Παθογένεση Ψωριασικής Αρθρίτιδας

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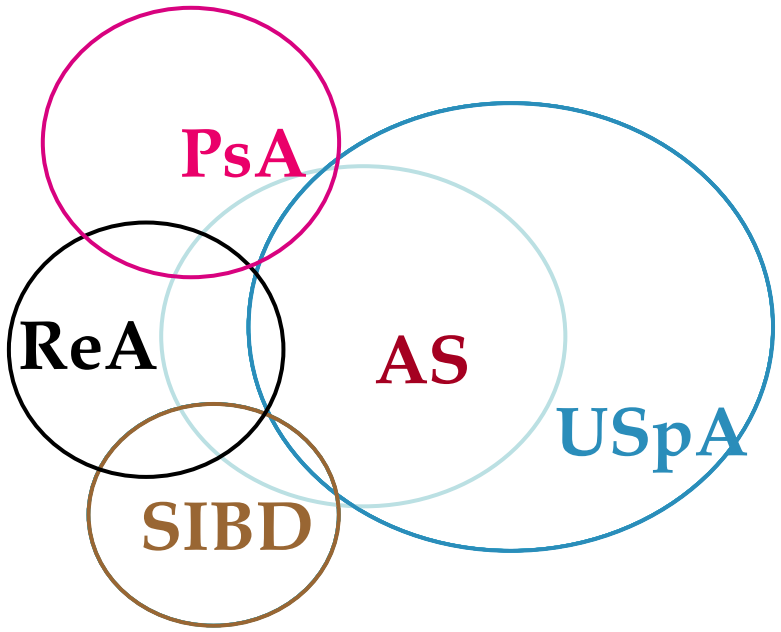
Οκτώβριος 2022

Spondyloarthritis

Psoriatic Arthritis

SpA: Overlapping entities



AS **Ankylosing spondylitis**

PsA **Psoriatic arthritis**

USpA **Undifferentiated SpA**

ReA **Reactive arthritis**

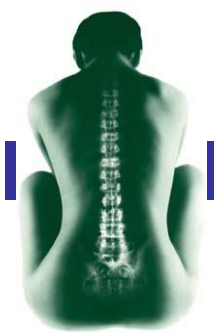
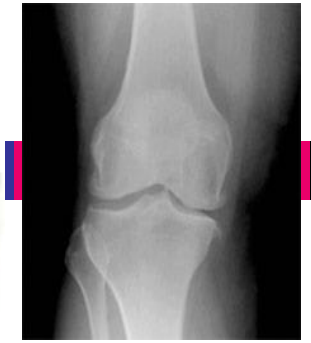
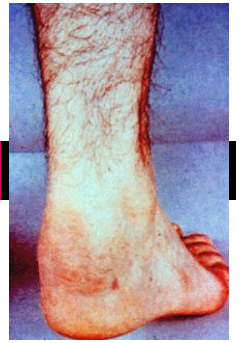
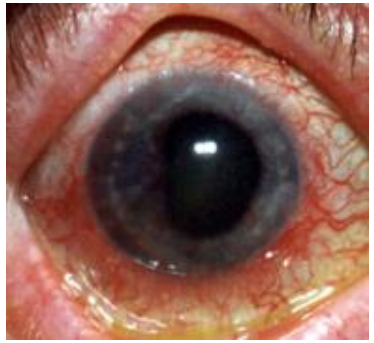
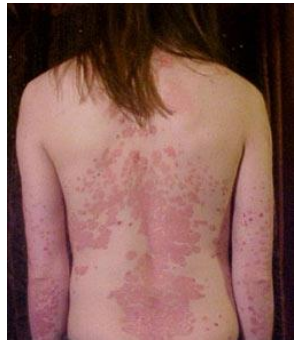
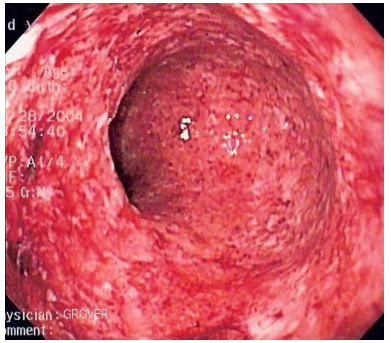
SIBD **SpA με IBD**

Davis JC & Mease PJ Semin Arthr & Rheum 2008

Psoriatic arthritis

Epidemiology

- Inflammatory arthritis
  - Affects
    - ✓ ~ 1-3% white Caucasian
    - ✓ 0.1-0.3% American/ African-American
    - ✓ ~ 30% of patients with psoriasis
  - Psoriasis usually (~70%) precedes of arthritis
  - 30-50 years old
  - ♀ = ♂

Chandran et al J Autoimmun 2010

Psoriatic Arthritis

Patterns of disease

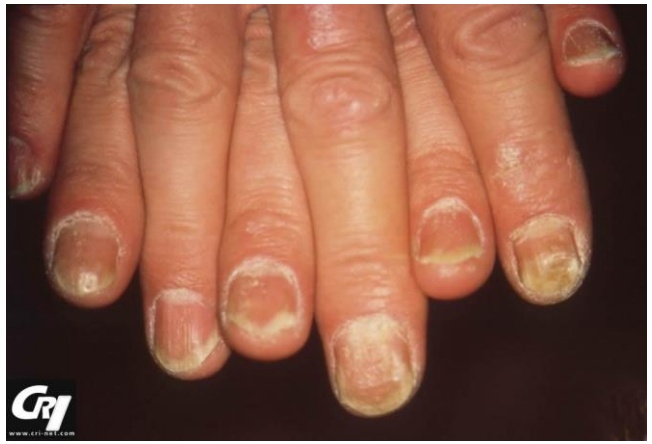
- Heterogeneous disease
  - Asymmetric oligoarthritis
  - Predominantly distal interphalangeal disease
  - Peripheral polyarthritis (rheumatoid-like)
  - Dominant axial disease (sacroiliitis/spondylitis)
  - “Arthritis mutilans” (a mutilating type of disease - digits)

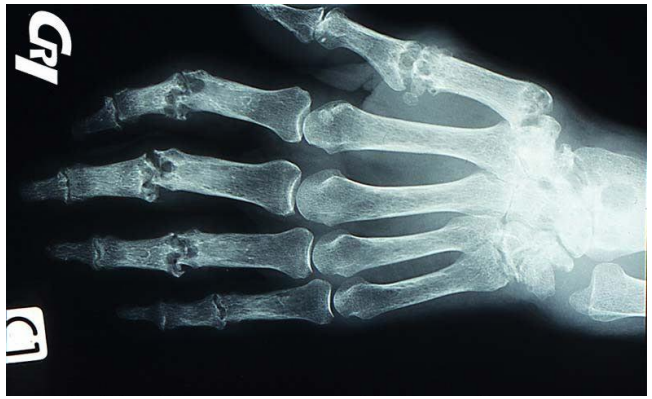
Eder & Gladman Curr Rheum Rep 2013

Psoriatic Arthritis

Common Findings

- Other common findings
  - Enthesitis (entheses: tendon/ligament attaches to the bone)
  - Dactylitis - sausage-shaped swelling of digits
  - Nail involvement
  - Radiologically
    - juxta-articular new bone formation and erosions





Brockbank JE Ann Rheum Dis 2015

Psoriatic arthritis

...or psoriatic disease

- Metabolic component
  - Diabetes (11-20%)
  - Obesity (16-60%)
    - Associates with PsA development and worse prognosis
  - Hypertension/CVD (28-47%/21-62%)
    - ⇧ CVD risk
      - ✓ Does not fully explained by classic CVD risk factors
  - Mental disorders
    - Depression (9-27%)
    - Anxiety (6-37%)

- Inflammatory Bowel Disease
  - Crohn (not for UC)
    - Risk Ratio
      - Vs Healthy: 2.96 (1.40 - 6.00)
      - Vs Psoriasis 3.60 (1.83 – 7.10)
- Ocular manifestations
  - Risk Ratio
    - Vs Healthy: 3.35 (2.21 - 5.70)
    - Vs Psoriasis 2.13 (1.40 – 3.24)

Kimball AB J Am Acad Dermatol. 2008
Krishnadas R Brain Behav Immun 2016
Nikiphorou E, Fragoulis GE Ther Adv Musculoskelet Dis. 2018

Charlton R et al Ann Rheum Dis 2018
McDonough E et al J Rheum 2014
Khraishi M et al Clin Rheum 2014
Husted JA et al Arthritis Care and Res 2014

Psoriatic arthritis (PsA)

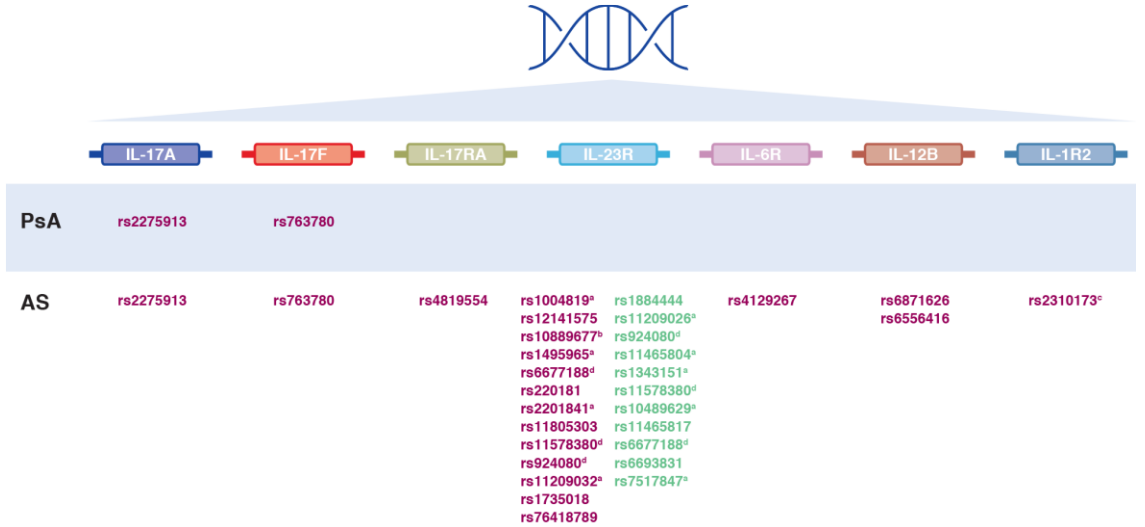
Pathogenesis

- Genetic factors
- Environmental factors
  - Microbiome
- Mechanical stress

PsA pathogenesis

Genetics HLA

- HLA-B27
  - In about 20% 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

PsA 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

PsA pathogenesis

Environmental factors

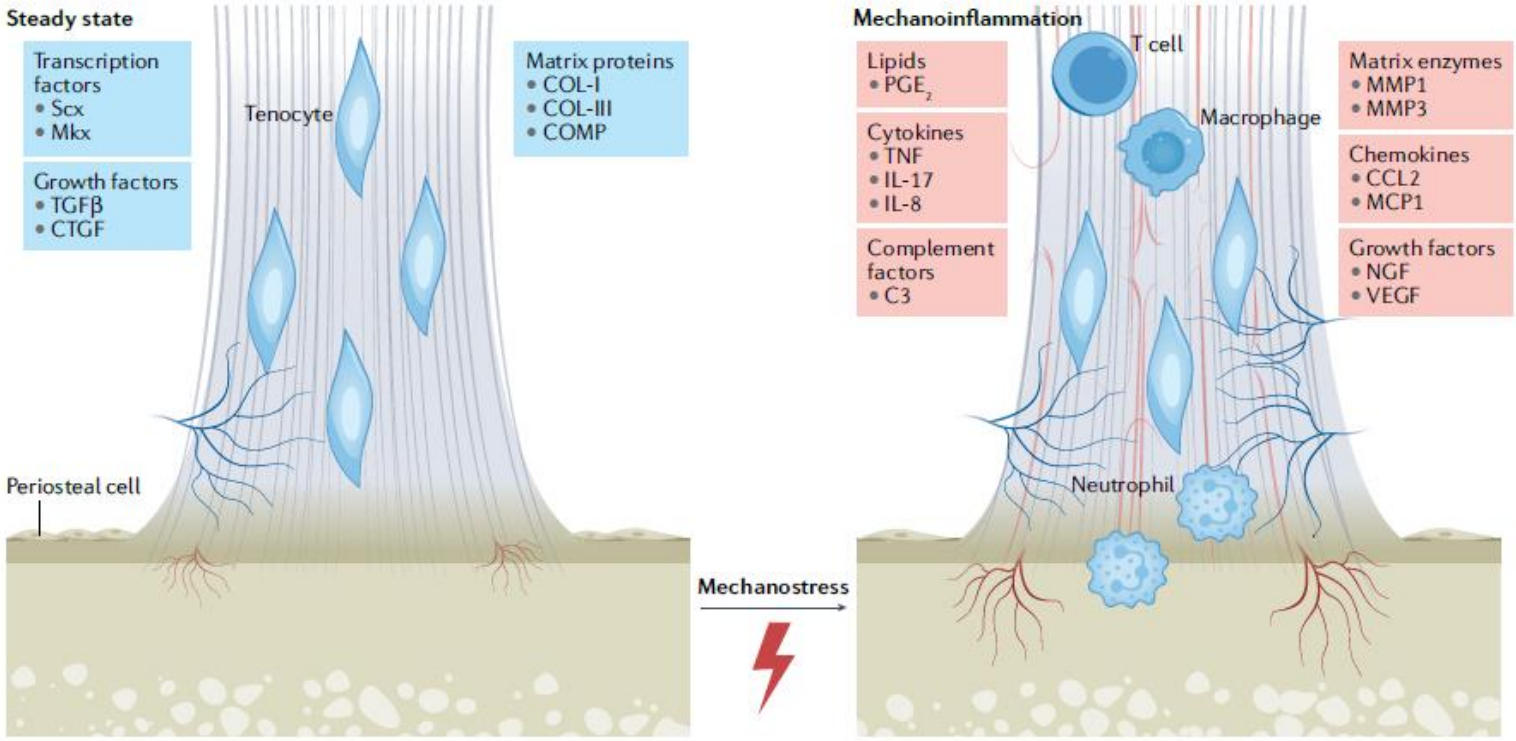
- Environmental factors
  - Microbiome
- HLA-B27 Tg mice or SKG mice
  - IBD-like, psoriasis-like rash, arthritis, sacroiliitis
    - Lees pronounced in germ free conditions
- Psoriatic arthritis Vs Healthy individuals
  - ⇩ Akkermansia/Ruminococcus/Coprococcus

