



Hepatocyte Transporter Network 2019
Les Diablerets, Switzerland
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Hepatocyte concentrations induced by transporter activity in isolated and perfused rat livers

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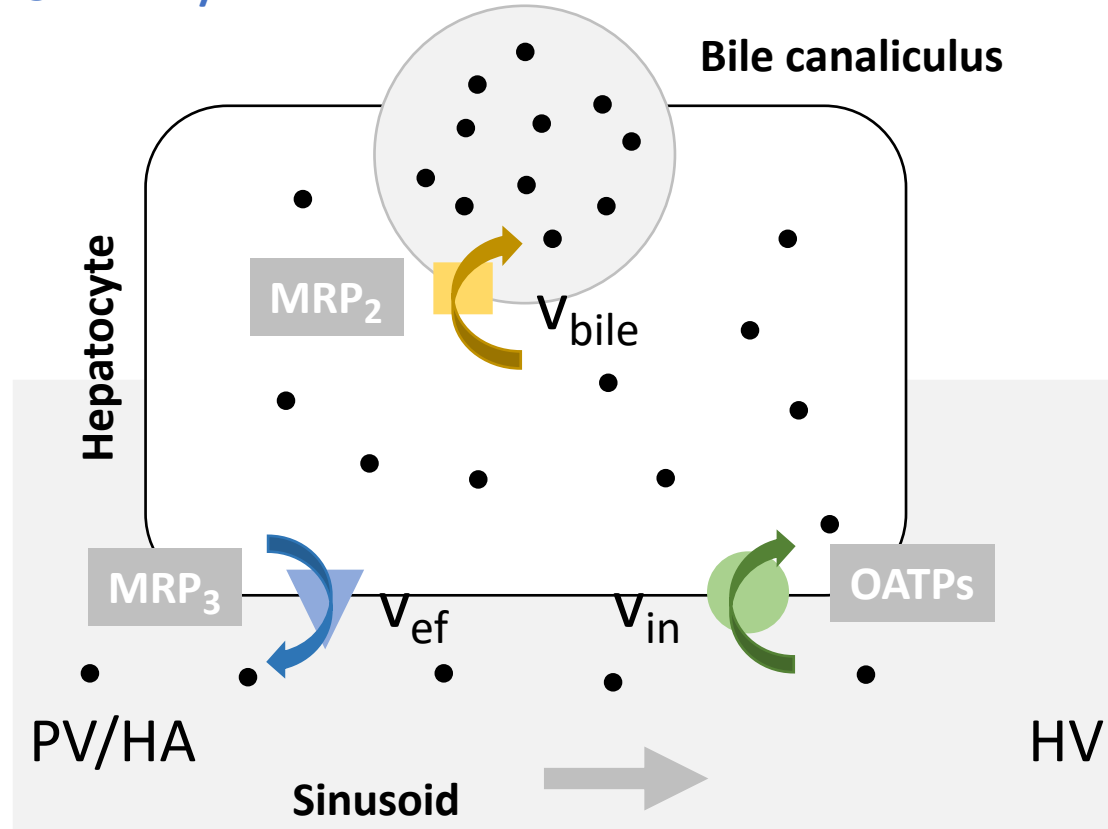
Drug hepatocyte concentrations

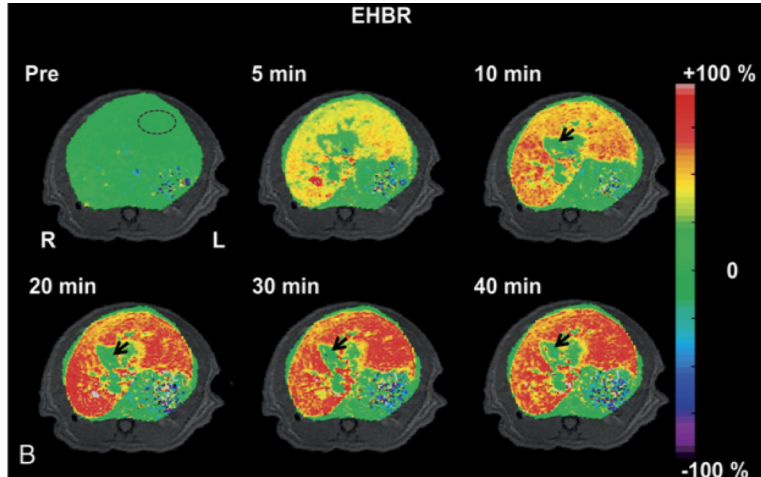
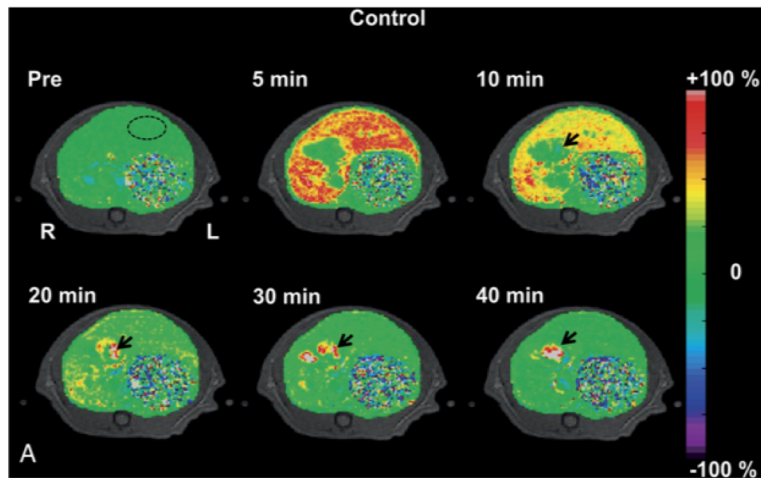
- **Concentrations** are important parameters for drugs targeting hepatocytes
- Concentrations should be high enough to be effective (statins) but low enough to avoid toxicity by accumulation
- **Liver imaging** may quantify these concentrations

