Drug transporters in the skin: Role in dermal absorption

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Drug transporters in the skin: Role in dermal absorption

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2019 GMP Symposium
16th October 2019, Lyon - France

GMP
Groupe de Métabolisme et Pharmacocinétique

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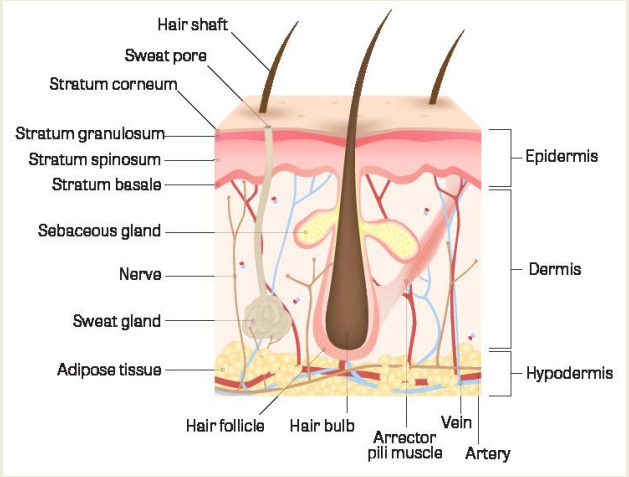
Human skin

- 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



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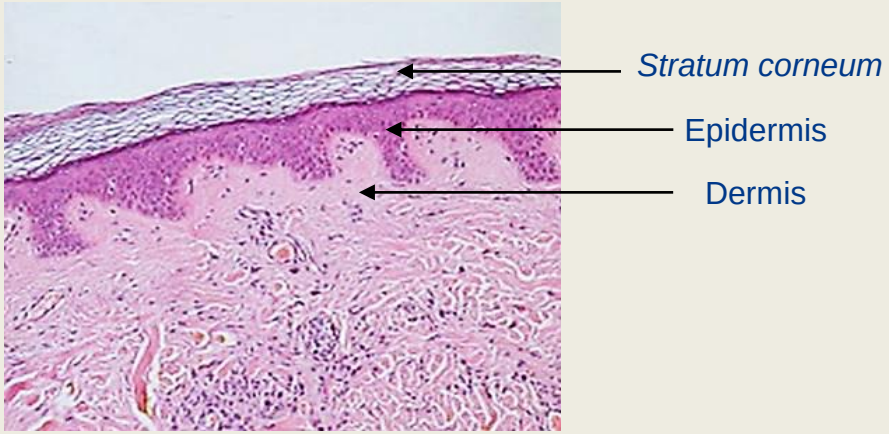
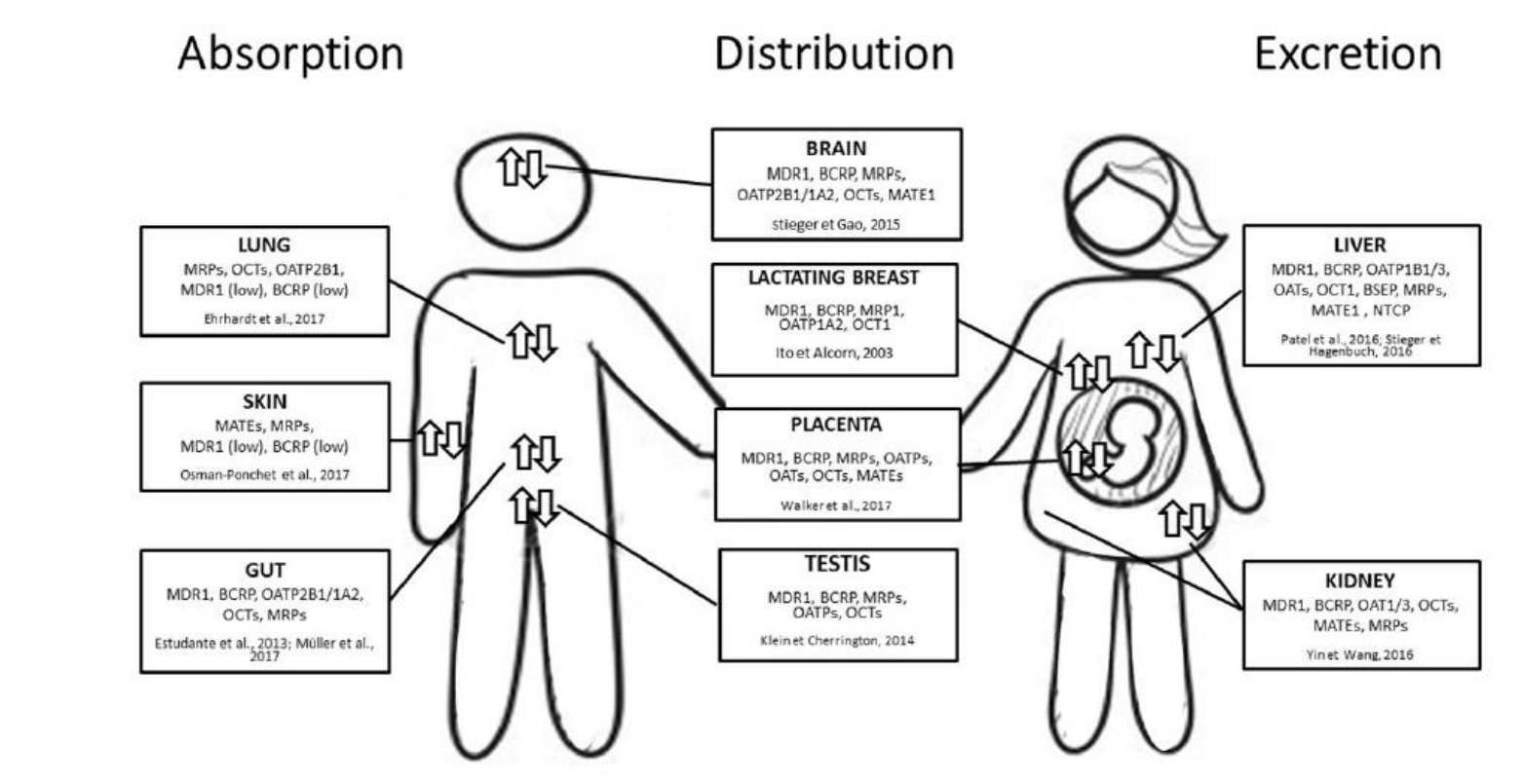