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

PsA Pathogenesis

Mechanical stress

- In normal tendons
  - Tenocytes
    - control extracellular matrix by producing collagen or degrading it via proteases
  - are notoriously mechanosensitive
    - transcription factors
      - ✓ scleraxis and mohawk
      - ✓ drive expression of mechanical stress-activated genes
- In vitro
  - stretching of tendon and ligament stromal cells induces the production of an array of pro-inflammatory mediators,
    - Chemokines, cytokines and complement factors



Schett G et al Nat Rev Rheum 2022

PsA Pathogenesis

Mechanical stress

- Mechanical stress
  - "unloaded mice": less enthesitis
  - PsA studies
    - 9-25% injury preceded
    - Koebner-phenomenon analogy
  - Psoriasis patients
    - Joint/bone injury

Table 2 HR of incident psoriatic arthritis (PsA) by trauma exposure among patients with psoriasis

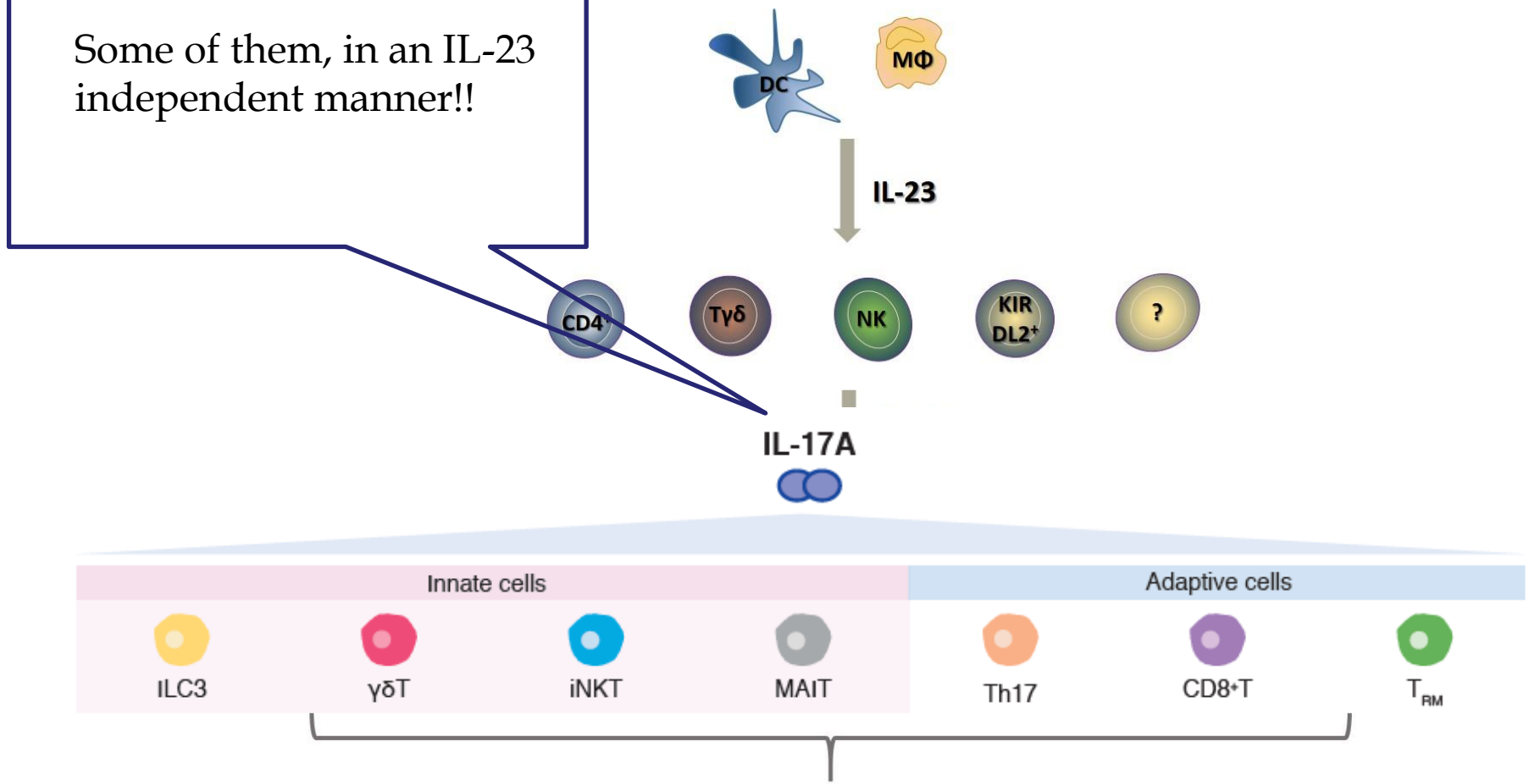
	Trauma exposure					
	Unexposed	All	Joint	Bone	Nerve	Skin
Cases of PsA, N	745	265	122	56	15	63
IR/10 000 person-years	22.0 (21.0 to 24.0)	30.0 (26.0 to 34.0)	35.0 (29.0 to 41.0)	28.0 (21.0 to 37.0)	30.0 (17.0 to 49.0)	23.0 (17.0 to 29.0)
HR (95% CI)	1.00 (reference)	1.34 (1.15 to 1.56)	1.53 (1.22 to 1.92)	1.45 (1.05 to 2.01)	1.71 (0.89 to 3.28)	0.93 (0.69 to 1.26)
Multivariate HR (95% CI)*	1.00 (reference)	1.32 (1.13 to 1.54)	1.50 (1.19 to 1.90)	1.46 (1.04 to 2.04)	1.66 (0.84 to 3.29)	0.91 (0.67 to 1.23)

Scarpa R et al Ann Rheum Dis 1992
Taurog J et al JEM 1994
Thorarensen SM ARD 2017

PsA Pathogenesis

The IL-23/IL-17 axis

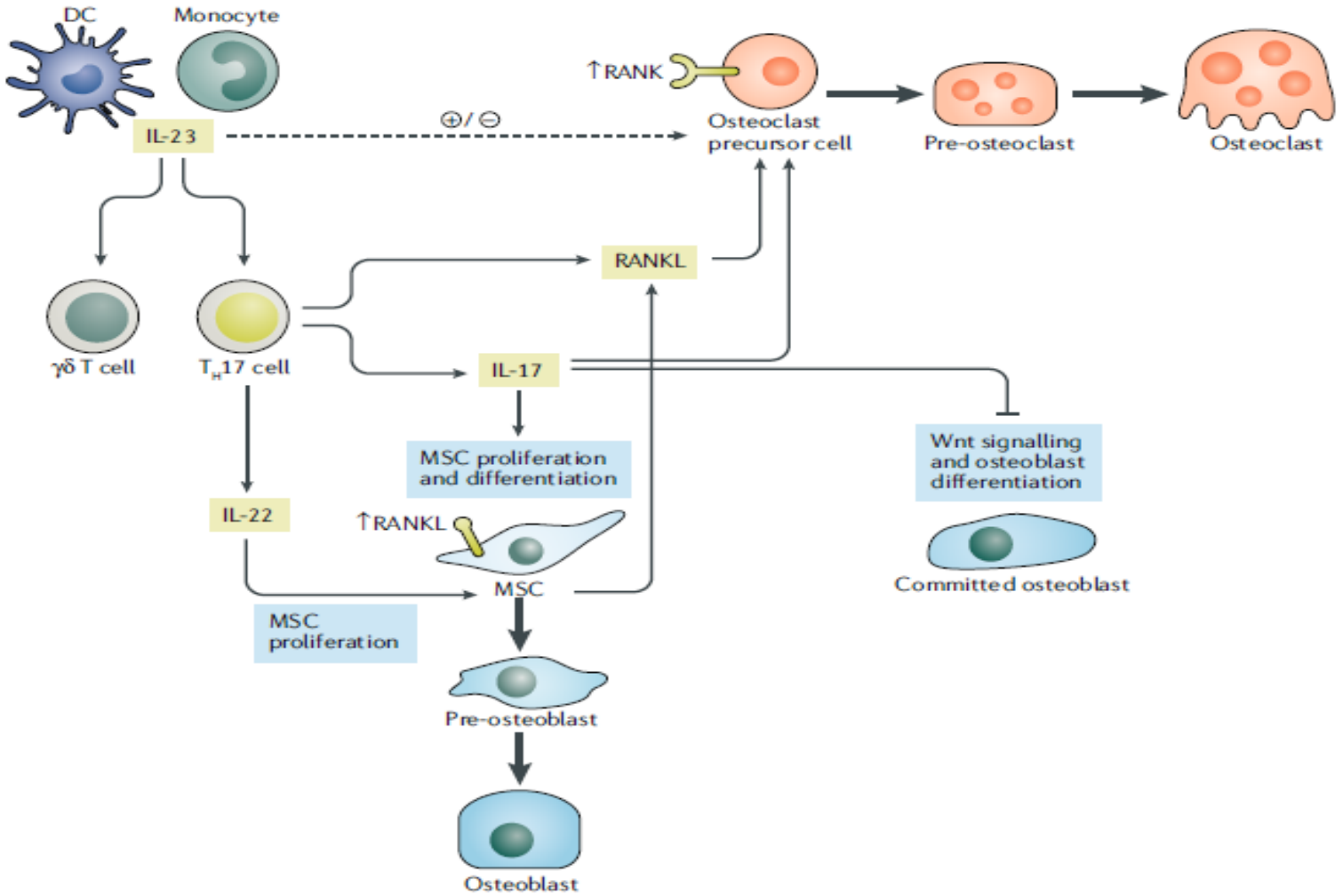
Some of them, in an IL-23 independent manner!!



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

Bone formation



Veale D et al Lancet 2018
Gravallese E & Schett G Nat Rev Rheum 2018

IL-23

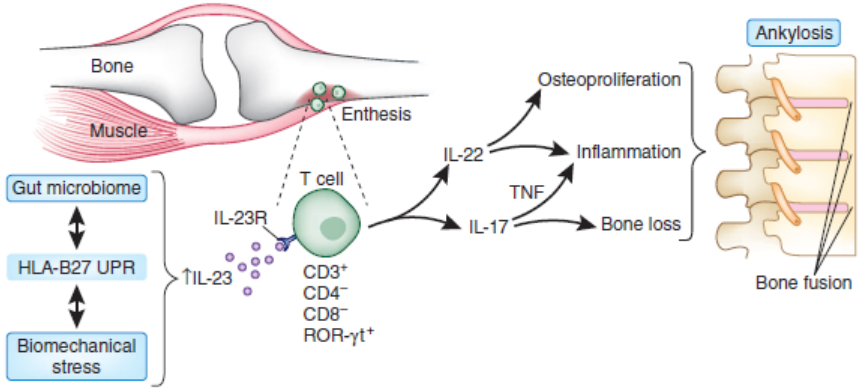
Evidence for PsA

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

Psoriatic arthritis

Enthesitis

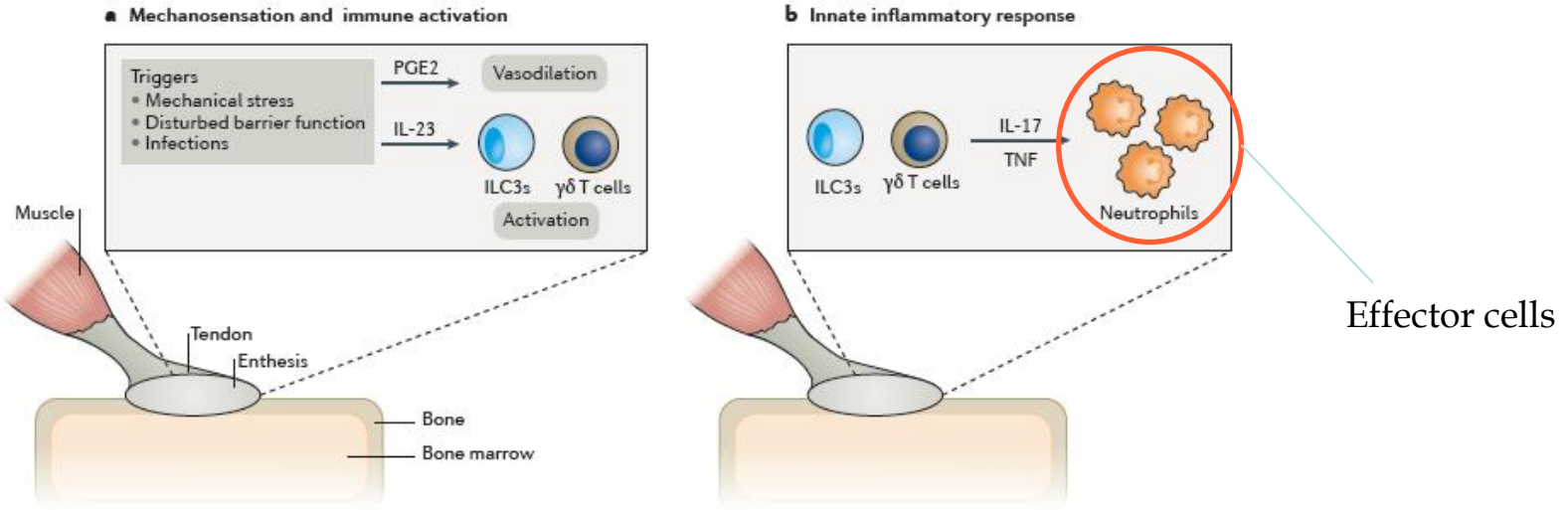
- Enthesis organ "synovio-entheseal concept"
- Could enthesis be the start of everything??
- T-cells at the sites of tendon insertion into bone (entheses)
  - express IL-23 receptor
  - respond to systemically-administered IL-23 to produce IL-17, IL-22 and IL-6



