INTERLEUKIN-22 REGULATES ANTI-TUMOR IMMUNITY IN MOUSE MODELS OF LUNG AND BREAST CARCINOMA

D. Brukhovetska*, J. Suarez-Gosalvez, M. Schübel, A. Markota, J. Jobst, J. Dörr, F. Märkl, M. Schwedtfeiger, A. Öner, M. Seifert, A. Gottschlich, S. Endres, S. Kobold. Center of Integrated Protein Science Munich (CPS-M) and Division of Clinical Pharmacology, Department of Medicine IV, Klinikum der Universität München, LMU, Munich, Germany

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Background High expression of CD155 (poliovirus receptor, PVR) is associated with a poor prognosis of lung adenocarcinoma (LUAD) and triple-negative breast cancer (TNBC) patients. When overexpressed, this molecule inhibits the anti-tumor function of NK and cytotoxic T cells through binding to its inhibitory co-receptors TIGIT and CD96, and downregulation of stimulatory CD226 (DNAM-1). However, the exact mechanism of CD155 overexpression on the tumor cells remains unclear. Here we demonstrate that interleukin-22 (IL-22), a cytokine known to promote cancer progression, induces upregulation of CD155 on tumor cells in mouse models of breast and lung cancer and may, thus, inhibit antitumor immunity and promote lung metastasis.

Materials and Methods To study the influence of IL-22 on antitumor immunity, we utilize IL-22-deficient animals in syngeneic mouse models of metastatic breast and lung cancer. For this purpose, we generated tumor cells deficient in IL-22 receptor (IL-22R) or in CD155 and tumor cells, that constantly express CD155 independent of its natural regulation. Here, we determine the incidence of metastasis and antitumor NK and T cell responses in the lung, the primary site of metastasis.

Results We demonstrate that murine cancer cells upregulate CD155 surface expression upon treatment with recombinant IL-22, whereas this effect is abolished in the absence of IL-22R. Furthermore, IL-22-deficient animals have a lower metastatic burden in the lung and demonstrate a dramatic increase in IFN-γ production in NK, and, to a lower extent, cytotoxic T cells. Moreover, this effect is reversed when CD155 is expressed on the tumor cells independent of its natural regulation, which enables lung metastases in IL-22 deficient animals. Phenotypically, NK cells in IL-22 knockout mice have a higher expression of co-stimulatory receptor CD226, which is linked to the antitumor potential of these cells.

Conclusions Here we demonstrate a novel pathway of cytokine-mediated cancer progression, where IL-22 is capable of inducing CD155 on the tumor cells and, therefore, promotes an immunosuppressive tumor microenvironment. This highlights the potential of IL-22 as a target for immunotherapy considering the complexity of the CD155-dependent immunoregulatory network.


A LIBRARY OF NOVEL CANCER TESTIS SPECIFIC T-CELL RECEPTORS FOR T-CELL RECEPTOR GENE THERAPY

MAJ de Rooy*, DM Steen, D Remst, A Wouters, MGD Kester, RS Hagedoorn, PA van Veelen, EME Verdegaal, JHF Falkenburg, MHH Heemskerk. LUMC, Leiden, Netherlands

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Background The positive clinical effect of T-cell receptor (TCR) gene therapy on tumor regression has previously been demonstrated by NY-ESO-1 TCR-gene therapy. To seriously increase the number of cancer patients that can be treated with TCR-gene therapy we aim to identify a novel set of high-affinity Cancer Testis (CT) specific TCRs targeting different CT-antigens in a variety of prevalent HLA-class I alleles.

Materials and Methods In this study, we selected by bioinformatic tools the most promising CT-genes to target, and from these genes we identified by HLA-peptidomics the naturally processed and presented HLA-class I peptides. With these peptides HLA-tetramers were generated, and by MACS enrichment and single cell sorting CT-specific CD8+ T-cell clones were selected from the allo-HLA repertoire of healthy donors. By performing several different functional assays the high function avidity CT-clones with a safe recognition pattern were selected. To evaluate the potential for clinical application in TCR-gene therapy, TCRs were sequenced, and transferred into peripheral blood derived CD8+ T cells.

Results In total we identified, 7 novel CT-specific TCRs that effectively target MAGE-A1, MAGE-A3, MAGE-A6 and MAGE-A9 expressing tumors cells in the context of HLA-A1, -A2, -A3, -B7, -C7 and -B35.
Conclusions With this set of 7 novel CT-specific TCRs we expand the arsenal of tumor specific TCRs. With this expanding library of TCRs it would be possible to select in future for each cancer patient, based on HLA typing and gene expression, a useful TCR to generate a personalized TCR-gene therapy products. In addition, patients could be treated with multiple TCRs to enhance the efficacy and increase the durability of clinical responses by reducing the likelihood of tumor escape.


Poster Presentations
P01 Emerging concepts/new agents

P01.01 SAFETY AND EFFICACY STUDY OF PEMBROLIZUMAB IN COMBINATION WITH LENVATINIB IN PARTICIPANTS WITH HEPATOCELLULAR CARCINOMA (HCC) BEFORE LIVER TRANSPLANT AS NEOADJUVANT THERAPY—PLENTY RANDOMIZED CLINICAL TRIAL
H Feng*, Q Xia, PLENTY committee. Renji Hospital affiliated to Shanghai Jiao Tong University, Shanghai, China

Background Patients with hepatocellular carcinoma (HCC) who exceed standard Milan criteria suffered from high post-transplant recurrence rate. This study will evaluate the safety and efficacy of pembrolizumab in combination with lenvatinib as neoadjuvant therapy in participants with HCC exceeding Milan criteria before liver transplant.

Materials and Methods Participants would be randomly assigned (1:1) to experimental or Comparator/Control by computer-generated allocation based on the envelope method and the hierarchical block randomization method (hierarchy: BCLC stage and AFP level). The envelopes are sealed opaque, and sequentially numbered. Randomization is performed by the trial coordinator. The random number table and the block assignment number table will be kept confidential by the full-time coordinator. The random number table and the block assignment number table will be kept confidential by the full-time secretary of this project. Center-stratified block-permutated randomization is used in this trial. Then permuted block randomization is used for each stratum with a block size of 4.

Results The initial first patient was recruited in August 2020, the primary hypothesis of this study are that neoadjuvant pembrolizumab plus lenvatinib is superior to regularly waiting in the list with respect to: 1) recurrence-free survival (RFS) as assessed by blinded independent central review (BICR); and 2) Objective Response Rate (ORR). The investigators design a clinical study to explore whether the combination above as a neoadjuvant treatment in patients with advanced HCC before liver transplant could reduce postoperative recurrence and to analyze potential immune biomarker of therapeutic response.

Conclusions The study is still ongoing and the preliminary short term outcome was positive. HCC patients who exceeded milan criteria may benefit from neoadjuvant immunotherapy combined with TKI before liver transplantation.

Disclosure Information H. Feng: None. Q. Xia: None.