Department of Dermatology and Allergy
Charité - Universitätsmedizin Berlin

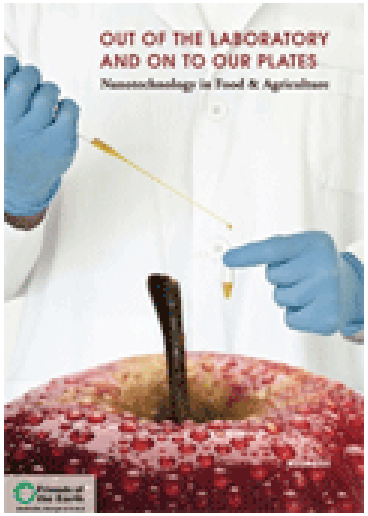
Safety aspects of skin penetration of nanoparticles in topically applied cosmetics / pharmaceuticals

A. Patzelt, H. Richter, W. Sterry, J. Lademann

Center of Experimental and Applied Cutaneous Physiology (CCP)

Safety aspects of skin penetration of nano-sized particles

Center of Experimental and Applied Cutaneous Physiology

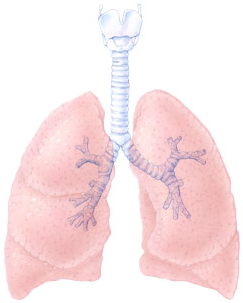


Safety aspects of skin penetration of nano-sized particles

Center of Experimental and Applied Cutaneous Physiology

Potential risks of NP – a public debate

Principal human health risk may be from inhalation of NP!



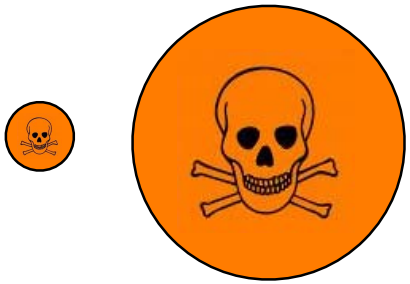
Potential dangers may be from contact of NP with skin?

Safety aspects of skin penetration of nano-sized particles

Center of Experimental and Applied Cutaneous Physiology

Key questions

Do topically applied NP pose new risks when compared to traditional cosmetic products?



➔ **Material versus Size?**

Do topically applied NP remain on the skin or do they pass the skin barrier and gain access to systemic compartments?

Which biological effects can be induced when NP enter the organism?

Safety aspects of skin penetration of nano-sized particles

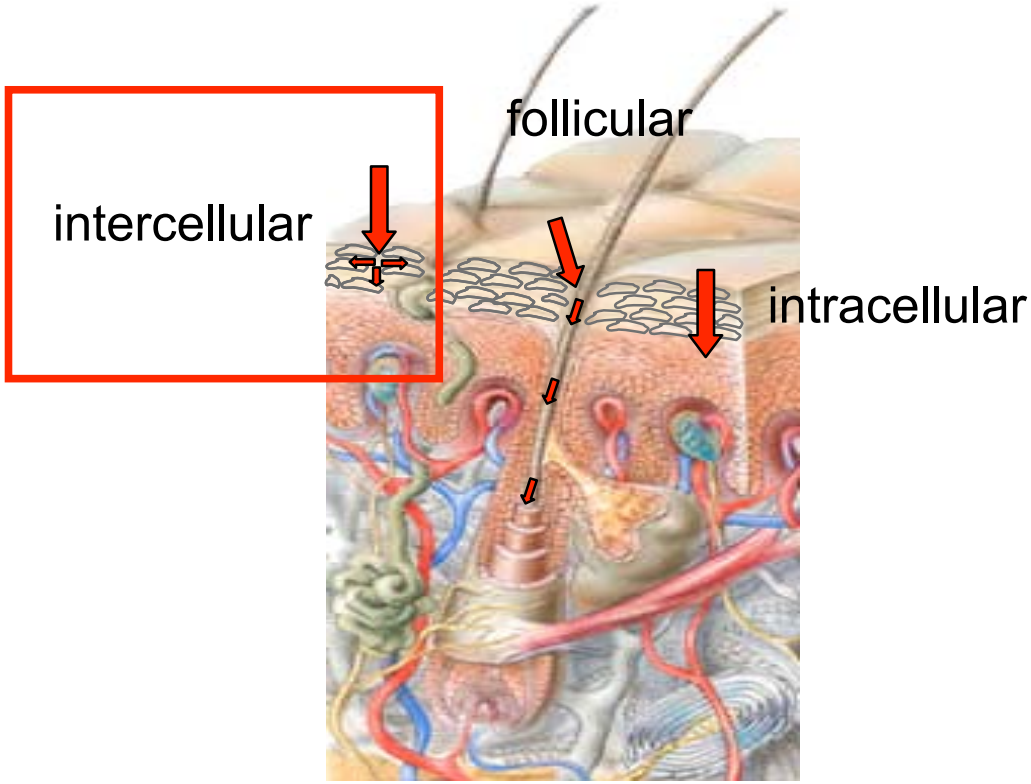
Center of Experimental and Applied Cutaneous Physiology

Are nano-sized particles able to cross the skin barrier?

Safety aspects of skin penetration of nano-sized particles

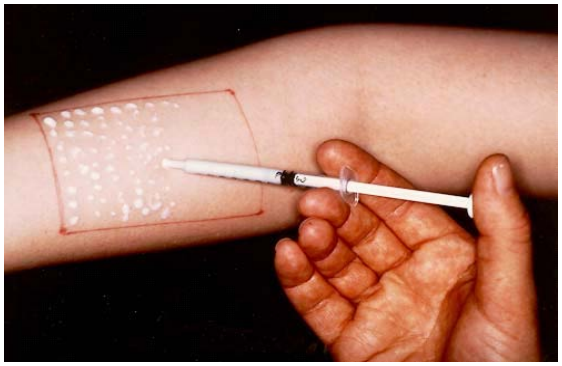
Center of Experimental and Applied Cutaneous Physiology

Penetration pathways

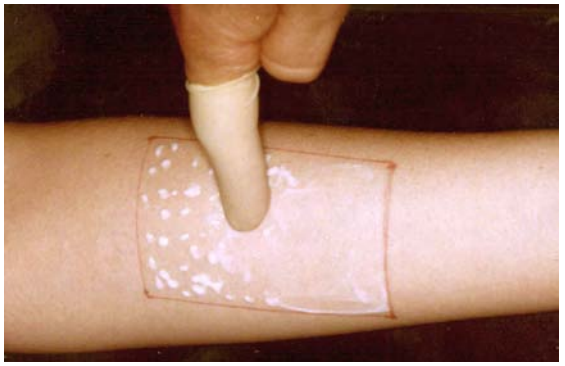


Center of Experimental and Applied Cutaneous Physiology

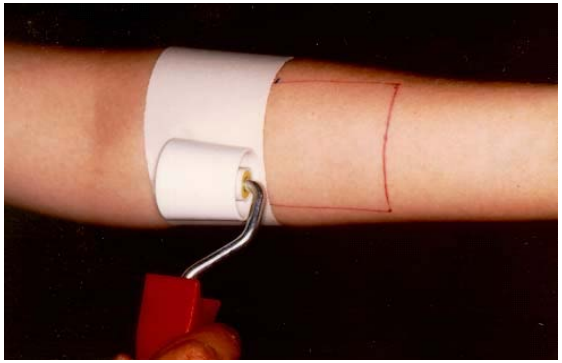
Investigation of intercellular penetration of titanium dioxide by tape stripping