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

Psoriatic arthritis

Enthesitis

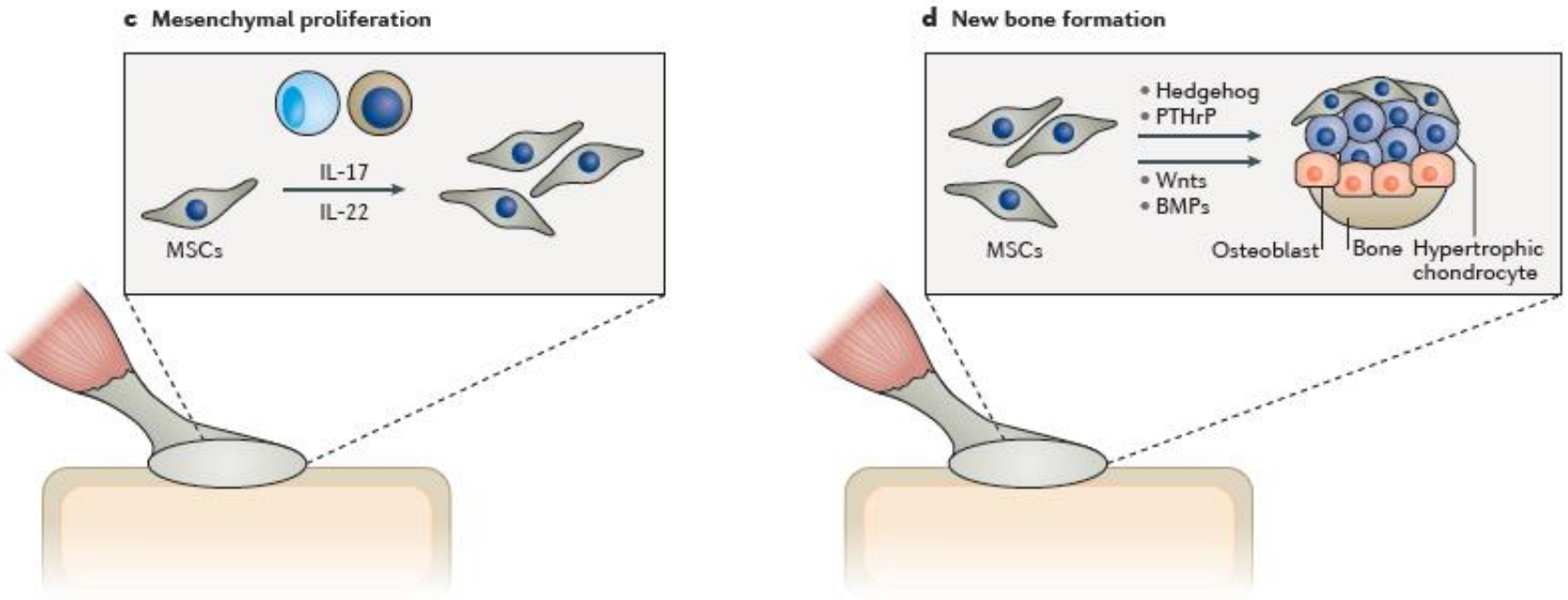


- PGE2
  - Response to mechanical stress
  - Mesenchymal cells – COX2 expression
  - Induces IL-17 expression

Schett G et al Nat Rev Rheum 2017

Psoriatic arthritis

Enthesitis

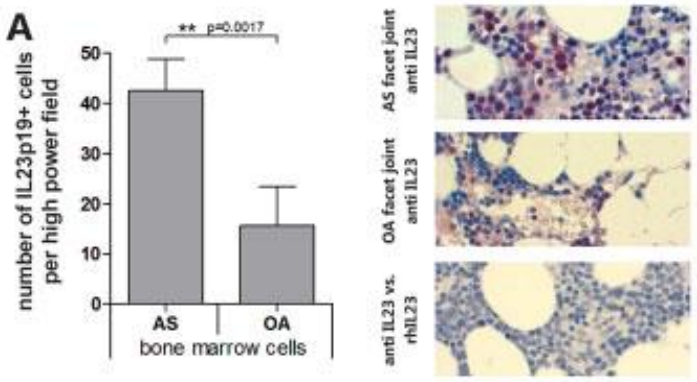


Schett G et al Nat Rev Rheum 2017

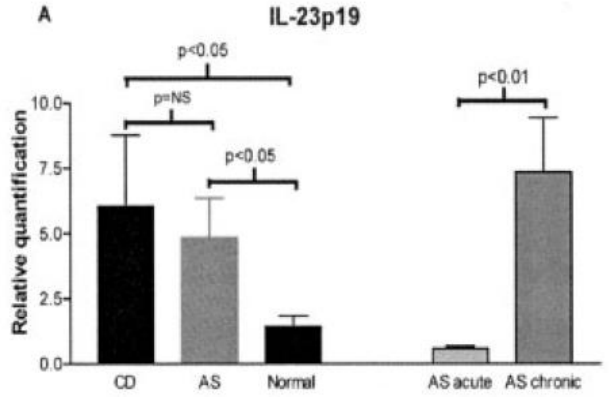
SpA

IL-23 in the spine/bowel

- Spine
  - ⇧ IL-23 facet SpA > OA
  - myeloid CD14+ cells expressing IL-23 in spinal entheses obtained from healthy individuals



- Bowel
  - By infiltrating monocytes
  - Paneth cells

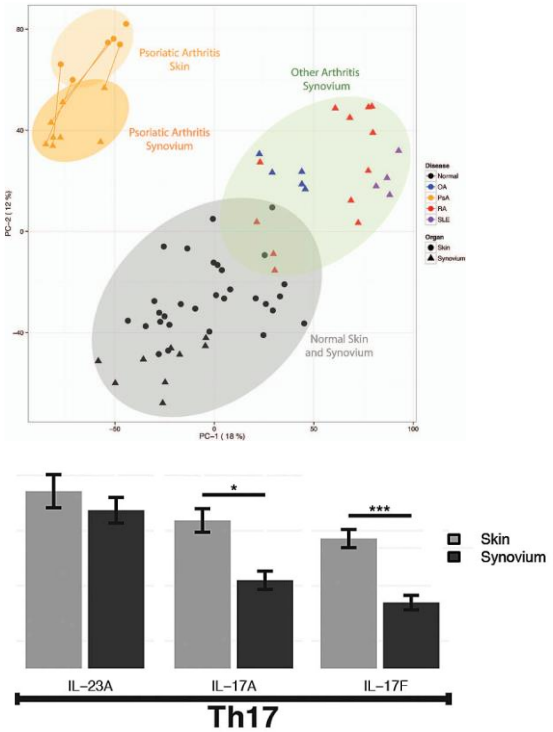


Appel H et al Arthr & Rheum 2013
Siebert S et al Ann rheum Dis 2018
DG McGonagle et al ARD 2019
Bridgewood C et al Ann Rhem Dis 2019

Psoriatic arthritis

IL-23 in Synovium and Skin

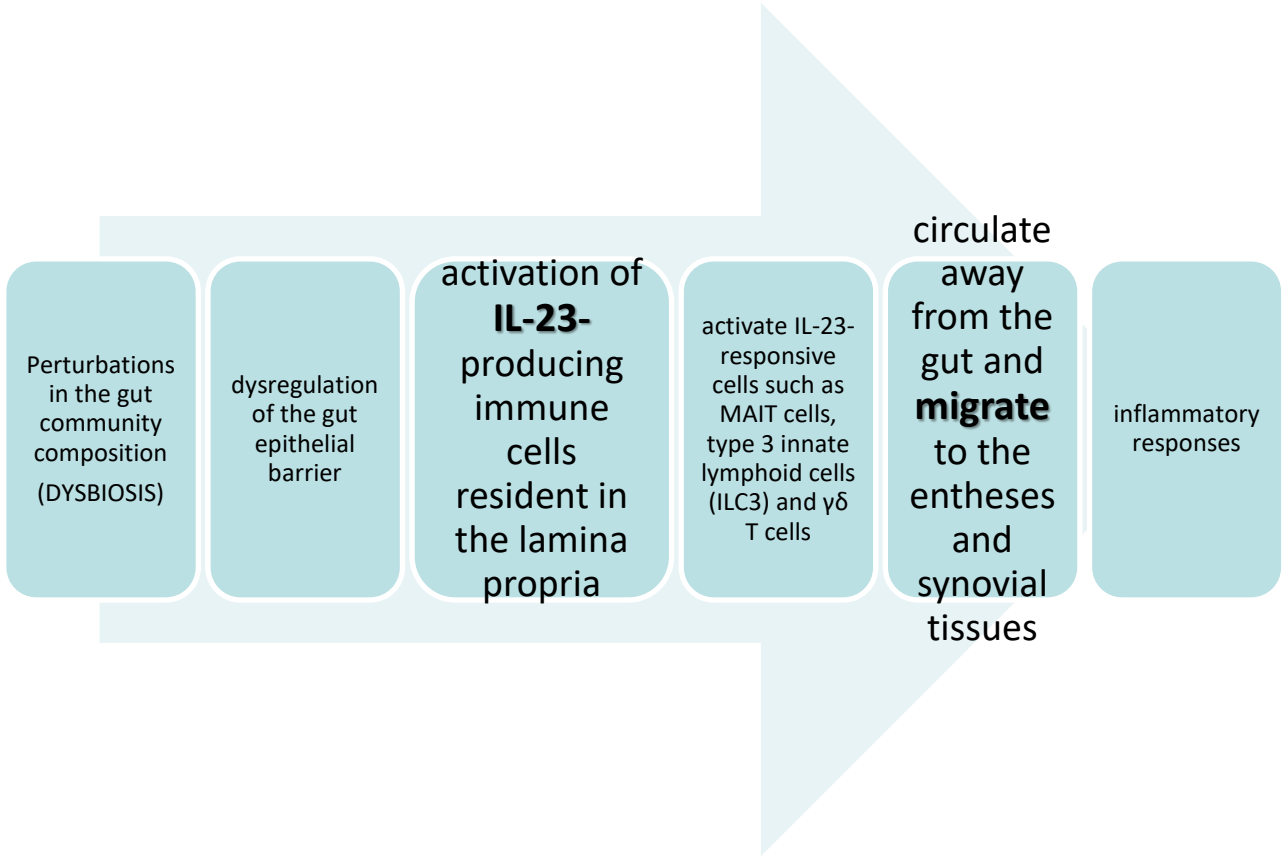
- Similarities & differences
  - TNF pathway, VEGF, TGF-β1 and IL-6
    - More activated in synovium
  - IL-23/-17 axis
    - More active in the skin



Belasco J et al Arthr Rheum 2015

PsA pathogenesis

The microbiome (gut-joint axis)

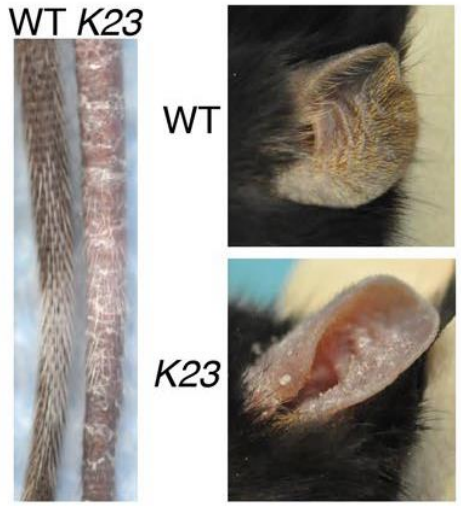


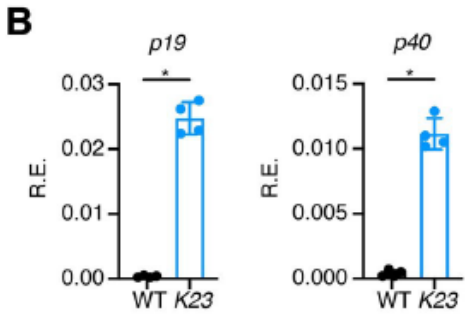
Schett G et al Nat Rev Rheum 2022

PsA Pathogenesis

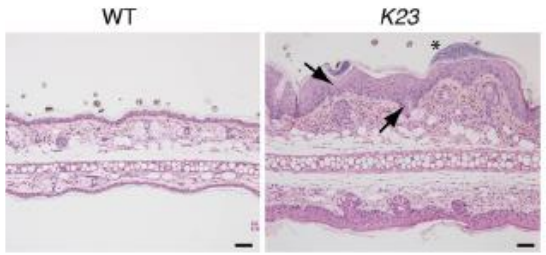
Could all start from IL-23?

