Cytokines' network in PsA/SpA

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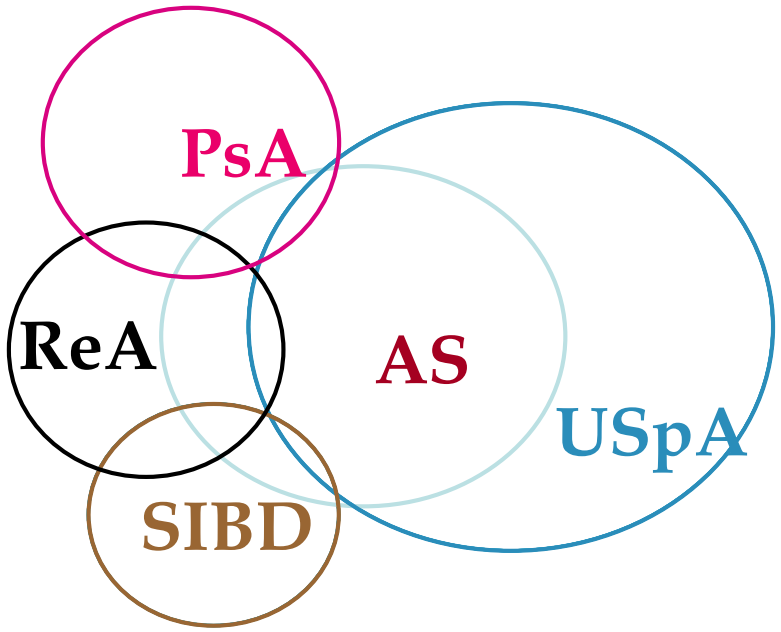
Conflicts of interest

- Honoraria/Speaker fees
  - Abbvie, Aenorasis, Pfizer, Novartis, UCB, Janssen, Lilly, Amgen

Spondyloarthritis

Axial spondyloarthritis (AxSpA) and Psoriatic arthritis (PsA)

SpA: Overlapping entities



AS **Ankylosing spondylitis**

PsA **Psoriatic arthritis**

USpA **Undifferentiated SpA**

ReA **Reactive arthritis**

SIBD **SpA με IBD**

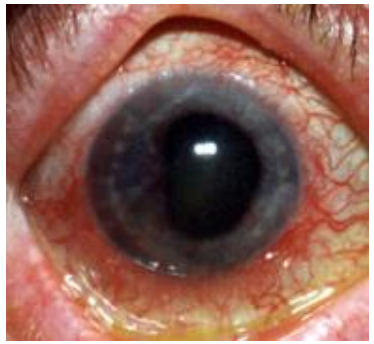
Davis JC & Mease PJ Semin Arthr & Rheum 2008

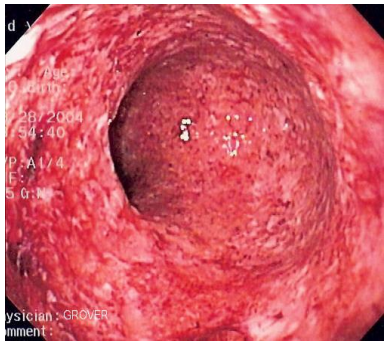
SpA

Shared Clinical manifestations

- PsA and AxSpA
  - Share clinical manifestations
  - Inflammatory bowel disease (AxSpA [15-30%] > PsA [5%])
  - Uveitis (AxSpA [10-20%] > PsA [5%])
  - Psoriasis (PsA>AxSpA [10%])
  - Peripheral arthritis (PsA>AxSpA)
  - Axial Disease (AxSpA [100%] > PsA [25%])





Chandran et al J Autoimmun 2010

SpA

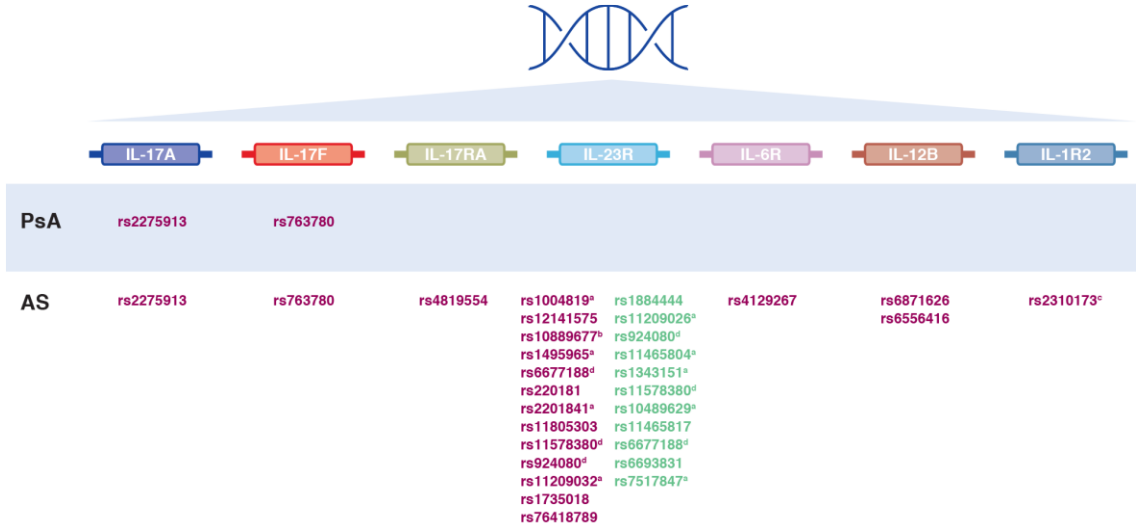
Pathogenesis

- Genetic factors
- Environmental factors
  - Microbiome
- Mechanical stress

Pathogenesis

Genetics HLA

- HLA-B27
  - In AxSpA
  - In about 20-30% of PsA
  - Associated with
    - Axial disease
    - Dactylitis
    - Uveitis
    - Poor prognosis



McGonagle D et al Ann Rheum Dis 2019

Queiro R Rheumatology (Oxford) 2016
Rauner N et al. J Rheum 2009
Aschermann S Joint Bone Spine 2006
Neerinckx B et al RMD Open 2017

SpA pathogenesis

Genetics…..and non-HLA

- Genetic factors
  - Outside HLA – mainly in pathways
    - IFN
    - TNF
    - IL-23/-17

Gene	PSO	PsA
HLA		
PSORS1	X	X
HLA-C*0704	X	
HLA-C*1203	X	
HLA-B27	X	X
HLA-B57	X	X
HLADQA1	X	
HLA-B13		X
HLA-B08		X
HLA-B37	X	
HLA-B38		X
HLA-B39		X
HLA-DRB1*04		X
IFN signalling		
ELMO1	X	
SOCS1	X	
RNF114	X	
IFIH1	X	
MDA5	X	
DDX58	X	
TYK2	X	X
IL-23/17 signalling		
IL-23A (p19)	X	X
IL-12B (p40)	X	X
IL-23R	X	X
TYK2	X	X
JAK2	X	
STAT3	X	X
TRAF3IP2	X	X
SOCS1	X	
ETS1	X	

(modif)Cafaro G, McInnes IB Clin Rheum 2018

SpA pathogenesis

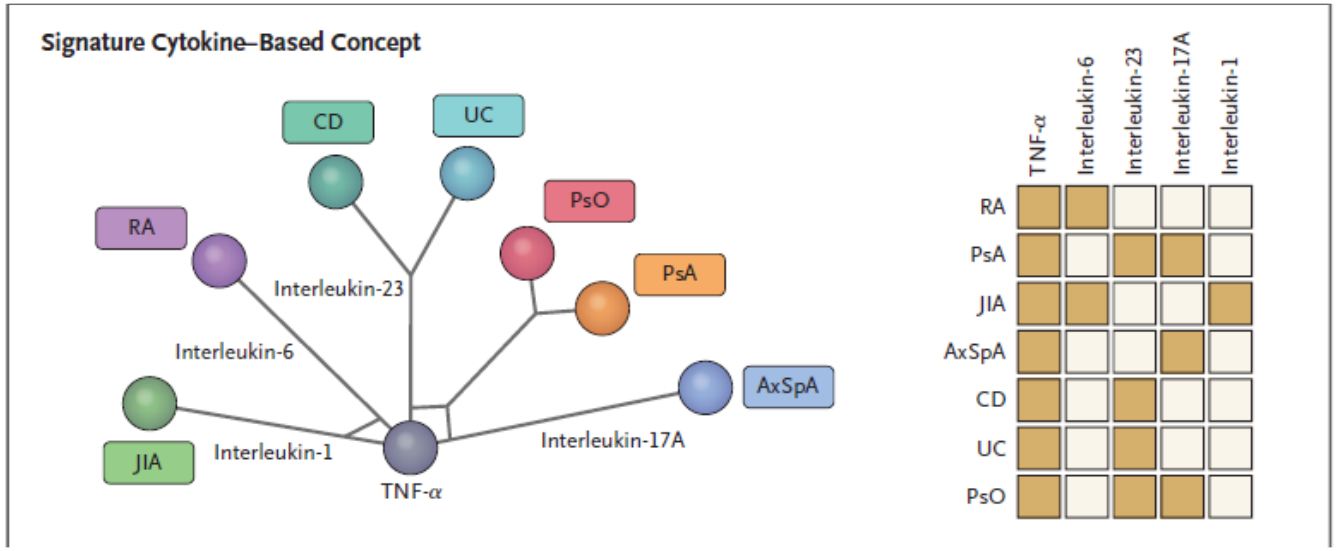
Environmental factors

- Environmental factors
  - Microbiome
- HLA-B27 Tg mice or SKG mice
  - IBD-like, psoriasis-like rash, arthritis, sacroiliitis
    - Lees pronounced in germ free conditions
- Psoriatic arthritis Vs Healthy individuals
  - ⇩ Akkermansia/Ruminococcus/Coprococcus

Scher J et al Arthr Rheum 2015
Taurog J et al JEM 1994

Cytokines

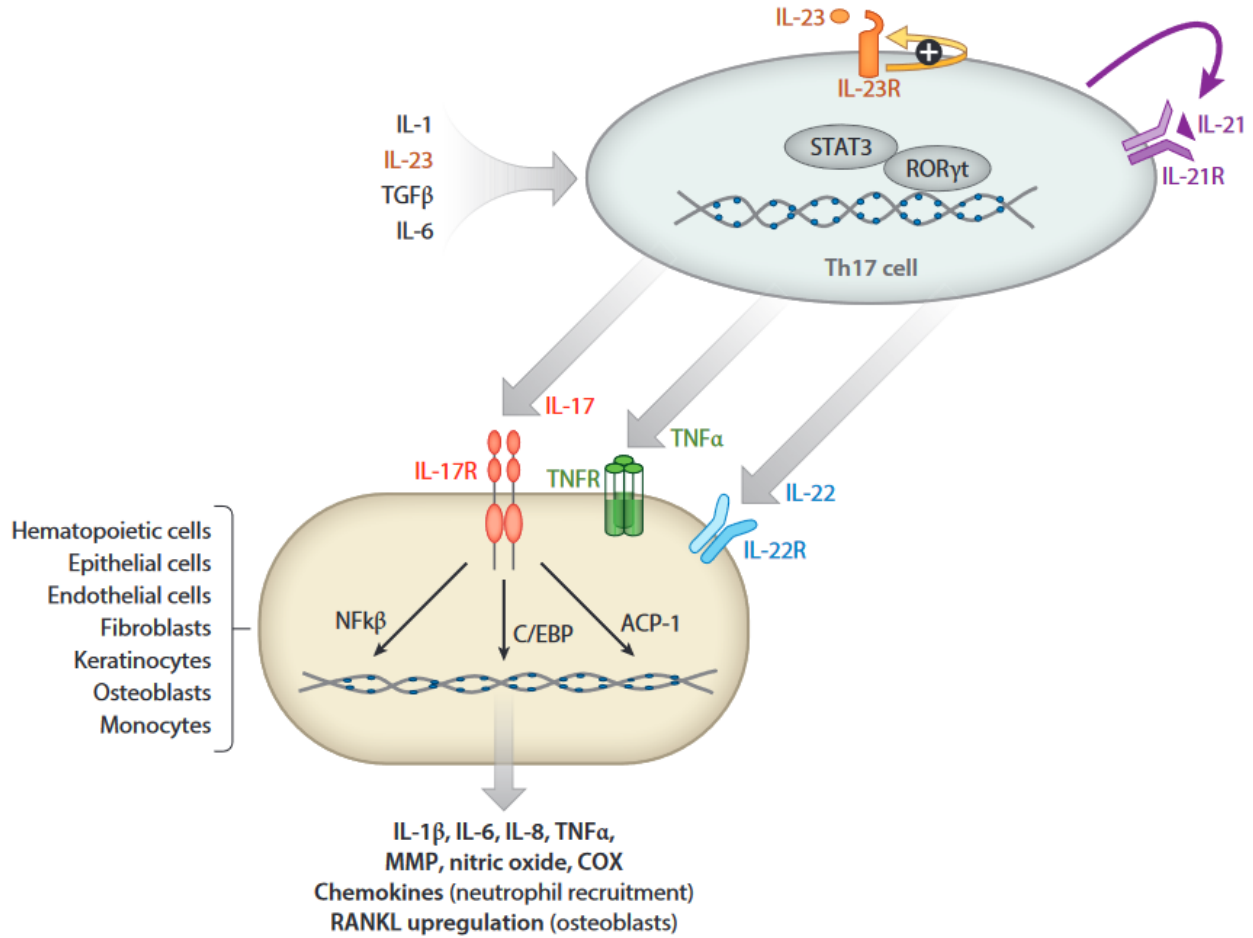
Different drivers according to disease type? (Updated?)



Schett G et al. NEJM 2021

The cytokines

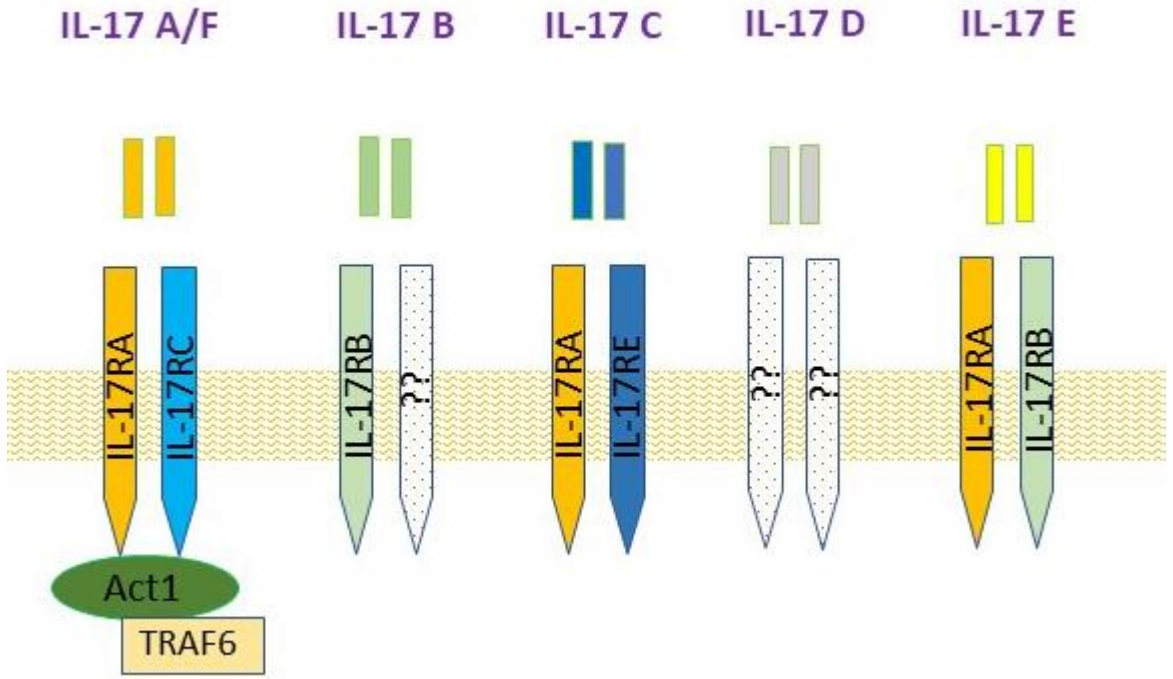
IL-23/IL-17/TNF/IL-22



Gaffen et al Immunology 2014
Fragoulis et al Ann Rev Med 2016
Frleta et al Curr Rheum Rep 2014

IL-17
the players

- 6 members (IL-17A through -F)
  - IL-17A and IL-17F the most well characterized
  - Form homodimers and heterodimers
    - which act with diverse affinity
    - through the five IL-17 receptors (IL-17Rs)



Fragoulis & Siebert, Oxford Textbook Rheumatology 2023

IL-17

PsA

- Mononuclear cells
  - Synovial fluid (SF)
  - PsA (n = 20), RA (n = 20), OA (n = 20)
    - ⇧ Th17 in PsA (SF)

Table 1 Enrichment of CD4+ IL-17+ T lymphocytes in the synovial fluid of psoriatic arthritis patients compared to the controls

Study group	%CD4+IL-17+ T lymphocytes (mean ± SD)	
	SFMC	PBMC
Psoriatic arthritis ($n = 12$)	7.9 ± 2.8*	0.9 ± 0.6
Rheumatoid arthritis ($n = 8$)	8.2 ± 3.1*	1.0 ± 0.6
Osteoarthritis ($n = 12$)	0.7 ± 0.3	0.6 ± 0.2
Healthy volunteers ($n = 12$)	Not done	0.6 ± 0.2

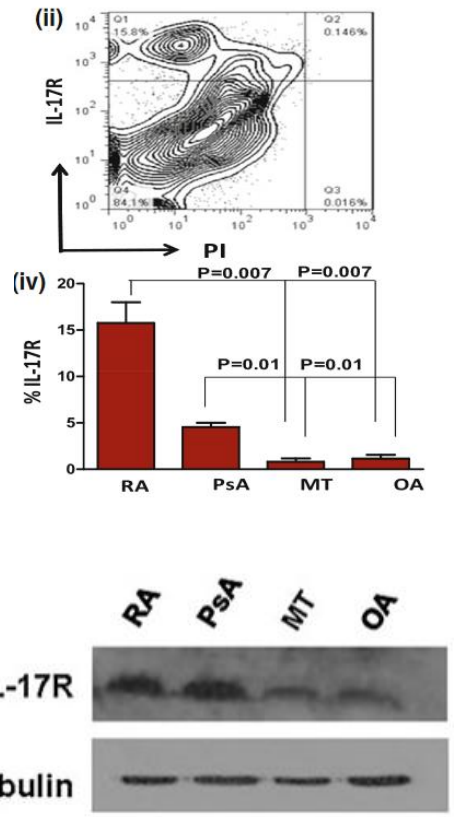
* $P < .001$, Student t test, comparison between psoriatic arthritis and osteoarthritis; and rheumatoid arthritis and osteoarthritis. *SFMC* synovial fluid mononuclear cells, *PBMC* peripheral blood mononuclear cells

