ACR Convergence
Where Rheumatology Meets
#ACR22

Blocking IL-1, IL-33 and IL-36 Signaling with the Anti-IL1RAP Antibody mCAN10 Ameliorates Inflammation and Fibrosis in Preclinical Models of Systemic Sclerosis

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Disclosures

I have the following relevant financial relationship(s) to disclose:

Shareholder: Cantargia AB

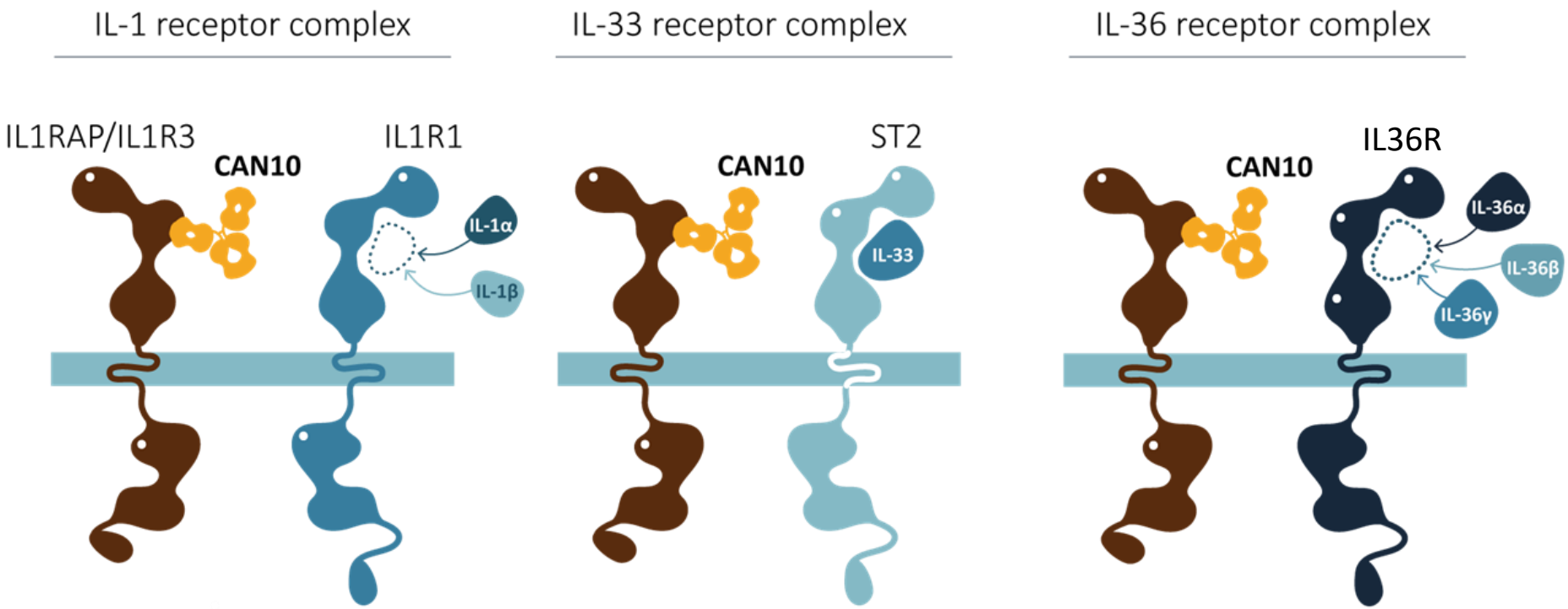
Employee: Cantargia AB

Patent: Coinventor of patent covering the anti-IL1RAP Ab CAN10, Cantargia AB

SR, PS, and DL are employees and shareholders of Cantargia AB. SR and DL are coinventors of the anti-IL1RAP Ab CAN10 patent

JHWD has consultancy relationships with AbbVie, Active Biotech, Anamar, ARXX, AstraZeneca, Bayer Pharma, Boehringer Ingelheim, Celgene, Galapagos, GSK, Inventiva, Janssen, Novartis, Pfizer, and UCB. JHWD has received research funding from Anamar, ARXX, BMS, Bayer Pharma, Boehringer Ingelheim, Cantargia, Celgene, CSL Behring, Galapagos, GSK, Inventiva, Kiniksa, Sanofi-Aventis, RedX, UCB. JHWD is stock owner of 4D Science

CAN10 – a humanized monoclonal antibody blocking IL1RAP signaling



IL1RAP blockade by CAN10 for diseases involving multiple IL1RAP-dependent pathways