- Transgenic expression of IL-23 in mice





p19/p40
expression
in the ears

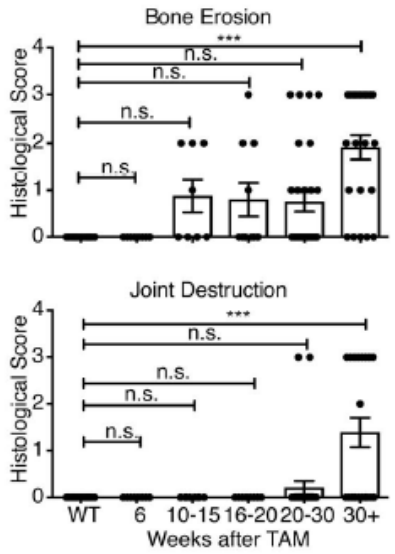


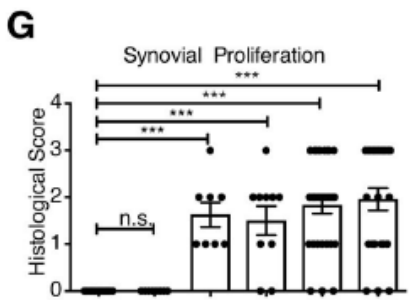
H&E, ears
6 weeks

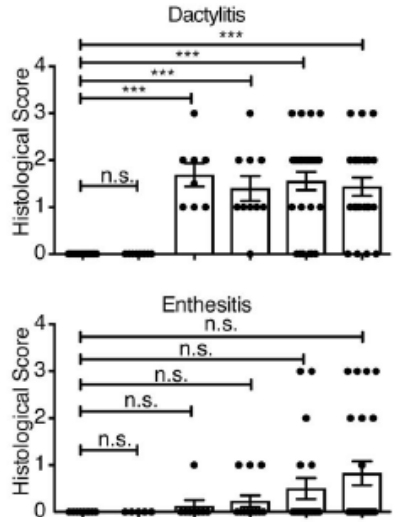
Chen L et al, Sci Rep 2020

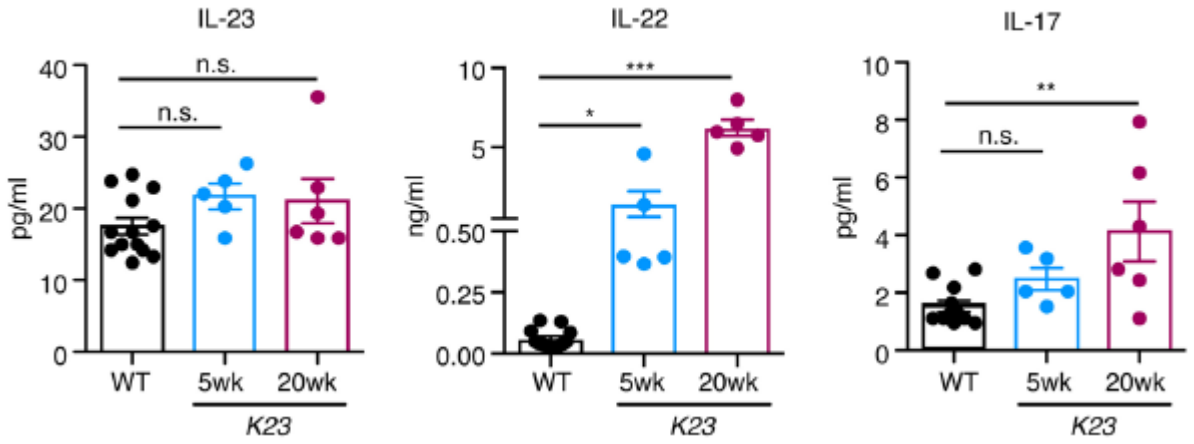
IL-23 mice model

PsA features & cytokines expression





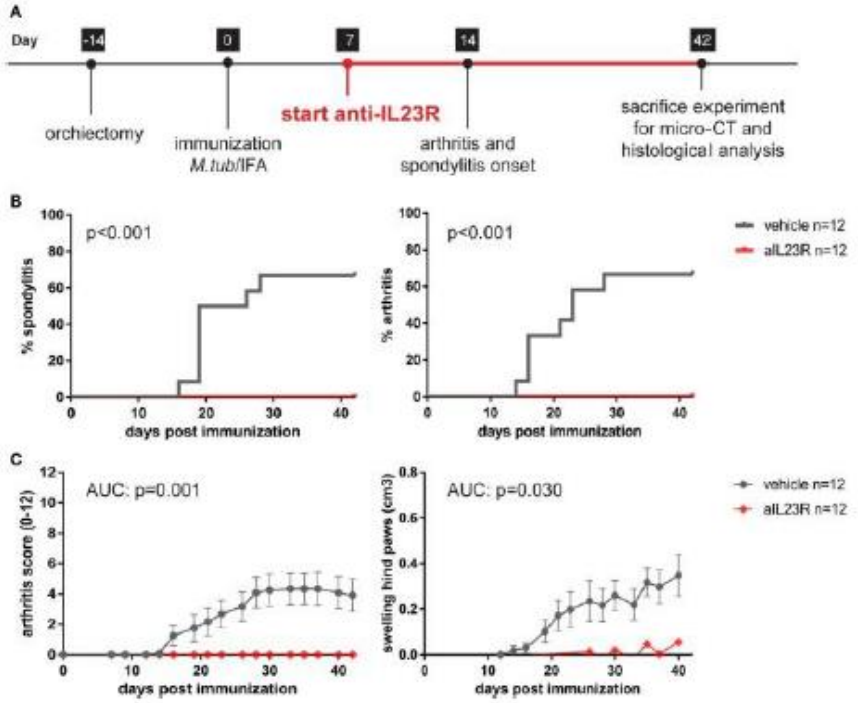




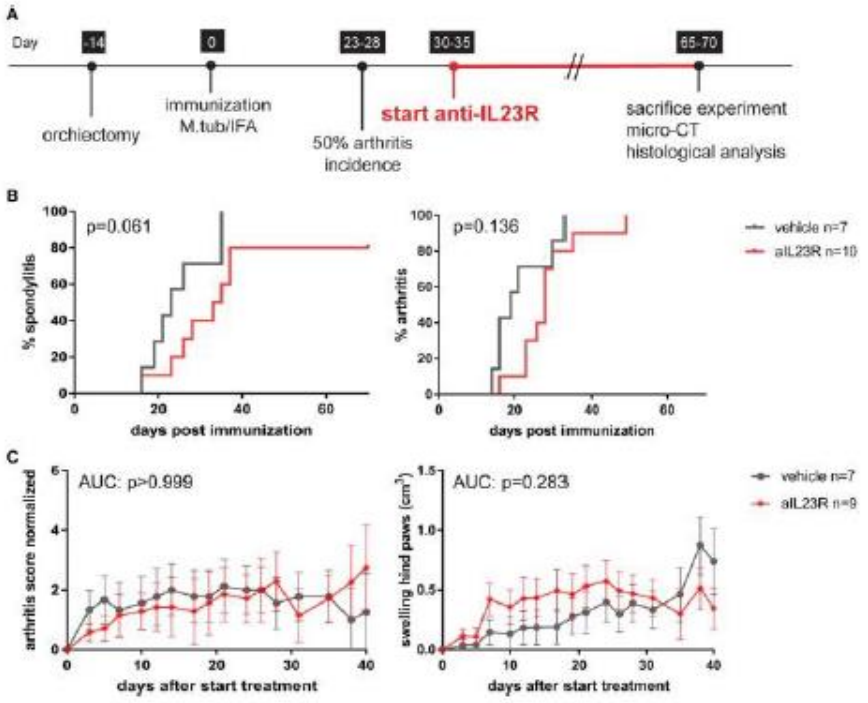
IL-23

Initiation but not perpetuation of disease

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



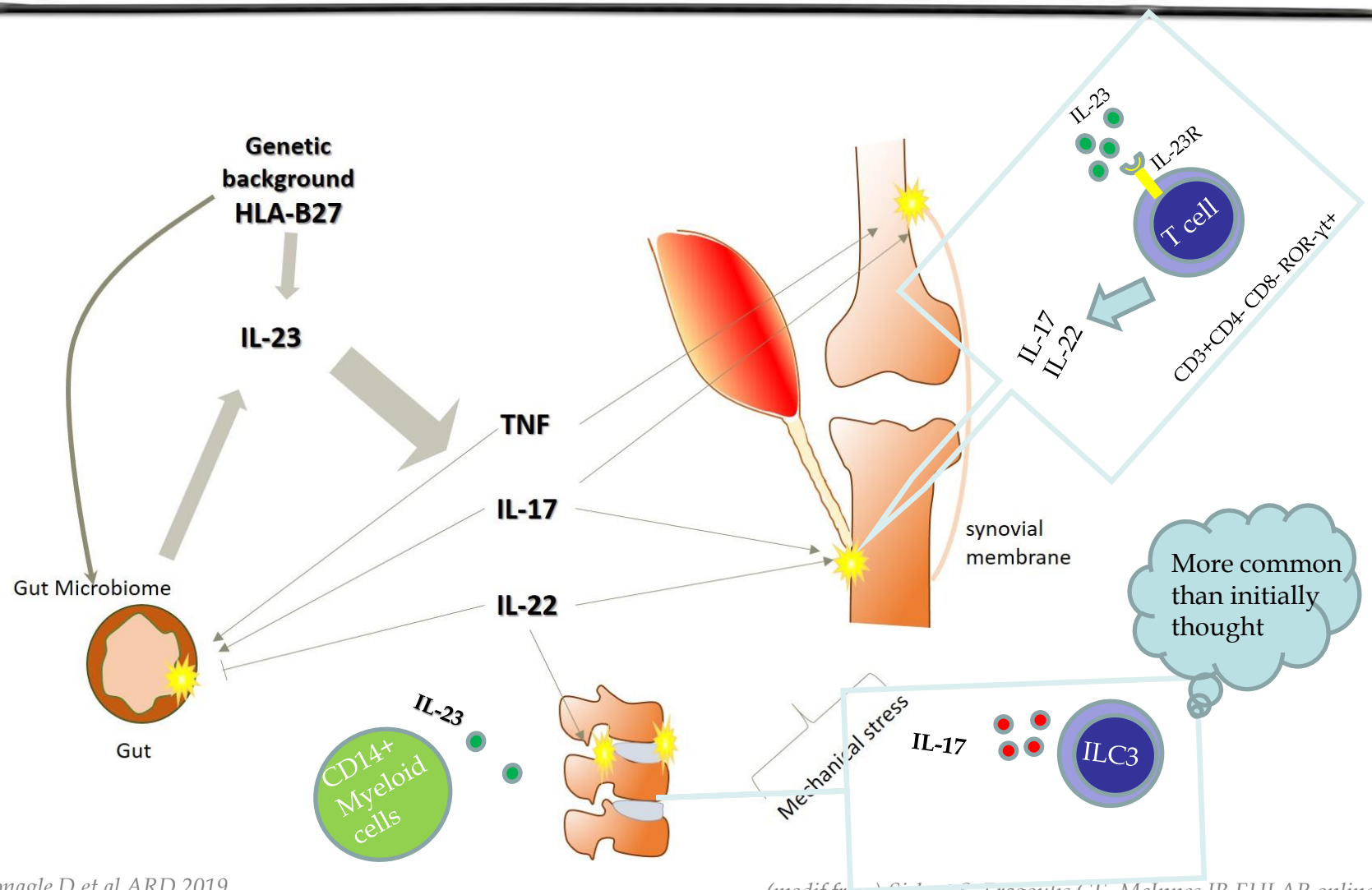
Anti-IL23R failed to suppress spondylitis and arthritis in HLA-B27tg rats



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

PsA

Pathogenesis overview



McGonagle D et al ARD 2019
Bridgewood et al ARD 2019

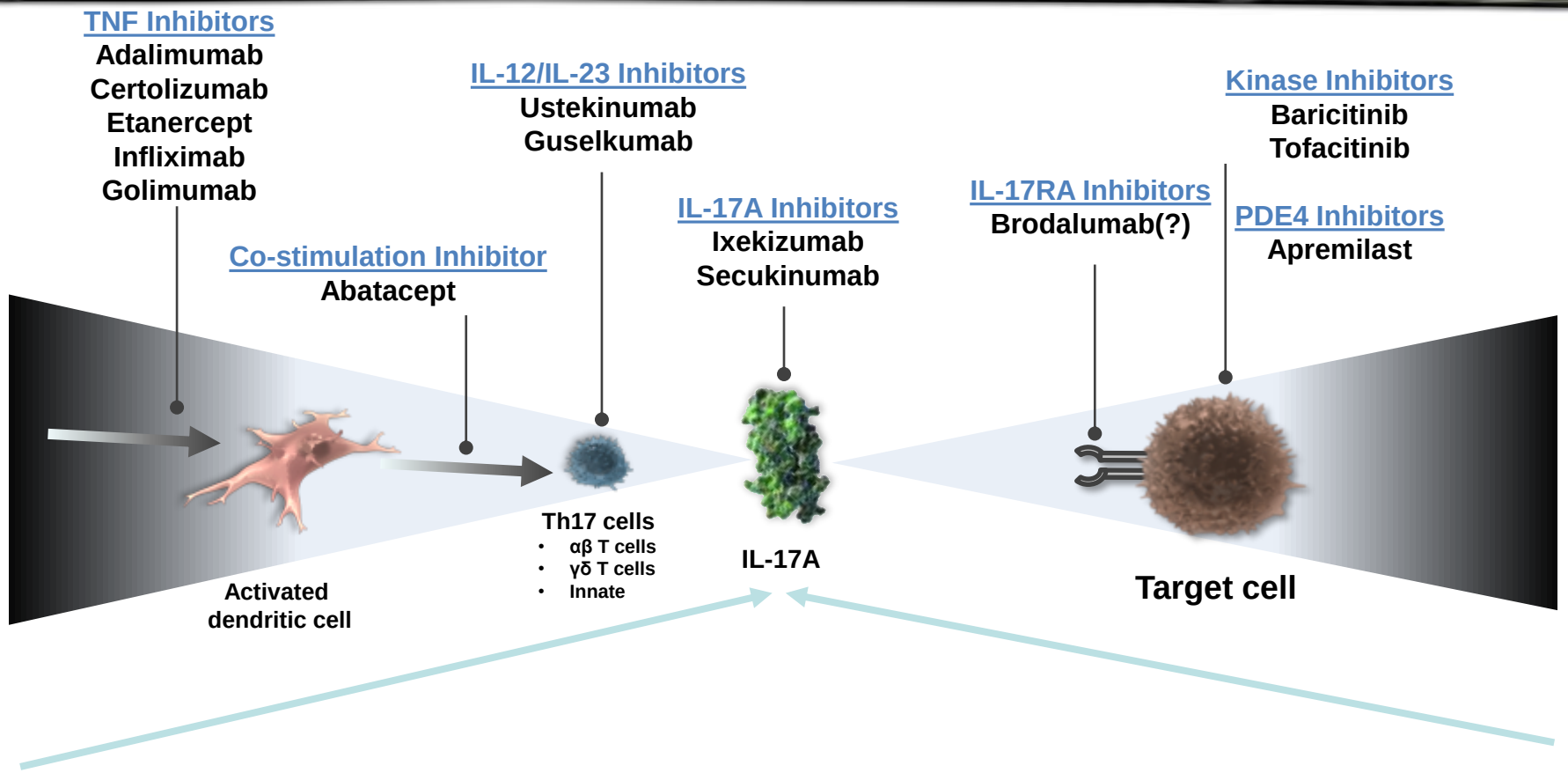
(modif from) Siebert S, Fragoulis GE, McInnes IB EULAR online course 2016
Gravallese and Schett Nat Rev Rheum 2018

