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**Abstracts**

622 PD-L1 IS A POTENTIAL PREDICTIVE BIOMARKER FOR RESPONSE TO RM-1929 TREATMENT IN RECURRENT HEAD AND NECK SQUAMOUS CELL CARCINOMA PATIENTS

C Daniel De Magalhaes Filho*, Chung-Wein Lee, Nikolai Suslov, Jerry Fong, Miguel Garcia-Guzman, Rakuten Medical, San Diego, CA, USA

Background RM-1929 is an antibody-drug conjugate comprised of cetuximab covalently linked to the photoactivable dye, IRDye® 700DX (IR700). After systemic infusion of RM-1929, illumination of the tumor with 690 nm non-thermal red light activates the drug and results in targeted and rapid tumor necrosis. Previous preclinical data have shown that RM-1929 treatment triggers immunogenic cell death and activates the innate and adaptive immune response. A retrospective analysis of PD-L1 expression from the phase I/IIa clinical trial in patients with recurrent head and neck squamous cell carcinoma (rHNSCC) (NCT02422979) was conducted. The analysis explored correlations of PD-L1 expression, including combined proportion score (CPS) and tumor proportion score (TPS), with clinical outcomes such as response rate and overall survival.

Methods PD-L1 expression prior to RM-1929 treatment was assessed by immunohistochemistry in 18 out of 30 patients enrolled in Part II of the trial, based on sample availability. PD-L1 expression was evaluated using TPS and CPS. Responders were defined as patients that achieved complete response or partial response, and non-responders had either stable disease or progressive disease. Overall survival (OS) was analyzed using the Kaplan-Meier method.

Results Responders (n=10) had a TPS of 4.3±2.4 (mean ±SEM), which was substantially lower than in non-responders (n=8) with a TPS of 39.4±11.8. Similarly, CPS was lower in responders (8.6±2.3) compared to non-responders (50.0±13.5). The best target response rate for all patients included in this analysis was 56%. Patients with CPS>40 had a response rate of 76.9% (n=13) compared to 0% in patients with CPS>40 (n=5). This suggests that a CPS cut-off of 40 led to enrichment of the best target response rate. The median OS of patients with CPS>40 (13.0±2.8 months) was also higher than in patients with CPS>40 (3.1±0.8 months) and in all patients (12.0±2.9 months).

Conclusions These results suggest that rHNSCC patients with lower PD-L1 expression levels may be more responsive to RM-1929 treatment and CPS/TPS could potentially be predictive biomarkers in identifying patients with a higher probability of benefiting from this treatment. Given the limited number of patients in this analysis, additional clinical trials will be needed to validate PD-L1 expression as an effective predictive biomarker for RM-1929 treatment.

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Trial Registration NCT02422979

Ethics Approval The trial was approved by the following Institution Ethics Boards and IRB#: as listed: UCSF Institutional Review Board (#17-21904), Thomas Jefferson University, IRB (#16C.328), University of Oklahoma Health Sciences Center Institutional Review Board (#5723), University of Texas MD Anderson Cancer Center - Institutional Review Board (#IRB 2 IRB00002203), Quorum Review IRB (#30458/1), Rush University Medical Center Institutional Review Board (#1503601-IRB01), and Catholic Health Initiatives Institute for Research and Innovation (CIRI) Institutional Review Board (CHIRB) (# IRB00009715).

Consent N/A

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623 IMMUNO STATS: LEVERAGING PROTEIN ENGINEERING TO EXPAND AND TRACK ANTIGEN-SPECIFIC T CELLS IN VIVO

1Stad Zeigler, 2Andrew Woodham, 1Mengyan Li, 2Elia Zeyang, 2Stephen Kilibrath, 4Mohammad Rashidian, 1Kaitlyn O’Connor, 2Rodolfo Chaparro, 2Ronald Seidel, 2Maia Meynier, 2Ross Cheloha, 2Jason Dearing, 2Phaneendra Duddempudi, 4Alex Celiigil, 2Scott Garforth, 2Alan Packard, 2Harris Goldstein, 2Hidde Ploegh, 2Steven Almo*, 1Albert Einstein College of Medicine, Bronx, NY, USA; 2Boston Children’s Hospital, Boston, MA, USA; 3Massachusetts Institute of Technology, Cambridge, MA, USA; 4Dana Farber Cancer Institute, Boston, MA, USA; 5Cue Biopharma, Cambridge, MA, USA

Background Immunotherapies are highly promising and effective strategies for the treatment of cancer; however, continuing challenges persist, including 1) untargeted global immune modulation, resulting in serious side effects; 2) lack of therapeutics capable of in vivo expansion of tumor-specific T cells; 3) inability to visualize in vivo tumor-specific T cell responses; and 4) lack of flexible platforms to rapidly and efficiently explore new therapeutic strategies and immune-escape mechanisms. To address these challenges, we developed a novel class of precision biologics to treat cancer, autoimmunity diseases and infectious diseases. We describe a modular platform constructed around an Fc-based covalent pMHC dimer, referred to as synTac (artificial synapse for T cell activation; also termed ImmunoSTATs for Selective Targeting and Alteration of T cells), which selectively delivers different cargoes, including costimulatory, coinhibitory or cytokine signals and other modalities to primary T cells of defined specificity. The inherent modularity supports broad applications. Changing the encoded peptide enables targeting of different T cell specificities to address different diseases, while altering the cargo allows for evaluation of different co-modulatory mechanisms or the delivery of mechanistically informative probes.

Methods Sortase A-mediated enzymatic coupling supported site-specific and stoichiometric installation of positron emission tomography (PET)-active radiolabels on synTacs to visualize the in vivo localization of antigen-specific T cells. The NSG humanized mouse model allowed for the evaluation of synTac/ImmunoSTATs to drive the in vivo antigen-specific expansion of human CD8 T cells.

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 intrasplenically 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, synTac/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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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 cell redirector comprised of an affinity-enhanced TCR recognising 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 (MRAEs). These include vitiligo/skin hypopigmentation, leukotrichia, and hyperpigmentation and, collectively, are associated with better overall survival in uveal patients receiving tebentafusp (Orloff et al, AACR 2020). In this study, we dissected the mechanisms by which tebentafusp may induce MRAE and highlight the potential clinical significance.

Methods In vitro studies were conducted to assess the direct and indirect effects of tebentafusp on epidermal melanocytes from healthy donors. Expression of gp100 and the gp100:HLA*A02:01 target complex by melanocytes were quantified at the mRNA level and on the cell surface by confocal microscopy, respectively. Melanocytes co-cultured with PBMC and CMV-specific human CD8 T cells populating their spleens, respectively. In vivo administration of HIV- and CMV-specific synTacs/Immuno-STATs to immunodeficient mice intrasplenically 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, synTac/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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BISPECIFIC PERSONALIZED APATMER FOR THE TREATMENT OF SOLID TUMORS


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. Aummine’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 Aummine’s innovative platform, 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