



Nestlé Skin Health



Drug transporters in the skin

Importance in dermal absorption

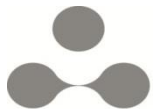
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Skin Metabolism Meeting
University of Sunderland
27th - 29th November 2017

Confidential / 1

Nestlé Skin Health - Galderma



Nestlé Skin Health

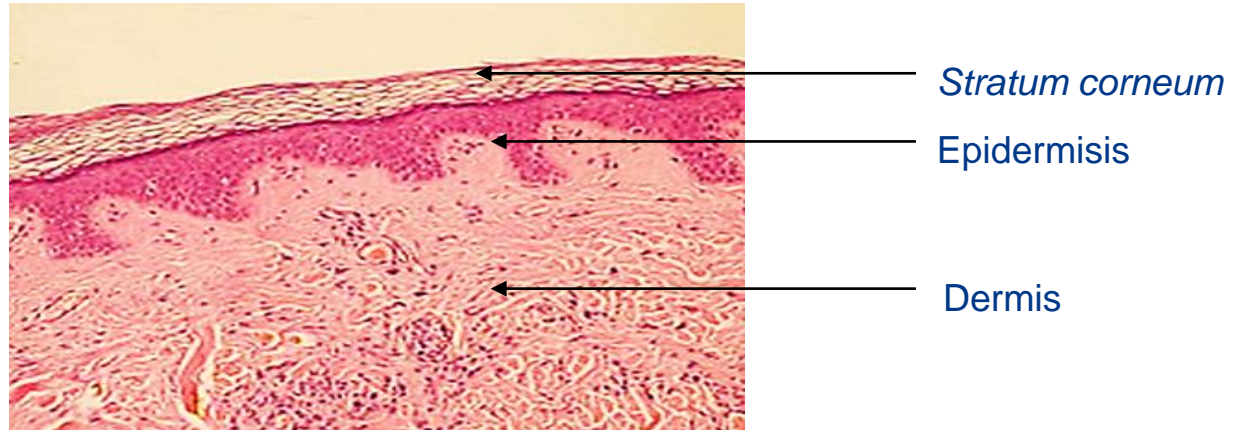


Committed to the future of dermatology
Science-based solutions for the skin, hair and nails



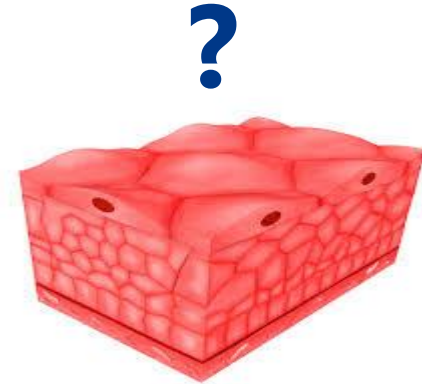
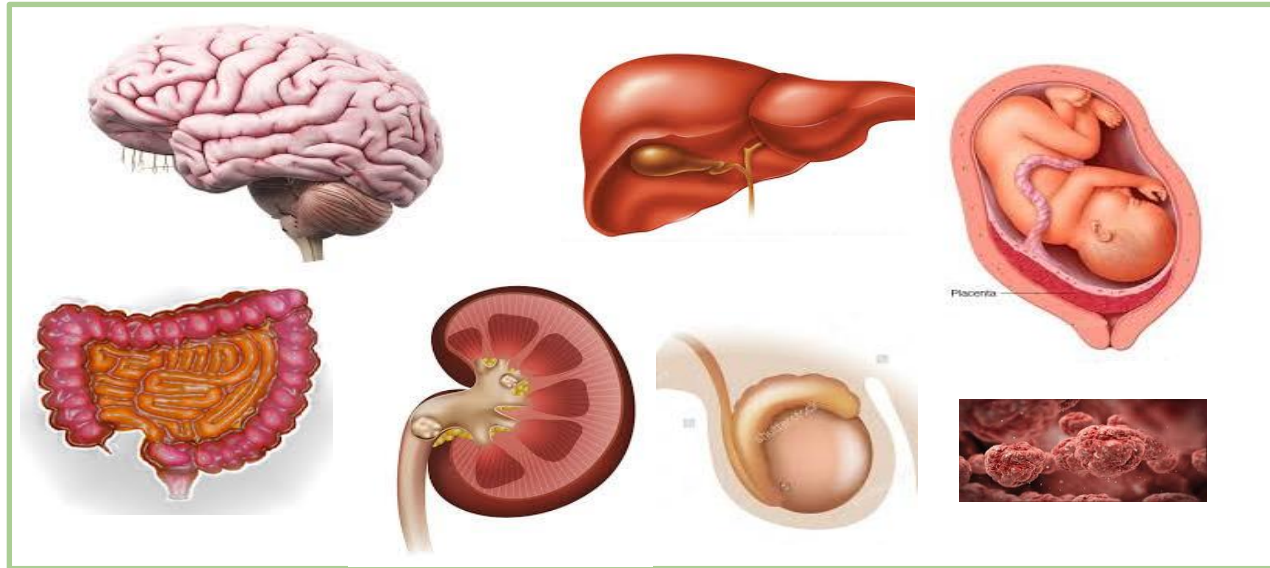
Human skin

