IL23

Origine, principaux rôles, implication en physiopathologie, traitements

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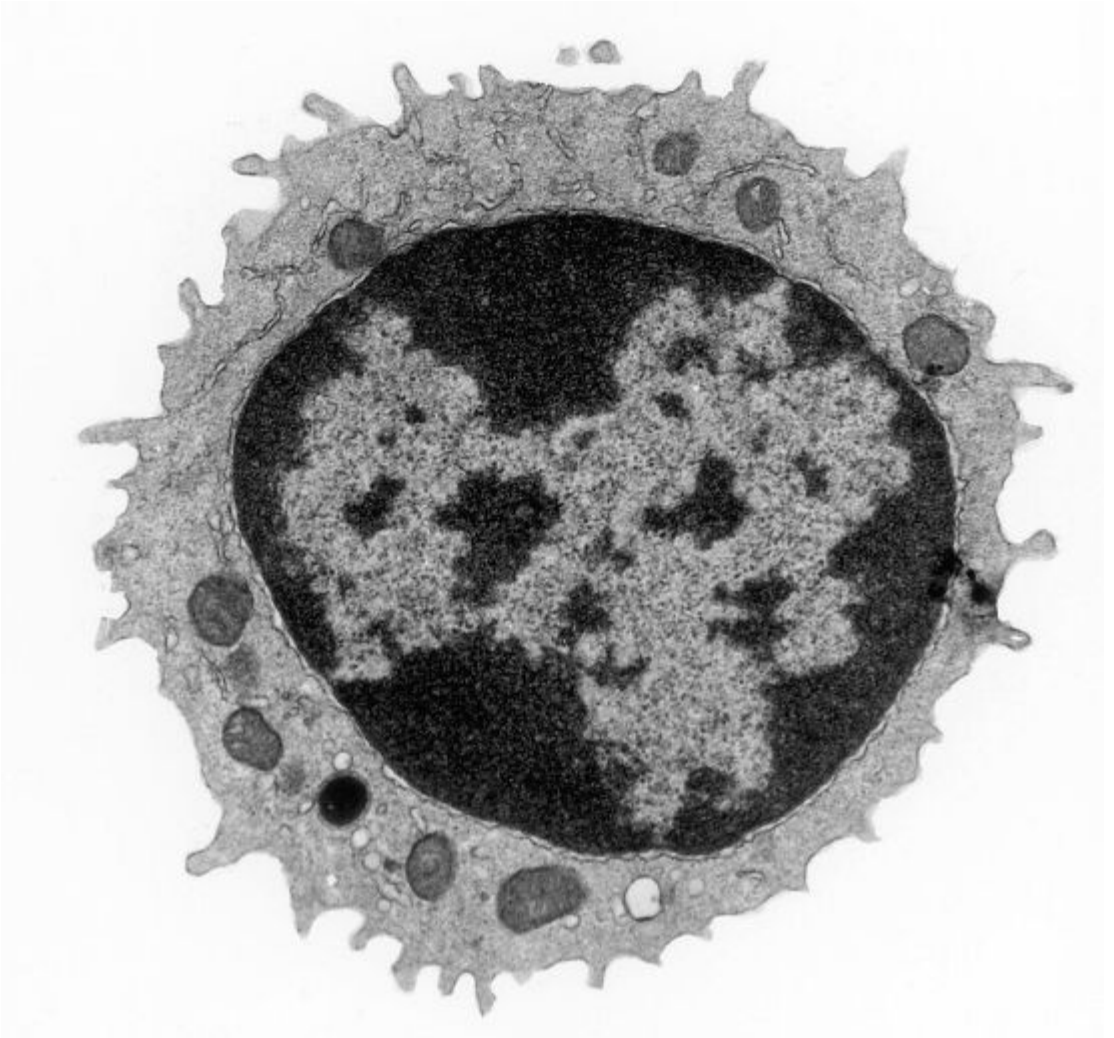
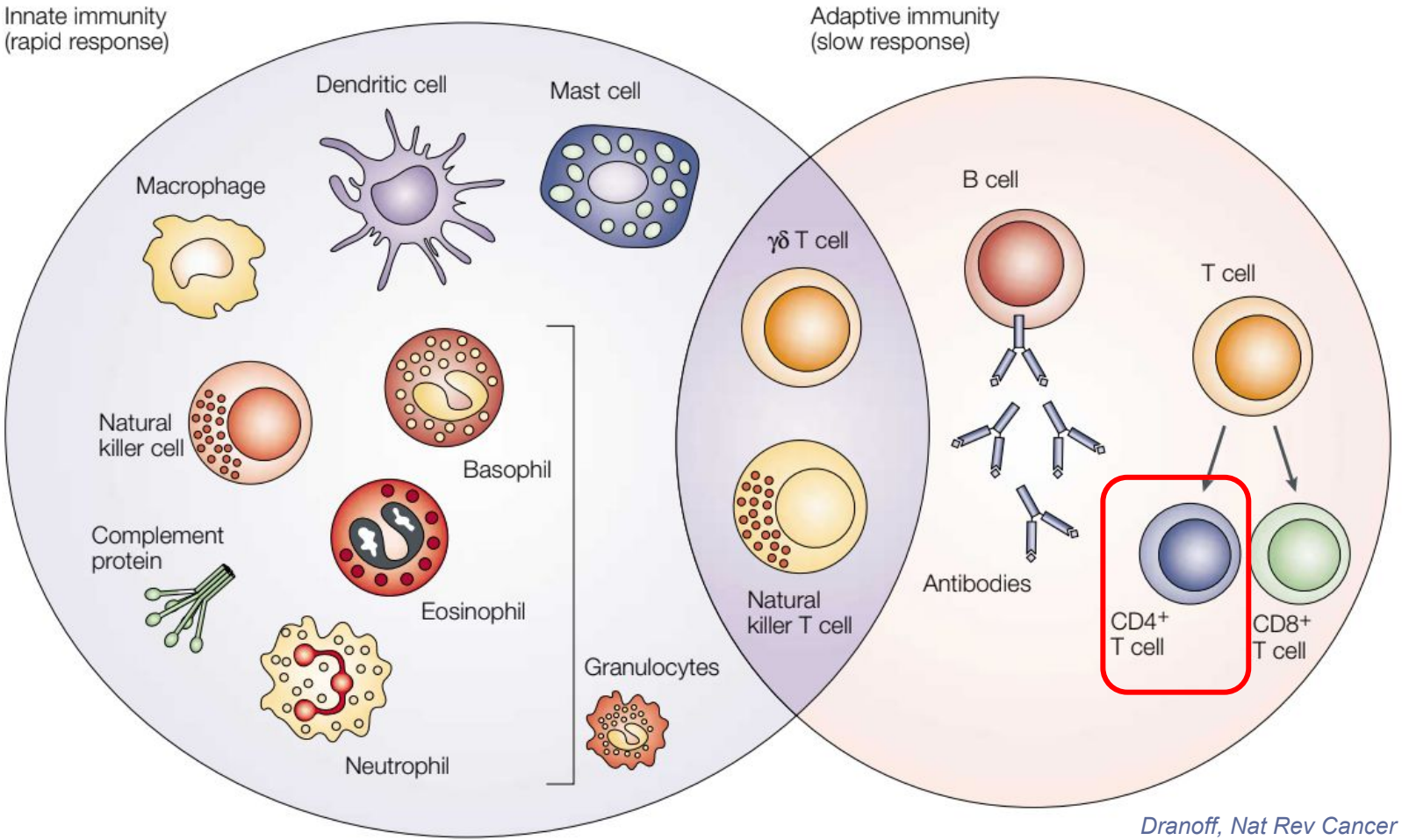
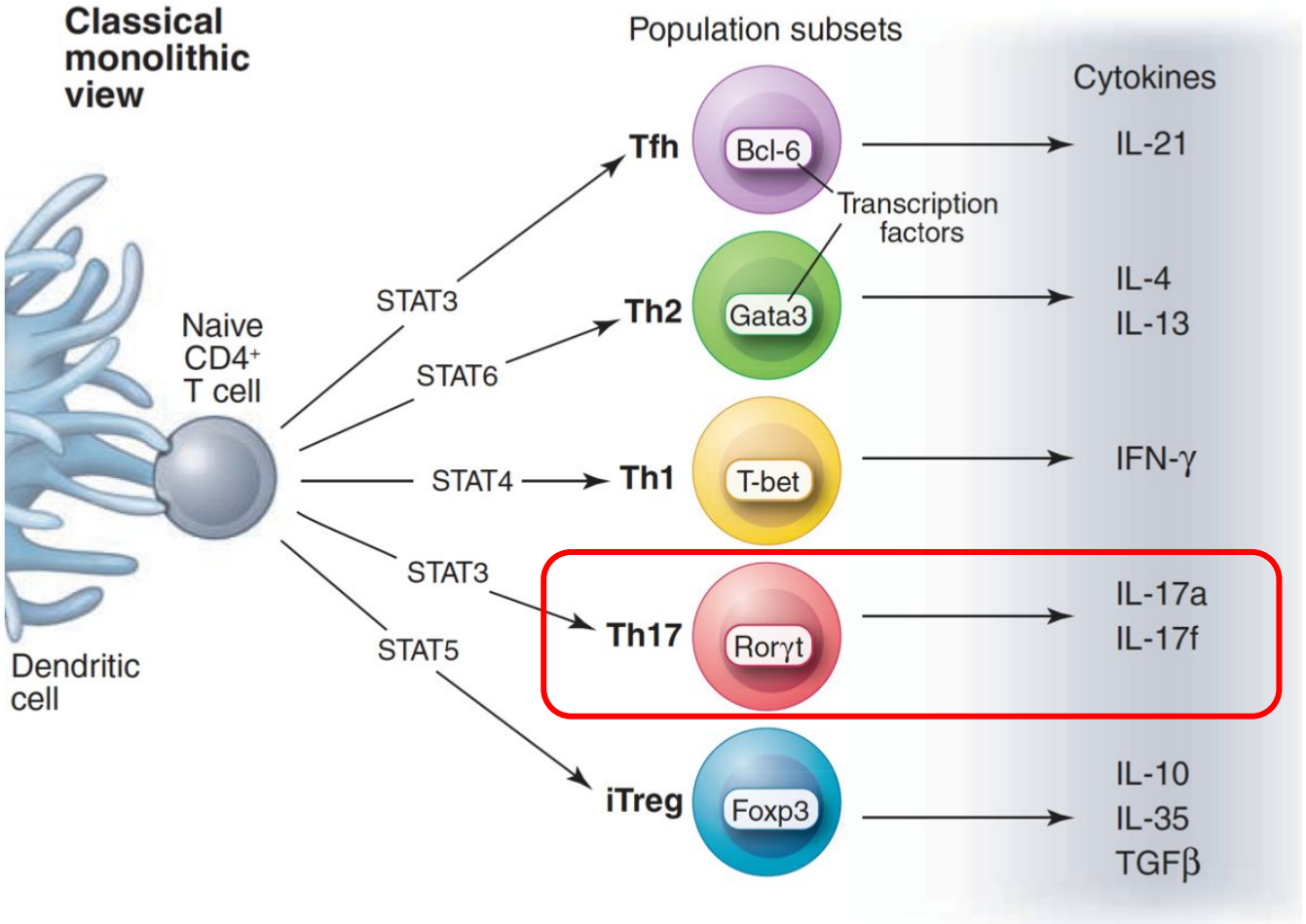
SRO 05/04/2024

