Auto-anticorps anti-cytokines

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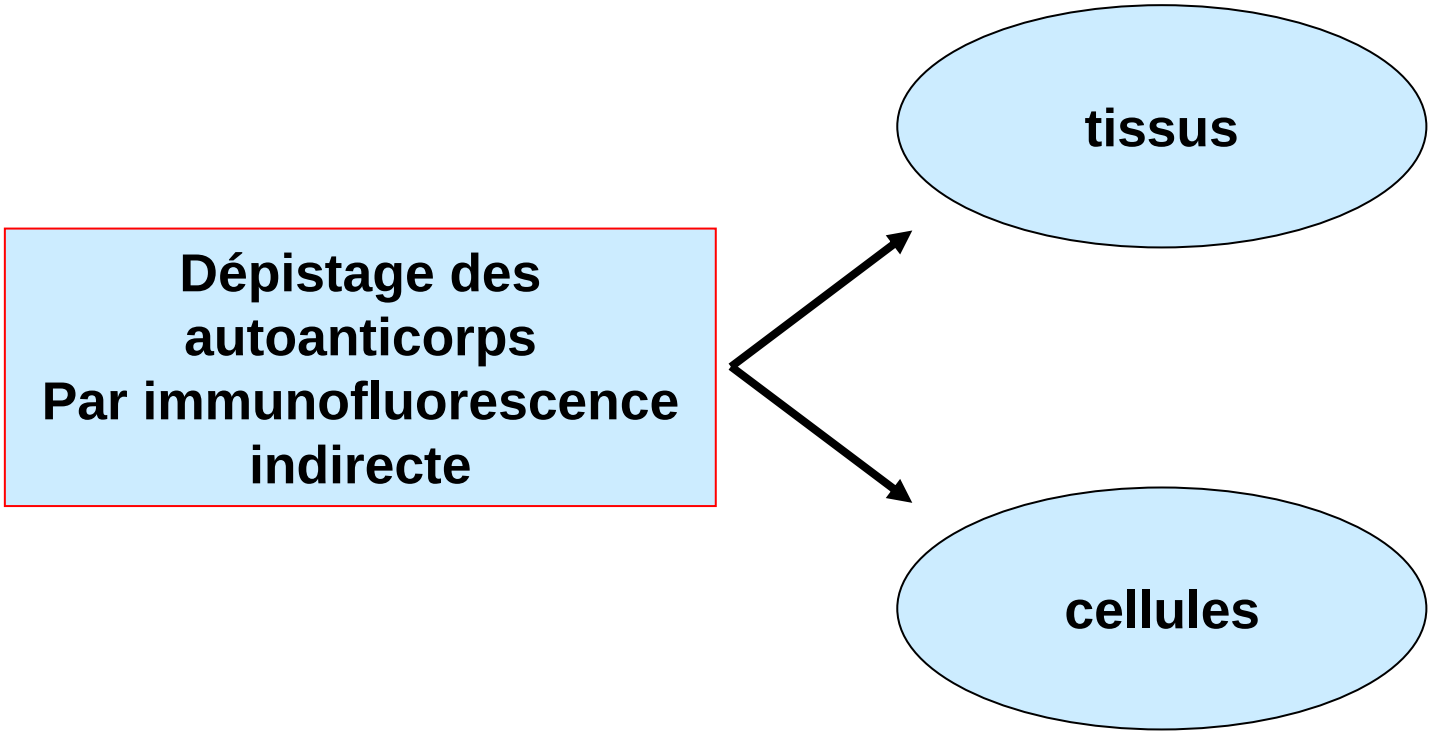
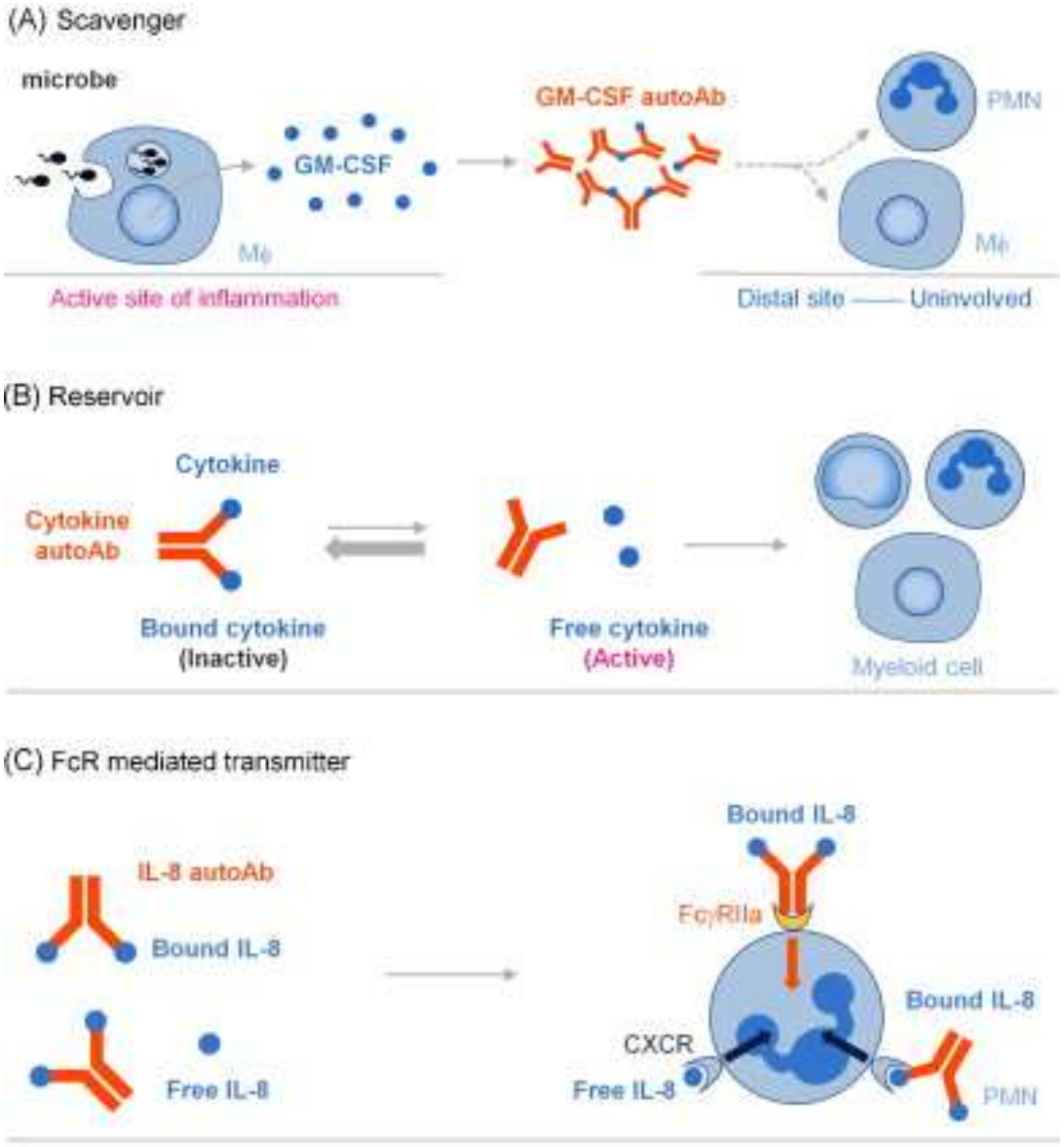


