ΕΛΛΗΝΙΚΗ ΔΗΜΟΚΡΑΤΙΑ
Εθνικόν και Καποδιστριακόν Πανεπιστήμιον Αθηνών
ΙΔΡΥΘΕΝ ΤΟ 1837

Novel Cytokine Inhibitors

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University of Glasgow

Heraklion October 2021

Introduction

Cytokines - properties

- Cytokines
  - are key effectors in the pathogenesis of several human ARDs
    - Single-cytokine targeting useful in several ARDs
      - ✓ e.g RA, PsA, GCA and others
  - mediate a wide variety of immunologic actions
    - Pleiotropic functions
    - Synergistic interactions
  - Render them intriguing therapeutic targets
  - But also could be associate with side-effects

Gabay C & McInnes IB, Arthr Res & Ther 2009

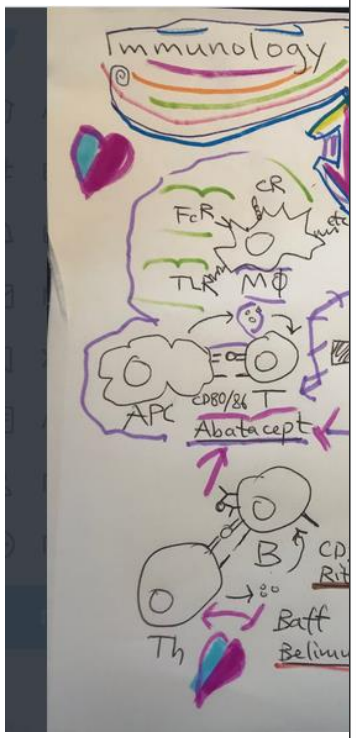
Introduction

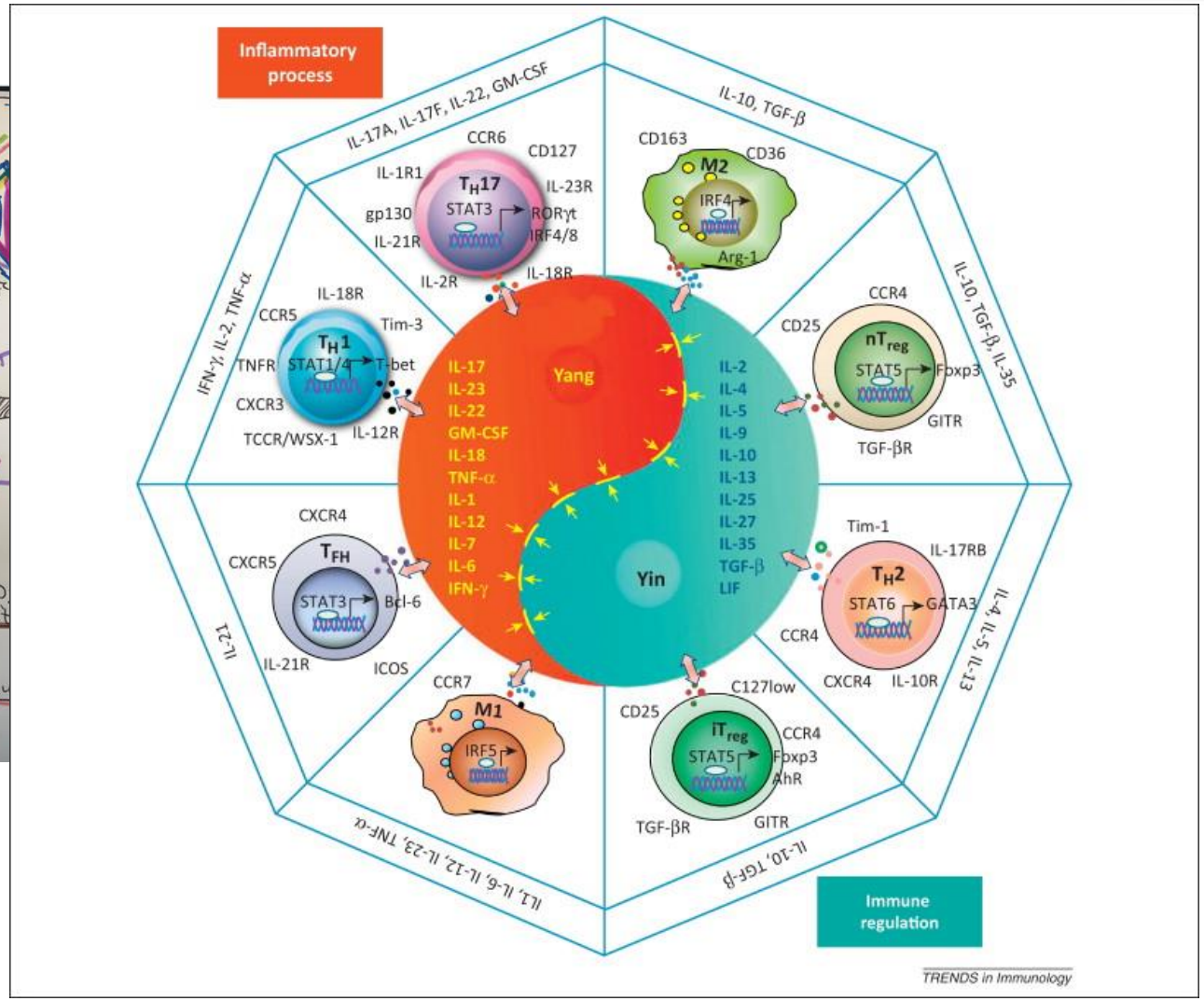
What do we need from cytokine-based treatment?

- Control of inflammation
- Protection of targeted tissues (e.g bone and cartilage)
- Promoting the re-establishment of immune tolerance
- Healing of previously damaged tissues
- Preservation of host immune capability
  - to avoid profound immune suppression

Conell C & McInnes IB, Best Practice Research Clin Rheum 2006

The complexity of Immune System

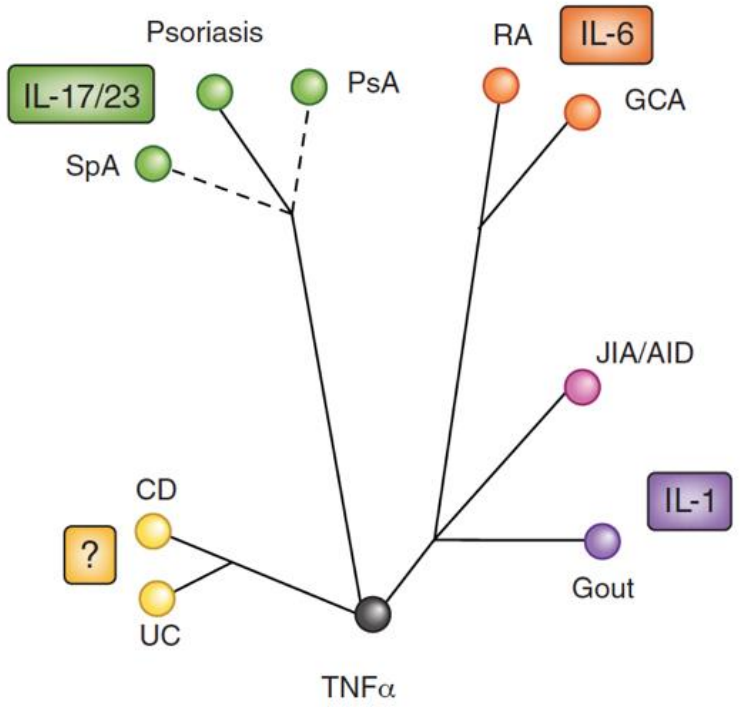




Liu et al. Trends in Immun 2012

Cytokines

Different drivers according to disease type?

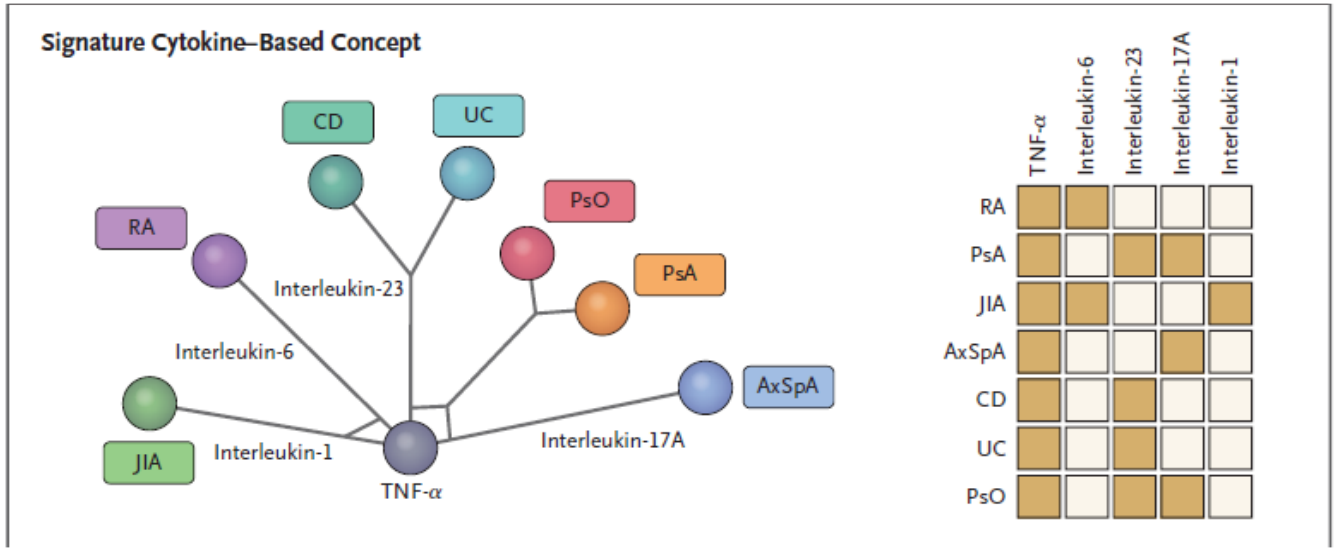


Chronic inflammatory disease	Cytokine targets: TNF	IL-6R	IL-1	IL-12/IL-23	IL-17A	IL-23
Rheumatoid arthritis	✓	✓	✓	−	−	−
Autoinflammatory disease/sJIA	✓	✓	✓			
Crohn's disease	✓			✓	−	+
Ulcerative colitis	✓			+	−	+
Psoriasis	✓			✓	✓	✓
Psoriatic arthritis	✓	+		✓	✓	+
Ankylosing spondylitis/ axSpA	✓	−	−	−	✓	−
Multiple sclerosis	−					

Schett G et al. Nat Med 2013
Bravo A et al Nat Rev Rheum 2019

Cytokines

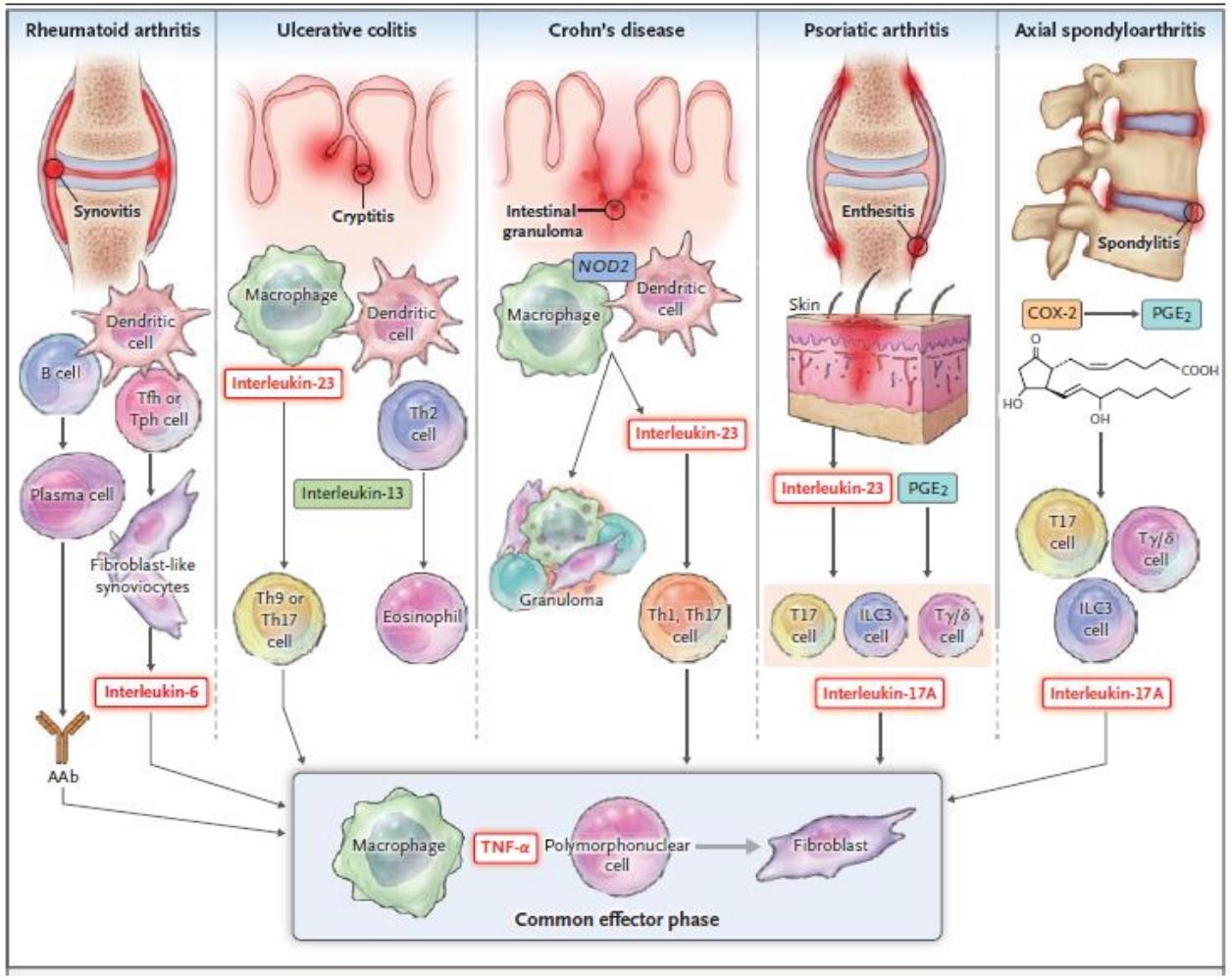
Different drivers according to disease type? (Updated?)



