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Blocking IL1RAP function counteracts pathways associated with human SSc and reduces skin and lung fibrosis in a sclerodermatous GvHD model

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INTRODUCTION

The IL1 receptor accessory protein (IL1RAP) is a coreceptor required for signaling from the IL1, IL33, and IL36 receptors. We have developed a fully humanized IgG1-LALA antibody (CAN10) that binds IL1RAP with high affinity and disrupts IL1α, IL1β, IL33, IL36α, IL36β and IL36γ signaling, without inducing ADCC. CAN10 is currently undergoing the final stages of preclinical development in preparation for clinical studies in systemic sclerosis (SSc) and myocarditis.

IL1, IL33 and IL36 affect several cell types known to be important for the pathophysiology of SSc e.g., fibroblasts, endothelial cells and immune cells, and could be a highly relevant target for severe multiorgan diseases involving both inflammation and fibrosis. The present study aims to describe the potential of therapeutic IL1RAP blockade by CAN10 in a mouse model of SSc, sclerodermatous graft vs host disease (scIGvHD) using a surrogate antibody with a similar functional profile (mCAN10).

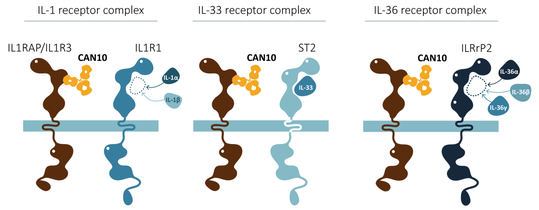

Figure 1. CAN10 binds IL1RAP and blocks IL1/33/36 signaling.
CAN10 binds to IL1RAP and blocks association to the IL1 receptor (IL1R1), the IL33 receptor (ST2) and the IL36 receptor (ILRrP2). This results in disrupted IL1α, IL1β, IL33, IL36α, IL36β and IL36γ signaling.

STUDY OBJECTIVES

- To study the potency and benefit of IL1RAP-blockade by the antibody mCAN10 as an anti-inflammatory and anti-fibrotic strategy to treat established disease in a mouse model of SSc (sclerodermatous chronic graft vs host disease model (cGvHD))
- To study the expression of genes related to IL1RAP signaling in skin from SSc patients compared to healthy individuals

RESULTS

Genes related to IL1RAP signaling are upregulated in skin from SSc subjects

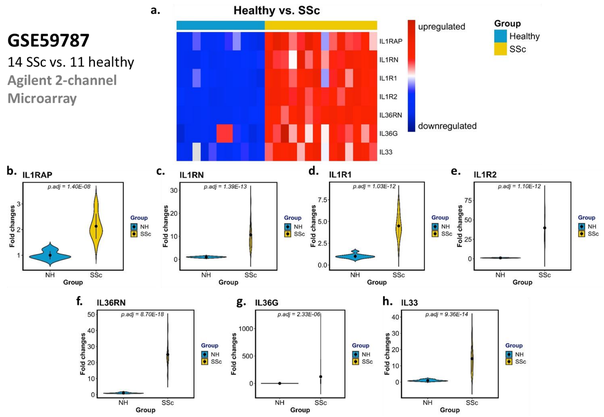

Figure 2. IL1RAP and the IL1/33/36 pathways are upregulated in SSc patient skin
IL1RAP, IL1RN, IL1R1, IL1R2, IL36RN, IL36G and IL33 were upregulated in skin from patients with SSc compared to healthy individuals, indicating that targeting IL1RAP could be a valuable treatment strategy in SSc. ST2, IL36R, IL1α, and IL1β were not detectable. NH, healthy; SSc, systemic sclerosis

