La recherche clinique et translationnelle sur la sclérodermie

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CERAINO
FHU Precision Health In Complex Inflammatory Diseases (PRECISE)
University of Lille
Lille University Hospital

on behalf....

Recherche Clinique

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Fédération Hospitalo-Universitaire (FHU) PRECISE

Responsable du projet : Pr David LAUNAY (PU-PH, médecine interne CHU de Lille)

Précise
Santé de précision dans les maladies inflammatoires chroniques

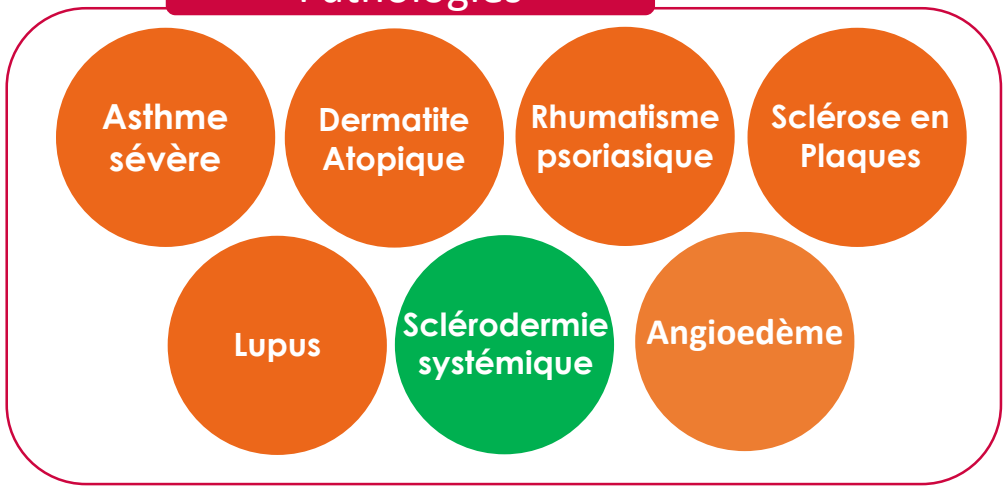
WP1	Création de la plateforme PRECISE : une plateforme clinico-biologique commune interrégionale	WP leaders : Pascal VIVIER, Céline PODEVIN
	Tâche 1.1 : Extension de la base de données locales (IMMINENT) à l'inter-région du G4	Tâche 2.2 : Mise en place d'une biobanque inter-régionale

OBJECTIF : création d'une **cohorte clinico-biologique prospective sur les maladies inflammatoires chroniques** à médiation immune (IMIDs), par la structuration de l'observation médicale associée à une biobanque

Travail initié dans le cadre du précédent FHU :
⇒ Actuellement uniquement **lillois**, avec 7 pathologies

✓ Réglementaire ✓ Technique / organisationnel

Pathologies



⇒ **Extensions** *(nouveaux centres, nouvelles pathologies) prévues* dans le cadre du FHU PRECISE

Données collectées

- **Données du soin structurées**
- Incluant des **données communes** à l'ensemble des pathologies *(métier, niveau d'étude, expositions, autres maladies inflammatoires ou auto-immunes, cancer, FDR cardiovasculaires, toxiques, grossesses, vaccins, hospitalisation, infection sévère, …)*
- **Données de qualité de vie** (SF-12)

Biobanque

- **Sérum**
- **Plasma** + récupération des buffy coat
- **PBMC** (cellules mononuclées)

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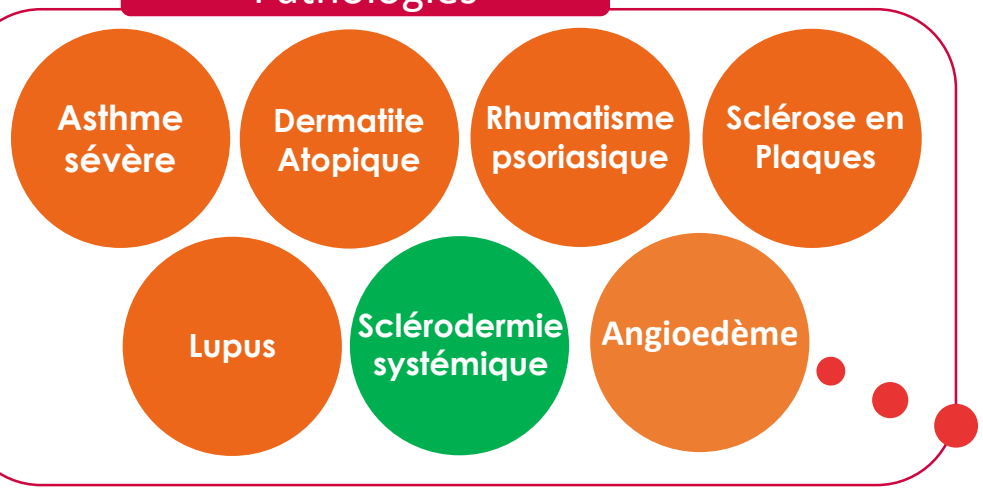

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CeRAiNO
Centre de référence des maladies auto-immunes systémiques rares du Nord et Nord-Ouest

Focus SSc au 07/03/2022 : **250 patients inclus** dans la cohorte
Complétant les 450 inclus dans la cohorte n°1 (plasma/serum)

Intérêt de de la TEP au 18 F-FDG positron dans la SSc (Ledoult E, et al. Arthritis Res Ther. 2021) montrant que cet examen pouvait permettre de prédire l'évolution de l'atteinte pulmonaire et était corrélé avec sa sévérité.