- Skin is the largest organ of the body
 - 2 m² surface area
 - 0.5 – 4 mm thickness
 - 16% body weight
- Skin plays a crucial role in body protection from:
 - Damage, infection, and drying out



Drug transporters

- Drug transporters are well characterized in many key tissues but very little is known about them in the skin



SKIN





Outline

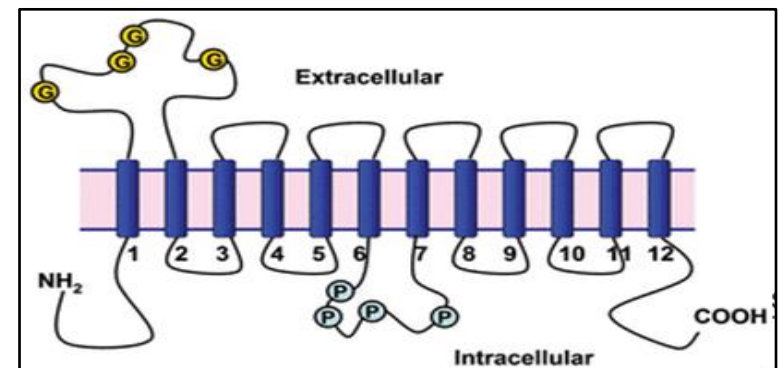
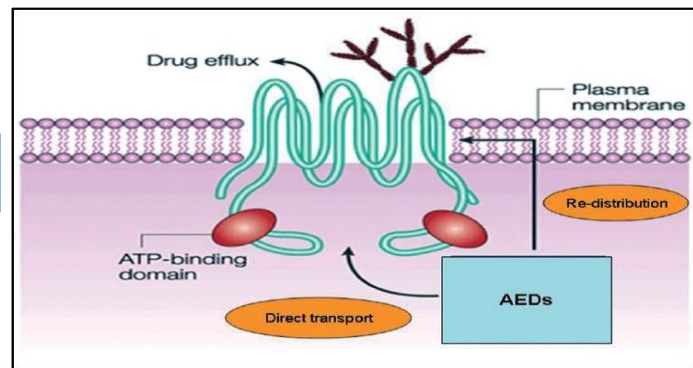
- General overview of drug transporters
 - ABC and SLC transporters
 - Regulatory perspectives
- Characterization of drug transporters in the skin
 - Expression & Regulation (*ex vivo* skin & 3D *in vitro* models)
 - Localization
 - Function
- Conclusion



Drug transporters

- ATP-binding cassette (ABC)  Drug Efflux (Out)
 - ABCB1: MDR1 (Multi-drug resistance) or P-gp
 - ABCC1/2: MRP1/2 (Multidrug resistance-associated protein)
 - ABCG2: BCRP (Breast cancer resistance protein)
- Solute Carrier (SLC)  Drug Uptake (In)
 - SLCO: OATP1B1/3 (organic anion transporting polypeptide) Liver
 - SLC22: OCT1/2 (organic cation T), OAT1/3 (organic anion T), Kidney
 - SLC47: MATE1/2-K (multidrug and toxin extrusion) Kidney, Liver, Skin

ABC



SLC

Genetic diseases related to drug transporters

- In humans, 15 severe genetic diseases are caused by the dysfunction of ABC transporters:
 - ABCC6 : Pseudoxanthoma elasticum
 - ABCA12 : Lamellar ichthyosis
 - ABCA1 : Tangier disease
 - ABCB4 : Cholestasis
 - ABCC2 : Dubin–Johnson syndrome
 - ABCC7 : Cystic fibrosis



Pseudoxanthoma elasticum

<http://flipper.diff.org>



Lamellar Ichthyosis

Dr. Ibrahim Md Sharaf



Role of drug transporters

- Physiological role:
 - Transport of glucose, lipids, creatinine, steroid conjugates, thyroid hormones, bile salts
- Tissue distribution – drug disposition:
 - Highly abundant in the gastrointestinal tract, liver, kidney, brain, skin
 - Significantly modulate the absorption, distribution and elimination
 - Efficacy and toxicity of pharmacological agents
- Mediate drug interactions*
 - Result from altered tissue distribution of a drug that is a substrate of a transporter. May not be apparent by measuring systemic drug exposures

**Giacomini, Huang, et al. 2010; Brouwer, Keppler, et al. 2013; Giacomini and Huang 2013; Tweedie, Polli, et al. 2013; Zamek-Gliszczynski, Lee, et al. 2013.*



Regulatory perspectives

- Due to contribution of drug transporters to drug-drug interactions, European, US and Japanese regulatory agencies require evaluation of key drug transporters during drug development
 - FDA (Draft Guidance October 2017):
 - EMA (Guidance 2013)
 - Japanese PMDA (Draft Guidance 2014)
- Key transporters: P-gp, BCRP, OATP1B1/B3, OAT1/3, OCT1/2, MATE1/2-K, and BSEP



Objectives

- Drug transporters are well characterized in liver, kidney, intestine, and brain, but little is known about skin
- Objective of this work was to characterize drug transporters in the skin :
 - mRNA expression & regulation in the skin
 - Localization in the skin
 - Role in dermal absorption
- In order to meet regulatory agencies requirement for topically applied drugs, and to improve prediction using PBPK modeling