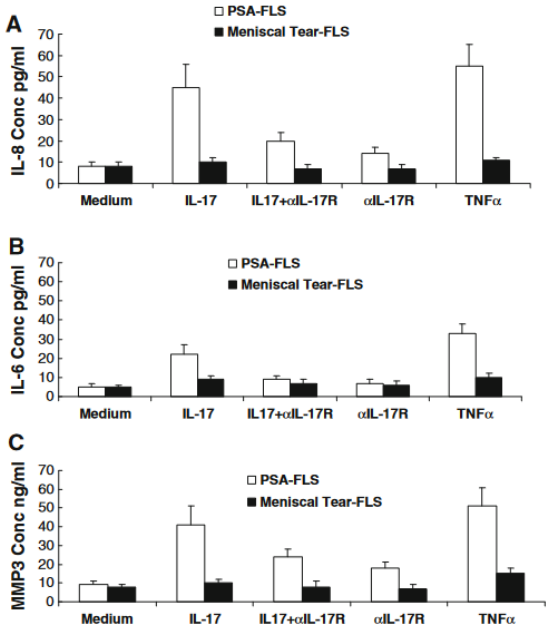
Raychaudhuri et al Mol Cell Bioch 2012

IL-17

PsA

- Synoviocytes (FLS)
  - PsA (n = 5), RA (n = 5), OA (n = 5)
  - IL-17R
    - Higher in PsA
    - rIL-17 induced
      - ✓ IL-6, IL-8, and MMP-3 production in PsA-FLS
    - anti-IL-17RA antibody inhibited the production of IL-6, IL-8, and MMP-3



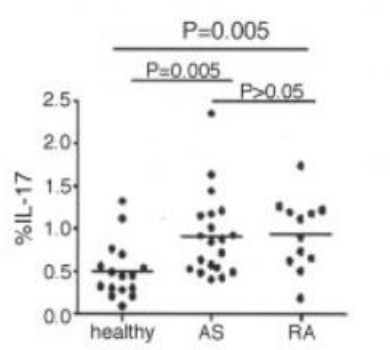


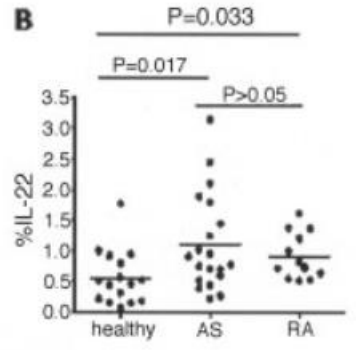
Raychaudhuri et al Mol Cell Bioch 2012

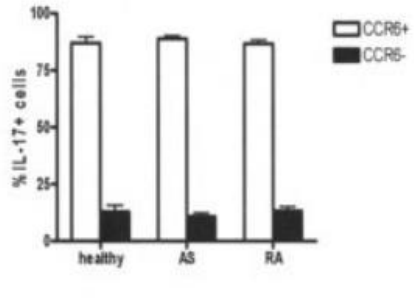
IL-17

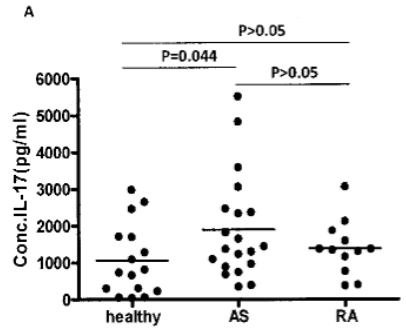
AxSpA

- PBMCs
  - AS (n=20)Vs RA (n=12) Vs HC (n=16)
  - ⇧ AS Vs HC
    - PBMCs: % of IL-17–CD4+ T cells
    - PBMCs: % IL-22–CD4+ T cells
    - IL-17







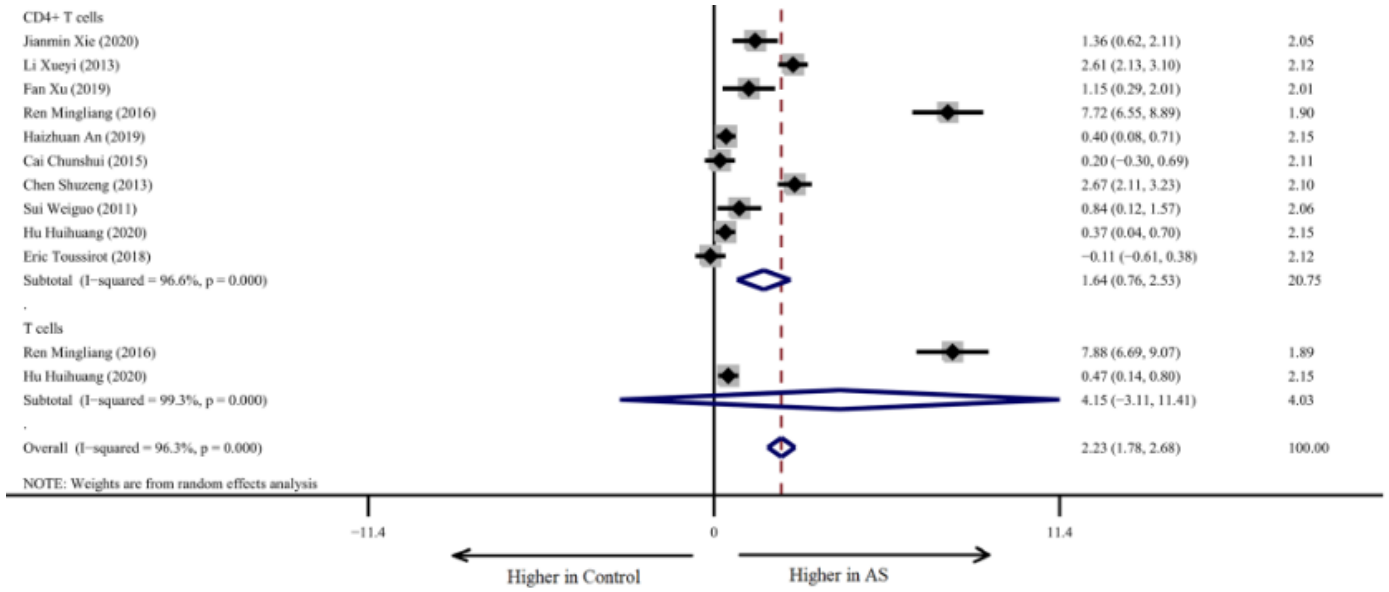


Shen et al Arthr & Rheum 2019

IL-17

SpA – meta-analysis

- 138 studies
- ⇧ AS vs HC
  - % Th17 cells
    - ⇧ in active AS



Su et al Adv Ther 2022

IL-17

SpA – meta-analysis

- Levels of IL-17
  - ⇧ AS vs HC

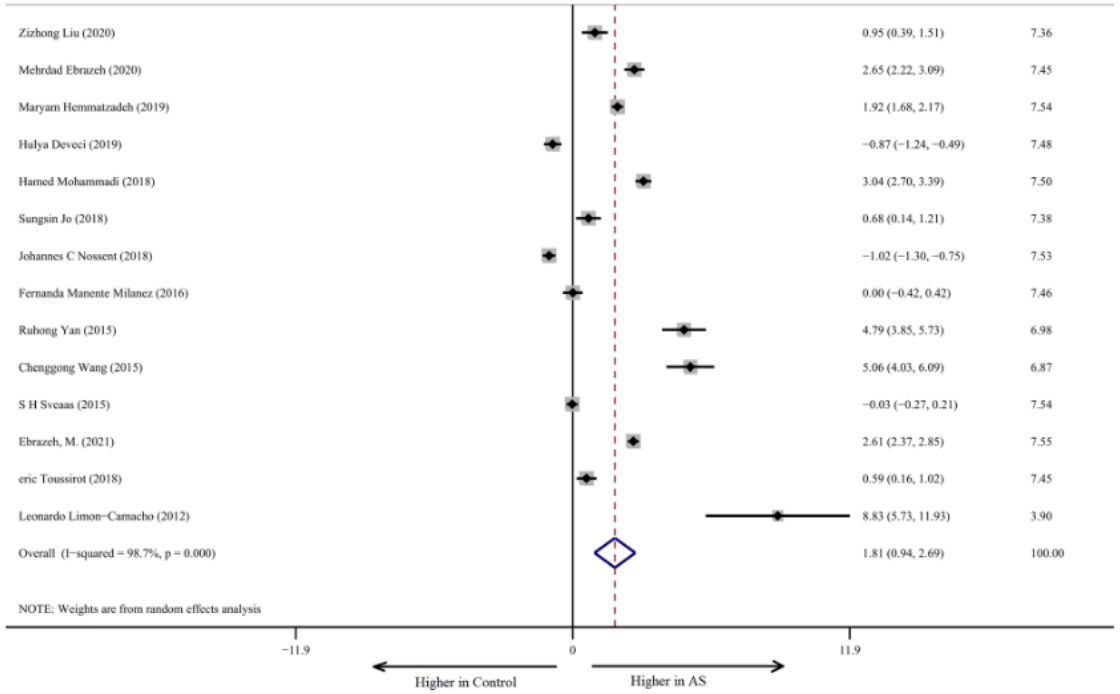
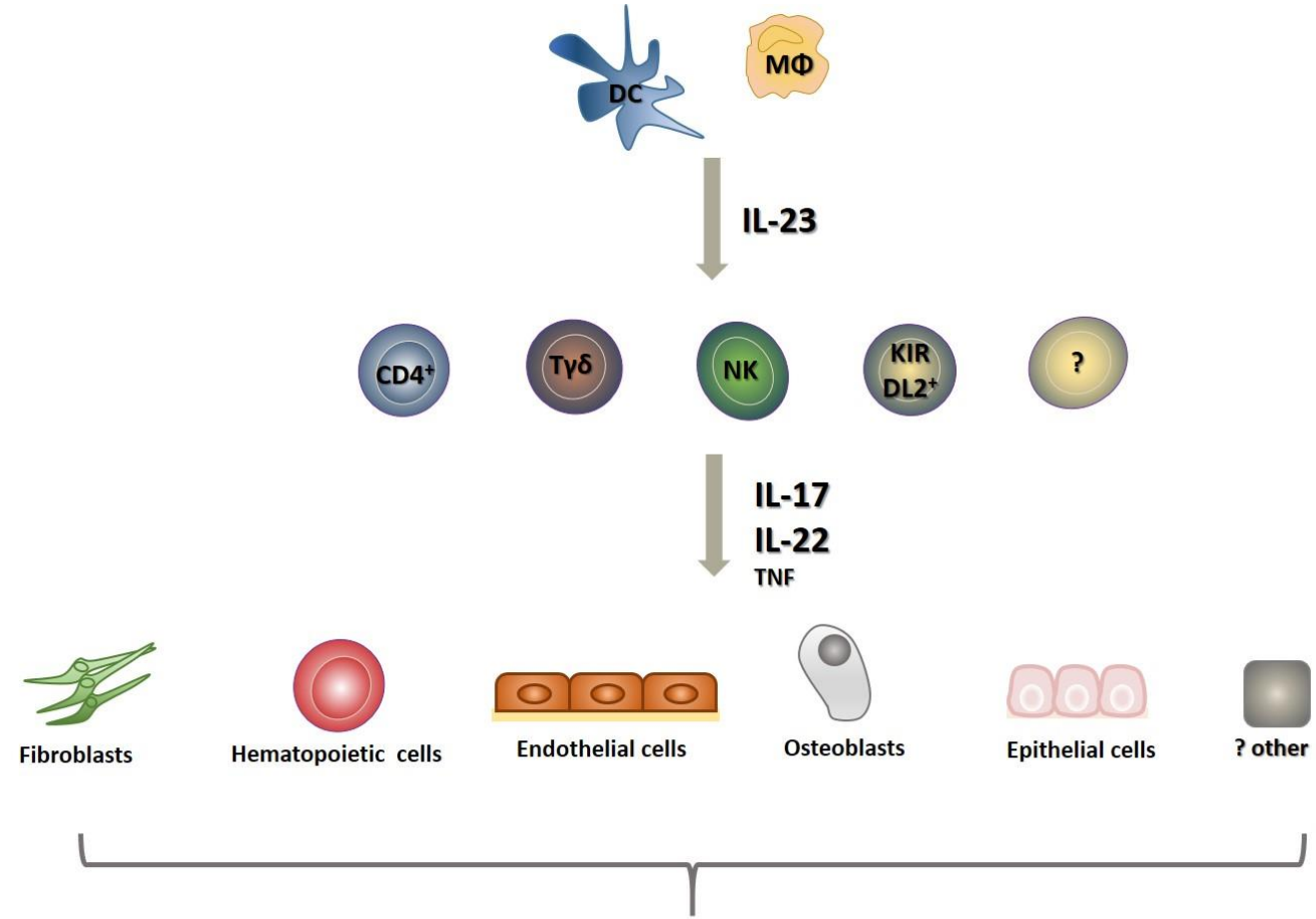


Fig. 6 Forest plot of IL-17A. The level of peripheral IL-17A was higher in patients with AS (*AS*) than in healthy controls

Su et al Adv Ther 2022

Pathogenesis

The IL-23/IL-17 axis

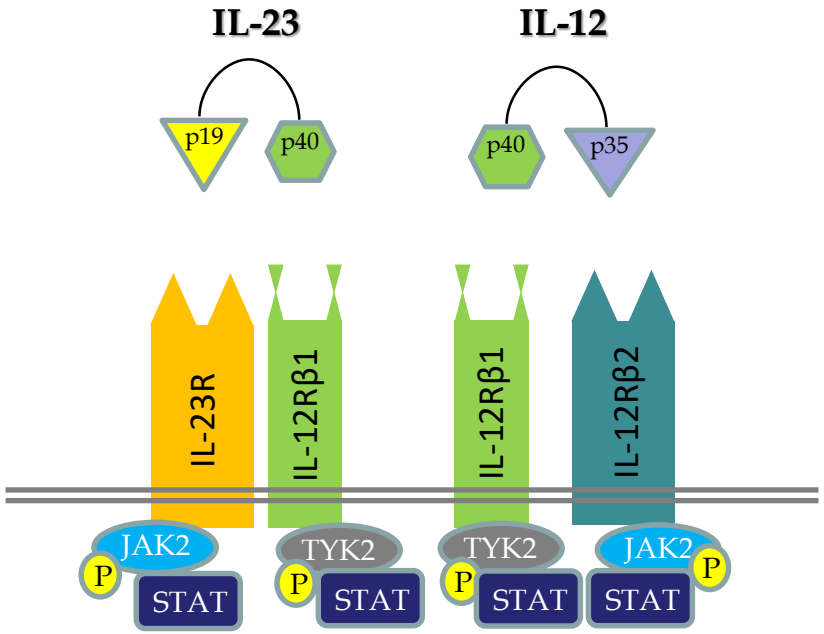


McGonagle D et al Ann Rheum Dis 2019
Sieper J et al Nat Rev Rheum 2019
Siebert S, Fragoulis GE, McInnes IB EULAR online course 2016

IL-23

Mode of action

- Engagement of IL-23 with the IL-23R
  - Signalling, mainly through JAK2 and TYK2
    - Phosphorylation of STAT3
    - Subsequent expression of the transcription factor RORγt and production of IL-17



Fragoulis GE & Siebert S, Musc Care 2022 (in press)

IL-23

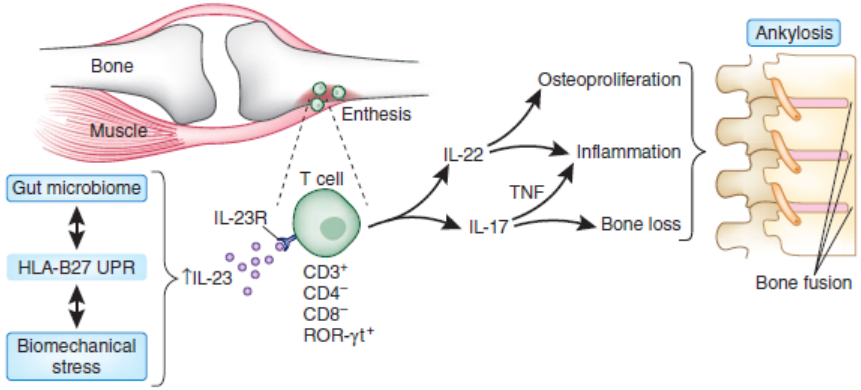
Evidence for SpA

- In
  - Entheses
  - Spine
  - Bowel
  - Joints
  - Skin

IL-23

Enthesis

- Enthesis organ "synovio-entheseal concept"
- Could enthesis be the start of everything??
- T-cells at the sites of tendon insertion into bone (entheses)
  - express IL-23 receptor
  - respond to systemically-administered IL-23 to produce IL-17, IL-22 and IL-6

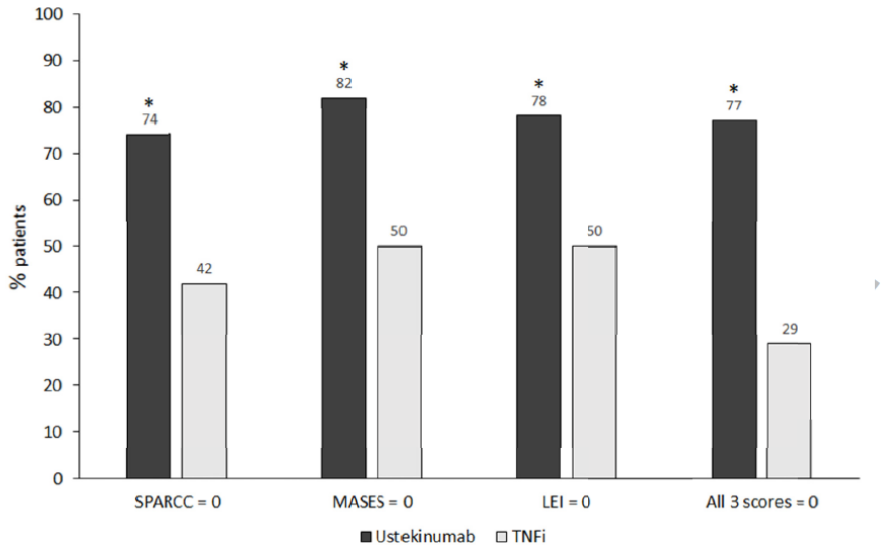


Lories J and McInnes IB Nat Med 2012
Sherlock JP Nat Med 2012

ECLIPSA

Enthesitis

- Prospective randomized RCT
- Ustekinumab (n=23) >> TNFi (n=24)
- At week 24
- more ustekinumab- than TNF-treated patients
  - SPARCC Enthesitis Index = 0 (74% versus 42%, respectively; p = 0.018)
- similar results observed for MASES = 0, LEI = 0, and for all three scores = 0