Fig. 3 Visual examination of FDG PET/CT scans. Transverse slides of the FDG PET/CT scans of **a** a SSc-ILD with an abnormal interstitial lung pattern of FDG uptake and **b** a SSc-ILD without an abnormal interstitial lung pattern of FDG uptake

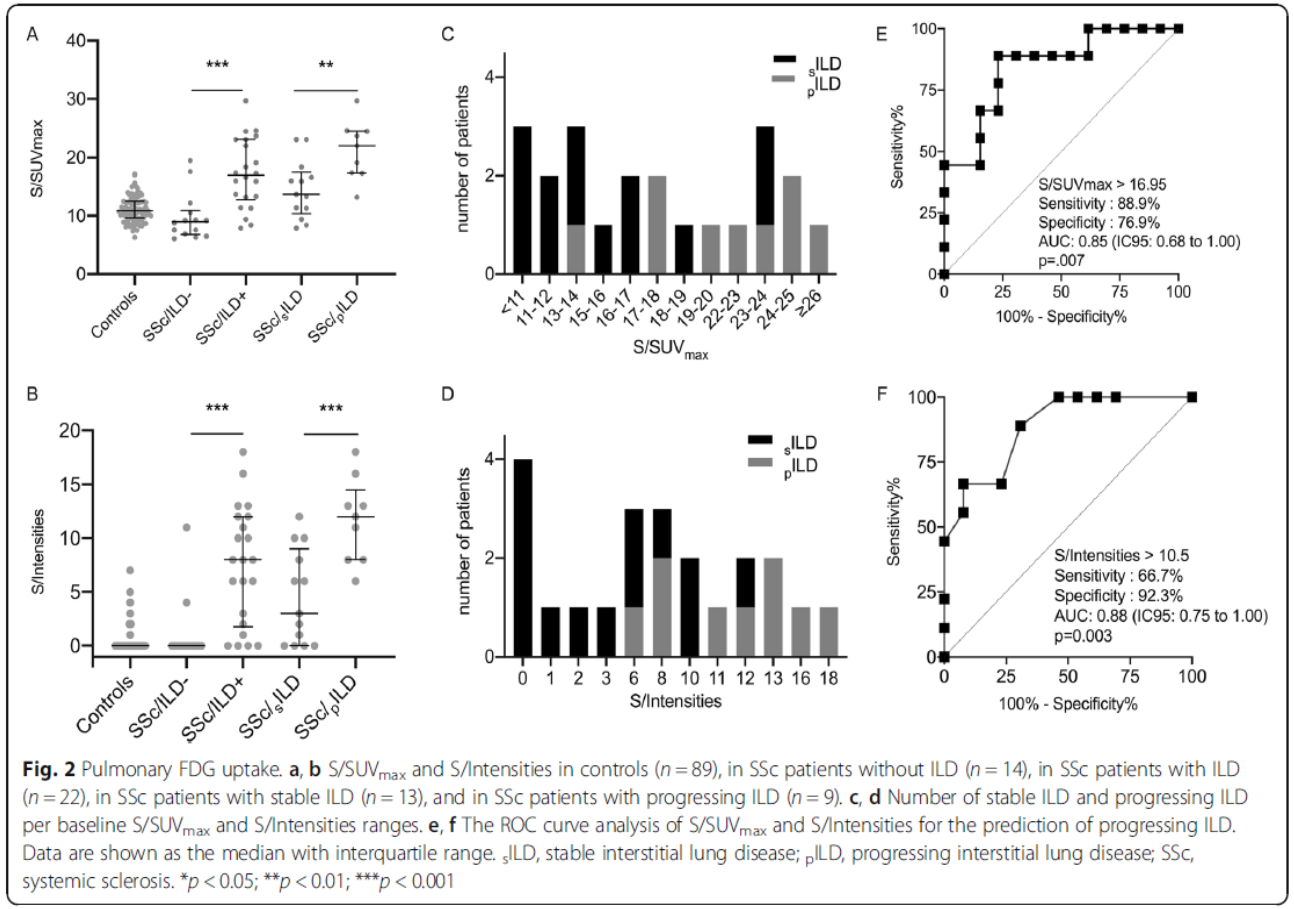
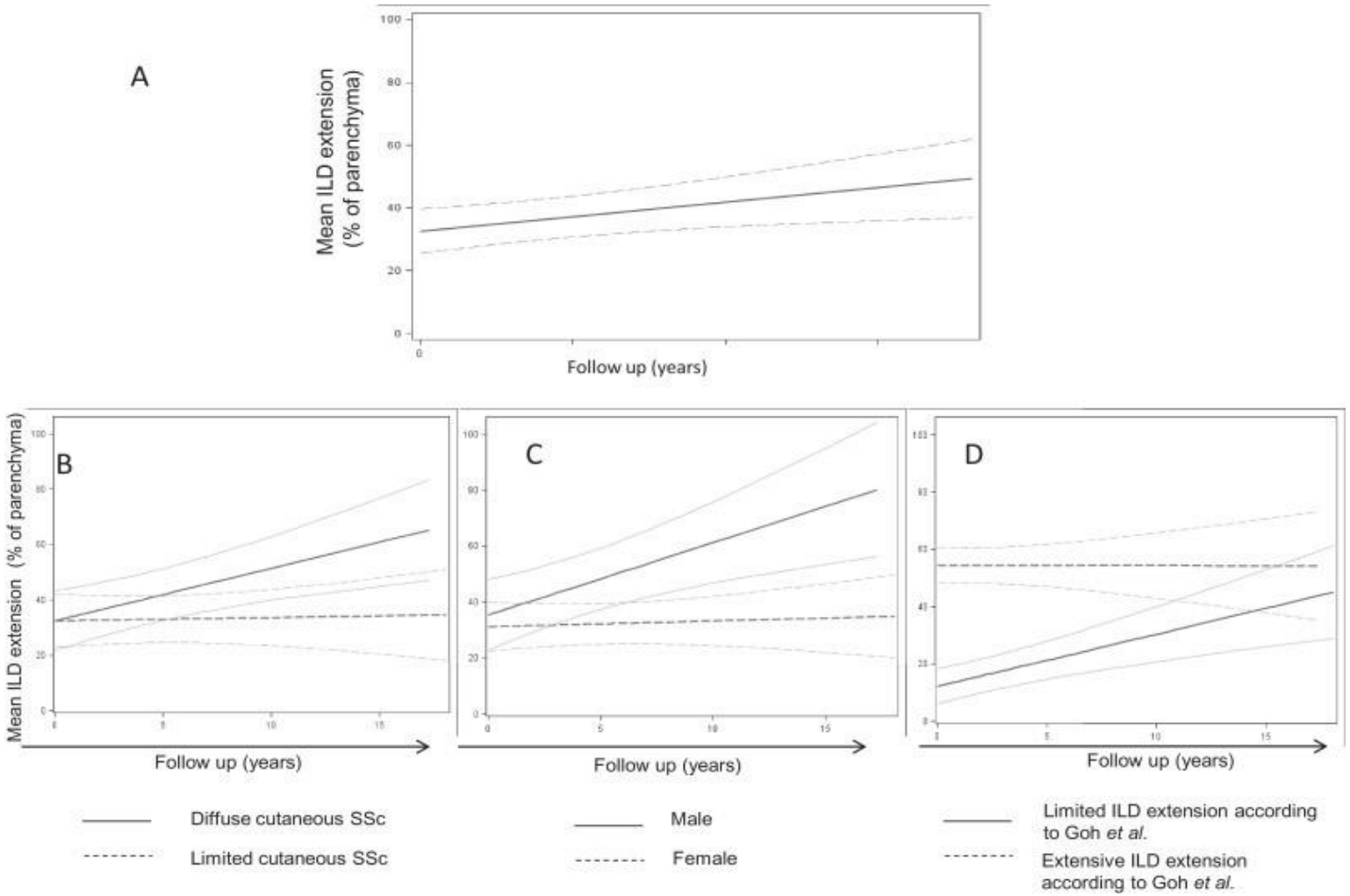


