EXPRESSION PROFILES OF DRUG TRANSPORTERS IN HUMAN AND MINIPIG SKIN, LIVER AND KIDNEY

Magali Kouidhi, Alexandre Gaborit, Karine Sevin, Claire E. Wilson* and Hanan Osman-Ponchet

***In vitro* Models, DMPK - Research, Galderma R&D, Sophia-Antipolis, France**

BACKGROUND

Drug transporters contribute to variability in drug concentration and response, and should be considered for evaluation during drug development. Minipig is frequently used as an animal model in pharmacology and toxicology screening. However, transcriptional profiles of drug transporters are poorly characterized in this model, mainly in the skin.
This work was conducted to compare the expression profiles of drug transporters in the skin, liver, and kidney of minipig and human tissue.

METHODS

➢Drug transporters chosen were those included in the EMA guidance as the most likely clinical sources of drug interactions, among them 11 uptake transporters belonging to SLC family and 4 efflux transporters belonging to ABC family.

➢ Human skin in organ-culture, hepatocytes in primary culture and kidney total RNA were used to analyze gene expression by TaqMan Real-time RT-PCR (Figure 1).

➢ Skin and liver from male and female and kidney total RNA from kidney of female Göttingen minipig were used for analysis (Figure 2).

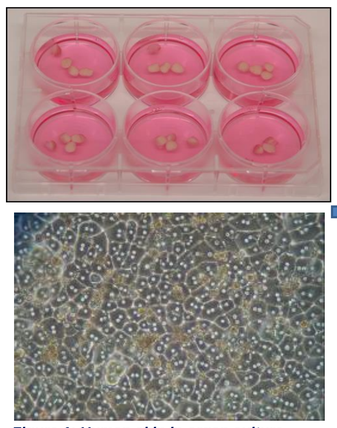
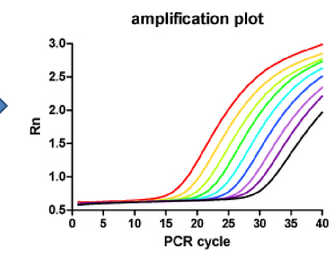


Figure 1: Human skin in organ culture and human hepatocytes in primary culture



TaqMan real-time RT-PCR amplification plot

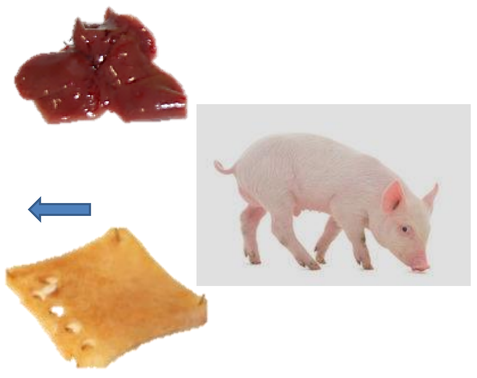
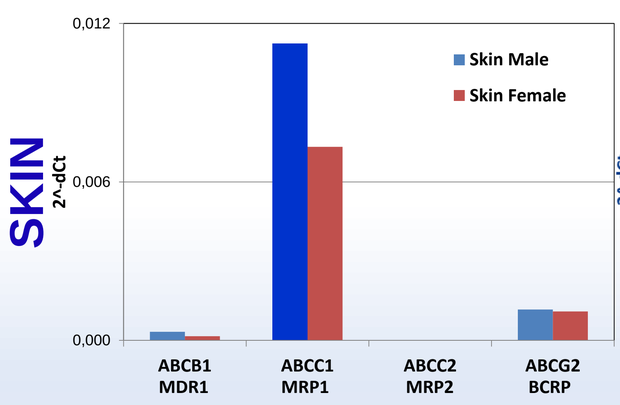


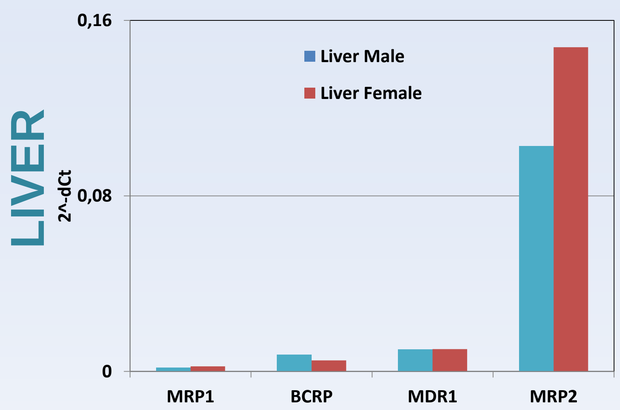
Figure 2: Skin and liver samples from Göttingen minipig