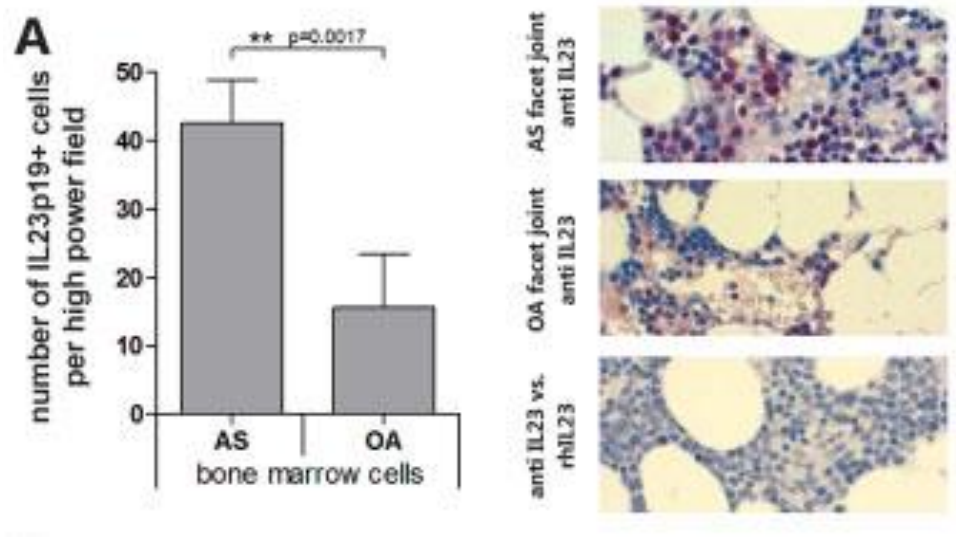


Rossini et al,Exp Op Biol Ther 2020
Araujo et al Semin Arth Rheum 2019

IL-23

Axial entheses

- IL-23
  - ⇧ IL-23 facet SpA

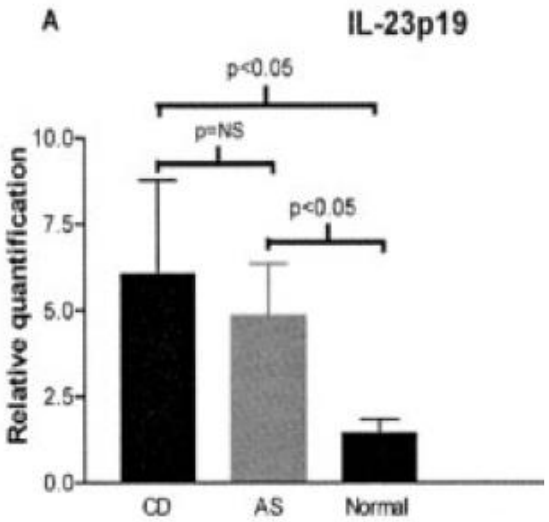


Appel H et al Arthr & Rheum 2013
Siebert S et al Ann rheum Dis 2018
DG McGonagle et al ARD 2019
Bridgewood C et al Ann Rhem Dis 2019

IL-23

Bowel

- IL-23 has been found to be overexpressed in the gut of AS patients
  - By infiltrating monocytes
  - Paneth cells

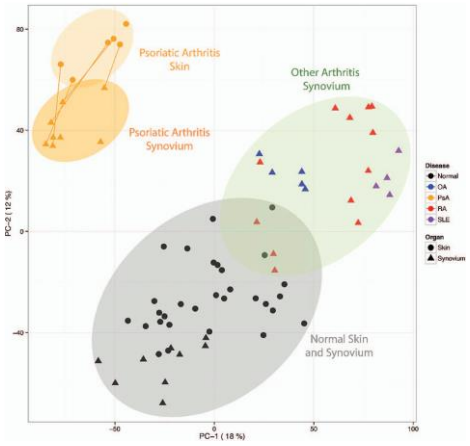


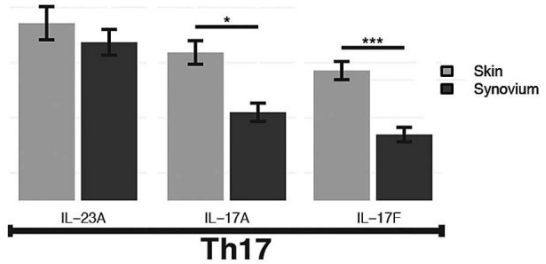
Ciccia et al Arth & Rheumatol 2009

IL-23

Synovium Vs Skin

- Similarities & differences
  - IL-23/-17 axis
    - More active in the skin Vs synovium



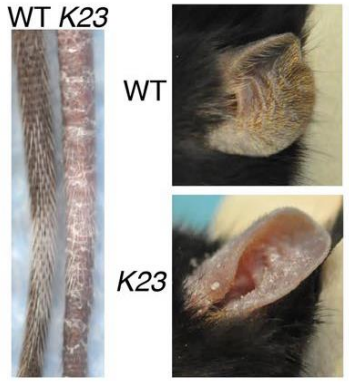


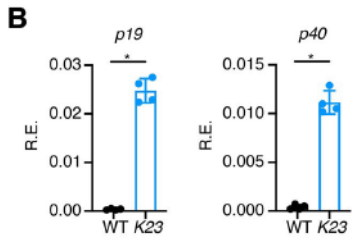
Belasco J et al Arthr Rheum 2015

PsA Pathogenesis

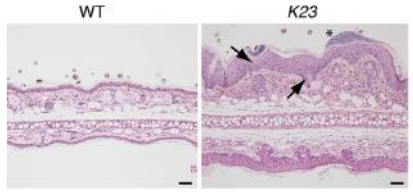
Could all start from IL-23?

- Transgenic expression of IL-23 in mice





p19/p40 expression in the ears

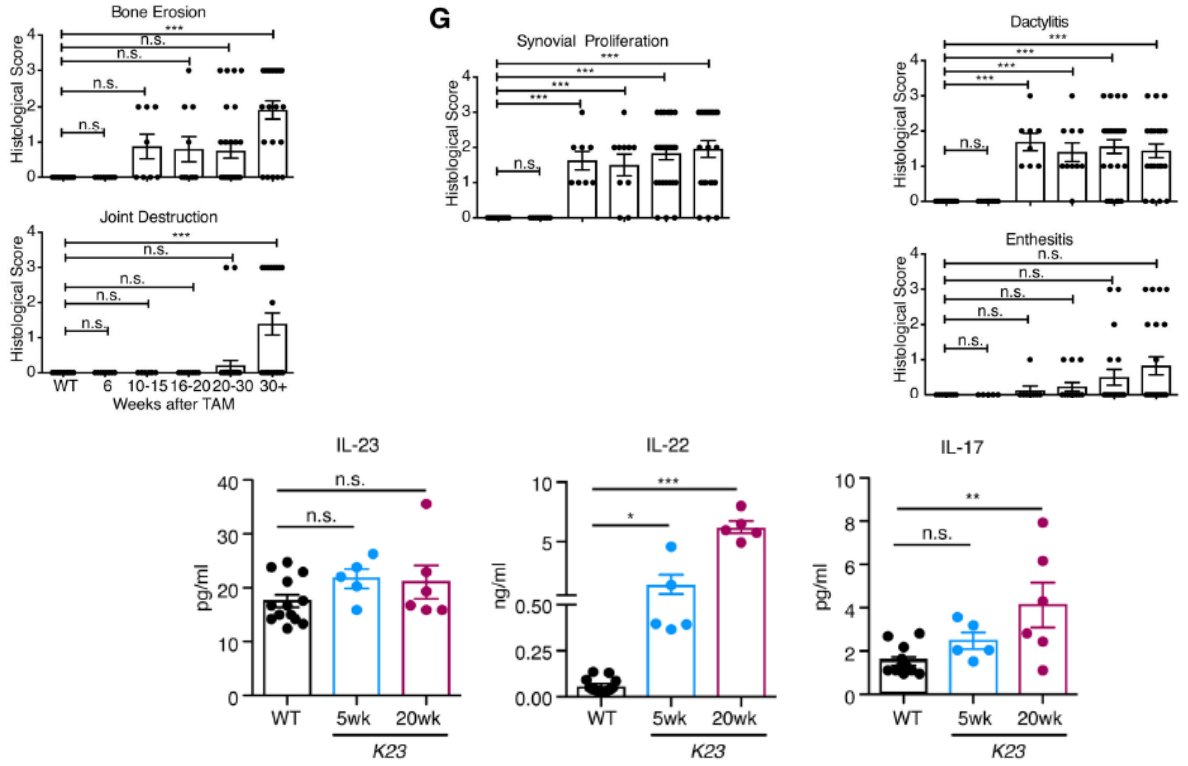


H&E, ears
6 weeks

Chen L et al, Sci Rep 2020

IL-23 mice model

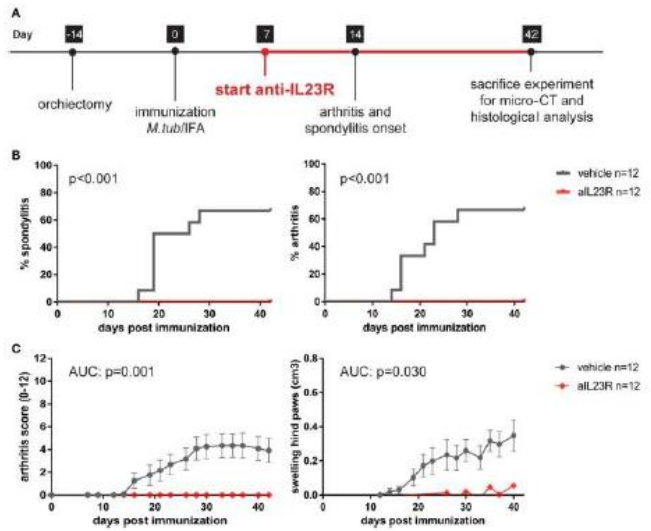
PsA features & cytokines expression



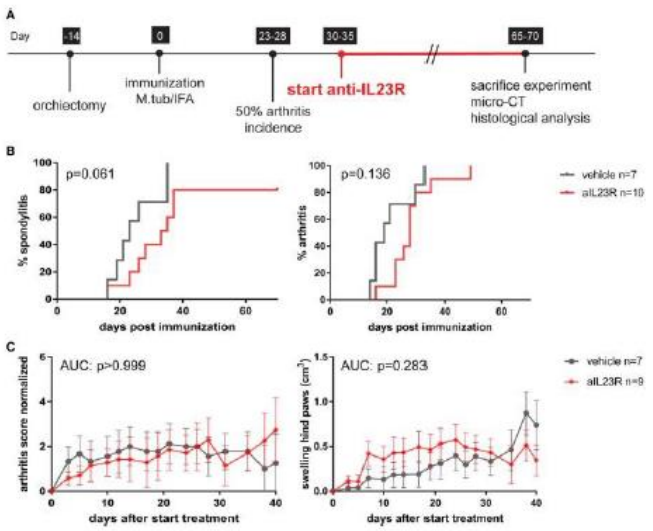
IL-23

Initiation but not perpetuation of disease

Anti-IL-23R prevented initiation of spondylitis and arthritis development in HLA-B27tg rats



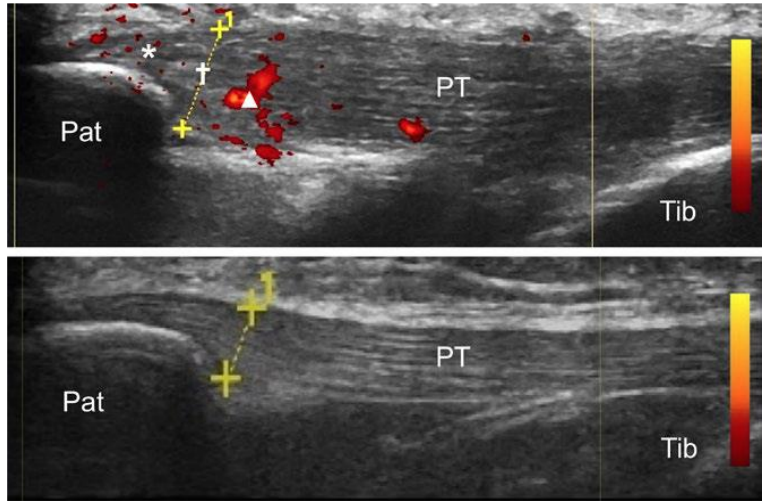
Anti-IL23R failed to suppress spondylitis and arthritis in HLA-B27tg rats

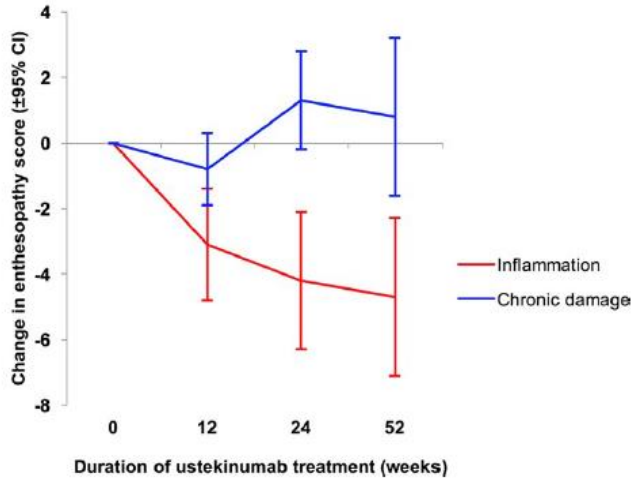


van Tok MN, et al. Front Immunol.2018;9:1550

IL-23 in early enthesitis

- 73 new pso patients (topical Tx)
  - 49% had US enthesitis
    - 23 consented to participate
      - ✓ Compared with healthy volunteers
      - ✓ Entheseal abnormalities (thickening, PD): 24.2% Vs 4.5 %
      - ✓ Damage: 15.9% vs 6%
    - Treatment with Ustekinumab
      - ✓ Improved Enthesitis
      - ✓ But not damage



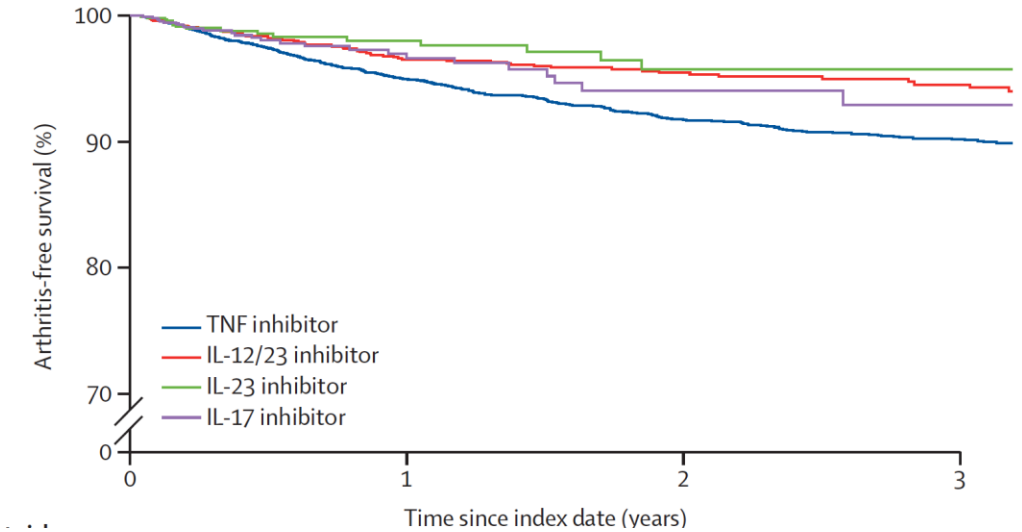


Savage et al Arthr & Rheumatol 2023

IL-23 inhibitors

Disease interception ?

- USA electronic health records
  - 15.501 PsO patients
    - 6.3% developed PsA
    - cumulative incidence of 2·6 cases per 100 person-years
- Treatment with IL-23i Vs TNFi or IL-17
  - According to first biologic class prescribed
  - associated with ⇩ risk of progression to PsA inflammatory arthritis
    - The results persisted in al 6 sensitivity analyses (e.g other definitions, drug switching etc)

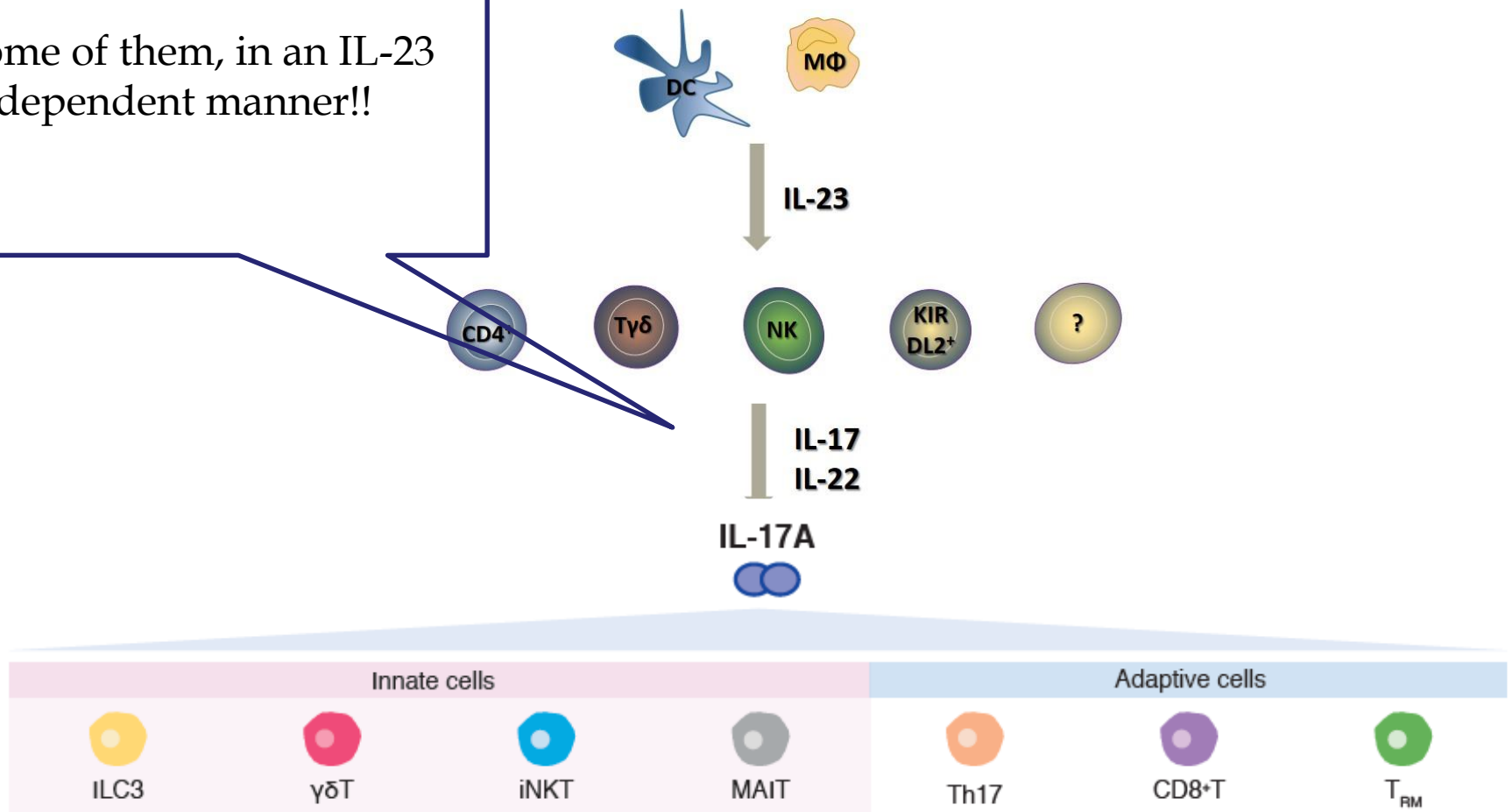


Shikha S. et al, Lancet Rheumatology 2023

PsA Pathogenesis

The IL-23/IL-17 axis

Some of them, in an IL-23 independent manner!!



