

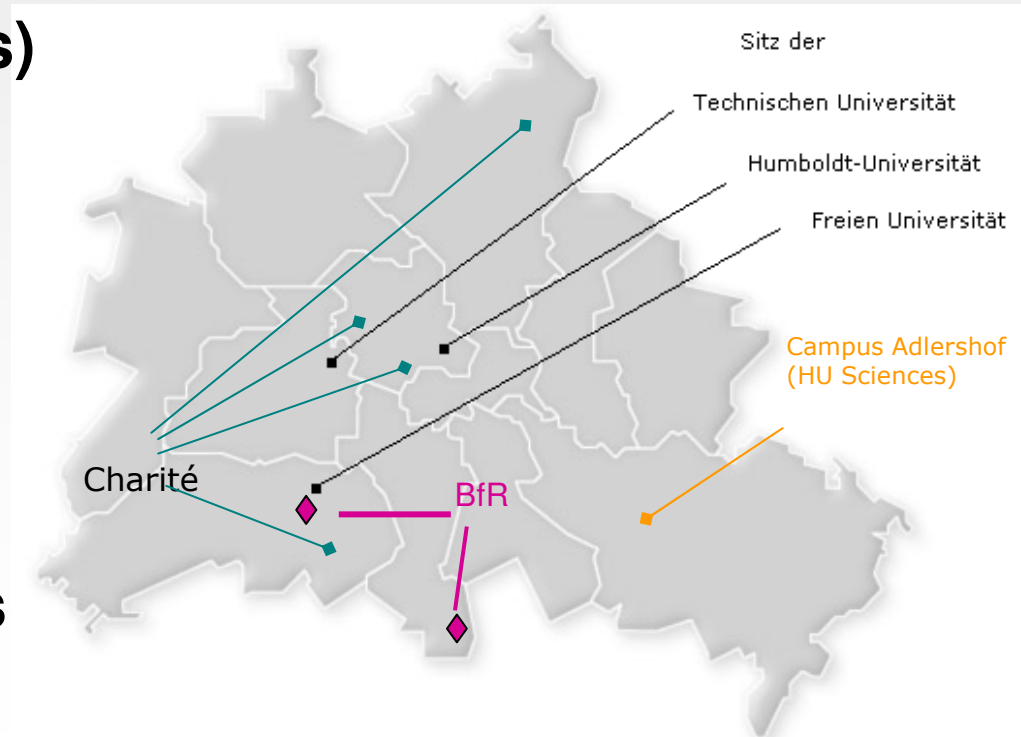


Cooperation between FU Berlin and ZEBET on Alternatives

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Freie Universität Berlin, Germany

Berlin – Science City

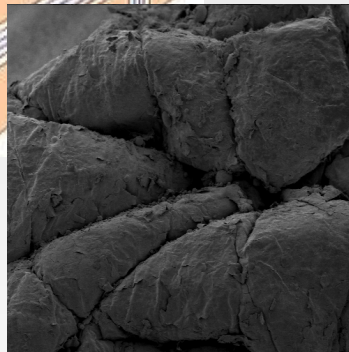
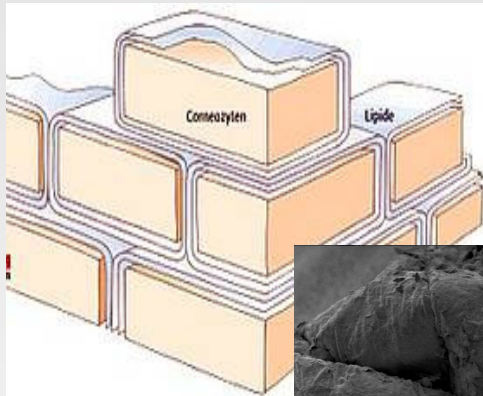
- Berlin – a multicultural city in Central Europe
- 3.4 m inhabitants (about 14% foreigners)
- 134.500 Students
(about 14 % internationals)
- 4 Universities
- 3 Schools of Arts
- 11 Universities
of Applied Sciences
- 15 Private Universities
- > 70 Other
research institutions



