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### **Research interests**

The major focus of our laboratory is to understand the molecular pathways leading to diseases such as cancer using the mouse as a model system. Specifically, we are focusing on tumor/tissue cell intrinsic mechanisms by analysing how signalling via the Epidermal Growth Factor Receptor (EGFR), a receptor tyrosine kinase frequently amplified and overexpressed in human tumors, affects the development of epithelial and glial cells and tumors. Moreover, we are also studying tumor/tissue cell extrinsic mechanisms focusing on the role of innate and adaptive immune cells in normal and diseased skin as well as in anti-tumor immune responses and inflammation. The ultimate goal is to translate this knowledge to patients to develop rational and effective therapies for disease treatment.

### **Thesis projects**

#### Project 1: Role of EGFR in skin inflammation and cancer

Targeted therapies against the EGFR are used in several cancer patients. However, treatment with EGFR-Inhibitors is associated with cutaneous side effects like folliculitis, an acne-like papulopustular rash. Interestingly, the intensity of the side effects positively correlates with treatment success. Similar and even stronger skin alterations can be observed in mice lacking the EGFR in the epidermis. The aim of this project is therefore to understand why and how EGFR inhibition leads to skin inflammation by employing conditional EGFR knock-out mice. The results obtained in these experiments will be validated in human skin samples from patients treated with EGFR inhibitors.

#### Project 2: Mechanism of action of Imiquimod in basal cell carcinoma: Interaction of EGFR and Ptch signaling

We have previously shown that the TLR-7/8 agonist Imiquimod (Imi) can be used for the treatment of melanoma in mice which is accompanied by massive inflammation. In humans Imi is even more successfully used for the treatment of basal cell carcinoma (BCC). BCC is frequently caused by mutations in the hedgehog / patched (ptch) / Smoothed (Smo) / Gli-pathway. We could recently show that EGFR signaling synergizes with the HH pathway to increase tumor cell proliferation and survival. Additionally, the EGFR has been implicated in the regulation of TLR expression and its inhibition causes skin inflammation. The aim of the project will be to investigate the mechanisms of action of Imi in the resolution of BCC by employing mouse models for BCC. The therapeutic effect of Imi will be analyzed in the presence or absence of a functional EGFR.

Both these projects will employ a broad range of state-of-the-art molecular and cellular approaches aimed at addressing gene function *in vivo* in genetically modified mice. Methods

include primary cell isolation and purification, modern cell sorting approaches, FACS analysis, biochemical analysis of signaling pathways, histology, immunohistochemistry, conventional and inducible transgenic and ES cell methodologies as well as various experimental *in vivo* mouse procedures.

### **Selected publications**

Lichtenberger BM, Tan PK, Niederleithner H, Ferrara N, Petzelbauer P, **Sibilia M.** "Autocrine VEGF signaling synergizes with EGFR in tumor cells to promote epithelial cancer development". ***Cell***, 140, 268-279, (2010)

Holcman M, Stoitzner P, Drobits B, Luehrs P, Stingl G, Romani N, Maurer D, **Sibilia M.** "Skin inflammation is not sufficient to break tolerance induced against a novel antigen", ***J. Immunology*** 183, 1133-43, (2009).

Natarajan A. Wagner B. and **Sibilia M.** "The EGF receptor is required for efficient liver regeneration", ***PNAS*** 104, 17081-17086 (2007).

Palamara F, Meindl S, Holcman M, Luehrs P, Stingl G, **Sibilia M.** "Identification and characterization of 'pDC-like cells' in normal mouse skin and melanomas treated with Imiquimod", ***J. Immunology*** 173, 3051-3061, (2004).