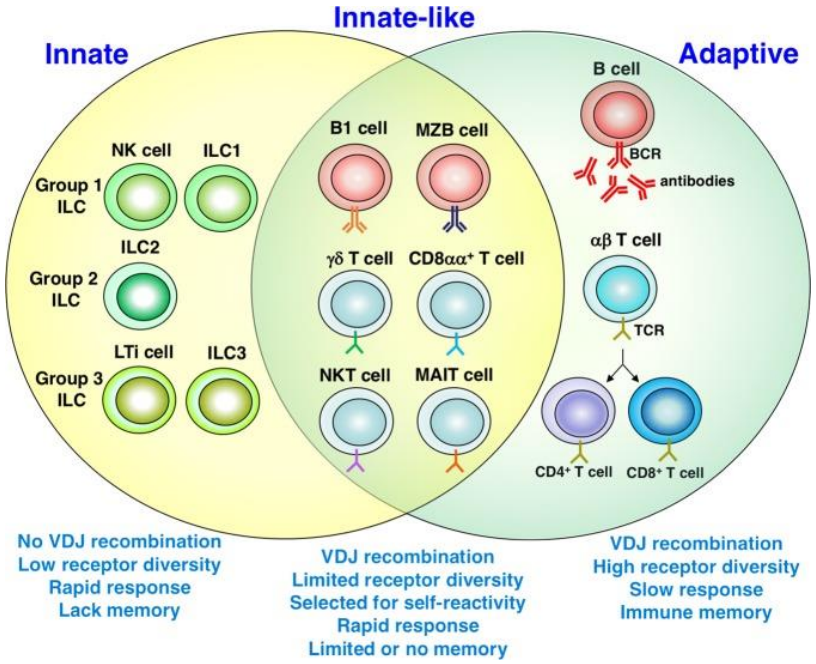
Inflammatory cytokines, chemokines, RANKL, cell activation

McGonagle D et al Ann Rheum Dis 2019
Sieper J et al Nat Rev Rheum 2019
Siebert S, Fragoulis GE, McInnes IB EULAR online course 2016

PsA pathogenesis

Rare subpopulations

- MAIT
- ILC
- Tgd

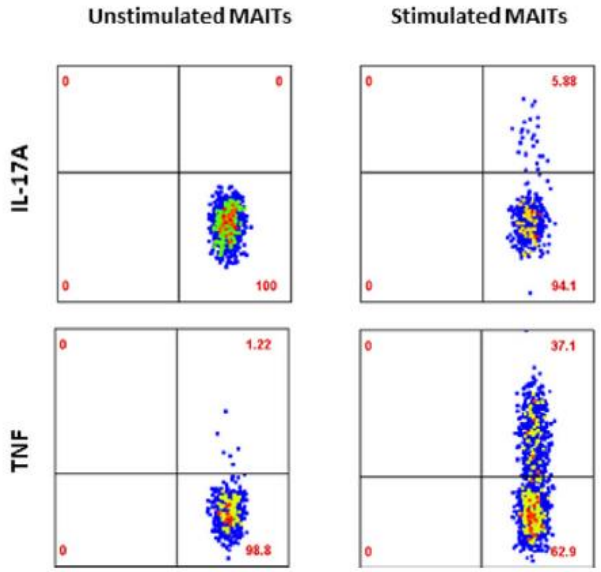


Van Kaer et al Cell and Mol Immun 2019

MAIT

Healthy

- Present in
  - Axial entheses
    - ✓ Able to produce TNF and IL-17
    - ✓ AHR, JAK1, STAT4, and TGFβ1, CCR6, CCR3 expression
  - Blood
    - ✓ Able to produce IL-17
    - ✓ Transcripts expressed in T circulating lymphocytes

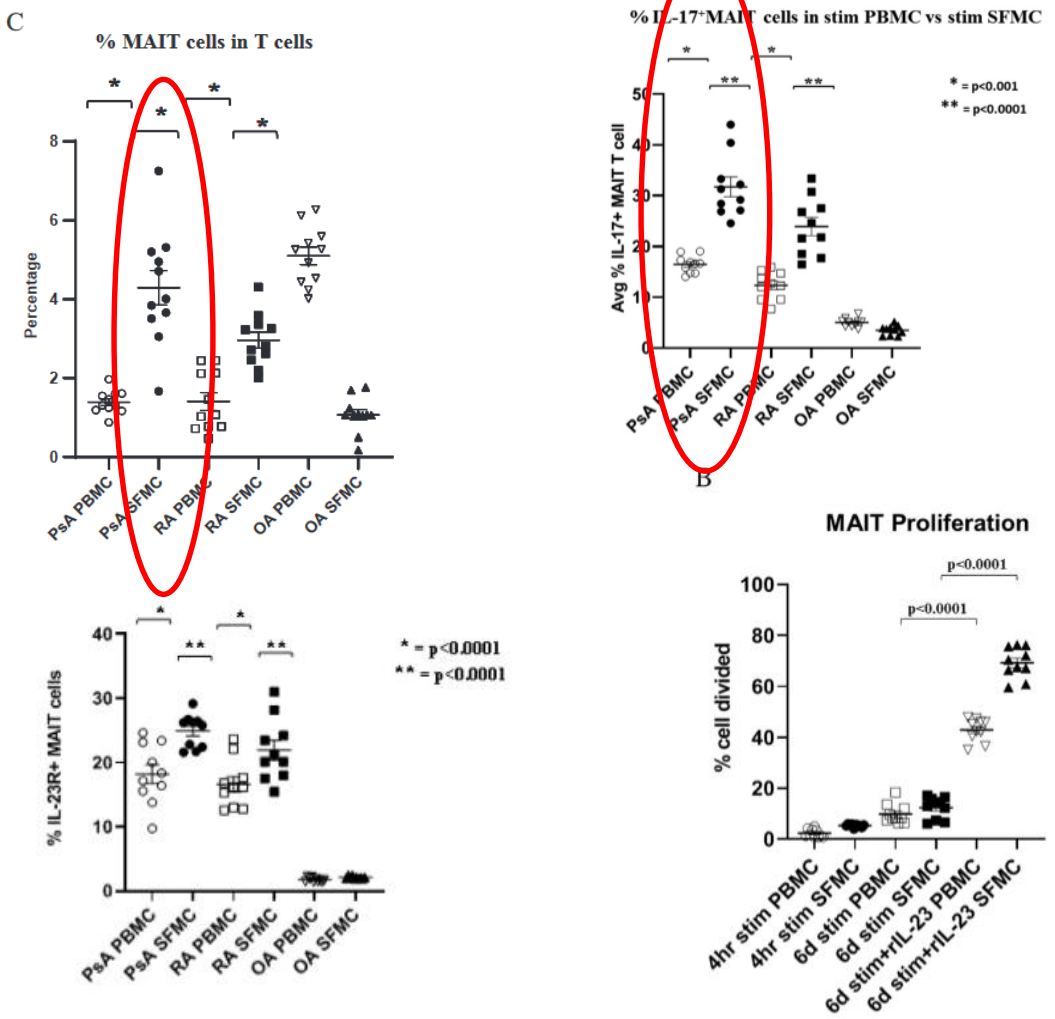


Rosine et al Arthr & Rheum 2022

MAIT

In PsA – not many data

- PBMCs and SF
- PsA, RA, HC, n=10 each
  - MAIT cells were enriched in synovial fluid of PsA
- Upon stimulation SFMC MAIT cells
  - produced ⇧ IL-17A in PsA Vs RA, OA
  - upregulation of IL-23R
    - IL-23R was functionally active

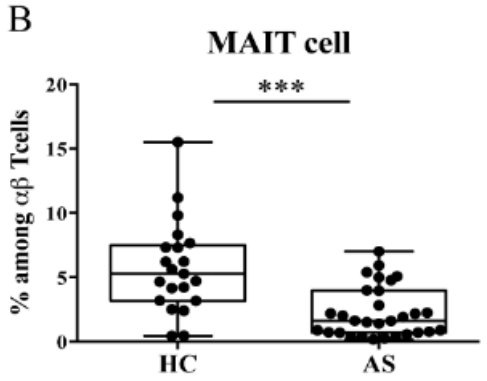


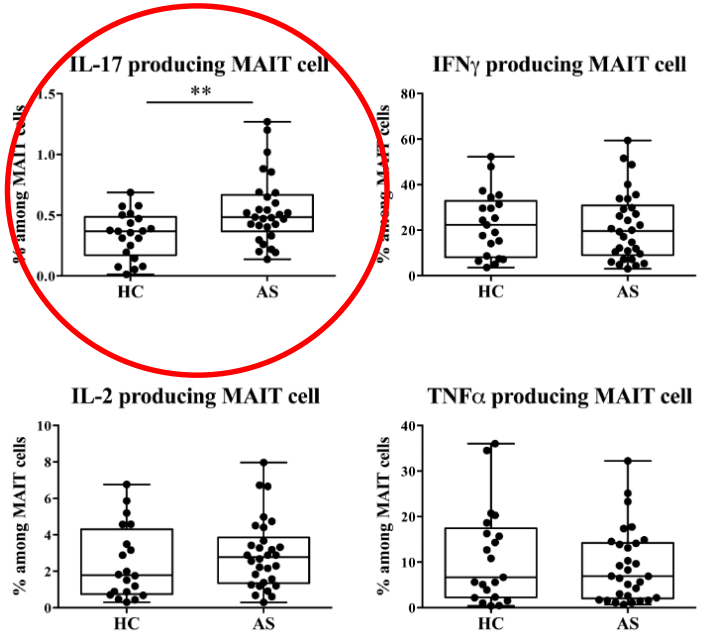
Raychaudhuri et al, Cytokine 2020

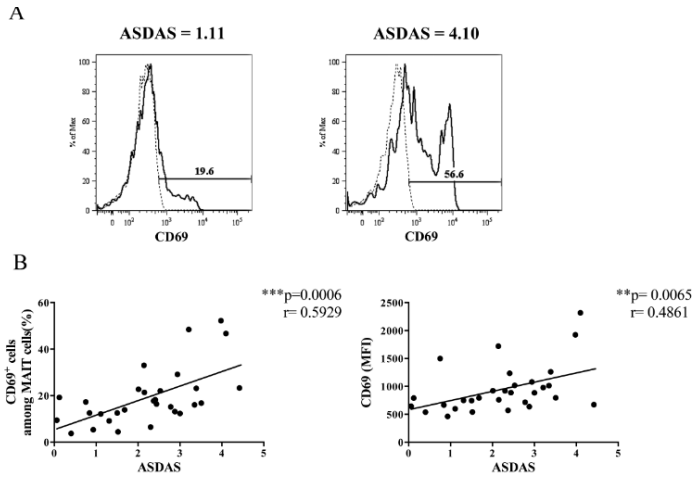
MAIT

AS - blood

- 30 AS Vs 21 HC
- % MAIT was reduced
  - ⇧ MAIT producing IL-17
  - ⇧ activated (CD69) MAIT
    - Associated with disease activity





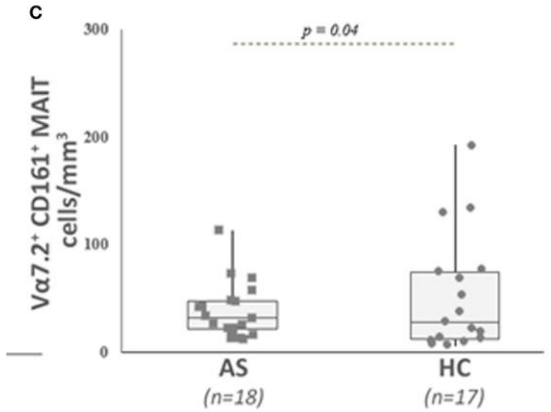


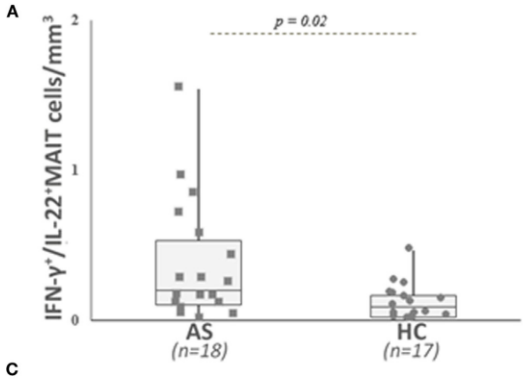
Hayashi et al J Rheum 2016

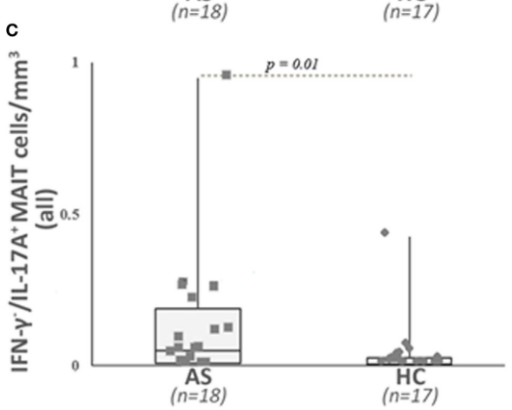
MAIT

AS - blood

- Peripheral blood 36 AS Vs 55 HC
  - MAIT
    - ⇩ Vs HC
    - ⇧ IFN-γ+/IL-17A+ MAIT cells
    - ⇧ IL-22+ MAIT



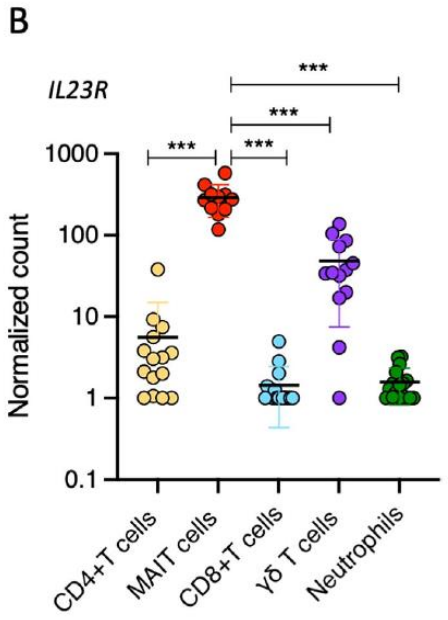


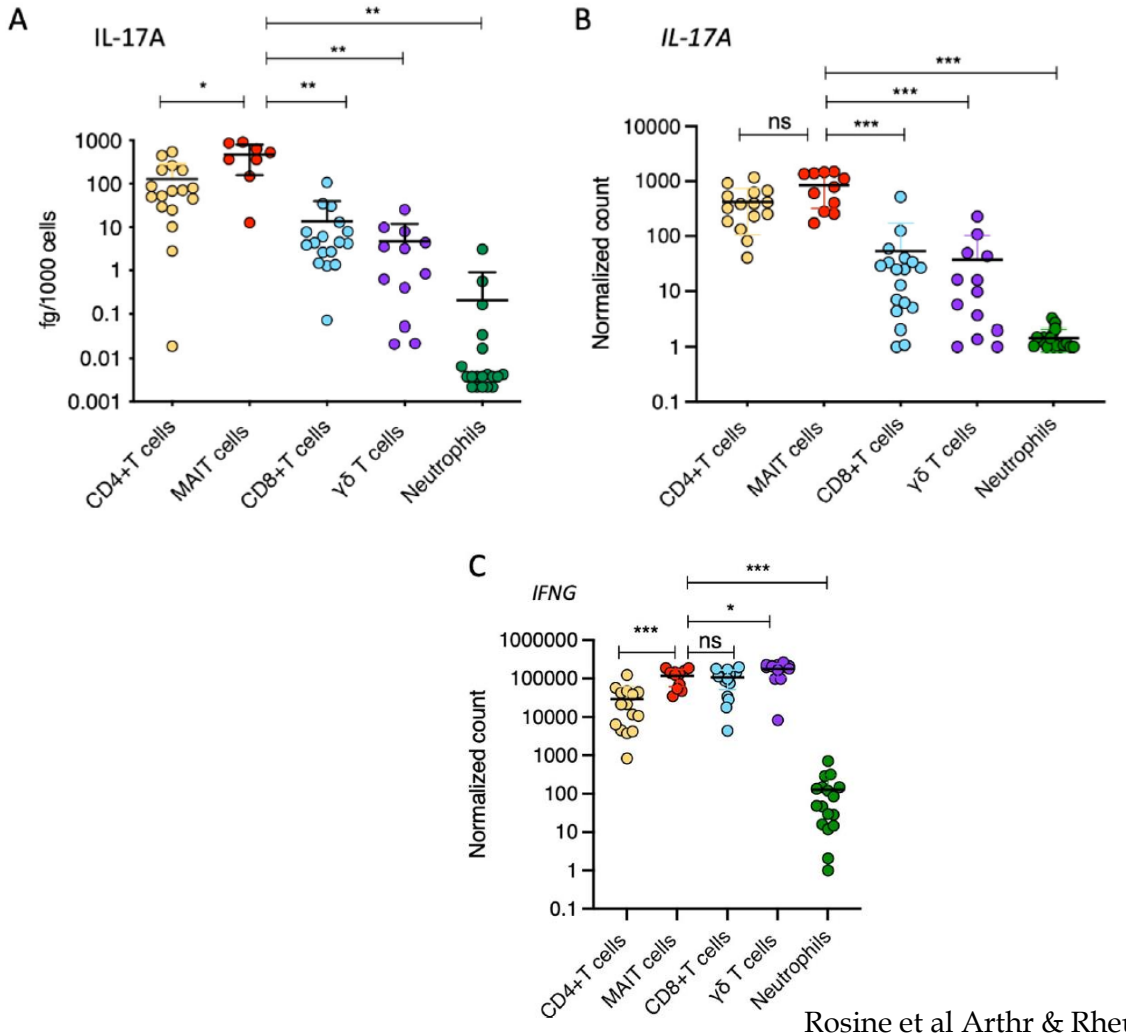


Toussirot et al Front Immun 2018

MAIT
AxSpA - blood

- 18 AxSpA pts
  - MAIT produce
    - IL-17
    - IL-23R
    - IFNg



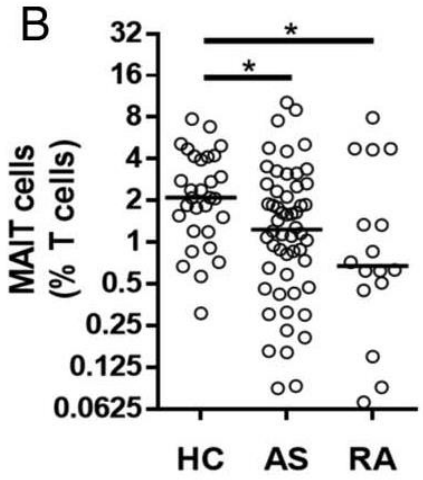


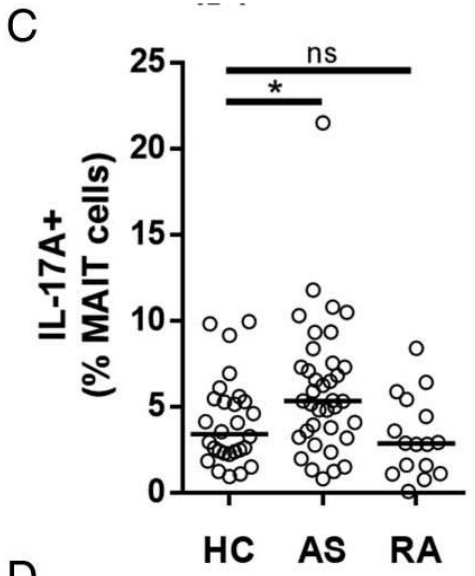
Rosine et al Arthr & Rheum 2022

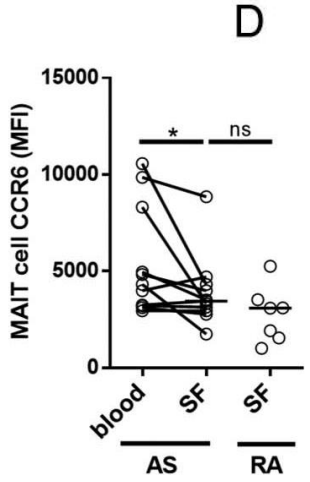
MAIT

AxSpA - blood

- AxSpA, RA, HC
  - Peripheral blood
  - In AxSpA
    - MAIT were less
    - But produced more IL-17
      - ✓ Especially in males
    - Homing molecules (CCR6)
      - ✓ ⇧ peripheral blood