- Research:
Skin Penetration and Skin Metabolism (BMBF)
Angiogenesis Model Development (ZEBET)
- Teaching
Undergraduates (Biology, Chemistry, Pharmacy)
PhD Students
- Continuing Education
INVITROTRAIN (EFRE)
DUW: Drug Research & Management
- BfR - Scientific Advisory Board
- Deutscher Tierschutzforschungspreis - Jury

Since 1995

Barrier Function of Human Skin



Relevant for

- toxic agent
- drugs
- actives of cosmetics

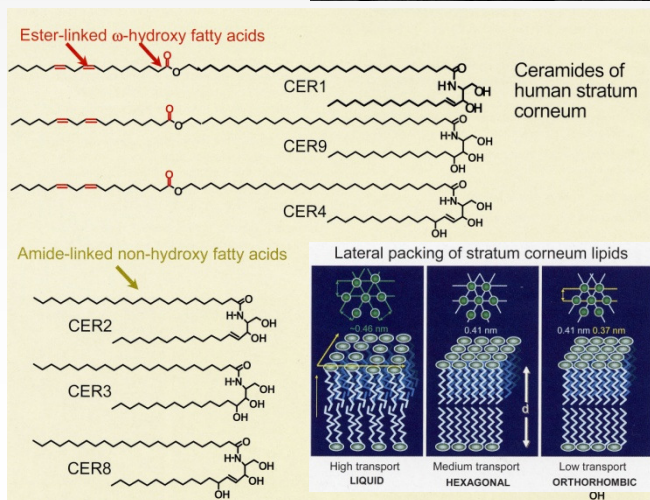
Cosmetic directive
REACH

Stratum corneum

Corneocytes: rich in keratin

Intercellular space:

highly hydrophobic lipides



Skin penetration:

Mw < 400 (- 800) g/mol; logP 1-3

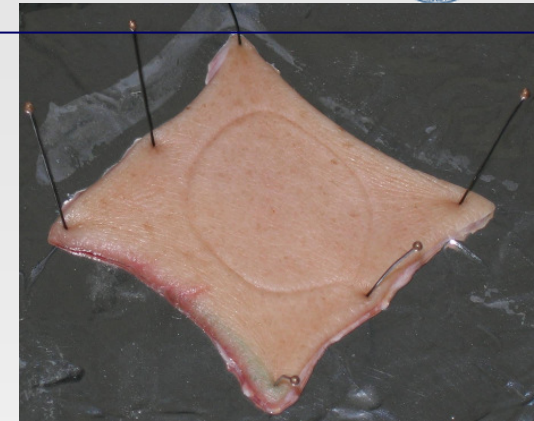
Validation - Modular Approach

- Characterisation of the test matrix reflecting target structure in vivo (GD 431)
- **Method development** (close to TGD 28)
- **Method transfer**
- **Prevalidation**
- **Validation (Biostatistics!)**
- Prediction model

Hartung et al., 2004

The German Study

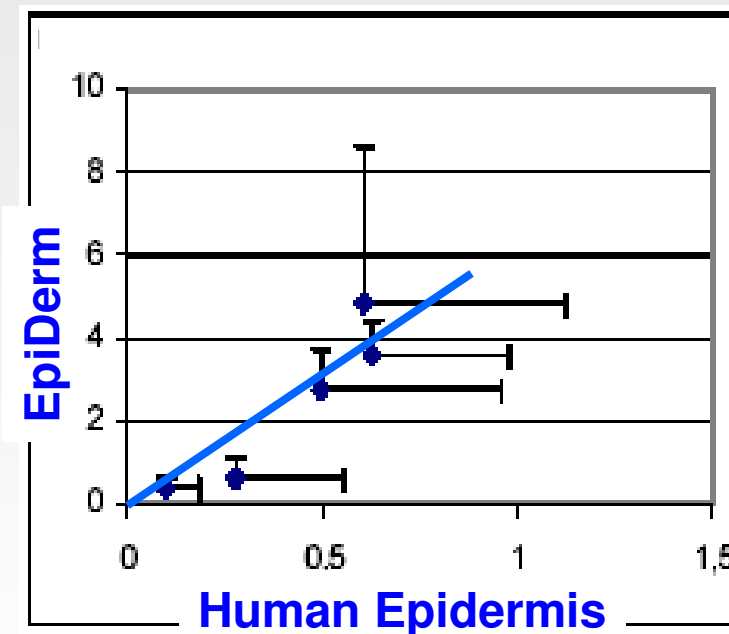
- Skin: human, pig
- 3 commercially available RHE
- 3 OECD standard compounds
6 other compounds
including ivermectin,
digoxin, mannilol
- Infinite / finite doses
- 3 Laboratories per skin