DARRAS Manon
VIALLE Charlotte





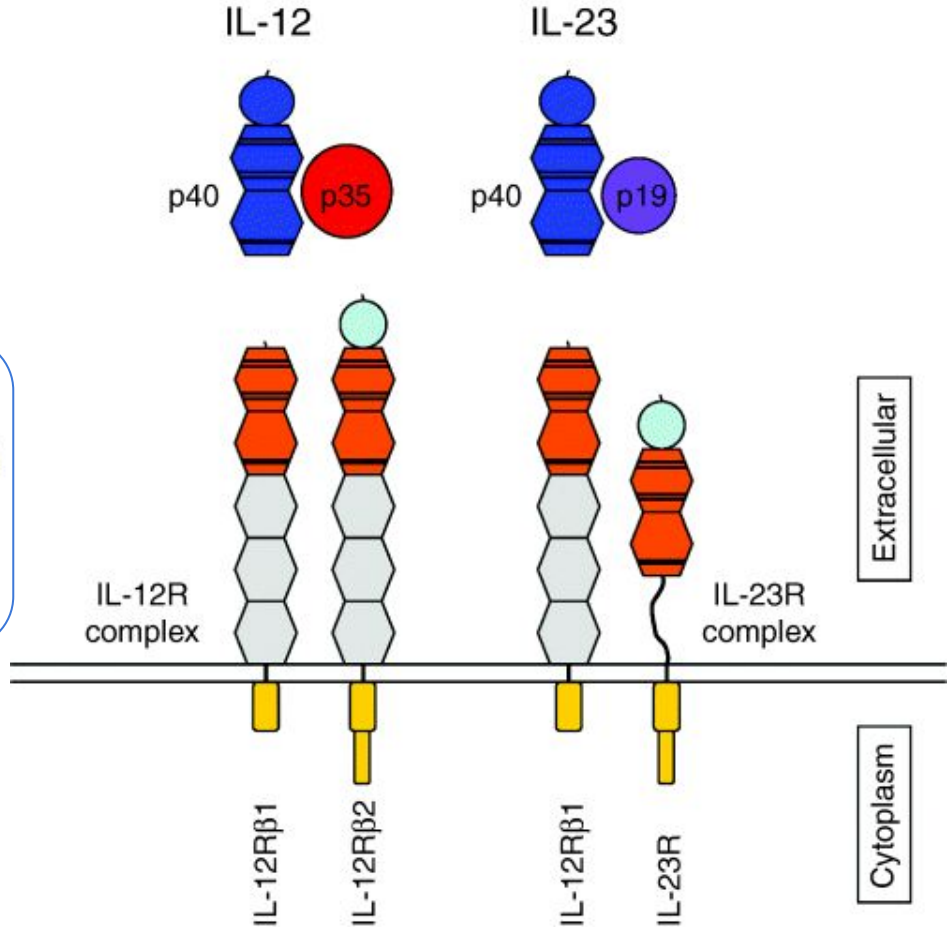
Dranoff, Nat Rev Cancer 2004



O'shea, Science, 2010

Immunity, Vol. 13, 715–725, November, 2000, Copyright ©2000 by Cell Press

Novel p19 Protein Engages IL-12p40 to Form a Cytokine, IL-23, with Biological Activities Similar as Well as Distinct from IL-12

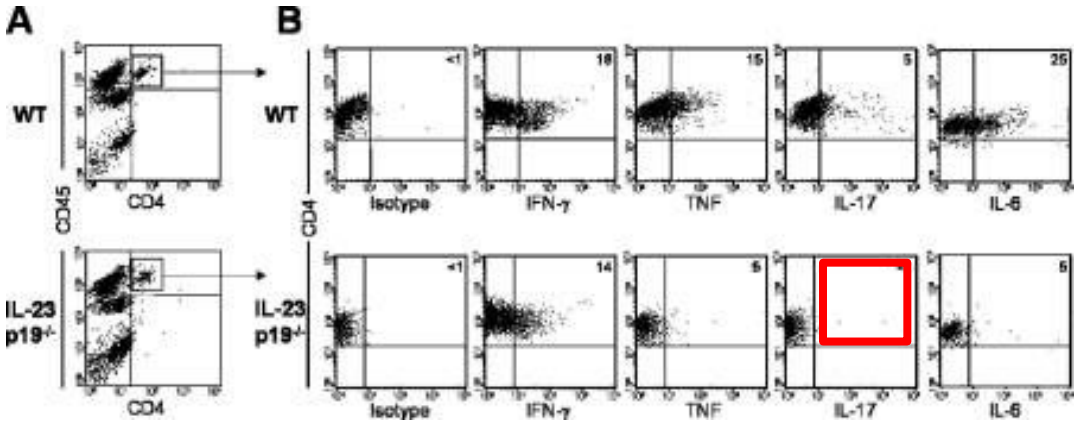


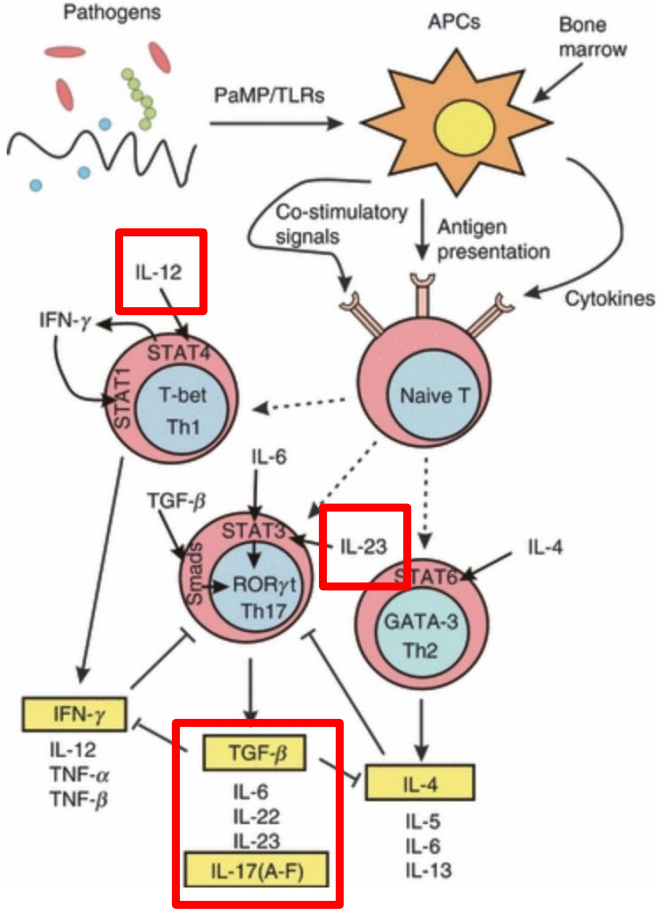
Langrish, C.L.IL-12 and IL-23: master regulators of innate and adaptive immunity. Immunological Reviews.

J Exp Med. 2005 Jan 17;201(2):233-40. doi: 10.1084/jem.20041257.

IL-23 drives a pathogenic T cell population that induces autoimmune inflammation

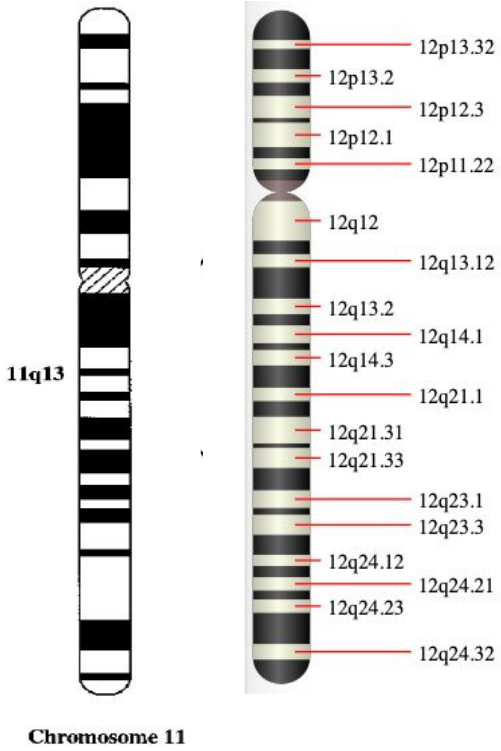
Claire L Langrish [1], Yi Chen, Wendy M Blumenschein, Jeanine Mattson, Beth Basham,

