Shared resistance mechanisms in immunotherapy and targeted inhibitor therapy of melanoma

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Malignant transformation of pigment-producing melanocytes in the skin gives rise to cutaneous melanoma. Until recently, the median survival of patients with advanced metastatic disease was only 6–12 months, due to the lack of effective treatment options. This dramatically changed with the clinical implementation of (1) small molecule inhibitors targeting oncogenic mitogen-activated protein kinase (MAPK) signaling (MAPKi) and (2) immune-modulating antibodies (termed immune checkpoint blockade, ICB). The median overall survival for patients having access to one of these therapies is now 24 months or even longer. However, a large subgroup of patients who initially responded to MAPKi and ICB will eventually die from the disease due to acquired therapy resistance, indicating the importance to elucidate resistance mechanisms in order to improve clinical outcome.

It is well accepted that cytotoxic tumor-reactive CD8+ T lymphocytes play a major role in clinical responses to therapy to MAPKi and ICB. Those T cells infiltrate melanoma lesions and have the capability to specifically recognize and kill autologous tumor cells. Our research group elucidated several mechanisms that enable melanoma cells to escape from surveillance by cytotoxic CD8 T lymphocytes (https://www.uni-due.de/zmb/members/annette-paschen-zmb.php). So far, we mainly addressed tumor cell-intrinsic genetic and non-genetic mechanisms that are involved also in resistance to therapy (Sucker et al., 2017, PMID: 28561041; Horn et al., 2018, PMID: 29917141; Pieper et al., 2018, PMID: 30221038 ; Such et al., 2020, PMID: 32427578; Harbers et al., 2021, PMID: 33798535). But, therapy resistance is established not only at the tumor cell level. Within the tumor microenvironment CD8+ T lymphocytes receive multiple suppressive signals that dampen their activity and contribute to therapy resistance. It is still unclear whether T-cell suppression in melanomas with acquired resistance to MAPKi and ICB is mediated by distinct or shared mechanisms, though this knowledge is of importance as it could guide decision making in treatment of affected patients.

This project aims to compare CD8+ T cells from resistant lesions growing out under MAPKi and ICB therapy with respect to their phenotype and function. We will determine the transcriptome and epigenome of sorted CD8 tumor-infiltrating T cells and apply multiplex flow cytometry to define the T cell's phenotype and function. We expect that systematic data analyses will lead to the identification of signaling pathways, epigenetic regulators or phenotypic markers that could be targeted to improve T cell function under MAPKi and/or ICB.

Applicant should have as strong background in tumor immunology with a specific focus on CD8+ T cells and should be interested to work in a multidisciplinary team of basic researchers and clinicians (https://hautklinik.uk-essen.de/).

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