THE WORKGROUP: Translational Skin Cancer Research, DKTK, University Medicine Essen, Head: Jürgen C. Becker

The Institute of Translational Skin Cancer Research (TSCR) is a multidisciplinary research environment dedicated to the molecular and immunological characterization of skin cancers, including melanoma, Merkel cell carcinoma (MCC), cutaneous squamous cell carcinoma, and cutaneous T-cell lymphoma.

Our work centers on understanding the molecular regulation of tumor progression, metastasis, and immune escape. To address these questions, we employ a comprehensive and integrative technological portfolio: single-cell multi-omics (including sc/snRNA-seq, scVDJ-seq, scATAC-seq, scDNTR-seq), spatially resolved transcriptomics (Visium, Open-ST, Xenium,), epigenetic profiling (MethylationEPIC, ATAC-seq), and antibody-based proteomics (Akoya PhenoCycler, MANTRA). These approaches are applied to patient-derived tumor material and are tightly coupled with advanced bioinformatic and statistical analyses **(Figure 1A and B)**.

In parallel, we utilize a broad range of experimental model systems for functional validation, including in vitro platforms (3D and organoid cultures, gene knockdown/knockout/editing, and molecular and functional assays) and in vivo models such as chicken CAM, *Caenorhabditis elegans*, and *Drosophila melanogaster* **(Figure 1C)**. This integrative strategy allows us to mechanistically validate findings and facilitate their translation into clinically relevant applications.

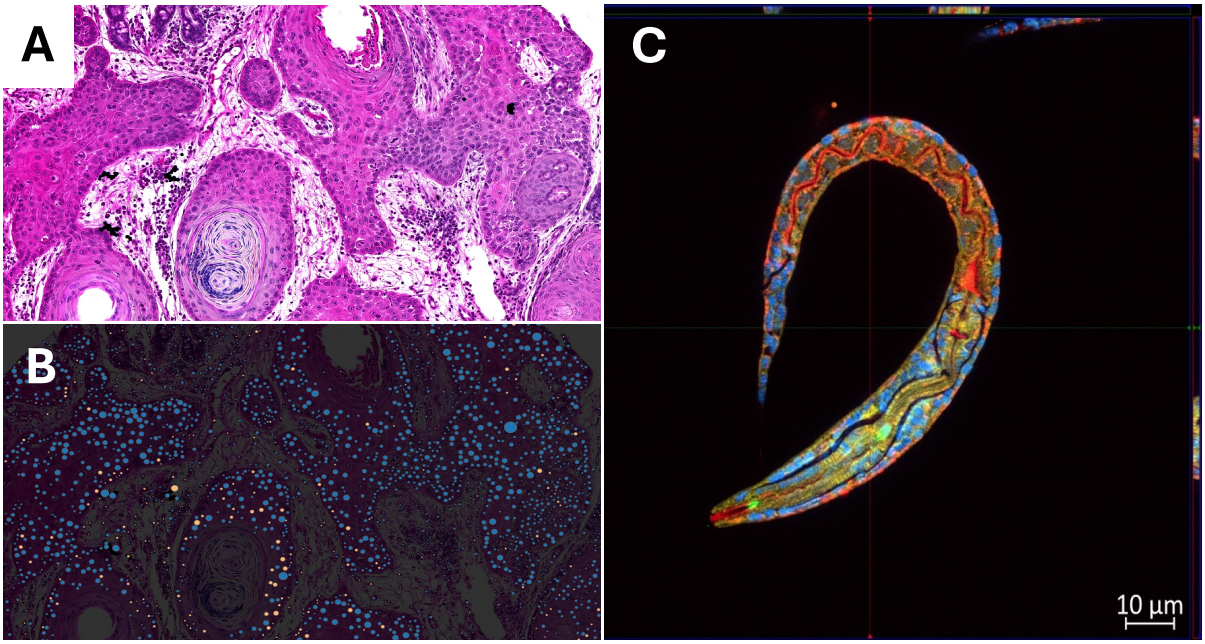

Figure 1. Technological approaches and model systems. (A, B) High-definition Visium Spatial transcriptomics: H&E image of a cutaneous squamous cell carcinoma (A); annotations of cell segmentation and transcriptomic clustering (B). **(C)** *Cell Painting* image of *C. elegans*.

A key strength of our workgroup is its close integration with the clinical Department of Dermatology at the University Hospital Essen and national research networks such as ADO/DeCOG. This collaboration ensures a continuous bidirectional transfer between clinical observation and experimental investigation. The department hosts one of the largest skin cancer biobanks in Germany, comprising fresh and formalin-fixed paraffin-embedded tumor tissues, peripheral blood mononuclear cells, sera, and plasma—comprehensively annotated with clinical data—providing an exceptional resource for translational research.

A growing body of evidence suggests that tumors do more than evading the immune system—they actively reprogram their identity to suppress it. At the TSCR, we are at the forefront of uncovering how neuronal-like fate switches in cancer cells reshape tumor–immune interactions. Leveraging cutting-edge single-cell and spatial technologies, comprehensive patient-derived resources, and innovative model systems, we aim to translate fundamental discoveries into new therapeutic strategies for aggressive skin cancers.