IL1RAP is involved in both inflammation and fibrosis

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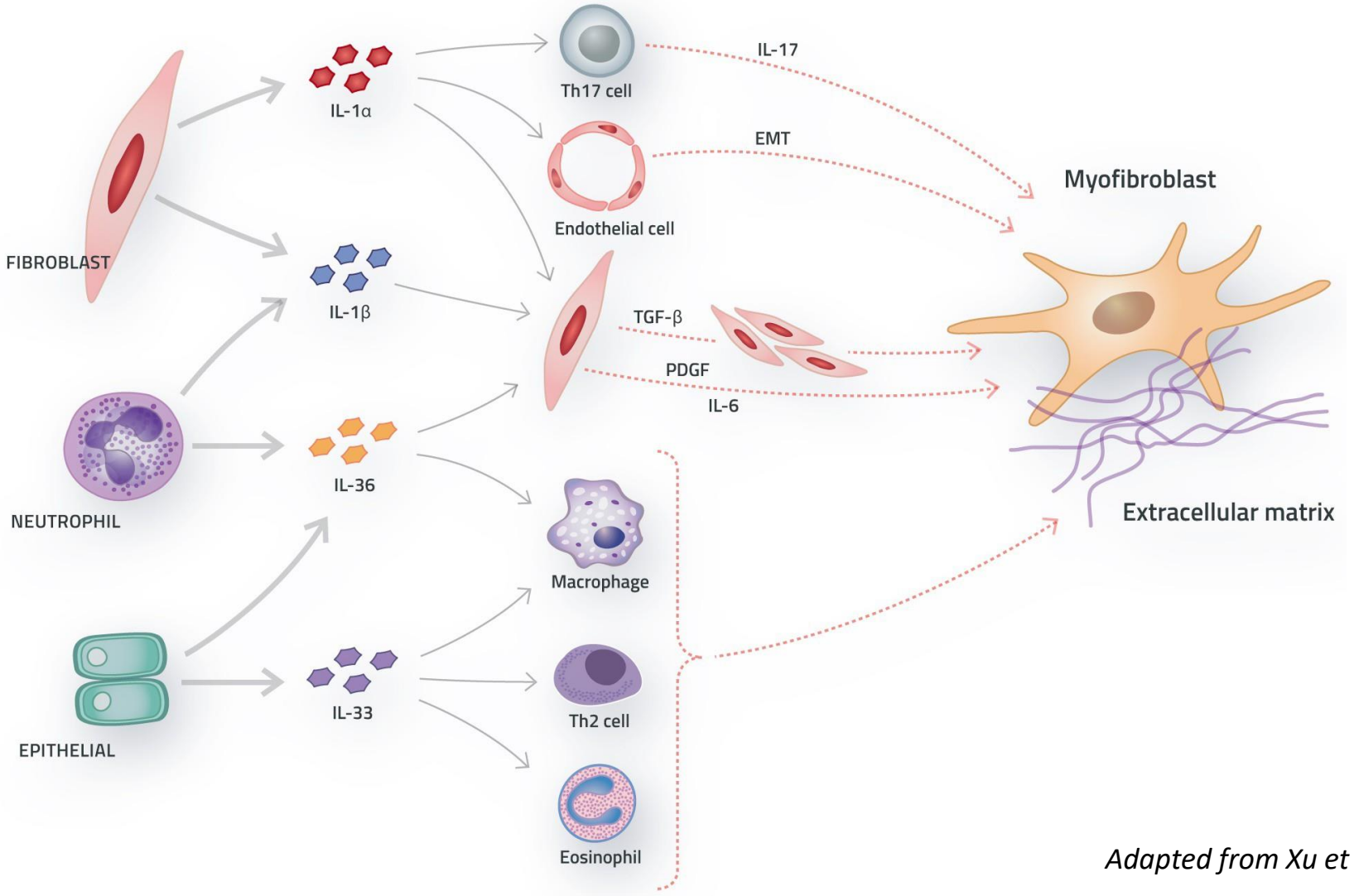
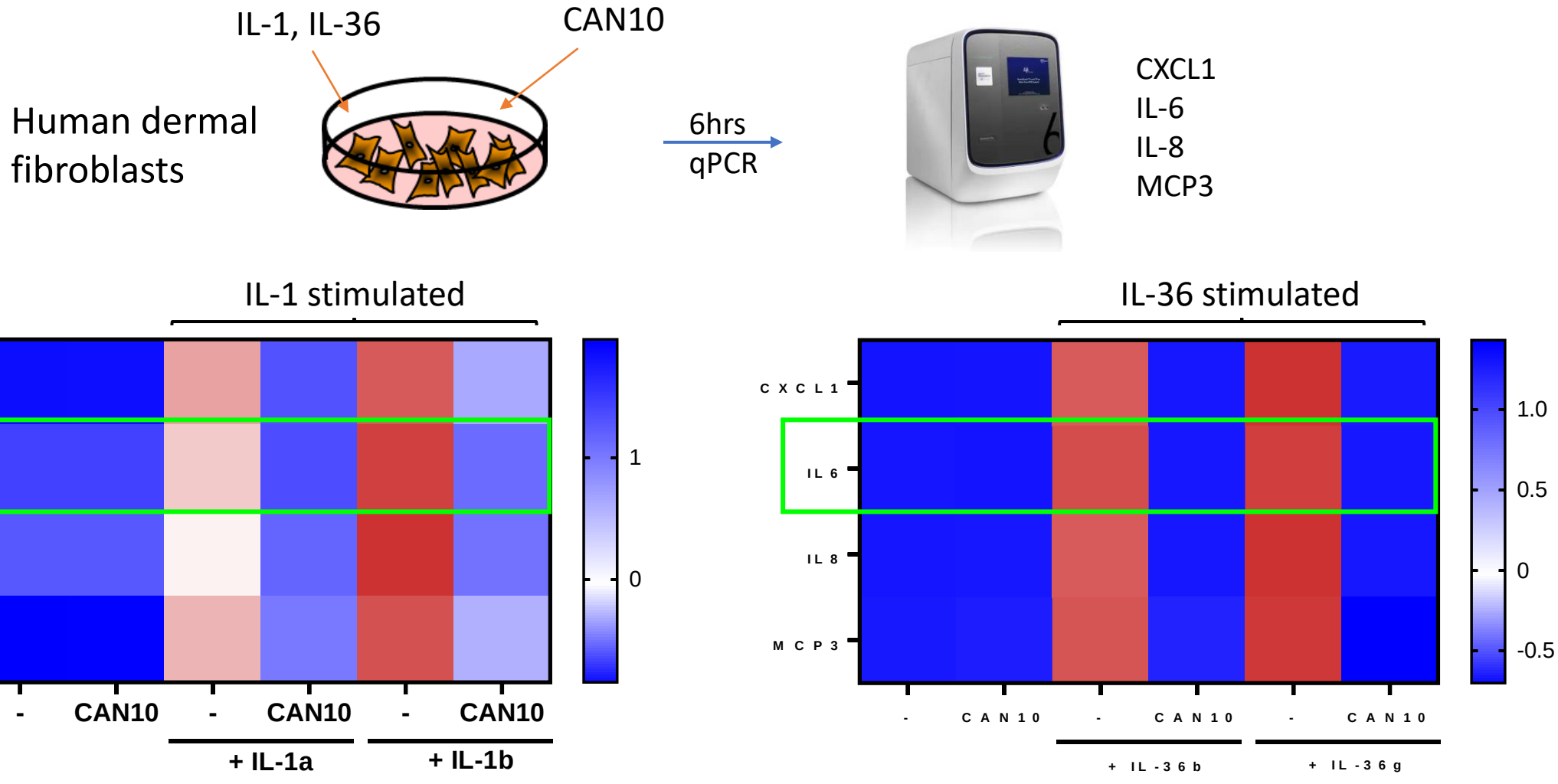


