

CHARACTERIZATION OF DRUG TRANSPORTERS INVOLVED IN DRUG-DRUG INTERACTIONS IN HUMAN SKIN

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BACKGROUND

Recent research indicates that some of the ATP-binding Cassette (ABC) and Solute Carrier (SLC) transporters play an important role in the absorption, distribution and excretion of drugs, and are involved in clinically relevant drug-drug interactions for systemic drugs. However, very little is known about the role of drug transporters in human skin in the disposition of topically applied drugs and their involvement in drug-drug interactions. The aim of this work was to compare the expression in human skin (vs human hepatocytes and kidney) of ABC and SLC transporters included in the EMA guidance as the most likely clinical sources of drug interactions.

METHODS

- Gene expression of 11 SLC and 4 ABC transporters was analyzed by TaqMan Real-time RT-PCR in human skin in organ-culture (Figure 1), hepatocytes and kidney.
- Localization of MRP1 transporter in human skin was performed by immunohistochemistry.
- Functional analysis of MRP1 in human skin was performed using specific substrate and inhibitor in skin absorption model (Figure 2).



Figure 1: Skin organ-culture

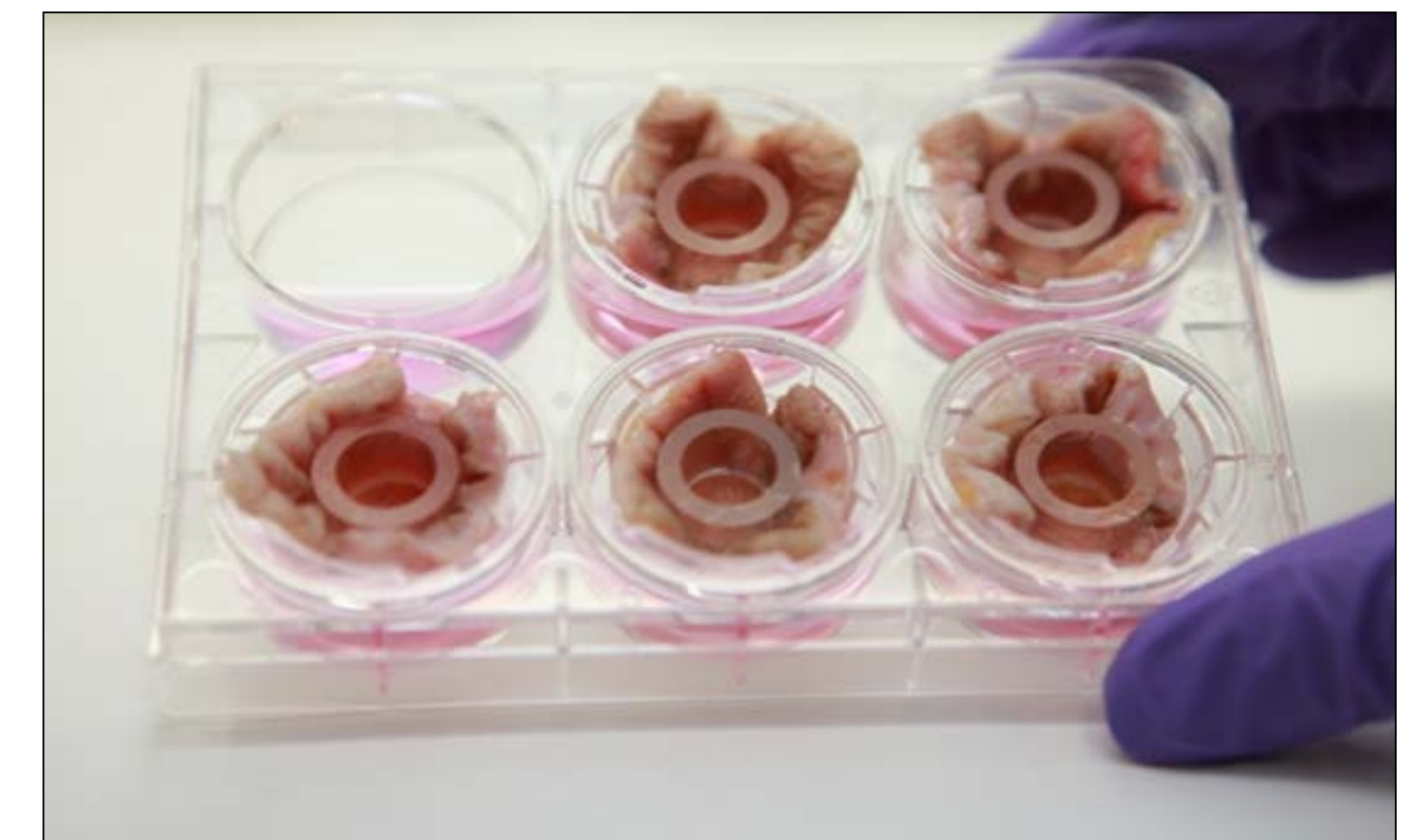
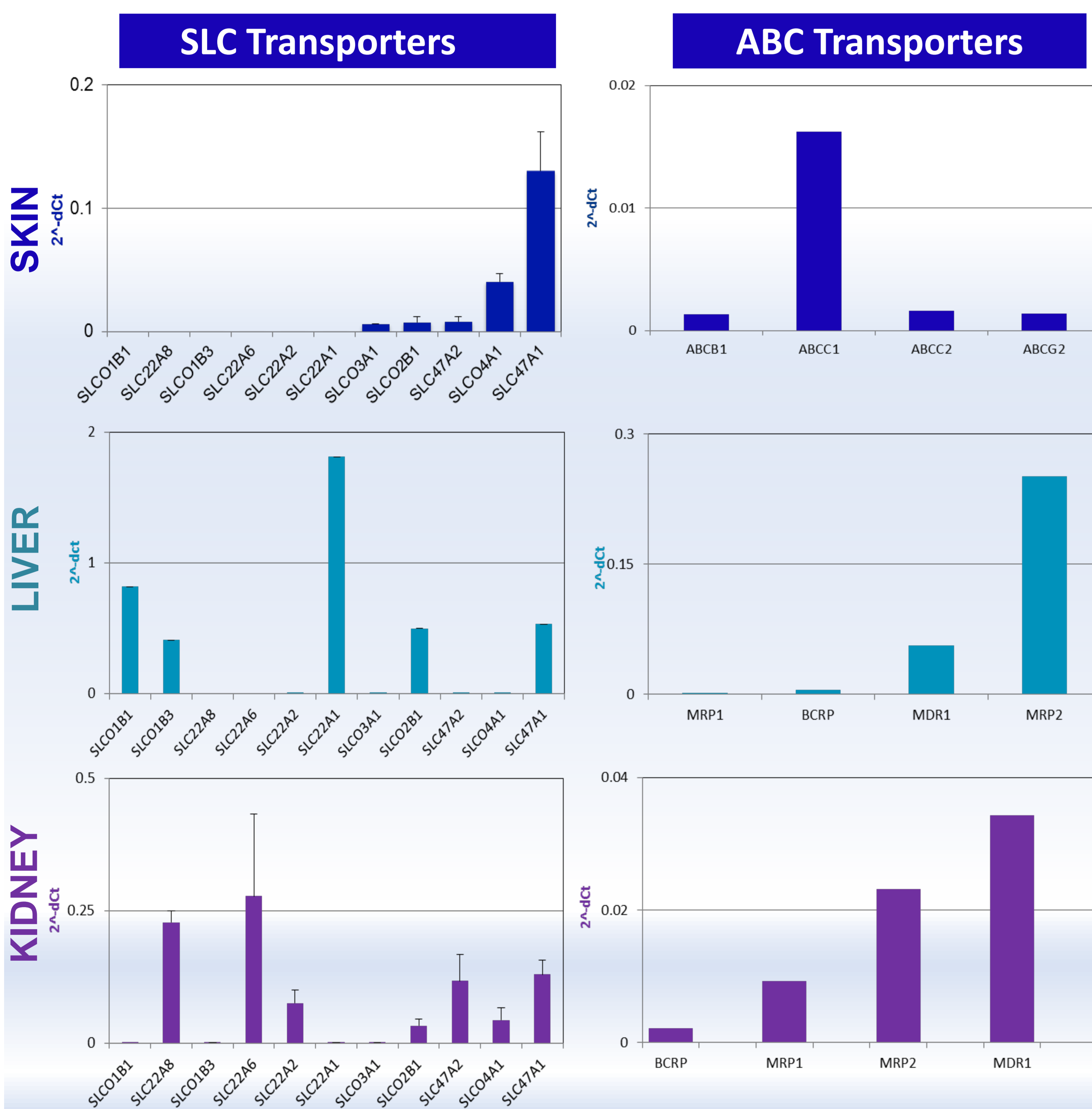