Ne détecte pas les Ac dirigés contre des antigènes circulants

- **anti-oxLDL (athérosclérose)**
- **anti-cytokines**

Rôles physiologiques (potentiels)



Neutralisation
(↘ effet endocrine)

protection
(↗ ½ vie)

présentation
(↗ bio-activité)

Watanabe M *et al.* Cytokine Growth Factor Rev. 2010 Aug;21(4):263-73

Auto-Ac anti-cytokines et pathologies

 # Ac thérapeutiques

Déficits immunitaires acquis

Anti - IFNγ
- IL-6
- IL-17

Modification de l'activité d'une maladie auto-immune

 # Disease-modifying anti-rheumatic drugs (DMARDs)

Anti - INFα
- TNFα
- BAFF
- IL-1α

Autres complications

Anti - G-CSF
- GM-CSG
- IL-8

Auto-Ac anti-cytokines
et
déficits immunitaires acquis

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Adult-Onset Immunodeficiency in Thailand and Taiwan

Sarah K. Browne, M.D., Peter D. Burbelo, Ph.D., Ploenchan Chetchotisakd, M.D., Yupin Suputtamongkol, M.D., Sasisopin Kiertiburanakul, M.D., Pamela A. Shaw, Ph.D., Jennifer L. Kirk, B.A., Kamonwan Jutivorakool, M.D., Rifat Zaman, B.S., Li Ding, M.D., Amy P. Hsu, B.A., Smita Y. Patel, M.D., Kenneth N. Olivier, M.D., Viraphong Lulitanond, Ph.D., Piroon Mootsikapun, M.D., Siriluck Anunnatsiri, M.D., Nasikarn Angkasekwinai, M.D., Boonmee Sathapatayavongs, M.D., Po-Ren Hsueh, M.D., Chi-Chang Shieh, M.D., Ph.D., Margaret R. Brown, B.S., Wanna Thongnoppakhun, Ph.D., Reginald Claypool, R.N., Elizabeth P. Sampaio, M.D., Ph.D., Charin Thepthai, M.Sc., Duangdao Waywa, M.Sc., Camilla Dacombe, R.N., Yona Reizes, R.N., Adrian M. Zelazny, Ph.D., Paul Saleeb, M.D., Lindsey B. Rosen, B.S., Allen Mo, B.S., Michael Iadarola, Ph.D., and Steven M. Holland, M.D.

N ENGL J MED, AUGUST 23, 2012, 367;8 p725-34

203 patients et contrôles de Taiwan et Thaïlande répartis en 5 groupes

Groupe 1	**Infections disséminées à mycobactéries atypiques**	**n = 52**
Groupe 2	**Infections opportunistes autres +/- mycob. Atypiques** (41/45)	**n = 45**
Groupe 3	**Tuberculose disséminée**	**n = 9**
Groupe 4	**Tuberculose pulmonaire**	**n = 49**
Groupe 5	**Contrôles sains (donneurs de sang)**	**n = 48**

