Cytokine inhibitors in autoimmune diseases from basic science to translational application

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Heraklion November 2019

Outline

- Introduction - The Complexity of Immune system
- The Players - Drugs targeting cytokines and their receptors
- The IL-23/-17 axis
- IL-1 & the inflammasome
- IL-6
- Conclusion

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

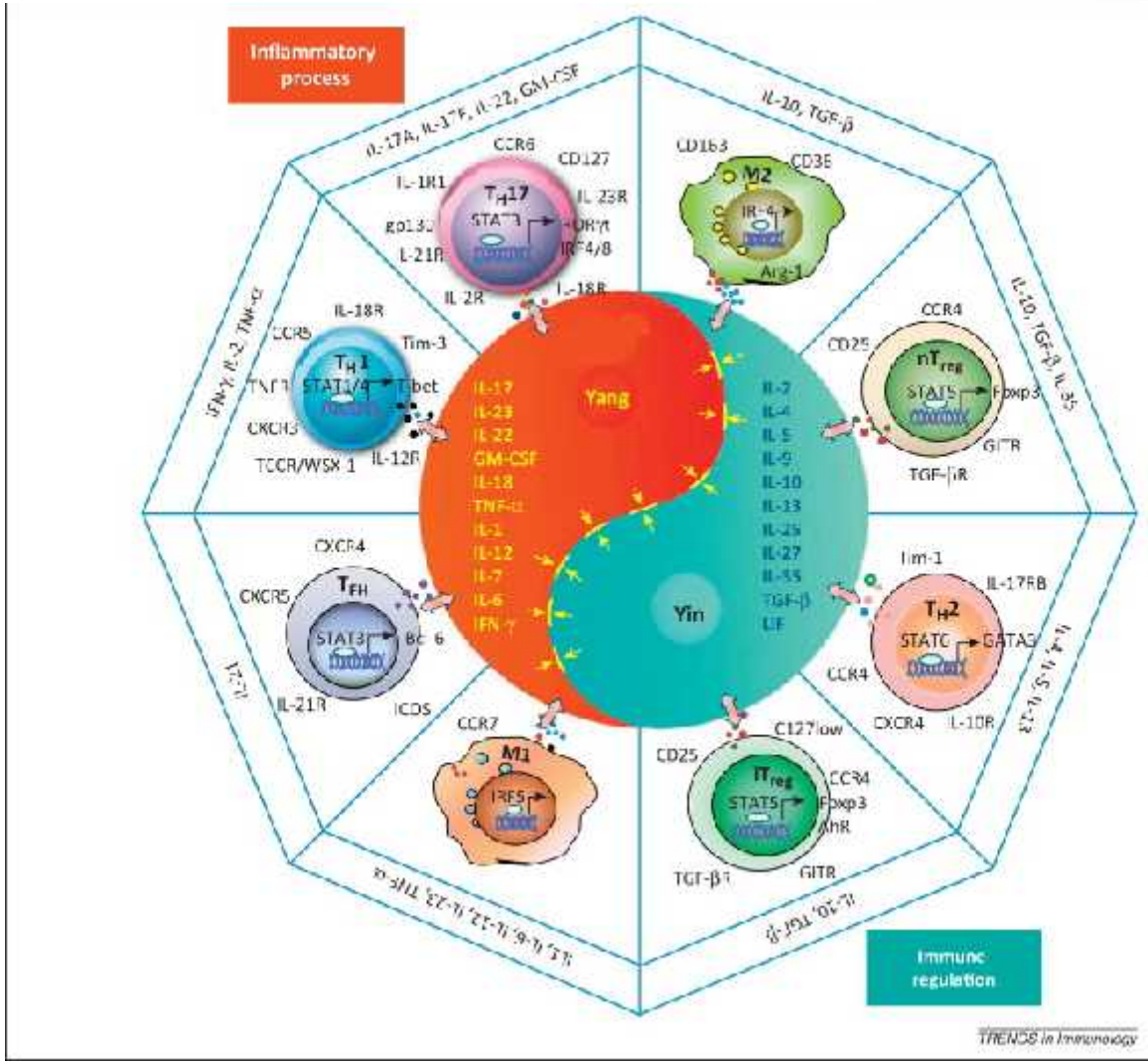
Introduction

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
- Amelioration of associated co-morbidities
- Preservation of host immune capability
  - to avoid profound immune suppression and

