

17^e JOURNÉE SCIENTIFIQUE DU GRPSO ET DU GREAT

Groupe de Recherche sur le **PSO**riasis

Groupe de Recherche sur l'**Eczéma AT**opique
DA (Dermatite Atopique)

**VENDREDI
6 OCTOBRE
2023**

ESPACE DU CENTENAIRE
Maison de la RATP - Paris



Sous l'égide de la





Production of functional plasmacytoid dendritic cells-targeted CAR-T cells from patients with immune-mediated inflammatory diseases

Dr Blandine CAËL

PharmD, AHU Immunologie

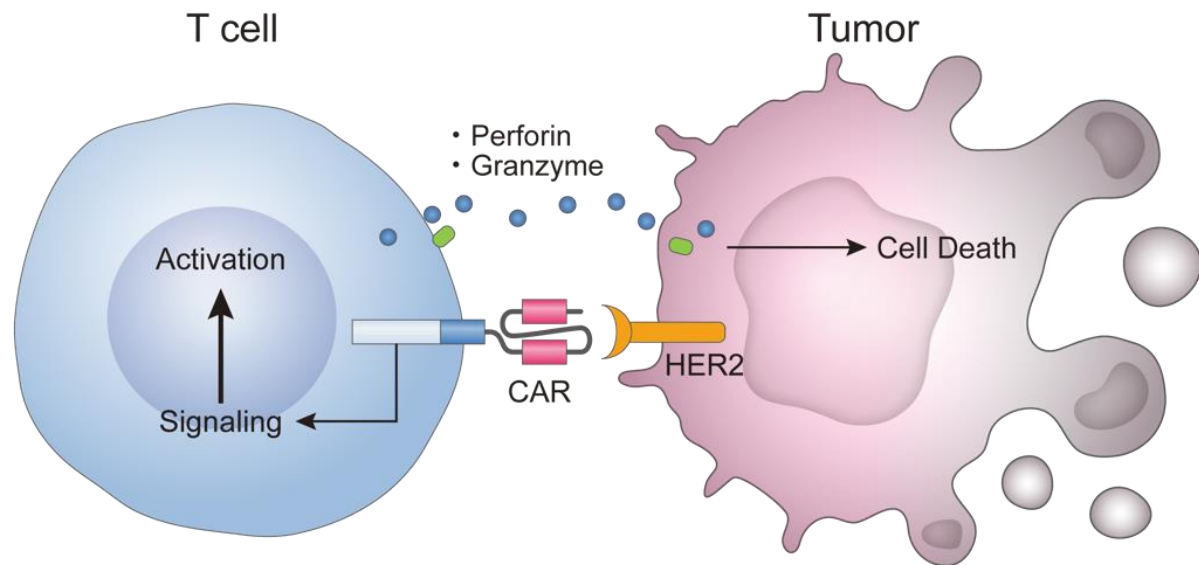
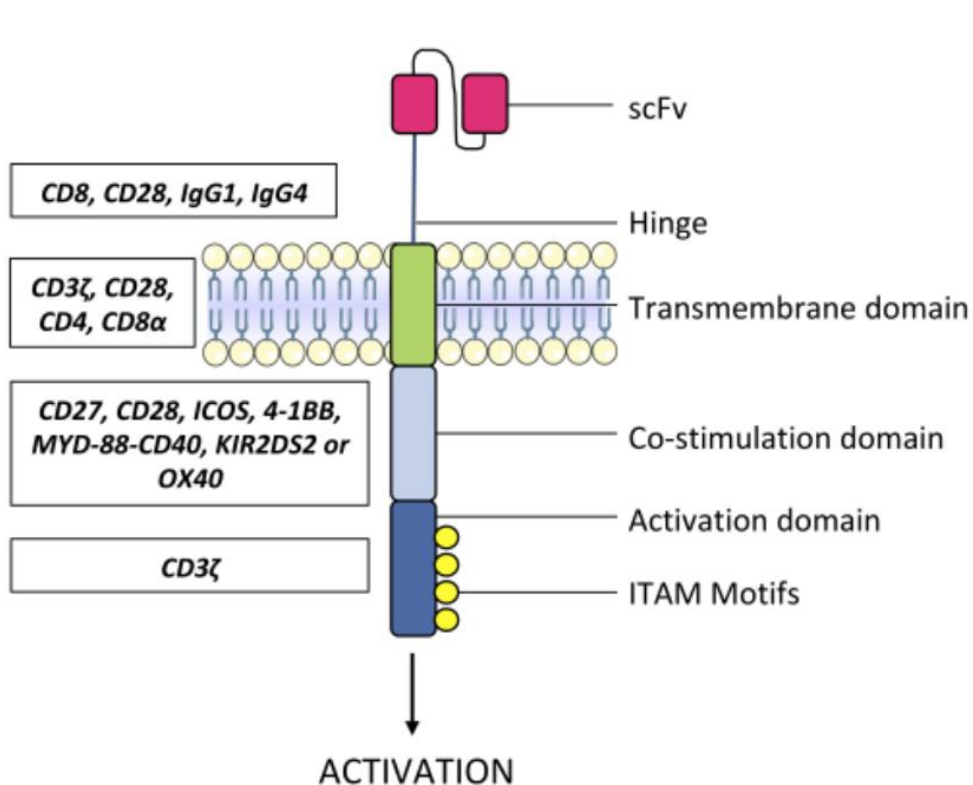
PhD Student

Inserm UMR 1098 RIGHT Besançon

CAR-T cell therapy

Targeted immunotherapy: Antigen-specific

Chimeric Antigen Receptor (CAR)

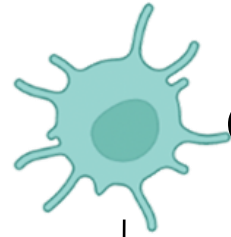


Avouac J. Rev du Rhum.2021

- Diversification of targets
- 6 marketing authorisations in France, 6 FDA
- Expansion to other domains : autoimmunes diseases



Plasmacytoid dendritic cell : dysfunction in autoimmune diseases

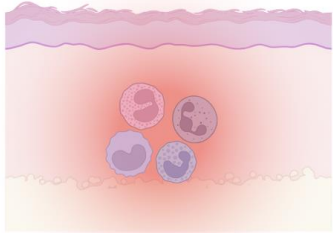


Dysfonctionnal pDCs

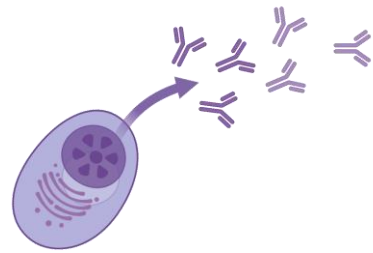
(Lupus, systemic sclerosis, psoriasis...)