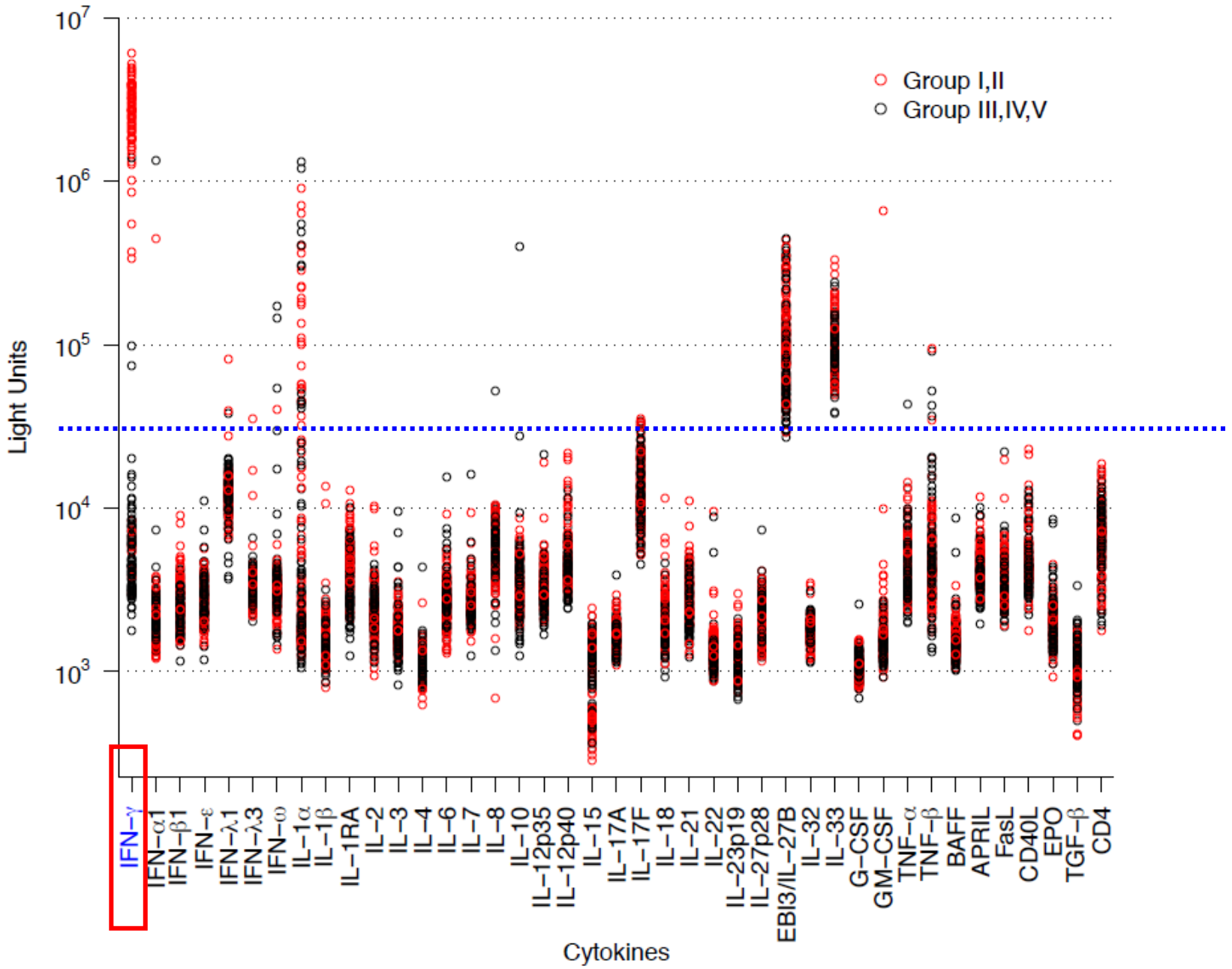
- **Pas d' ATCD de Kc**
- **Pas de ttt immunosuppresseur**
- **Pas de déficit immunitaire congénital**
- **Pas de lymphopénie T-CD4**
- **HIV-**

- **NFS**
- **fonction rénale et hépatique**
- **dosage pondéral des Ig**
- **phénotypage lymphocytaire**

- **ANA**
- **anticorps anti-cytokines**

Screeening par immunoprécipitation avec évaluation de 41 cibles (!!):

IFNγ, α1, β1, ε, λ1, λ3, ω; IL-1α et 1β, IL-1Ra, IL-2, 3, 4, 6, 7, 8, 10, 12p35, 12p40, 15, 17A, 17F, 18, 21, 22, 23p19, 27p28, 27b, 32, 33; G-CSF, GM-CSF, TNF-α, TNF-β, BAFF, APRIL, FasL, CD40L, EPO, TGFβ, CD4R.



Seuls les Ac anti-IFNγ distinguent groupes 1/2 des groupes 3/4/5 (p<0.001)