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

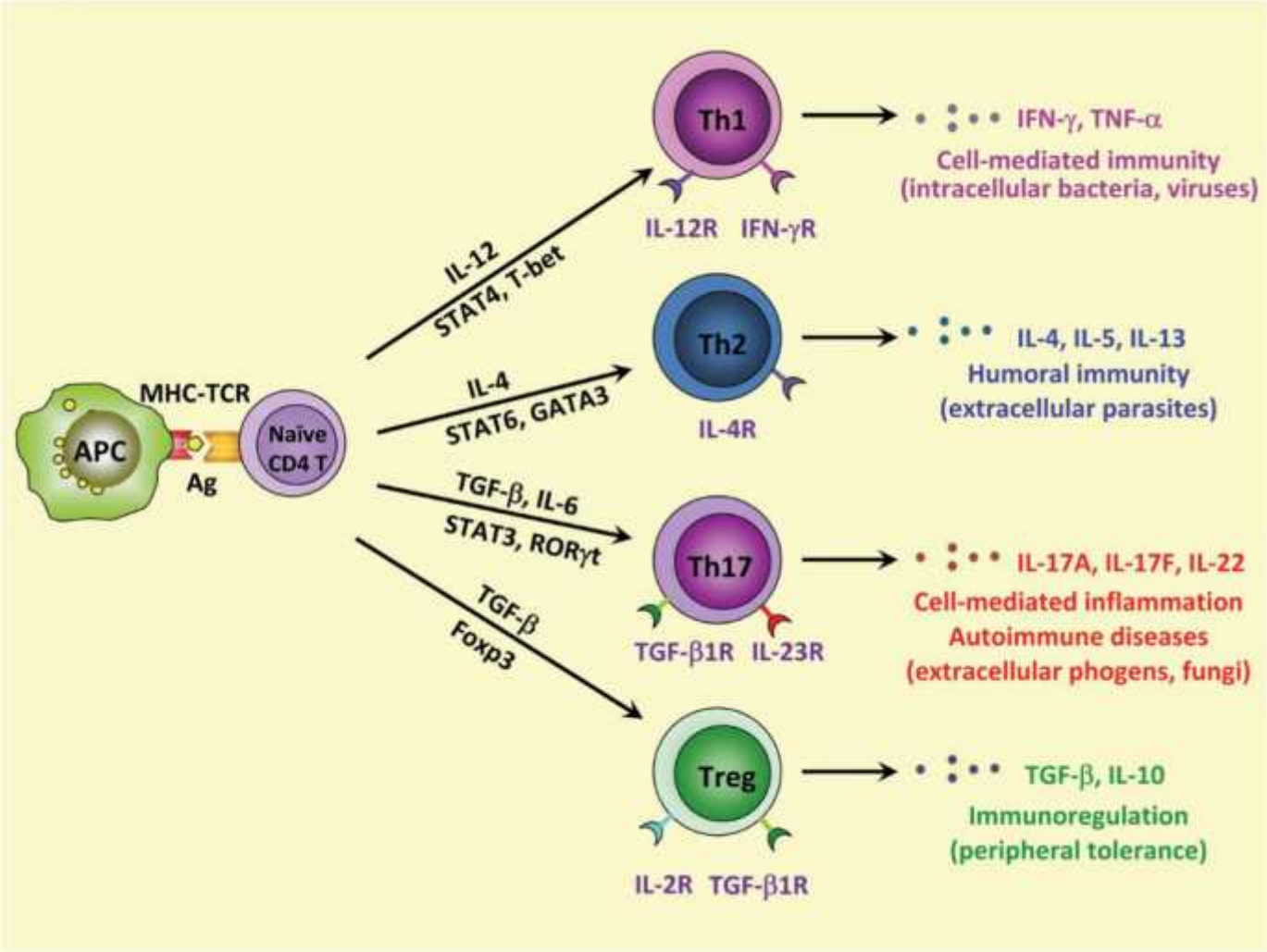
The complexity of Immune System



Liu et al. Trends in Immun 2012

Cytokines

Different T cell subsets

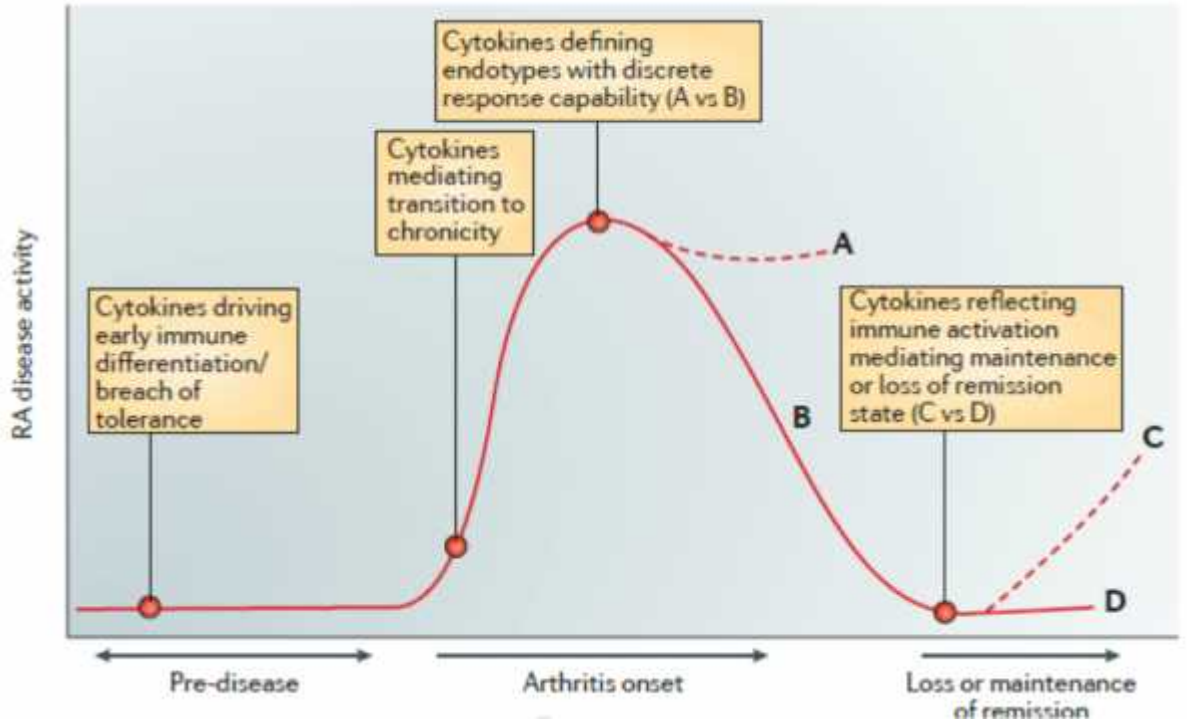


Leung et al CMI 2010

Cytokines

Diverse drive according to disease stage?

- Groups of cytokines (e.g. IL-6, IL-21, IL-23, IL-17) likely
  - drive adaptive immune activation/differentiation
  - loss of tolerance
  - in preclinical or early arthritis, whereas
- distinct profiles might dominate
  - the transition to chronicity or the maintenance of established disease (e.g. TNF, IL-6),