Drug transporters

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



Clerbaux et al., 2019

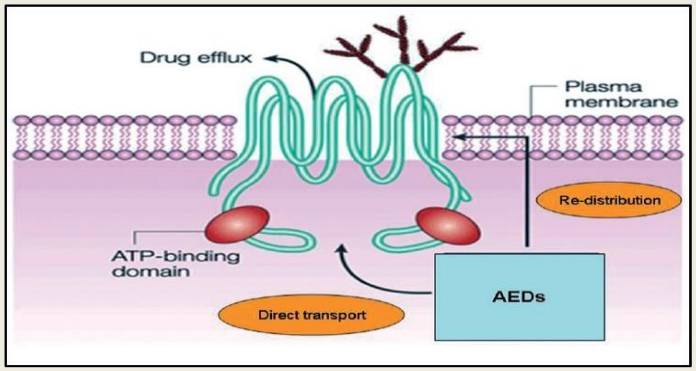
Outline

- 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

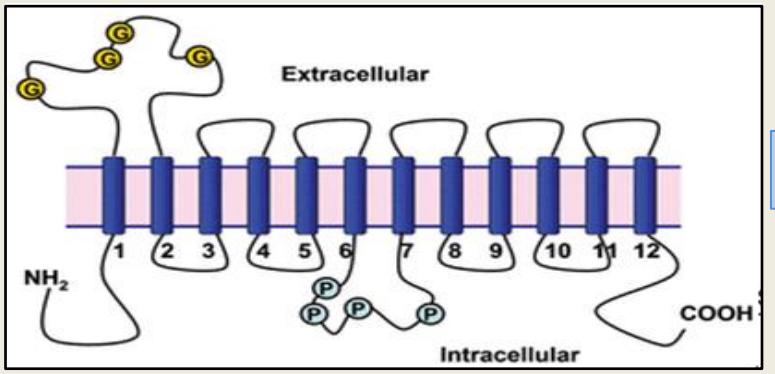
Drug transporters

- 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



A. Das et al; Indian J Human Genetics (2011)



K. Sanjay et al; Physiological Reviews (2015)

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

- 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

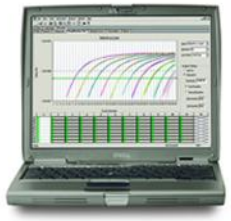
Tissue homogenisation

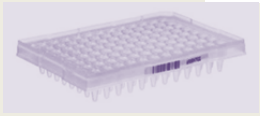
Reverse transcription

Skin organ-culture
& Treatment 3 days

Total RNA extraction