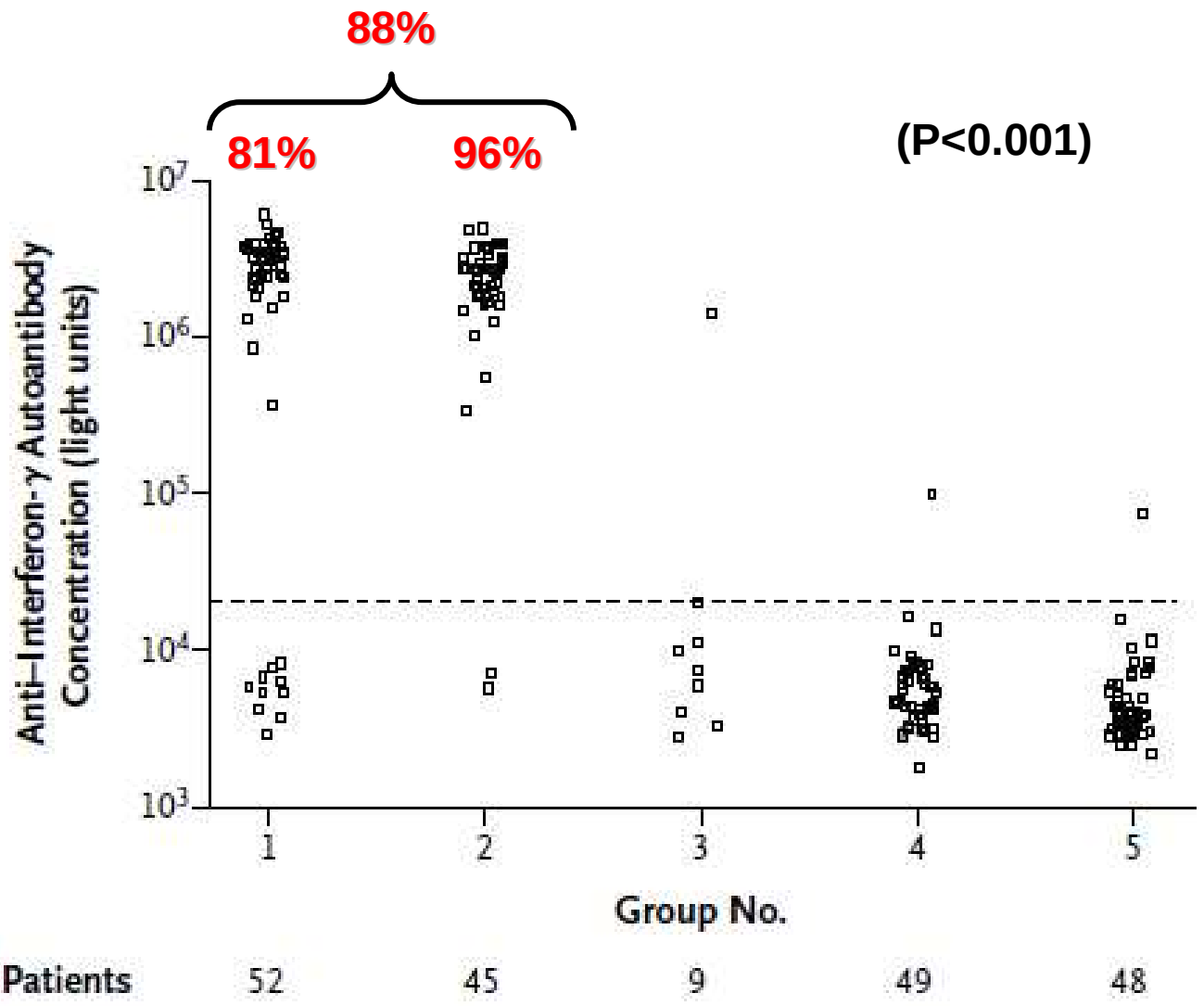


Figure 2. Anti–Interferon-γ Autoantibody Concentrations in 203 Participants, According to Study Group.

Th2

IL-4
IL-5
IL-13

Réponse humorale (Ac)
➔ LB, PNEo, PNB, masto

Germes extracellulaires
Helminthes

Th1

IL-2
IFNγ
TNF

Réponse cellulaire
➔ macrophages
➔ CD8 cytotoxiques

Germes intracellulaires

Th17

IL-17A
IL-17F
IL-21
IL-22
GM-CSF

Réponse cellulaire
➔ PNN

bactéries extracellulaires
Champignons

Treg

TGFβ
IL-10

Immunorégulation
⊣ TH1-TH2-TH17

Auto-Ac neutralisants anti-IFNγ

➔ **Déficit immunitaire acquis**

- ➔ **Infections opportunistes à germes intra-cellulaires**
- ➔ **Surtout mycobactéries atypiques (96%)**
- ➔ **Début à l'âge adulte**

- ➔ **En Asie du sud-est…**

Polyendocrinopathie autoimmune de type 1 (PAI-1)

= syndrome APECED

Auto-immune Polyendocrinopathy Candidiasis Ectodermal Dystrophy

Mutation *AIRE* ➔ défaut de sélection thymique
➔ multiples atteintes auto-immunes

- **Hypoparathyroïdie**
- **insuffisance surrénalienne**
- **insuffisance ovarienne…**