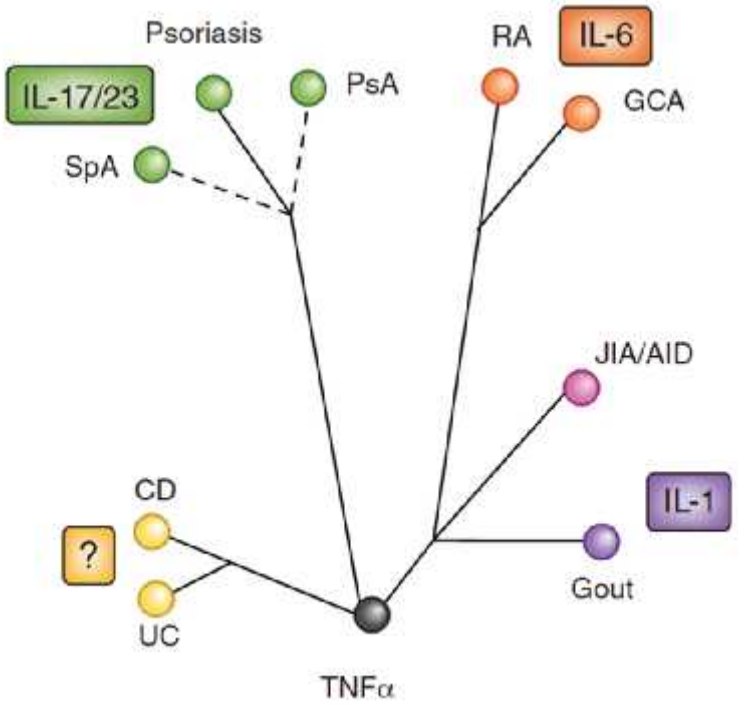


Cytokine profiles could yield new biomarker profiles, or novel insights into the rational, 'pathogenesis stage-dependent' application of cytokine-targeting therapeutics

McInnes et al. Nat Rev Rheum 2015

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

Outline

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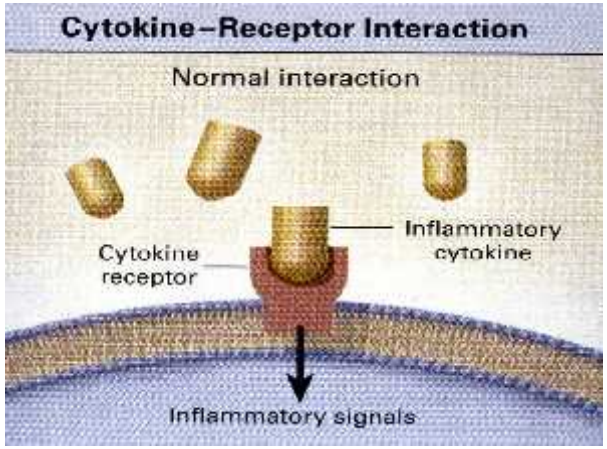
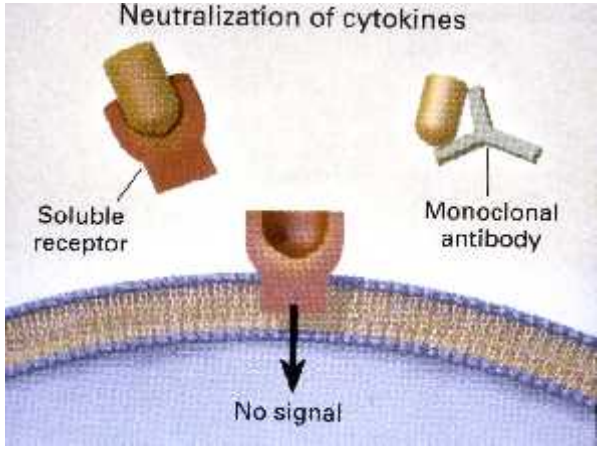
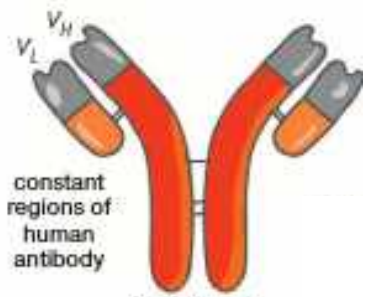
The Players

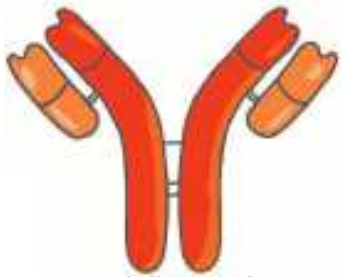
The TNF inhibitors



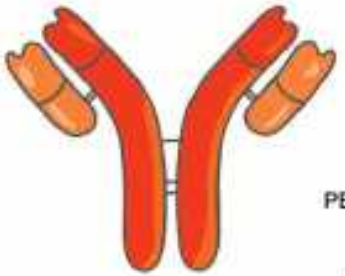




infliximab (chimeric antibody)