Hepatobiliary imaging substrates

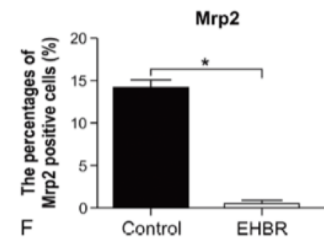
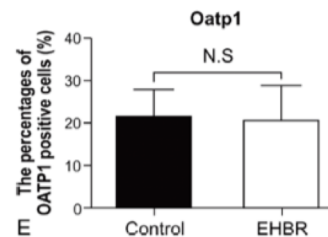
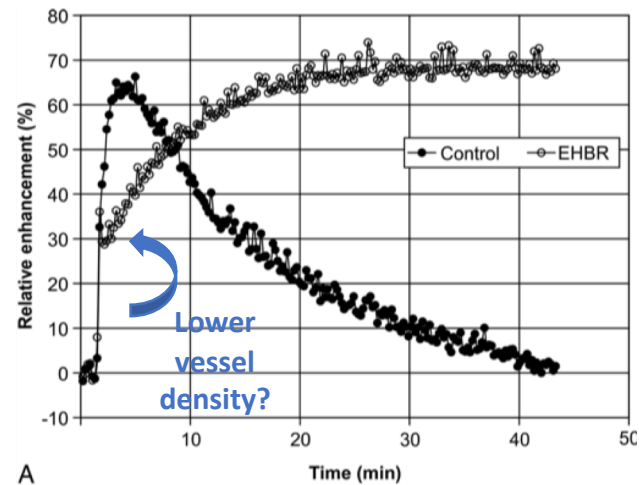
- MRI hepatobiliary contrast agents: Gd-BOPTA (**BOPTA**), MultiHance[®] and Gd-EOB-DTPA (**EOB-DTPA**), Primovist[®]
- Hepatobiliary SPECT tracer: mebrofenin (**MEB**), Choletec[®]
- Various hepatobiliary PET tracers
- Hepatobiliary imaging substrates are transported across membrane proteins
- Complex mechanisms generate hepatocyte concentrations