*Gilliet M. Arch Dermatol, 2004
Nestle F.O. J.Exp.Med, 2005
Kajafa S. JCI Insight, 2018
Ah Kioon M.D. Sci Transl Med, 2018*

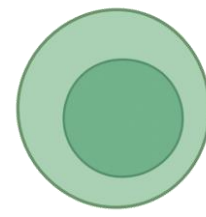
Intense secretion of IFN-I and other cytokines (CXCL4, IL-6, TNF- α ,...)



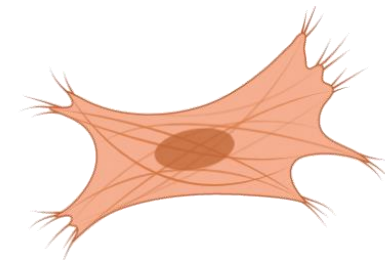
Recruitment of immune cells to the affected tissue
Inflammation



B-cells and plasma cells activation and secretion of autoantibodies

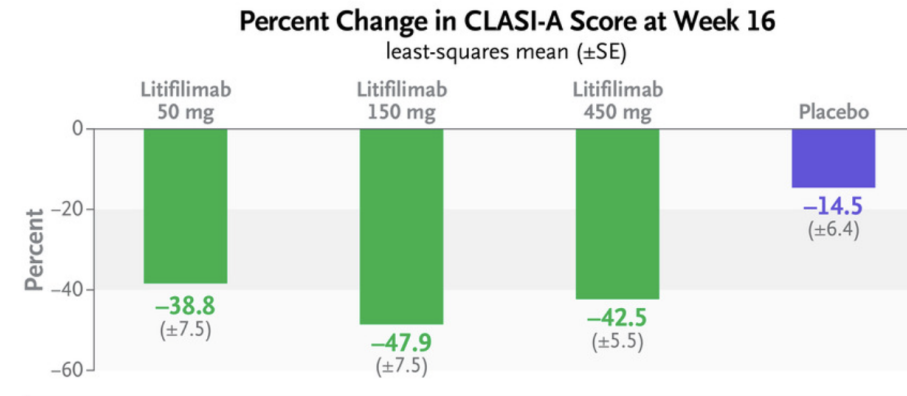
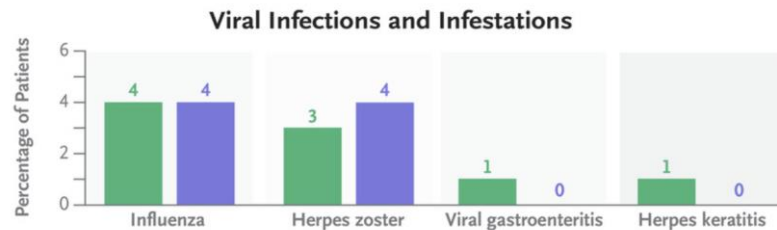
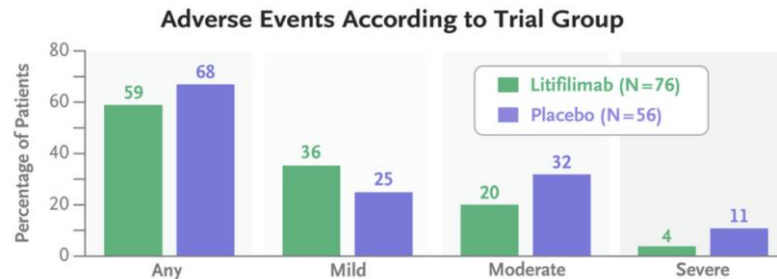
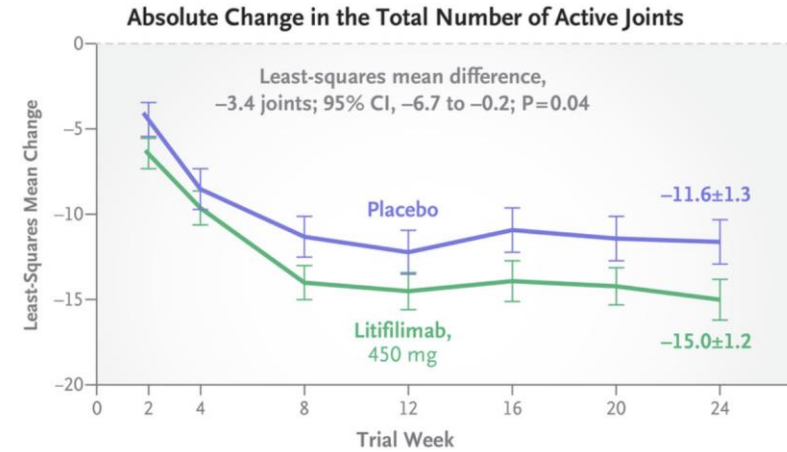
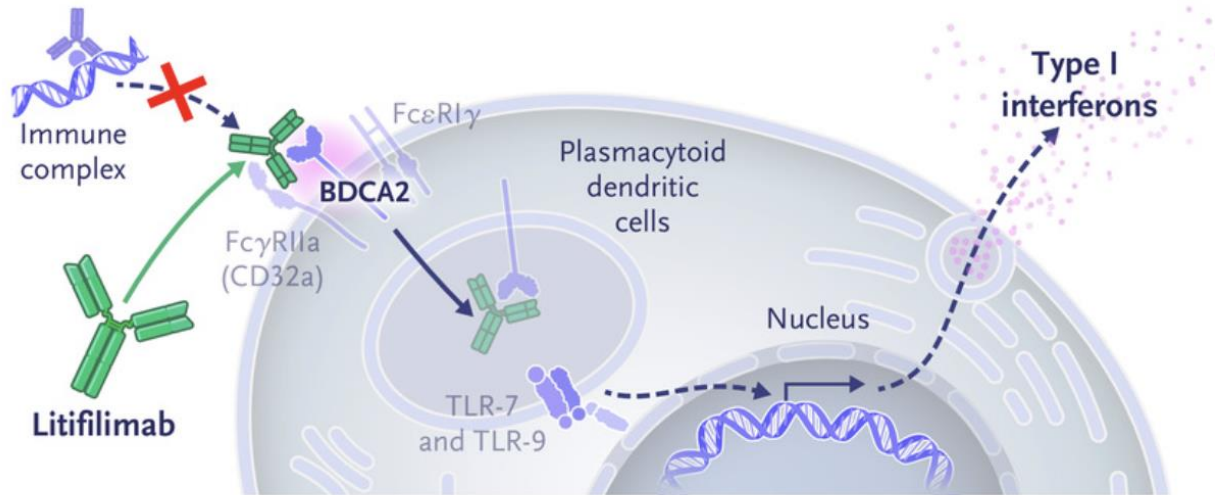


Polarization of T-cells (Th17...)



