

presence of a bispecific antibody (BiAb) cross-linking the receptor with a tumor-associated antigen. While we could show efficacy of the SAR platform in different models, limited infiltration and immune suppression still hamper its function. We could previously demonstrate that T cell infiltration can be enhanced by transduction with carefully chosen chemokine receptors like CXCR6, CCR4 and CCR8. At the same time, gene silencing of checkpoint molecules like PD-1 can make T cells more resistant to immunosuppression, thus we assumed that combining these approaches might generate a desired T cell product.

Materials and Methods All constructs had been generated previously by overlap-extension cloning. The EGFRvIII (E3) SAR consists of extracellular EGFRvIII, transmembrane CD28 and intracellular CD28 and CD3 ζ . Human CXCR6-GFP, CCR4-GFP and CCR8-GFP are composed of the chemokine receptors fused to GFP via a 2A sequence. Primary human T cells were retrovirally transduced to stably express the SAR and chemokine receptors. We analyzed migration, cytotoxicity and activation of the single and double (E3 SAR and chemokine receptor) transduced T cells. In addition, PD-1 was knocked out using CRISPR-Cas9 and killing kinetics of target cells and T cell activation were assessed.

Results Co-transduction with chemokine receptors significantly increased migration of E3 SAR T cells to their respective ligand while lysis of target-expressing tumor cell and T cell activation in the presence of BiAb were not affected *in vitro*. Additionally knocking out PD-1 enhanced killing kinetics and activation of E3 SAR and E3 SAR + CXCR6-GFP transduced T cells compared to corresponding mock electroporated T cells.

Conclusions Using the controllable and modular SAR – BiAb platform SAR T cell activation can be limited by stopping BiAb dosing if adverse events occur. In addition, SAR T cells can be redirected to an alternative tumor-associated antigen by exchanging the BiAb in the case of antigen escape. Here we present add-ons to this approach for increased tumor infiltration and resistance to immunosuppression. Since migration is enhanced upon co-transduction with chemokine receptors and target cell lysis is accelerated upon PD-1 knockout *in vitro* these two additional modifications seem very promising options to further improve tumor control *in vivo*.

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P06.07 **IN VIVO STUDIES OF IMMUNOMODULATORY A-CTLA-4 ANTIBODY IN A HUMANIZED MOUSE MODEL**

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Background Recent findings in cancer immunotherapy have reinforced the hypothesis that the immune system is able to control most cancers. Immunomodulatory antibodies can

enhance immune responses, having the potential to generate anti-cancer immunity.¹⁻⁴

Materials and Methods Most current studies addressing this question are performed in murine mouse model systems or use *in vitro* culture systems, which do not reflect the human *in vivo* situation, potentially leading to results that cannot be fully translated into human cancer therapy. Therefore, it is necessary to establish a new mouse model, which allows the study of cancer immunotherapy in the context of a human immune system. We focused on the establishment of a humanized mouse model, in which different immunomodulatory antibodies can be tested in the presence of a human immune system.

Results First experiments concerning the suitability to test immunomodulatory antibodies in the humanized mouse model, revealed that effects of checkpoint-control antibody a-CTLA-4 were similar to the effects seen in patients of clinical studies. To analyse the anti-tumor activities of immunomodulatory antibodies *in vivo* we are establishing a human melanoma-like tumor model in humanized mice.

Conclusions This enables us to test the efficacy of immunomodulatory agonistic antibodies (such as CP-870,893) and checkpoint control antibodies (such as anti-CTLA-4) in eliminating a melanoma-like tumor. Furthermore, parameters like tumor infiltrating human cells and cytokine/chemokine production can be analysed.

REFERENCES

- Schuster M, Nechansky A, Loibner H. Cancer immunotherapy. *Biotechnol J* 2006;1:138–147.
- Mellman I, Coukos G, Dranoff G. Cancer immunotherapy comes of age. *Nature rev* 2011;480:480–489.
- Finn OJ. Immuno-oncology: understanding the function and dysfunction of the immune system in cancer. *Annals of Oncology* 2012;23:vii6–vii9.
- Langer LF, Clay TM, Morse MA. Update on anti-CTLA-4 in clinical trials. *Expert Opin Biol Ther* 2007;8:1245–1256.

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P07 Cell therapy in haematologic diseases

P07.01 **A MODULAR AND CONTROLLABLE T CELL THERAPY PLATFORM FOR AML**

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Background Targeted immunotherapies have shown limited success in the context of acute myeloid leukemia (AML). The mutational landscape, heterogeneity attributed to this malignancy and toxicities associated with the targeting of myeloid lineage antigens, it has become apparent that a modular and controllable cell therapy approach with the potential to target multiple antigens is required. We propose a controlled ACT