

INMUNAUTAS

Beyond the gut - Explorando las fronteras entre las IMIDs.

Evento de Educación Médica
Organizado y Financiado por:

Johnson&Johnson

EM-196046 Enero 2026 Jassen Cilag S.A

Proyecto



Comité Científico:

Yago González-Lama. *Gastroenterologist, Hospital Universitario 12 de Octubre, Madrid, Spain*
Luis Menchén. *Gastroenterologist, Hospital Gregorio Marañón, Madrid*
Rubén Francés. *Professor of Immunology, Grupo de Immunobiología Hepática e Intestinal, CIBER*

Ponentes invitados:

Daniel Cua. *Distinguido Fellow VP de Inmunología, J&J*
Azucena Salas. *PhD, Jefa de Grupo de EII, IDIBAPS; Profesora Asociada de Inmunología, Universidad de Barcelona*

I Beyond the gut - Explorando las fronteras entre las IMIDs

Viernes 23 de enero

- 19:45-20:00 h **Bienvenida a Inmunautas 3ª Edición.**
Comité Científico
- 20:00-21:00h **Why IL-23?**
Daniel Cua
- Mesa Redonda: todos los ponentes

Sábado 24 de enero

- 09:30-10:00 h **Beyond the gut- Explorando las fronteras entre las IMIDs**
Yago González-Lama
- Mesa Redonda: todos los ponentes
- 10:00-11:00 h **Taller EII y Psoriasis:**
Yago González-Lama y Rubén Francés
- Mesa Redonda: todos los ponentes
- 11:00-11:30 h **Café**
- 11:30-12:30 h **Taller EII y EspA:**
Luis Menchén y Azucena Salas
- Mesa Redonda: todos los ponentes
- 12:30-13:00 h **Futuro de la EII:**
Luis Menchén
- Mesa Redonda: todos los ponentes
- 13:00-13:15 h **Conclusiones y clausura**
Comité Científico

DISCLOSURE

- Esta charla está organizado y financiado por Janssen, Compañía Farmacéutica del Grupo Johnson&Johnson
- Los puntos de vista expresados en las presentaciones son propiedad de los ponentes y no necesariamente coinciden con los puntos de vista de Janssen
- Las presentaciones pueden incluir discusiones sobre la utilización de fármacos fuera de ficha técnica
- Cualquier alusión a casos clínicos hará referencia a supuestos clínicos ficticios

CONFLICTOS DE INTERÉS

YG: He sido ponente, consultor y miembro asesor o he recibido financiación para investigación de: Abbvie, Takeda, Janssen, Pfizer, Biogen, Amgen, Ferring, Faes Farma, Chiesi, Gebro Pharma.

LM: He recibido ayudas para la investigación de MSD, Abbvie y Kern, y he servido como ponente y miembro de consejos de asesoría de MSD, Abbvie, Pfizer, Janssen, Takeda, Biogen, Sandoz, Gaápagos, Dr. Falk-Pharma, FAES, Ferring, General Electric y Medtronic

RF: He sido ponente, consultor o he recibido financiación para investigación de: Abbvie, Johnson&Johnson, Takeda, Pfizer, Novartis, Adacyte, UCB, Biogen, Almirall, GSK, Astra Zeneca, Boehringer.

AS: He recibido financiación de Takeda, Nestle, Pfizer, Roche-Genentech, AbbVie, GSK, Scipher Medicine, Alimentiv, Inc, Boehringer Ingelheim, Agomab, Galapagos, AdBio Partners, HotSpot Therapeutics, GoodGut.

DC: Empleado de Janssen (Johnson & Johnson).

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20:00-21:00h **Why IL-23?**
Daniel Cua

Mesa Redonda: todos los ponentes

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Bienvenidos a Inmunautas

3ª Edición
Comité científico

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En ediciones anteriores...

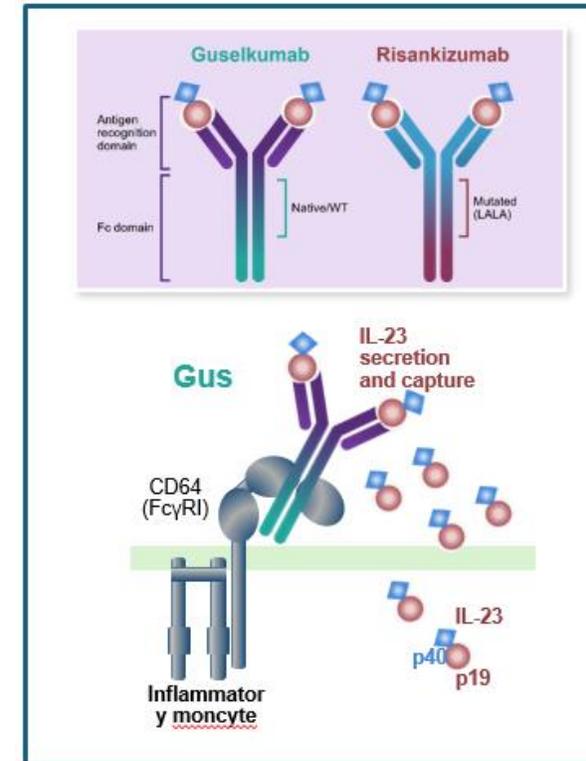
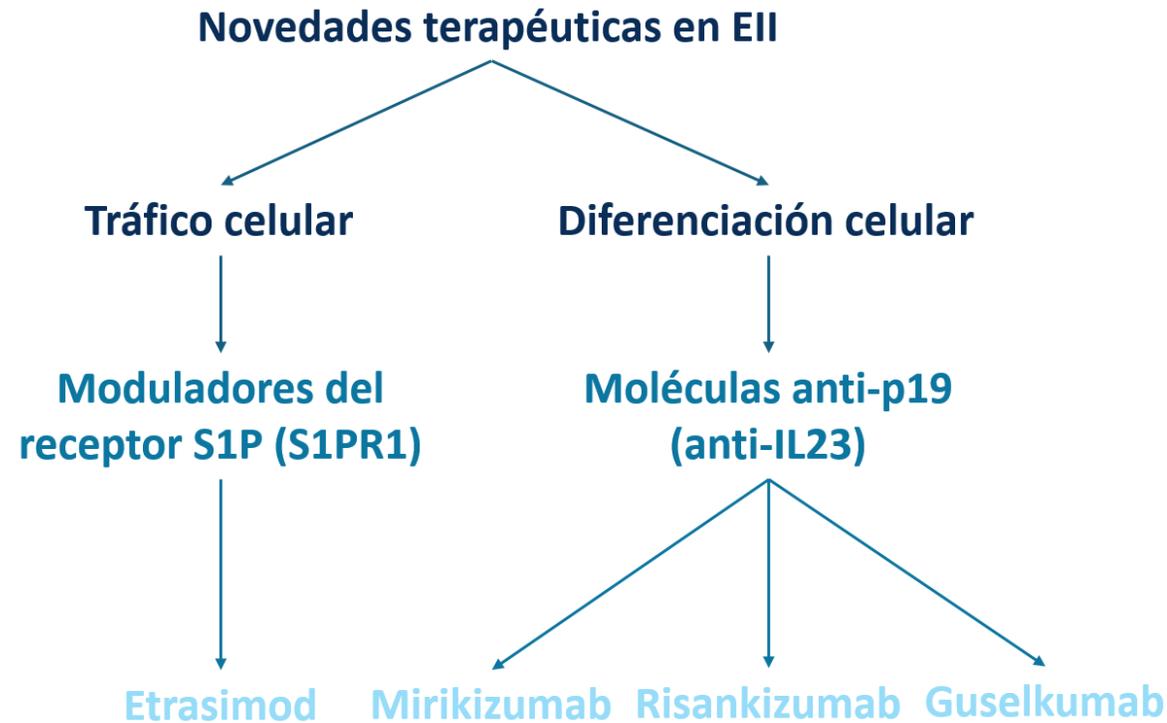
- La desregulación del sistema inmune a nivel intestinal es compleja y tiene lugar en diferentes lugares.
- El conocimiento de las alteraciones del sistema inmune da pie a la identificación de dianas terapéuticas concretas y a tratamientos específicos.

The best is yet to come.

Frank Sinatra.



Conectamos puntos en el complejo universo de la inmunología de la EII



Conectamos puntos en el complejo universo de la inmunología de la EII

**Inmunidad innata y
Enfermedad precoz**



**Inmunidad adaptativa y
Enfermedad avanzada**

¿Qué le está pasando a mi paciente a nivel del epitelio?

Este daño es previo al desarrollo de EII, ¿está ocurriendo desde hace tiempo? ¿se puede detectar precozmente?

¿Podemos modular la disfunción de la barrera intestinal que caracteriza la EII precoz?

...

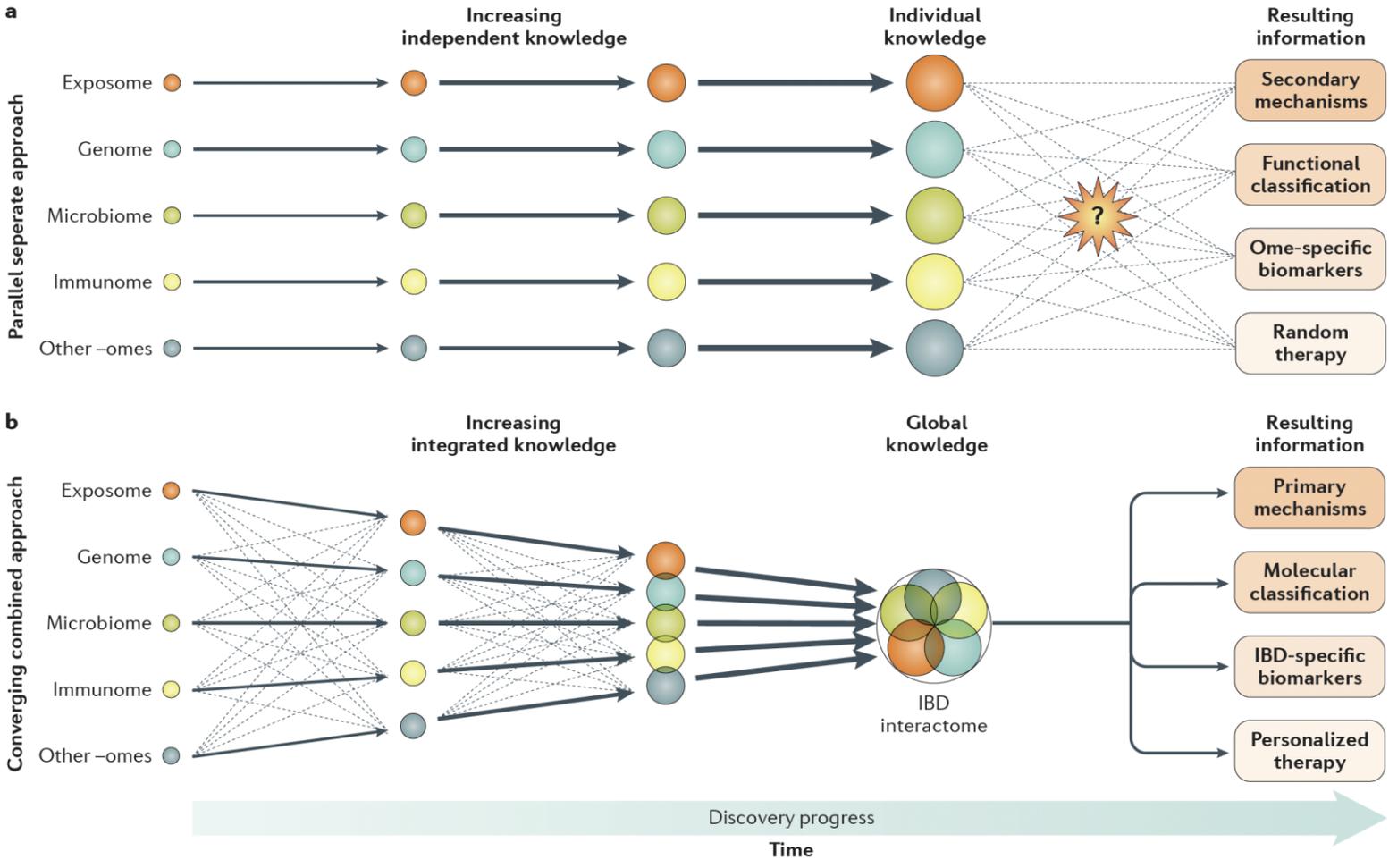
¿Qué le está pasando a mi paciente en relación con la inmunidad adaptativa?

La activación de la inmunidad adaptativa puede ocurrir antes del diagnóstico.

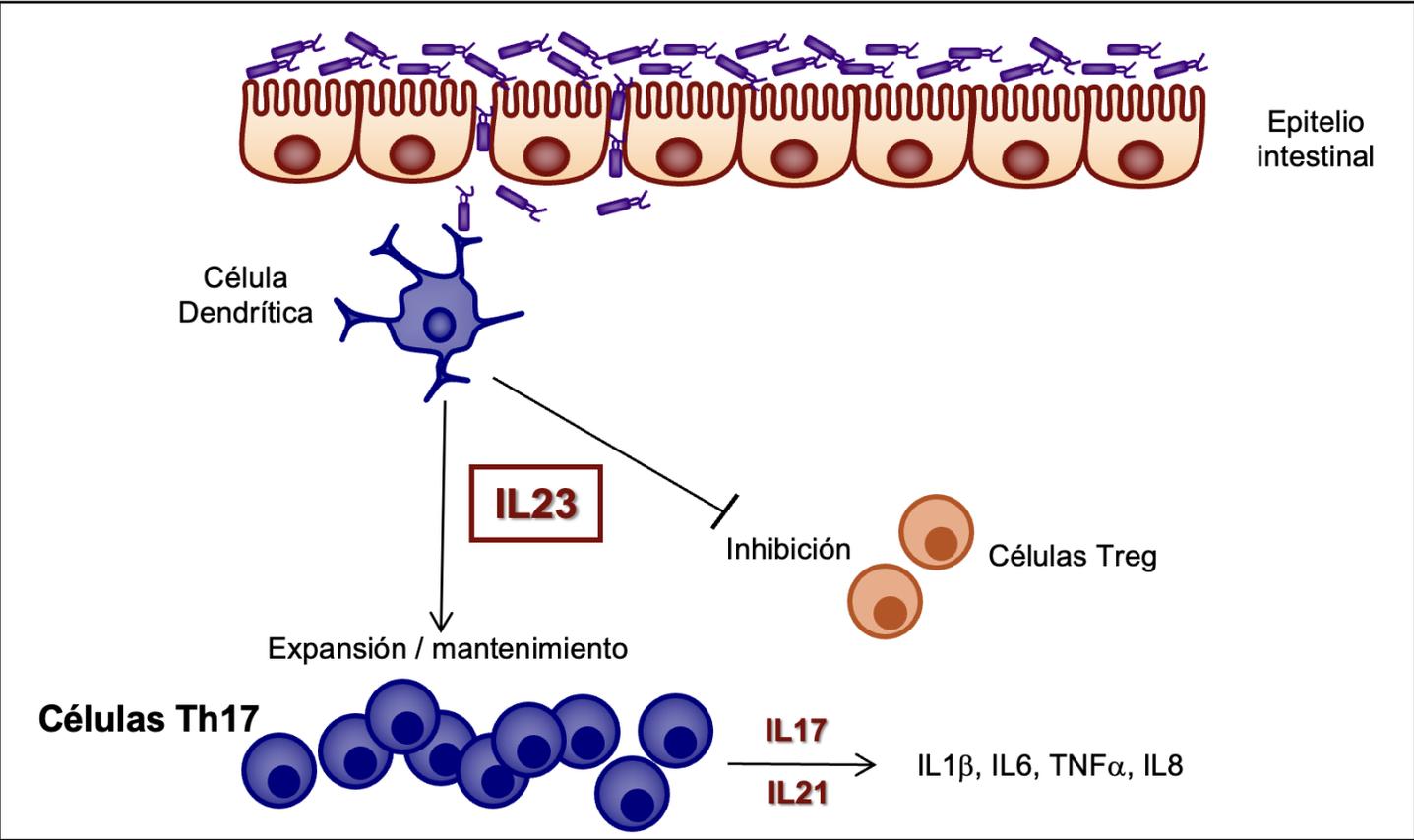
La enfermedad avanzada presenta cambios en la respuesta inmunitaria

...

Is everything as simple as it seems?



Is everything as simple as it seems?

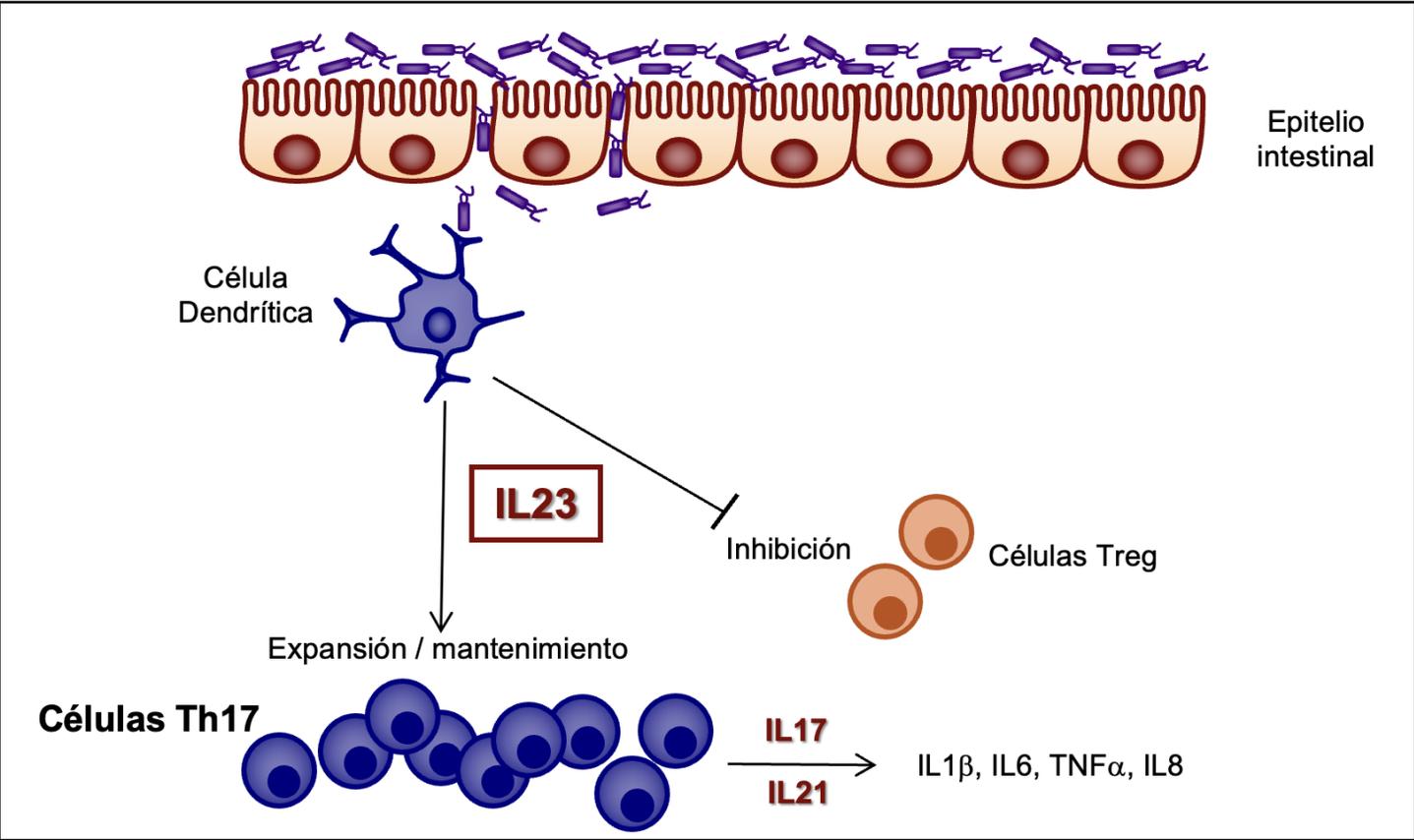


The Journal of Clinical Investigation <http://www.jci.org> Volume 116 Number 5 May 2006

IL-23 is essential for T cell-mediated colitis and promotes inflammation via IL-17 and IL-6

David Yen,¹ Jeanne Cheung,¹ Heleen Scheerens,¹ Frédérique Poulet,² Terrill McClanahan,³ Brent McKenzie,¹ Melanie A. Kleinschek,¹ Alex Owyang,¹ Jeanine Mattson,³ Wendy Blumenschein,³ Erin Murphy,³ Manjiri Sathe,³ Daniel J. Cua,¹ Robert A. Kastelein,¹ and Donna Rennick¹

Is everything as simple as it seems?



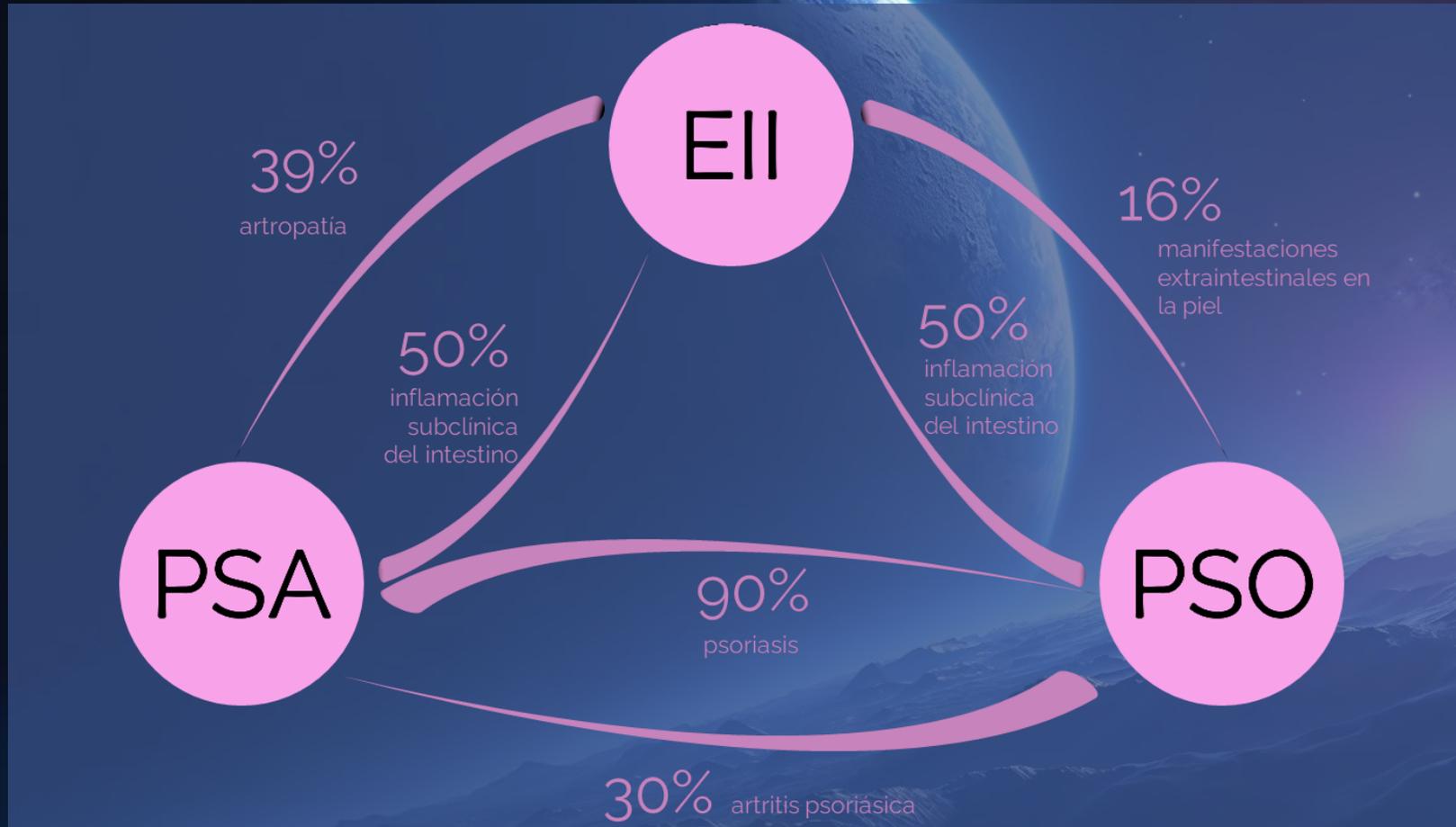
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Let's get started!

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1. Ciccia F, et al. Arthritis Rheumatol. 2016;68:1922-31.; 2. Mease PJ, Armstrong AW. Drugs. 2014;75:423-41; 3. Ciocon DH, Kimball AB. Br J Dermatol. 2007;157:850-60; 4. Sanchez IM, et al. Curr Dermatol Rep. 2018;7:59-74; 5. Arvikar SL, Fisher MC. Curr Rev Musculoskel Med. 2011;4:123-31; 6. Greuter T, et al. Clin Rev Allergy Immunol. 2017;53:413-27.; 7. Liu JT, et al. World J Orthop. 2014;5:537-43; 8. Suzuki E, et al. Autoimmunity Rev. 2014;13:496-502; 9. Lowes MA, et al. Annu Rev Immunol. 2014;32:227-55; 10. Levine JS, Burakoff R. Gastroenterol Hepatol (N Y). 2011;7:235-41; 11. Matricon J, et al. Self NonSelf. 2010;1:299-309; 12. Mease PJ, et al. J Am Acad Dermatol. 2013;69:729-35; 13. Tremfya (guselkumab) SmPC EMA; 14. Skyrizi (risankizumab) SmPC EMA; 15. Ormvo (mirikizumab) SmPC EMA

EM-196046 Enero 2026 Janssen Cilag S.A



Bienvenidos a la 3ª Edición

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Let's get excited about the IL-23 pathway!

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Beyond the gut - Explorando las fronteras entre las IMIDs.

IL-23: *The Why*

Dr. Daniel Cua
Comité científico

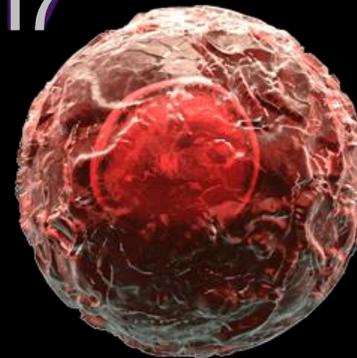
Why IL-23?

- **Discovery of IL-23 as a key axis in IMiDs (PSO, PSA, IBD)**
- **IL-23 activates Th17 cells that secrete pro-inflammatory cytokines, perpetuating damage**
- **IL-23 is responsible for triggering autoimmune diseases**

Krueger JG, *et al.* Front Immunol. 2024;15:1331217.

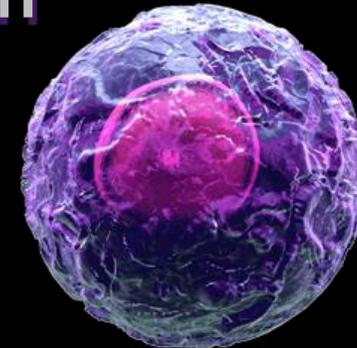


Th17



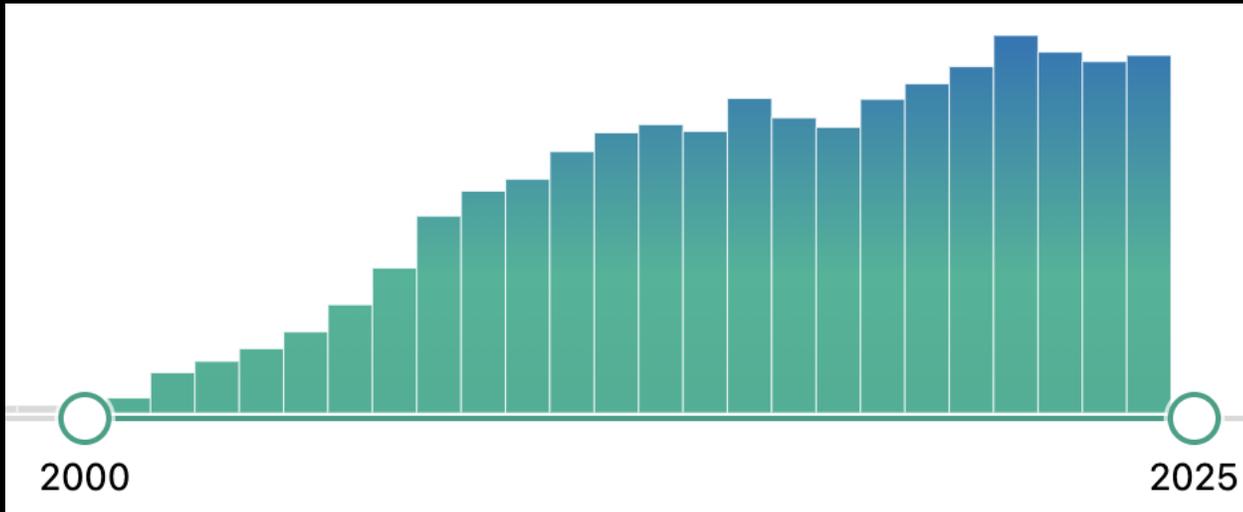
Wound healing

Th1



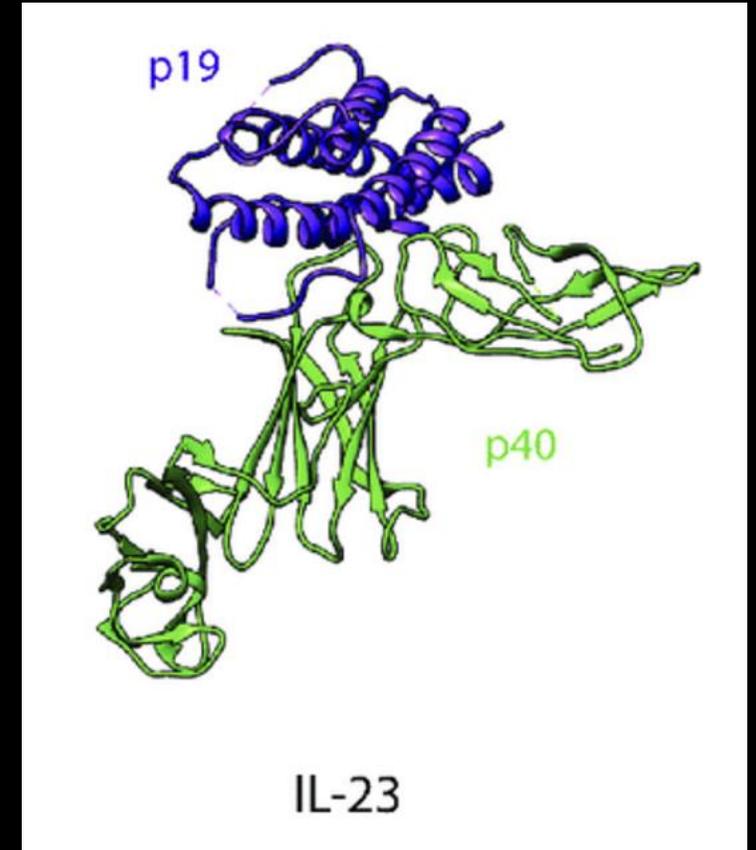
Fight infections

IL-23: from 2000 to 2025 → 11,400 published works



Discovery [\[edit\]](#)

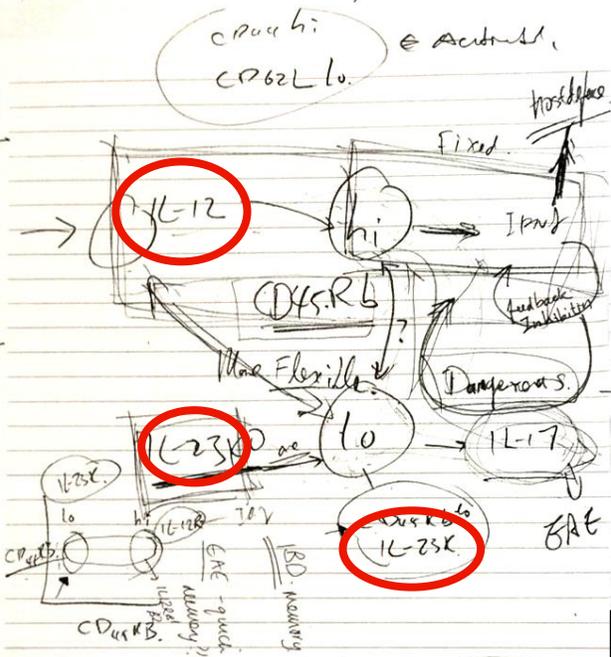
IL-23 was first described by Robert Kastelein and colleagues at the DNAX research institute using a combination of [computational](#), [biochemical](#) and cellular [immunology](#) approaches.^[1]



Two Working Hypotheses for "Alternative T cell" activation Pathway induced by IL-23:

Hypothesis One

Some of the CD45Rb^{hi} cells become CD45Rb^{lo} memory cells, while most will apoptose after activation. IL-23 re-activates these Rb^{lo} memory cells to make IL-17 leading to Autoimmunity.



In a meeting with Craig Murphy and Claire Longmire, we discussed the two distinct T cell populations that are driven by IL-12 and IL-23.

IL-12 promotes induction of Th1 cell secreting IFN-γ, consistent with Anna O'Garra's work. These IFN-γ secreting cells are CD45Rb^{hi}.

These IFN-γ producing cells have a... (faded)

2003

My work suggest existence of a novel IL-23R+ T cell subset

Highly pathogenic Th17 cells that drive disease

Note: When analyzing CD45Rb expression, be sure to look at only the CD45⁺ cells. There are many other myeloid/lymphoid cells that might cloud the picture.

Daniel Cua
6/5/03

IL-23, by contrast, promotes induction of IL-17 producer express lower level of CD45Rb → (CD45Rb^{lo}). ~~Since~~ either CD45Rb^{lo} cell preferentially expressed IL-23R. IL-23 induce ~~a~~ changes in CD45Rb expression level.

→ have a CD45Rb^{hi} population of T cells. IL-23 KO mice ~~don't~~ have CD45Rb^{lo} population of T cells. To p19KO T cell culture change the CD45Rb^{hi} → CD45Rb^{lo}

Ilmuth
6/5/03

these as IFN-γ producers?

Hypothesis I: Th17 develops from a subset of Th1 cells that survives activation induced cell death, becoming CD45Rb^{lo} memory T cells that express IL-23R. IL-23 then activates these CD45Rb^{lo} cell to become effector T cells producing IL-17 and maintains/induce autoimmunity.

Daniel Cua
6/5/03

Hypothesis II: Th17 comes from a "common precursor population" that can respond to both IL-12 and IL-23. Each of these two cytokine directs development of distinct subset of T cells: that fraction as Th1-IFNγ... Th17-IL-17 producing cells involved in autoimmunity.

Interleukin-23 rather than interleukin-12 is the critical cytokine for autoimmune inflammation of the brain

Daniel J. Cua*, Jonathan Sherlock*, Yi Chen*, Craig A. Murphy*,

IL-23 past, present, and future: a roadmap to advancing IL-23 science and therapy

James G. Krueger¹, Kilian Eyerich^{2,3}, Vijay K. Kuchroo⁴, Christopher T. Ritchlin⁵, Maria T. Abreu⁶, M. Merle Elloso⁷, Anne Fourie⁸, Steven Fakhrazadeh⁹, Jonathan P. Sherlock^{10,11}, Ya-Wen Yang⁹, Daniel J. Cua^{10*} and Iain B. McInnes^{12*}

The Importance of Interleukin-23 in Immune-Mediated Diseases

 Daniel Cua, Ph.D., Vice President, IL-23 Pathway Area Leader at the Janssen Pharmaceutical Companies of Johnson & Johnson
Published Oct 20, 2021

 Wikipedia
https://en.wikipedia.org/wiki/Interleukin_23

Interleukin 23

IL-23 imbalance and increase is associated with autoimmune diseases and cancer. ... ^ Cua

DJ, Sherlock J, Chen Y, Murphy CA, Joyce B, Seymour B, et al ...

Article | January 18 2005

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

Claire L. Langrish, Yi Chen, Wendy M. Blumenschein, Jeanine Mattson, Beth Basham, Jonathan D. Sedgwick, Terrill McClanahan, Robert A. Kastelein, Daniel J. Cua

Science Immunology

Local IL-23 is required for proliferation and retention of skin-resident memory T_H17 cells

SARAH K. WHITLEY , MUSHI LI , SAKEEN W. KASHEM , TOSHIRO HIRAI , BOTOND Z. IGYÁRTÓ , KELLEY KNIZNER, JONHAN HO , LAURA K. FERRIS,

CASEY T. WEAVER , DANIEL J. CUA, MANDY J. MCGEACHY, AND DANIEL H. KAPLAN  [fewer](#) [Authors Info & Affiliations](#)

 **The Journal of Clinical Investigation**

Anti-IL-23 therapy inhibits multiple inflammatory pathways and ameliorates autoimmune encephalomyelitis

Yi Chen, ... , Robert A. Kastelein, Daniel J. Cua

J Clin Invest. 2006;116(5):1317-1326. <https://doi.org/10.1172/JCI25308>.

Generation of IL-23 p19 deficient mice

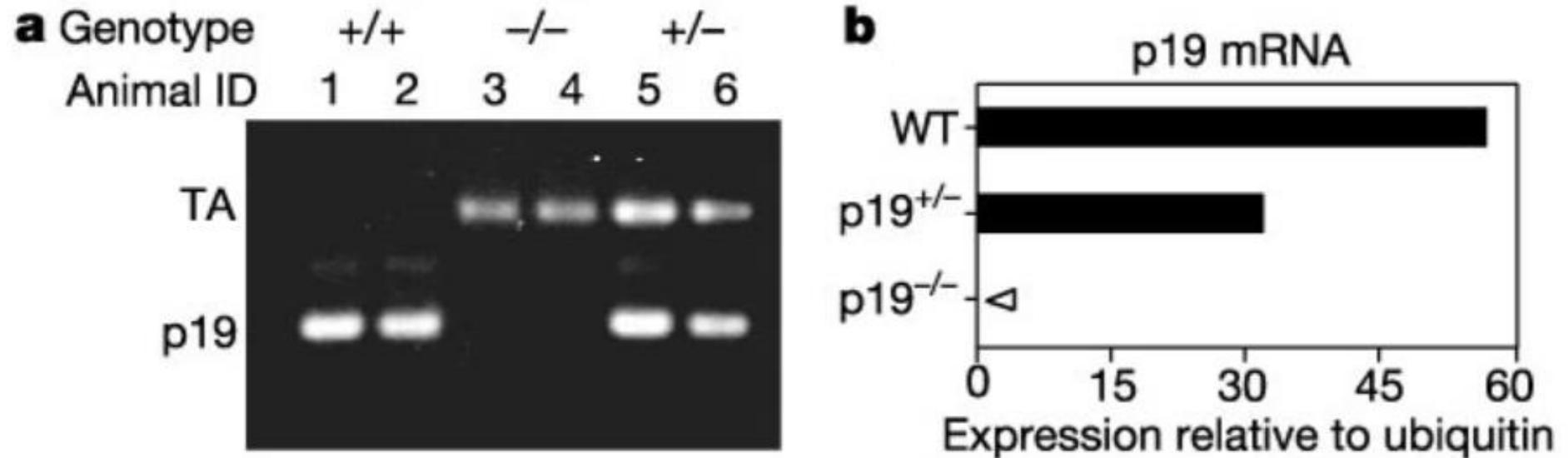
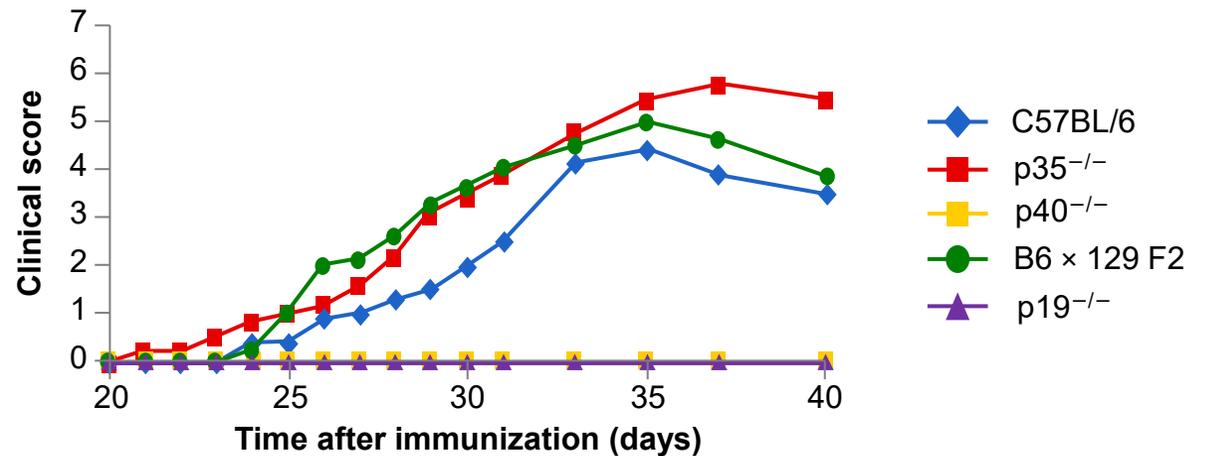
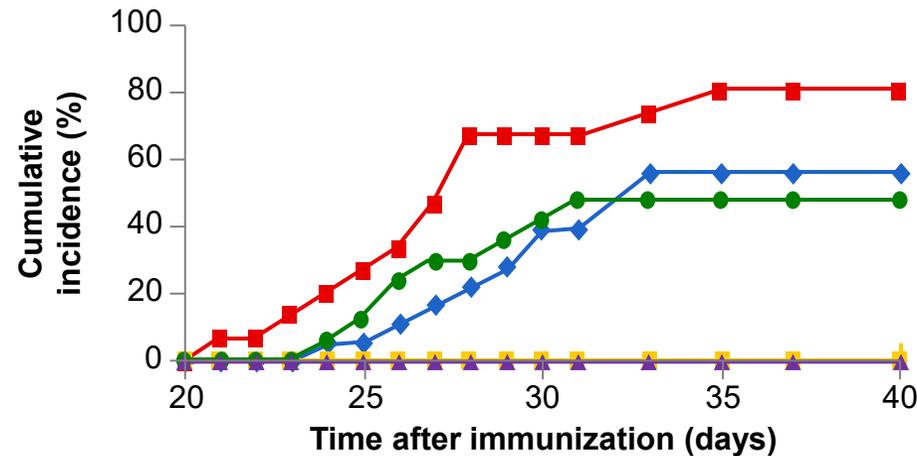


Figure 1: Generation of IL-23-deficient mice

See Supplementary Information for the targeting strategy. **a**, PCR analysis of wild type (+/+), heterozygous (+/-) and homozygous IL-23 p19-deficient (-/-) mice, showing presence of the targeted allele (TA) and absence of the *p19* gene in *p19*^{-/-} mice. **b**, Quantitative RT-PCR analysis of the expression of *IL-23 p19* mRNA in lymph node tissue.

IL-23 promotes joint injury response: a model of enthesal inflammation

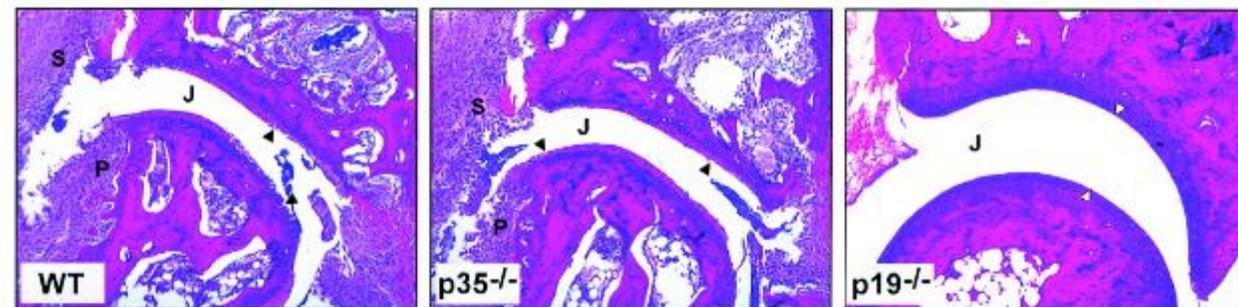
Cumulative incidence and mean clinical score of mice that developed CIA



Disease incidence^a, disease severity^b, and day of onset of CIA

CIA in WT, p19 ^{-/-} , p35 ^{-/-} and p40 ^{-/-} mice			
Genotype	Incidence, diseased/total	Clinical score ^c , median (range)	Day of onset ^c , mean (± SEM)
C57BL/6	10/18	4.0 (1–11)	29.8 (± 1.0)
p35 ^{-/-}	12/15	6.0 (2–12)	27.0 (± 1.1)
p40 ^{-/-}	0/9	N/A	N/A
B6 × 129 F2	8/17	3.5 (2–12)	27.3 (± 0.9)
p19 ^{-/-}	0/20	N/A	N/A

Histopathology of decalcified paws at Day 42

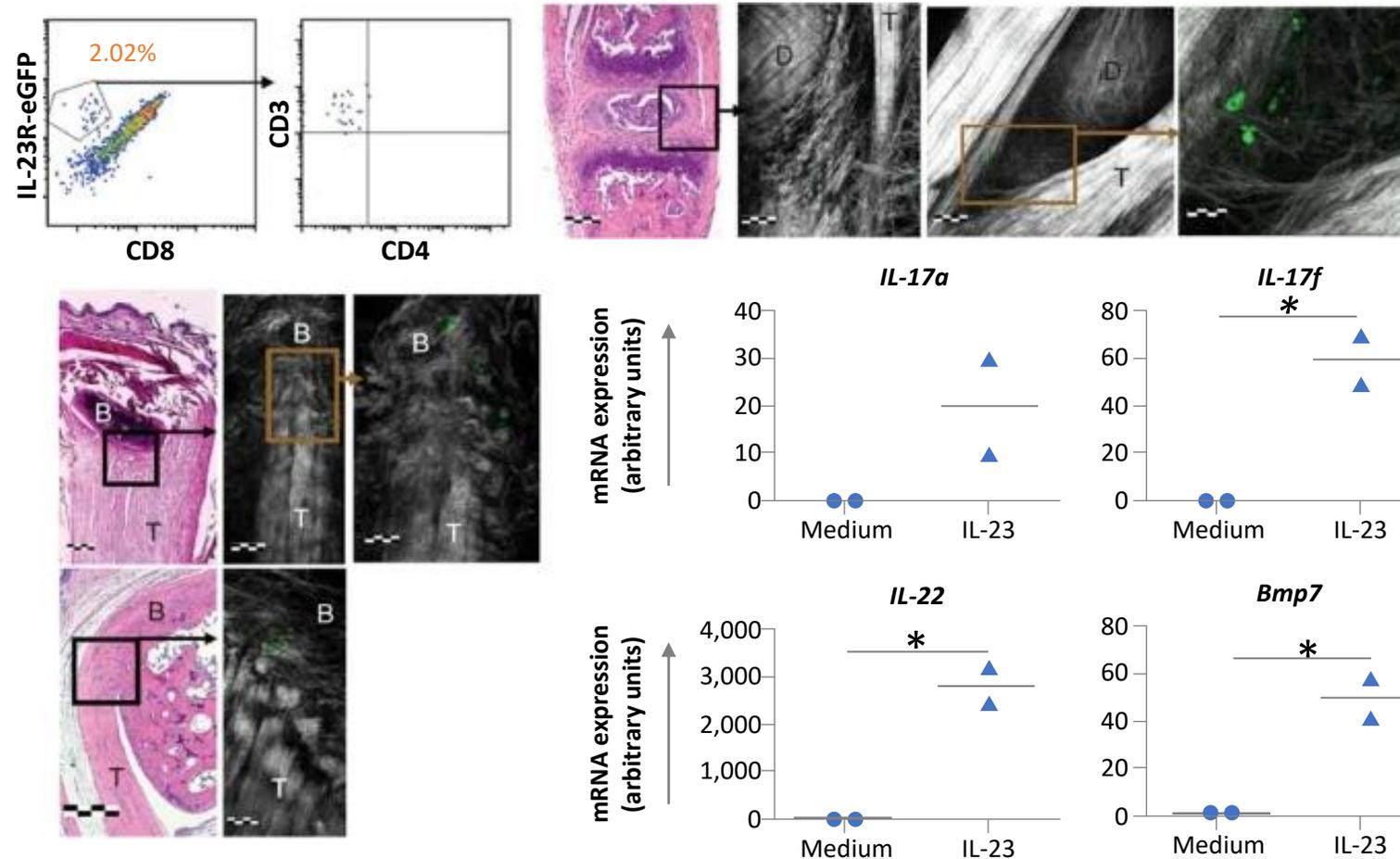


^a Number of diseased mice/total mice in group. ^b Median maximum disease score attained and range of clinical scores. ^c Only mice that developed clinical signs of disease were analyzed.

CIA, collagen-induced arthritis; N/A, not applicable; SEM, standard error of the mean.

IL-23R⁺ tissue-resident cells within entheseal tissues promote chronic injury responses

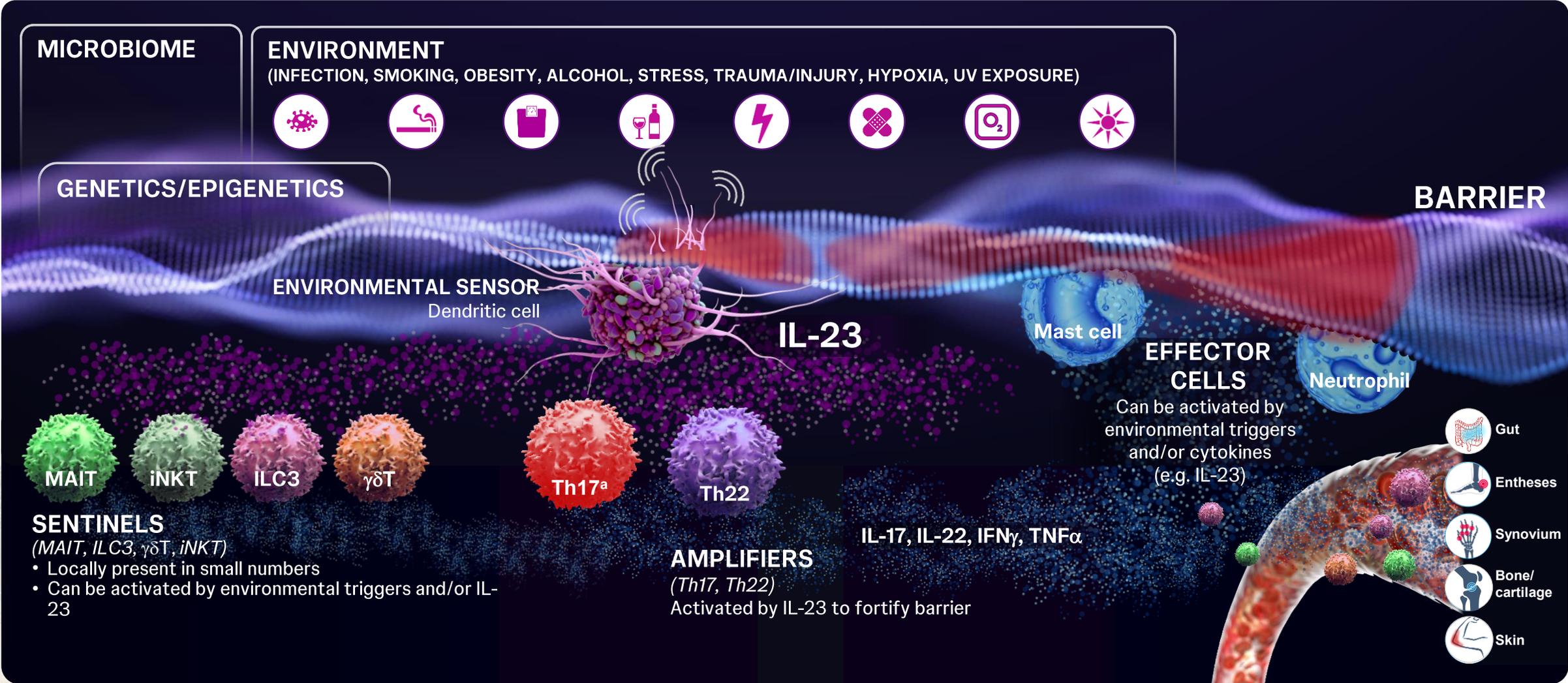
Entheses contain an IL-23R⁺ resident cell population



*p < 0.01 by t-test.

Bmp7, bone morphogenic protein 7; CD, cluster of differentiation; eGFP, enhanced green fluorescent protein; IL-23R, IL-23 receptor.

Shared cytokines across the autoimmune axis ¹⁻¹⁶



NOTE: This is not intended to be a complete depiction of cells and cytokines possibly contributing to immune-mediated inflammatory conditions.
 a Other cytokines that facilitate differentiation of Th17 cells include TGF- β , IL-1, and IL-6, while IL-23 promotes the survival and expansion of Th17 cells.^{12,13}
 $\gamma\delta$ T, gamma delta T cell; ILC3, group 3 innate lymphoid cells; iNKT, invariant natural killer T cell; MAIT, mucosal-associated invariant T cell; TNF, tumor necrosis factor; UV, ultraviolet.
 1. Boyapati R, et al. F1000Prime Rep. 2015;7:44. 2. Szilagyi A. Clin J Gastroenterol. 2020;13:139-52. 3. Swanson GR, et al. Alcohol. 2010;44:223-8. 4. Chandra S, Kronenberg M. Adv Immunol. 2015;127:145-201. 5. Chen F, et al. J Immunol. 2016;196:4390-9. 6. Tecchio C, et al. Front Immunol. 2014;5:508. 7. De Winter BY, et al. Biochim Biophys Acta. 2012;1822:66-73. 8. Scher JU. J Rheumatol Suppl. 2018;94:32-5. 9. Scher JU, et al. Arthritis Rheumatol. 2015;67:128-39. 10. Manasson J, et al. Arthritis Rheumatol. 2020;72:645-57. 11. Mailliet J, et al. Joint Bone Spine. 2016;83:665-68. 12. Boutet MA, et al. Int J Mol Sci. 2018;19:530. 13. Eken A, Oukka M. Interleukin 23 in IBD Pathogenesis. New Insights into Inflammatory Bowel Disease. 2016. IntechOpen. 14. Gracey E, et al. Curr Opin Rheumatol. 2019;31:62-9. 15. Toussiot E, Saas P. RMD Open. 2018;4:e000821. 16. Gaffen SL, et al. Nat Rev Immunol. 2014;14:585-600.

IL-23 dysregulation drives autoimmune inflammation



Skin



Keratinocyte proliferation & inflammation

A diagram of a single skin cell, specifically a keratinocyte, shown in a purple and white color scheme.

GI tract



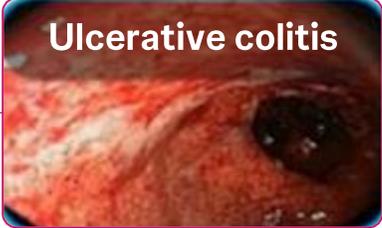
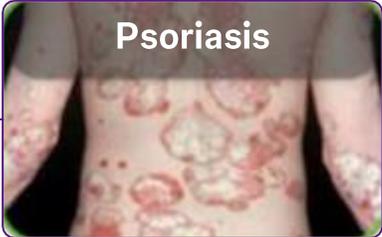
Epithelial cell barrier compromised

A diagram showing a cross-section of the gastrointestinal tract's epithelial layer, with some cells appearing to be missing or damaged, indicating a compromised barrier.

Entheses



Inflammation & calcification

A diagram of a joint, likely a knee, showing the bones and the area where they meet (the enthesis), with red and yellow colors indicating inflammation and calcification.

IL-23 plays a key role in initiating autoimmune diseases

Interleukin-23 is a crucial cytokine deeply involved in promoting many autoimmune and chronic inflammatory diseases by driving the expansion and survival of pro-inflammatory Th17, leading to conditions like PSO, PSA, and IBD. It acts as a key mediator, stimulating the production of other inflammatory cytokines like IL-17 and IL-22, which perpetuates chronic inflammation and tissue damage.

How IL-23 Drives Autoimmunity

- 1. Activates Th17 Cells:** IL-23 is essential for the differentiation, proliferation, and survival of Th17 cells, a specific subset of T cells that produce potent inflammatory cytokines.
- 2. Induces Pro-inflammatory Cytokines:** It promotes the production of IL-17, IL-22, IFN γ , GM-CSF, which are central to autoimmune responses and tissue inflammation.
- 3. Creates a Vicious Cycle:** In infections, the IL-23 pathway helps fight pathogens, but if the system fails to turn off, the continued overproduction of IL-23 causes chronic inflammation, damaging tissues.
- 4. Linked to Genetic Risk:** Genetic variations in the IL23R are associated with increased risk for diseases like PSO, AS, & IBD, suggesting heightened IL-23 signaling contributes to disease susceptibility.

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Not all IL-23 inhibitors are the same

- **Myeloid cells expressing CD64 are a major source of IL-23 in inflamed tissues**
- **Dual-acting GUS binds to CD64 and inhibits IL-23 at the cellular source of cytokine production**

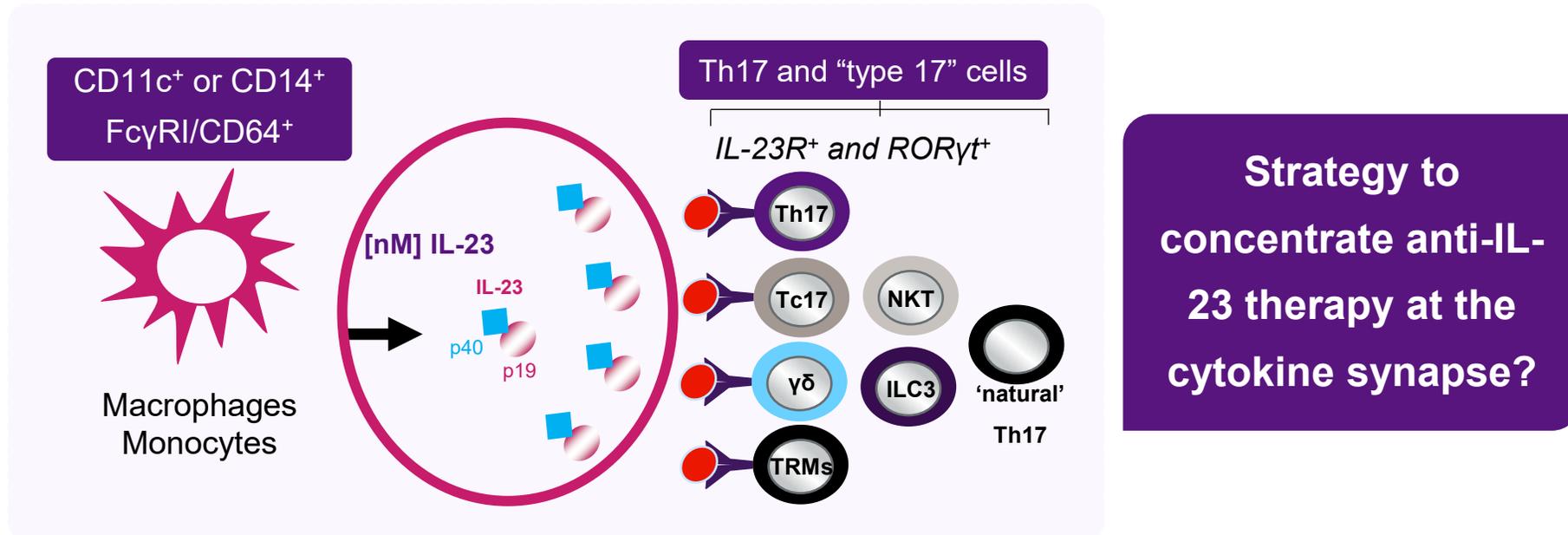
Sachen KL, et al. Front Immunol. 2025;16:1532852.

The biological characteristics of IL-23 suggest that it mainly operates within inflamed tissues

High concentration of IL-23 at the 'cytokine synapse' between myeloid cells and lymphoid cells

IL-23 level

- Undetectable to low in serum^{1,2}
- pM concentration in inflamed tissues^{2,3}
- nM concentration of IL-23 is required to activate type 17 cells³
- IL-23 is highly concentrated within the immune synapse of myeloid cells and T cells³⁻⁶



CD, cluster of differentiation; Fc γ RI; Fc gamma receptor I; IL-23R, IL-23 receptor; nM, nanomolar; NKT, natural killer T cell; pM, picomolar; ROR γ , RAR-related orphan receptor gamma; Tc17, IL-17-producing CD8⁺ T cell; TRM, tissue-resident memory T cell.