Modification of target cell phenotypes (fibroblasts, keratinocytes...)

Plasmacytoid dendritic cell : a interesting target cell



Project objectives

CD28/4-1BB CD123 CAR T cells in blastic plasmacytoid dendritic cell neoplasm

[Elodie Bôle-Richard](#), [Maxime Fredon](#), [...] [Francine Garnache-Ottou](#) 

Leukemia **34**, 3228–3241 (2020) | [Cite this article](#)

Preclinical proof of concept : CD123 CAR-T in BPDCN (leukemia)



Evaluation of the benefit to use CD123 CAR-T to eliminate pDCs in dermatological autoimmune diseases

Capacity to produce CAR-T from T cells of patients

First preliminary results (*Caël et al., Br J Dermatol, 2023*)

Functionnality of CD123 CAR-T

- *In vivo* models



Project objectives

CD28/4-1BB CD123 CAR T cells in blastic plasmacytoid dendritic cell neoplasm

[Elodie Bôle-Richard](#), [Maxime Fredon](#), [...] [Francine Garnache-Ottou](#) ✉

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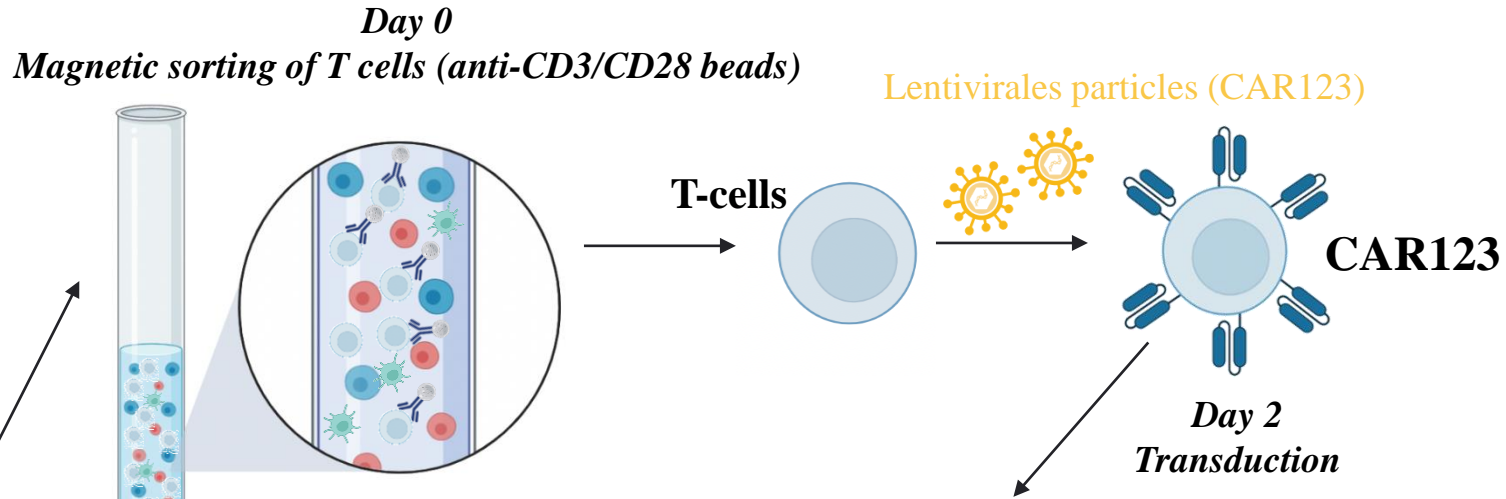
First preliminary results (*Caël et al., Br J Dermatol, 2023*)

Functionnality of CD123 CAR-T

- *In vivo* models



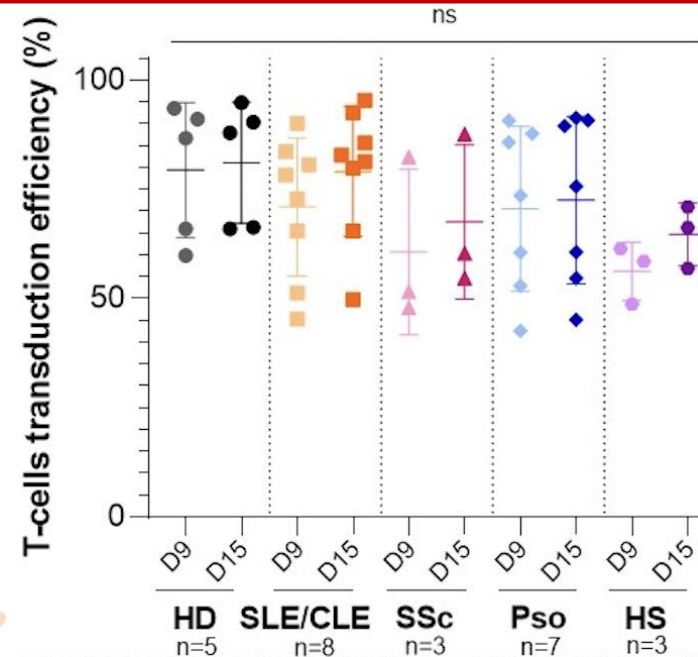
Production of CAR-T CD123



T-cells from patients were able to genetically modified to express a CAR123

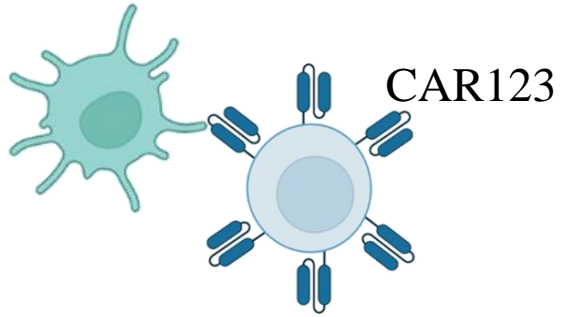
Samples of patients
n=21

- Systemic/cutaneous lupus erythematosus (n=8) SLE/CLE
- Systemic sclerosis (n=3) SSc
- Psoriasis (n=7) PSO
- Hidradenitis suppurativa (n=3) HS