Fig. 2 Pulmonary FDG uptake. **a**, **b** S/SUV_{max} and S/Intensities in controls ($n = 89$), in SSc patients without ILD ($n = 14$), in SSc patients with ILD ($n = 22$), in SSc patients with stable ILD ($n = 13$), and in SSc patients with progressing ILD ($n = 9$). **c**, **d** Number of stable ILD and progressing ILD per baseline S/SUV_{max} and S/Intensities ranges. **e**, **f** The ROC curve analysis of S/SUV_{max} and S/Intensities for the prediction of progressing ILD. Data are shown as the median with interquartile range. $_{s}$ILD, stable interstitial lung disease; $_{p}$ILD, progressing interstitial lung disease; SSc, systemic sclerosis. $^{*}p < 0.05$; $^{**}p < 0.01$; $^{***}p < 0.001$

==> Etude prospective SCLEROTEP

Evolution des TDM thoraciques au cours de la SSc (Le Gouellec et al. Semin Arthritis Rheum 2020) permettant de mettre en évidence des facteurs pronostiques de l'aggravation pulmonaire tels les antitopoisomérase 1 et la forme diffuse de SSc.



Evaluation des trajectoires du score de Rodnan au cours du temps chez les patients SSc (Ledoult et al. Arthritis Res Ther 2020).

Cette étude a caractérisé 5 trajectoires d'évolution du score de Rodnan avec des implications pronostiques :

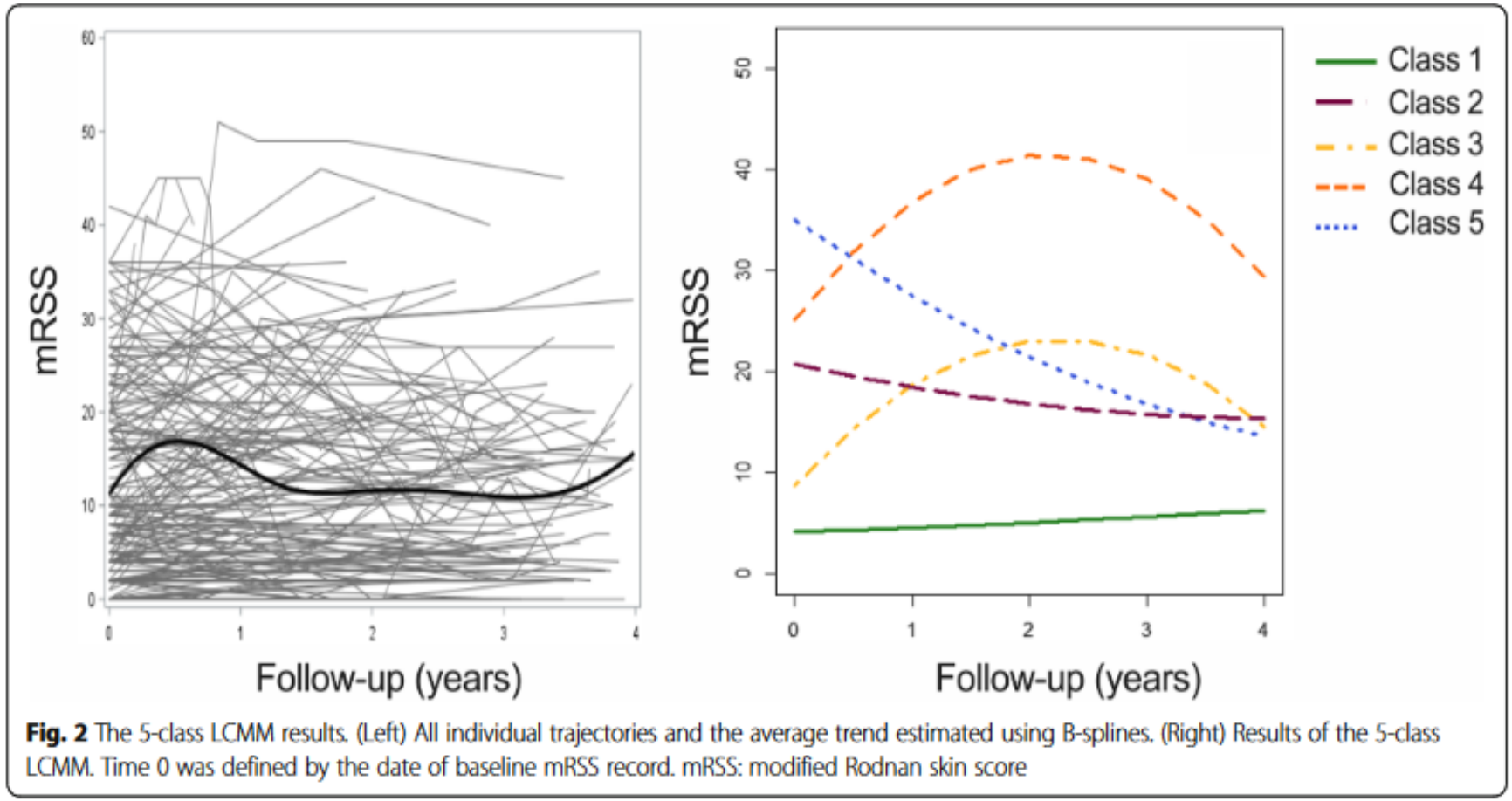


Fig. 2 The 5-class LCMM results. (Left) All individual trajectories and the average trend estimated using B-splines. (Right) Results of the 5-class LCMM. Time 0 was defined by the date of baseline mRSS record. mRSS: modified Rodnan skin score

La survie de l'HTAP de la SSc avait augmenté pour les patients de moins de 70 ans entre 2006 et 2017 (Hachulla et al. Chest 2020).

