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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Disclosure Information S. Dey: None. E. Sutanto-Ward: None. K.L. Kopp: A. Employment (full or part-time); Significant; IO Biotech. J.B. DuHadaway: None. A. Mondal: None. I. Lecoq: A. Employment (full or part-time); Significant; IO Biotech. M. Zocca: A. Employment (full or part-time); Significant; IO Biotech. M.H. Andersen: A. Employment (full or part-time); Significant; IO Biotech. A.W. Pedersen: A. Employment (full or part-time); Significant; IO Biotech. A.J. Muller: F. Consultant/Advisory Board; Modest; IO Biotech.

P04.04

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

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10.1136/jitc-2020-ITOC7.73

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.

Disclosure Information S. Schmitt: None. A. Lohner: None. K. Deiser: None. A. Maier: None. M. Rothe: None. C. Augsberger: None. A. Moosmann: None. H. Leonhardt: None. N. Fenn: None. M. Griffioen: None. K. Hopfner: None. M. Subklewe: None.

P04.05

MODULATING TUMOR MICROENVIRONMENT WITH ARGINASE-1 SPECIFIC T CELLS

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10.1136/jitc-2020-ITOC7.74

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,

such as presence of T_H2 cytokines IL-4 or IL-13 *in vitro* (Martinenaitė *et al.*, 2019, DOI: 10.1038/s41423-019-0231-3 and DOI: 10.1007/s00262-019-02425-6).

Methods and Results In order to explore if arginase-1-specific T cells have a potential role in modulation of immune homeostasis, human arginase-1-specific memory T cells were isolated and expanded for functional characterization. We show that arginase-1-specific T cells specifically recognize arginase-1 expressing cells, such as mRNA transfected autologous dendritic cells (DCs) and B cells as well as M2 polarized macrophages *in vitro*. In addition, activated arginase-1-specific T cells produce pro-inflammatory cytokines IFN γ and TNF α . Secretion of TH1 cytokines by these T cells suggests potential role as potent immune modulators in the tumor microenvironment, since many arginase-1 expressing myeloid cells are not terminally differentiated and they can be re-polarized to an immunostimulatory, M1-like phenotype. We also observed that targeting of M2-polarized arginase-1 expressing monocytic leukemia cell line THP-1 with arginase-1-specific CD4⁺ T cells induces upregulation of PD-L1 on the THP-1 cells. Furthermore, we demonstrate that an arginase-1-derive peptide vaccine has a therapeutic effect in syngeneic mouse tumor models (B16 and MC38), both as monotherapy and in combination with anti-PD-1 treatment. The therapeutic effect was associated with increased immune infiltration in the peptide vaccinated mice compared to the control.

Conclusions Our study provides evidence that immune modulatory vaccination targeting arginase-1 is an intriguing way of targeting the immune suppressive microenvironment.

Disclosure Information E. Martinenaitė: A. Employment (full or part-time); Significant; IO Biotech. M. Aaboe Joergensen: None. R.E. Johansson Mortensen: None. S. Munir Ahmad: None. S.E. Weis-Banke: None. M. Orebo Holmström: None. A. Wakatsuki Pedersen: A. Employment (full or part-time); Significant; IO Biotech. Ö. Met: None. I.M. Svane: F. Consultant/Advisory Board; Significant; IO Biotech. M. Hald Andersen: A. Employment (full or part-time); Significant; IO Biotech.

P04.06 MUCOSAL IMMUNIZATION WITH A CDC1-TARGETED CTA1 ADJUVANT VACCINE CONFERS PROTECTION AGAINST MELANOMA METASTASIS

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10.1136/jitc-2020-ITOC7.75

Background Specific targeting of anti-cancer vaccines to dendritic cells (DCs) has been shown to mount efficient immune responses against tumor cells. Classical CD103⁺ dendritic cells (also called cDC1) have an inherent ability to cross-present antigens to CD8⁺ cytotoxic T cells. Here we have explored an anti-tumor vaccine that specifically targets cDC1 cells for protection against and elimination of metastatic melanoma. The vaccine contains the cholera toxin A1 subunit (CTA1) adjuvant and is targeted to cDC1 cells through an anti-CD103 single chain antibody (CD103 scFv).

Material and Methods C57BL/6 mice were injected with wild type or ovalbumin (OVA) expressing B16 melanoma cells

either subcutaneously (s.c.) to establish solid tumors, or intravenously (i.v.) to allow the formation of pulmonary metastases. Before or after establishment of tumors, mice were intranasally inoculated with a vaccine composed of a CD103 scFv element fused to the adjuvant CTA1 and the MHC I H2kd-restricted OVA epitope SIINFEKL together with the MHC II H2kd-restricted OVA epitope p323 or just the p323 peptide alone (*i.e.* CTA1-SIINFEKL-p323-CD103 and CTA1-p323-CD103, respectively). Control mice were inoculated with PBS. The growth of solid tumors was carefully monitored and the development of pulmonary metastases was determined 2–3 weeks after tumor cell injection. In addition, antigen-specific T cell immunity following intranasal immunization was evaluated.

Results Targeting MHC I and MHC II tumor cell epitopes to cDC1, via CD103 ScFv, in conjunction with the CTA1 adjuvant elicited strong tumor specific and protective CD8⁺ T cell responses as well as CD4⁺ T cell immunity. Immunization with the CTA1-SIINFEKL-p323-CD103 vaccine significantly reduced the growth of established solid B16F1-OVA melanomas ($P < 0.001$) and potentially prevented metastasis formation ($P < 0.01$). Control immunizations with the CTA1-p323-CD103 vaccine tended to reduce metastasis, but tumor-specific CD8⁺ T cells were required for full therapeutic protection.

Conclusion Targeting tumor specific CD8⁺ T cell epitopes to cDC1, in the context of a powerful adjuvant such as CTA1, leads to the development of efficient anti-tumor immune responses. Our results point towards the utility of cDC1-targeted vaccines in the treatment of established tumors or as a means to prevent metastasis formation.

Disclosure Information M. Arabpour: None. S. Paul: None. R. Kiffin: None. H.G. Wiktorin: None. K. Hellstrand: None. N. Lycke: None. A. Martner: None.

P04.07 ABSTRACT WITHDRAWN

P04.08 VIRUS LIKE VACCINES: A NOVEL IMMUNOTHERAPY STRATEGY AGAINST THE CANCER-ASSOCIATED ENDOGENOUS RETROVIRUS

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10.1136/jitc-2020-ITOC7.76

In face of the necessity of broadly acting and highly effective vaccines capable of eliminating/preventing human cancers with insufficient mutated antigens, we introduced the concept of Virus-Like Vaccines (VLVs). This strategy combines a replication-deficient retrovirus encoding virus structural proteins. These proteins assemble into secreted virus-like particles (VLPs) that deliver the target antigen to the immune system rising both humoral and cellular immune responses. Here, we use an adenoviral vector encoding the group specific antigen (Gag) and the glycoprotein of the viral envelope (Env) from endogenous retrovirus (ERV). Since ERV Env is reported to have immunosuppressive properties that support tumor establishment and development, we designed a modified vaccine that includes a mutation on the Env immunosuppressive domain (ISD) that