Psoriatic arthritis

Treatment options

- NSAIDs
- Glucocorticoids
- Conventional synthetic DMARDs
  - Methotrexate, Leflunomide, Sulfasalazine, Cyclosporin
- **Targeted synthetic DMARD**
  - Apremilast (PDE4 inhibitor) and JAK-inhibitors
- **Biologic DMARDs (“Biologics”)**

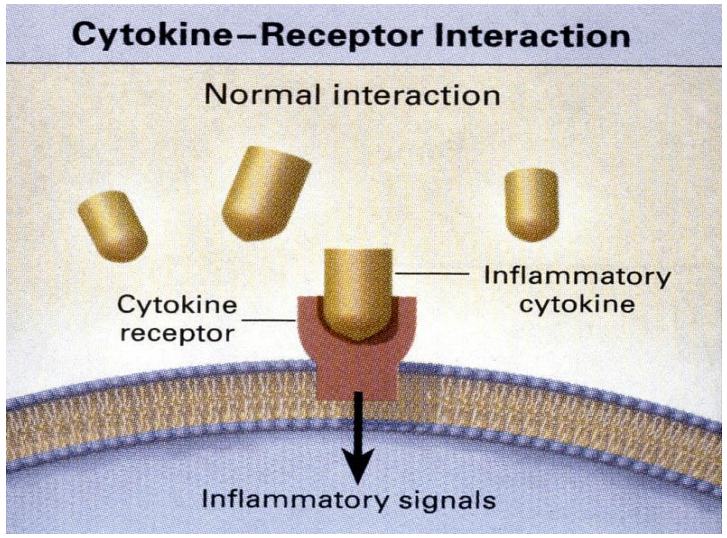
Current and novel treatment options for PsA

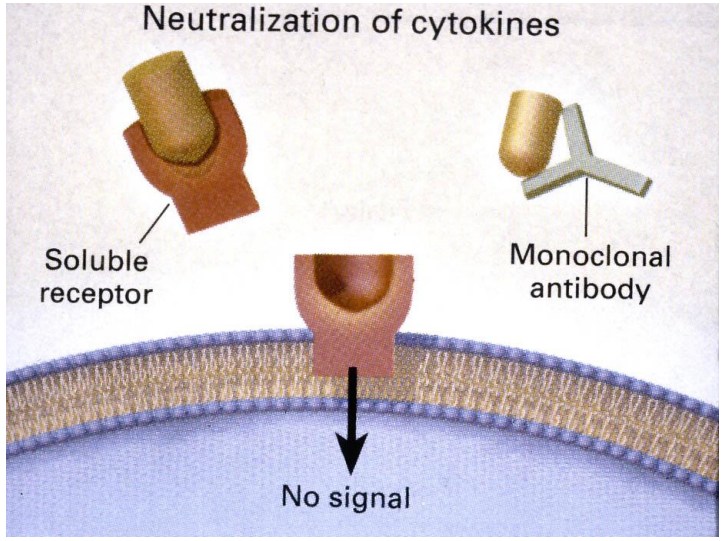


PDE4, phosphodiesterase type 4; Th17, T helper 17 cell.
Adapted from Nestle F, et al. *N Engl J Med*. 2009;361:496–509;
Kopf M, et al. *Nat Rev Drug Discov*. 2010;9:703–718; Garber K. *Nat Biotechnol*. 2011;29:563–566

anti-TNF

Mode of action

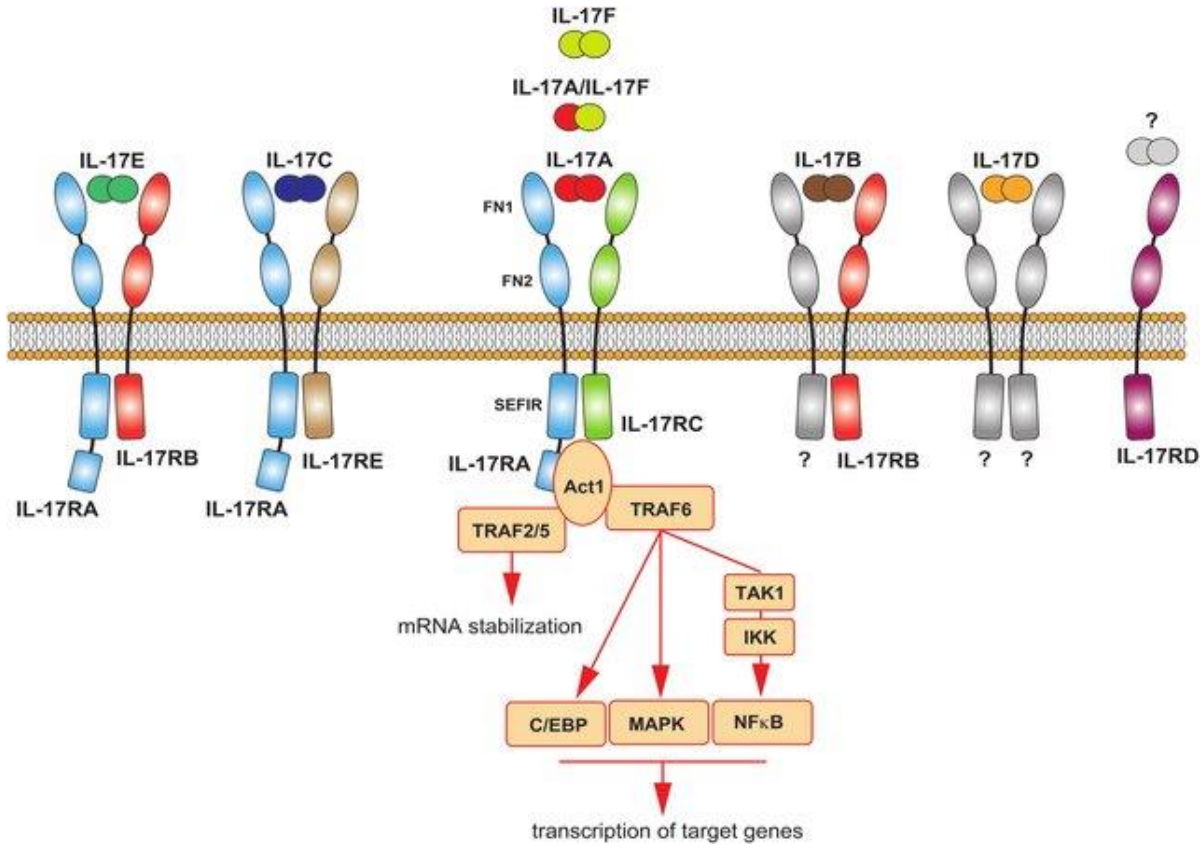




Anti-IL-17

Mode of action

- IL-17 family
  - 6 members which share similar structure
    - IL-17A and IL-17F: the most well characterized
  - and five receptors (IL-17RA to IL-17RE)
    - Can form heterodimers
  - Under normal conditions protects from fungal infections

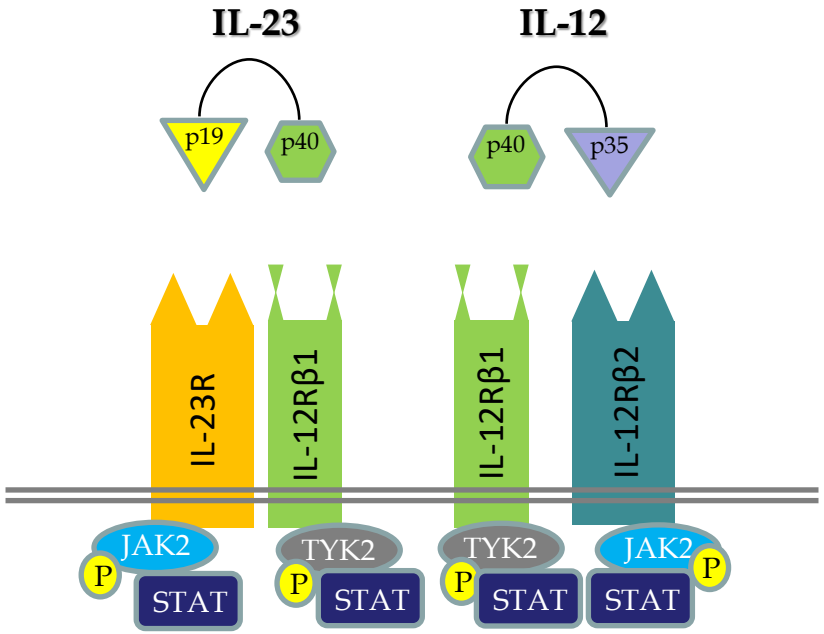


Brembilla et al. Front immun 2018
Fragoulis & Siebert Oxford Textbook in Rheumatology (In Press)

Anti-IL-23

Mode of action

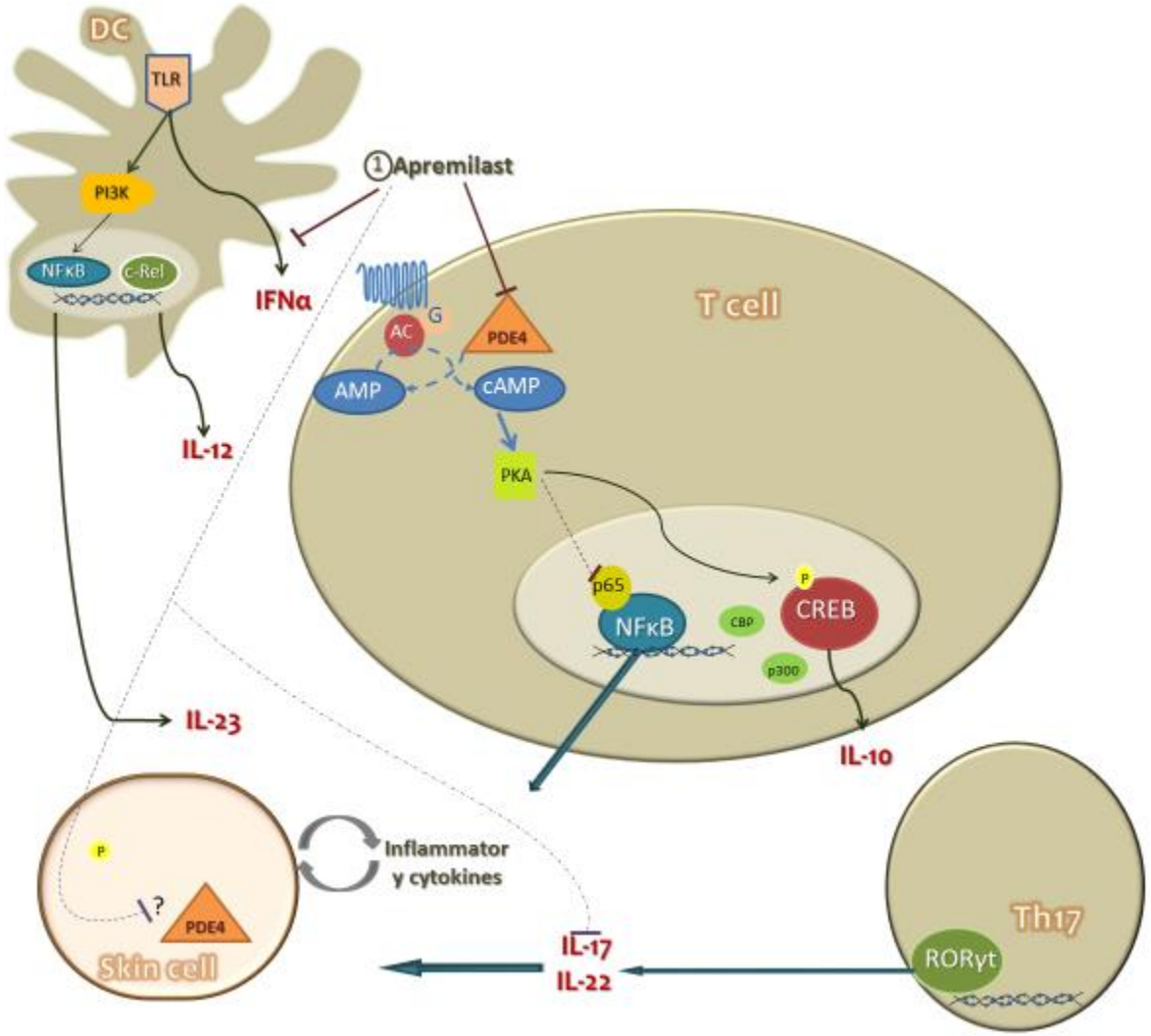
- Engagement of IL-23 with the IL-23R
  - Signalling, mainly through JAK2 and TYK2
    - Phosphorylation of STAT3
    - Subsequent expression of the transcription factor RORγt and production of IL-17