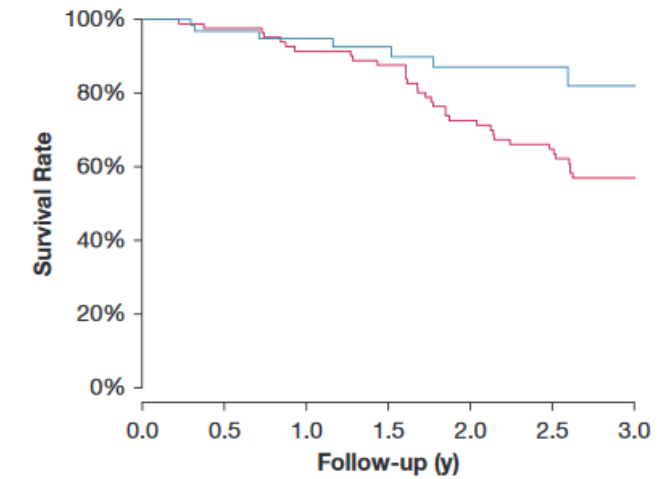


Figure 2 – *Kaplan-Meier survival curve in patients with systemic sclerosis-associated pulmonary arterial hypertension aged ≤ 70 years for the two study periods. See Figure 1 legend for expansion of abbreviation.*

Ongoing

- Neurosclérodermie : IRM3T/spectroscopie cérébrale (PHRC)
- Rôle pronostique de biomarqueurs simples
- Influence du groupe sanguin
- Atteinte cardiaque
- ….

Recherche translationnelle et fondamentale

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Infinite

contract 2020-2024

Institute for Translational Research in Inflammation

INFINITE U1286

Inserm | Université de Lille | CHU de Lille

Director: Laurent Dubuquoy, PhD

Deputy director: David Launay, MD, PhD

Université de Lille

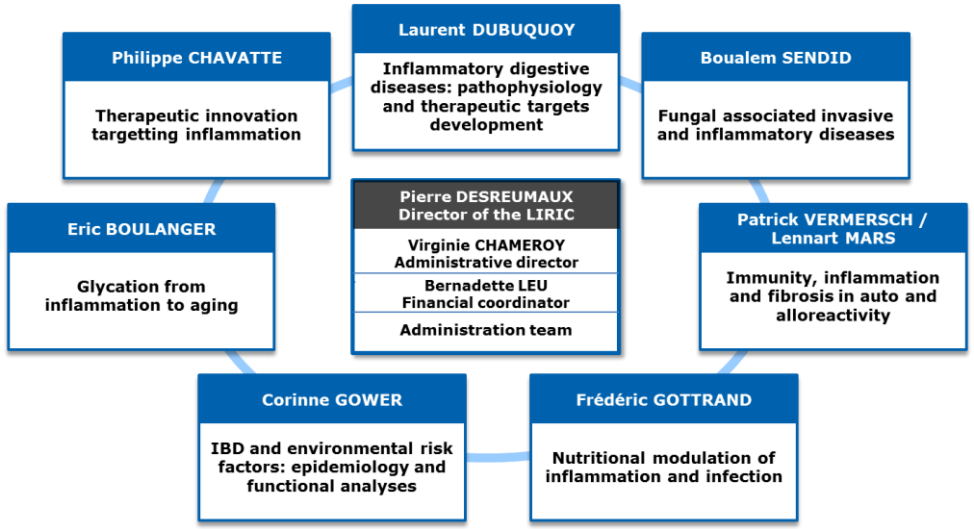
ufr3s Sciences de Santé et du Sport

CHU LILLE

Inserm

Restructuration

LIRIC → Infinite



LIRIC = 7 teams (2015-2019)

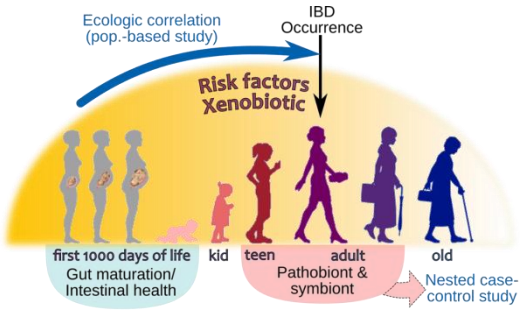
INFINITE = 1 team (2020-2024)

Inflammation, aging, neuroinflammation and glycobiology

1 theme: inflammation from its origin to its consequences

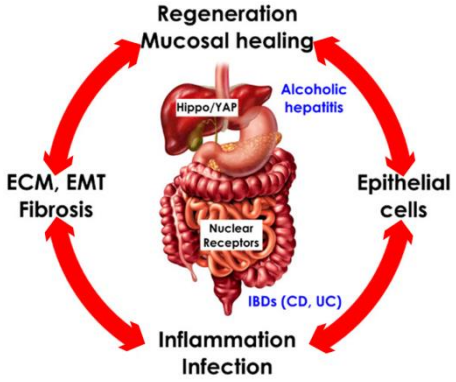
Global scientific strategy: inflammation

