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1 *Imiquimod mouse model*
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IMIQUIMOD MOUSE MODEL OF A PSORIASIS-LIKE SKIN CONDITION

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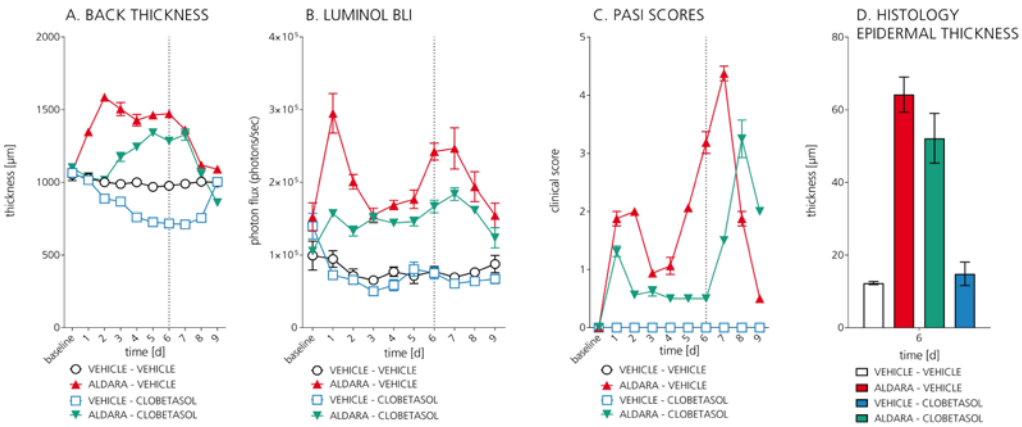
Psoriasis

Skin conditions are linked to processes occurring throughout the body, and they can become risk factors that are linked to other types of illness or injury. Psoriasis is an autoimmune disorder in which cells multiply too quickly and form shiny scales on the skin's surface, psoriasis often occurs alongside arthritis or other joint diseases. Affected individuals develop red, raised and scaling skin lesions sometimes affecting the majority of the skin, have a shorter lifespan and are at higher risk of cardiovascular diseases, obesity, metabolic dysregulation/ diabetes and psoriatic arthritis.

Imiquimod mouse model

Imiquimod (IMQ, Aldara) is a chemotherapeutic agent for many skin-associated diseases, but it has also been associated with inflammatory side effects. Clinical observations, namely an exacerbation of symptoms in psoriasis-patients using IMQ and induction of such symptoms in patients not suffering from psoriasis, have led to the concept of using IMQ as a murine model for psoriasis-like skin inflammation.
The IMQ-induced psoriasis model develops skin pathology which highly correlates to that of human psoriasis and is considered a potential preclinical psoriasis model. Imiquimod is a ligand for the Toll-Like Receptors (TLR) 7 and 8. TLRs play an important role in the function of the immune system. Basically, activation of TLR leads to a subsequent activation of the immune system and therefore IMQ is a potent immune activator.

At the Fraunhofer IME Branch for Translational Medicine and Pharmacology, we apply Aldara cream, containing IMQ, on the shaved back and on one ear of the mice for several consecutive days.



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Traditionally, the severity of the inflammation of the ear/skin is scored which is based on the clinical Psoriasis Area and Severity Index (PASI), a tool used to measure the severity and extent of psoriasis. The intensity of redness, thickness and scaling of the psoriasis is assessed. Our aim is to extend the in vivo measures for IMQ-induced skin abnormalities.

Endpoints

Our most important daily measures include: Ear/skin thickness using a digital micrometer and **luminol-based bioluminescent imaging (BLI) of myeloperoxidase (MPO) activity**.
The **IVIS Spectrum (Caliper Life Sciences)** is used as optical imaging technology to facilitate non-invasive longitudinal monitoring of disease progression (e.g. inflammation), cell trafficking and gene expression patterns in living animals. Luminol-based BLI, a measure of MPO activity is employed as an in vivo marker of inflammation.

Outcome parameters

- Normalized ear thickness: (thickness treated ear – baseline thickness treated ear) – (thickness untreated ear – baseline thickness untreated ear)
- Back thickness
- BLI of back and ear
- PASI scores
- H&E staining: thickness stratum spinosum and basale

Histopathology and Fluorescence-Associated Cell Sorting analysis

- FACS / immunohistochemistry (IHC) analysis of tissue and blood samples
- Analysis of profile of cytokines / chemokines / lipids in tissue and blood samples
- **Hematoxylin and eosin (H&E) staining** of skin tissue sections
- Several inflammatory skin diseases are associated with enhanced vascularity and vascular hyperpermeability. The **vascular (hyper)permeability** (Evans blue) responses are investigated.
- **Multi-Epitope Ligand Cartography (MELC)** allows multiple immunohistology by visualizing up to 40 antibodies on the same specimen. This is done in collaboration with the Institute of Clinical Pharmacology (Pharmazentrum Frankfurt/ZAFES, Frankfurt am Main).

Quality management and validation

The model has been validated with the clinical reference compound clobetasol.

Selected publications

- Hofmann MCJ., Schmidt M, Arne O, Geisslinger G, Parnham MJ, de Bruin NMWJ. Non-invasive bioluminescence imaging as a standardized assessment measure in mouse models of dermal inflammation. J Dermatol Sci. 2018; 91:153-63. doi: 10.1016/j.jdermsci.2018.04.013.
- Pierre S, Linke B, Suo J, Tarighi N, Del Turco D, Thomas D, et al. GPVI and Thromboxane Receptor on Platelets Promote Proinflammatory Macrophage Phenotypes during Cutaneous Inflammation. J Invest Dermatol 2017;137:686–95. doi:10.1016/j.jid.2016.09.036.
- Homann J, Suo J, Schmidt M, de Bruin N, Scholich K, Geisslinger G, et al. In Vivo Availability of Pro-Resolving Lipid Mediators in Oxazolone Induced Dermal Inflammation in the Mouse. PLoS One 2015;10:e0143141. doi:10.1371/journal.pone.0143141.
- Thomas D, Suo J, Ulshöfer T, Jordan H, de Bruin N, Scholich K, et al. Nano-LC-MS/MS for the quantitation of prostanoids in immune cells. Anal Bioanal Chem 2014;406:7103–16. doi:10.1007/s00216-014-8134-8.

1 *Effects of IMQ on:*
A. Back thickness
B. Back luminol BLI
C. PASI scores
D. Epidermal thickness (histology)
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