Schett G et al. NEJM 2021

Cytokines

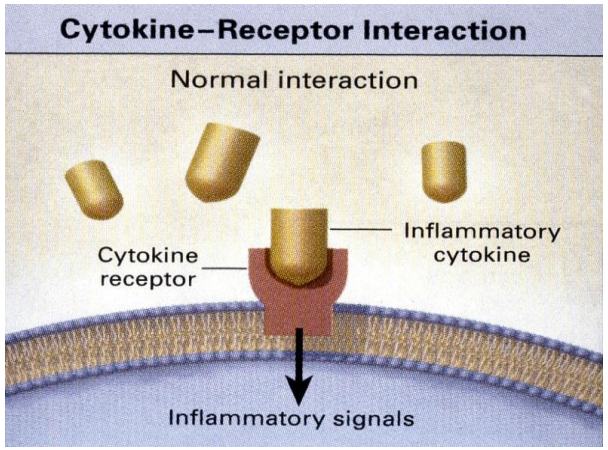
Same but different…

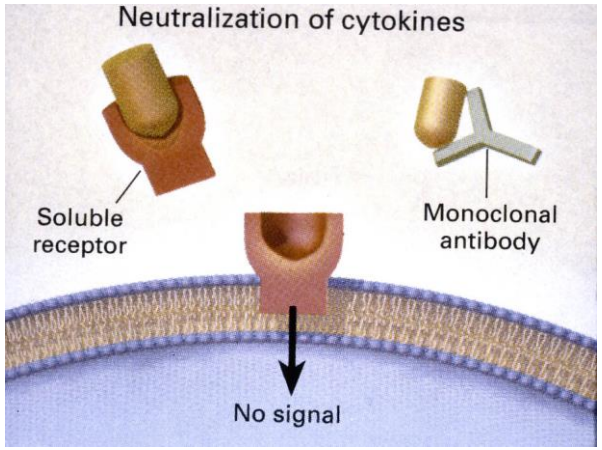


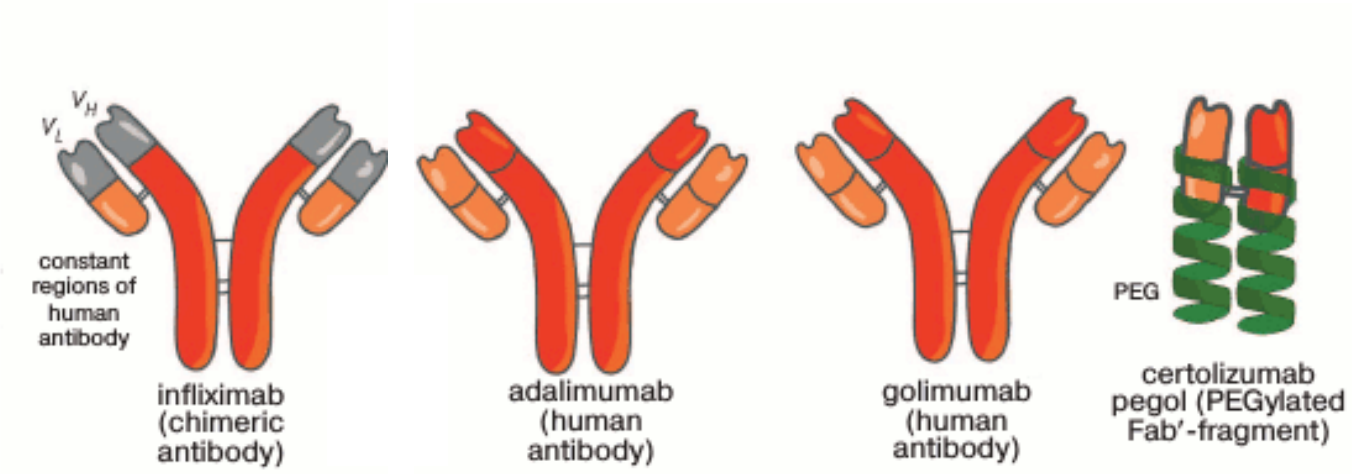
Schett G et al. NEJM 2021

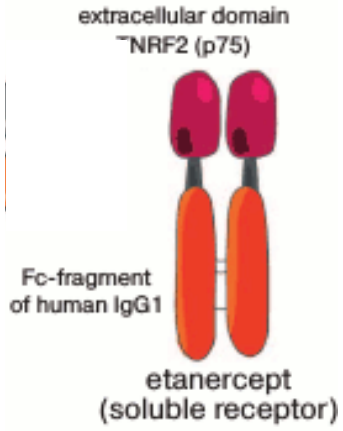
The Players

The TNF inhibitors



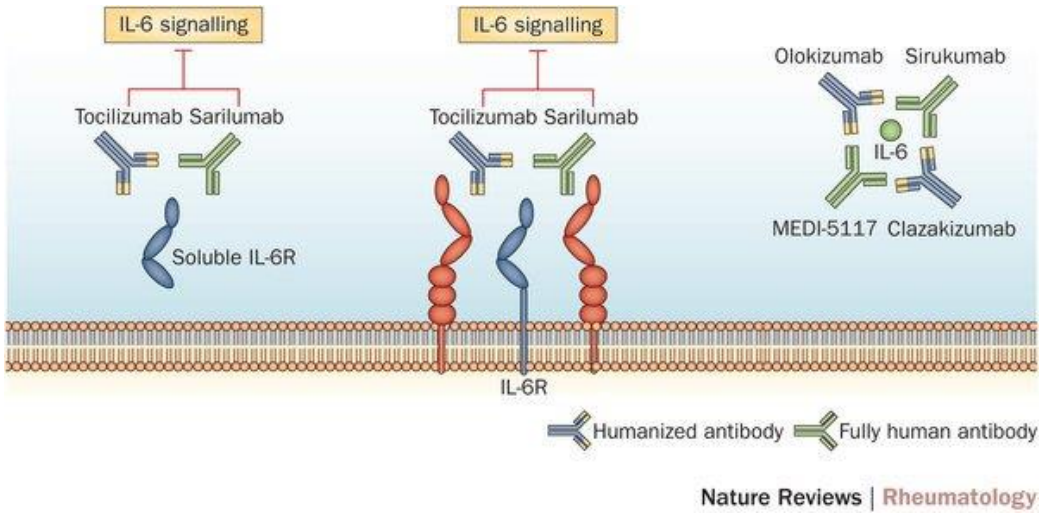


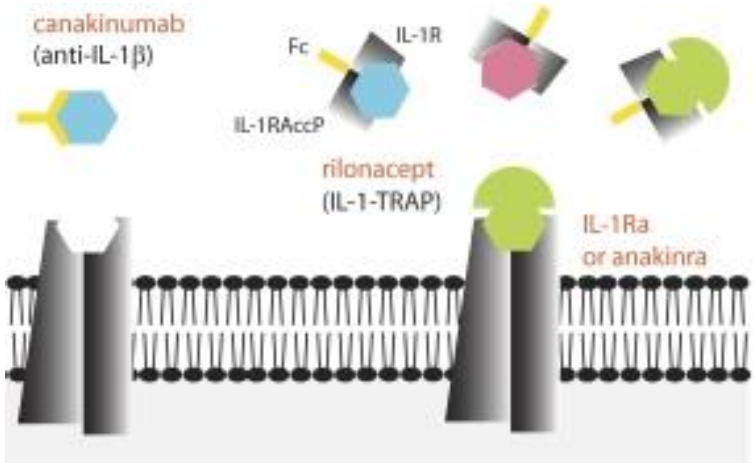




The Players

Against IL-6 / IL-1



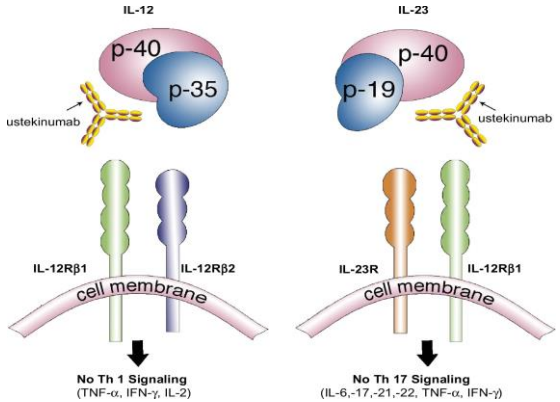


Tanaka T et al, CSHBP 2014
Doherty T et al, JLB 2011

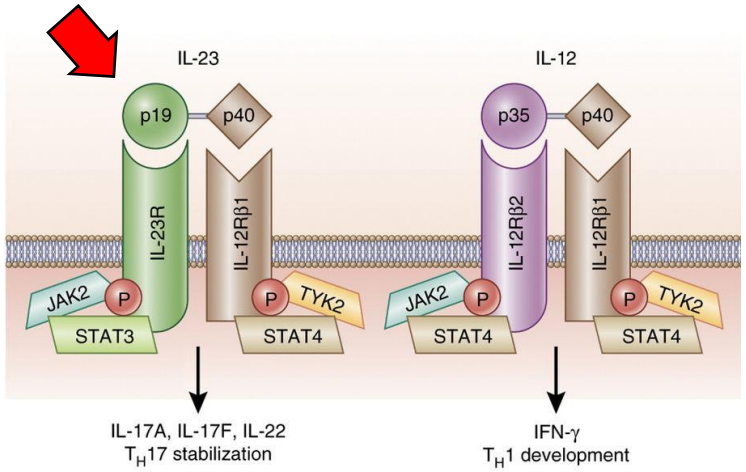
The Players

Against IL-23 / IL-17

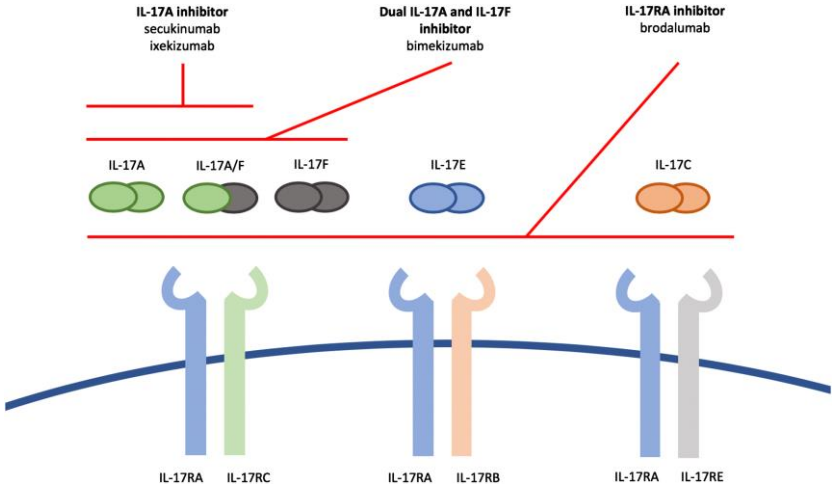
against p40 subunit IL-12/-23



against p19 subunit IL-23



against IL-17



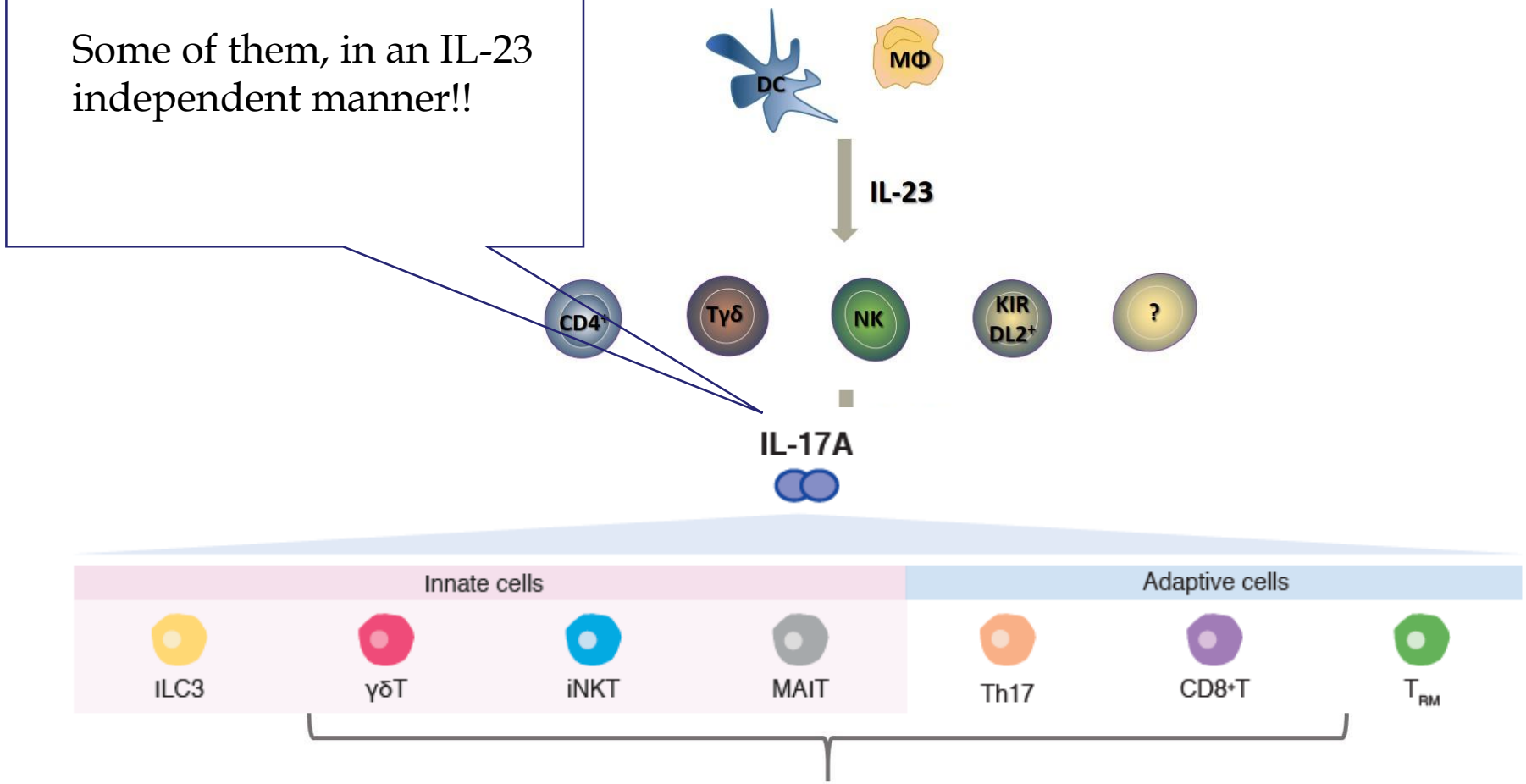
Risankizumab
Guselkumab
Tildrakizumab

Dinarello CA et al. Nat Rev Rheum 2019
Koutruba N et al Ther Clin Risk Management 2010
Reis J et al Biodrugs 2019
Teng MWL et al Nat Med 2015

Anti-23/-12, Anti-IL-17

Why they work??

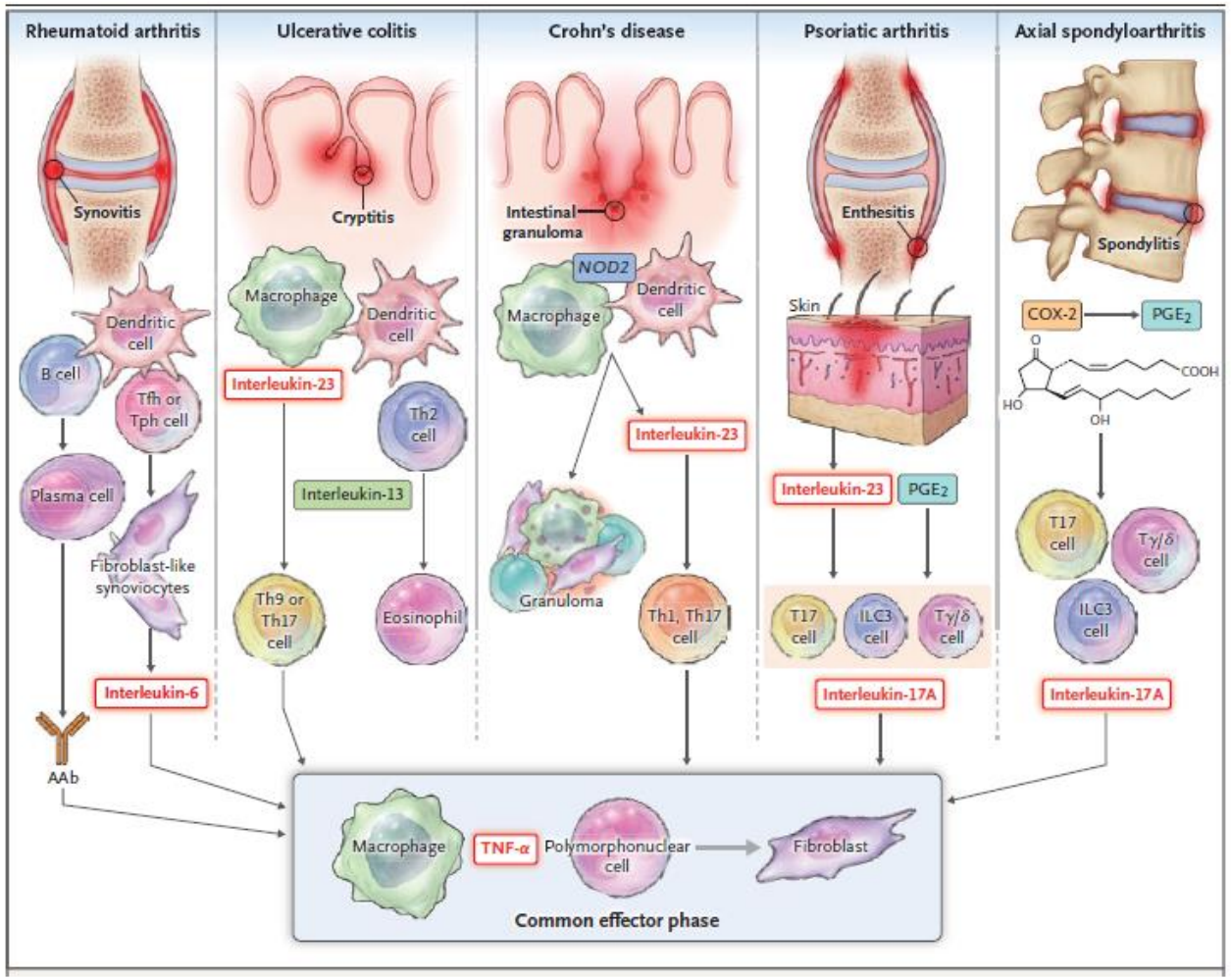
Some of them, in an IL-23 independent manner!!