1. Gordon KB, et al. J Invest Dermatol. 2019;139:2437-46.

2. Pirowska M, et al. Postepy Dermatol Alergol. 2018;35:360-6.

3. Piskin G, et al. J Immunol. 2006;176:1908-15.

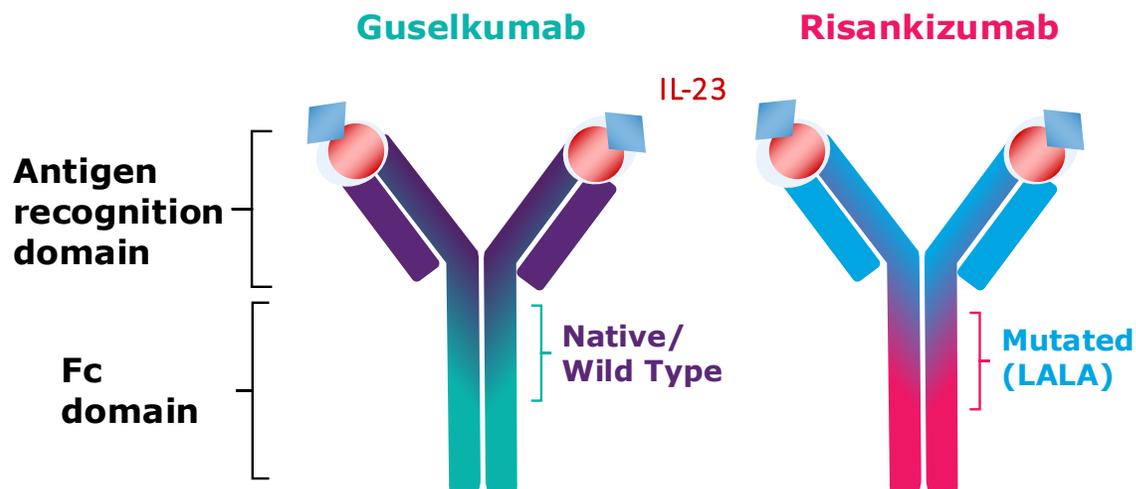
4. Mehta H, et al. J Invest Dermatol. 2021;141:1707-18.

5. Pastor-Fernández G, et al. Cells. 2020;9:2044.

6. Sherlock JP, Cua DJ. Rheumatology (Oxford). 2021;60(Suppl 4):iv1-3.

Not all IL-23 inhibitors are the same

GUS is all Natural



RIS has Mutations

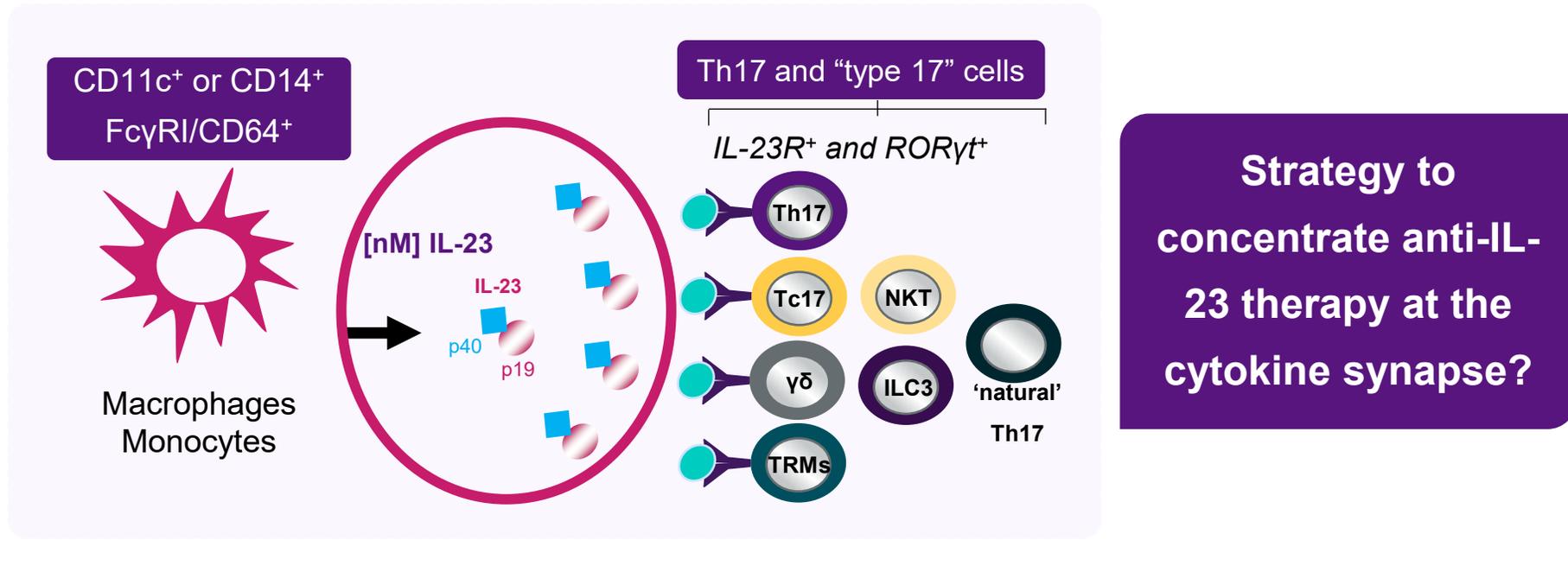
Antibody	Fully human	Humanized
Isotype	IgG1	IgG1
Antigen	IL-23 p19	IL-23 p19
Fc domain	Native/ Wild type	Mutated/LALA
Immunogenicity @ 52 week	6% anti-drug Ab 0.4% neutralizing Ab	24% anti-drug Ab 14% neutralizing Ab

Tissue is the issue...WHY?

- High concentration of IL-23 at the 'cytokine synapse' between myeloid cells and lymphoid cells

IL-23 level

- Undetectable to low in serum^{1,2}
- pM concentration in inflamed tissues^{2,3}
- nM concentration of IL-23 is required to activate type 17 cells³
- IL-23 is highly concentrated within the immune synapse of myeloid cells and T cells³⁻⁶



CD, cluster of differentiation; FcγRI; Fc gamma receptor I; IL-23R, IL-23 receptor; nM, nanomolar; NKT, natural killer T cell; pM, picomolar; RORγ, RAR-related orphan receptor gamma; Tc17, IL-17-producing CD8⁺ T cell; TRM, tissue-resident memory T cell.

1. Gordon KB, et al. J Invest Dermatol. 2019;139:2437-46.

2. Pirowska M, et al. Postepy Dermatol Alergol. 2018;35:360-6.

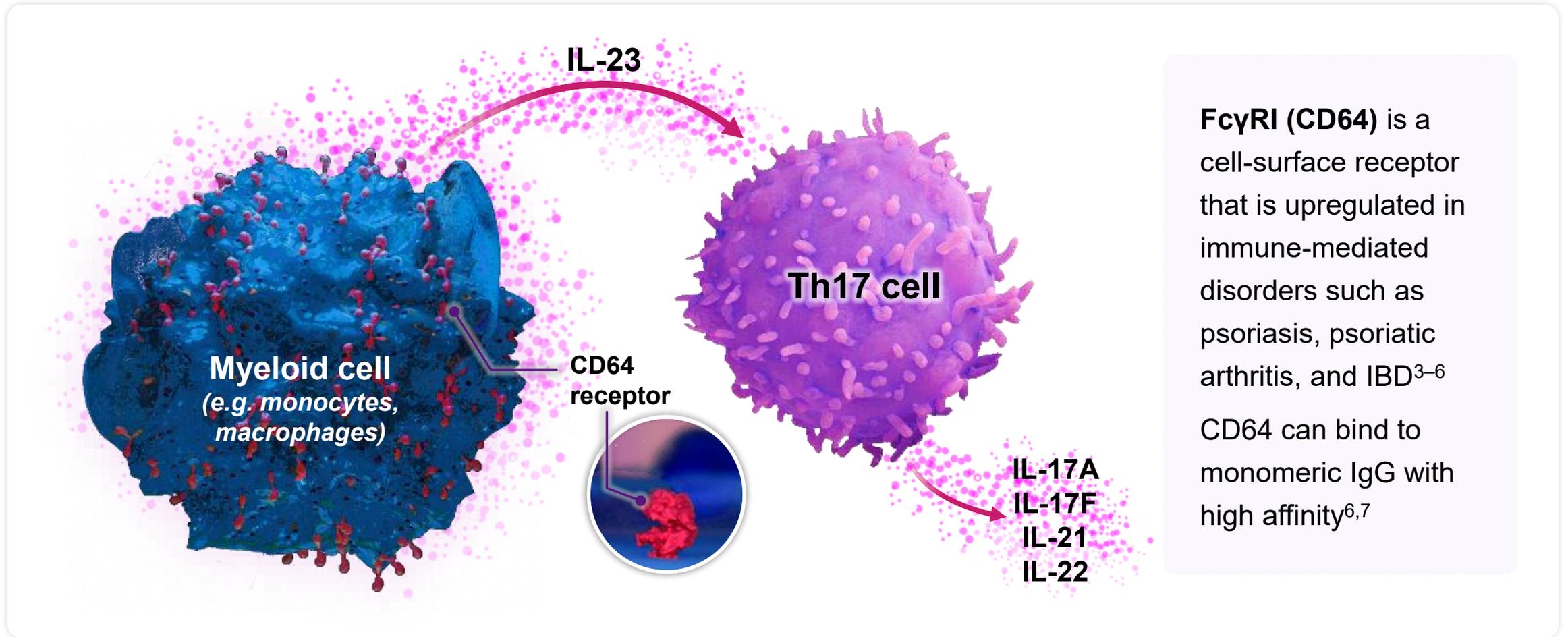
3. Piskin G, et al. J Immunol. 2006;176:1908-15.

4. Mehta H, et al. J Invest Dermatol. 2021;141:1707-18.

5. Pastor-Fernández G, et al. Cells. 2020;9:2044.

6. Sherlock JP, Cua DJ. Rheumatology (Oxford). 2021;60(Suppl 4):iv1-3.

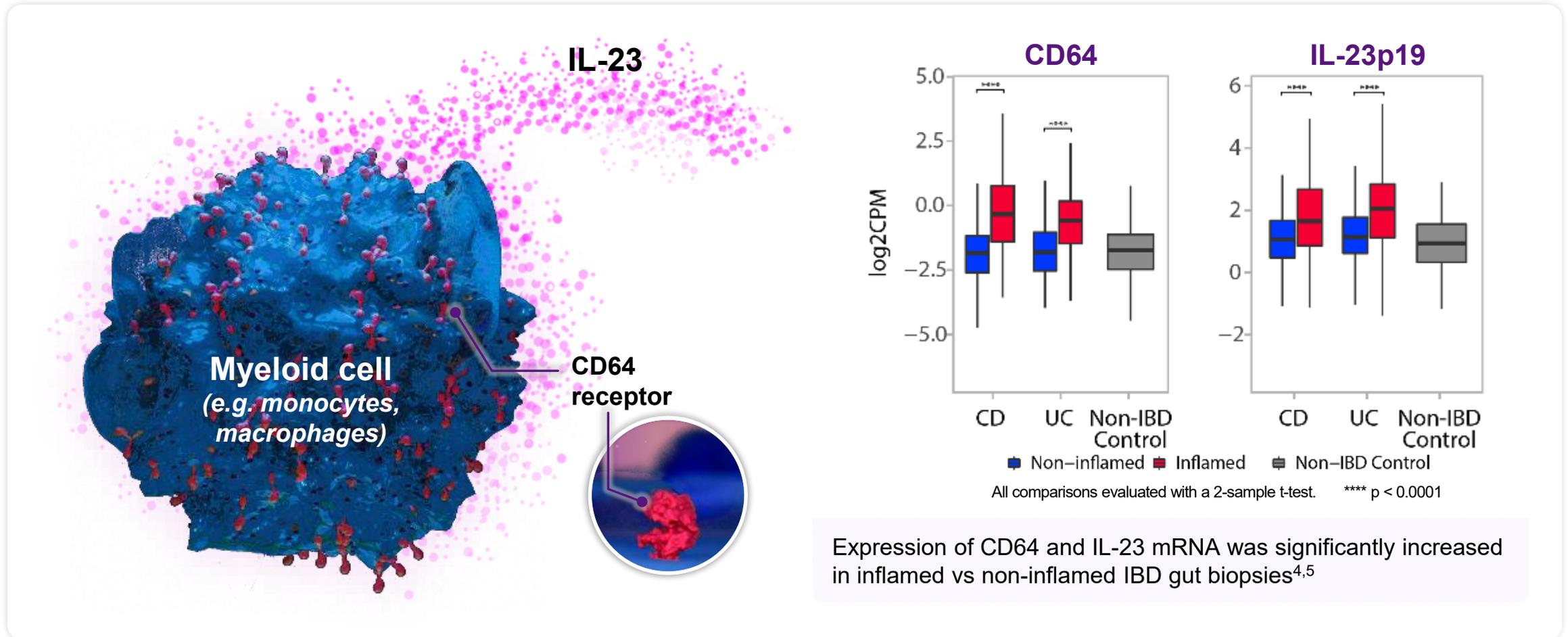
Myeloid cells expressing CD64 are a major source of IL-23 in inflamed gut tissue (1) ¹⁻³



FcγRI (CD64) is a cell-surface receptor that is upregulated in immune-mediated disorders such as psoriasis, psoriatic arthritis, and IBD³⁻⁶

CD64 can bind to monomeric IgG with high affinity^{6,7}

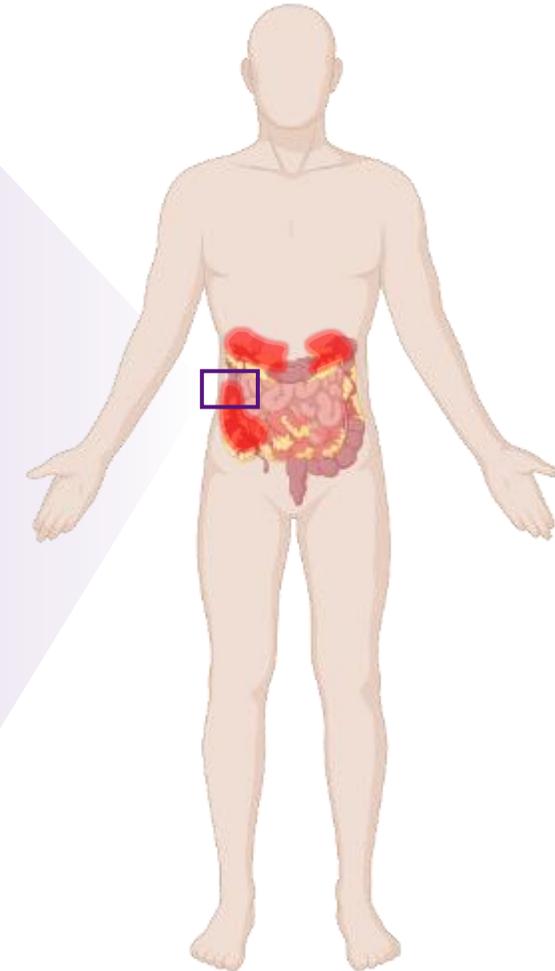
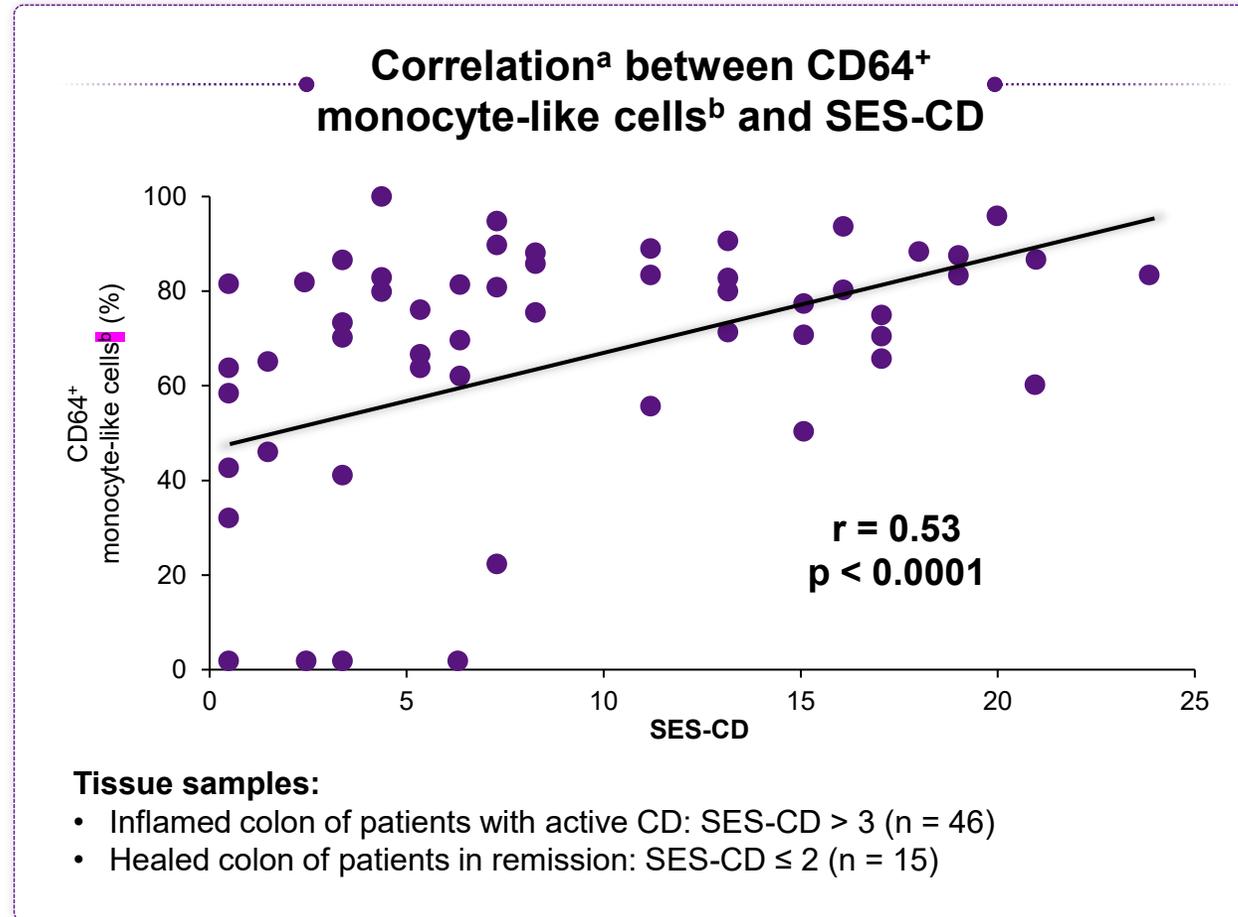
Myeloid cells expressing CD64 are a major source of IL-23 in inflamed gut tissue (2) ¹⁻³



Expression of CD64 and IL-23 mRNA was significantly increased in inflamed vs non-inflamed IBD gut biopsies^{4,5}

CD, Crohn's disease; CPM, counts per million; mRNA, messenger ribonucleic acid; UC, ulcerative colitis.
1. Kamada N, et al. J Clin Invest. 2008;118:2269-80. 2. Chapuy L, et al. J Crohns Colitis. 2020;14:79-95. 3. Chapuy L, et al. Mucosal Immunol. 2019;12:703-19. 4. Matt P, et al. Scand J Rheumatol. 2015;44:464-73. 5. Wang Y, et al. Sci Rep. 2019;9:5310. 6. Akinrinmade OA, et al. Biomedicines. 2017;5:56. 7. Bournazos S, et al. Nat Rev Immunol. 2020;20:633-43.

CD64⁺ monocyte-like cells correlate with endoscopic disease severity¹



^a Spearman's rank correlation test.

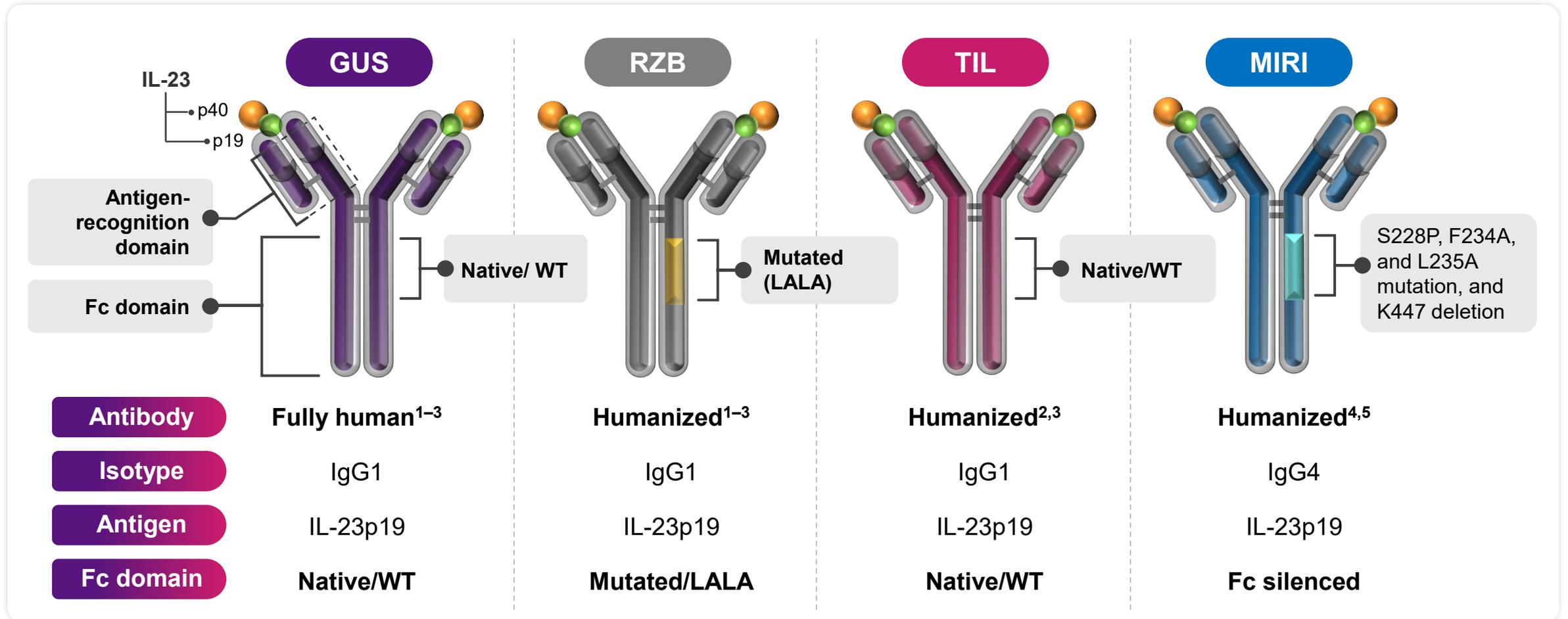
^b Monocyte-like cells defined as CD64⁺CD163⁺/dim. CD163 is a macrophage marker. SES-CD, Simple Endoscopic Score for Crohn's Disease.

Graph adapted from Chapuy L, et al. Mucosal Immunol. 2019;12:703-19.

1. Chapuy L, et al. Mucosal Immunol. 2019;12:703-19.

2. Thornton S, et al. J Immunol. 2019;202:1635-43.

Not All IL-23is are the Same



Note: not shown brazikumab, which are other IL-23p19 monoclonal antibodies. Brazikumab is a fully human IgG2 that contains a native Fc domain.

Fc, fragment crystallizable; LALA, leucine to alanine substitution at positions 234 and 235; MIRI, mirikizumab; RZB, risankizumab;

TIL, tildrakizumab; WT, wild type.

1. Atreya R, et al. Poster presented at ECCO 2023; poster P504.

2. Zhou L, et al. MABs. 2021;13:1964420.

3. Eyerich K, et al. Poster presented at AAD 2023; poster P43272.

4. Dumet C, et al. MABs. 2019;11:1341-50.

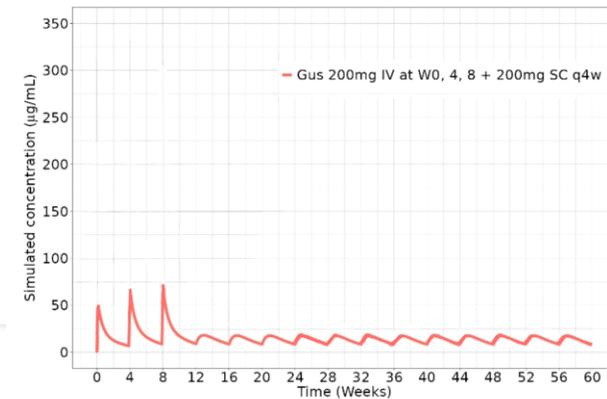
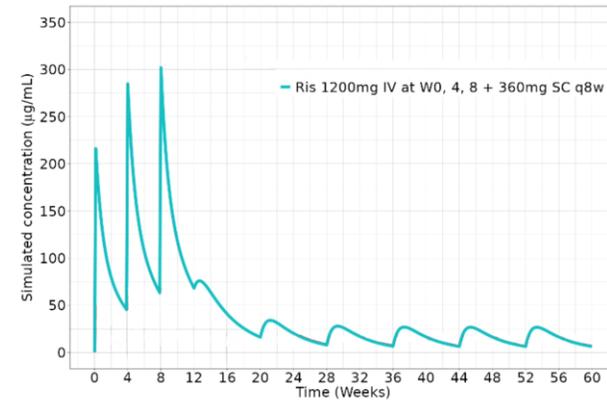
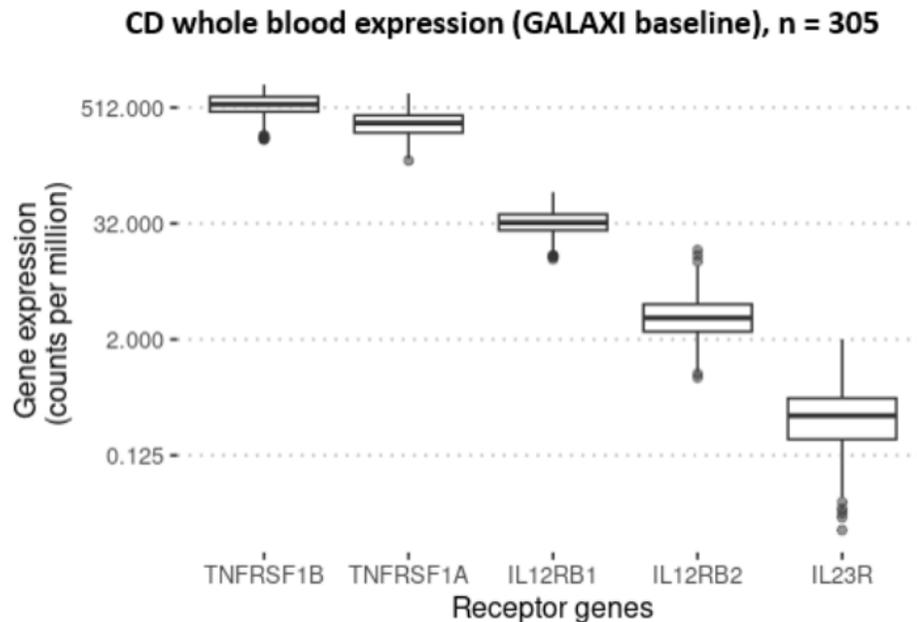
5. Strohl WR. Antib Ther. 2024;7:132-56.

LALA mutation in Fc Domain

GUS does not contain Fc LALA mutation

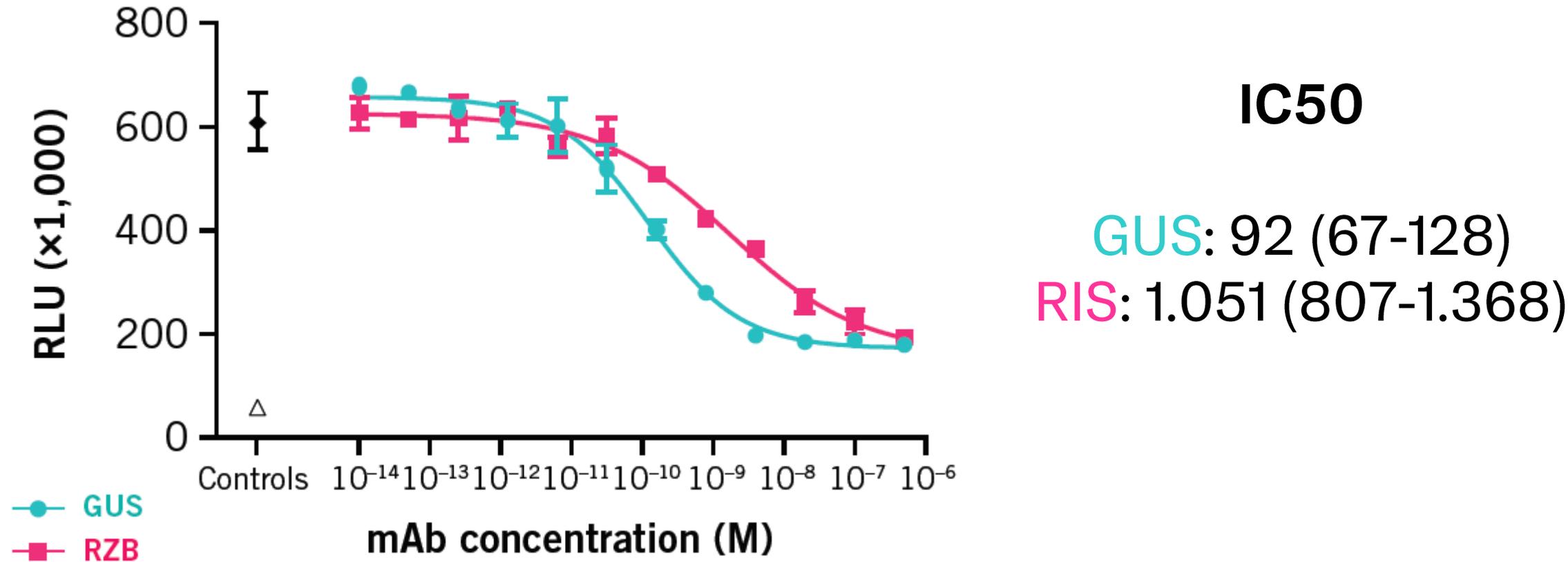
- Fc LaLa mutation designed for long serum $\frac{1}{2}$ life may alter tissue biodistribution
- IL-23R biology does not occur in **serum**.
- The site of IL-23 action is in inflamed tissue (**Tissue is the Issue**).

The long serum $\frac{1}{2}$ life and high serum drug exposure of mutated Fc antibody is **NOT** an advantage.



Serum antibody drug exposure of RIS and GUS calculated from Clinical dosing regimen approved for Ulcerative Colitis.

Guselkumab demonstrates 10-fold greater potency compared to risankizumab in a co-culture of IL-23–producing CD64+ myeloid cells and IL-23–responsive cells



*Based on *in vitro* studies in a model of inflammatory monocytes. The clinical significance of these findings is unknown.

Molecular Differentiation of IL-23i

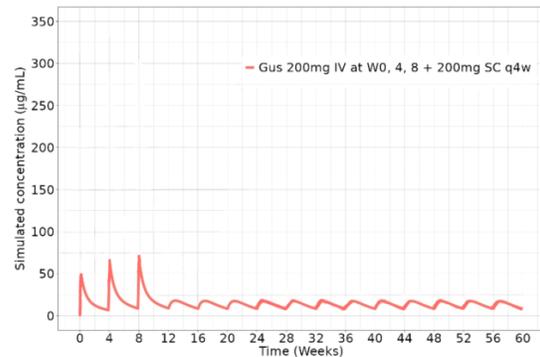
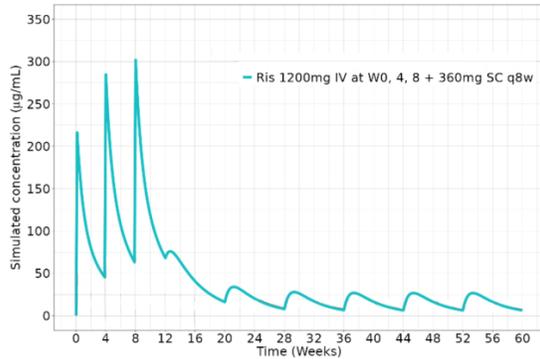
	Guselkumab	Risankizumab
Antibody Molecular Attributes:	Fully human IgG1 Native/Wildtype Fc	Humanized IgG1 Mutated/LALA Fc
High Affinity Binding to IL-23¹⁻²	✓	✓
Potent inhibition of IL-23 signaling¹⁻²	✓	✓
CD64 binding & capture of IL-23 at the cellular source of production¹⁻³	✓	✗
Internalization of IL-23 by CD64⁺ macrophages¹	✓	✗
Bio-distribution profile enables subcutaneous treatment induction	✓	✗

Tremfya (guselkumab). SmPC. 2025; Skyrizi (risankizumab). SmPC. 2025. .

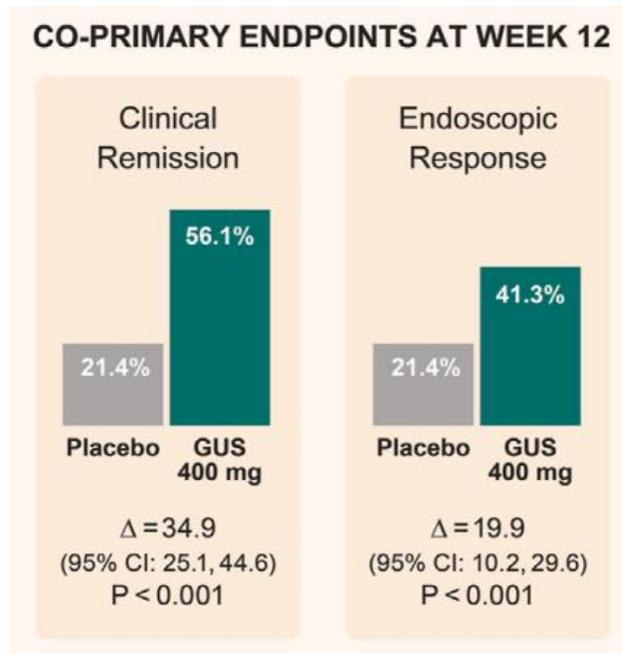
IgG, immunoglobulin G; IL, interleukin; LALA, leucine to alanine substitution at positions 234 and 235.

GUS bio-distribution profile enables subcutaneous treatment induction

Emerging data shows RIS IR switch to GUS = disease remission (Endoscopic Response)



Phase 3 GRAVITI study results



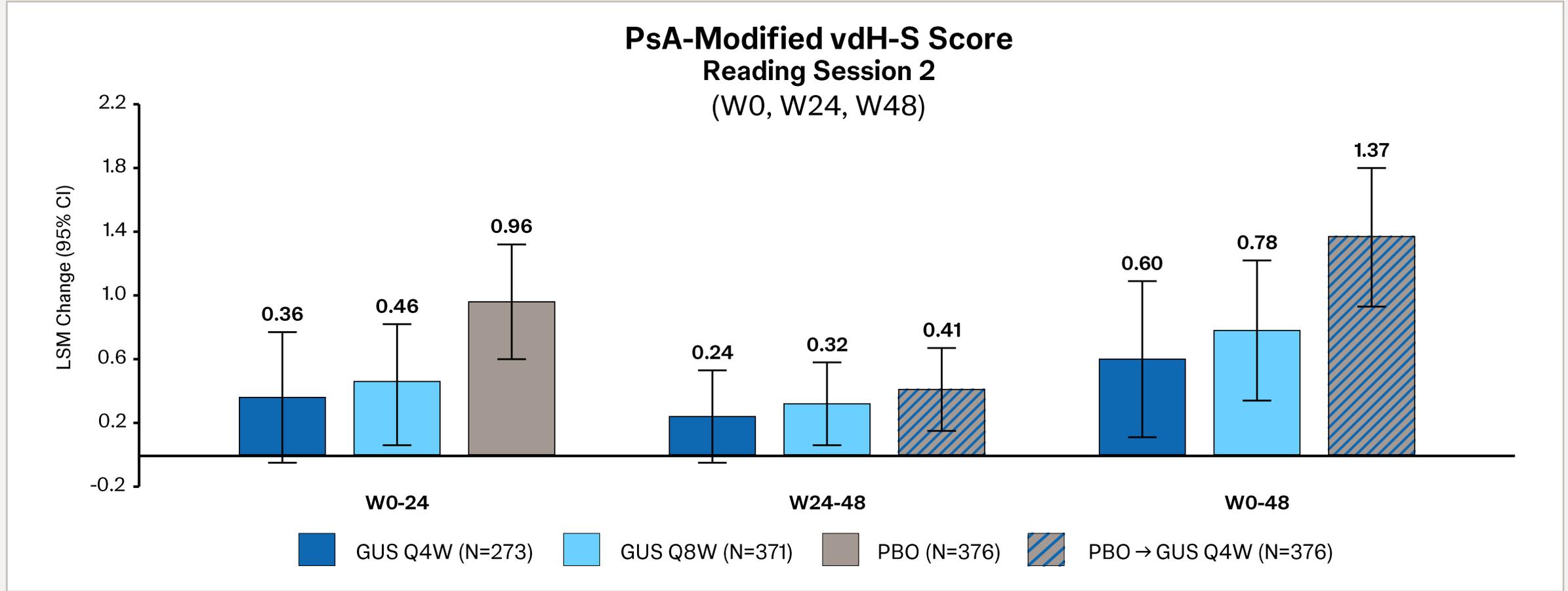
Induction Dosing in IBD

Disease state	Risankizumab	Guselkumab
CD	600 mg IV	200 mg IV or 400 mg SC
UC	1,200 mg IV	200 mg IV or 400 mg SC

Guselkumab 400 mg SC q4w → 100 mg SC q8w
 Guselkumab 400 mg SC q4w → 200 mg SC q4w

Inhibition of structural damage progression with GUS was durable through W48

This material was presented at the scientific meeting and is not for promotional use. Provided in response to a medical information request; no further use permitted.



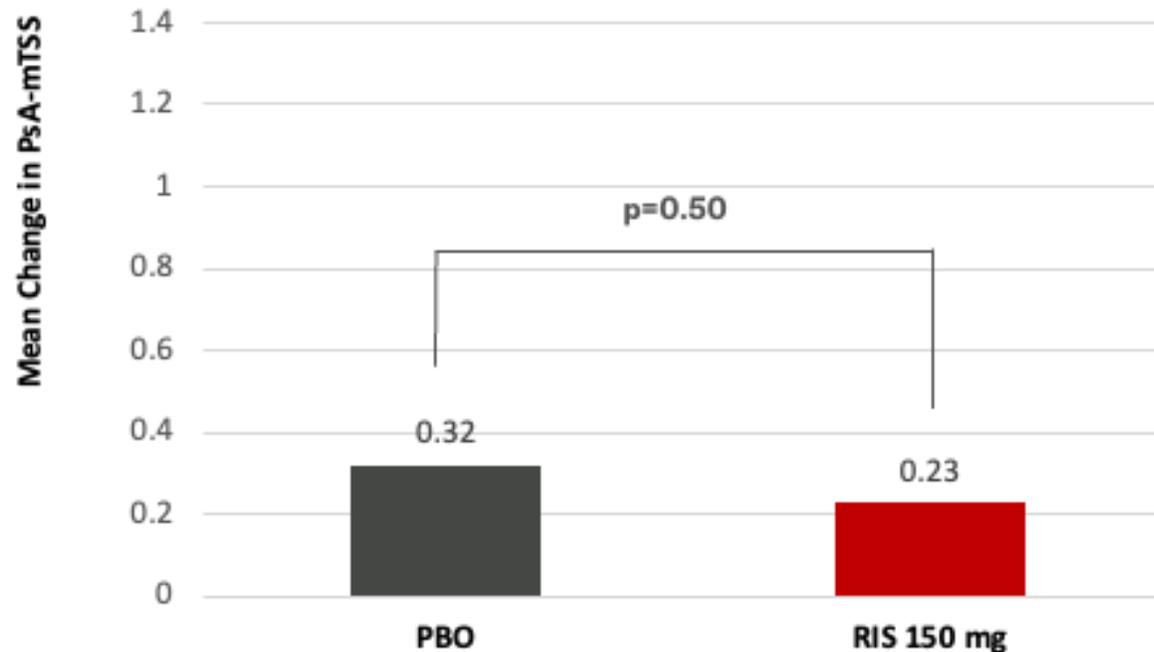
Treatment with GUS from W24-48 reduced the rate of radiographic progression among PBO-randomized pts

For pts with missing W48 radiographs, W0/24 radiographs were not re-read during reading session 2; W0/24 data from reading session 1 was used if available. The same readers were used for reading sessions 1 and 2. Score change was assessed in the mFAS according to the Adjusted Treatment Policy Estimand: irrespective of background PsA medication or adherence to study intervention; in situations when ND/MD occurred, observed data collected after ND/MD was not used; data for visits after ND/MD and missing data were imputed using full conditional specifications MI. LSM change and CIs based on combining ANCOVA model (explanatory variables: baseline modified vdH-S score, treatment group, and randomization stratification level) results from each MI dataset. ANCOVA=Analysis of Covariance, CI=confidence interval, GUS=guselkumab, LSM=least squares mean, mFAS=modified full analysis set, MI=multiple imputation, ND/MD=natural disaster or major disruption, PBO=placebo, PsA=psoriatic arthritis, pts=participants, Q4W/Q8W=every 4/8 weeks, vdH-S=van der Heijde-Sharp, W=week. Presented by Steven Fakharzadeh at the 6th Inflammatory Skin Disease Summit (ISDS); November 12-15, 2025; New York, NY, USA. 39

Risankizumab Did Not Inhibit Progression of Structural Damage in Psoriatic Arthritis

- **Risankizumab (150 mg) every 12 weeks at Week 24 did not show evidence of a significant difference vs placebo for inhibition of structural damage¹**

KEEPSAKE 1: Mean Change in PsA-mTSS at Week 24¹



Clinical Differentiation of guselkumab

Disease state	Clinical attribute	Guselkumab	Risankizumab
PsO	High level, durable skin clearance	✓	✓
PsA	High level, durable joint efficacy	✓	✓
PsA	Inhibition of progression of structural damage	✓	X
IBD	Durable endoscopic and histologic efficacy	✓	✓
IBD	Low dose induction regimen	✓	X
IBD	Subcutaneous induction dosing option	✓	X

No head-to-head studies have been conducted, IBD studies planned

IBD=inflammatory bowel disease, PsA=psoriatic arthritis, PsO=psoriasis. Tremfya (guselkumab). SmPC. 2025; Skyrizi (risankizumab). SmPC. 2025; Steven Fakharzadeh at the 6th Inflammatory Skin Disease Summit (ISDS); November 12-15, 2025; New York, NY, USA; McInnes IB et al. Long-Term Efficacy and Safety of Guselkumab, a Monoclonal Antibody Specific to the p19 Subunit of Interleukin-23, Through Two Years: Results From a Phase III, Randomized, Double-Blind, Placebo-Controlled Study Conducted in Biologic-Naive Patients With Active Psoriatic Arthritis. Arthritis Rheumatol. 2022 Mar;74(3):475-485. doi: 10.1002/art.42010. Epub 2022 Feb 7. PMID: 34719872; PMCID: PMC9305108; Mease PJ et al Inhibition of structural damage progression with the selective interleukin-23 inhibitor guselkumab in participants with active PsA: results through week 24 of the phase 3b, randomised, double-blind, placebo-controlled APEX study. Ann Rheum Dis. 2025 Dec;84(12):1983-1994. doi: 10.1016/j.ard.2025.08.006. Epub 2025 Sep 17. PMID: 40962616. Reich K, Gordon KB, Strober BE, Armstrong AW, Miller M, Shen YK, You Y, Han C, Yang YW, Foley P, Griffiths CEM. Five-year maintenance of clinical response and health-related quality of life improvements in patients with moderate-to-severe psoriasis treated with guselkumab: results from VOYAGE 1 and VOYAGE 2. Br J Dermatol. 2021 Dec;185(6):1146-1159. doi: 10.1111/bjd.20568. Epub 2021 Sep 8. PMID: 34105767.

Take-home messages

- IL-23 promotes skin, joint, and gut autoinflammatory diseases by activating pathogenic Th17 cells
- **IL-23 is a tissue cytokine**; IL-23 is most highly concentrated at the myeloid / T cell interface where the signalling occurs
- Both GUS and RIS display high affinity binding to IL-23; GUS has a native Fc domain, while RIS has a mutated Fc domain carrying LALA mutation
- **Dual-acting GUS binds to CD64 and simultaneously capture IL-23** at the cellular source of production, leading to internalization and degradation of IL-23 by CD64⁺ macrophages
- **GUS favorable bio-distribution profile enables subcutaneous treatment induction**

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Beyond the gut - Explorando las fronteras entre las IMIDs.

Evento de Educación Médica
Organizado y Financiado por:

Johnson&Johnson

EM-196046 Enero 2026 Jassen Cilag S.A

Proyecto



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Beyond the gut - Explorando las fronteras entre las **IMiDs**.

Más allá del intestino

Reflexiones de un clínico “motivao”

Yago González Lama

*Jefe de Sección de Gastroenterología y
Unidad de Enfermedad Inflamatoria Intestinal
Sº Aparato Digestivo.
H.U. 12 de Octubre. Madrid.*



*@YagoGlezLama
@DigestivoHU120*

La magnitud del problema



En realidad ¿Qué es una MEI?



patología inflamatoria que ocurre en un paciente con EII, que se localiza fuera del intestino y que está mediada por:

- *el mismo mecanismo inmunológico que la inflamación intestinal*
- *mecanismos independientes pero promovidos por la inflamación intestinal.*

Ejemplos

Ejemplos	Ejemplos	Ejemplos	Fenómenos
Espondiloartritis periférica	Espondiloartritis axial	Espondiloartritis axial	tromboembólicos
Uveítis, episcleritis	Uveítis	Uveítis	Osteoporosis
Eritema nodoso	Urticaria	Urticaria	Queilitis angular
Piodermia gangrenosa	Alteraciones de la piel	Alteraciones de la piel	Nefrolitiasis
Colangitis esclerosante	Colangitis esclerosante	Colangitis esclerosante	Amiloidosis
Paradoja	Paradoja	Paradoja	Paradoja

Enfermedades asociadas

Consecuencias de la EII

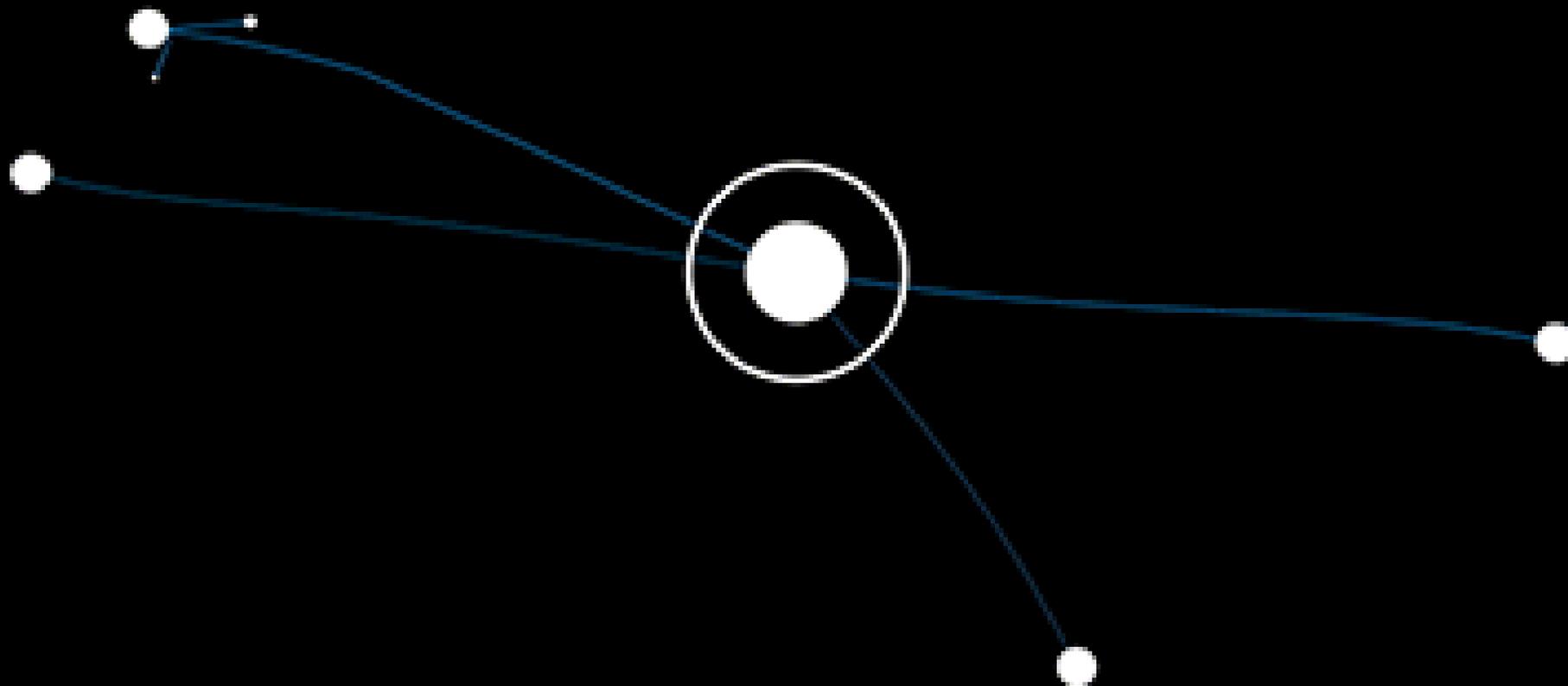
En general, 2 vías de conexión entre inflamación intestinal y en otros órganos

Dos mecanismos no mutuamente excluyentes y podrían contribuir en distinto grado en diferentes MEI

- La MEI puede surgir por la **extensión extraintestinal de una respuesta inmune específica**
- La MEI sería el resultado de un proceso **inflamatorio independiente** pero iniciado o perpetuado por la presencia de EII en el mismo individuo, o por compartir factores **genéticos o ambientales** con la EII.



Espectro de IMID: Complejas interrelaciones



Múltiples mecanismos fisiopatológicos

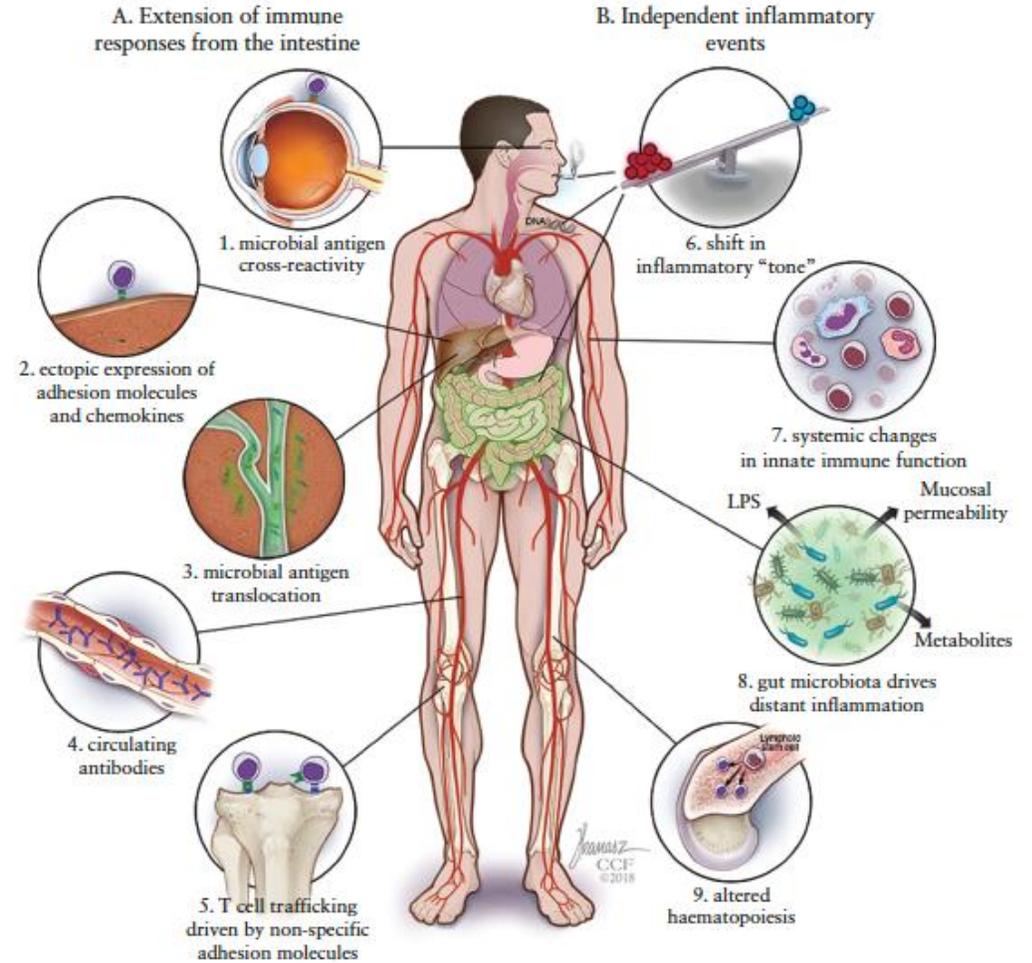
Journal of Crohn's and Colitis, 2019, 541–554
doi:10.1093/ecco-jcc/jjy191
Advance Access publication November 15, 2018
ECCO Scientific Workshop Paper

OXFORD

ECCO Scientific Workshop Paper

The Pathogenesis of Extraintestinal Manifestations: Implications for IBD Research, Diagnosis, and Therapy

C. R. H. Hedin^{a,o}, S. R. Vavricka^b, A. J. Stagg^c, A. Schoepfer^d, T. Raine^e,
L. Puig^f, U. Pleyer^g, A. Navarini^h, A. E. van der Meulen-de Jongⁱ, J. Maul^{j,k},
K. Katsanos^l, A. Kagramanova^m, T. Greuter^{n,o}, Y. González-Lama^p,
F. van Gaalen^q, P. Ellul^r, J. Burisch^{s,t}, D. Bettenworth^u, M. D. Becker^v,
G. Bamias^w, F. Rieder^x

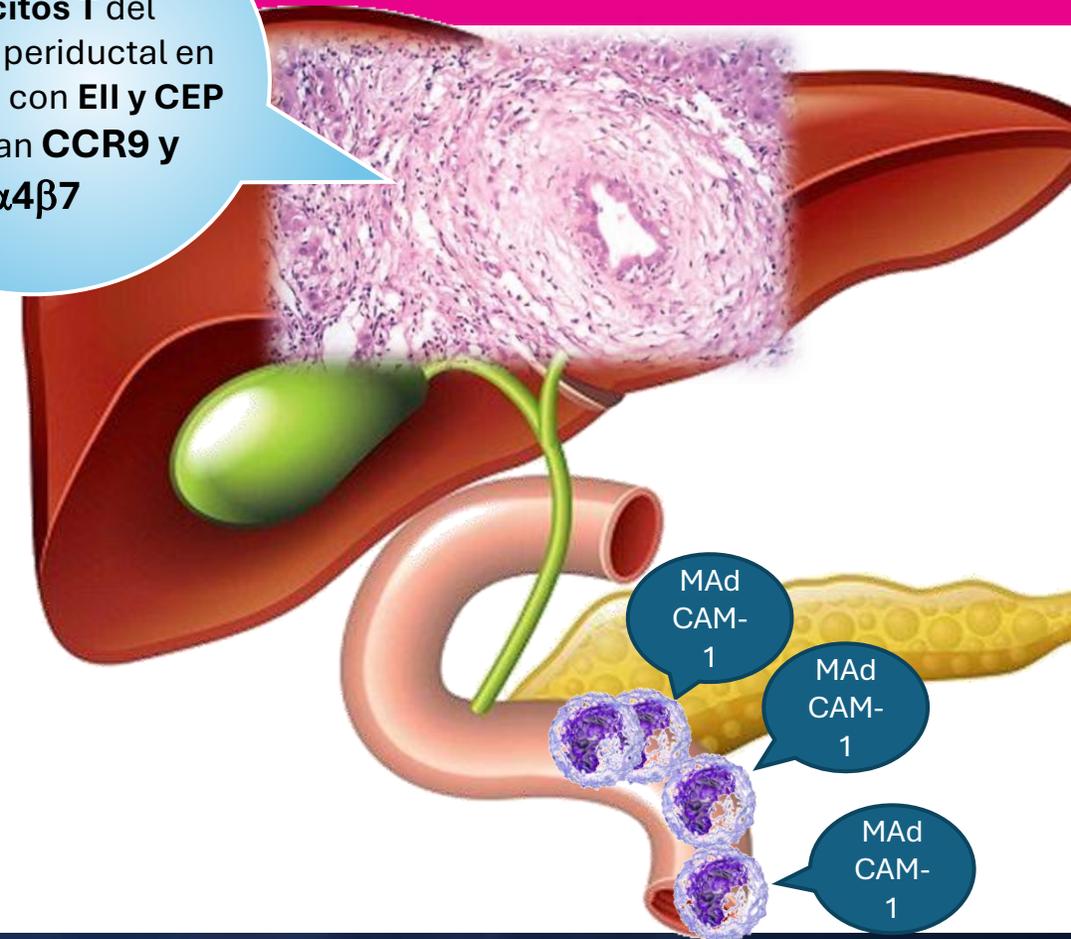


MEI como extensión de la respuesta inmune más allá del intestino

expresión ectópica de citoquinas y moléculas de adhesión

- La expresión de las moléculas de adhesión MAdCAM-1, restringida al tejido intestinal, promueve la expresión de la **integrina $\alpha 4\beta 7$** en los linfocitos T de forma que éstos se dirigen selectivamente a la mucosa intestinal en el contexto de la EII.
- La citoquina **CCL25**, también atrae al intestino a los linfocitos que expresan **CCR9**
- Se ha encontrado expresión de MAdCAM-1 en el tracto portal de pacientes con **colangitis esclerosante primaria**

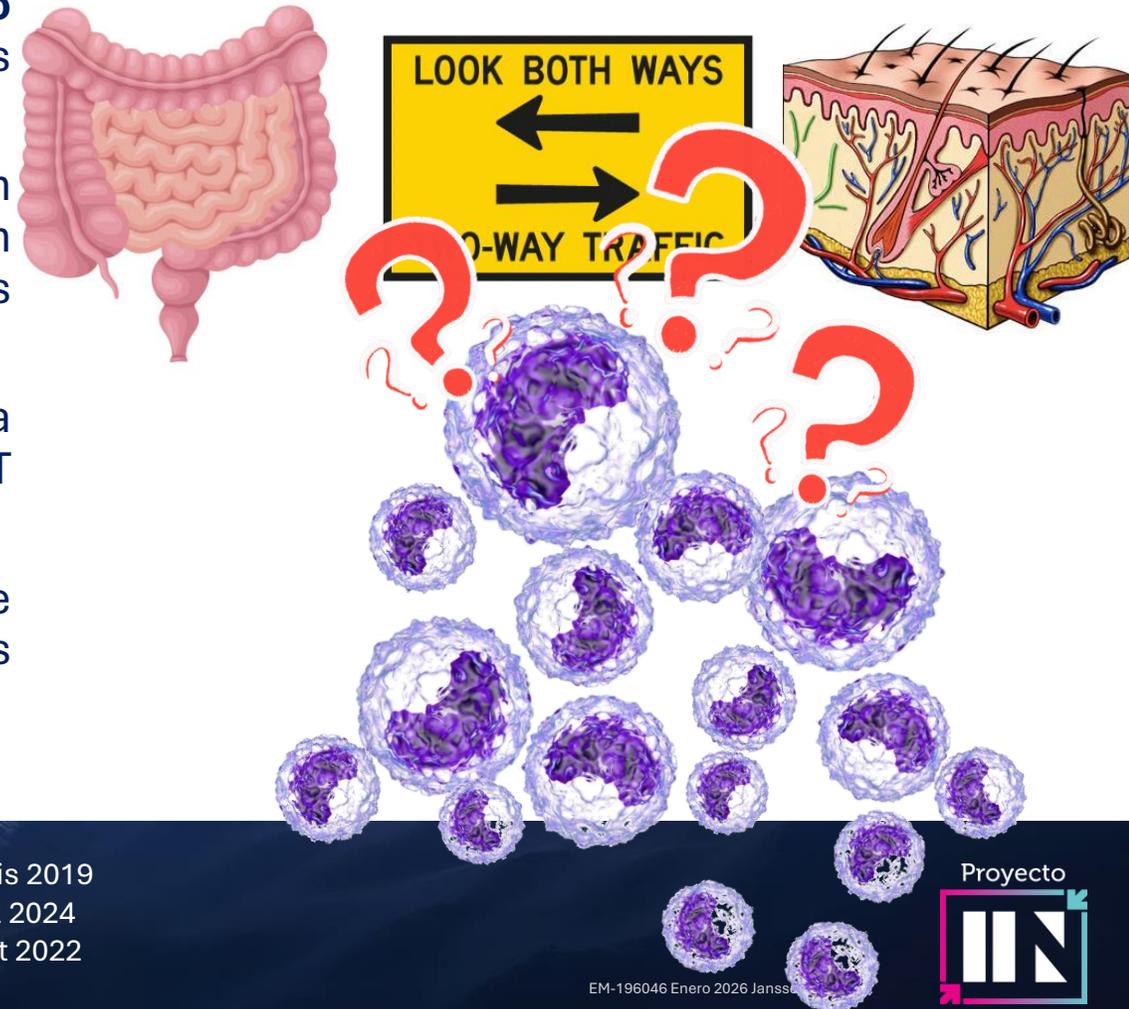
hasta el **20%** de los **linfocitos T** del infiltrado periductal en pacientes con **EII y CEP** expresan **CCR9 y $\alpha 4\beta 7$**



MEI como extensión de la respuesta inmune más allá del intestino

expresión ectópica de citoquinas y moléculas de adhesión

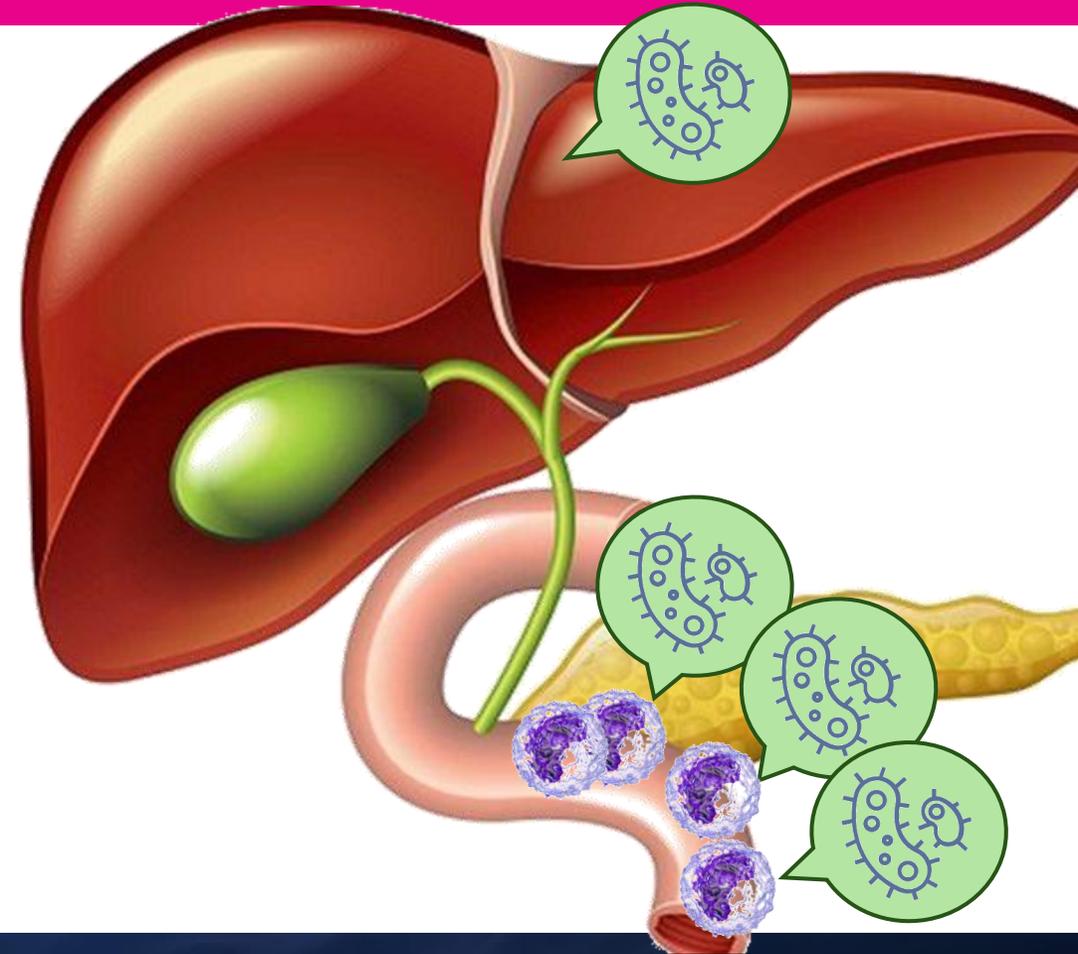
- Se ha comprobado la co-expresión de $\alpha 4\beta 7$ con el **antígeno leucocitario cutáneo (CLA)** en algunas células T de pacientes con EI y MEI dermatológicas
- Células dendríticas intestinales pueden **inducir** la co-expresión de CLA y $\alpha 4\beta 7$ en los linfocitos T ("**dual-tropic cells**"). Son células con fenotipo **pro-inflamatorio** (producen citoquinas inflamatorias como IFN- γ).
- El tejido intestinal inflamado expresa **CCL27** (una quimiocina que normalmente solo está en la piel), atrayendo células T cutáneas al intestino.
- Estas "dual-tropic cells" juegan un papel en el desarrollo de muchas MEI dermatológicas al encontrarse en ambos tejidos inflamados.