- BOPTA/EOB-DTPA/MEB



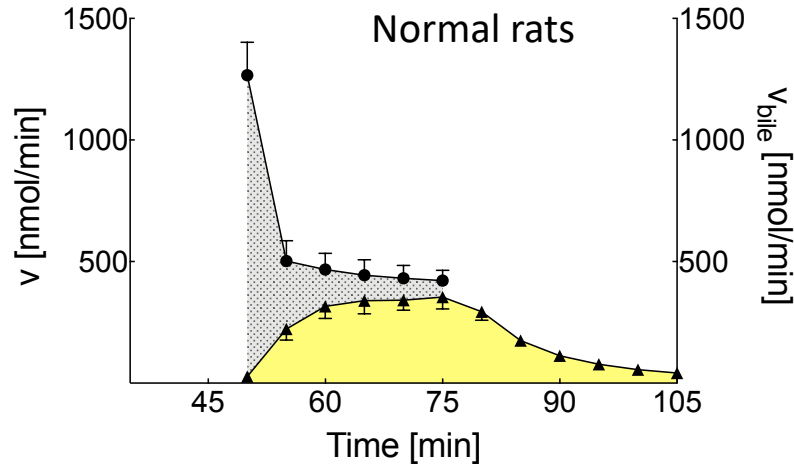


EOB-DTPA injection in rats lacking MRP₂



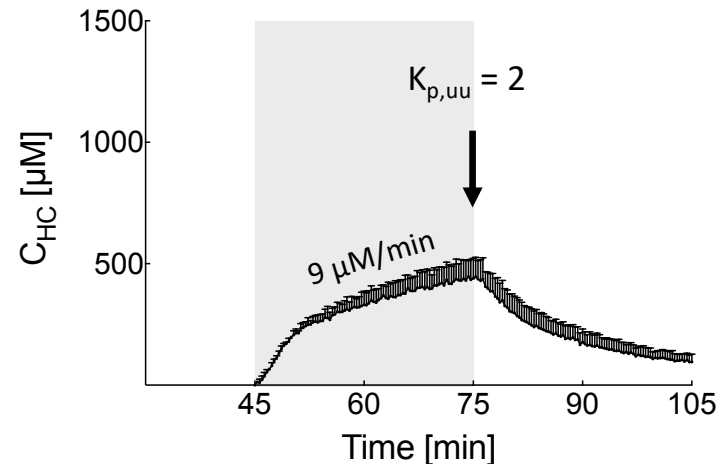
BOPTA accumulates in rat hepatocytes

BOPTA perfusion: 200 μM



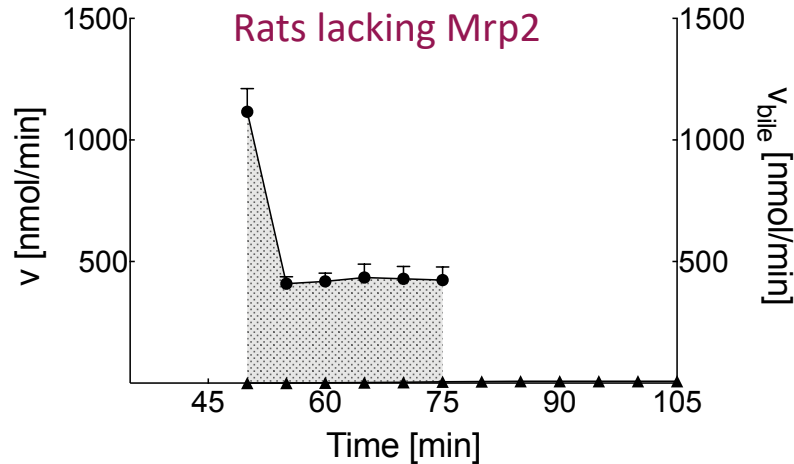
v : BOPTA removal rate from sinusoids

v_{bile} : BOPTA bile excretion rate



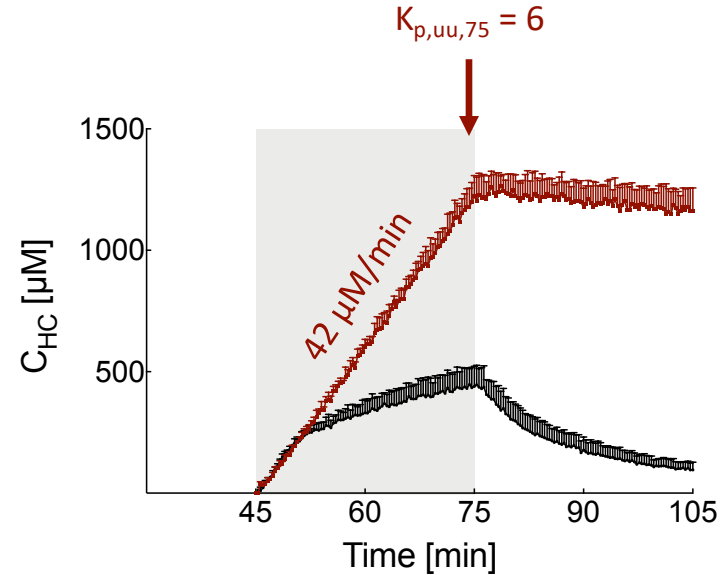
BOPTA concentrations in rats lacking Mrp2