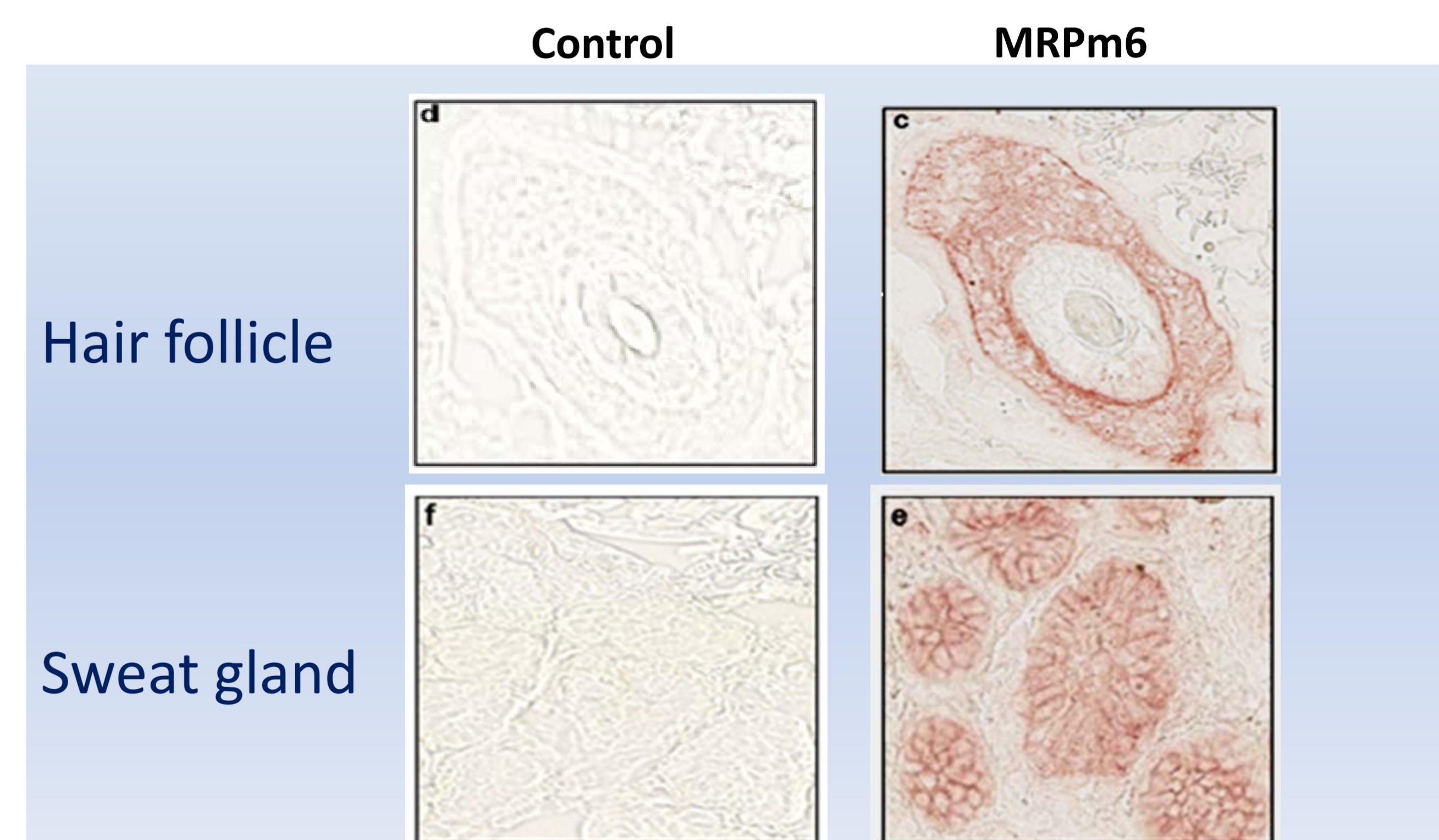
Figure 2: Skin absorption model

RESULTS

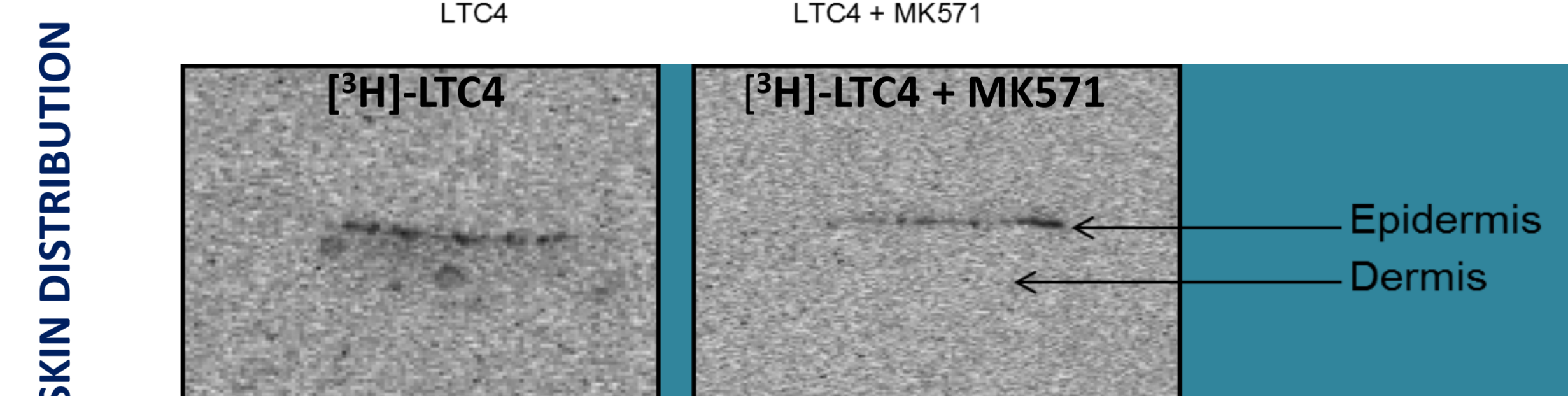
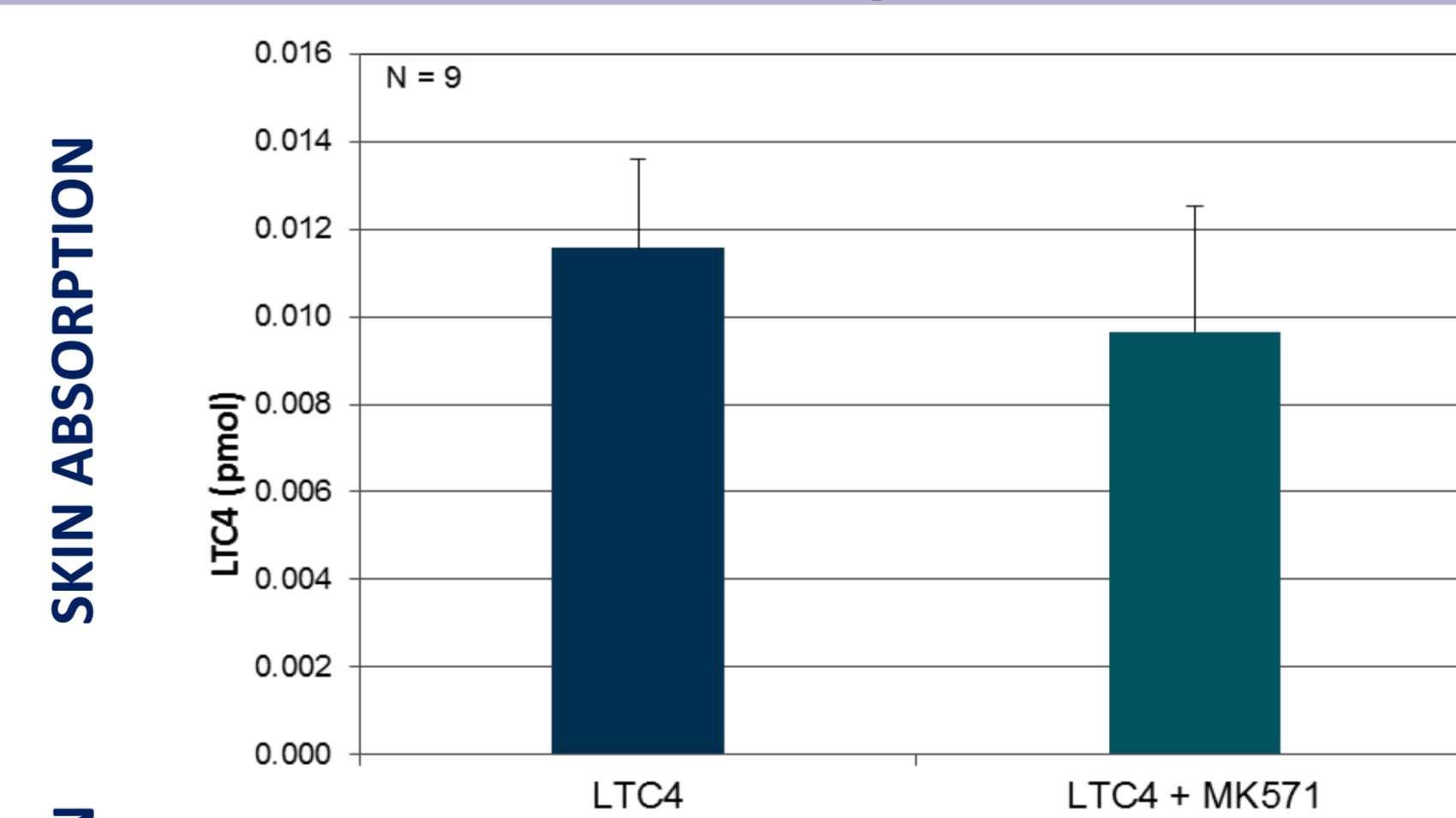
1. GENE EXPRESSION OF SLC and ABC TRANSPORTERS



2. LOCALIZATION OF MRP1 IN SKIN CRYOSECTION



3. EFFECT OF MK571 (MRP1 INHIBITOR) ON SKIN ABSORPTION OF LTC4 (MRP1 SUBSTRATE)



Inhibition of MRP1 by MK571 significantly decreases skin absorption and distribution of LTC4.

SLC and ABC transporters have a very specific expression profile in human skin with SLCO4A1 (OATPE), SLC47A1 (MATE1) and ABCC1 (MRP1) being the most expressed. SLCO4A1 and ABCC1 are about 70 times and 15 times more expressed in human skin than in hepatocytes, respectively. Moreover, MRP1 was mainly expressed in the hair follicle and sweat gland, and involved in drug uptake in human skin.

CONCLUSION

This is the first time that there is evidence for the expression of MATE transporters and the localization of MRP1 transporter in human skin. Further investigations are needed to characterize the functional role of MATE transporters in human skin.