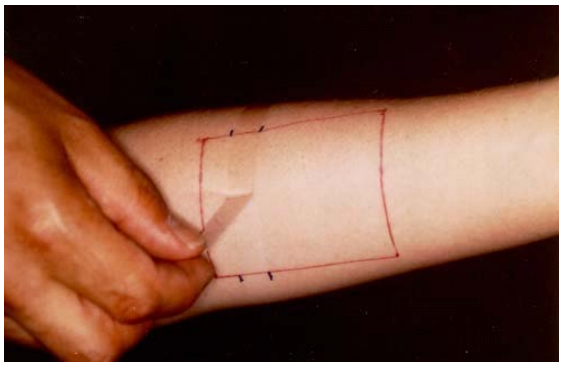
Application of the emulsion



Homogeneous distribution



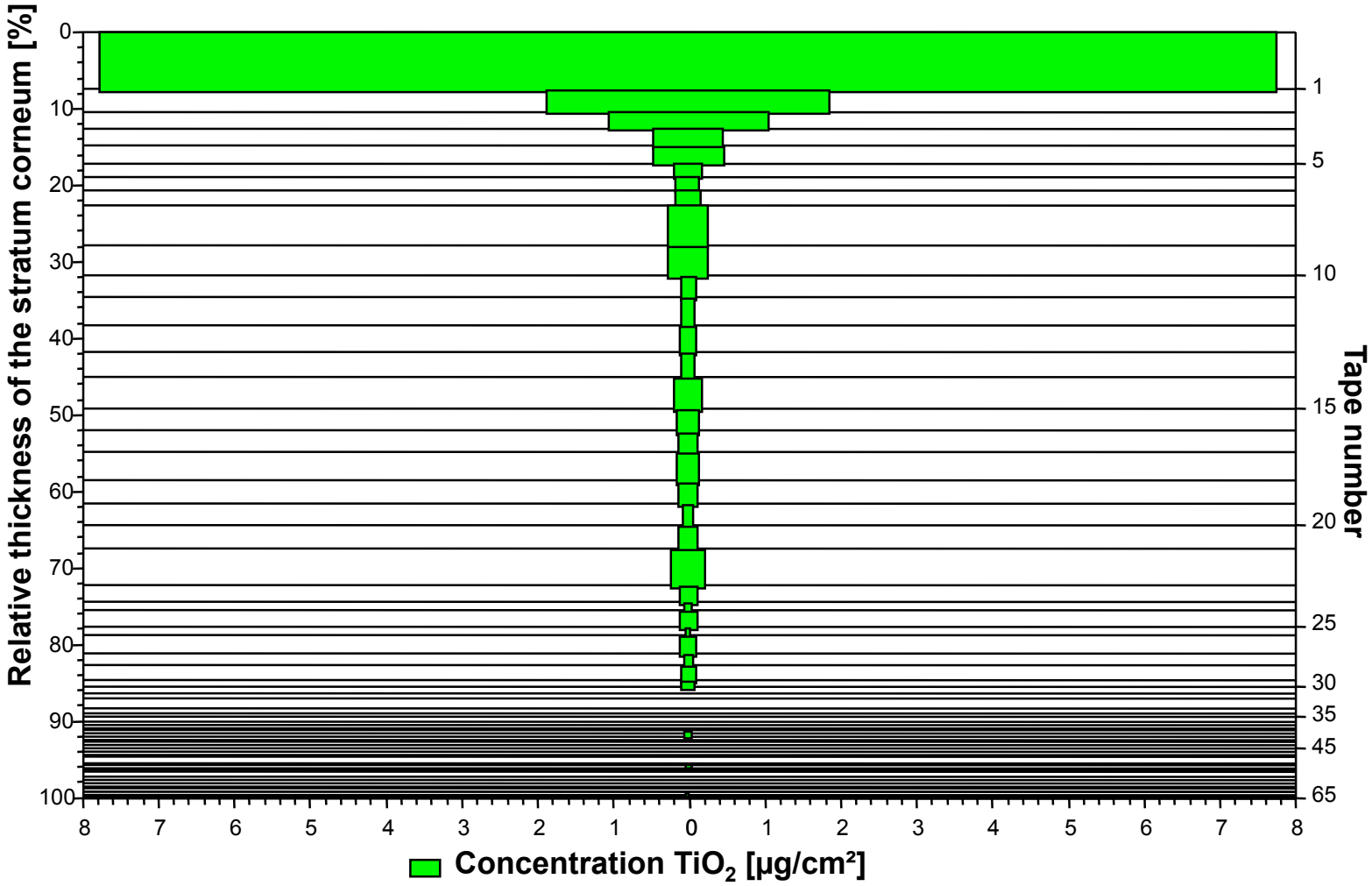
Pressing the tape with a roller



Removal of the adhesive film

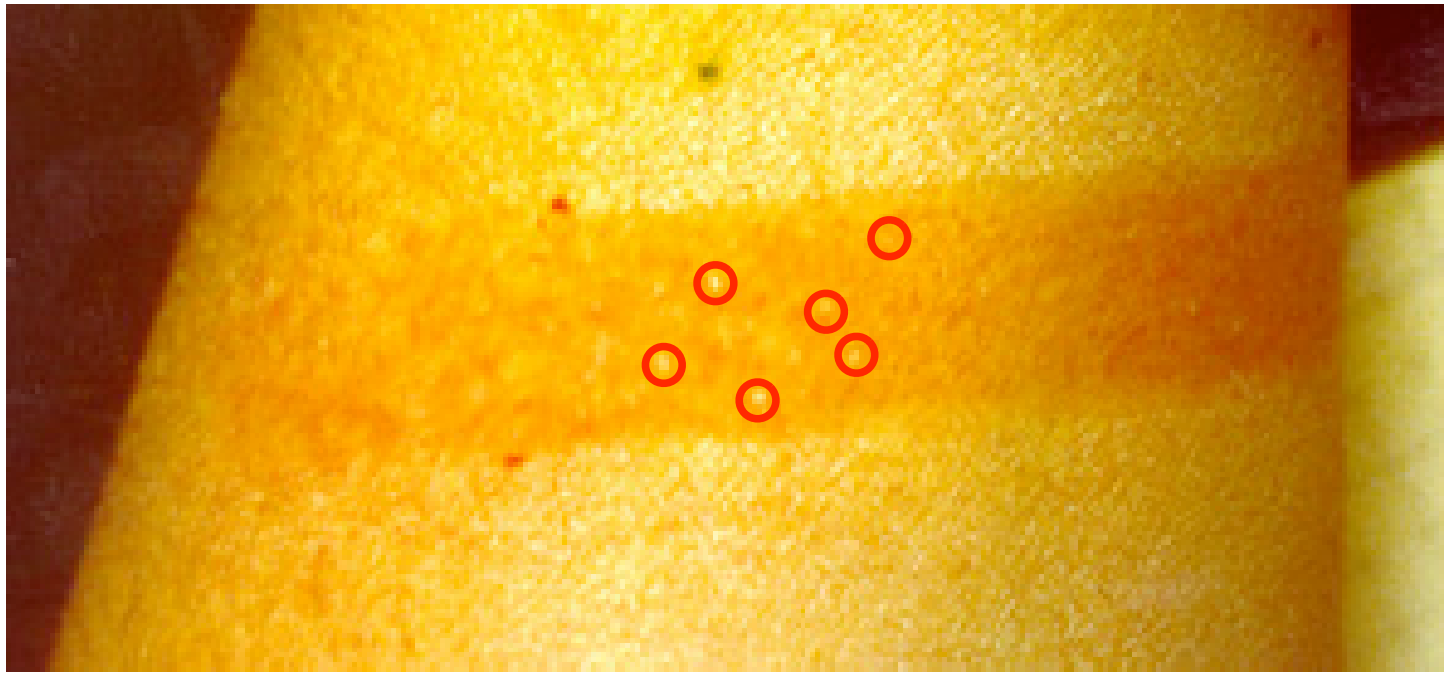
Center of Experimental and Applied Cutaneous Physiology

Penetration profile of titanium dioxide



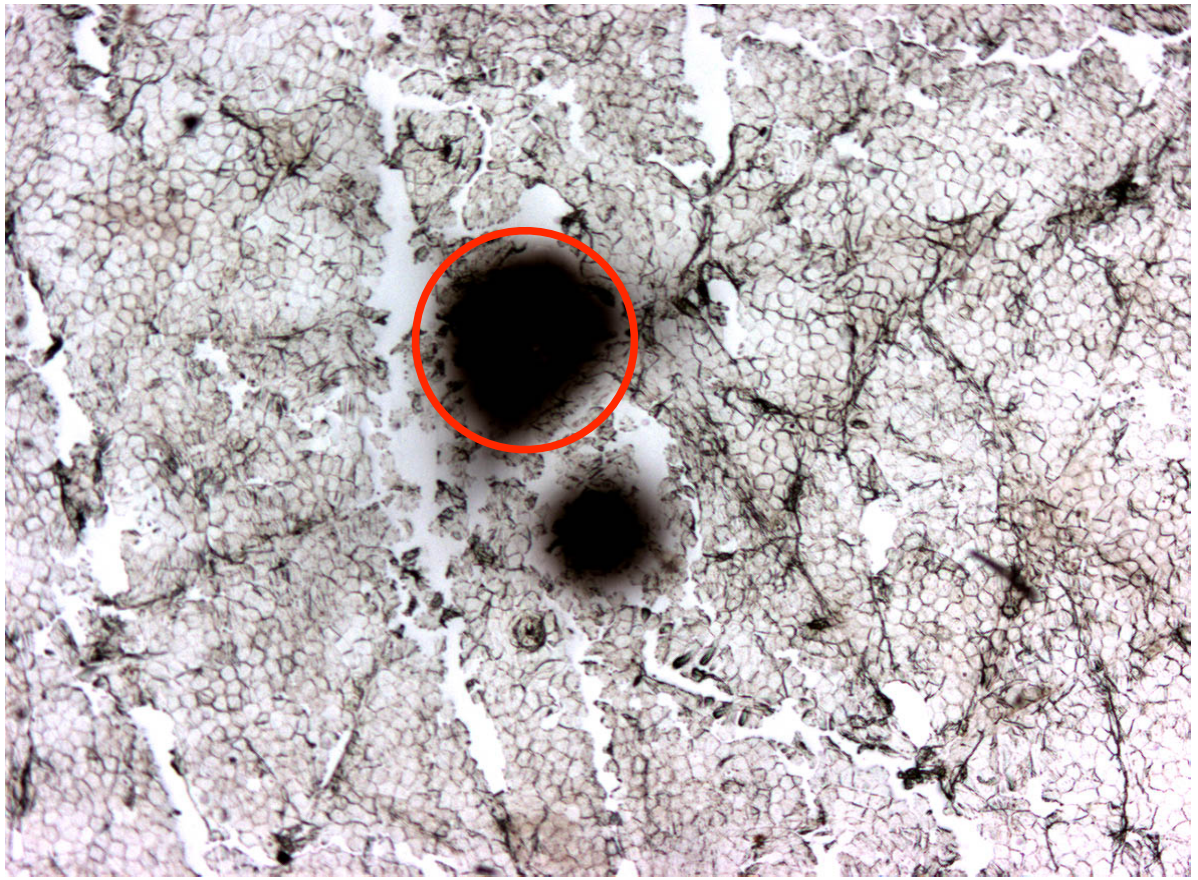
Center of Experimental and Applied Cutaneous Physiology