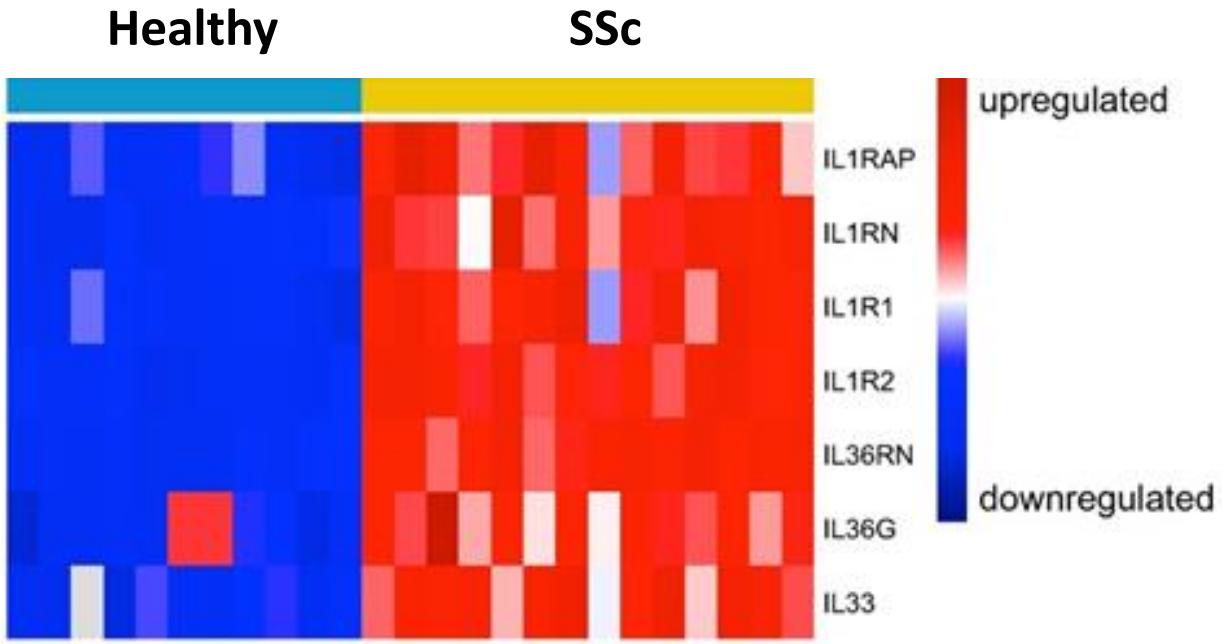
Adapted from Xu et al., Front. Immunol. 2019

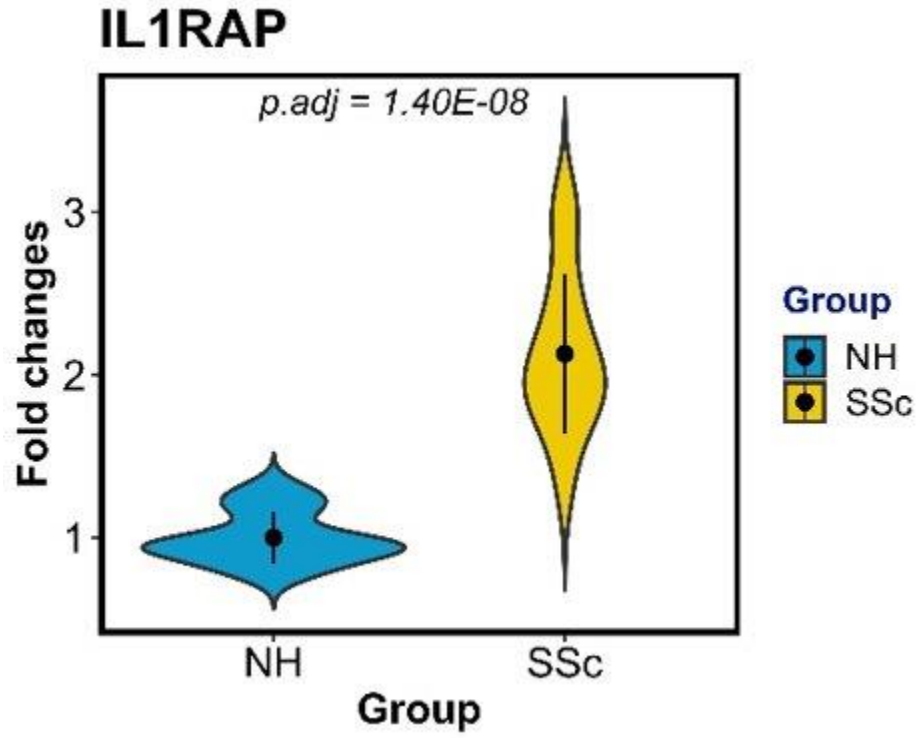
CAN10 blocks human dermal fibroblast activation by IL-1 and IL-36



