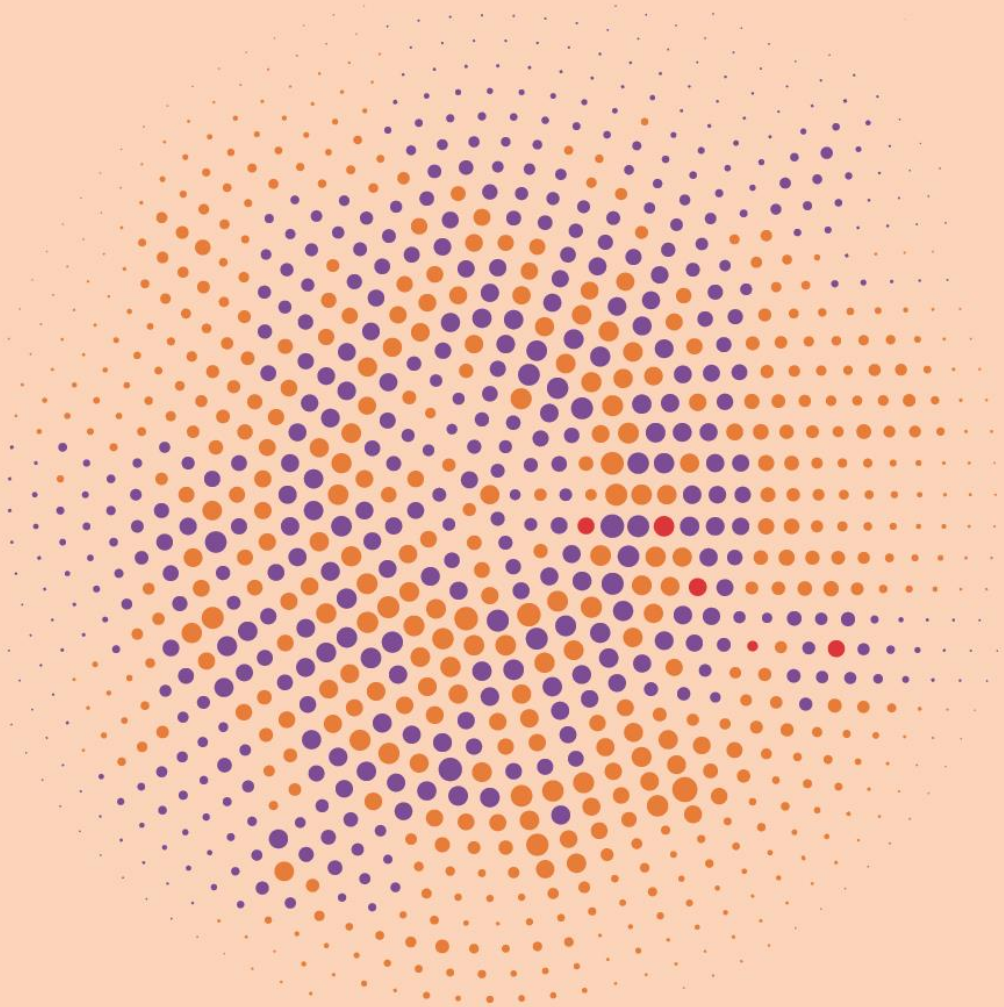

# 16e Journée Scientifique conjointe du Groupe de Recherche sur le PSORIASIS et du Groupe HS France

**Vendredi 7 octobre 2022**
Espace du Centenaire
Maison de la RATP – Paris

GRPso
Groupe de Recherche sur le Psoriasis

HS-France

Sous l'égide de la
Société Française de Dermatologie

16e Journée Scientifique conjointe
du Groupe de Recherche sur le PSORIASIS et du Groupe HS France

Vendredi 7 octobre 2022
Espace du Centenaire
Maison de la RATP – Paris

# Quoi de neuf en recherche

*Réunion annuelle du GrPSO – Octobre 2022*

***Pr Denis Jullien***
*Hôpital E. Herriot*
*Lyon*
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centre de référence maladies rares

**Dermatoses bulleuses toxiques et toxidermies graves**

GRPso
HS-France
Sous l'égide de la Société Française de Dermatologie

## Conflits d’intérêts D Jullien

*Orateur invité, et/ou membre d’advisory board, et/ou consultant, et/ou investigateur et/ou bénéficiaire de l’hospitalité de la part / pour les compagnies pharmaceutiques suivantes :*

- Abbvie
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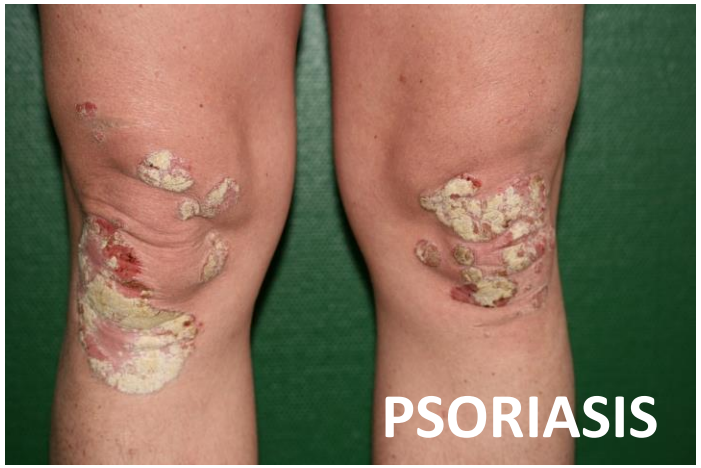
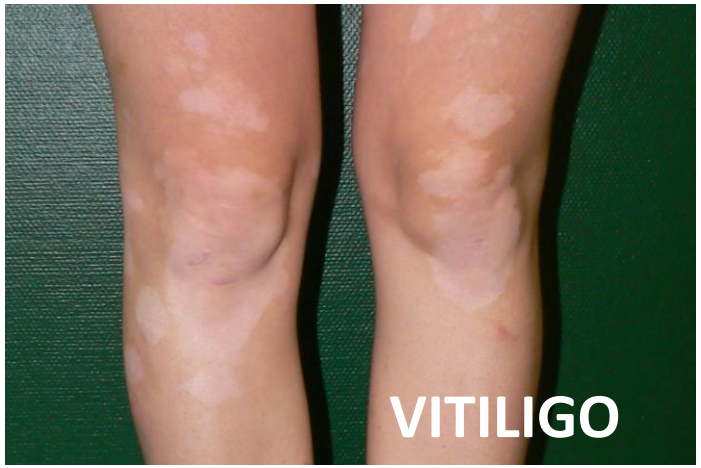
Le Monde, 03/04/2019 – étude Formindep sur la prévention des COI dans les 32 CHU




# Bilateral symmetric lesions in certain anatomic regions of the body

*The cellular and molecular mechanisms that orchestrate the patterned activities of immune cells in the skin of patients remain elusive.*

Article

## Anatomically distinct fibroblast subsets determine skin autoimmune patterns

https://doi.org/10.1038/s41586-021-04221-8
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Zijian Xu[1,9], Daoming Chen[1,2,9], Yucheng Hu[3], Kaiju Jiang[1], Huanwei Huang[1], Yingxue Du[1], Wenbo Wu[1], Jiawen Wang[1], Jianhua Sui[1], Wenhui Wang[4], Long Zhang[4], Shuli Li[5], Chunying Li[5], Yong Yang[6], Jianmin Chang[7]✉ & Ting Chen[1,8]✉

The skin serves as a physical barrier and an immunological interface that protects the body from the external environment[1–3]. Aberrant activation of immune cells can induce common skin autoimmune diseases such as vitiligo, which are often characterized by bilateral symmetric lesions in certain anatomic regions of the body[4–6]. Understanding what orchestrates the activities of cutaneous immune cells at an organ level is necessary for the treatment of autoimmune diseases. Here we identify subsets of dermal fibroblasts that are responsible for driving patterned autoimmune activity, by using a robust mouse model of vitiligo that is based on the activation of endogenous auto-reactive CD8⁺ T cells that target epidermal melanocytes. Using a combination of single-cell analysis of skin samples from patients with vitiligo, cell-type-specific genetic knockouts and engraftment experiments, we find that among multiple interferon-γ (IFNγ)-responsive cell types in vitiligo-affected skin, dermal fibroblasts are uniquely required to recruit and activate CD8⁺ cytotoxic T cells through secreted chemokines. Anatomically distinct human dermal fibroblasts exhibit intrinsic differences in the expression of chemokines in response to IFNγ. In mouse models of vitiligo, regional IFNγ-resistant fibroblasts determine the autoimmune pattern of depigmentation in the skin. Our study identifies anatomically distinct fibroblasts with permissive or repressive IFNγ responses as the key determinant of body-level patterns of lesions in vitiligo, and highlights mesenchymal subpopulations as therapeutic targets for treating autoimmune diseases.