WP1 Environmental contributions to mucosal homeostasis and IBD susceptibility

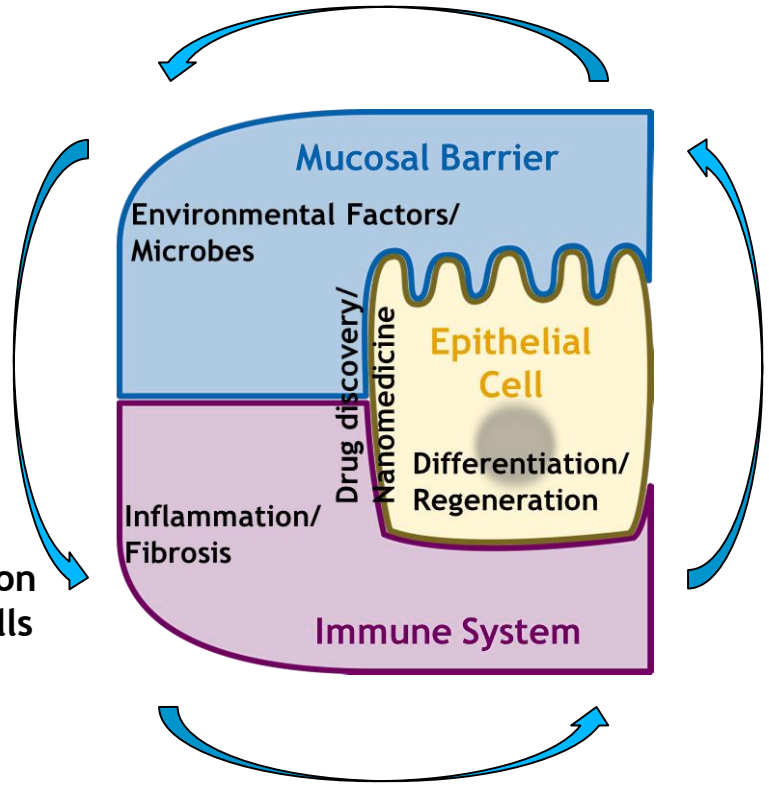


Origin of inflammation

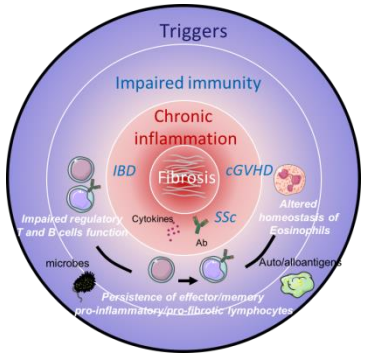
WP2 Epithelium integrity: from pathologic regeneration to homeostasis



Consequences of inflammation

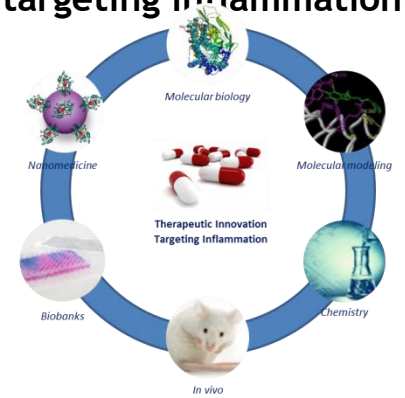


WP3 From chronic inflammation to fibrosis: role of immune cells



Consequences & mechanisms of inflammation

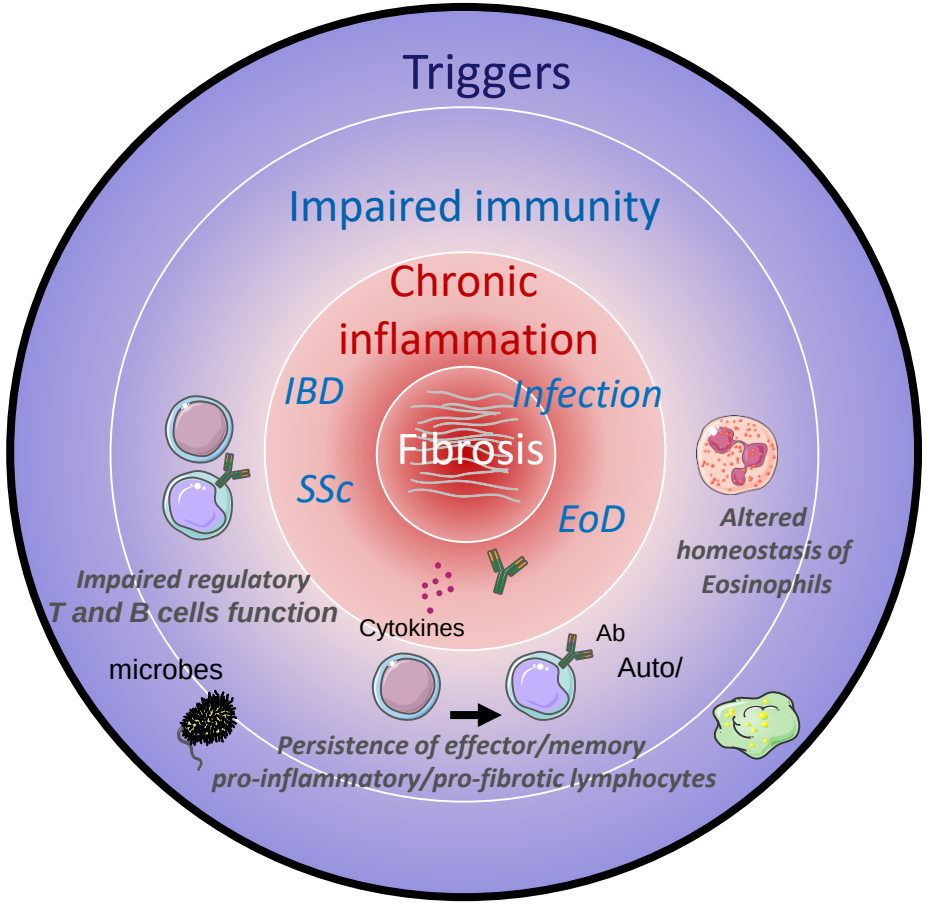
WP4 Therapeutic innovation targeting inflammation



New treatments and biomarkers

WP3- From chronic inflammation to fibrosis: Role of immune cells

Fibrosing chronic inflammatory diseases



Task 1
Inflammatory Bowel Diseases (IBD)
Mucosal immune responses in intestinal diseases: Innate, T and B lymphocytes

PI: B. MERESSE

Task 2
Systemic sclerosis (SSc)
The pathogenic role of B cells and their interaction with memory T cells

PI: Pr D. LAUNAY / Pr S. DUBUCQUOI

Task 3
Infection (CMV, COVID-19)/ Eosinophilic disorders (EoD)
T cells and Eosinophils

PI: Pr M. LABALETTE / Dr G. LEFEVRE

Infinite

Environment | Epithelial tissue | Immunity | Fibrosis | Therapeutics

WP3/Task 2: Fibrosis & Inflammation (FIRE)

Pr David Launay/Pr Sylvain Dubucquoi/Pr Vincent Sobanski

AJose-Garcia, postdoc
A Filiot, data scientist
A Largy, ASI
A Chépy, PhD
A Collet, M2R
E Ledoult, CCU-AH
L Bourel, PhD
L Guilbert, Tec
M Jendoubi, IE
M Le Maître, PhD
S Sanges,MCU-PH
S Speca, IR
S Vivier, PhD
T Guerrier, IR
T Machet, M2R