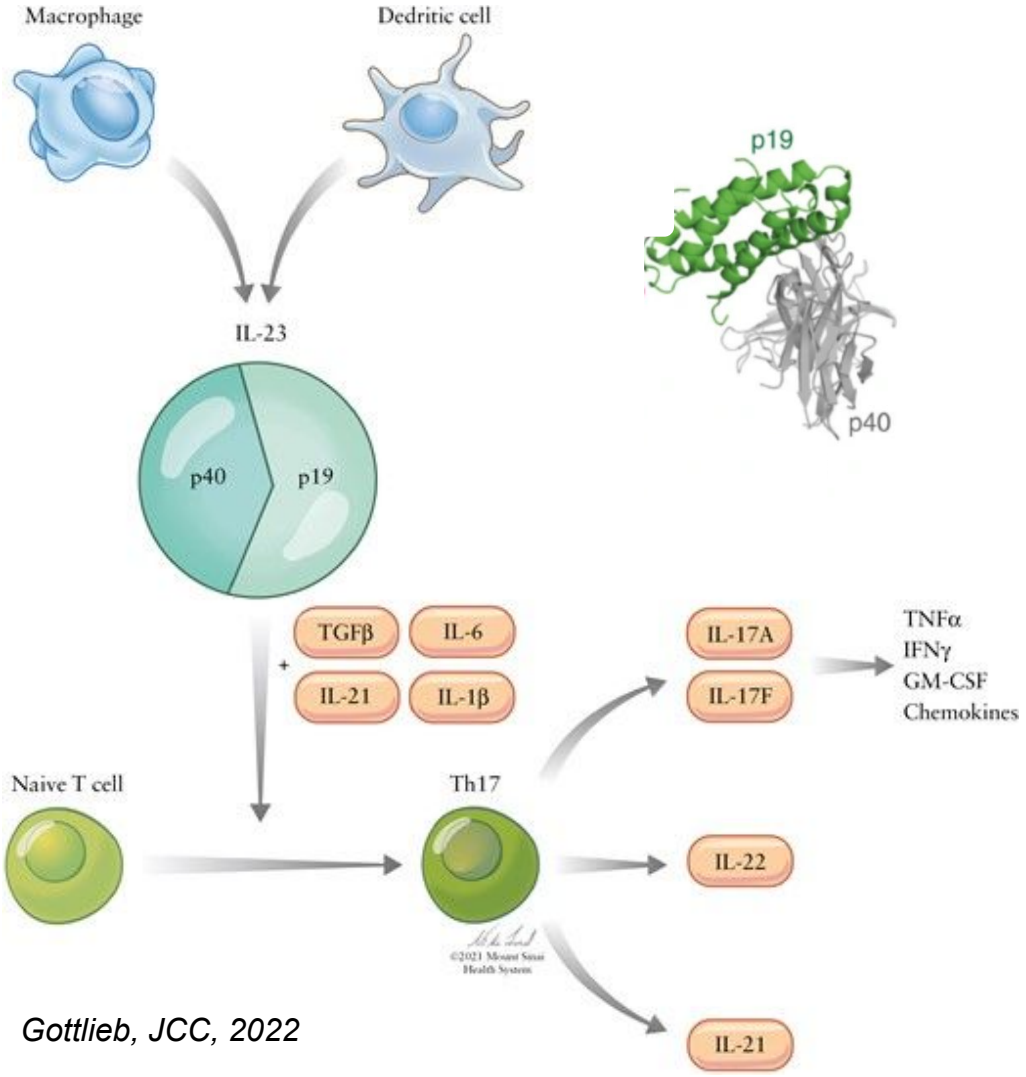




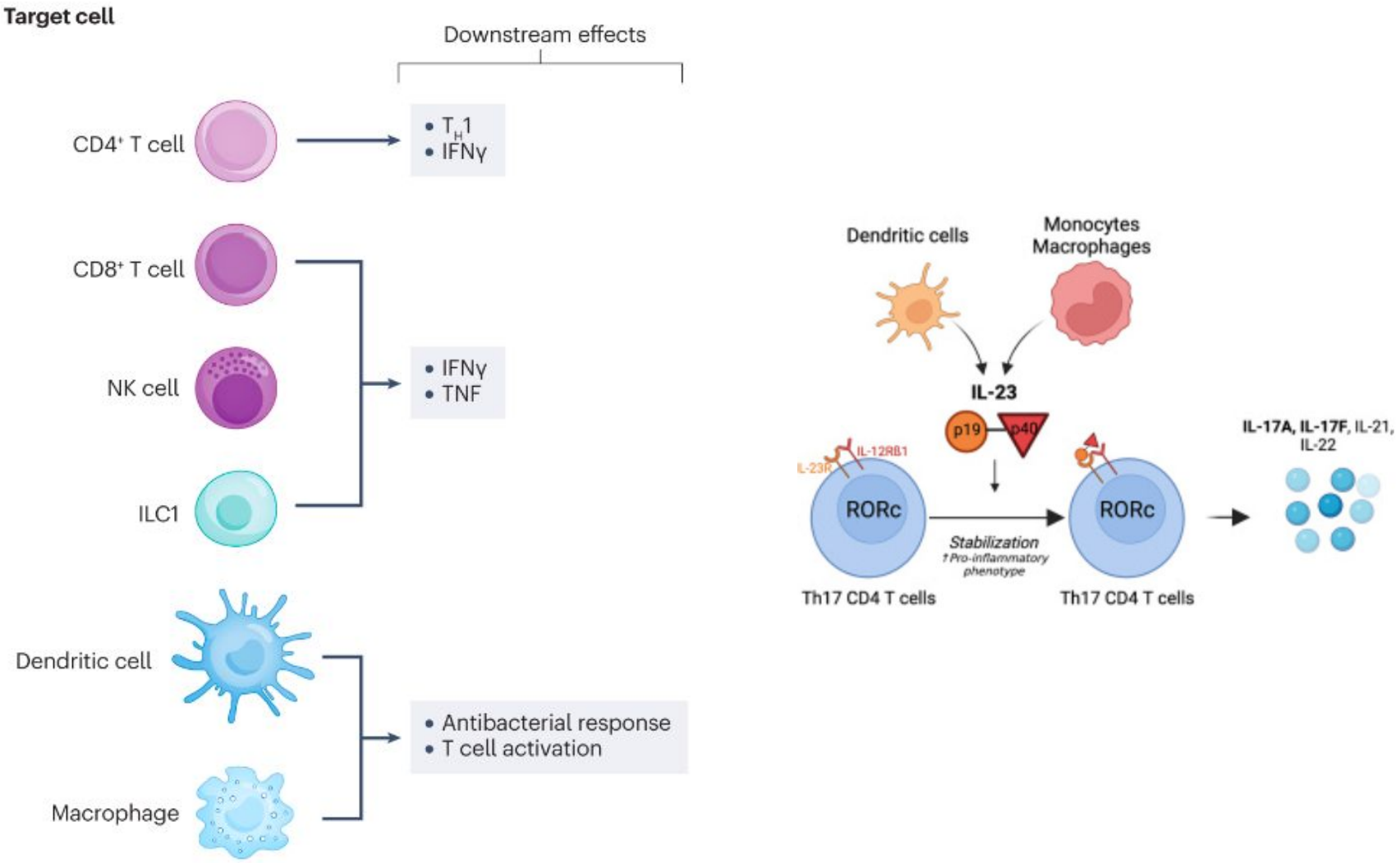
Tang, Chunlei et al. Immunology (2012)

Cr 12q13.2 (p19) et 11q1.3 (p40)





Gottlieb, JCC, 2022


Target cell
Downstream effects
CD4⁺ T cell
• T_H1
• IFNγ
CD8⁺ T cell
NK cell
ILC1
• IFNγ
• TNF
Dendritic cell
Macrophage
• Antibacterial response
• T cell activation
Dendritic cells
Monocytes
Macrophages
IL-23
p19
p40
IL-23R
IL-12Rß1
RORc
Stabilization
↑Pro-inflammatory phenotype
RORc
IL-17A, IL-17F, IL-21, IL-22
Th17 CD4 T cells
Th17 CD4 T cells

