An Abrocitinib Surrogate Molecule Reduces Disease Severity and Protects Skin Barrier Integrity in a Humanized Mouse Model of Atopic Dermatitis Flare-Ups

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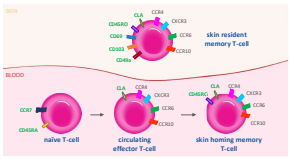
Background

Atopic dermatitis (AD) is a chronic inflammatory skin disorder characterized by immune cell activation, impairment of the skin barrier and waves of disease recurrence [1, 2]. AD recurrences are suggested to be mediated by memory T-cells (see Figure on the right) [3]. Key disease pathways of AD include the Th2-derived cytokines IL-13 and IL-4. Indeed, their blockade by biologics prompted significant improvements in patients with moderate-to-severe AD [4]. However, unlike other skin inflammatory diseases, targeting those cytokines only resolves AD in around 38% of the patients [5]. Thus, more efficient treatments are sought after, which also reduce disease reappearances. The janus activated kinase 1 (JAK1) inhibitor Abrocitinib has demonstrated efficacy in clinical studies in AD patients [6]. JAK signalling is induced by various cytokines, including IL-4, -13, -31, -6, -15, -22 or interferons, and regulates T-cell differentiation and function [7]. Given its broad spectrum of activity, the beneficial effects of Abrocitinib in ameliorating AD may exceed the scope of clinical findings [6].



Naive T-cells are characterized by CCR7 and CD45RA expression, which are downregulated on effector and memory T-cells. While blood circulating memory T-cells upregulate only CD45RO and CLA, skin resident memory T-cells are also positive for CD103, CD69 and CD49a. CCR4, CXCR3, CCR6, and CCR10 further distinguish Th1, Th2, Th17, Th17+1, and Th22 cells. Adapted from [8-11].

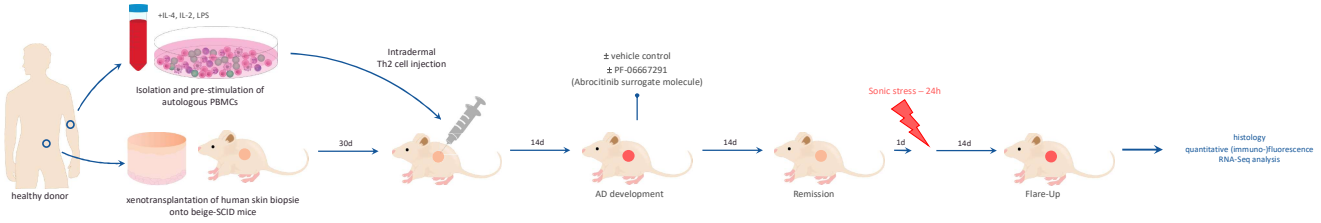
Aim of the study

To investigate mechanisms whereby Abro reduces AD disease recurrence using a humanized AD mouse model in which disease relapse can be observed following exposure to sonic stress.

Take-home Message

"Abrocitinib reduces **AD disease relapses** ín humanized mice, characterized by increased barrier function, potentially via **keratinocyte responses to Abro** and/or **interference with the expansion and/or survival of skin homing CLA+ memory T-cells**"

Methods



Abdominal skin from 3 healthy donors was transplanted onto 60 beige-SCID mice. 30 days after transplantation, the grafted skin was injected intradermally with autologous *in vitro* IL-4,IL-2,LPS-treated PMBCs to induce AD. 14 days after PBMC injection, treatments started. Mice received a daily oral administration of 2% Tween 20/0.5% methylcellulose (drug-vehicle) or PF-06667291 (abrocitinib surrogate molecule) for another 14 days. One day after treatment was discontinued, mice were exposed to sonic stress for 24h. 14 days later, the experiment was terminated and xenografts were used for further analysis

Results

Treatment with PF-06667291 significantly reduces epidermal thickness, and increases Filaggin and Claudin-1 expression also after disease flare-ups, while Involucrin and Keratin 1 expression are not affected