RNA quantification

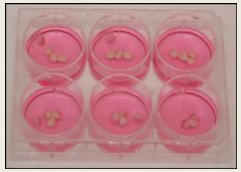




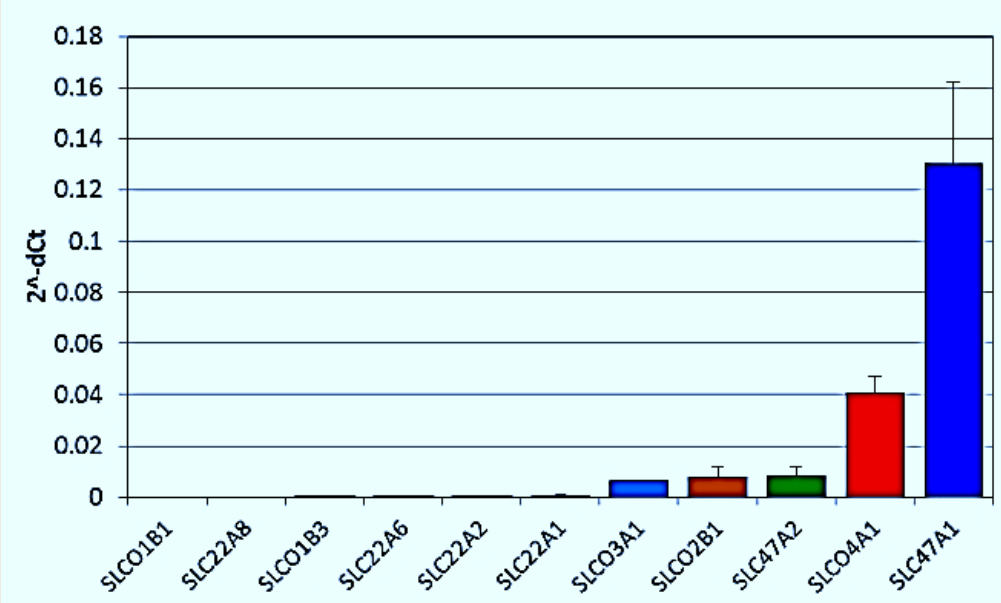
Real-Time qPCR
TaqMan technology

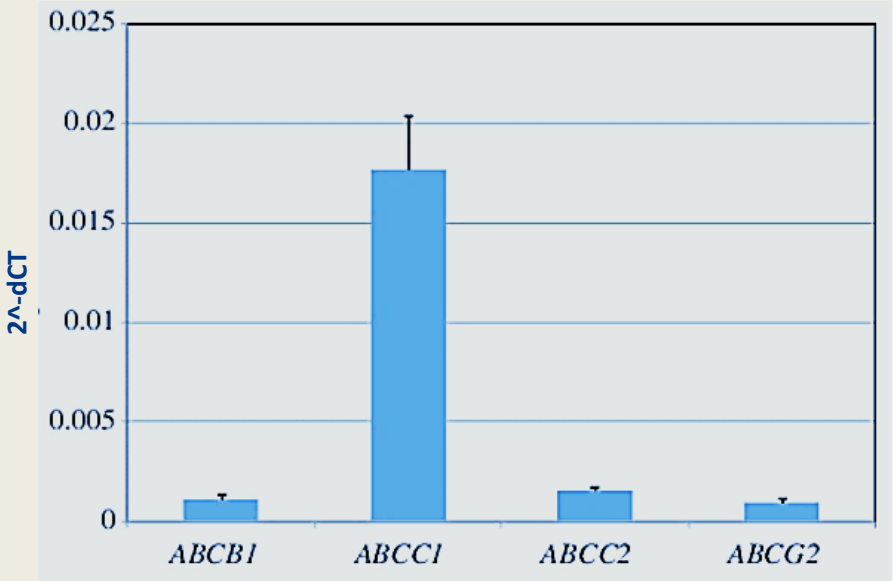
Expression of drug transporters in *ex vivo* human skin

SLC Transporters



ABC Transporters

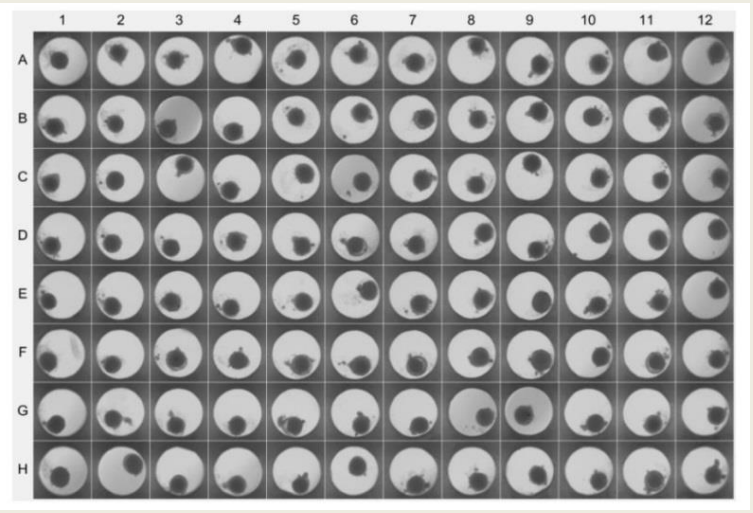


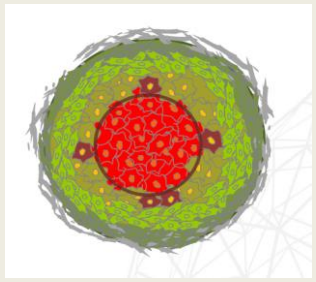


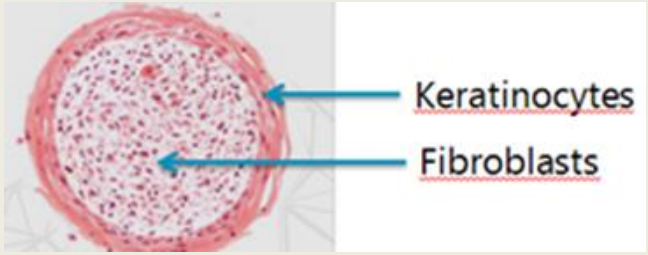
- 5 SLC transporters over 11 are expressed in human skin,
  MATE1 (SLC47A1) is the most expressed in human skin
- All key ABC transporters are expressed in human skin,
  MRP1 (ABCC1) is the most expressed in human skin

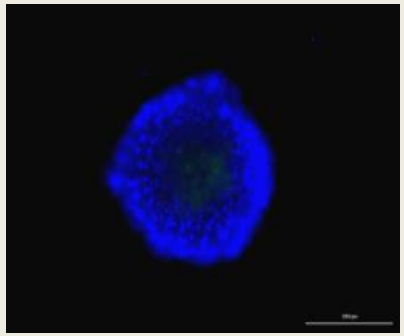
Expression of drug transporters in 3D human skin microtissue (InSphero)

