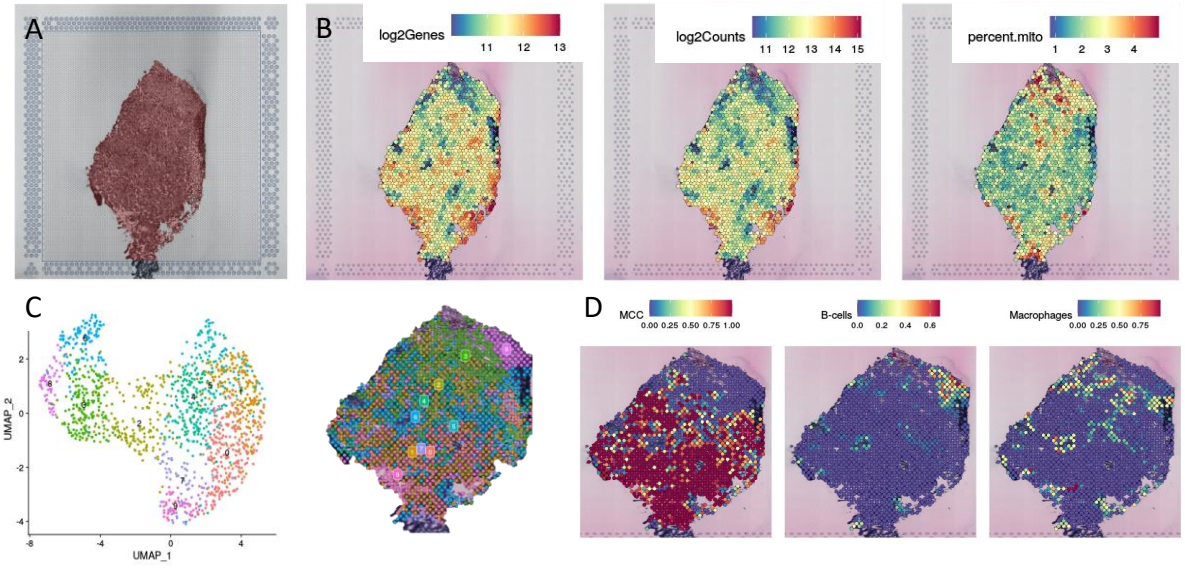
The workgroup:

The Institute of **Translational Skin Cancer Research (TSCR)** is a multidisciplinary research group addressing the **molecular and immunological characterization** of different types of **skin cancer** (melanoma, Merkel cell carcinoma, cutaneous squamous cell carcinoma, cutaneous lymphoma). The main focus of our investigations is the molecular regulation of **tumor progression, metastasis and immune escape**. This includes the application of **state-of-the-art technologies** such as ***single cell [10X Genomics, smartSeq2] and spatially resolved [Visium, MERFISH, RNAScope] transcriptomics***, ***epigenetics [MethylationEPIC, ATAC-seq]***, and ***antibody based proteomics [Akoya PhenoCycler, MANTRA]*** of patient-derived tumor tissue as well as the respective **bioinformatic and statistical analyses**. We equally use in vitro [3D and organoid cultures, gene k.d./k.o./editing, functional and molecular assays] and in vivo [CAM, PDX, GEMMs] models to functionally validate our findings and to establish their mechanistic relevance and thus ease their **translation into clinical applications**. The translation from the clinic into the lab and back is facilitated by our close cooperation with the clinical **Department of Dermatology, University Hospital Essen**. The Department is one of the **leading skin cancer centers in Germany**, with more than 10,000 patient contacts per year. The Department is hosting the **largest skin cancer biobank** in Germany, including fresh as well as formalin-fixed paraffin-embedded tissue samples, peripheral blood cells (PBMC), sera and plasma; **all materials annotated with clinical data** of the respective patients.

