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1 *Bleomycin mouse model*

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BLEOMYCIN MOUSE MODEL FOR SYSTEMIC SCLEROSIS

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Systemic sclerosis

Systemic sclerosis (SSc) or scleroderma is an inflammatory rheumatic connective tissue disease that is characterized by fibrosis of the skin and various internal organs. SSc is characterized by the excessive accumulation of extracellular matrix proteins in (among others) the skin, vascular injury and immunological abnormalities.

Bleomycin model

One of the animal models available for SSc is the murine bleomycin-induced dermal fibrosis model. Bleomycin is an antibiotic anti-tumor agent that has several actions, such as the production of free radicals, induction of apoptosis and the upregulation of extracellular matrix protein gene expression. Chronic application of bleomycin to the (shaved) skin by subcutaneous (s.c.) injections in the lower back area has been shown to induce skin fibrosis. This is accompanied by infiltration of the injected skin with several immune cells such as T cells, monocytes, macrophages and mast cells.

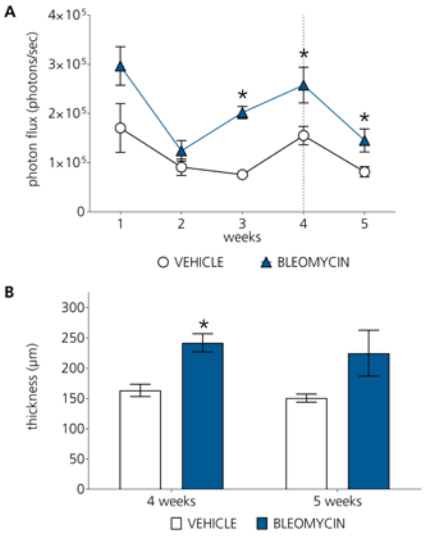
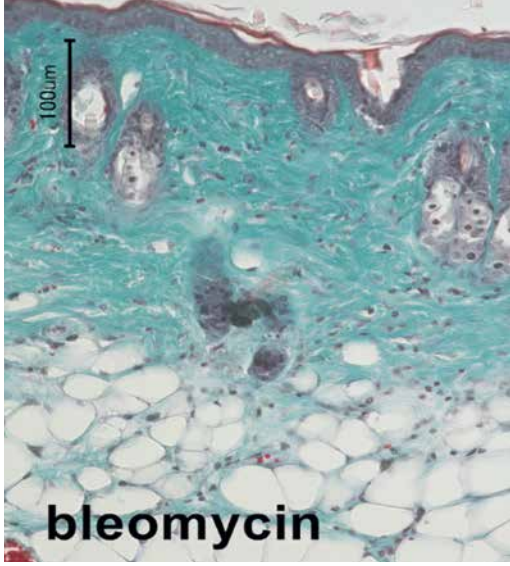


Figure 1 Bleomycin slow release
A Luminol BLI
B Histology - collagen thickness.



Endpoints/Outcome parameters

The progression of the cellular infiltration and inflammatory response induced in the skin by bleomycin can be monitored in vivo by **luminol-based bioluminescence imaging (BLI)**.

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 **myeloperoxidase (MPO) activity** is employed as an in vivo marker of inflammation.

At the end of the experiment, histological analysis of the skin can be performed such as the **Masson trichrome stain for fibrosis**.

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).

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, Ferreiros N, Stegner D, Frölich S, Sisignano M, Meyer Dos Santos S, deBruin N, Nüsing RM, Deller T, Nieswandt B, Geisslinger G, Scholich K. 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.

2 *The Masson's Trichrome staining is widely used for a variety of purposes, primarily to visualize collagen fibers, which appear in green © Fraunhofer IME / Martine Hofmann, Mike Schmidt.*