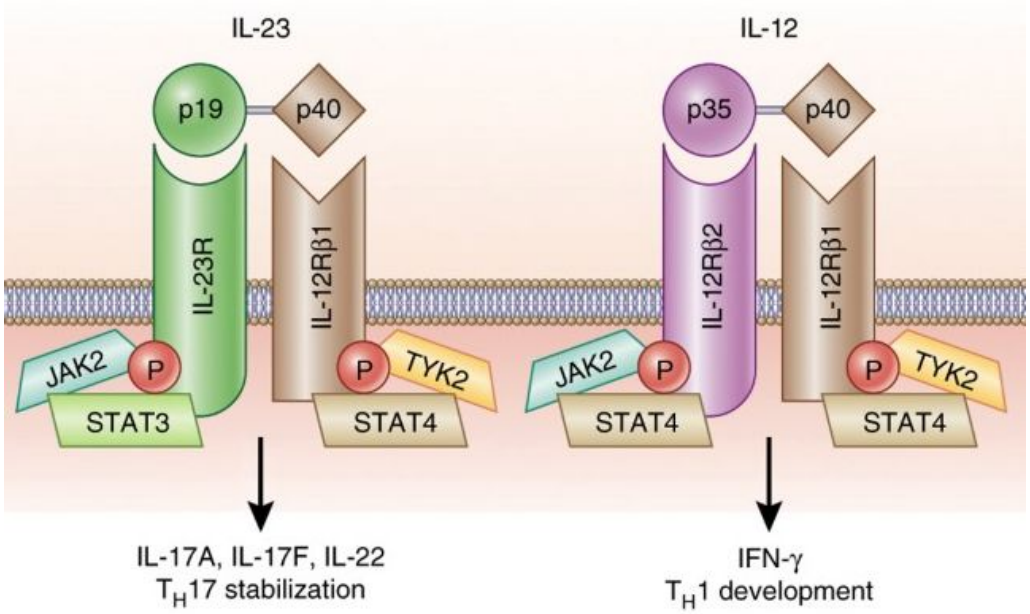
Récepteur IL 23

Absent des Th0

Hétérodimère

- p19 se fixe sur IL-23Rα
- p40 se fixe sur IL-12Rβ1

Exprimés par cellules Tγδ , NK, monocytes & macrophage, cellules dendritiques



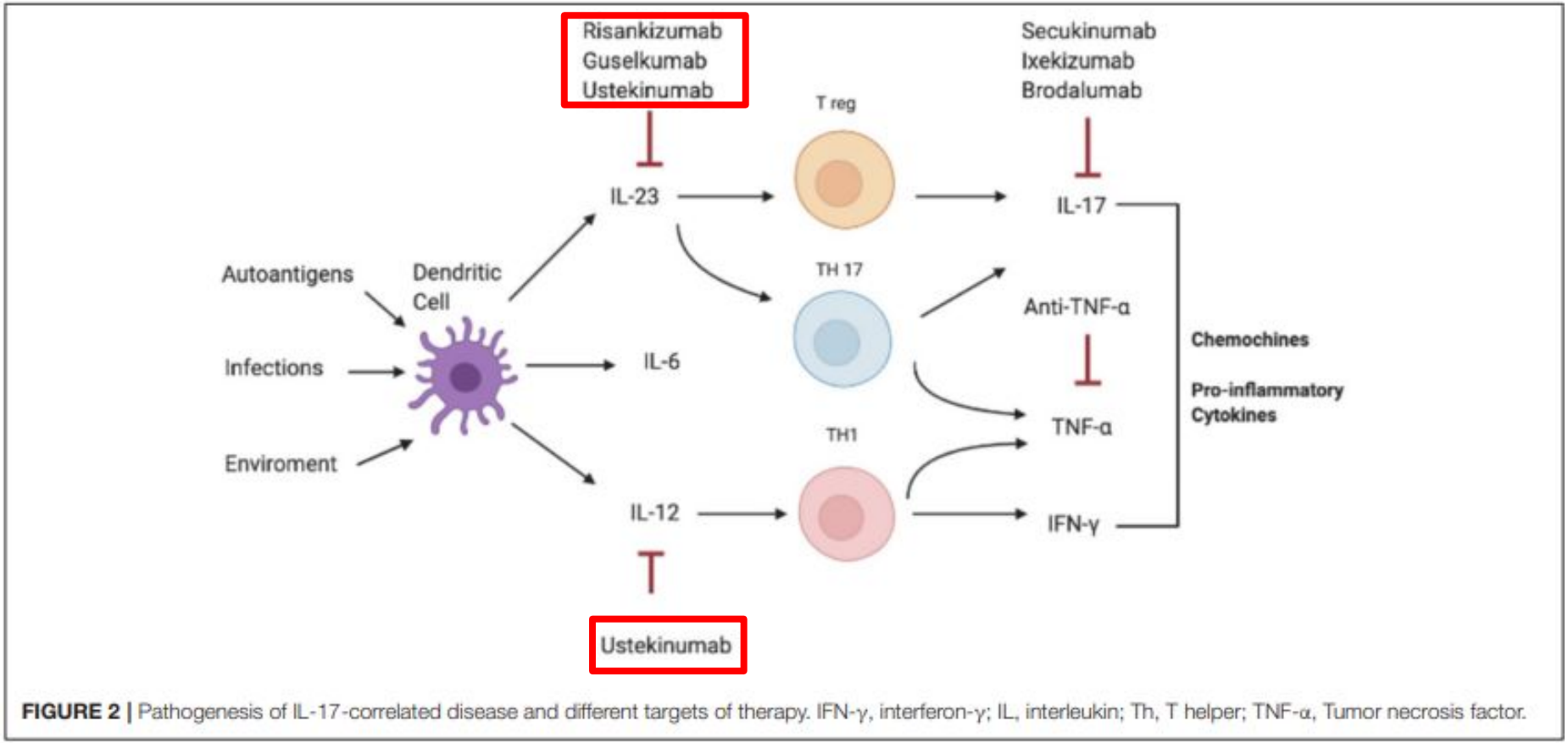


FIGURE 2 | Pathogenesis of IL-17-correlated disease and different targets of therapy. IFN-γ, interferon-γ; IL, interleukin; Th, T helper; TNF-α, Tumor necrosis factor.

Schinocca C, et al. Role of the IL-23/IL-17 Pathway in Rheumatic Diseases: An Overview. Front Immunol. 2021

Target cytokine	Structure	Drug	Clinical application	Under investigation (phase IIb or III)
IL-23	Anti-p40 mAb	Ustekinumab	Psoriasis, PsA, UC, CD	Idiopathic inflammatory myositis (NCT03981744) Takayasu arteritis (NCT04882072)
	Anti-p19 mAb	Guselkumab	Psoriasis, PsA	UC (NCT04033445) CD (NCT03466411, NCT04397263)
		Risankizumab	Psoriasis	PsA (26,27) UC (NCT03398135, NCT03398148) CD (NCT03104413, NCT03105102, NCT03105128, NCT04524611)
		Tildrakizumab	Psoriasis	PsA (NCT03552276, NCT04314544, NCT04314531, NCT04991116)
		Mirikizumab		Psoriasis (NCT03482011, NCT03535194, NCT03556202) UC (NCT03518086, NCT03519945, NCT03524092) CD (NCT03926130, NCT04232553)

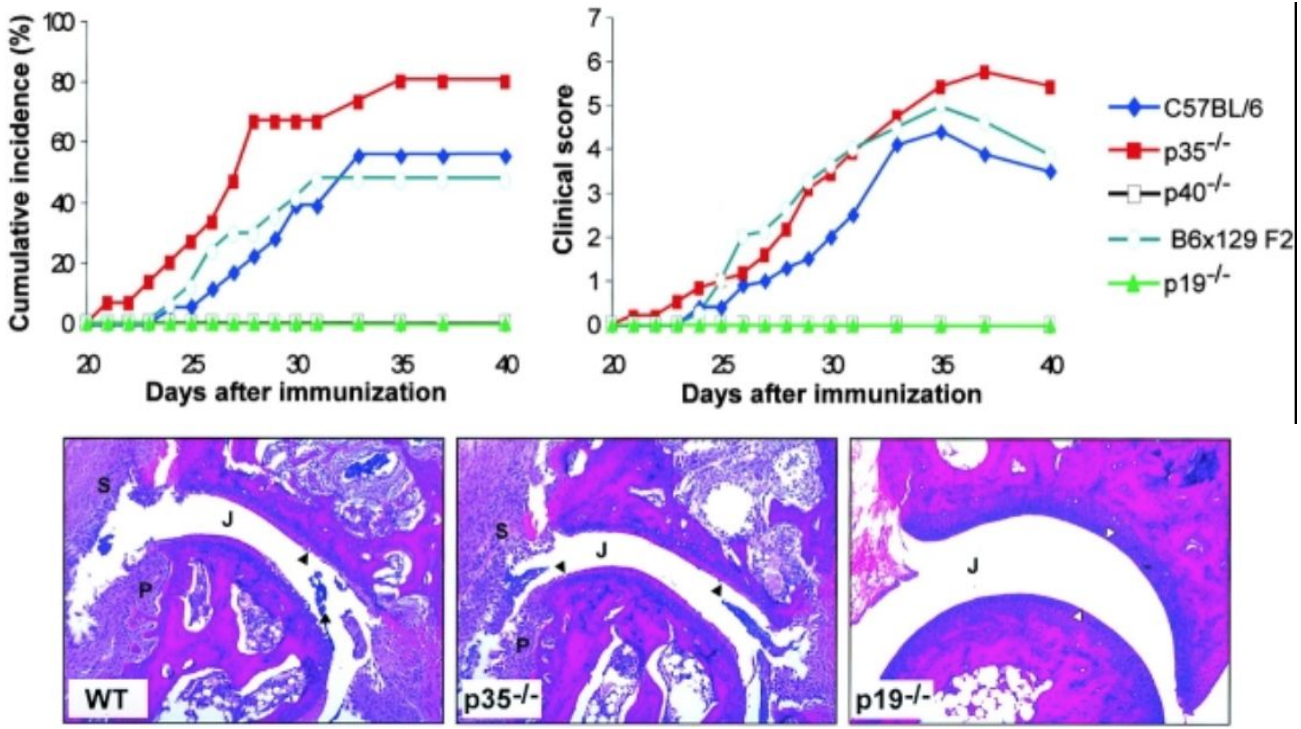
Jung SM, Kim WU, Février 2022

Polyarthrite rhumatoïde

> J Exp Med. 2003 Dec 15;198(12):1951-7. doi: 10.1084/jem.20030896. Epub 2003 Dec 8.

Divergent pro- and antiinflammatory roles for IL-23 and IL-12 in joint autoimmune inflammation

Craig A Murphy [1], Claire L Langrish, Yi Chen, Wendy Blumenschein, Terrill McClanahan,