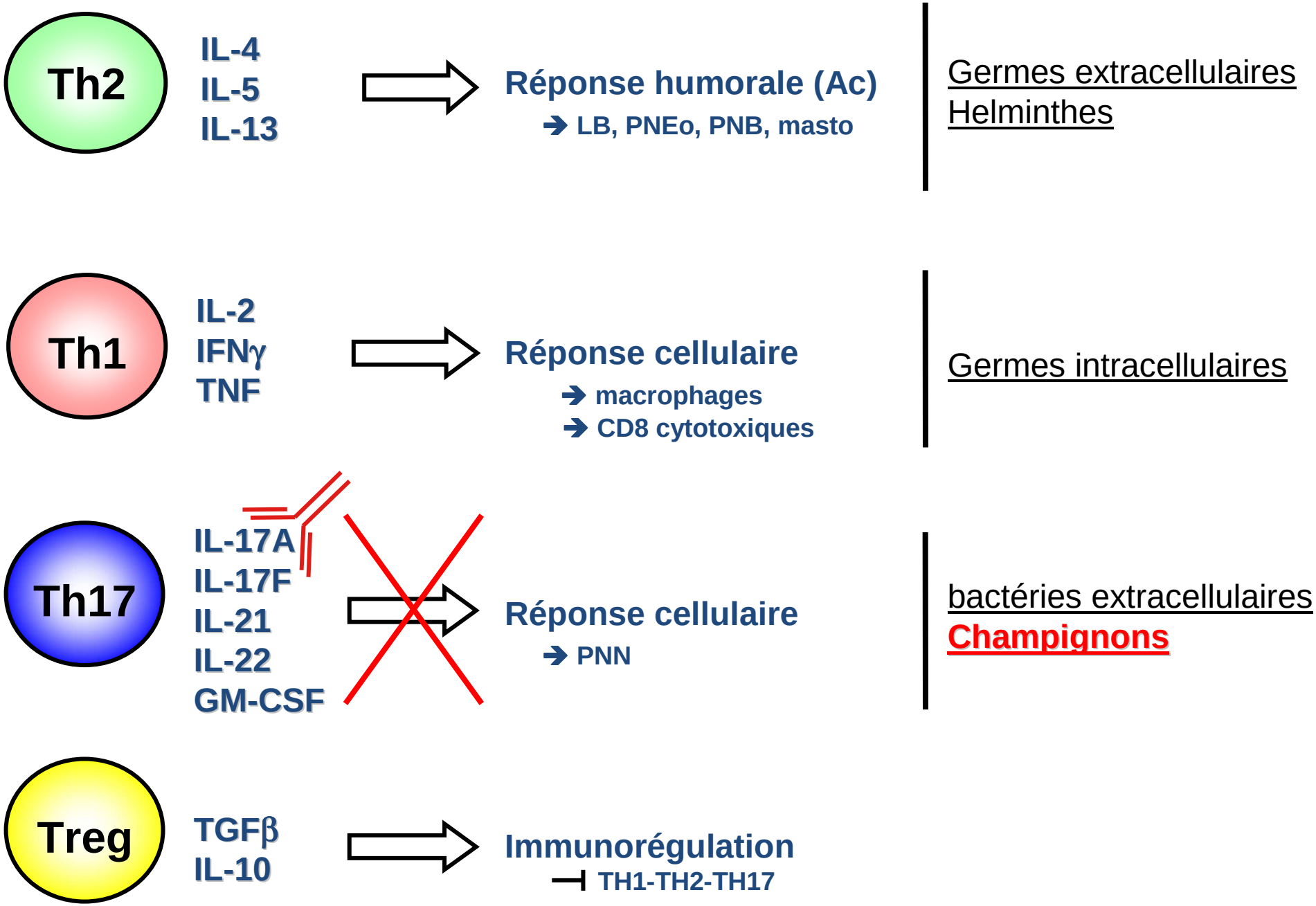
Et une candidose cutanéo-muqueuse chronique…

Autoantibodies against IL-17A, IL-17F, and IL-22 in patients with chronic mucocutaneous candidiasis and autoimmune polyendocrine syndrome type I

Anne Puel,[1,2] Rainer Döffinger,[3] Angels Natividad,[1,2] Maya Chrabieh,[1,2] Gabriela Barcenas-Morales,[4] Capucine Picard,[1,2,5] Aurélie Cobat,[1,2] Marie Ouachée-Chardin,[8] Antoine Toulon,[2,6] Jacinta Bustamante,[1,2] Saleh Al-Muhsen,[9] Mohammed Al-Owain,[10] Peter D. Arkwright,[11] Colm Costigan,[12] Vivienne McConnell,[13] Andrew J. Cant,[14] Mario Abinun,[14] Michel Polak,[2,15] Pierre-François Bougnères,[16] Dinakantha Kumararatne,[3] László Marodi,[17] Amit Nahum,[18] Chaim Roifman,[18] Stéphane Blanche,[2,7] Alain Fischer,[2,7,19] Christine Bodemer,[2,6] Laurent Abel,[1,2,20] Desa Lilic,[21] and Jean-Laurent Casanova[1,2,7,20]

J. Exp. Med. 2010 Vol. 207 No. 2 291-297

Most patients with autoimmune polyendocrine syndrome type I (APS-I) display chronic mucocutaneous candidiasis (CMC). We hypothesized that this CMC might result from autoimmunity to interleukin (IL)-17 cytokines. We found high titers of autoantibodies (auto-Abs) against IL-17A, IL-17F, and/or IL-22 in the sera of all 33 patients tested, as detected by multiplex particle-based flow cytometry. The auto-Abs against IL-17A, IL-17F, and IL-22 were specific in the five patients tested, as shown by Western blotting. The auto-Abs against IL-17A were neutralizing in the only patient tested, as shown by bioassays of IL-17A activity. None of the 37 healthy controls and none of the 103 patients with other autoimmune disorders tested had such auto-Abs. None of the patients with APS-I had auto-Abs against cytokines previously shown to cause other well-defined clinical syndromes in other patients (IL-6, interferon [IFN]-γ, or granulocyte/macrophage colony-stimulating factor) or against other cytokines (IL-1β, IL-10, IL-12, IL-18, IL-21, IL-23, IL-26, IFN-β, tumor necrosis factor [α], or transforming growth factor β). These findings suggest that auto-Abs against IL-17A, IL-17F, and IL-22 may cause CMC in patients with APS-I.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bactéries extracellulaires
Champignons
Treg
TGFβ
IL-10
Immunorégulation
⊣ TH1-TH2-TH17

Recurrent Staphylococcal Cellulitis and Subcutaneous Abscesses in a Child with Autoantibodies against IL-6[1]