Gracey eta al Ann Rheum Dis 2016

CCR6 - migration

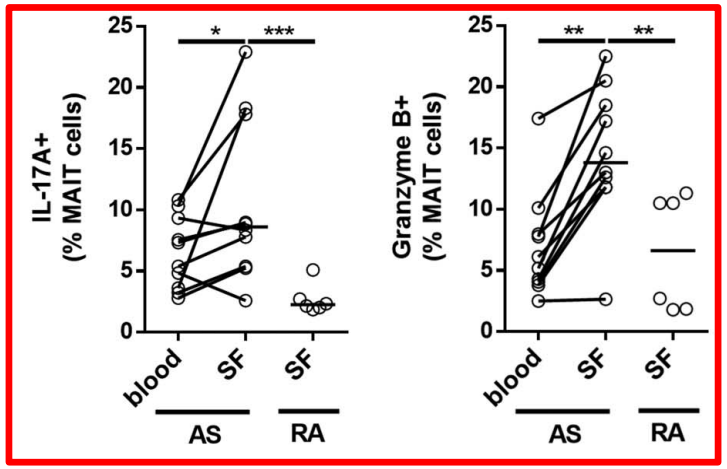
- CCR6
  - Involved in cells migration
  - present on B and T cells as well as dendritic cells (DCs).
  - Bind to CCL20
    - only known ligand
  - Both CCR6 and CCL20 are expressed by Th17 cells

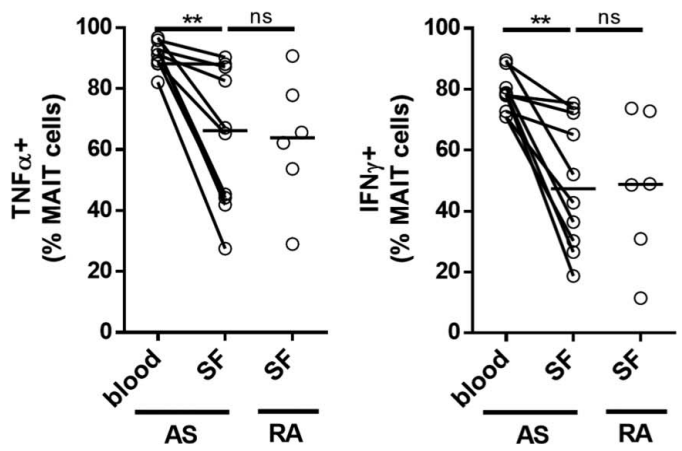
Lee et al Front Immun 2013

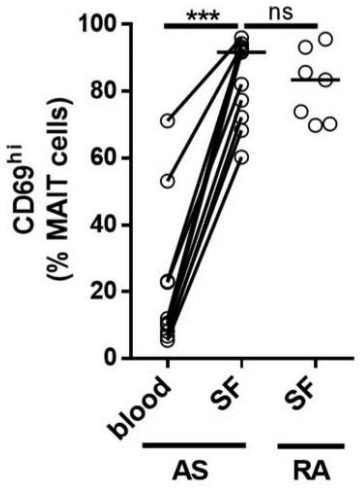
MAIT

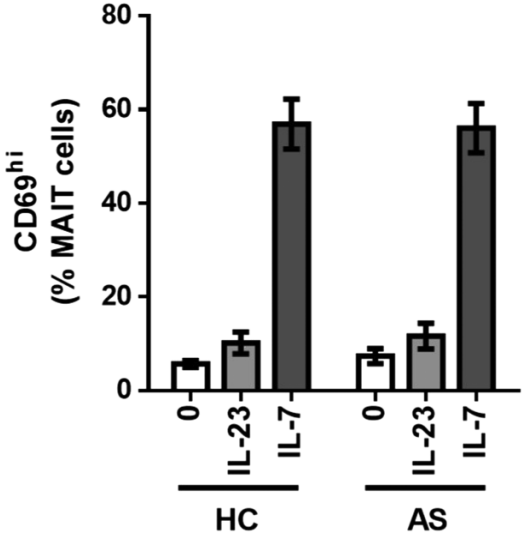
AxSpA - synovial fluid

- AxSpA
  - Even more in SF
    - Phenotype towards
      - ✓ IL-17
      - ✓ Granzyme B+
    - Activated (CD69)
      - ✓ IL-7 but not IL-23 dependent









Gracey eta al Ann Rheum Dis 2016

IL-7

SpA - Synovial fluid

- SpA (n=10), RA (n=8), OA (n=5)
- IL-7 in the synovial fluid of SpA patients

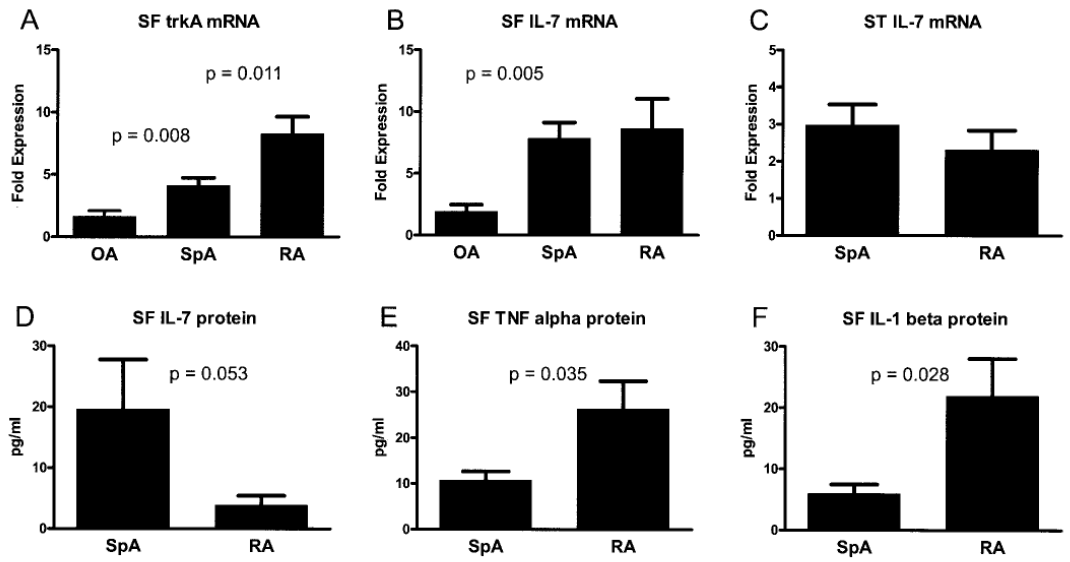


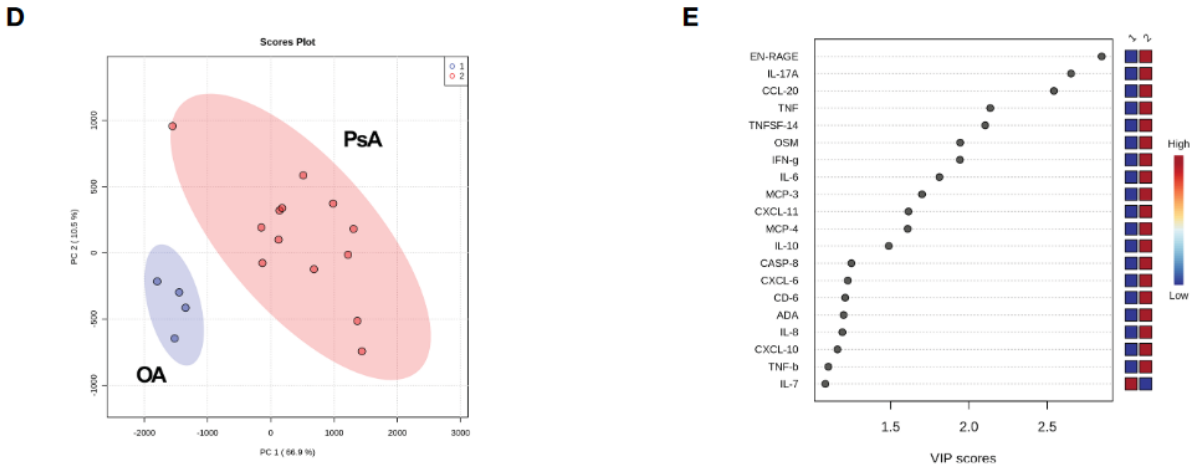
Figure 2. Expression of candidate molecules, as assessed at the mRNA level by quantitative reverse transcriptase–polymerase chain reaction study of synovial fluid (SF) cells (**A** and **B**) or synovial tissue (ST) (**C**), and at the protein level by enzyme-linked immunosorbent assay of SF (**D–F**). Synovial samples were obtained from patients with spondylarthritis (SpA), rheumatoid arthritis (RA), and osteoarthritis (OA). Values are the mean and SEM. IL-7 = interleukin-7; TNF = tumor necrosis factor.

Rihl et al Arthr & Rheum 2007

IL-7

PsA - Synovial fluid

- Synovial fluid
  - 13 PsA vs 4 OA
    - 39 proteins were found ⇧ in SF PsA Vs OA patients
      - ✓ Among these
        - ~ TNF
        - ~ IL-17A,
        - ~ IL-6
        - ~ IL-10
        - ~ IFNg
        - ~ IL-7

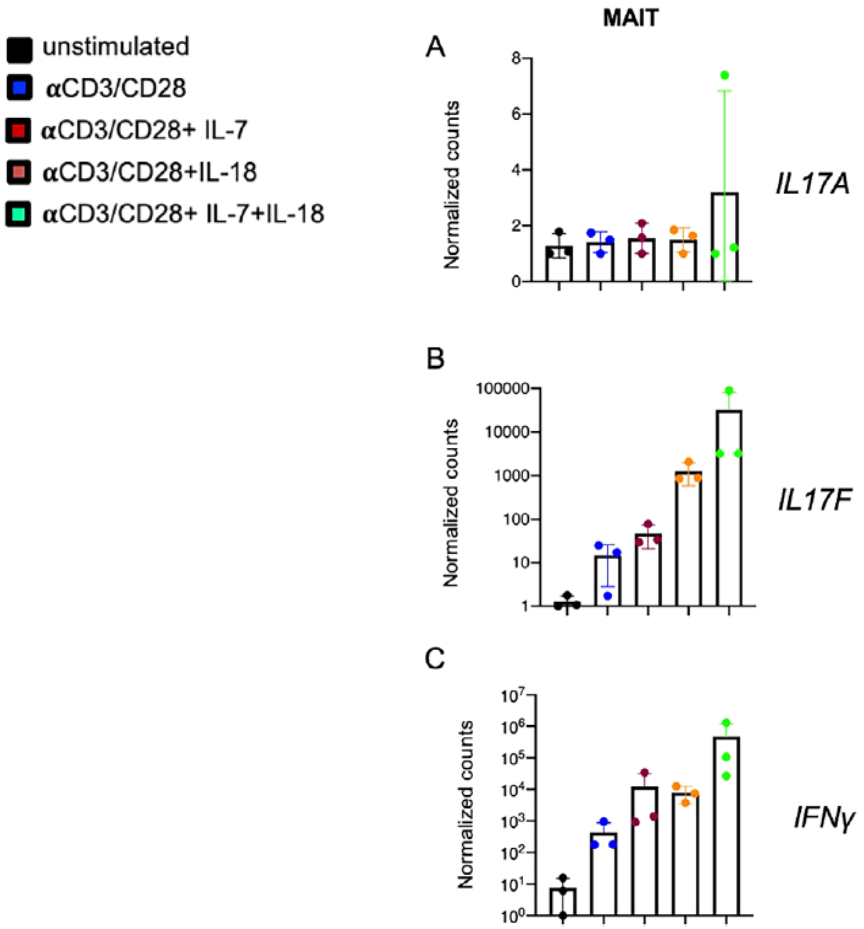


Barbarroja et al Front Immun 2023

MAIT

AxSpA – blood (IL-17)

- IL-17 MAIT in AxSpA
  - Driven by IL-7 and IL-18

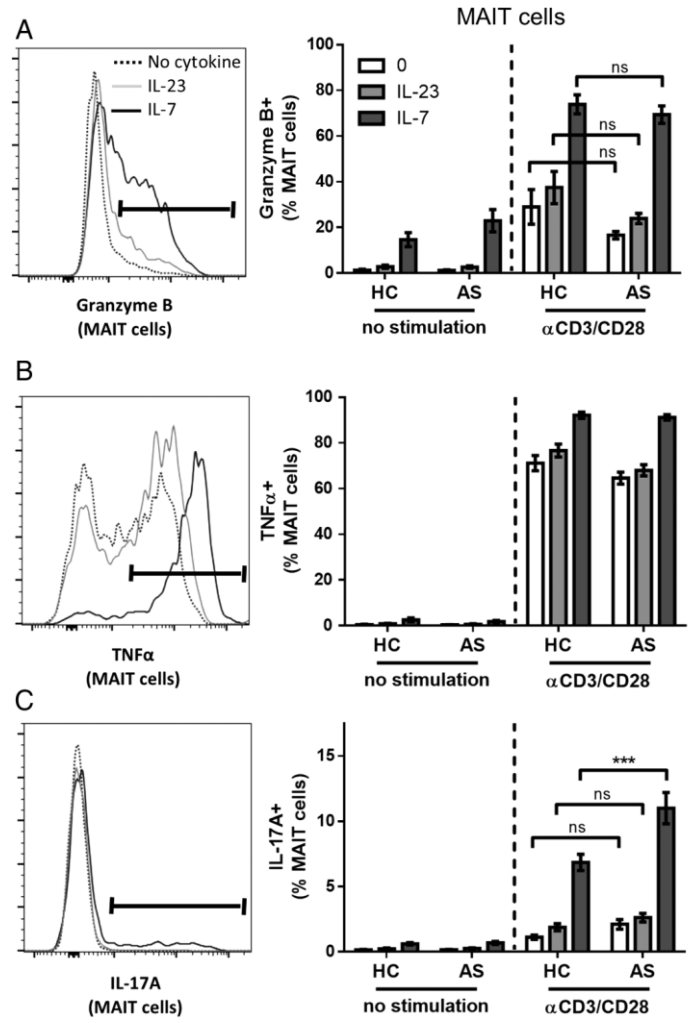


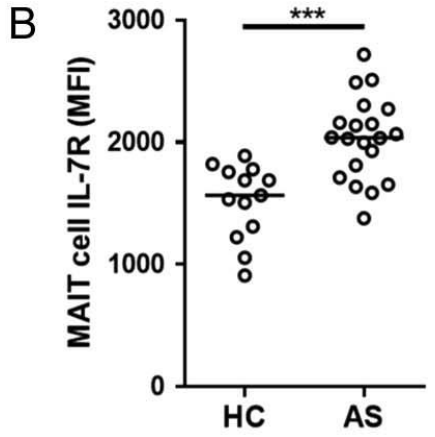
Rosine et al Arthr & Rheum 2022

MAIT

AxSpA - IL-7

- PBMCs
  - Express IL-7R (AxSpA>HC)
  - Produce, upon priming with IL-7
    - Granzyme B
    - TNFa
    - IL-17
      - ✓ Different Vs HC

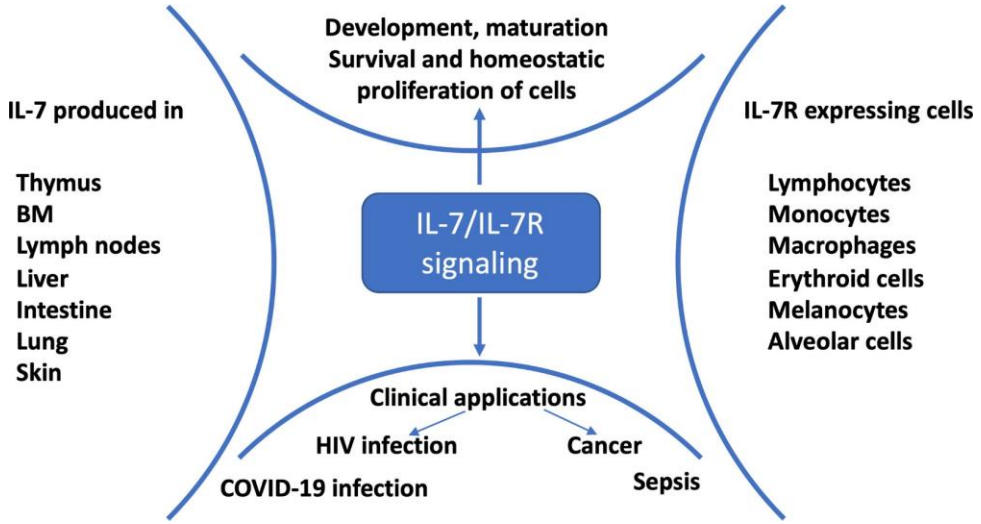




Gracey eta al Ann Rheum Dis 2016

IL-7

- IL-7/IL-7R signaling
  - IL-7 is mainly produced by
    - stromal cells
    - epithelial cells
    - Keratinocytes
    - dendritic cells
  - consumed by IL-7R expressing cells for
    - Development
    - Proliferation
    - Survival
    - maintenance