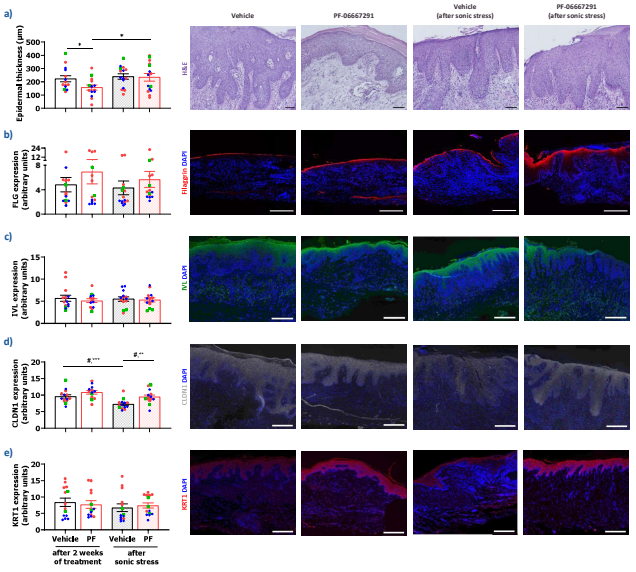


Figure 1. Analysis of PF-06667291 (abrocitinib surrogate molecule) treated AD-induced xenotransplanted skin 2 weeks after treatment and after disease flare up induction by sonic stress exposure. Skin barrier function was determined by quantifying (a) epidermal thickness (H&E staining), (b) Filaggrin (FLG), (c) involucrin (IVL), (d) Claudin 1 (CLDN1) and (e) Keratin 1 (Krt1) expression. Representative images are shown on the right. mean±SEM, n=10-14 mice/experimental group from n=3 independent human donors D'Agostino & Pearson test for normal distribution. Mann Whitney or Students tests; *p<0.05, **p<0.01, ***p<0.001 and Kruskal Wallis or one-way Anova #p<0.05.

Treatment with PF-06667291 induces a trend towards reduced CD3+ T cells, CD3+CD45RO+ memory T cells, and skin homing CD3+CLA+ T cells.

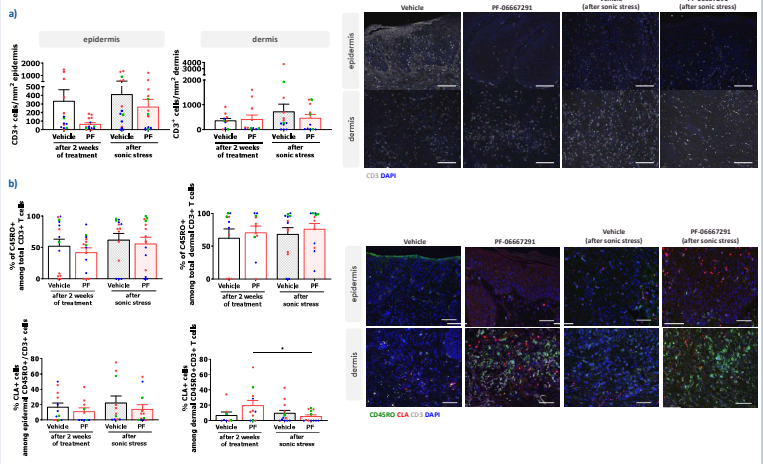


Figure 2. Analysis of PF-06667291 (abrocitinib surrogate molecule) treated AD-induced xenotransplanted skin 2 weeks after treatment and after disease flare up induction by sonic stress exposure. (a) The number of CD3+ T-cells was determined in the dermis and epidermis. Representative images are shown on the right. (b) The number of skin resident CD3+CD45RO+ T cells, and skin homing CD3+CLA+ T cells was determined in the dermis and epidermis. Representative images are shown on the right. mean±SEM, n=10-14 mice/experimental group from n=3 independent human donors D'Agostino & Pearson test for normal distribution. Mann Whitney tests; *p<0.05.

RNASeq analysis after induction of disease recurrence reveals upregulation of genes associated with skin barrier and lower expression of genes associated to inflammation, Th1 , Th17 and Th2 responses

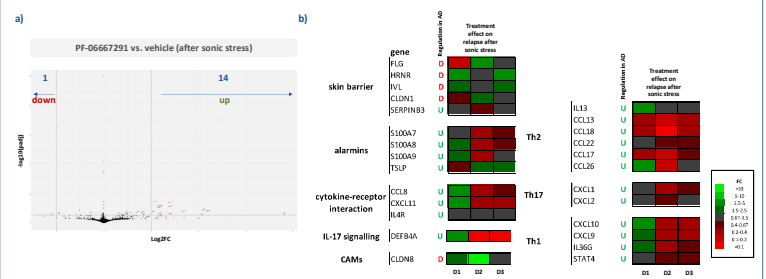


Figure 3. Volcano plot showing the significantly down regulated genes (DESeq2: padj ≤0.05, log2FC ≥1/≤-1) in PF-06667291-treated xenografts after sonic stress compared to vehicle-treated xenografts after sonic stress and heatmaps showing the fold-change of differentially expressed genes between PF-0667291-treated xenografts vs vehicle-treated xenografts after sonic stress from n=3 different donors (D1-D3). Displayed genes have been described to be dysregulated in AD (D: down-regulated in AD, U: up-regulated in AD).

Conclusion

PF-06667291 reduces the severity of sonic stress-induced inflammatory relapses and enhances barrier integrity in AD-induced xenografts. These findings indicate that keratinocyte responses to Abro may play a role in its capacity to prevent the recurrence of AD flares. Additionally, PF decreases the number of skin-homing CLA+CD3+ T cells, further implicating a role for these cells in the recurrence of AD flare-ups.

REFERENCES

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DISCLOSURES

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