Vitiligo is an acquired polygenetic autoimmune disease[9]. Its defining feature is skin depigmentation, in which affected skin is unable to spontaneously recover owing to the activity of auto-reactive CD8⁺ T cells, which causes a loss of epidermal melanocytes[7,8,10–15]. Vitiligo affects 0.5% to 2% of the population worldwide[16–18]. More than 80% of patients with vitiligo have bilateral symmetric patterns of depigmentation across the central body axis, which is classified as non-segmental vitiligo[4–6]. Previous studies using a mouse model of vitiligo have shown that IFNγ is important for T cell-induced depigmentation in skin[19–21]. Although various studies have proposed underlying mechanisms[22–27], the identity of IFNγ-responsive cells that mediate this function is largely unknown. Hypotheses about the reason behind the bilateral symmetric patterns that are observed in vitiligo pathology include regional variations in microbiota distribution; the pattern of antigen expression in melanocytes; and different distributions of neuropeptides released by nerve endings[28–32]. Despite these studies, the cellular and molecular mechanisms that orchestrate the patterned activities of immune cells in the skin of patients with vitiligo remain elusive.

### Cellular IFNγ responses in vitiligo-affected skin

To understand the cellular and molecular mechanisms that lead to patterned autoimmune activity in vitiligo-affected skin (Fig. 1a, Extended Data Fig. 1a), we first analysed skin biopsies from patients with vitiligo. Immunofluorescent staining showed that melanocytes were absent within the lesion but evenly distributed in the basal epidermis of the perilesion region (Fig. 1b). Notably, the majority of the infiltrated CD8⁺ T cells were concentrated at the junction area between the lesion and the perilesion skin, which implied a local recruitment mechanism for CD8⁺ T cells.

Next we used single-cell RNA sequencing (scRNA-seq) to analyse all cell types present in patient skin (Extended Data Fig. 1b, c). Unsupervised clustering of more than 50,000 cells from 10 patients with vitiligo and 5 healthy donors yielded 8 main cell types defined by signature genes (Extended Data Fig. 1d–h, Supplementary Table 1). Further analysis of melanocytes revealed two distinct sub-clusters

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# Psoriatic Fibroblasts Induce Hyperproliferation of Normal Keratinocytes in a Skin Equivalent Model in Vitro

Abstract. *A skin equivalent model has been used to fabricate tissues with psoriatic and normal cells. Psoriatic fibroblasts can induce hyperproliferative activity in normal keratinocytes. The psoriatic epidermis from lesions continues to proliferate at high rates for at least 15 days in this model, and normal fibroblasts are unable to suppress this hyperproliferation. The primary defect in psoriatic skin may reside in the dermal fibroblast.*

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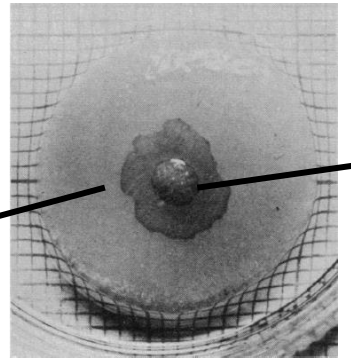
*Hôpital Henri Mondor*

**Dermal Equivalent Fibroblasts**
**F**NN
**F**PN
**F**PP



**PUNCH BIOPSIES**
NN
PN
PP

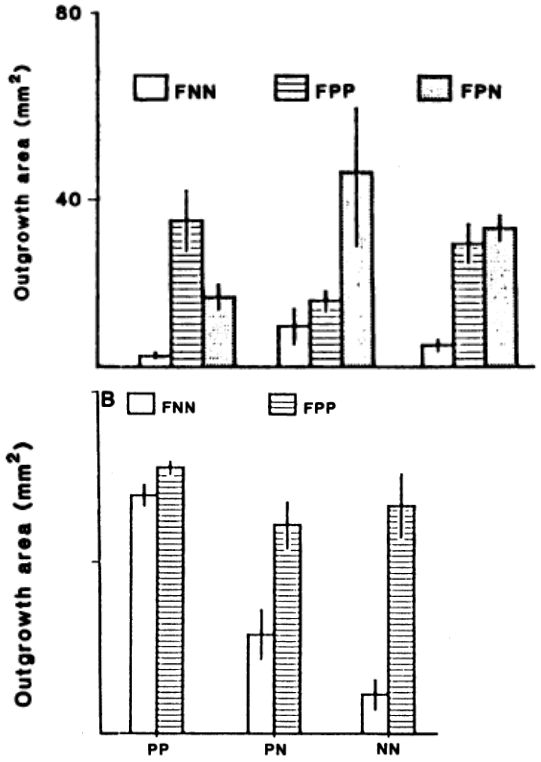



Fig. 2. Outgrowth of keratinocytes from NN biopsies taken from the same specimen of normal skin on dermal equivalents made up with FPP, FPN, or FNN strains (9 days in culture). Each of three psoriatic patients provided a strain of FPP and of FPN. Three normal volunteers each provided an FNN strain. The epidermal outgrowth on FPN and FPP dermal equivalents was significantly greater than that obtained with FNN ($P < 0.002$, Wilcoxon test) with one exception seen in the middle set of data for FPP (bar, ± standard error of the mean). In other

Fig. 3.Epidermal outgrowth at day 9 from PP, PN (harvested from five psoriatic patients), or NN (harvested from five normal volunteers) biopsies on dermalequivalents made up with FPP or FNN strains. One strain of FPP and one of FNN were used.

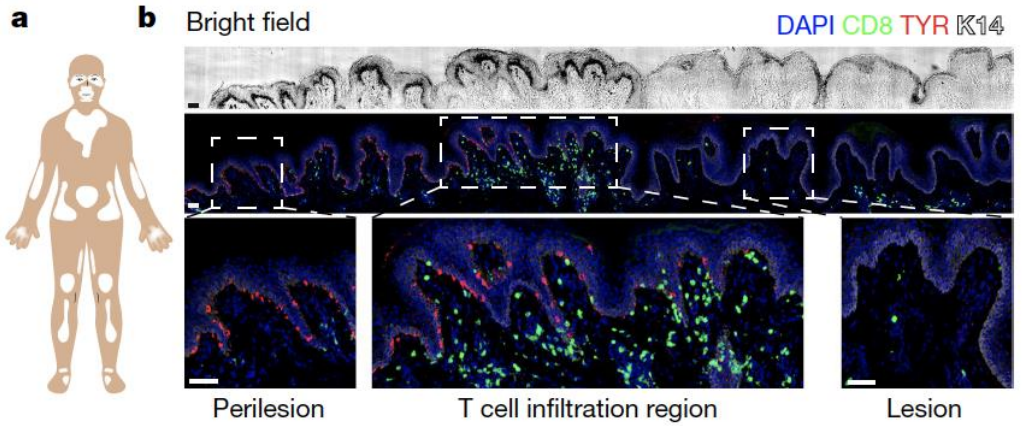
**« we propose that a primary defect of psoriatic skin may reside in the dermal fibroblasts »**