Bekele et al Front Immun 2021

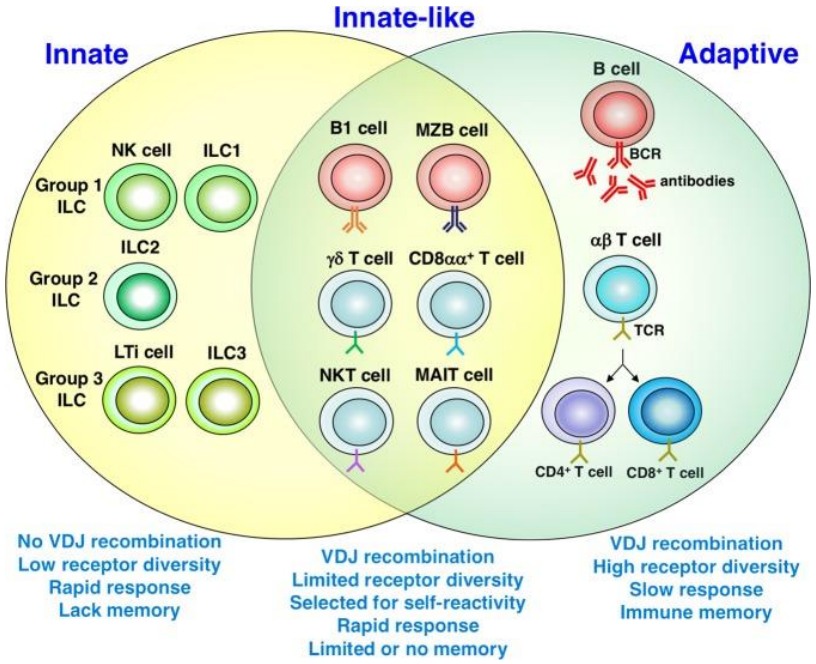
Summary

- MAIT
  - Present and active in axial entheses
  - Main producers of IL-17 (blood)
    - Under IL-7
  - Migrate to joints? (CCR6)
  - More data needed for PsA

PsA pathogenesis

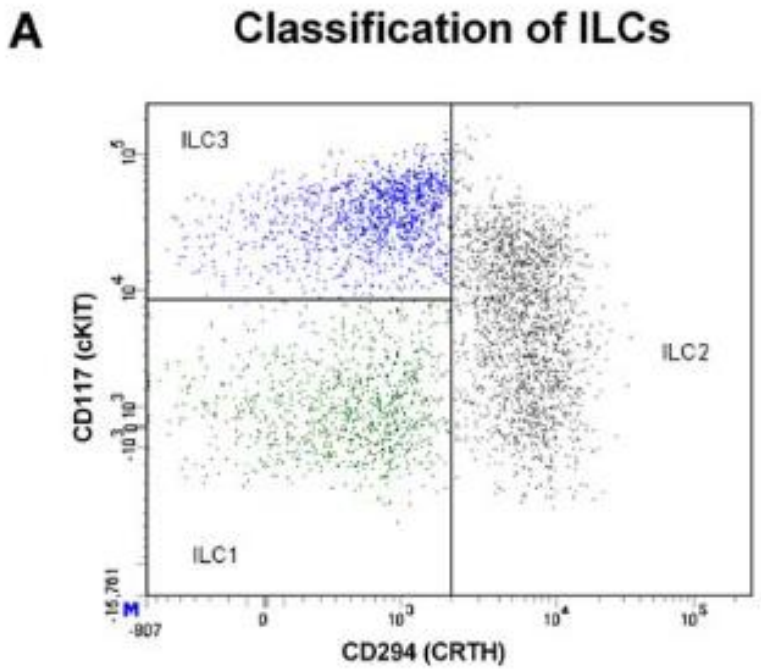
Rare subpopullations

- MAIT
- ILC
- Tgd



Van Kaer et al Cell and Mol Immun 2019

A

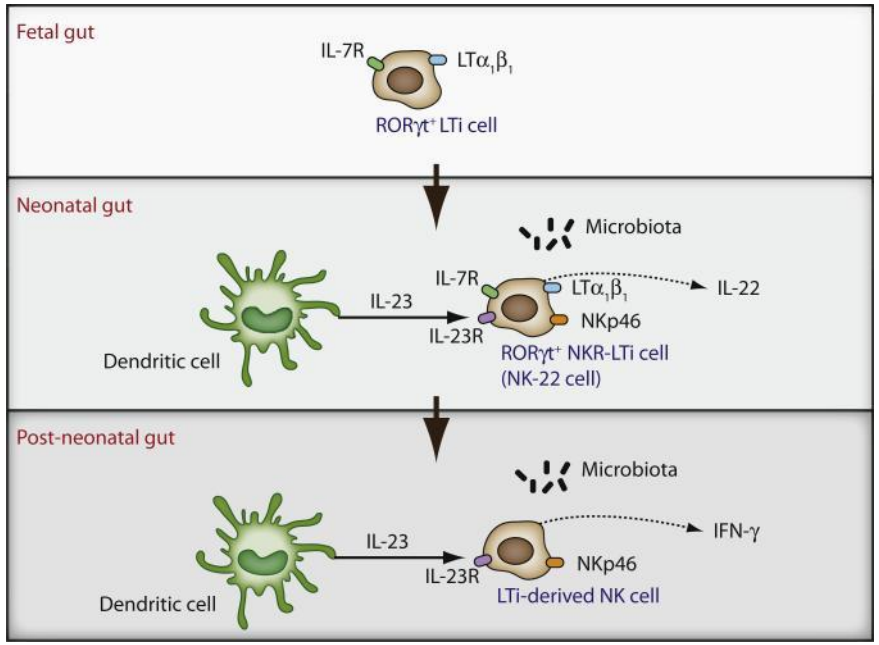


Leijten et al Arthr & Rheum 2015

ILC3

- Related to lymphoid tissue induced cells (LTi)
  - Induced by IL-7

- LTi (lymphoid tissue inducer cells)
  - Appear in lymphoid organs
    - Fetal>adults (intestine)
  - Produce lymphotoxin (LTα1β1) and tumor necrosis factor (TNF)
    - Stimulating the mesenchymal cell production of chemokines and adhesion molecules essential for lymphoid organogenesis
    - Some of them express receptors found in NK cells
  - Express RORγt & IL-23R
  - Produce IL-22, IFNg

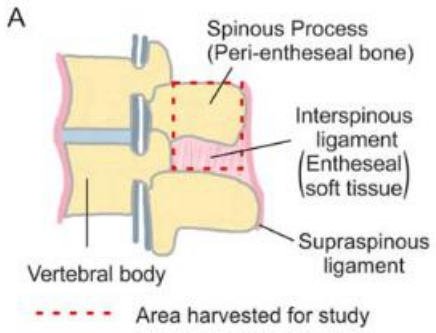


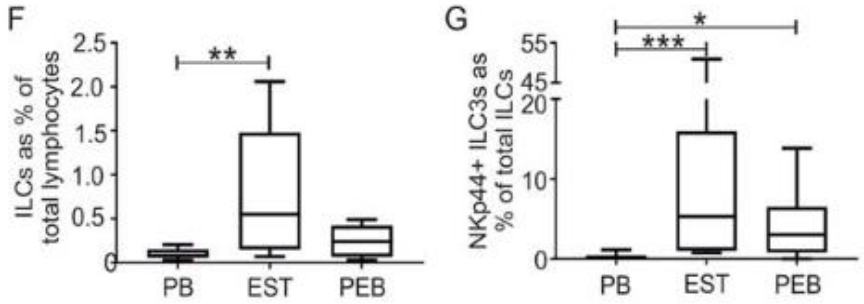
Strober et al Immunity 2012

ILCs

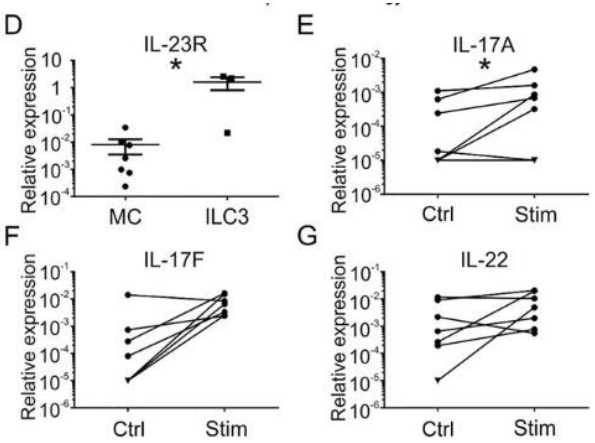
In healthy

- Interspinous ligament and spinous process bone (healthy)
  - Higher % in entheses > blood
  - Produce IL-17 under IL-23





EST: enthesis
PEB: perientheseal bone
PB: periph blood
MC: mononuclear cells

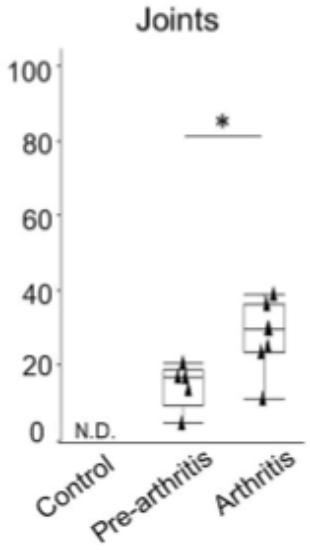


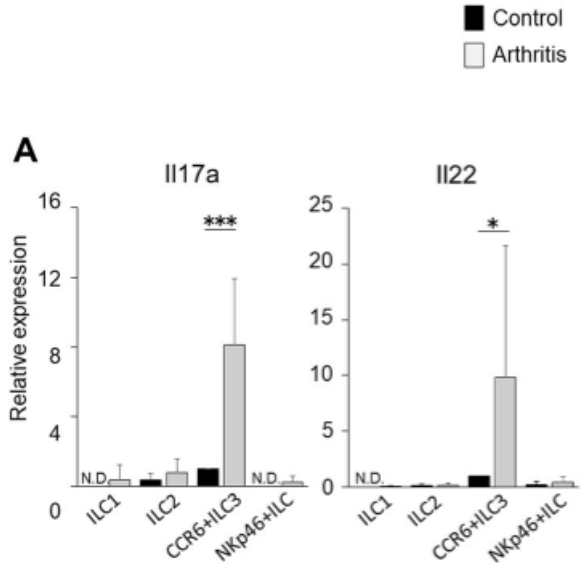
Cuthbert et al Arthr & Rheumat 2017

ILC3

mice

- CIA mice
  - CCR6+ ILC3s in joints with arthritis
    - ⇧ Vs non-arthritic joints
    - expressed ⇧ IL-17A and IL-22 mRNA Vs control mice



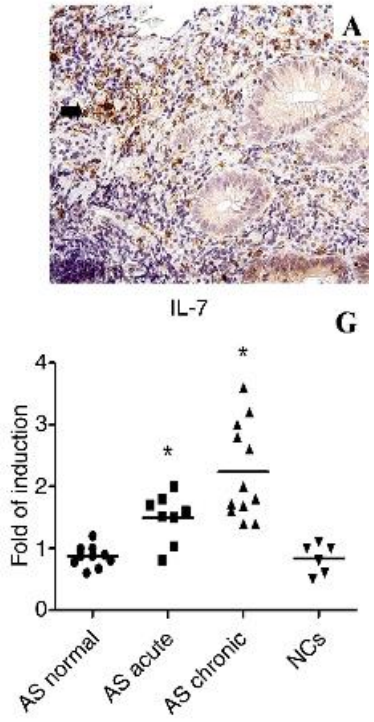


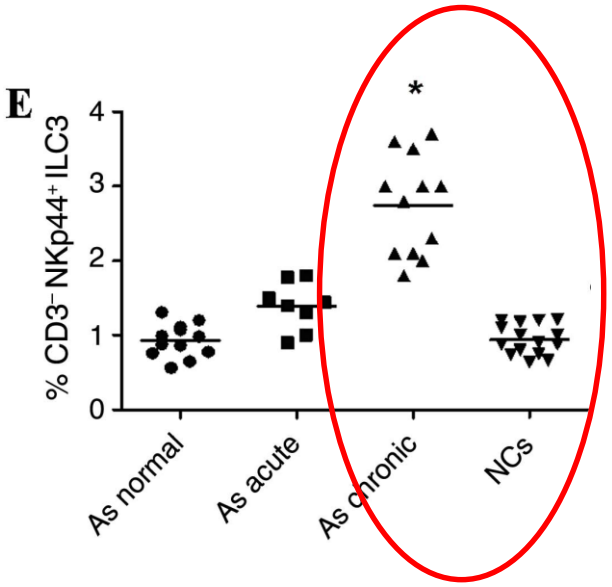
Takaki-Kuwahara et al Arthr Res & Ther 2019

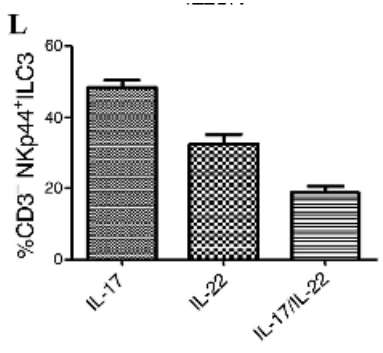
ILC3

AS - Gut

- Gut of AS patients
  - Overexpression of IL-7
  - ⇧ ILC3
    - Produce IL-22
    - Produce IL-17







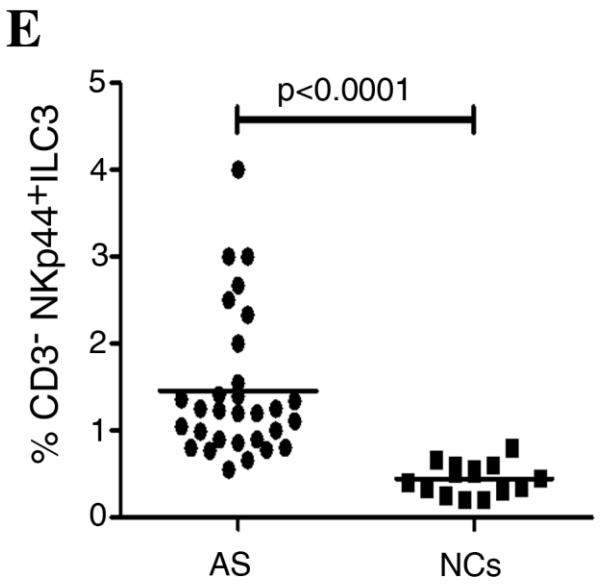
Ciccia et al Arthr & Rheum 2011
Ciccia et al Ann Rheum Dis 2015

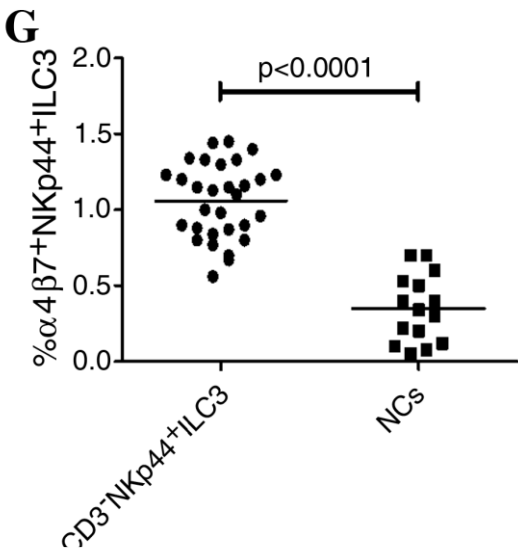
ILC3

AS-blood

- ILC3
  - ⇧ in AS Vs HC
    - ⇧ IL-17 & IL-22
    - Express integrin α4β7

Peripheral blood



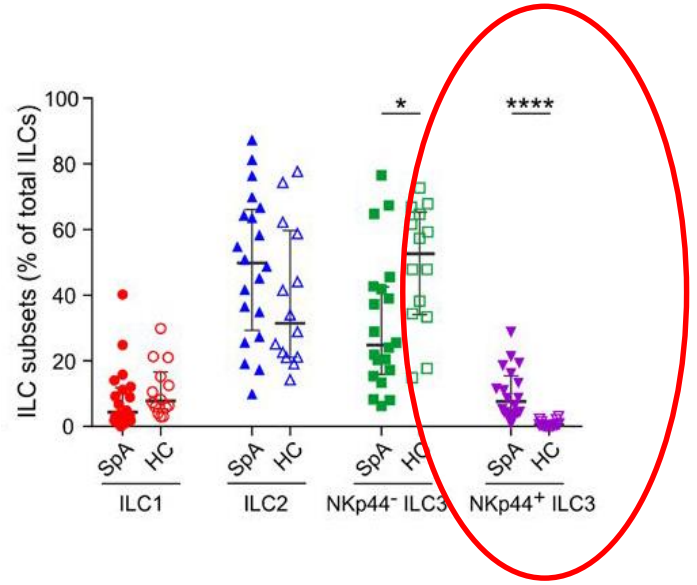


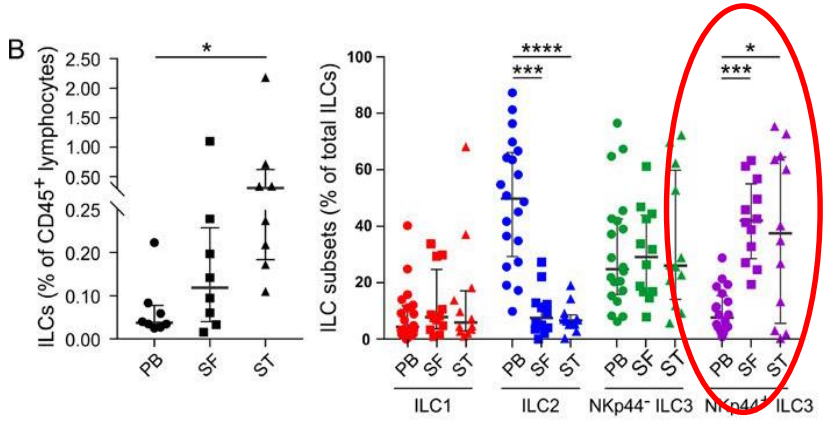
Ciccia et al Ann Rheum Dis 2015

ILC3

peripheral SpA – blood & synovial tissue

- per SpA (n=26), Knee arthritis
- Blood
  - ⇧ % of ILC3 (NKp44+)
- Matched synovial tissue (ST), synovial fluid (SF), and peripheral blood (PB) samples
  - ⇧ % of ILC3 in ST in SpA



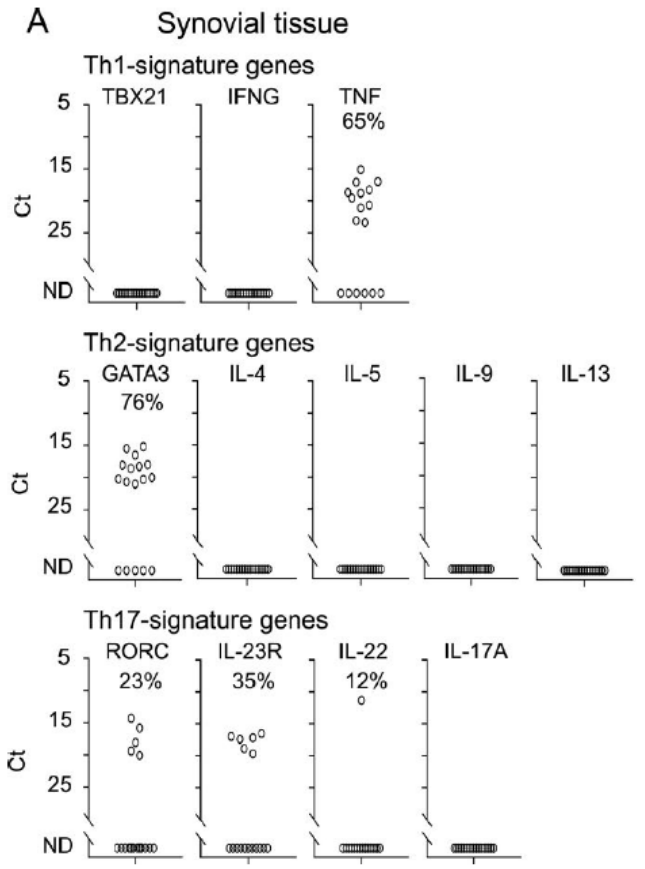


Blijdorp et al Arthr & Rheum 2019

ILC3

In peripheral SpA

- Synovial tissue
- ⇧ Th17 signature transcripts (e.g *RORC*, *AHR*, and *IL23R)*
  - capable of inducing expression of *IL-22*
  - BUT not *IL-17A*, in response to in vitro restimulation.