MEI como extensión de la respuesta inmune más allá del intestino

Traslocación de antígenos bacterianos

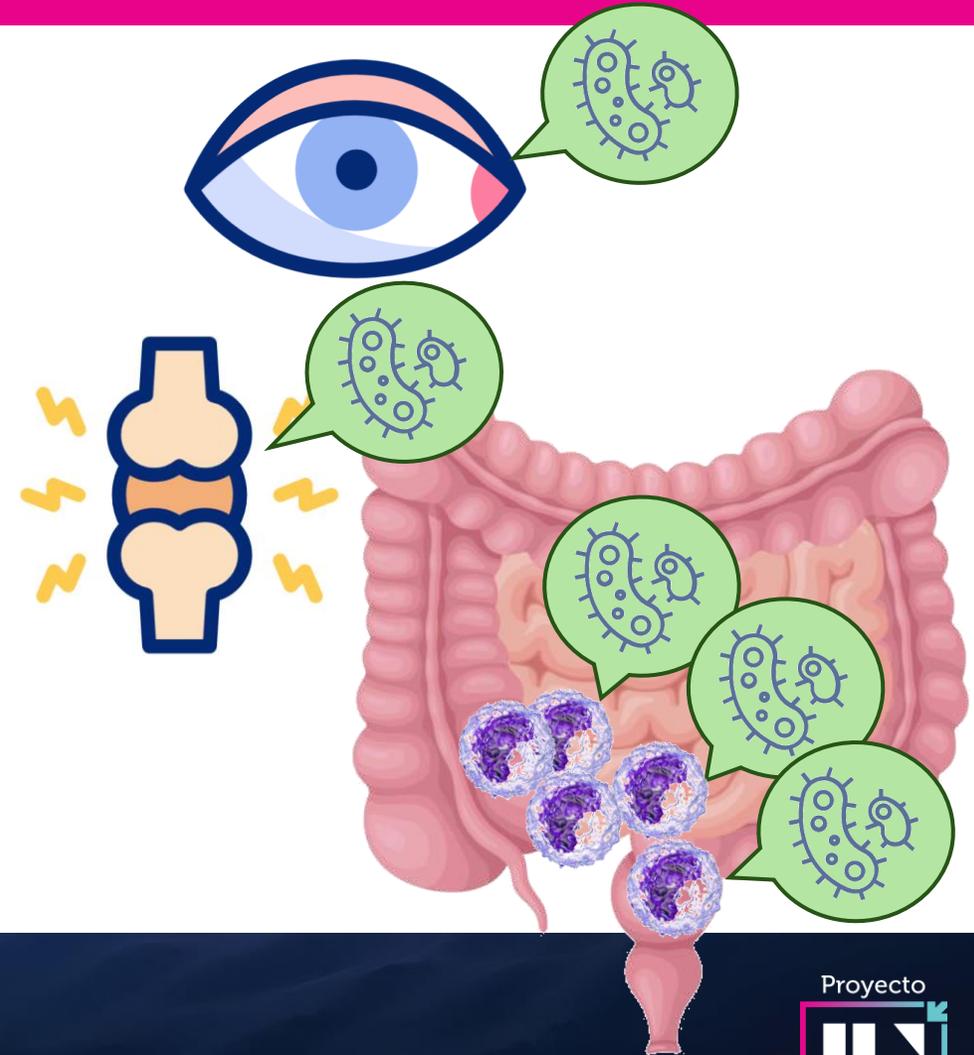
- **Antígenos derivados de la microbiota intestinal** podrían ser la diana de células efectoras T a nivel intestinal en la EII, y que el transporte de estos antígenos hacia otros lugares, como el hígado a través de la circulación portal, podría activar las interacciones vía $\alpha 4\beta 7$ -MAdCAM-1 a este nivel
- La presencia de **una microbiota particular** en pacientes con **colangitis esclerosante** primaria sugiere que este mecanismo está favorecido por algún grupo de bacterias en particular
- Se ha descrito un fenómeno parecido con las células T específicas de la retina y que ocasionan uveítis en ratones



MEI como extensión de la respuesta inmune más allá del intestino

Traslocación de antígenos bacterianos

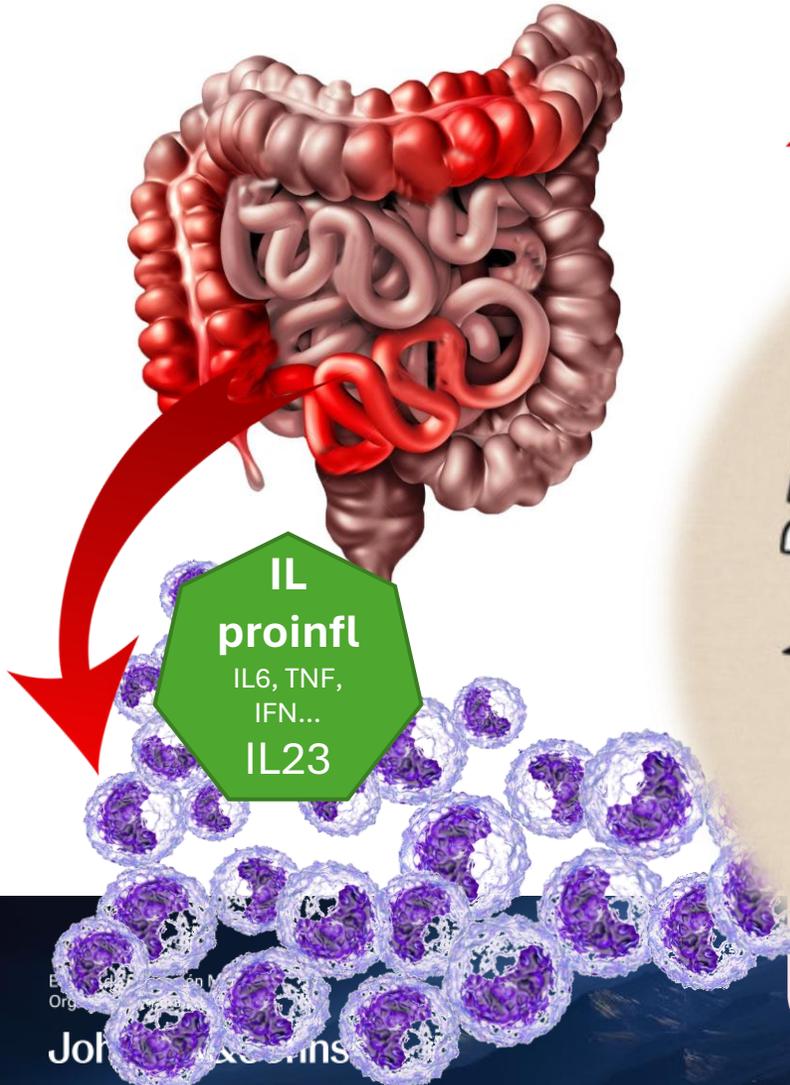
- Se ha demostrado que cél. T de la tejidos inflamados de pacientes con **uveítis** y **espondiloartritis** reconocen **péptidos de bacterias entéricas**.
- Estas cél. T expresan CD161, integrin $\alpha 4\beta 7$, and CCR6, lo que demuestra que se han diferenciado y sensibilizado a nivel intestinal y han migrado (¿persiguiendo esos péptidos bacterianos?): **Gut-primed trafficking T cells**.
- Se ha encontrado DNA bacteriano entérico y Gut-primed trafficking T Cells en **tejido sinovial y entésico**



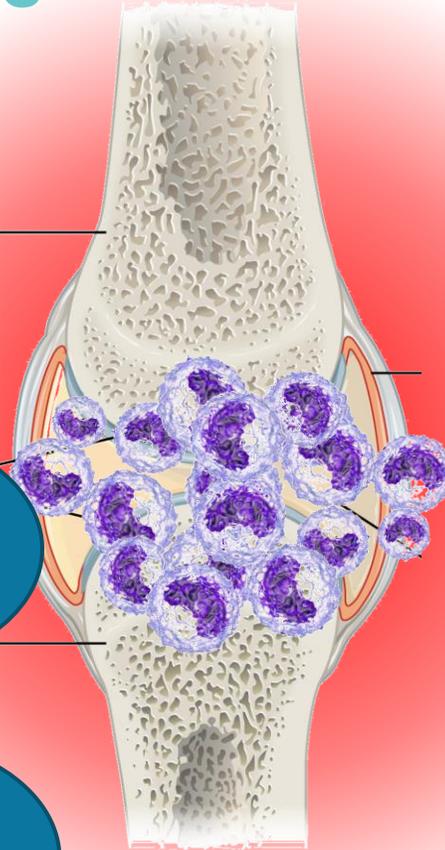
MEI como extensión de la respuesta inmune más allá del intestino y proceso inflamatorio independiente

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Centros entre las IMiDs.

citoquinas y moléculas de adhesión no selectivas del intestino: El tono inflamatorio



eficaces: -1
eficaces: -1



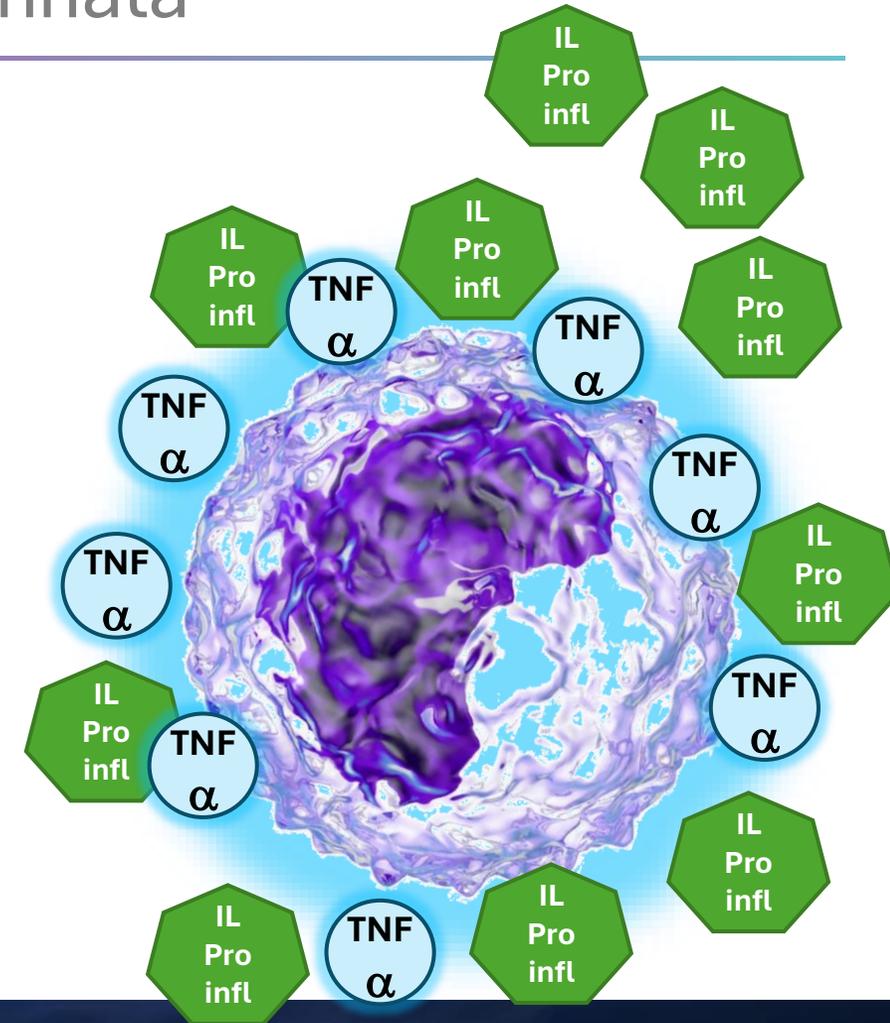
Hedin J Crohn Colitis 2019
Salmi J Exp Med 1995
Salmi J Immunol 2001
Park Autoimm Rev 2017
Sherlock Nat Med 2012



MEI como proceso inflamatorio independiente

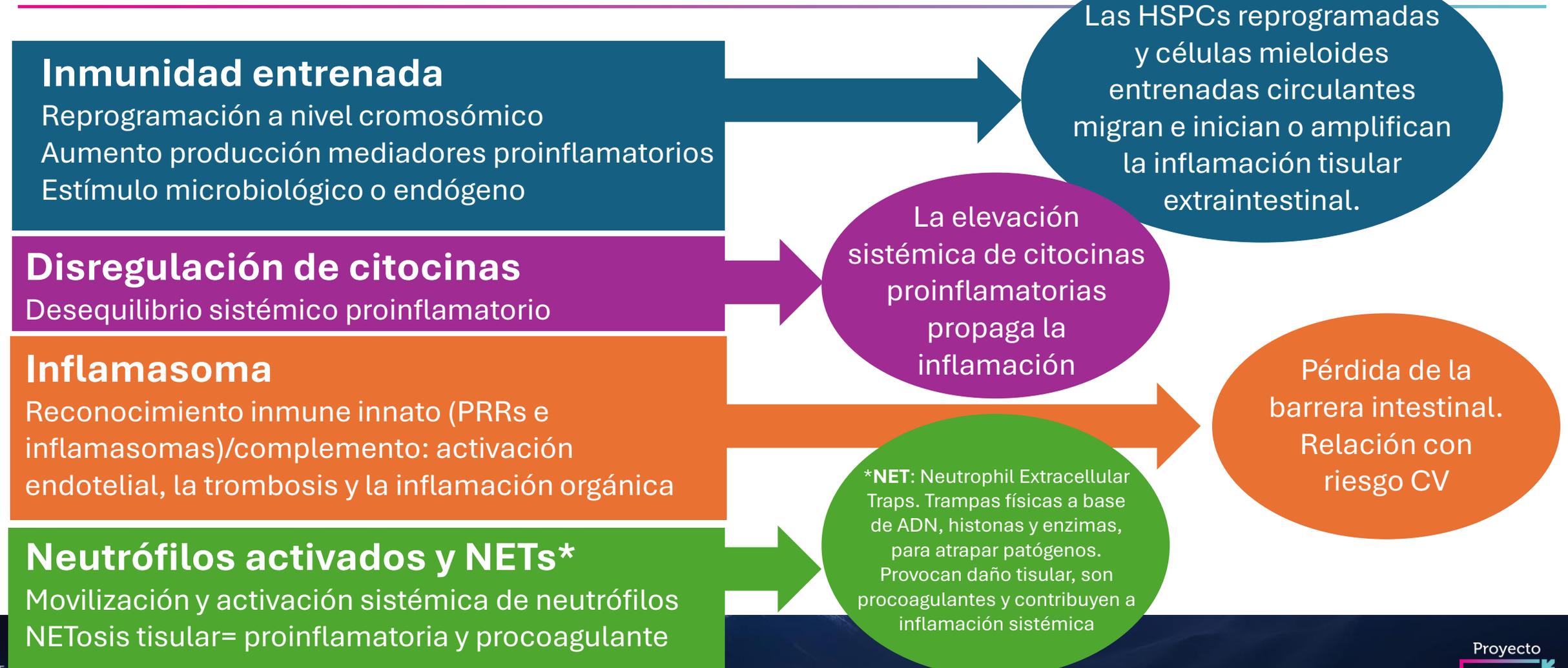
cambios sistémicos en la respuesta inmune innata

- La exposición de los neutrófilos a **citoquinas proinflamatorias** puede aumentar su respuesta al ser activados: “**neutrophil priming**”
- Los neutrófilos circulantes en pacientes con EI tienen **características morfológicas** que demuestran su estado de **activación**, habiéndose demostrado en ellos el fenómeno de “priming” *in vitro* lo que incluye **sobreexpresión** de moléculas proinflamatorias como el **TNF α**
- Otros cambios en las células inmunes circulantes en pacientes con EI sugieren cambios a nivel **hematopoyético**; es posible que las citoquinas proinflamatorias sistémicas induzcan cambios en la generación de las células que originan la **respuesta inmune innata**.



MEI como proceso inflamatorio independiente

cambios sistémicos en la respuesta inmune innata



Disbiosis y microbiota en la patogenia de las MEI

- La microbiota intestinal es probablemente uno de los principales **determinantes de la respuesta inmune en la EI**, causando la **activación de células T** específicas el intestino, por lo que podría jugar un papel en el desarrollo de las MEI.
- Se ha comprobado que los pacientes con **espondiloartritis**, al igual que con **artritis psoriásica** o con **colangitis esclerosante primaria**, tienen menor diversidad microbiana intestinal; hasta el punto de que se ha demostrado la relación de determinadas bacterias con la actividad de la EspA.
- No está claro si las **variaciones en la microbiota** pueden seleccionar a aquellos pacientes con EI que desarrollarían determinadas MEI.



Genética y MEI

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and the gut - Explorando las fronteras entre las IMiDs.

- Existen datos suficientes como para suponer que muchas MEI comparten **predisposición genética** con la EII. De hecho, se ha comprobado una gran concordancia entre familiares con EII y MEI, y se sabe que una MEI aumenta el riesgo de padecer otra MEI.
- Existen **solapamiento genético** entre la EII y algunas MEI, fundamentalmente las relacionadas con la EspA, habiéndose llegado a asociar el gen **NOD2** tanto con enfermedad de Crohn ileal como con sacroileítis y uveítis.
- Muchos de los estudios genéticos sobre la patogénesis de las MEI en la EII se basan en el sistema **HLA**: Se han relacionado muchos genes HLA con diferentes MEI.
- Los grandes estudios de asociación genómica (**GWAS**) han encontrado varios *loci* en común entre la EII y la EspA, psoriasis, eritema nodoso o colangitis esclerosante primaria, algunos de ellos con una fuerte asociación.



Conclusiones



Las MEI son el resultado de múltiples interacciones complejas.



No existe un mecanismo único para cada MEI.



Los mecanismos por los que un paciente con EII pueden desarrollar MEI son múltiples, y estamos aun lejos de comprenderlos bien.



Aun así, comprender los mecanismos fundamentales de cada MEI o grupos de MEI pueden ayudarnos a tratar mejor a nuestros pacientes

INMUNAUTAS

Beyond the gut - Explorando las fronteras entre las IMiDs.

¡Gracias por vuestra atención!

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Beyond the gut - Explorando las fronteras entre las IMIDs.

Workshop EII - Psoriasis

Yago González-Lama & Rubén Francés

Evento de Educación Médica
Organizado y Financiado por:

Johnson&Johnson

EM-196046 Enero 2026 Janssen Cilag S.A

Proyecto



Os presento a Carlos

35 años. Soltero. Trabaja en una consultora.

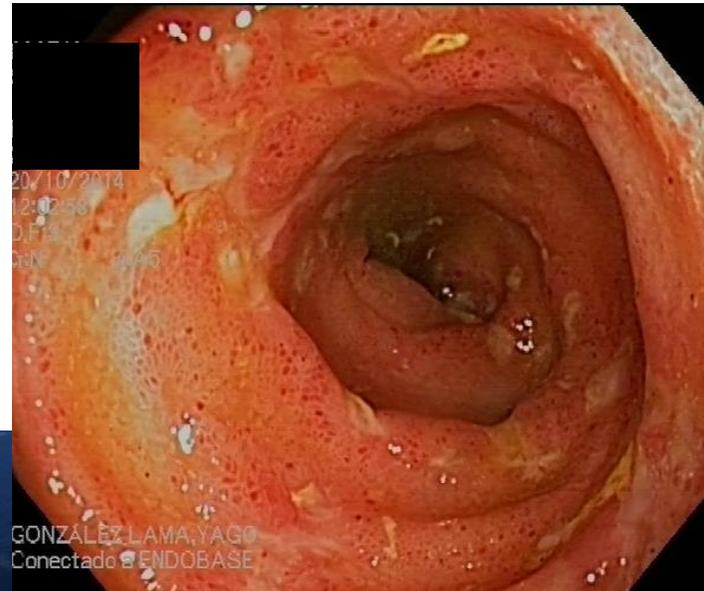
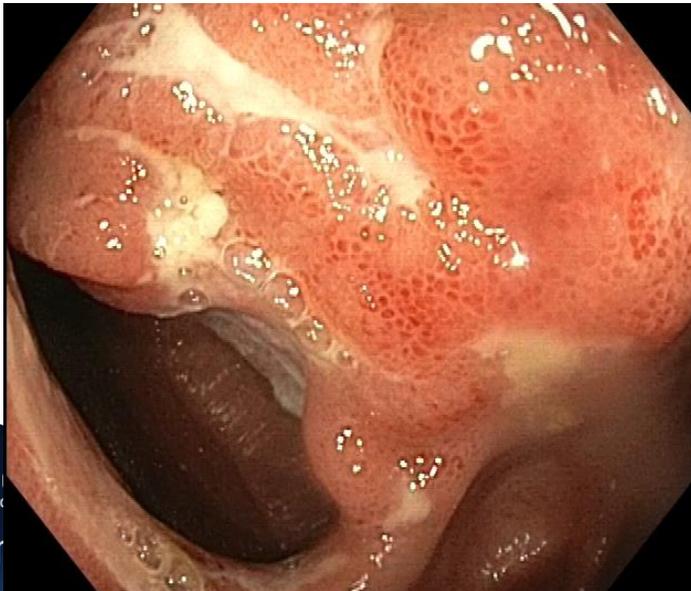
Diagnosticado de **Psoriasis** en placas muy **leve** desde hace 5 años.

No ha llevado tratamiento salvo tópico y esporádicamente.



Os presento a Carlos

- Arrastra un cuadro de **astenia** y su MAP detectó anemia y ferropenia.
- Al interrogatorio dirigido, parece que lleva un tiempo además con aumento del número de deposiciones, algo de urgencia y de dolor abdominal.
- Se remitió a digestivo, donde se pidió una **calprotectina**, que fue claramente patológica, y se hizo una **colonoscopia** que demostró **ileítis** endoscópicamente grave.

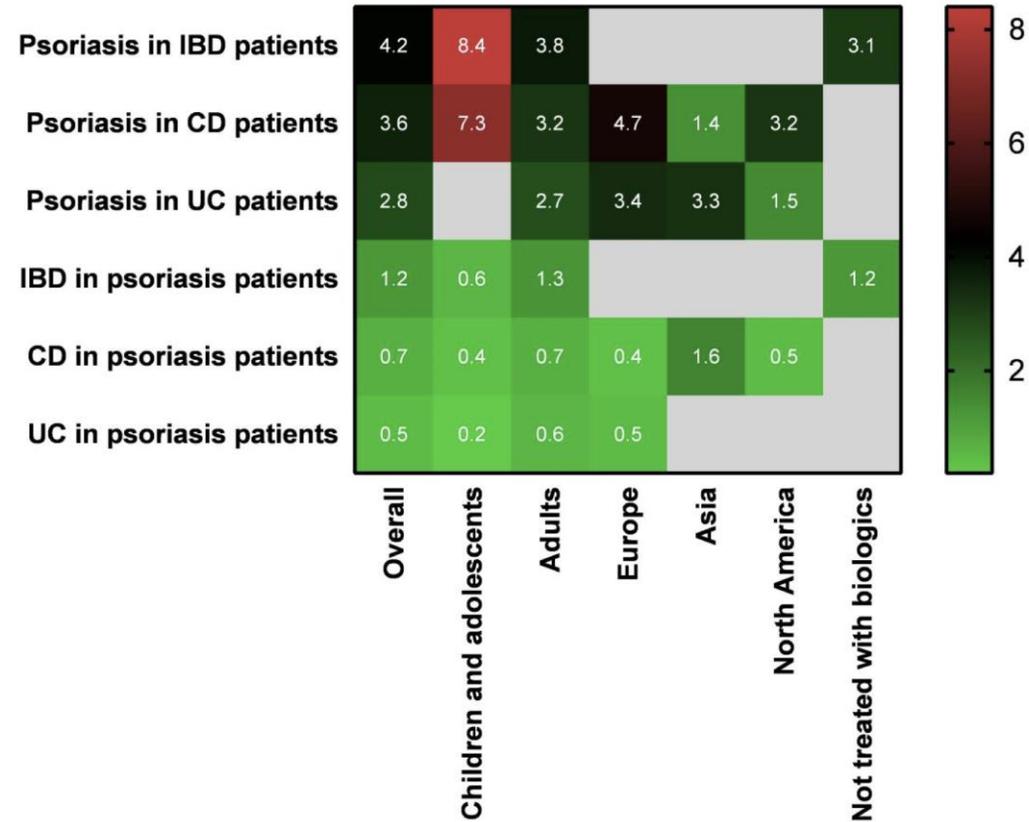


INMUNAUTAS

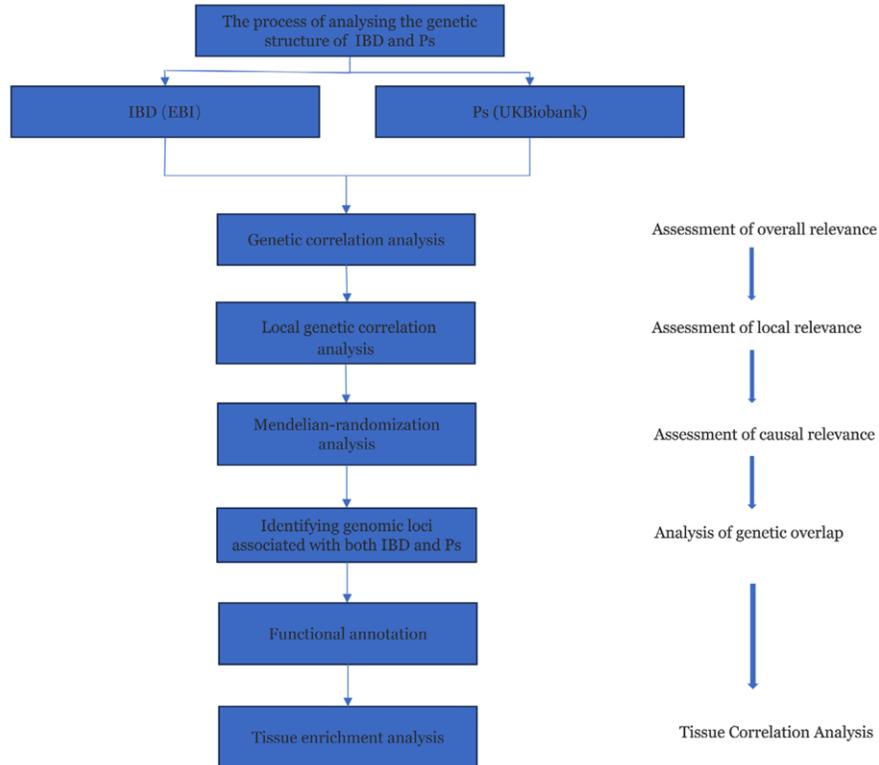
Beyond the gut - Explorando las fronteras entre las IMiDs.

Pregunta 1. ¿Existen bases genéticas que justifiquen la asociación de EII y psoriasis?

Bidirectional Association Between IBD and Psoriasis

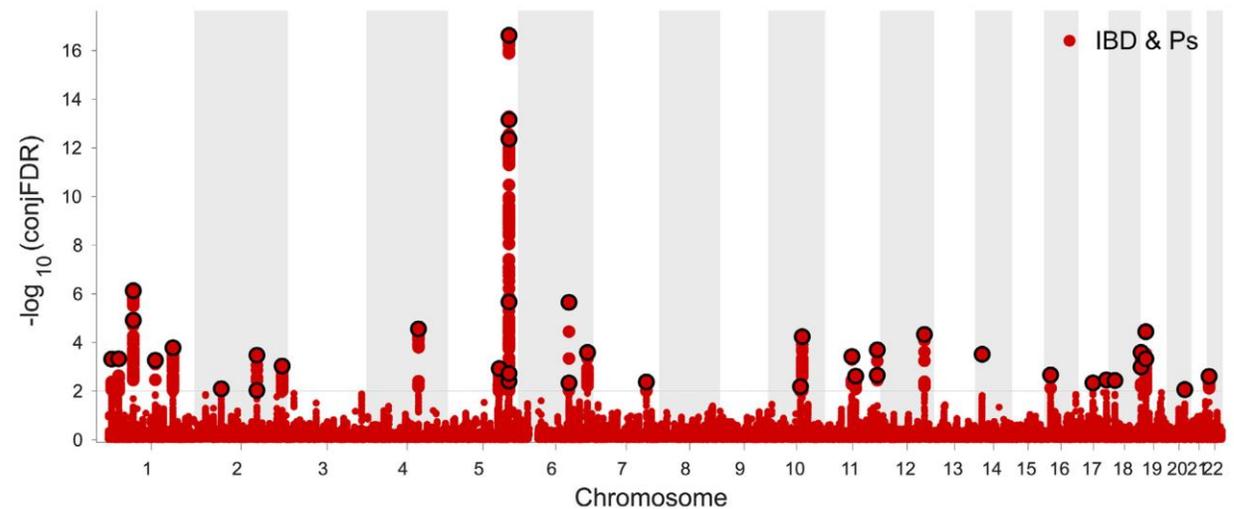


Shared risk loci between IBD and Psoriasis



(GWAS ID: ebi-a-GCST004131): 25,042 IBD cases and 34,915 controls
(GWAS ID: ukb-b-10537): 5314 Pso cases and 457,619 controls

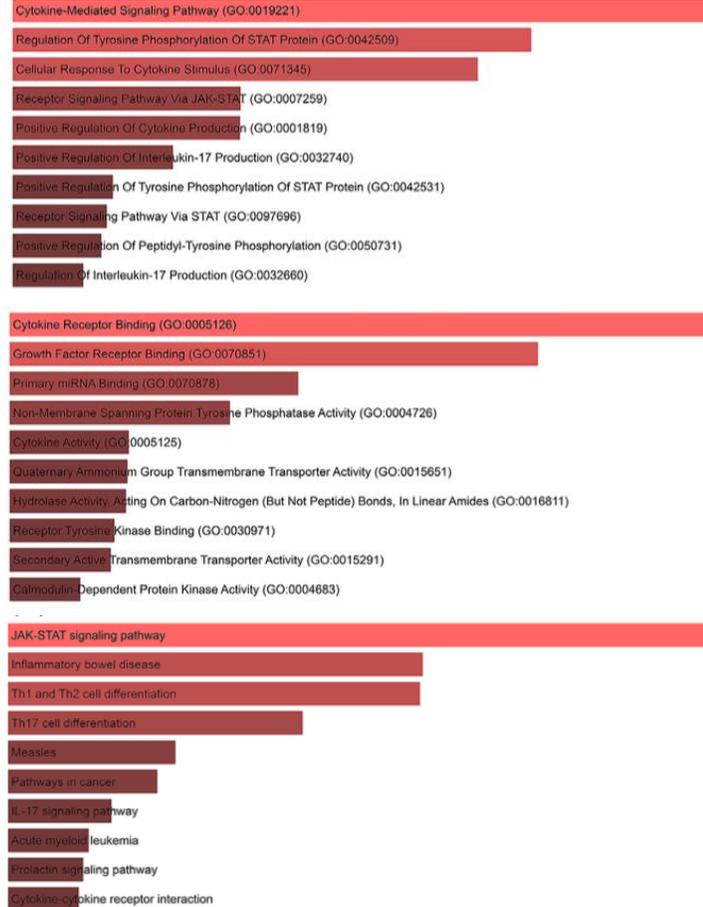
43 shared loci (1885 candidate SNPs)



Enrichment analysis for shared loci between IBD and Ps

TABLE 1 The 43 LD-independent loci jointly associated with IBD and Ps identified by conjFDR analyses.

SNP	A1	A2	Gene	function	CADD	zscore_IBD	zscore_Ps	conjFDR_IBD_Ps	pval_IBD	pval_Ps
rs6125877	A	G	TREX1	downstream	0.013	16.56856	4.617776	0.000243	1.18E-61	3.88E-06
rs5754100	T	G	UBE2L3	ncRNA_intronic	0.46	16.475231	4.617776	0.000243	5.53E-61	3.88E-06
rs118115488	G	A	PDE4A	ncRNA_intronic	3.861	16.481794	4.581618	0.000284	4.96E-61	4.61E-06
rs11672021	T	G	PDE4A	ncRNA_intronic	7.249	16.448919	4.581618	0.000284	8.54E-61	4.61E-06
rs35138525	G	T	RP11-770G2.5	intergenic	1.889	4.241125	-4.458299	0.000471	2.22E-05	8.26E-06
rs71639217	A	G	RP11-431K24.1	intergenic	0.079	-4.216824	4.452106	0.000483	2.48E-05	8.50E-06
rs2074452	C	A	SBN02	ncRNA_intronic	7.996	16.645986	4.42622	0.000535	3.24E-62	9.59E-06
rs35665378	G	T	POLR2E	ncRNA_intronic	1.647	16.987018	4.201433	0.00129	1.02E-64	2.65E-05
rs2847266	T	C	RP11-973H7.1	ncRNA_intronic	3.007	16.918868	4.201433	0.00129	3.27E-64	2.65E-05
rs111585196	T	C	CYTH1	ncRNA_intronic	7.415	16.879043	4.182069	0.00138	6.42E-64	2.89E-05
rs2021511	T	C	RM12	upstream	0.508	16.795431	4.155728	0.00153	2.64E-63	3.24E-05
rs696	A	G	NFKBIA	upstream	0.344	16.842921	4.14756	0.00158	1.18E-63	3.36E-05
rs8072566	T	C	STAT3	ncRNA_exonic	1.649	16.817379	4.117458	0.00176	1.82E-63	3.83E-05
rs61907765	A	G	ETS1	upstream	3.397	16.691497	4.110494	0.0018	1.51E-62	3.95E-05
rs10774624	T	C	RP3-473L9.4	upstream	5.477	16.711123	4.090739	0.00195	1.09E-62	4.30E-05
rs10059288	A	G	AC008697.1	intergenic	1.544	3.781152	-4.14756	0.00232	0.000156	3.36E-05
rs4921230	A	G	LINC01845	intergenic	0.619	3.71533	-4.14756	0.00294	0.000203	3.36E-05
rs11221249	G	A	LINC02098	upstream	3.848	-10.369931	-3.926914	0.00354	3.40E-25	8.60E-05
rs2052352	T	C	CAMK2G	intergenic	0.551	-4.908544	3.877204	0.00422	9.18E-07	0.000106
rs12724239	A	G	DENND1B	upstream	0.101	-4.753317	3.851966	0.00462	2.00E-06	0.000117
rs78703675	A	G	RORC	intergenic	0.739	-4.801241	3.851966	0.00462	1.58E-06	0.000117
rs10193928	C	T	LINC01185	ncRNA_intronic	0.15	-4.743749	3.82901	0.005	2.10E-06	0.000129
rs17716942	A	G	KCNH7	intergenic	0.481	-4.77829	3.82901	0.005	1.77E-06	0.000129
rs72673802	G	A	SLC35D1	intergenic	1.903	-4.803602	3.82901	0.005	1.56E-06	0.000129
rs11236797	C	T	RP11-672A2.7	upstream	0.818	3.563157	-4.211751	0.00502	0.000366	2.53E-05
rs4728142	G	A	IRF5	intergenic	3.007	3.522565	-4.132033	0.00576	0.000427	3.60E-05
rs1004819	G	A	IL23R	intergenic	1.536	-4.754852	3.788472	0.00577	1.99E-06	0.000152
rs367254	C	T	TRAF3IP2	intergenic	0.038	3.519888	-4.155728	0.00582	0.000432	3.24E-05
rs17674015	C	A	CTB-1121.1	intergenic	2.084	3.503015	-4.132033	0.00616	0.00046	3.60E-05
rs76198205	C	T	SLC16A10	intergenic	0.533	3.499623	-4.172955	0.00623	0.000466	3.01E-05
rs10056700	A	G	RAD50	intergenic	0.704	3.469422	-4.139668	0.00688	0.000522	3.48E-05
rs9989746	A	G	SP140	intergenic	6.206	-6.033795	3.737534	0.0069	1.60E-09	0.000186
rs6861973	T	C	RP11-431K24.1	intergenic	0.063	3.458696	-4.155728	0.00714	0.000543	3.24E-05
rs13169581	A	G	AC008697.1	intergenic	0.369	3.455223	-4.124634	0.00723	0.00055	3.71E-05
rs6887065	C	A	AC008697.1	intergenic	6.846	3.451672	-4.155728	0.00731	0.000557	3.24E-05
rs34470843	G	A	CTB-1121.1	intergenic	1.623	3.438201	-4.172955	0.00764	0.000586	3.01E-05
rs212396	C	T	RP1-111C20.4	intergenic	1.465	3.435589	-4.124634	0.00771	0.000591	3.71E-05
rs4921488	A	G	AC008697.1	intergenic	1.711	3.419159	-4.14756	0.0081	0.000628	3.36E-05
rs2063113	T	G	RP11-84D1.2	intergenic	1.251	-5.201167	3.669873	0.00869	1.98E-07	0.000243
rs942793	C	T	ZMIZ1	intergenic	7.825	3.396983	-4.182069	0.00875	0.000681	2.89E-05



GO - Biological processes
Cytokine-mediated signaling pathway

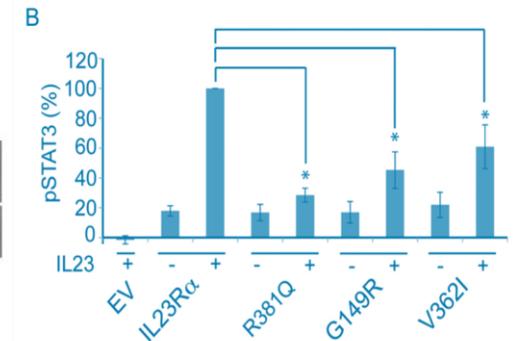
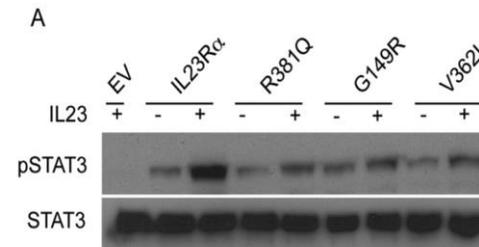
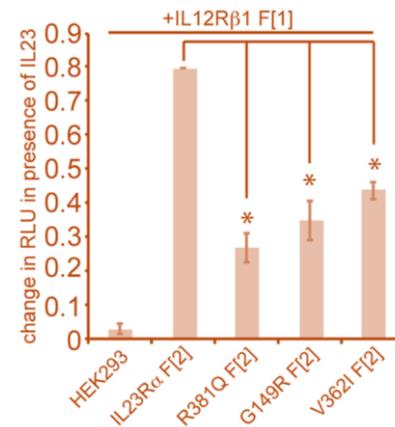
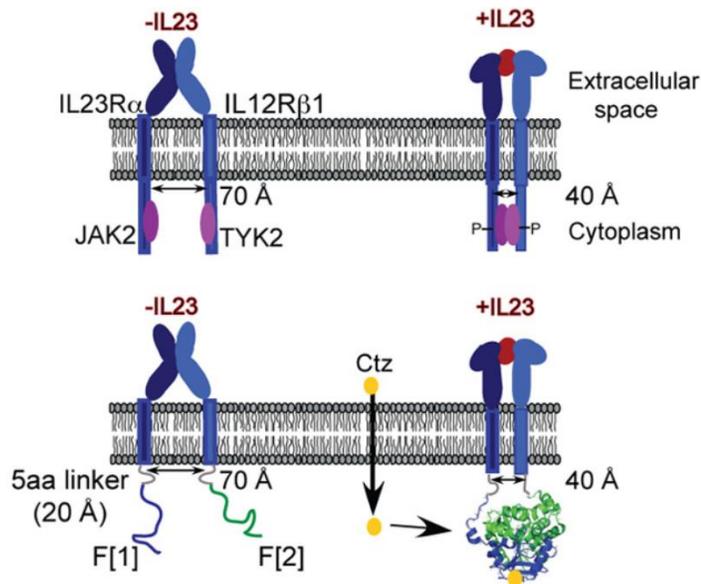
GO - Molecular function
Cytokine receptor binding

KEGG - Enriched pathway
JAK-STAT signaling pathway

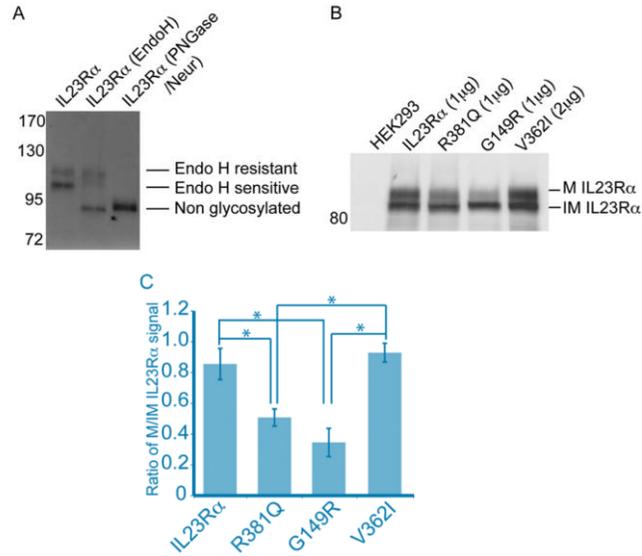
IL23R α variants show the reduction in activation by IL23

IL23R variants reduce their ability to interact with IL12R β 1 upon IL-23 stimulation

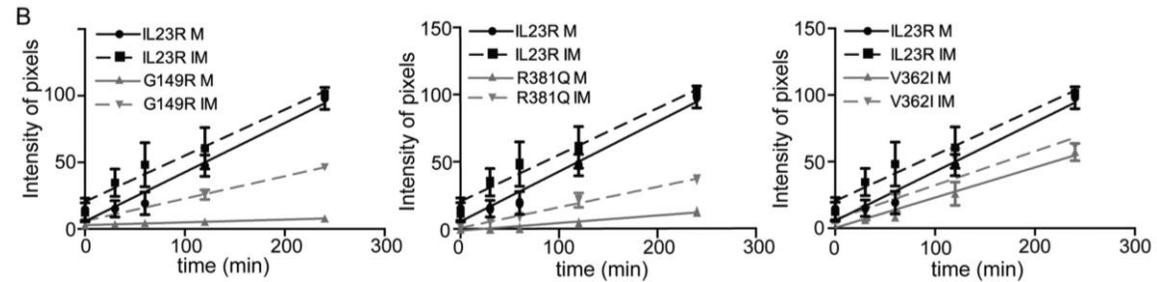
IL23R α protective variants R381Q, G149R, and V362I display reduction in receptor signaling



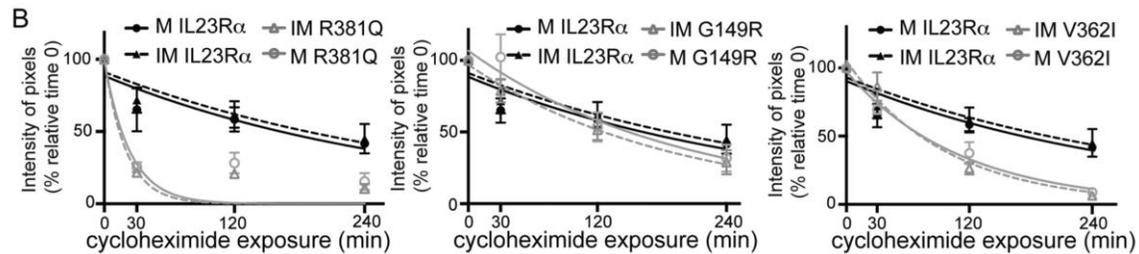
IL23R α -protective variants display different receptor maturation and stability



IL23R α -protective variants display different receptor maturation

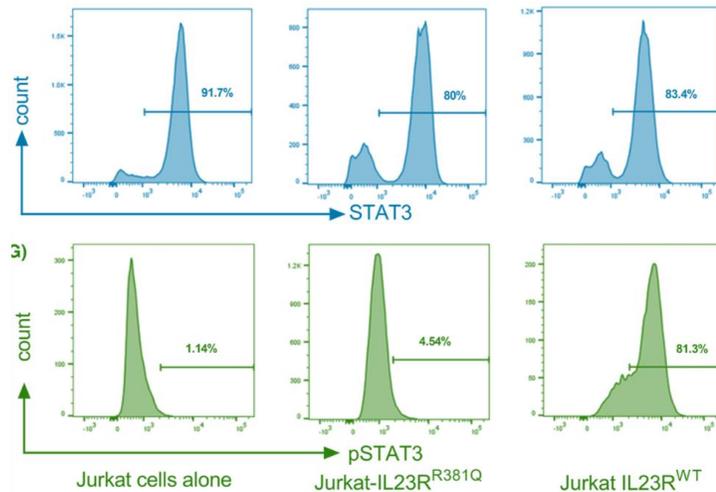


IL23R α -protective variants display less stability

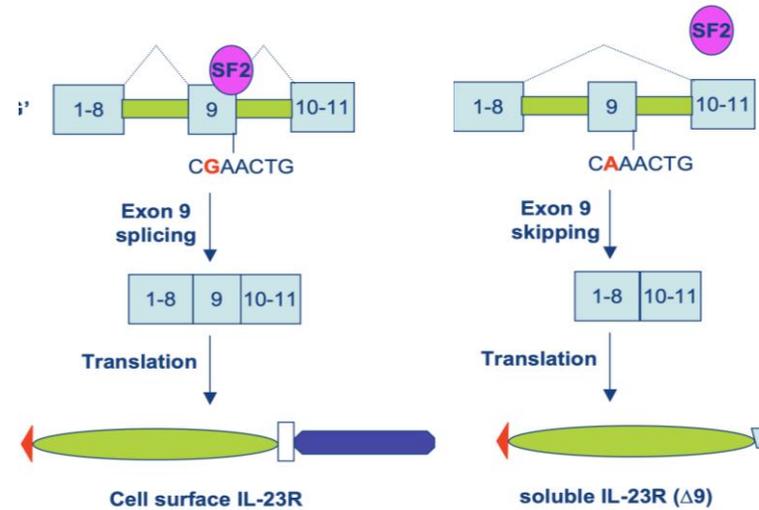


R381Q reverses IL23R dependent STAT3 activation reducing membrane bound receptor

IL23 stimulated T cells intracellularly stained for STAT3 and pSTAT3 expression



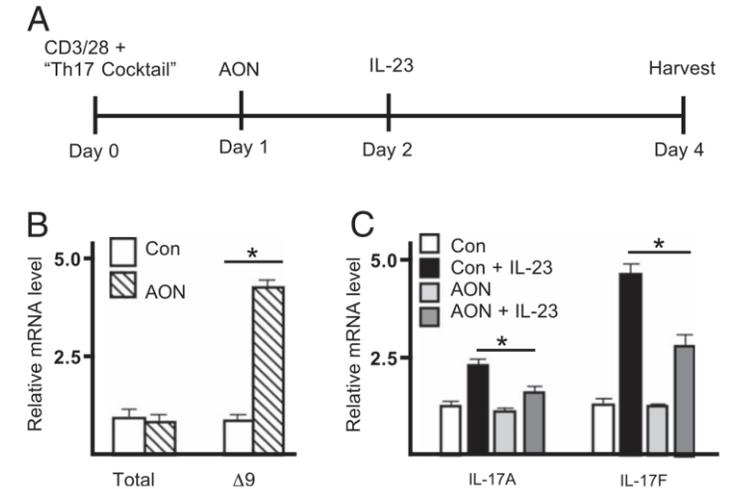
rs11209026 favors exon 9 skipping by reducing the binding of the splicing enhancer SF2



Common allele: 1142G

SNP rs11209026
Variant allele: 1142A

AON treatment diminished the maturation of human Th17 cells.

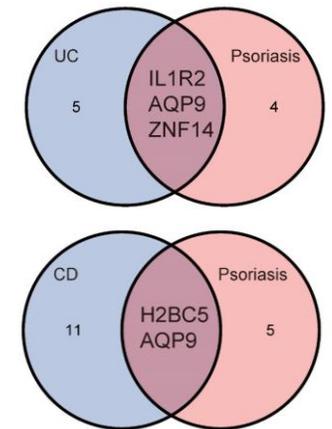
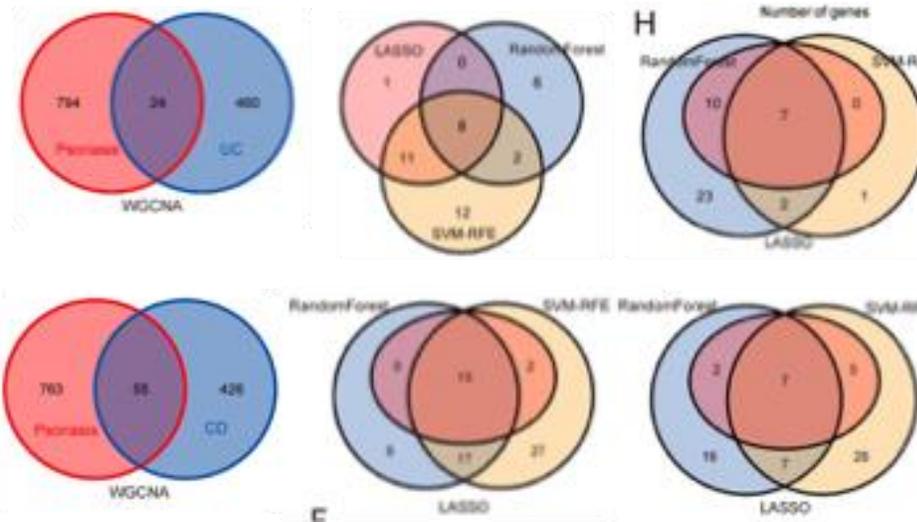
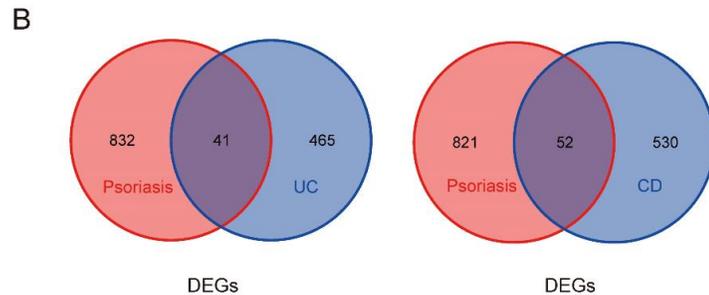
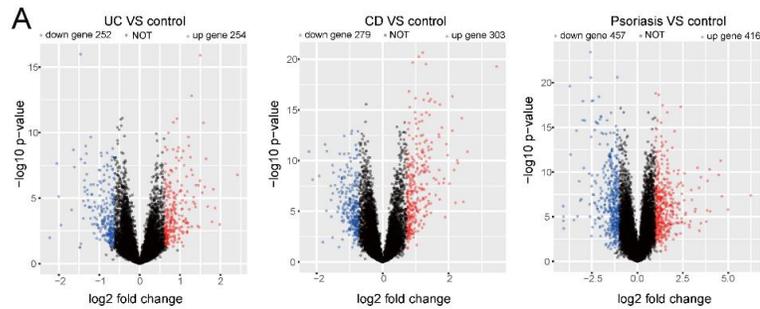


AQP9 as shared diagnostic gene in IBD and Psoriasis

GSE3365 from the GPL96 platform : 127 transcriptome datasets, comprising 42 normal, 26 UC, and 59 CD samples
 GSE14905 from the GPL570 platform: 82 transcriptome datasets: 21 normal and 61 psoriasis samples

WGCNA to investigate crucial module genes in diseases.
 Soft threshold method to create a co-expression network.

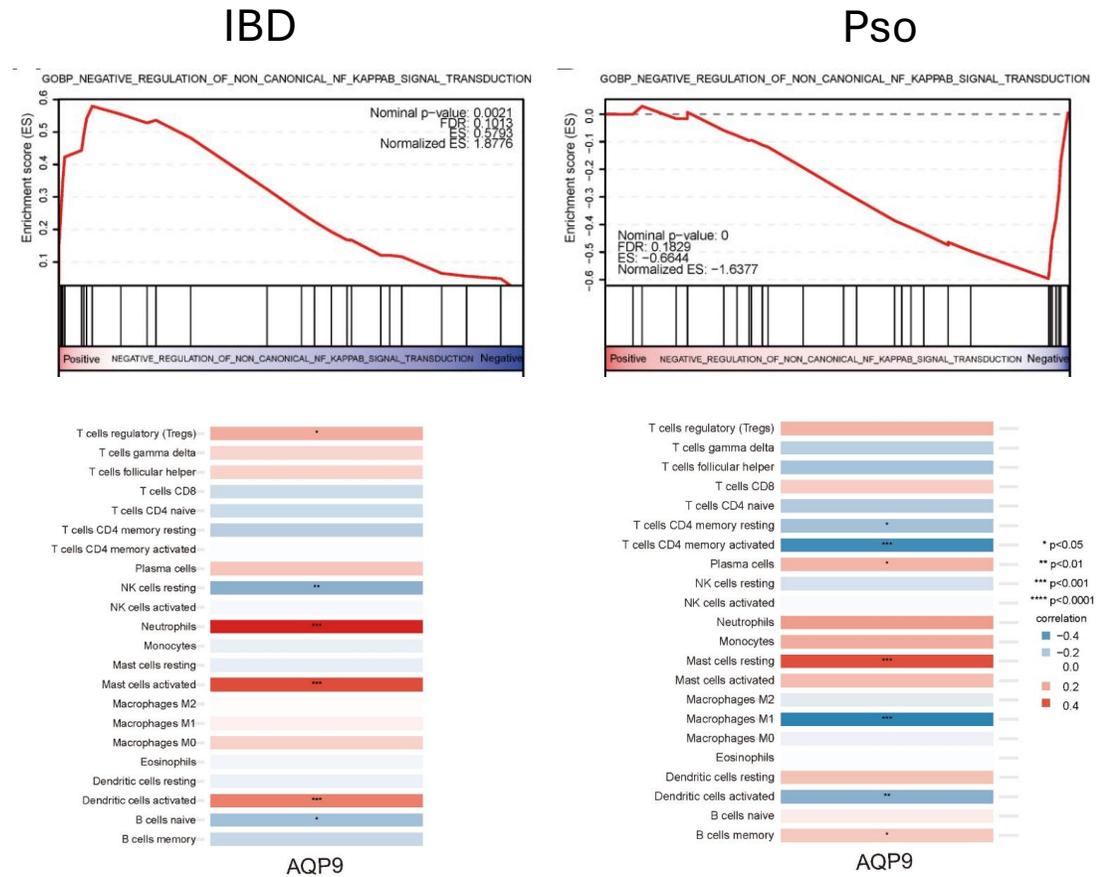
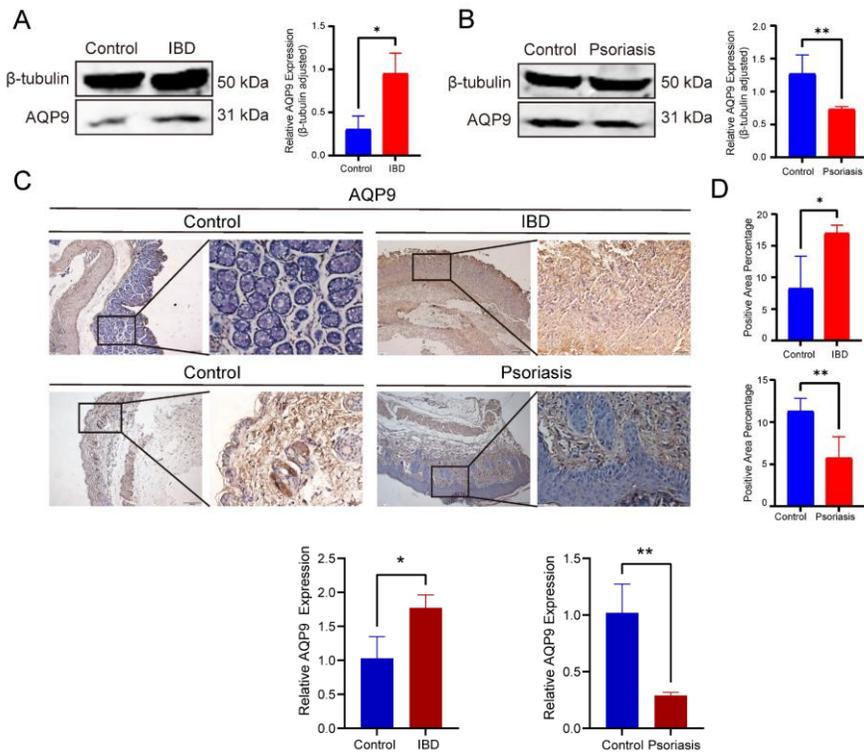
GSE75214 and GSE52471 as validation datasets



ble 3. AUC values of shared diagnostic genes in validation asets.