IL1RAP is expressed in SSc skin

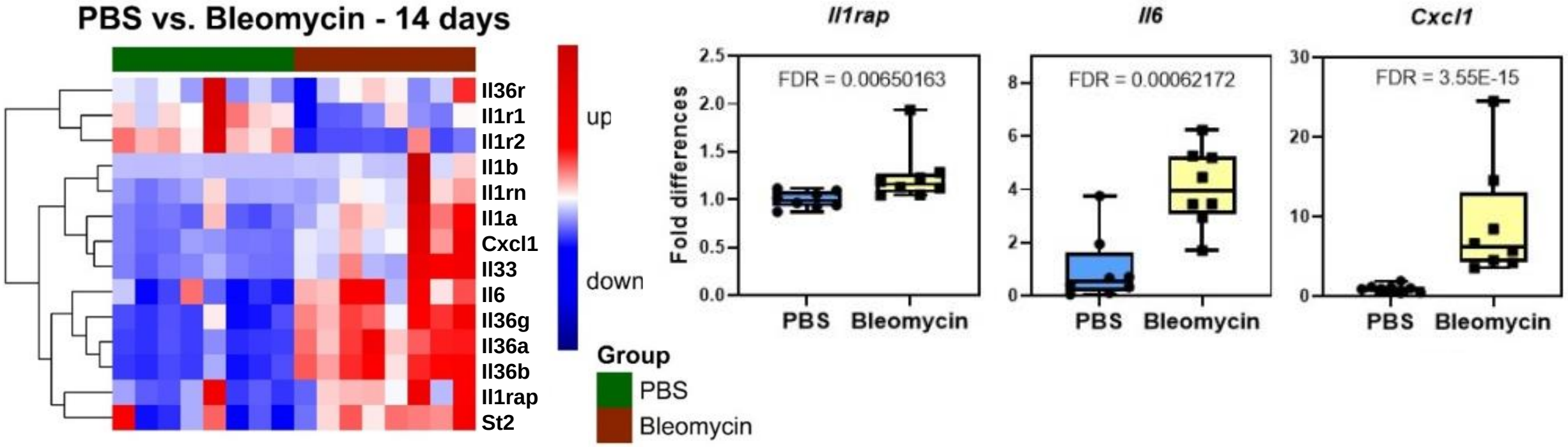
2 publicly available human SSc cohorts show differential expression of IL1RAP and associated genes in SSc skin





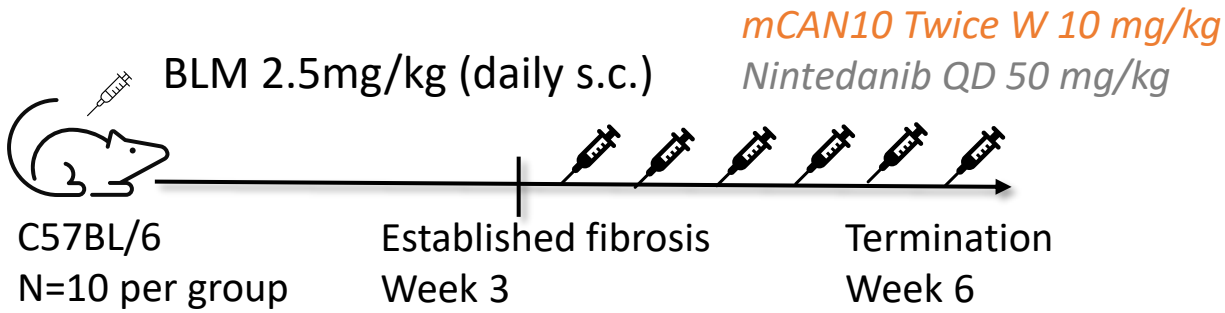
Mahoney et al. 2015 GSE59787
Skaug et al. Ann Rheum Dis 2020. GSE130955

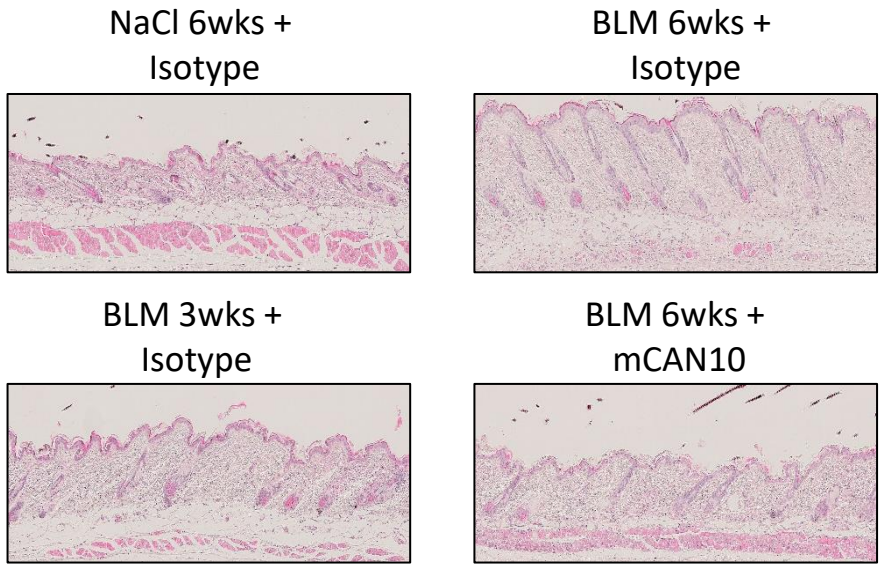
Bleomycin induces IL1RAP and related genes in mouse skin