**Science**. 1985 Nov 8;230(4726):669-72.

# Vitiligo

## CD8⁺ T cell infiltrating plays a direct role in melanocyte disappearance.

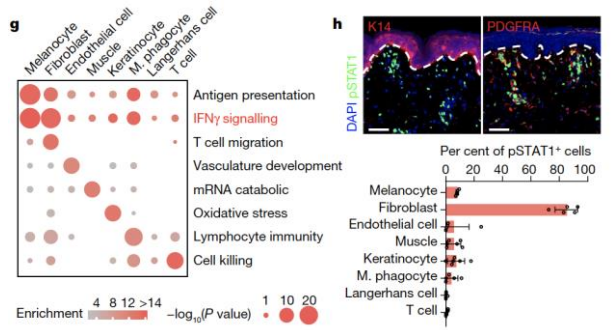
▶ infiltrated **CD8+T cells** concentrated at the junction area between the lesion and the perilesion sugesting **local recruitment**

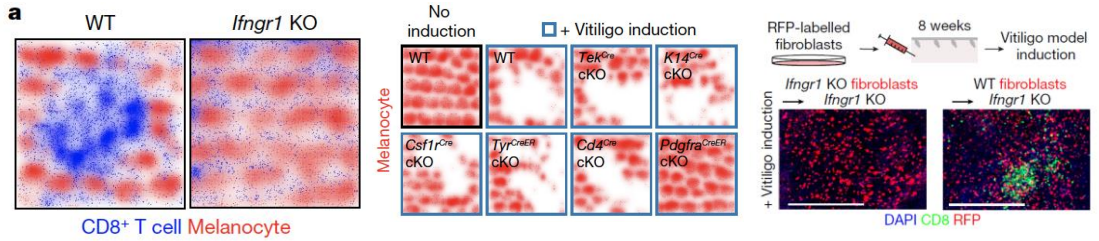


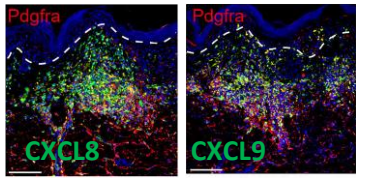

## Previous studies showed that IFNγ signalling is important for the progression of vitiligo in mouse models

*sc-RNAseq, GeneOntology, pSTAT, Models of vitiligo, skin engraftment, adoptive T-cell transfer, lineage tracing experiments, cell specific IFN KO strategy , …*

- *Among **IFNγ-responsive cell types in the skin of patients** with vitiligo, **dermal fibroblasts** accounted for around 80% of the pSTAT1+ cells in patient skin*
- ***IFNγ-responsive skin stromal cells are required to drive auto-reactive CD8+ T cell-mediated vitiligo in a paracrine manner**.*
- *Only Pdgfra$^{CreER}$;Ifngr1$^{fl/fl}$ mice did not develop vitiligo*
- ***….***



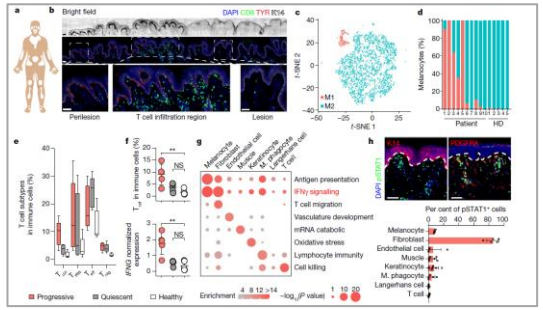



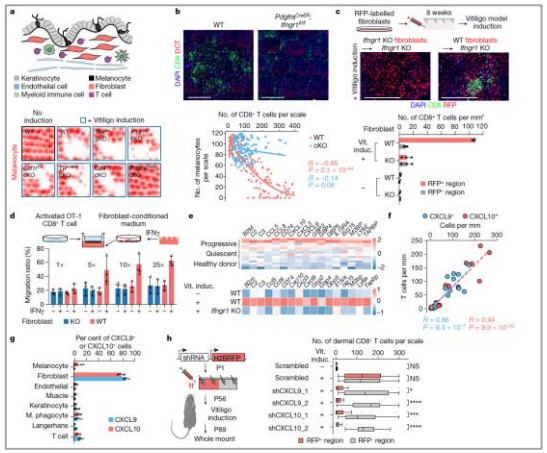

fibroblasts
Vitiligo Patients

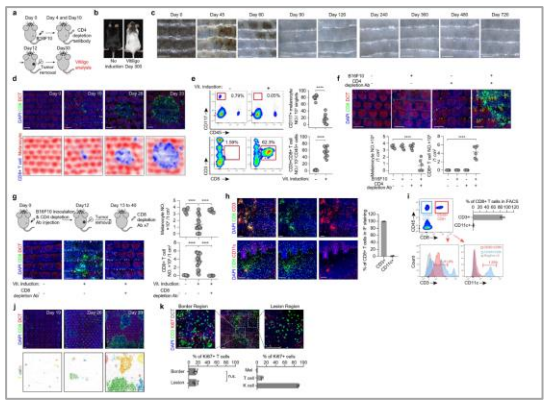
▶ **Vitiligo requires**
- **IFNγ-responsive fibroblasts**
- **that mediate local aggregation of autoreactive CD8+ T cells**
- **in a paracrine manner**
- **through the CXCL9/CXCL10–CXCR3 axis.**

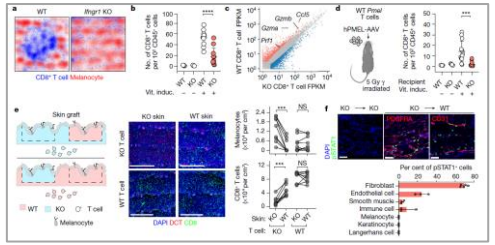
Xu Z, ET AL. Anatomically distinct fibroblast subsets determine skin autoimmune patterns. Nature. 2022 Jan;601(7891):118-124.

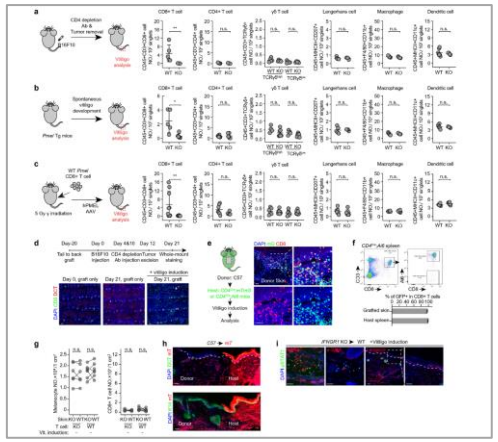
# 2022 - What it takes to demonstrate and convince Nature editor