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

IL-23

PsA

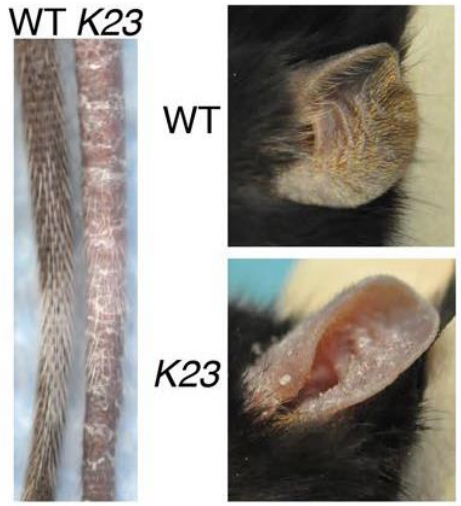


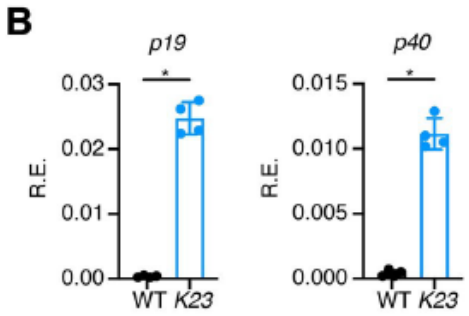
- IL-23
  - Act more systemically
  - From distant sites (gut/skin)
    - Gut-joint axis
      - ✓ MAIT in PsA joints

Schett G et al. NEJM 2021

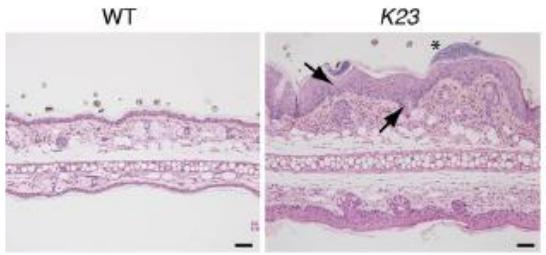
IL-23 mice model

- Transgenic expression of IL-23 in skin of mice





p19/p40
expression
in the ears

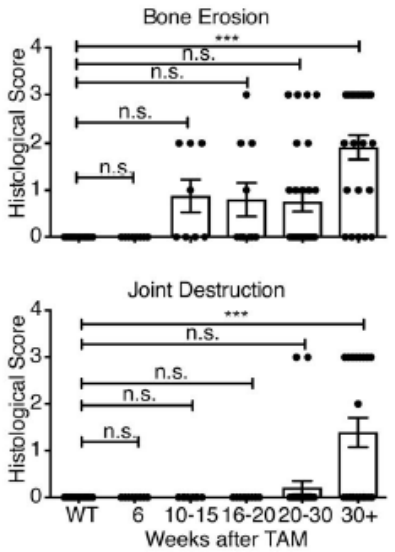


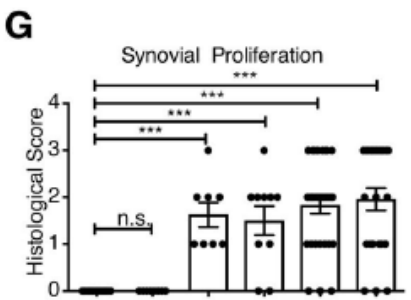
H&E, ears
6 weeks

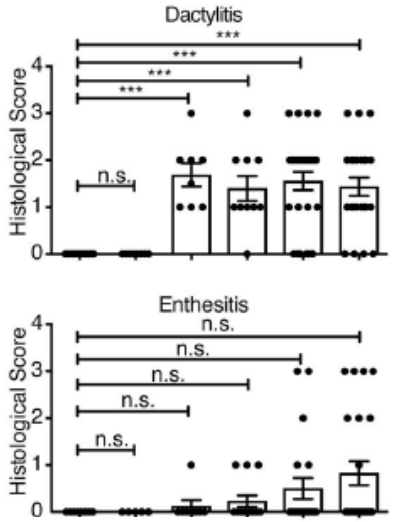
Chen L et al, Sci Rep 2020

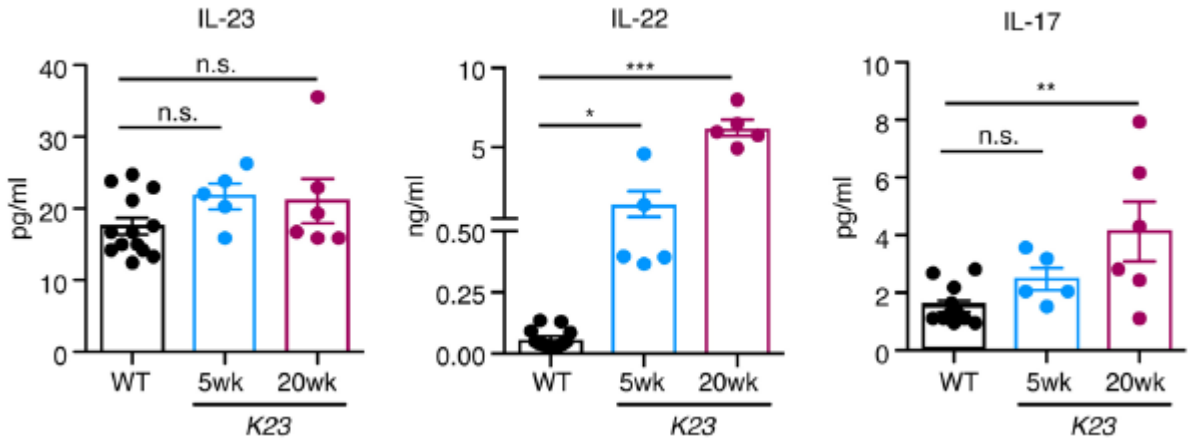
IL-23 mice model

PsA features & cytokines expression









Anti-IL-23

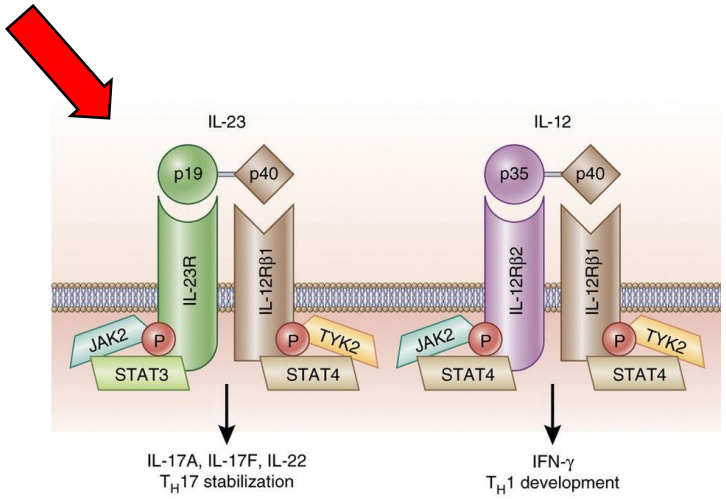
Treatment modalities

Target	Generic name (trade name, where relevant)	Type of monoclonal antibody	Route, half life
p40 subunit of IL-23 and IL-12	Ustekinumab (Stelara®)	Human, IgG1	SC, 20 days
	Briakinumab (withdraw)	Human, IgG1	SC, 9 days
IL-23p19	Guselkumab (Trefmya®)	Human, IgG1λ	SC, 12-19 days
	Risankizumab (Skyrizi®)	Humanized, IgG1κ	SC, 27days
	Tildrakizumab (Illumetri®, EU/ Illumya®, US)	Humanized, IgG1κ	SC, 25 days

Reviewd in Sakkas L et al. Front Pharmacol.2019

Anti-IL-23

New Treatment modalities



<u>Έναντι p19 υπομονάδας IL-23</u>

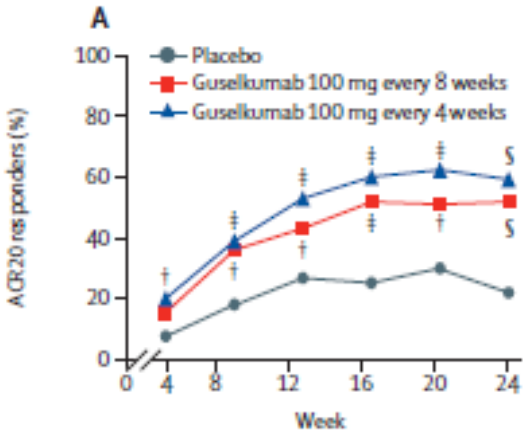
Guselkumab
Risankizumab
Tildrakizumab

Teng MWL et al Nat Med 2015

Guselkumab

Discover-1 (PsA biologic-experienced)

- phase 3, placebo-controlled study
  - biologic-naive patients with active psoriatic arthritis
  - guselkumab 100q4w/guselkumab100q8weeks/PBO
- ACR20 week 24
  - Gusq4w: 59%
  - Gusqq8w: 52%
  - PBO:22% p<0·0001
- No safety concerns

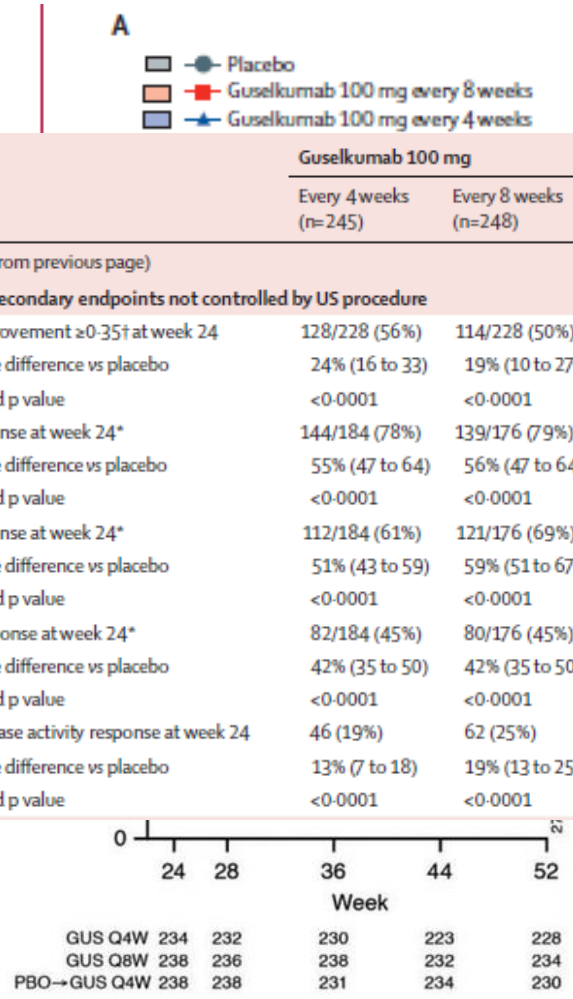


Deodhar et al, Lancet 2020

Guselkumab

Discover-2 (PsA biologic-naïve)

- phase 3, placebo-controlled study
  - biologic-naive patients with active psoriatic arthritis
  - guselkumab 100q4w/guselkumab100q8weeks/PBO
- ACR20 week 24
  - Gusq4w: 64%
  - Gusqq8w: 64%
  - PBO:33% p<0 ·0001
- Continued to improve over week 52
- ACR20
  - Gusq4w 70.6
  - Gusq8w 74.6
- No safety concerns



	Guselkumab 100 mg		Placebo (n=246)
	Every 4 weeks (n=245)	Every 8 weeks (n=248)	
(Continued from previous page)			
Additional secondary endpoints not controlled by US procedure			
HAQ-DI improvement ≥0·35† at week 24	128/228 (56%)	114/228 (50%)	74/236 (31%)
Percentage difference vs placebo	24% (16 to 33)	19% (10 to 27)	--
Unadjusted p value	<0·0001	<0·0001	--
PASI75 response at week 24*	144/184 (78%)	139/176 (79%)	42/183 (23%)
Percentage difference vs placebo	55% (47 to 64)	56% (47 to 64)	--
Unadjusted p value	<0·0001	<0·0001	--
PASI90 response at week 24*	112/184 (61%)	121/176 (69%)	18/183 (10%)
Percentage difference vs placebo	51% (43 to 59)	59% (51 to 67)	--
Unadjusted p value	<0·0001	<0·0001	--
PASI100 response at week 24*	82/184 (45%)	80/176 (45%)	5/183 (3%)
Percentage difference vs placebo	42% (35 to 50)	42% (35 to 50)	--
Unadjusted p value	<0·0001	<0·0001	--
Minimal disease activity response at week 24	46 (19%)	62 (25%)	15 (6%)
Percentage difference vs placebo	13% (7 to 18)	19% (13 to 25)	--
Unadjusted p value	<0·0001	<0·0001	--

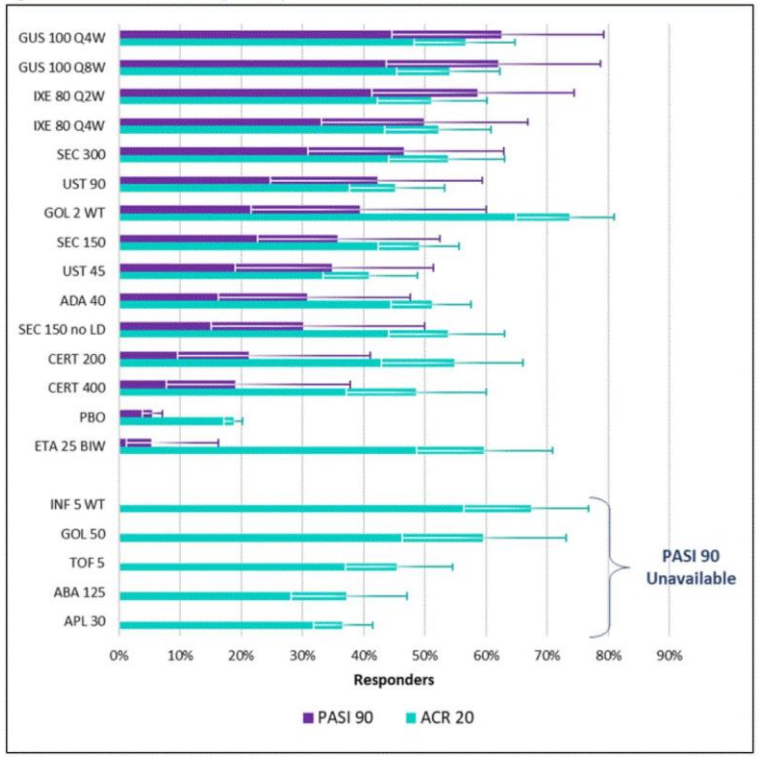
Mease et al, Lancet 2020
McInnes IB, ARD 2020 (ab)

Guselkumab

SLR & network meta-analysis

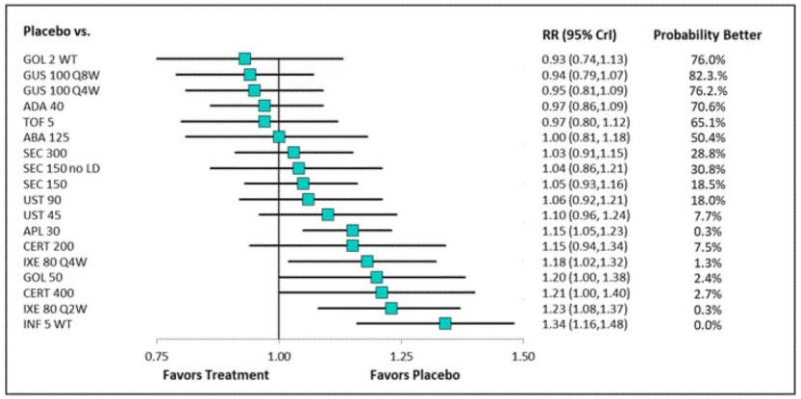
- SLR & network meta-analysis (RCTs 2000-2018)
- 26 phase 3 studies: For ACR20 ranked 5th and 8th (q4w and q8w), For PASI90: 1st and 2nd

Figure 1: Absolute Probability of Response for PASI 90 & ACR 20



Median proportion of PASI 90 (purple) and ACR 20 (teal) responders with associated 95% credible intervals according to best-fitting NMAs.