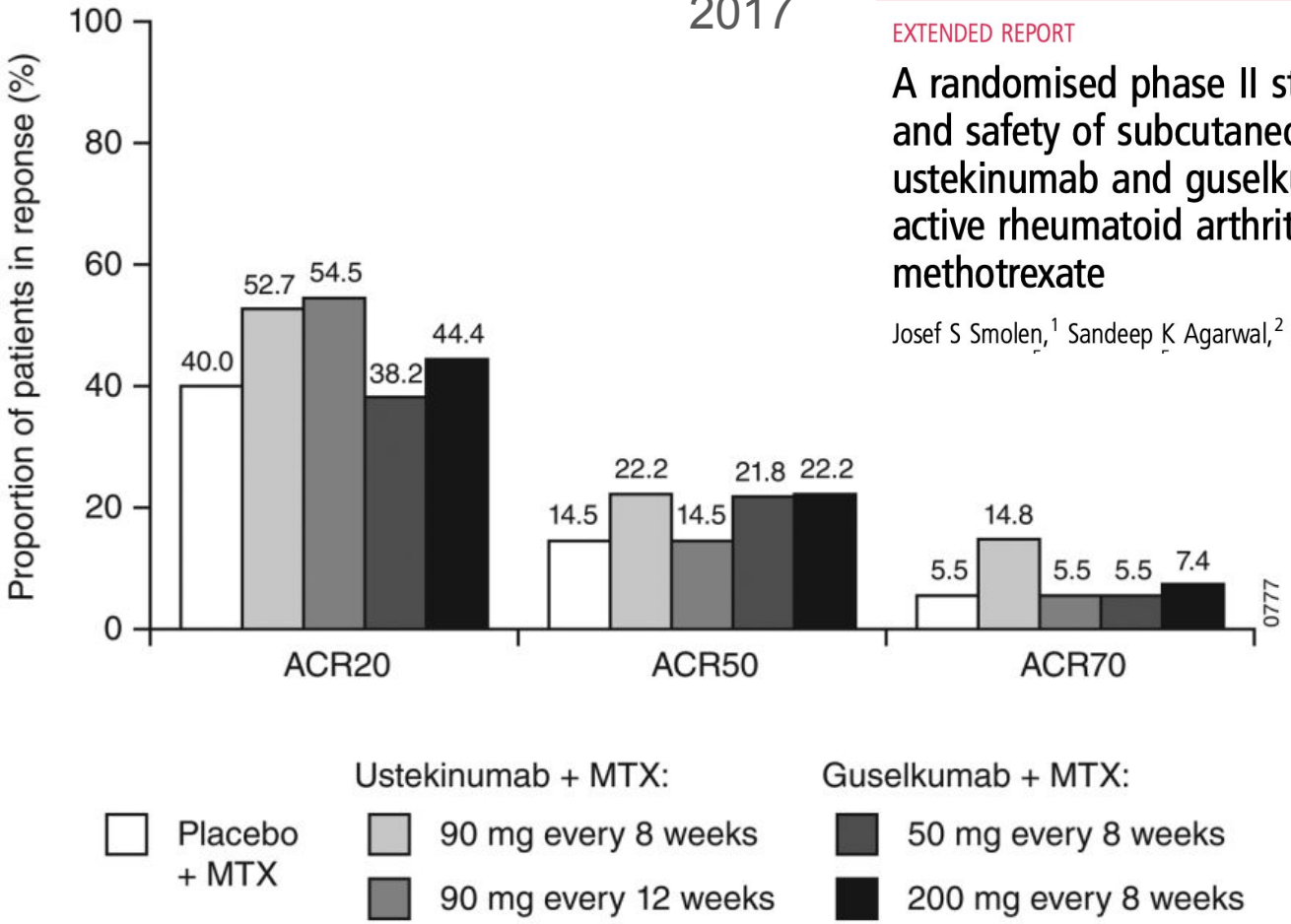


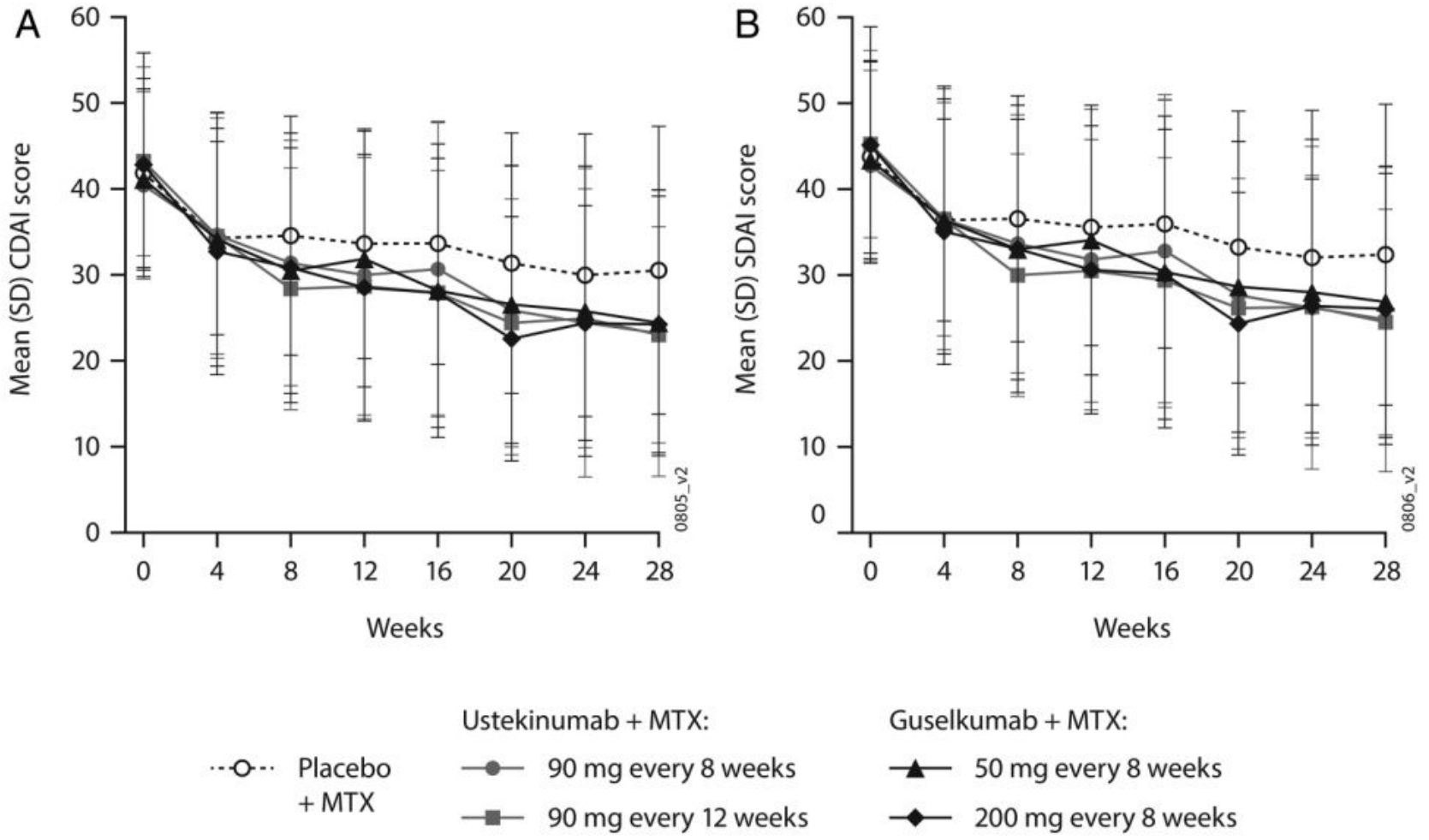
2017

EXTENDED REPORT

A randomised phase II study evaluating the efficacy and safety of subcutaneously administered ustekinumab and guselkumab in patients with active rheumatoid arthritis despite treatment with methotrexate

Josef S Smolen,[1] Sandeep K Agarwal,[2] Elena Ilivanova,[3] Xie Lillian Xu,[4] Ye Miao,[5]

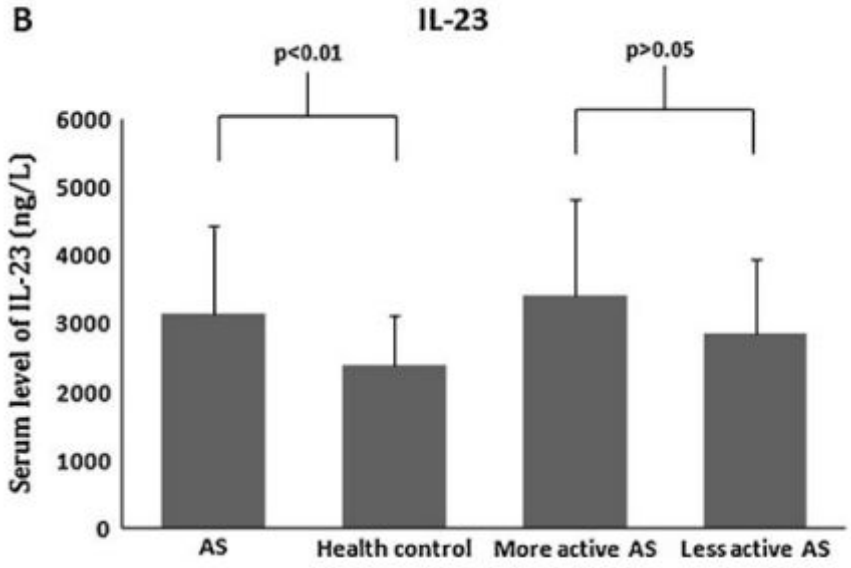



A
Mean (SD) CDAI score
60
50
40
30
20
10
0
0
4
8
12
16
20
24
28
Weeks
0805_v2
B
Mean (SD) SDAI score
60
50
40
30
20
10
0
0
4
8
12
16
20
24
28
Weeks
0806_v2
Placebo + MTX
Ustekinumab + MTX:
90 mg every 8 weeks
90 mg every 12 weeks
Guselkumab + MTX:
50 mg every 8 weeks
200 mg every 8 weeks

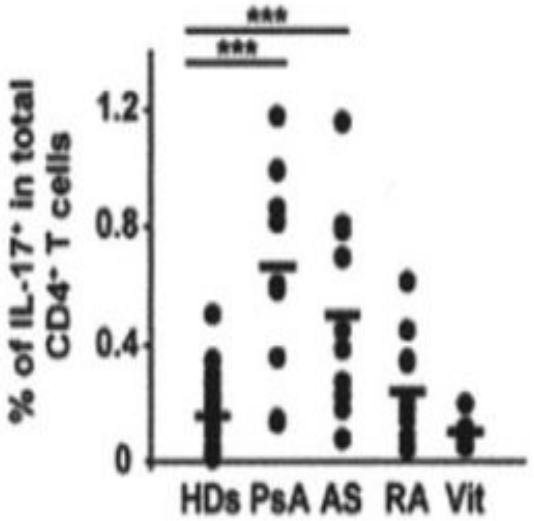
Spondylarthrite ankylosante

Axe IL-23/IL-17 → axe d'activation principal dans la maladie

- ↑ **taux IL-23 et IL-17** dans les <u>sérums</u> des patients atteints de SpA
- ↑ nombre de **cellules Th17** dans le sang périphérique des patients atteints de SpA



Mei, Y., Pan, F., Gao, J. et al, 2010



Jandus C, Bioley G et al 2008

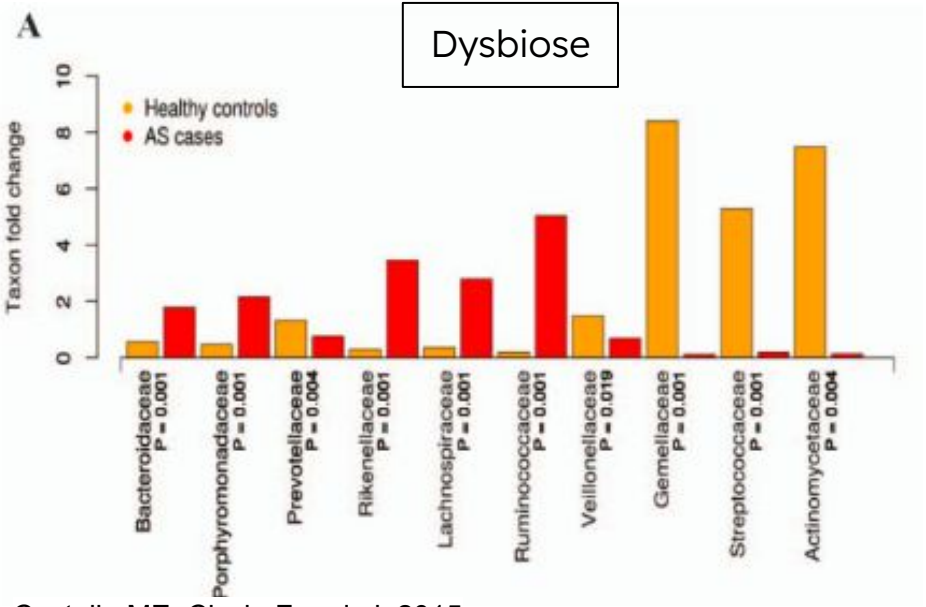
1/ Modification de la forme de HLA-B27 : altération du domaine de liaison aux protéines

Guiliano DB, Fussell H and all, 2014

2/ SNP (polymorphismes nucléotides simples) au niveau de l'axe IL-23/IL-17 dans les **gènes codant pour l'IL-23R** = STAT3 et TYK2 *Di Meglio P, Di Cesare A and al, 2011*