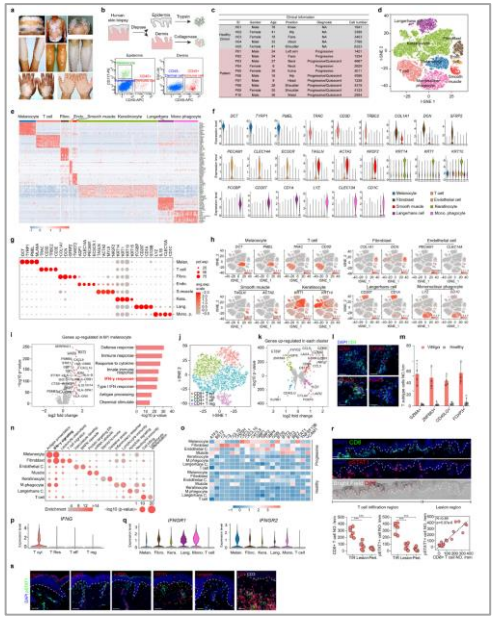


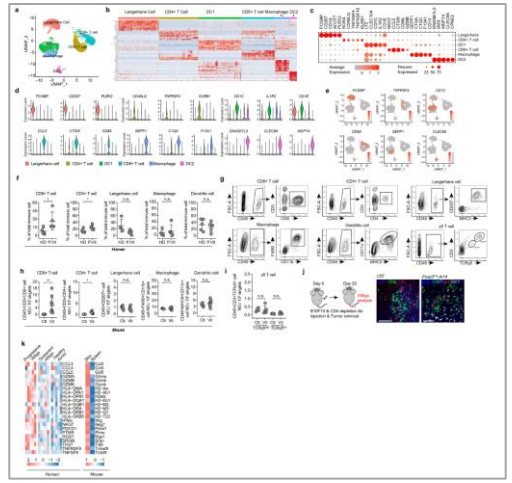


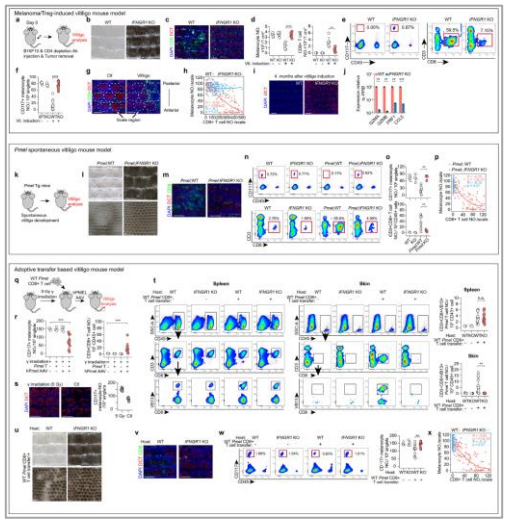






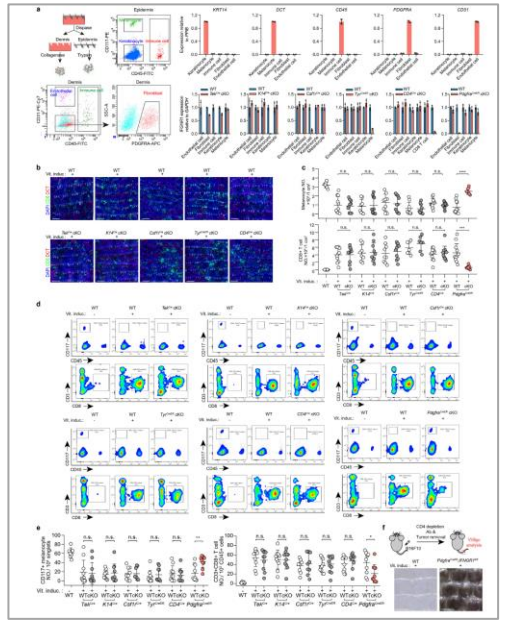


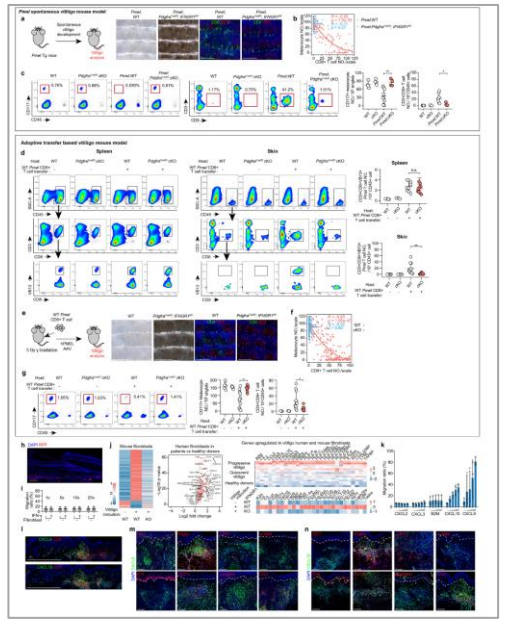


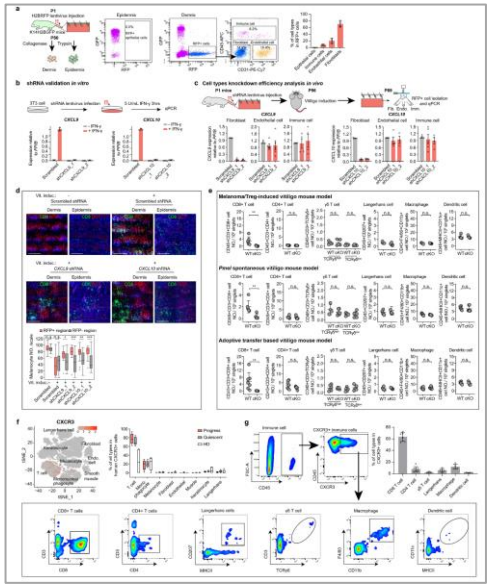








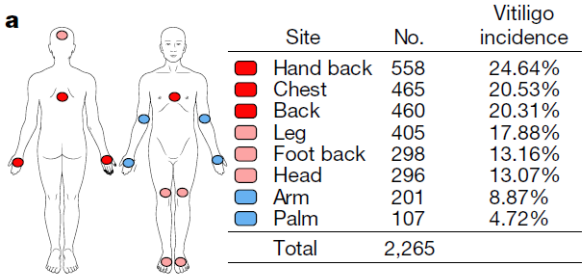


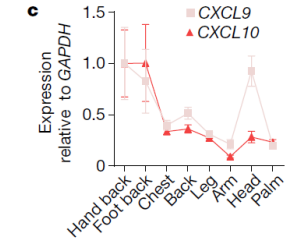


## fibroblasts from different anatomic skin regions are intrinsically different (HOX genes). Whether they are different in regulating the activity of cutaneous immune cells is unknown.

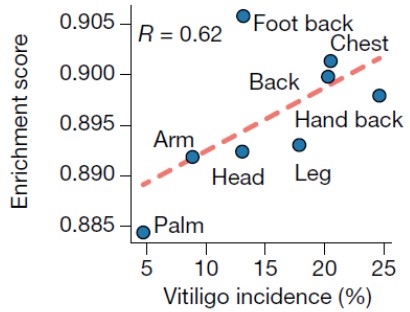
frequencies of vitiligo lesions at different anatomic regions of 2,265 patients, RNA-seq analysis of in vitro IFNγ-treated primary human dermal fibroblasts isolated from these eight anatomic regions.

*Most susceptible to vitiligo : back of the hand, chest, back,*
*Least susceptible to vitiligo : palm and arm*
*All Fibroblast similar levels of IFNγ signaling pathway genes BUT multiple* ***IFNγ-induced chemokine genes (CXCL9, CXCL10) significantly upregulated in fibroblasts isolated from anatomic regions with a higher incidence of vitiligo***




**▸ Regional fibroblasts differ in IFNγ response and % of vitiligo incidence positively correlated with the intrinsic IFNγ response of dermal fibroblasts at different anatomic regions**



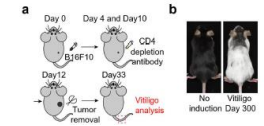

Correlation analysis of fibroblasts IFNγ response enrichment score versus vitiligo incidence frequency

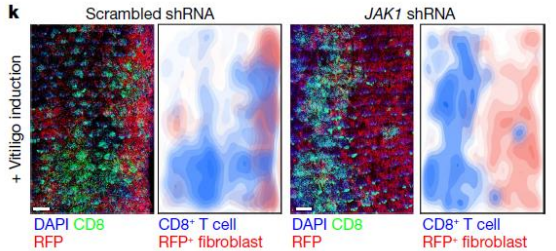
## functional relevance of this correlation ?