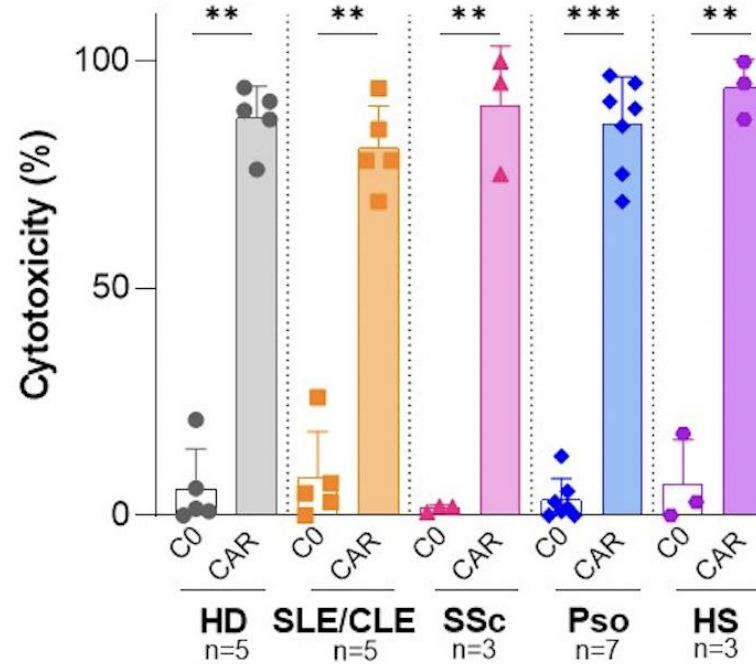
Production of CAR-T CD123

Autologous pDCs



6h of co-culture

Evaluation of target cell death by flow cytometry

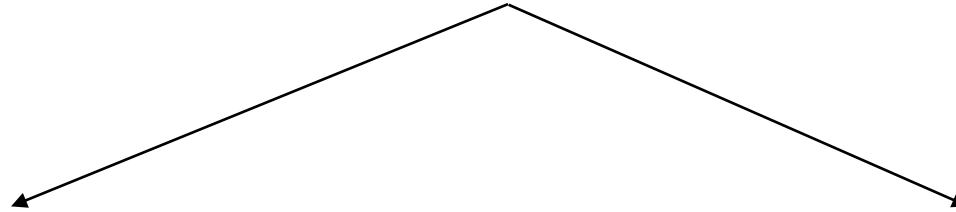


CAR-T cells from patients were able to lyse autologous pDCs *in vitro*



Project objectives

Evaluation of the benefit to use CD123 CAR-T to eliminate pDCs in dermatological autoimmune diseases



Quality assessment of T-cells

First preliminary results (*Caël et al., Br J Dermatol, 2023*)

→ **CARDA-2I** (DRCI, 2023-A00432-43, CHU Besançon)

Functionality of CD123 CAR-T

- *In vivo* models



Project objectives

Evaluation of the benefit to use CD123 CAR-T to eliminate pDCs in dermatological autoimmune diseases

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Functionality of CD123 CAR-T