Results: P_{app} Values

Pearson Correlation		r^2
Pig Skin	EPISKIN®	0.920
Pig Skin	SkinEthic®	0.918
Pig Skin	EpiDerm™	0.842
Pig Skin	HES	0.861
HES	EPISKIN	0.707
HES	SkinEthic	0.803
HES	EpiDerm	0.932
EpiDerm	EPISKIN	0.637
EpiDerm	SkinEthic	0.853
SkinEthic	EPISKIN	0.906

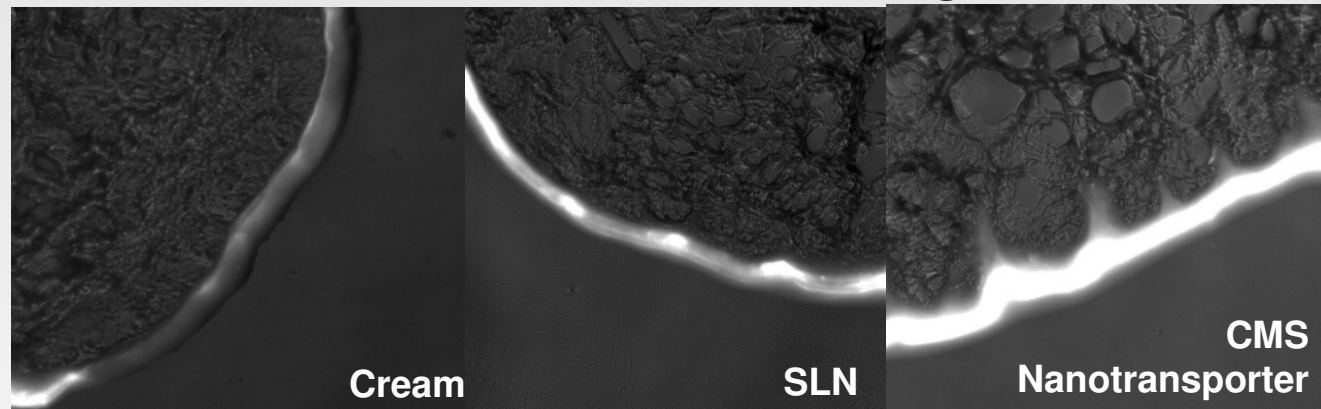
Scatter Plot P_{app}



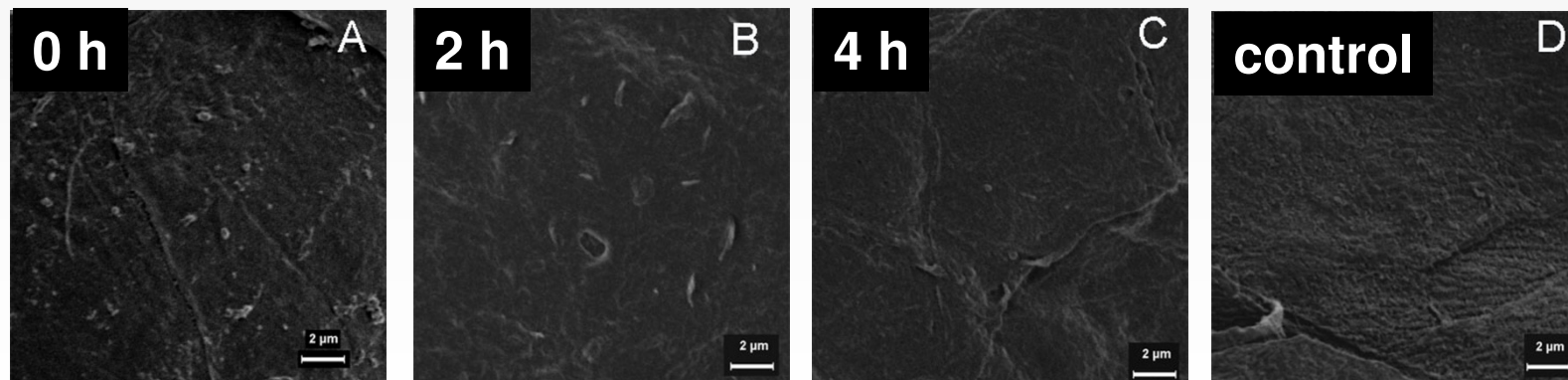
Schäfer-Korting et al., ATLA 2008

- Freie Universität Berlin
Universität des Saarlandes
Tierärztliche Hochschule Hannover
Ludwig-Maximilians-Universität München
Technische Universität Braunschweig