Skin after removal of 25 tape strips



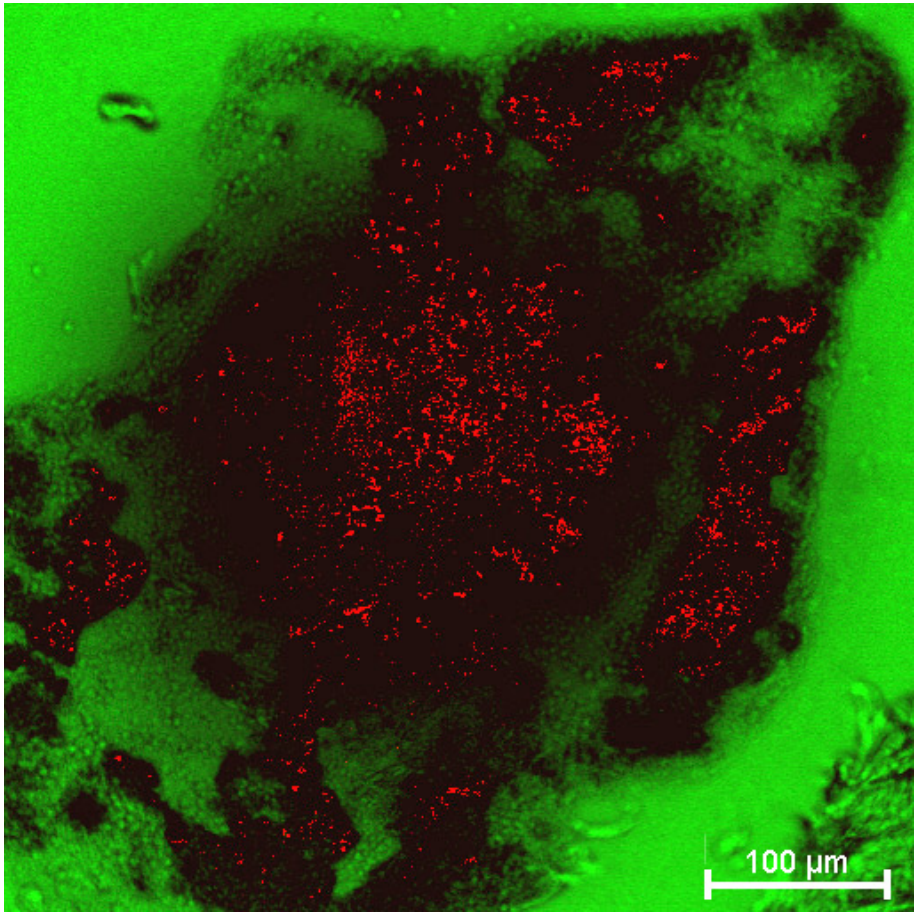
Center of Experimental and Applied Cutaneous Physiology

Position of hair follicles on tape strips with OsO_4 staining



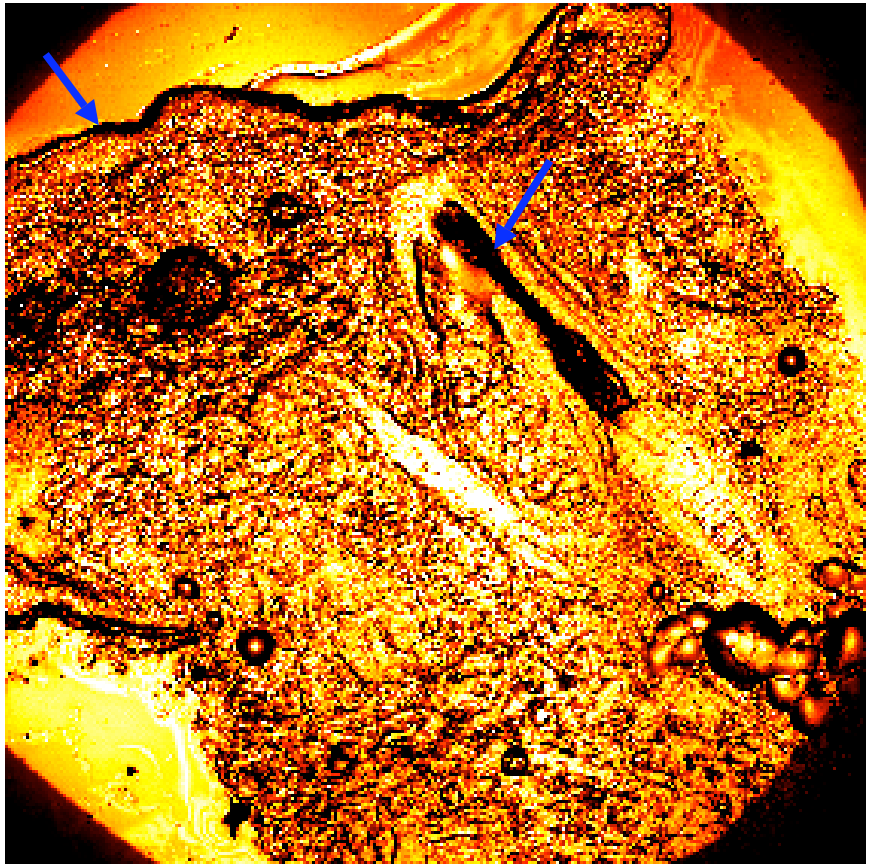
Center of Experimental and Applied Cutaneous Physiology

Detection of titanium dioxide on the removed tape strips in follicular areas



Center of Experimental and Applied Cutaneous Physiology

Biopsy after application of titanium dioxide



Center of Experimental and Applied Cutaneous Physiology

No penetration of titanium dioxide via the intercellular pathway into the living tissue

Tan et al., 1996

Landsdown and Taylor, 1997

Dussert and Gooris, 1997

Lademann et al., 1999

Pflücker et al. 2001

Schulz et al, 2002

Gottbrath and Müller-Goymann, 2003

Grontier et al. 2004

Mavon et al. 2007

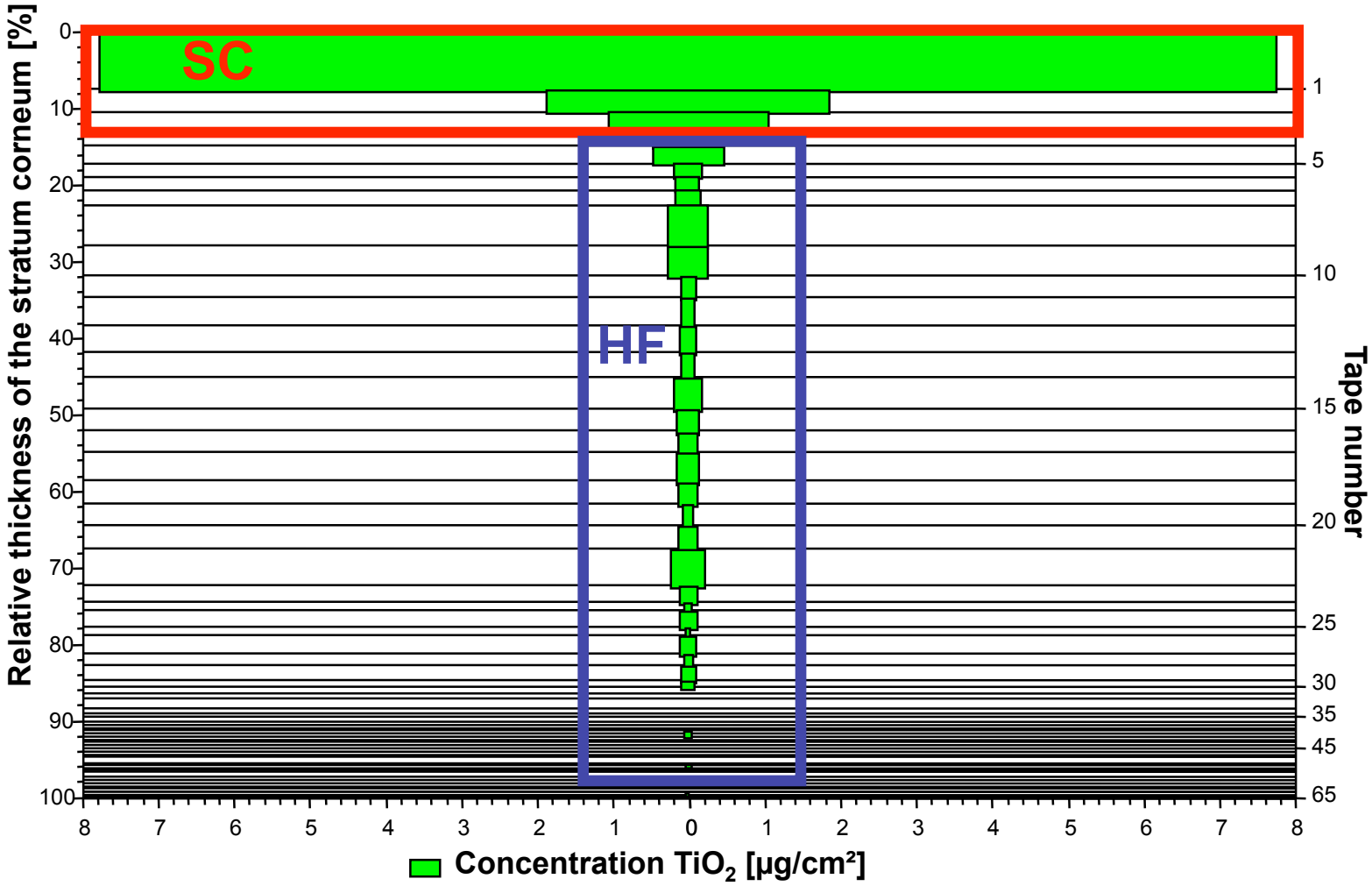
Nohynek et al, 2007

etc.