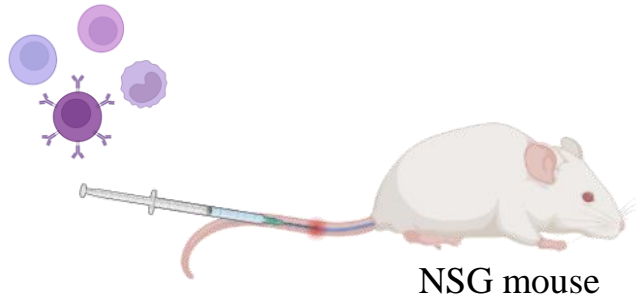
- *In vivo* models



In vivo models

Pseudo-humanisation

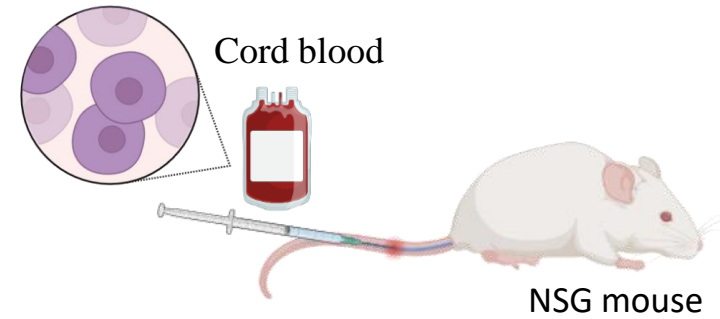
Injection of human PBMCs



Chen J. Front Immunol, 2021
Park MJ. Exp and Mol Medicine, 2022

Humanisation

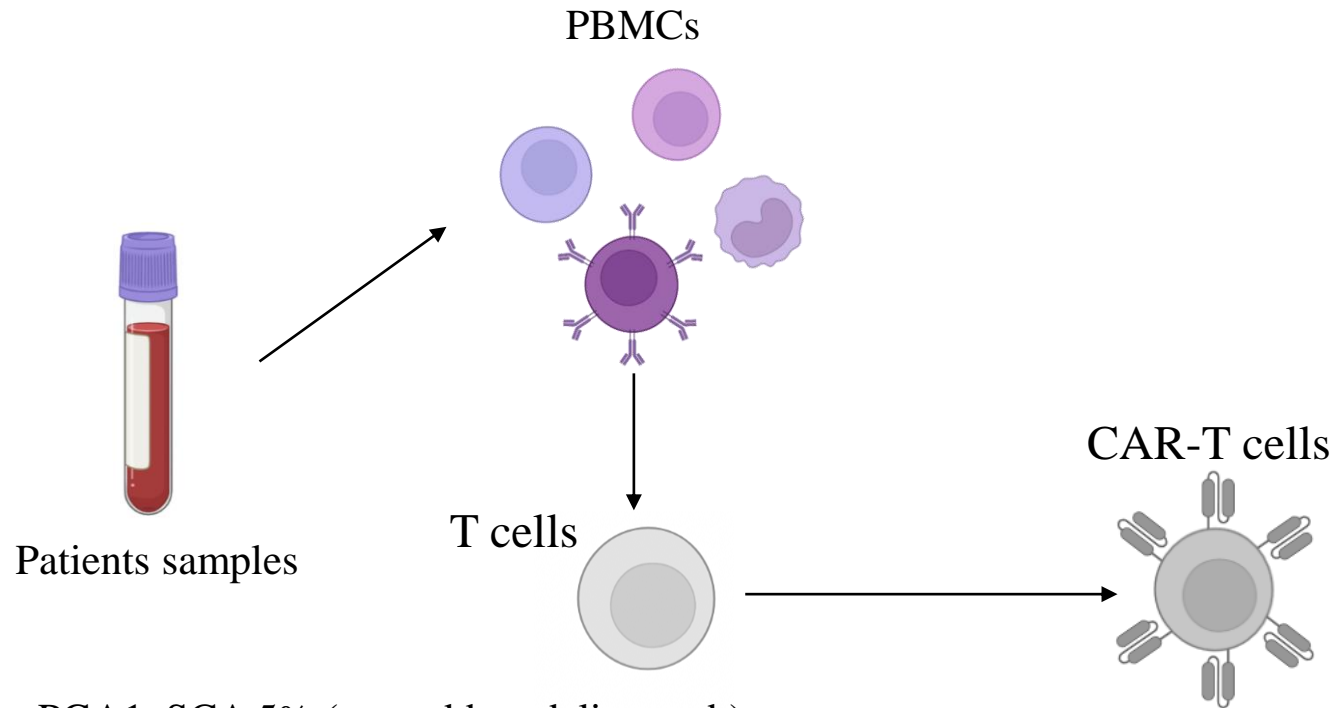
Injection of CD34+ stem cell



Humanisation rate



In vivo model : psoriasis



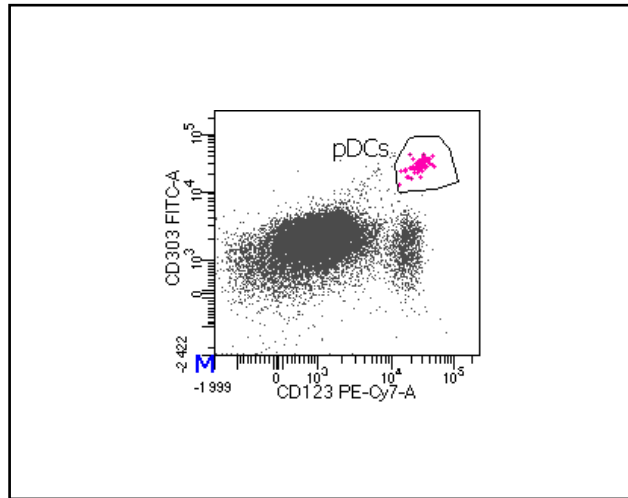
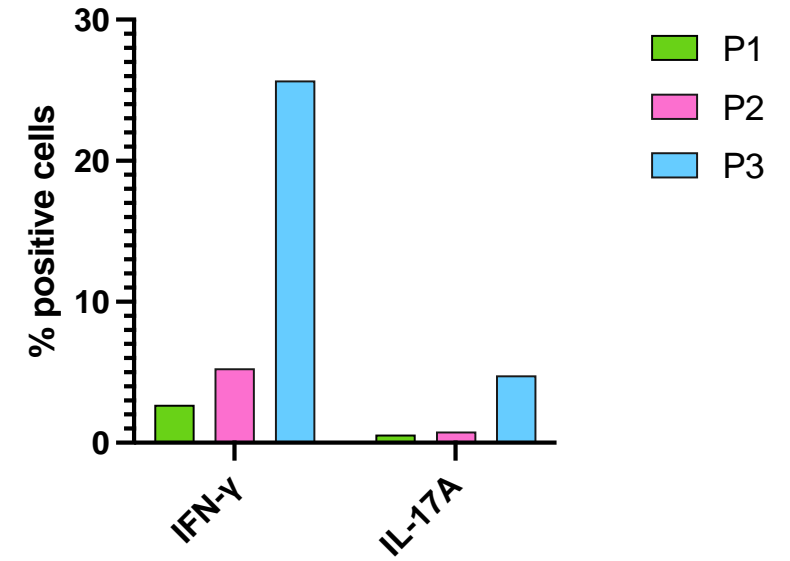
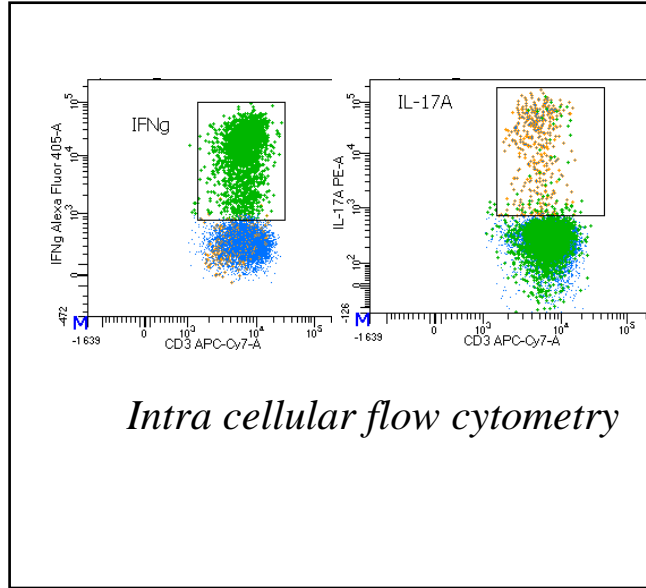
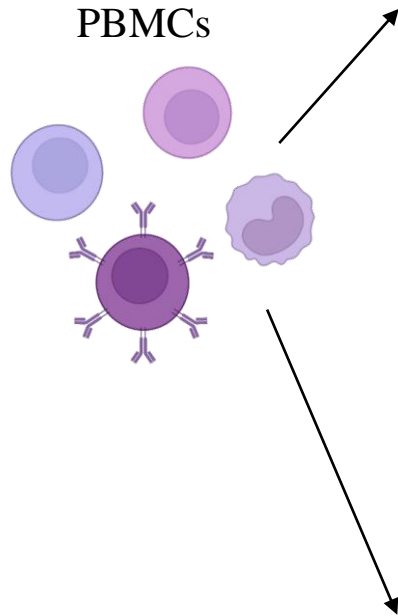
- P1** : PGA1, SCA 5% (treated by adalimumab)
- P2** : PGA3, SCA 40% (not treated)
- P3** : PGA 4-5, SCA 50% (resistant to several therapies)