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

Apremilast

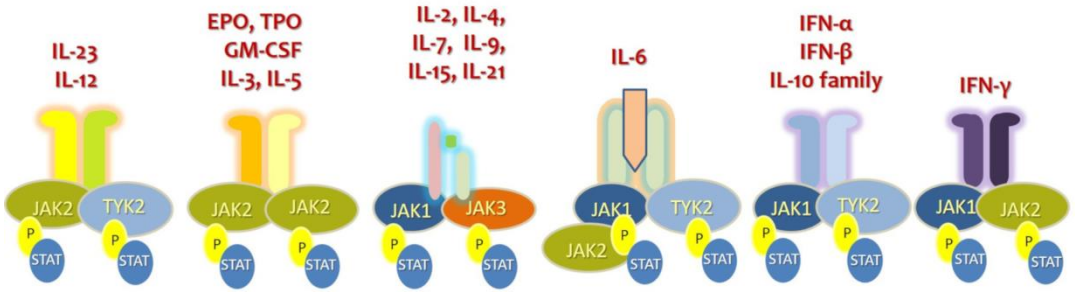
Mode of action



Fragoulis GE, McInnes IB (Oxford Textbook of Psoriatic Arthritis, 2018)

JAKi

Mode of action



<u>JAK inhibitors</u>

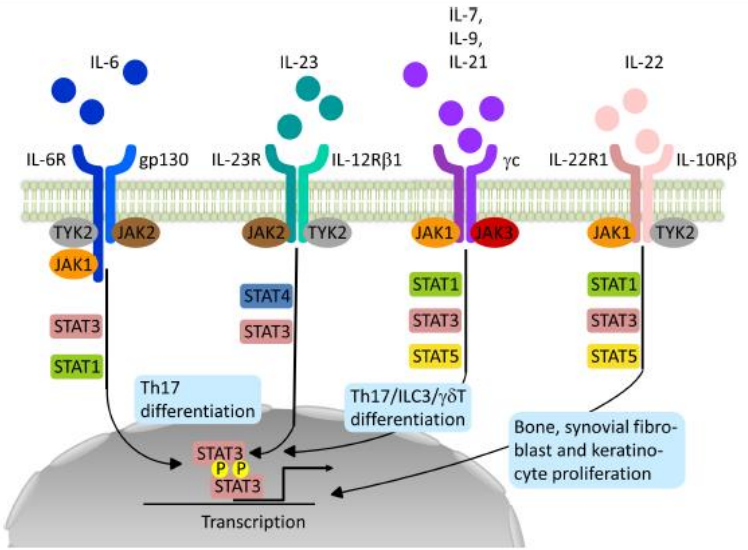
Tofacitinib (JAK3/1>2)
Baricitinib (JAK1/2)
Filgotinib (JAK1)
Upadacitinib (JAK1)
Others

Teng MWL et al Nat Med 2015
Fragoulis GE et al Rheumatology 2018 (In Press)

JAK-inhibitors in PsA/SpA

Why?

- Cytokines involved in this IL-23/IL-17 axis exert their function through the JAK/STAT pathway
- Polymorphisms in JAK2 and TYK2 have been reported in association with axSpA
- Animal studies
- Ex-vivo data

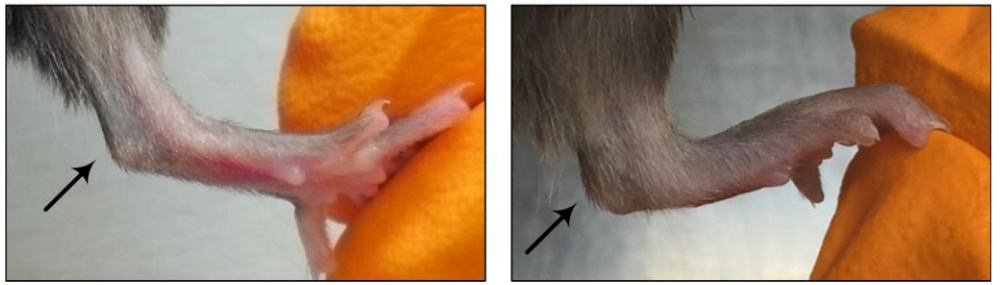


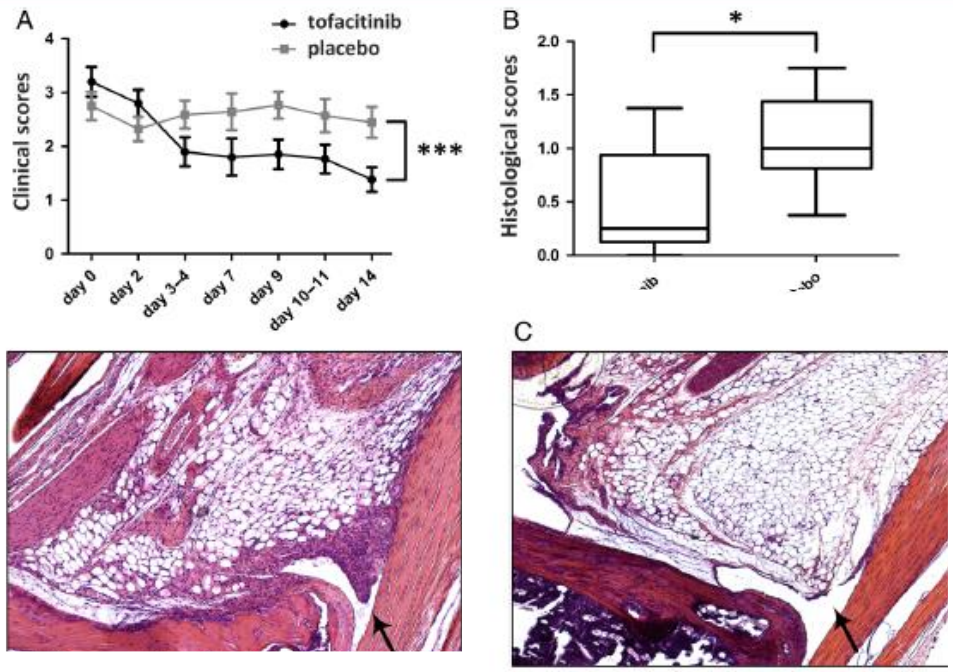
Dendrou et al Sci Transl Med. (2016)
Fragoulis et al JACI 2021
Hammitzsch et al Front Imm 2020

Animal models

The A-20 knock-out example

- A-20 Knock-out mice
  - A-20 negative regulate NFkB
  - SpA like enthesitis/arthritis
  - Treatment with Tofacitinib
    - ⇩ disease activity,
    - ⇩ inflammation of the synovial–entheseal complex

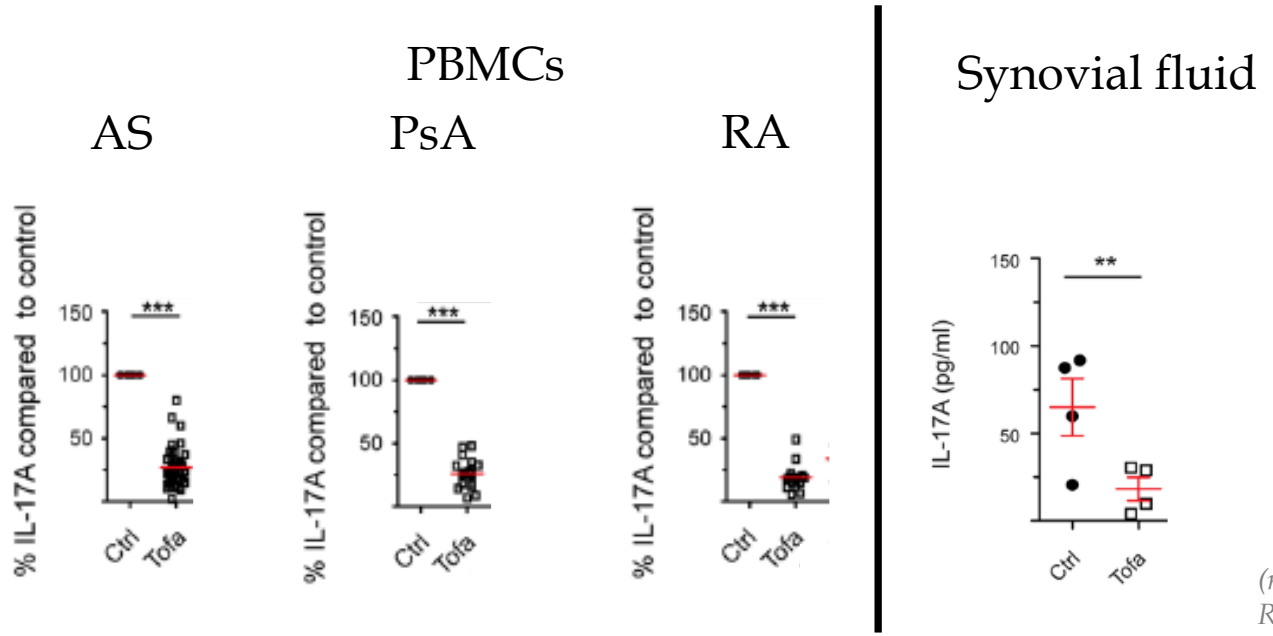




De Wilde et al Ann Rheum Dis 2017

Ex-vivo data

- CD4 T cells
  - AS, PsA, RA
    - JAKinibs ⇩ responses IL-17A, IL-17F, IL-22
    - in cultured CD4 T cells under Th17-promoting conditions (PBMC or synovial fluid)



(modified from) Hammitzsch et al Sci Rep 2018

Safety & Co-morbidities

Should be also considered…

- Inflammatory bowel disease, Uveitis
  - Contra-indication
    - Anti-IL-17
    - Etanercept
- Cardiovascular disease
- Mental-health disorders

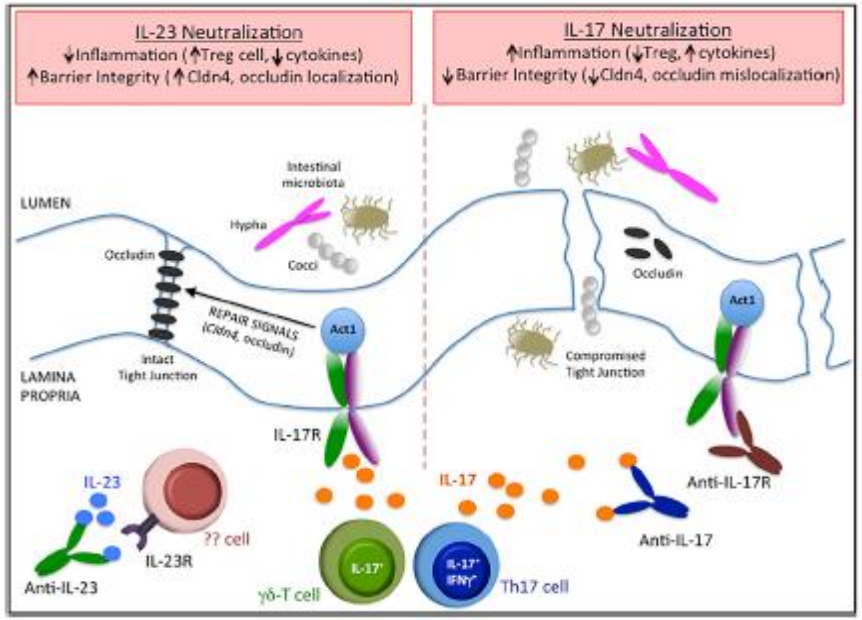
Whitlock SM et al J Am Acad Derm 2018
Feagan BG et al Lancet 2017

Sharma S et al Best clin Prac & Res Clin Rheum 2018

Inflammatory bowel disease

The IL-17 story

- Anti-IL-17 & Inflammatory bowel disease
  - RCTs in Crohn disease: negative
  - Pathogenetic mechanisms
    - Candida growth (IL-17 fungal protection)
    - Occludin traslocation (tight junction protein)
      - ✓ Production of IL-17 from Tγδ upon intestinal injury



Doedhar et al Arthritis Rheumatol. 2016; 68 (suppl 10)
Fobelo Lozano MI J Crohns Colitis 2018
Heuber W et al Gut 2012
Gaffen SL et al Nat Rev Immun 2012
Colombeel JF et al 2013
Whibley N et al Immunity 2015

SpA/PsA and CVD risk

- Less evidence compared to RA
  - However…..PsA: worse metabolic profile compared RA
    - Many data derived from psoriasis studies
  - Lack of evidence for newer drugs

Fragoulis et al, Ther Adv M. Dis 2020

PsA

Increased CVD risk

- SLR
- ⇧ CVD morbidity and mortality risk
- ⇧ rates of risk factors for CVD (e.g hypertension, overweight)

Table 5 Cardiovascular risk factors in PsA

Cardiovascular risk factor	No of studies	Findings
Dyslipidaemia*	6	Dyslipidaemia was more prevalent in PsA patients than in controls[18 24 26 28–30] • Reduced total cholesterol and HDL-cholesterol levels[26 28 30] • Reduced LDL-cholesterol levels[28 30] • Increased LDL and triglycerides levels[26]
Hypertension	6	Hypertension was more prevalent in PsA patients than in controls[17 18 24 26 28 29]
Obesity or BMI	3	Patients with PsA had higher BMI than controls[24 26 28]
Diabetes mellitus	4	Diabetes mellitus was more prevalent in PsA patients than in controls[18 24 28 29]
Smoking	3	There was no statistical differences between patients and controls.[24 28 29]

*Dyslipidaemia is defined as abnormalities in lipid profile predisposing to cardiovascular diseases.
BMI, body mass index; HDL, high-density lipoprotein; LDL, low-density lipoprotein; PsA, psoriatic arthritis.