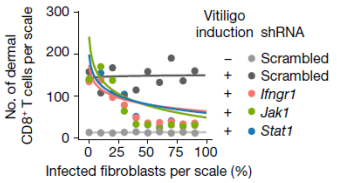
melanoma–Treg-induced mouse model of vitiligo (*dorsal and ventral skin hair back most susceptible to vitiligo, and paw the least), fibroblast mosaic KO experiments*

*- Cxcl9 and Cxcl10 higher expression in dorsal and ventral fibroblasts compared to paw*
*- medium from IFNγ-treated dorsal skin induced more CD8+ migration than from paw*
*- in a field with* ***uneven fibroblast responses to IFNγ****, CD8+ T cells preferentially aggregate towards a region with fibroblasts capable of stronger IFNγ responses, hence generating a patterned loss of melanocytes.*

**CD8+ T cells preferentially aggregate toward a region with fibroblasts capable of stronger IFNγ responses, generating a patterned loss of melanocytes.**



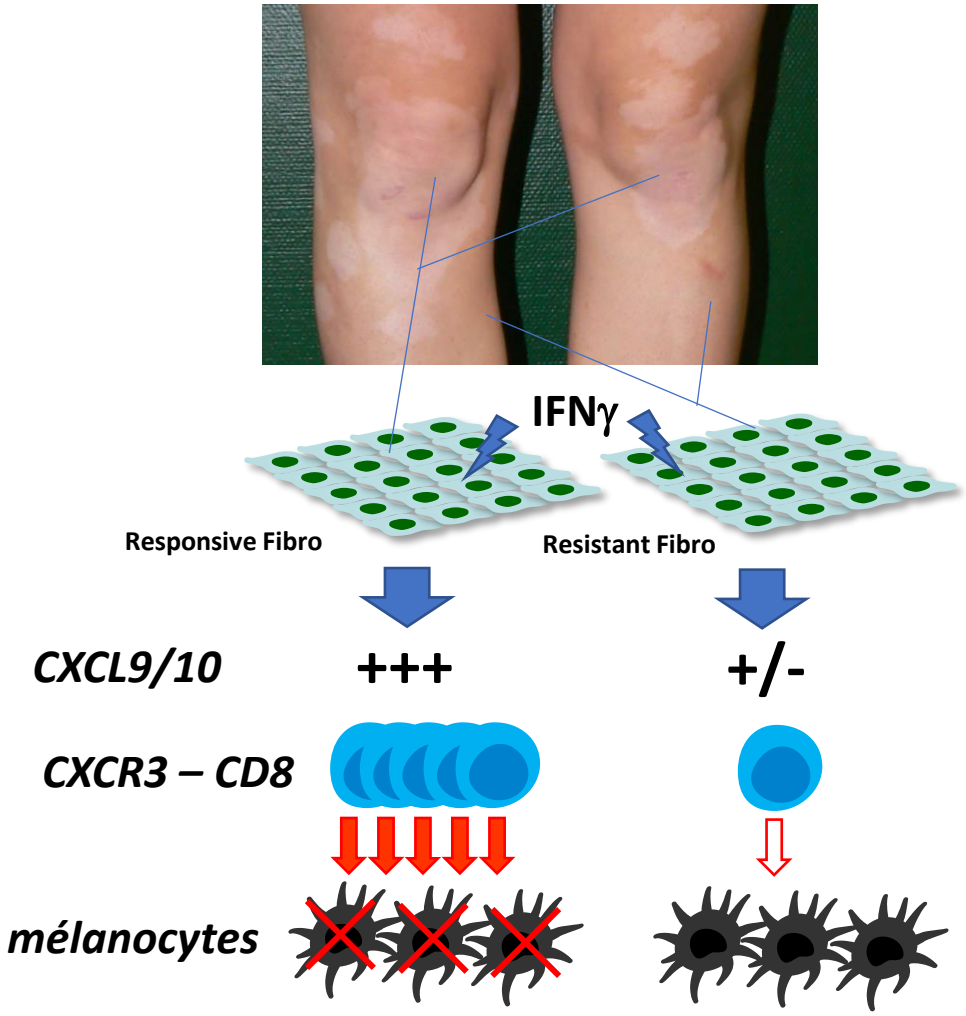




Representative whole-mount and density plot images and correlation analysis of the number of T cells versus the percentage of infected fibroblasts in the in vivo mosaic fibroblast knockdown experiment

Xu Z, ET AL. Anatomically distinct fibroblast subsets determine skin autoimmune patterns. Nature. 2022 Jan;601(7891):118-124.

**Vitiligo - Regional distinct fibroblasts determine the autoimmune pattern of depigmentation in the skin.**

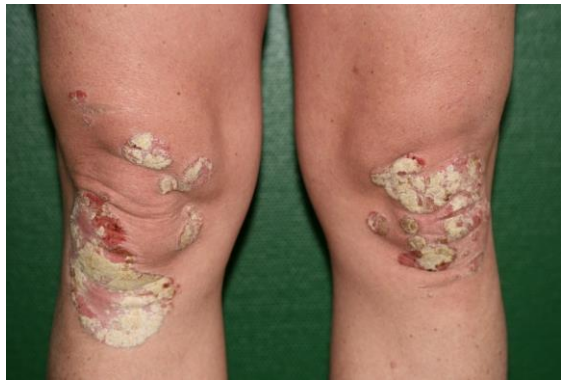



***Feedforward system between mobile CD8+ T cells and immobile fibroblasts***

- progressive aggregation of CD8+ T cells in areas with IFNγ-responsive fibroblasts
- Sharp decline of CD8+ T cells in areas with IFNγ-resistant fibroblasts.

▶ **prioritize allocation of collective cytotoxicity and elimination of target cells**

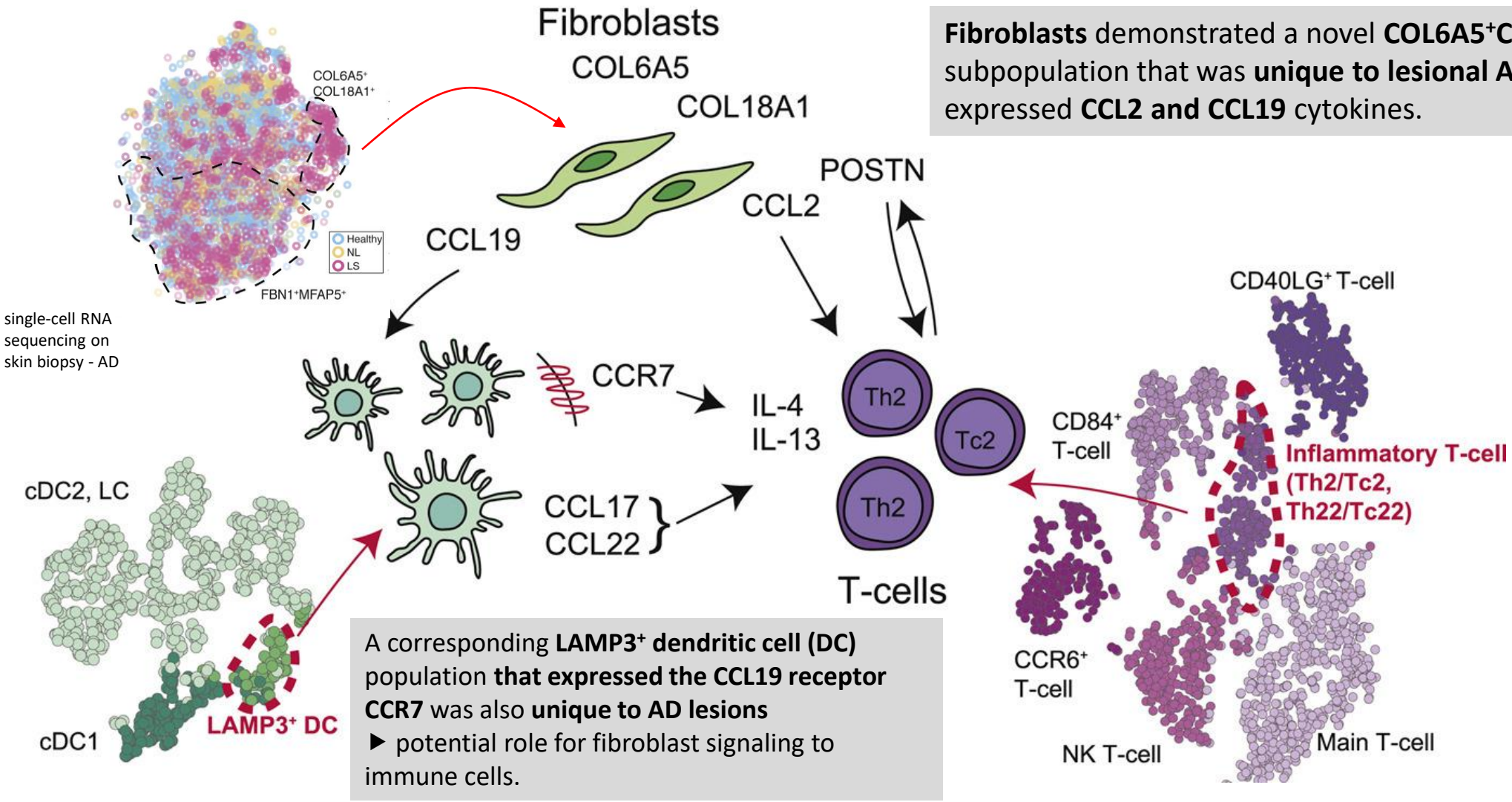
"Many other autoimmune skin diseases exhibit regional preference with symmetric distributions"