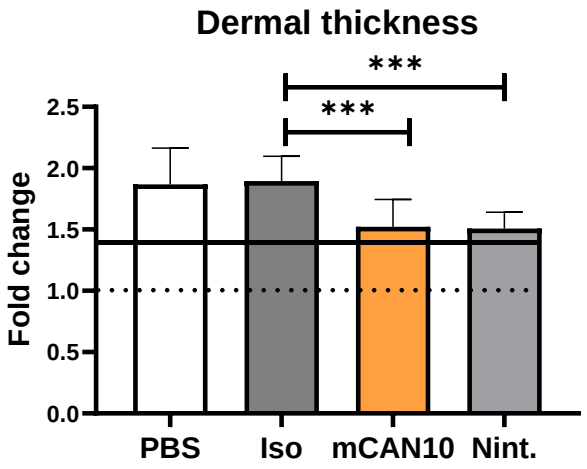


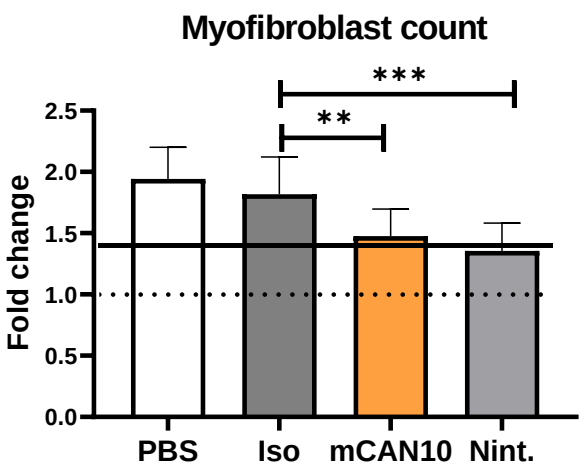
Decato et al. 2022, GSE132869

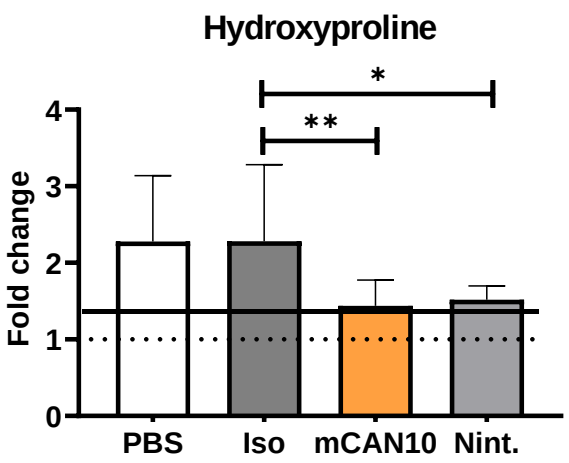
IL1RAP-blockade inhibits bleomycin-induced skin fibrosis











Baseline fibrosis at 3 weeks

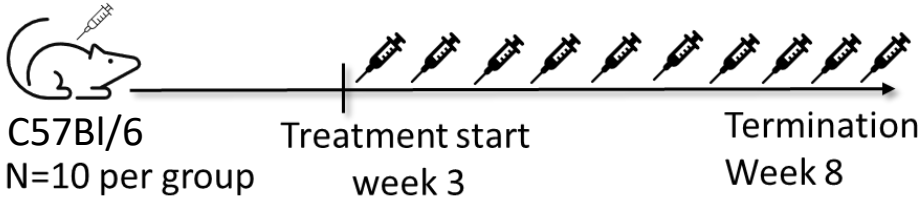
No BLM control (no fibrosis)

Therapeutic treatment with mCAN10 in two additional experimental SSc models

Mouse model:	BLM	Topo	cGvHD
Skin fibrosis	+	+	+
Lung fibrosis		+	+
Topo autoantibodies		+	
Resemble severe patients		(+)	+

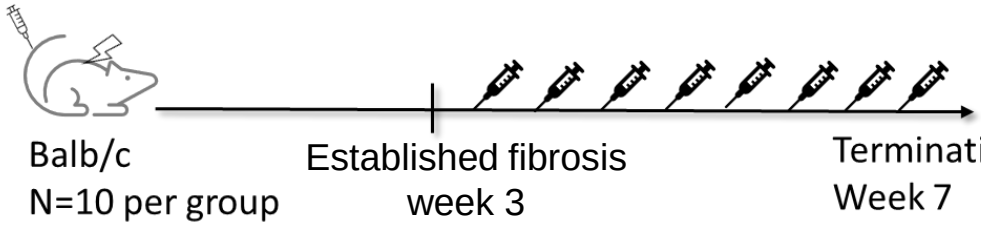
Topo I

Topoisomerase I 500 U/ml
in CFA (every other week)



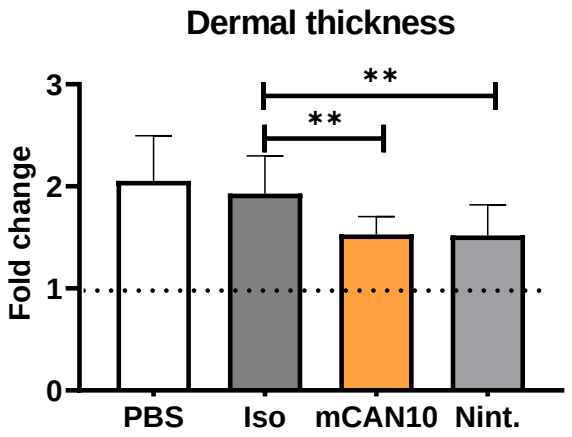
cGvHD

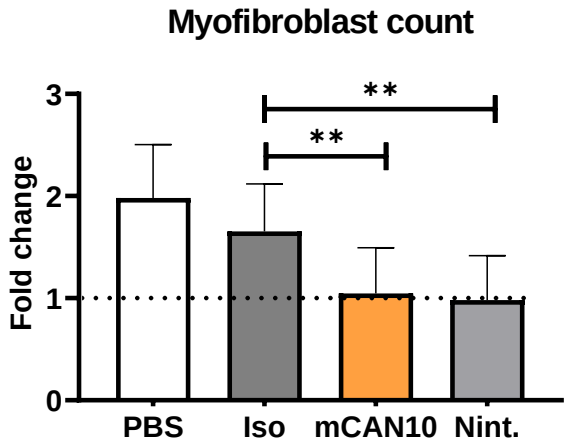
2 million bone marrow cells
+ 5 million splenocytes

