binders (both CTA-derived and mutation-derived peptides) in the homozygous cohort. Our findings demonstrate a reduced amount of potentially immunogenic peptides in EGA patients with HLA-homozygosity for at least one locus, which may result in impaired cancer immunosurveillance. In line with this observation, we also found increased levels of CTA expression in homozygous compared to heterozygous patients. After artificial modification of the genotype of homozygous patients to a heterozygous genotype, the set of predicted good-binding peptides was comparable to the heterozygous cohort.

Conclusion Our results highlight the effect of HLA-I homozygosity on the immunopeptidome as important prerequisite of anti-tumor immunity. The high frequency of genomic HLA-I homozygosity observed in the EGA cohort may reflect an increased cancer risk for these patients. Together with previous reports demonstrating reduced survival after checkpoint therapy, our study suggests consideration of germ-line HLA-homozygosity for the design and interpretation of immunotherapeutic trials.

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

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10.1136/jitc-2021-ITOC8.3

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.

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

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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.

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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

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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 secretary of this project. Center-stratified block-permuted 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.

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P01.02 TLR-MEDIATED SUPPRESSION OF THE CCL22-CCR4 AXIS AS A NEW TARGET FOR TUMOR IMMUNOTHERAPY

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Background Unmethylated CpG-DNA is a potent ligand for the endosomal Toll-like-receptor-9, important for the immune activation to pathogen-associated molecules.¹ CpG and other TLR-ligands show effective immunotherapeutic capacities in cancer treatment by inducing an antitumorigenic immunity.² They are able to reduce tumor progression by reduction of intratumoral secretion of the immunoregulating chemokine CCL22³ and subsequent recruitment of immunosuppressive regulatory T cells (Treg), which express CCR4 the only so far known receptor for CCL22.⁴ Our recent work has shown that CCL22 secretion by dendritic cells (DC) in the lymph node, mediates tolerance by inducing DC-Treg contacts.⁵ Indeed, in the absence of CCL22, immune responses to vaccination were stronger and resulted in tumor rejection.⁶ Therefore, we are aiming to investigate the effects of TLR-ligands on systemic CCL22 levels, elucidating all involved mechanisms to identify new targets for cancer immunotherapy.

Materials and Methods T, B and CD11c⁺ DCs of wildtype (wt) and RAG1^{-/-} mice were isolated from splenocytes by magnetic-activated cell sorting for *in vitro* assays. Different co-cultures were incubated with CpG and GM-CSF, known as an CCL22 inducer.⁵ For *in vivo* experiments, wt mice were treated with CpG, R484 or poly(I:C) alone and in combination with GM-CSF. CCL22-levels in a number of organs were analyzed.

Results Analyzing the different immune cell compartments *in vitro*, we found that DCs in whole splenocytes secrete CCL22 during culture while DC cultured alone showed no CCL22 secretion. When treated with CpG, CCL22-levels were reduced in splenocytes, while it was induced in DC culture alone. The same results were seen when RAG splenocytes, that lack functional B and T cells, were cultured with CpG. CpG treated B cells were able to suppress CCL22 secretion by DC unlike T cells alone. Co-cultures of T and B cells treated with CpG, however, induced the strongest CCL22 suppression in DC. *In vivo*, we could show that all TLR ligands tested reduced CCL22 in a number of organs significantly. Furthermore, CpG showed the strongest suppression of CCL22 even in the presence of the CCL22 inducer GM-CSF.⁵

Conclusions We could show that B cells with T cells mediate CCL22 suppression by TLR ligands. The fact that CpG was able to reduce CCL22 levels even in the presence of the inducer GM-CSF demonstrates the potent CCL22 suppressive capacity of TLR ligands.

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