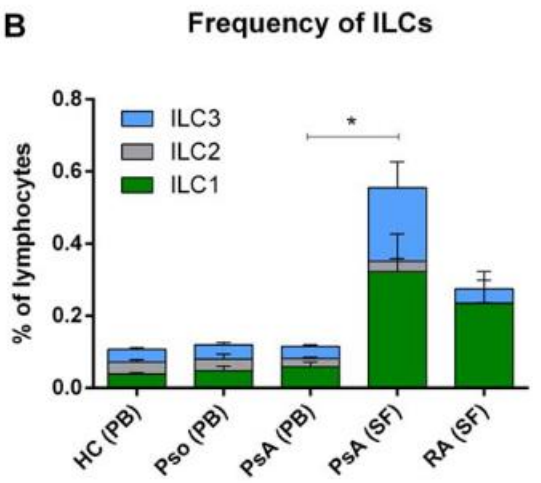


Blijdorp et al Arthr & Rheum 2019

ILC3

PsA - blood & synovial fluid

- HC (n=12), psoriasis (n=8), PsA (n=13)
  - Peripheral blood and synovial fluid
- ILCs
  - ⇧ in PsA SF > PB
  - ⇧ in PsA SF > RA SF

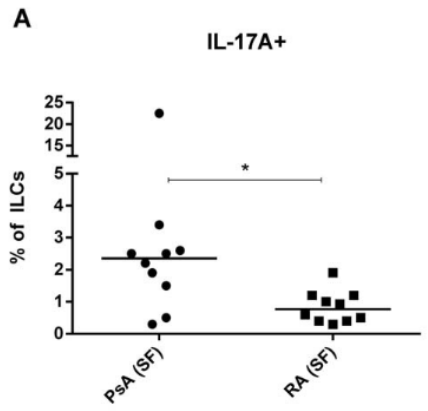


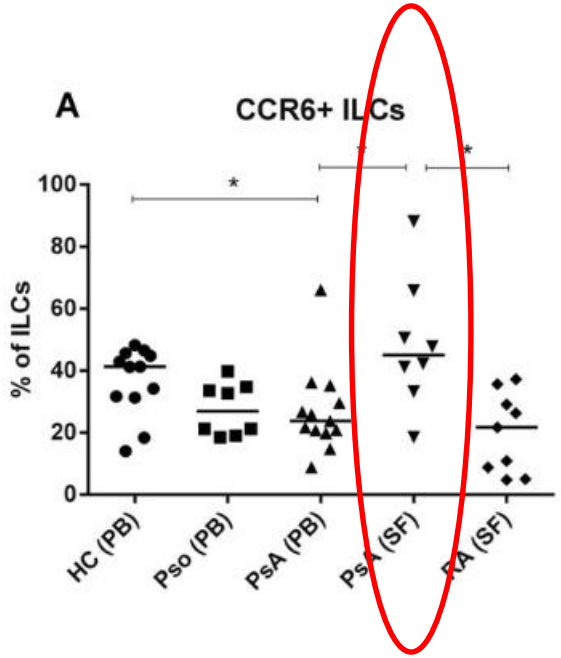
Leijten et al Arthr & Rheum 2015

ILC3

PsA – synovial fluid

- ILCs in synovial fluid
  - IL-17 producing Vs RA
  - enriched for CCR6
    - Vs PsA PB
    - Vs RA SF





Leijten et al Arthr & Rheum 2015

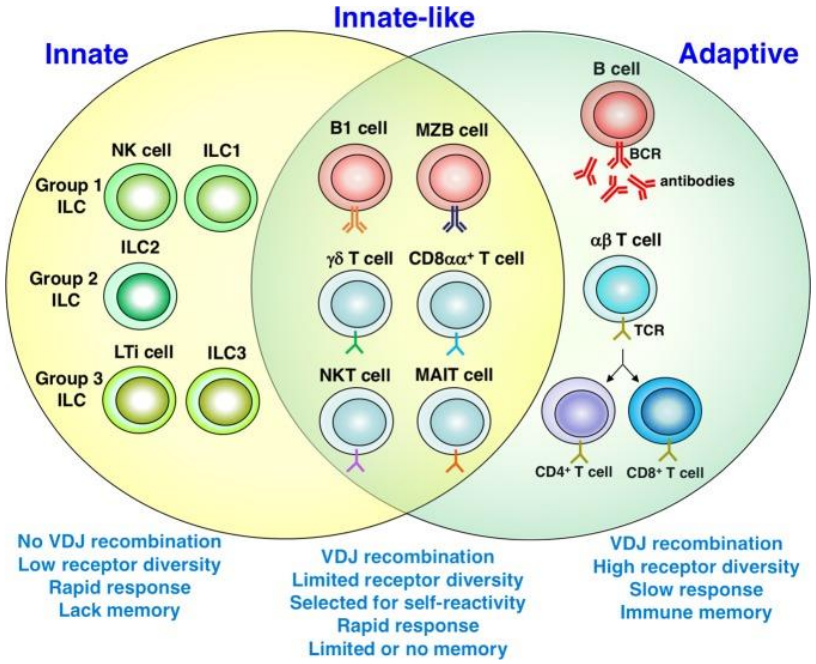
summary

- ILC
  - ILC3 more important
    - Bowel ?
  - ⇧ SpA/PsA
  - Target tissues>blood
    - migration
  - Produce IL-22
  - IL-17 in **some** cases

PsA pathogenesis

Rare subpopullations

- MAIT
- ILC
- Tgd

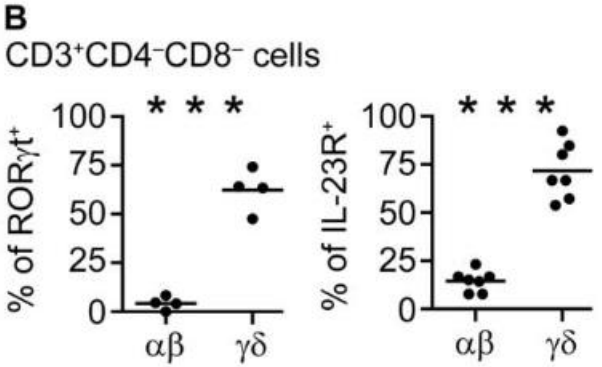


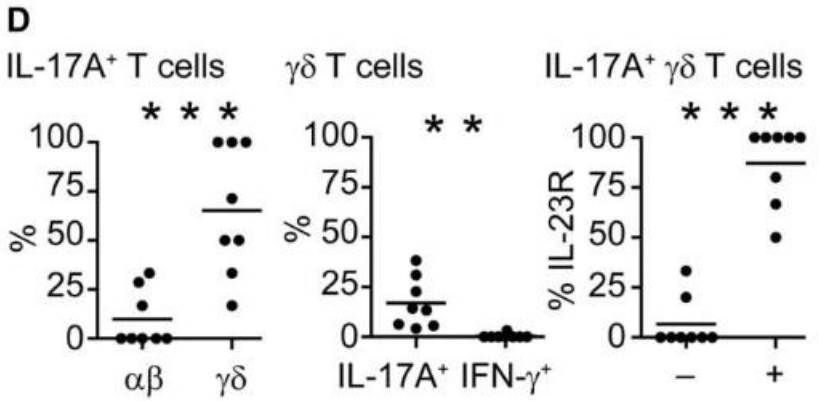
Van Kaer et al Cell and Mol Immun 2019

Tgd Mice

- In Tcrd-H2BeGFP mice
- Tgd
  - abundant in uninflamed entheseal tissue
  - constituted the large majority of RORgt, IL-23R+ enthesis- resident lymphocytes
  - Produce IL-17
    - Under IL-23

In entheses





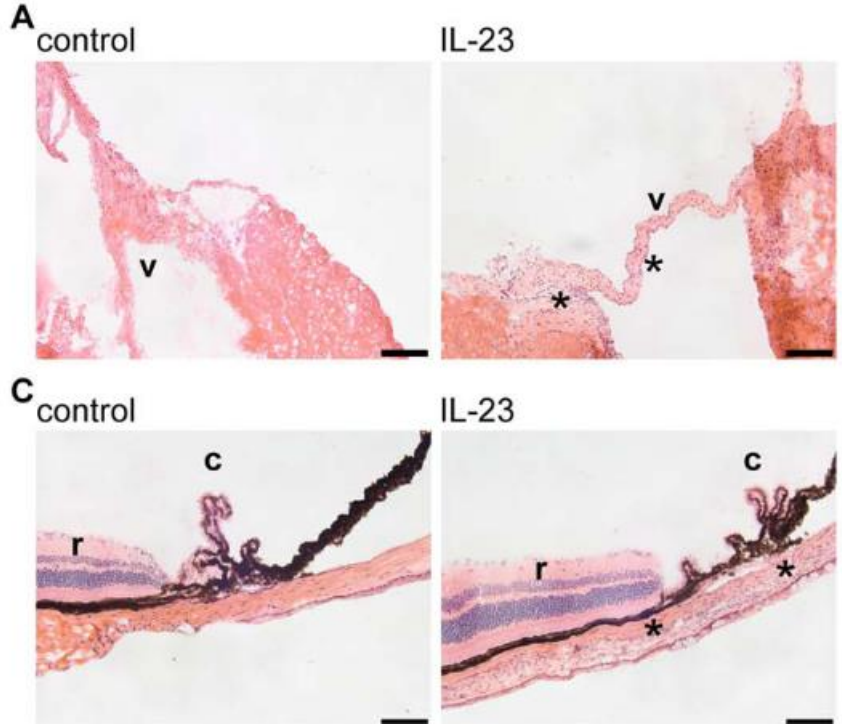
Stimulated with IL-23

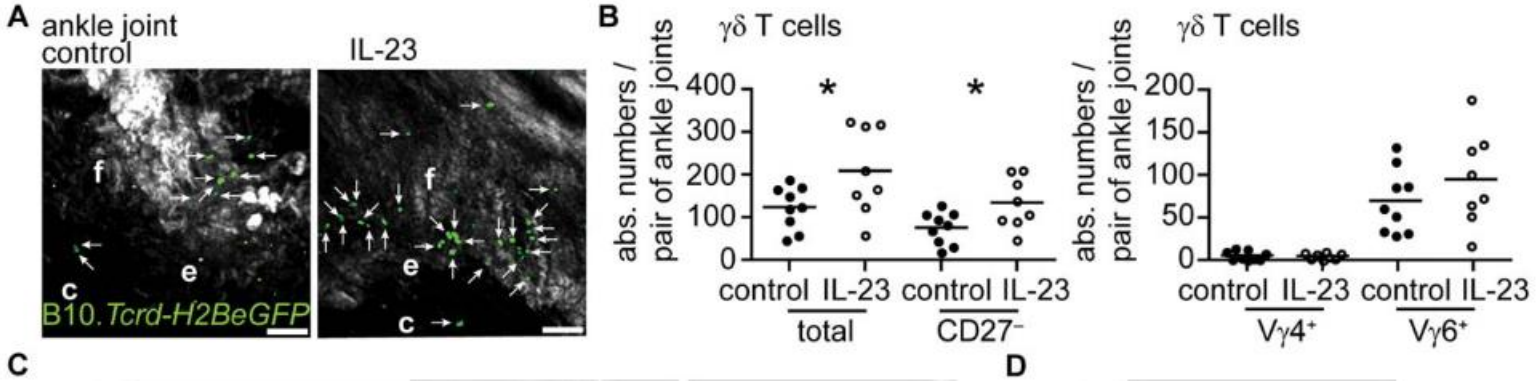
Reinhardt Arthr & Rheum 2016

Tgd

Accumulating in IL-23 overexpressing conditions

- In mice overexpressing IL-23
  - Accumulation of Tgd cells
    - In entheses
    - In aortic root
    - In eye (ciliary body)

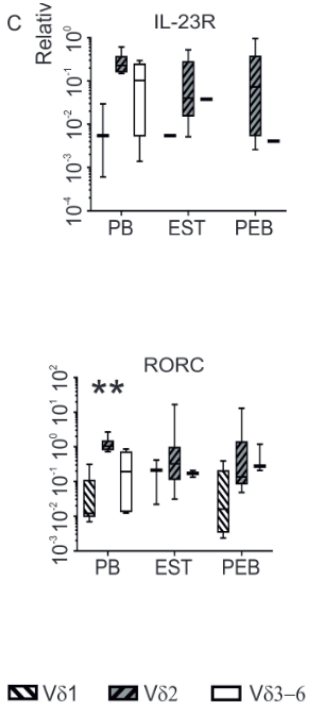


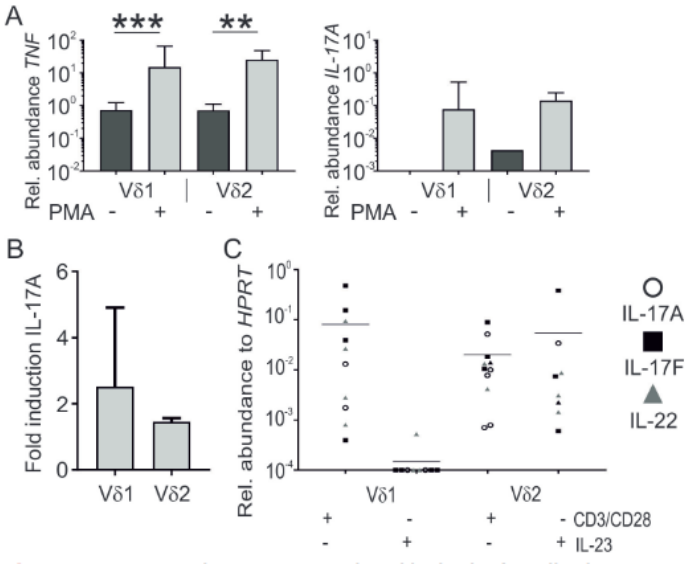


Reinhardt Arthr & Rheum 2016

Tgd
In Healthy

- Spinal processes
  - Entheses and bone
  - Tgd cells
    - 2 subsets
    - Vδ2
      - ✓ ⇧ IL-23/17-associated transcripts (e.g IL-23R, RORC)
    - Vδ1
      - ✓ almost completely lacked detectable IL-23R transcript
    - Produce IL-17
      - ✓ Dependent OR NOT from IL-23

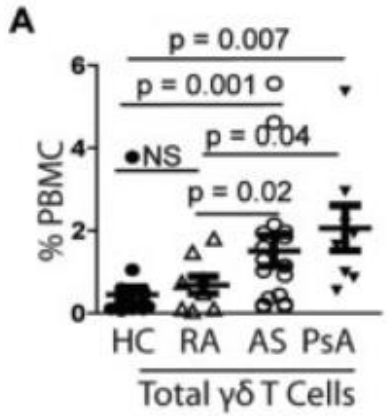


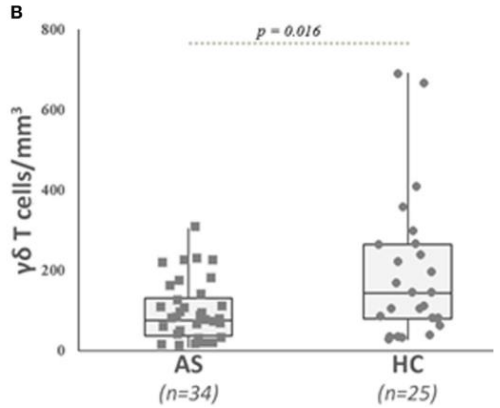


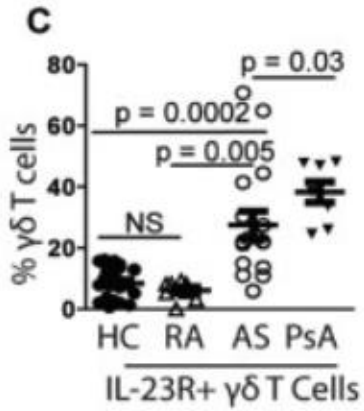
Cuthbert et al Ann Rheum Dis 2019

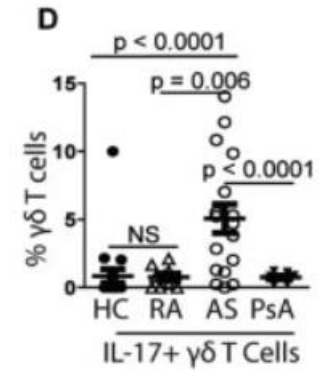
Tgd
AS/PsA - blood

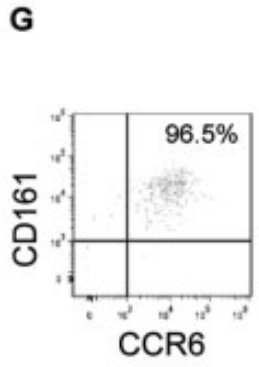
- Peripheral blood
  - % of Tgd cells in AS & PsA
    - Contradicting results
  - ⇧ % of IL-23R+ Tgd in AS and PsA
  - ⇧ % of IL-17 Tgd in AS ≠ PsA
    - ⇧ ⇧ ⇧ Express CCR6











Kenna et al Arthr & Rheum 2012
Toussirot et al Front Immun 2018

- ILC
  - ILC3 more important
    - Bowel?
  - ⇧ SpA/PsA
  - Target tissues>blood
    - migration
  - Produce **IL-22**
  - IL-17 in **some** cases
- Tgd
  - Important in entheses
  - Produce IL-17
    - Irrespective or not of IL-23
    - AS ≠ PsA ?
    - Migration
- MAIT
  - Present and active in axial entheses
  - Mani producers of IL-17 (blood)
    - Under IL-7
  - Migrate to joints?