Disease	Internal validation				External validation			
	IL1R2	AQP9	ZNF14	H2BC5	IL1R2	AQP9	ZNF14	H2BC5
UC	83.7	93.681	83.974	–	65.933	90.394	50.914	–
CD	–	89.629	–	93.543	–	93.909	–	61.333
Psoriasis	78.728	78.689	92.194	80.562	75.641	82.906	93.162	51.709

AQP9 negatively regulates NFκβ and modulates immune cell infiltration



No parece tan fácil la cosa

- Se pautó Adalimumab con buena respuesta desde el punto de vista intestinal
- Sin embargo, parece que ha empeorado en los últimos tiempos y le ha aparecido en el cuero cabelludo, y presenta además algo de **onicopatía** y recientemente se ha añadido **dactilitis**.



INMUNAUTAS

Beyond the gut - Explorando las fronteras entre las IMiDs.

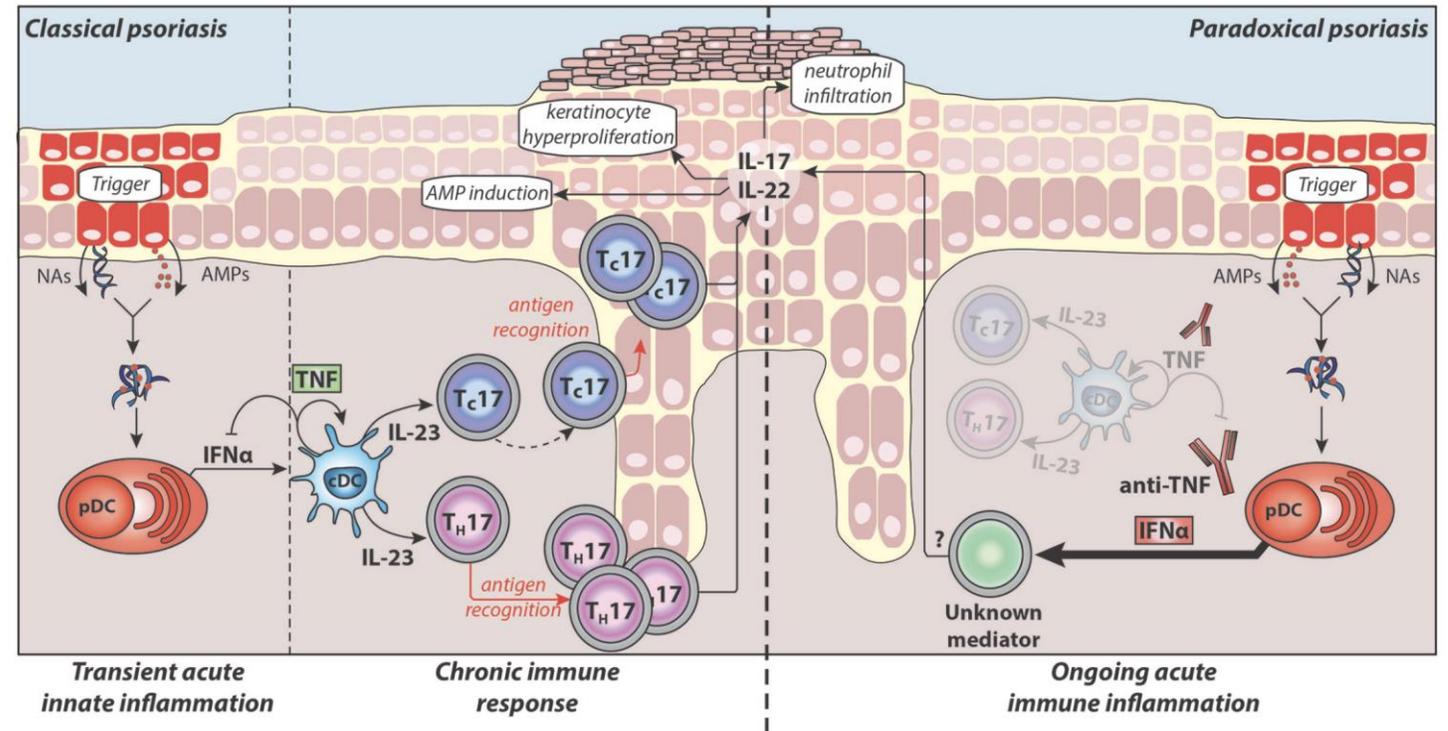
Pregunta 2. ¿Se puede interpretar como una psoriasis paradójica? ¿Cuál es el mecanismo inmunopatogénico de este fenómeno?

Uncontrolled IFN- α signalling unleashed by TNF blockade

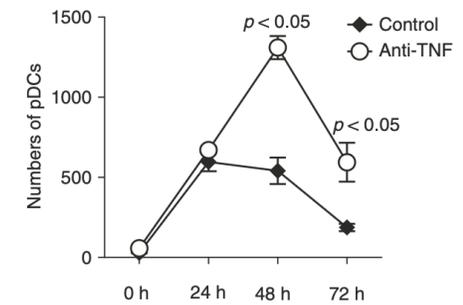
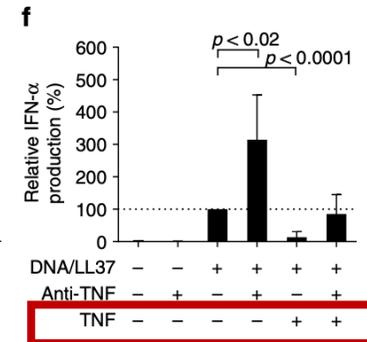
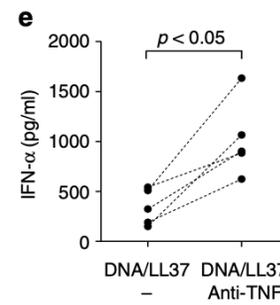
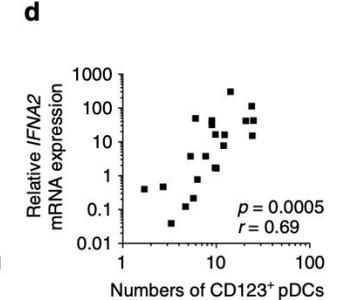
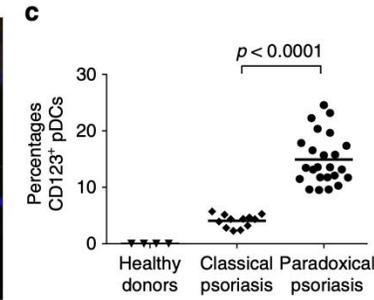
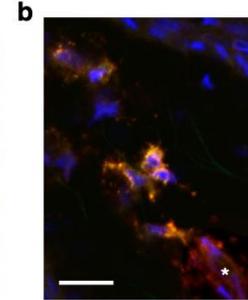
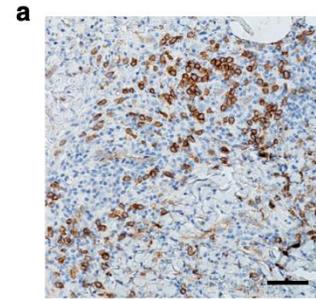
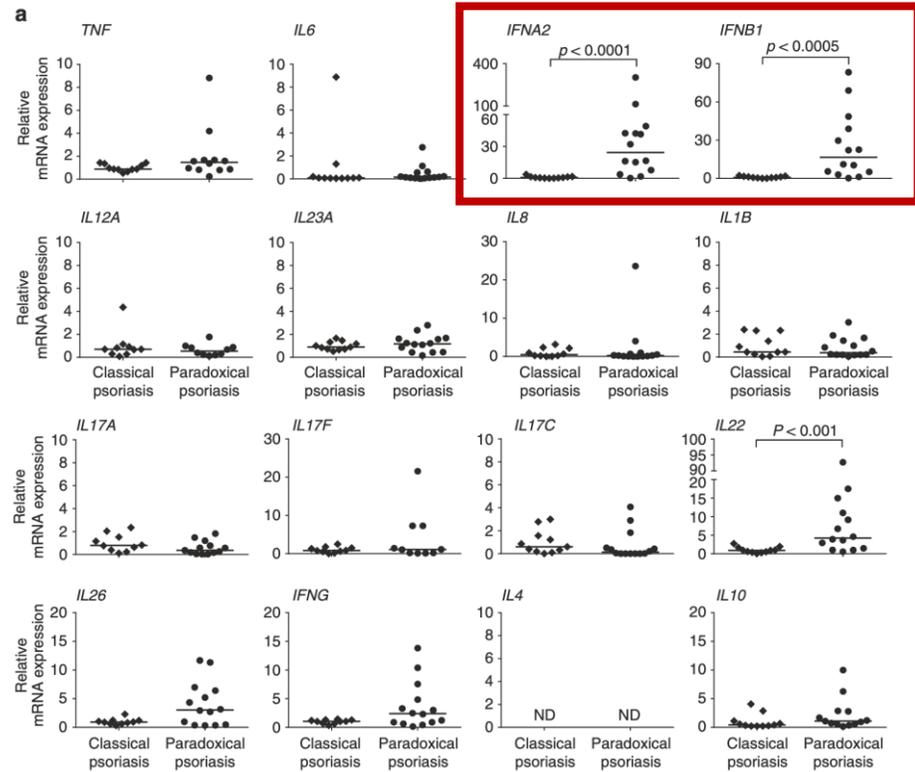
Worsening of existing psoriasis in patients undergoing treatment with a targeted therapy

or

New -onset psoriasiform reaction in patients treated with a targeted therapy for a different disease



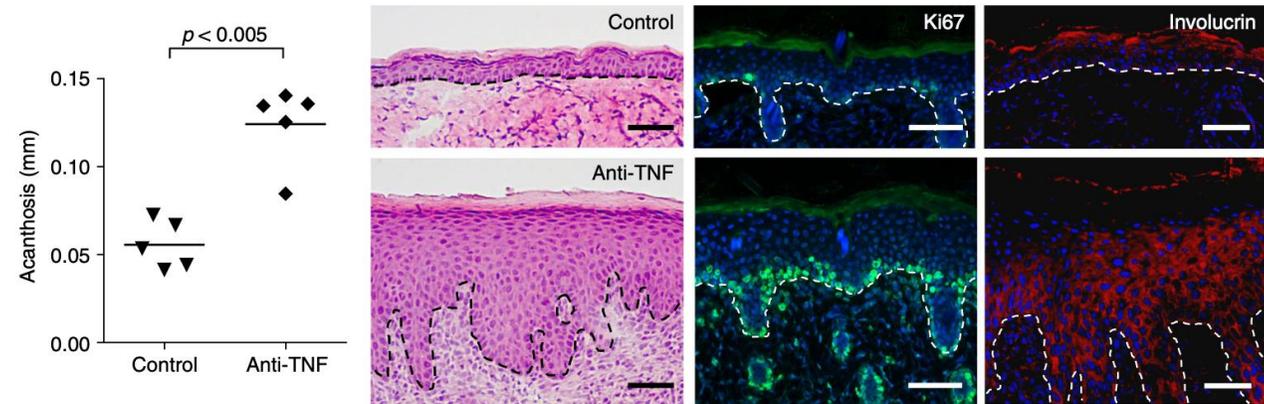
Increased type I interferon in skin lesions of paradoxical psoriasis



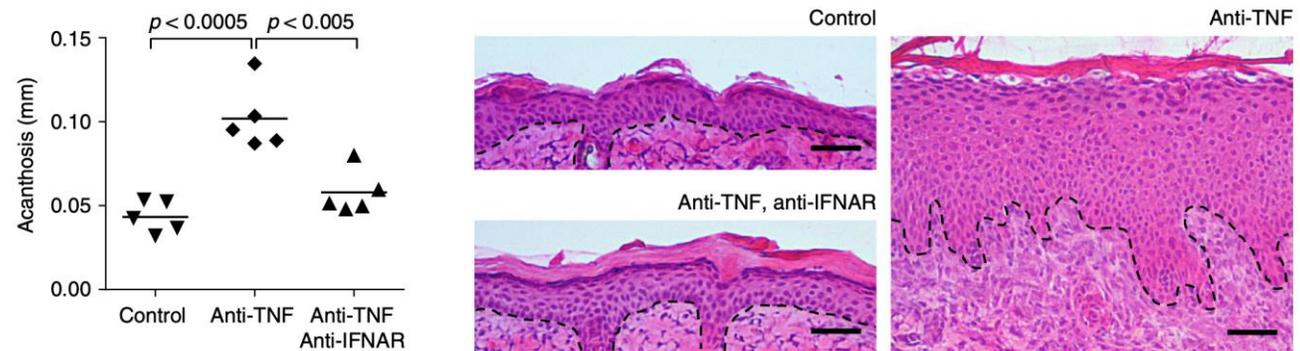
TNF blockade significantly enhanced IFN- α production by stimulated pDCs measured 48h after stimulation

Type I interferon-dependent psoriasis-like skin phenotype induced by anti-TNF.

Epidermal thickening (acanthosis) in mice treated with or without anti-TNF antibody 7 days after mechanical injury by tape stripping.

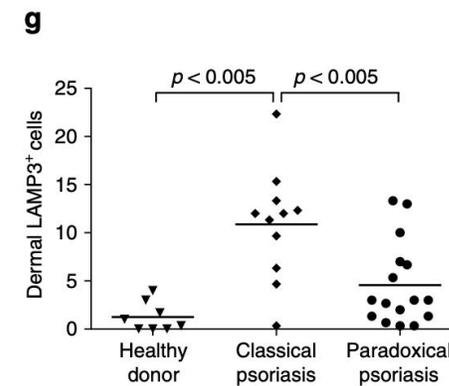
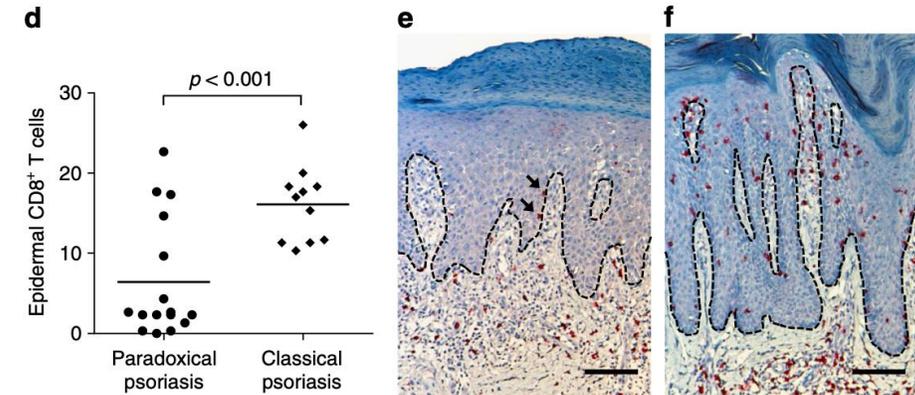
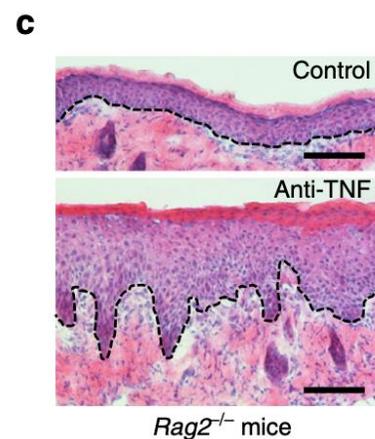
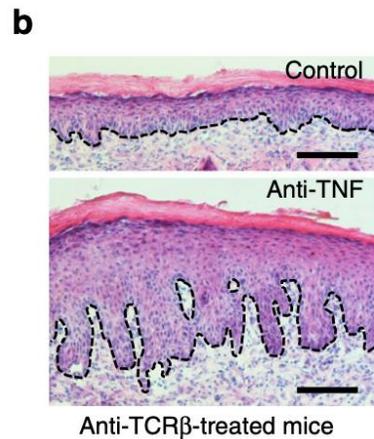
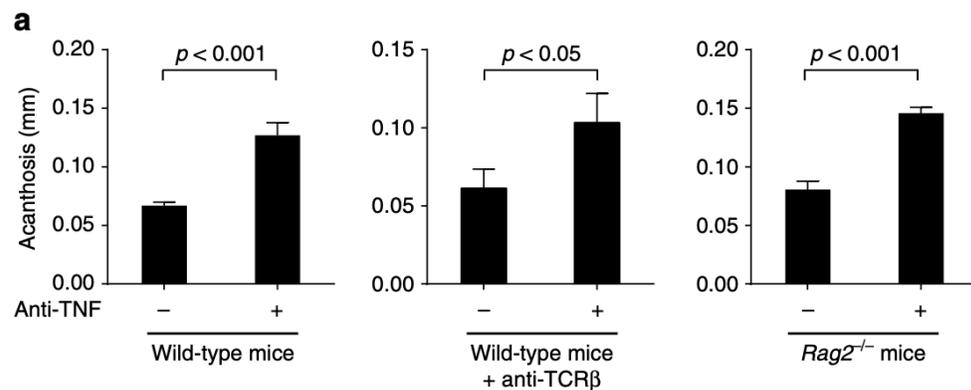


Inhibition of type I IFN signaling decreased the anti-TNF induced psoriatic phenotype to levels indistinguishable from control mice

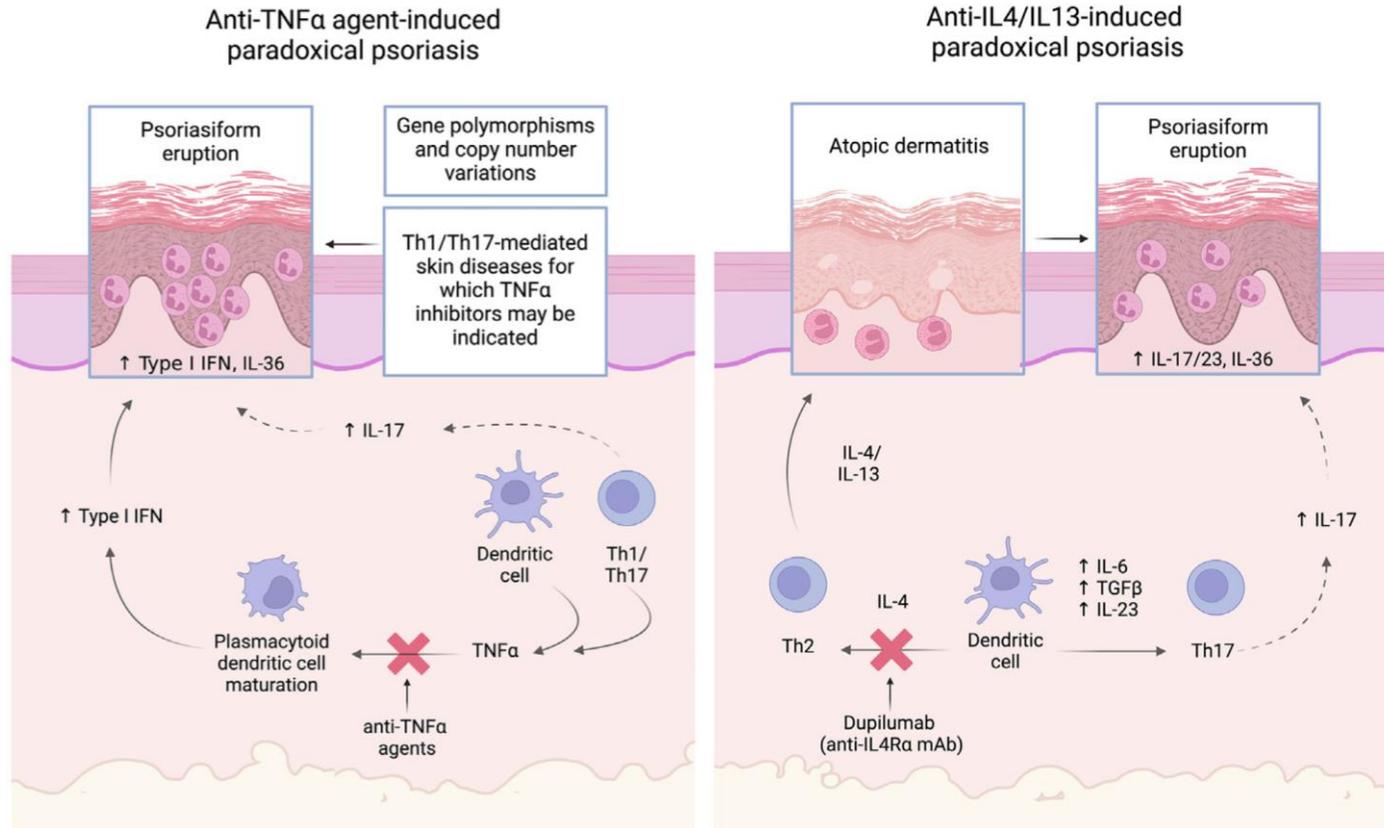


T-cell-independent induction of paradoxical psoriasis

Neither conventional T cells nor γ/δ -T cells are required for the type I IFN-driven keratinocyte hyperproliferation.



Paradoxical Psoriasis induced by other therapies



Paradoxical vs classic Psoriasis

Characteristics	Classical psoriasis	Paradoxical psoriasis
Clinico-phenotypic presentation	Well-demarcated erythematous plaques covered with silvery-white scales.	Presence of different psoriatic patterns including plaque-type, guttate, pustular forms as well as eczematiform presentation. Palmoplantar zones affected more often. Non-cicatricial alopecia regularly noted.
Histo-pathological appearance	Characteristic psoriatic histology: Epidermal hyperplasia (acanthosis), papillomatosis, hyper-/parakeratosis, dermal, and epidermal immune cell infiltrates.	Three different patterns: -classical psoriatic pattern -eczematiform pattern with spongiosis -lichenoid pattern with interface dermatitis often all these patterns are simultaneously present at variable degrees.
Recurrence	Relapsing.	Non-relapsing (upon cessation of anti-TNF).
Genetic associations	Many known (and established): <i>HLA-Cw6</i> , <i>IL12B</i> , <i>IL23A</i> , <i>IL23R</i> , and various components along type-I interferon signalling, NF-KB signalling, and other signalling pathways.	Few proposed: <i>IL23R</i> (an allele that is protective concerning classical psoriasis), and <i>FBXL19</i> , <i>CTLA4</i> , <i>SCL12A8</i> , <i>TAP1</i> which have an unclear role in paradoxical psoriasis and the outcome of the allele is undetermined.
Role of TNF	Driven by TNF.	Induced by blockade of TNF.
Role of adaptive immunity	T-cell mediated. Intraepidermal and dermal (autoimmune) T_H/T_C 17-cells found throughout skin lesions.	T-cell independent. Significant reduced numbers of intraepidermal $CD8^+$ T_C -cells as compared to classical psoriasis.
Role of innate immunity	Transiently driven by pDC derived type-I IFN during the early phase of psoriasis development. Mature cDCs and neutrophils present in large numbers in skin lesions of chronic/late phase of classical psoriasis.	Driven by unabated type-I IFN produced by non-maturing pDCs. Immature dendritic cells, and neutrophils often present in lesions. Role for other cell types not known (particularly in mediating the psoriatic phenotype).
Pathogenic mechanism	Chronic (autoimmune) T_H/T_C 17-mediated inflammation	Unabated, ongoing type-I IFN-driven innate inflammation, absence of T-cell autoimmunity.

Mechanism	Description	References
Cytokine dysregulation	Dysregulation in cytokine balance is one of the most common and most accepted theories. In PP, TNFi blocks TNF α , which inhibits the maturation of conventional dendritic cells (cDCs) and pDC, leading to an increased production of IFN α . As a result, the overexpression of IFN α leads to the failure of activation of autoimmune T cells and memory T cells.	Mylonas A et al., 2018 [9] Toussiroot É et al., 2016 [13] Lu J et al., 2023 [33] Conrad C et al., 2018 [34]
JAK-STAT pathway	TNFi blocks TNF α , leading to an overexpression of IFN α , which binds to its specific receptors on cells, activates JAK1 and TYK2, and leads to the phosphorylation and activation of STAT1 and STAT2. These induce the expression of proinflammatory genes, resulting in amplified inflammation and potentially explaining the development of psoriasis. Also, the elevated levels of IL-23 activate JAK2/TYK2, which activates STAT3, leading to Th17 cell differentiation and subsequent inflammation. This activation may have a potential role in the pathogenesis	Woodbury MJ et al., 2024 [35] Zhang Y et al., 2024 [36]
CXCR3 ligands and T cell migration	TNF inhibitors may cause aberrant lymphocyte movement and increase CXCR3 ligands, such as CXCL9, CXCL10, and CXCL11, supporting a Th1-skewed inflammatory response and contributing to psoriasis lesions.	Tillack C et al., 2013 [38]
Role of T cells and dendritic cells	T cells produce cytokines such as TNF α and IL-17, sustaining inflammation, while dendritic cells produce IFN α . Both play crucial roles in paradoxical adverse events.	Kumar BV et al., 2018 [39]
Genetic factors	Certain SNPs in genes like <i>IL23R</i> , <i>FBXL19</i> , <i>CTLA4</i> , <i>SLC12A8</i> , <i>TAP1</i> , and others predispose individuals to paradoxical psoriasis.	Cabaleiro T et al., 2015 [22]
Microbiota involvement and dysbiosis	Changes in the gut or skin microbiota might influence systemic inflammation, contribute to the pathogenesis and progression of IBD or psoriasis, and could trigger or exacerbate psoriasis, including paradoxical forms. Certain modifications in the composition of the microbiota can potentially result in an immune system response alteration, ultimately leading to the development of an inflammatory response.	Zákostelská Z J et al., 2023 [40]

Parece que no fue bien la cosa...

- Se suspendió el antiTNF.
- Se propusieron tratamientos tópicos e incluso fototerapia, sin demasiada mejoría

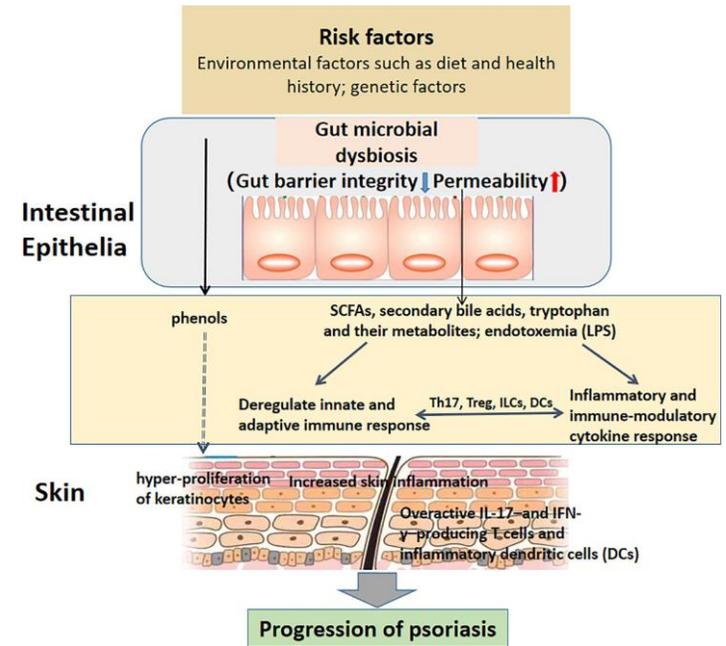
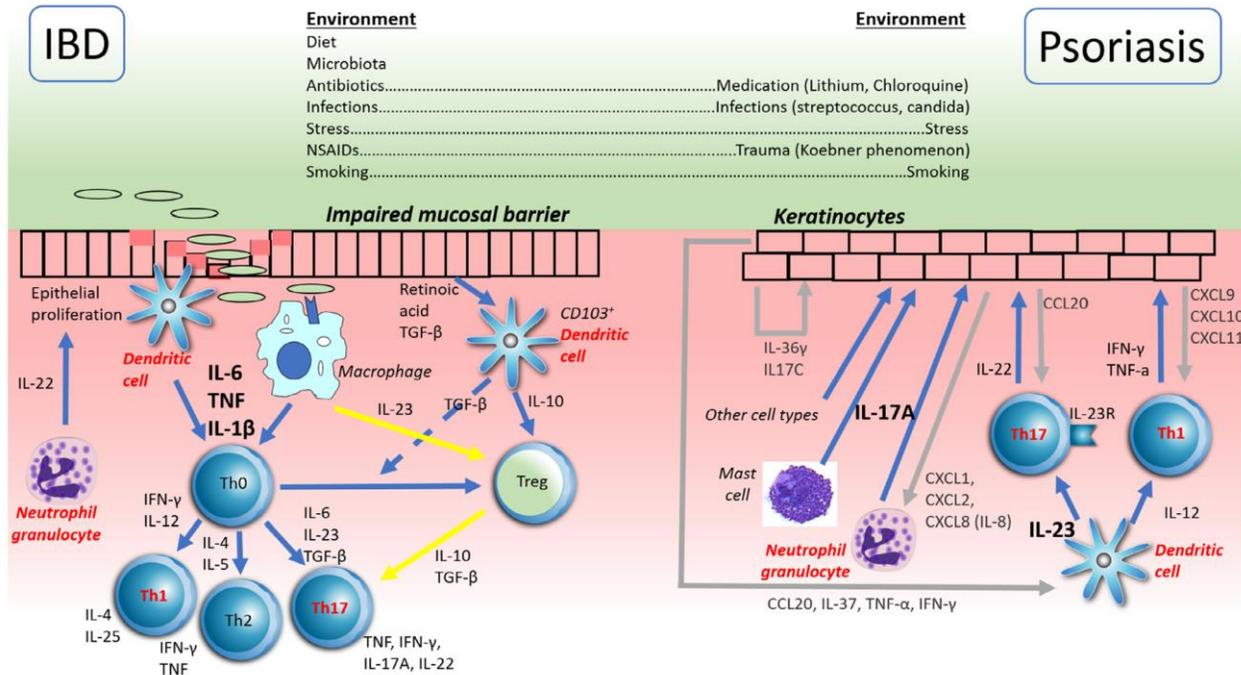


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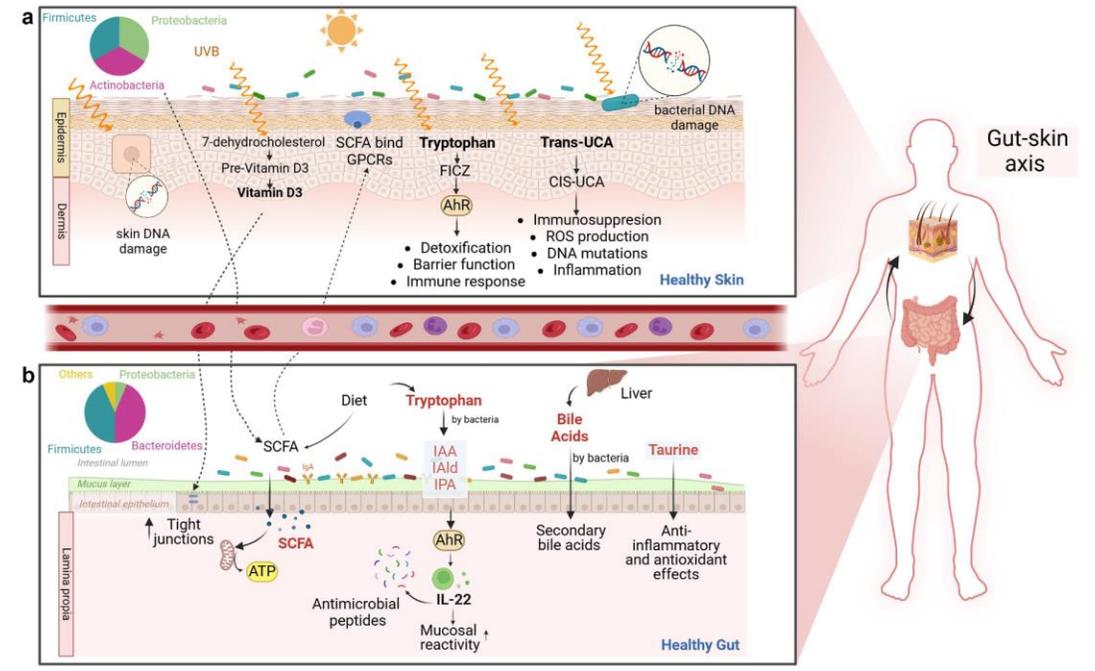
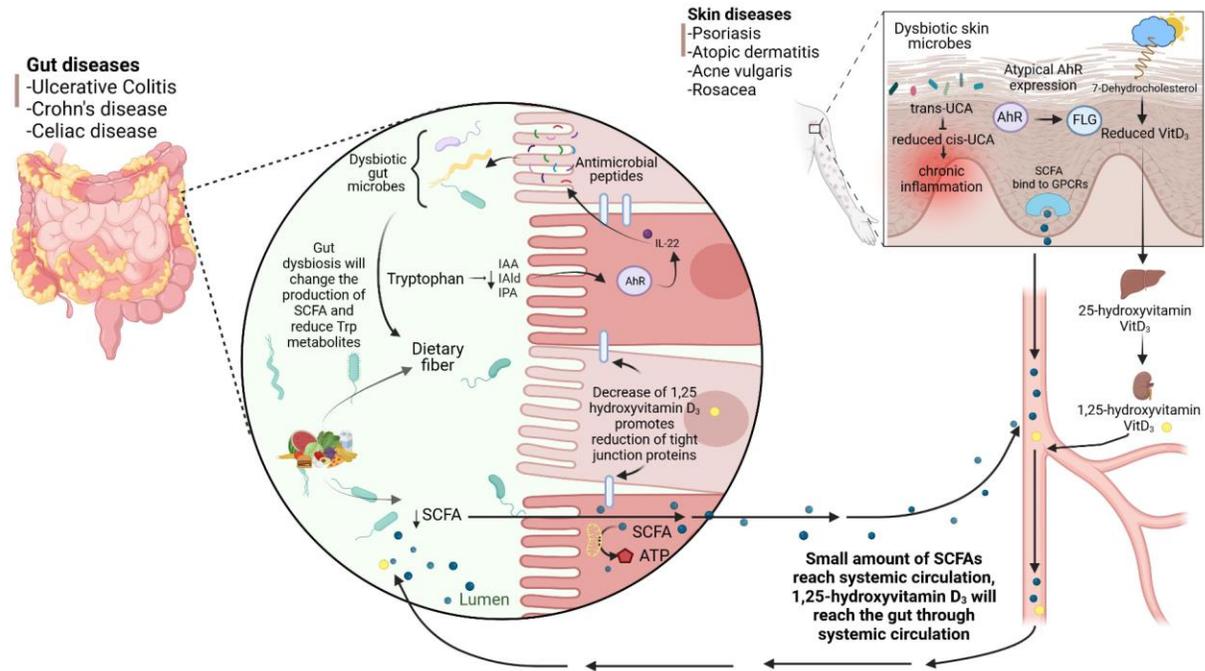
Beyond the gut - Explorando las fronteras entre las IMiDs.

Pregunta 3. ¿Cuáles son los mecanismos comunes que permiten la asociación entre EII y psoriasis en un mismo paciente?

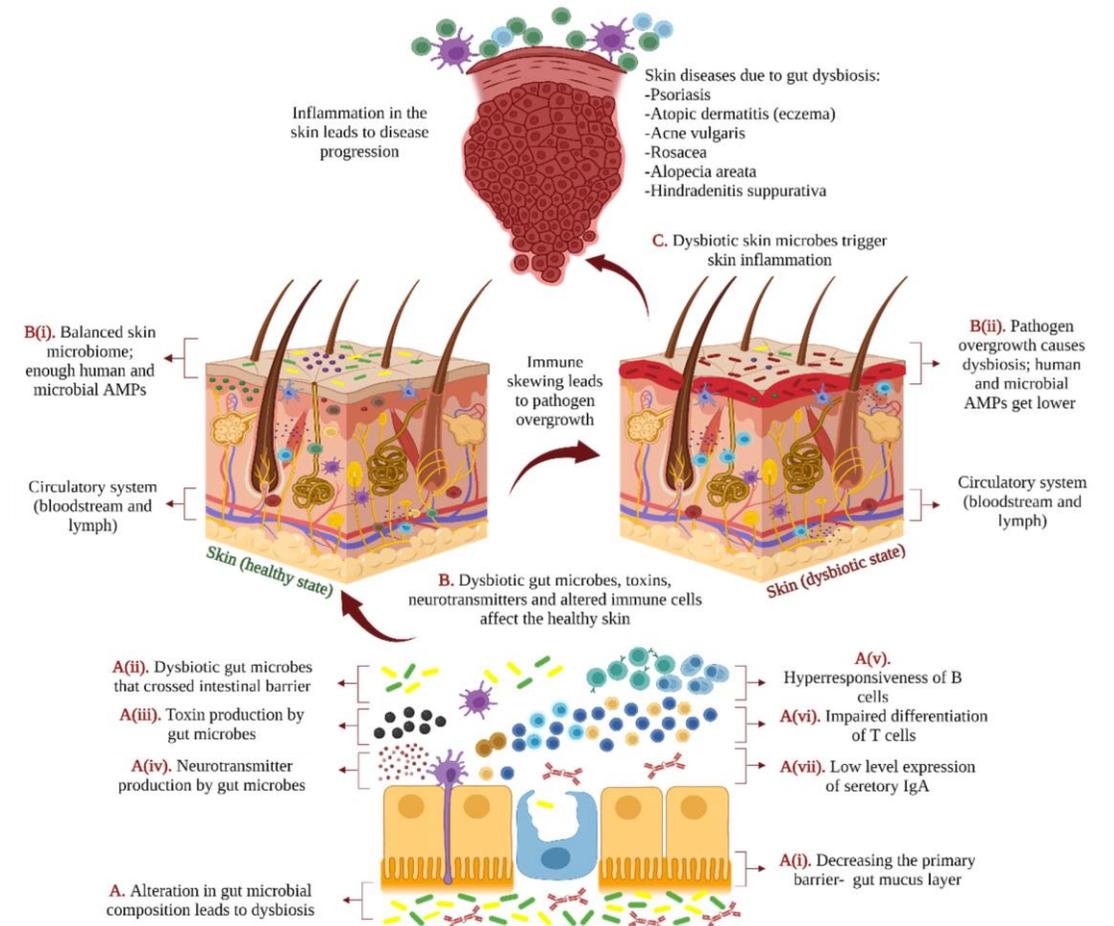
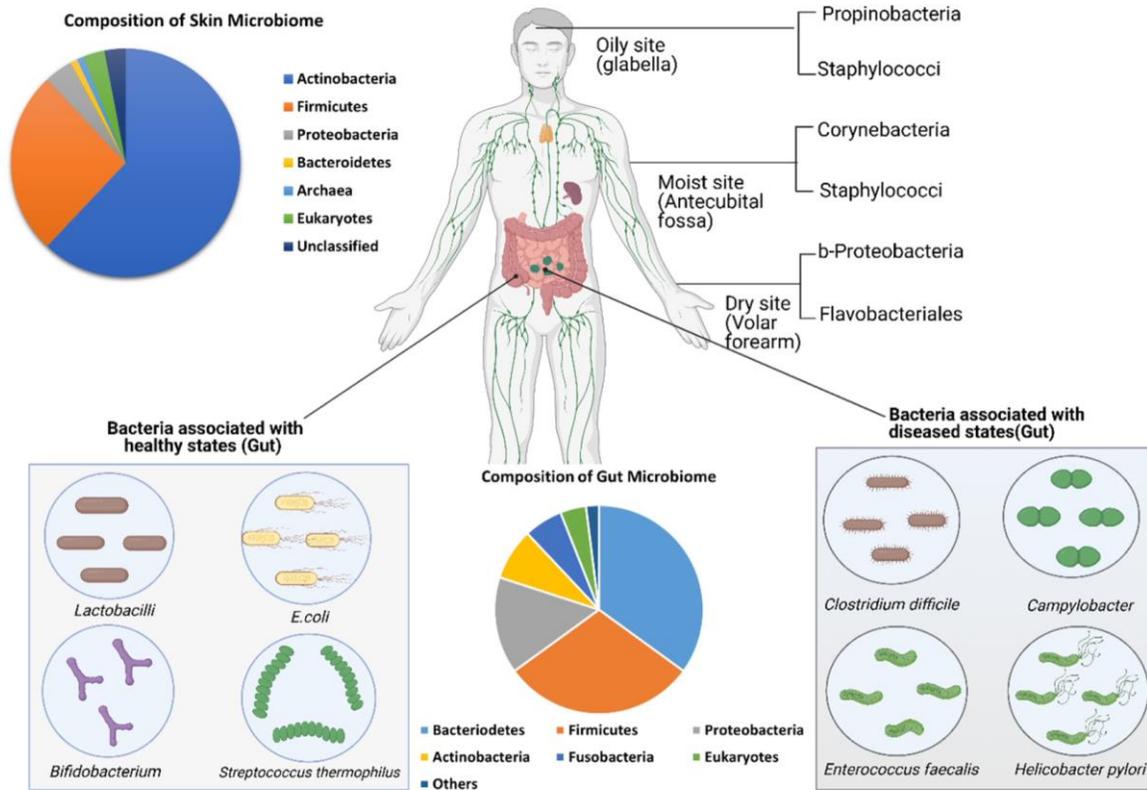
Environmental triggers of epithelial disruption



Microbiota-driven relationship between IBD and Pso



Microbial composition of gut and skin and mechanisms of interaction



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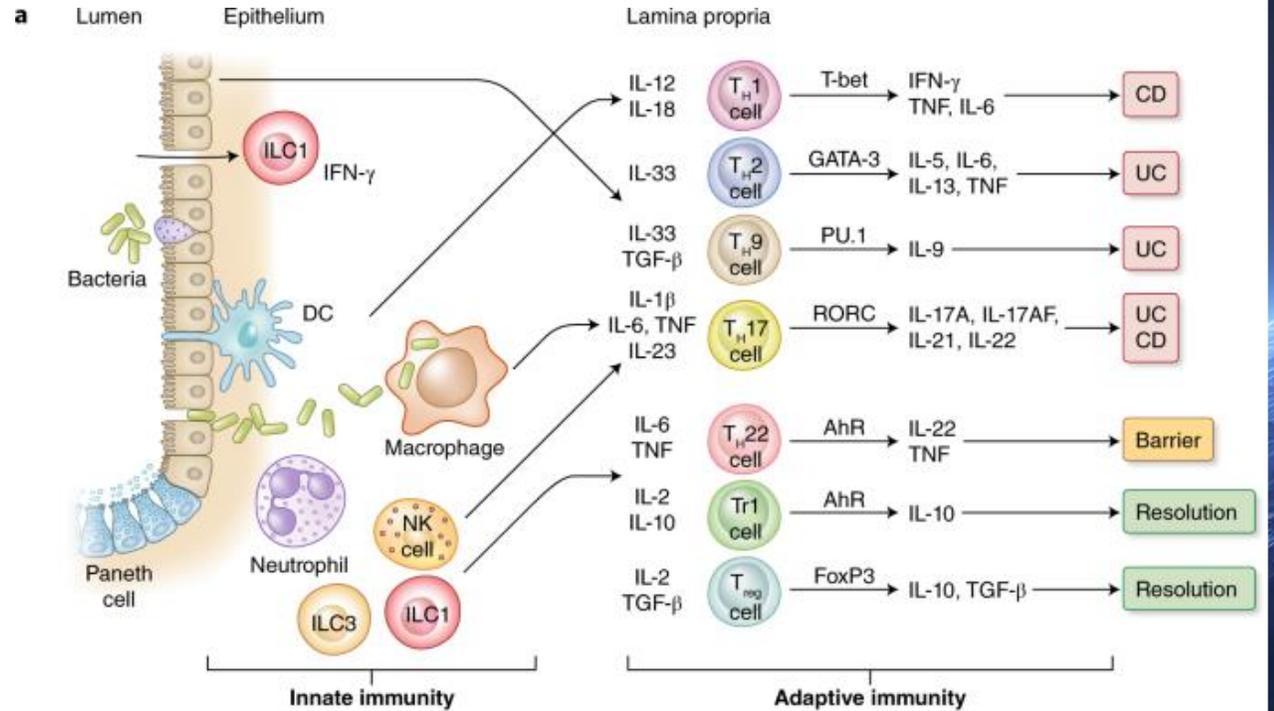
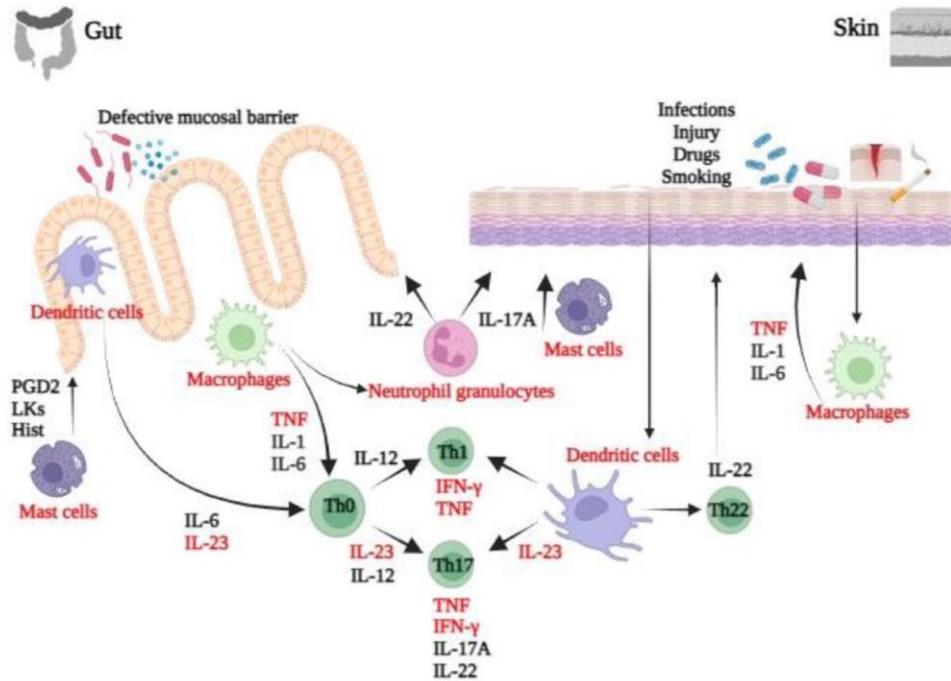
Pregunta 4 ¿Qué alternativas terapéuticas pueden combatir ambas entidades?

¿Puede llegar a ser razonable combinar tratamientos?

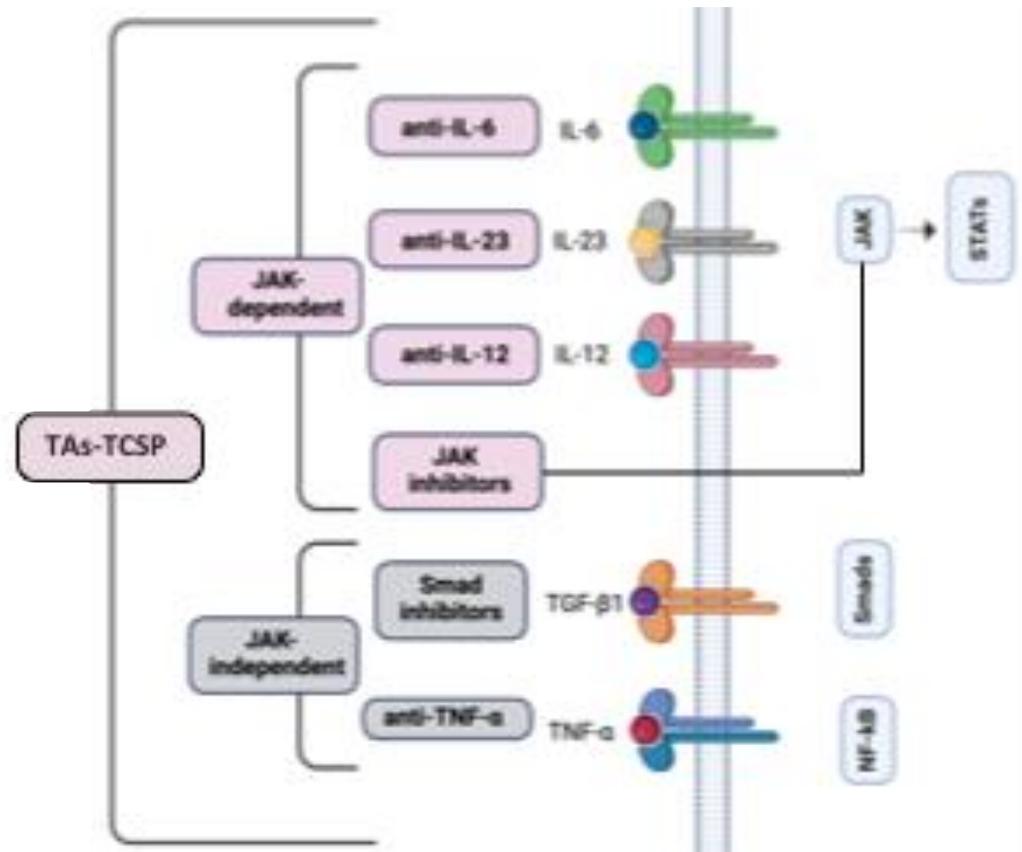
Preferred, alternative and avoidable therapies

		Preferred medication option	Alternative medication option	Medications to avoid
Cardiovascular diseases	 HF (NYHA Functional Class III and IV)	<ul style="list-style-type: none"> • Anti-integrin • Anti-interleukins 	<ul style="list-style-type: none"> • JAK inhibitors 	<ul style="list-style-type: none"> • Anti-TNF
	 Vasculopathy and Coronary Disease	<ul style="list-style-type: none"> • Anti-TNF • Anti-integrin • Anti-interleukins 		<ul style="list-style-type: none"> • JAK Inhibitors
Malignancy diseases	 Solid Tumors	<ul style="list-style-type: none"> • Anti-integrin • Anti-interleukins • S1p modulators 	<ul style="list-style-type: none"> • Anti-TNF • JAK inhibitors 	Avoid Advanced Therapies During Chemotherapy
	 Melanoma or Lymphoma	<ul style="list-style-type: none"> • Anti-integrin • Anti-interleukins 	<ul style="list-style-type: none"> • JAK inhibitors 	<ul style="list-style-type: none"> • Anti-TNF • S1p modulators • Thiopurines (in lymphoma)
Joint's EIM	 Axial spondyloarthritis	<ul style="list-style-type: none"> • Anti-TNF 	<ul style="list-style-type: none"> • JAK inhibitors 	
Skin EIM	 <ul style="list-style-type: none"> • Psoriasis • Hidradenitis Suppurativa 	<ul style="list-style-type: none"> • PsO or PsA: Anti-interleukines • HS: Anti-TNF 	<ul style="list-style-type: none"> • Anti-TNF • JAK inhibitors 	Avoid Anti-TNF in Anti-TNF-Induced Paradoxical Psoriasis
Recurrent infections	 Recurrent Infections and Increased Infection Susceptibility	<ul style="list-style-type: none"> • Anti-integrin • Anti-interleukins • S1p modulators 		<ul style="list-style-type: none"> • Anti-TNF • JAK inhibitor (if an Effective Alternative is Available)
Age	 Elderly Individuals	<ul style="list-style-type: none"> • Anti-integrin • Anti-interleukins 	<ul style="list-style-type: none"> • Anti-TNF • S1p modulators 	<ul style="list-style-type: none"> • Thiopurines • JAK inhibitors
Pregnancy	 Pregnancy or Conception Planning	<ul style="list-style-type: none"> • Anti-TNF • Anti-integrin • Anti-interleukin 12/23 	<ul style="list-style-type: none"> • Anti-interleukin 23 	<ul style="list-style-type: none"> • Methotrexate • JAK Inhibitor • S1p modulators

Common immune pathways



Combined advanced therapy



Hay que ponerse de acuerdo

- Se suspendió el antiTNF y se propusieron tratamientos tópicos e incluso fototerapia, sin demasiada mejoría
- Su dermatóloga pondera su buena experiencia tratando este tipo de psoriasis con anti-IL17, y argumenta que el paciente se encuentra bien de su EII en este momento.

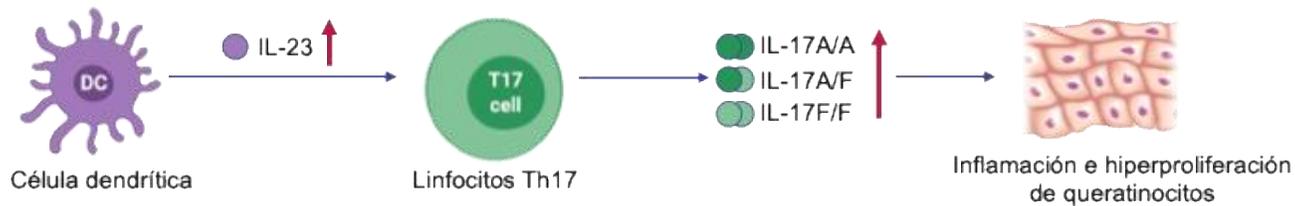


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Pregunta 5 ¿Es buena idea plantear un tratamiento anti IL17?

¿Cuál sería la justificación inmunopatológica?

Th-17 pathway in IBD and Psoriasis



Drug	IBD	Cancer	HF	DM	Obesity	Depression	KD	MS	Lupus
Infliximab	++	+/-	P/C	++	+	+	++	C	-
Adalimumab	++	+/-	P/C	++	+	++	++	C	-
Etanercept	+								
Certolizumab pegol	++								
Brodalumab	NR								
Ixekizumab	P								
Secukinumab	NR								
Guselkumab	+								
Risankizumab	+								
Ustekinumab	++								
Tildrakizumab	+	+	++	?	++	?	++	+	+

DOCUMENTO DE CONSENSO

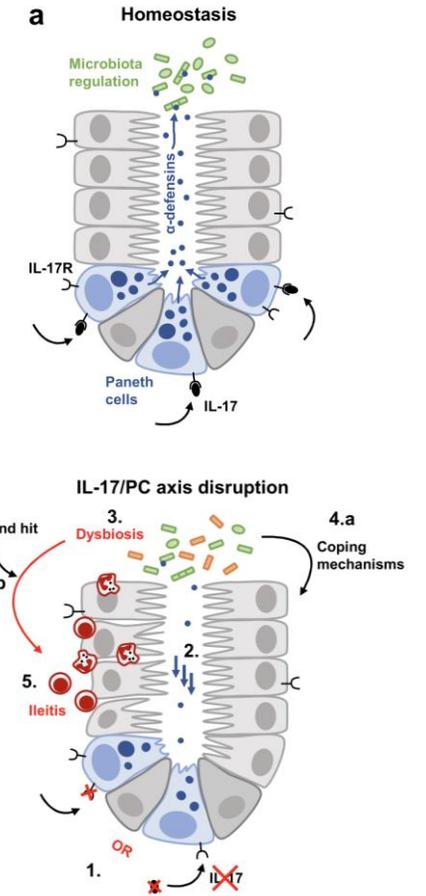
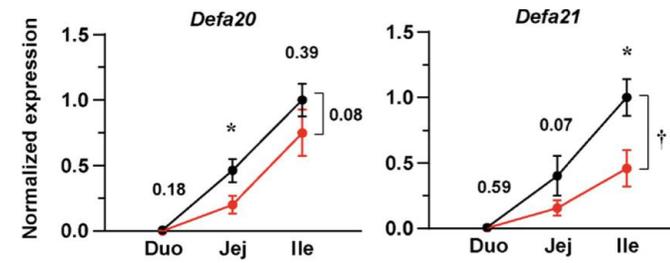
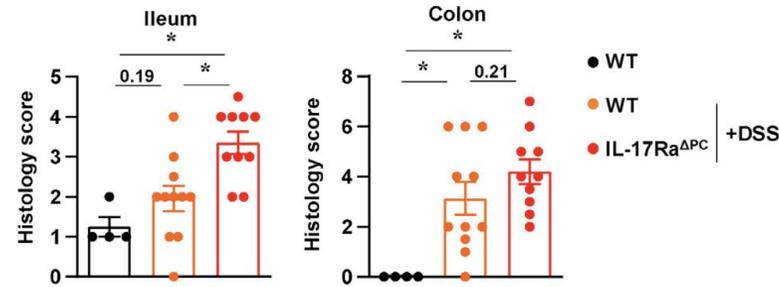
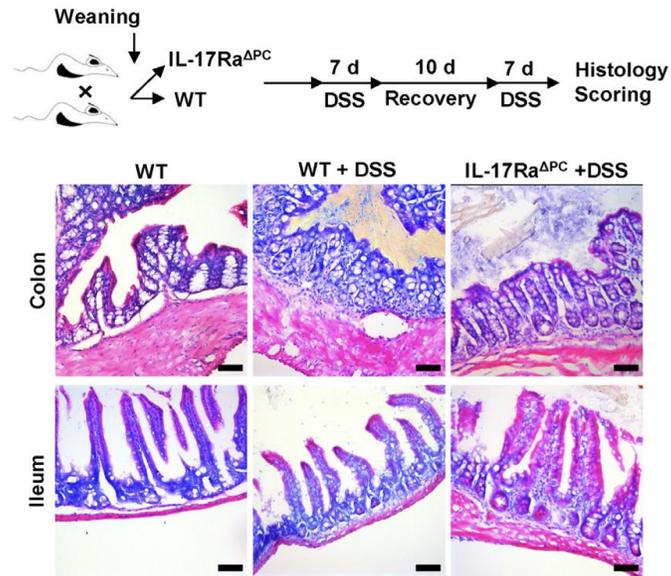
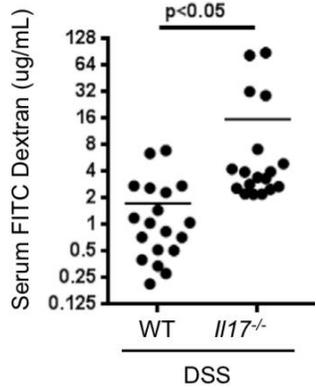
DOI: 10.1016/j.ad.2022.01.024 [Open Access](#)

Actualización práctica de las recomendaciones del Grupo de Psoriasis de la Academia Española de Dermatología y Venereología (GPS) para el tratamiento de la psoriasis con terapia biológica. Parte 2 «Manejo de poblaciones especiales, pacientes con comorbilidad y gestión del riesgo»

Practical Update of the Guidelines Published by the Psoriasis Group of the Spanish Academy of Dermatology and Venereology (GPs) on the Treatment of Psoriasis With Biologic Agents: Part 2 — Management of Special Populations, Patients With Comorbid Conditions, and Risk

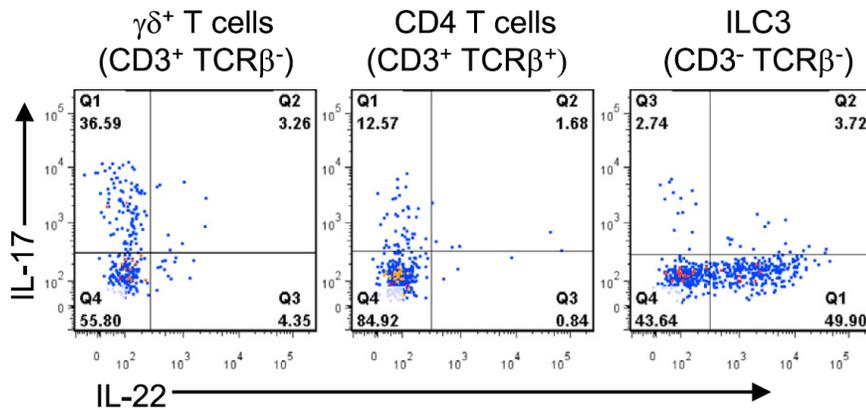
Role of IL-17 in epithelial protection

Regulation of gut permeability and stimulation of anti-microbial peptides by PCs

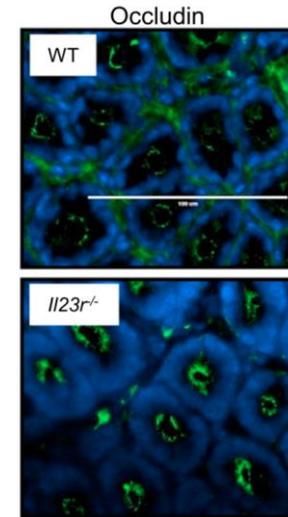
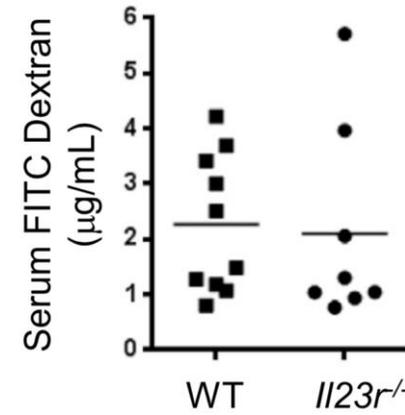
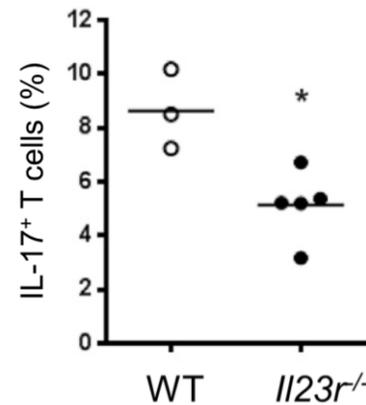


Do IL-17 and IL-23 belong together?... Not always

Different cellular sources of IL-17

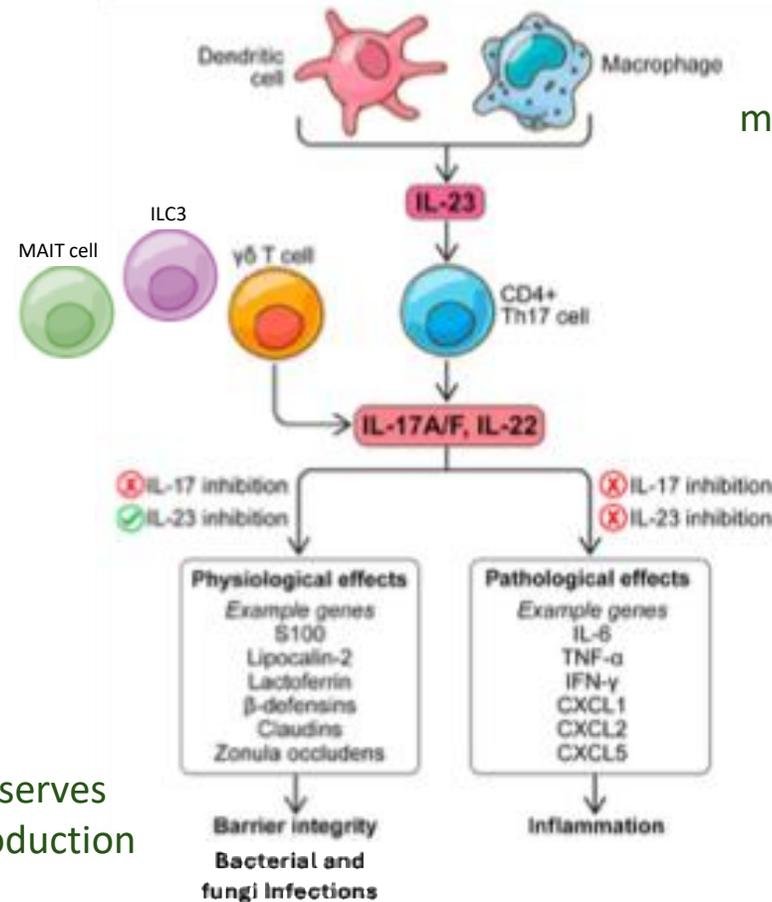


IL-17 does not require IL-23 in all cases.
Lack of IL23R improves barrier function



Do IL-17 and IL-23 belong together?... Not always

Innate cell types can produce IL-17 regardless IL-23



IL-23 is produced by DCs, macrophages and neutrophils and it licenses IL-17 production by Th17 cells

Anti-IL-23 preserves innate IL-17 production

Anti-IL-23 inhibits pathogenic Th17 expansion

Hay que ponerse de acuerdo

- Finalmente se inició tratamiento **Guselkumab**, con buena respuesta desde el punto de vista dermatológico.
- Al cabo de un año, el paciente persiste en remisión profunda de su EI.



