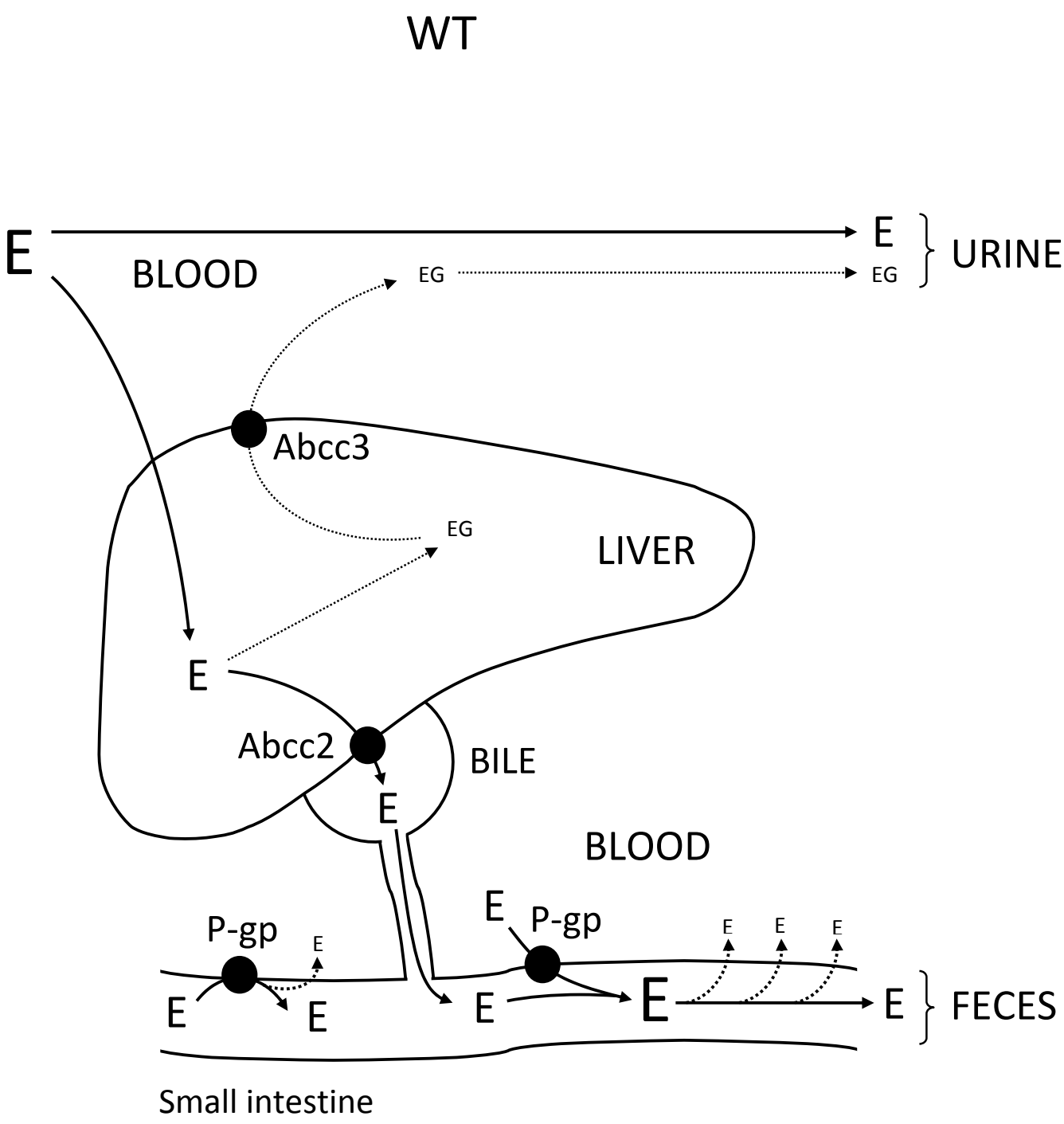
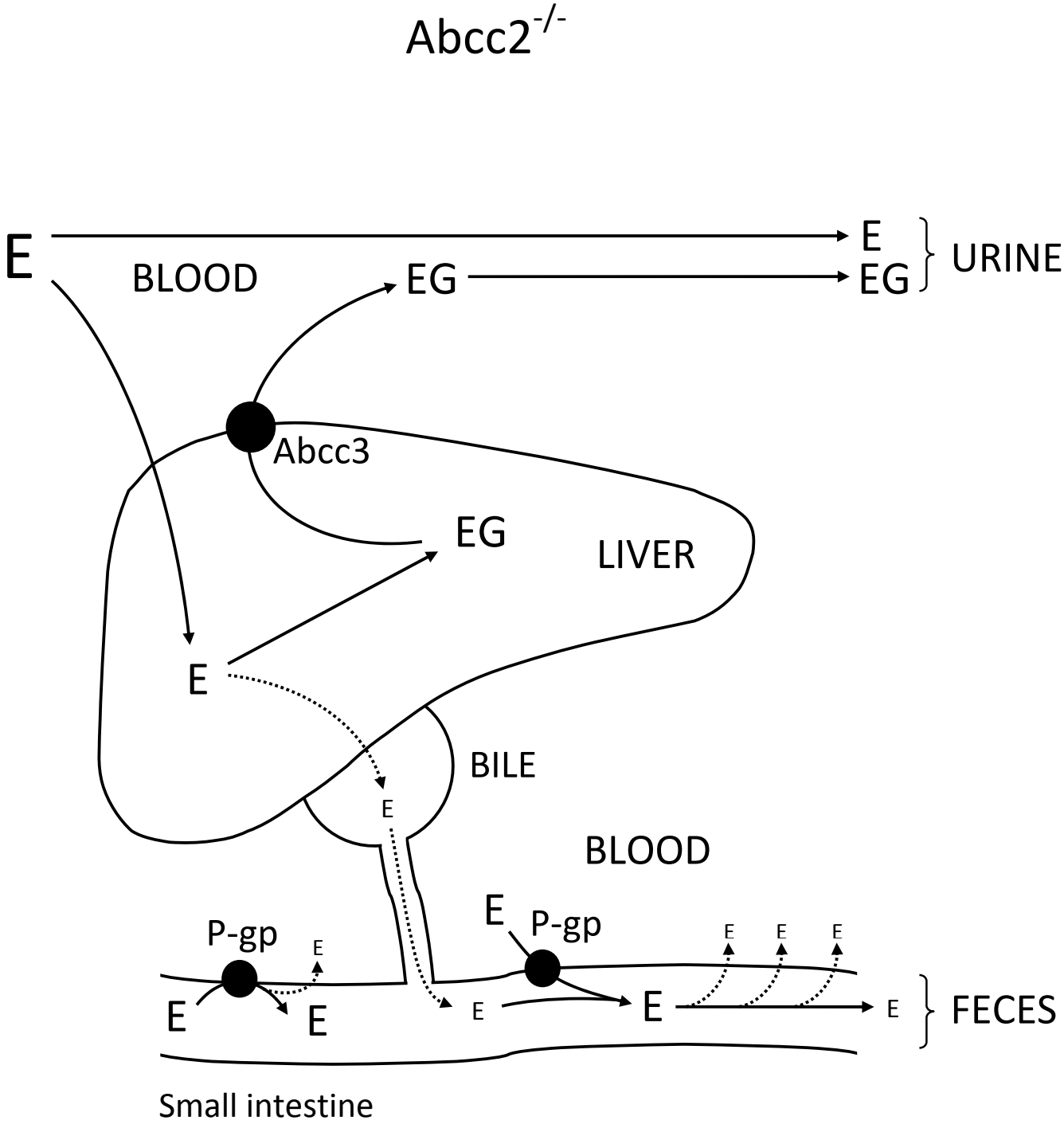
Suppl. fig. 1A


