A NOVEL STRATEGY TO TREAT ADVANCED, LATE-STAGE TUMOURS WITH REAL-TIME TUMOUR VACCINATION

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10.1136/esmoopen-2018-EACR25.942

Introduction Novel anti-cancer immune therapeutic strategies, like various new antibody formats and/or tumour vaccines, show promising results in patients.

However, due to the ‘immune-escape phenomenon’ driven by tumor-secreted Transforming Growth Factor-beta (TGF-beta), the host immune system of cancer bearing patients frequently fails to control tumour re-growth.

Real-Time Tumour Vaccination (RealTVac) approach aims at avoiding this ‘immune-escape phenomenon’ by intratumoral inhibition of active TGF-beta isotypes while simultaneously and synergistically inducing an efficient immune response by a highly potent combination of immune stimulating factors.

Material and methods The synergistic effects of the proposed combination of a TGF-beta inhibitor with immunostimulating cytokines are demonstrated in in-vitro and in-vivo experiments:

1. Effects of RealTVac components (ALK5-Inhibitor SD208 combined with T-cell stimulating interleukin-2 (IL-2) and Dendritic Cell (DC)-stimulating Granulocyte/Macrophage-Colony Stimulating Factor (GM-CSF) in a pharmaceutical composition upon human peripheral blood mononuclear cells (PBMCs) proliferation and allogeneous cytotoxicity against human malignant glioma cells were studied in-vitro (Cell Proliferation Assay, CARE-LASS Assay).

2. Effects of intratumoral RealTVac components (see above) upon in-vivo growth of malignant melanoma were studied in a syngeneic B16-Mouse Model.

Results and discussions Both, immune cell proliferation and tumour cell cytotoxicity were significantly enhanced using components of RealTVac therapy.

Initial experiments in a syngeneic B16 melanoma xenograft model in immunocompetent mice indicate that Real-Time Tumour Vaccination of established subcutaneous B16 tumour xenografts reduced local tumour growth compared to untreated controls.

Conclusion Real-time tumour vaccination (RealTVac) activates human immune cells in vitro and inhibits growth of established B16 subcutaneous melanoma tumours in vivo.

We hypothesised that local, intratumoral generation of tertiary lymphoid structures by combined activation of T-cells and DC by immunostimulating/modulating cytokines in TGF-beta-free context induces the host anti-tumour immune responses to personalised Tumor-Associated Antigens (TAAs) in real-time mode.

Thus, intratumoral immunisation as applied for RealTVac may create a new paradigm for cancer therapy in the near future (Marabelle et al., Clin. Cancer Res., 2014).

SMALL MOLECULES, PEPTIDES AND ANTIBODIES – THE COMPARISON OF PD-1/PD-L1 BLOCKING POTENTIAL IN AN IN VITRO IMMUNE CHECKPOINT BLOCKADE ASSAY

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10.1136/esmoopen-2018-EACR25.943

Introduction Programmed cell death-1 (PD-1, CD279) protein is a surface receptor belonging to immunoglobulin superfamily. The receptor is expressed mostly on activated T cells and serves as an emergency brake for turning off the destructive action of these cells. Its natural ligand, PD-L1, is expressed on several types of immune cells to prevent from autoimmune reactions and provide T cell homeostasis. Due to its immunosuppressive function, PD-L1 is also utilised by a variety of cancer types to evade the deadly impact of activated T cells.

In the recent years cancer immunotherapy utilising antibodies targeting PD-1/PD-L1 interaction has been proved to be exceptionally effective in multiple clinical studies. Due to extraordinary clinical outcome the use of both anti-PD-1 and anti-PD-L1 antibodies has been approved for the treatment of several cancer types. Despite great achievements of the use of therapeutic antibodies, a strikingly less progress has been done in the field of small molecules targeting this interaction.

In this report the comparison of the in vitro activity of therapeutic antibodies, Bristol-Myers Squibb (BMS) small molecules and cyclic peptides is presented.

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