1182 MODULATING THE TUMOR MICROENVIRONMENT BY A TARGETING TGFB1 WITH VACCINE-INDUCED IMMUNE RESPONSES

Brian Weinert*, Tine Hannibal, Preeyam Patel, Evelina Martinenaite, Marion Chapellier, Marco Carretta, Alireza Alavi, Ayako Pedersen, Muhammad Al-Hajj. *IO Biotech, Copenhagen, Denmark*

Background Recent clinical results[1] provide a rationale for cancer immunotherapy based on activation of "anti-regulatory" T cells. Anti-regulatory T cells recognize antigens expressed by immunosuppressive cells and thereby target pro-inflammatory signals to the tumor microenvironment.[2] TGFB1 promotes immune suppression in diverse cancers. We hypothesize that activating T cells against TGFB1 may allow targeting of pro-inflammatory immune response to TGFB1-expressing tumors while avoiding the toxicities associated with TGFB1 pan-inhibition. TGFB1-specific T cells are frequently detected in humans.[3] Vaccination with a TGFB1 peptide ameliorates fibrosis in a model of chronic colitis [4] and enhances the anti-tumor activity of an HPV16 E7-specific vaccine[5], indicating a therapeutic potential of a TGFB1 vaccine. Here we sought to enhance the specificity anti-TGFB1 immune responses and identify peptides with high TGFB1 selectivity (vs TGFB2/3), thereby mitigating potential off-target toxicities. To understand the TGFB1 landscape in human tumors we performed a multiplexed IHC analysis of TGFB1 expression on tumor cells and the multiplicity of cells in the tumor microenvironment.

Methods PBMCs were assayed by ELISPOT to measure responses to peptides from TGFB1, TGFB2, and TGFB3. TGFB1 expression was examined by multiplex immunofluorescence in a tissue microarray panel of tumor indications with hyperplexed visualization of markers on a single section. Vaccination is evaluated in mouse models expressing TGFb1. Tumor growth monitored, organs and tumor samples collected. Histopathological examination is performed on multiple tissues. Vaccine activity is determined and immune infiltrate analysis conducted by FACS and RNAseq.

Results Healthy human donors exhibited robust immune responses to TGFB1 peptides selected for improved TGFB1-specificity. Stimulation of PBMCs with TGFB1 peptides did not result in cross-reactivity to homologous TGFB2 or TGFB3 peptides. Analysis of TGFB1 expression showed widespread TGFB1 expression in cancers and provides a rationale for targeting TGFB1 in selected indications. Anti-TGFB1 T cell clones functional activity and TGFB1-specificity were confirmed. Therapeutic activity of TGFb1 vaccine in mouse models and in addition to the cellular and molecular analysis of the tumors in the various cohorts will be presented.

Conclusions A TGFb1 vaccine is an attractive new approach for cancer immune therapy. Optimal synthetic long peptides able to elicit robust and highly selective TGFB1-immune responses were developed. These peptides showed ability to change an immune suppressive TME to a pro-inflammatory state and drive efficacy in mouse models. These data support the preclinical development of an TGFb1 vaccine for the treatment of multiple solid tumors.

REFERENCES

1. Kjeldsen JW, Lorentzen CL, Martinenaite E, Ellebaek , Donia M, Holmstroem RB, Klausen TW, Madsen CO, Ahmed SM, Weis-Banke SE, Holmstrom MO, Hendel HW, Ehrnrooth E, Zocca MB, Pedersen AW, Andersen MH, Svane IM. A phase 1/2 trial of an immune-modulatory vaccine against IDO/PD-L1 in combination with nivolumab in metastatic melanoma. *Nat Med* 2021;**27**(12):2212–2223.
2. Andersen MH. The T-win(R) technology: immune-modulating vaccines. *Semin Immunopathol* 2019;**41**(1):87–95.
3. Holmstrom MO, Mortensen REJ, Pavlidis AM, Martinenaite E, Weis-Banke SE, Aaboe-Jorgensen M, Bendtsen SK, Met O, Pedersen AW, Donia M, Svane IM, Andersen MH. Cytotoxic T cells isolated from healthy donors and cancer patients kill TGFbeta-expressing cancer cells in a TGFbeta-dependent manner. *Cell Mol Immunol* 2021;**18**(2):415–426.
4. Ma Y, Q Guan, Bai A, Weiss CR, Hillman CL,Ma A, Zhou G, Qing G, Peng Z. Targeting TGF-beta1 by employing a vaccine ameliorates fibrosis in a mouse model of chronic colitis. *Inflamm Bowel Dis* 2010;**16**(6):1040–50.
5. Chu X, Li Y, Huang W, Feng X , Sun P, Yao Y, Yang X, Sun W, Bai H, Liu C, Ma Y. Combined immunization against TGF-beta1 enhances HPV16 E7-specific vaccine-elicited antitumour immunity in mice with grafted TC-1 tumours. *Artif Cells Nanomed Biotechnol* 2018;**46**(sup2):1199–1209.

http://dx.doi.org/10.1136/jitc-2022-SITC2022.1182