Expression of drug transporters in human skin

Methods



Skin biopsy



Tissue homogenisation



Skin organ-culture
& Treatment 3 days



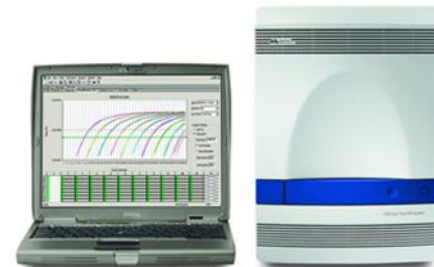
Total RNA extraction



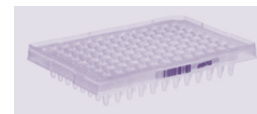
Reverse transcription



RNA quantification

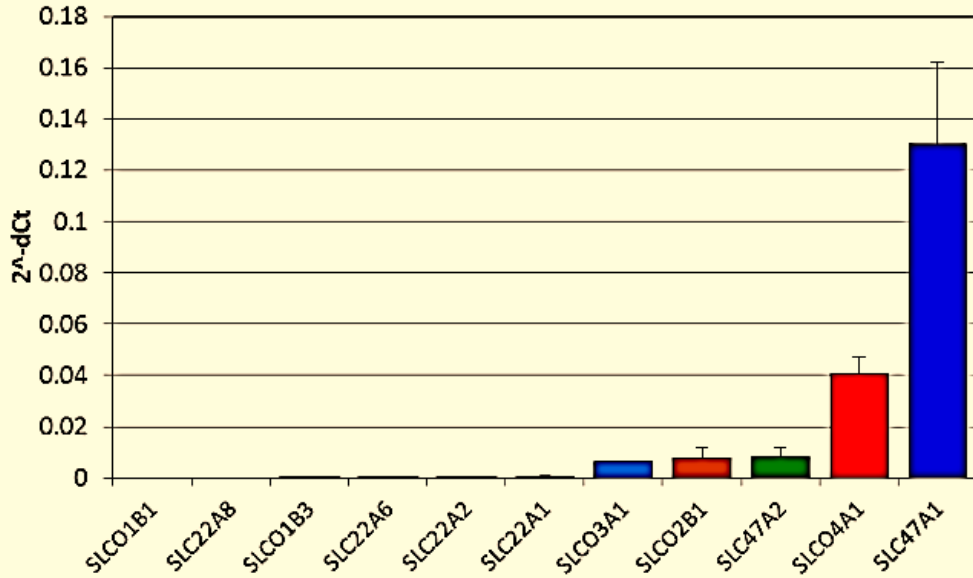


Real-Time qPCR
TaqMan technology

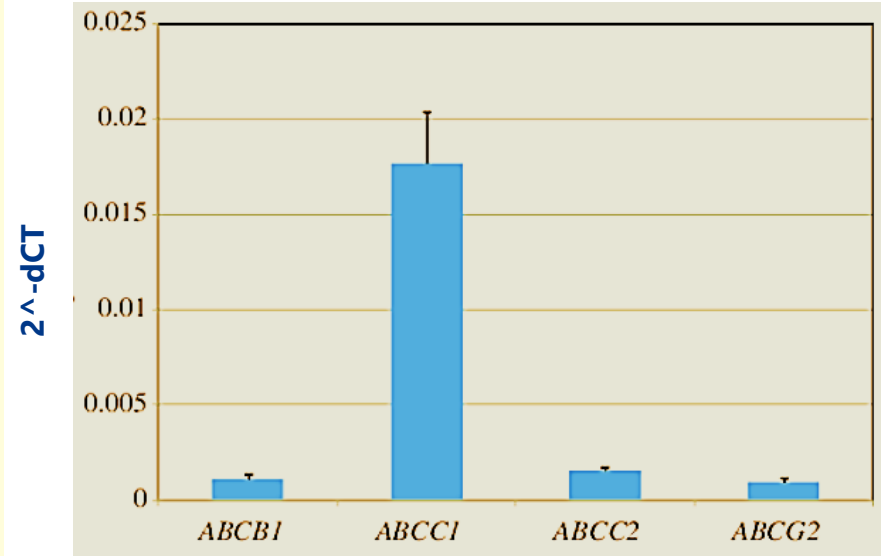


Expression of drug transporters in *ex vivo* human skin

SLC Transporters



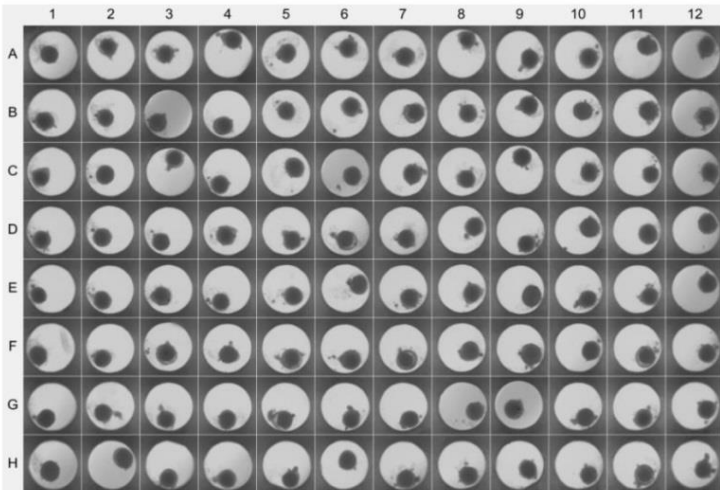
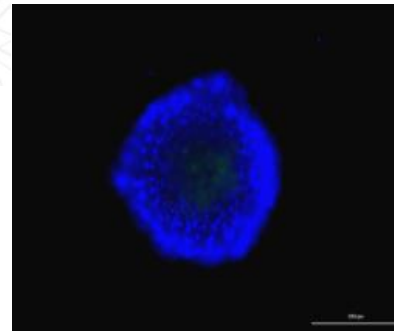
