CD13+ 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 and Highlights
- Tagraxofusp is FDA approved, and is commercially available in the U.S. for the treatment of patients with blastic plasmacytoid dendritic cell neoplasm (BPDCN), a malignancy derived from the plasmacytoid dendritic cell (pDC) precursor.
- 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.
- pDCs are immune cells that express CD123, secrete IFNα, and play a role in inflammation and disease pathogenesis observed in systemic sclerosis (SSc) and lupus patients.1,3
- Therapeutic depletion of pDCs or attenuation of pDC function, may represent a novel approach to treating SSc patients.

Tagraxofusp mechanism of action
- 2x10^6 pDC enriched PBMCs (3-6% pDCs) were cultured for 24hr with tagraxofusp (0.01-100 ng/ml), 0.17 pM-1.7 nM) in the presence or absence of CpG-274 (0.5 μM) for DC activation/maturation.
- pDC survival was assessed by flow cytometry (CD14+, CD3- BDCA4+ CD123+) and survival graphed against tagraxofusp concentration.
- Tagraxofusp was cytotoxic to pDCs from both HVs and SSc patients to a similar extent. ED50 of tagraxofusp in HVs and SSc patients was 4.3 and 3.2 ng/ml (74.4 and 55.4 μM) respectively.
- A 68-fold reduction in CpG-induced IFNα protein secretion was observed in pDC-enriched patient PBMCs cultured with tagraxofusp; this was accompanied by a 3-fold reduction in the expression of the type 1 IFN-induced gene, GBP.
- The effect of tagraxofusp on CpG-induced cytokine secretion by PBMCs from SSc patients was assessed by measuring cell culture supernatant by Luminex technology for IL-1α, IL-6, IL-8, IFNα, IFNγ IP-10, TNFα, MIP-1α/β, MCP1 and RANTES.

Conclusions and Next Steps
- CD123 expression on pDCs from HV and SSc patients is comparable.
- Tagraxofusp is cytotoxic against CD123+ pDCs from HVs and SSc patients.
- In SSc patients, pDC depletion by tagraxofusp was accompanied by a 68-fold reduction in CpG-induced IFNα protein secretion, and a 3-fold reduction in expression of the IFNα-induced gene, GBP.
- Tagraxofusp concentrations effective at eliminating inflammatory pDCs in this study were lower than peak plasma concentrations observed in BPDCN patients treated with the drug.
- These data present a potentially novel approach of targeting pDCs and inflammation in the treatment of SSc and warrant further investigation. A clinical trial is planned in autoimmune disease.

Flow cytometry analysis of CD123 expression on pDCs of HVs and SSc patients
- CD123 expression on pDCs from healthy volunteers was compared to SSc patients by flow cytometry. MFI data shows a similar level of expression on samples tested.

References
5. Sun, Q. Blood 2008; 112 (8): 3103-11
7. Sun, Q. Blood 2008; 112 (8): 3103-11