

## Human organo-typical (HOT) co-culture models

### EDI-CO skin:

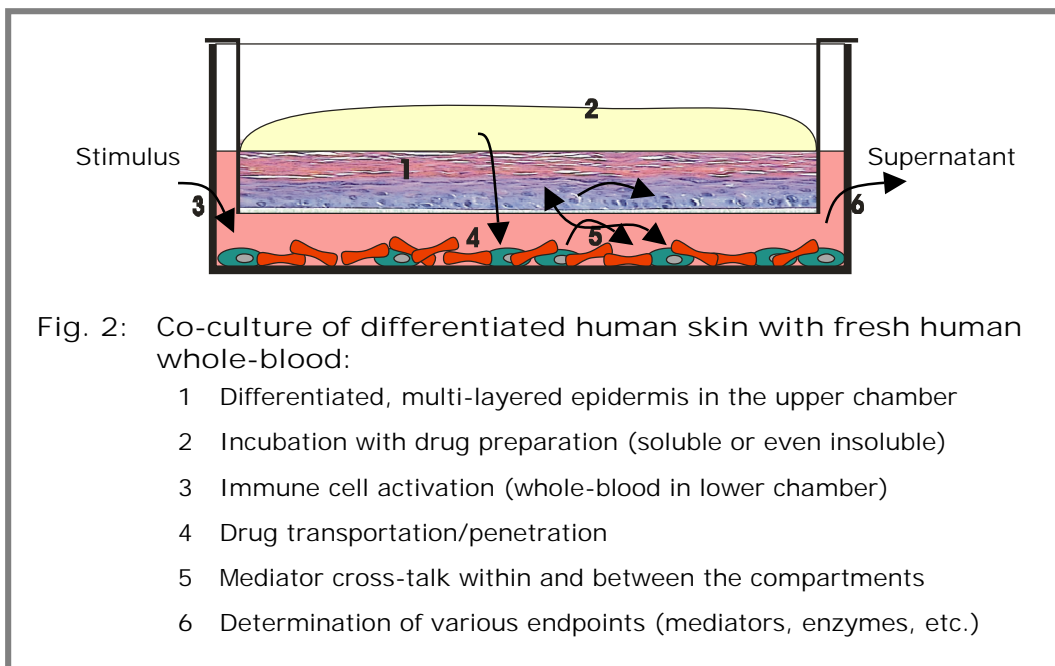
Functionally differentiated human epidermis  
together with human whole-blood

Multilayered (3-dimensional) cultures of human keratinocytes form a central building block in characterising toxicological profiles of new and old drug substances. Highly standardised skin models for in vitro research (Fig. 1) are prepared by SkinEthic (Nice, France), a leading manufacturer in this field.



**Fig. 1: Differentiated human skin on filter support showing several vital as well as corneous layers**

These human epidermal models are used in our newly developed co-culture system, EDI-CO skin for dermatological immuno-pharmacology (see Fig. 2).



**Fig. 2: Co-culture of differentiated human skin with fresh human whole-blood:**

- 1 Differentiated, multi-layered epidermis in the upper chamber
- 2 Incubation with drug preparation (soluble or even insoluble)
- 3 Immune cell activation (whole-blood in lower chamber)
- 4 Drug transportation/penetration
- 5 Mediator cross-talk within and between the compartments
- 6 Determination of various endpoints (mediators, enzymes, etc.)

The lower compartment of this co-culture model consists of a particular human whole-blood culture system (see above). The major advantage of the latter - in contrast to the more common PBMC (peripheral blood mononuclear cell) cultures - is that whole-blood cultures provide a much more complete and lifelike representation of the cross-talk between all different cellular as well as non-cellular elements of the human immune system. Furthermore, all cellular activation takes place in a physiological environment (artificial stimulation by plastic adherence is eliminated).

Only soluble products can pass the porous membrane between the two compartments. There is no direct contact of the cells in this co-culture model. The signalling cross-talk therefore includes the transport of drug substances as well as the secretion of mediators on both sides, the gut epithelium as well as the leukocyte compartment.