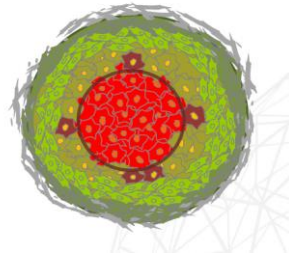
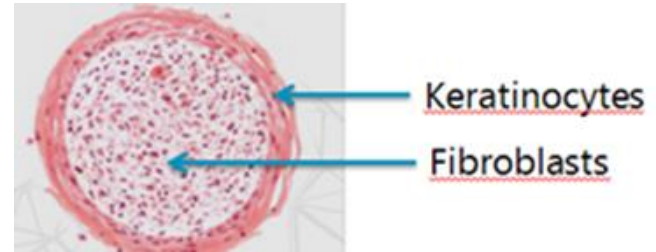
ABC Transporters



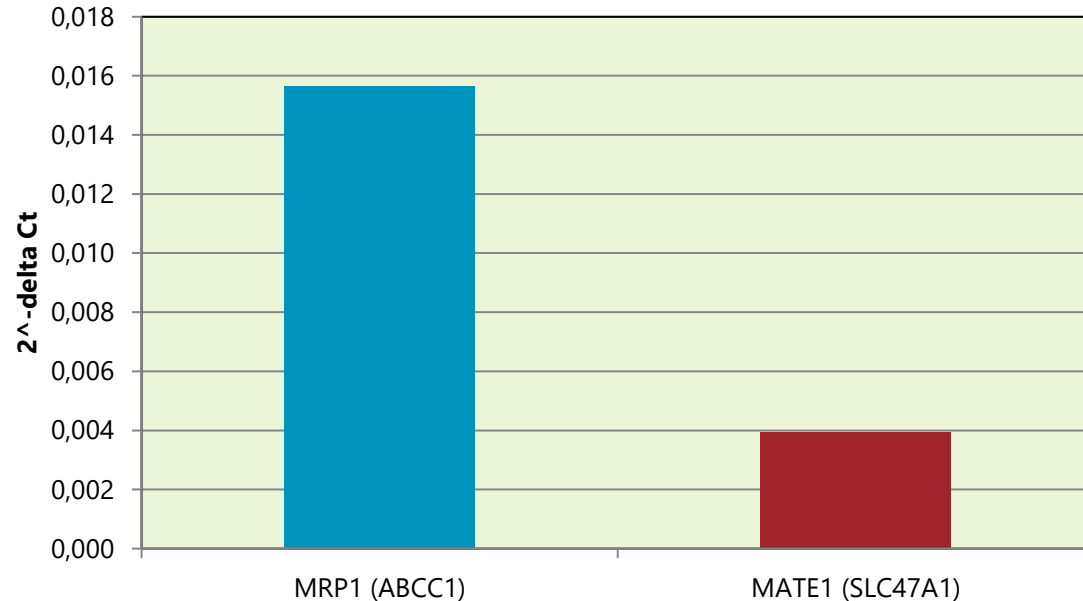
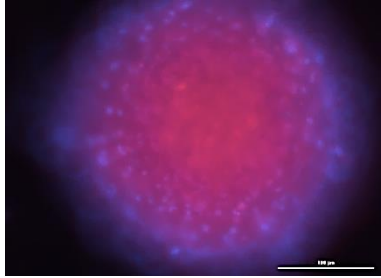
- 5 SLC transporters over 11 are expressed in human skin
 - MATE1 (SLC471) is the most expressed
- All key ABC transporters are expressed in human skin
 - MRP1 (ABCC1) is the most expressed

Expression of drug transporters in 3D human skin microtissue (InSphero)

- Biological system:
 - 3D Human skin microtissue : Sphere of fibroblasts surrounded by keratinocytes
 - One tissue per well of 96-well plate

