Results Using radiolabeled synTacs/Immuno-STATs loaded with the appropriate peptides, we employed positron emission tomography to localize human papillomavirus (HPV16)-specific CD8 T cells to implanted HPV16-positive tumors in mice, as well as influenza A virus (IAV)-specific CD8 T cells in the lungs of IAV-infected mice. In vivo administration of HIV- and CMV-specific synTacs/Immuno-STATs to immunodeficient mice intraperitoneally engrafted with human donor PBMCs resulted in the marked and selective expansion of HIV-specific and CMV-specific human CD8 T cells populating their spleens, respectively.

Conclusions We demonstrate the remarkable flexibility of the synTacs/Immuno-STAT platform for addressing a broad range of applications, including the first report of the in vivo imaging of antigen-specific CD8 T cell populations and in vivo antigen-selective expansion of human CD8 T cells. These results suggest that, in addition to broad therapeutic applications, synTacs/Immuno-STATs may provide prognostic/diagnostic information. Most notably, these results demonstrate the presence of synTacs/Immuno-STAT biologics in the tumor or infected tissues where they can elicit T cell restimulation and expansion necessary for target killing and enhanced therapeutic efficacy.

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624 IFNγ SECRETED BY TEBENTAFUSP (IMCGP100)-REDIRECTED T CELLS INHIBITS EXPRESSION OF MELANIN SYNTHESIS PATHWAY GENES IN HEALTHY MELANOCYTES


Background Tebentafusp (IMCgp100) is a bispecific T cellredirector comprised of an affinity-enhanced TCR recognizing melanocyte lineage antigen gp100 and a T cell engaging anti-CD3 scFv domain. Tebentafusp has shown activity as monotherapy in advanced cutaneous and uveal melanoma (Middleton et al., ASCO 2019), and we have previously reported that over half of uveal melanoma patients treated with tebentafusp display melanocyte-related adverse events (MRAE). These include vitiligo/skin hypopigmentation, leukotrichia, and hyperpigmentation and, collectively, are associated with better over half of uveal melanoma patients treated with tebentafusp.

Methods Results Healthy melanocytes expressed 2 to 3-fold lower levels of gp100 peptide-HLA complexes on their surface compared to gp100-positive melanoma cell lines. In the presence of tebentafusp, this lower target expression translated into 3 to 6 fold lower levels of IFNγ and more than 100 fold lower granzyme B production by redirected T cells and these melanocytes were resistant to direct tebentafusp-induced killing (EC50 for melanocytes greater than 1nM vs E50 melanoma cell lines of 23–50 pM). Supernatants from T cells activated in response to melanoma cancer cells by tebentafusp downregulated the melanin content of healthy melanocytes (20–30%) reduction. Western blotting revealed 30–40% inhibition of two key components of the melanin synthesis pathway; the tyrosinase-related protein (TRP)-1 and TRP-2. This inhibition was reversed by blocking IFNγ in supernatants from activated T cells.

Conclusions MRAEs, especially vitiligo, associated with response to tebentafusp, may be explained, at least in part, by the downregulation of melanin biosynthesis pathway genes by IFNγ secreted by tebentafusp-activated T cells.

Ethics Approval The study was approved by the South Central - Oxford A Research Ethics Committee (UK), REC reference 13/SC/0226

REFERENCES

625 BISPECIFIC PERSONALIZED APTAMER FOR THE TREATMENT OF SOLID TUMORS

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Background Despite substantial progress observed in the field of targeted therapies for cancer, there is still a major unmet clinical need for truly personalized medicine approaches. Aummune’s innovative proprietary technology enables a personalized anti-cancer treatment based on a process of selecting and identifying specific functional aptamers – structured single-stranded DNA (ssDNA) oligonucleotides, that are able to bind a large variety of targets with high affinity and specificity.

Methods The Bispecific Personalized Aptamer is comprised of two ssDNA oligonucleotides arms joined together by a dimerization site. One arm of the Bispecific Personalized Aptamer is the outcome of Aummune’s innovative platform,1 identifying functional aptamer sequences with the ability to kill tumor target cells, while leaving healthy tissue intact. The second arm is a constant aptamer sequence that binds to cytotoxic T lymphocytes. The two aptamer arms of the bispecific structure are bridged together by complementary sequences that form a CpG-rich domain designed to induce TLR9-mediated Antigen Presenting Cells (APCs) stimulation.

Results We have demonstrated a successful identification of a personalized aptamer arm using HCT116 colon carcinoma cells as a target. When hybridized to the constant, T cell engager arm, the bispecific entity has demonstrated potent yet