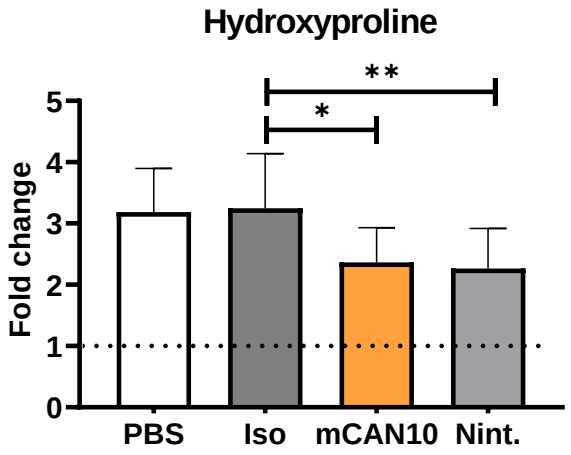


Therapeutic treatment with mCAN10 reduces Topo I and cGvHD skin fibrosis

Topo I

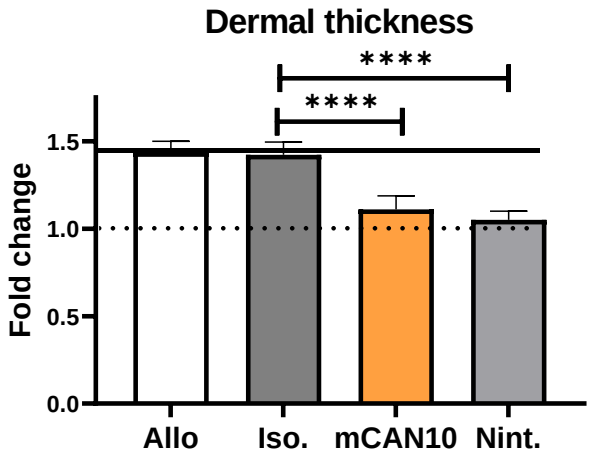


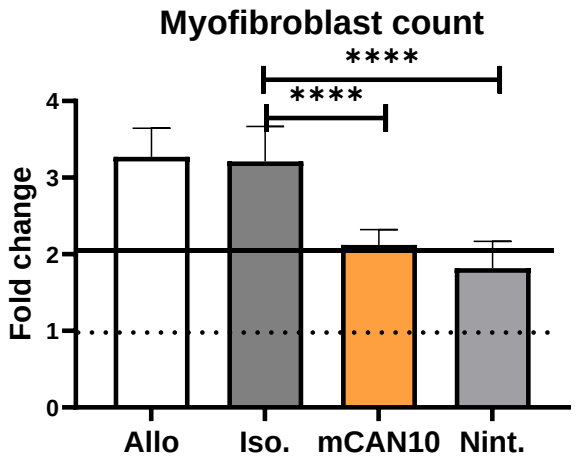


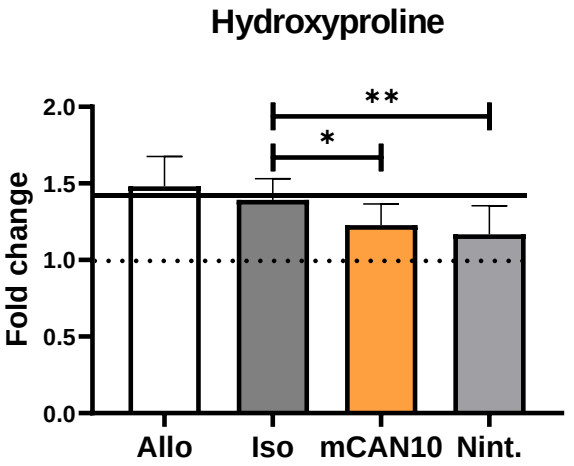


..... No fibrosis control (CFA/NaCl)

cGvHD



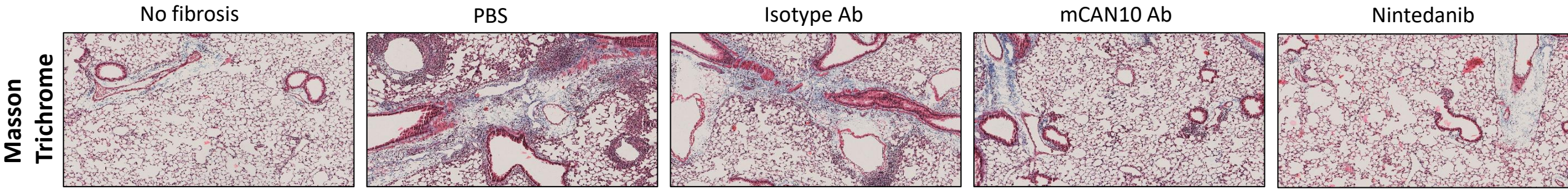




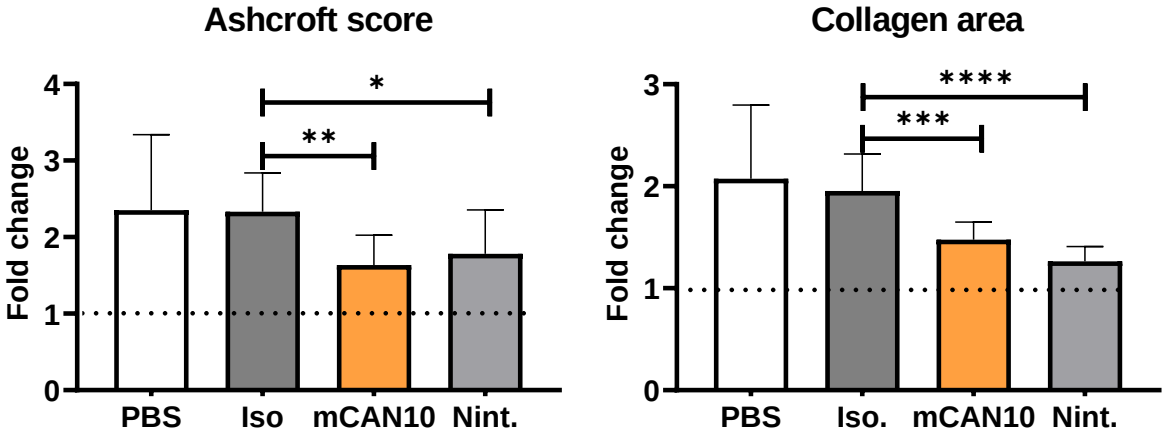
——— Baseline fibrosis at 3 weeks

..... No fibrosis control (syngeneic transfer)

