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Combined blockade of IL-1, IL-33 and IL-36 signaling by targeting IL1RAP to treat inflammatory skin diseases

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Introduction

IL-1 receptor accessory protein (IL1RAP) is a coreceptor required for signaling of the IL-1, IL-33, and IL-36 receptors. We have developed a fully humanized IgG1-LALA antibody (CAN10) that binds IL1RAP with high affinity (Kd=167 pM) and disrupts IL-1 (α/β), IL-33 and IL-36 (α/β/γ) signaling, without inducing ADCC.

CAN10 is currently in phase 1 clinical development in healthy volunteers and subjects with psoriasis (NCT06143371). Here, we investigate the potential of targeting IL1RAP in preclinical models of skin inflammation to strengthen the scientific rationale for clinical development of CAN10 in inflammatory skin diseases with involvement of IL-1, IL-33 and IL-36, such as hidradenitis suppurativa (HS) and psoriasis.

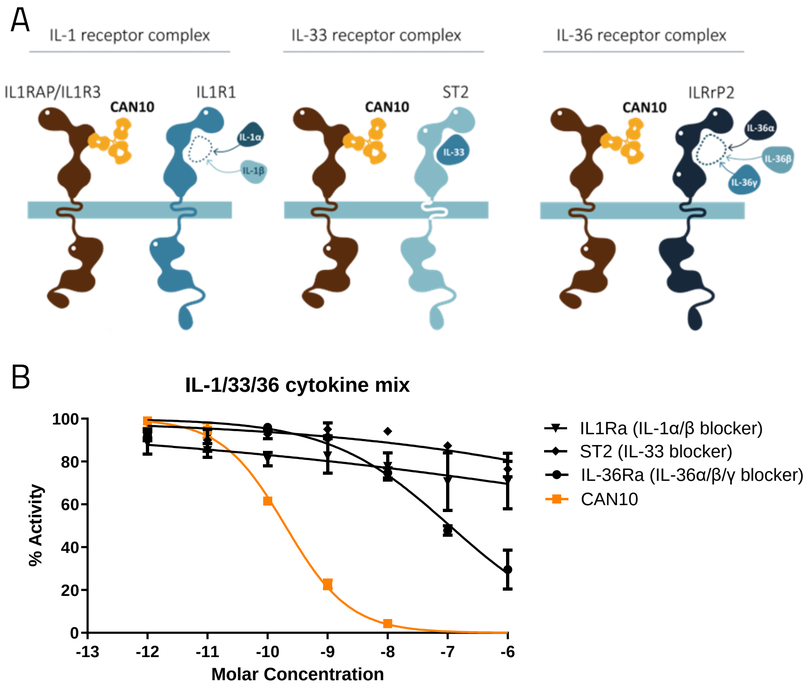

Figure 1. CAN10 targets IL1RAP and blocks IL-1/33/36 signaling.
A) IL1RAP associates with IL1R1, ST2 (IL-33R, IL1RL1) or IL1Rrp2 (IL-36R, IL1RL2) to allow for IL-1α/IL-1β, IL-33 and IL-36α/β/γ signaling. **B)** Signaling inhibition by CAN10 or the natural antagonists IL1Ra, sST2, IL36Ra in HEK-Blue cells stimulated with all six cytokines.

Study Objectives

- To study the potency and benefit of IL1RAP-blockade as an anti-inflammatory strategy
- To study the effect of blocking IL1RAP in inflammatory skin conditions
- To study the expression of IL1RAP in human inflammatory skin conditions

Results

IL1RAP blockade has potent anti-inflammatory properties in vivo that is qualitatively different from IL-1 blockade