Jamnitski et al ARD 2013

PsA

Comparable CVD-burden with DM?

- Study comparing PsA vs RA Vs DM

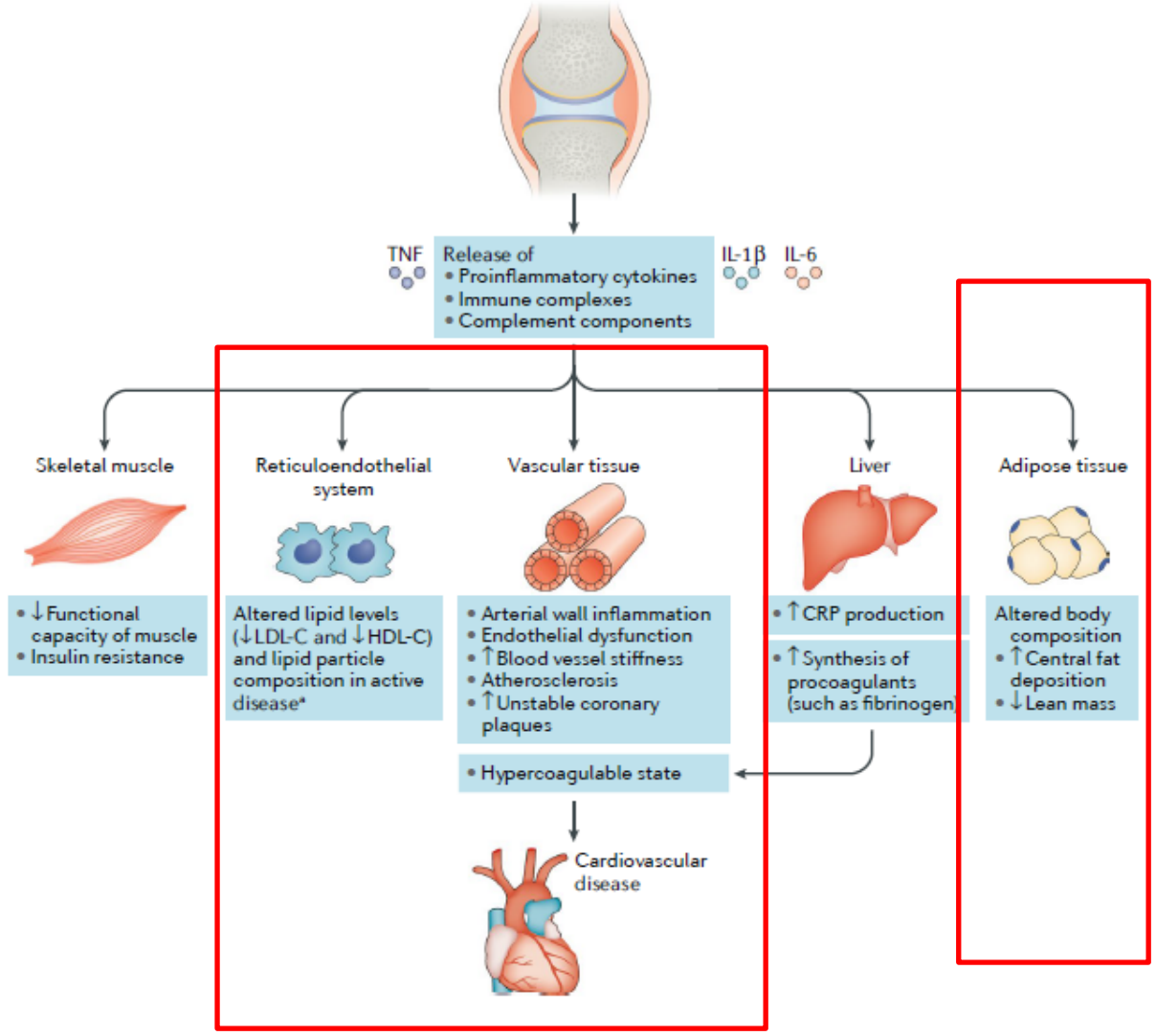
Table 3. Comparison of comorbidities between psoriatic arthritis, rheumatoid arthritis and diabetes mellitus patients.

Comorbidity	PsA *n* = 215	RA *n* = 215	DM n = 215	PsA *versus* RA		PsA *versus* DM	
				Crude OR (95% CI)	Adjusted OR (95% CI)	Crude OR (95% CI)	Adjusted OR (95% CI)
Smoking	76 (35.4)	62 (28.8)	85 (39.5)	1.35 (0.90–2.03)		0.84 (0.57–1.24)	
Hyperlipidaemia	101 (47.0)	67 (31.2)	101 (47.0)	1.96 (1.32–2.90)	–	1	–
Hypertension	62 (28.8)	51 (23.8)	97 (45.1)	1.30 (0.84–1.99)	–	0.49 (0.33–0.74)	–
Obesity	50 (29.4)	24 (12.8)	79 (36.7)	2.83 (1.65–4.86)		0.72 (0.47–1.10)	
Coronary disease	10 (4.7)	10 (4.7)	16 (7.4)	1 (0.41–2.45)	1.05 (0.31–3.57)[a]	0.61 (0.27–1.37)	0.66 (0.23–1.91)[a]
Stroke	8 (3.7)	2 (0.9)	7 (3.3)	4.12 (0.86–19.6)	5.06 (0.80–32.1)[a]	1.15 (0.41–3.22)	1.20 (0.35–4.12)[a]
MACEs	12 (5.6)	12 (5.6)	22 (10.2)	1 (0.44–2.28)	1.20 (0.40–3.63)[a]	0.52 (0.25–1.08)	0.42 (0.16–1.10)[a]
Osteoporosis	12 (5.6)	24 (11.2)	2 (0.9)	0.46 (0.21–1.03)	0.67 (0.28–1.64)[b]	6.22 (1.33–29.2)[b]	–
Depression[c]	42 (19.5)	15 (7.0)	12 (5.6)	3.24 (1.74–6.04)	3.02 (1.57–5.81)[d]	4.11 (2.10–8.05)	4.85 (2.37–9.93)[d]
Malignancy	12 (5.6)	7 (3.3)	–	1.76 (0.68–4.55)	1.60 (0.60–4.26)[e]	–	–

Fragoulis Ther Adv M Dis 2021

Cytokines and Comorbidities

Cardiovascular risk – the big picture

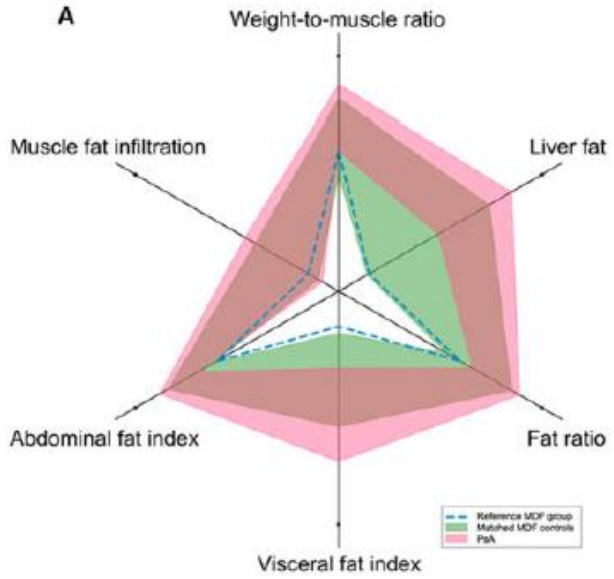


Feguson L et al, Nat Rev Rheum 2019

PsA

Adipose tissue - comparable with diabetes

- **PsA** (n=26) Vs Healthy (n=130) Vs Diabetes (n=454)
  - MRI body fat composition
    - 26 PsA / 130 age, sex and BMI-matched controls / 454 DM type2
  - Vs 130 age/sex matched **healthy**
    - ⇧ visceral adipose tissue (VAT) volume [mean 5.89 l (S.D. 2.10 l)] compared Vs matched-controls [mean 4.34 l (S.D. 1.83 l)] (P <0.001)
    - ⇧ liver fat percentage [median 8.88% (interquartile range 4.42–13.18%)] Vs matched-controls [3.29% (1.98–7.25%)] (P <0.001).
  - Vs 454 **DM2**
    - No statistically significant differences in VAT, liver fat or muscle fat infiltration (MFI) between PsA and type 2 diabetes.

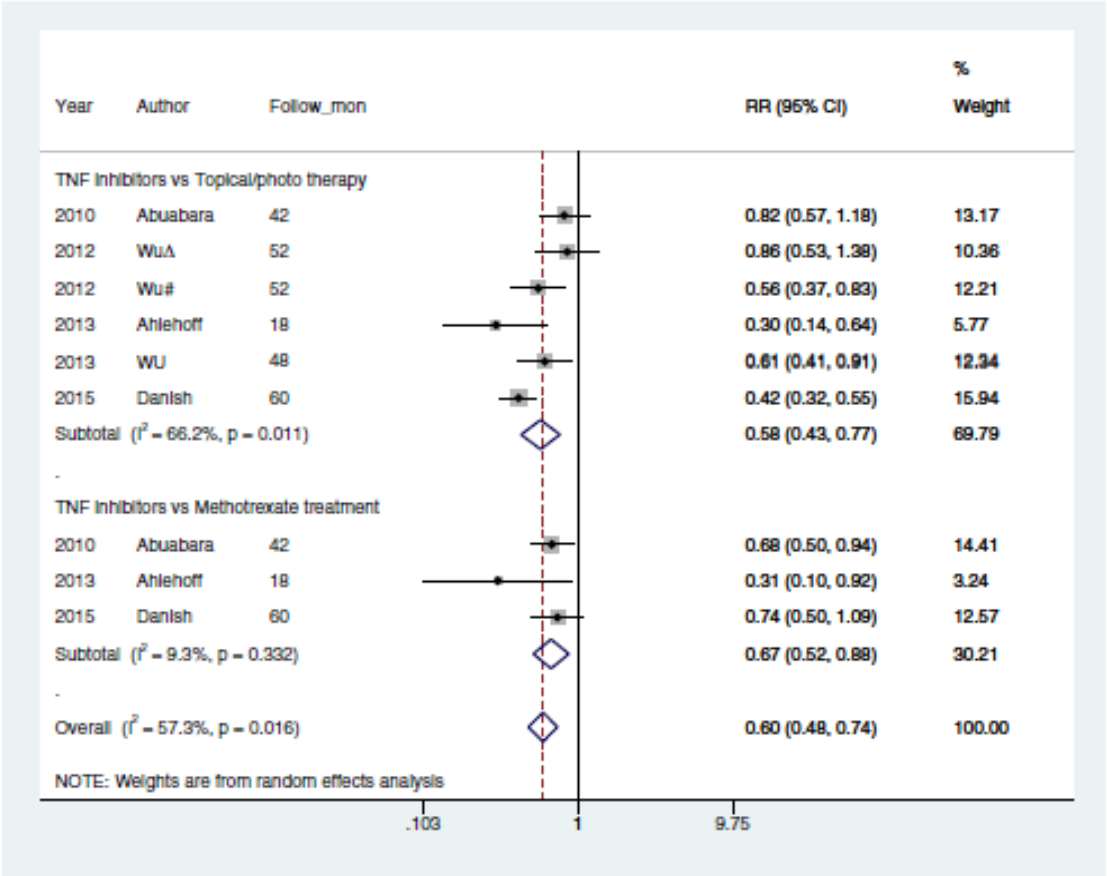


Feguson L et al, Rheumatology (Oxf) 2021

PsA (PsO) – TNFi clinical outcomes

- Meta-analysis TNFi Vs topical therapy (psoriasis)
  - ⇩ risk for all CVD
    (RR, 0.58; 95 % CI, 0.43 to 0.77; P < 0.001)
  - ⇩ risk for MI
    (RR, 0.73; 95 % CI, 0.59 to 0.90; P = 0.003)
- Meta-analysis TNFi Vs MTX
  - ⇩ risk risk for CVD
    (RR, 0.67; 95 % CI, 0.52 to 0.88; P = 0.003)
  - ⇩ risk for MI

    (RR, 0.65; 95 % CI, 0.48 to 0.89; P = 0.007)



Yang ZS et al, Clin Rev All Immun 2016
Roubille C et al, ARD 2015
Lee MP et al, JAMA Dermatol 2019

Effects of IL-17A mAb treatment on atherosclerotic plaques in apoE−/− mice.