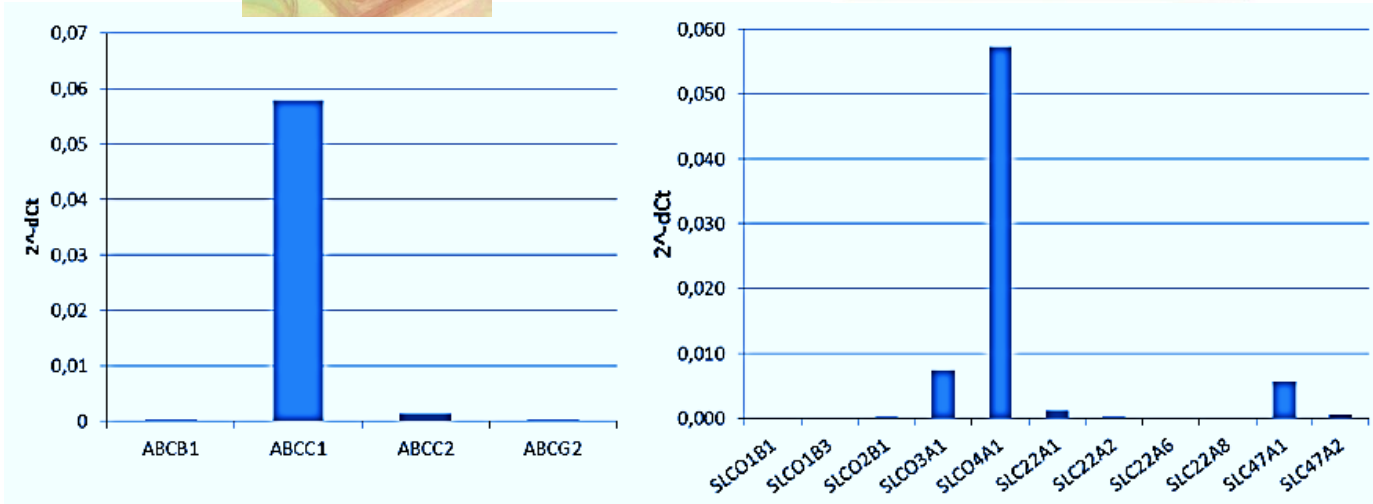
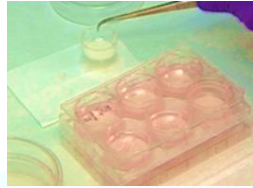


Expression of drug transporters in 3D human skin microtissue (InSphero)



- MRP1 and MATE1 are expressed in 3D Human skin microtissue

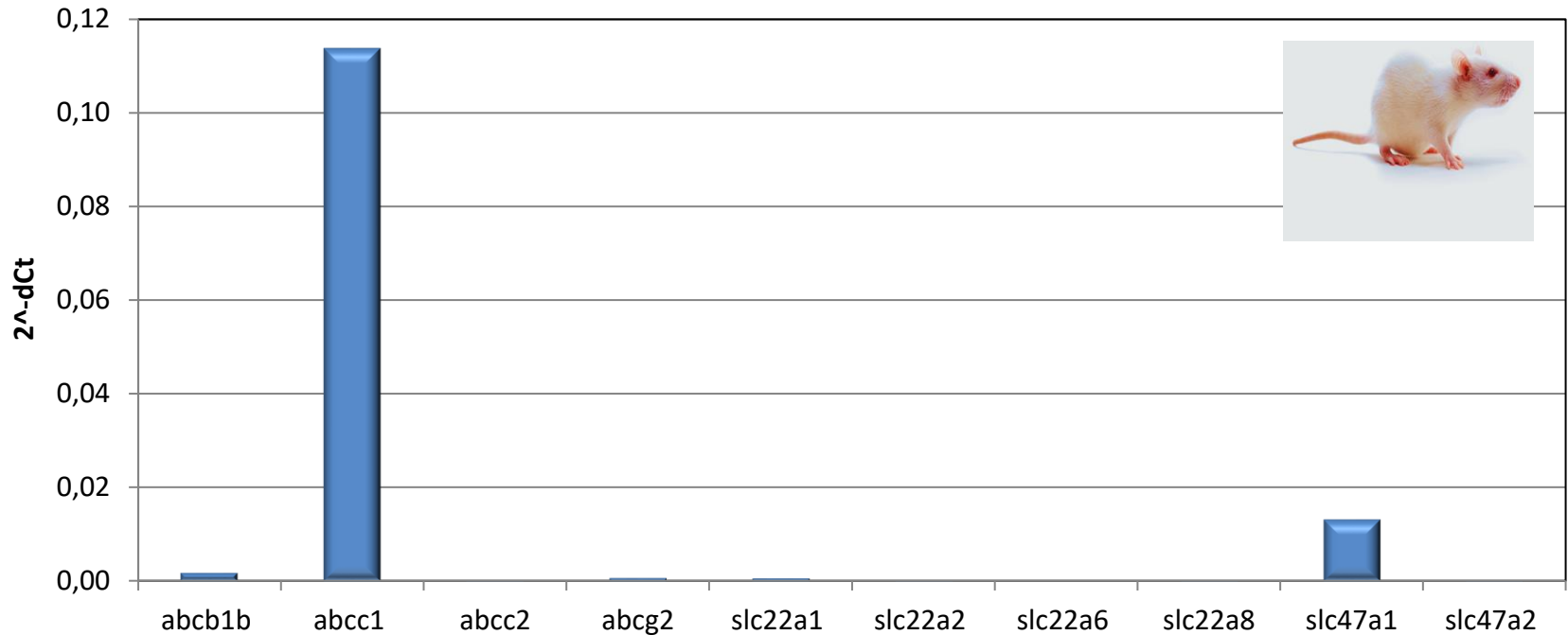
Expression of drug transporters in 3D reconstructed human epidermis (Episkin)