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

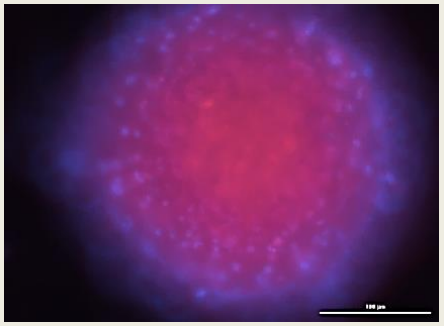


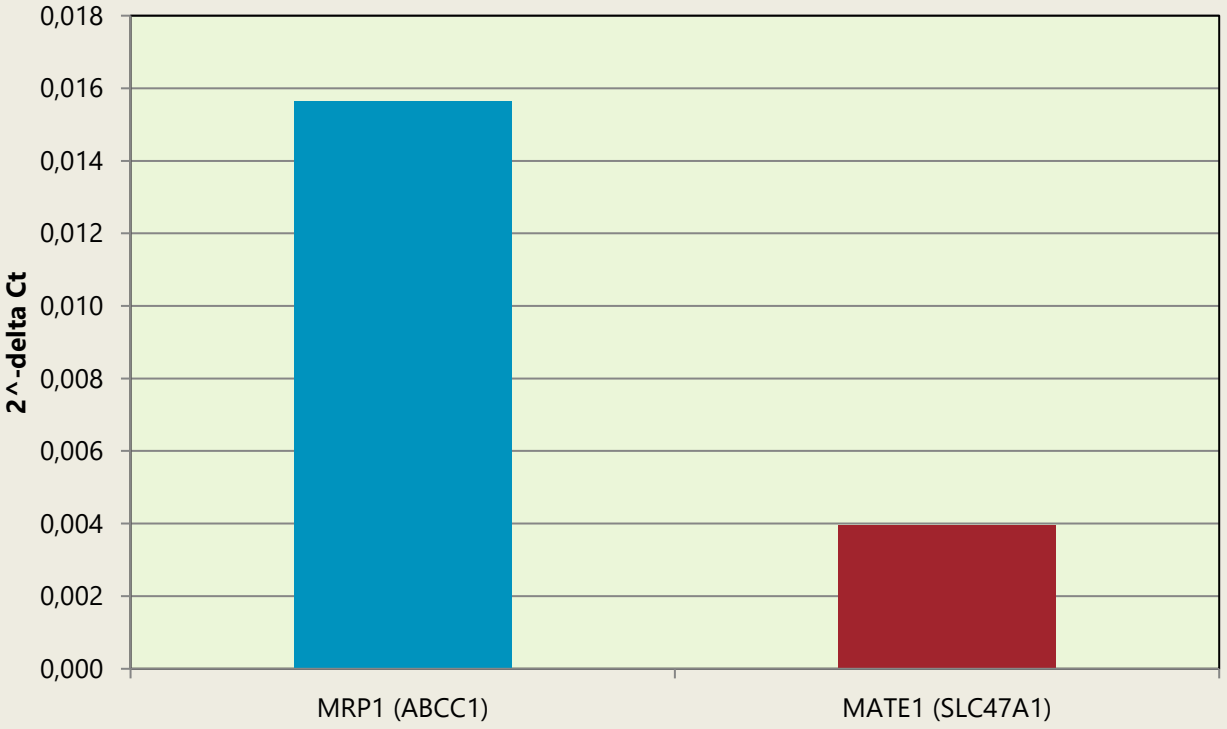






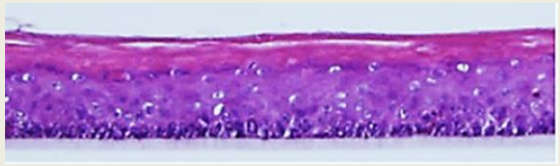
Expression of drug transporters in 3D human skin microtissue (InSphero)