WT
E
BLOOD
EG
E
EG
URINE
Abcc3
EG
LIVER
E
Abcc2
BILE
E
BLOOD
P-gp
E
E
E
P-gp
E
E
E
E
E
E
E
FECES
Small intestine

Suppl. fig. 1B


Abcc2-/-
E
BLOOD
EG
E
EG
URINE
Abcc3
EG
LIVER
E
BILE
E
BLOOD
E
P-gp
P-gp
E
E
E
E
E
E
E
E
E
E
FECES
Small intestine

Supplementary Figure S1. Schematic overview of our data, showing the contributions of Abcc2, Abcc3 and P-gp to the plasma pharmacokinetics and elimination of etoposide in mice. When etoposide is given intravenously, a substantial amount is taken up by the liver. In WT mice (*A*), a relatively small fraction of etoposide (**E**) is converted in the liver to etoposide glucuronide (**EG**) and excreted to the blood circulation by Abcc3, located in the sinusoidal (blood-facing) membrane of the hepatocyte. The majority of E is excreted from the liver into the bile by Abcc2 located in the bile canalicular membrane. P-gp, present in the epithelial cells of the small intestine, pumps E directly from the blood into the gut lumen and partly restricts the re-uptake of E from the gut. P-gp also restricts the uptake of E from the gut after oral administration and a reduced fraction of E reaches the systemic circulation (see lower left quadrant of scheme). A substantial amount of etoposide is excreted directly from the circulation into urine by the kidneys (top arrow).

In Abcc2 deficient mice (*B*), excretion of E into the bile is seriously impaired due to the absence of Abcc2 from the canalicular membrane and the majority of E in the liver is now conjugated to EG. Abcc3, which is upregulated in the livers of Abcc2 deficient mice, pumps EG from the liver toward the systemic blood. As a consequence, urinary excretion of EG is highly increased in *Abcc2*$^{-/-}$ mice. Urinary excretion of etoposide itself is not substantially altered. Furthermore, due to the absence of Abcc2, fecal excretion of E is decreased but not abrogated, as P-gp still mediates excretion of E across the gut wall from blood to the intestinal lumen.