Safety aspects of skin penetration of nano-sized particles

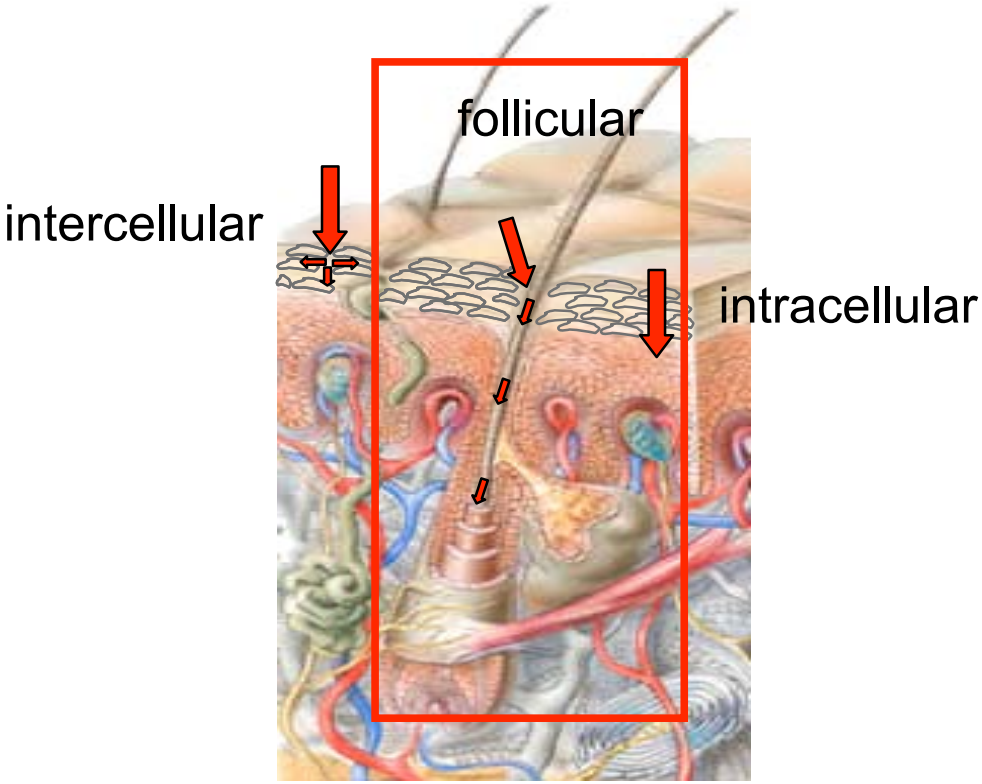
Center of Experimental and Applied Cutaneous Physiology

Penetration profile of titanium dioxide



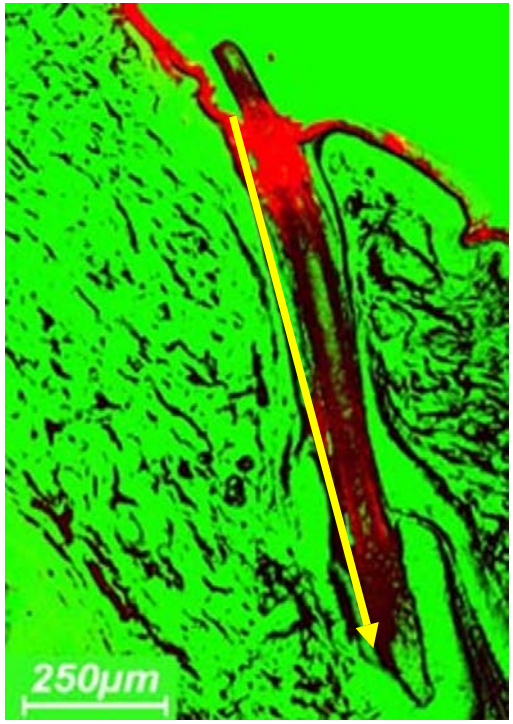
Center of Experimental and Applied Cutaneous Physiology

Investigation of follicular penetration of NP

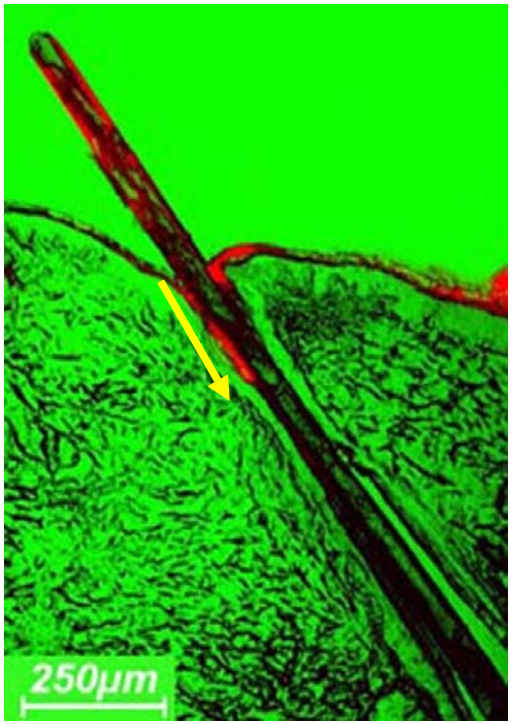


Center of Experimental and Applied Cutaneous Physiology

Investigation of follicular penetration of NP



320 nm NP formulation

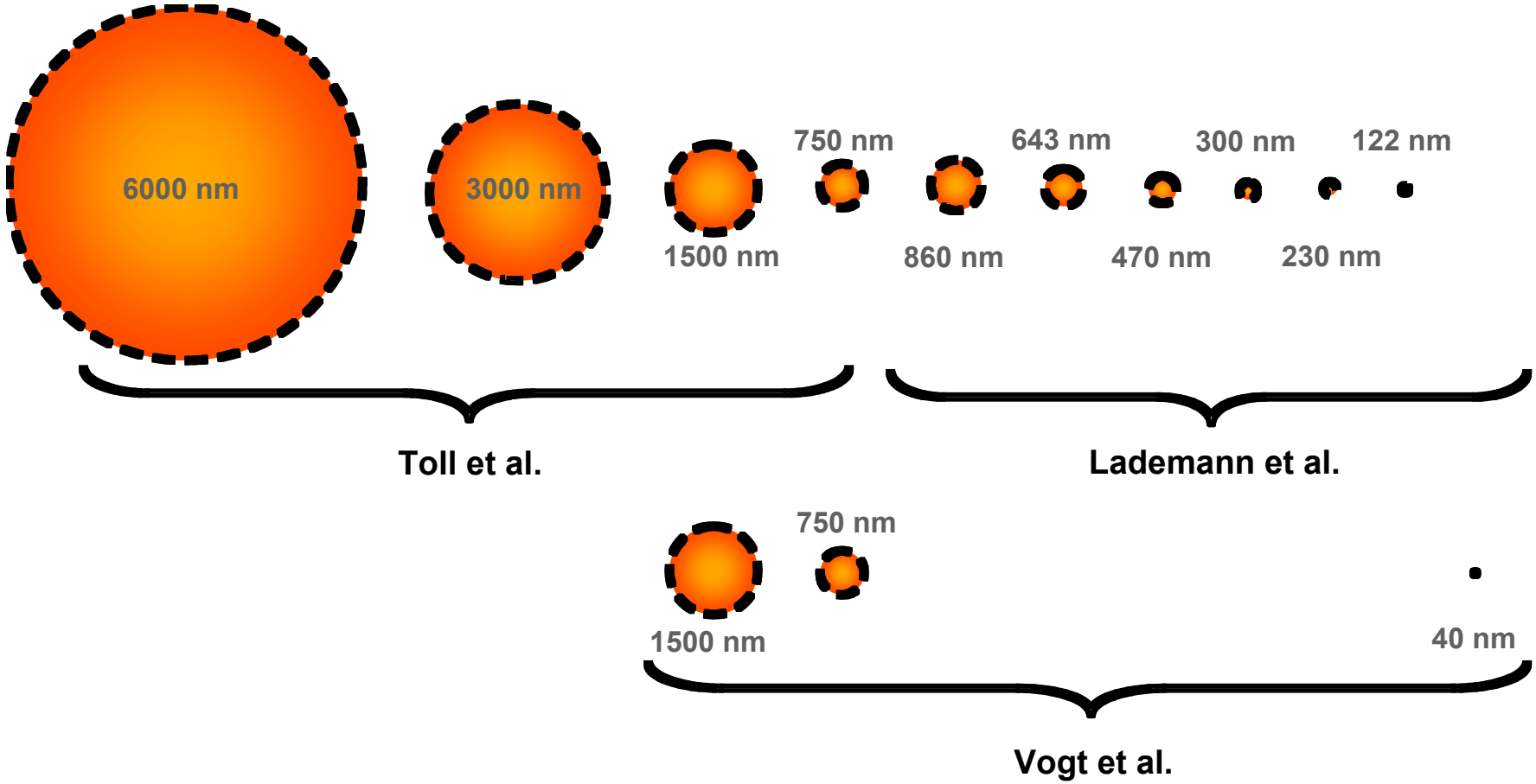


non-particle containing formulation

Lademann et al., *Eur J Pharm Biopharm*, 2007, 66, 159

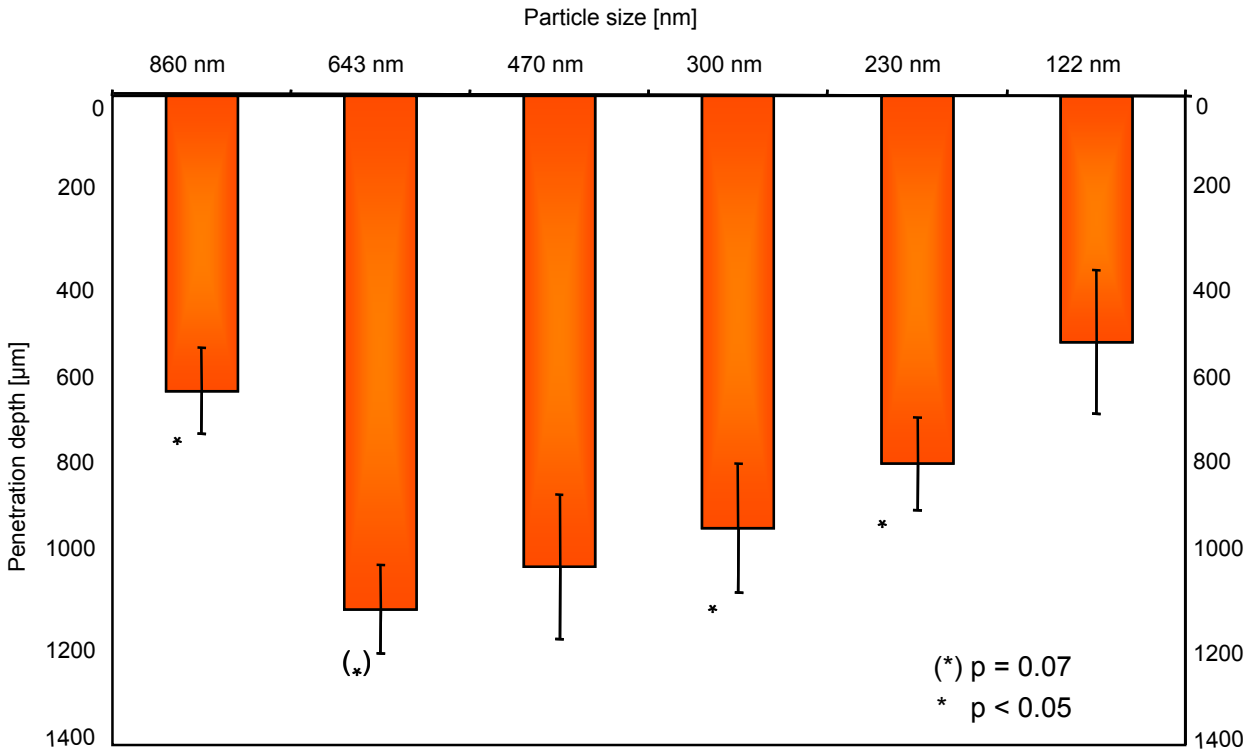
Center of Experimental and Applied Cutaneous Physiology