- Fraunhofer Institut IGB, Stuttgart
- Across Barriers, Saarbrücken
BASF, Ludwigshafen
Beiersdorf, Hamburg
Cognis, Düsseldorf
- ZEBET am BfR, Berlin
- **Funding: BMBF 2002-2006**

Nilred Penetration of Pig Skin



SLN: Interaction with Pig Skin ex vivo

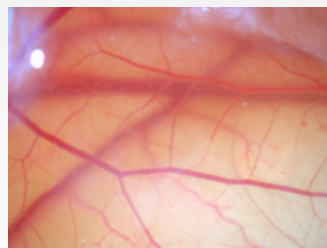
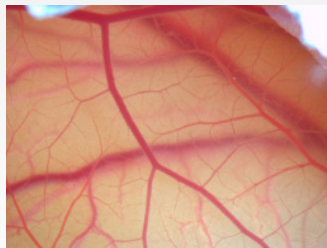


Küchler et al, EJPB 2009

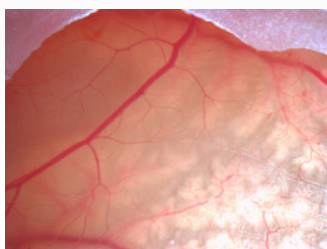
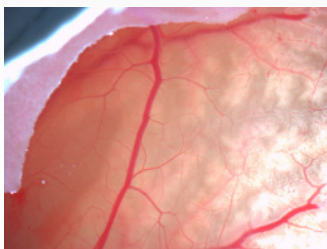
Eye Irritation (HET-CAM Test)

baseline

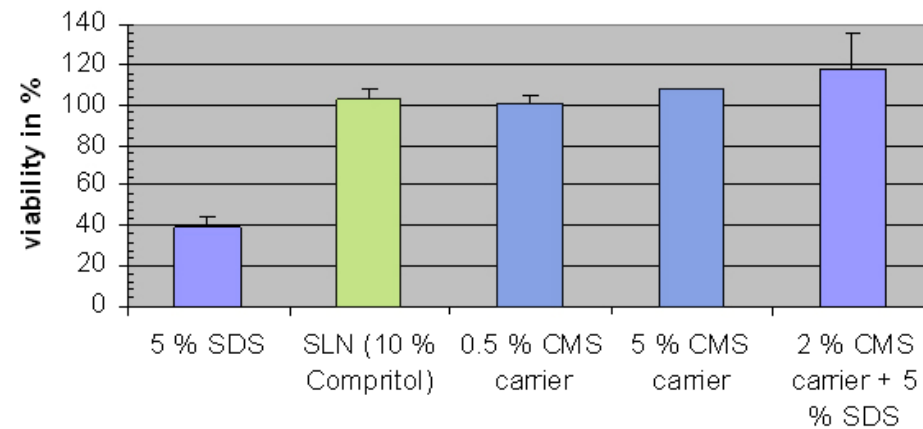
NP (50 μ l)