In vivo model : psoriasis



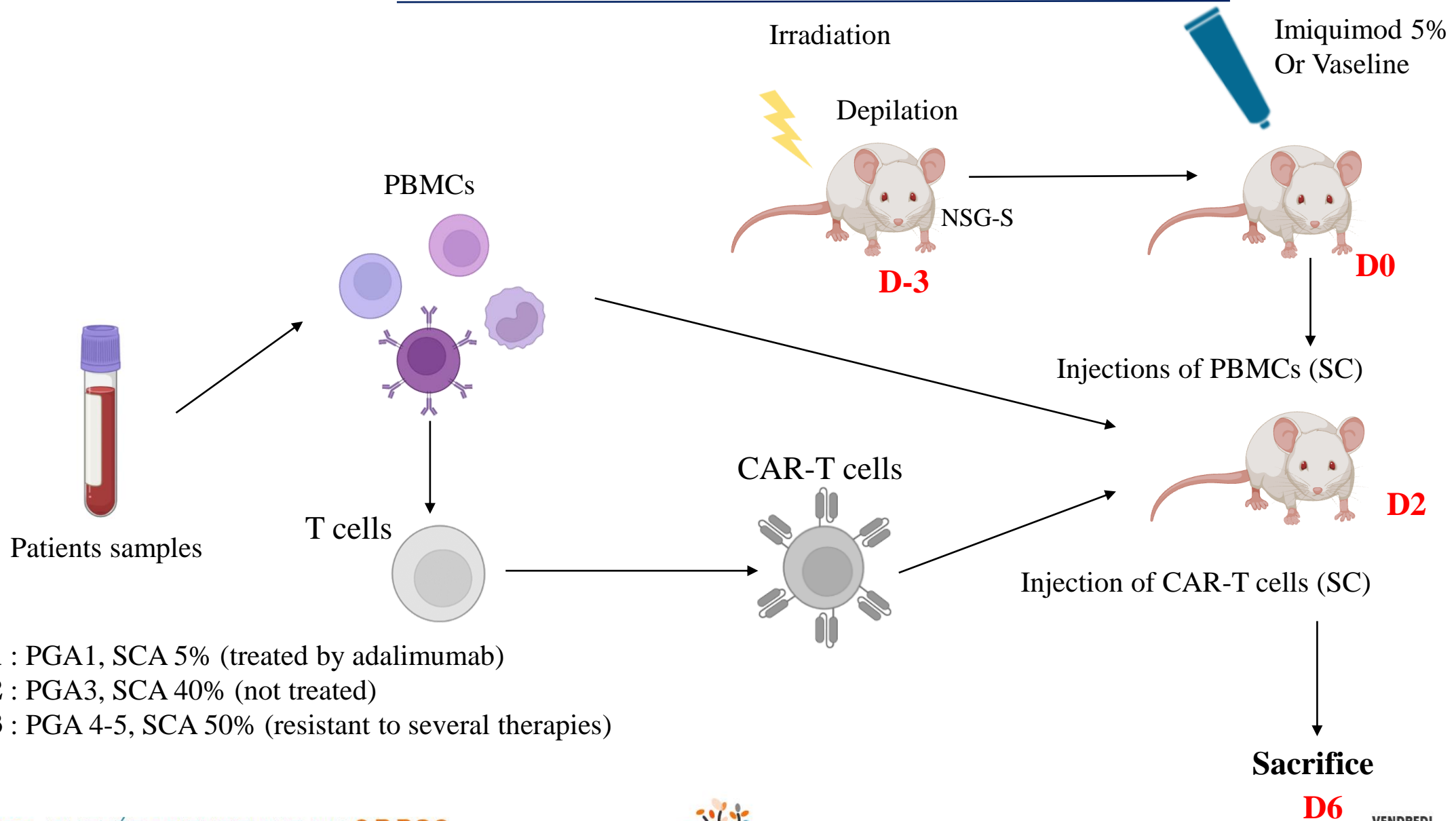
Patients samples



- P1** : PGA1, SCA 5% (treated by adalimumab)
- P2** : PGA3, SCA 40% (not treated)
- P3** : PGA 4-5, SCA 50% (resistant to several therapies)



In vivo model : psoriasis



- P1 : PGA1, SCA 5% (treated by adalimumab)
- P2 : PGA3, SCA 40% (not treated)
- P3 : PGA 4-5, SCA 50% (resistant to several therapies)



In vivo model : psoriasis

Mice groups

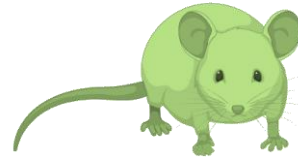


Not treated (NT) (n=3)



Imiquimod (IMI) (n=3)

P1



Imiquimod + PBMCs (n=1)
Imiquimod + PBMCs + CAR-T (n=1)

P2



Imiquimod + PBMCs (n=1)
Imiquimod + PBMCs + CAR-T (n=1)