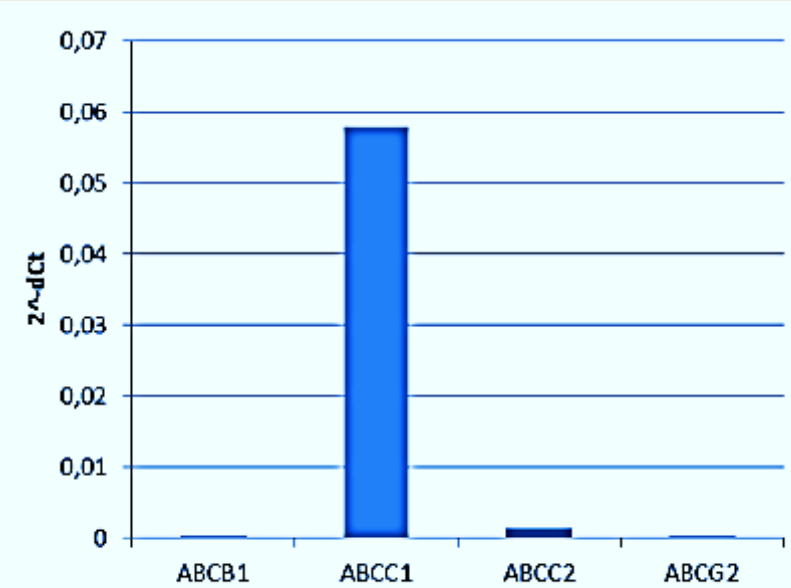


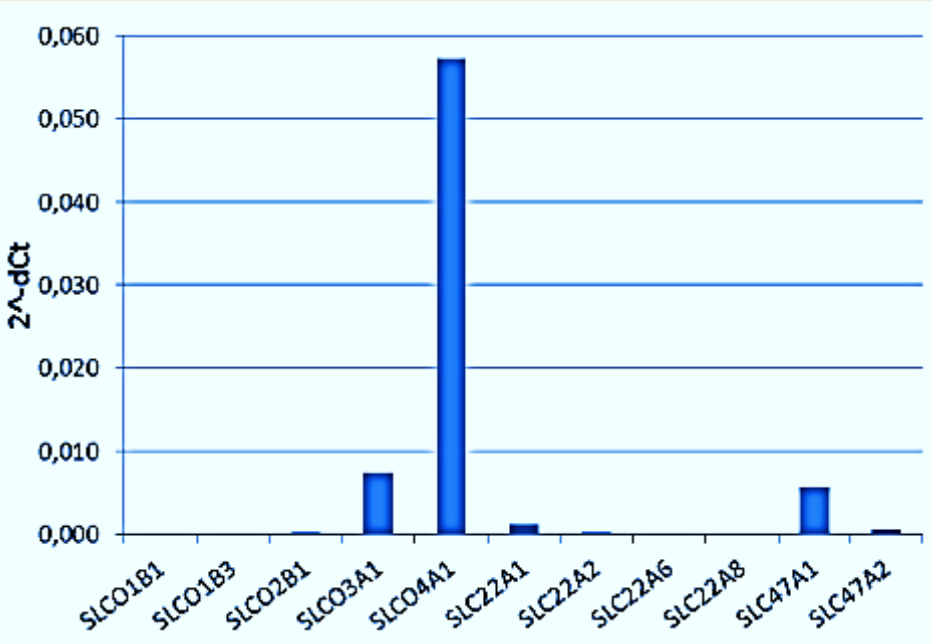


- MRP1 and MATE1 are expressed in 3D Human skin microtissue

Expression of drug transporters in 3D reconstructed human epidermis

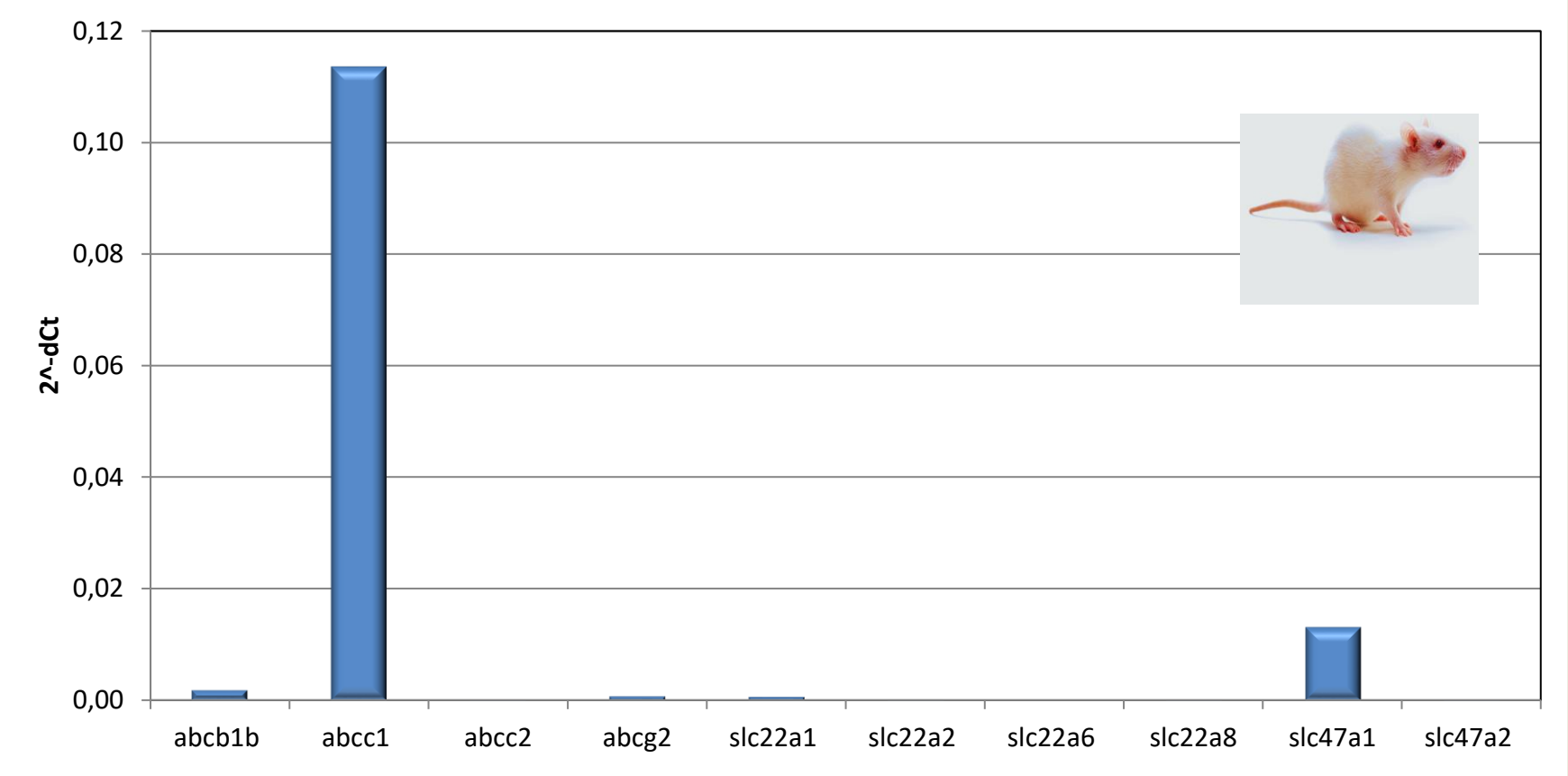