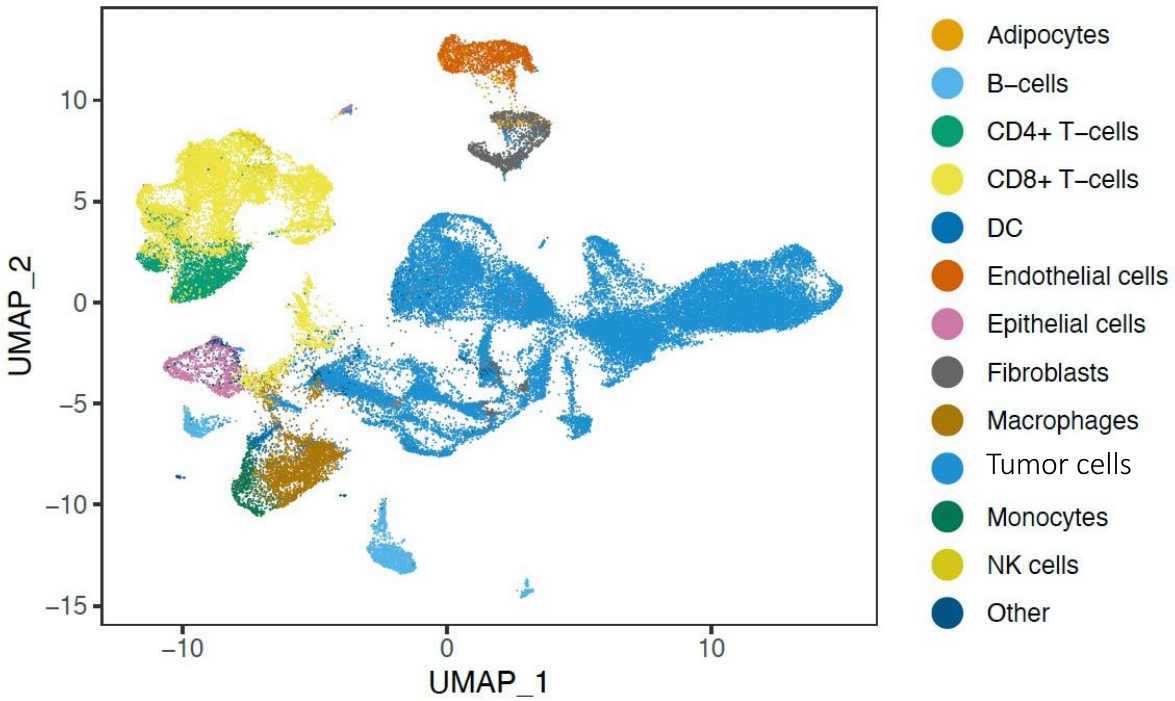


Spatially resolved transcriptomics exemplified in a case of Merkel cell carcinoma. (A) Microscopic evaluation. **(B)** Quality control of sequencing data with respect to number of genes, transcript counts and percentage for individual spots. **(C)** Dimension reduction for Seurat clustering and reprojection to the original. **(D)** Cell type deconvolution for each individual spot.

The project:

It is increasingly recognized that **immune escape mechanisms** of solid cancers are not solely depending on characteristics of the malignant or the stromal cells, but are caused and maintained to a significant extent by the dynamic interaction of all cell types present in the **tumor microenvironment**. ***This notion will be scrutinized by the candidate together with the TSCR team using the highly aggressive*** **Merkel cell carcinoma (MCC)** ***as a model tumor.***
Initial single cell analyses of primary and metastatic MCC tissue indicated complex interactions of different cell types based on the respective expression of ligands and receptors by them.

Presumed cellular reactions inferred by epigenetic characteristics, transcription factor activity as well as ratios of spliced and non-spliced mRNA counts confirmed this mutual influence of cell-cell interactions. For example, chronic inflammation caused by cancer cells favors the presence of B cells producing immunosuppressive cytokines and small metabolites such as the neurotransmitter GABA. These soluble factors cause the polarization of macrophages, which in turn inhibit the recruitment and activation of cytotoxic T cells. Knowledge of the epigenetic and transcriptional signatures in the cells of the tumor microenvironment facilitates and refines the deconvolution of bulk epigenetic and transcriptomic data, which in turn allows to extend the otherwise for logistic and economic reason limited number of analyzed tissue samples to larger cohorts. Furthermore, the availability of spatially resolved transcriptomics together with antibody-based proteomics prepares the possibility to train AI-based algorithms for the analysis of conventional histology sections to already infer from them the dynamic interactions in the tumor microenvironment, which constitutes the prerequisite to further train the model using the bulk epigenetic and transcriptomic data.



Single cell transcriptomics of primary and metastatic tumor lesions. UMAP representation of 58,201 cells from 12 patients colored of major cellular components

Further information as well as the combined publication list is provided at the following web-links:

https://dktk.dkfz.de/en/sites/essen-duesseldorf/core_facilities
https://www.uni-due.de/zmb/members/juergen-becker.php
https://dktk.dkfz.de/en/research/dktk-researchers/jurgen-becker
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