Study design and body weight in sclerodermatous cGvHD

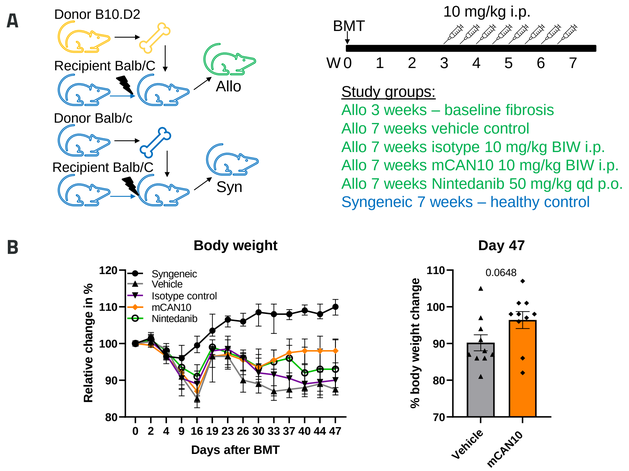

Figure 3. Study outline and treatment schedule in cGvHD
A) Balb/C mice received splenocytes and bone marrow transfer (BMT) from either Balb/C mice (syngeneic controls) or B10.D2 mice (allogeneic). Approximately 2 weeks after BMT, leukocytes infiltrate the tissue and stimulate resident fibroblasts to release large amounts of extracellular matrix proteins. One week later, cGVHD mice develop pulmonary and dermal fibrosis. Mice receiving allogeneic BMT were treated i.p. with vehicle (PBS), mCAN10 or isotype control twice a week or with Nintedanib p.o. daily. Mice were treated in a therapeutic setting starting at day 21 after BMT, *i.e.* when fibrosis was established. Body weight change is shown in B). Mice treated with mCAN10 (orange line and column) showed a tendency to a reduced weight loss compared to control or Nintedanib treated mice.

mCAN10 treatment decreases fibrosis in both skin and lung of cGvHD mice

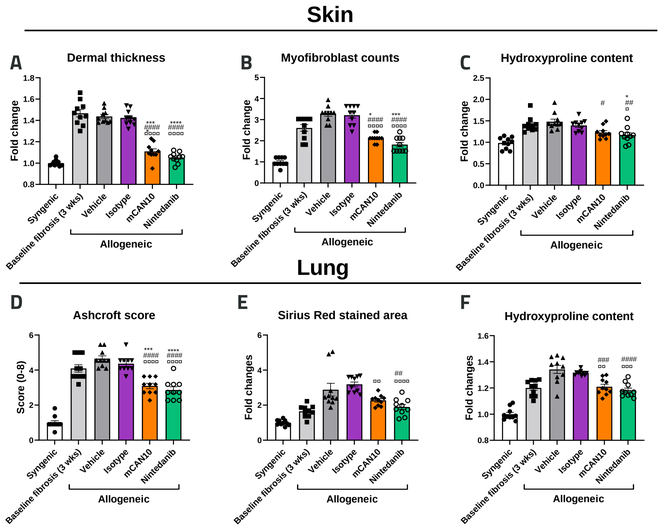

Figure 4. mCAN10 treatment decreases both skin and lung fibrosis in the cGvHD mouse model
mCAN10 treatment decreased; A) dermal thickness, B) skin myofibroblast counts, C) skin collagen content, D) Lung ashcroft score (0-8) E) Sirius Red staining in lung (collagen percentage) and F) lung collagen content, after allogeneic BMT in the cGvHD mouse model. mCAN10 also significantly decreased dermal thickness, myofibroblast counts in skin and Ashcroft score in the lung compared to the 3 wks baseline fibrosis group, indicating that mCAN10 can reverse skin fibrosis and the lung pathology developing in cGvHD mice. The fold change was calculated by comparing values from healthy mice receiving syngeneic BMT and thereby not developing cGvHD.

mCAN10 treatment affects several disease-related genes, in cGvHD mice, that are also dysregulated in SSc patients

Figure 5. mCAN10 treatment normalizes the global gene expression profile in skin from cGvHD mice and targets key SSc genes also present in the human disease. RNAseq gene expression analyses of skin biopsies from mice receiving syngeneic or allogeneic BMT revealed 2308 DEGs, 1023 of which were up- and 1285 of which were down-regulated (p-value ≤ 0.05 and |log2FC| ≥ 1.5) A) Functional evaluation using g:Profiler and GSEA demonstrated normalization of processes and pathways related to inflammation and fibrosis with mCAN10 vs allo. B) Heatmap of DEGs show substantial differences between mice receiving syngeneic or allogeneic BMT, while treatment of allogeneic BMT mice with mCAN10 normalized the gene expression profile. C) A comparison of the gene expression profile in skin between allogeneic BMT SSc mice and SSc patients (GSE130955 from PRESS cohort) revealed 449 genes that were differentially expressed in both the mouse disease model and the human disease. Interestingly, mCAN10 treatment affected 177 of these shared genes (39%).

SUMMARY

- Skin from individuals with SSc display upregulation of IL1RAP-related genes
- IL1RAP-blockade by mCAN10 counteracts both skin and lung inflammation and fibrosis in a mouse model of SSc
- IL1RAP-blockade normalizes the global gene expression profile in skin and affects several key SSc genes that are deregulated in human SSc skin
- These studies highlight the potential of CAN10 to treat inflammatory and fibrotic diseases such as SSc

References: *Wei et al., Front. Immunol. 2019; Cho et al., Fron Immunol. 2018; Distler et al., Arthritis and Reumatology 2010*

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