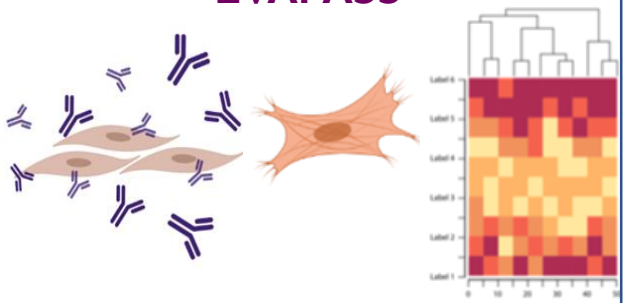
WP3/Task 2:

The pathogenic role of immune cells in fibrosis in IMIDs (FIRE)

Systemic sclerosis (SSc) as a model

Pathogenic autoantibodies

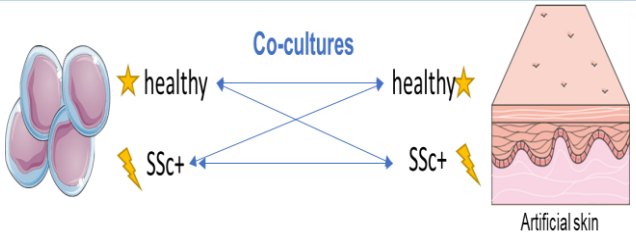
EVAPASS

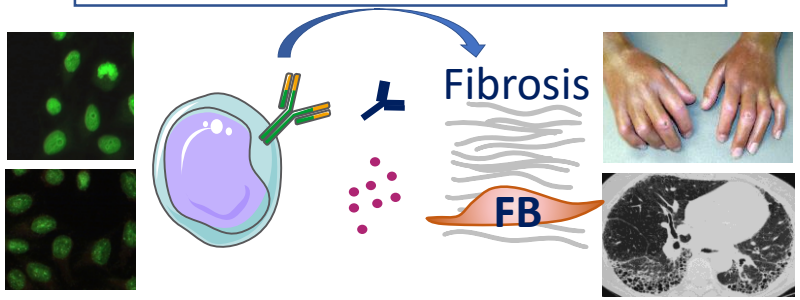


Multi-Omics data

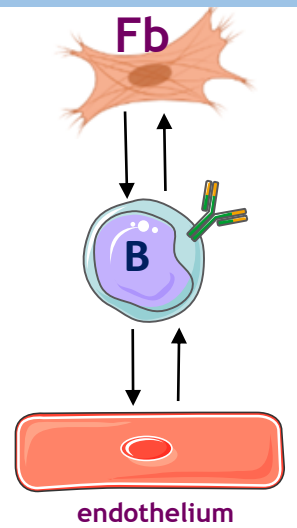
IMPLICITE

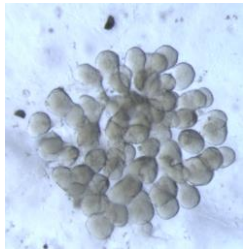
Immune cells skin infiltration



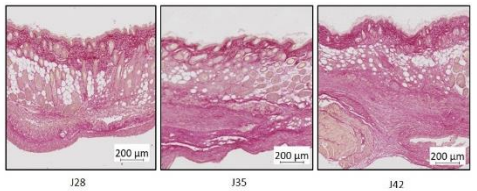


Cells interaction





Skin and lung organoids



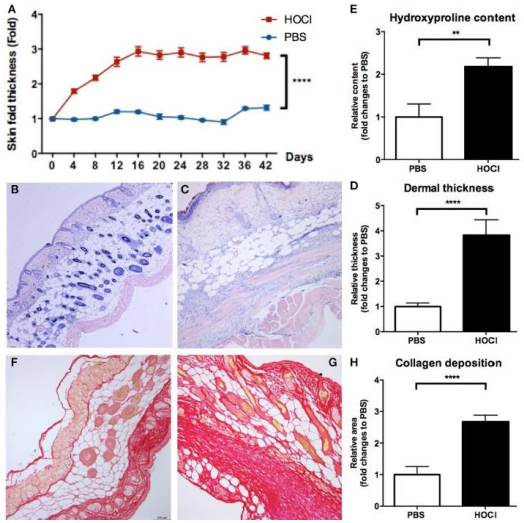
Model characterisation

Mouse models of inflammatory fibrosis

Extracorporeal photopheresis

drugs

Infinite



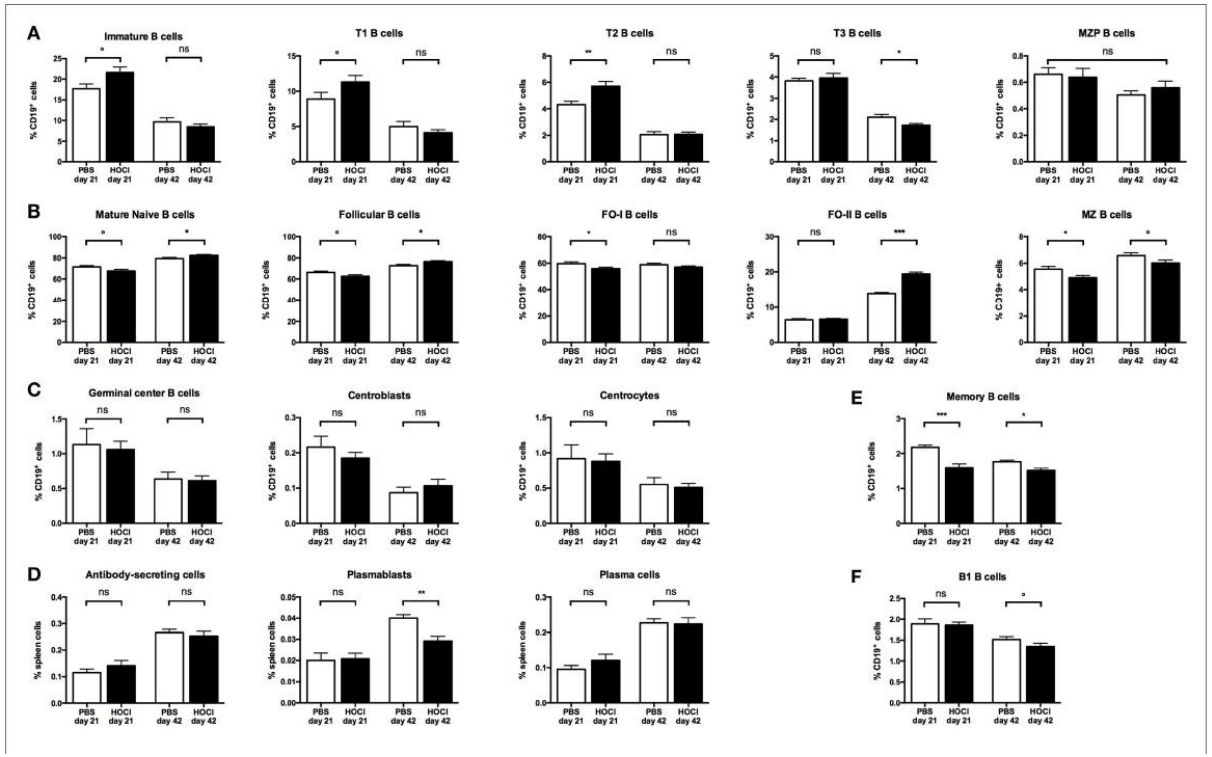
frontiers in Immunology

ORIGINAL RESEARCH
published: 07 February 2017
doi: 10.3389/fimmu.2017.00063

B Cell Homeostasis and Functional Properties Are Altered in an Hypochlorous Acid-Induced Murine Model of Systemic Sclerosis

*Sébastien Sanges[1,2,3,4], Manel Jendoubi[1,2], Niloufar Kavian[5], Carine Hauspie[1,2,6], Silvia Speca[1,2], Jean-Charles Crave[7], Thomas Guerrier[1,2], Guillaume Lefèvre[1,2,3,4,6], Vincent Sobanski[1,2,3,4], Ariel Savina[8], Eric Hachulla[1,2,3,4], Pierre-Yves Hatron[1,2,3,4], Myriam Labalette[1,2,6], Frédéric Batteux[5], Sylvain Dubucquoi[1,2,6] and David Launay[1,2,3,4]**