- Apo-e -/- mice treated with anti-IL-17
  - Inhibition of IL-17A
    - ⇩ atherosclerotic lesion area ($p < 0.001$), maximal stenosis ($p < 0.001$)
    - ⇩ cellular infiltration
    - ⇩ activation markers on endothelium and immune cells (e.g., VCAM-1)
    - ⇩ cytokine/chemokine secretion (e.g., IL6, TNFalpha, CCL5)

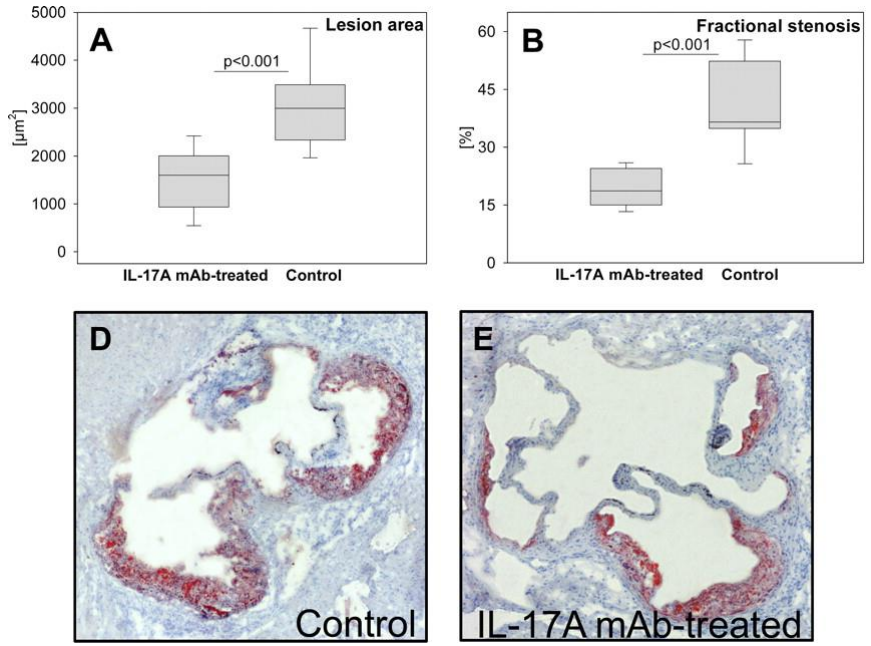


Table V. *Quantitative tissue PCR results for different cytokines, chemokines, adhesion molecules and transcription factors from the thoracic aorta*[a]

Variable	IL-17 mAb-treated (n = 15) $\Delta C_T \pm SD$	Control (n = 10) $\Delta C_T \pm SD$	*p* value
CD3ε	3.11 ± 2.02	8.58 ± 2.47	<0.001
Endothelial NO synthase	0.35 ± 0.18	0.24 ± 0.10	n.s.
LCK	3.26 ± 2.10	6.75 ± 4.09	0.01
IL4	0.33 ± 0.19	0.18 ± 0.09	0.01
FOXP3	1.06 ± 0.43	0.67 ± 0.41	0.006
IL1β	2.76 ± 1.93	1.37 ± 1.27	0.01
TNFα	3.24 ± 2.18	4.28 ± 4.43	0.04
IL6	78.46 ± 51.39	157.27 ± 193.99	0.04
MCP-1 (*CCL2*)	63.44 ± 24.65	64.36 ± 28.74	n.s.
MIP-1a (*CCL3*)	2.62 ± 0.94	2.54 ± 0.86	n.s.
TR2 (*TNFRSF14*)	0.02 ± 0.02	0.35 ± 0.85	0.03
VCAM1	22.19 ± 0.87	64.30 ± 28.02	<0.001
Caspase3	5.28 ± 2.76	11.59 ± 3.80	0.005
IFNγ	2.01 ± 1.35	1.41 ± 0.85	n.s.
CCL5	30.08 ± 18.24	52.57 ± 24.96	0.007
CCR5	18.95 ± 16.79	57.53 ± 45.67	0.1

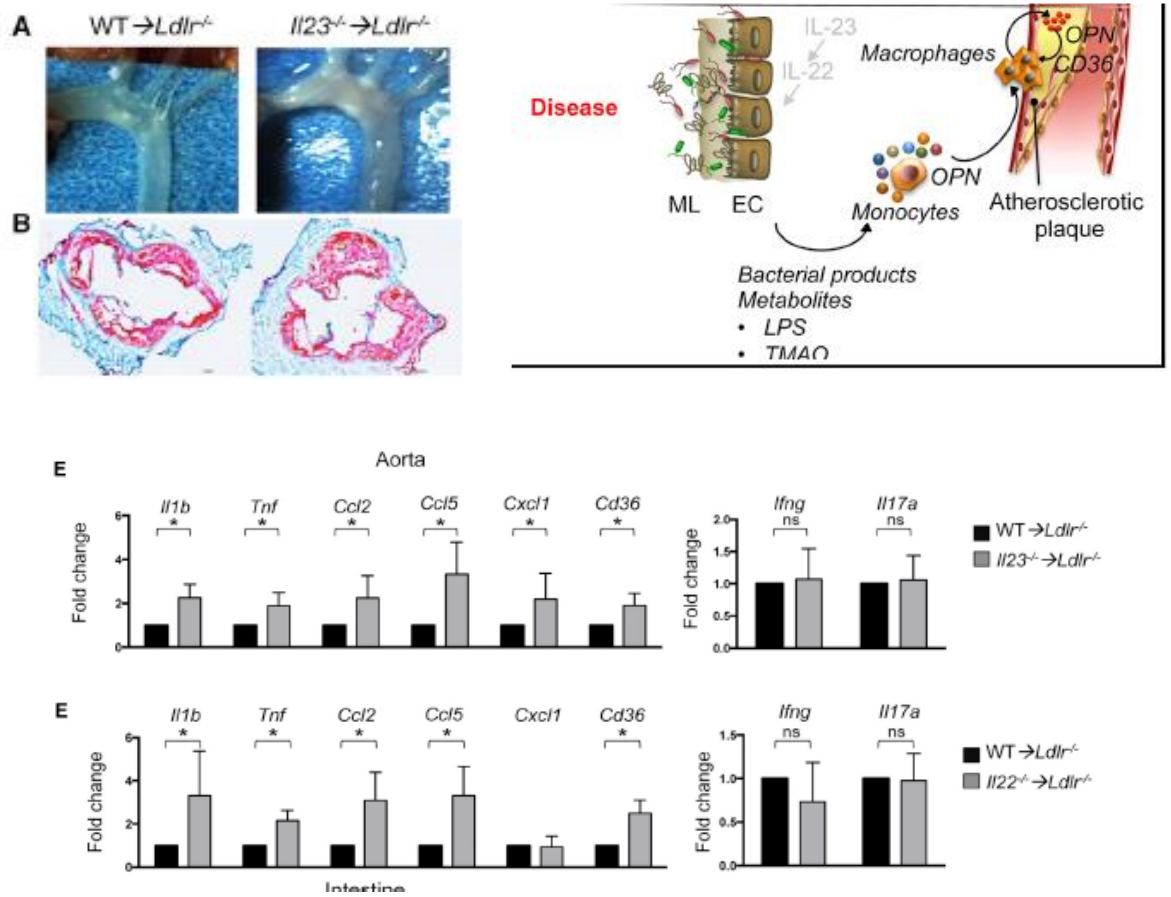
[a] Values are normalized to β-actin and expressed as cDNA copies/1000 β-actin copies. All values are shown as mean ± SD. n.s., Not significant.

Christian Erbel et al. J Immunol 2009;183:8167-8175

IL-23

Atherogenesis

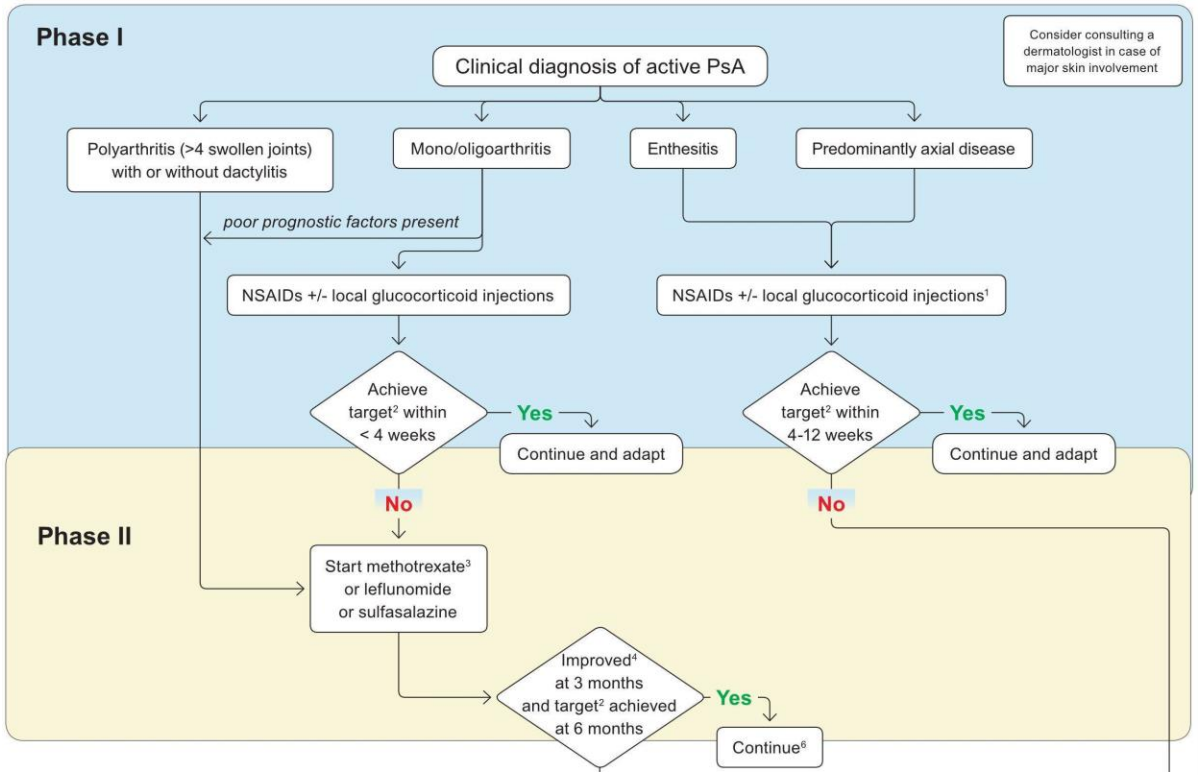
- IL-23 and its downstream target IL-22
  - ⇩ atherosclerosis by **repressing** pro-atherogenic microbiota.
    - Inactivation of IL-23-IL-22:
      - ✓ deterioration of the intestinal barrier
      - ✓ expansion of pathogenic bacteria causing systemic increase in pro-atherogenic metabolites (e.g LPS, TMAO)
    - Microbiota transfer from IL-23-deficient mice accelerated atherosclerosis
    - Microbial depletion or IL-22 supplementation reduced inflammation and ameliorated disease.

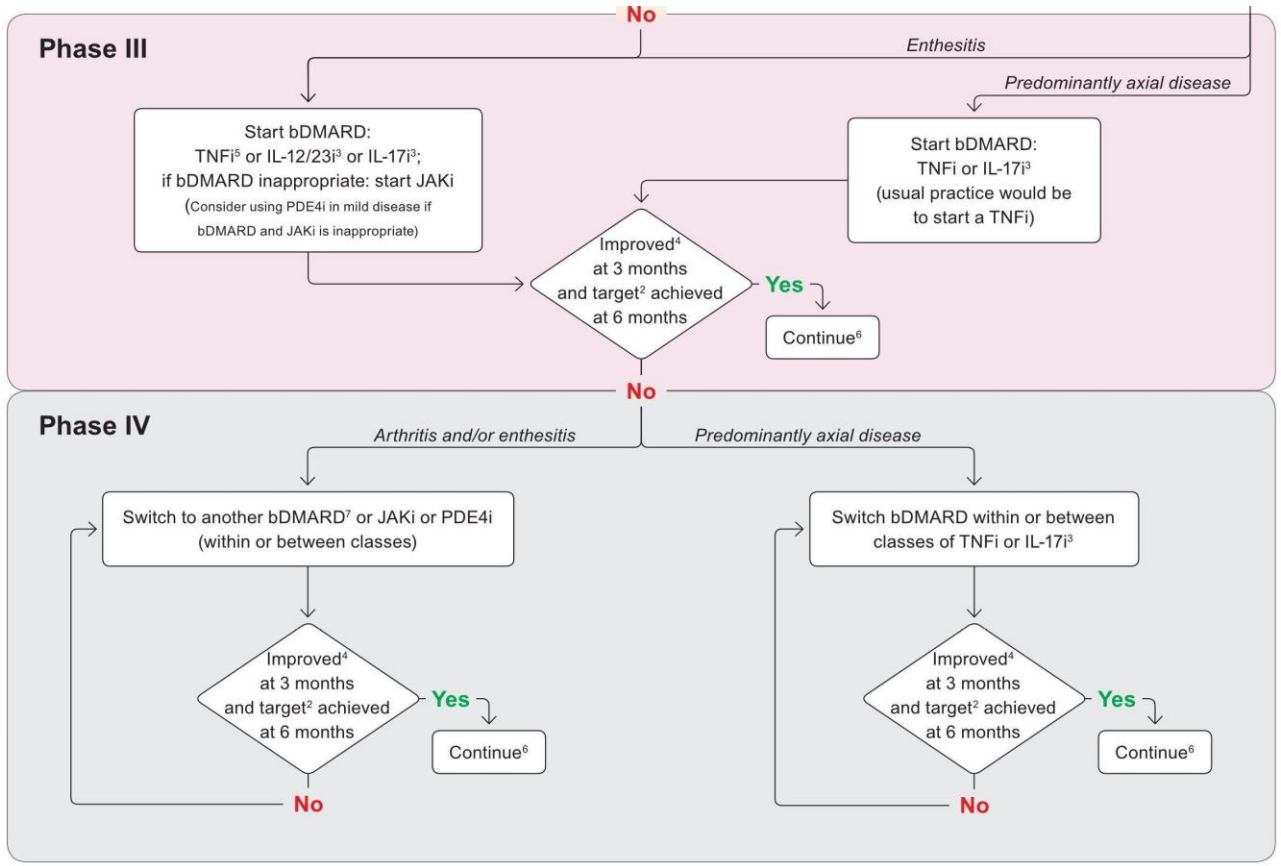


Fatkhullina et al, Immunity 2018

Psoriatic arthritis

EULAR recommendations





Gossec L et al Ann Rheum Dis 2020