Size dependency of follicular penetration of NP



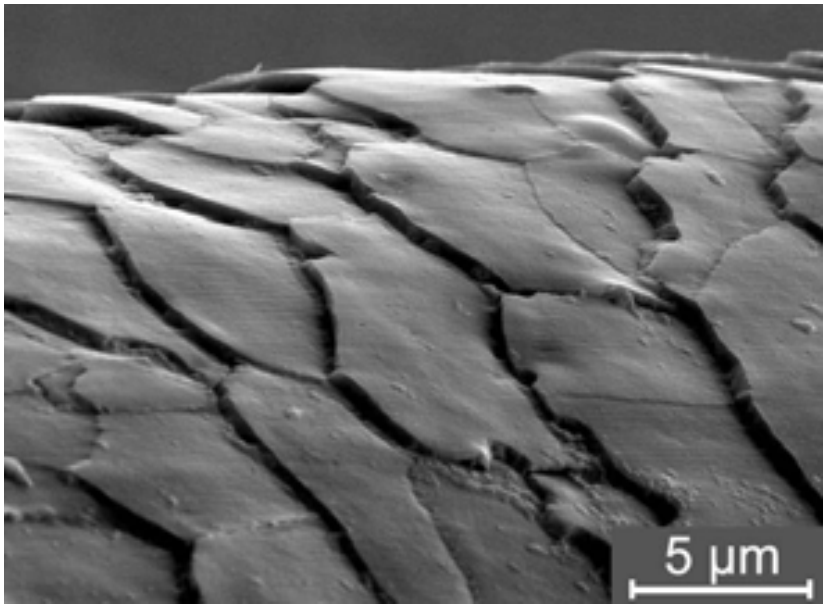
Center of Experimental and Applied Cutaneous Physiology

Size dependency of follicular penetration of NP



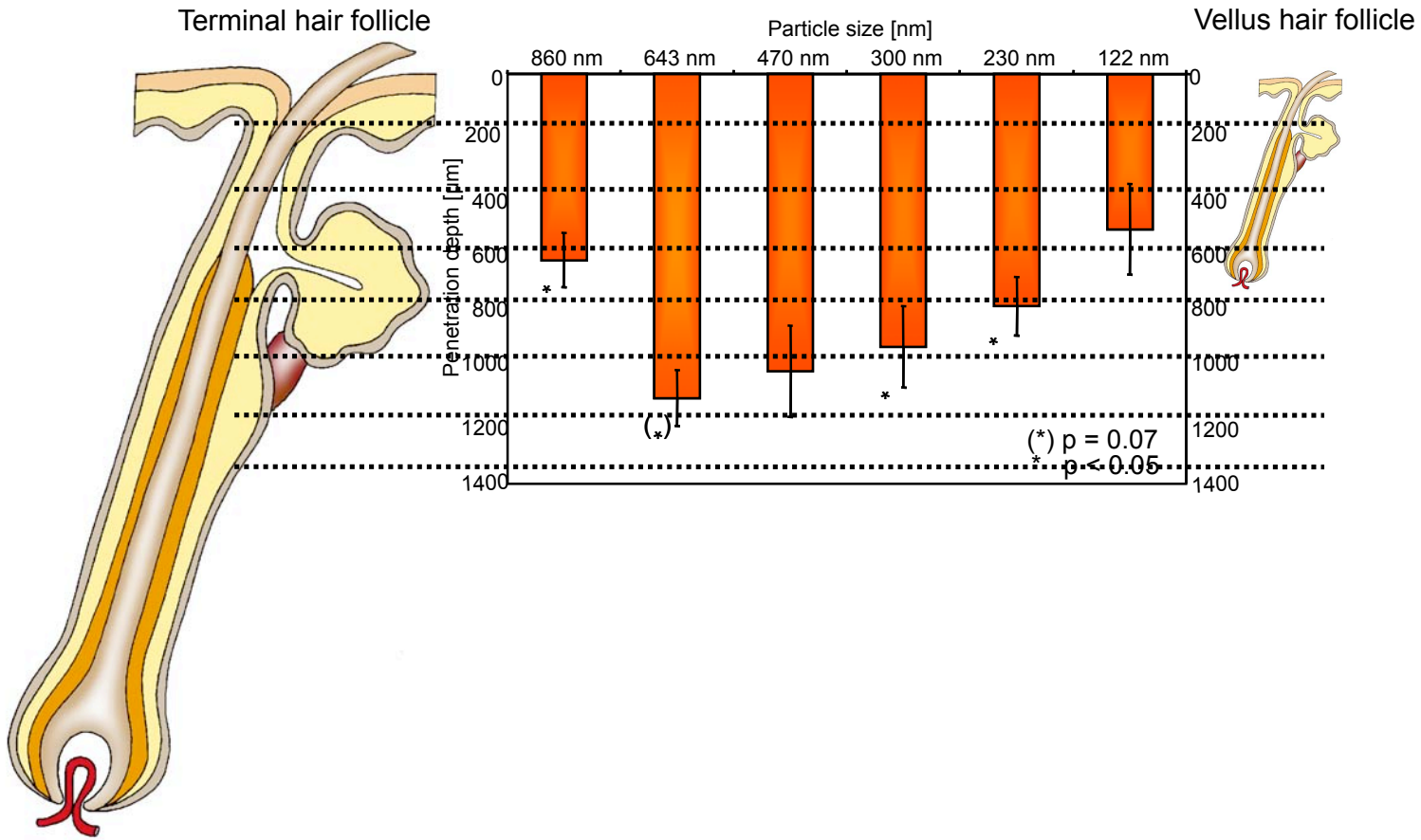
Center of Experimental and Applied Cutaneous Physiology

Hair follicle pump



Center of Experimental and Applied Cutaneous Physiology

Size dependency of follicular penetration of NP



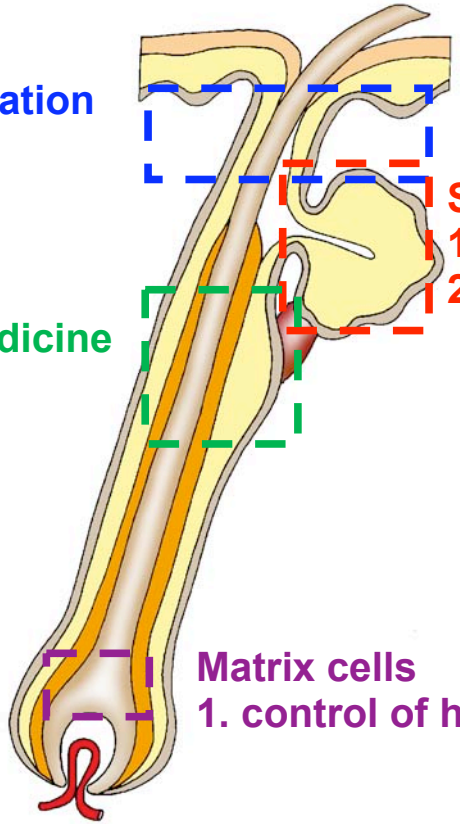
Safety aspects of skin penetration of nano-sized particles

Center of Experimental and Applied Cutaneous Physiology

Hair follicle targeting

Infundibulum:
1. transfollicular penetration
2. immunotherapy
   topical vakzination

