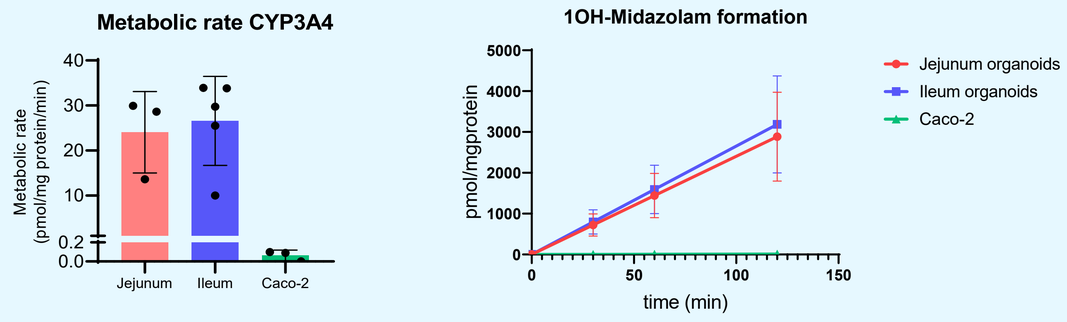
Similar efflux (B>A) transport in pediatric organoids



A>B = apical to basolateral transport; B>A = basolateral to apical transport

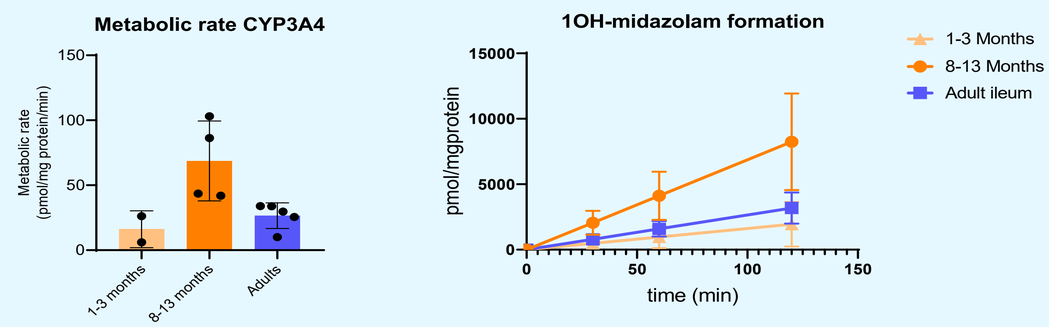
Adult monolayer metabolism by CYP3A4

More CYP3A4 metabolism in organoid monolayers compared to Caco-2



Pediatric vs adult CYP3A4 metabolism in organoid monolayers

Higher CYP3A4 metabolism in children ±1 year old



Take home messages:

- Patient derived adult and pediatric organoids can be cultured and applied for PK research
- Intestinal organoid monolayers from adults show ***region specific functionality trends of MDR1 and BCRP*** [2,3] and more **CYP3A4 functionality** compared to Caco-2 monolayers
- ***Pediatric*** intestinal organoid monolayers 8-13 months old show a ***possible higher CYP3A4 metabolism*** compared to adults
- ***Pediatric*** intestinal organoid monolayers show ***similar drug transport*** compared to adults
- More (young) donors will be included to further study population variation in intestinal drug transport and metabolism
- Organoid metabolism will be ***compared with fresh tissue functionality*** data and gene expression

Questions? Eva Streekstra, MSc; eva.streekstra@radboudumc.nl;

[1] Matsui, T., & Shinozawa, T. (2021). Human organoids for predictive toxicology research and drug development. Frontiers in Genetics, 2119.doi: 10.3389/fgene.2021.767621 [2] Müller J, et al. Expression, regulation and function of intestinal drug transporters: an update. Biol Chem. 2017 Feb 1;398(2):175-192. doi: 10.1515/hsz-2016-0259. [3] Grangeon A, et al. Determination of CYP450 Expression Levels in the Human Small Intestine by Mass Spectrometry-Based Targeted Proteomics. Int J Mol Sci. 2021 Nov 26;22(23):12791. doi: 10.3390/ijms222312791.

TNO innovation for life

Institute for Health Sciences
Radboudumc