**Psoriasis ?**

**The immune cell activity regulated by regional fibroblasts could provide a general paradigm through which the progression and regional pattern of skin autoimmune diseases are regulated."**

# Novel inflammatory fibroblasts cross-talk with DCs and T-cells, and may orchestrate T-cell migration and Th2/Tc2 polarization in AD



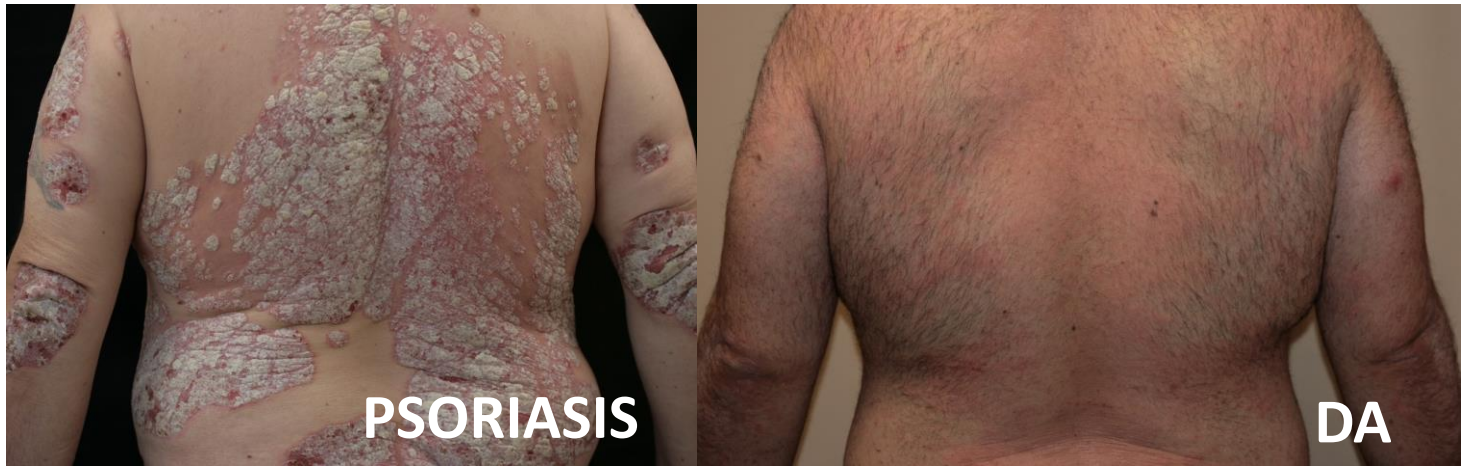

single-cell RNA sequencing on skin biopsy - AD

**Fibroblasts** demonstrated a novel **COL6A5⁺COL18A1⁺** subpopulation that was **unique to lesional AD** and expressed **CCL2 and CCL19** cytokines.

A corresponding **LAMP3⁺ dendritic cell (DC)** population **that expressed the CCL19 receptor CCR7** was also **unique to AD lesions**
► potential role for fibroblast signaling to immune cells.

single-cell RNA sequencing on skin biopsy specimens from 5 patients with AD (4 lesional samples and 5 nonlesional samples) and 7 healthy control subjects

He H, …, Guttman-Yassky E. Single-cell transcriptome analysis of human skin identifies novel fibroblast subpopulation and enrichment of immune subsets in atopic dermatitis. J Allergy Clin Immunol. 2020 Jun;145(6):1615-1628. doi:




# Obese patients have more severe disease and exhibit resistance to therapies that are effective in lean patients

*The mechanisms underlying these observations remain unclear*

Article

## Obesity alters pathology and treatment response in inflammatory disease

https://doi.org/10.1038/s41586-022-04536-0
Received: 18 March 2021
Accepted: 8 February 2022
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Check for updates

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Decades of work have elucidated cytokine signalling and transcriptional pathways that control T cell differentiation and have led the way to targeted biologic therapies that are effective in a range of autoimmune, allergic and inflammatory diseases. Recent evidence indicates that obesity and metabolic disease can also influence the immune system[1–7], although the mechanisms and effects on immunotherapy outcomes remain largely unknown. Here, using two models of atopic dermatitis, we show that lean and obese mice mount markedly different immune responses. Obesity converted the classical type 2 T helper ($T_H2$)-predominant disease associated with atopic dermatitis to a more severe disease with prominent $T_H17$ inflammation. We also observed divergent responses to biologic therapies targeting $T_H2$ cytokines, which robustly protected lean mice but exacerbated disease in obese mice. Single-cell RNA sequencing coupled with genome-wide binding analyses revealed decreased activity of nuclear receptor peroxisome proliferator-activated receptor-γ (PPARγ) in $T_H2$ cells from obese mice relative to lean mice. Conditional ablation of PPARγ in T cells revealed that PPARγ is required to focus the in vivo $T_H$ response towards a $T_H2$-predominant state and prevent aberrant non-$T_H2$ inflammation. Treatment of obese mice with a small-molecule PPARγ agonist limited development of $T_H17$ pathology and unlocked therapeutic responsiveness to targeted anti-$T_H2$ biologic therapies. These studies reveal the effects of obesity on immunological disease and suggest a precision medicine approach to target the immune dysregulation caused by obesity.

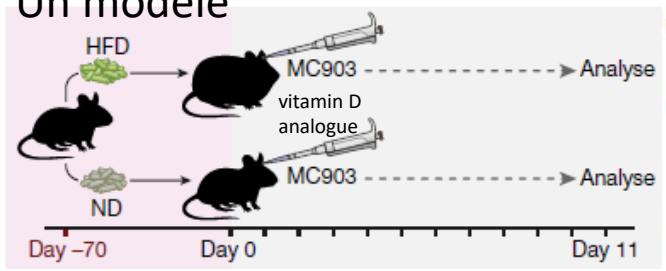
Emerging clinical data of multiple immunological diseases including atopy and asthma indicate that obese patients have more severe disease and exhibit resistance to therapies that are effective in lean patients[8–13], although the mechanisms underlying these observations remain unclear. To gain mechanistic insights into the immunopathological effects of obesity, we employed a well-characterized mouse model of atopic dermatitis[14,15] (AD). We challenged obese mice fed high-fat diet (HFD) and lean controls with the vitamin $D_3$ analogue MC903 to induce AD on the ear (Fig. 1a). The obese mice displayed a markedly increased inflammatory response, evidenced by an approximately twofold to fourfold increase in ear thickness relative to lean mice that received the same MC903 treatment (Fig. 1b). The MC903-treated ears of the obese mice had more severe erythema and scale, hallmarks of dermal inflammation (Fig. 1c). Histological evaluation demonstrated greater expansions of the epidermal and dermal layers in obese mice, along with a marked increase in leukocytic infiltration (Fig. 1d, dashed line). Of note, studies modulating duration of the HFD (Extended Data Fig. 1a–d) and using monogenic models of obesity on normal or HFD (Extended data Fig. 1e–j) suggested that the increased ear thickness and inflammation seen in obesity was at least partially dependent on HFD. Further, we observed a persistent inflammatory effect of obesity, even after weight loss (Extended Data Fig. 1k–m). Additionally, obesity increased disease severity, including after weight loss, in a second model of AD (Extended Data Fig. 2a–g), involving sensitization to ovalbumin (OVA) followed by serial tape-stripping and exposure to a mixture of OVA and papain (TOP). Finally, this increased inflammatory response was not limited to atopic diseases of the skin, as challenging lean and obese mice in an experimental model of allergic airway disease (ovalbumin sensitization and challenge) yielded increased cellular infiltration across multiple immune subsets in the bronchial–alveolar lavage fluid of obese mice and increased $CD4^+$ and $CD8^+$ T cells in the draining lymph node of obese mice (Extended Data Fig. 2h–j). Together, these results show that obesity exacerbates multiple mouse models of atopic disease.

