Project abstract

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Group homepage: Please visit our website for further information on our research and recent publications.	***www.dkfz.de/en/neuroimmunologie/index.php***

PROJECT PROPOSAL

Our group aims at developing and improving immune therapeutic approaches to target brain tumors by understanding molecular mechanisms of immunosuppression and exploiting novel immunotherapeutic treatment modalities. With expertise in comprehensive cellular and imaging-based analysis of tumor microenvironments, transcriptomics, and immunoreceptor profiling and utilization, and using clinical samples and mouse models, we strongly focus on clinical translation.

In the past years we have identified immunosuppressive functions and mechanisms of key metabolites that are produced by brain tumors. The discovery that TDO-derived tryptophan metabolites (kynurenines) drive growth of brain tumors and immunosuppression via the activation of the aryl hydrocarbon receptor (AHR) opened the way to novel therapeutic targets and implied further questions which we currently address using tumor models. Our findings that IDH-mutant glioma cell-derived 2HG actively and directly inhibits adaptive cellular and innate immune responses by affecting immune cell function in the tumor microenvironment pave the way towards novel concepts of immunotherapeutic combination treatments which we are currently investigating in preclinical animal glioma models.

A second line of investigations addresses the discovery of novel target antigens and T cell receptors for targeted immunotherapy of gliomas. We have shown therapeutic efficacy of an IDH1 mutation-specific vaccine and completed a phase I clinical trial to test immunogenicity

and tolerability of this vaccine in brain tumor patients, showing strong immunogenicity, enhanced pseudoprogression as a surrogate marker for immune cell infiltration and successful anti-tumor immune response. Ongoing projects now focus on identification of further mutational antigens for specific immunotherapy and on specific TCR discovery for use in transgenic T cell therapy for glioma patients. A workflow for the development of a patient-specific targeted immunotherapy for patients with gliomas based on T cell receptor identification and validation has been developed including bioinformatics-based approaches for tumor-infiltrating reactive T cell selection for such TCR discovery based on high throughput state-of-the-art single cell RNA, single cell VDJ, as well as TCRbeta deep sequencing.