Anne Puel,[2*‡] Capucine Picard,[*‡§] Mathie Lorrot,[‖] Charlotte Pons,[‖] Maya Chrabieh,[*‡] Lazaro Lorenzo,[*‡] Maria Mamani-Matsuda,[†‡] Emmanuelle Jouanguy,[*‡] Dominique Gendrel,[‖] and Jean-Laurent Casanova[*‡¶]

We investigated an otherwise healthy patient presenting two episodes of staphylococcal cellulitis and abscesses, accompanied by high fever and biological signs of inflammation but, paradoxically, with no detectable increase in serum levels of C-reactive protein (CRP), an IL-6-responsive protein synthesized in the liver. Following in vitro activation of whole blood cells from the patient with multiple cytokines, TLR agonists, heat-killed bacteria, and mitogens, we observed a profound and specific impairment of IL-6 secretion. However, the patient's PBMCs, activated in the same conditions but in the absence of the patient's plasma, secreted IL-6 normally. The patient's serum contained high titers of IgG1 autoantibodies against IL-6, which specifically neutralized IL-6 production by control PBMCs as well as IL-6 responses in the human hepatocellular carcinoma cell line Hep3B. These anti-IL-6 autoantibodies were detected over a period of 4 years, in the absence of any other autoantibodies. Our results indicate that these Abs probably prevented an increase in CRP concentration during infection and that impaired IL-6-mediated immunity may have contributed to staphylococcal disease. Patients with severe bacterial infections and low serum CRP concentrations should be tested for anti-IL-6 autoantibodies, especially in the presence of other clinical and biological signs of inflammation. *The Journal of Immunology*, 2008, 180: 647–654.

Infections sévères à Staphylocoque doré + CRP normale

(Tocilizumab: 3 cas d'infections disséminées à Staph. Doré)

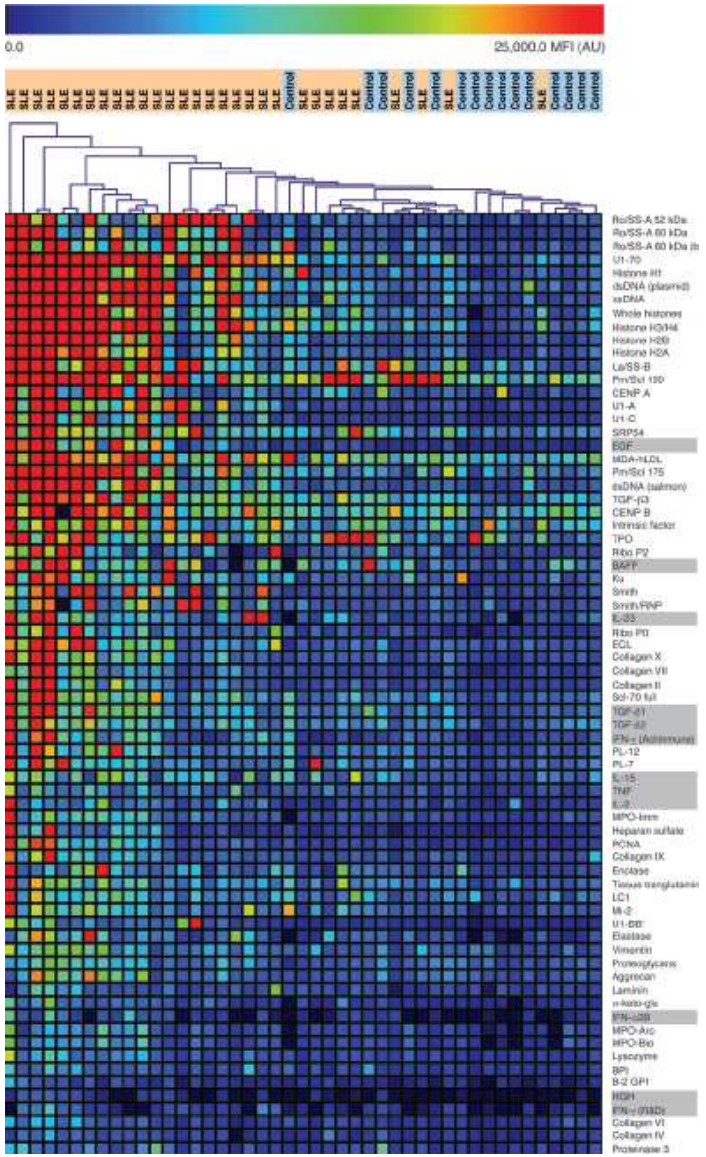
Auto-Ac anti-cytokines
et
déficits immunitaires acquis

- **Complications infectieuses sévères +++**

- **mais rares**

Auto-Ac anti-cytokines associés à une maladie auto-immune

Lupus érythémateux systémique



Auto-Ac anti-

- **IL-23**
- **BAFF**
- **TGF-β**
- **IFN-α**
- **IFN-γ**
- **IL-15**
- **TNFα**
- **IL-2**

Price JV *et al* . J Clin Invest. 2013; 123 (12): 5135-45

Auto-Ac anti-cytokines et Lupus érythémateux systémique

Rôle protecteur

- IFN-α (13-27%)
- TNF-α (10-20%)

➔ Corrélation inverse titre / SLEDAI

Rôle aggravant

- BAFF (15%)