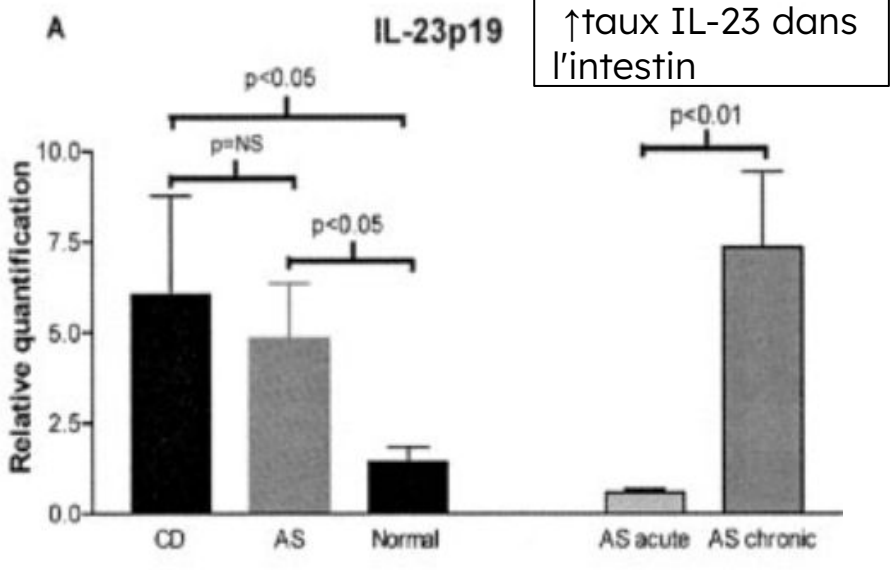
3/ The "joint-gut theory" : grande interface environnement/système immunitaire

Dysbiose



Costello ME, Ciccia F and al, 2015

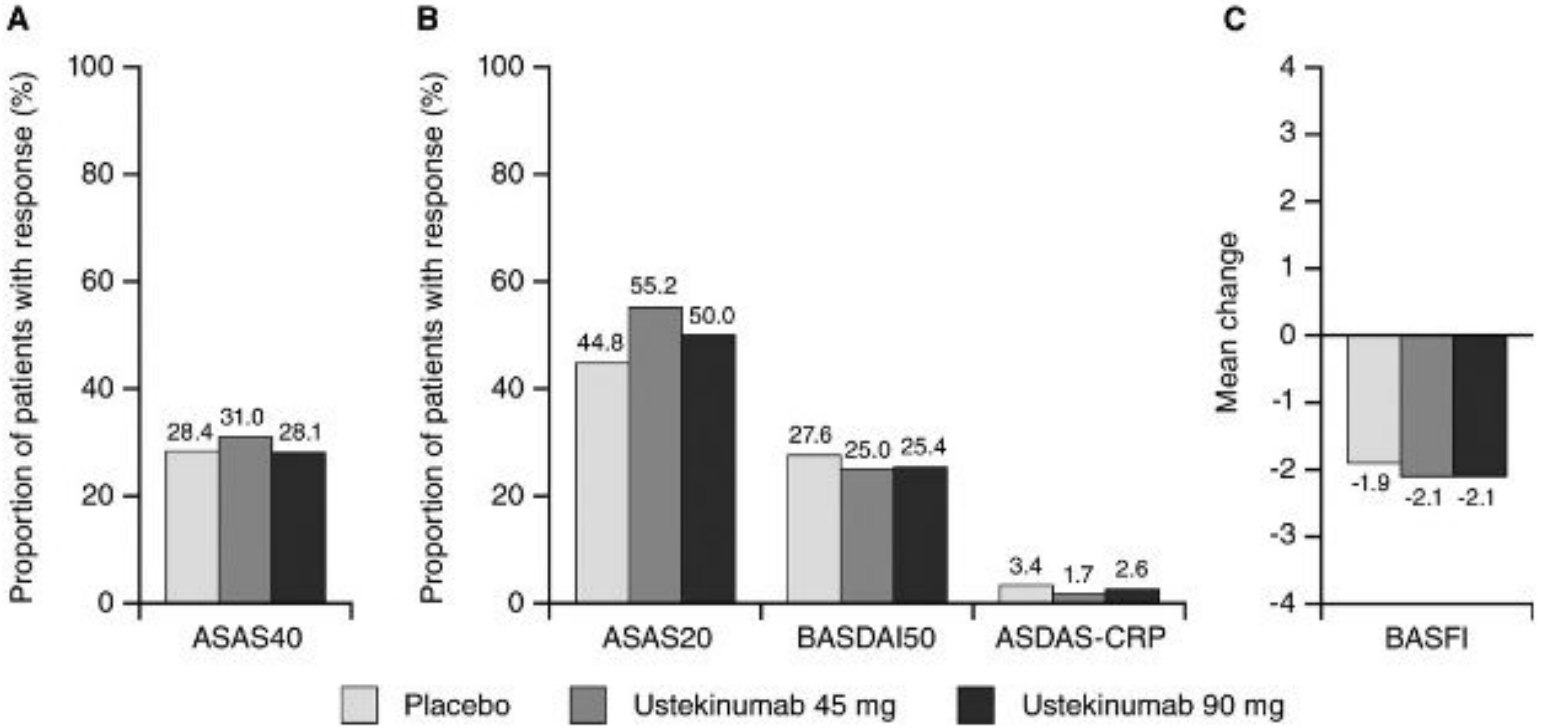
↑taux IL-23 dans l'intestin

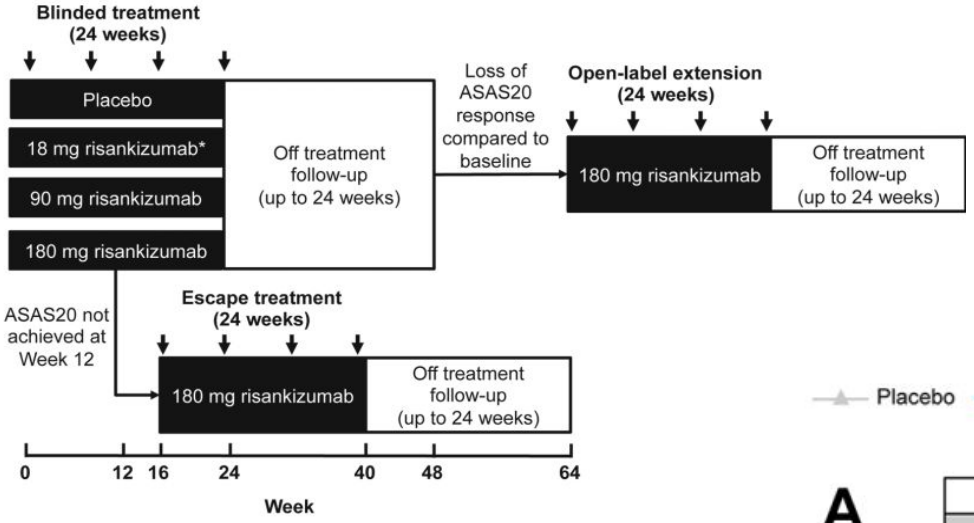


Ciccia F, Bombardieri M and al, 2008

Three Multicenter, Randomized, Double-Blind, Placebo-Controlled Studies Evaluating the Efficacy and Safety of Ustekinumab in Axial Spondyloarthritis

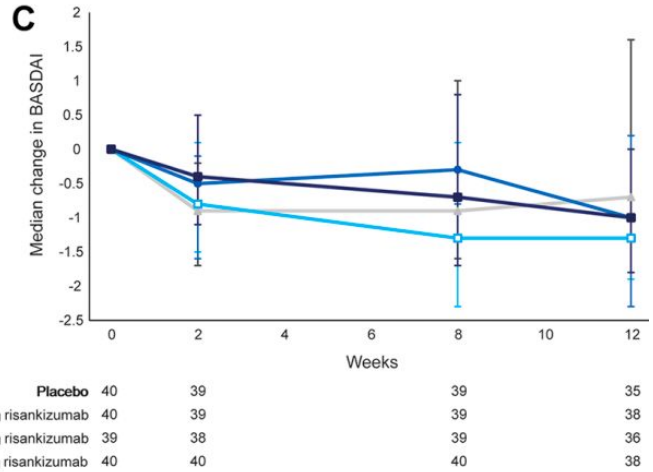
Atul Deodhar,[1] Lianne S. Gensler,[2] Joachim Sieper,[3] Michael Clark,[4] Cesar Calderon,[4] Yuhua Wang,[4] Yiying Zhou,[4]

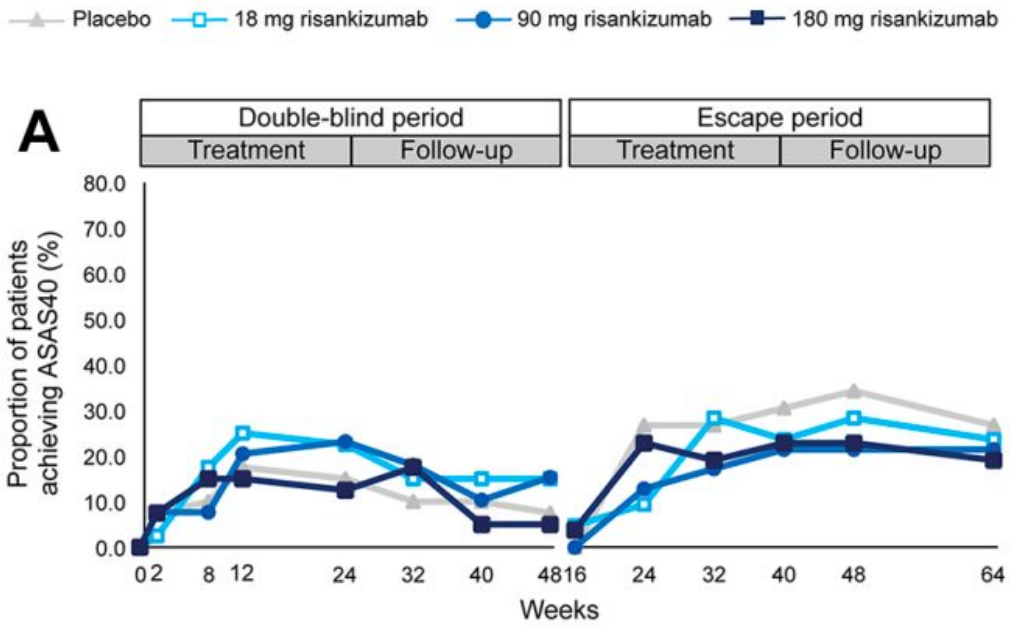




Risankizumab, an IL-23 inhibitor, for ankylosing spondylitis: results of a randomised, double-blind, placebo-controlled, proof-of-concept, dose-finding phase 2 study

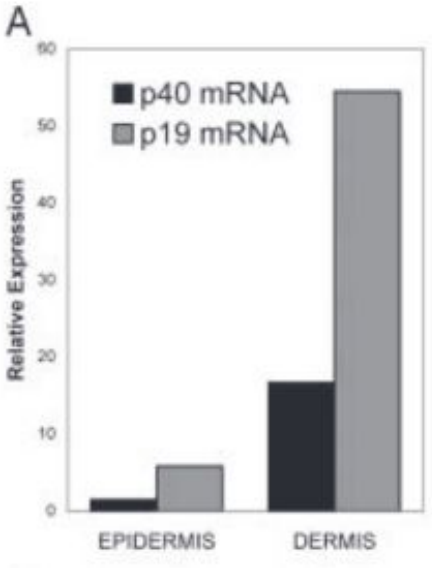
Dominique Baeten,[1] Mikkel Østergaard,[2,3] James Cheng-Chung Wei,[4,5]