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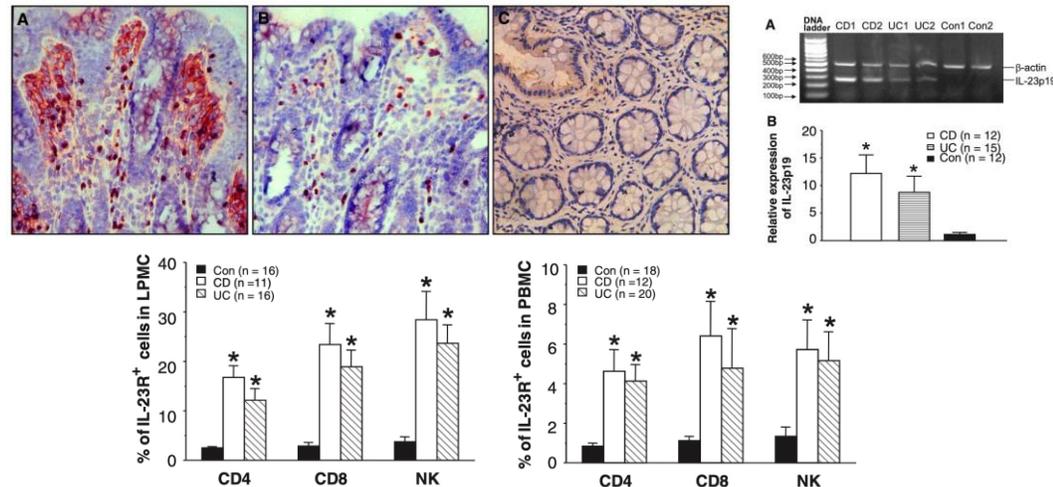
Beyond the gut - Explorando las fronteras entre las IMiDs.

Pregunta 6. ¿Qué está pasando?

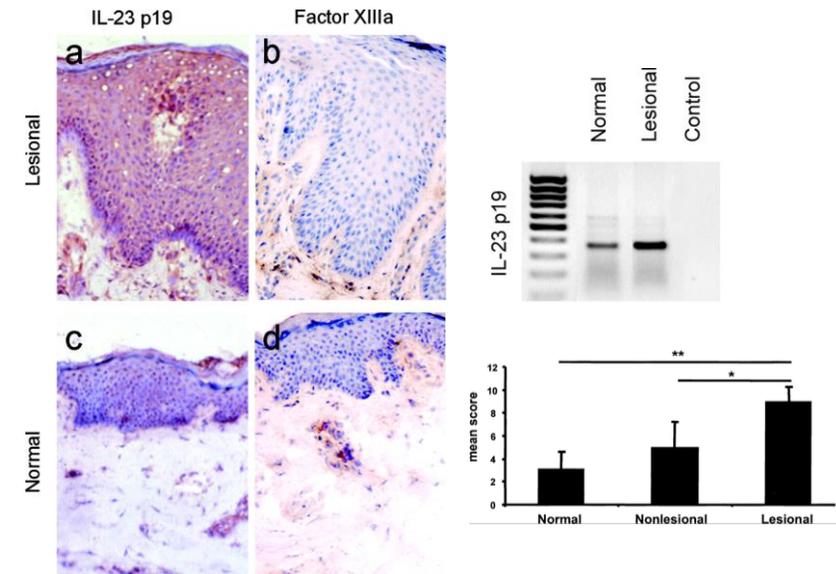
¿Por qué bloquear la IL23 favorece la resolución de ambas entidades?

IL-23 in inflamed tissue in IBD and Psoriasis

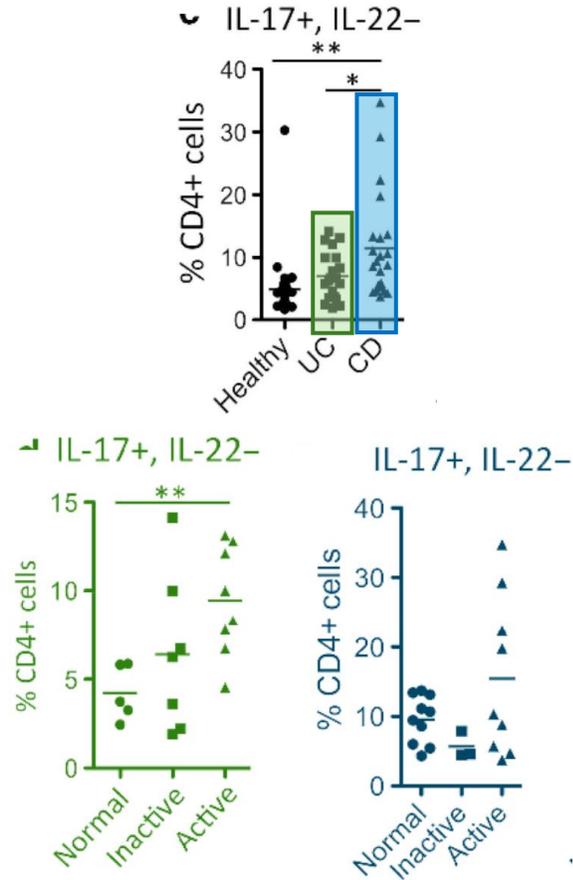
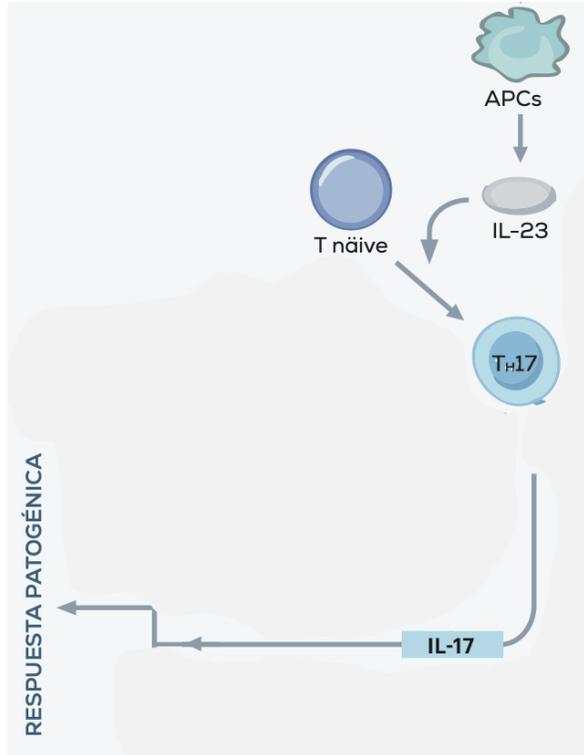
IL-23 is highly expressed in inflamed mucosa of IBD



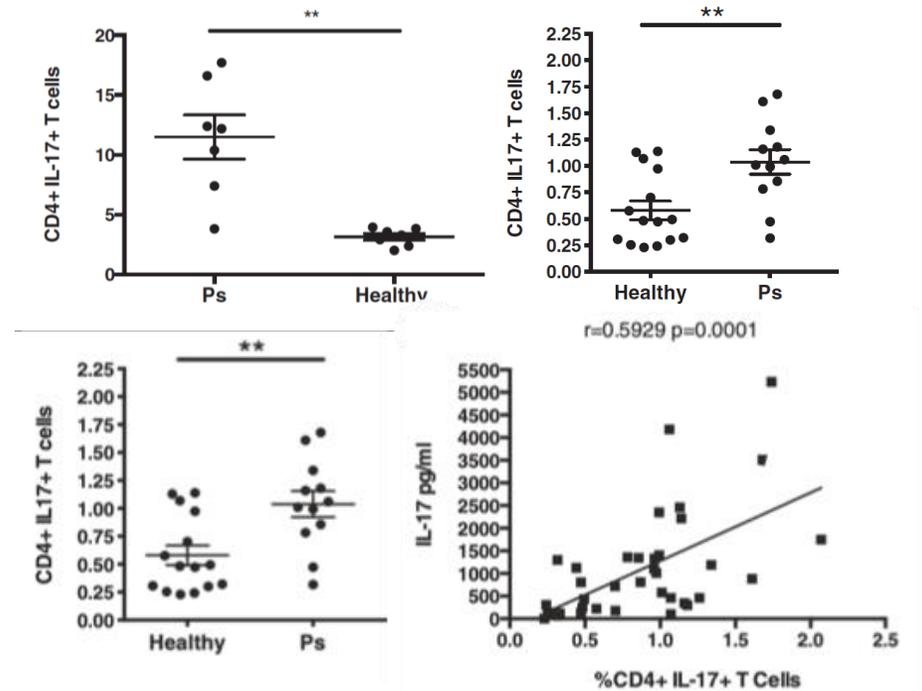
IL-23 is increased in lesional tissue in Psoriasis



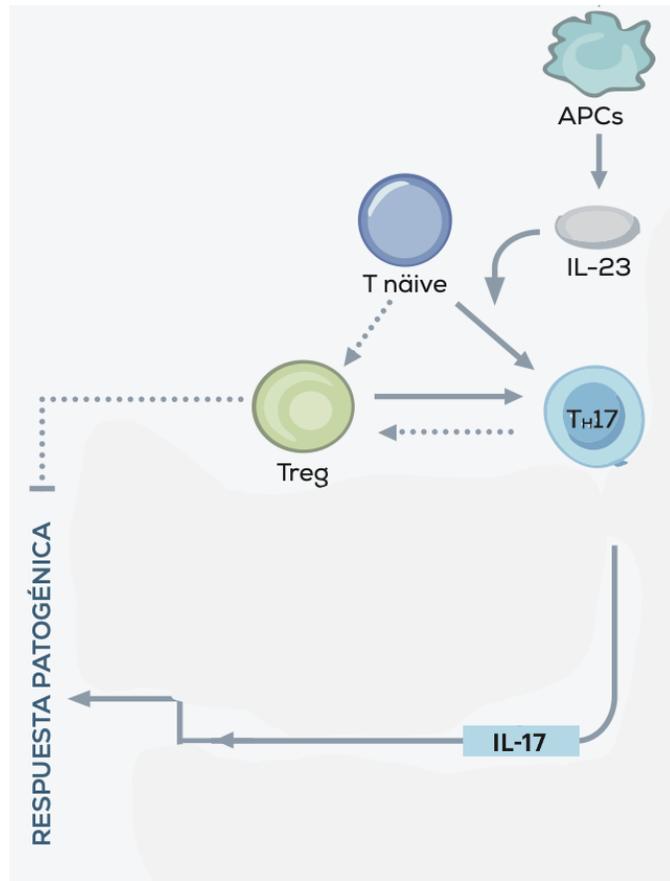
Th-17 drives inflammation during IBD and Pso



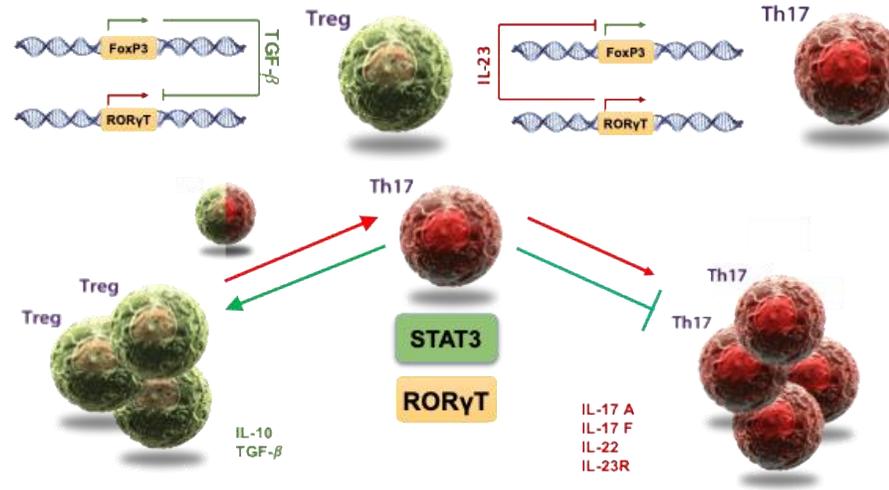
Th17 cell increase in skin and peripheral blood of Pso patients



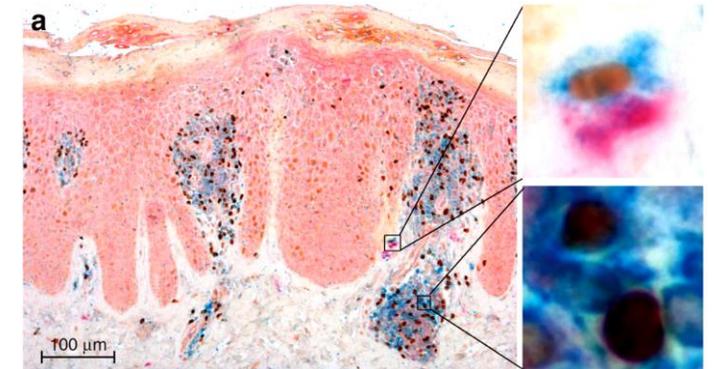
Regulatory T cell activity inhibition during chronic inflammation



Th17 – Treg plasticity



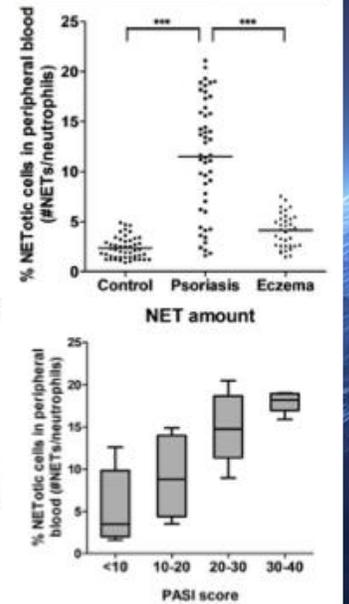
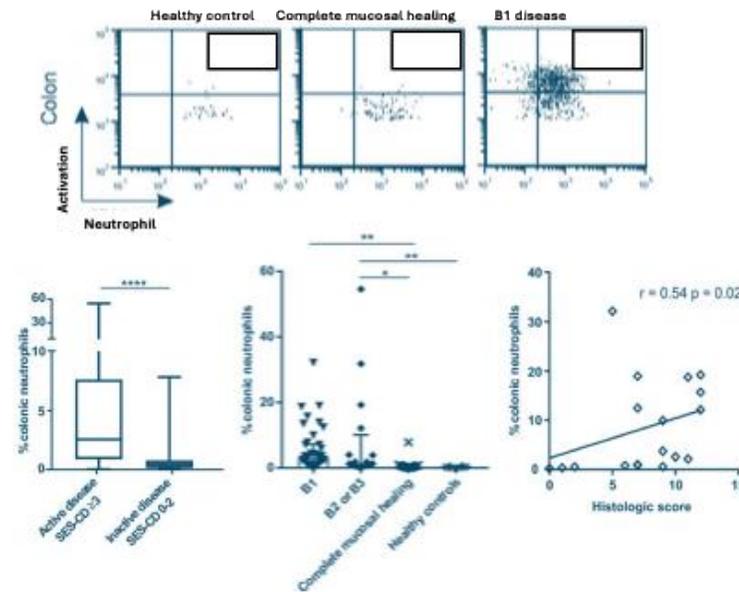
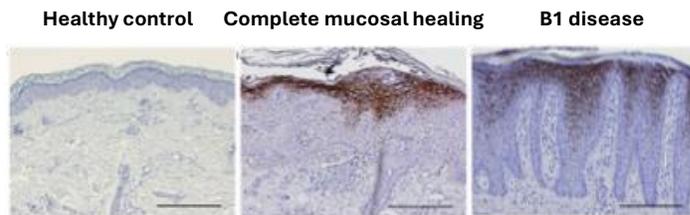
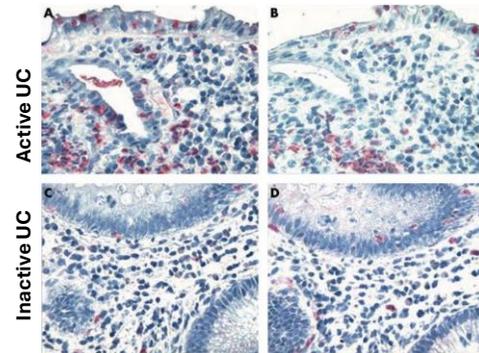
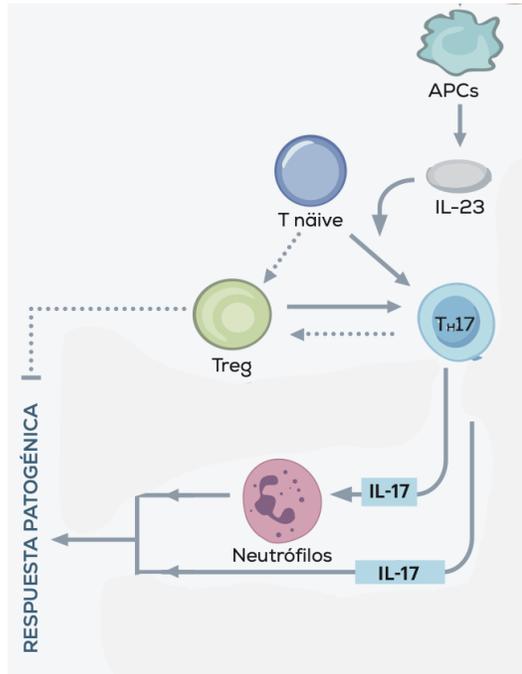
Foxp3+ Regulatory T Cells of Psoriasis Patients Easily Differentiate into IL-17A-Producing Cells and Are Found in Lesional Skin



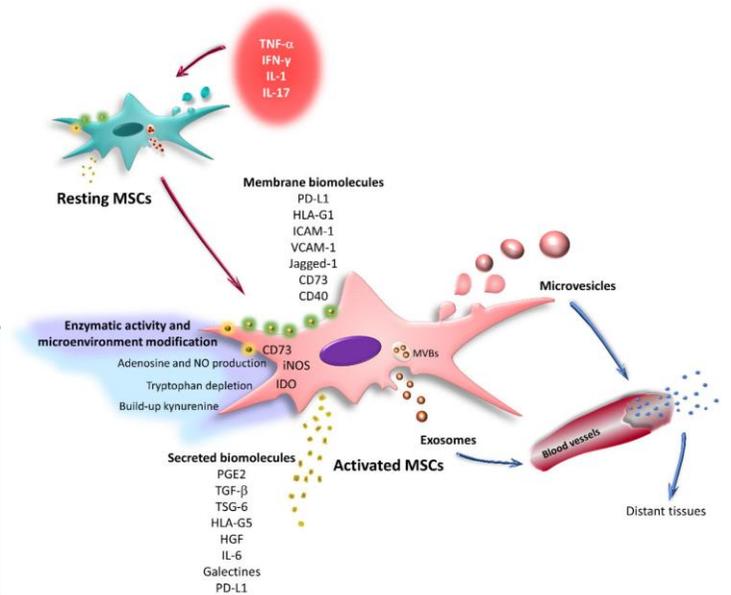
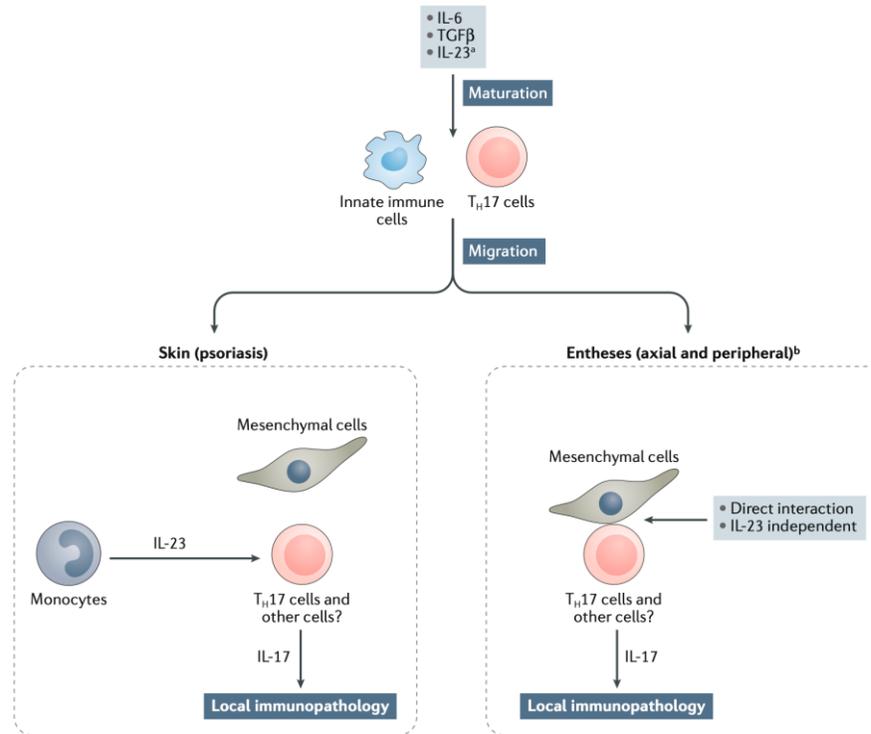
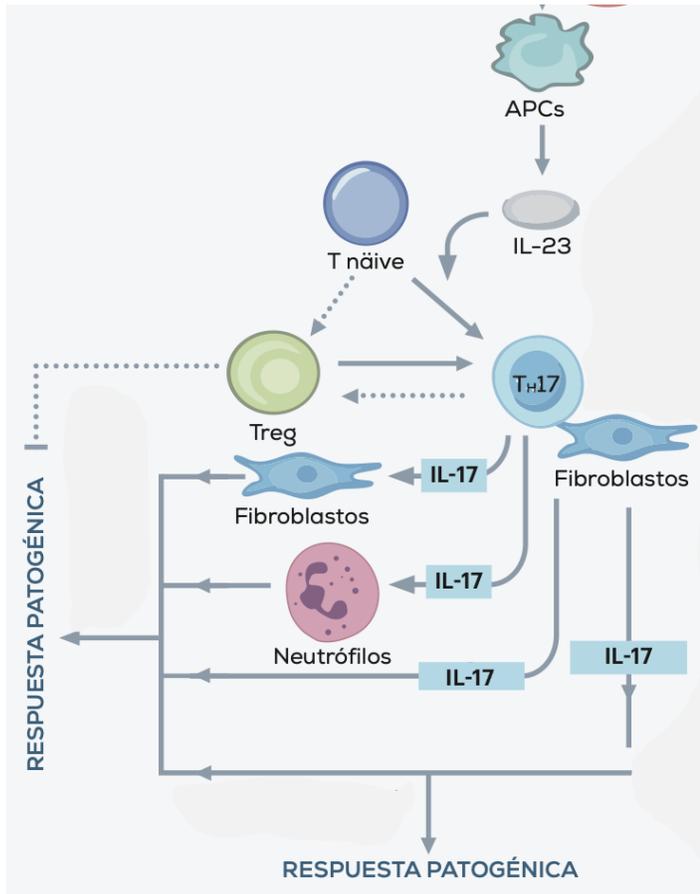
Sustained neutrophil activation

LP neutrophil infiltration in IBD

Recruitment of activated neutrophils correlates with disease severity in adult Crohn's disease



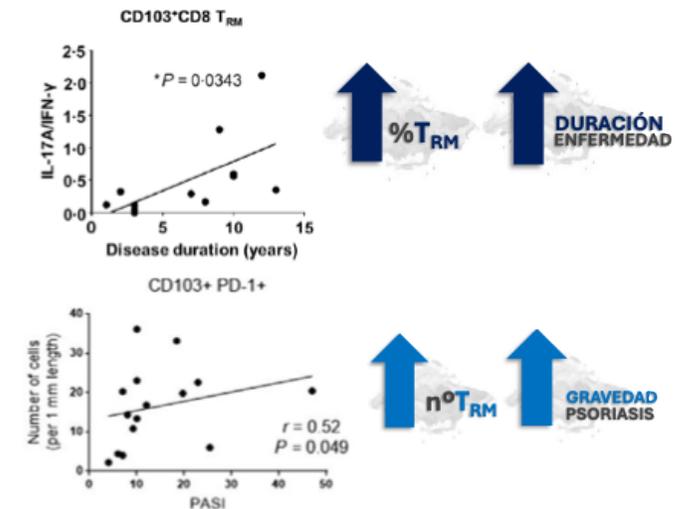
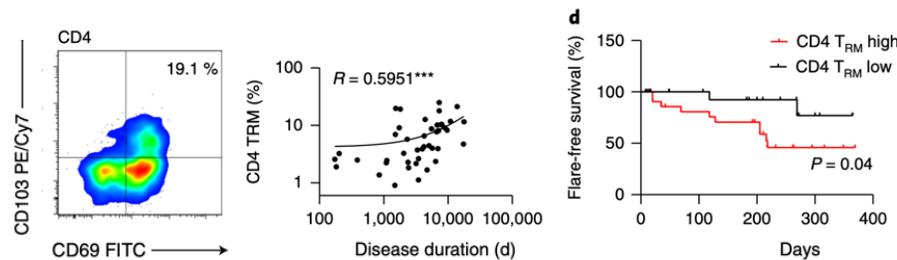
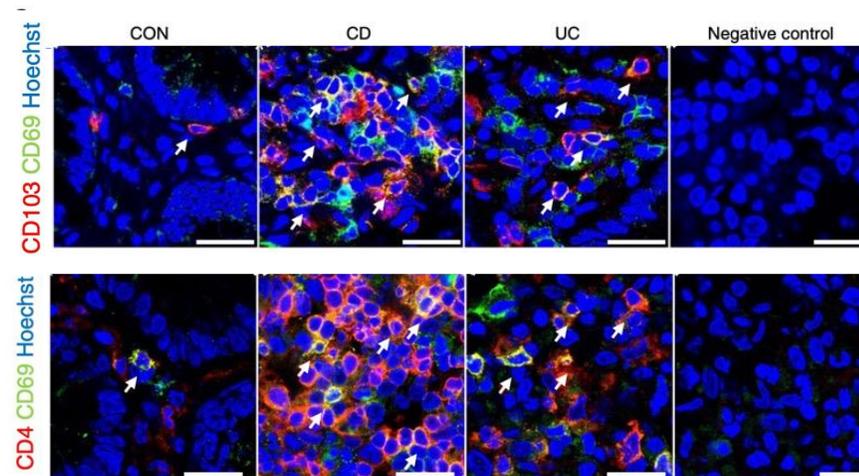
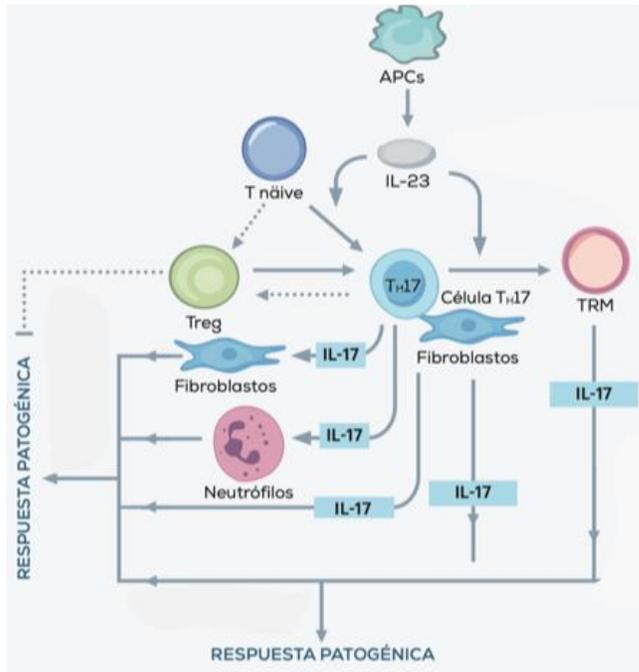
IL-17 induced fibroblast activation



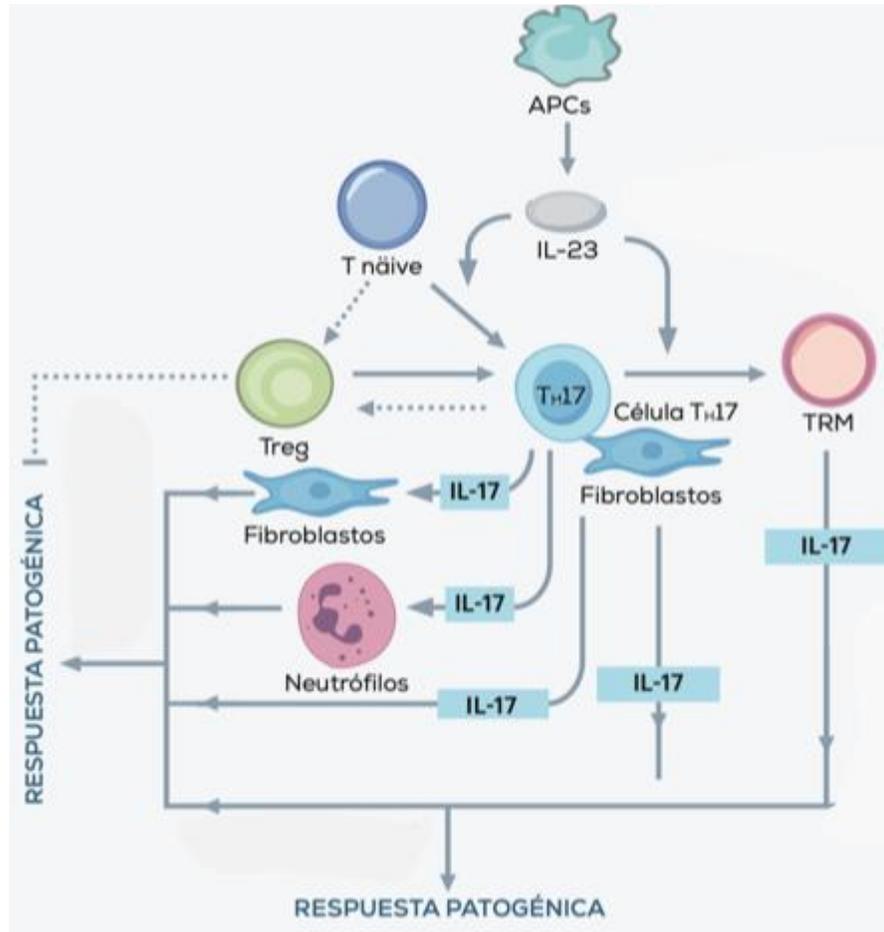
Resident memory T cells in IBD and Psoriasis

CD4+ intestinal TRM cells are associated with clinical flares of IBD

Correlation between T_{RM} cells, psoriasis duration and severity



Inflammatory breakdown during IL-23 antagonism



Inhibits functional Th-17 expansion (IL17-producing CD4⁺ cells)

Induces tolerogenic regulatory T cells

Reduces neutrophil and stromal cell activation

Limits Th17 differentiation into tissue resident memory T cells (TRM)

Conclusions on the Gut-Skin Axis



Psoriasis is a frequent comorbidity in IBD (shared genetic and environmental triggers).



Paradoxical Pso may be induced by biologic therapy (mainly antiTNF). Alternative immune circuits involved.



Adaptive Th17 is expanded in IBD and Psoriasis (Anti-ILs available).



Anti-IL23 breaks down the (multiple) inflammatory cascade in IBD and Pso, preserving the physiological activity of IL-17 at the gut epithelial tissue.

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¡GRACIAS!

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Proyecto



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Workshop EII - Espondiloartritis

Luis Menchén & Azucena Salas

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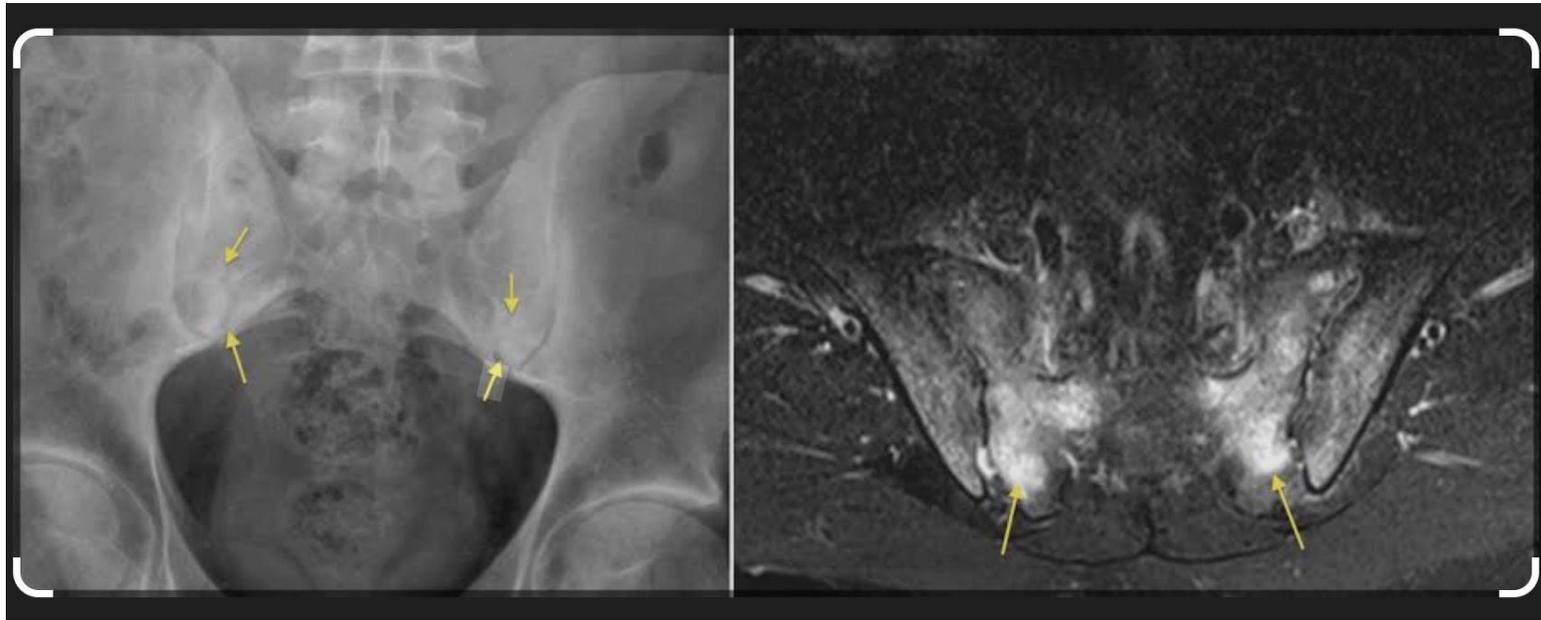
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Proyecto



Caso clínico

- Varón de 29 años. Fumador de 20 cig/d
- Diagnosticado de **Sacroilitis radiológica** hace 4 años. Curso clínico leve. HLA-B27
- Tratamiento con AINEs a demanda



Caso clínico

- **Anemia** ferropénica y por déficit de vitamina B12 en análisis de control
- Asintomático desde el punto de vista digestivo
- Aparición de artralgia con semiología inflamatoria en rodilla izda. y entesitis de talón dcha.
- **Calprotectina fecal 860**
- **Colonoscopia** sugestiva de enfermedad de Crohn ileocólica leve

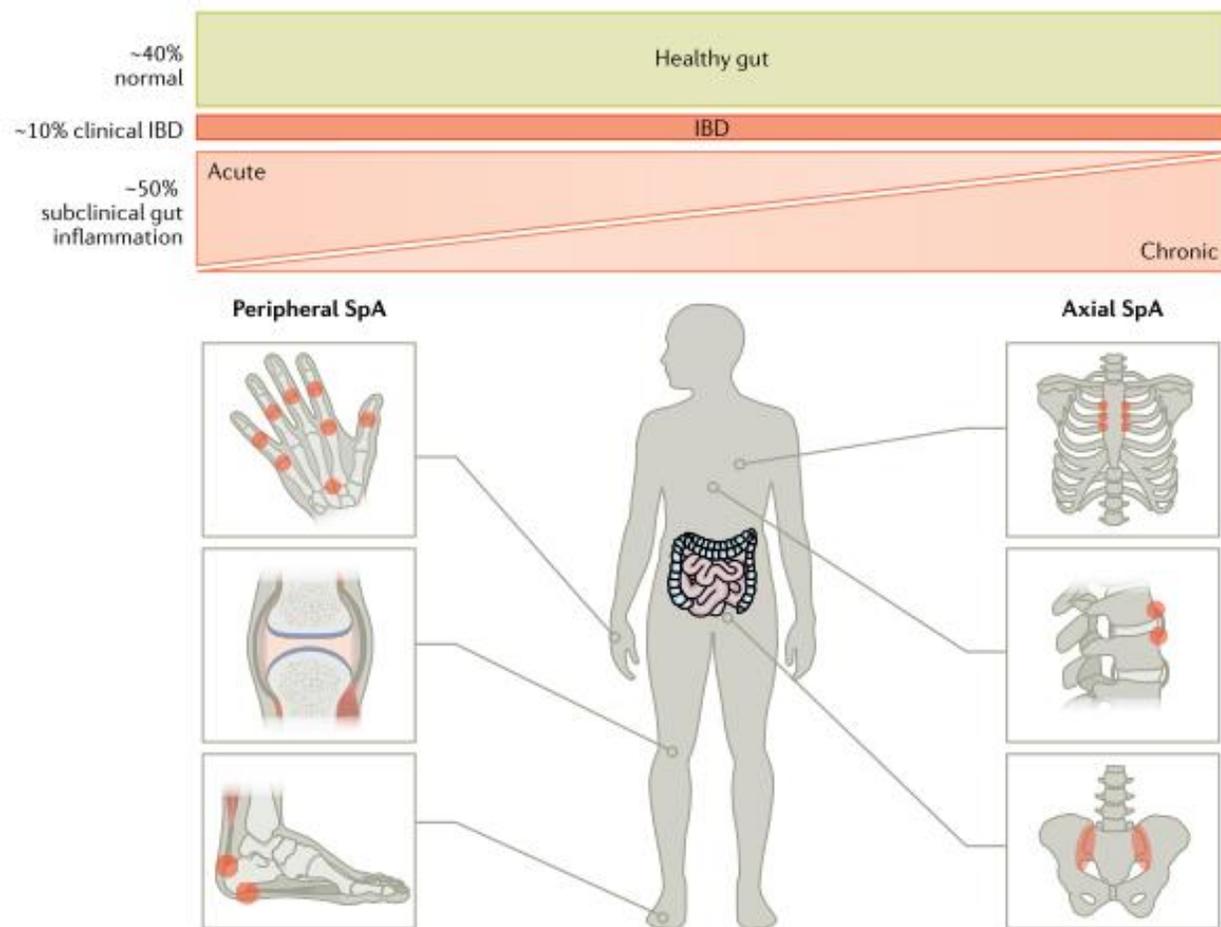


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Pregunta 1.

¿Existen bases genéticas que justifiquen la asociación de EII y las SpA?

EII y Espondiloartritis: influencia genética



- Los estudios GWAS demuestran un **importante solapamiento** entre la EII y la Espondilitis Anquilosante y otras espondiloartritis a nivel genético.
- La **Espondilitis Anquilosante** es una de las enfermedades inflamatorias con más carga genética: se estima una heredabilidad de >90%, siendo **HLA-B27** el gen más significativo para la Espondiloartritis. Sin embargo **HLA-B27 no se asocia a EII**.
- Polimorfismos en el gen **IL23R** se **asocian a ambas patologías**.

IL-23 signalling	IL12RB	T _H 17 cell differentiation	CCR6
	STAT3		FOSL2
	IL12B (IL-12p40)		TNFRSF6 (DR3)
	IL23R		TNFSF15 (TL1A)
	JAK2		VDR
TYK2	GPR65		
Effector cytokines	IL21		IL1R2
	IL22		IL6R
	IL27		RORC (ROR γ t)
Recruitment	CCR2		IL1R1
	CCR6		
	ITGA4 (α 4 integrin)		

Barrier repair and integrity	OSM
	OSMR
	PTGS2 (COX2)
	GPR35
	NKX2-3
	PTGER4 (EP4)
Mucus production and bacteria interaction	PTPN2
	TNFRSF1A (TNFRI)
	ITLN1
	MUC19
	ZFP36L1 (butyrate response factor)
	FUT2

Cell development	NFIL3	Antigen processing and presentation	HLA-C
	PRDM1 (BLIMP1)		ERAP2
	BACH2		ERAP1
	ETS1		HLA-B (HLAB27)
	EOMES		NPEPPS
	RUNX3		
Activation	TBX21 (T-bet)		
	IL18R1		
	IL18RAP		
	IL7R (CD127)		

Osteoclast and/or osteoclast function	TNFSF11 (RANKL)
	PTGER4 (EP4)
	PTGS1 (COX1)
	TNFRSF11A (RANK)
BMP or TGF β signalling	SMAD7
	SMURF1
	TAB1
	SMAD3

■ Genes associated with Crohn's disease
■ Genes associated with both Crohn's disease and AS
■ Genes associated with AS

Autophagy	ATG16L1	NF- κ B regulation	MAP3K7IP2 (TAB2)
	ATG4B		NFKB2
	LRRK2		RELA (NFKB3)
	IRGM		TRAF3IP2
PRR	CARD9		NFKBIA
	LACC1		TLR4
	NOD2 (CARD15)	TNFAIP3 (A20)	
	RIPK2	NFKB1	
	IFIH1 (MDA5)		
Myeloid cell function		CCL2	
		CCR2	
		SKAP2	
		CXCR2 (IL8RB)	
		MST1	
		NOS2	
	SH2B3 (LNK)		

Gracey E et al. Nat Rev Rheumatol 2020

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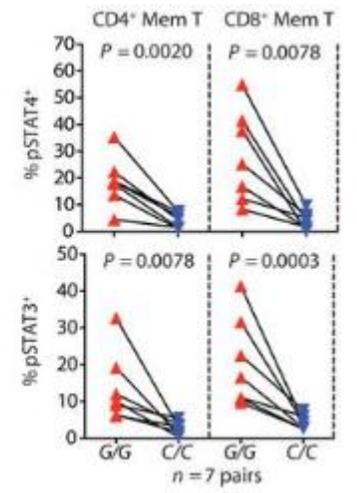
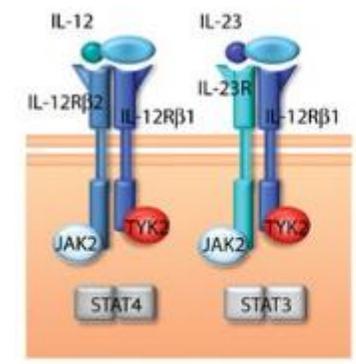
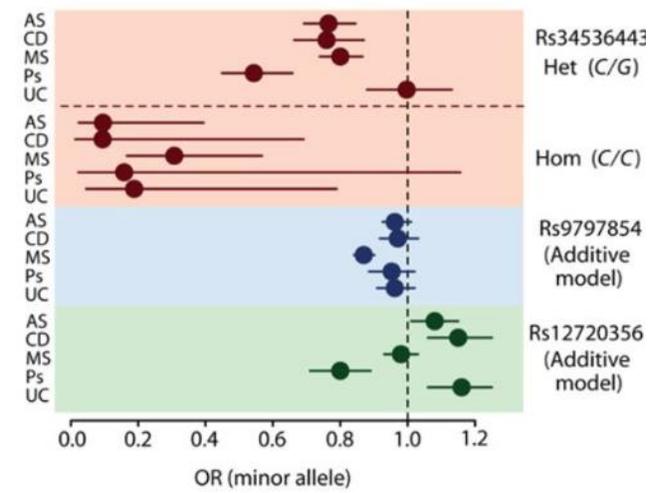


Loss of function Tyk2 mutations have a protective effect

IL-23 signalling	T _H 17 cell differentiation
IL12RB	CCR6
STAT3	FOSL2
IL12B (IL-12p40)	TNFRSF6 (DR3)
IL23R	TNFSF15 (TL1A)
JAK2	VDR
TYK2	GPR65
Effector cytokines	IL17 cell differentiation
IL21	IL1R2
IL22	IL6R
IL27	RORC (ROR γ t)
Recruitment	IL1R1
CCR2	
CCR6	
ITGA4 (α 4 integrin)	

■ Genes associated with Crohn's disease
■ Genes associated with both Crohn's disease and AS
■ Genes associated with AS

Genetic associations in the TYK2 gene region across AIDs



Rs34536443 is associated with decreased pSTAT positivity in response to type I IFN, IL-12 and IL-23.

Gracey E et al. Nat Rev Rheumatol 2020

Dendrou CA et al Science Trans Med 2016

Caso clínico

- Inicio de tratamiento con infliximab 5 mg/kg en sem. 0-2-6 y mantenimiento cada 8 semanas
- Respuesta clínica articular favorable: ausencia de dolor axial, mejoría clínica articular periférica
- Calprotectina sem. 12: 134

INMUNAUTAS

Beyond the gut - Explorando las fronteras entre las IMIDs.

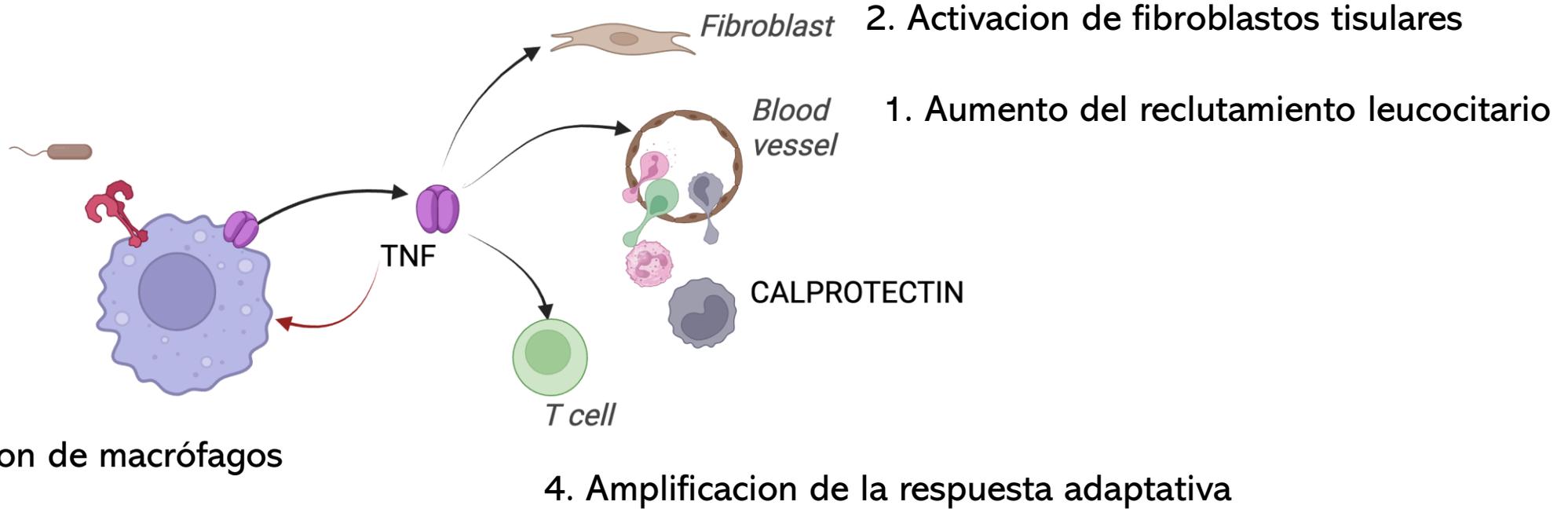
Pregunta 2. ¿Existen mecanismos inmunopatogénicos comunes entre ambas entidades?

Fármacos en uso en EI y SpA

Target	Drug class	Therapeutics	Approval status			
			Peripheral SpA	Axial SpA	Crohn's disease	Ulcerative colitis
TNF	mAb	Adalimumab; infliximab; certolizumab; golimumab	Approved by the FDA and/or EMA	Approved by the FDA and/or EMA	Approved by the FDA and/or EMA (only adalimumab, infliximab and certolizumab)	Approved by the FDA and/or EMA (only adalimumab, infliximab and golimumab)
p40 subunit (IL-12/IL-23)	mAb	Ustekinumab	Approved by the FDA and/or EMA	Not effective	Approved by the FDA and/or EMA	Approved by the FDA and/or EMA
p19 subunit (IL-23)	mAb	Risankizumab	Approved by the FDA and/or EMA	Not effective	Approved by the FDA and/or EMA	Ongoing phase III clinical trial
JAK1 and JAK3	Small molecule	Tofacitinib	Approved by the FDA and/or EMA	Approved by the FDA and/or EMA	Not effective	Approved by the FDA and/or EMA
JAK1	Small molecule	Upadacitinib	Approved by the FDA and/or EMA	Approved by the FDA and/or EMA	Phase III clinical trial with positive results	Approved by the FDA and/or EMA

IBD, inflammatory bowel disease; JAK, Janus kinase; mAb, monoclonal antibody; SpA, spondyloarthritis.

TNF: ¿Por qué su bloqueo es tan efectivo?



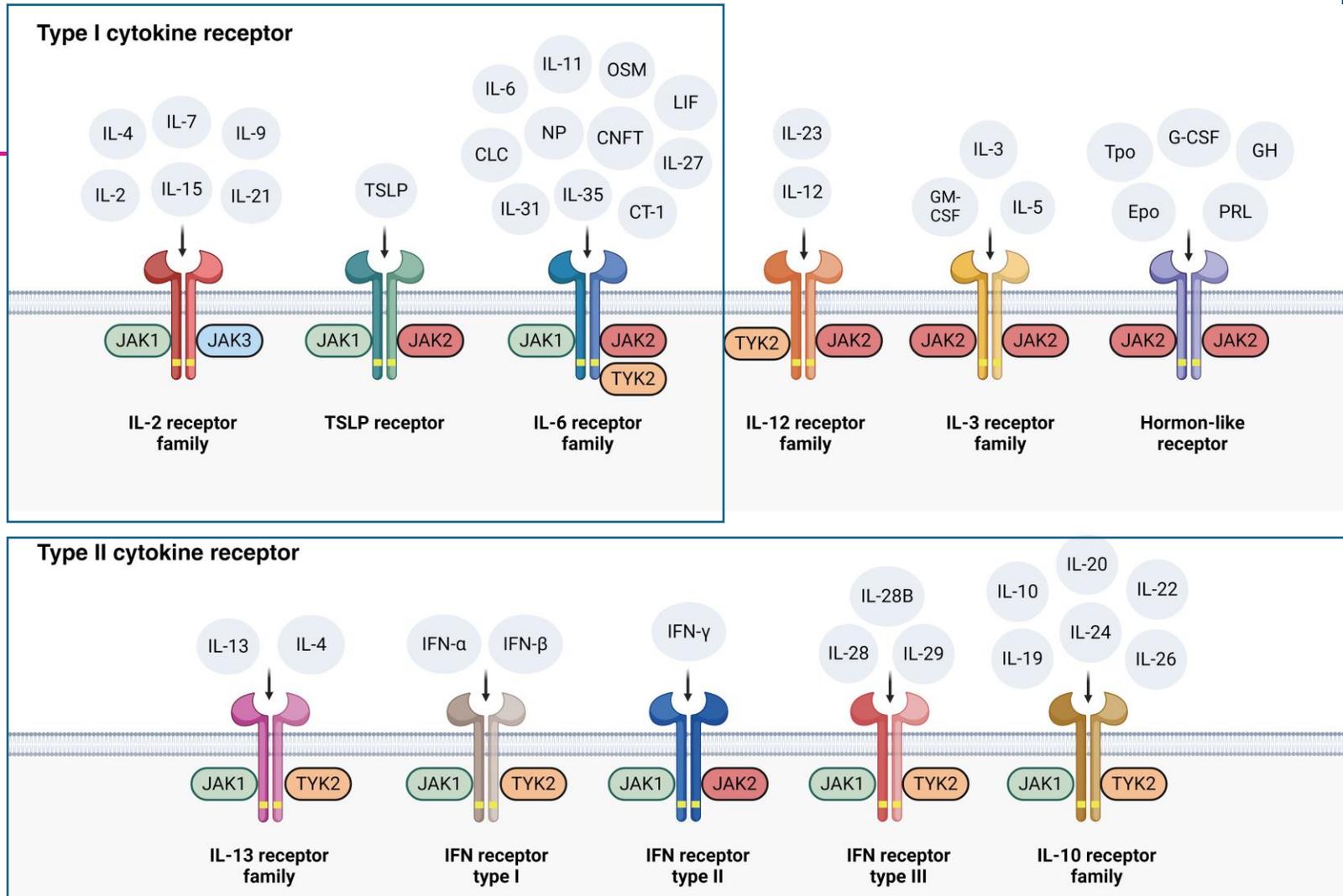
3. Activacion de macrófagos

4. Amplificacion de la respuesta adaptativa

Fármacos en uso en EI y SpA

Target	Drug class	Therapeutics	Approval status			
			Peripheral SpA	Axial SpA	Crohn's disease	Ulcerative colitis
TNF	mAb	Adalimumab; infliximab; certolizumab; golimumab	Approved by the FDA and/or EMA	Approved by the FDA and/or EMA	Approved by the FDA and/or EMA (only adalimumab, infliximab and certolizumab)	Approved by the FDA and/or EMA (only adalimumab, infliximab and golimumab)
p40 subunit (IL-12/IL-23)	mAb	Ustekinumab	Approved by the FDA and/or EMA	Not effective	Approved by the FDA and/or EMA	Approved by the FDA and/or EMA
p19 subunit (IL-23)	mAb	Risankizumab	Approved by the FDA and/or EMA	Not effective	Approved by the FDA and/or EMA	Ongoing phase III clinical trial
JAK1 and JAK3	Small molecule	Tofacitinib	Approved by the FDA and/or EMA	Approved by the FDA and/or EMA	Not effective	Approved by the FDA and/or EMA
JAK1	Small molecule	Upadacitinib	Approved by the FDA and/or EMA	Approved by the FDA and/or EMA	Phase III clinical trial with positive results	Approved by the FDA and/or EMA

IBD, inflammatory bowel disease; JAK, Janus kinase; mAb, monoclonal antibody; SpA, spondyloarthritis.

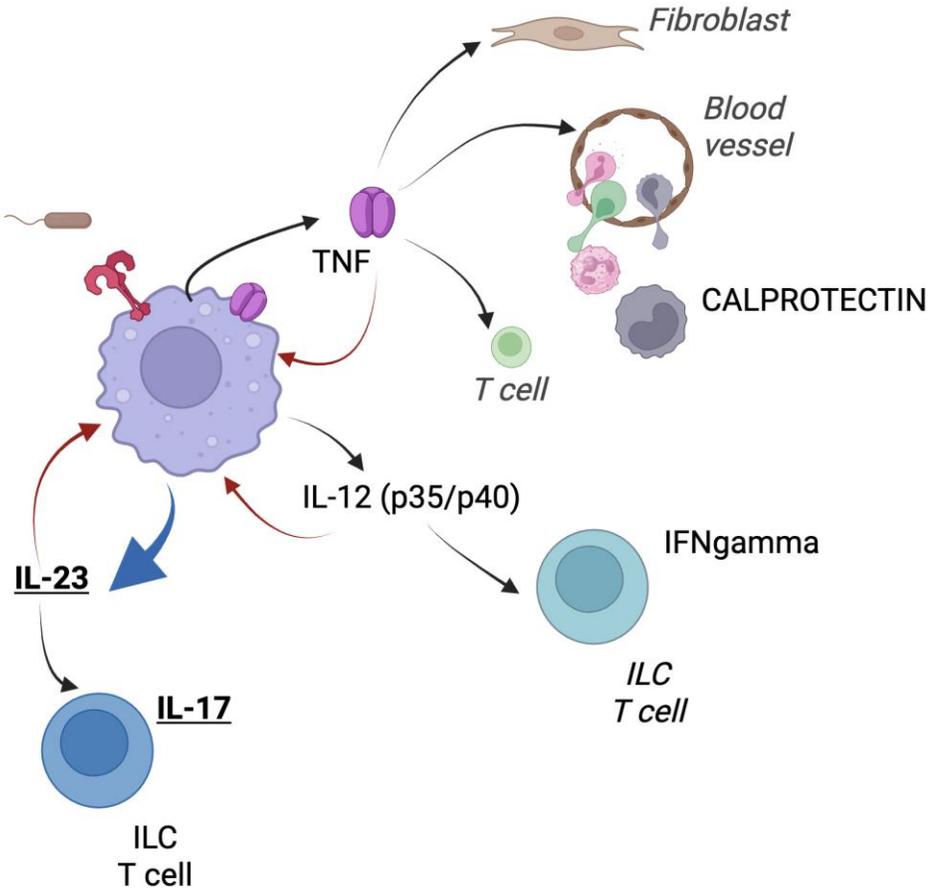


Fármacos en uso en EI y SpA

Target	Drug class	Therapeutics	Approval status			
			Peripheral SpA	Axial SpA	Crohn's disease	Ulcerative colitis
TNF	mAb	Adalimumab; infliximab; certolizumab; golimumab	Approved by the FDA and/or EMA	Approved by the FDA and/or EMA	Approved by the FDA and/or EMA (only adalimumab, infliximab and certolizumab)	Approved by the FDA and/or EMA (only adalimumab, infliximab and golimumab)
p40 subunit (IL-12/IL-23)	mAb	Ustekinumab	Approved by the FDA and/or EMA	Not effective	Approved by the FDA and/or EMA	Approved by the FDA and/or EMA
p19 subunit (IL-23)	mAb	Risankizumab	Approved by the FDA and/or EMA	Not effective	Approved by the FDA and/or EMA	Ongoing phase III clinical trial
JAK1 and JAK3	Small molecule	Tofacitinib	Approved by the FDA and/or EMA	Approved by the FDA and/or EMA	Not effective	Approved by the FDA and/or EMA
JAK1	Small molecule	Upadacitinib	Approved by the FDA and/or EMA	Approved by the FDA and/or EMA	Phase III clinical trial with positive results	Approved by the FDA and/or EMA

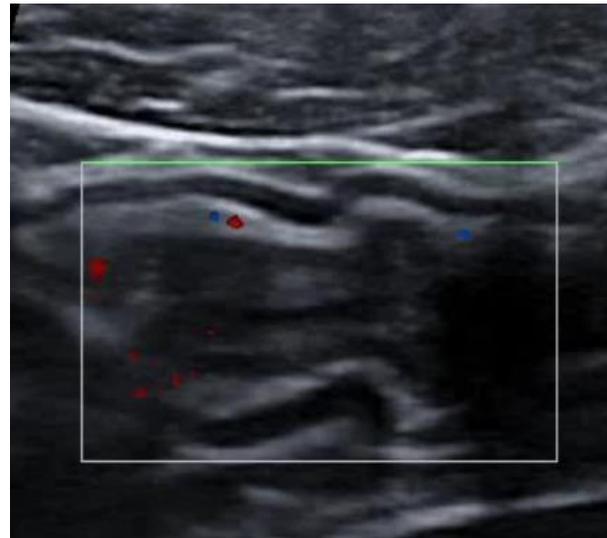
IBD, inflammatory bowel disease; JAK, Janus kinase; mAb, monoclonal antibody; SpA, spondyloarthritis.