Supernatants and/or cell contents are collected at the end of culture to test for various parameters such as:

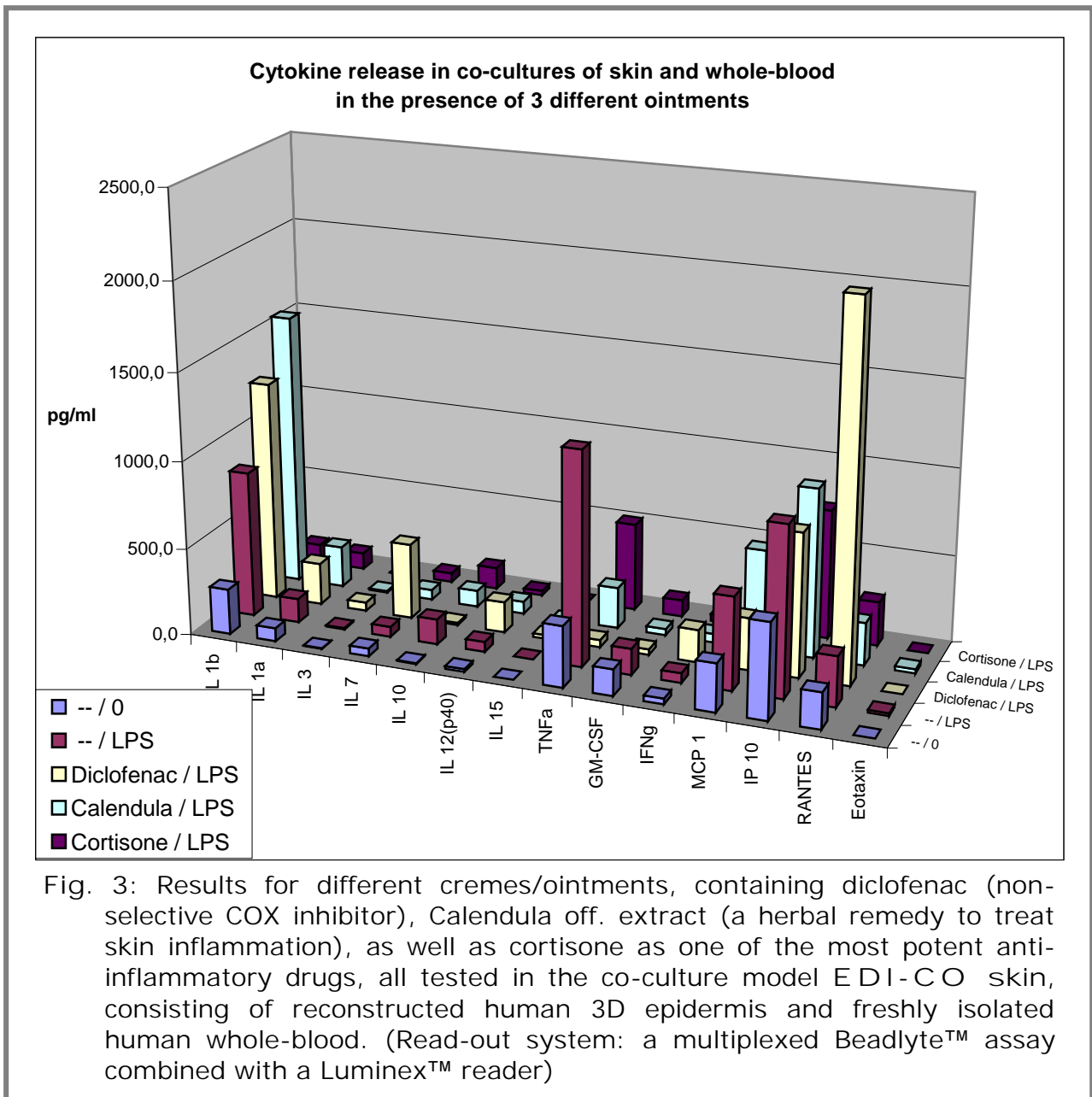
Cell type	Cytokines	Chemokines	Others
Granulocytes	–	–	Elastase
Monocytes	IL-1 $\beta$ , IL-6, IL-12 TNF $\alpha$ , TGF $\beta$ etc.	IL-8, MCP-1, etc.	MMPs
T-lymphocytes	IL-2, IL-4, IL-5, IFN $\gamma$ etc.	IL-8, MCP-1, RANTES, etc.	–
B-Lymphocytes	IL-10	–	–
Epidermal cells	IL-1 $\beta$	IL-8	substance transport

But also multiplex testing for pattern recognition of more than 20 different parameters from the same co-culture is possible (see Fig. 3).

Organo-typical conditions to investigate drug effects on human tissues can be obtained e.g. by combining differentiated human 3-D epidermis together with human whole-blood cultures in a two-chamber culture model.

An additional specific development of EDI was the construction of a peculiar applicator that avoids any mechanical damage of the differentiated epidermis during the addition of solid or semi-solid drug samples. Hence, this new organo-typical co-culture system can also be used to screen for pharmacological effects not only of soluble pharmaceuticals but also of solid probes (like cremes, ointments, lotions etc.; see Fig. 3 for sample results).

## EDI-CO skin: Sample results



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