SLN



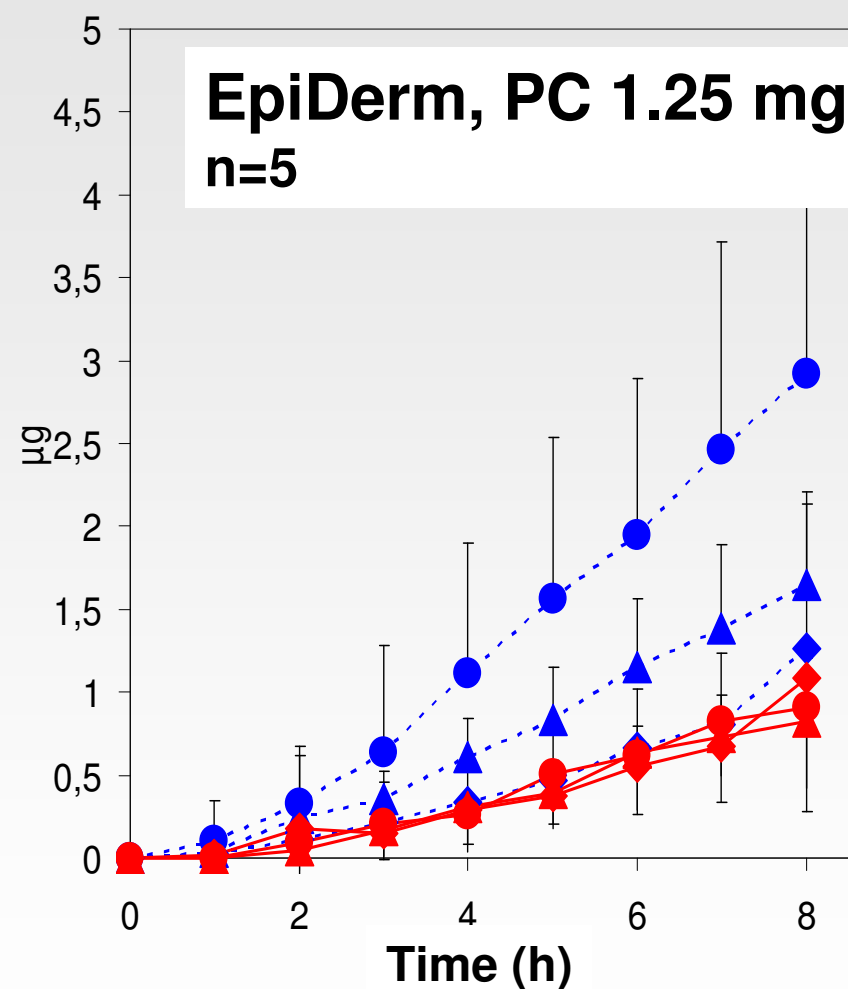
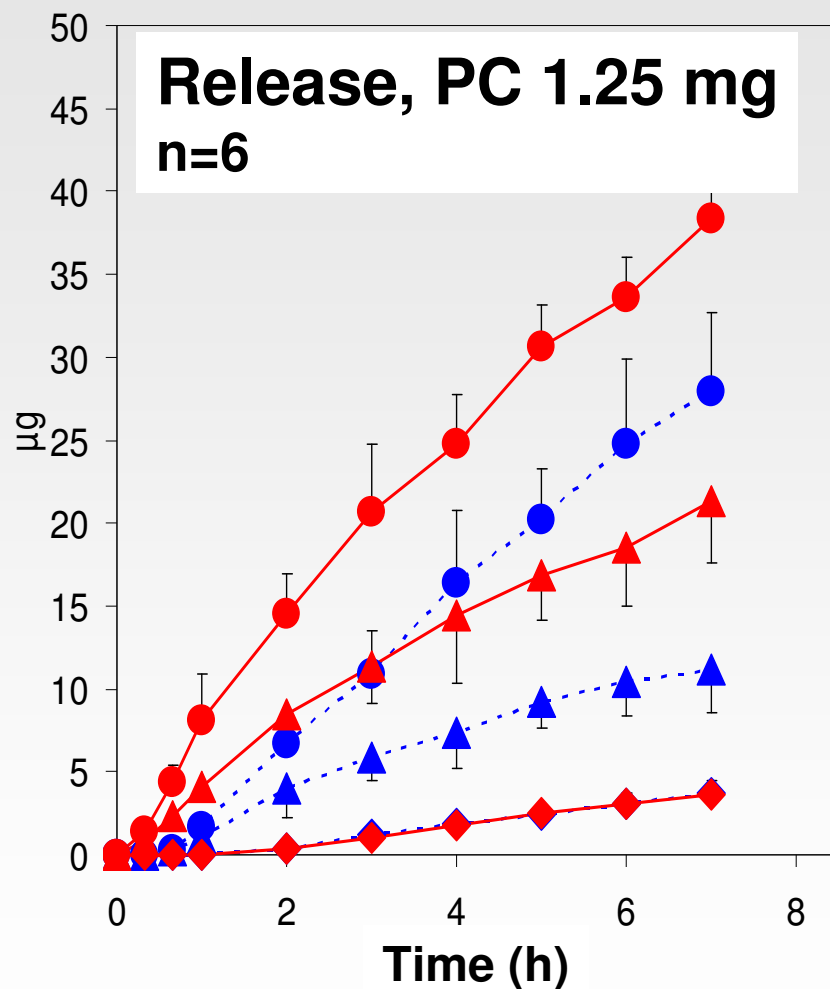
CMS NT