Figure 2: Forest Plot of Adverse Events vs. Placebo



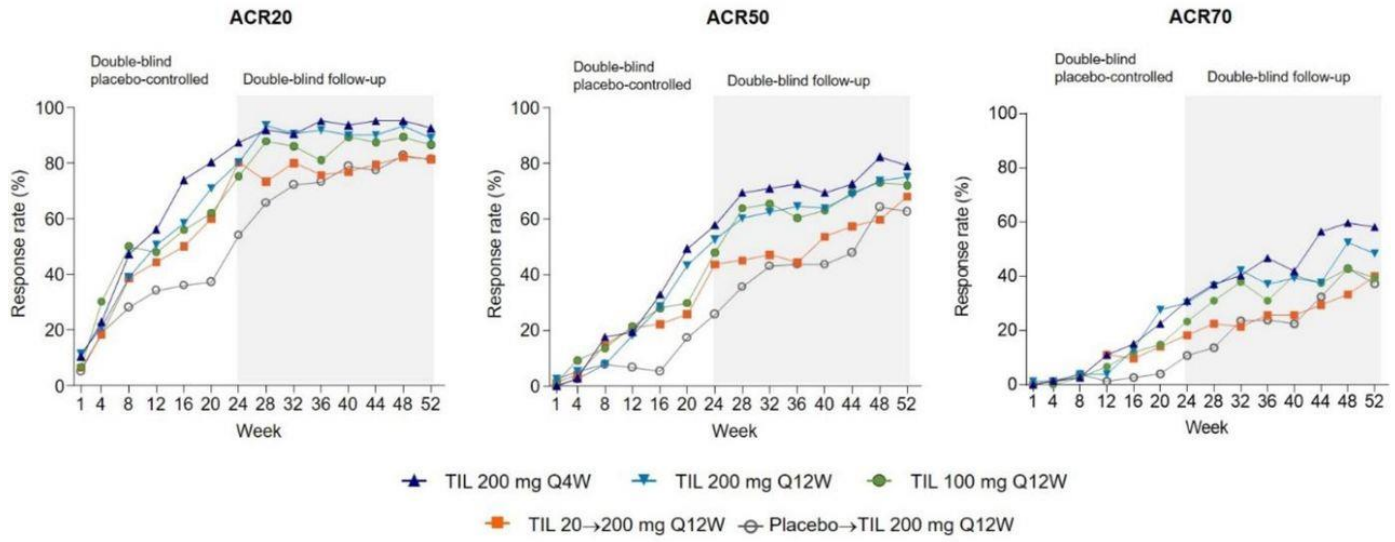
Forest plot comparing relative risks (RR) and 95% credible interval (CrI) versus placebo for adverse events. Probability better than placebo shown on the right.

McInnes et al, ARD (ab) 2020

Tildrakizumab

- Phase 2 (n=391)
- PsA pts were randomised 1:1:1:1:1 to 5 different schemes (one PBO)
- No new safety concerns

Figure 1. ACR20/50/70 through W52



Mease P et al, ARD 2020 (ab)

Risankizumab

- Phase 2 (n=185)
- PsA pts were randomized 1:1:1:1:1 to 5 different schemes (one PBO)
- No new safety concerns

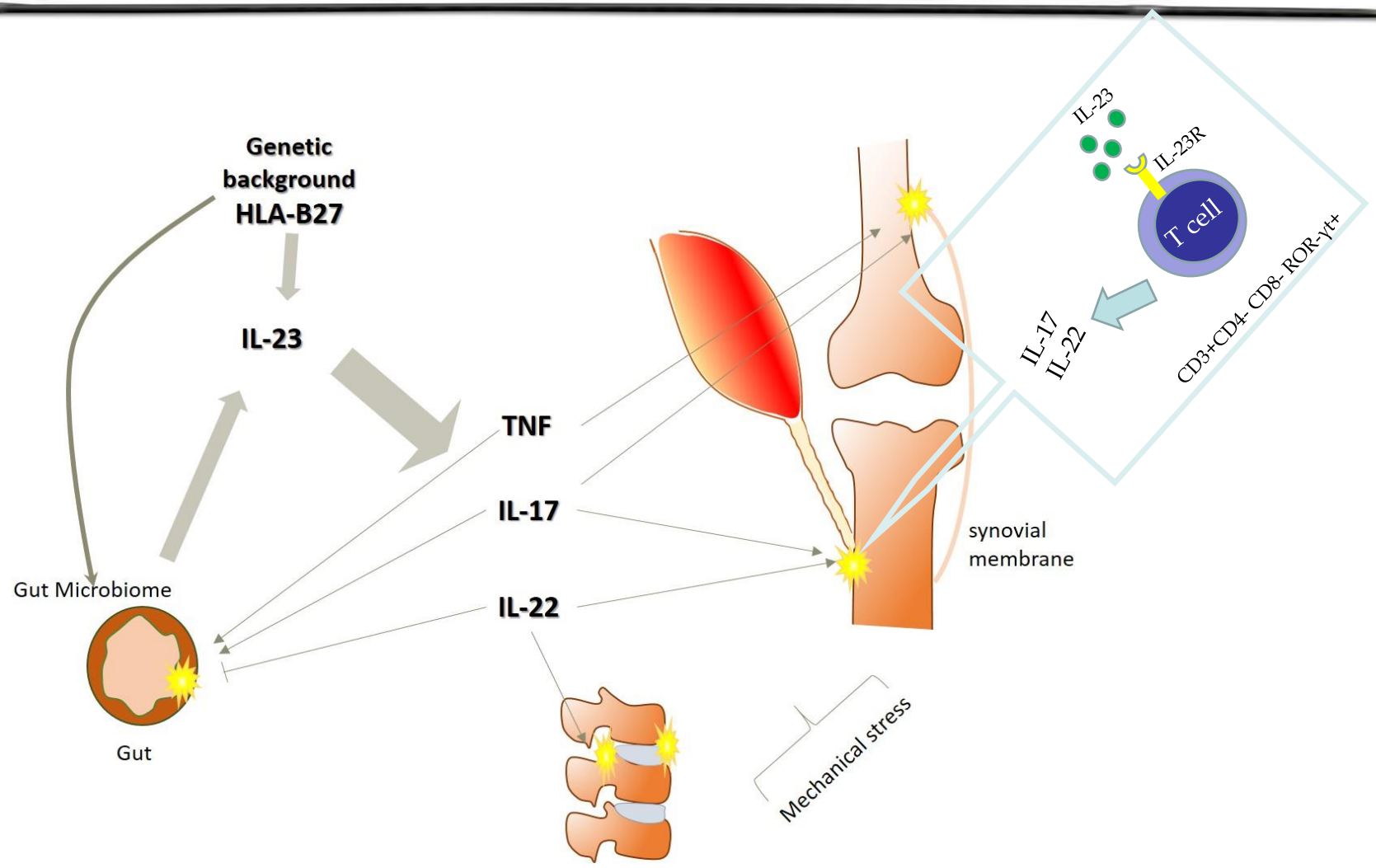
Endpoints	Risankizumab (RZB)					Placebo
	Arm 1 N=42	Arm 2 N=42	Arm 3 N=39	Arm 4 N=20	Arms 1–4 N=143	Arm 5 N=42
ACR20 (%)	42.9	47.6	59.0**	40.0	48.3*	31.0
ACR50 (%)	19.0	16.7	33.3**	20.0	22.4**	7.1
ACR70 (%)	11.9	11.9	15.4*	15.0	13.3**	2.4
PASI 75 (%)[b]	68.8***	70.0***	69.6***	55.6*	67.6***	14.3
PASI 90 (%)[b]	60.0***	52.9**	47.6**	55.6**	53.2***	10.0
PASI 100 (%)[b]	46.7**	35.3**	28.6*	44.4*	37.1***	5.0
MDA (%)	19.0	28.6**	25.6*	30.0*	25.2***	7.1

Week 24

Mease P et al, ARD 2018 (ab)

Psoriatic arthritis

Pathogenesis



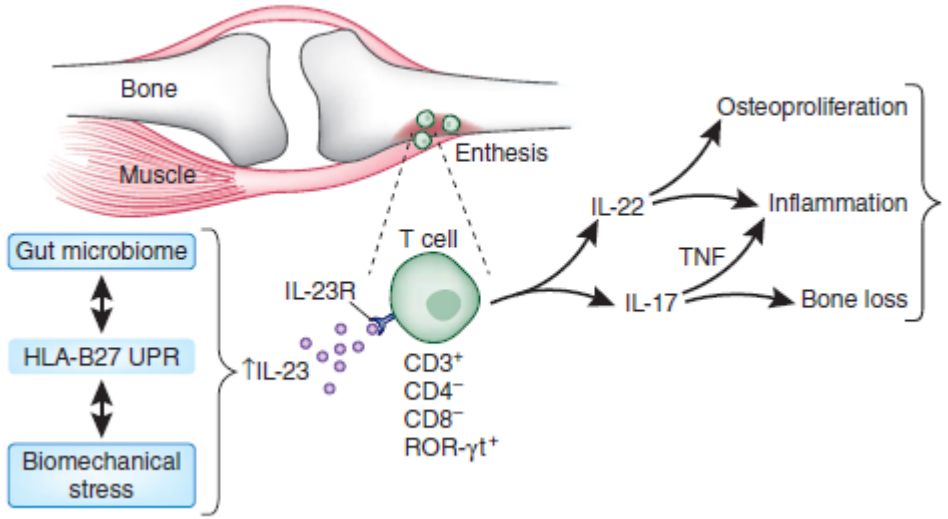
McGonagle D et al ARD 2019
Bridgewood et al ARD 2019

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

Psoriatic Arthritis

Enthesitis

- Enthesis organ "synovio-entheseal concept"
  - bursae, tendon sheaths, fibrous tissue, fat pads, fasciae
- Can everything start from the entheses ??

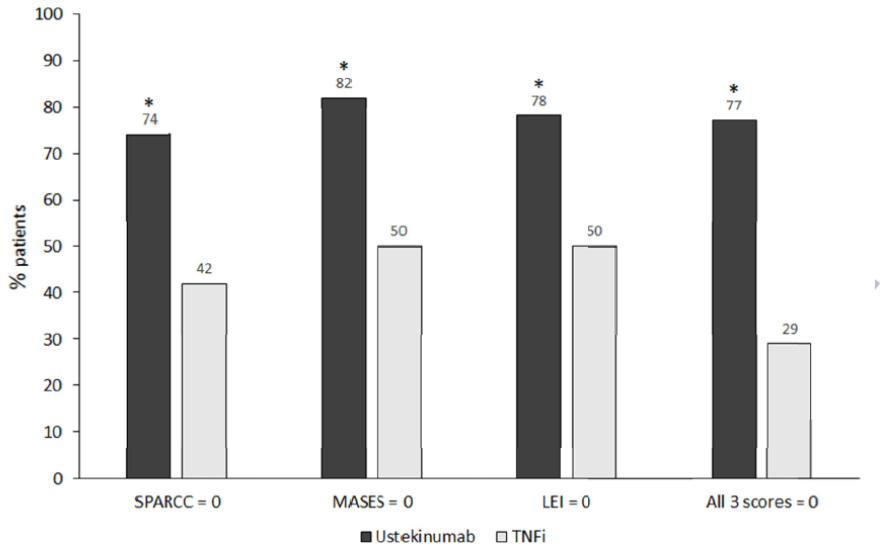


Lories J and McInnes IB Nat Med 2012
Sherlock JP Nat Med 2012

ECLIPSA

Enthesitis

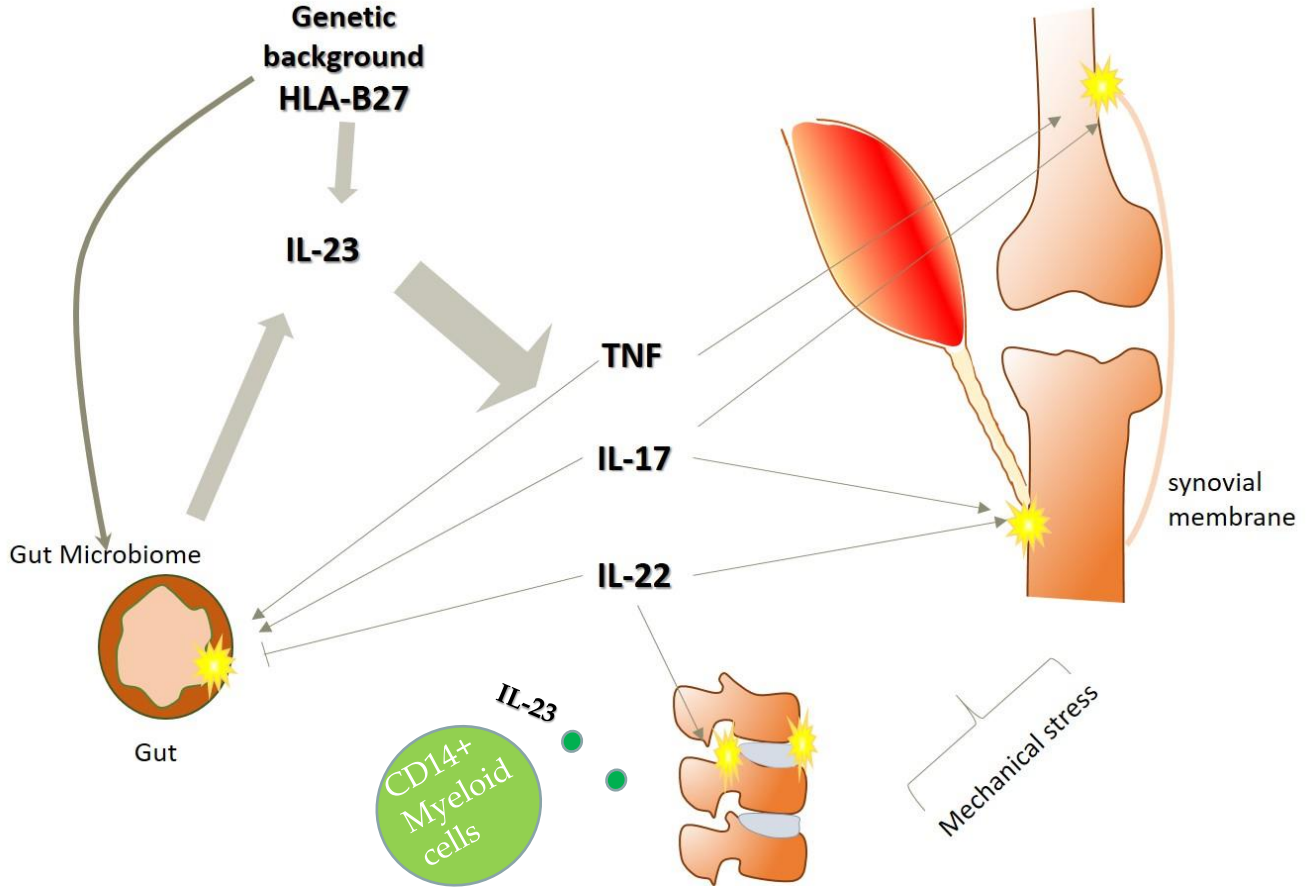
- Prospective randomized CT
- Ustekinumab (n=23) >> TNFi (n=24)
- At week 24
- more ustekinumab- than TNF-treated patients
  - SPARCC Enthesitis Index = 0 (74% versus 42%, respectively; p = 0.018)
- similar results observed for MASES = 0, LEI = 0, and for all three scores = 0



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

Psoriatic arthritis/SpA

Pathogenesis



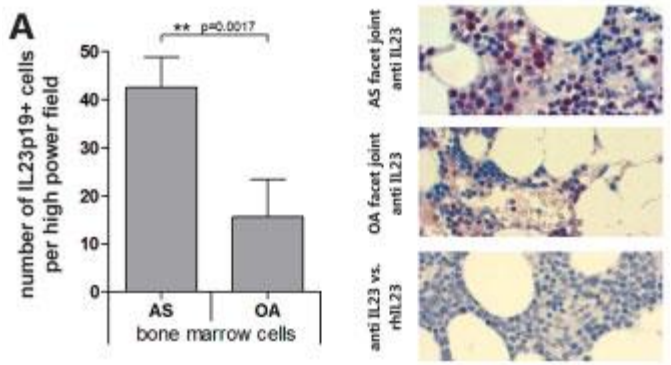
McGonagle D et al ARD 2019
Bridgewood et al ARD 2019

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

Axial spondylartritis

IL-17 but not IL-23…

- anti-IL-17 works but not anti-IL-23 ??
  - In peripheral blood of AS patients
    - ⇧ number of γδ T cells secreting IL-17 & expressing IL-23R
  - ⇧ IL-23 facet AS **but**



