other IDO1-targeting approaches, as well as decoding the underlying mechanism of cooperativity between anti-PD-1 antibody and IDO1 peptide vaccines.

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P04.04

MULTIFUNCTIONAL ANTIBODY CONSTRUCT FOR *IN VIVO* TARGETING OF DENDRITIC CELLS AS A THERAPEUTIC VACCINATION STRATEGY IN AML

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Background Dendritic cells (DCs) are antigen-presenting cells that induce antigen-specific T-cell responses. Therefore, they are used as tools and targets for anti-tumor vaccination. In contrast to T-cell based immunotherapies, that are often limited to surface antigens, DC-based vaccination strategies open up new therapeutic options by utilizing highly abundant intracellular tumor antigens as a target source. Among those, recent interest has been focused on the identification of neoantigens derived from tumor-specific mutations. Especially mutated Nucleophosmin 1 (Δ NPM1) is a considered candidate for targeted therapy in acute myeloid leukemia (AML). We developed a multifunctional antibody construct consisting of a peptide domain including a variable T-cell epitope that is fused to an α CD40 single chain variable fragment (scFv) with agonistic function to target and activate dendritic cells *in vivo*. To potentiate therapeutic efficacy, toll-like receptor (TLR) agonists can be attached as co-stimulatory domains, thereby aiming to enhance cross-presentation of conjugated (neo)antigens to CD8⁺ T cells.

Materials and Methods Flow cytometry and microscopy-based binding and internalization experiments were performed using monocyte-derived dendritic cells (moDCs). Upregulation of surface markers (CD80, CD83, CD86, HLA-DR) as well as cytokine secretion (IL-6 and IL-12) indicated DC maturation. To validate peptide processing and presentation, moDCs were co-cultured with autologous as well as allogeneic T cells. IFN- γ and TNF- α secretion served as a readout for T-cell activation, peptide-MHC multimer staining for T-cell proliferation.

Results For proof-of-principle experiments, the multispecific antibody derivative was developed by fusing the α CD40 scFv to a cytomegalovirus (CMV)-specific peptide. The α CD40.CMV construct bound CD40 agonistically and showed efficient internalization into early endosomal compartments on immature moDCs. In co-cultures of immature and mature moDCs with autologous or allogeneic T cells, α CD40.CMV induced a significantly increased T-cell activation and proliferation compared to the control. The co-administration of α CD40.CMV with various TLR agonists as vaccine adjuvants resulted in a significant upregulation of DC maturation markers in comparison to α CD40.CMV only. Interestingly, not all adjuvants were able to enhance the T-cell response. To translate this principle to the AML setting, the CMV peptide sequence was replaced with the Δ NPM1-derived and HLA-A*02:01-binding neoantigen CLAVEEVSL. Cross-presentation to CD8⁺ T cells transduced with a Δ NPM1-specific T-cell receptor was proven by IFN- γ and TNF- α secretion in co-cultures with moDCs that have been pre-incubated with α CD40. Δ NPM1. The optimal vaccine adjuvant has yet to be identified.

Conclusions We successfully demonstrated the development of a multifunctional antibody construct that specifically targets and stimulates DCs by an agonistic α CD40 scFv. It simultaneously delivers a T cell-specific peptide with a vaccine adjuvant to induce an efficient T-cell response. As neoantigens are promising targets and under intense investigation, the α CD40. Δ NPM1 fusion protein is of high therapeutic interest. Thus, our approach displays a promising DC vaccination option for the treatment of AML.

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MODULATING TUMOR MICROENVIRONMENT WITH ARGINASE-1 SPECIFIC T CELLS

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Background Cancer progression is associated with an increased immune suppression at the tumor site. Arginase-1 is an enzyme well-known for its involvement in metabolic immune regulation. At the tumor site, arginase-1 acts by reducing availability of L-arginine to the infiltrating immune cells thus reducing T cell functionality and proliferation. While arginase-1 is expressed by some tumor cells, it has also been shown to be produced by immune inhibitory myeloid cells, such as myeloid derived suppressor cells (MDSCs), tumor associated macrophages (TAMs) and is associated with poor prognosis. Previously, we demonstrated that spontaneous CD4⁺ and CD8⁺ T-cell immune responses against arginase-derived, HLA-restricted peptides can be found in both cancer patients and healthy individuals (Martinenaite *et al*, 2018, DOI: 10.1080/2162402X.2017.1404215). These T cells are present in the memory T cell compartment, and that they are activated in arginase-1 inducing conditions,