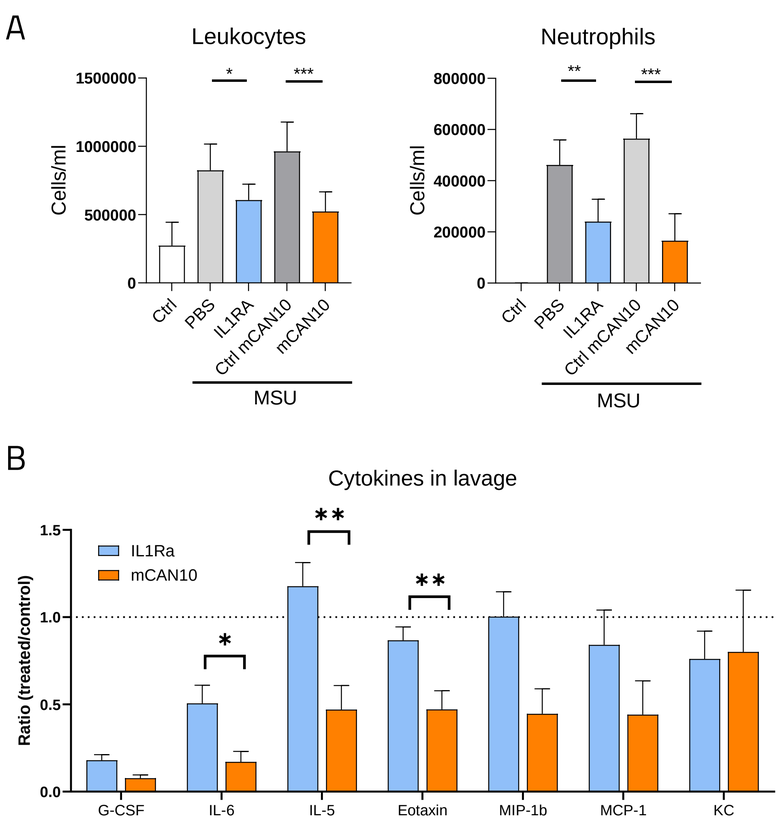

Figure 2. IL1RAP blockade decreased inflammation in monosodium urate crystal (MSU) induced acute peritonitis.
MSU was given i.p. at 0 hours and mice were terminated after 6 hours. mCAN10, an anti-mouse IL1RAP surrogate of CAN10 (20 mg/kg) or equimolar concentration of IL1RA (IL-1 receptor antagonist, blocking IL-1α and IL-1β, 2.3 mg/kg) were given i.p 1 hour prior to MSU. Infiltrating cells **(A)** and cytokines **(B)** were measured in the peritoneal lavage. *p<0.05, **p<0.01, ***p<0.005.

IL1RAP inhibition reduces skin and joint inflammation as well as systemic IL-17 levels

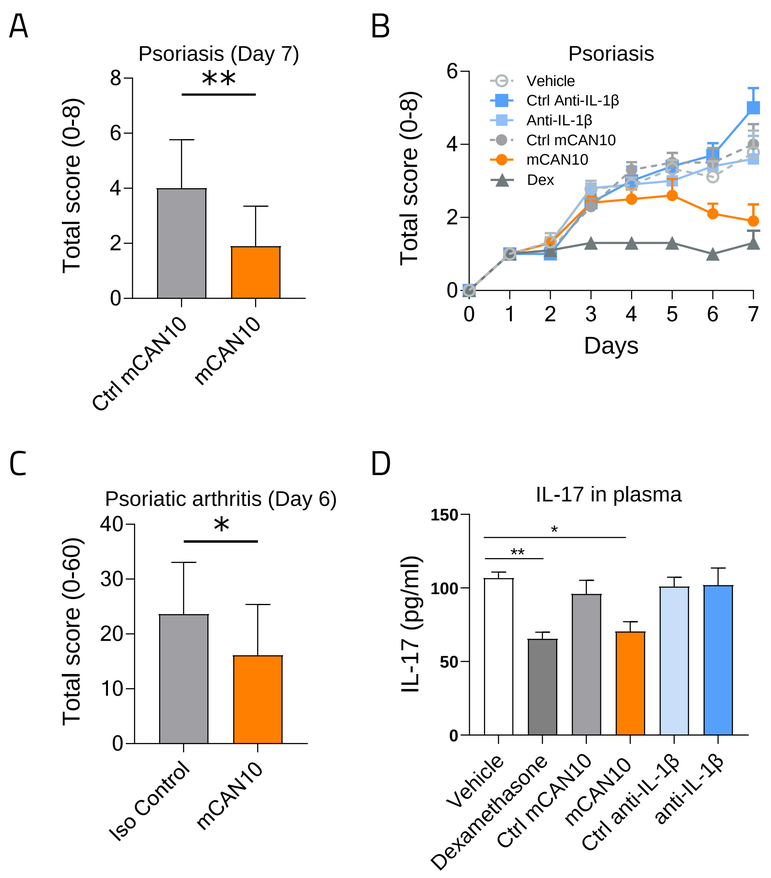

Figure 3. mCAN10 decreases inflammation in psoriasis and psoriatic arthritis while IL-1β blockade does not. A-B) Imiquimod was administered daily to the back skin and mice were scored for scaling and skin erythema. mCAN10 or anti-IL-1β mAbs were administered days 0, 3, 5 and daily dexamethasone was used as positive control. **C-D)** Mannan was injected i.p. and arthritis was scored in the paws. Blood samples were taken at termination and IL-17 levels were measured in plasma.