- MRP1 and MATE1 are also expressed in 3D reconstructed human epidermis



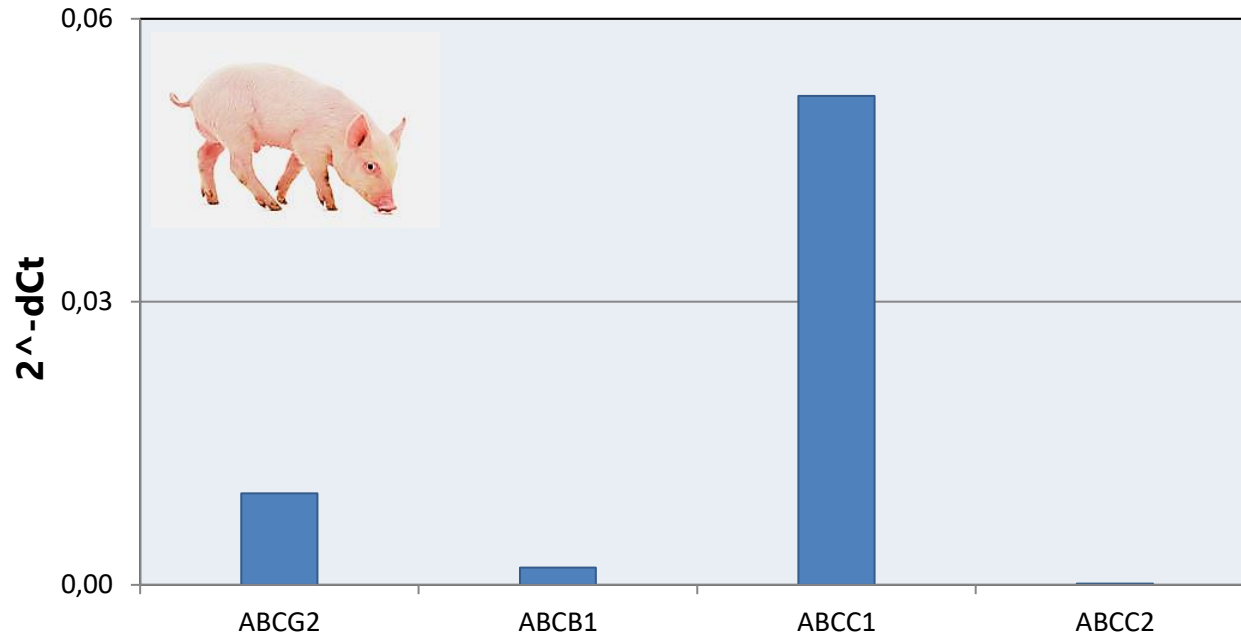
Expression of drug transporters in Rat skin



- MRP1 and MATE1 are expressed in Rat skin



Expression of drug transporters in Minipig skin

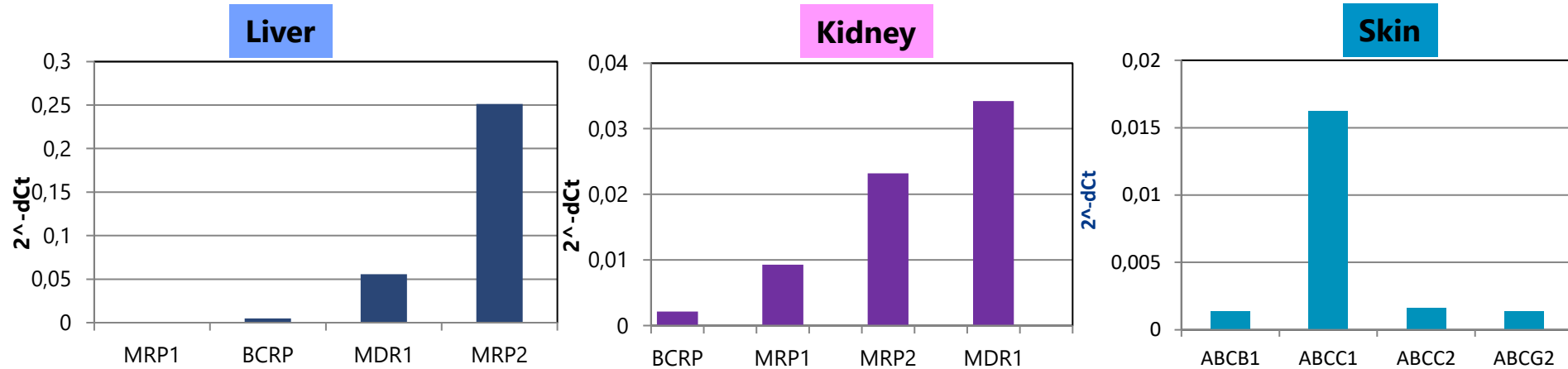


- MRP1 is the main ABC transporter in Minipig skin



Expression of ABC transporters in human tissues

Comparison of ABC transporters in Skin, Liver and kidney



- Expression profile very different according to tissue
 - ABCC1 (MRP1) most expressed in skin
 - ABCC2 (MRP2) most expressed in liver
 - ABCB1 (MDR1) most expressed in kidney