Stem cells
1. regenerative medicine
2. wound healing
3. gene therapy

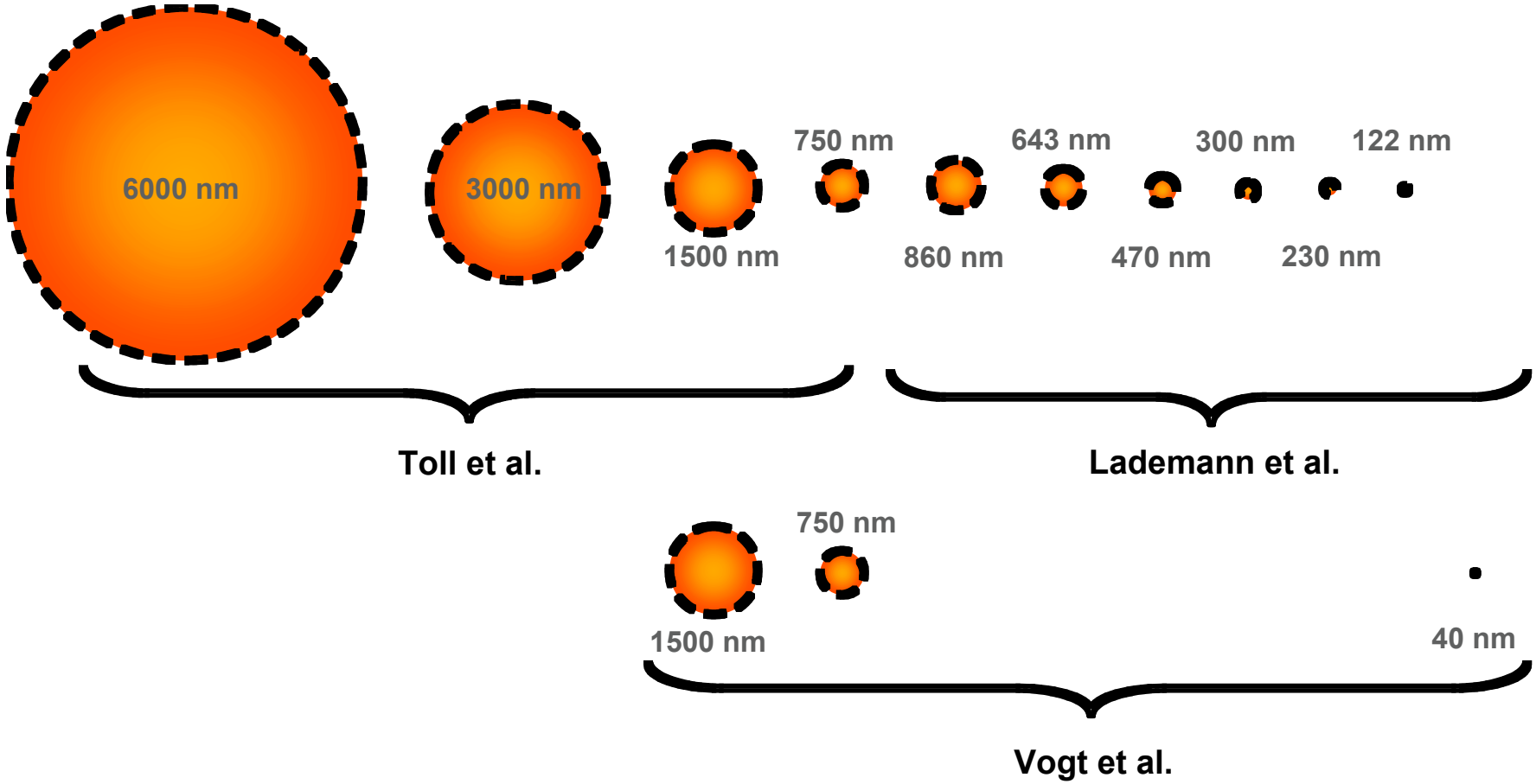


Sebaceous gland
1. Acne
2. Androgenetic Alopecia

Matrix cells
1. control of hair growth

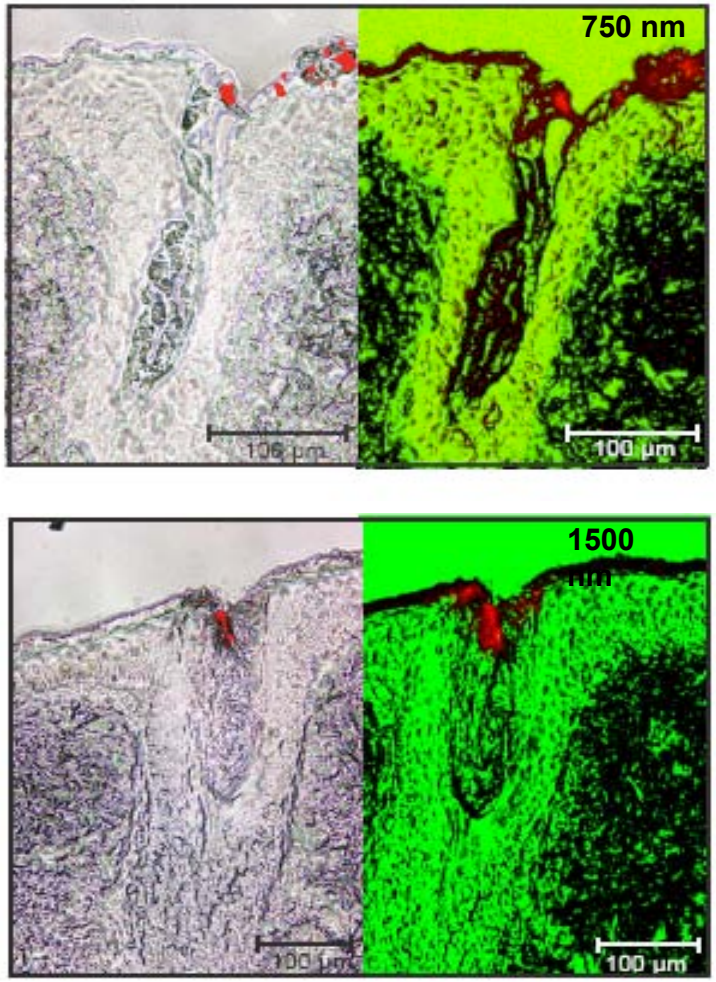
Center of Experimental and Applied Cutaneous Physiology

Size dependency of follicular penetration of NP

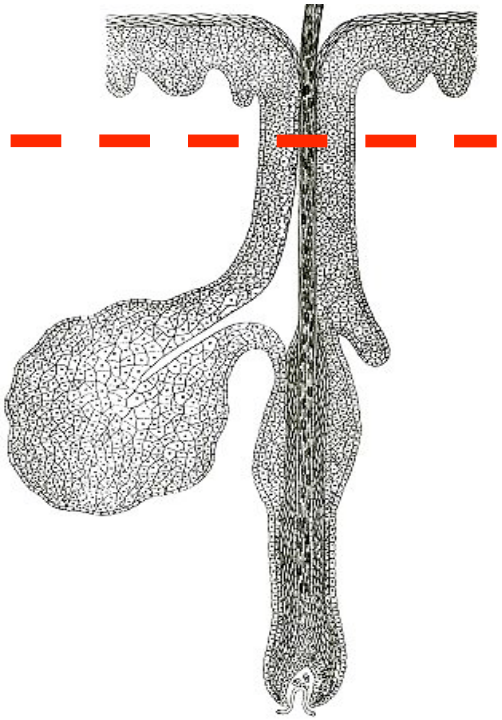


Center of Experimental and Applied Cutaneous Physiology

Size dependency of follicular penetration of NP



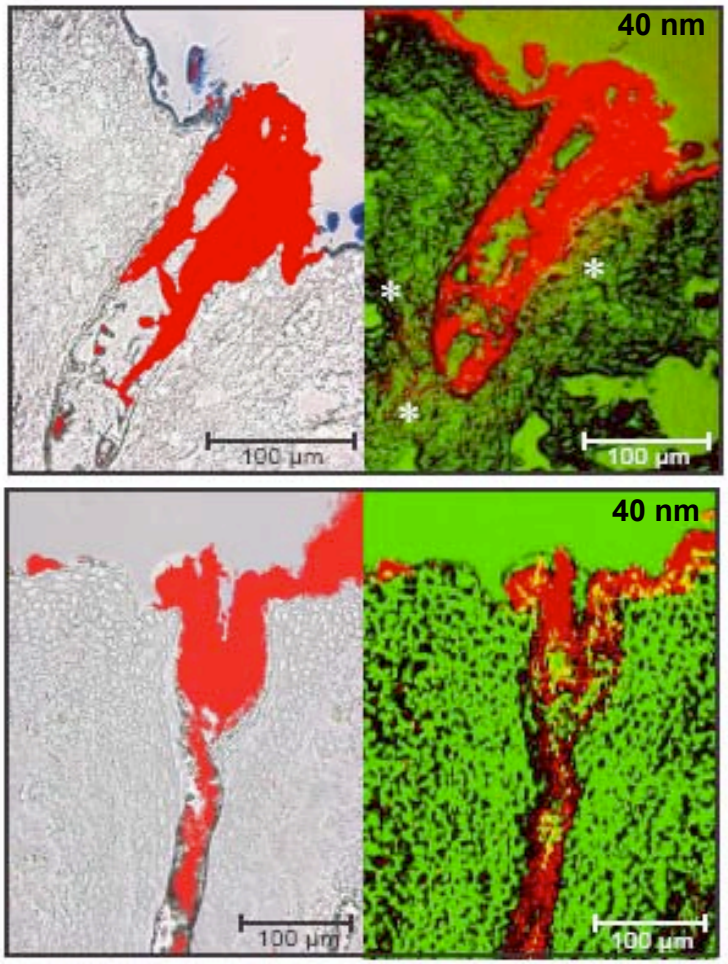
Microparticles
750 nm
1500 nm



Vogt et al. *J Invest Dermatol,* 2006

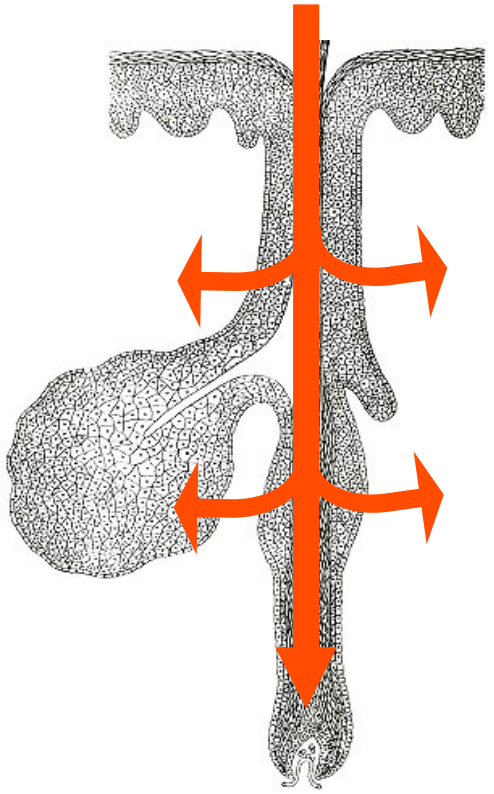
Center of Experimental and Applied Cutaneous Physiology