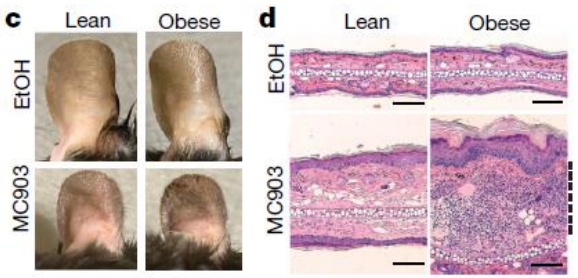
A list of affiliations appears at the end of the paper.

# Dermatite Atopique

## Obesity exacerbates multiple mouse models of atopic disease

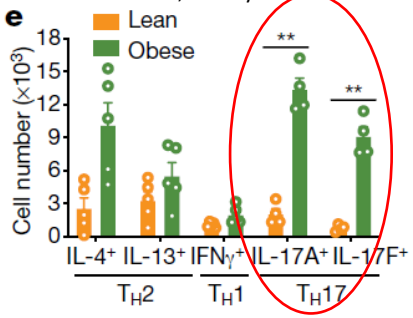
Un modèle




## Obesity alters the TH-response in AD .. to include substantial TH17 inflammation in addition to canonical TH2 inflammation found in lean mice

Total cytokine-competent CD4+ T cell from whole ear, on day 11

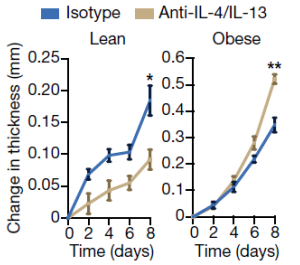


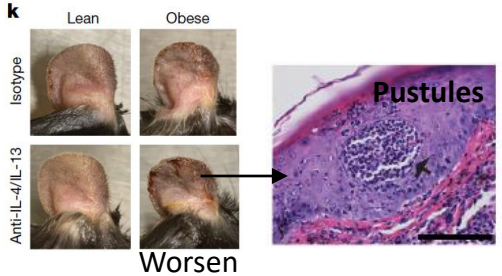

*scRNA-Seq to profile T cells from inflamed skin-* ***Transcriptional trajectories study***: differences in the **degree of TH17** differentiation between lean and obese mice

**LM**: **TH17 in 'early' position** (expressing TH17 lineage-defining transcription factor *Rorc*, but <u>not</u> effector cytokines *Il17a*, *Il17f* or *Il22*, or *Il23r*).

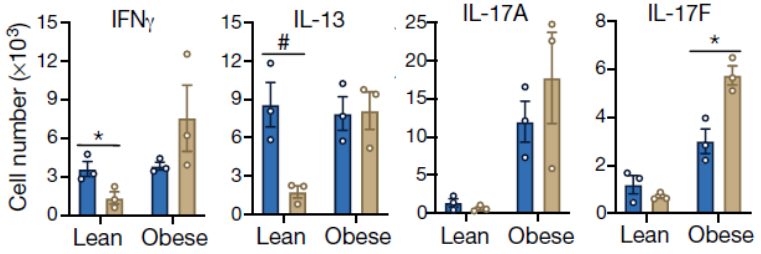
**OM**: **TH17 in 'late' position** (expressing both Rorc AND effectors Il17a, Il17f or Il22, or Il23r) ← egress of lymphocytes from secondary lymphoid organs

## Anti-IL-4/IL-13 TH2 blockade exacerbates non-TH2 inflammation in the obese animals and worsens disease




Worsen




lesional CD4+ T cells

**LM** : ↓ IFNg+, IL13+ & ↓ IL17A/F+ CD4

**OM** : ↑ IFNg+, & ↑ IL17A/F+ CD4

**<u>Hypothesis</u> :**

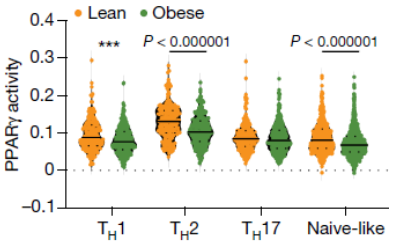
**Obesity downregulate a transcription factor (TF) that protects the dominance of the TH2 response**

**PPARγ :**

*- TF of the nuclear hormone receptor family (sensitive to systemic changes in physiologic and metabolic state)*

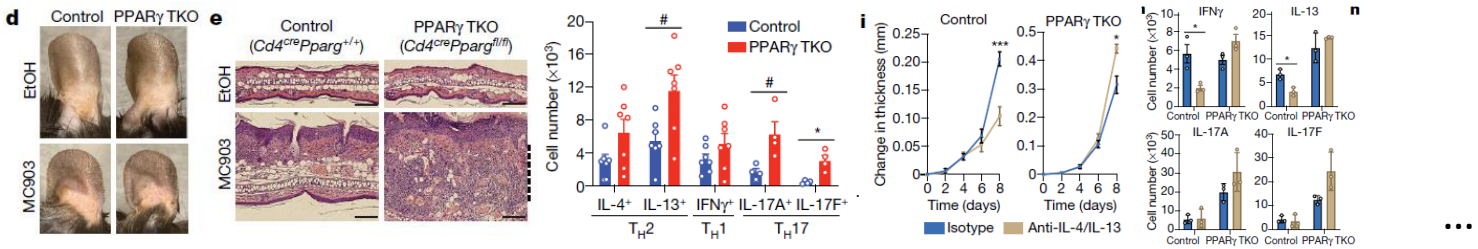
*- highly and differentially expressed in TH2 cells vs. TH1 and TH17 cells; Important for regulating transcriptional networks in TH2 cells*

**Expression of PPARγ-regulated genes is decreased in TH2 cells and naive-like T cells from obese mice.**



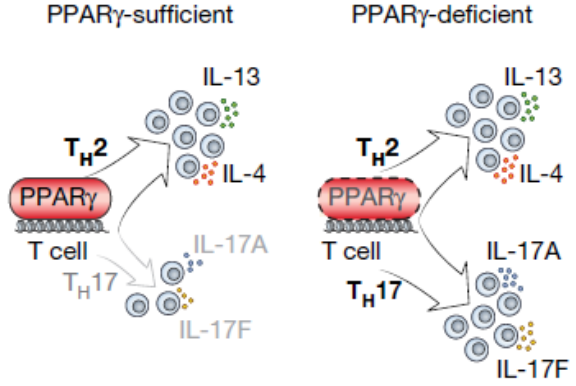

Single-cell RNA sequencing coupled with genome-wide binding analyses

**Mice with T cell-specific PPARγ deficiency largely phenocopy obese PPARγ-sufficient mice upon experimental AD challenge**




The maintenance of TH2 responses by PPARγ seems to prevent the amplification of a more pathological TH17-type inflammation