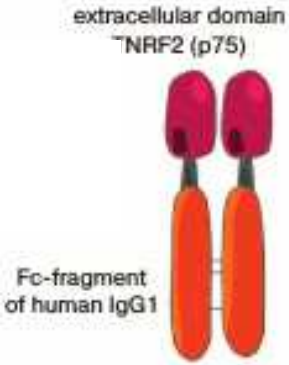


adalimumab (human antibody)



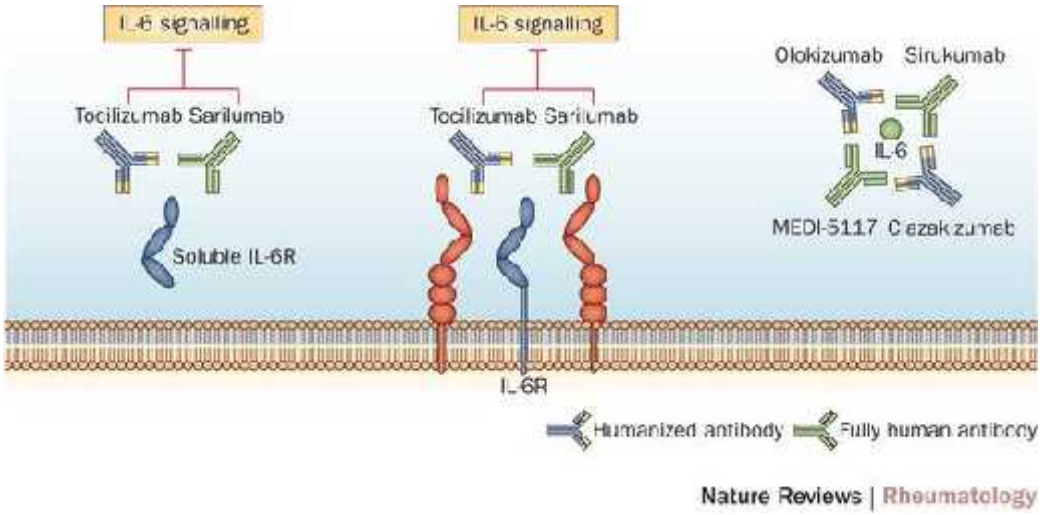
golimumab (human antibody)

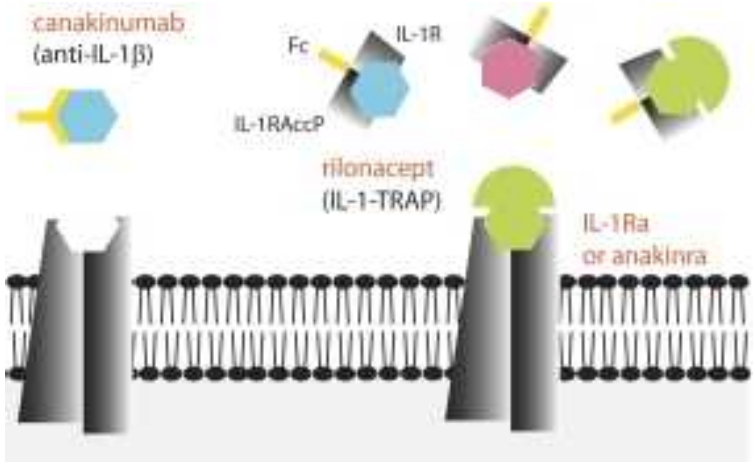
certolizumab pegol (PEGylated Fab'-fragment)



etanercept (soluble receptor)

