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SAT0284 CD123+ PLASMACYTOID DENDRITIC CELLS (PDCS) FROM SYSTEMIC SCLEROSIS PATIENTS ARE SUSCEPTIBLE TO THE CYTOTOXIC ACTIVITY OF TAGRAXOFUSP, A CD123-TARGETED THERAPY

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Background: Tagraxofusp is a novel targeted therapy directed to the interleukin-3 receptor (CD123). Tagraxofusp is comprised of human IL-3 recombinantly fused to a truncated diphtheria toxin (DT) payload engineered such that IL-3 replaces the native DT receptor-binding domain. In this way, the IL-3 domain of tagraxofusp directs the cytotoxic DT payload to cells expressing CD123. Upon internalization, tagraxofusp irreversibly inhibits protein synthesis and induces apoptosis of the target cell. Tagraxofusp was recently approved by the FDA for the treatment of patients with blastic plasmacytoid dendritic cell neoplasm (BPDCN), a malignancy derived from the plasmacytoid dendritic cell (pDC) precursor. pDCs are immune cells that express CD123, secrete IFN- α , and play a role in inflammation and disease pathogenesis observed in systemic sclerosis (SSc) patients^{1,2}. Therapeutic depletion of pDCs or attenuation of pDC function may represent a novel approach to treating SSc patients.

Objectives: To assess the ability of tagraxofusp to selectively deplete pDCs from SSc patients *ex vivo*.

Methods: Patients fulfilled the 2013 ACR/EULAR classification criteria for SSc³. PBMCs from either SSc patients or healthy volunteers (HV) were prepared using Ficoll-Paque density gradient from fresh blood. pDCs were isolated from PBMCs as previously described and used to enrich the frequency of pDCs in an additional draw of PBMCs⁴. pDC-enriched PBMCs (3-6% pDCs) were cultured at 2×10^5 cells per well in the presence or absence of CpG-274 (0.5 μ M) to activate pDCs and then incubated with tagraxofusp (0.01-100 ng/ml, 0.17 pM-1.7 nM) at 37°C, 5% CO₂, and 95% humidity. After 24 h of culture, pDC survival was assessed by flow cytometry (CD14-, CD3- BDCA4+ CD123+), and supernatants were collected for cytokine quantification by a multiplexed Luminex assay. Changes in gene expression were measured by PCR on 10 μ g cDNA,

and calculated based on relative threshold cycle and expression of a ubiquitin housekeeping gene.

Results: Tagraxofusp was cytotoxic towards pDCs from both HV (n=5) and SSc donors (n=5) to a similar extent. The ED₅₀ of tagraxofusp in pDCs from HV and SSc was 4.3 and 3.2 ng/ml (74.4 and 55.4 pM), respectively; no effect was observed on B or T cells across the tagraxofusp dose range tested (Fig.1A). Tagraxofusp-mediated pDC depletion was further accompanied by a 68-fold reduction in secreted IFN- α and a 3-fold downregulation of GBP, a type 1 IFN-induced gene (Fig. 1B).

Conclusion: Tagraxofusp is a novel CD123-targeted therapy that is cytotoxic towards pDCs from SSc patients. These data present a novel approach of targeting pDCs in the treatment of SSc, and a clinical trial is under design.

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SAT0285 EVALUATION OF CHRONIC PAIN IN PATIENTS WITH SYSTEMIC SCLEROSIS COMPARED TO THOSE WITH CHRONIC HEADACHE AND RHEUMATOID ARTHRITIS

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Background: Systemic Sclerosis (SSc) is a chronic systemic disease frequently leading to disability and low quality of life. Chronic pain (CP), due to severe disease complications and internal organs involvement, is often underestimated. Based on available data around a 60-70% of patient with SSc suffer of chronic pain but we still lacking of fine tools to better evaluate it and follow up patients

Objectives: Evaluate pain in SSc patients, in terms of its intensity, sensory and affective components, the interference with physical and social activities, impact on quality of life and correlation with main SSc clinical manifestations.

Methods: From January 2013 to January 2018 we retrospectively evaluated 98 patients with a diagnosis of SSc [F/M=87/11; Limited/Diffuse SSc 63/35 anti-Scl70/ACA/ANA nucleolar positivity 45/39/14; mean age 55.6 ± 12.6 DS; mean disease duration 9.9 ± 7.6 DS] according to 2013 ACR/EULAR criteria; 47 patients with a diagnosis of chronic headache (CH) as defined by the International Classification for Headache Disorders, Third Edition beta version (ICHD-3 beta) criteria [F/M 37/10; mean age 52.6 ± 14.2 DS; mean disease duration: 7 ± 2 yrs DS] and 46 patients with Rheumatoid Arthritis [F/M 36/10, mean age 61 ± 13 , mean disease duration 10 ± 2 yrs, DS]. All patients fulfilled self-completing questionnaires for the evaluation of pain and quality of life: Visual Analogic Scale (VAS), Numeric Rating Scale (NRS), Short Form-McGill Pain Questionnaire (SF-MPQ), Brief Pain Inventory Score (BPI) e Health Assessment Questionnaire (HAQ).