Results: Phenotypic analyses showed an early expansion of transitional B cells, followed by a late expansion of the mature naive subset and decrease in plasmablasts and memory B cells. These anomalies are similar to those encountered in SSc patients.



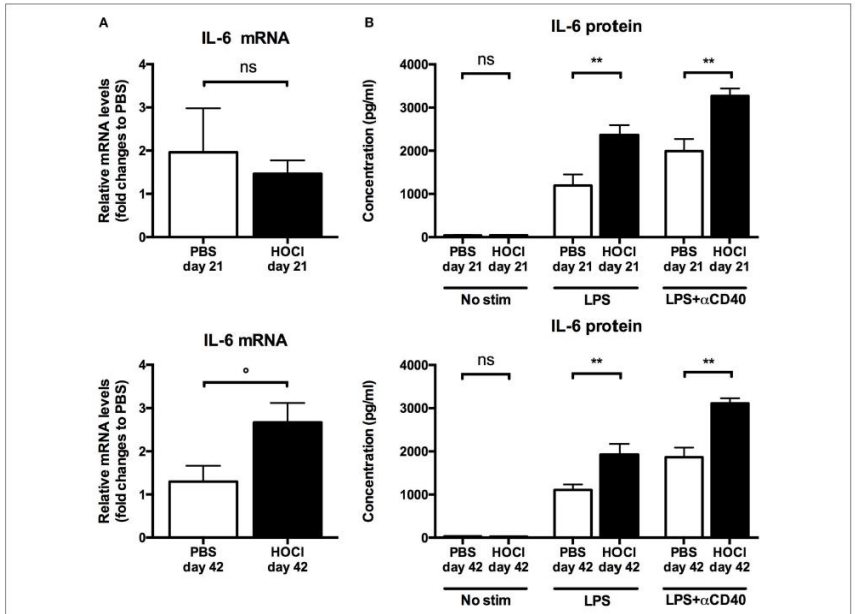


FIGURE 9 | Interleukin (IL)-6 production by splenic B cells in phosphate-buffered saline (PBS) and HOCl mice at day 21 and day 42. **(A)** IL-6 mRNA levels in splenic B cells after collection and sorting, normalized to GUSB and expressed as fold changes to PBS day 21 for day-21 groups (top row), and to PBS day 42 for day-42 groups (bottom row) (n = 4–6 per group). **(B)** IL-6 supernatant levels after culture of splenic B cells for 48 h with various stimulation conditions [none, lipopolysaccharide (LPS), LPS + anti-CD40 antibody] at day 21 (top row) and day 42 (bottom row), expressed in picograms per milliliter (n = 6–8 per group).

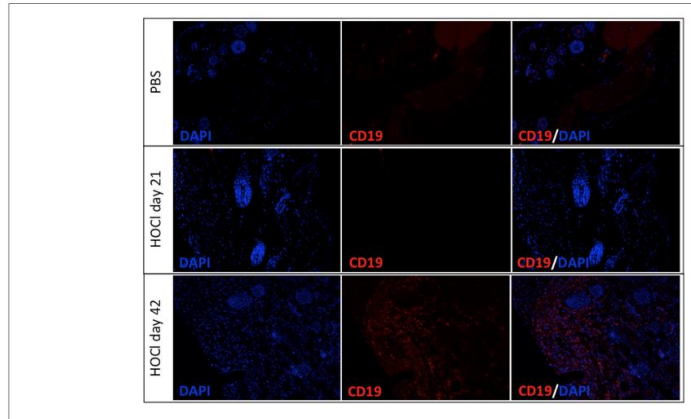
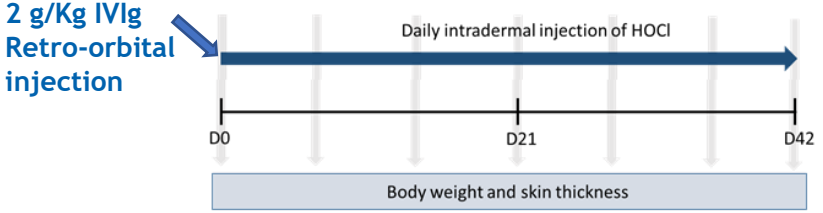