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

AxSpA

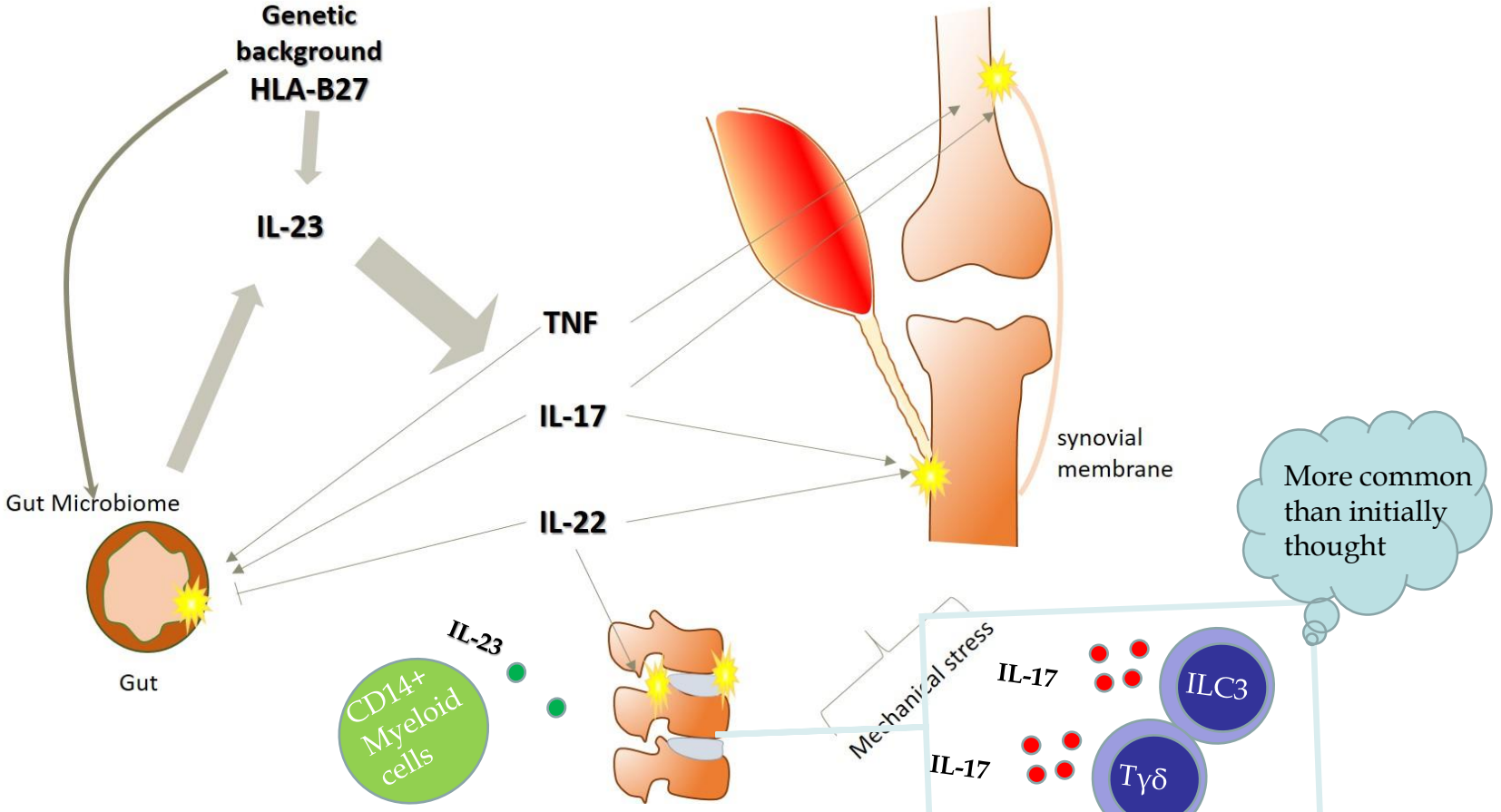
IL-23 does not work

- Ustekinumab
  - Despite some good results in small open label studies
  - phase III AS trials & non-radiographic axSpA
    - Primary endpoints were not achieved
- Risankizumab
  - Not good clinical and radiologic results in AS

Baeten D et al Ann Rheum Dis. 2018
Siebert S et al Ann rheum Dis 2018

PsA/SpA

Pathogenesis overview

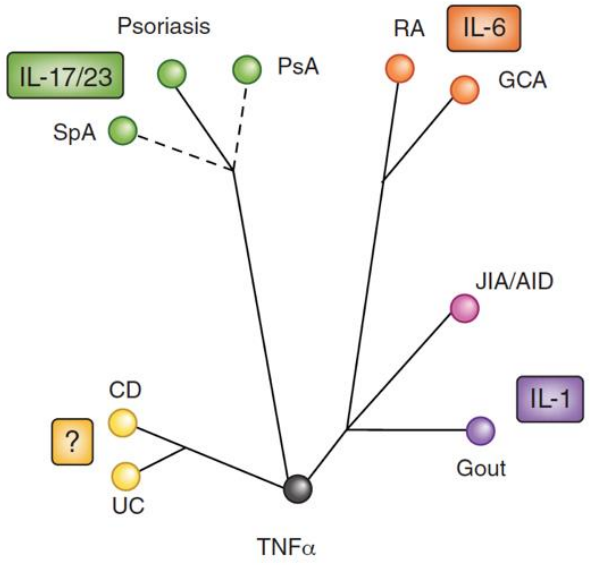


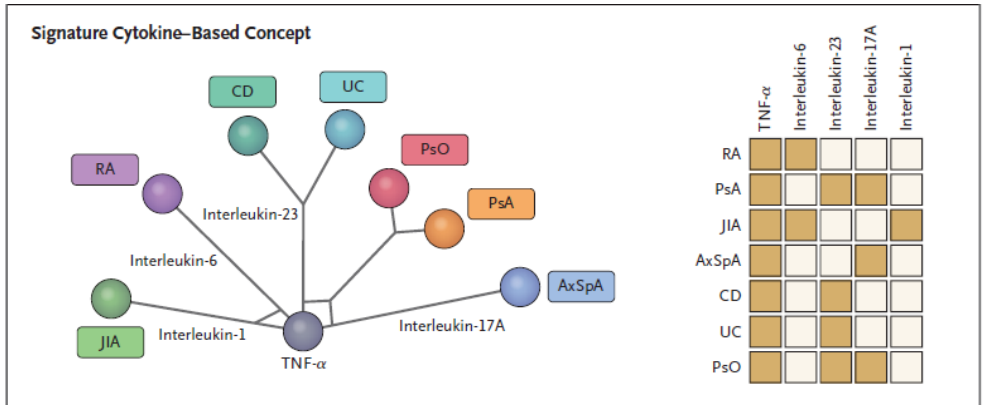
McGonagle D et al ARD 2019
Bridgewood et al ARD 2019

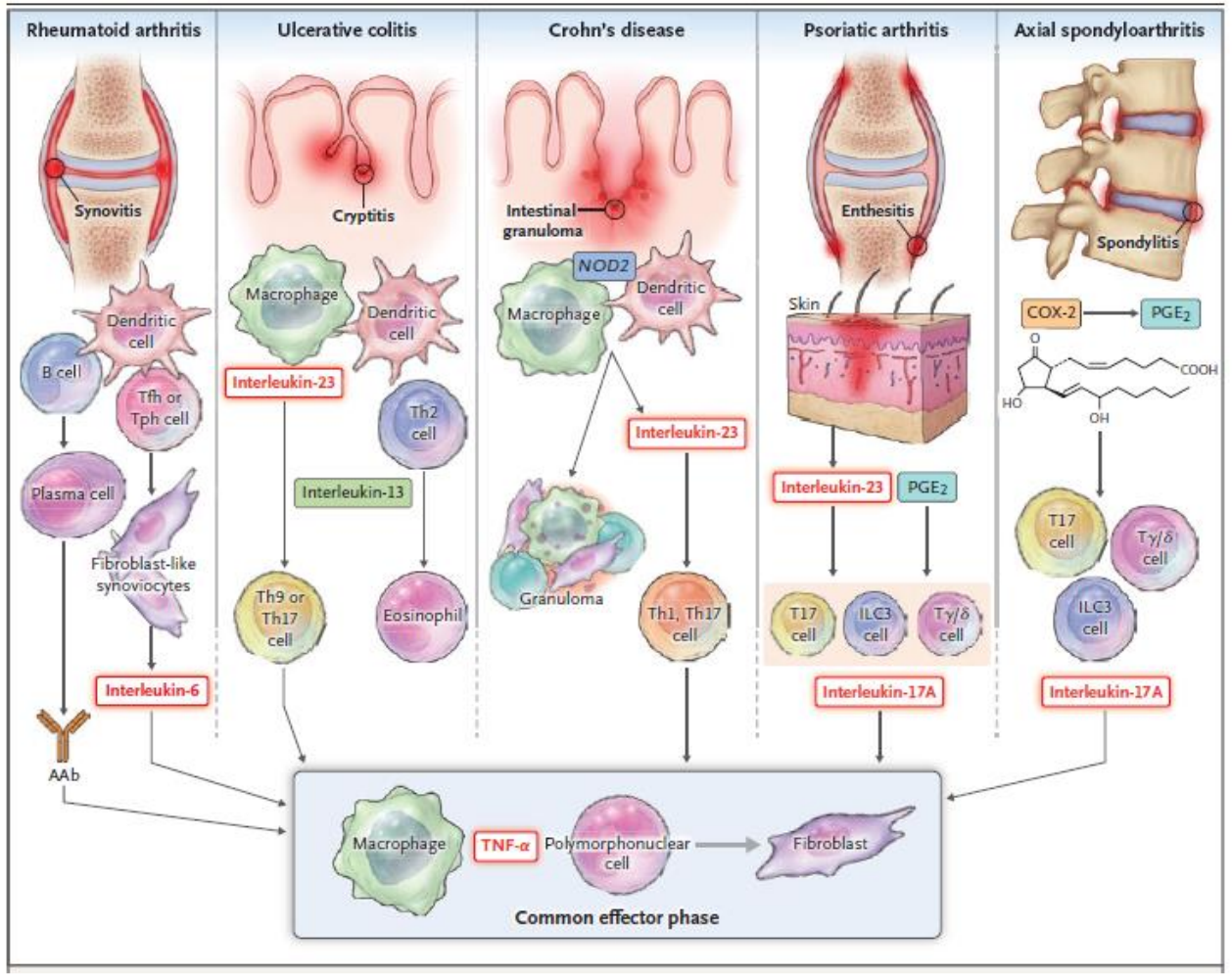
(modif from) Siebert S, Fragoulis GE, McInnes IB EULAR online course 2016
Gravallese and Schett Nat Rev Rheum 2018

Cytokines

Different drivers according to disease type? (Updated?)







Schett G et al. NEJM 2021

Axial PsA Vs AS

similarities & differences

TABLE 2 The comparison of the baseline and longitudinal clinical characteristics between the four groups

Variable	Ankylosing spondylitis		Psoriatic arthritis		
	Psoriasis ($n = 91$)	No psoriasis ($n = 675$)	Axial ($n = 477$)	Peripheral ($N = 826$)	*P*-value
At baseline					
Active joints (tender + swollen), mean (S.D.)	1.3 (3.1)	1.1 (3.5)	8.5 (10.1)	9.2 (9.9)	<0.001
Damaged joints, mean (S.D.)	0.7 (4.6)	0.2 (1.3)	5.5 (9.9)	1.8 (5.0)	<0.001
Joints after surgery, mean (S.D.)	0.1 (0.6)	0.1 (0.5)	0.3 (1.6)	0.1 (0.6)	0.44
Presence of inflammatory or mechanical back pain, *n* (%)	82 (90)	618 (92)	100 (21)	253 (31)	<0.001
ASDAS-ESR, mean (S.D.)	2.8 (1.3)	2.6 (1.1)	4.8 (3.0)	2.6 (1.1)	0.05
Patient global assessment, mean (S.D.)	4.9 (3.0)	4.7 (2.8)	1.9 (1.7)	4.9 (2.5)	0.25
BASMI, mean (S.D.)	3.1 (2.4)	2.3 (2.3)	1.9 (1.7)	1.2 (1.3)	<0.001
Enthesitis, *n* (%)	12 (13)	75 (11)	68 (14)	150 (18)	0.001
Dactylitis, *n* (%)	0	0	146 (31)	213 (26)	0.08
Iritis, *n* (%)	2 (3)	9 (2)	2 (0)	0 (0)	<0.001
Elevated ESR, *n* (%)	31 (34)	198 (29)	70 (15)	288 (35)	<0.001
Receiving biologics, *n* (%)	26 (29)	145 (21)	327 (69)	56 (7)	<0.001
Receiving NSAIDs, *n* (%)	47 (52)	340 (50)	216 (45)	435 (53)	0.04
Receiving DMARDs, *n* (%)	12 (13)	84 (12)	5.2 (6.5)	232 (28)	<0.001
Over time, adjusted mean (S.D.)					
Total active joint	1.5 (3.5)	0.9 (2.2)	5.2 (6.5)	5.6 (6.6)	<0.001
BASMI	2.9 (2.2)	2.2 (2.1)	1.8 (1.4)	1.4 (1.2)	<0.001
ASDAS-ESR	2.3 (0.9)	2.2 (0.9)	2.2 (1.0)	2.1 (0.8)	0.58
BASDAI	4.1 (2.0)	3.9 (2.1)	3.5 (2.2)	3.6 (2.0)	0.02
Patient global assessment	4.3 (2.2)	4.1 (2.2)	2.1 (0.6)	3.9 (2.0)	0.34
Physician global assessment	2.4 (0.9)	2.2 (0.8)	4.0 (2.3)	2.0 (0.7)	<0.001

Feld et al Rheumatology 2019

Axial PsA Vs AS

similarities & differences

Table 4 Axial radiographic pattern and morphology in PsSpA (n=118) and AS (n=157) cases

	PsSpA n (%)	AS n (%)	AS versus PsSpA OR	95% CI	p Value
Pattern					
Radiographic					
Sacroiliitis	79 (67)	157 (100)	–	–	–
Spondylitis (cervical and/or lumbar)	84 (71)	109 (69)	0.94	0.52 to 1.69	0.83
Sacroiliitis pattern					
Bilateral	65/79 (82)	142/147 (97)	6.14	2.08 to 18.15	0.001
Symmetrical grade	60/79 (76)	119/147 (81)	1.17	0.59 to 2.32	0.65
Spondylitis pattern					
Cervical vertebrae	52/116 (45)	85 (54)	1.20	0.65 to 2.25	0.56
Cervical facet joint	29 (25)	60 (38)	1.48	0.81 to 2.72	0.20
Lumbar vertebrae	50/117 (43)	85 (54)	1.37	0.75 to 2.50	0.30
Morphology					
Sacroiliac joint					
Sclerosis bilaterally (grade 2)	6 (5)	9 (6)	1.75	0.56 to 5.48	0.34
Erosion (grade 3)	42 (36)	53 (34)	1.07	0.63 to 1.81	0.80
Partial ankylosis (grade 3)	25 (21)	46 (29)	1.08	0.56 to 2.10	0.81
Complete ankylosis (grade 4)	18 (15)	68 (43)	2.96	1.42 to 6.15	0.004
Vertebral					
Erosion, n (%)	3 (3)	6 (4)	1.58	0.38 to 6.57	0.53
Non-bridging syndesmophyte	47 (40)	58 (37)	0.93	0.57 to 1.56	0.79
Bridging syndesmophyte	12 (10)	36 (23)	2.78	1.49 to 5.18	0.001

*Multivariate reverse-stepwise logistic regression model (adjusted as required for the following potential covariates: sex, age at radiographic assessment, disease duration at radiographic assessment, *HLA-B*27* status, anti-TNF use ever, synthetic DMARD use ever, smoking and BMI).
Anti-TNF, antitumour necrosis factor; AS, ankylosing spondylitis; BMI, body mass index; DMARD, disease modifying antirheumatic drug; PsSpA, psoriatic spondyloarthritis.