IL1RAP is upregulated on fibroblasts, endothelial cells and immune cells in inflammatory skin

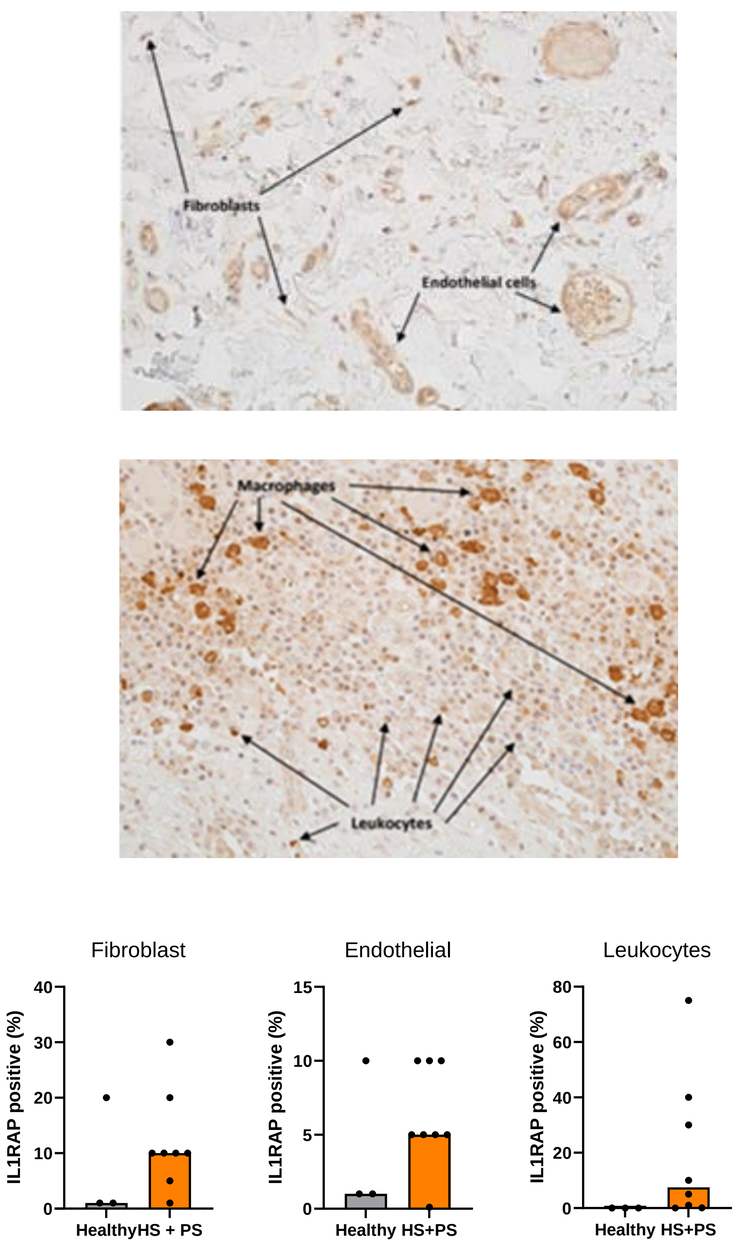

Figure 4. IL1RAP is upregulated in inflammatory skin conditions such as hidradenitis suppurativa and psoriasis.
IL1RAP levels in skin were determined by immunohistochemistry. IL1RAP was shown to be expressed on fibroblasts, endothelial cells, and leukocytes, and present at higher levels in inflammatory (HS and PS) skin compared to healthy skin. HS; hidradenitis suppurativa, PS; psoriasis

IL1RAP blockade blocks inflammatory signaling in human skin fibroblasts and endothelial cells