P3

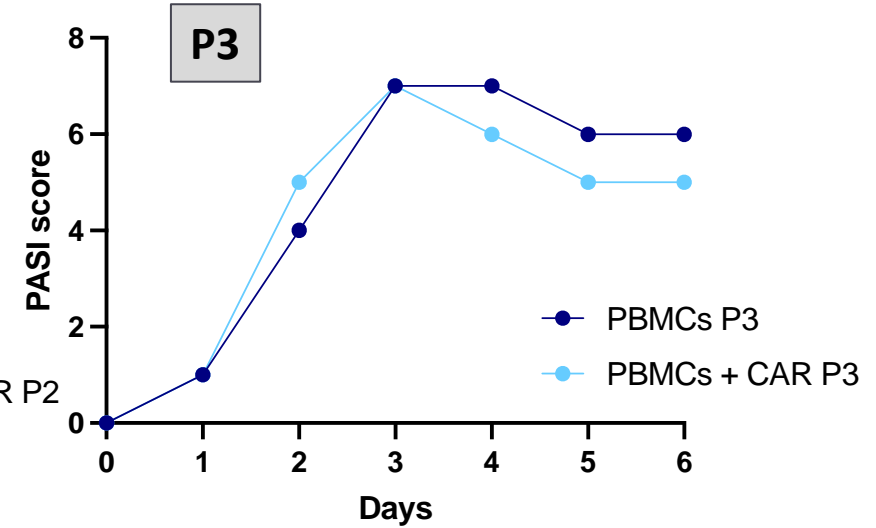
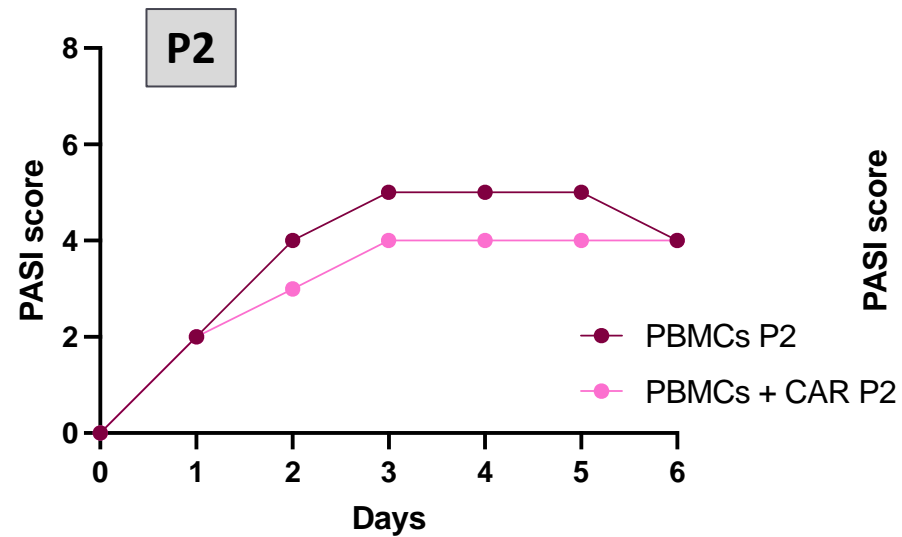
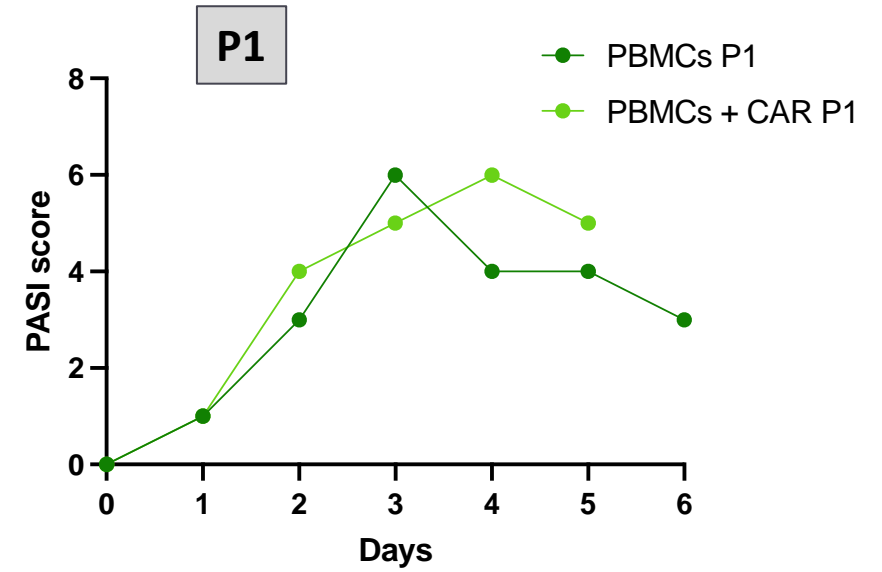
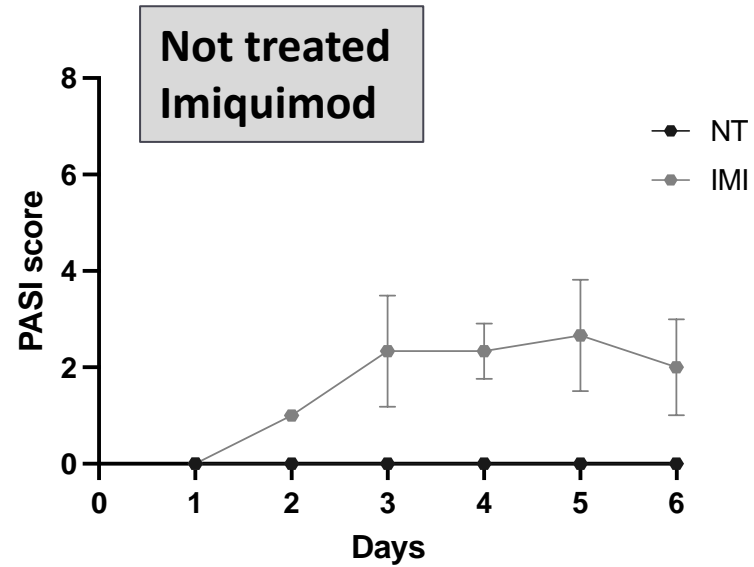
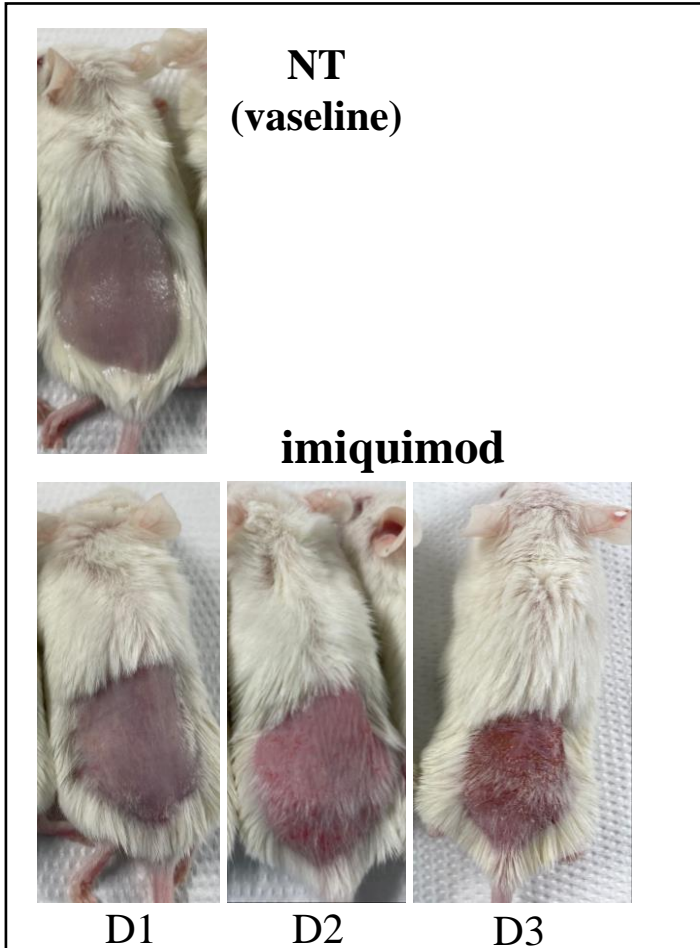


Imiquimod + PBMCs (n=1)
Imiquimod + PBMCs + CAR-T (n=1)