Y la IL-12/IL-23?



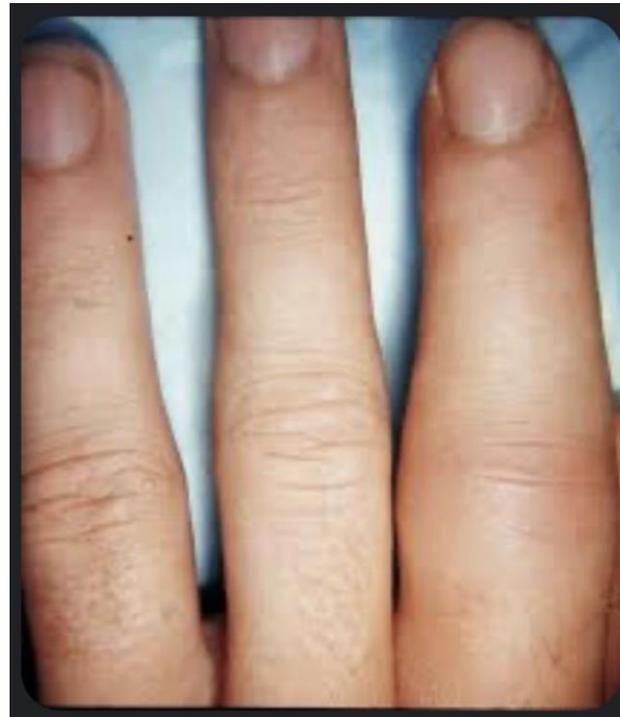
Dos años más tarde

- Pérdida de respuesta clínica articular: dolor lumbar, rigidez. Artralgias periféricas.
- Actividad clínica intestinal progresiva a lo largo de los últimos 3 meses
 - 5 dep/d, blandas, con sangre mezclada ocasional
 - Dolor FID intermitente
 - Calprotectina 632. Niveles IFX indetectables. ATIs > 50
 - Eco: actividad inflamatoria ileal



Dos años más tarde

- Se suspendió el infliximab y se inició tratamiento con ustekinumab
- Remisión clínica, bioquímica y ecográfica intestinal
- Persistencia de clínica articular axial, empeoramiento franco artralgiás en rodillas, tobillo izdo. y dactilitis



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Beyond the gut - Explorando las fronteras entre las IMiDs.

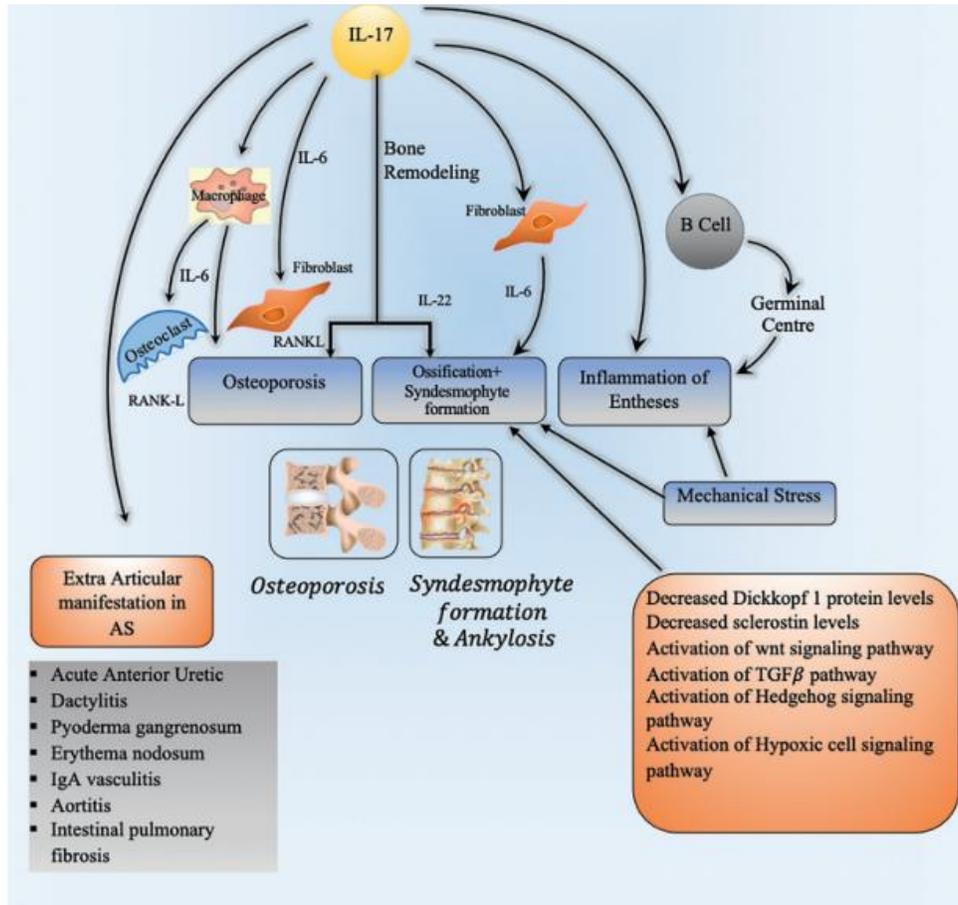
Pregunta 3.
¿Porqué algunos fármacos para la EII no son eficaces para la SpA y a la inversa?

Perspectivas terapéuticas en EII-EII

Target	Drug class	Therapeutics	Disease			
			Peripheral SpA	Axial SpA	Crohn's disease	Ulcerative colitis
IL-17RA	mAb	Brodalumab	Phase III clinical trial with positive results	Phase III clinical trial with positive results	Not effective	Not evaluated
p19 subunit (IL-23)	mAb	Guselkumab	Approved by the FDA and/or EMA	Ongoing phase IV clinical trial in axial PsA	Ongoing phase III clinical trial	Ongoing phase III clinical trial in ulcerative colitis
JAK1	Small molecule	Filgotinib	Phase III clinical trial with positive results	Phase II clinical trial with positive results	Phase III clinical trial with negative results	Approved by the FDA and/or EMA
TYK2	Small molecule	Deucravacitinib	Ongoing phase III clinical trial	Not evaluated	Ongoing phase II clinical trial	Ongoing phase II clinical trial
TYK2 and JAK1	Small molecule	Brepocitinib	Phase II clinical trial with positive results	Not evaluated	Ongoing phase II clinical trial	Phase II clinical trial with positive results
PDE4	Small molecule	Apremilast	Approved by the FDA and/or EMA	Not effective	Not evaluated	Phase II clinical trial with positive results
Integrin $\alpha 4\beta 7$	Small molecule	Vedolizumab	Discordant results in observational studies	Discordant results in observational studies	Approved by FDA and/or EMA	Approved by the FDA and/or EMA

IBD, inflammatory bowel disease; IL-17RA, IL-17 receptor subunit A; JAK, Janus kinase; mAb, monoclonal antibody; PDE4, phosphodiesterase 4; SpA, spondyloarthritis; TYK2, tyrosine kinase 2.

IL-17 es mediadora de daño músculo esquelético y extra-articular detectado en la Espondilitis Anquilosante



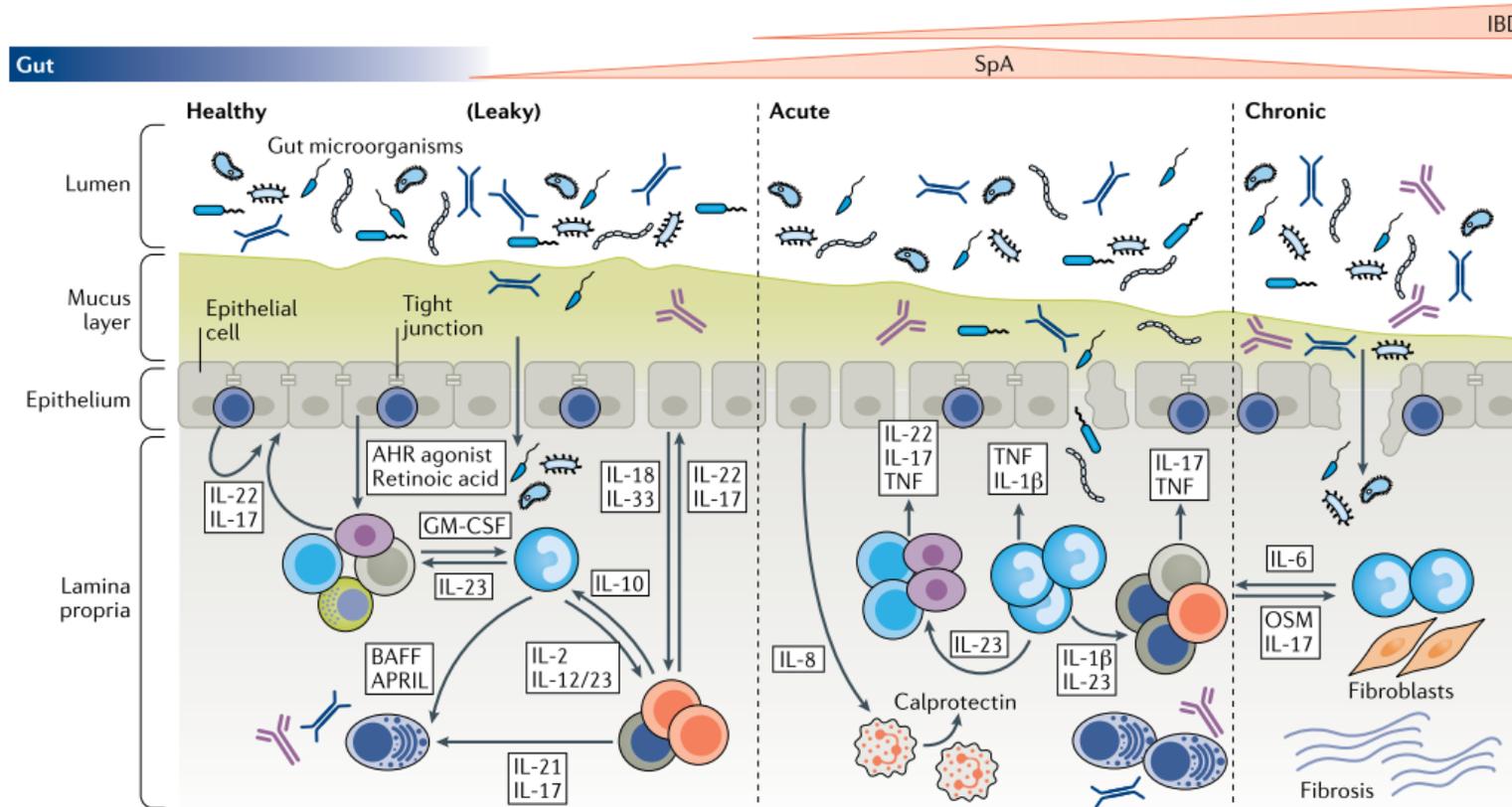
• **Función de la IL-17:** la interleucina-17 (IL-17) influye en varios tipos de células, incluidos macrófagos, fibroblastos y células B, para impulsar los procesos de inflamación y remodelación ósea.

• **Remodelación ósea y osteoporosis:** IL-17 e IL-6 contribuyen a la osteoporosis al promover la formación y actividad de los osteoclastos a través de la señalización RANKL.

• **Formación de sindesmofitos y anquilosis:** el estrés mecánico y las vías de señalización específicas (como la disminución de los niveles de Dickkopf 1 y esclerostina, y la activación de las vías Wnt y TGF-β) se asocian a la osificación y formación de sindesmofitos, lo que en última instancia conduce a la anquilosis.

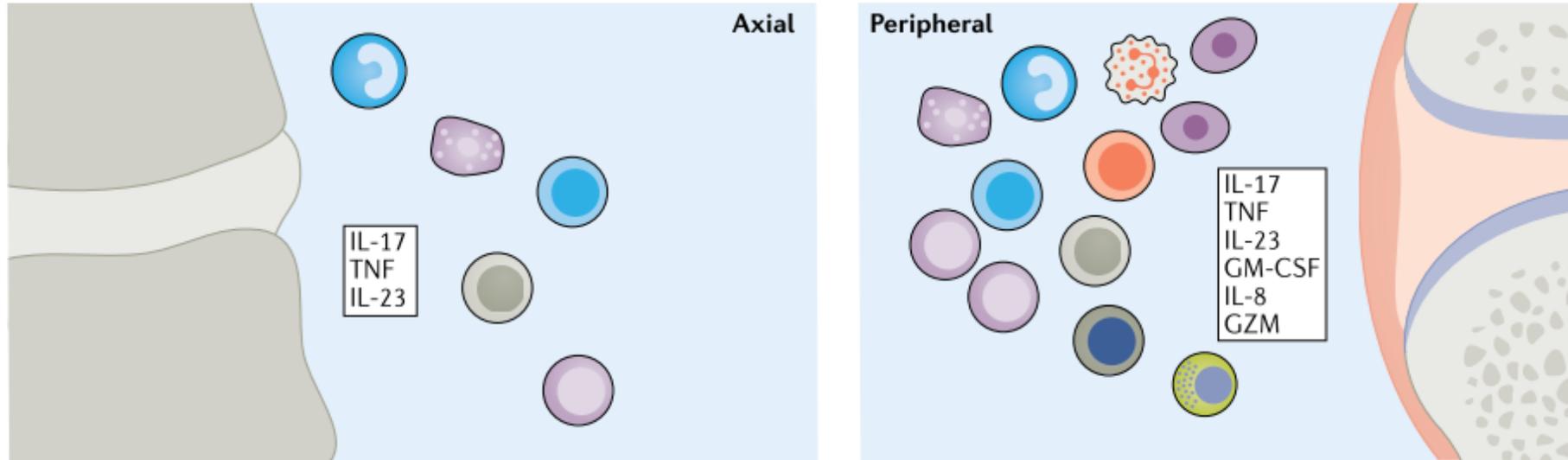
Cambios inmunológicos en el eje intestino-articulaciones

Homeostasis:
Células CD8+ intraepiteliales (IELs), producen IL-17 y son cruciales para la inmunidad de barrera.



Inflamación:
El aumento en la producción de IL-17 es común al intestino y las articulaciones en pacientes con espondilitis anquilosante o artritis psoriática.

Cambios inmunológicos en el eje intestino-articulaciones



Immune cells and cytokines are detectable in bone, enthesal tissue in peripheral and axial joints, and in the synovial fluid of peripheral joints.

Immunity

Interleukin-23-Independent IL-17 Production Regulates Intestinal Epithelial Permeability

Highlights

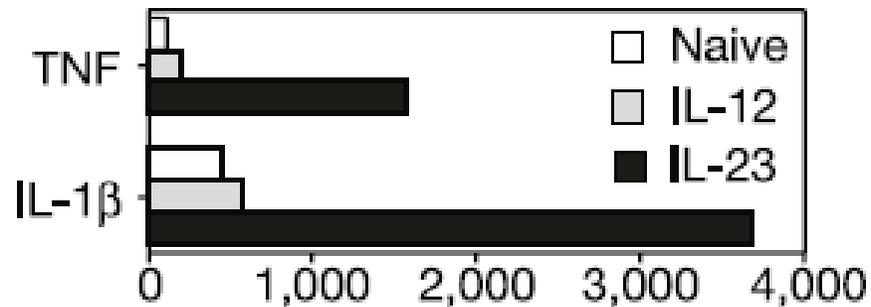
- Neutralizing IL-17 results in increased gut permeability in a DSS injury model
- $\gamma\delta$ T cells are the major source of gut-protective IL-17 and are IL-23 independent

Authors

Jacob S. Lee, Cristina M. Tato, Barbara Joyce-Shaikh, ..., Terrill K. McClanahan, Xiaoxia Li, Daniel J. Cua

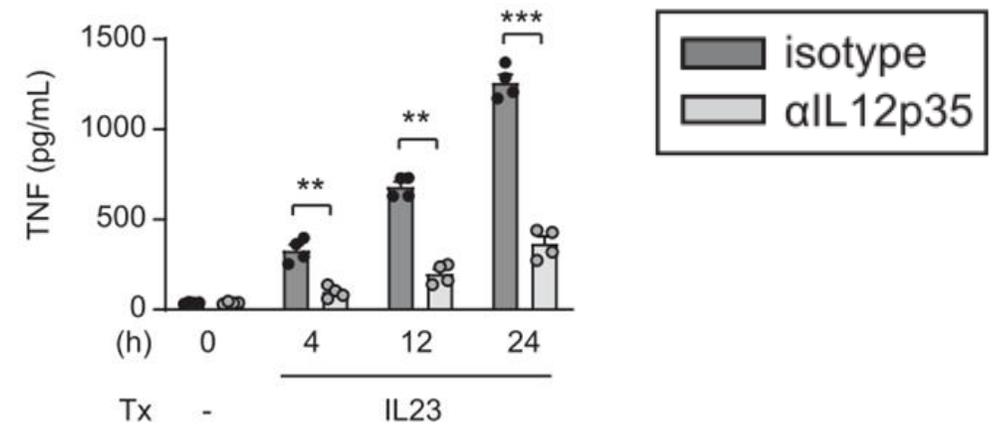
Macrophages respond to IL-23

Macrófagos peritoneales estimulados con IL-23



Cua DJ et al. Nature 2023

Macrófagos humanos estimulados con IL-23

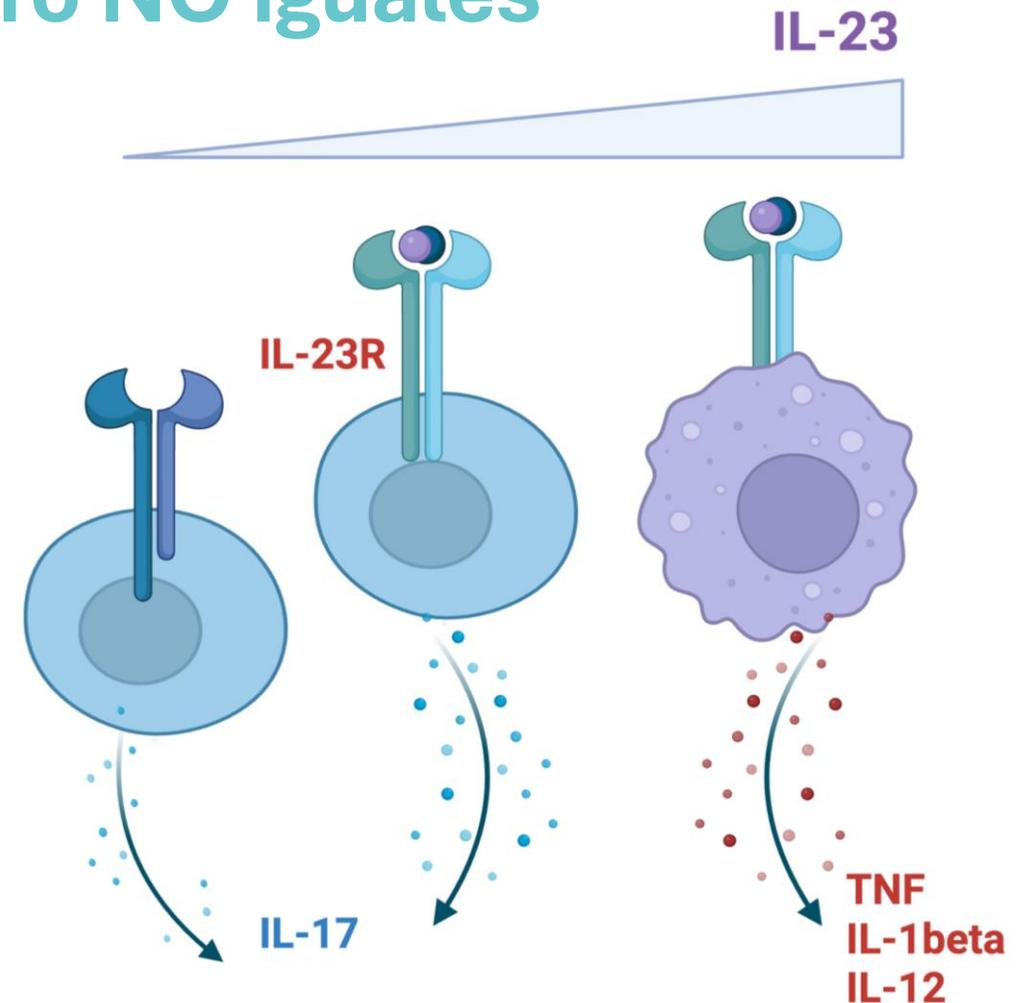


- IL-23 induce la producción de IL-12, IL1b y TNF en macrófagos.
- Este aumento es en parte amplificado por la propia IL-12.

Sun R and Abraham C. Cell Mol Gastro Hepatol 2020

IL-17 e IL-23: relacionados pero NO iguales

- La IL-17 cumple importantes funciones protectoras en las **barreras epiteliales**.
- La IL-17 puede producirse independientemente de la IL-23.
- La producción de IL-23 es dependiente del entorno inflamatorio.
- La neutralización de IL-23 reduce la inflamación en tejidos preservando la función protectora de la IL-17.



Vedolizumab en Espondiloartritis?

- Se ha asociado el uso de Vedolizumab con la aparición o reactivación de manifestaciones articulares.
 - *Dubash, S. et al. Rheumatology. 2019;58(6):963–8*
 - *Varkas G et al. Case report: Ann Rheum Dis. 2017 May;76(5):878-881*
 - *Zheng D et al. Meta analysis: J Gastroenterol Hepatol. 2024 Sep;39(9):1745-1759*
- Un estudio prospectivo contradice esta observacion:
 - *Rohekar S. et al. UEGJ 2024; 12(7):859-69*

Received: 28 March 2024 | Accepted: 31 May 2024

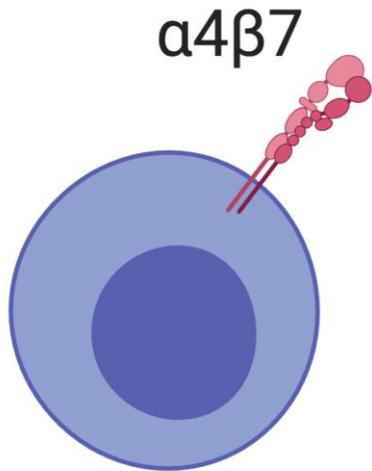
DOI: 10.1002/ueg2.12621

ORIGINAL ARTICLE

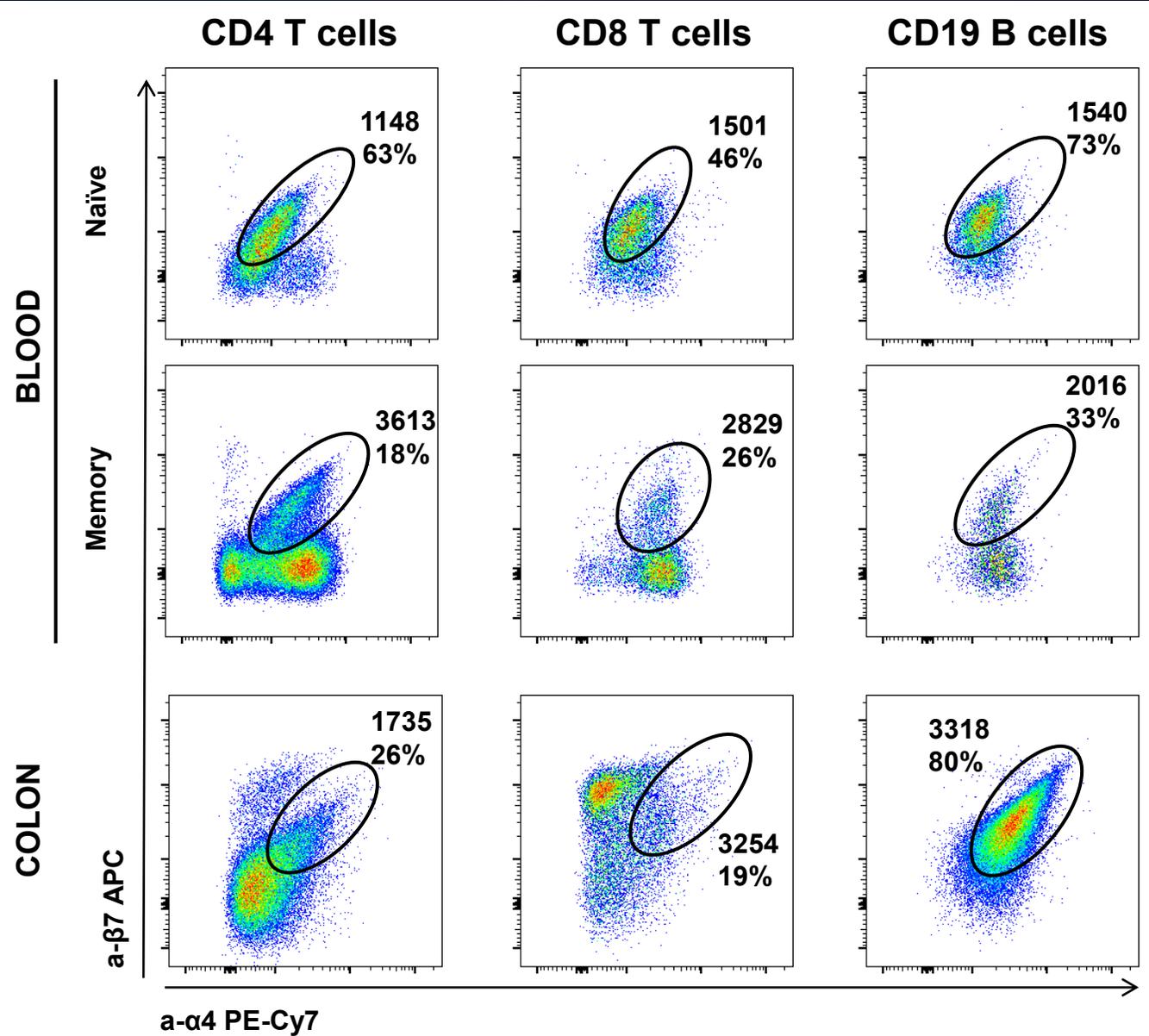
UNITED EUROPEAN
GASTROENTEROLOGY
ueg journal WILEY

Initiation of vedolizumab did not provoke new-onset spondylarthritis in patients with inflammatory bowel disease: A prospective 24-week study with imaging assessments

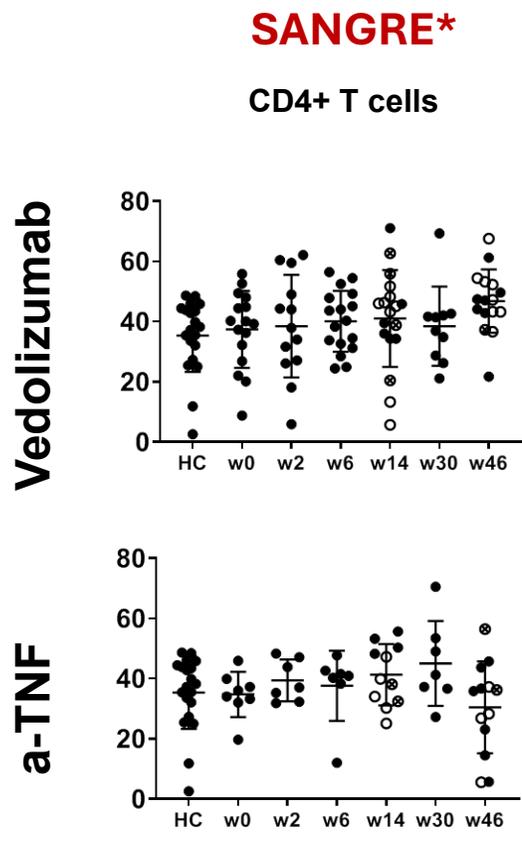
$\alpha 4\beta 7$ expression



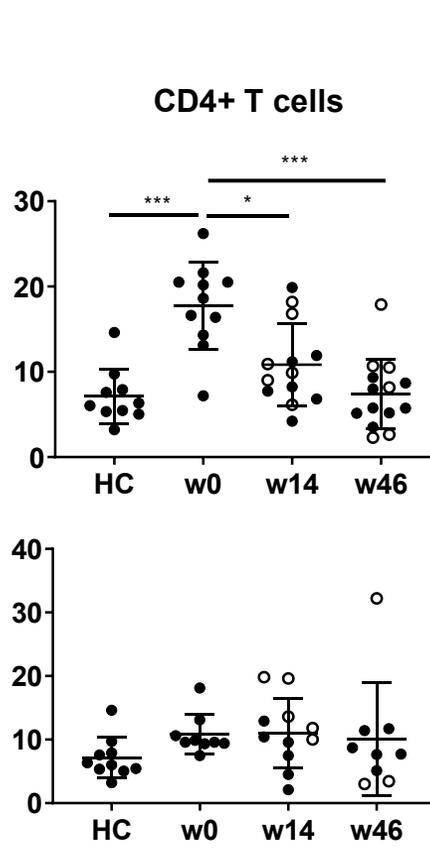
Veny M et al. JCC 2020



Efecto de VDZ vs IFX en linfocitos



* % CD8+ cambios similares

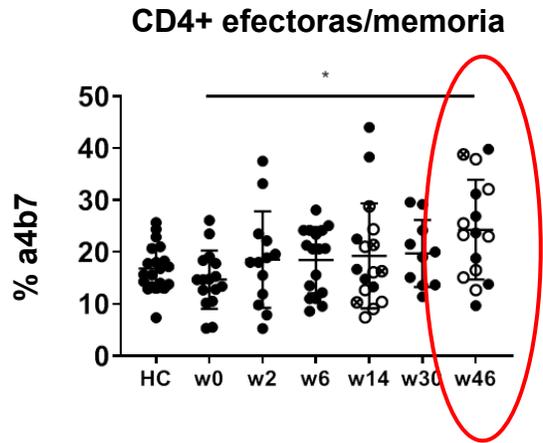


Veny M et al. JCC 2020

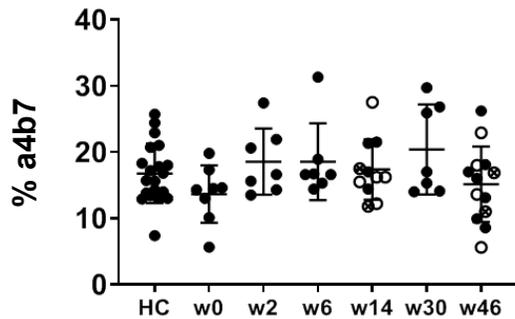
VDZ vs IFX: linfocitos $\alpha 4\beta 7+$

SANGRE

Vedolizumab



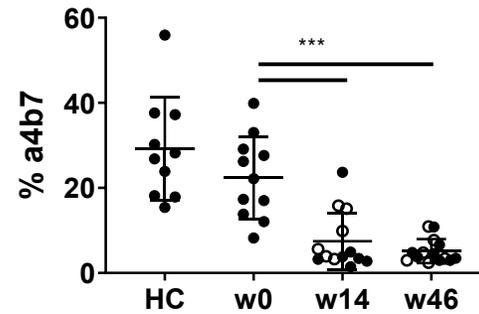
a-TNF



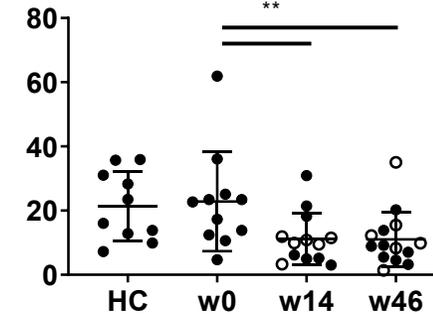
- Non-responder
- Responder

COLON

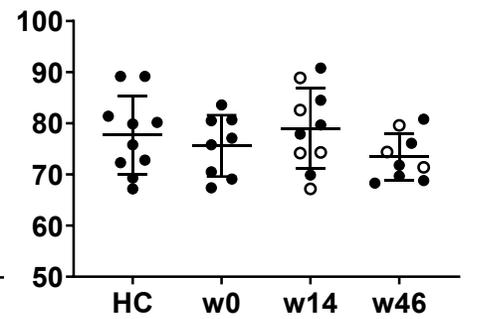
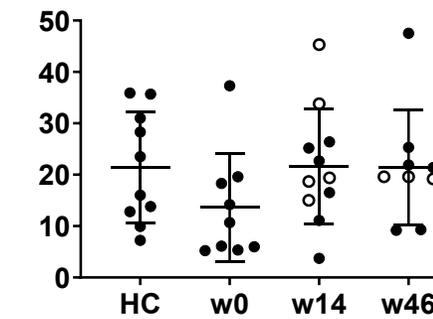
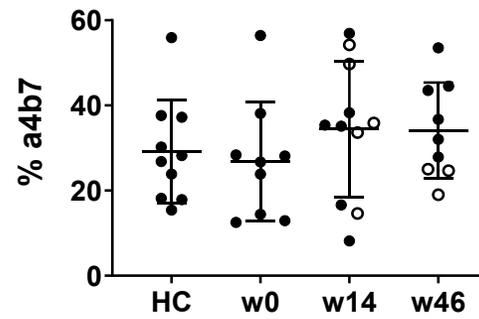
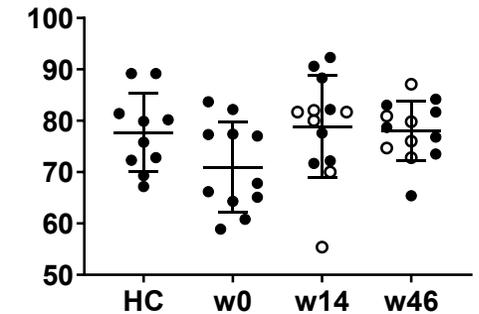
CD4+ T cells



CD8+ T cells



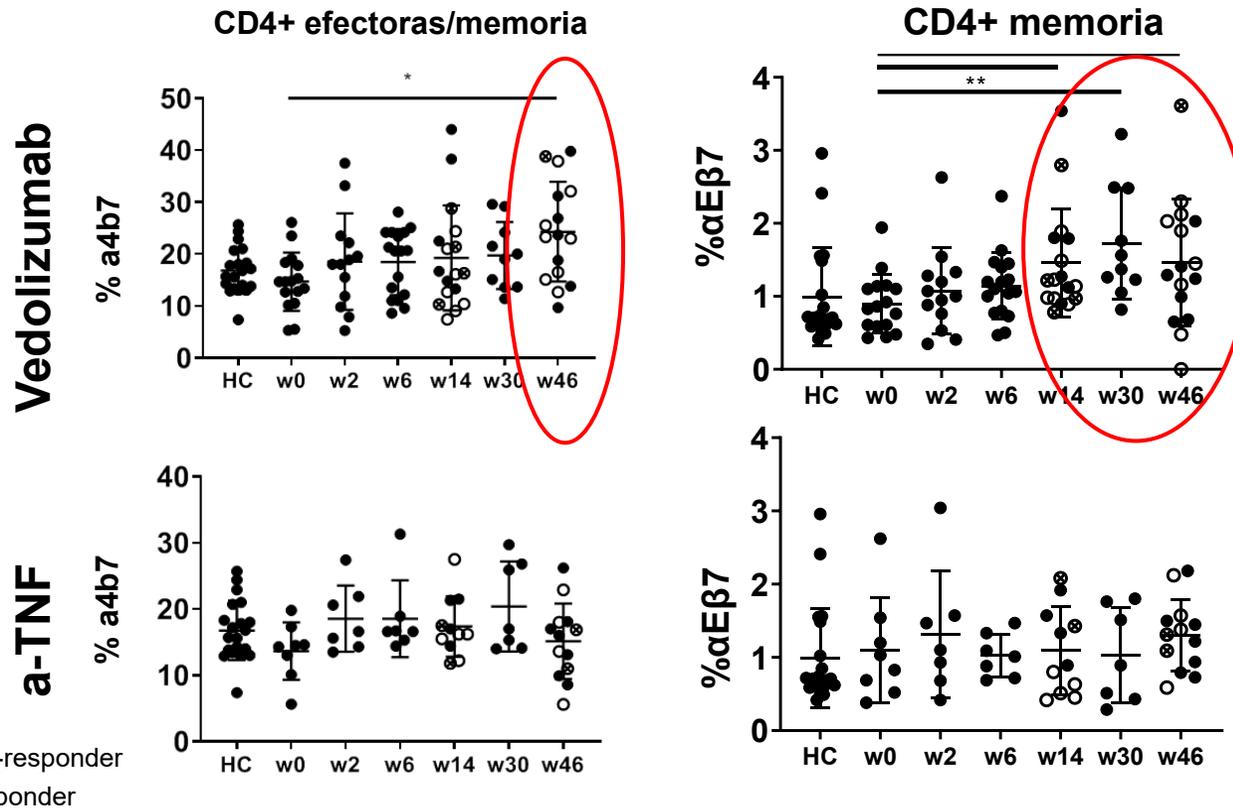
B cells



Veny M et al. JCC 2020

VDZ aumenta el número de $\alpha E\beta 7$ en sangre

SANGRE



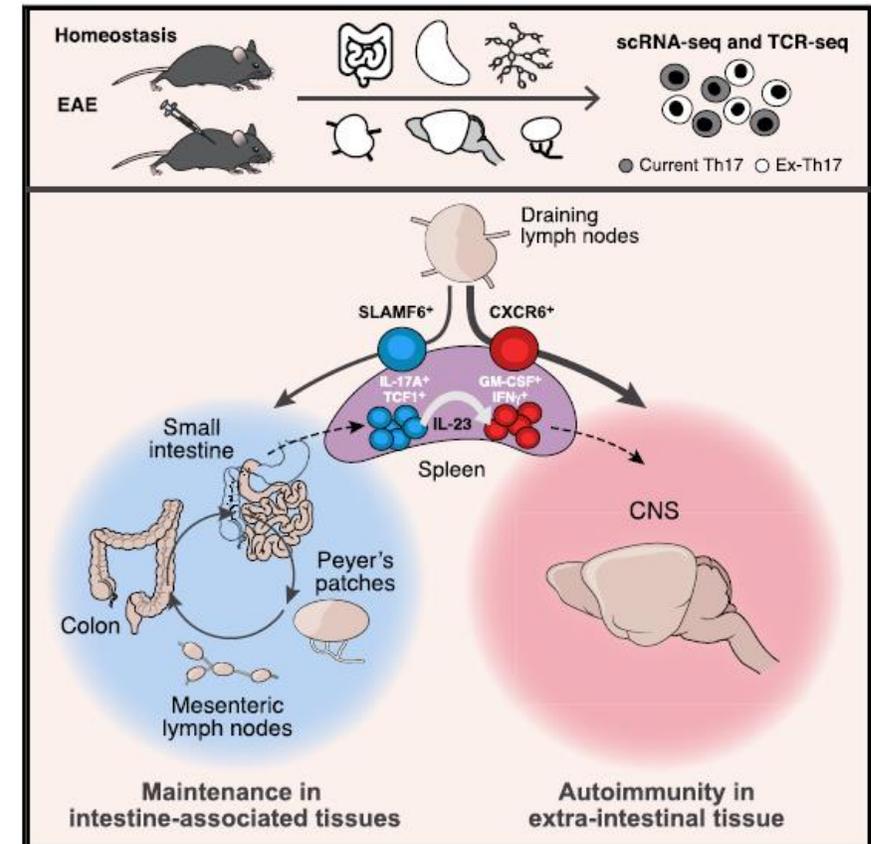
Veny M et al. JCC 2020

Células CD8+ T (CD49a+ $\alpha E\beta 7$ CD29+) son más prevalentes en el synovium de Epondilitis Anquilosante que de pacientes con AR y podrían jugar un papel en la patofisiología de la SpA.

Qaiyum, Z et al. Ann Rheum Dis 2019

Stem-like intestinal Th17 cells give rise to pathogenic effector T cells during autoimmunity

Schnell A et al. Cell 2021; 184, 6281–6298



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Beyond the gut - Explorando las fronteras entre las IMiDs.

Pregunta 4.
**¿Qué opciones terapéuticas para
ambas entidades tienen más
“sentido inmunológico”?**

Anti-p19 anticuerpos: ¿todavía una opción?

- Risankizumab no demostró eficacia en el tratamiento de la SpA en un estudio fase II (NCT02047110).
- Risankizumab es eficaz en la PsA (KEEPsAKE trial).
Kristensen LE et al Ann Rheum Dis 2022.
- Guselkumab es eficaz PsA (DISCOVER trials) y la PsA con síntomas axiales (posthoc analysis de los estudios DISCOVER).
Mease PJ et al. The Lancet Rheumatol 2021.
- Un estudio fase IV está en marcha para evaluar la eficacia de guselkumab versus placebo en pacientes con **PsA axial** (NCT04929210). **A Study of Guselkumab Administered Subcutaneously in Bio-naive Participants With Active Psoriatic Arthritis Axial Disease (STAR)**
ONGOING RECRUITMENT

Time to lift the moratorium on IL-23 inhibitors for axial psoriatic arthritis

Antonio Tonutti, Kerem Abacar, Tom Macleod, Carlo Selmi, Dennis McGonagle

A Axial spondyloarthritis with psoriasis

Prioritise other treatments over IL-23 inhibitors

Skin psoriasis



HLA-B27-positive
Male sex



Sacroiliitis
Positive MRI, bilateral,
subchondral bone
marrow oedema



Rare peripheral
arthritis



No nail psoriasis



B Axial psoriatic arthritis

Consider using IL-23 inhibitors

Skin psoriasis



Axial involvement
Rare sacroiliitis,
cervical-thoracic
predominant, patchy,
asymmetrical, positive
or negative MRI



Peripheral arthritis
commonly present

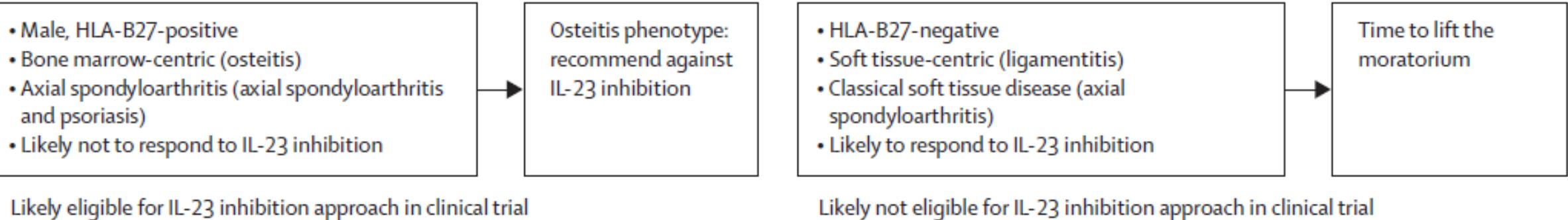


Frequent nail psoriasis



Time to lift the moratorium on IL-23 inhibitors for axial psoriatic arthritis

Antonio Tonutti, Kerem Abacar, Tom Macleod, Carlo Selmi, Dennis McGonagle



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¡GRACIAS!

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Organizado y Financiado por:

Johnson&Johnson

EM-196046 Enero 2026 Janssen Cilag S.A

Proyecto



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El futuro de la EII

Una visión personal

Luis Menchén



Evento de Educación Médica
Organizado y Financiado por:

Johnson&Johnson

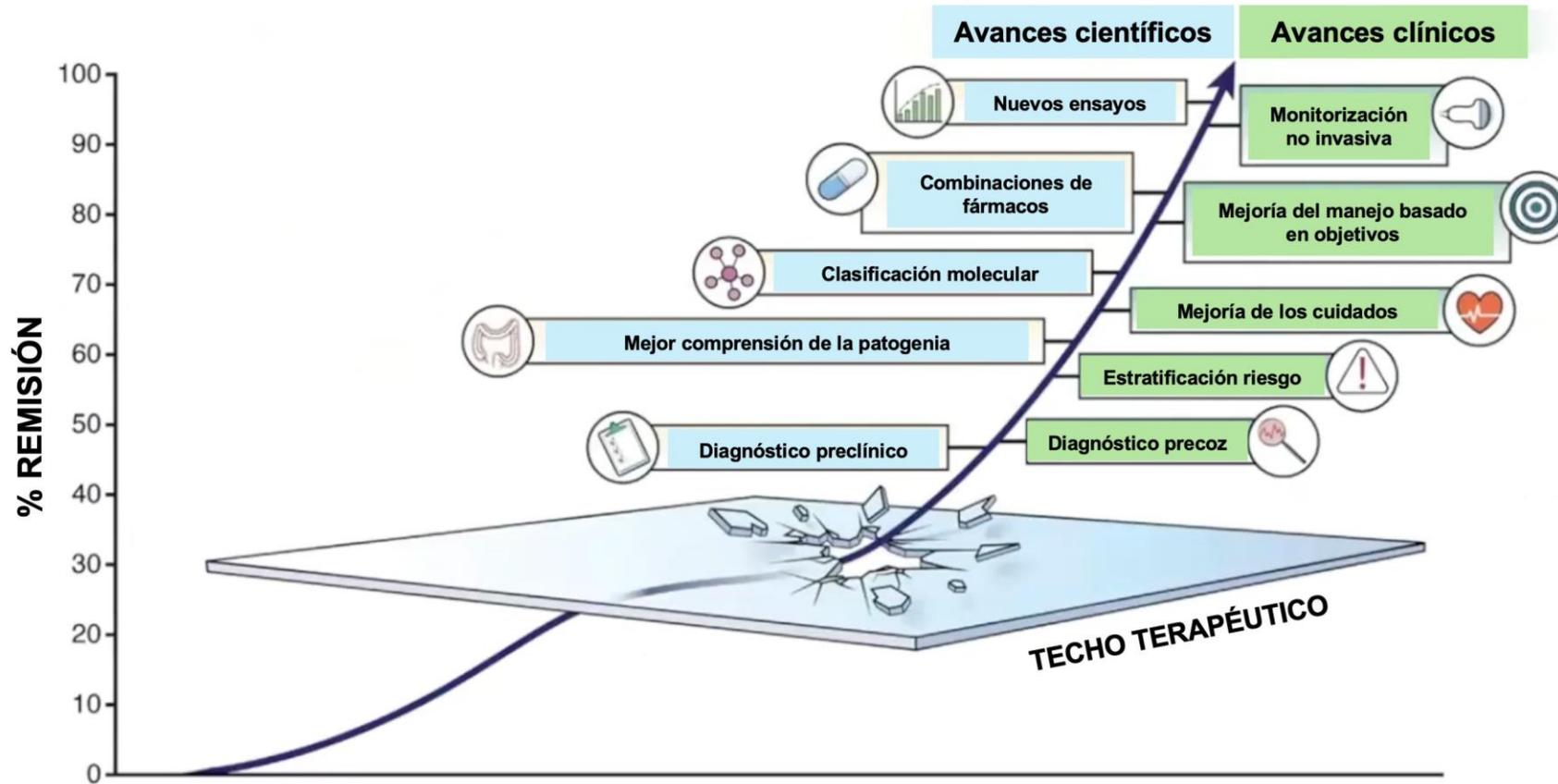
EM-196046 Enero 2026 Janssen Cilag S.A

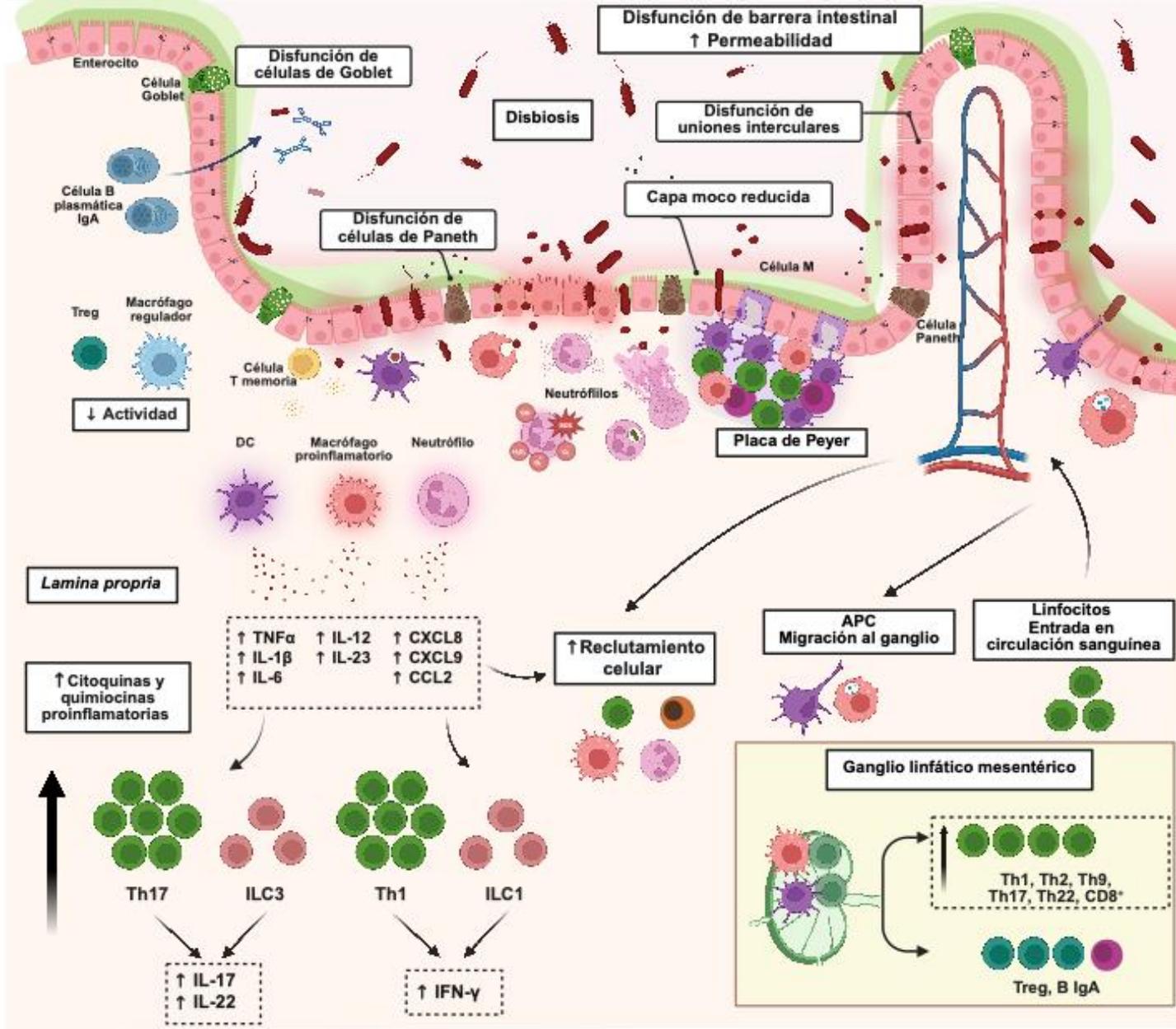


El futuro de la EII

- Reclasificación
- Predicción. Nuevas herramientas de monitorización
- Nuevos objetivos terapéuticos
- Nuevas dianas terapéuticas
- Nuevas estrategias terapéuticas: combinación, posicionamiento
- Terapias celulares
- Medicina basada en valor

El futuro de la EII





Reclasificación de la EII

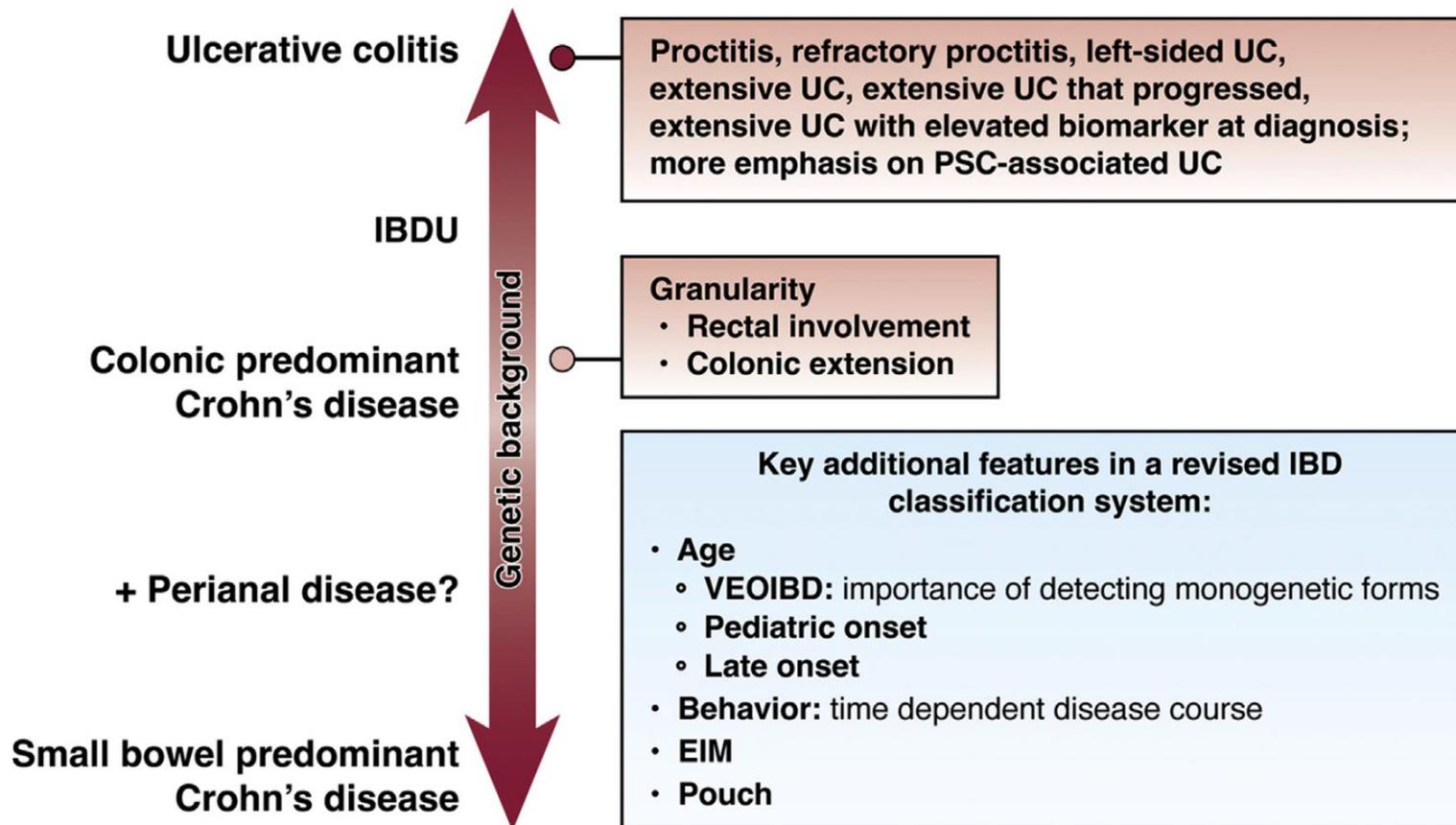
Gastroenterology 2022;162:1370-1382

DISEASE CHARACTERIZATION

Time to Revisit Disease Classification in Inflammatory Bowel Disease: Is the Current Classification of Inflammatory Bowel Disease Good Enough for Optimal Clinical Management?



Brian Verstockt^{1,2} Brian Dessel³ Helena Martinez-Lozano⁴ Dermot McGovern⁵ Mark S. Silverberg⁶

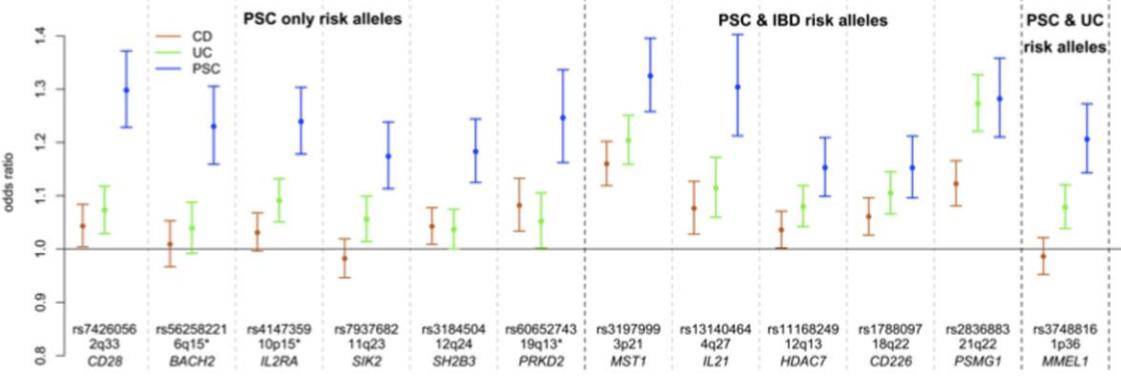


Reclasificación de la EII

Nat Genet. 2013 Jun; 45(6): 670-675. doi:10.1038/ng.2616.

Dense genotyping of immune-related disease regions identifies nine new risk loci for primary sclerosing cholangitis

Jimmy Z. Liu^{1,2}, Johannes Raikund Nov^{1,2,3,4,5,6,7}, Trine Falasenas^{1,2,4,5,6,7}, Eva Ellinghaus^{1,2}, Simon M. Bushnell^{1,2,3,4}, Henrich T. Doochevel^{1,2,3,4}, Ole A. Andreassen^{1,2,3,4}, Rineke K. Weerama^{1,2}, Tobias J. Waltemate^{1,2,3,4}, Bertus Eksteen^{1,2}, Pieter Invernizzi^{1,2}, Gidon M. Hershlag^{1,2}, Daniel Nis Gochman^{1,2}, Albert Panes^{1,2}, David Ellinghaus^{1,2}, Yajna Shah^{1,2}, Brian D. Juran^{1,2}, Piotr Milkiewicz^{1,2,3,4}, Christian Rust^{1,2}, Christoph Schweser^{1,2}, Tobias Müller^{1,2}, Biprajit Sanyal^{1,2,3,4}, Georges Delbecq^{1,2,3,4}, Marcus M. Mühlbauer^{1,2,3,4}, Stefan Herberich^{1,2}, Juliana Winkelmann^{1,2,3,4}, Milica Milovic^{1,2}, Felix Braun^{1,2}, Cyril Y. Panigrahy^{1,2}, Peter J. Crookson^{1,2}, Martin Sternes^{1,2}, Andreas Tiedel^{1,2}, Andrew L. Mason^{1,2}, Janina Saarela^{1,2}, Virpi Leppä^{1,2}, Rikako Dorfman^{1,2}, Domingo Alvarez^{1,2}, Annarosa Flisanti^{1,2}, Bana Chengel-Dumitrescu^{1,2}, Stephen S. Rich^{1,2,3,4}, Wesley K. Thompson^{1,2}, Andrew J. Schork^{1,2}, Sigrid Nass^{1,2,3,4}, Ingo Thomas^{1,2}, Gabriele Mayr^{1,2}, Inke R. König^{1,2}, Kristian Heem^{1,2}, Isabelle Claryen^{1,2}, Javier Gutierrez-Achury^{1,2}, Iñaki Ricarte-Ponce^{1,2}



Gut 2016;0:1-9

The gut microbial profile in patients with primary sclerosing cholangitis is distinct from patients with ulcerative colitis without biliary disease and healthy controls

Martin Kurmen,^{1,2,3,4} Kristian Holm,^{1,4} Jani Andresson,^{1,4} Sille Nygård,^{5,6,7} Mette Vesterhus,^{1,8} Marte L. Helvik,⁹ Marius Tjørdal,^{1,2,10} Hanns-Ulrich Marschall,¹¹ Erik Schrupp,^{1,2} Bjørn Mørum,^{1,2} Jielge Røtge,^{1,2} pbl Aukrust,^{2,3,4,10} Tom H. Karlsen,^{1,2,4,5,10,12} Johannes R. Hov^{2,3,4,14}

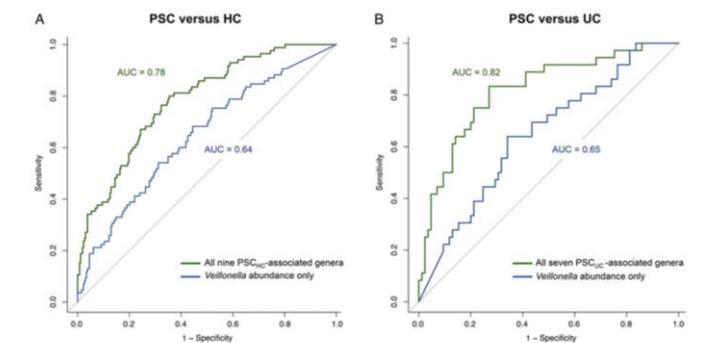


Figure 5 (A) Gut microbiota-based PSC classification using AUROC analysis (in the combined panel) using the relative abundance of the *Veillonella* genus (AUC=0.64, 95% CI 0.58 to 0.71, p<0.0001). When using each individual's arcsine square root transformed abundance of the nine genera differing between PSC and HC (and validated by all secondary analyses, denoted as PSC_{UC}), together with the coefficients from multivariate logistic regression, the AUC increased to 0.78 (0.73 to 0.84, p<0.0001). (B) The same analysis was repeated for PSC and UC. The *Veillonella* genus alone gave an AUC of 0.65 (0.54 to 0.75, p<0.05), and the seven genera differing between PSC and UC (denoted as PSC_{UC}) gave an AUC of 0.82 (0.73 to 0.90, p<0.0001). AUC, area under the curve; AUROC, area under the receiver operating characteristics curve; HC, healthy controls; PSC, primary sclerosing cholangitis.