...and lung fibrosis in the same models

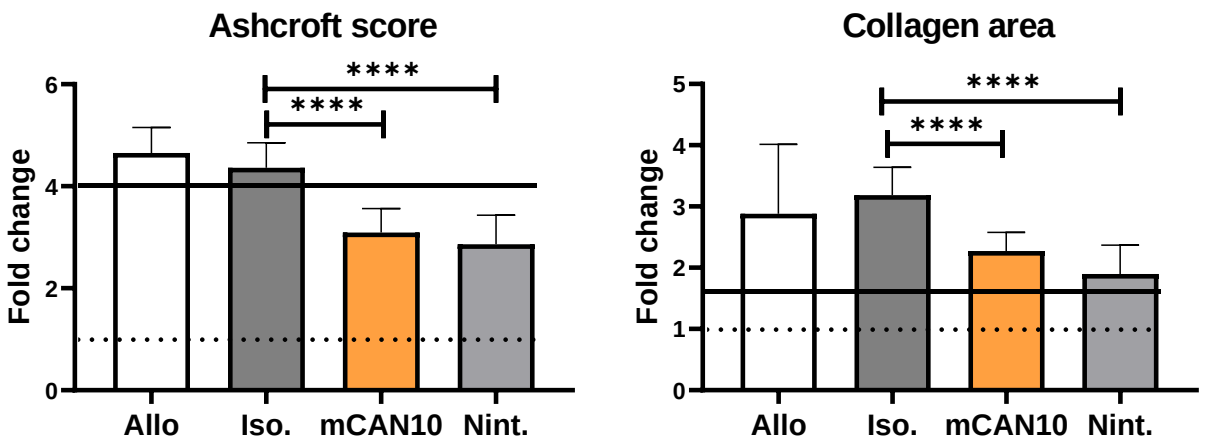


Topo model



No fibrosis (NaCl/CFA)