In vivo model : psoriasis

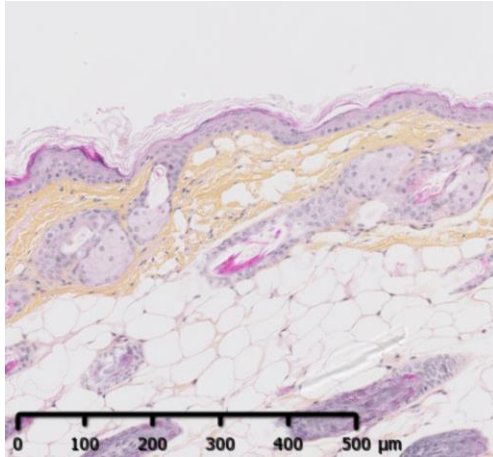
PASI Score



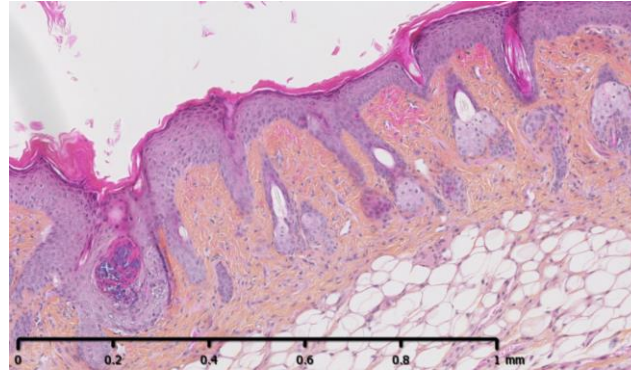
In vivo model : psoriasis

Epidermal thickness

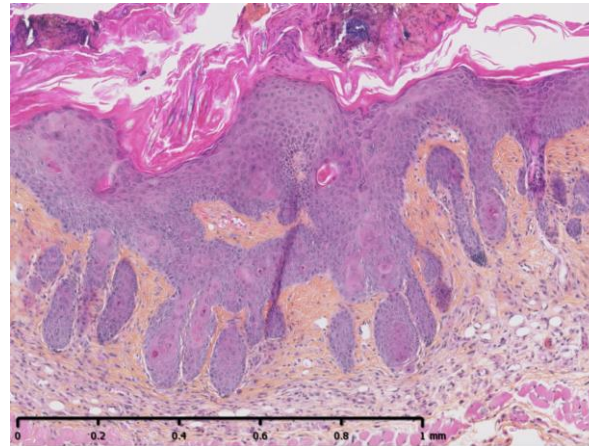
NT



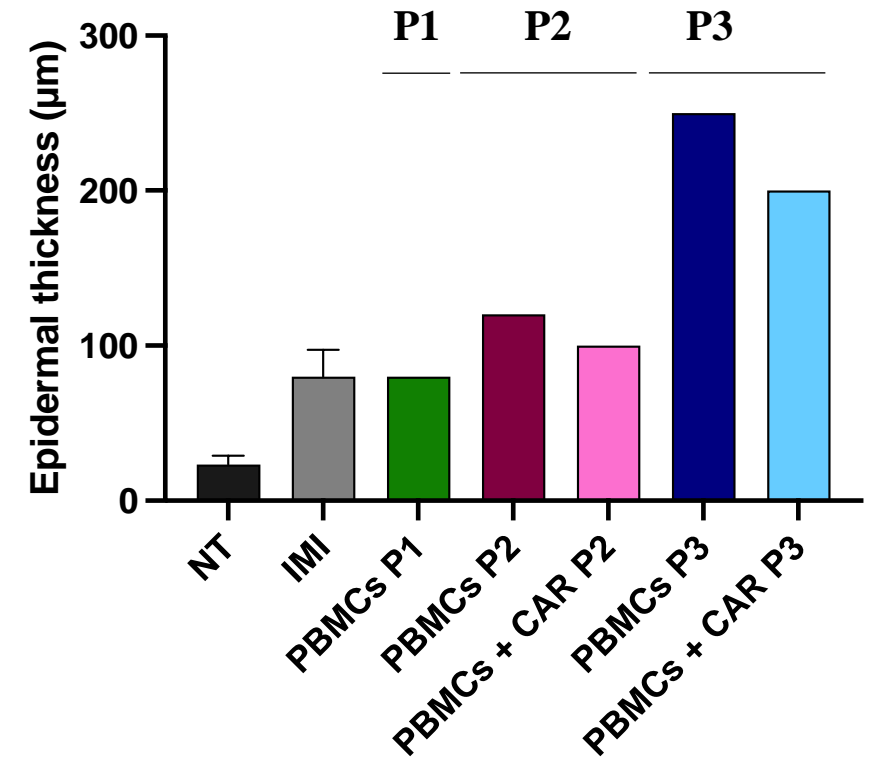
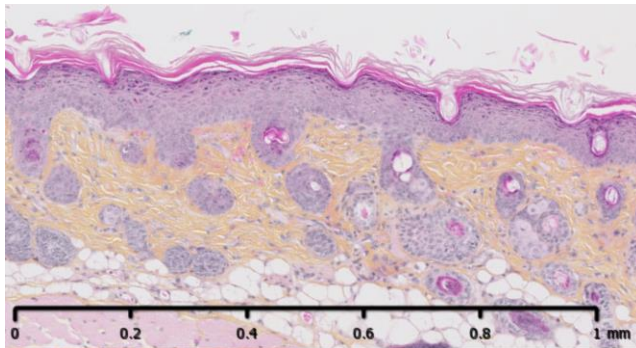
PBMCs P2



PBMCs P3



IMI



x100



Conclusion/perspectives

Development of mouse models

Pseudo-humanisation

Humanisation

Optimisations of the model

Technique mastered in the laboratory
Next step





UMR1098

Pr Francine Garnache-Ottou

Dr Elodie Bôle-Richard

Pr Olivier Adotevi

Pr Yann Godet

Sabeha Biichle

Francis Bonnefoy

Blandine Baffert

Dr Jeanne Galaine

Plateforme de Biomonitoring EFS BFC

Service de dermatologie CHU Besançon

Pr François Aubin

Dr Irène Gallais-Sérézal

Dr Julie Castagna

17^e JOURNÉE SCIENTIFIQUE DU GRPSO Groupe de Recherche sur le PSOriasis
ET DU GREAT Groupe de Recherche sur l'Eczéma ATopique DA (Dermatite Atopique)

Thank you for your attention



ImmunoConcept Bordeaux

Pr Patrick Blanco

Dr Vanja Sisirak



Université Rennes 1

Dr Cédric Ménard



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