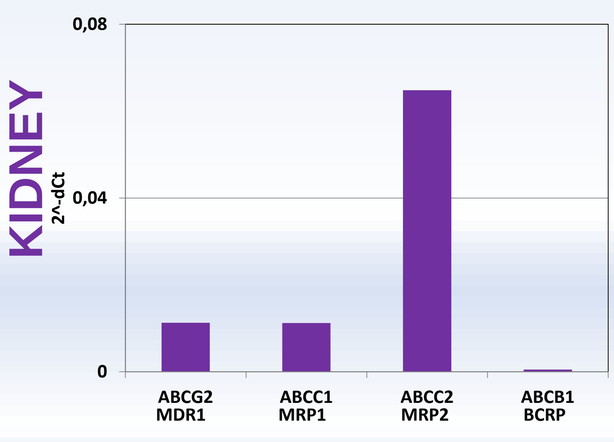
RESULTS

GENE EXPRESSION OF ABC TRANSPORTERS

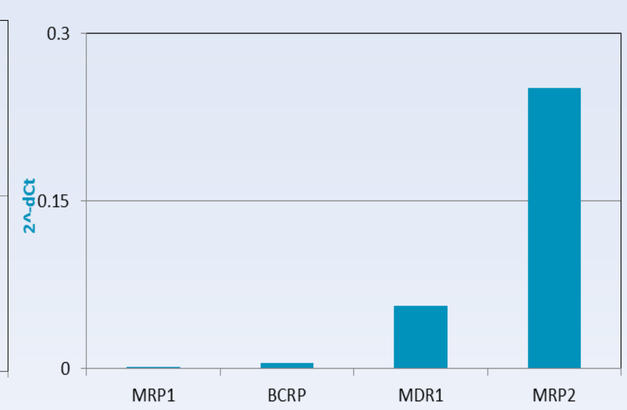
Minipig

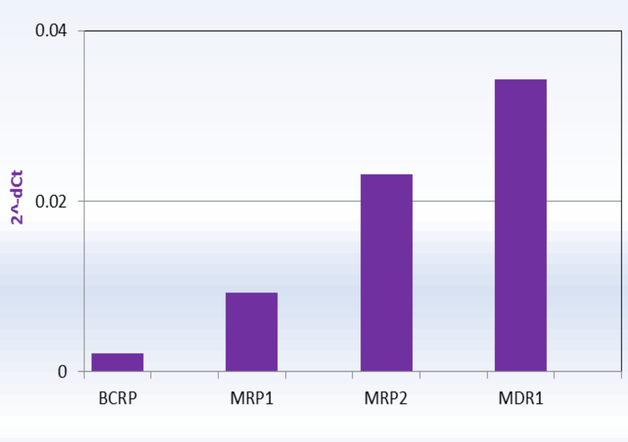






Human



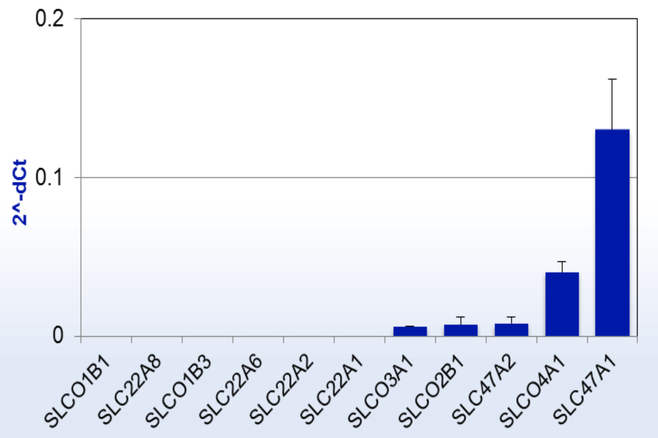


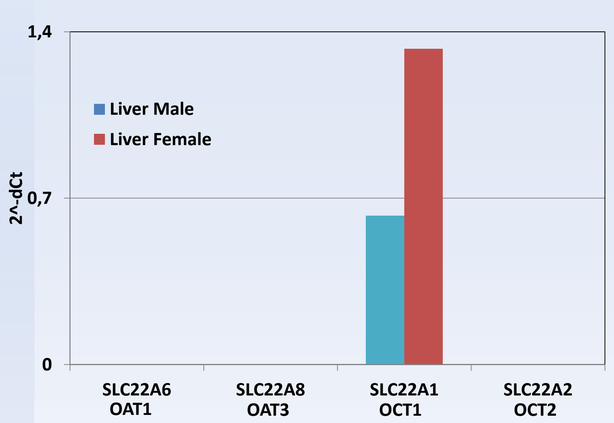
GENE EXPRESSION OF SLC TRANSPORTERS

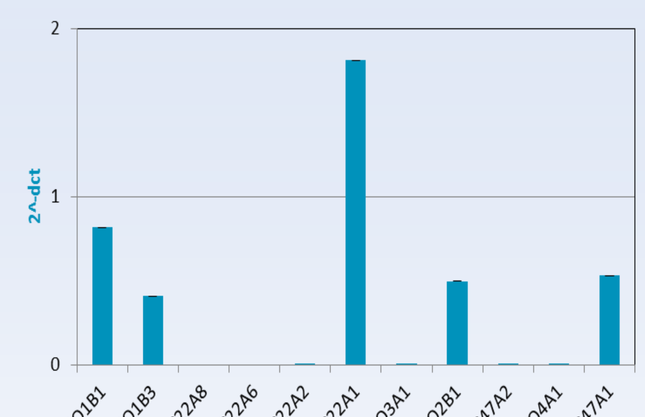
Minipig

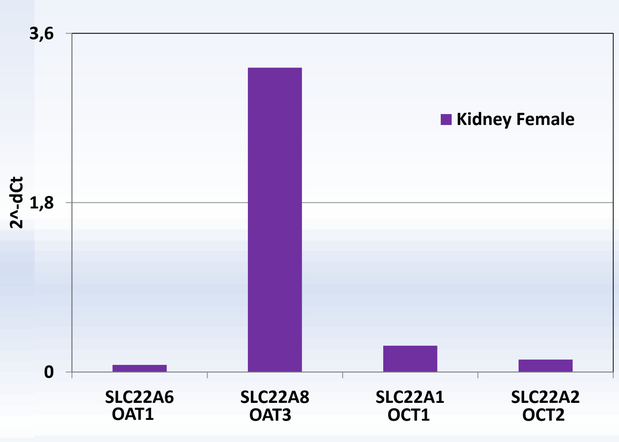
Non detected

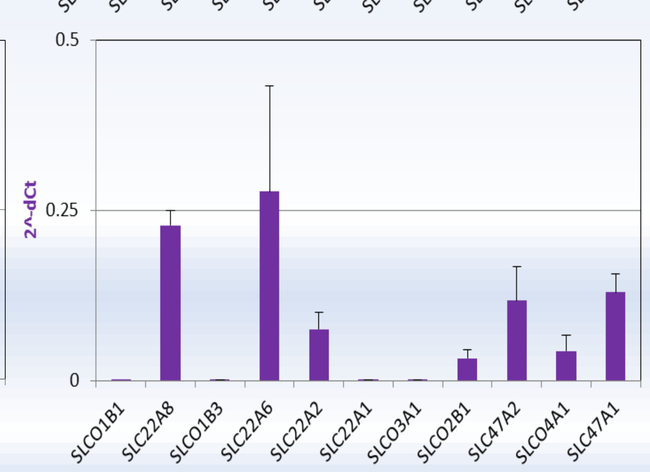
Human











ABCC1 (MRP1) was expressed at the highest levels in the skin and ABCC2 (MRP2) was the main transporter in the liver in both species. In minipig kidney, MRP2 was expressed at the highest levels, whereas in human kidney MDR1 was the main transporter, followed by MRP2. SLC47A1 (MATE1) was expressed at the highest levels in human skin (not cloned in minipig). None of the four SLC transporters analyzed was detected in minipig skin. In the liver, SLC22A1 (OCT1) was expressed at the highest levels in both species. In minipig kidney, SLC22A8 (OAT3) was expressed at the highest levels whereas in human kidney OAT1 and OAT3 where the main transporters.

CONCLUSION

Despite some differences, quantitative comparison of the expression of drug transporters in minipig and human tissue will help to improve the quality of predictions from animal to humans. To the best of our knowledge, this is the first work describing expression of drug transporters in minipig tissues, particularly in the skin.

Corresponding author: hanan.osman-ponchet@galderma.com