Skin Irritation (Episkin Test)

Wolf et al., EJPB 2009

Formulation Effects

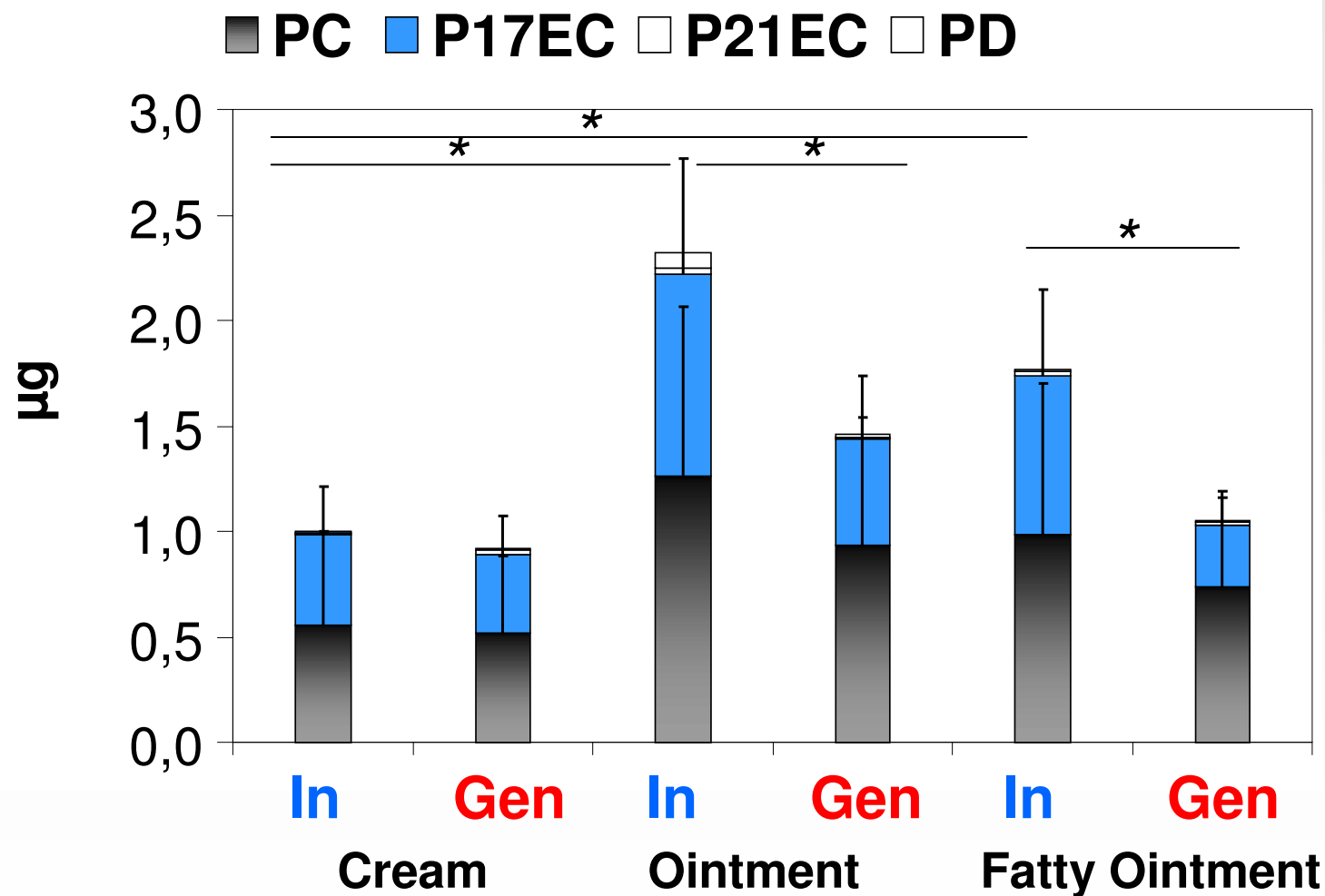


Cream ◆◆, Ointment ●●, Fatty Ointment ▲▲

MW $\pm$ SE

Lombardi Borgia et al., EJPB 2008

Formulation Effects

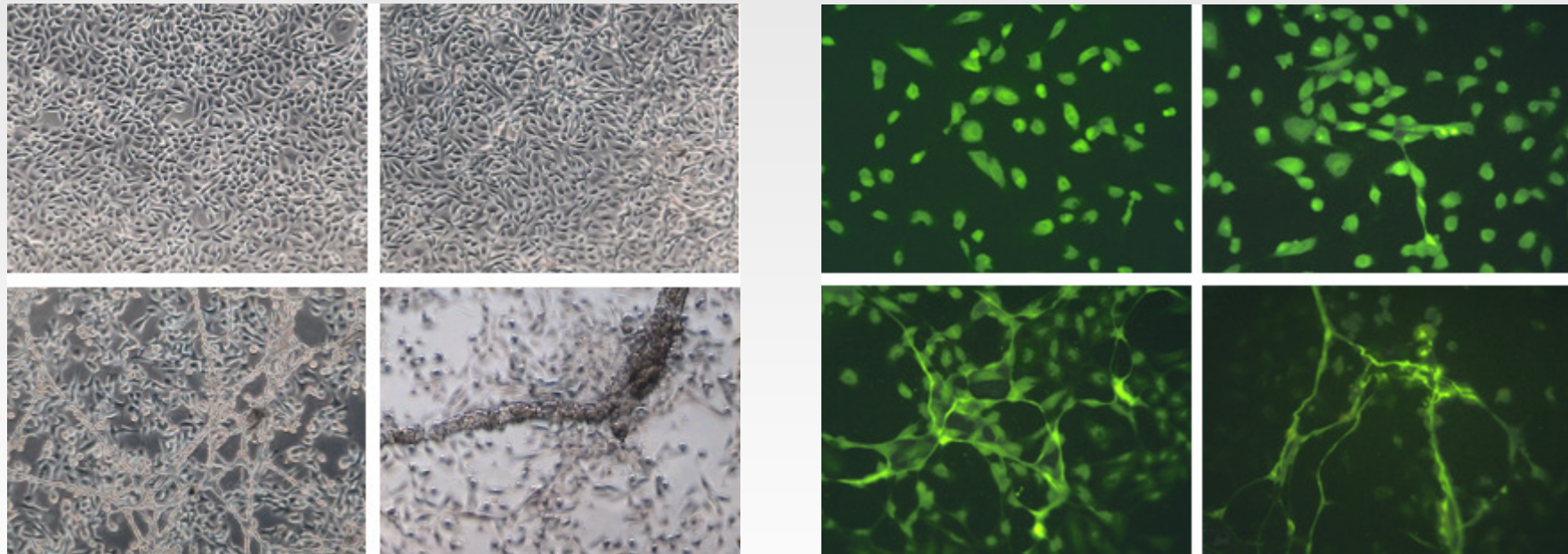


MW ± SE
n=6, 8 h
p ≤ 0.05

Lombardi Borgia et al., EJPB 2008

Angiogenesis - Antiangiogenesis

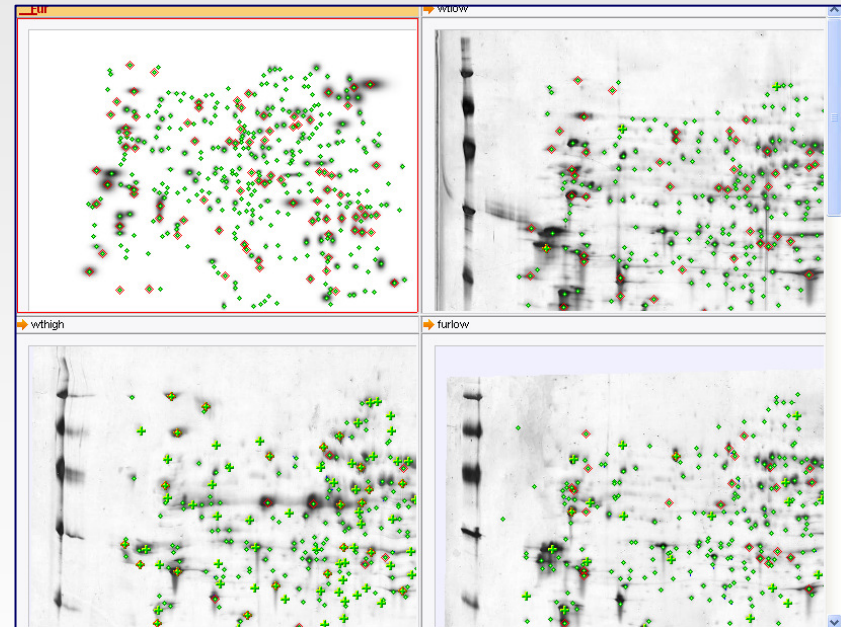
