than traditional T cells in the host. We explored the characteristics of CpG-expanded T cells and found that T cells generated from a CpG culture incur a unique proteomic and cell surface signature phenotype. Of all the cell types present in the starting culture (CD4+ T cells, NK cells, B cells, DCs, macrophages), B cells were the only cell type critical to achieve a more potent T cell therapy with CpG. In a direct comparison of CpG class A (targeting DCs) and CpG class B (targeting B cells), only the B cell-activating CpG improved cell therapy. Finally, we found that B cells alone could improve purified CD8+ T cells for ACT when the co-culture was activated with CpG, indicating that B cells become potent APCs in this context.

Conclusions Collectively, our findings indicate a novel way to use TLR agonists to improve ACT and reveal a critical role for B cells in the expansion of potent anti-tumor CD8+ T cells. Translating these findings to ACT therapies could provide dramatic improvements in patients with late stage malignancies.

Acknowledgements Proteomic analysis was performed at the Mass Spectrometry Facility, a University Shared Research Resource at the Medical University of South Carolina, using instrumentation acquired through the NIH shared instrumentation grant program (S10 OD010731-Orbitrap Elite Mass Spectrometer or Orbitrap Fusion Lumos ETD/VD MS (S10 OD025126).

Trial Registration NA

Ethics Approval All animal procedures were approved by the Institutional Animal Care & Use Committee of the Medical University of South Carolina, protocol number 0488.

Consent NA

REFERENCES

1. NA

<http://dx.doi.org/10.1136/jitc-2020-SITC2020.0160>

161

DEVELOPMENT OF A CD8 CO-RECEPTOR INDEPENDENT T CELL RECEPTOR SPECIFIC FOR TUMOR-ASSOCIATED ANTIGEN MAGE-A4 FOR NEXT GENERATION T CELL-BASED IMMUNOTHERAPY

¹Kathrin Davari*¹Tristan Holland, ¹Laura Prassmayer, ¹Giulia Longinotti, ²Kenneth Ganley, ²Lisa Pechilis, ²Iulia Diaconu, ²Prashant Nambiar, ²Mike Magee, ³Dolores Schendel, ¹Daniel Sommermeyer, Christian Ellinger, ¹Rer Nat. ¹Medigene Immunotherapies GmbH, Planegg-Martinsried, Germany; ²Bluebird Bio Inc., Cambridge, MA, USA; ³Medigene AG, Planegg-Martinsried, Germany

Background The cancer-testis antigen MAGE-A4 is an attractive target for T cell-based immunotherapy, especially for indications with unmet clinical need like non-small-cell lung carcinoma or triple-negative breast cancer. Overcoming high tumor burden using adoptive transfer of T cells modified to express a transgenic T cell receptor (TCR) demands optimal recognition of the corresponding target on tumor cells by the TCR-modified T cells (TCR-Ts). Here we describe the isolation and pre-clinical characterization of high avidity TCR-Ts expressing a human leucocyte antigen (HLA)-A*02:01-restricted MAGE-A4-specific TCR that is fully functional in T cells irrespective of CD4 or CD8 co-receptor expression.

Methods An unbiased CD137-based sorting approach was first used to identify an immunogenic MAGE-A4-derived candidate epitope that was properly processed and presented on HLA-A2 molecules encoded by the HLA-A*02:01 allele. To isolate

high avidity T cells via subsequent multimer sorting, an in vitro priming approach using HLA-A2-negative donors (allogeneic-HLA-restricted priming approach) was conducted to bypass central tolerance to this self-antigen. Pre-clinical parameters of safety and activity were assessed in a comprehensive set of in vitro and in vivo studies of the lead TCR candidate derived from a selected T cell clone.

Results A TCR recognizing the MAGE-A4-derived decapeptide GYDGREHTV was isolated from primed T cells of a non-tolerant HLA-A2-negative donor. The respective TCR-T cell product bbT485, expressing the lead TCR in T cells from healthy donors, was demonstrated pre-clinically to have a favorable safety profile and superior in vivo potency compared to TCR-Ts made using a TCR derived from an HLA-A2-positive donor bearing a tolerized T cell repertoire to self-antigens. The natural high avidity allogeneic (allo)-derived TCR was found to be CD8 co-receptor-independent, allowing effector functions to be elicited in transgenic CD4+ T helper cells. These CD4+ TCR-T cells not only supported an anti-tumor response by direct killing of MAGE-A4-positive tumor cells, but also upregulated hallmarks associated with helper function, such as CD154 expression and release of key cytokines upon tumor-specific stimulation.

Conclusions The extensive pre-clinical assessment of safety and in vivo potency of this non-mutated high avidity, CD8 co-receptor-independent, MAGE-A4-specific HLA-A2 restricted TCR provide the basis for its use in clinical TCR-T immunotherapy studies. The ability of this co-receptor-independent TCR to activate all transduced T cells (irrespective of CD4 or CD8 expression) could potentially provide enhanced cellular responses in the clinical setting through the induction of functionally diverse T cell subsets that goes beyond what is currently tested in the clinic.

<http://dx.doi.org/10.1136/jitc-2020-SITC2020.0161>

163

NICE: NEOANTIGEN-CYTOKINE-CHEMOKINE MULTIFUNCTIONAL ENGAGER FOR NK CELL IMMUNOTHERAPY OF SOLID TUMORS

Xue Yao*, Sandro Matosevic. Purdue University, Lafayette, IN, USA

Background The effectiveness of natural killer cell-based immunotherapy against solid tumors is limited by the lack of specific antigens and the immunosuppressive tumor microenvironment. To improve the clinical efficacy and specificity of NK cell therapy, we are designing, developing, and characterizing a new generation of multi-specific killer engagers, which consists of a neoantigen-targeting moiety, together with cytokine and chemokine-producing domains.

Methods Targeting a neoantigen-an antigen formed specifically in response to tumor genome mutations-enables substantially enhanced tumor specificity to be achieved. We evaluated the responsiveness of NK cells to Wilms Tumor 1 (WT1) antigen in GBM by synthesizing an antibody that is able to recognize the WT1/HLA complex. Incorporation of cytokine (namely IL-2, IL-15, and IL-21)-essential for the maturation, persistence, and expansion of NK cells in vivo-favors the proliferation and survival of NK cells in the tumor microenvironment, thereby leading to more sustained anti-tumor responses. Additionally, our data have indicated that the chemokine CXCL10 plays an important role in the infiltration of immune cells into GBM, yet the chemokine itself is expressed at low levels in GBM. Incorporation of a CXCL10-producing element into our