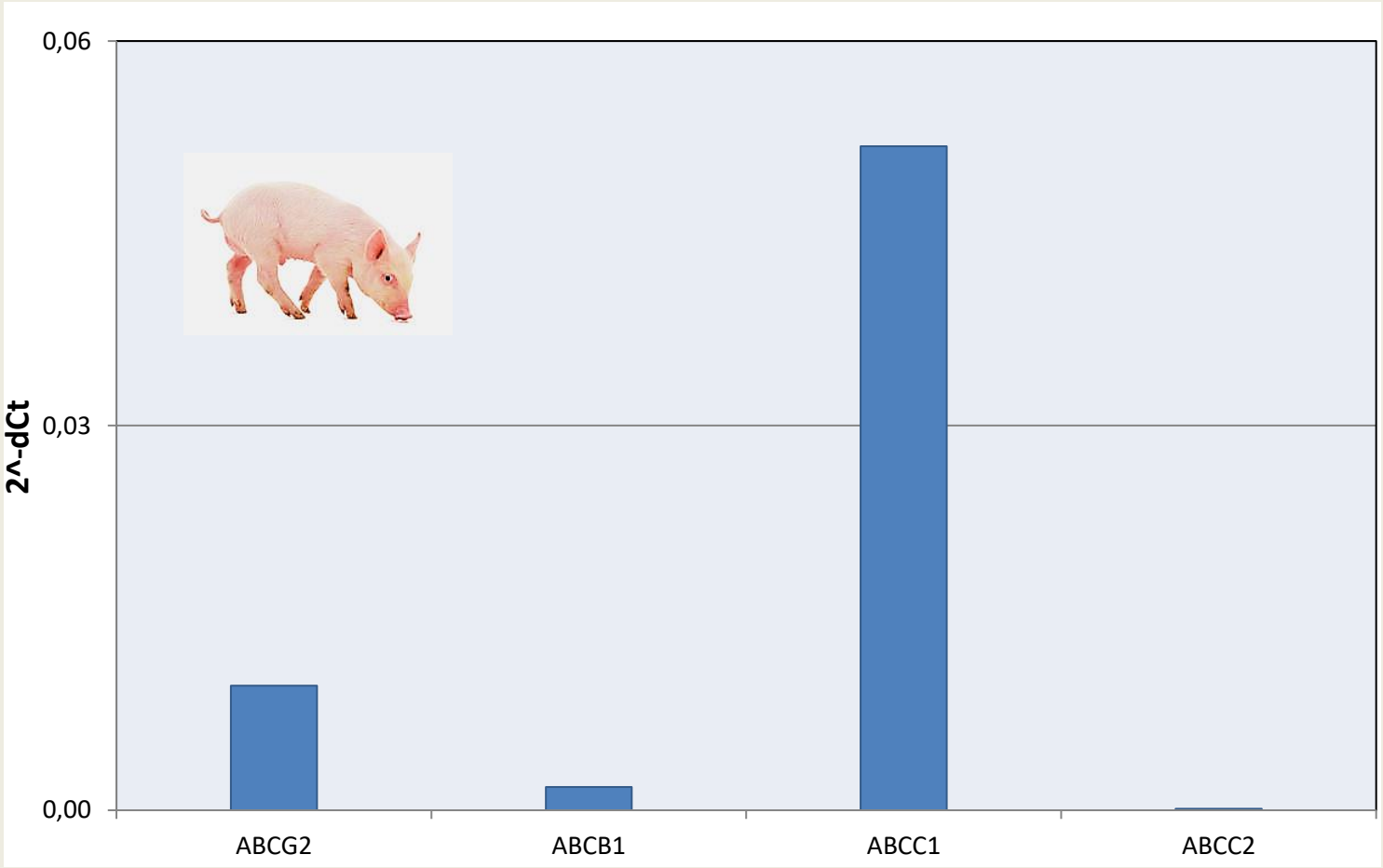
- MRP1 and MATE1 are also expressed in 3D reconstructed human epidermis

Expression of drug transporters in Rat skin



- MRP1 and MATE1 are expressed in Rat skin

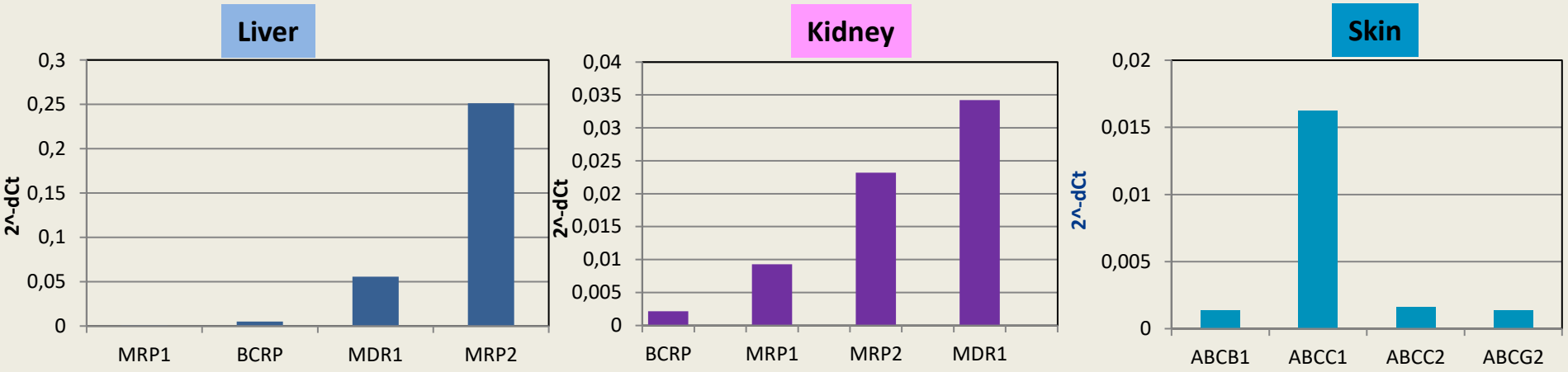
Expression of drug transporters in Minipig skin