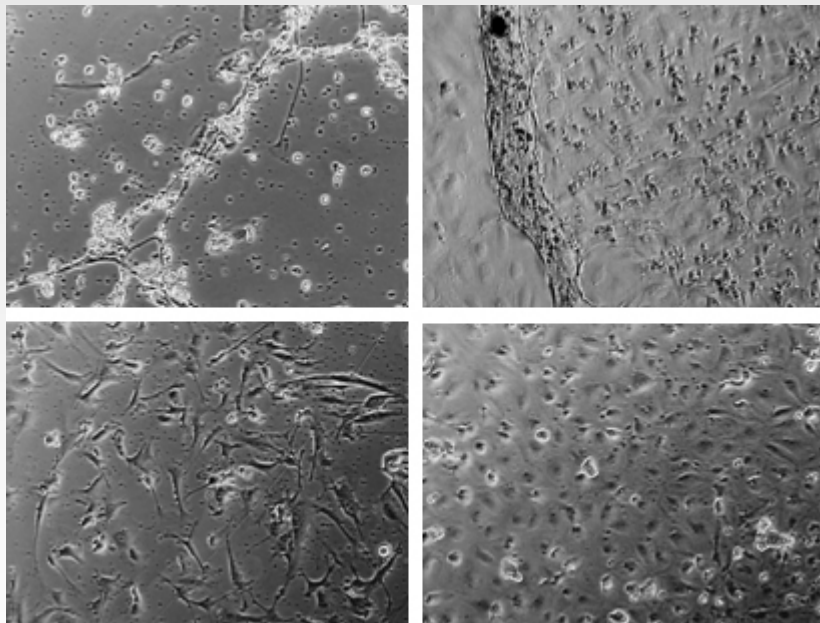
1. In vitro test protocol



All in one in vitro assay for quantitation of angiogenesis and antiangiogenesis

*Prof. Johanna Plendl (Freie Universität Berlin), Prof. Fred Sinowatz (LMU München)
1999 – 2002*

2. Profiling of angiogenic markers for standardised use of endothelial cells



Protein expression differences in endothelial cell cultures by 2D-SDS-PAGE

Dr. Mahtab Bahramsoltani, Prof. Johanna Plendl, 2007 – 2010



Cooperation between FU Berlin and ZEBET on Alternatives

**FU Berlin would like to give special thanks to scientists
of ZEBET for many years of great cooperation**

**In particular: Dr. M. Liebsch, Dr. Dr. A. Luch,
Prof. H. Spielmann**

Seed money of ZEBET is gratefully acknowledged

Thank you very much for your attention