The human skin transplant model of psoriasis

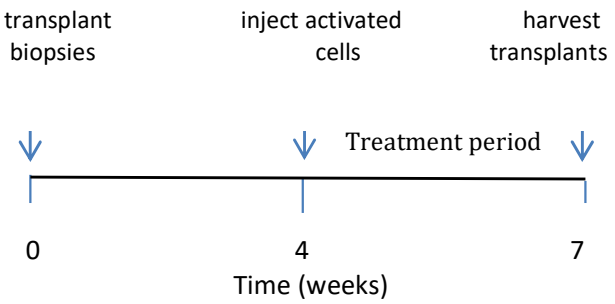
Psoriasis is a complex, chronic, immuno-inflammatory skin disease characterized by thickening and scaling of the skin. Although it is generally accepted that type 1 helper T-cells, and mediators released by them, play a central role in the development of psoriasis, it is likely that other cell types (e.g. dendritic and natural killer cells) are also involved. The transplant model of psoriasis, in which a psoriatic lesion is induced in non-lesional psoriasis skin transplanted onto immune-deficient mice by injecting activated autologous white blood cells intradermally into the transplant, is the only one in which chronic interactions between the skin and regulatory cells can be studied and manipulated. For this reason it is considered to be the gold standard for testing anti-psoriatic therapeutics. Derphartox has developed and validated the use of small biopsies (5 mm diameter) in this model so that it can be used routinely for the testing/development of new drugs.

Basic protocol

In this psoriasis model the procedures are depicted in figure 1.

- Mice are transplanted the same day as the biopsies are obtained and we usually transplant all mice needed for a project within 3 days
- Treatment can be started before cells are injected (prophylactic protocol) or 1 week after (therapeutic protocol)
- Mice can be treated by all routes of administration used to treat patients
- At the end of the treatment period transplants are harvested, embedded in Tissue-Tek® and stored frozen until needed

Figure 1. Time schedule basic protocol



Collection of other material; The PBMC incubation medium, mouse serum/plasma and samples of the transplant can be taken and analysed using standard biochemical, immunological and molecular biological methods.

End points

In this psoriasis model the endpoints are presented in figure 2.

Figure 2a. Epidermal ridge thickness. H&E stained section of a transplant injected with activated cells. The average epidermal ridge thickness is calculated from measurements of epidermal ridge thickness (see black arrows) made at regular intervals over the length of the human epidermis.

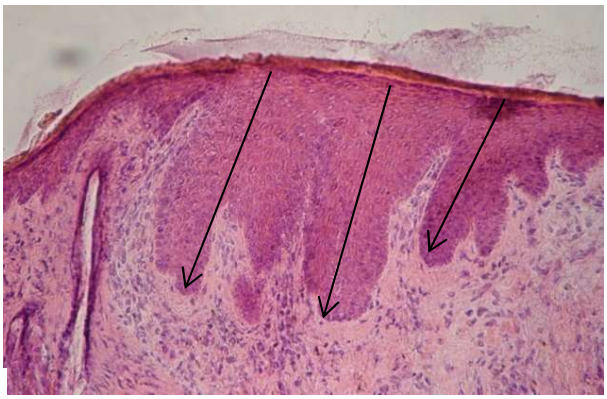
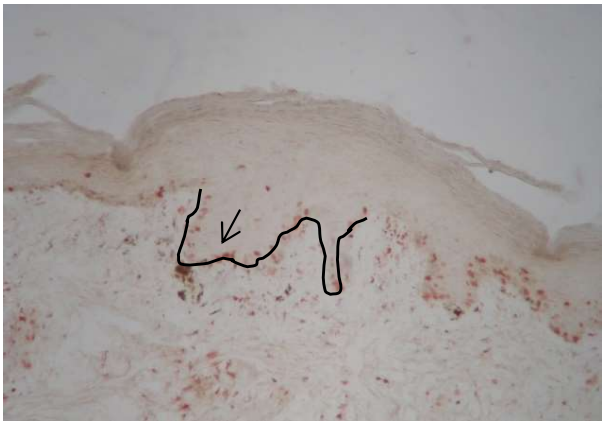


Figure 2b. Ki67 index. The Ki67 index is the number of Ki67 positive cells / mm basal membrane.



Reproducibility

Table 1. Epidermal ridge thickness data (µm) for the therapeutic and prophylactic models.

Prophylactic model	Expt 1	Expt 2	Expt 3
Control	217	205	187
Betamethasone	115	112	98

Therapeutic model	Expt 1	Expt 2	Expt 3
Control	202	195	182
Betamethasone	109	112	111

Data are average epidermal ridge thickness values (µm), n = 5-8. The effects of betamethasone dipropionate vs control are significant ($p<0.05$)
Betamethasone dipropionate (15mg, 0.05%) was applied topically 2x day for 3 weeks.

Reference compounds

Table 2. Compounds that reduce epidermal ridge thickness and keratinocyte proliferation.

Compound	Drug type
Diprolene	Betamethasone di-propionate, a glucocorticoid receptor agonist
Dermoval	Clobetasol propionate, a glucocorticoid receptor agonist
Daivonex	Calcipotriol, a vitamin-D derivative
Daivobet	Betamethasone di-propionate + Calcipotriol
Cyclosporine A	A calcineurin inhibitor
Tacrolimus	A calcineurin inhibitor
Etomoxir	A carnitine palmitoyltransferase inhibitor
Remicade	Infliximab, a chimeric monoclonal antibody against tumour necrosis factor alpha
Stelara	Ustekinumab, an anti-IL12/23 human monoclonal antibody
UR-13870	A p38 kinase inhibitor
KdPT	A tripeptide derivative of alpha-melanocyte-stimulating hormone

Advantages of the model

- Interactions are between human tissues (skin and regulatory cells)
- Compounds can be tested chronically
- Compounds can be administered by all routes used to treat patients

Time lines

Upon the administration of the first dose we agree the final report within 6 months.

Associated (disease) models

- Normal and diseased human skin explant culture
- Imiquimod mouse model of psoriasis
- Mouse oxazolone-induced delayed type hypersensitivity model (also for pruritus)
- Wound healing (in vitro and mouse and humanized mouse models)

For more info please email

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References

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