- 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



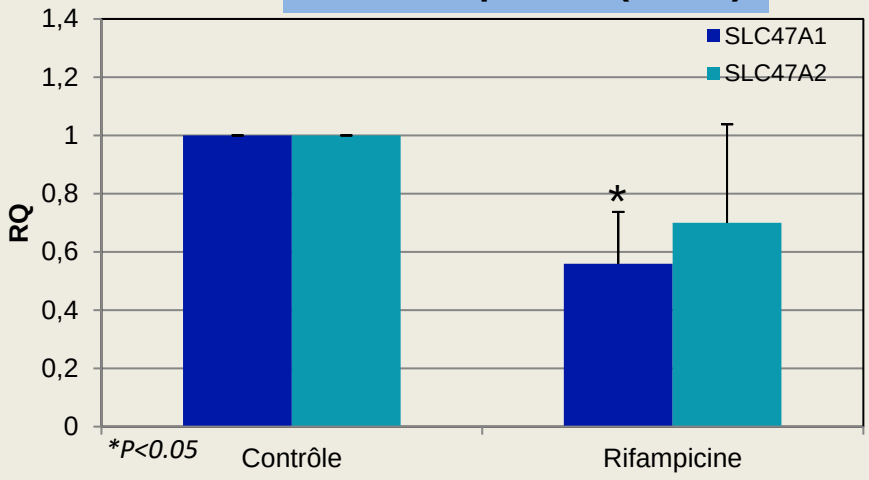
- Expression profile very different according to tissue
  - ABCC1 (MRP1) most expressed in skin
  - ABCC2 (MRP2) most expressed in liver
  - ABCB1 (MDR1) most expressed in kidney

Regulation of drug transporters in human skin

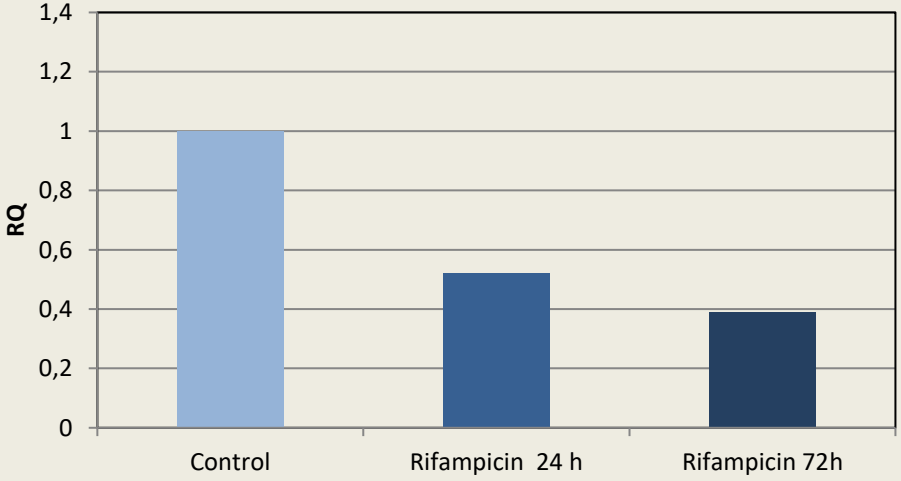
Effect of Rifampicin on ABC and SLC transporters in Skin

Rifampicin: 50 µM for 72 h
Human skin biopsies in organ-culture
N = 2 or 3 donors

SLC transporters (MATE)



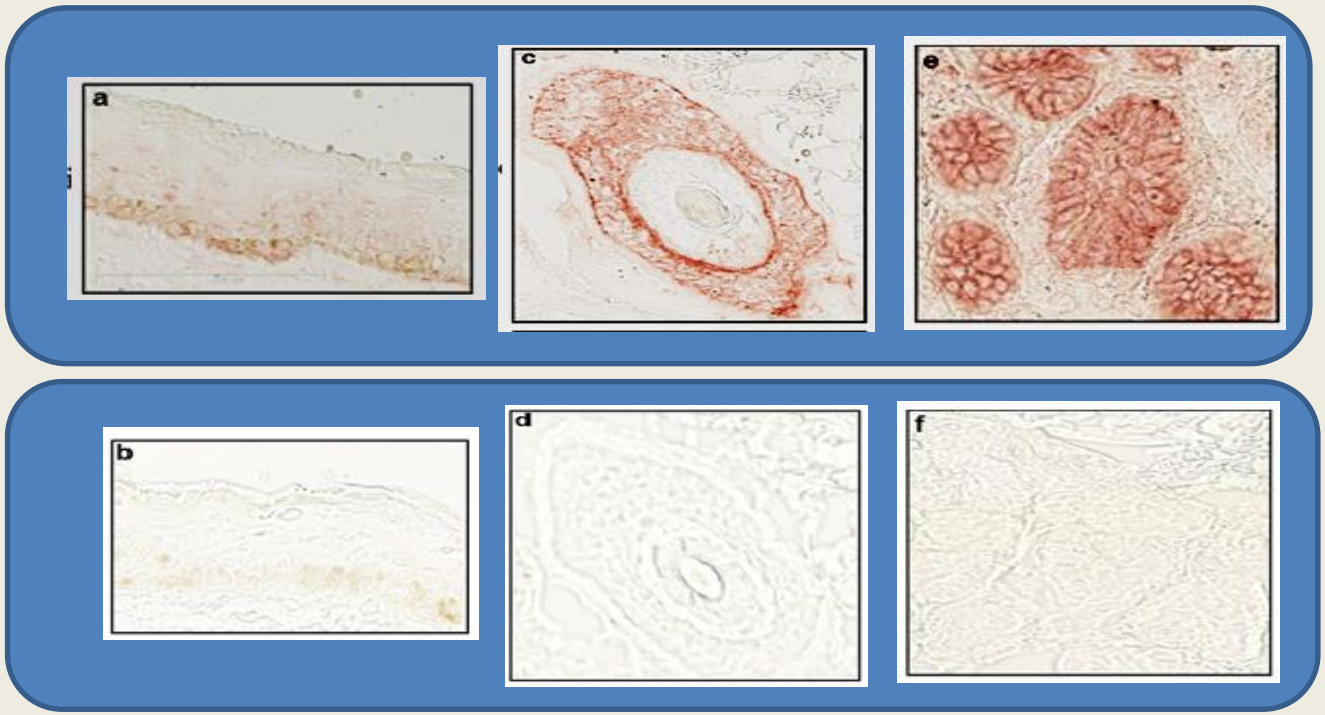
ABC transporters (MRP1)