Reclasificación de la EII

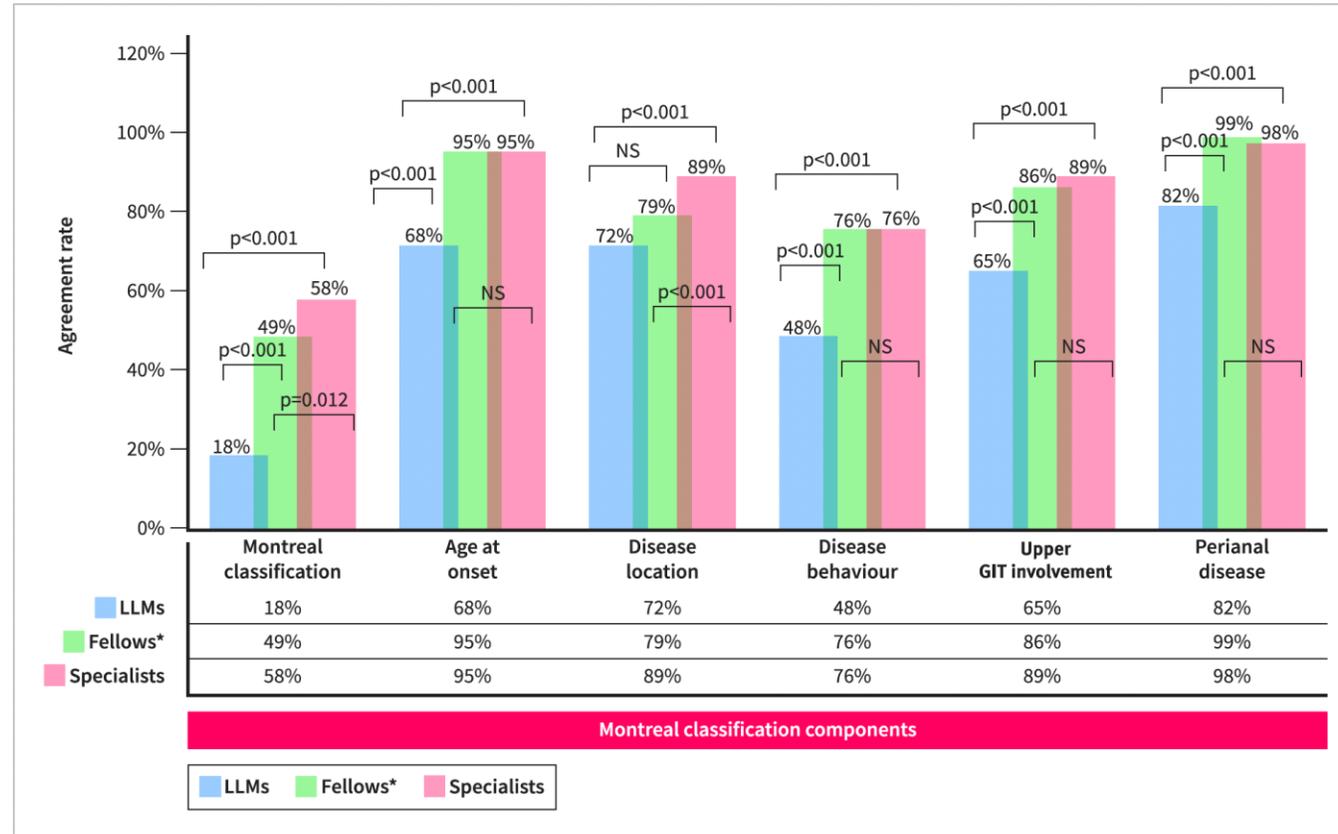


FIGURE 2 | The agreement rates with the inflammatory bowel disease board's consensus among the study groups. GIT, gastrointestinal tract; LLMs, language learning models. *Including young specialists with up to 2 years of experience.

Predicción del desarrollo y curso clínico de la EI

(A)

Predictors of response in Crohn's disease	Anti-TNF alpha	Vedolizumab	Ustekinumab
Patient-related factors			
Young age at initiation	Positive predictor	Insufficient data or controversy	Insufficient data or controversy
Smoking	Negative predictor	Negative predictor	Not examined
High BMI	Negative predictor	Insufficient data or controversy	Not examined
Disease-related factors			
Shorter duration of disease	Positive predictor	Insufficient data or controversy	Insufficient data or controversy
Severe disease activity at induction	Negative predictor	Negative predictor	Negative predictor
Complicated phenotype (stricturing, penetrating)	Negative predictor	Negative predictor	Negative predictor
History of intestinal resection	Negative predictor	Not examined	Negative predictor
Ileocolonic disease	Positive predictor	Not examined	Positive predictor
Elevated inflammatory biomarkers	Positive predictor	Negative predictor	Insufficient data or controversy
No recent hospitalisation (12 months)	Not examined	Positive predictor	Not examined
Treatment-related factors			
Early response	Positive predictor	Positive predictor	Positive predictor
Mucosal healing	Positive predictor	Not examined	Not examined
Low trough level of biologic	Negative predictor	Negative predictor	Negative predictor
Anti-drug antibodies	Negative predictor	Insufficient data or controversy	Insufficient data or controversy
No prior anti-TNF exposure	Positive predictor	Positive predictor	Not examined
Concomitant steroid use	Not examined	Negative predictor	Not examined
Concomitant immunomodulator use	Positive predictor	Insufficient data or controversy	Positive predictor
Others			
Genetic: Fas-ligand-843 TT, caspase-9 93 CC/CT	Negative predictor	Not examined	Not examined
Microbiome: higher alpha diversity	Not examined	Positive predictor	Not examined

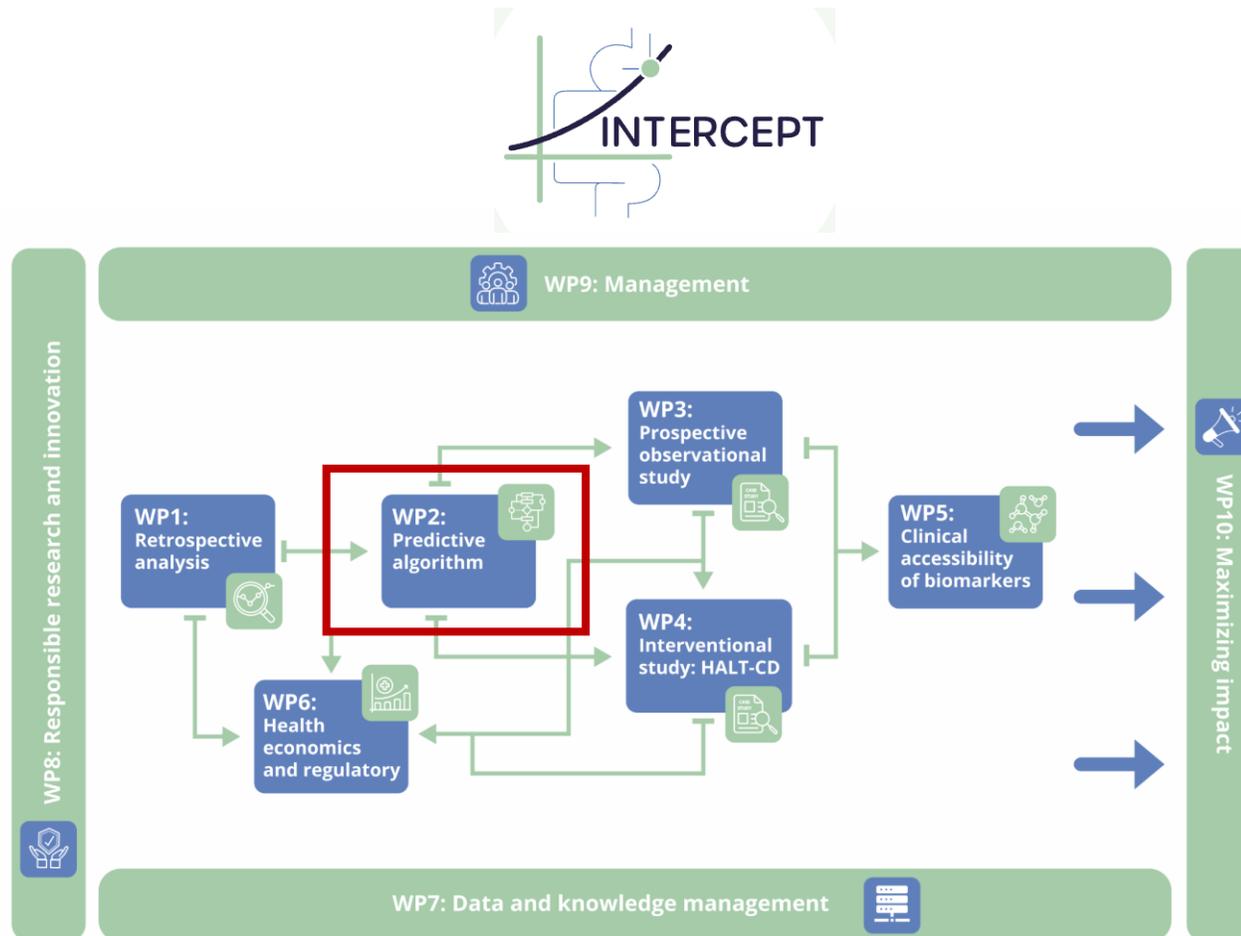
(B)

Predictors of response in ulcerative colitis	Anti-TNF alpha	Vedolizumab
Patient-related factors		
Young age	Positive predictor	Not examined
High BMI	Negative predictor	Insufficient data or controversy
Disease-related factors		
Severe disease activity at induction	Negative predictor	Negative predictor
Disease extent	Negative predictor	Not examined
Elevated inflammatory biomarkers	Insufficient data or controversy	Negative predictor
High hemoglobin at baseline	Positive predictor	Not examined
Low serum albumin	Negative predictor	Insufficient data or controversy
pANCA +	Negative predictor	Not examined
Treatment-related factors		
Early response	Positive predictor	Positive predictor
Mucosal healing	Positive predictor	Not examined
Low trough level of biologic	Negative predictor	Negative predictor
Anti-drug antibodies	Negative predictor	Insufficient data or controversy
No prior anti-TNF exposure	Positive predictor	Positive predictor
Concomitant steroid use	Not examined	Negative predictor
Concomitant immunomodulator use	Positive predictor	Not examined
Others		
Genetic: high expression oncostatin M, TNF receptor 1 36G	Negative predictor	Not examined

■ Positive predictor ■ Insufficient data or controversy
■ Negative predictor ■ Not examined

FIGURE 1 Comparison of predictors of response currently available in the literature for anti-TNF therapies, vedolizumab and ustekinumab in Crohn's disease (A) and ulcerative colitis (B)

Predicción del desarrollo y curso clínico de la EI

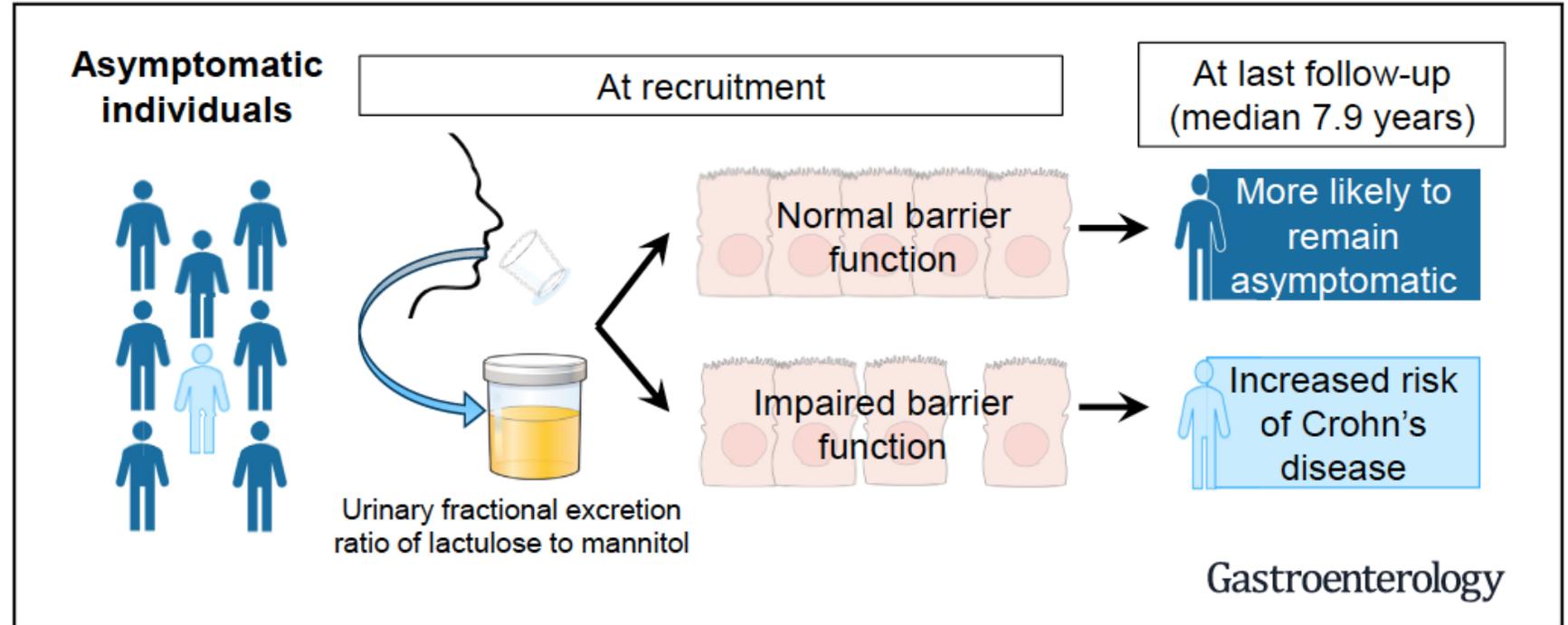


Predicción del desarrollo y curso clínico de la EI

Gastroenterology 2020;159:2092-2100

Increased Intestinal Permeability Is Associated With Later Development of Crohn's Disease

Williams Turpin,^{1,2*} Sun-Ho Lee,^{1,2*} Juan Antonio Raygoza Garay,^{1,2} Karen L. Madsen,³ Jonathan B. Meddings,⁴ Larbi Bedrani,⁵ Namita Power,¹ Osvaldo Espin-Garcia,⁶ Wei Xu,⁷ Michelle I. Smith,⁷ Anne M. Griffiths,⁸ Paul Moayyedi,⁹ Dan Turner,¹⁰ Ernest G. Seidman,¹¹ A. Hillary Steinhart,¹² John K. Marshall,¹³ Kevan Jacobson,^{11,12} David Mack,¹³ Hien Huynh,¹⁴ Charles N. Bernstein,¹⁵ Andrew D. Paterson,^{15,16} The Crohn's and Colitis Canada Genetic Environmental Microbial Project Research Consortium, and Kenneth Croitoru^{1,2}



Predicción del desarrollo y curso clínico de la EII

Marcadores moleculares

Marcadores pronósticos

PredictSURE IBD: PCR de 17 genes en sangre periférica (PROFILE trial)
Perfil de proteínas séricas (NORDTREAT trial)

Marcadores predictivos de eficacia terapéutica

Marcadores transcriptómicos en mucosa (IL13RA2, OSM, TREM1)
HLA-DQA1*05 y antiTNF (predicen inmunogenicidad)
Marcadores multiómicos (ninguno validado)

Marcadores predictivos de efectos adversos

HLA-DQA1 – HLA-DRB1 y pancreatitis por tiopurinas
NUDT15 – TPMT y mielosupresión por tiopurinas

Predicción del desarrollo y curso clínico de la EI

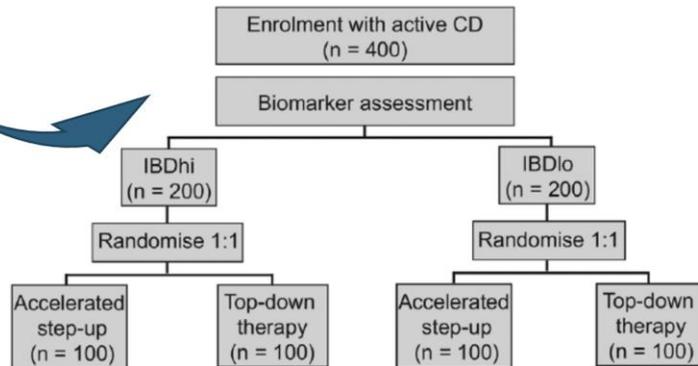
Marcadores moleculares



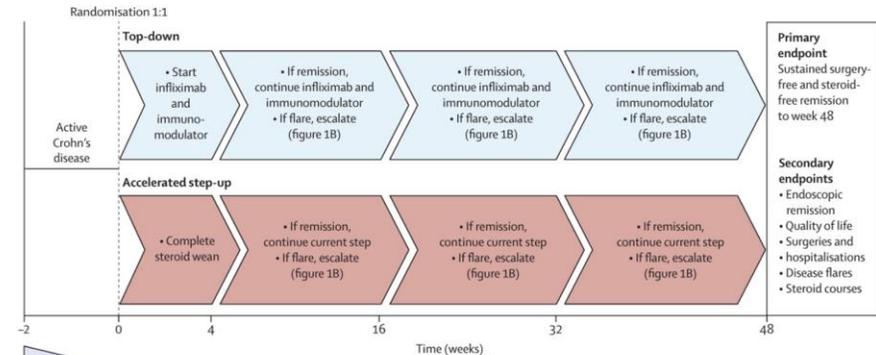
Predicting **O**utcomes **F**or **C**rohn's **d**isease using a **m**olecular **b**iomarker (**PROFILE**): protocol for a multicentre, randomised, biomarker-stratified trial

Miles Parkes,¹ Nurulamin M Noor,¹ Francis Dowling,² Harvey Leung,² Simon Bond,^{2,3} Lynne Whitehead,⁴ Sara Upponi,⁵ Paul Kinnon,⁶ Andrew P Sandham,⁶ Paul A Lyons,^{1,6} Eoin F McKinney,^{1,6} Kenneth G C Smith,^{1,6} James C Lee¹

Parkes M, et al. *BMJ Open* 2018



A biomarker-stratified comparison of top-down versus accelerated step-up treatment strategies for patients with newly diagnosed Crohn's disease (PROFILE): a multicentre, open-label randomised controlled trial



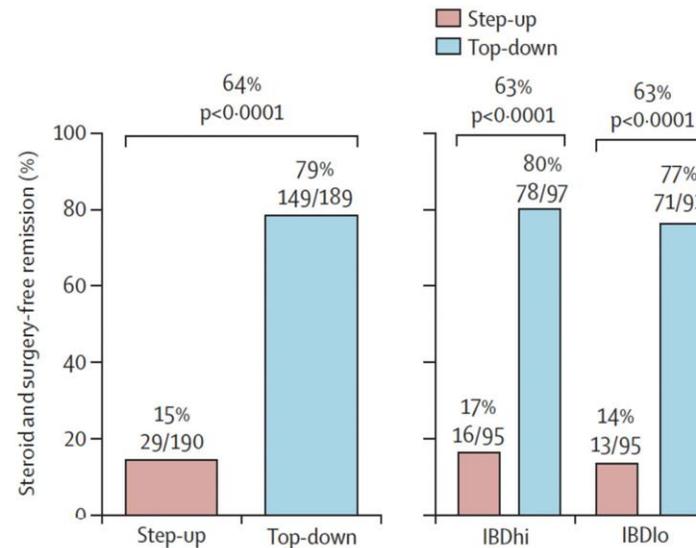
Trial visit	Accelerated step-up	Top-down
Week -2 (screening)	Start steroid induction for active Crohn's disease	Start steroid induction for active Crohn's disease
Week 0 (randomisation)	Following randomisation, continue steroid taper	Following randomisation, start infliximab and immunomodulator, and continue steroid taper
Week 4, 16, 32, 48 (after randomisation)	If in remission, continue on current step of treatment If flare 1, start steroids and immunomodulator If flare 2, start infliximab alongside immunomodulator	If in remission, continue infliximab and immunomodulator If flare 1, additional course of steroid medication If flare 2, consider non-response and trial withdrawal

Noor N et al. *Lancet Gastroenterol Hepatol* 2024

Predicción del desarrollo y curso clínico de la EI

Marcadores moleculares

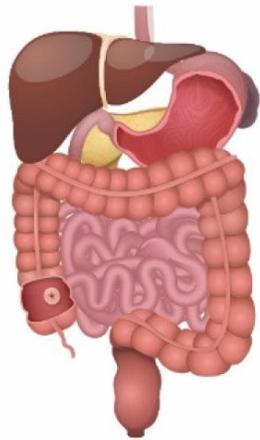
Biomarker-based stratification does not demonstrate clinical utility in large randomized trial



Noor N et al. Lancet Gastroenterol Hepatol 2024

Predicción del desarrollo y curso clínico de la EI

Inteligencia Artificial



Data Sources

Electronic health records

- Clinical characteristics
- Disease scoring reports
- Lifestyle (diet, smoking, biosensor data)
- Laboratory reports

Imaging technologies

- Endoscopy
- CT Enterography
- MR Enterography
- Histopathology

High throughput omics data

- Genomics
- Transcriptomics
- Proteomics
- Metabolomics



Data Analysis

Artificial intelligence

- Machine learning
 - Unsupervised learning
 - Supervised learning
- Deep learning
 - Neural networks
- Computer-aided detection/diagnosis



Implementation

- Improved diagnosis
- Patient profiling
- Avoids need for biopsies
- Biomarker investigation
- Patient stratification
- Drug response prediction
- Personalized treatment
- Improved prognosis

Predicción del desarrollo y curso clínico de la EI

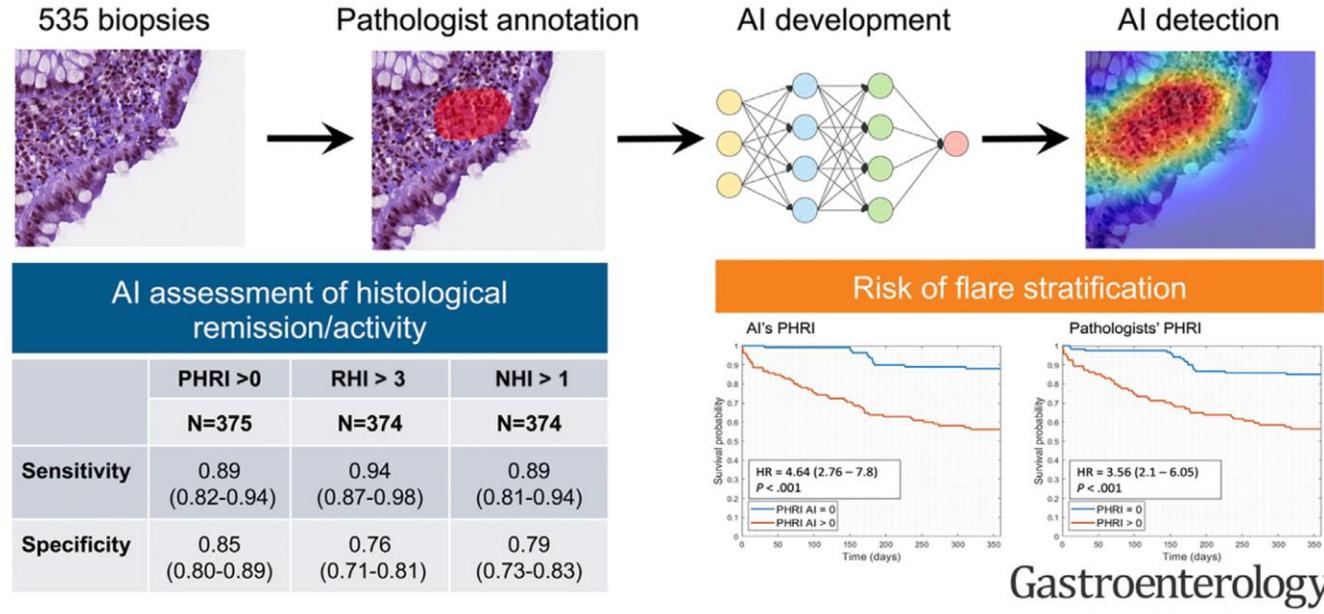
Inteligencia Artificial

Gastroenterology 2023;164:1180-1188

INFLAMMATORY BOWEL DISEASE

Artificial Intelligence Enabled Histological Prediction of Remission or Activity and Clinical Outcomes in Ulcerative Colitis

Marietta Iacucci,^{1,2,3,4,*} Tommaso Lorenzo Parigi,^{1,*} Rocio Del Amor,^{5,6,*} Pablo Meseguer,^{2,*} Giulio Mandelli,⁸ Anna Bozzola,⁹ Alina Bazarova,⁷ Pradeep Bhandari,⁸ Raf Bisschops,⁷ Silvio Danese,^{10,11} Gert De Hertogh,¹² Jose G. Ferraz,¹³ Martin Goetz,¹⁴ Enrico Grisan,^{15,16} Xianyong Gui,¹⁷ Bu Hayee,¹⁸ Ralf Kiesslich,¹⁰ Mark Lazarev,²³ Riemo Panaccione,¹⁹ Adolfo Parra-Blanco,^{21,22} Luca Pastorelli,²³ Timo Rath,²⁴ Elin S. Rayset,²⁵ Gian Eugenio Tortini,^{16,25} Michael Vieth,²⁶ Davide Zardo,²⁸ Subrata Ghosh,⁴ Valery Naranjo,⁸ and Vincenzo Villanacci⁸



Predicción del desarrollo y curso clínico de la EI

Apps para monitorización

JOURNAL OF MEDICAL INTERNET RESEARCH Aguas et al

Original Paper

Telemonitoring of Active Inflammatory Bowel Disease Using the App TECCU: Short-Term Results of a Multicenter Trial of GETECCU

Mariam Aguas^{1,2*}, MD, PhD; Javier Del Hoyo^{1,2*}, MD, PhD²; Raquel Vicente², MD; Manuel Barreiro-de Acosta¹, MD, PhD; Luigi Melcarne³, MD; Alejandro Hernandez-Camba⁴, MD, PhD; Lucia Madero^{3,8}, MD; Maria Teresa Arroyo⁵, MD, PhD; Beatriz Sicilia¹⁰, MD, PhD; Maria Chaparro^{6,11}, MD, PhD; Maria Dolores Martin-Arranz^{2,13}, MD, PhD; Ramón Pajares¹⁴, MD; Francisco Mesonero¹⁵, MD; Miriam Mañosa^{8,16}, MD, PhD; Pilar Martínez¹⁷, MD, PhD; Silvia Chacón¹⁸, MD, PhD; Joan Tosca¹⁹, MD; Sandra Marín²⁰, MD; Luciano Sanroman²¹, MD; Marta Calvo²², MD, PhD; David Monfort²³, MD; Empar Saiz²⁴, MD; Yamile Zabana²⁵, MD, PhD; Ivan Guerra²⁶, MD, PhD; Pilar Varela²⁷, MD; Virginia Baydal¹, RNC; Raquel Faubel^{28,29}, PhD; Pilar Corsino³, RNC, PhD; Sol Porto-Silva⁴, RNC; Eduard Brunet⁴, MD, PhD; Melodi González⁴, RNC; Ana Gutiérrez⁷, MD, PhD; Pilar Nos^{1,2}, MD, PhD

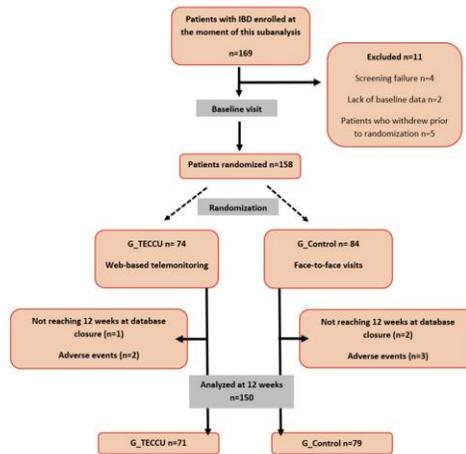
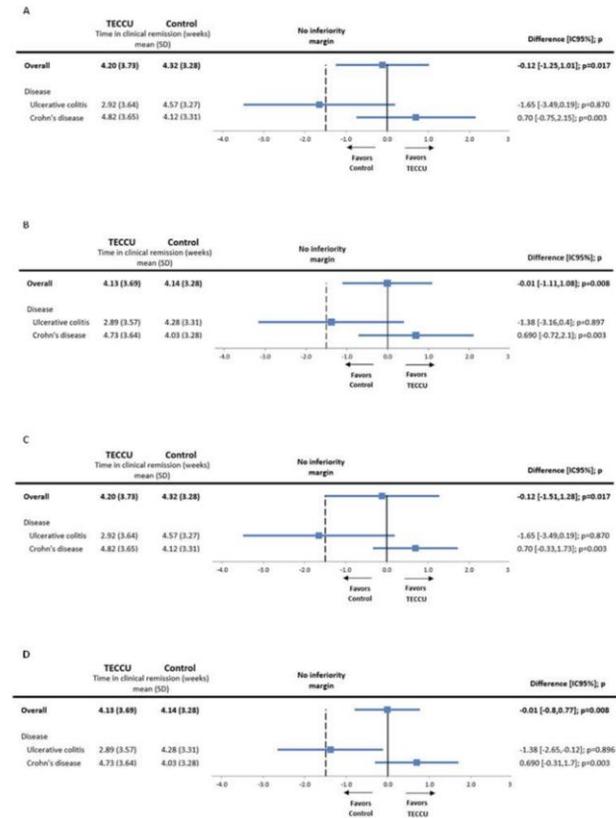


Figure 3. (A) Differences in the time in clinical remission between the 2 arms by the PP population. (B) Differences in the time in clinical remission between the 2 arms by the PP population in multiplicity adjustments. (C) Differences in the time in clinical remission between the 2 arms by the ITT population in multiplicity adjustments. (D) Differences in the time in clinical remission between the 2 arms by the ITT population in multiplicity adjustments. The data are shown for the whole cohort of patient analyzed and for specific subgroup (patients with UC or CD) analysis. Control: group of IBD patients receiving standard care with in-person visits; TECCU: group of IBD patients receiving remote monitoring. The dashed vertical line represents the non-inferiority margin of -1.5 weeks. CD: Crohn disease; ITT: intention to treat; PP: per-protocol; TECCU: Telemonitorización de la Enfermedad de Crohn y Colitis Ulcerosa or Telemonitoring of Crohn's Disease and Ulcerative Colitis; UC: ulcerative colitis.



Predicción del desarrollo y curso clínico de la EI

Apps para monitorización

frontiers | Frontiers in Immunology

TYPE: Original Research
PUBLISHED: 28 July 2022
DOI: 10.3389/fimmu.2022.915578

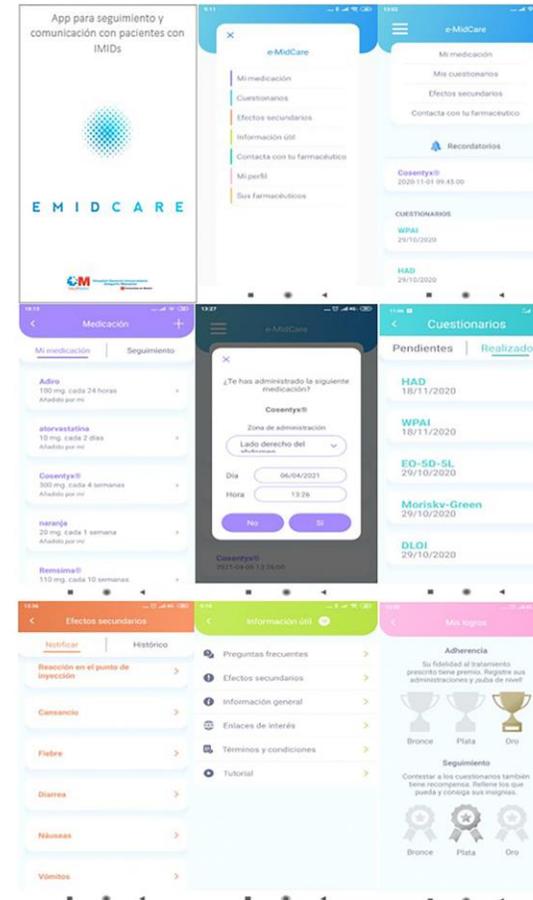
Check for updates

Design and implementation of a mobile app for the pharmacotherapeutic follow-up of patients diagnosed with immune-mediated inflammatory diseases: eMidCare

Rosa Romero-Jimenez^{1,2}, Vicente Escudero-Vilaplana^{1,2*}, Esther Chamorro-de-Vega^{1,2}, Arantza Ais-Larigoitia^{1,2}, Elena Lobato-Matilla^{1,2}, Beatriz Somoza-Fernández^{1,2}, Paula Ruiz-Briones^{1,2}, Carlos González^{2,3}, Ofelia Baniandrés^{2,4}, Luis Menchén^{2,5}, Carmen Lobo-Rodríguez^{2,6}, Ana Herranz^{1,2} and María Sanjurjo^{1,2}

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SPECIALTY SECTION
This article was submitted to Autoimmune and Autoinflammatory Disorders, a section of the journal Frontiers in Immunology



Nuevos objetivos terapéuticos

Gastroenterology 2021;160:1570-1583

STRIDE-II: An Update on the Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE) Initiative of the International Organization for the Study of IBD (IOIBD): Determining Therapeutic Goals for Treat-to-Target strategies in IBD

Dan Turner,^{1*} Amanda Ricciuto,^{2*} Ayanna Lewis,^{3*} Ferdinando D'Amico,^{4*} Jasbir Dhallwal,^{5**} Anne M. Griffiths,⁶ Dominik Bettenworth,⁶ William J. Sandborn,⁷ Bruce E. Sands,⁸ Walter Reinisch,⁹ Jürgen Schölmerich,¹⁰ Willem Bemmelman,¹¹ Silvio Danese,¹ Jean Yves Mary,¹² David Rubin,¹³ Jean-Frederic Colombel,¹⁴ Laurent Peyrin-Biroulet,¹⁵ Iris Dolan,¹⁶ Maria T. Abreu,³ and Axel Dignass,¹⁷ on behalf of the International Organization for the Study of IBD

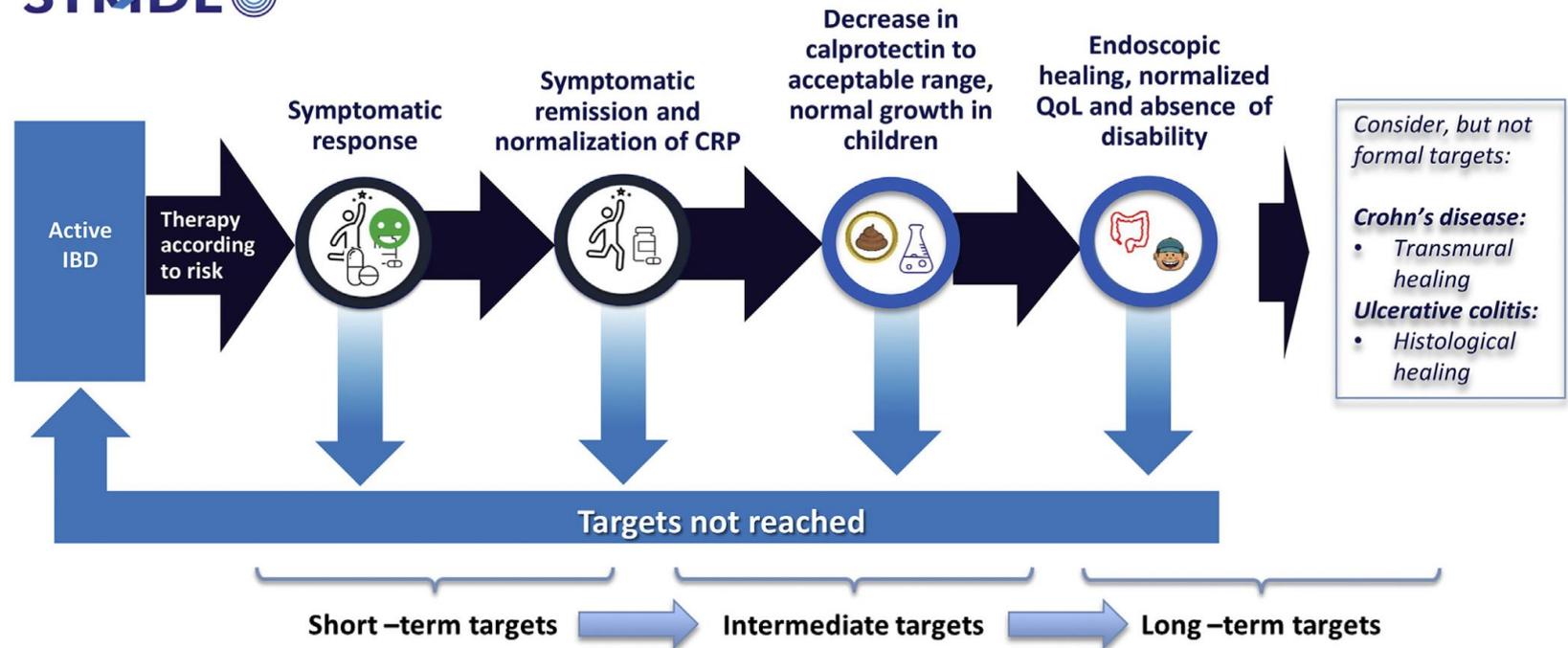


Figure 2. Treatment targets in CD and UC.

Nuevos objetivos terapéuticos

Crohn's & Colitis 360, 2024, 6, otas055
<https://doi.org/10.1093/crocol/otaa055>
 Advance access publication 10 October 2024
 Observations and Research



Clinical Approach to STRIDE-II in Real-Life Settings: Analysis and Practical Recommendations

Elena Ricart, MD, PhD,^{1,2} Guillermo Bastida, MD, PhD,³ Daniel Carpio, MD, PhD,⁴
 Daniel Ceballos, MD, PhD,⁵ Daniel Ginard, MD, PhD,⁶ Ignacio Marin-Jiménez, MD, PhD,⁷
 Luis Menchén, MD, PhD,⁸ Fernando Muñoz, MD, PhD,⁹ and Yago González-Lama, MD, PhD¹⁰

Table 6. Barriers to the implementation of STRIDE-II and suggested solutions.

Source	Barrier	Solution
STRIDE-II recommendations	-Lack of robust evidence	<ul style="list-style-type: none"> - Standardization of definitions and outcomes to facilitate clearer communication between professionals and patients - Research (validation studies, prognosis studies): Promote clinical research focusing on the validation of STRIDE-II targets, particularly in prognostic studies, to provide stronger evidence supporting the recommendations
	-Ambitious or stringent treatment goals (eg, transmural healing)	<ul style="list-style-type: none"> - Alternative treatment goals: Adopt flexible treatment goals that consider various disease states and patient responses. For example, setting more practical and achievable goals for patients who cannot meet more stringent criteria like transmural healing - Generation of composite scores: Use composite indices that combine several indicators of disease activity to better evaluate patient progress - More flexible cutoffs: Implement less rigid thresholds to account for patient variability in achieving clinical goals, ensuring treatment remains realistic - New drugs and new treatment strategies
	-Scope too general (eg, no subgroups, complex patients)	<ul style="list-style-type: none"> - Subgroup analysis: Perform detailed subgroup analyses in clinical studies to provide personalized treatment strategies for specific populations (eg, pediatric or elderly patients) - Patient stratification: Stratify patients based on disease severity, comorbidities, and response to previous treatments, allowing for more tailored treatment protocols - Adaptations to specific profiles: Adjust treatment strategies to match individual patient profiles, considering factors like genetics, disease phenotype, and lifestyle
Gastroenterologists	-Lack of knowledge and skills	<ul style="list-style-type: none"> - Educational activities: Organize continuous medical education (CME) workshops, webinars, and certifications aimed at increasing the awareness and competencies of gastroenterologists regarding STRIDE-II recommendations
	-Lack of time	<ul style="list-style-type: none"> - Consultation optimization: Streamline patient consultations by incorporating tools like pre-consultation questionnaires or digital health monitoring platforms to ensure efficient data gathering before meetings - Checklists generation: Develop checklists for key clinical steps in implementing STRIDE-II targets, ensuring that important aspects of patient care are not overlooked during time-constrained consultations
Health system	-Poor access (eg, MRE, ultrasound)	<ul style="list-style-type: none"> - Improve availability: Advocate for the allocation of more resources and infrastructure that allow for the wider availability of diagnostic tools like MRE and ultrasound in healthcare settings
	-Lack of resources	<ul style="list-style-type: none"> - Local adaptations: Tailor STRIDE-II implementations based on local health system limitations, allowing for the use of available technologies or alternative methods for monitoring disease progress
	-Lack of knowledge and skills in other health professionals (eg, endoscopists)	<ul style="list-style-type: none"> - Educational activities: Offer specialized training for health professionals such as endoscopists and radiologists, helping them better understand how to apply STRIDE-II targets and accurately interpret diagnostic findings within the framework of IBD care

Nuevos objetivos terapéuticos

AP&T

Letters to the Editors

Letter: psychological remission - a future endpoint in inflammatory bowel disease?

M. Barreiro-de Acosta* & J. P. Gisbert[†]

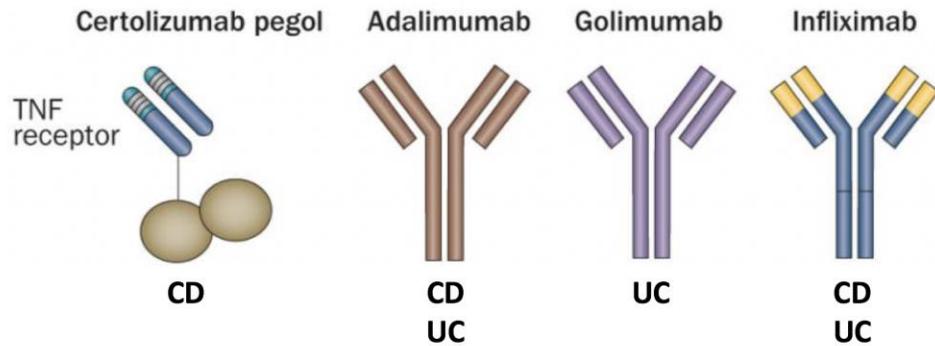
*Department of Gastroenterology, Hospital Clínico Universitario de Santiago de Compostela, Santiago, Spain.

[†]Department of Gastroenterology and Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBEREHD), Hospital Universitario de La Princesa, Instituto de Investigación Sanitaria Princesa (IP), Madrid, Spain.

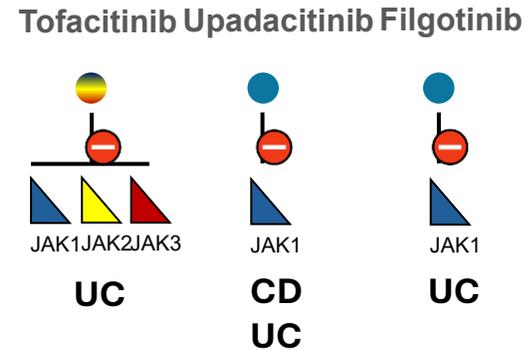
E-mail: manubarreiro@hotmail.com

Nuevas dianas terapéuticas

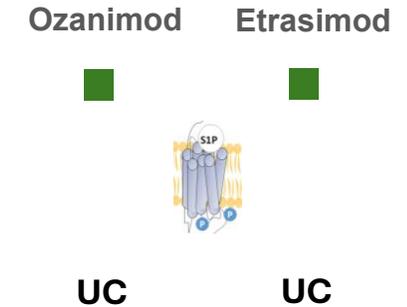
Anti-TNF



Inhibidores JAK

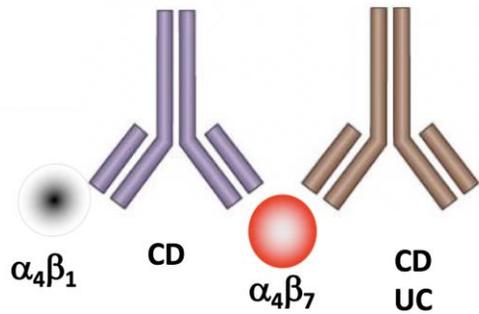


Moduladores S1P



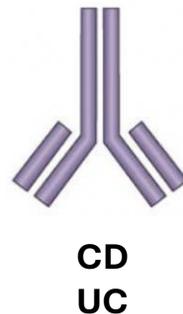
Natalizumab

Vedolizumab



Anti integrinas

Ustekinumab

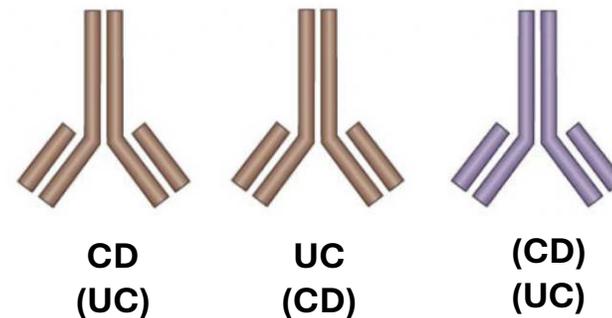


Anti-IL-12/23

Risankizumab

Mirikizumab

Guselkumab

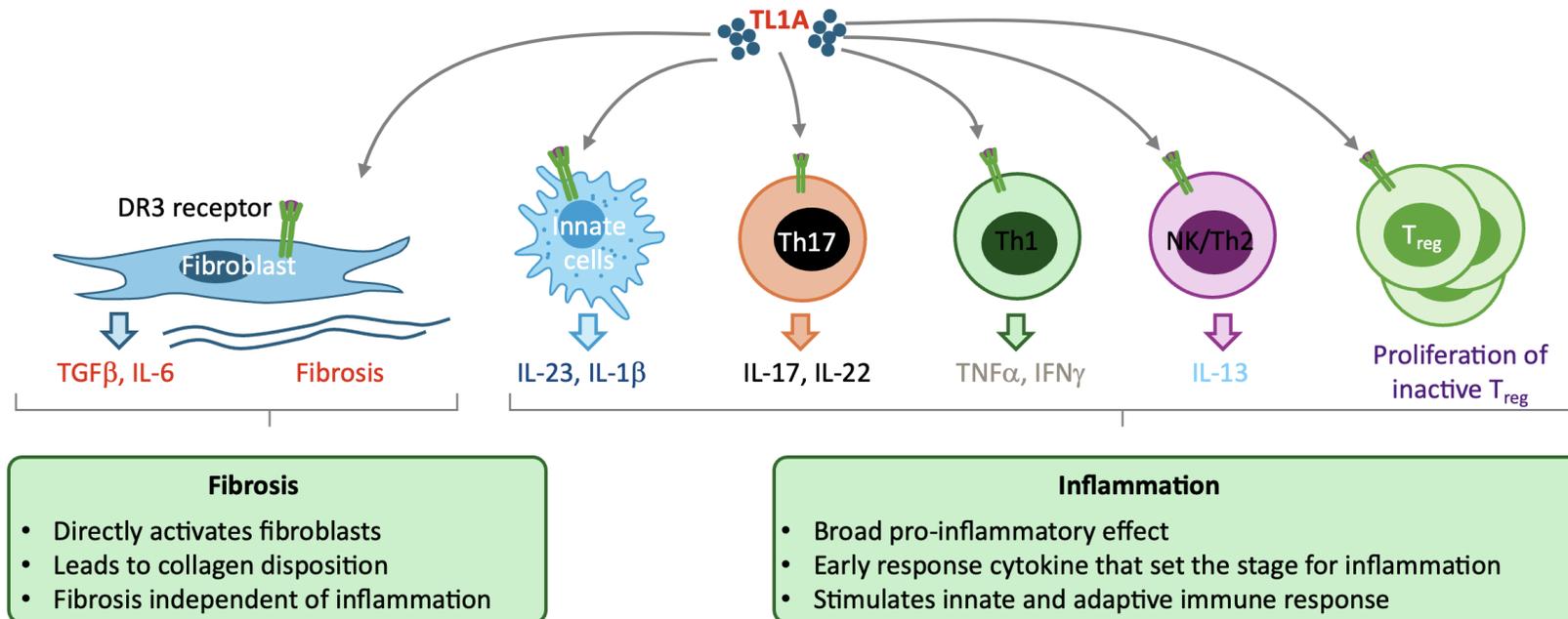


Anti-IL-23

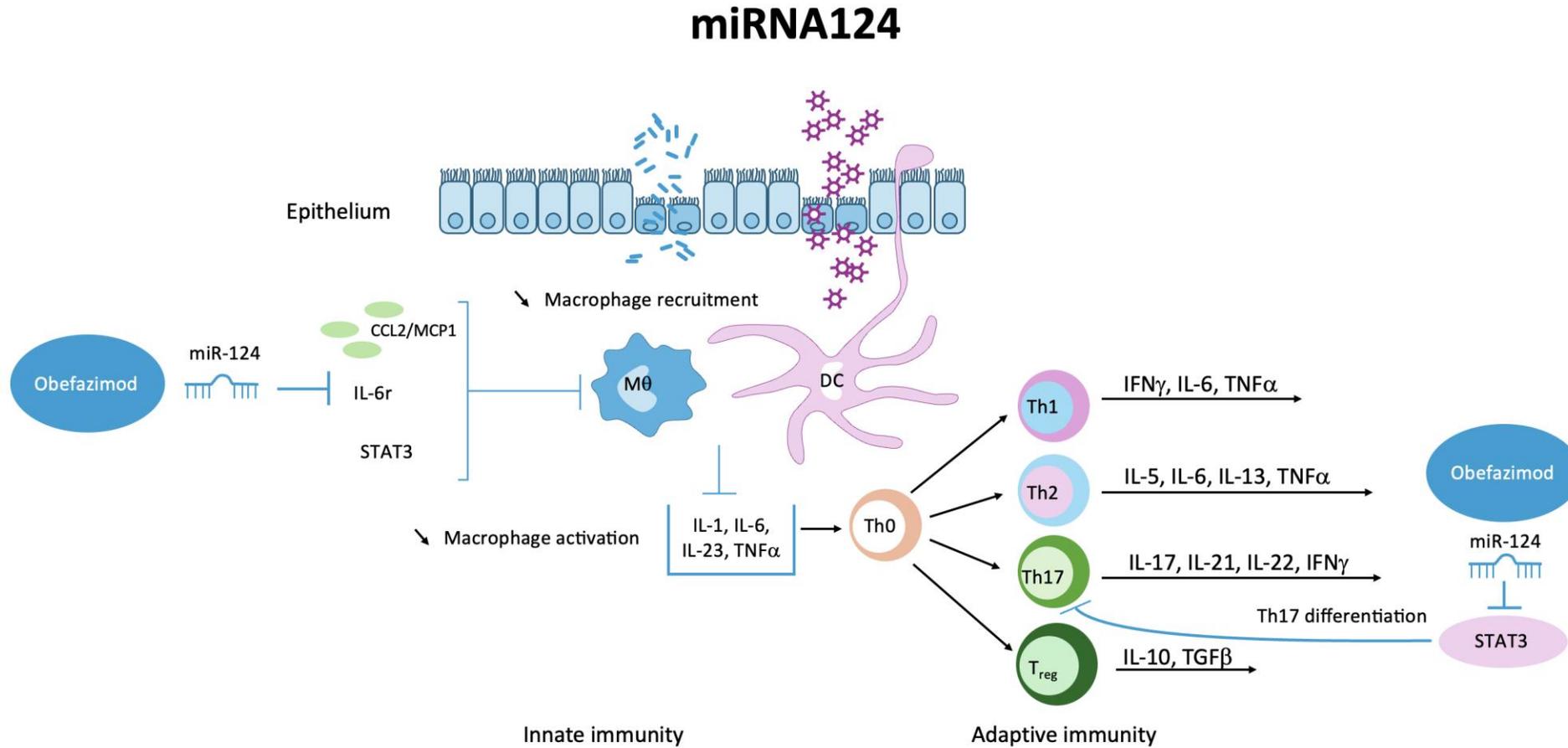
Nuevas dianas terapéuticas

Anti-TL1A

TL1A independently mediates both inflammation and fibrosis



Nuevas dianas terapéuticas



Nuevas dianas terapéuticas

Article

Bidirectional CRISPR screens decode a GLIS3-dependent fibrotic cell circuit

<https://doi.org/10.1038/s41586-025-09907-x>

Vladislav Pokatayev^{1,2,3,7}, Alok Jaiswal^{1,2,7}, Angela R. Shih⁴, Åsa Segerstolpe⁵, Bihua Li^{2,3}, Elizabeth A. Creasey^{1,4}, Yanhua Zhao⁶, Crystal Lin⁶, Shane Murphy⁷, Chih-Hung Chou⁷, Daniel B. Graham^{1,2,3,6,10} & Ramnik J. Xavier^{1,2,3,6,10}

Received: 19 December 2023

Accepted: 12 November 2025

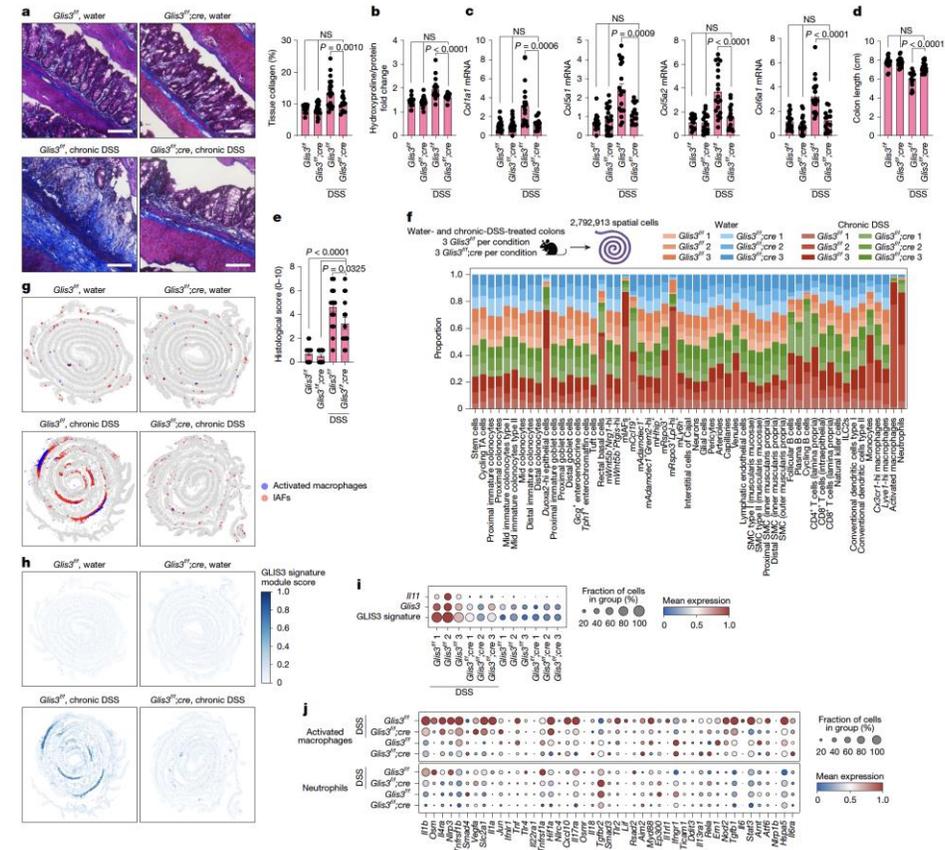


Fig. 5 | **GLIS3 is required for IAF induction and aberrant collagen deposition during colitis.** **a**, Masson's trichrome-stained *Glis3^{fl}* and *Glis3^{fl}*;cre mouse colons (5–18 weeks) treated with water or chronic DSS (left). Quantification of total

Glis3^{fl};cre mice. **h**, Spatial projection of the GLIS3 signature module score on colonic Swiss rolls of water- or chronic-DSS-treated *Glis3^{fl}* and *Glis3^{fl}*;cre mice. **i**, Dot plot showing expression of #11, *Glis3* and the GLIS3 signature for each

Nuevas dianas terapéuticas

nature COMMUNICATIONS

ARTICLE

<https://doi.org/10.1038/s41467-021-24470-5> OPEN

Artificial intelligence guided discovery of a barrier-protective therapy in inflammatory bowel disease

Debashis Sahoo^{1,2,3,10}, Lee Swanson^{4,10}, Ibrahim M. Sayed^{5,9,10}, Gajanan D. Katkar⁴, Stella-Rita Ibeawuchi⁶, Yash Mittal⁷, Rama F. Pranadinata⁴, Courtney Tindle⁴, Mackenzie Fuller⁴, Dominik L. Stec⁴, John T. Chang⁷, William J. Sandborn⁷, Soumita Das⁶ & Pradipta Ghosh^{3,4,7,8}

PMID: 27813479

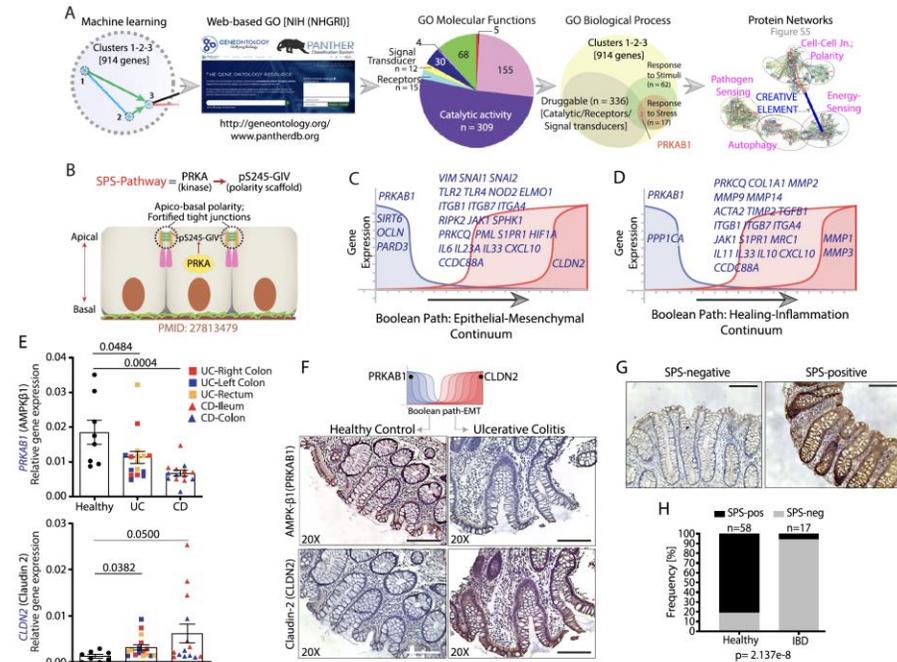


Fig. 3 Identification of PRKAB1 as a therapeutic target to promote intestinal barrier function. **A** Computational workflow for identification of PRKAB1 as a druggable target for promoting a barrier-protective transcriptional program within the IBD network. **B** Schematic summarizing key components of the SPS-pathway used in fortifying tight junctions and promoting apical-basal polarity. **C, D** Detailed view of two prominent disease paths identifying downregulation of PRKAB1 as a shared early event in IBD pathogenesis [see a complete list of genes in Table 1]. **E** The expression of PRKAB1 and CLDN2 transcript levels (qPCR) was assessed in the ileum and colon biopsies of IBD patients (UC = 16 and CD = 14) or healthy controls (n = 8). The different locations of the tissue specimens from UC and CD subjects were shown in different colors, as stated in the figure. Data represented as mean ± S.E.M. and two-tailed Mann-Whitney test using $p = 0.05$ cutoff was used to calculate significance. **F** IHC of IBD patient colon biopsies assessed for expression of PRKAB1 and CLDN2. Representative images are shown [expanded selection of IHC in Supplementary Fig. S9]. **G** Activation status of SPS-pathway was analyzed in FFPE colon biopsies from UC/CD patients using an anti-pS²⁴⁵-GIV antibody. Representative images are shown. Scale bars = 100 μ m. The method for assessing the SPS-pathway and details regarding the phospho-specific antibody is included in Supplementary Fig. S10. **H** Bar graphs showing the frequency of SPS pathway activation in healthy vs. IBD patients. Two-sided Fisher's exact test was used to calculate significance. Source data are provided as a Source Data file.