CyTOF

- Simultaneous –in depth analysis of cells subpopullations

Distinct innate and adaptive immunity phenotypic profile at the circulating single-cell level in Psoriatic Arthritis

George E. Fragoulis[1,3], Eleni-Kyriaki Vetsika[2], Maria Kyriakidi[2], Kleio-Maria Verrou[2], George Kollias[2], Maria G Tektonidou[1], Iain B. Mcinnes[3], Petros P. Sfikakis[1,2]

Clin Immun 2023 (In Press)

Antibodies' panel (n=30)

Metal isotope	Target
89Y	CD45
141Pr	CD196/CCR6
143Nd	CD123
144Nd	CD19
145Nd	CD4
146Nd	CD8a
147Sm	CD11c
148Nd	CD16
149Sm	CD45RO
150Nd	CD45RA
151Eu	CD161
152Sm	CD194/CCR4
153Eu	CD25
154Sm	CD27
155Gd	CD57
156Gd	CD183/CXCR3
158Gd	CD185/CXCR5
160Gd	CD28

Metal isotope	Target
161Dy	CD38
163Dy	CD56/NCAM
164Dy	TCRgd
166Er	CD294
167Er	CD197/CCR7
168Er	CD14
170Er	CD3
171Yb	CD20
172Yb	CD66b
173Yb	HLA-DR
174Yb	IgD
176Yb	CD127

Intercalator	Role
103Rh	live/dead cell discrimination
191Ir 193Ir	single nucleated cells/doublets discrimination

47 Immunocytic populations

A/A	Cells populations
1	**Granulocytes**
2	Neutrophils
3	Eosinophils
4	Basophils
5	$CD66b^-$ Neutrophils
6	**Dentritic Cells (DC)**
7	Myeloid (mDC)
8	Palsmatocytoid (pDC)
9	**Monocytes**
10	Classics
11	Intermediate
12	Non-classic

A/A	Cells populations
13	**Lymphocytes**
14	**$CD3^+$ T cells**
15	**$CD8^+$ cells**
16	Immature
17	Central memory (CM)
18	Effector memory (EM)
19	TE
20	$CD27^-CD28^-$
21	Senescent(Tsen)
22	Senescent $CD45RA^+$ (Tsen-TEMRA)
23	Activated
24	$CD127^+$ Activated
25	$CD45RA^+$ Activated
26	**$CD4^+$ T cells**
27	Immature
28	Central memory (CM)
29	Effector memory (EM)
30	TE

A/A	Cells populations
31	T regulatory (Tregs)
32	Th1
33	Th2
34	Th17
35	**MAIT/NKT**
36	**γδ T cells**
37	**B cells**
38	Immature
39	Memory
40	IgD^+ memory
41	IgD^- memory
42	Age-associated B κύτταρα (ABCs)
43	Plasmablasts
44	**Natural Killer cells (NK)**
45	Immature
46	Mature
47	**Innate lymphoid cells (ILCs)**

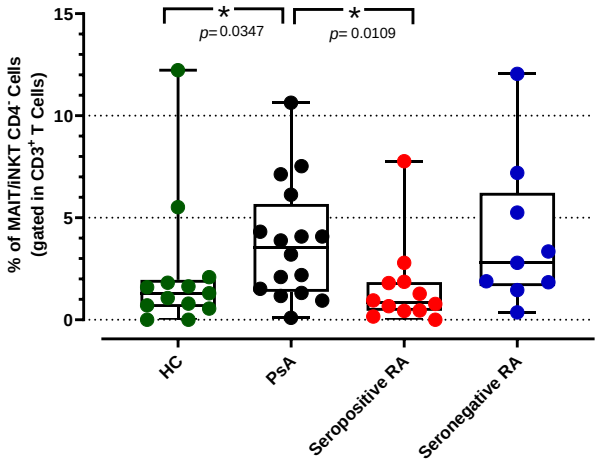
Patients' characteristics

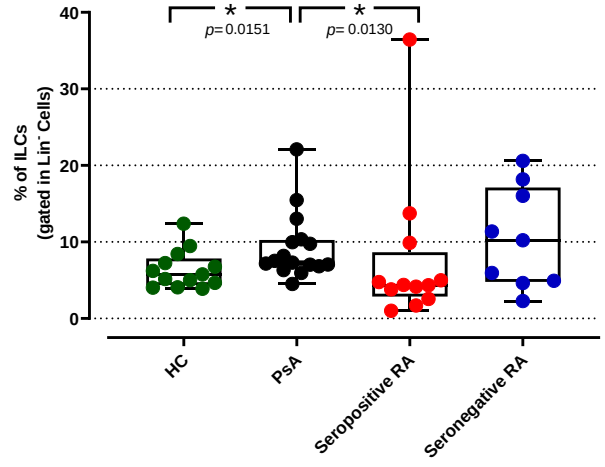
Characteristics	PsA (n= 16)	RA (n= 21)	HC (n= 13)
Age (years)			
Median (range)	49 (19-63)	55 (23-77)	51 (38-60)
Gender			
Female	12 (75%)	20 (95%)	9 (69%)
Male	4 (25%)	1 (5%)	4 (31%)
Smoking			
No	13 (81%)	14 (67%)	9 (69%)
Yes	3 (19%)	7 (33%)	4 (31%)
Treatment			
Naïve	5 (31%)	6 (29%)	-
csDMARDs-experienced	4 (25%)	11 (52%)	-
bDMARDs	7 (44%)	4 (19%)	-
CRP (mg/L)			
Mean (SEM)	8,31 (1,93)	20,54 (12,49)	-
ESR (mm/h)			
Mean (SEM)	25,56 (4,08)	35,33 (5,04)	-
Disease activity score	**DAPSA**	**DAS28**	
Mean (SEM)	16,86 (1,32)	4,91 (0,19)	-

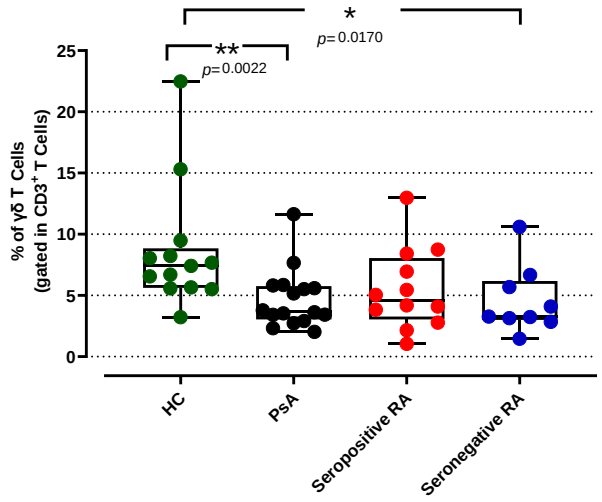
	RA (n= 21)
Seropositivity	
Seronegative	9 (43%)
Seropositive	12 (57%)

MAIT/iNKT, ILCs and γδ T cells
PsA and RA – peripheral blood

- PsA
  - ⇧ MAIT
  - ⇧ ILC
  - ⇩ Tgd
  - Similarities with seronegative but not seropositive RA

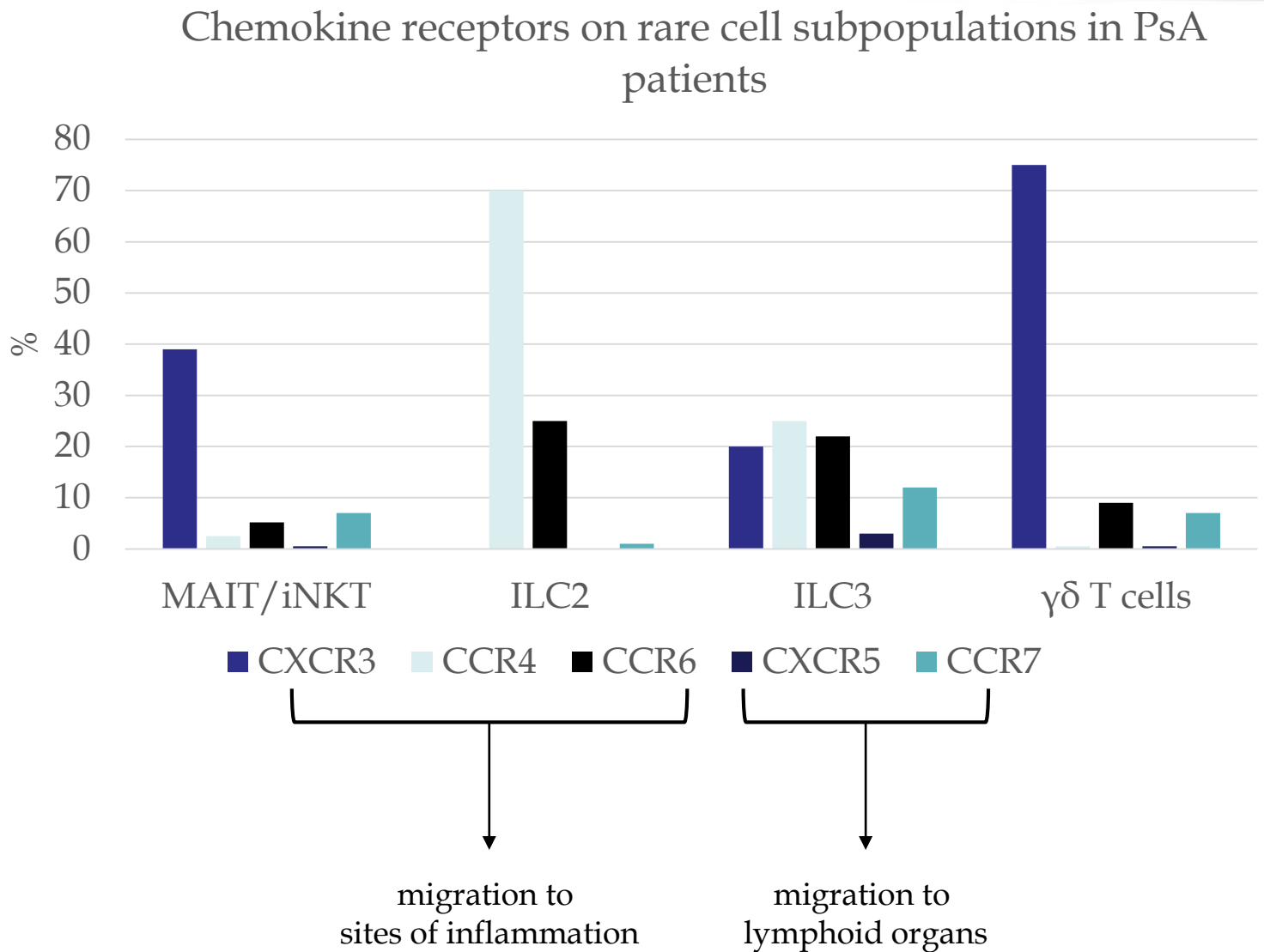




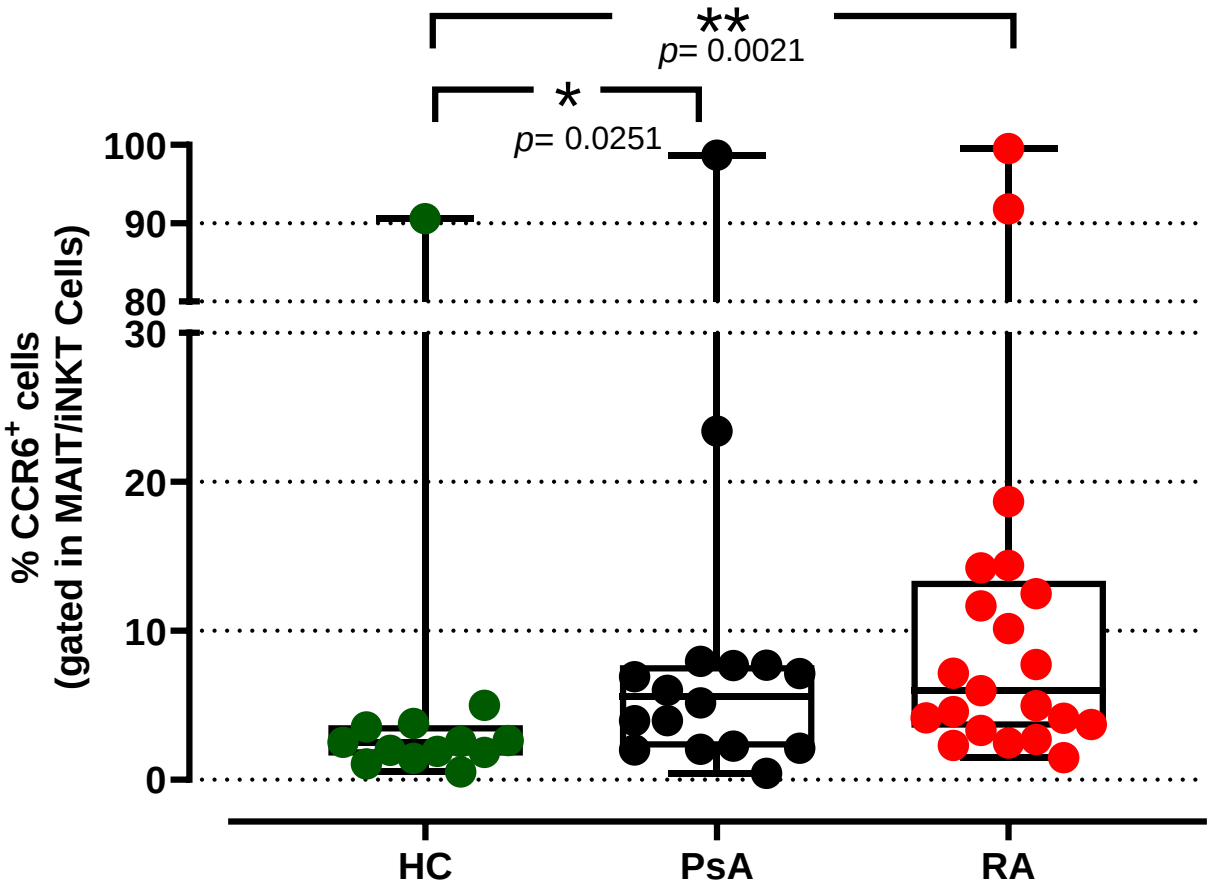


HC= 13
PsA= 16
Seropositive RA= 12
Seronegative RA= 9

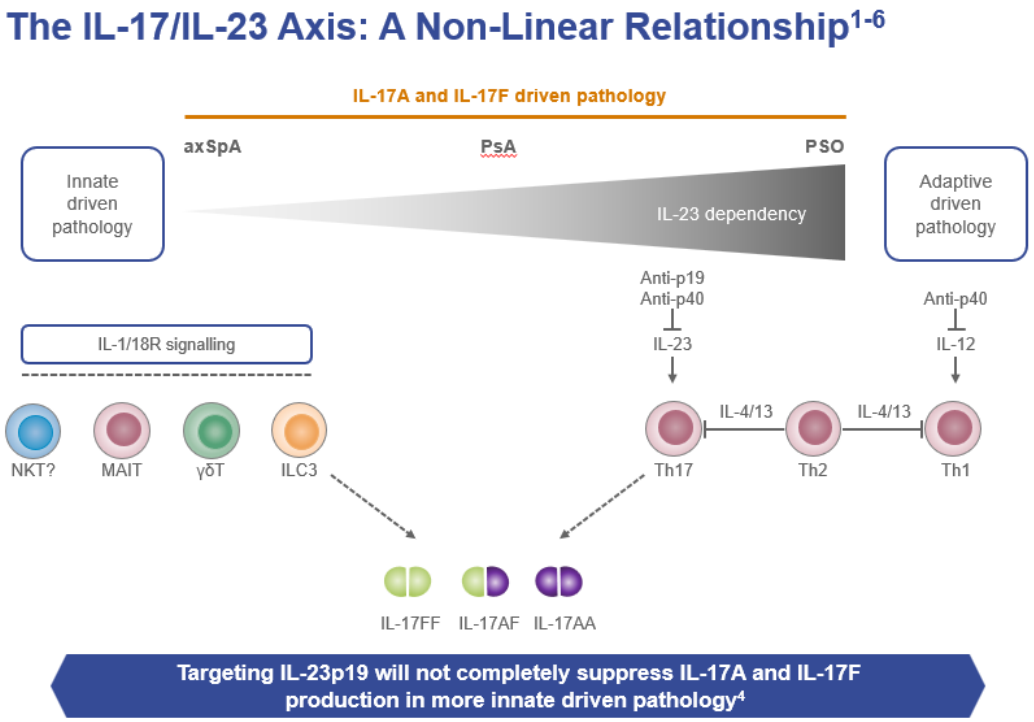
MAIT/iNKT, ILCs and γδ T cells & Migration
PsA peripheral blood



MAIT/iNKT
Peripheral blood CCR6 (Increased in PsA)



IL-23, IL-17 & migration



Perturbations in the gut community composition (DYSBIOSIS)

dysregulation of the gut epithelial barrier

activation of **IL-23-** producing immune cells resident in the lamina propria

activate IL-23-responsive cells such as MAIT cells, type 3 innate lymphoid cells (ILC3) and γδ T cells

circulate away from the gut and **migrate** to the entheses and synovial tissues

inflammatory responses

Sieper et al Nat Rev Rheum 2019

Conclusion, problems and questions

- SpA vs PsA
- Cell migration is important…
- Different tissues
  - Peripheral entheses Vs Axial entheses
    - Vs gut….Vs eye….

Thank you for your attention !! ☺