Think big and scale down: development of a multi-organ-on-the-chip-model for analysis of immune cell/skin interactions

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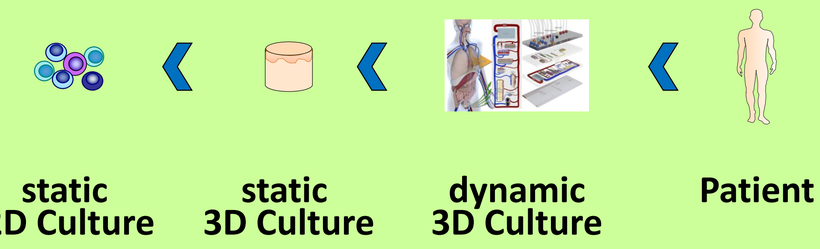
INTRODUCTION

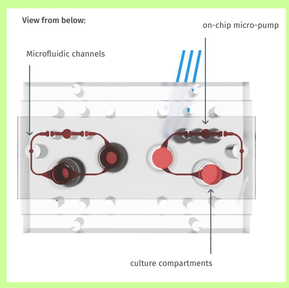
Dynamic 3D cultures allow testing of disease models close to the patient's situation

To date the interaction between skin and immune system in the context of chronic inflammatory skin diseases is poorly understood, complicating the development of targeted therapeutic strategies. So far, static 2D or 3D cultures, which are human but not systemic (A), or animal models, which are systemic but not human, can be used for testing. To be more close to the patient's situation, we established a multi-organ-on-the-chip system (B) in which human skin and immune cells can be cultured together in a dynamic miniaturized human chip culture. This technology – for the first time ever – provides preclinical insight on a systemic level using human tissue. The system closely resembles the activity of multiple human organs in their true physiological context at the smallest possible biological scale. The suitability of multi-organ chips combining skin and immune cells was tested exemplary by establishing a "***skin allograft on-the-chip model***". Human skin biopsies are cultured together with allogeneic Peripheral Blood Mononuclear Cells (PBMC) to induce skin rejection.

[A]



[B]



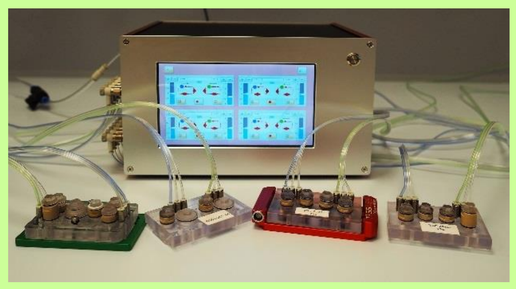
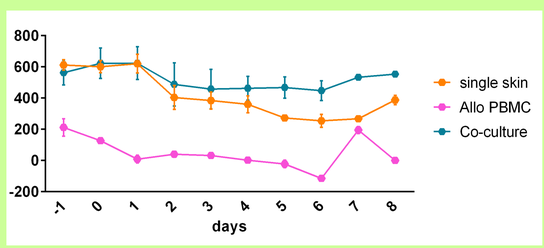


Fig. 1. **[A]** Dynamic 3D cultures are as close to the patient as possible.. **[B]** Design of the TissUse Two-Organ-Chips, which are connected to control units.

RESULTS

PBMC can be tracked in the skin

[A]