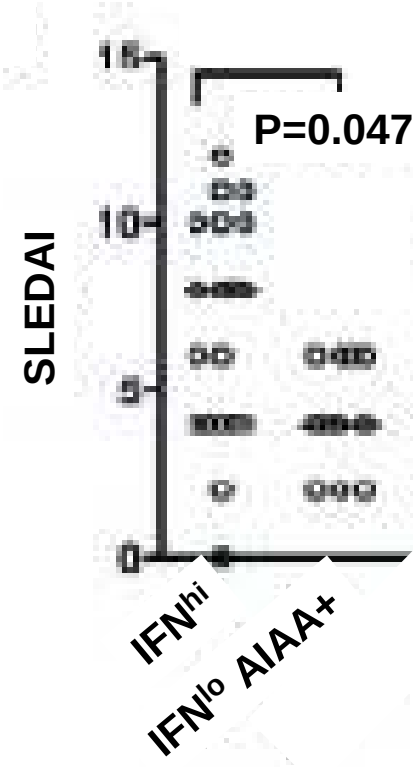
➔ Formes évolutives et sévères

(Price JV *et al* . J Clin Invest. 2013; 123 (12): 5135-45)

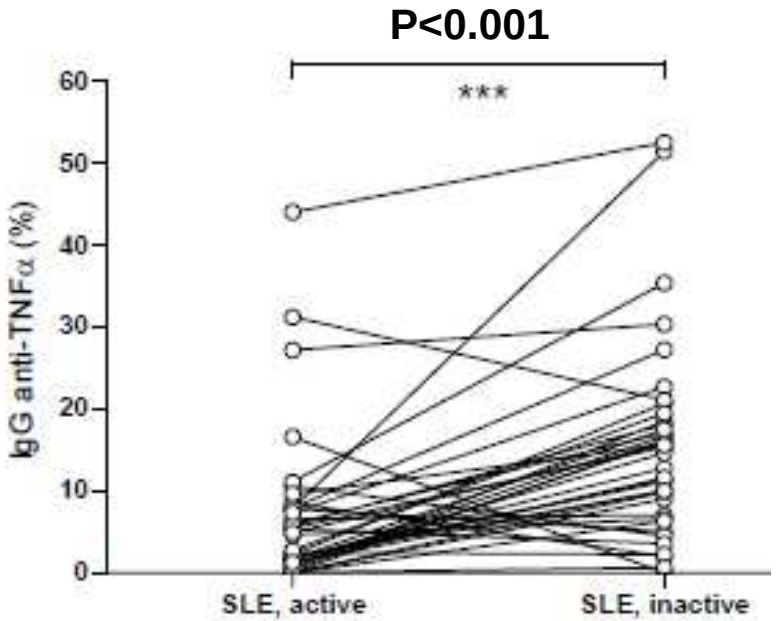
Auto-Ac anti-cytokines et Lupus érythémateux systémique

Intérêt pronostique ?? ⇒ **??**

Exemple des Ac anti-IFNα



Exemple des Ac anti-TNFα



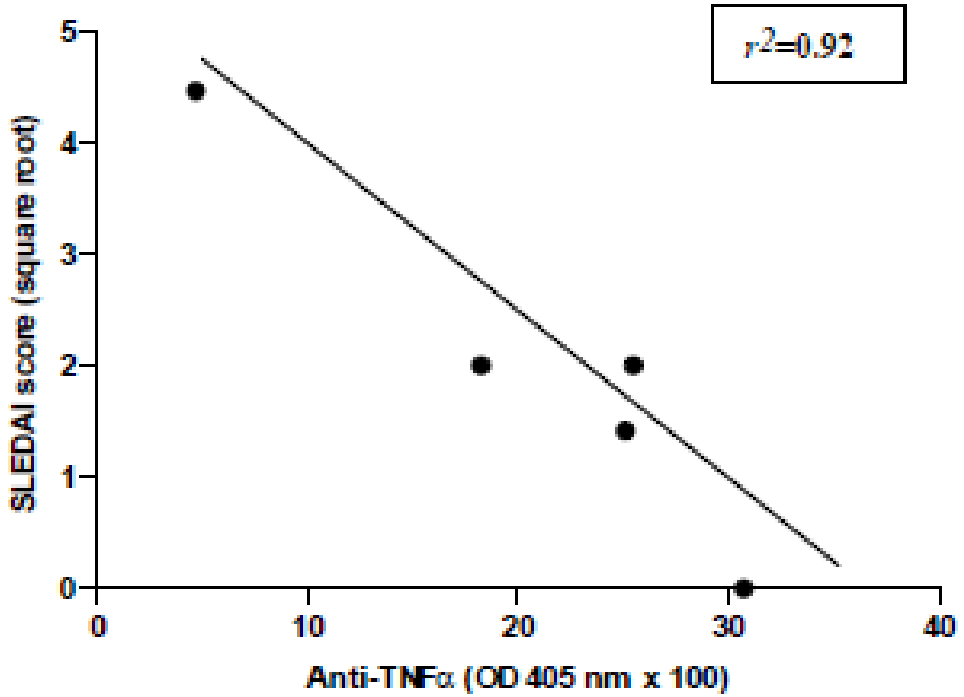
Morimoto AM *et al.* Arthritis Rheum. 2011; 63(8): 2407-15.