Size dependency of follicular penetration of NP



Microparticles

40 nm



Vogt et al. *J Invest Dermatol,* 2006

Safety aspects of skin penetration of nano-sized particles

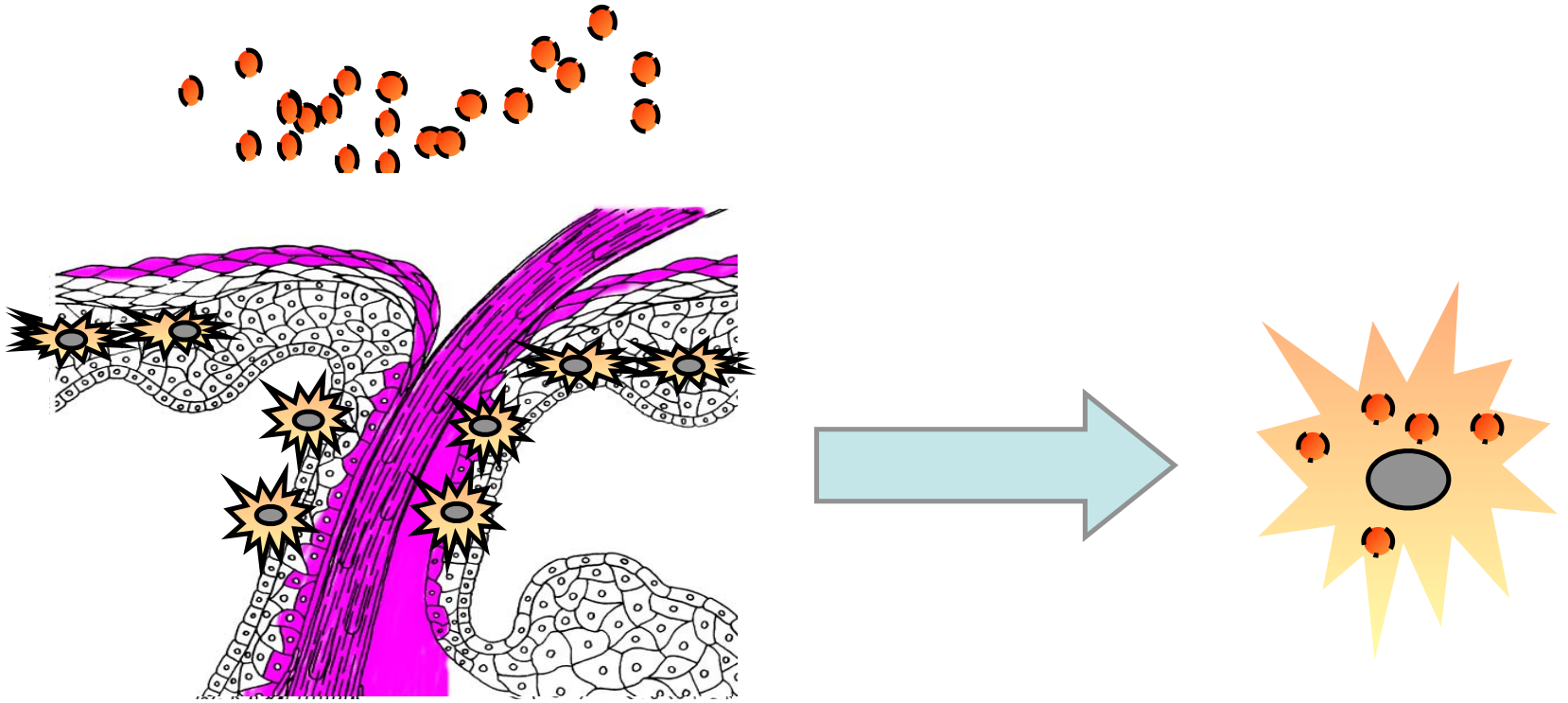
Center of Experimental and Applied Cutaneous Physiology

Review of literature:

Author	Particle size	Study
Ryman-Rasmussen et al., 2006	4.6 and 12 nm	QD penetrated through porcine skin, applied in alkaline solution
Gopee et al., 2006		QD penetrated only through mouse skin after dermabrasio
Baroli et al, 2007	5.9 nm	Metallic NP penetrated through skin, experiments in diffusion cell
Rouse et al, 2007	Fullerene particles	Fullerenes penetrated through porcine skin after skin flexing, experiment in diffusion cell
Vogt et al, 2006	40 nm	NP penetrated into the living tissue, after CSSS
Gopee et al, 2007	10, 30, 100 nm	No penetration in healthy porcine skin in vivo but in damaged skin
Zhang et al., 2008	ca. 40 nm	QD penetrated into upper SC layers in intact skin, reached living cells in damaged skin

Skin damage enables skin penetration of NP

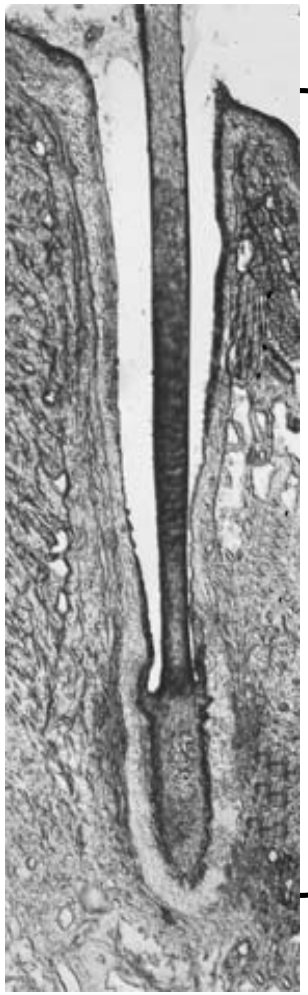
Center of Experimental and Applied Cutaneous Physiology



Vogt et al. *J Invest Dermatol,* 2006

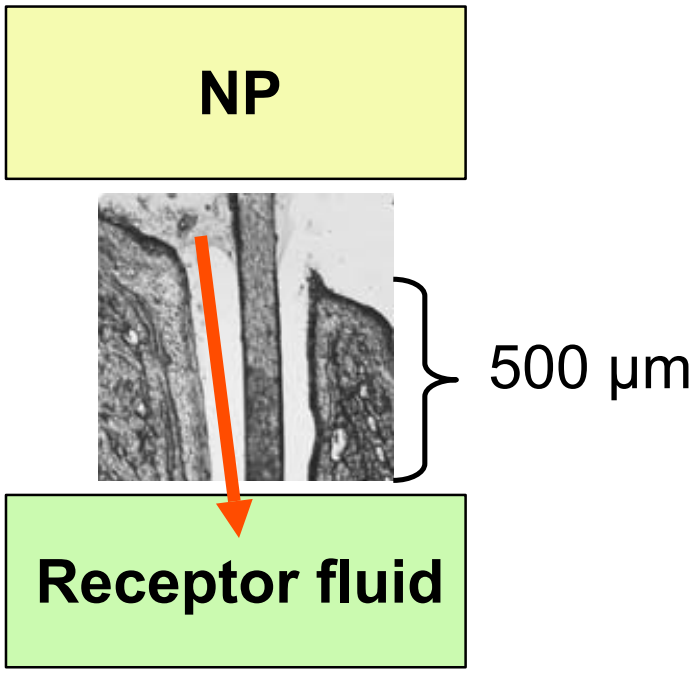
Center of Experimental and Applied Cutaneous Physiology

Skin damage enables skin penetration of NP



2500 µm

Diffusion cell



Center of Experimental and Applied Cutaneous Physiology

Summary

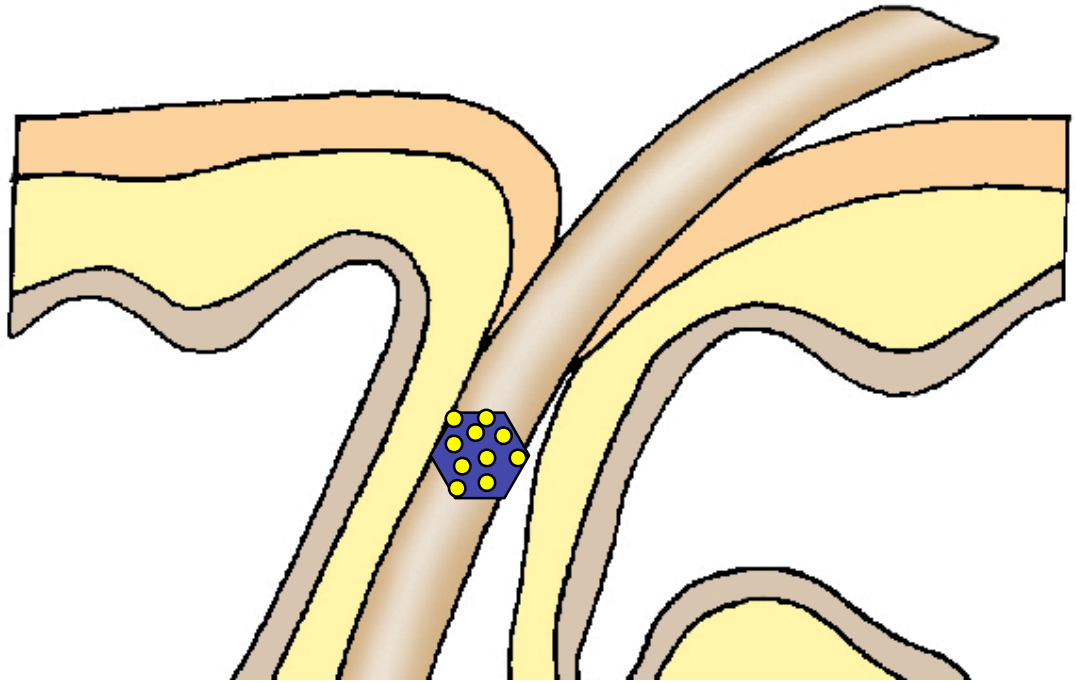
NP > 100 nm seem not penetrate through the intact skin barrier