BOPTA perfusion: 200 μM



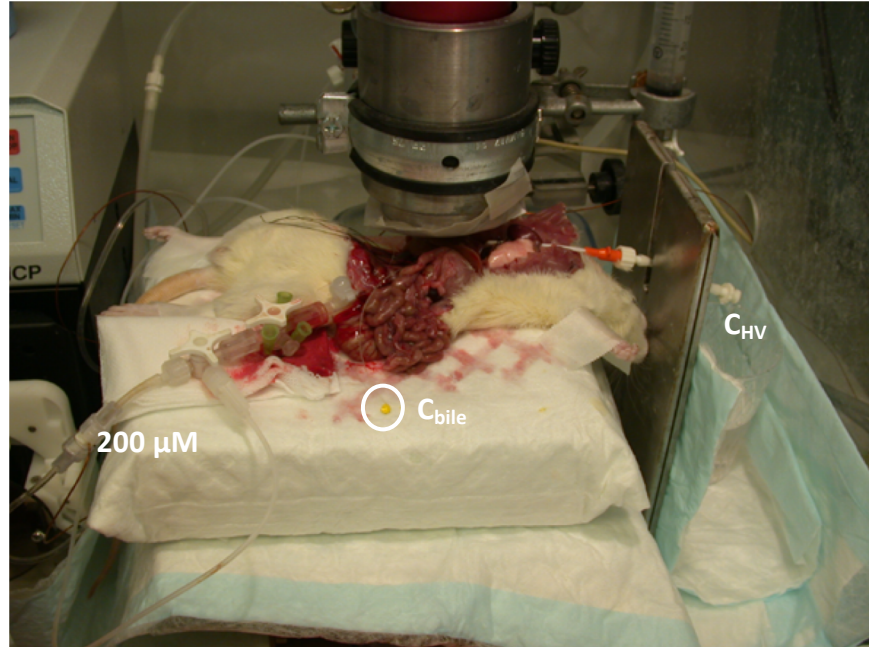
v : BOPTA removal rate from sinusoids

v_{bile} : BOPTA bile excretion rate



Quantification of transfer rates and concentrations in liver compartments

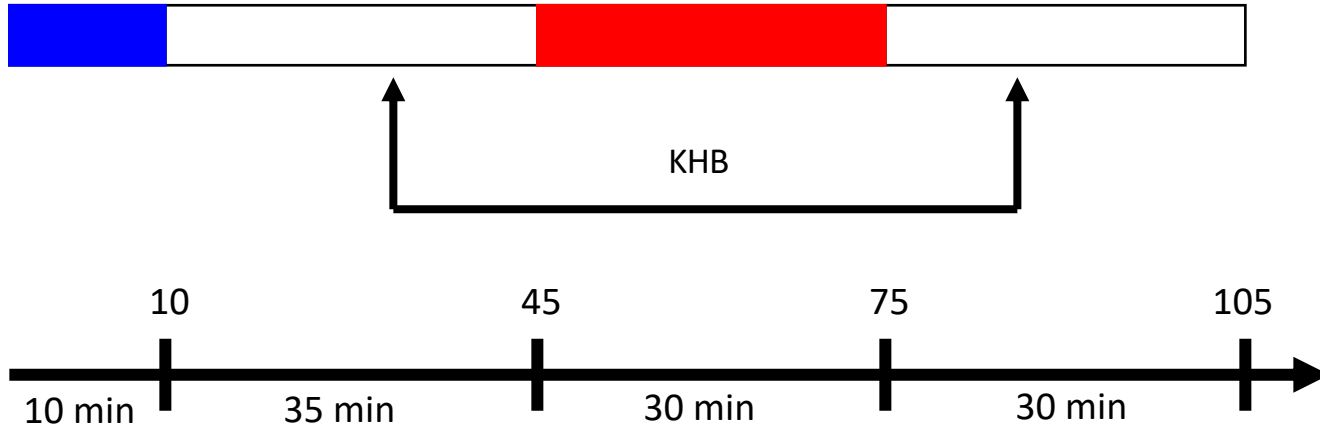
- $^{153}\text{Gd-BOPTA}$ removal rate from sinusoids (v)
- BOPTA bile excretion rate (v_{bile})
- Bile and HV concentrations (μM)
- Liver concentrations (γ counter)

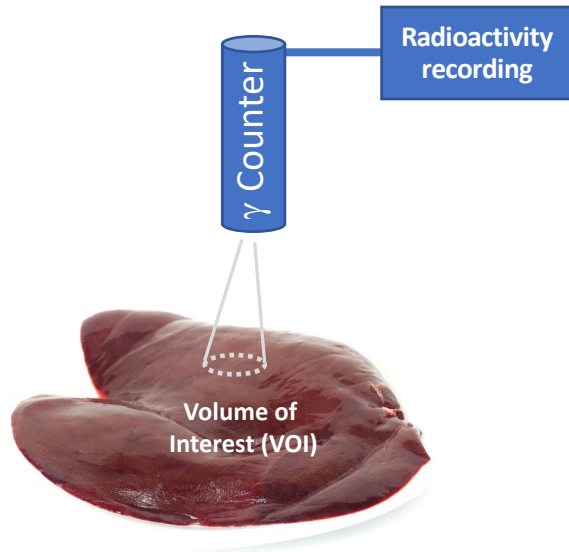


Protocol of perfused solutions

200 μM $^{153}\text{Gd-DTPA}$
64 μM $^{99\text{m}}\text{Tc-DTPA}$

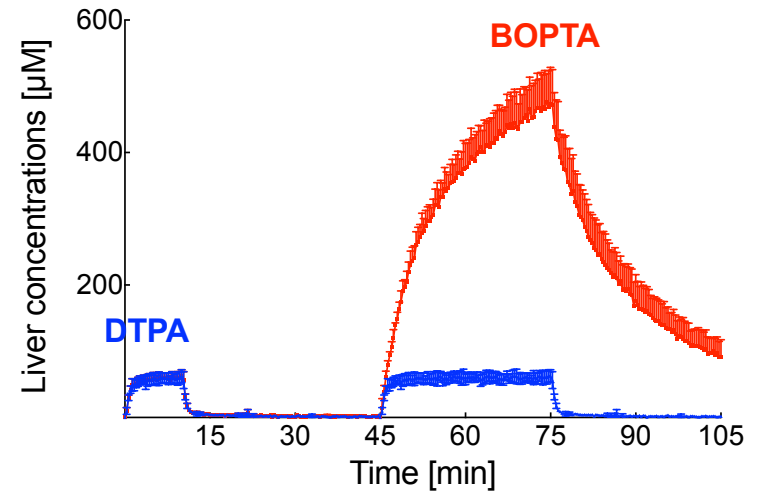
200 μM $^{153}\text{Gd-BOPTA}$
64 μM $^{99\text{m}}\text{Tc-MEB}$



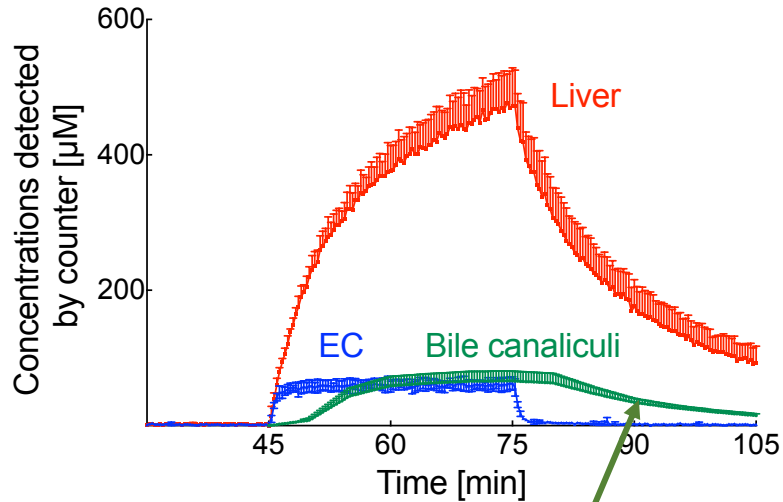


VOI Extracellular volume: 16%
 Hepatocytes: 80%
 Bile Canaliculi: 0.43%
 Condition: homogeneous tissue