Regulation of drug transporters in human skin

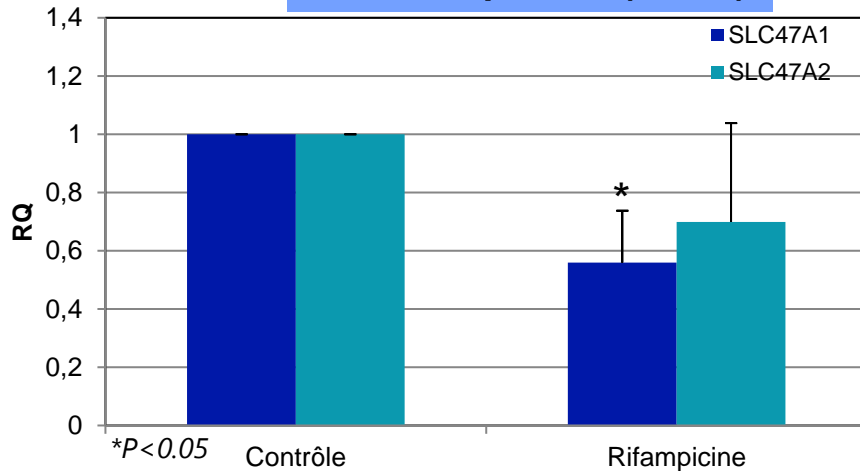
Effect of Rifampicin on ABC and SLC transporters in Skin

Rifampicin: 50 μ M for 72 h

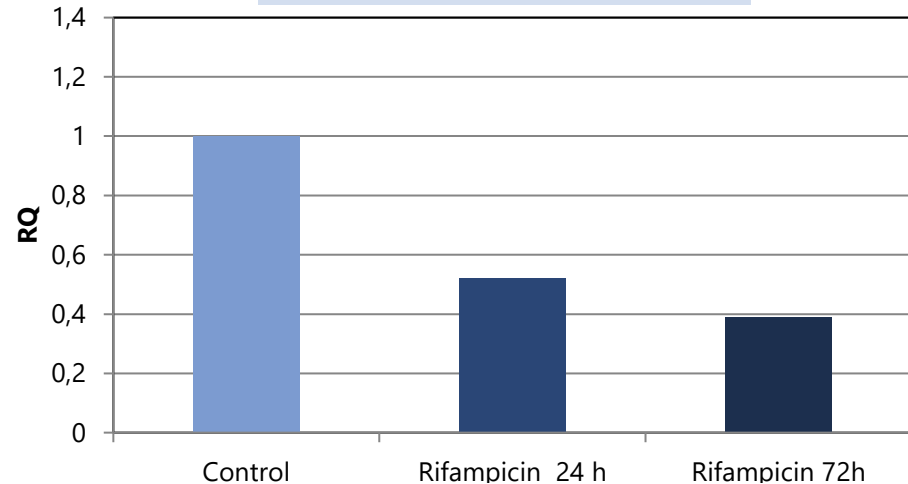
Human skin biopsies in organ-culture

N = 2 or 3 donors

SLC transporters (MATE)



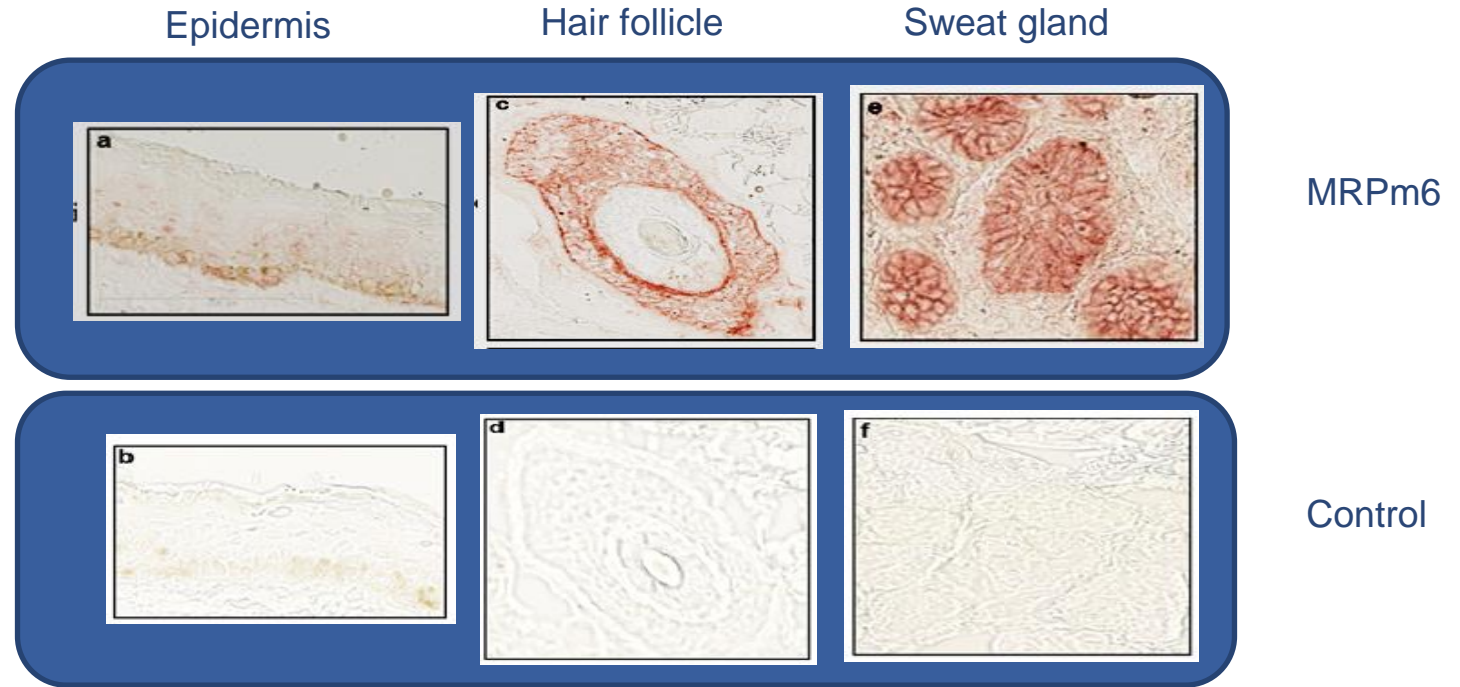
ABC transporters (MRP1)