Sjöwall C *et al.* J Autoimmun. 2004 Jun;22(4):315-23

Auto-Ac anti-cytokines et Lupus érythémateux systémique

Intérêt pronostique ?? → **??**

Exemple des Ac anti-TNFα



Sjöwall C *et al.* J Autoimmun. 2004 Jun;22(4):315-23

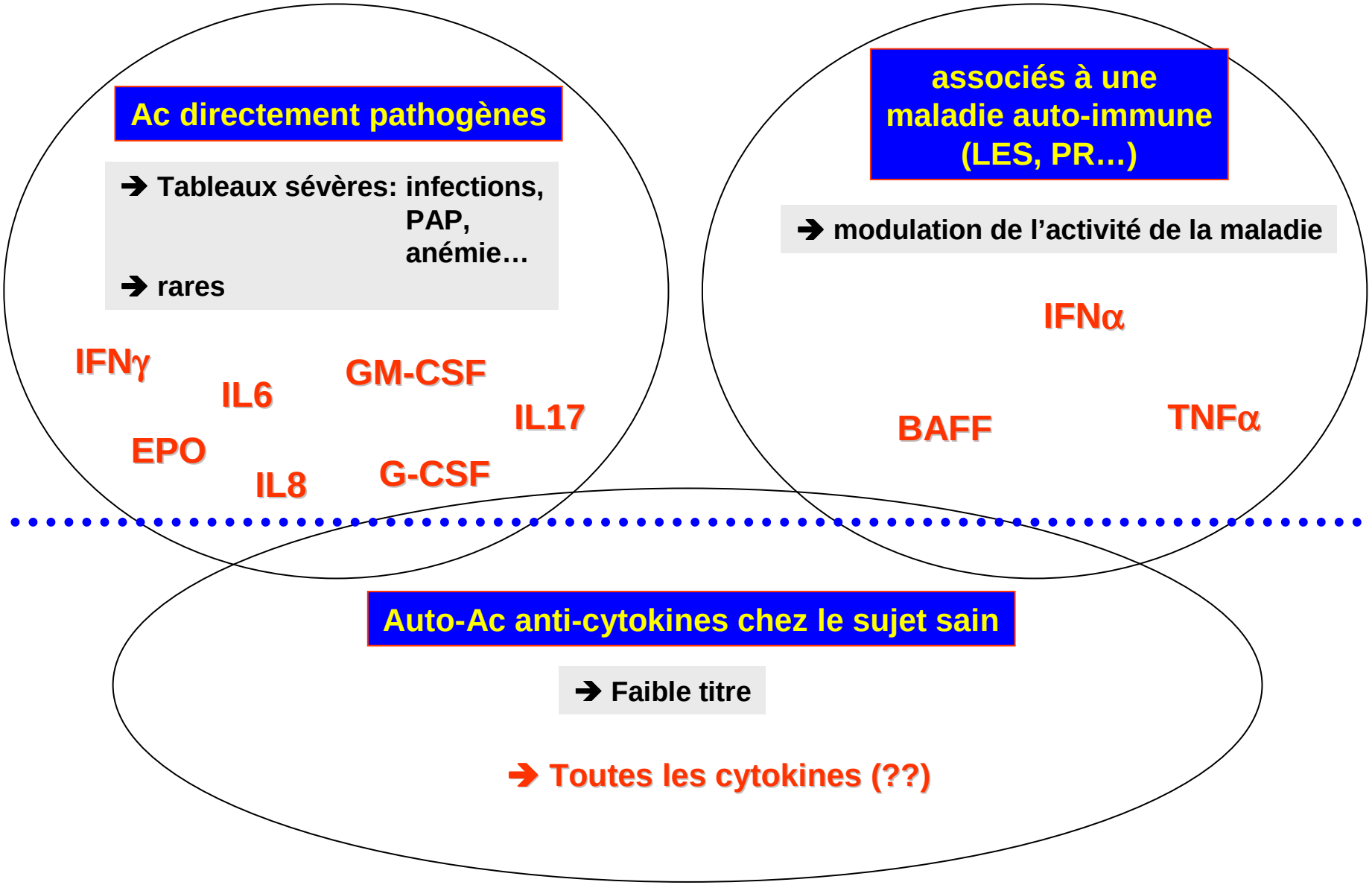
Auto-Ac associés à une maladie auto-immune

- fréquents
- souvent multiples
- capables de modifier l'évolution de la maladie

Autres auto-Ac anti-cytokines

Cytokine cible	clinique	références
IL-1α	**Rhumatismes inflammatoires chroniques (rôle protecteur)**	- Ann Rheum Dis 2002;61:598-602 - Scand J Immunol 1997;46(4):413-8
G-CSF	**PR ou LES + Neutropénie**	- Arthritis Rheum 2002;46(9):2384-91
GM-CSF	**Protéinose alvéolaire pulmonaire (PAP) acquise**	- J Exp Med 1999;190(6):875-80 - Blood 2004;103:1089-98 - PNAS 2013;110(19):7832-7
IL-8	**syndrome de détresse respiratoire aiguë (SDRA)**	- Am J Physiol Lung Cell Mol Physiol 2004;286:L1105-13
EPO	**Anémie par érythroblastopénie**	- NEJM 1996 Mar 7;334(10):630-3

conclusion


Ac directement pathogènes
➔ Tableaux sévères: infections, PAP, anémie…
➔ rares
IFNγ
IL6
GM-CSF
IL17
EPO
IL8
G-CSF
associés à une maladie auto-immune (LES, PR…)
➔ modulation de l'activité de la maladie
IFNα
BAFF
TNFα
Auto-Ac anti-cytokines chez le sujet sain
➔ Faible titre
➔ Toutes les cytokines (??)


Merci pour votre attention !!