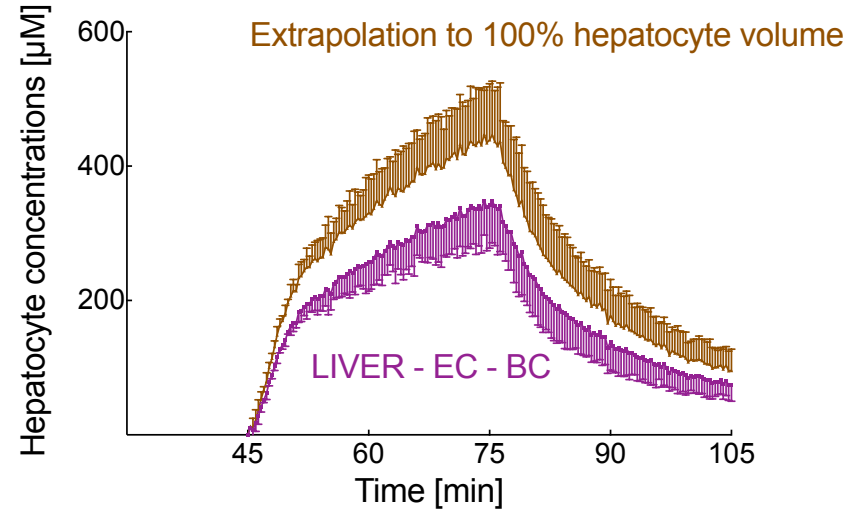
DTPA and BOPTA liver concentrations



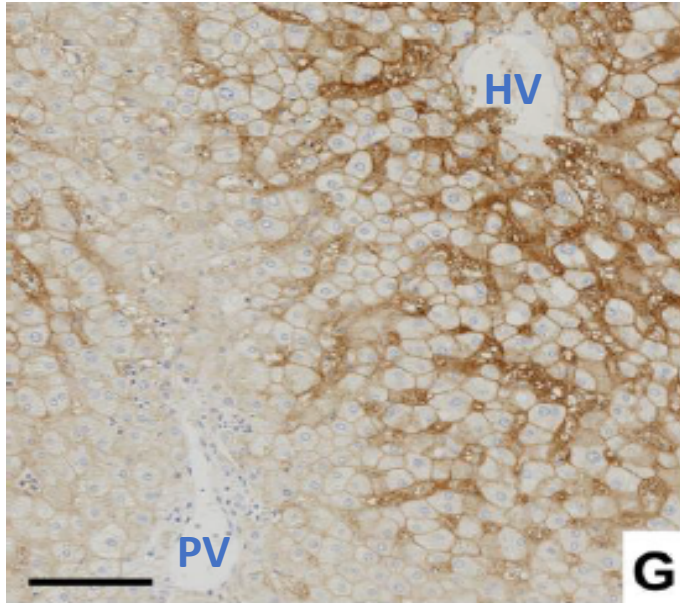
Hepatocyte concentrations?



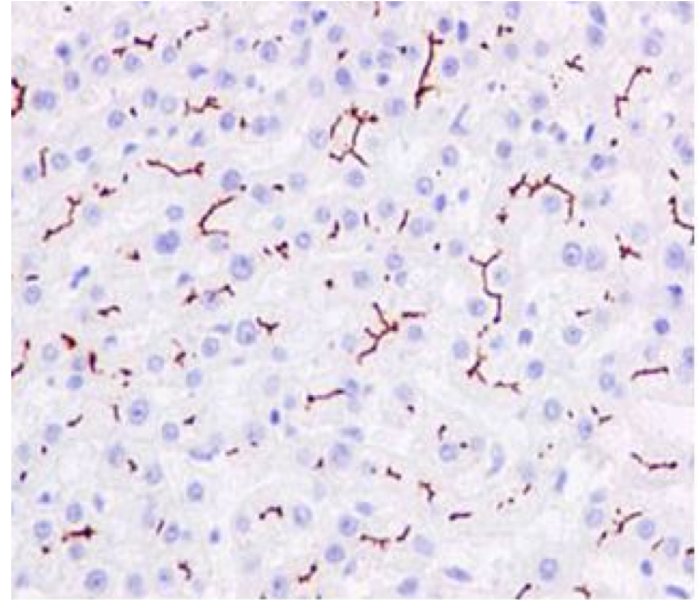
$C_{\text{bile}} \times 0.43\%$ or volume
occupied by bile canaliculi in
VOI