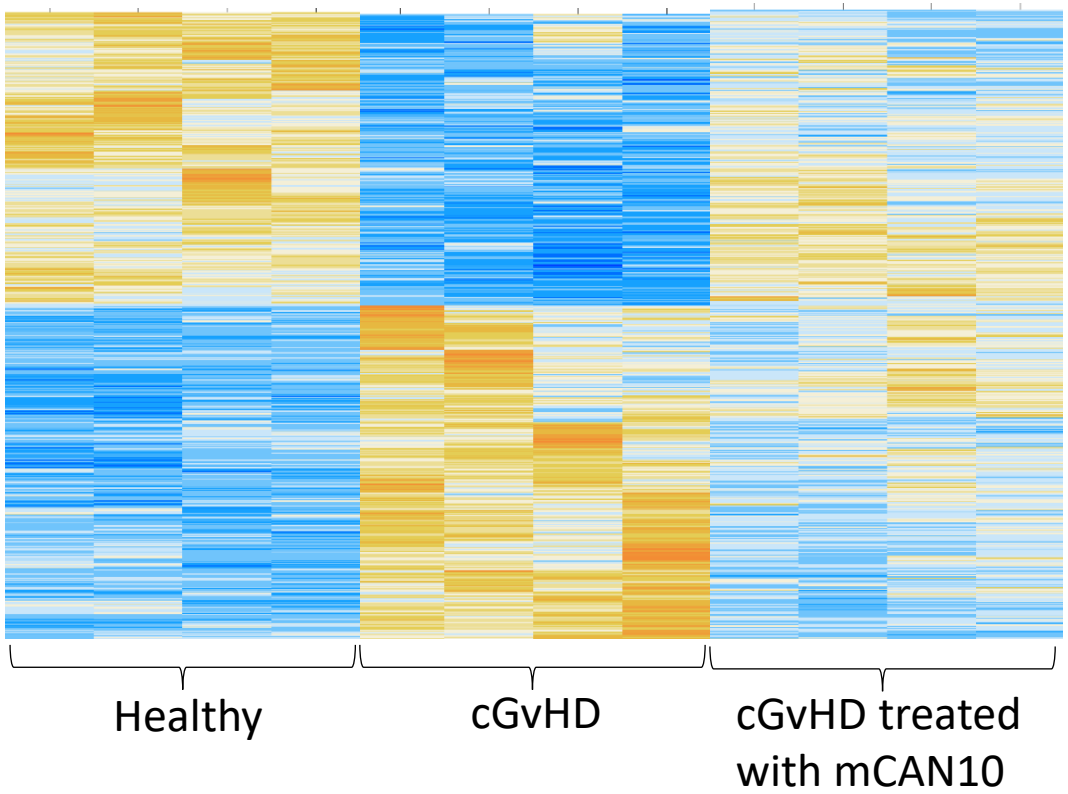
cGvHD model



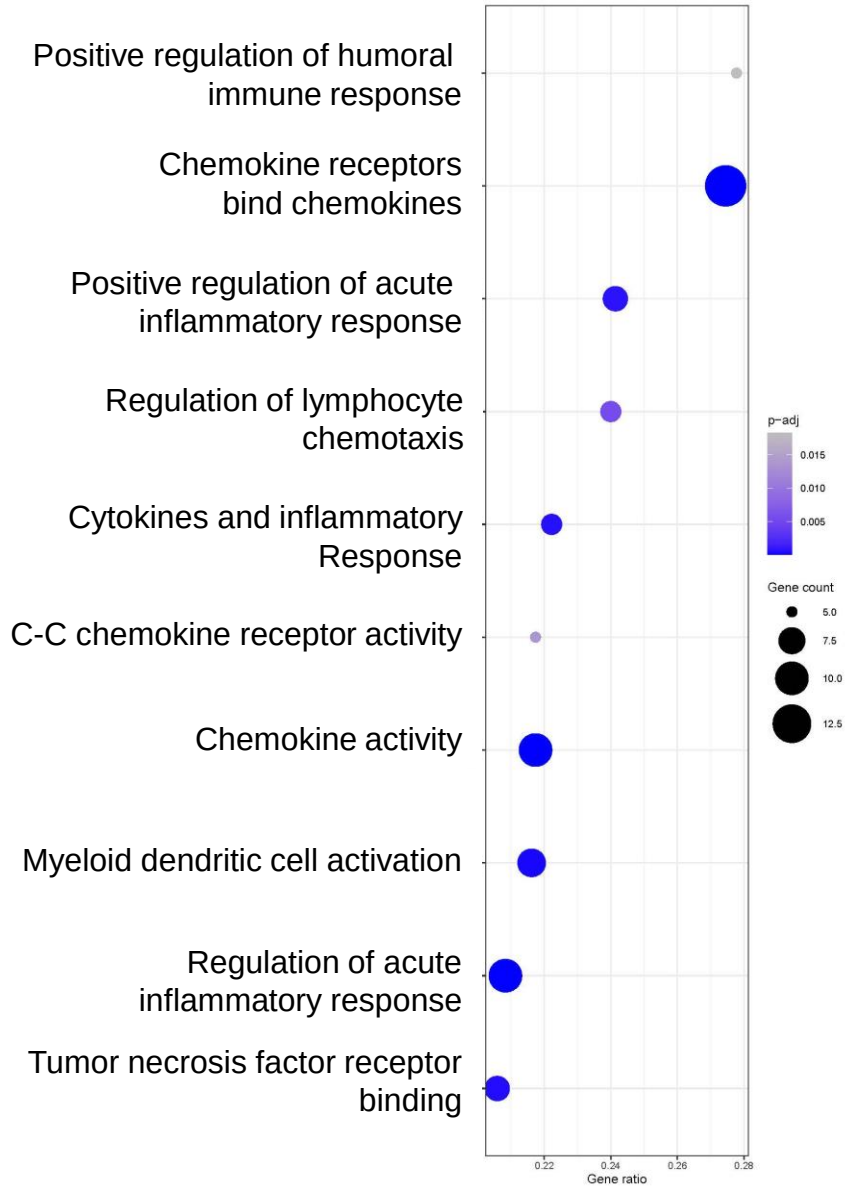
Baseline fibrosis at 3 weeks

No fibrosis (syngeneic transfer)

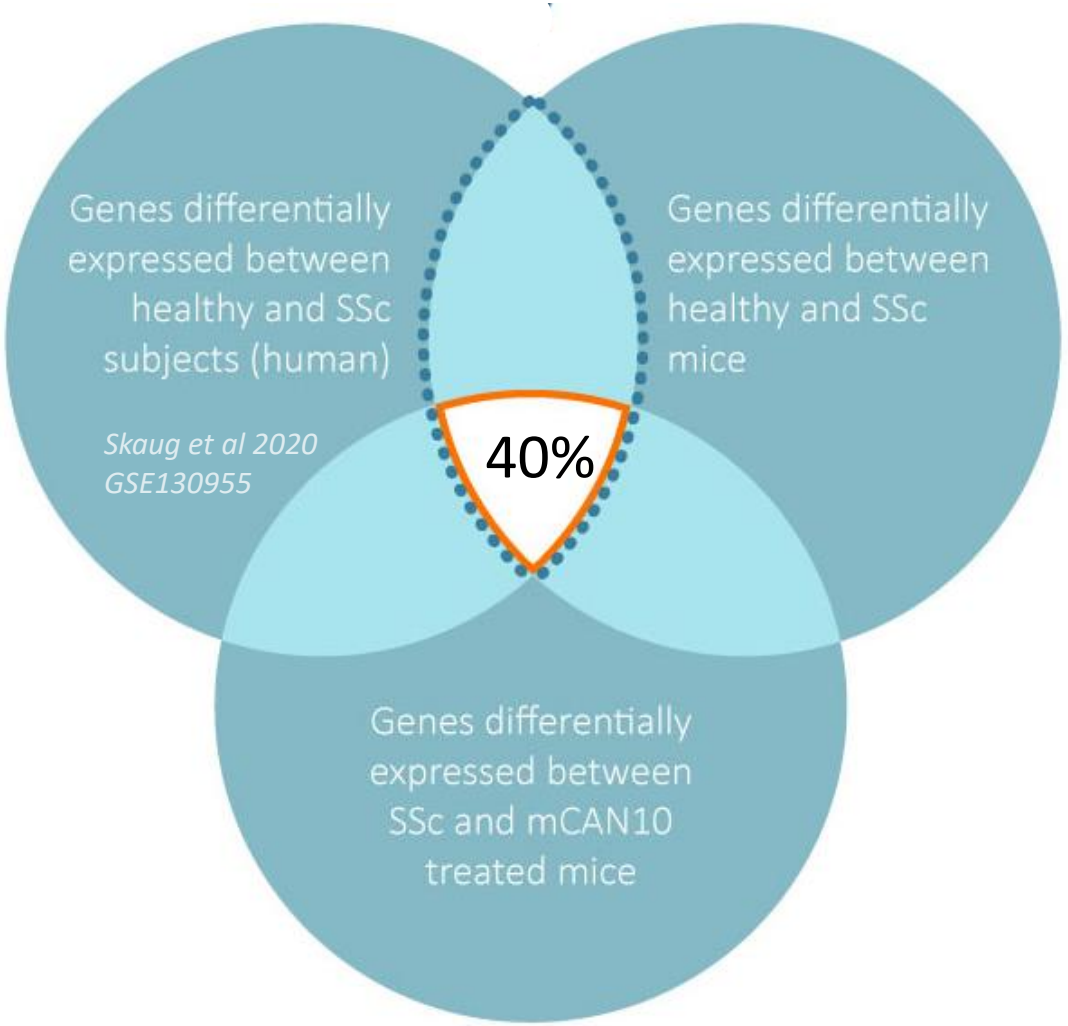
mCAN10 resets gene expression in cGvHD skin



VCAM1
ICAM1
IL-6
CXCL9
CCL5 (RANTES)
MCP3 (CCL7)
CCL1
CCL3 (MIP-1a)
LOX
…



Generation of a molecular fingerprint of CAN10 treatment



Differentially expressed genes in human systemic sclerosis skin were compared to differentially expressed genes in the scGvHD model

↓

449 genes were commonly deregulated in the mouse model and the human disease, CAN10 treatment affected 40% of these genes

↓

Machine learning identified a molecular fingerprint of CAN10 treatment that is being further investigated in translational studies

IL1RAP is a novel and promising target in treatment of SSc

- IL1RAP is required for signaling through the IL-1, IL-33 and IL-36 receptors
- IL1RAP and the IL-1/-33/-36 signaling systems have multiple roles in inflammation and fibrosis
- IL1RAP and related genes are upregulated in skin of SSc patients
- Therapeutic blockade of IL1RAP in 3 models of SSc show strong anti-fibrotic effects in both skin and lung
- IL1RAP blockade resets skin gene expression in a severe model of SSc, including several genes that are also deregulated in the human disease
- A gene signature of CAN10 treatment response is under evaluation in human SSc samples

- *CAN10 will enter phase 1 clinical trials next year*

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