Jadon et al Ann Rheum Dis 2016

Axial PsA Vs AS

similarities & differences

Table I. Baseline characteristics and treatment received. Comparison between axial-PsA and AS.

	axial-PsA (n=79)	AS (n=129)	*p*-value
Male gender, n (%)	36 (45.6)	78 (60.5)	**0.04**
Age (years), mean ± SD	52.1 ± 11.3	48.9 ± 13.4	**0.05**
Age at diagnosis, mean ± SD	45.7 ± 11.2	41.0 ± 15.7	**0.002**
Disease duration (months), mean ± SD	76.4 ± 64.1	97.5 ± 71.3	0.100
Weight (kg), mean ± SD	86.4 ± 19.6	77.5 ± 14.9	**0.005**
Height (cm), mean ± SD	172.1 ± 9.4	171.6 ± 10.2	0.753
Smoke (current), n (%)	33 (41.8)	62 (48.1)	0.393
BMI, mean ± SD	28.6 ± 5.9	26.2 ± 4.2	**0.006**
Family history of psoriasis, n (%)	32 (40.5)	6 (4.7)	**0.001**
Family history of SpA, n (%)	7 (8.9)	13 (10.1)	1.000
HLA-B27 status, n (%)	8/38 (21.1)	72/89 (80.1)	**0.001**
BASDAI, mean ± SD	3.37 ± 1.93	2.96 ± 1.95	0.212
ASDAS-CRP, mean ± SD	2.05 ± 0.77	2.08 ± 0.83	0.808
cDMARDs, n (%)	45 (56.9)	36 (27.9)	**0.001**
bDMARDs, n (%)	51 (64.5)	100 (77.5)	0.103
NSAIDs (ever), n (%)	44 (55.7)	105 (81.3)	**0.001**
Past use of bDMARDs, number, median (IQR)	0 (0-1)	0 (0-1)	0.856

Table II. Articular, extra-articular manifestations and radiologic findings: comparison between axial-PsA and AS.

	axial-PsA (n=79)	AS (n=129)	OR (95%CI)	*p-value*
Articular and extra-articular manifestations				
Low back pain[1]	67 (85.9)	108 (75.5)	0.92 (0.42-1.99)	1.000
Back pain (other regions)[1]	25 (32.1)	30 (21.0)	0.65 (0.35-1.22)	0.198
Anterior chest wall pain[1]	6 (7.7)	11 (7.7)	1.00 (0.35-2.81)	1.000
Peripheral arthritis[2]	72 (91.1)	55 (42.6)	0.07 (0.03-0.17)	**0.001**
Mono/oligo-arthritis	26 (32.9)	46 (35.7)	1.13 (0.62-2.04)	0.764
Polyarthritis	46 (58.2)	9 (7.0)	0.05 (0.02-0.12)	**0.001**
Current/past psoriasis, n (%)	79 (100.0)	17 (13.2)	5.64 (3.67-8.69)	**0.001**
Dactylitis[1]	16 (20.2)	7 (5.4)	0.22 (0.08-0.58)	**0.001**
Nail involvement[1]	30 (37.9)	0 (0.0)	0.01 (0.01-0.09)	**0.001**
Enthesitis[1]	18 (22.8)	21 (16.3)	0.65 (0.32-1.33)	0.274
Eye involvement[1]	2 (2.5)	30 (23.2)	11.66 (2.70-50.33)	**0.001**
Bowel involvement[1]	3 (3.8)	22 (17.1)	5.21 (1.51-18.03)	**0.004**
Radiologic findings				
Sacroiliitis on x-ray/MR				
Abnormal^	41/62 (62.1)	114/114 (100.0)	3.78 (2.91-4.91)	**0.001**
Unilateral	29/62 (46.7)	19/114 (16.7)	0.23 (0.11-0.45)	**0.001**
Bilateral	12/62 (19.3)	95/114 (83.3)	19.58 (8.77-43.70)	**0.001**
Cervical spine x-ray/MRI				
Abnormal^	20/27 (74.1)	40/56 (71.4)	0.87 (0.31-2.47)	1.000
Thoracic spine x-ray/MRI				
Abnormal^	9/17 (52.9)	26/39 (66.7)	1.78 (0.56-5.68)	0.378
Lumbar spine x-ray/MRI				
Abnormal^	14/27 (51.8)	51/72 (70.8)	2.25 (0.90-5.60)	0.098

Fragoulis GE Clin Exp Rheum 2021

Ustekinumab in Axial PsA

Data from Psummit-1 & 2

- Pooled data from PSUMMIT 1 & 2
- Week 24
  - UST Vs PBO
    - neck/back/hip pain (−1.99 vs −0.18)
    - mBASDAI (−2.09 vs −0.59).
    - ⇧ % of UST Vs PBO achieved ASDAS clinically important improvement
      - ✓ decrease ≥ 1.1; 49.6% vs 12.7%; nominal p<0.05

Helliwell PS et al, RMDOpen 2020

Guselkumab in Axial PsA

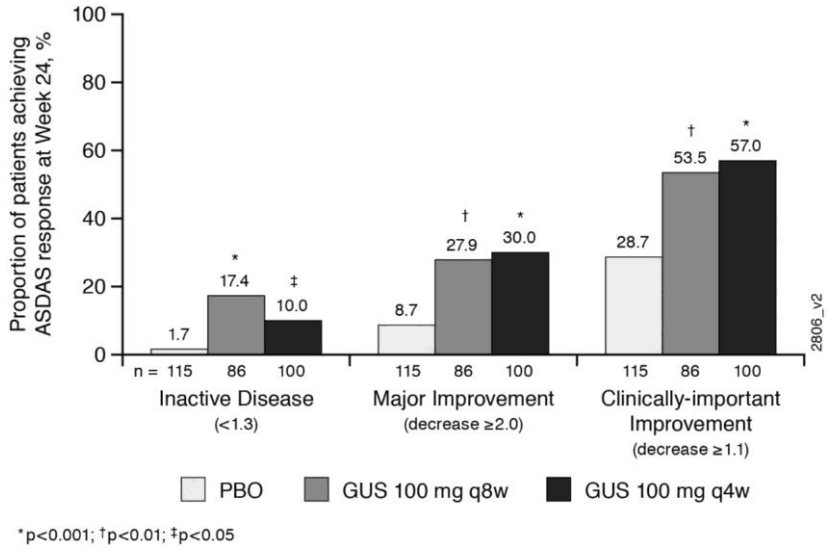
Data from Discover-1 & 2

- 312 pts with axial PsA (imaging confirmed SI)

Table. Efficacy of GUS in PsA patients with axial involvement at week 24.[a]

	PBO (n=118)	GUS 100 mg every 8 weeks (n=91)	GUS100 mg every 4 weeks (n=103)
LS Mean change in BASDAI	-1.35	-2.67*	-2.68*
LS Mean change in spinal pain[b]	-1.30	-2.73*	-2.48*
BASDAI50[c], %	21/110 (19.1%)	34/84 (40.5%)**	36/95 (37.9%)**
LS Mean change in modified BASDAI[d]	-1.13	-2.16*	-2.18*
LS Mean change in ASDAS-CRP	-0.71	-1.43*	-1.46*

[a]Pts with axial involvement consistent with sacroiliitis at baseline and either a history of imaging confirmation or pelvic X-ray at screening (pooled data from DISCOVER-1 & 2)
[b]Question 2 of the BASDAI.
[c]Pts with BASDAI > 0 at baseline.
[d]Excludes question 3 of the BASDAI.
Unadjusted p-values as noted: *p < 0.001, ** p < 0.01

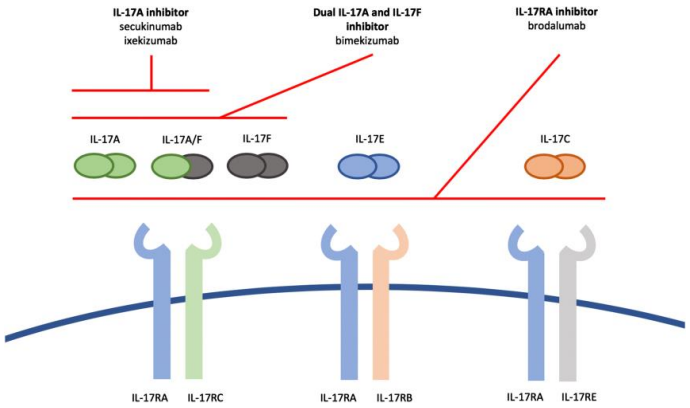


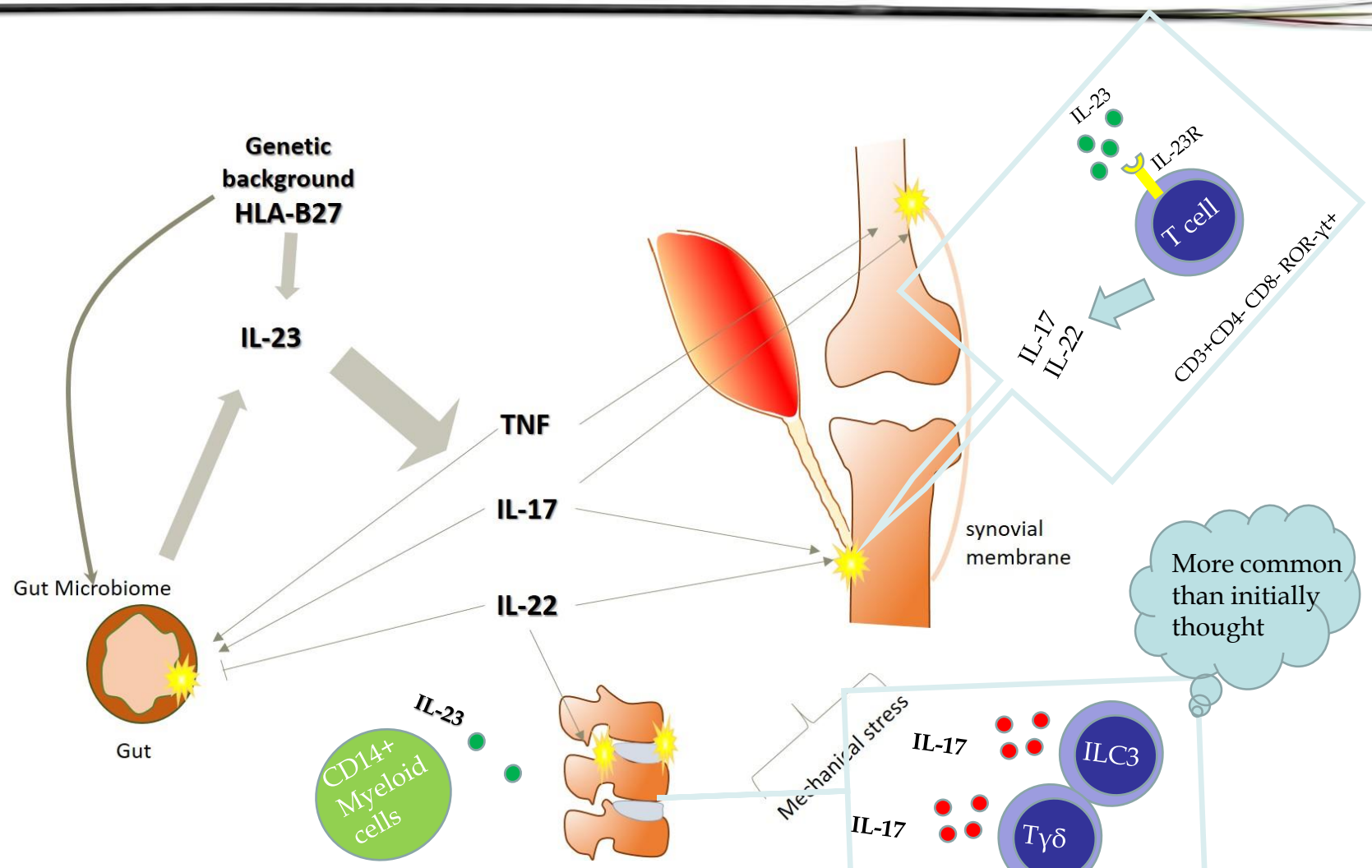
*p<0.001; †p<0.01; ‡p<0.05

Helliwell et al, ARD (ab) 2020

PsA/SpA

Pathogenesis overview



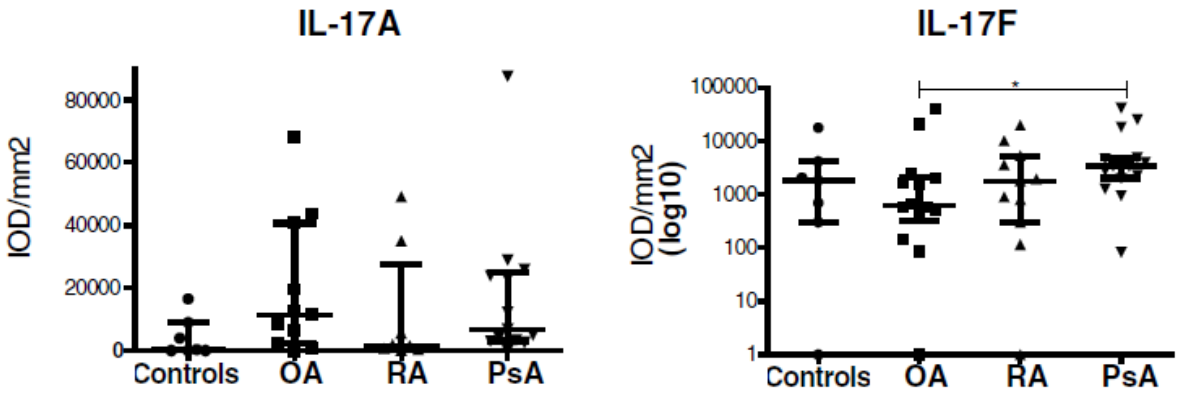


McGonagle D et al ARD 2019
Bridgewood et al ARD 2019

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

IL-17
blocking both IL-17A and F

- IL-17 family
  - IL-17F is the most structurally homologous (~50%) to IL-17A
  - IL-17F seems to be significantly increased in the synovium of PsA compared to osteoarthritis (OA) patients, unlike IL-17A
  - IL-17F seems to be the predominant subtype produced by Tγδ cells
    - capable of producing both IL-17 even independently of IL-23 stimulation
    - Special role in enthesis/axial disease



Van Baarsen et al, Arthr Res & Ther 2014
Oliveira et al Drug Des Dev and Ther 2021

IL-17
blocking both IL-17A and F

- Bimekizumab is a humanized monoclonal IgG1 antibody that selectively neutralizes both IL-17A and IL- 17F.
- Registered: psoriasis
- Phase III: AS, PsA

Table 1 Results from Published Trials Involving Bimekizumab in Psoriatic Arthritis

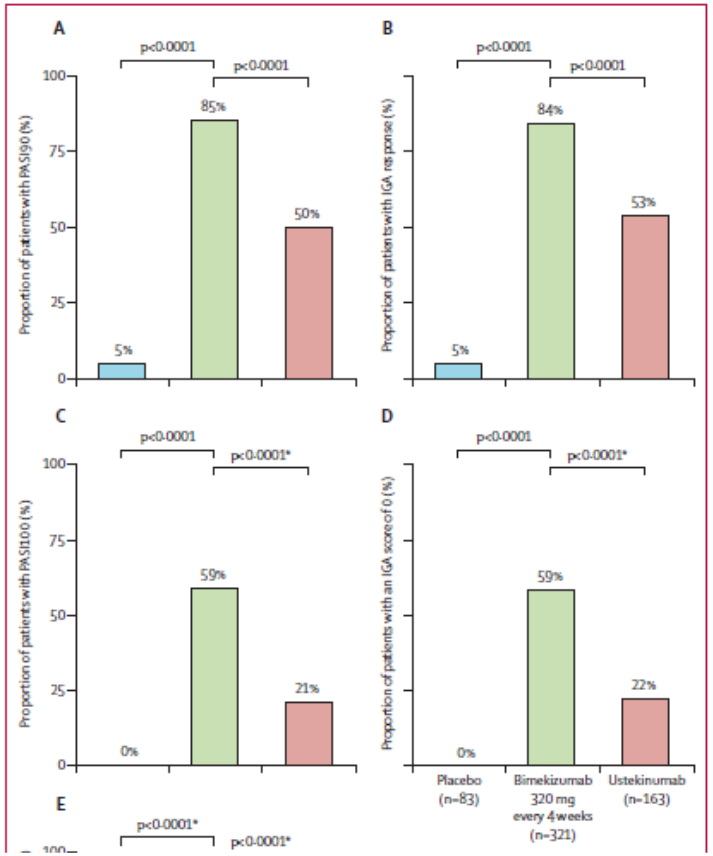
	Registration	ACR20	ACR50	PASI75	PASI100	PGA	PtGA
Phase I PA0007[7]	NCT02141763	Bimekizumab arm (at week 8)					
		80%	40%	100%	87%	−64%	− 59%
		Placebo arm					
		16.7%	8.3%	0%	0%	−29%	−17%
Phase II BE ACTIVE[8]	NCT02969525	Bimekizumab arm (at week 12)					
		59.75%*	34.5%**	64.75%***	35.25%****		
		Placebo arm					
		19%	7%	7%	7%		

Oliveira et al Drug Des Dev and Ther 2021

Bimekizumab

better than IL-23 for skin?