Hepatocytes in lobule are not all similar

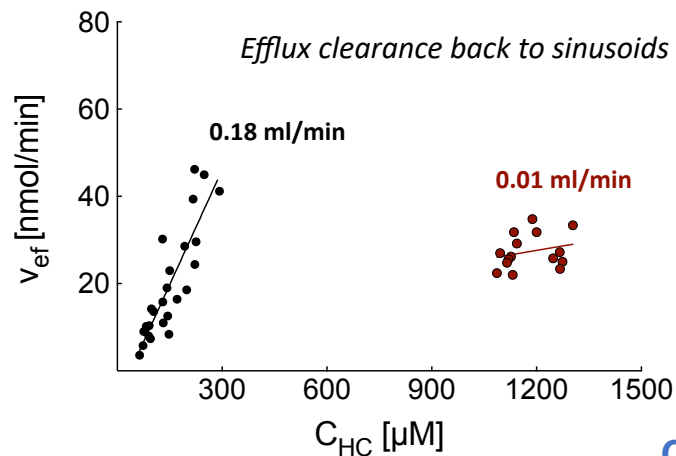
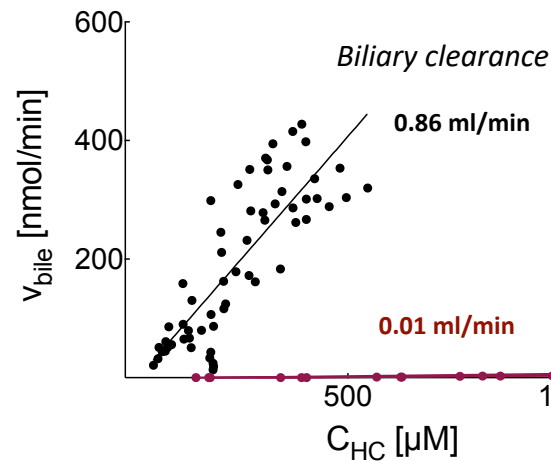
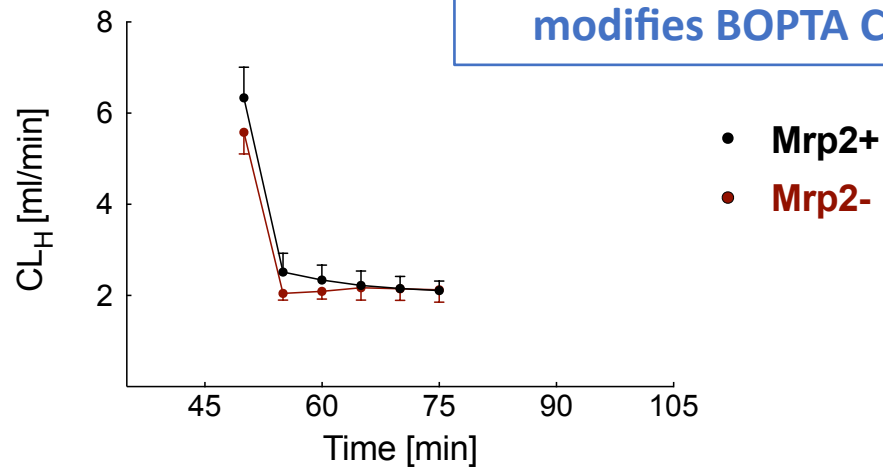
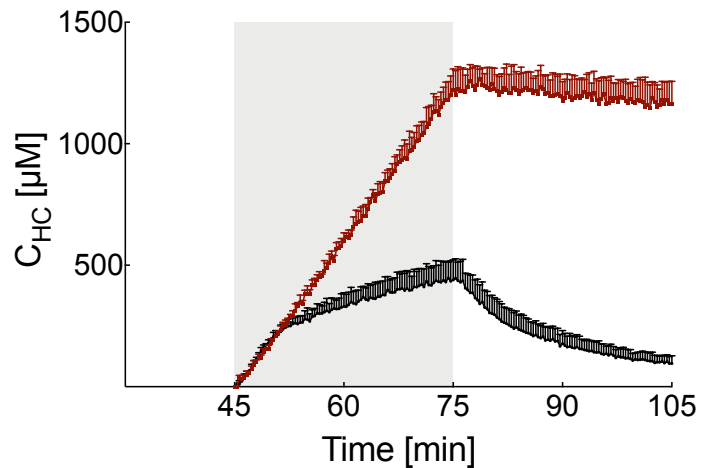


OATP1B1/B3 in normal livers



MRP2 is expressed in all hepatocytes

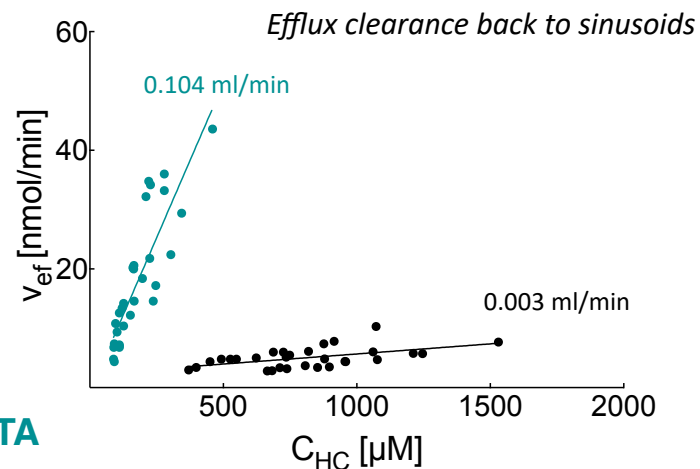
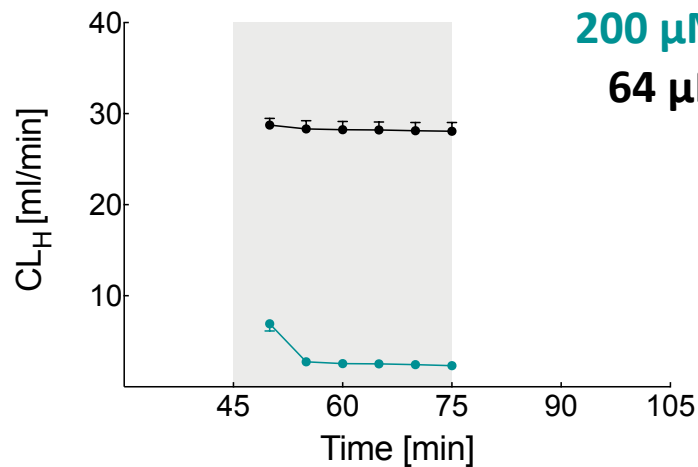
How the absence of Mrp2 modifies BOPTA C_{HC} ?