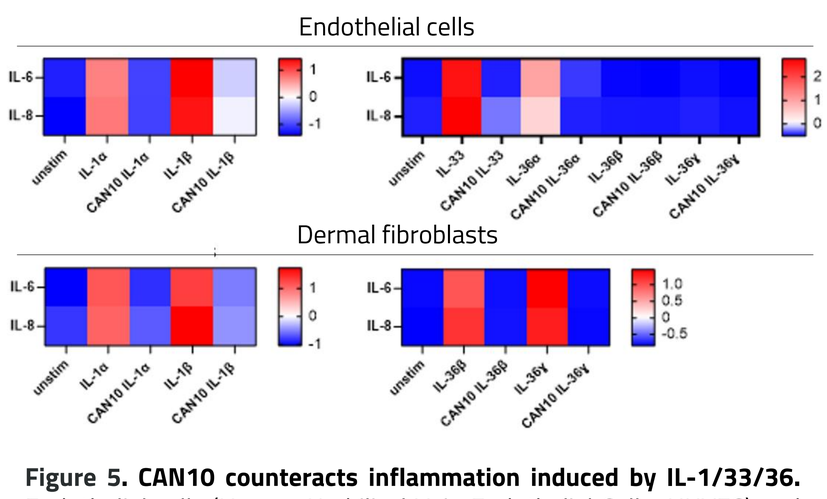

Figure 5. CAN10 counteracts inflammation induced by IL-1/33/36.
Endothelial cells (Human Umbilical Vein Endothelial Cells; HUVEC) and human dermal fibroblasts were treated with isotype or CAN10 and stimulated with IL-1, IL-33 or IL-36 *in vitro.* Dermal fibroblast did not show any activation of IL-6/IL-8 by IL-33, and HUVECs displayed low response to IL-36 stimuli. Heat maps are presented with Z-score.

IL1RAP blockade reduces IL-1/33/36 induced fibrosis by dermal fibroblasts

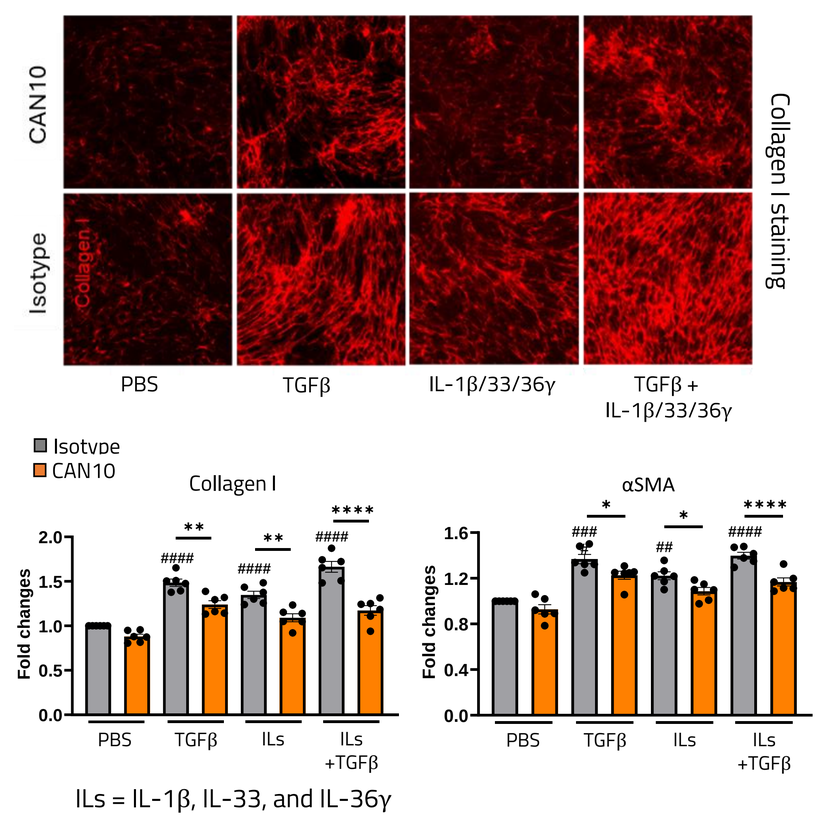

Figure 6. CAN10 counteracts fibrosis induced by IL-1/33/36.
Fibroblasts were isolated from skin of patients with systemic sclerosis (SSc) and treated with IL-1, IL-33 and IL-36 (ILs) *ex vivo*. Interleukin stimulation induce collagen I deposition and αSMA expression in SSc fibroblasts, which can be further enhanced by TGFβ.
# indicates differences of cytokine vs PBS stimulated fibroblasts. * indicates differences of fibroblasts treated with the CAN10 antibody and fibroblasts treated with isotype, at the same stimulus. #/* <0.05; ##/** <0.01; ###/*** <0.001; ####/**** <0.0001.

Summary

- CAN10 targets IL1RAP and blocks IL-1(α/β), IL-33 and IL-36(α/β/γ) signaling
- Blocking IL1RAP is a potent strategy to inhibit inflammation that is qualitatively different from IL-1 blockade.
- Blocking IL1RAP in mouse models of skin and joint inflammation reduces tissue inflammation and systemic IL-17 levels
- Skin from patients with inflammatory skin diseases have increased IL1RAP expression on immune cells, fibroblasts and endothelial cells, which respond to IL-1, IL-33 and/or IL-36 and can be targeted by CAN10
- CAN10 has potential for treatment of several inflammatory diseases, including gout, psoriasis, psoriatic arthritis and hidradenitis suppurativa
- CAN10 is currently in phase I clinical development (NCT06143371) including healthy and psoriasis subjects

References: *1) Field et al , 2024, Cell Reports 2) Grönberg et al 2024, ARD*

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