NP < 100 nm: up to now, no evidence for penetration through intact skin

➔ additional investigations have to be perfomed especially for NP < 10 nm

Center of Experimental and Applied Cutaneous Physiology

NP as carriers for drug delivery



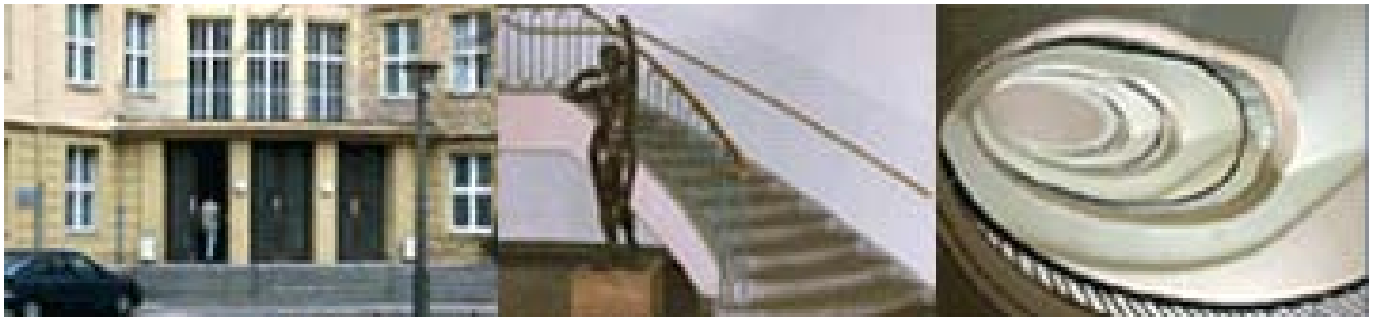
Thank you very much for your attention!

Center of Experimental and Applied Cutaneous Physiology

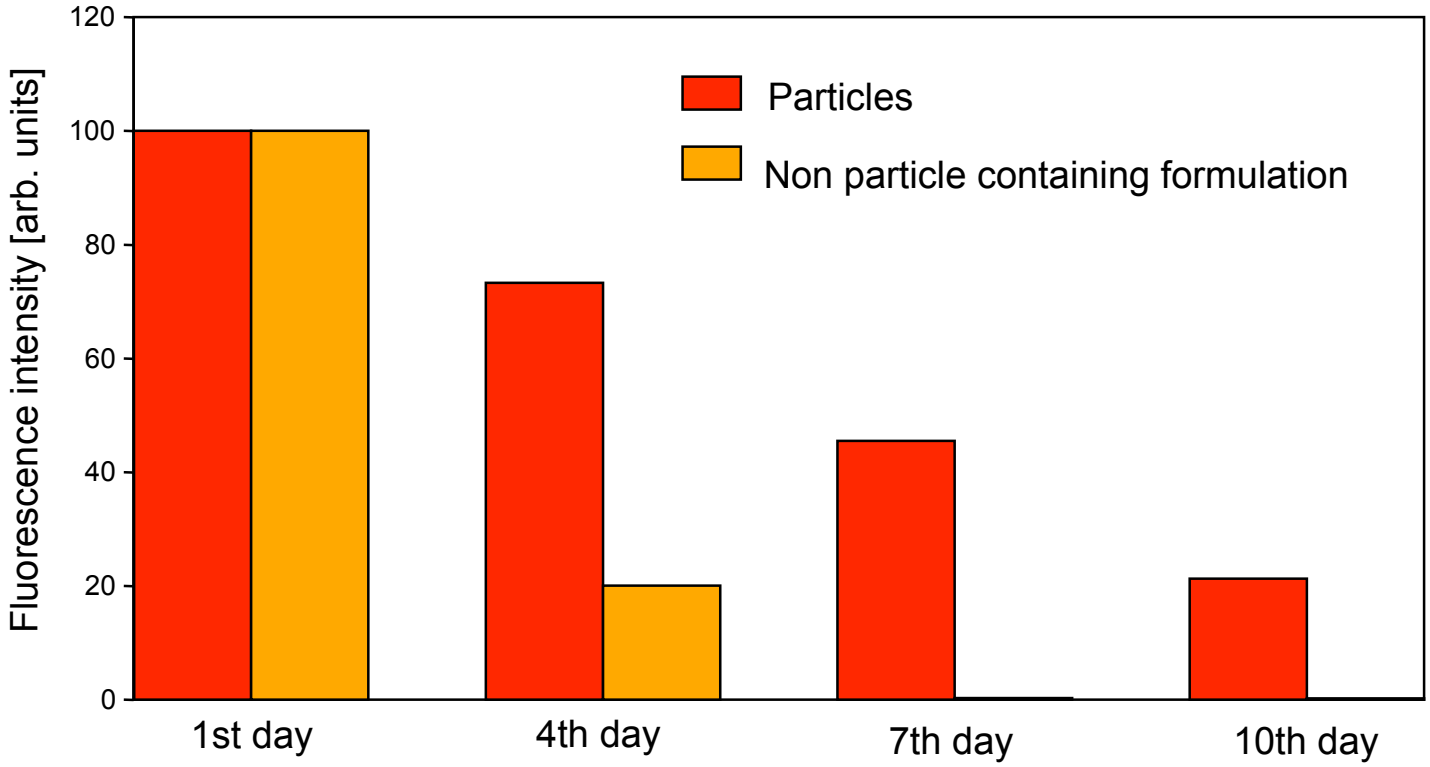
CHARITÉ

Department of Dermatology

Center of Experimental and Applied Cutaneous Physiology

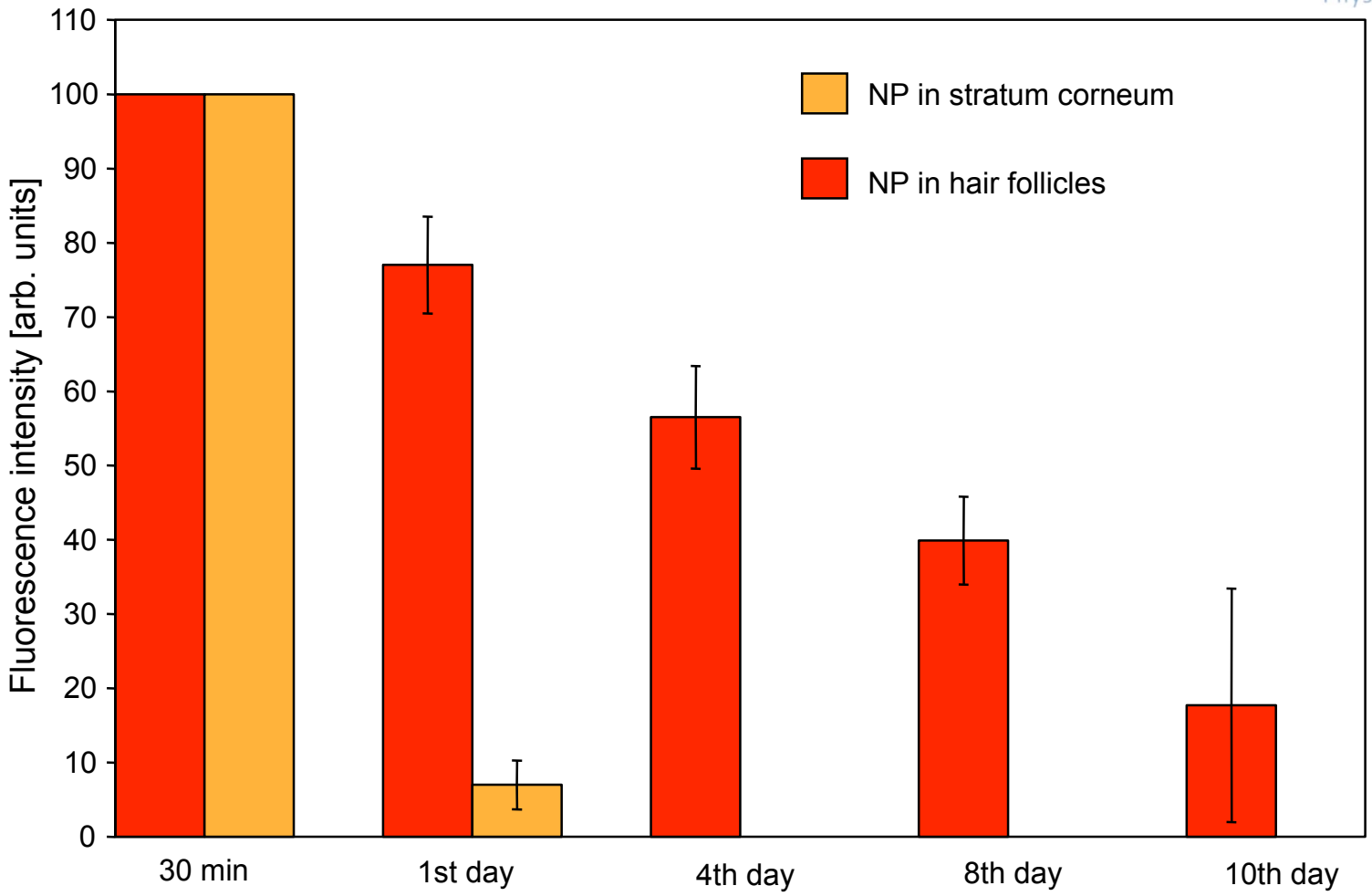


Long-term reservoir of NP in hair follicles



Center of Experimental and Applied Cutaneous Physiology

Long-term reservoir of NP in hair follicles



Lademann et al., Eur Jour Pharm and Biopharm 2007, 66, 139