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

Localization of MRP1 in human skin

Epidermis Hair follicle Sweat gland



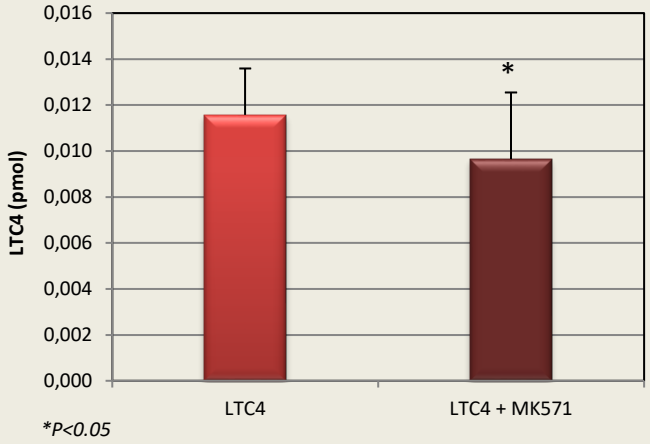
MRPm6

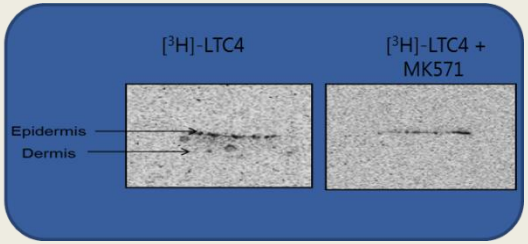
Control

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

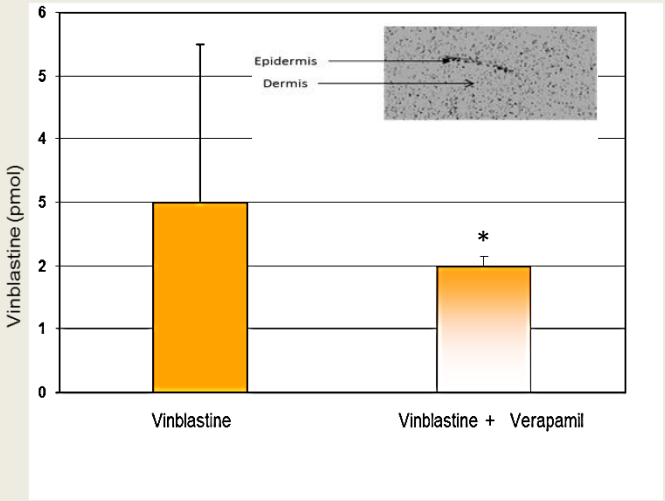
Role of MRP1 in dermal absorption

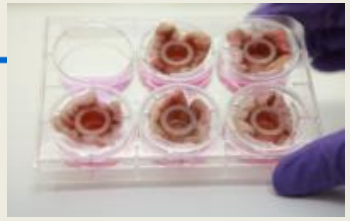
LTC4/MK571



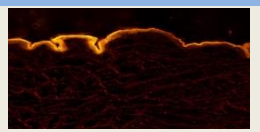


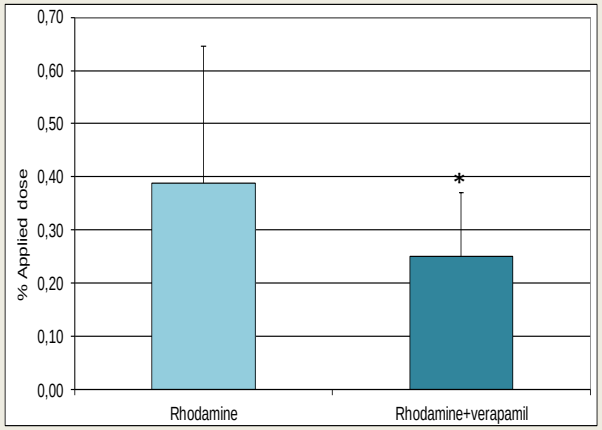
Vinblastine/Verapamil





Rhodamine 123/Verapamil

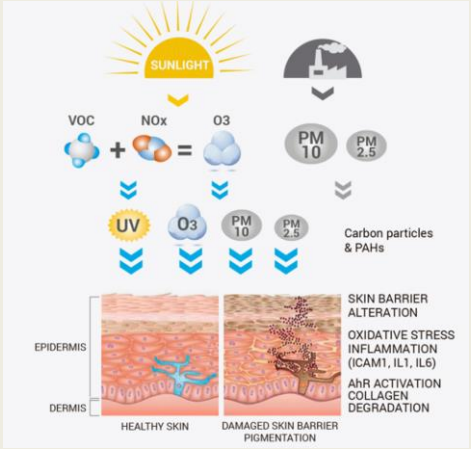




- MRP1 inhibitors significantly decrease dermal absorption of MRP1 substrates, indicating role of MRP1 in skin dermal absorption

Conclusion-Perspectives

- MRP1 plays important role in drug absorption in human skin
- Role of MATE1 and MATE2-K in the skin needs to be investigated
- What is the effect of environmental stress (air pollution and solar radiation) on drug transporters in the skin?



https://www.monteloeder.com/en/zero-pollution

Conclusion-Perspectives

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Review article

Membrane transporter data to support kinetically-informed chemical risk assessment using non-animal methods: Scientific and regulatory perspectives

Laure-Alix Clerbaux[a,1], Alicia Paini[a,*], Annie Lumen[b], Hanan Osman-Ponchet[c], Andrew P. Worth[a], Olivier Fardel[d]

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

L-A Clerbaux et al., 2019