- H2H comparison with Ustekinumab
  - 567 patients
    - 321 randomized to bimekizumab
    - 163 to ustekinumab
    - 83 to a placebo
  - bimekizumab > ustekinumab (week 16)
    - 85% vs 49.7% PASI 90 responses, p<0.001
    - Sustained till week 52 (81.6% vs 55.8%, p<0.001).

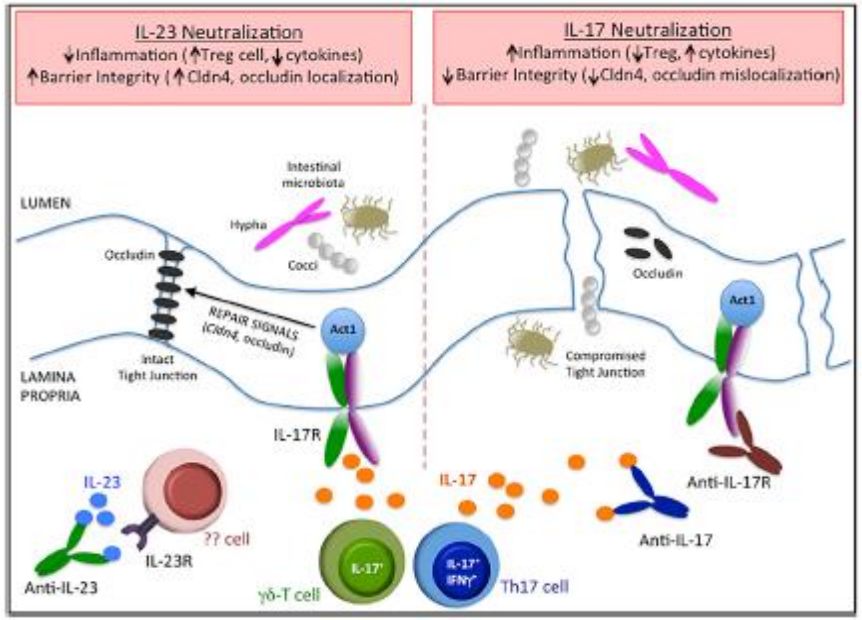


Oliveira et al Drug Des Dev and Ther 2021
Reich et al Lancet 2021

Anti-IL-17

Safety

- 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
    - New cases ??



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

Treatment

IL-17 & gastrointestinal manifestations

- 7355 patients (16.227 PY) 21 clinical trials
  - Patients exposed to anti-IL-17
- Pso: 5181 (14)
- PsA: 1380 (3)
- AS: 794 (4)
- Incidence did not increase over-time
- Most were new-onset

Table 2 EAIRs (95% CI) of IBD over the entire treatment period for patients taking any dose of secukinumab

	PsO Studies N=5181	PsA Studies N=1380	AS Studies N=794
Median exposure (min–max), days	505.0 (1–1825)	1067.5 (8–1827)	981.5 (1–1530)
Total exposure, PY	10 416.9	3866.9	1943.1
Incidence, identified by standard definition (preferred term)			
CD, EAIR per 100 PY (95% CI)	0.05 (0.02 to 0.11)	0.08 (0.02 to 0.23)	0.4 (0.2 to 0.8)
UC, EAIR per 100 PY (95% CI)	0.13 (0.07 to 0.23)	0.08 (0.02 to 0.23)	0.2 (0.1 to 0.5)
IBDU, EAIR per 100 PY (95% CI)	0.01 (0.00 to 0.05)	0.05 (0.01 to 0.19)	0.1 (0.0 to 0.3)

Schreiber Ann Rheum Dis 2018

Treatment

IL-17 & gastrointestinal manifestations

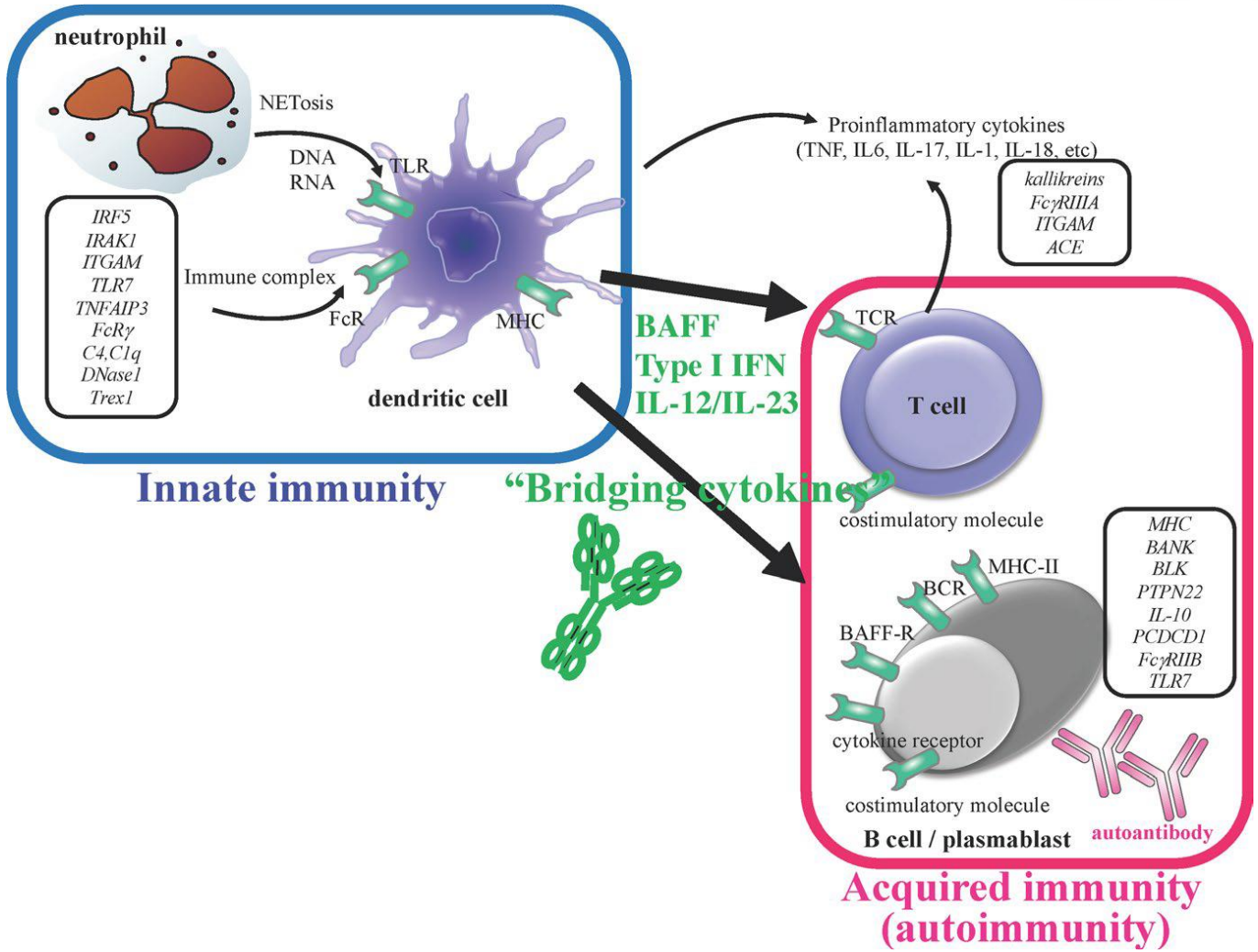
- 106 randomized trials: 40.053 patients
  - Inflammatory bowel disease cases were reported in 0.4% of patients exposed to IL-17i
- 61 uncontrolled or retrospective studies: 16.791 patients
  - Sixty (0.36%) inflammatory bowel disease cases were reported
- Most of them new onset

- New onset IBD or exacerbation of an old one seems to be uncommon

Caron B Exp Op Dr Saf 2021

IL-23-17 axis in other diseases

SLE

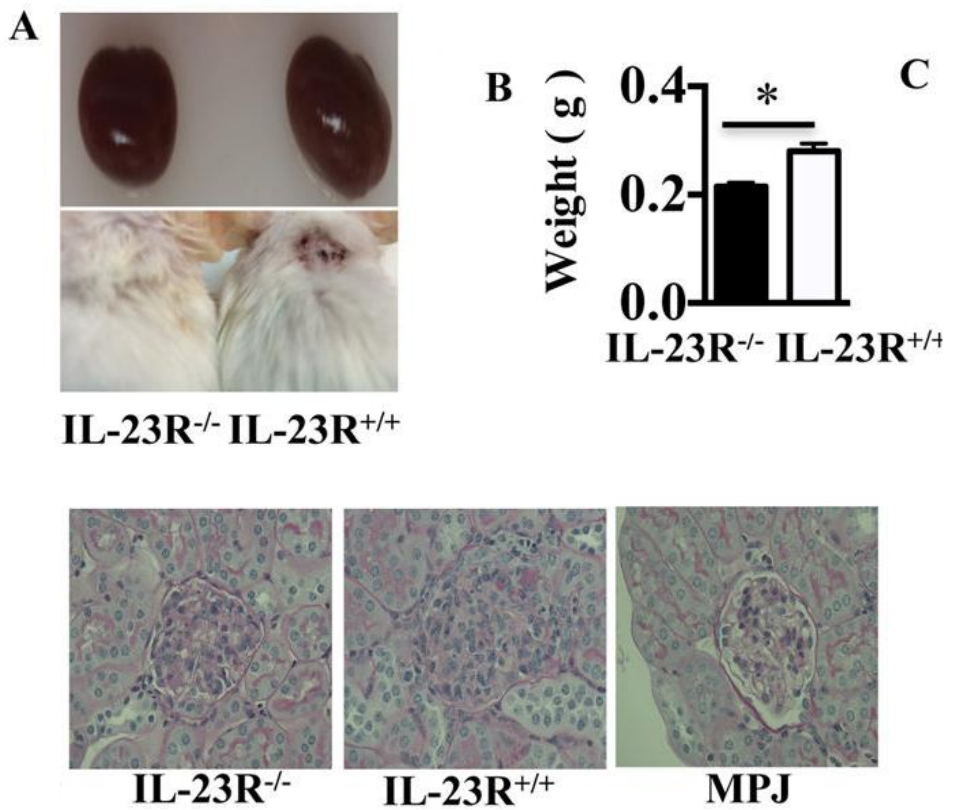


Tanaka Y et al, Int J Rheum Dis 2021

IL-23

SLE

- ⇧ IL-12, and IL-23 concentrations
- IL-23 ⇧ in SLE with active disease Vs patients with inactive disease and healthy controls
- IL-23R+/+ MRL.lpr mice Vs IL-23R-/- MRL.lpr mice
  - enlarged kidneys and severe skin lesions,
  - significantly worse glomerulonephritis as compared to IL-23R-/- MRL.lpr mice
  - ⇧ dsDNA



Dai et al, JI 2017
Guimaraez et al, Immun & Cell Biol 2017

Ustekinumab in SLE

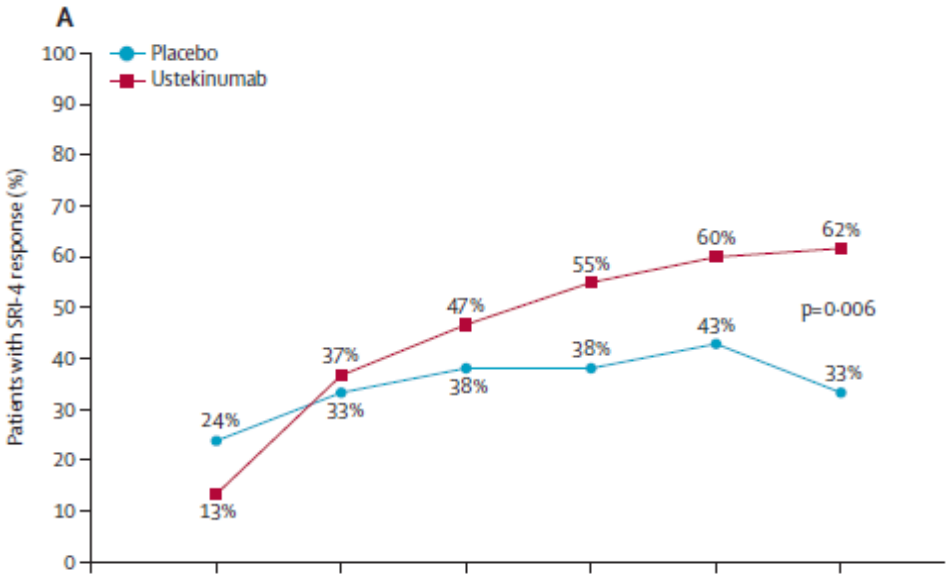
Phase II trial

- Multicentre, double-blind, phase 2, RCT
  - adult patients with active SLE randomly assigned (3:2) to the ustekinumab or placebo group
- IV ustekinumab followed by SC ustekinumab 90 mg q8weeks or intravenous placebo at week 0 followed by subcutaneous injections of placebo every 8 weeks
  - both in addition to standard-of-care therapy
- Primary endpoint @week24
  - % of patients achieving a SLEDAI-2K responder index-4 (SRI-4)

Ustekinumab in SLE

Phase II trial

- 102 patient
  - ustekinumab (n=60) or placebo (n=42).
- At week 24
  - **62% of patients in the ustekinumab group**
  - **33% in the placebo group**
  - **achieved an SRI-4 response (percentage difference 28% [95% CI 10–47], p=0·006).**
- Phase III……terminated! Due to poor efficacy



Vanvollenhoven et al, Lancet 2018
Liossis et al. Front Med 2021

IL-23-17 axis in other diseases

Behcet's disease (BD)

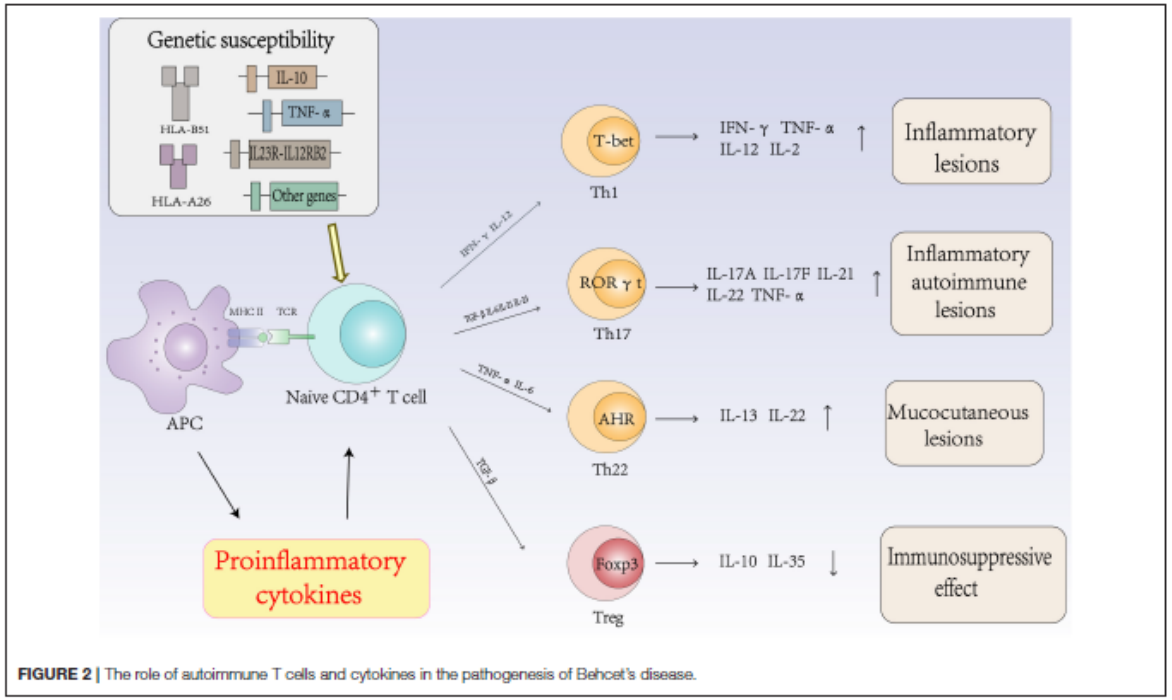


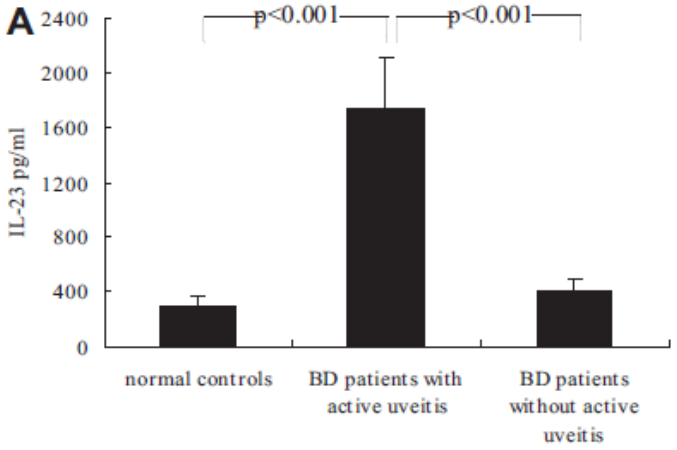
FIGURE 2 | The role of autoimmune T cells and cytokines in the pathogenesis of Behcet's disease.