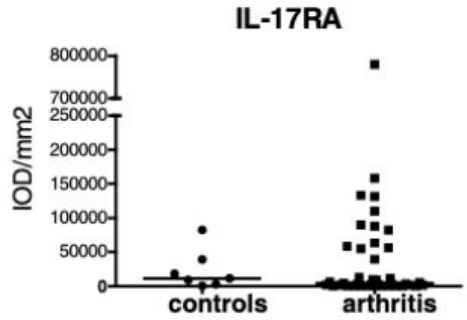


Rhumatisme psoriasique

Principales cellules effectrices dans les articulations + plaques cutanées : CDs, Macrophages, ¢ NK, mastocytes, PNN, ¢ Tγδ, ¢ T CD4+ & T CD8+
→ Phénotype sécrétoire prédominant d'**IL-17**
→ Cytokines produit par CDs dont **IL23** qui permet la différenciation des Th0 en Th17



Lee E, Trepicchio WL and al, 2004



Van Baarsen LG, Lebre MC and al, 2014

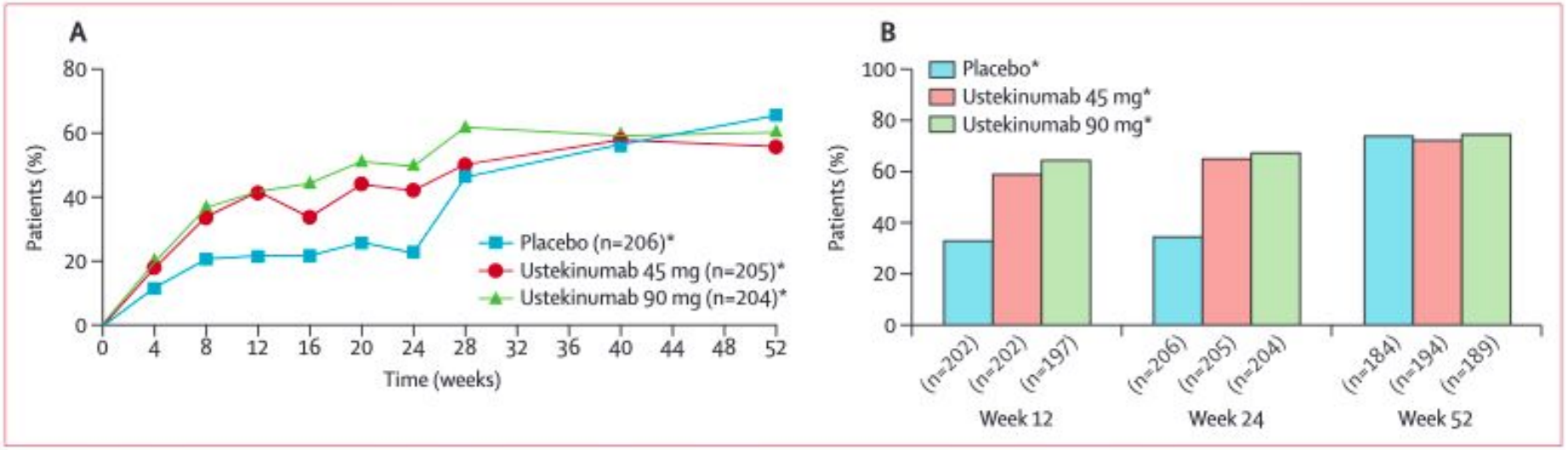
Nombre accru de cellules Th17 dans **sang + peau + liquide synovial**
Lee E, Trepicchio WL, 2004

Expression **IL23R, IL17R** majorés dans lésions cutanées psoriasiques et dans la synovite *Van Baarsen LG, Lebre MC and al, 2014*

Efficacy and safety of ustekinumab in patients with active psoriatic arthritis: 1 year results of the phase 3, multicentre, double-blind, placebo-controlled PSUMMIT 1 trial

Iain B McInnes*, Arthur Kavanaugh*, Alice B Gottlieb, Lluís Puig, Proton Rahman, Christopher Ritchlin, Carrie Brodmerkel, Shu Li, Yuhua Wang,

The Lancet, 2013

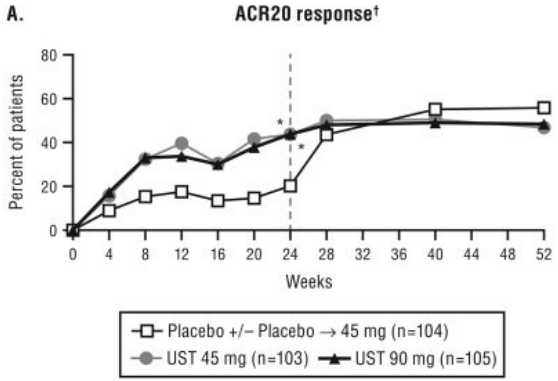


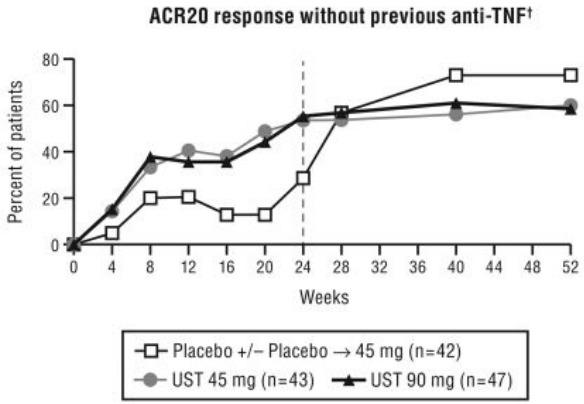
P-SUMMIT-2 : RP actif malgré ttt conventionnel avec échec/échappement aux anti-TNFa (**60%** des patients)

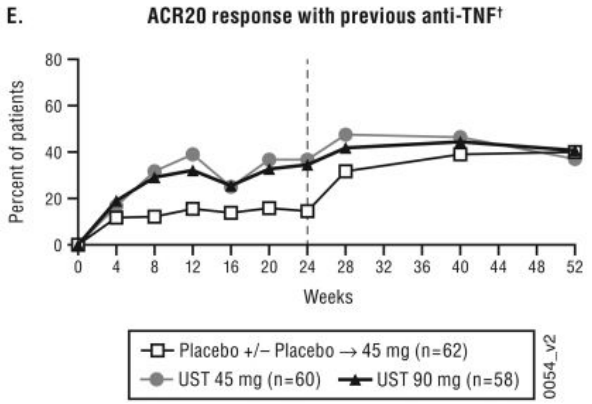
Efficacy and safety of the anti-IL-12/23 p40 monoclonal antibody, ustekinumab, in patients with active psoriatic arthritis despite conventional non-biological and biological anti-tumour necrosis factor therapy: 6-month and 1-year results of the phase 3, multicentre, double-blind, placebo-controlled, randomised PSUMMIT 2 trial

Christopher Ritchlin,[1] Proton Rahman,[2] Arthur Kavanaugh,[3] Iain B McInnes,[4]

Ann Rheum Dis. 2014





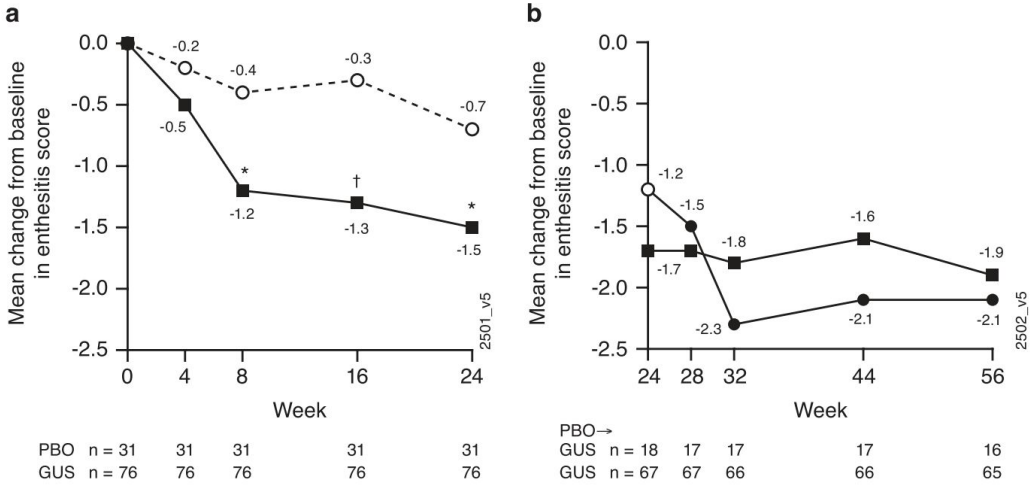


ORIGINAL RESEARCH

2020

Impact of guselkumab, an interleukin-23 p19 subunit inhibitor, on enthesitis and dactylitis in patients with moderate to severe psoriatic arthritis: results from a randomised, placebo-controlled, phase II study

Philip J Mease,[1,2] Dafna D Gladman,[3] Atul Deodhar,[4] Dennis G McGonagle,[5] Peter Nash,[6] Wolf-Henning Boehncke,[7] Alice Gottlieb,[8] Xie L Xu,[9] Stephen Xu,[10] Elizabeth C Hsia,[10,11] Chetan S Karyekar,[12] Philip S Helliwell[13]



Rheumatol Ther. 2024 Mar 18. doi: 10.1007/s40744-024-00654-5. Online ahead of print.

Efficacy and Safety of Risankizumab for Active Psoriatic Arthritis: 100-Week Results from the Phase 3 KEEPsAKE 1 Randomized Clinical Trial

Lars Erik Kristensen [1], Mauro Keiserman [2], Kim Papp [3 4], Leslie McCasland [5],

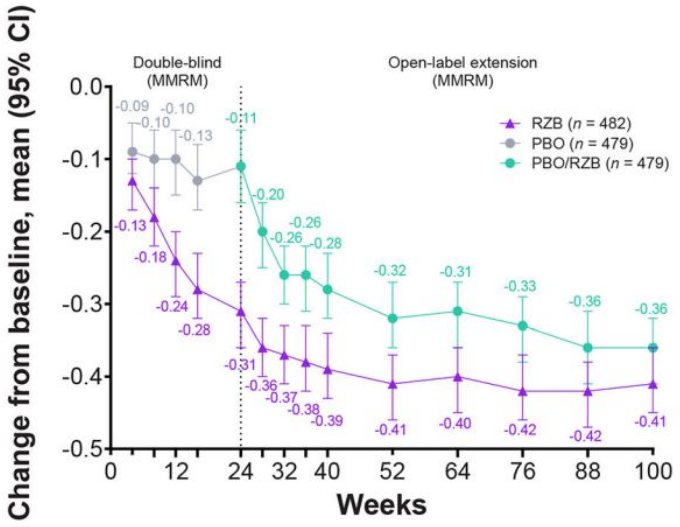


Fig. 3 Change from baseline over time in HAQ-DI.