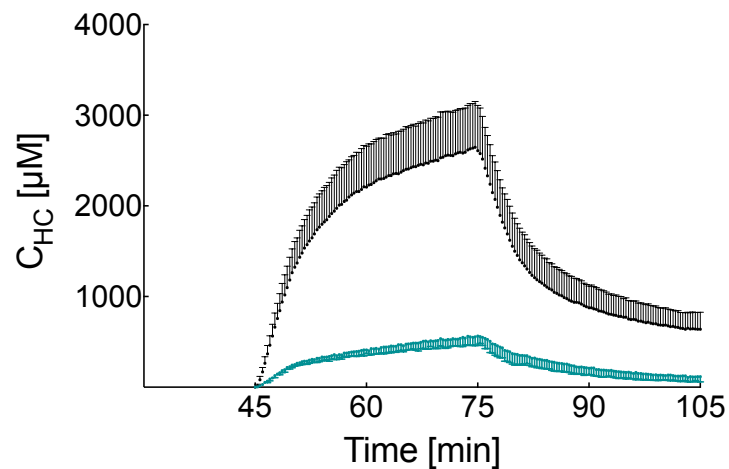
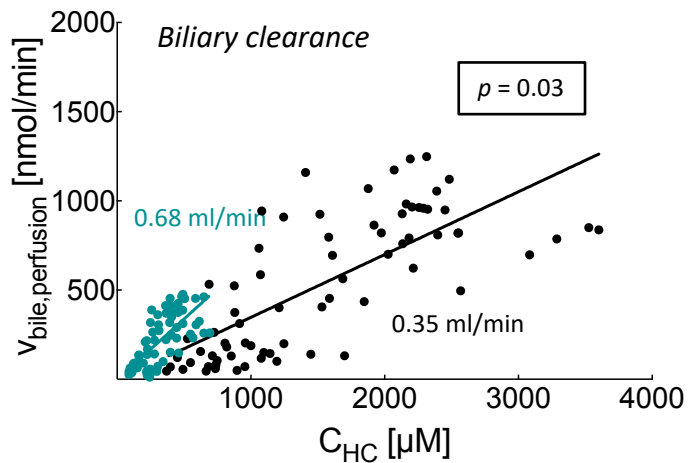
Substrate comparison

200 μM BOPTA

64 μM MEB

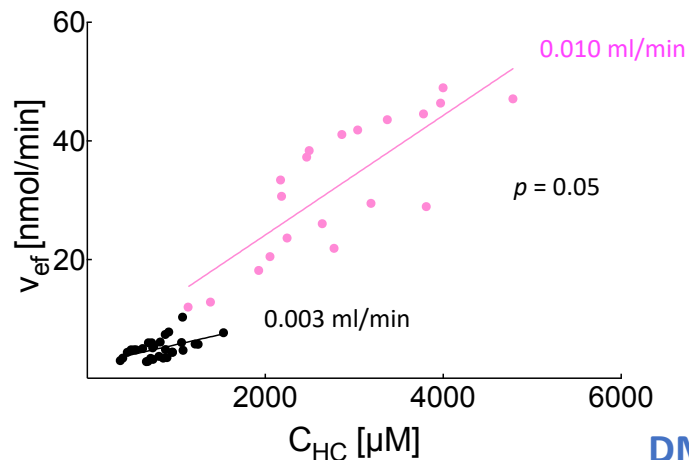
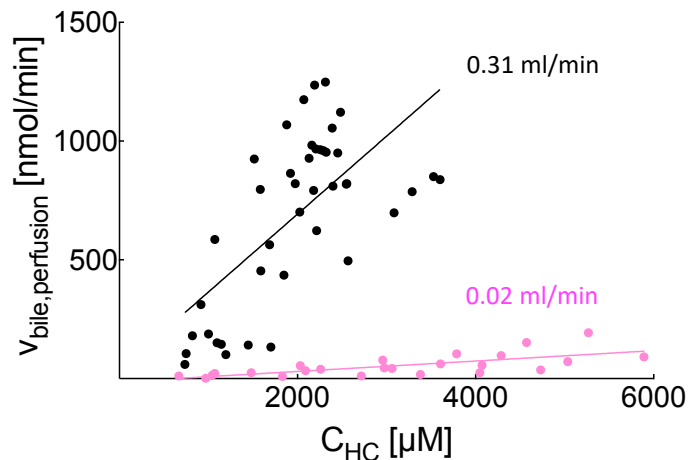
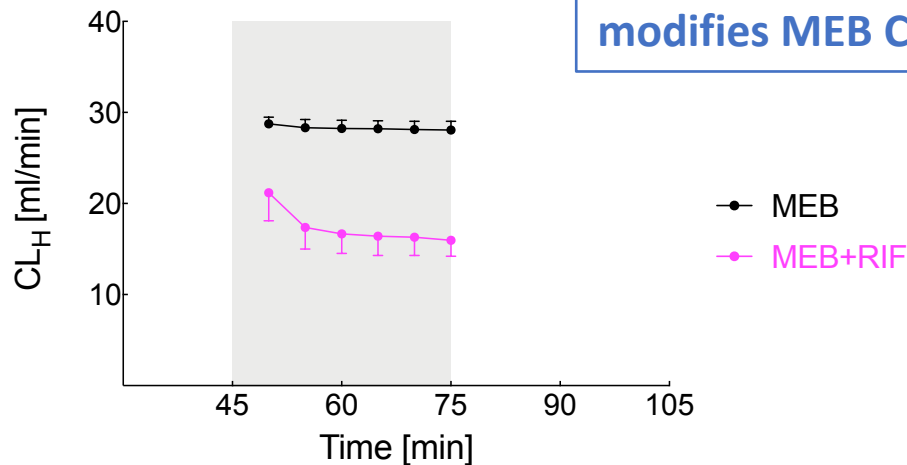
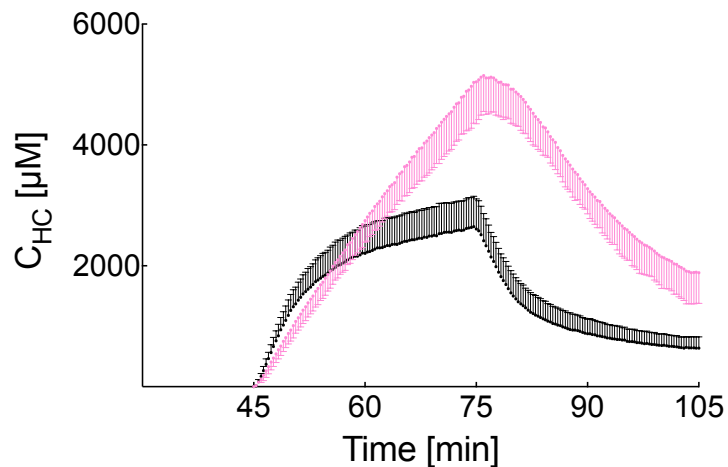