Nuevas moléculas: inhibidores IL23 v.o.

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Active, not recruiting

A Study of JNJ-77242113 in Participants With Moderately to Severely Active Ulcerative Colitis (ANTHEM-UC)

ClinicalTrials.gov ID **NCT06049017**

Sponsor **Janssen Research & Development, LLC**

Information provided by **Janssen Research & Development, LLC (Responsible Party)**

Last Update Posted **2025-12-19**

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Study Details | Researcher View | No Results Posted | Record History

On this page

- Study Overview
- Contacts and Locations
- Participation Criteria
- Study Plan
- Collaborators and Investigators
- Study Record Dates
- More Information

Study Overview

Brief Summary

The purpose of this study is to evaluate the safety and effectiveness of JNJ-77242113 compared with placebo in participants with moderately to severely active ulcerative colitis.

Official Title

A Phase 2b Multicenter, Randomized, Placebo- Controlled, Dose-Ranging Study to Evaluate the Efficacy and Safety of JNJ-77242113 for the Treatment of Moderately to Severely Active Ulcerative Colitis

Conditions

Colitis, Ulcerative

Study Start (Actual)

2023-10-09

Primary Completion (Actual)

2024-09-26

Study Completion (Estimated)

2026-01-16

Enrollment (Actual)

Nuevas estrategias terapéuticas

Intervención precoz: estratificación

- N=237. Cohorte Ibsen
- Prospectivo durante 10 años
- Incluye sólo a B1

EC AVANZADA

- Cirugía
- Necesidad de tiopurinas
- Progresión a B2 o B3



- N=489 EC
- Retrospectivo
- 5 años

DISABLING DISEASE

- Cirugía (excluyendo la inicial)
- > 2 hospitalización (excl. la inicial)
- 2 ciclos cort./año
- Cort.-dep y cort.-refractoriedad
- De novo B2 o B3
- Cambio IMM o anti-TNF



	GCS*	Colonic or ileocolonic disease at diagnosis (L2 or L3)		Small bowel disease at diagnosis (L1 or L4)	
		≥30 years at diagnosis§	<30 years at diagnosis	≥30 years at diagnosis	<30 years at diagnosis
ASCA† positive	YES	49.0% (40.1–57.9)	76.7% (69.1–84.2)	77.1% (69.6–84.6)	92.0% (87.2–96.9)
	NO	24.8% (17.1–32.5)	53.0% (44.0–61.9)	53.6% (44.7–62.6)	79.8% (72.6–87.0)
ASCA† negative	YES	21.5% (14.1–28.8)	48.3% (39.4–57.2)	49.0% (40.0–57.9)	76.6% (69.1–84.2)
	NO	8.6% (3.6–13.6)	24.3% (16.6–31.9)	24.8% (17.0–32.5)	52.9% (44.0–61.9)

Solberg I et al. Inflammatory Bowel Dis 2014

Table 3. Risk matrix showing the probability [%] of having disabling disease during the course of the disease.

	Age at diagnosis	Perianal Disease						Group S No IMM precoz
		No			Yes			
		B1	B2	B3	B1	B2	B3	
≤40	27% [21–36%]	60% [57–66%]	64% [62–65%]	72% [59–78%]	72% [67–87%]	85% [74–94%]	Group I IMM 1 ^o 6 meses	
>40	31% [17–39%]	43% [36–50%]	60% [49–62%]	66% [50–73%]	73% [58–83%]	76% [59–87%]		
≤40	85% [43–69%]	71% [67–79%]	77% [75–80%]	82% [75–90%]	90% [83–96%]	92% [84–97%]	Group S IMM 1 ^o 6 meses	
>40	45% [34–60%]	62% [58–72%]	69% [67–72%]	75% [67–86%]	86% [77–94%]	88% [78–96%]		
≤40	53% [42–66%]	71% [67–79%]	76% [74–77%]	81% [74–89%]	90% [83–96%]	91% [83–97%]	Group S IMM 1 ^o 6 meses	
>40	63% [52–75%]	78% [75–84%]	82% [81–84%]	86% [81–92%]	93% [88–98%]	94% [88–98%]		

Dias CC et al. J Crohns Colitis 2016

Nuevas estrategias terapéuticas

Intervención precoz: estratificación – profilaxis recurrencia postQx

Journal of Crohn's and Colitis, 2022, 17, 318–328
<https://doi.org/10.1093/ecco/ccj/cjaa1139>
 Advance access publication 17 September 2022
 Original Article

JCC OXFORD

Benefit of Risk-stratified Prophylactic Treatment on Clinical Outcome in Postoperative Crohn's Disease

Vincent Joustra,* Joris van Sabben,* Eline van der does de Willebois,* Marjolijn Duijvestein,* Nanne de Boer,* Jeroen Jansen,* Jarmila van der Bilt,* Wytze Lameris,* Willem Bemelman,* Christianne Buskens,* Geert D'Haens*

Benefit of risk-stratified prophylactic treatment on clinical outcome in post-operative Crohn's disease

```

  graph TD
    A[ECCO high-risk n=275] --> B[Risk stratification]
    B --> C[ECCO low-risk n=86]
    A --> D[Endoscopy <= 12 months? n=127]
    D -- No --> E[n=37 Prophylactic group]
    D -- Yes --> F[n=148 Endoscopy-driven group]
    C --> G[Endoscopy <= 12 months? n=31]
    G -- No --> H[n=31]
    G -- Yes --> I[n=55]
    I --> J[n=11 Prophylactic group]
    I --> K[n=44 Endoscopy-driven group]
  
```

Multicenter retrospective cohort
 376 adult Crohn's disease
 Ileocecal resection 2007–2018
 3 years clinical follow-up

Prophylactic vs. endoscopy-driven approach

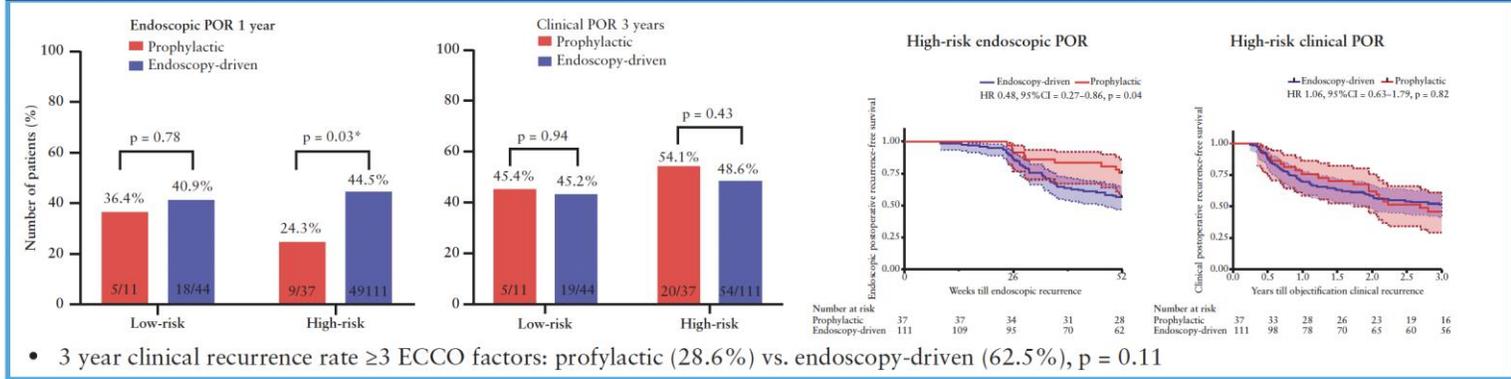
Clinical recurrence within 3 years
 IBD-related symptoms objectified with:

- CRP/F.calpro/colonoscopy/imaging or
- Start, switch or treatment intensification

Endoscopic recurrence within 1 year

- Rutgeert's $\geq 2b$

Our results indicate potential clinical benefit of prophylactic treatment in carefully selected patients with any ≥ 3 ECCO-defined risk factors and an endoscopy-driven approach in the remainder, potentially avoiding unnecessary treatment in a large number of patients.



Nuevas estrategias terapéuticas

Posicionamiento

Journal of Crohn's and Colitis, XX, 1-25
https://doi.org/10.1093/crocol/xx/xx/xx
Advance access publication 15 June 2024
ECCO Guidelines/Consensus Paper

JCC OXFORD

ECCO Guidelines on Therapeutics in Crohn's Disease: Medical Treatment

Hannah Gordon,¹ Silvia Minozzi,² Uri Kopylov,³ Bram Verstockt,^{4,5} Maria Chaparro,¹ Christianne Buskens,⁶ Janindra Warusavitame,⁷ Manasi Agrawal,⁸ Mariangela Allocca,⁹ Rajiv Atreya,¹⁰ Robert Battat,¹¹ Dominik Bettenworth,¹² Gabriele Bisleri,¹³ Steven Ross Brown,¹⁴ Johan Burtsch,¹⁵ Maria José Casanova,¹⁶ Wladyslawa Czuber-Dochan,¹⁷ Joline de Groof,¹⁸ Alaa El-Hussuna,¹⁹ Pierre Ellul,²⁰ Catarina Fidalgo,^{21,22} Gionata Fiorino,²³ Javier P Gisbert,²⁴ João Guedelha Sabino,²⁵ Jurij Hanzel,²⁶ Stefan Holubar,²⁷ Marietta Iacucci,²⁸ Nusrat Iqbal,²⁹ Christina Kapizioni,³⁰ Konstantinos Karmiris,³¹ Taku Kobayashi,³² Paulo Gustavo Kotze,³³ Gaetano Luglio,³⁴ Christian Maaser,³⁵ Gordon Moran,³⁶ Nurulamin Noor,³⁷ Konstantinos Papamichael,³⁸ Georgios Peros,³⁹ Catherine Reenaers,⁴⁰ Giuseppe Sica,⁴¹ Rotem Sigall-Boneh,⁴² Stephan R. Vavricka,⁴³ Henit Yanai,⁴⁴ Pär Myreliid,⁴⁵ Michel Adamina,⁴⁶ Tim Raine⁴⁷

Statement 5.1. We recommend **infliximab** as induction therapy with moderate-to-severe active CD [strong recommendation, moderate-quality evidence]. [Consensus: 100%]

Statement 6.1. We recommend **adalimumab** as induction therapy in patients with moderate-to-severe CD [strong recommendation, moderate-quality evidence]. [Consensus: 100%]

Statement 12.1. We recommend **vedolizumab** as induction therapy in moderate-to-severe CD [strong recommendation, moderate-quality evidence]. [Consensus: 100%]

Statement 9.1. We recommend **ustekinumab** as induction therapy in moderate-to-severe CD [strong recommendation, moderate-quality evidence]. [Consensus: 100%]

Statement 11.1. We recommend **risankizumab** as induction therapy in moderate-to-severe CD [strong recommendation, high-quality evidence]. [Consensus: 100%]

Statement 13.1. We recommend **upadacitinib** as induction therapy in moderate-to-severe CD [strong recommendation; high-quality evidence]. [Consensus: 100%]

3.9. Sequencing and combination of therapies in CD

3.9.1. Sequencing of advanced therapies in CD

Practice Point 3. There is currently **insufficient evidence** to direct how advanced therapies should be positioned in a therapeutic algorithm for luminal CD. Decisions should consider efficacy, safety, patient preferences and characteristics, disease characteristics, and cost or access to therapies. [Consensus: 97%]

Nuevas estrategias terapéuticas

Posicionamiento

Lancet 2022; 399: 2200-11

Ustekinumab versus adalimumab for induction and maintenance therapy in biologic-naive patients with moderately to severely active Crohn's disease: a multicentre, randomised, double-blind, parallel-group, phase 3b trial

*Bruce E Sands, Peter M Irving, Timothy Hoops, James L Izanec, Long-Long Gao, Christopher Gasink, Andrew Greenspan, Matthieu Allez, Silvio Danese, Stephen B Hanauer, Vipul Jairath, Tanja Kuehnbacher, James D Lewis, Edward V Loftus Jr, Emese Mihaly, Remo Panaccione, Ellen Scherl, Oksana B Shchukina, William J Sandborn, on behalf of the SEAVUE Study Group**

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Risankizumab versus Ustekinumab for Moderate-to-Severe Crohn's Disease

*L. Peyrin-Biroulet, J.C. Chapman, J.-F. Colombel, F. Caprioli, G. D'Haens, M. Ferrante, S. Schreiber, R. Atreya, S. Danese, J.O. Lindsay, P. Bossuyt, B. Siegmund, P.M. Irving, R. Panaccione, Q. Cao, E. Neimark, K. Wallace, T. Anschutz, K. Kligys, W.R. Duan, V. Pivorunas, X. Huang, S. Berg, L. Shu, and M. Dubinsky, for the SEQUENCE Study Group**

Lancet Gastroenterol Hepatol
2024; 9: 133-46

Efficacy and safety of 48 weeks of guselkumab for patients with Crohn's disease: maintenance results from the phase 2, randomised, double-blind GALAXI-1 trial

*Silvio Danese, Remo Panaccione, Brian G Feagan, Anita Afzali, David T Rubin, Bruce E Sands, Walter Reinisch, Julián Panés, Aparna Sahoo, Natalie A Terry, Daphne Chan, Chenglong Han, Mary Ellen Frustaci, Zijiang Yang, William J Sandborn, Tadakazu Hisamatsu, Jane M Andrews, Geert R D'Haens, for the GALAXI-1 Study Group**

Lancet 2024; 404: 2423-36

Efficacy and safety of mirikizumab in patients with moderately-to-severely active Crohn's disease: a phase 3, multicentre, randomised, double-blind, placebo-controlled and active-controlled, treat-through study

*Marc Ferrante, Geert D'Haens, Vipul Jairath, Silvio Danese, Minhu Chen, Subrata Ghosh, Tadakazu Hisamatsu, Jaroslaw Kierkus, Britta Siegmund, Sonja Michelle Bragg, Wallace Crandall, Frederick Durand, Emily Hon, Zhantao Lin, Michelle Ugolini Lopes, Nathan Morris, Marijana Protic, Hilde Carlier, Bruce E Sands, for the VIVID Study Group**

Nuevas estrategias terapéuticas

Combinación de terapias avanzadas

Lancet Gastroenterol Hepatol
2023; 8: 307-20

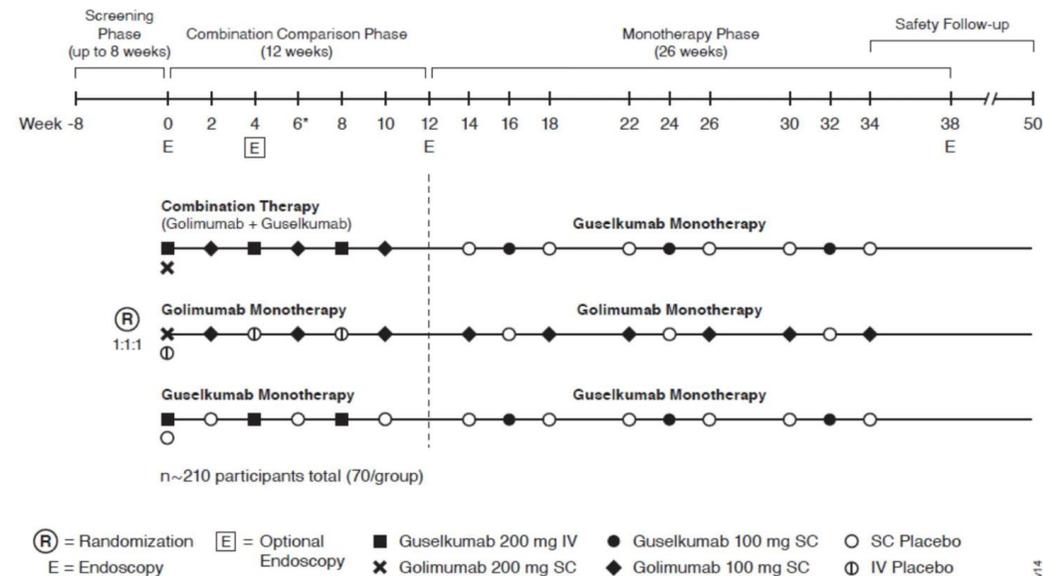
Guselkumab plus golimumab combination therapy versus guselkumab or golimumab monotherapy in patients with ulcerative colitis (VEGA): a randomised, double-blind, controlled, phase 2, proof-of-concept trial

Brian G Feagan, Bruce E Sands, William J Sandborn, Matthew Germinaro, Marion Vetter, Jie Shao, Shihong Sheng, Jewel Johans, Julidn Panés, for the VEGA Study Group*

- N=214. 18-65 a.
- Mayo 6 -12, endoscopia ≥ 2 . Stop IS
- Naive a biológicos excepto vedo / tofa
- Aleatorización 1:1:1
 - Golimumab + guselkumab
 - Golimumab
 - Guselkumab
- Objetivo primario: respuesta clínica semana 12

The primary endpoint was clinical response at week 12 (defined as $\geq 30\%$ decrease from baseline in the full Mayo score and a decrease of ≥ 3 points with either a decrease in rectal bleeding score of ≥ 1 point or a rectal bleeding score of 0 or 1). The major secondary endpoint was clinical remission at week 12 (defined as a full Mayo score of ≤ 2

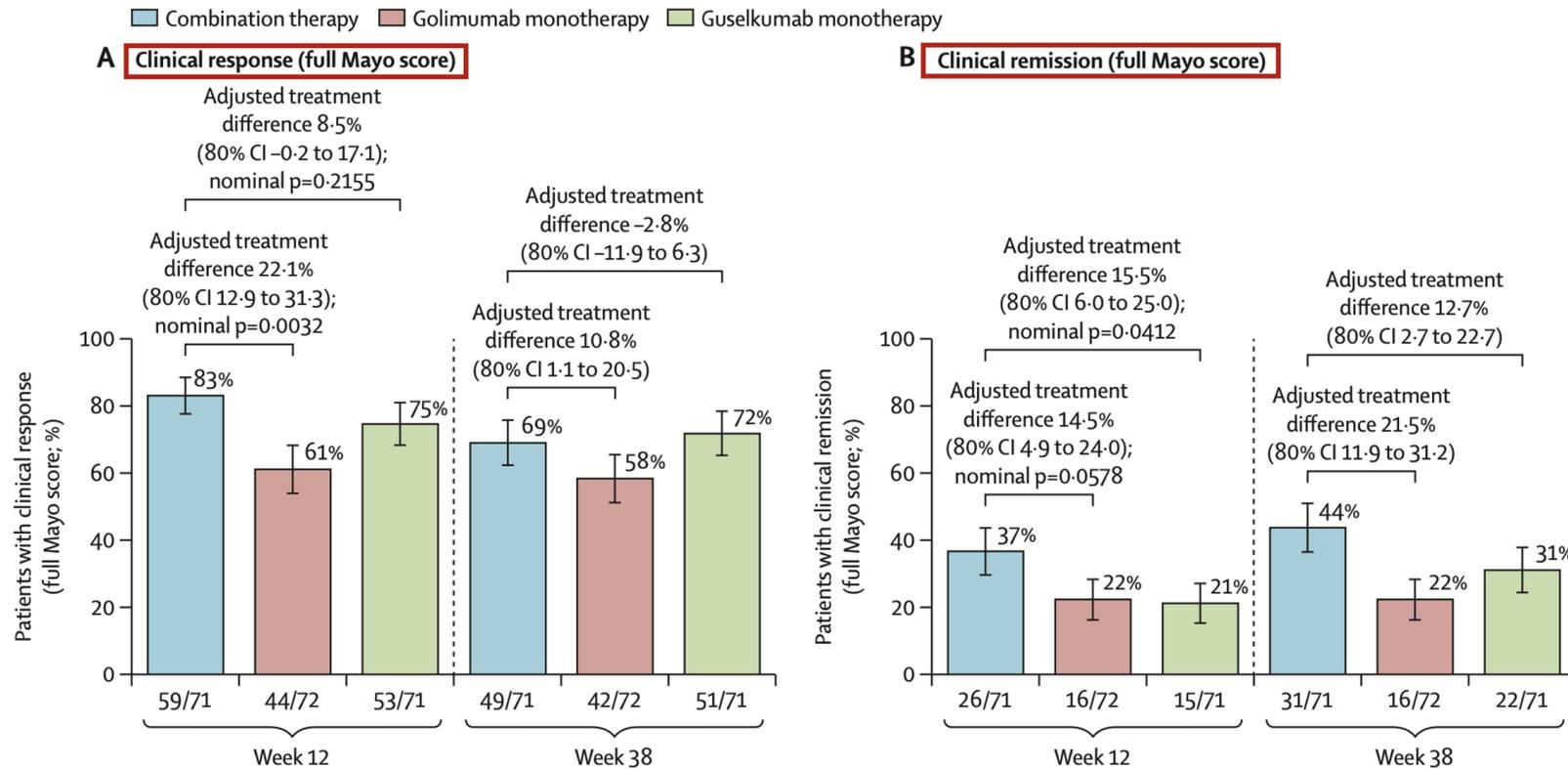
Figure S1: Study Design Schema



al remission according to the modified Mayo score (C) at weeks 12 and 38. (D) The proportion of patients in the combination group who achieved clinical remission at week 12 was significantly higher than in the monotherapy groups. The adjusted treatment difference between

Nuevas estrategias terapéuticas

Combinación de terapias avanzadas



Nuevas estrategias terapéuticas

Combinación de terapias avanzadas

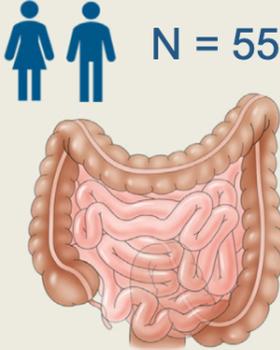
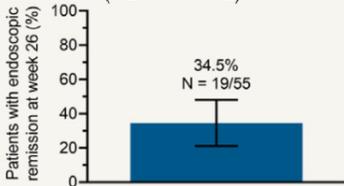
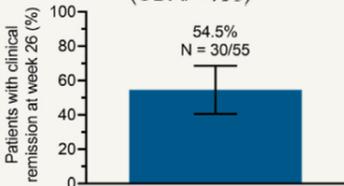
Clinical Gastroenterology and Hepatology 2024;22:1487-1496

Vedolizumab, Adalimumab, and Methotrexate Combination Therapy in Crohn's Disease (EXPLORER)

Jean-Frederic Colombel,¹ Ryan C. Ungaro,¹ Bruce E. Sands,¹ Corey A. Siegel,² Douglas C. Wolf,³ John F. Valentine,⁴ Brian G. Feagan,⁵ Blue Neustifter,⁶ Harisha Kadali,⁶ Pradeep Nazarey,⁶ Alexandra James,⁶ Vipul Jairath,⁷ and Rana M. Qasim Khan⁸

Check for updates

Phase 4, open-label study of vedolizumab, adalimumab, and methotrexate combination therapy in Crohn's disease

Patients	Treatment	Primary end point	Secondary end point
 <p>N = 55</p> <p>Biologic naïve patients with newly diagnosed, moderate to high risk CD</p>	<p>Triple combination therapy</p> <ul style="list-style-type: none"> IV vedolizumab 300 mg at weeks 0, 2, and 6 and every 8 weeks until week 102 SC adalimumab 160 mg at week 0, 80 mg at week 2, and 40 mg every 2 weeks until week 26 Oral methotrexate 15 mg weekly until week 34 	<p>Endoscopic remission at week 26 (SES-CD 0–2)</p>  <p>34.5% N = 19/55</p>	<p>Clinical remission at week 26 (CDAI <150)</p>  <p>54.5% N = 30/55</p>
		<p>Post hoc Bayesian analysis^a</p> <p>Probability that triple combination therapy produces higher endoscopic remission than benchmark rates for...</p> <ul style="list-style-type: none"> ...placebo ≥99.9% ...vedolizumab monotherapy = 86.3% ...adalimumab monotherapy = 71.4% 	

^aBeta(1.667, 5) prior. Posterior mean endoscopic remission rate = 33.5% (95% credible interval: 22.4, 45.7).
CD, Crohn's disease; CDAI, Crohn's Disease e Activity Index; IV, intravenous; SC, subcutaneous; SES-CD, Simple Endoscopic Score for Crohn's Disease

Clinical Gastroenterology and Hepatology

Nuevas estrategias terapéuticas

Combinación de terapias avanzadas

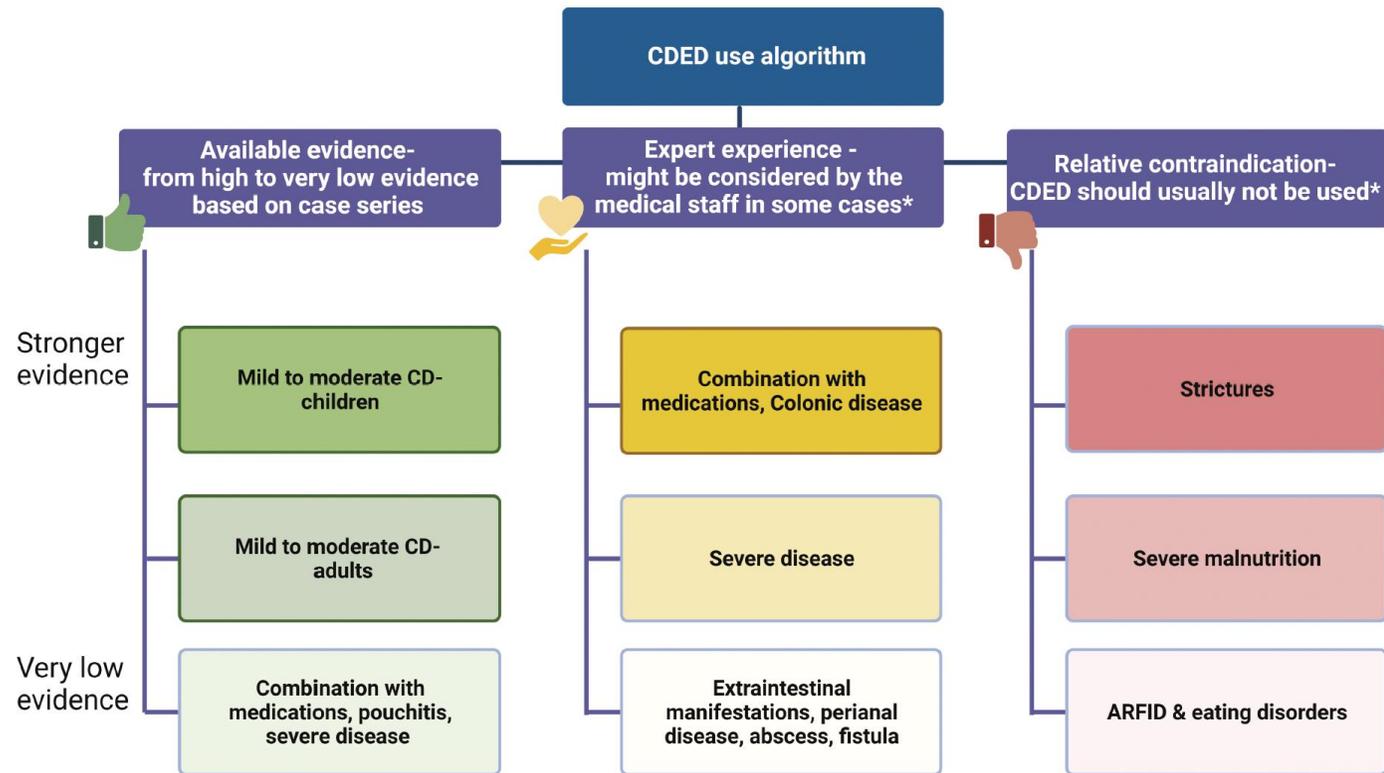


ClinicalTrials.gov

NCT Number	Study Title	Study URL	Study Status	Conditions
NCT06453317	Comparison of Ustekinumab, Infliximab and Combination Therapy in Moderately to Severely Active Ulcerative Colitis	https://clinicaltrials.gov/study/NCT06453317	NOT_YET_RECRUITING	Ulcerative Colitis Inflammatory Bowel Diseases
NCT06095596	Efficacy and Safety of Vedolizumab Combined With Upadacitinib in Patients With Ulcerative Colitis	https://clinicaltrials.gov/study/NCT06095596	RECRUITING	Crohn Disease
NCT06520397	Efficacy and Safety of Dual-targeted Therapy With Upadacitinib and Ustekinumab Versus Intensified Ustekinumab Therapy in Crohn's Disease	https://clinicaltrials.gov/study/NCT06520397	NOT_YET_RECRUITING	Crohn Disease
NCT05242471	A Study of Combination Therapy With Guselkumab and Golimumab in Participants With Moderately to Severely Active Crohn's Disease	https://clinicaltrials.gov/study/NCT05242471	ACTIVE_NOT_RECRUITING	Crohn's Disease
NCT00055536	Safety and Efficacy of Natalizumab in Combination With Remicade in the Treatment of Crohn's Disease	https://clinicaltrials.gov/study/NCT00055536	COMPLETED	Crohn's Disease
NCT05372939	Study of the Efficacy and Safety of AMT-101 in Combination With Adalimumab in Subjects With Ulcerative Colitis (MARKET)	https://clinicaltrials.gov/study/NCT05372939	COMPLETED	Ulcerative Colitis
NCT03662542	A Study of Efficacy and Safety of Combination Therapy With Guselkumab and Golimumab in Participants With Moderately to Severely Active Ulcerative Colitis	https://clinicaltrials.gov/study/NCT03662542	COMPLETED	Colitis, Ulcerative
NCT06598943	A Study of Etrekibart and Mirikizumab in Adult Patients With Moderately to Severely Active Ulcerative Colitis	https://clinicaltrials.gov/study/NCT06598943	NOT_YET_RECRUITING	Ulcerative Colitis Ulcerative Colitis Chronic
NCT05242484	A Study of Combination Therapy With Guselkumab and Golimumab in Participants With Moderately to Severely Active Ulcerative Colitis	https://clinicaltrials.gov/study/NCT05242484	ACTIVE_NOT_RECRUITING	Colitis, Ulcerative

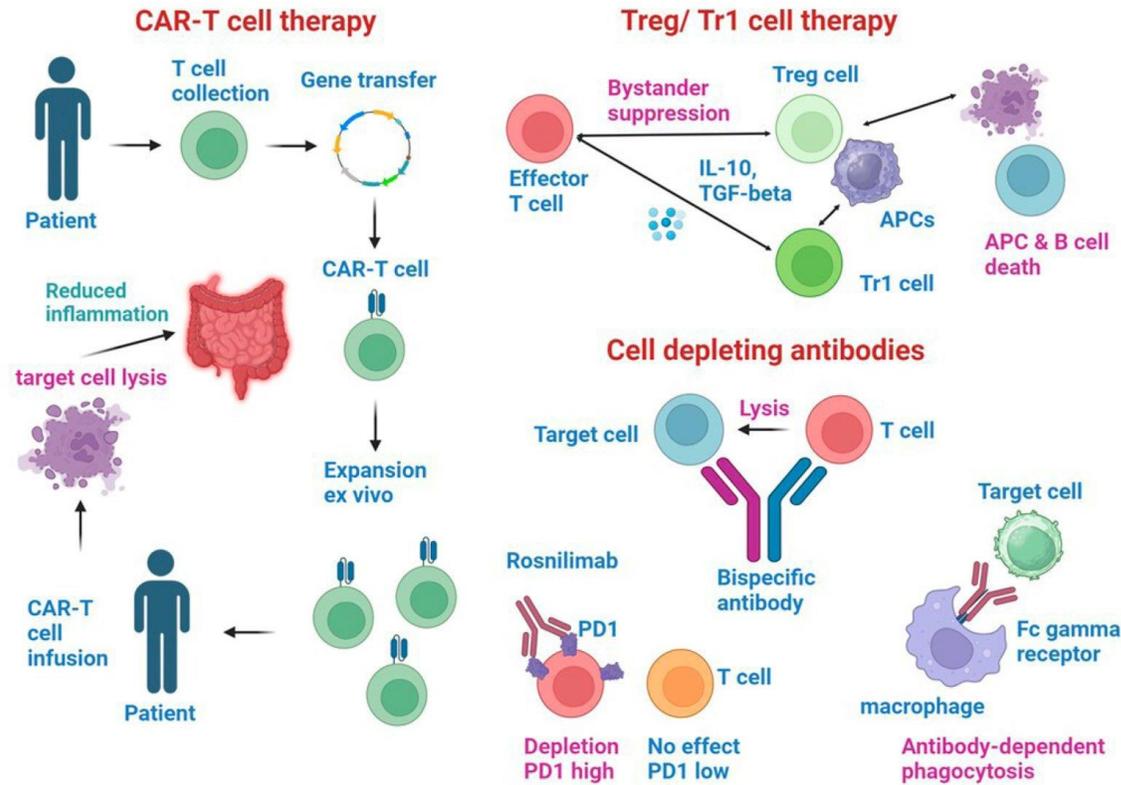
Nuevas estrategias terapéuticas

Dieta: Crohn´s Disease Exlcusion Diet



Nuevas estrategias terapéuticas

Terapia celular



Nuevas estrategias terapéuticas

Terapia celular

ARTICLES
<https://doi.org/10.1038/s41591-022-02017-5>

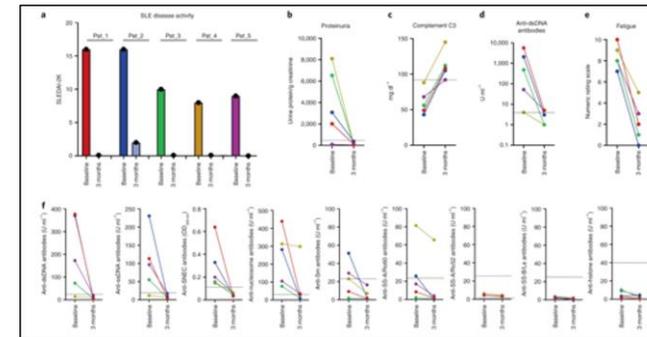
nature medicine

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Anti-CD19 CAR T cell therapy for refractory systemic lupus erythematosus

Andreas Mackensen^{1,2,8}, Fabian Müller^{1,2,8}, Dimitrios Mougiakakos^{1,2,3,8}, Sebastian Böltz^{2,4}, Artur Wilhelm^{2,4}, Michael Aigner^{1,2}, Simon Völkl^{1,2}, David Simon^{2,4}, Arnd Kleyer^{2,4}, Luis Munoz^{2,4}, Sascha Kretschmann^{1,2}, Soraya Kharboulji^{1,2}, Regina Gary^{1,2}, Hannah Reimann^{1,2}, Wolf Rösler^{1,2}, Stefan Uderhardt^{2,4}, Holger Bang⁵, Martin Herrmann^{2,4}, Arif Bülent Ekici⁶, Christian Buettner⁶, Katharina Marie Habenicht⁷, Thomas H. Winkler⁷, Gerhard Krönke^{2,4,8} and Georg Schett^{2,4,8}✉

Systemic lupus erythematosus (SLE) is a life-threatening autoimmune disease characterized by adaptive immune system activation, formation of double-stranded DNA autoantibodies and organ inflammation. Five patients with SLE (four women and one man) with a median (range) age of 22 (6) years, median (range) disease duration of 4 (8) years and active disease (median (range) SLE disease activity index Systemic Lupus Erythematosus Disease Activity Index: 16 (8)) refractory to several immunosuppressive drug treatments were enrolled in a compassionate-use chimeric antigen receptor (CAR) T cell program. Autologous T cells from patients with SLE were transduced with a lentiviral anti-CD19 CAR vector, expanded and reinfused at a dose of 1×10^6 CAR T cells per kg body weight into the patients after lymphodepletion with fludarabine and cyclophosphamide. CAR T cells expanded *in vivo*, led to deep depletion of B cells, improvement of clinical symptoms and normalization of laboratory parameters including seroconversion of anti-double-stranded DNA antibodies. Remission of SLE according to DORIS criteria was achieved in all five patients after 3 months and the median (range) Systemic Lupus Erythematosus Disease Activity Index score after 3 months was 0 (2). Drug-free remission was maintained during longer follow-up (median (range) of 8 (12) months after CAR T cell administration) and even after the reappearance of B cells, which was observed after a mean (\pm s.d.) of 110 ± 32 d after CAR T cell treatment. Reappearing B cells were naïve and showed non-class-switched B cell receptors. CAR T cell treatment was well tolerated with only mild cytokine-release syndrome. These data suggest that CD19 CAR T cell transfer is feasible, tolerable and highly effective in SLE.

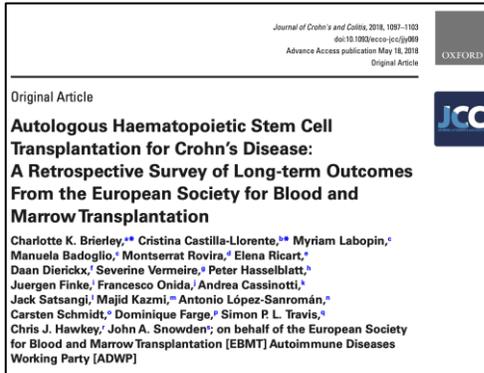


Remission of SLE according to DORIS criteria was achieved in all five patients after 3 months and the median (range) Systemic Lupus Erythematosus Disease Activity Index score after 3 months was 0 (2). Drug-free remission was maintained during longer follow-up (median (range) of 8 (12) months after CAR T cell administration) and even after the reappearance of B cells, which was observed after a mean (\pm s.d.) of 110 ± 32 d after CAR T cell treatment.

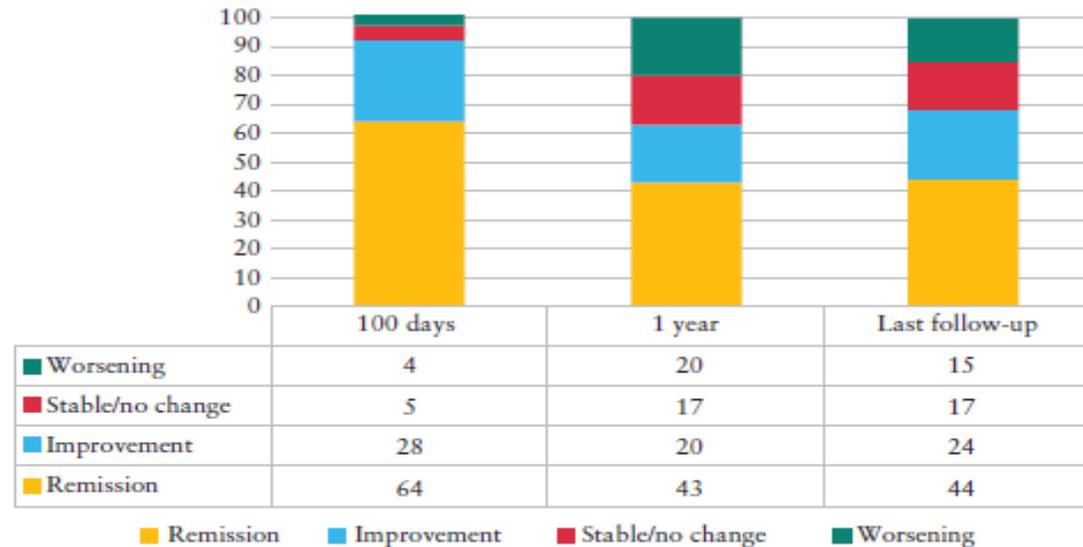


Nuevas estrategias terapéuticas

Terapia celular

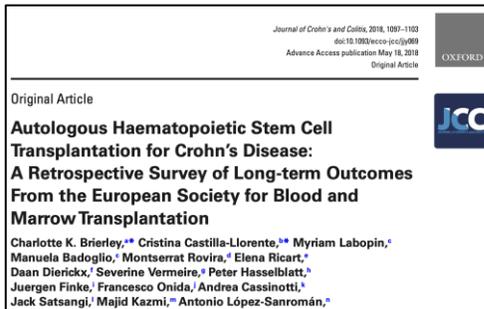


- N=82, 19 centros, 8 países; 1996-2015
- Fallo previo a una mediana de 6 fármacos; 74% cirugía previa
- Seguimiento mediano 41 m (6-174)

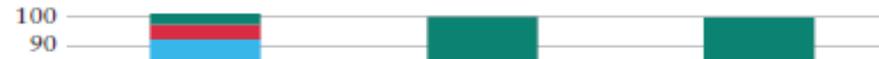


Nuevas estrategias terapéuticas

Terapia celular



- N=82, 19 centros, 8 países; 1996-2015
- Fallo previo a una mediana de 6 fármacos; 74% cirugía previa
- Seguimiento mediano 41 m (6-174)



68% remisión o mejoría significativa al final del seguimiento

27% sin necesidad de re-tto.

57% (24/42) remisión o mejoría significativa tras retratamiento

Improvement	28	20	24
Remission	64	43	44

Remission Improvement Stable/no change Worsening

Nuevas estrategias terapéuticas

Terapia celular



RESULTADO EXPEDIENTE - ICI24/00008

DATOS GENERALES

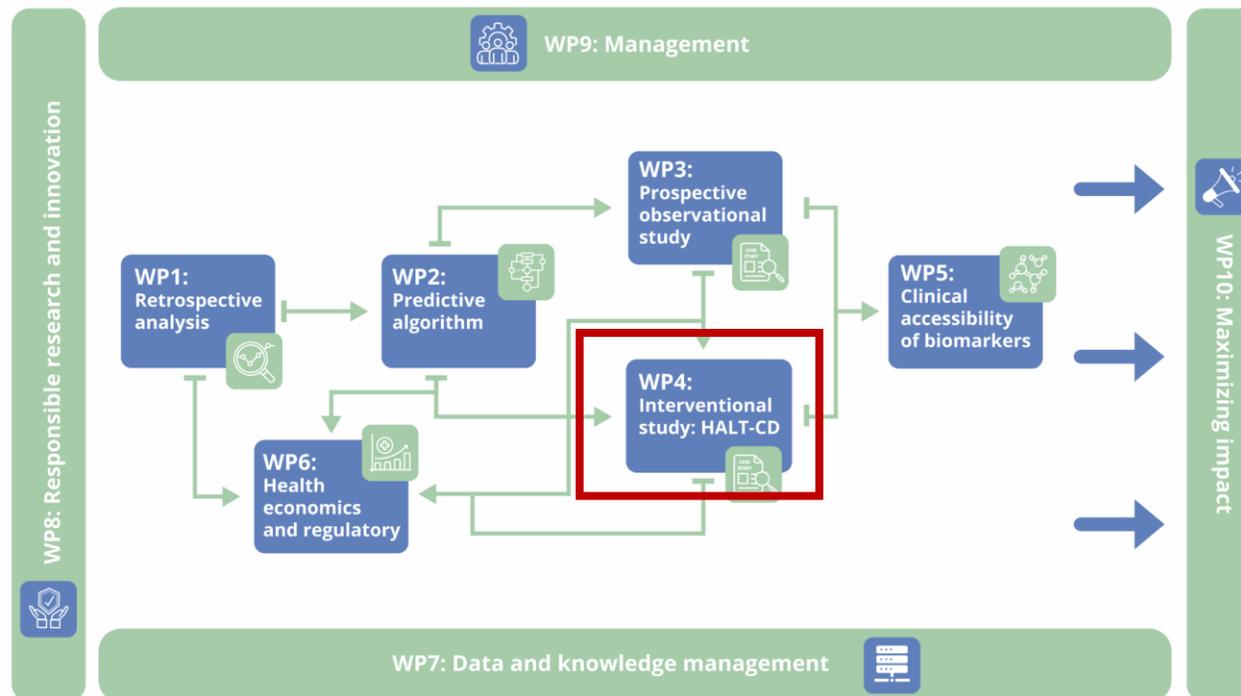
INVESTIGADOR PRINCIPAL	CORREA ROCHA, RAFAEL
COINVESTIGADOR PRINCIPAL	,
CENTRO SOLICITANTE	FUNDACION INVESTIGACION BIOMEDICA HOSPITAL GREGORIO MARAÑON
CENTRO DE REALIZACIÓN	INSTITUTO DE INVESTIGACION SANITARIA GREGORIO MARAÑON (IISGM)
CENTRO DE ADSCRIPCIÓN	FUNDACION INVESTIGACION BIOMEDICA HOSPITAL GREGORIO MARAÑON
TÍTULO	Ensayo clínico Fase I/IIa para determinar la eficacia de una terapia celular con células Treg obtenidas de tejido tímico (thyTreg) alogénicas y criopreservadas en el control de la inflamación en pacientes adultos con enfermedad de Crohn refractaria
ESTADO DE EVALUACIÓN:	FAVORABLE

RESOLUCIÓN PROVISIONAL DE CONCESIÓN

Ayuda susceptible de ser cofinanciada por FEDER

ESTADO DE RESOLUCIÓN PROVISIONAL DE CONCESIÓN: **CONCEDIDO**

Nuevas estrategias terapéuticas



Nuevas estrategias terapéuticas

JAMA. 2015;313(15):1541-1549. doi:10.1001/jama.2015.2928

Preliminary Communication

Effects of High-Dose Oral Insulin on Immune Responses in **Children at High Risk** for Type 1 Diabetes The Pre-POINT Randomized Clinical Trial

Ezio Bonifacio, PhD; Anette-G. Ziegler, MD; Georgeanna Klingensmith, MD; Edith Schober, MD;
Polly J. Bingley, MD; Marietta Rottenkolber, Dipl Stat; Anke Theil, PhD; Anne Eugster, PhD;
Ramona Puff, PhD; Claudia Peplow, Dipl Eoc Troph; Florian Buettner, PhD; Karin Lange, PhD;
Jörg Hasford, MD; Peter Achenbach, MD; for the Pre-POINT Study Group

Lancet 2024; 403: 838–49

Abatacept in **individuals at high risk** of rheumatoid arthritis (APIPPRA): a randomised, double-blind, multicentre, parallel, placebo-controlled, phase 2b clinical trial

Andrew P Cope, Marianna Jasencova, Joana C Vasconcelos, Andrew Filer, Karim Raza, Sumera Qureshi, Maria Antonietta D'Agostino,
Iain B McInnes, John D Isaacs, Arthur G Pratt, Benjamin A Fisher, Christopher D Buckley, Paul Emery, Pauline Ho, Maya H Buch, Coziana Ciurtin,
Dirkjan van Schaardenburg, Thomas Huizinga, René Toes, Evangelos Georgiou, Joanna Kelly, Caroline Murphy, A Toby Prevost, on behalf of the
APIPPRA study investigators*

Medicina basada en valor

Clinical Gastroenterology and Hepatology 2024;22:923-932

NARRATIVE REVIEWS

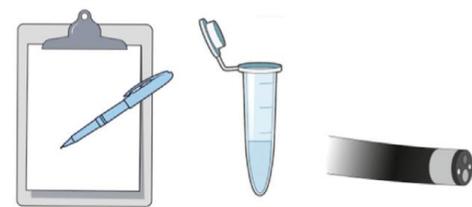
Charles J. Kahi, Section Editor

Common Instances of Low-value Care in Inflammatory Bowel Diseases

Siddharth Singh,^{1,2} Fernando S. Velayos,³ and David T. Rubin⁴

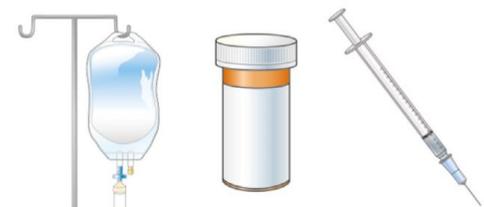
Check for updates

Diagnosis and monitoring



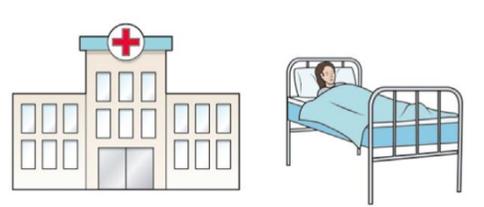
- Use of serology for diagnosis of IBD
- Over-reliance on symptoms for monitoring disease activity and major treatment decisions
- Failure to treat-to-target, particularly in symptomatic patients with IBD
- Annual surveillance colonoscopies for dysplasia surveillance in patients with IBD at low risk of developing dysplasia

Treatment



- Use of 5-aminosalicylates for treating CD
- Routinely continuing 5-aminosalicylates after escalation to immunosuppressive therapies in patients with IBD
- Chronic and/or repeated use of systemic corticosteroids, without attempting steroid-sparing strategies
- Step therapy in Crohn's disease in patients at high risk of disease-related complications
- Failure to optimize dosing of TNF antagonists, in patients with active disease
- Failure to consider de-escalation of TNF antagonists in patients who have achieved stable remission with intensive dosing regimens

Hospitalized patients



- Routine cross-sectional imaging with CT for patients presenting to Emergency Department
- Withholding pharmacological prophylaxis for venous thromboembolism in patients hospitalized with IBD flare
- Prolonged use of high dose intravenous corticosteroids despite lack of clinical improvement in patients hospitalized with acute severe ulcerative colitis

Medicina basada en valor

Gut 2025;0:1–34. doi:10.1136/gutjnl-2025-335023

British Society of Gastroenterology guidelines on colorectal surveillance in inflammatory bowel disease

James Edward East ¹, Morris Gordon ², Gaurav Bhaskar Nigam ¹, Vassiliki Sinopoulou ², Adrian C Bateman ³, Shahida Din ^{4,5}, Marietta Iacucci ⁶, Misha Kabir ⁷, Christopher Andrew Lamb ^{8,9}, Ana Wilson ^{10,11}, Ibrahim Al Bakir ¹², Anjan Dhar ^{13,14}, Sunil Dolwani ¹⁵, Omar Faiz ^{16,17}, Ailsa Hart ^{10,11}, Bu Hussain Hayee ¹⁸, Chris Healey ¹⁹, Simon John Leedham ^{1,20}, Marco R Novelli ²¹, Tim Raine ²², Matthew D Rutter ²³, Neil A Shepherd ²⁴, Venkataraman Subramanian ^{25,26}, Margaret Vance ¹⁹, Ruth Wakeman ²⁷, Lydia White ¹, Nigel J Trudgill ^{28,29}, A John Morris ³⁰

Risk Calculator

Please enter the following details:

What is the date of assessment?

dd/mm/yyyy

What was the year of IBD diagnosis?

YYYY

What is the age at diagnosis?

Select Age

Based on current or previous endoscopy, was there evidence of extensive disease (i.e., >50% colonic involvement or Montreal E3 disease)?

Yes No

Does the individual have a diagnosis of Primary Sclerosing Cholangitis (PSC)?

Yes No

Is there history of prior dysplasia (including indefinite for dysplasia (IND) or low-grade dysplasia (LGD), identified during current or previous procedures)?

Yes No

What is the gender of the individual?

Male Female

What was the type of IBD diagnosis?

Ulcerative Colitis or IBD-
Unclassified Crohn's
Disease

Were post-inflammatory polyps identified during current or previous procedures?

Yes No

What is the highest grade of endoscopic inflammation based on the current or most recent procedure?

Severe Moderate Mild No
Inflammation

Calculate Risk

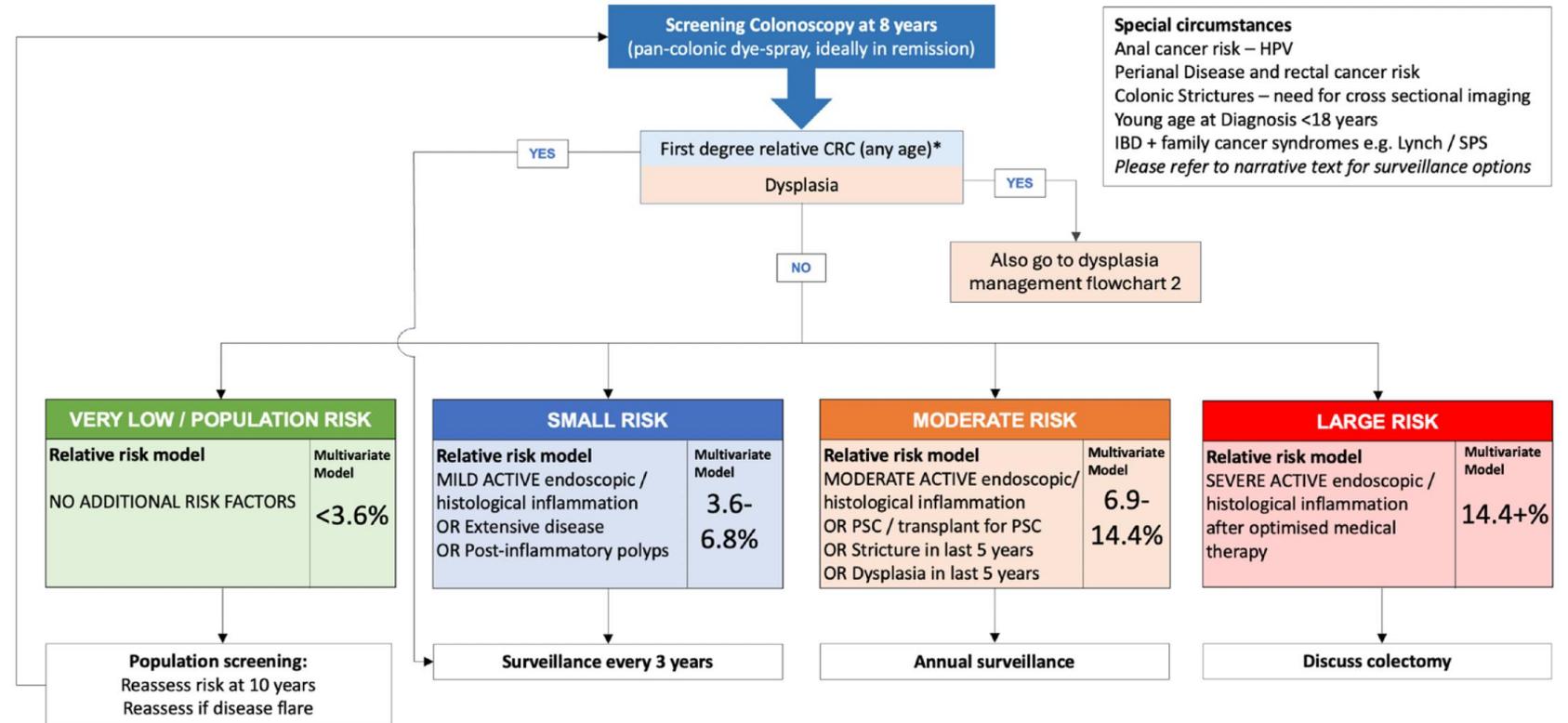
Medicina basada en valor

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British Society of Gastroenterology guidelines on colorectal surveillance in inflammatory bowel disease

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RISK STRATIFICATION FOR IBD SURVEILLANCE FLOWCHART 2025



Medicina basada en valor

Journal of Crohn's and Colitis, 2022, 17, 379–388
https://doi.org/10.1093/ecco-ccj/cjg145
Advance access publication 27 September 2022
Original Article

JCC OXFORD

What are the Unmet Needs and Most Relevant Treatment Outcomes According to Patients with Inflammatory Bowel Disease? A Qualitative Patient Preference Study

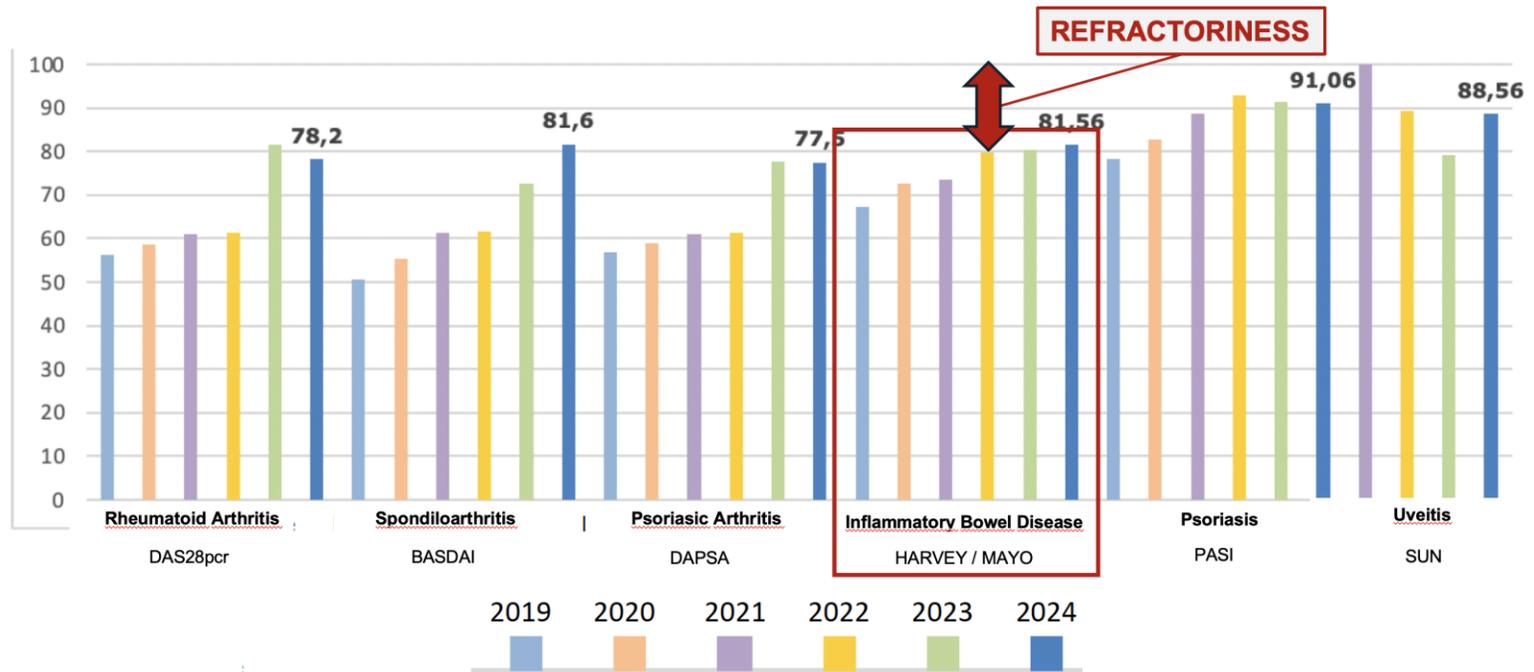
Elise Schoefs,^a Séverine Vermeire,^{b,c} Marc Ferrante,^{b,c} João Sabino,^{b,c} Tessy Lambrechts,^b Luisa Avedano,^d Isabella Haaf,^d Maria Stella De Rocchis,^d Andrea Broggi,^d Magdalena Sajak-Szczerba,^d Roberto Saldaña,^e Rosanne Janssens,^e Isabelle Huys^e

Table 2. Top ten characteristics identified in the attribute grading exercise

Rank	Characteristic	Mean score
1	Prevent surgery	9.55
2	Long-term clinical remission	9.45
3	Improved quality of life	9.36
4	Occurrence of urgency	9.27
5	Improved labour rate	9.27
6	Occurrence of diarrhoea	9.18
7	Occurrence of severe infections	9.18
8	Prevent hospitalization	9.09
9	Occurrence of joint pain	9.00
10	Prevent flare-ups	9.00

Medicina basada en valor

OUR DATA ON CLINICAL REMISSION (Steroid-free for IBD)



Agenda global de investigación en EII:

6 dominios prioritarios para el futuro

1. Comprender la carga epidemiológica global (7 prioridades)

- 1.2 Investigación poblacional de alta calidad sobre sistemas sanitarios
- 1.1 Análisis geoespacial y temporal en 4 etapas epidemiológicas
- 1.6 Investigación en poblaciones infrarrepresentadas

2. Modelos asistenciales (6 prioridades)

- 2.6 Colaboración multidisciplinar en Atención Primaria
- 2.5 Guías claras para derivación precoz
- 2.3 Impacto económico en sistemas sanitarios

3. Estrategias terapéuticas (6 prioridades)

- 3.1 Vías clínicas para diagnóstico e intervención precoz
- 3.6 Evaluación de fibrosis y complicaciones
- 3.4 Tratamientos combinados farmacológicos y no farmacológicos

4. Educación y concienciación (6 prioridades)

- 4.6 Educación del paciente en diagnóstico y remisión funcional
- 4.3 Recursos educativos para Atención Primaria
- 4.2 Formación con énfasis en dieta y nutrición

5. Pacientes y comunidad (6 prioridades)

- 5.5 Apoyo psicosocial y salud mental
- 5.1 Alineación de objetivos clínicos y del paciente
- 5.3 Acceso equitativo a centros especializados

6. Liderazgo y equidad (6 prioridades)

- 6.4 Modelos asistenciales en entornos con recursos limitados
- 6.6 Participación de organizaciones de pacientes
- 6.2 Indicadores mínimos de equidad sanitaria