- Rifampicin markedly decreases expression of MATE and MRP1 transporters in human skin



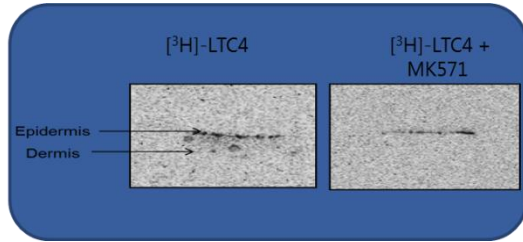
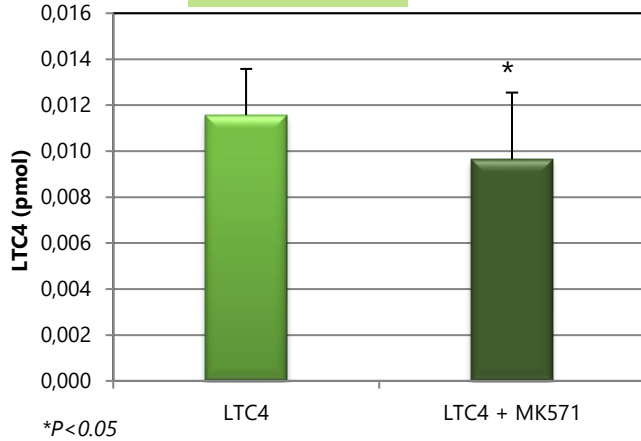
Localization of MRP1 in human skin



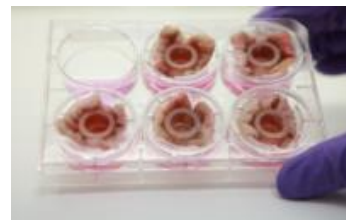
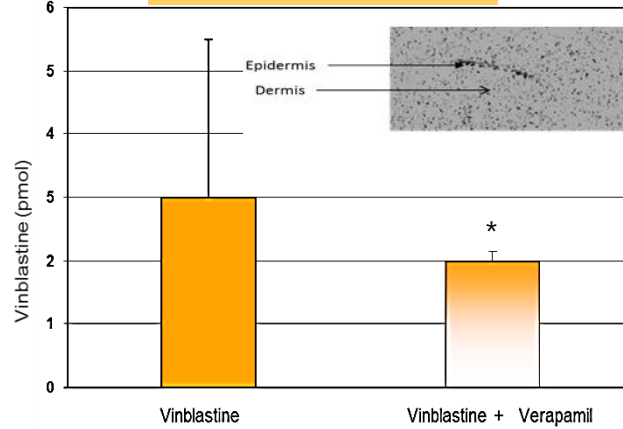
- MRP1 mainly localized in the hair follicle and sweat gland in the dermis  Role in dermal absorption

Role of MRP1 in dermal absorption

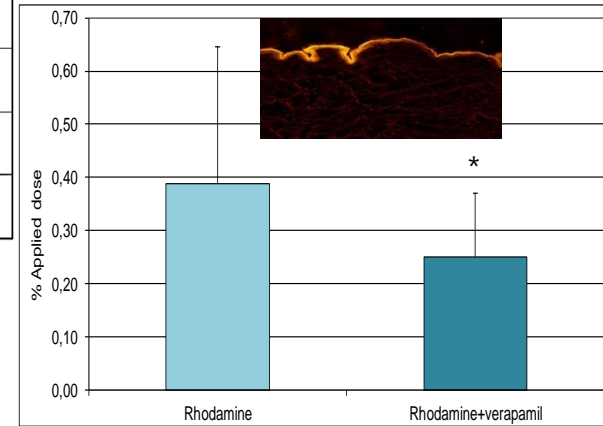
LTC4/MK571



Vinblastine/Verapamil



Rhodamine 123/Verapamil



- MRP1 inhibitors significantly decrease dermal absorption of MRP1 substrates, indicating role of MRP1 in skin dermal absorption



Conclusion

- MRP1 plays important role in drug absorption in human skin
- Role of MATE1 and MATE2-K in the skin need to be clarified
- Further studies needed to clarify the role of drug transporters in drug disposition in the skin and in clinical drug interactions with topically applied drugs

H. Osman-Ponchet et al., 2014, Drug Metabolism and drug interactions

M. Alriquet et al., 2015, ADMET & DMPK

H. Osman-Ponchet et al., 2017, ADMET & DMPK



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Thank you