THE PROJECT: Neuronal Fate Switches as Drivers of Immune Evasion in Cancer

The emerging field of cancer neuro-immunology highlights the complex interplay between the nervous system, tumor cells, and the immune microenvironment. Beyond the contribution of sensory nerve fibers, sympathetic neuronal signaling has been shown to promote immunosuppression and drive T-cell exhaustion **(Figure 2)**. In addition, specialized neuronal pacemaker cells can orchestrate synchronized calcium signaling, which activates key oncogenic pathways such as MAPK and NF-κB in tumor cells. These signals shape the tumor immune microenvironment, for example, by promoting regulatory T-cell recruitment and activation or by inducing the release of neuropeptides such as CGRP, directly affecting T-cell function.

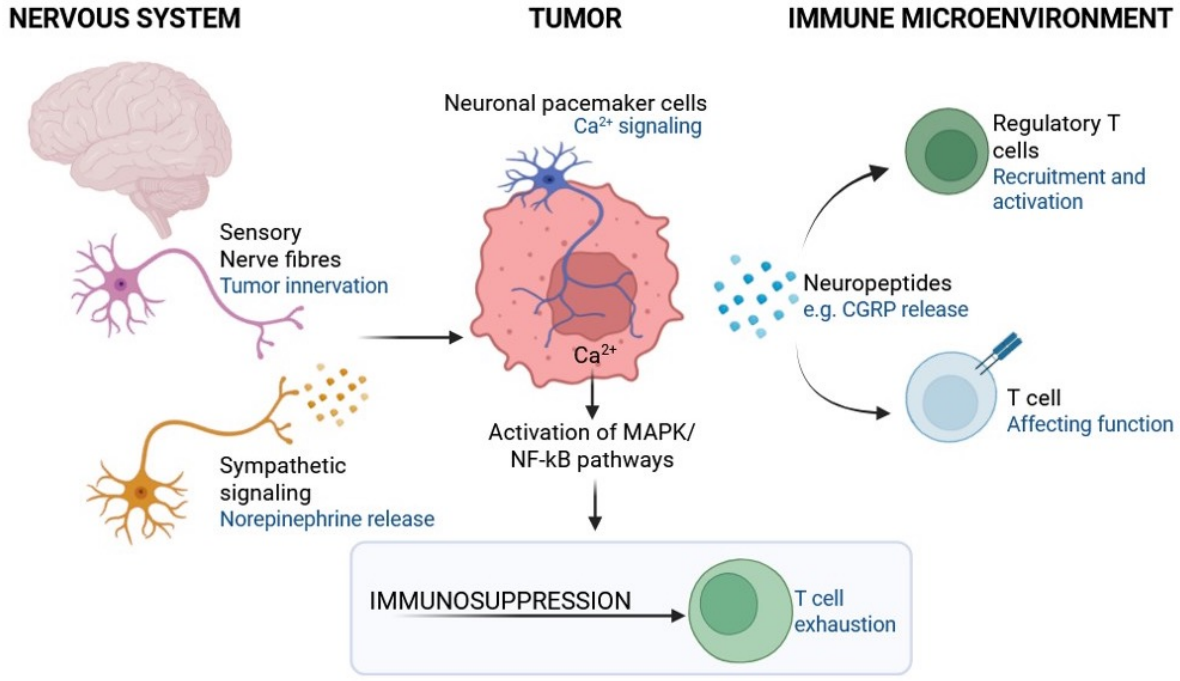

Figure 2. Cancer neuro-immunology: the complex interplay between the nervous system, tumor cells, and the tumor immune microenvironment (TiME).

Neuronal pacemaker-like features were initially described in neuronal malignancies; however, recent work from our group uncovered a comparable phenomenon in MCC, an aggressive skin cancer characterized by viral carcinogenesis and neuroendocrine differentiation. Specifically, we demonstrated that genetic silencing of Merkel cell polyomavirus-encoded proteins (large T antigen, LTA, and small T antigen, sTA) can induce neuronal transdifferentiation.

Importantly, spatial transcriptomic analyses of human MCC tissues revealed that such neuronal transdifferentiation also occurs spontaneously in vivo. These tumor regions are characterized by reduced LTA signaling and distinct rosette-like cellular architectures, accompanied by aberrant activation of the WNT/β-catenin pathway—a hallmark of neuronal pacemaker cells. Notably, MCC tumors exhibiting these features display highly aggressive clinical behavior despite limited proliferative activity and are associated with a sparse or absent inflammatory infiltrate.

Building on these observations, the aim of this project is to systematically investigate neuronal transdifferentiation, its interactions with the tumor microenvironment, and the mechanisms underlying the associated immune suppression. Using a combination of in situ, ex vivo, and in vitro approaches, the project seeks to define how neuronal fate switching contributes to immune evasion and to identify potential therapeutic strategies to counteract neuronal transdifferentiation-driven tumor progression.

Further information including the TSCR's publication list is provided at the following web-links:
https://dktk.dkfz.de/en/research/dktk-researchers/jurgen-becker
https://pubmed.ncbi.nlm.nih.gov/?term=becker-jc&sort=date&size=50