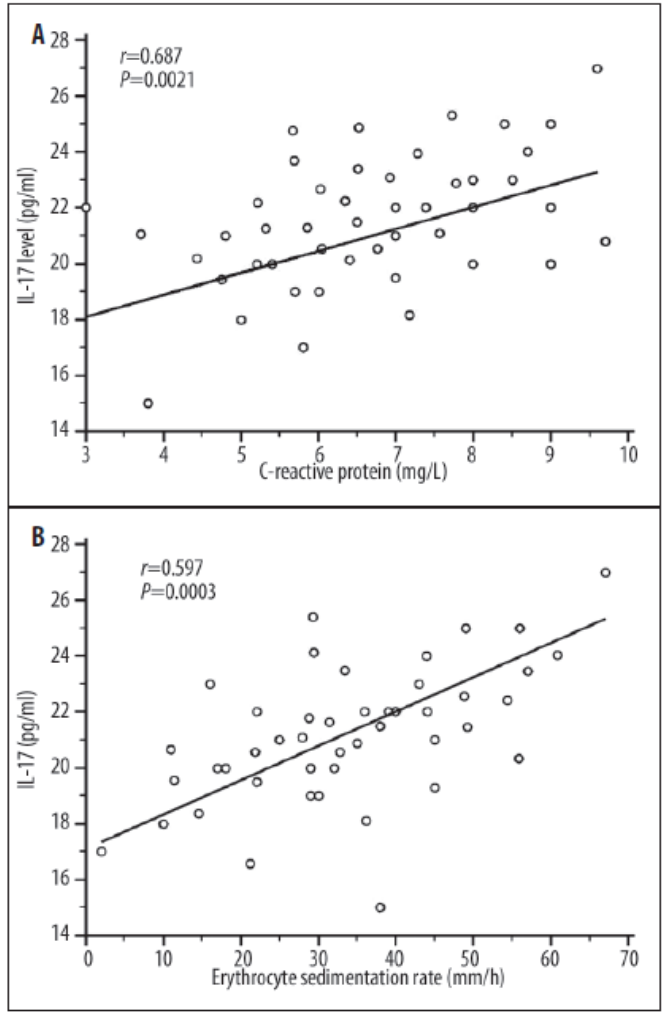
Tong et al, Fron Immun 2019

IL-23-17 axis

BD

- rs17375018 in the IL-23R gene had a strong correlation with BD uveitis
- IL-17, IL-23
  - Increased in serum
- frequencies of Th17 cells and their cytokines and transcription factor RORgt
  - ⇧ in active BD patients than those in inactive BD patients



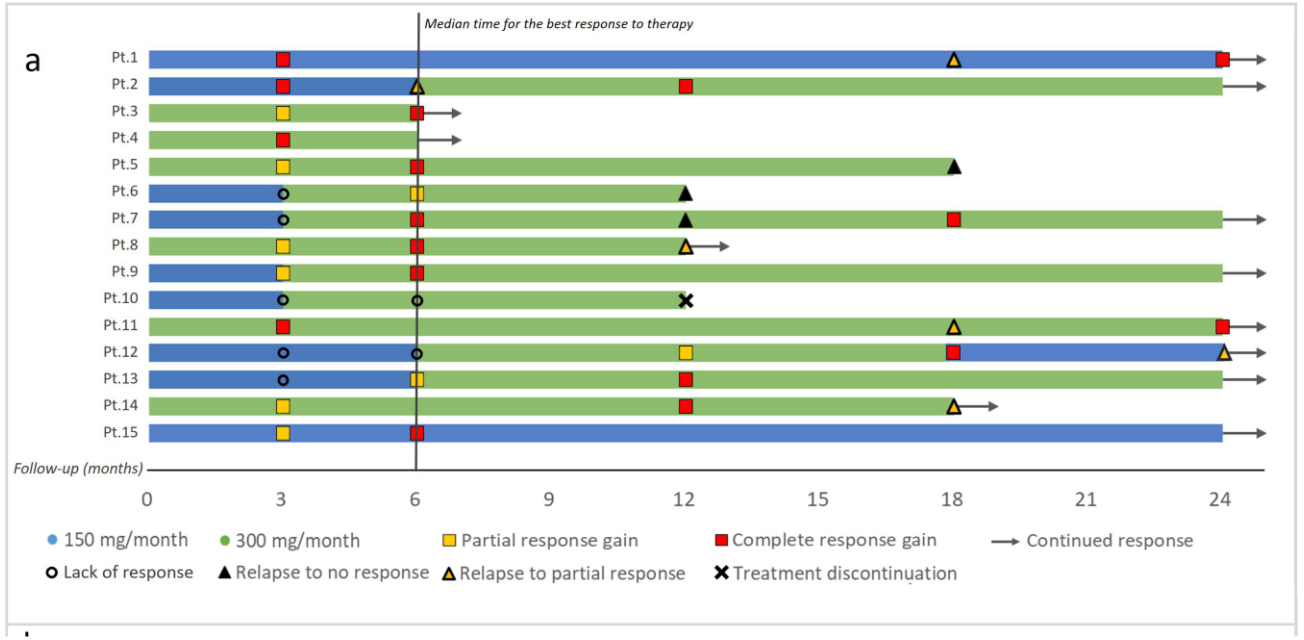


Chi et al, Inv Opth & Vis sci 2008
Jiang et al ARD 2010
Hamzaoui Med. Sci Monit 2011

Anti-IL-17

BD

- Multicentre retrospective study
  - 15 patients with a mucosal and articular BD phenotype
  - refractory to colchicine, disease-modifying antirheumatic drugs and at least one TNFi
  - Secukinumab from 150 to 300 mg per month
    - As add-on therapy
    - No TNFi
- 3 months of follow-up
  - 66.7% patients achieved a response (complete or partial)
  - further increased to 86.7% at 6 months, 76.9% at 12 months, 90.0% at 18 months and 100.0% after 24 months



Fagni et al, ARD 2020

Anti-IL-23

BD

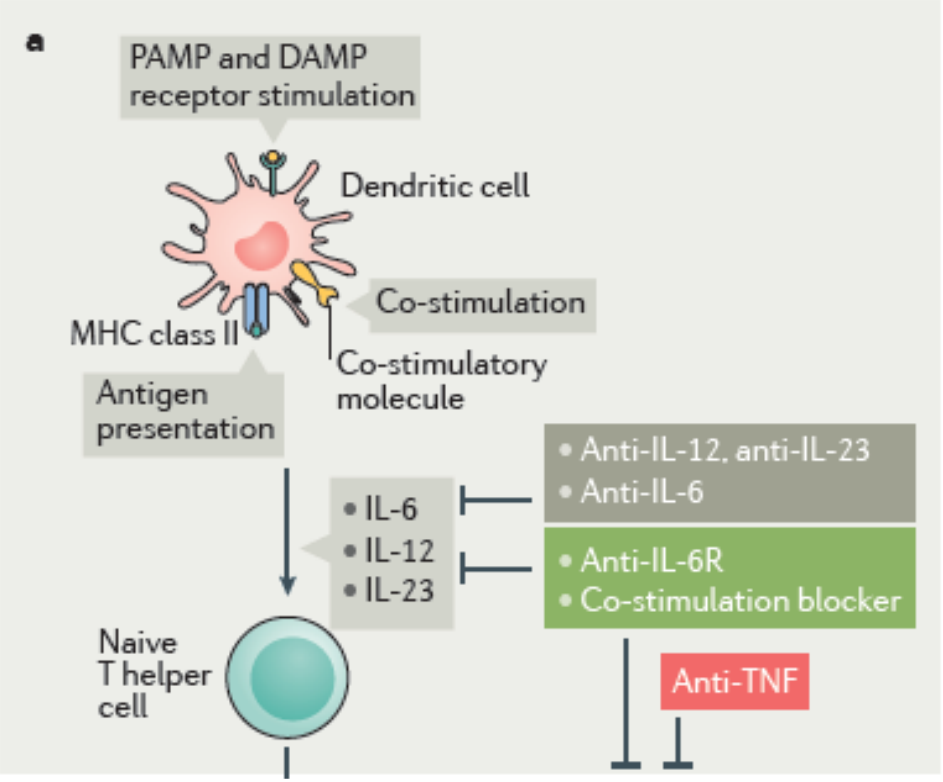
- open-label study included 30 patients
- Oral ulcers refractory to colchicine
- Ustekinumab week 0,4 and q12w
- primary end point: at week 12: % complete response (no ulcers)
- Results
  - The median No of oral was significantly ⇩ at week 12 compared to baseline (0 [IQR 0–1] versus 2 [IQR 2–3]; *P* < 0.0001)
  - Complete response was achieved in 60.0% and 88.9% of patients at weeks 12 and 24, respectively

Mirouse et al, Arhtr and Rheum 2019

IL-23-17 axis in other diseases

GCA

- Adventitia
  - important site of immune surveillance
    - rich in dendritic cells (DCs) and MΦ
    - expressing Toll-like receptors (TLRs)
- pathogen-associated molecular patterns (PAMPs), microorganism-associated molecular patterns (MAMPs) and damage-associated molecular patterns (DAMPs)
  - DC activation
  - leading to the production of pro-inflammatory cytokines such as IL-12 and IL-6, IL-23, IL-1
  - Naïve T cells activation



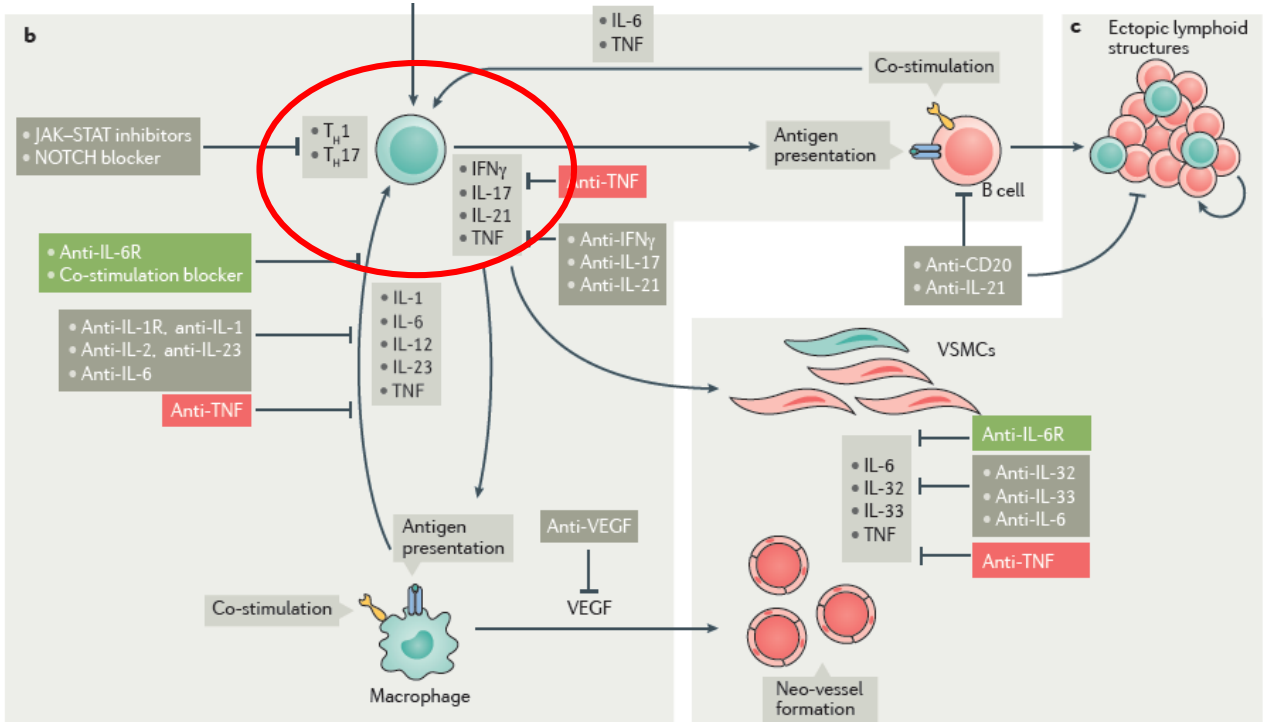
Dejaco C et al, Nat Rev Rheum 2017

GCA

IL-6 amplifying inflammation & chronic phase

- Maturation of DCs
- naive CD4+ T cells polarize
  - Th1 cells
    - Production IFNγ and TNF
  - Th17 cells
    - Production IL-17 and IL-21

- Recruit macrophages
  - produce IL-1, IL-6, IL-12, IL-23, TNF and VEGF
  - Might drive GC formation and VSMC proliferation



Dejaco C et al, Nat Rev Rheum 2017

GCA

Treatment / anti-TNF failed

- No clear explanation why TNFs failed
  - Possibly redundant pathways exist

Infliximab (TNF blocker)	Randomized, multicentre, double-blinded	44	New GCA (cranial)	54 weeks	Did not achieve primary and main secondary end points	Hoffman 2007 (REF. 134) (full paper)
Etanercept (TNF blocker)	Randomized, multicentre, double-blinded	17	GCA in remission, stable oral prednisone treatment	15 months	Cumulative glucocorticoid dose: 1.5 g in etanercept versus 3.0 g in control group ($p = 0.03$) other outcomes negative	Martinez-Taboada 2008 (REF. 137) (full paper)
Adalimumab (TNF blocker)	Randomized, multicentre, double-blinded	70	New GCA (cranial)	52 weeks	Did not achieve primary and main secondary endpoints	Seror 2014 (REF. 136) (full paper)

Dejaco C et al, Nat Rev Rheum 2017

GCA

Treatment – what about Ustekinumab?

- The "dual" role (IL-12 & IL-23) makes UST a potentially attractive treatment
- Open-label/small (n=25) study, 52 weeks
- refractory disease with either an inability to taper prednisolone to an acceptable dose or a history of multiple relapses during prednisolone
  - a reduction in
    - median prednisolone dose ($p < 0.001$)
    - CRP ($p = 0.006$)
  - No patients had a flare of GCA while treated with ustekinumab

Dejaco C et al, Nat Rev Rheum 2017
Low C & Conway R, Ther Adv Mus Res 2019
Conway R et al, Semin Arth Rheum 2018

GCA

Treatment – what about Ustekinumab?

- Open-label trial of UST in GCA
- All patients: a 24-week prednisone taper and SC UST 90 mg at baseline and at weeks 4, 12, 20, 28, 36, and 44.
- Primary endpoint: prednisone-free remission (absence of relapse through week 52 and normalization of the ESR and CRP level)
- 13 patients
  - Only 3 (23%) achieved the primary endpoint.
  - Of the 10 patients (77%) who failed to achieve the primary endpoint, 7 relapsed after a mean period of 23 weeks.
- **Conclusion:** UST combined with 24 weeks of prednisone was associated with a high rate of treatment failure in this prospective GCA trial.

Dejaco C et al, Nat Rev Rheum 2017
Low C & Conway R, Ther Adv Mus Res 2019
Conway R et al, Semin Arth Rheum 2018

GCA

Secukinumab

- Only case reports so far….

Trials. 2021 Aug 17;22(1):543. doi: 10.1186/s13063-021-05520-1.

Efficacy and safety of secukinumab in patients with giant cell arteritis: study protocol for a randomized, parallel group, double-blind, placebo-controlled phase II trial

Nils Venhoff [1], Wolfgang A Schmidt [2], Peter Lamprecht [3], Hans-Peter Tony [4], Christine App [5], Christian Sieder [5], Carolin Legeler [6], Claudia Jentzsch [7], Jens Thiel [1]

Take home Messages

- Are we going towards cytokine-based treatment?
  - Simple but complex
- Could that be that some cytokines are involved at an earlier stage of disease than others?
- Other (partly unidentified) cells are contributing to the cytokine milieu.