- **Rhumatisme psoriasique**

« STELARA, seul ou en association avec le méthotrexate (MTX), est indiqué dans le traitement du rhumatisme psoriasique actif chez l'adulte lorsque la réponse à un précédent traitement de fond antirhumatismal non-biologique (DMARD) a été inadéquate. »

Modéré	Le service médical rendu par STELARA 45 mg et 90 mg (ustékinumab), solution injectable en stylo prérempli, est modéré dans le traitement du rhumatisme psoriasique actif chez l'adulte lorsque la réponse à un précédent traitement de fond antirhumatismal non-biologique (DMARD) a été inadéquate.

Autres

LES (Lupus érythémateux disséminé)

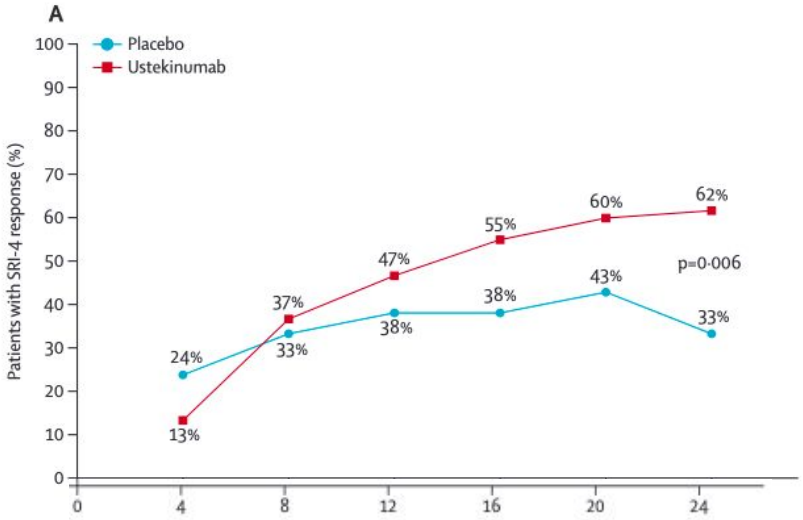
- ↑ **taux IL-17** & **IL-23 sérique** + ↑ **nombre cellules Th17 sériques** vs sujet sains
  → Taux corrélé à l'activité de la néphrite ; % Th17 circulant corrélé à l'activité du LES *Chen et al, 2012*
  → Taux sériques élevés IL-23 et IL-17 initiaux prédisent une réponse histopathologique défavorable

- Biopsies rénales : infiltrat de Lymphocytes T exprimant IL17
  → In vitro (souris) : majoration de l'expression de IL23R avec aggravation de la LN
  Fischer K, Przepiera-Bedzak H and al, 2017

Efficacy and safety of ustekinumab, an IL-12 and IL-23 inhibitor, in patients with active systemic lupus erythematosus: results of a multicentre, double-blind, phase 2, randomised, controlled study

Ronald F van Vollenhoven, Bevra H Hahn, George C Tsokos, Carrie L Wagner, Peter Lipsky, Zahi Touma, Victoria P Werth, Robert M Gordon, Bei Zhou, Benjamin Hsu, Marc Chevrier, Manon Triebel, Jarrat L Jordan, Shawn Rose

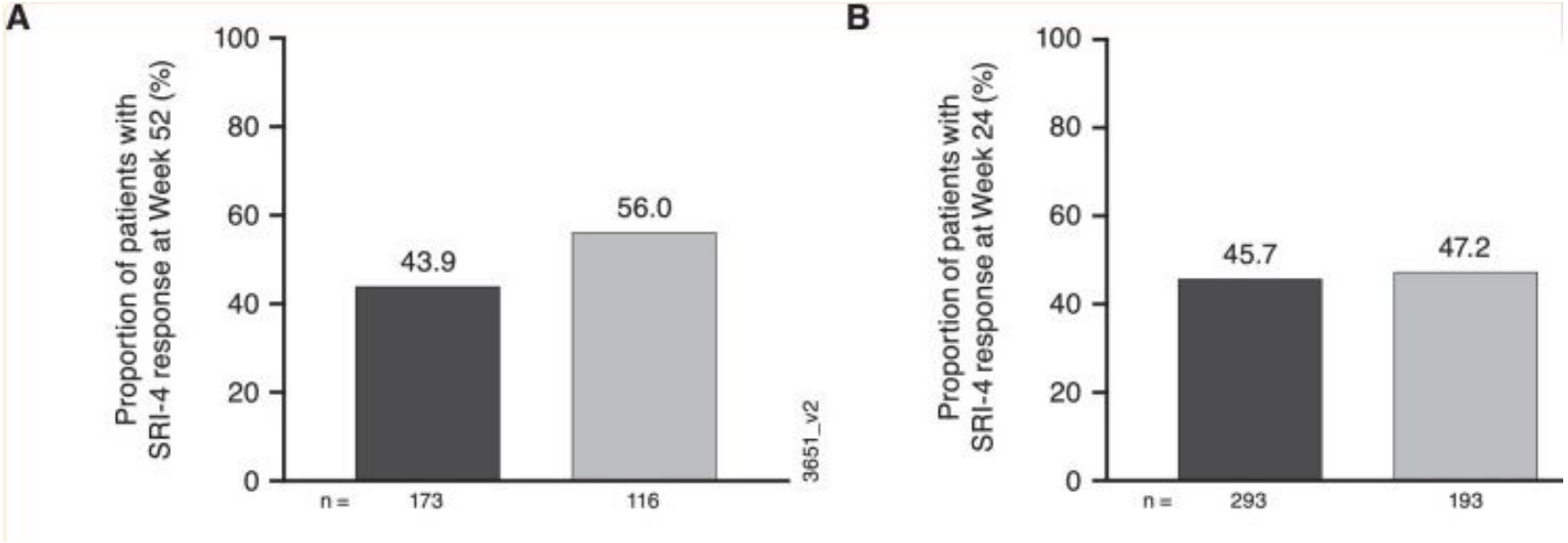
The Lancet, 2018



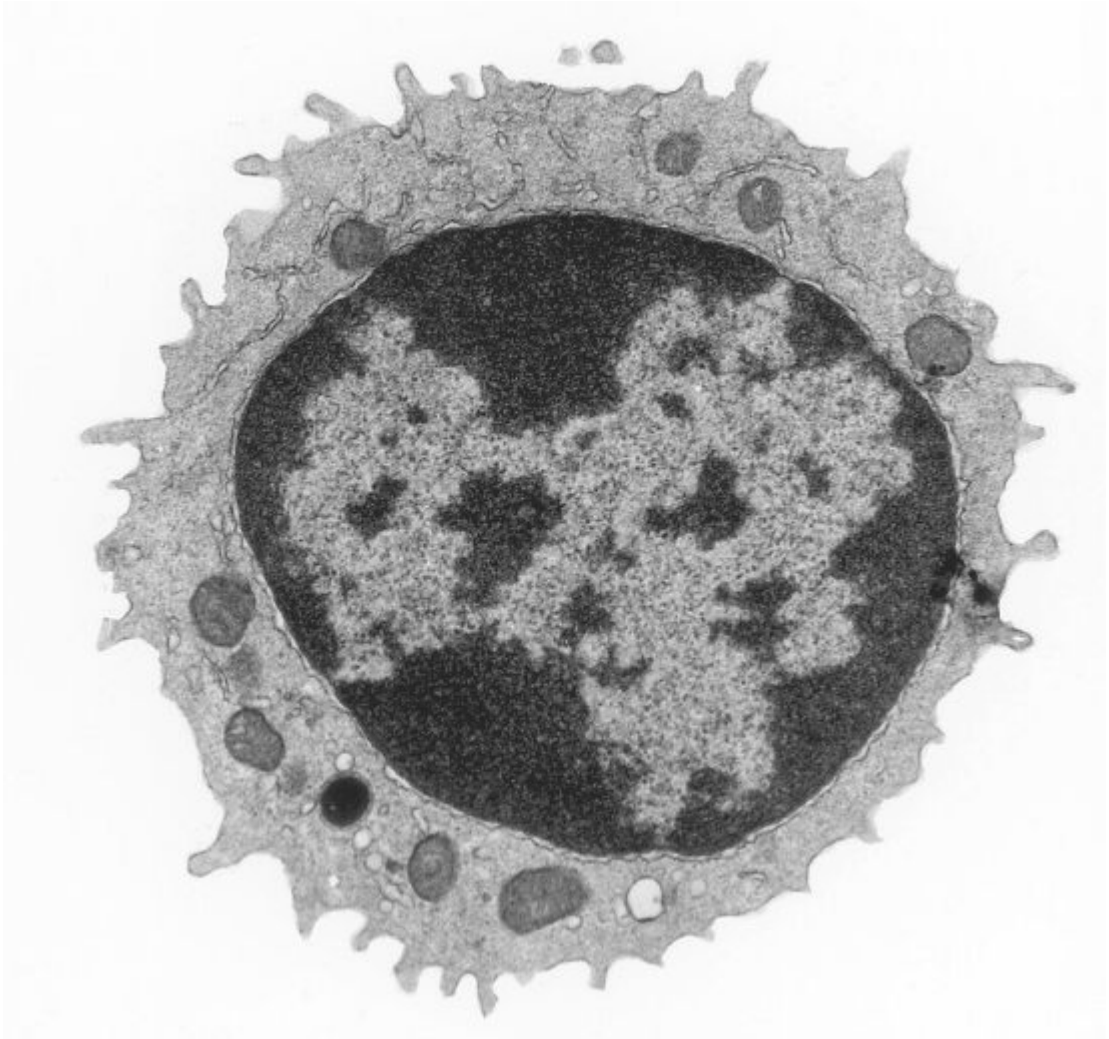
Phase 3, multicentre, randomised, placebo-controlled study evaluating the efficacy and safety of ustekinumab in patients with systemic lupus erythematosus

Ronald F van Vollenhoven [1], Kenneth C Kalunian [2], Thomas Dörner [3], Bevra H Hahn [4],

Ann Rheum Dis. 2022



Merci pour votre attention



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