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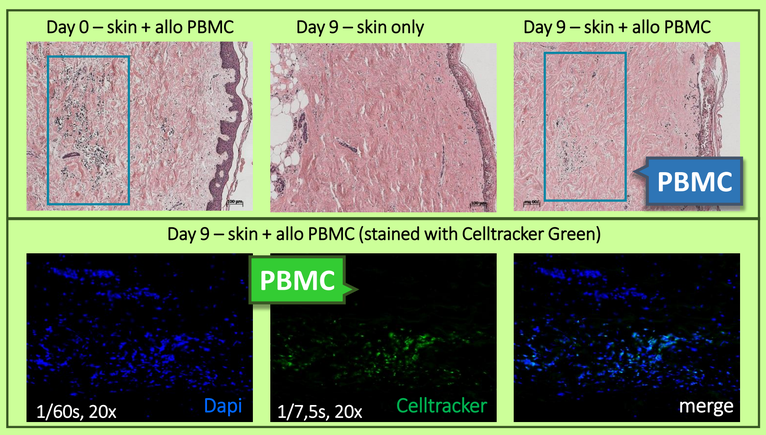
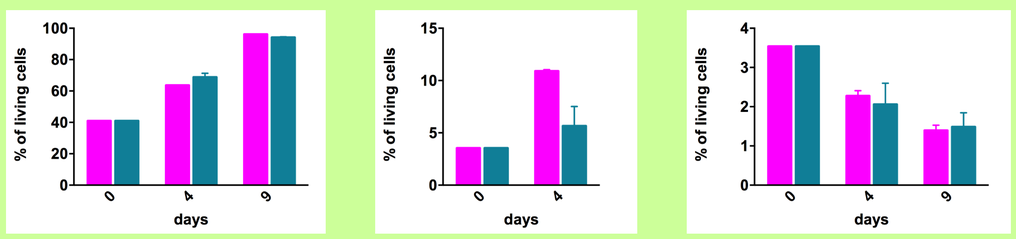


[C]

Fig. 2. **[A]** Glucose consumption as well as LDH production were analysed in medium. **[B]** H&E stain of skin freshly injected with allogeneic PBMC (day 0) and of single or co-culture at day 9. **[C]** Celltracker Green stained PBMC were injected into the skin, after 9 days nuclear counterstaining with Dapi was performed and fluorescence was recorded.

T cells preferentially survive and are more antigen-experienced in the co-culture

[A]



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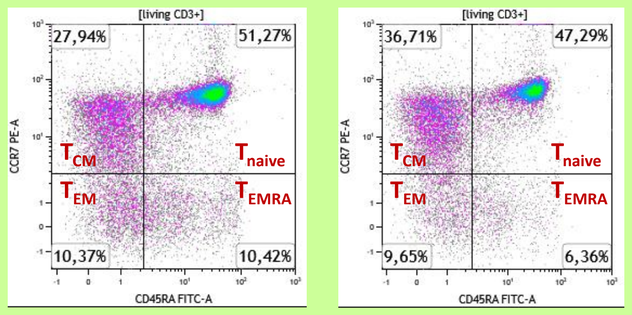

Fig. 3. **[A]** Expression of CD3, CD56 and CD19 on circulating PBMC was assessed by flow cytometry. **[B]** Flow cytometric analysis of CD3+ T cells for CD45RA and CCR7 expression at day 9. Gating for naive, effector memory (EM), central memory (CM) and terminally differentiated effector memory (EMRA) T cells is shown.

Enhanced IFNγ production in skin/immune cell co-culture

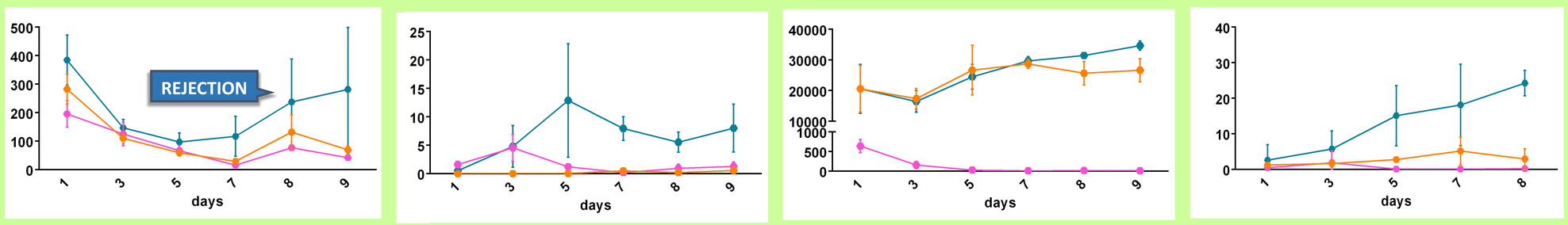

Fig. 4. Concentrations of IFNγ, IL2, IL6 and IL17A were measured by Meso Scale Discovery.

CONCLUSION

Our skin allograft on-the-chip model shows signs of rejection and might also be suitable to investigate pathogenetic mechanisms in chronic inflammatory diseases, e.g. psoriasis, or testing of novel therypeutic approaches with the advantage of reducing animal studies.