PPARγ is a focusing factor crucial to the in vivo TH2 response, serving to maintain TH2 responses against competing TH programs during an inflammatory challenge

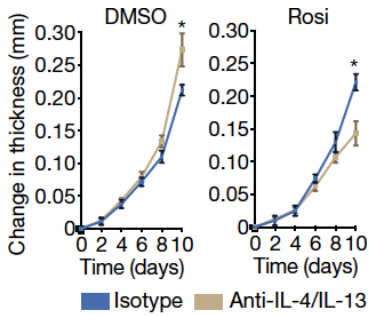


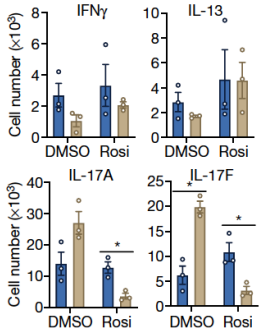
**Thiazolidinediones are PPARγ agonists used as insulin-sensitizing medications to manage type 2 diabetes**

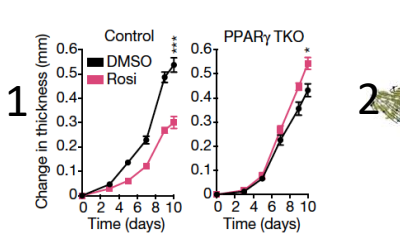
► *Treatment OM (control) and PPARγ-TKO mice with rosiglitazone or DMSO and challenge OM with AD.*

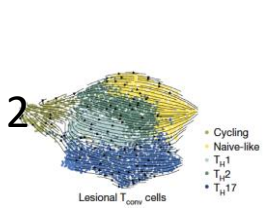
**Rosiglitazone in OM vs *PPARγ-TKO mice***

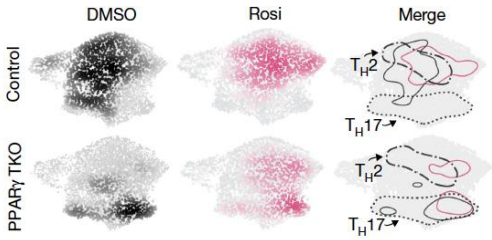
- **↓ AD severity and leukocytes infiltration [1]**
- **Collapse lesional CD4+ T cell compartment to the TH2 cluster [2]**
- **Strongly reduced the TH17 population [2]**
- **Increase activity of PPARγ-regulated genes in TH2 and TH17[3]**
- **restore the efficacy of anti-IL-4/IL-13 treatment**

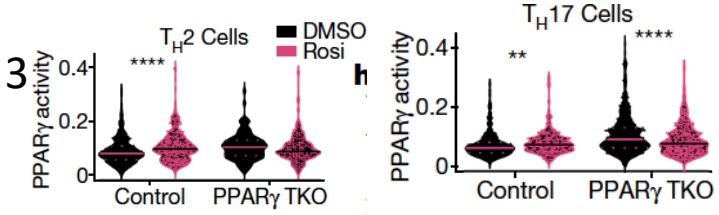


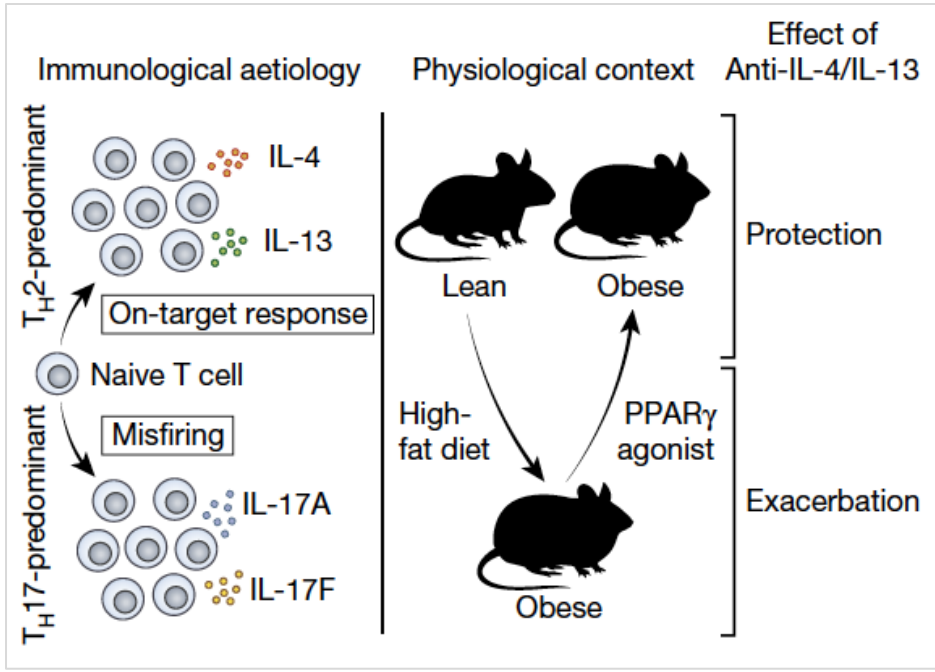




**Obesity exacerbates atopic disease by exaggerating pathological TH17 responses**

*- OM develop more severe disease associated with immunological 'misfiring' converting anti-IL-4/13 therapy to an anti-therapy*

*- PPARγ agonist can help to enforce an 'on-target' immunological response and restore efficacy*



# Évaluation de l'adhésion et de l'observance thérapeutique dans la prise en charge du psoriasis

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**Comité scientifique** : Dr Sandra Ly, Dr Antoine Fauconneau, Dr Mélanie Chamaillard,
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Dermatologues membres de Derm to Derm, réseau d'échanges professionnel de la prise en charge du psoriasis et à tous les dermatologues exerçant sur le territoire national

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**Attaché de Recherche Clinique (ARC) coordonnateur** : Christine Alfaro

**Direction technique digitale :** Laurent Elgard

# Étude prospective exploratoire en vie réelle non interventionnelle

- **Objectif principal :**

- Mesurer l'observance déclarée par le patient au cours du temps à 3, 6 et 9 mois après initiation ou modification d'un traitement pour son psoriasis.

- **Critère de jugement principal :**

- L'observance sera évaluée par le **score de Girerd** à 3, 6 et 9 mois renseigné par les patients, automatiquement sollicités par email ou SMS

- **Objectifs secondaires :**

- Évaluer l'adhésion thérapeutique du patient à l'issue de la première consultation par l'utilisation du questionnaire **de satisfaction d'adhésion thérapeutique (AdT)**.

- Rechercher des associations entre des facteurs cliniques (liés à la maladie, aux traitements et aux comorbidités) et socio-démographiques, et une bonne observance au traitement du psoriasis.

- Rechercher des associations entre des facteurs cliniques et socio-démographiques , et une bonne adhésion au traitement du psoriasis.

# Matériel et méthodes

- Inclusion **consécutivement** pendant 3 mois **tous** les patients atteints de psoriasis consultant pour **débuter ou modifier** un traitement
- Les investigateurs n'auront pas connaissance des données d'observance et d'adhésion renseignées par les patients en dehors de leur consultation.
- Après remise de la fiche d'information et recueil et signature du consentement pour participer à l'étude, le **questionnaire d'adhésion** AdT (inclusion) est adressé dans les 48 heures par voie électronique ou SMS à chaque patient selon le choix de celui-ci et un **questionnaire d'observance de Girerd** est rempli par chaque patient à 3, 6 et 9 mois.
- Au niveau statistique il est prévu d'inclure un nombre minimal de **650 patients** et les analyses seront réalisées avec le logiciel STATA (versions 13).
- La société ClinInfo a été sélectionnée pour la réalisation de la plateforme numérique qui met à disposition les questionnaires en ligne, et permet de notifier aux patients le moment où ils sont invités à y répondre (email, sms).

# Conclusion

- Financée par soutien institutionnel et Appel d’offre libéral de la SFD
- Nécessité de 650 inclusions
- Besoin d’une forte participation

Merci et pour en savoir plus

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