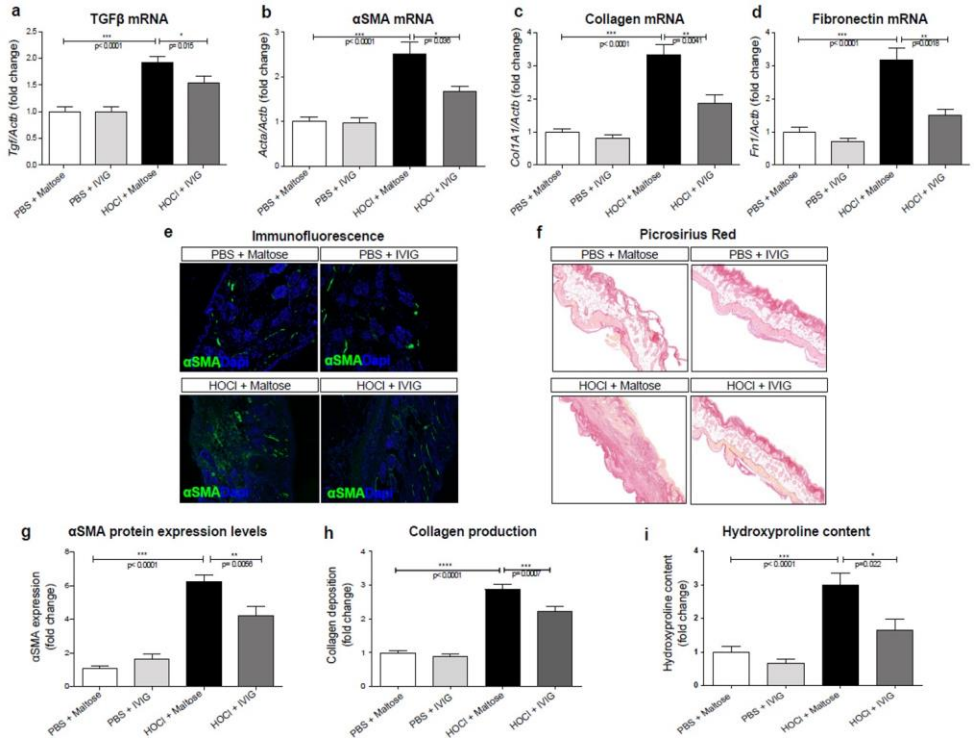
FIGURE 8 | Representative images of skin sections immunostained for CD19 in phosphate-buffered saline (PBS) and HOCl mice at day 21 and day 42. Representative images of PBS skin (top row), HOCl skin at day 21 (middle row), and HOCl skin at day 42 (bottom row) immunostained with DAPI (left column), with anti-CD19 antibody (middle column), and with both (right column) (n = 5 per group).

Murine model of HOCl-induced SS for therapeutic screening

IVIg administration controls skin fibrosis in mice

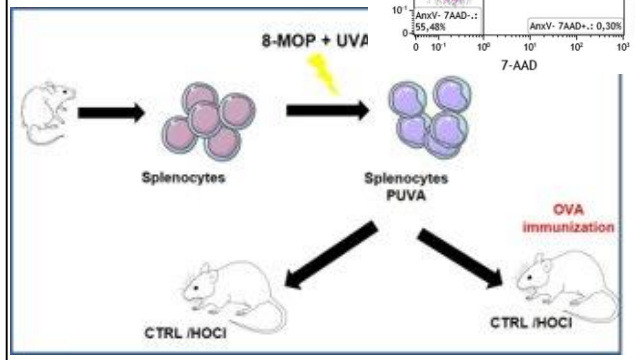
2 g/Kg IVIg
Retro-orbital injection

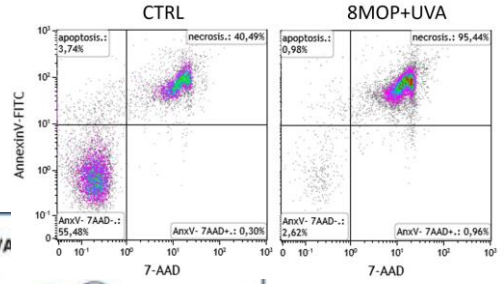




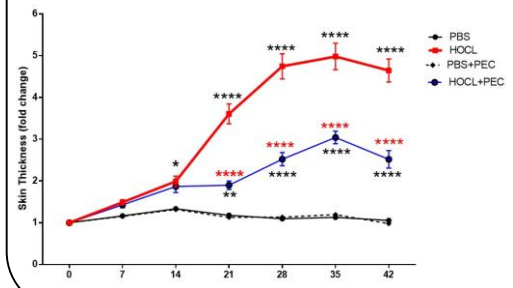
Pre-clinical study of Extracorporeal phothopheresis efficiency

Therakos Research Grant





Macroscopic skin thickness



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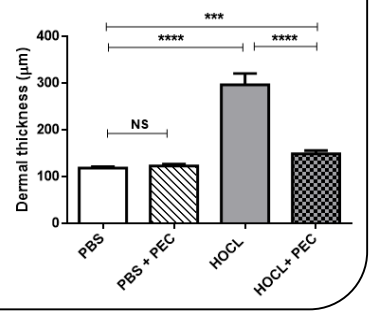

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Environment | Epithelial tissue | Immunity | Fibrosis | Therapeutics

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WP3- INRIA Team : ENDOMIC

Various sources of health data

Clinical data warehouses

Data produced routinely, collected in Electronic Health Records

French administrative healthcare database

INCLUDE

CHU LILLE

Inpatient data

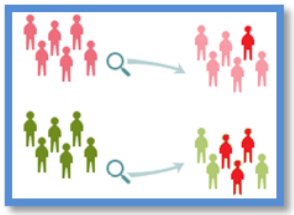
Open data (ecological data)

Prospective databases

Data produced specifically to answer a research question

Medical devices

Cohorts / Registries
Clinical trials



Omics

Proteomics
Proteomics and Systems Biology

Inria

I-SITE UNIVERSITÉ LILLE NORD-EUROPE

humAIn
Alliance Hauts-de-France en Intelligence Artificielle

IUF institut universitaire de France

Infinite

Environment | Epithelial tissue | Immunity | Fibrosis | Therapeutics

Strong academic and industrial consortium: Complementary leaders

PROMISE

CLINICAL RESEARCH TEAMS
Patient cohorts, CT scan

TRANSLATIONAL/BASIC RESEARCH TEAMS
Animal models, omics, data integration, sociome

Leaders in SSc :
Internists/Rheumatologists/Pulmonologists/Radiologists
French Reference Centres for SSc
EUSTAR
Patients associations

Valorization

Go@L-GFS

INDUSTRIAL PARTNERS:
Leaders in SSc drugs, AI and CT scan and biomarkers

Merci !

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