- BOPTA
- MEB



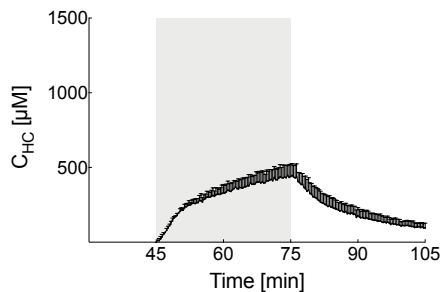
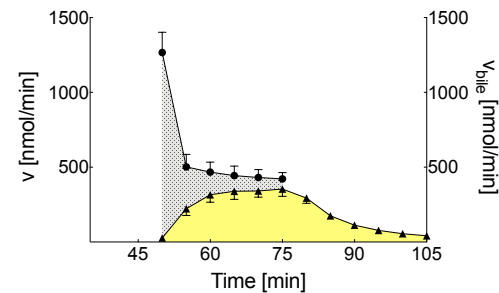
Perfusion concentrations: **64 μM MEB $\pm$ 100 μM rifampicin (RIF)**

**How rifampicin
modifies MEB C_{HC} ?**



1

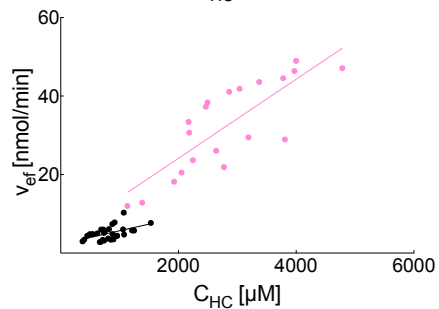
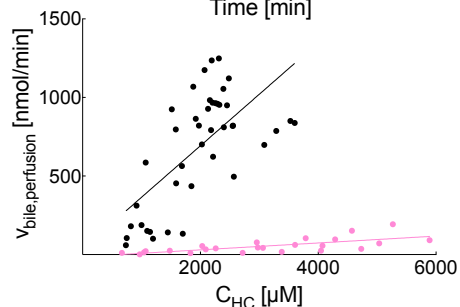
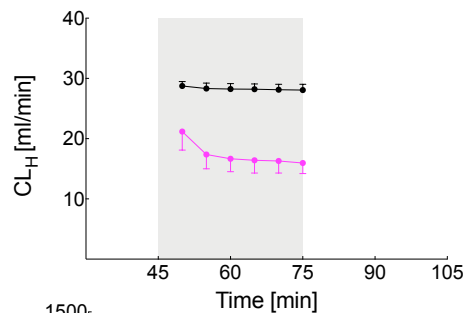
C_{HC} generation



Conclusions

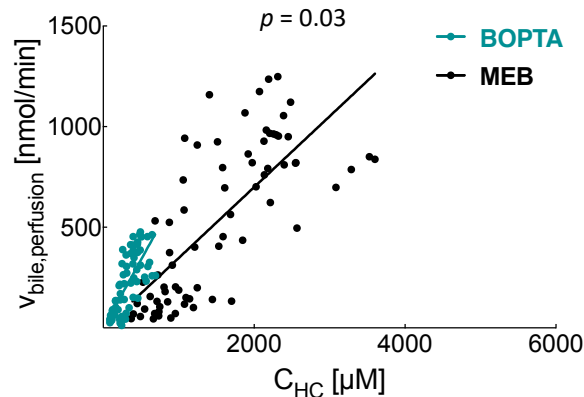
2

Transporter inhibition



3

Comparison of substrates



4

Mrp2 function