The Players
Against IL-6 / IL-1



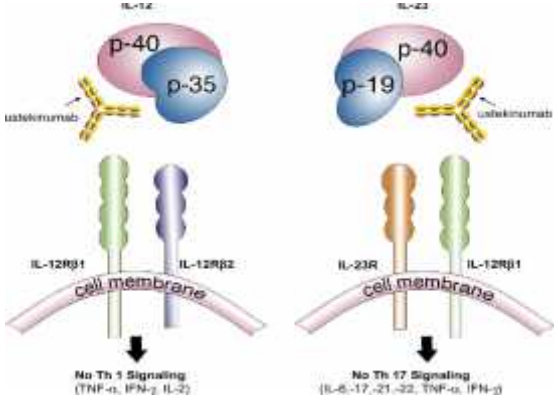


Tanaka T et al, CSHBP 2014
Doherty T et al, JLB 2011

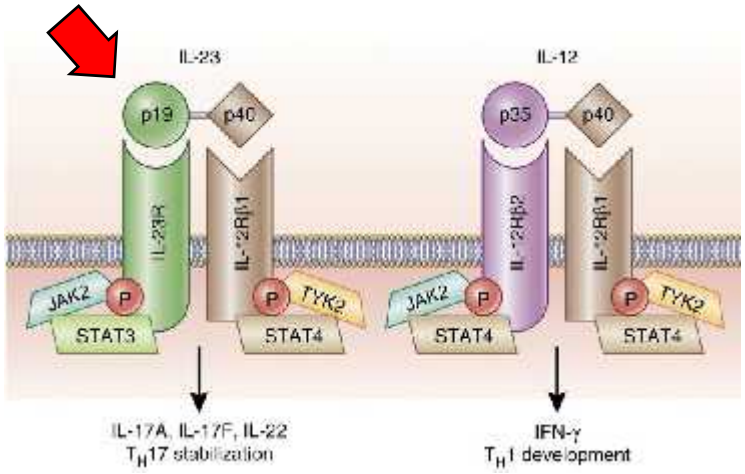
The Players

Against IL-23 / IL-17

against p40 subunit IL-12/-23

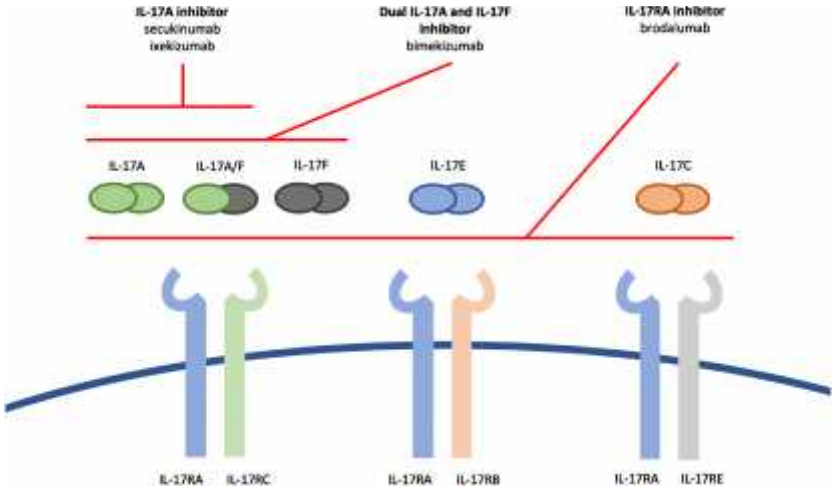


against p19 subunit IL-23



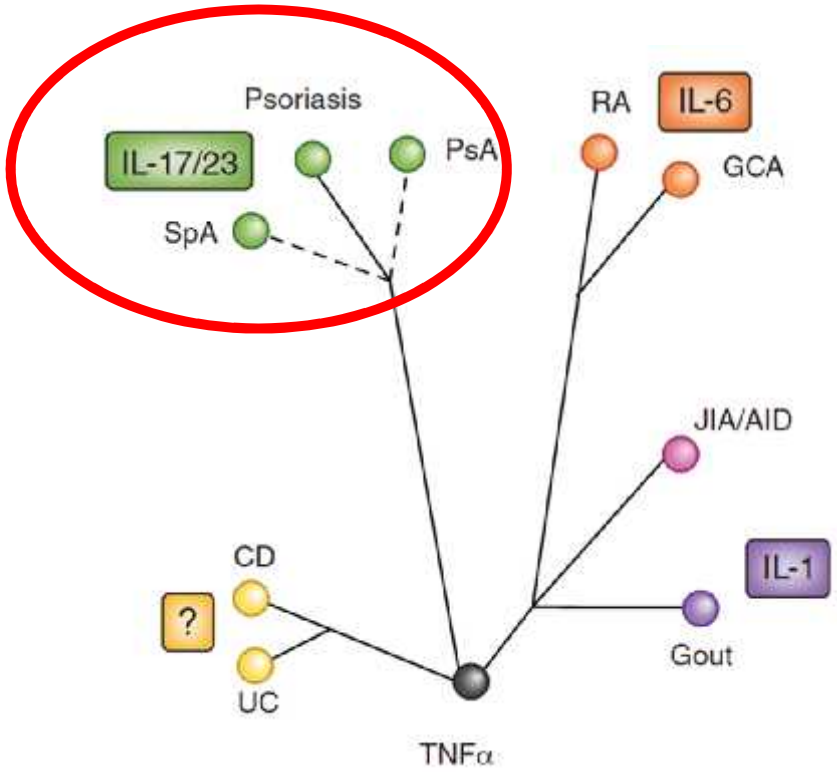
Risankizumab
Guselkumab
Tildrakizumab

against IL-17



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

The IL-23/-17 axis



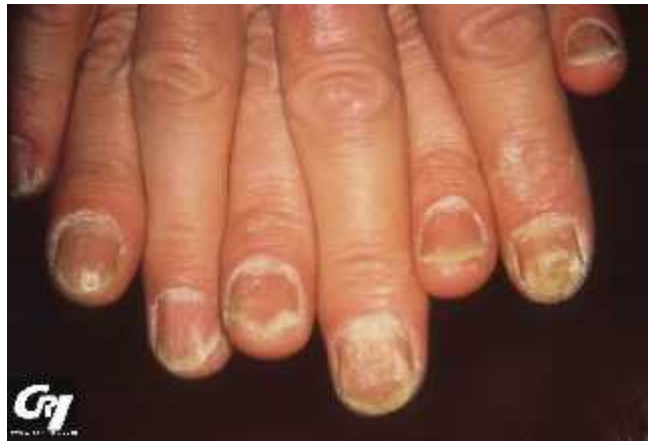
Psoriatic Arthritis
Patterns of disease

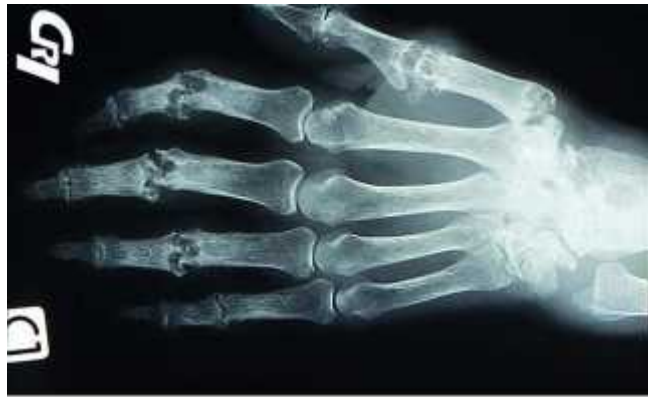
- Heterogeneous disease
  - Asymmetric oligoarthritis
  - Predominantly distal interphalangeal disease
  - Peripheral polyarthritis (rheumatoid-like)
  - Dominant axial disease (sacroiliitis/spondylitis)
  - "Arthritis mutilans" (a mutilating type of disease - digits)

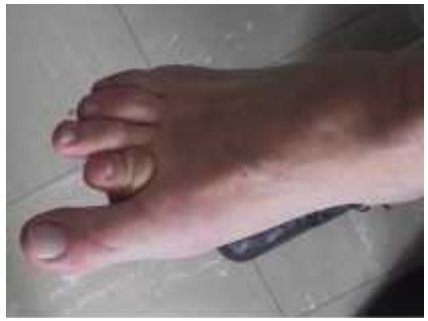
Eder & Gladman Curr Rheum Rep 2013

Psoriatic Arthritis
Common Findings

- Other common findings
  - Enthesitis (entheses: tendon/ligament attaches to the bone)
  - Dactylitis - sausage-shaped swelling of digits (40-50%)
  - Nail involvement







Brockbank JE Ann Rheum Dis 2015

www.cri-net.com

Psoriatic Arthritis….

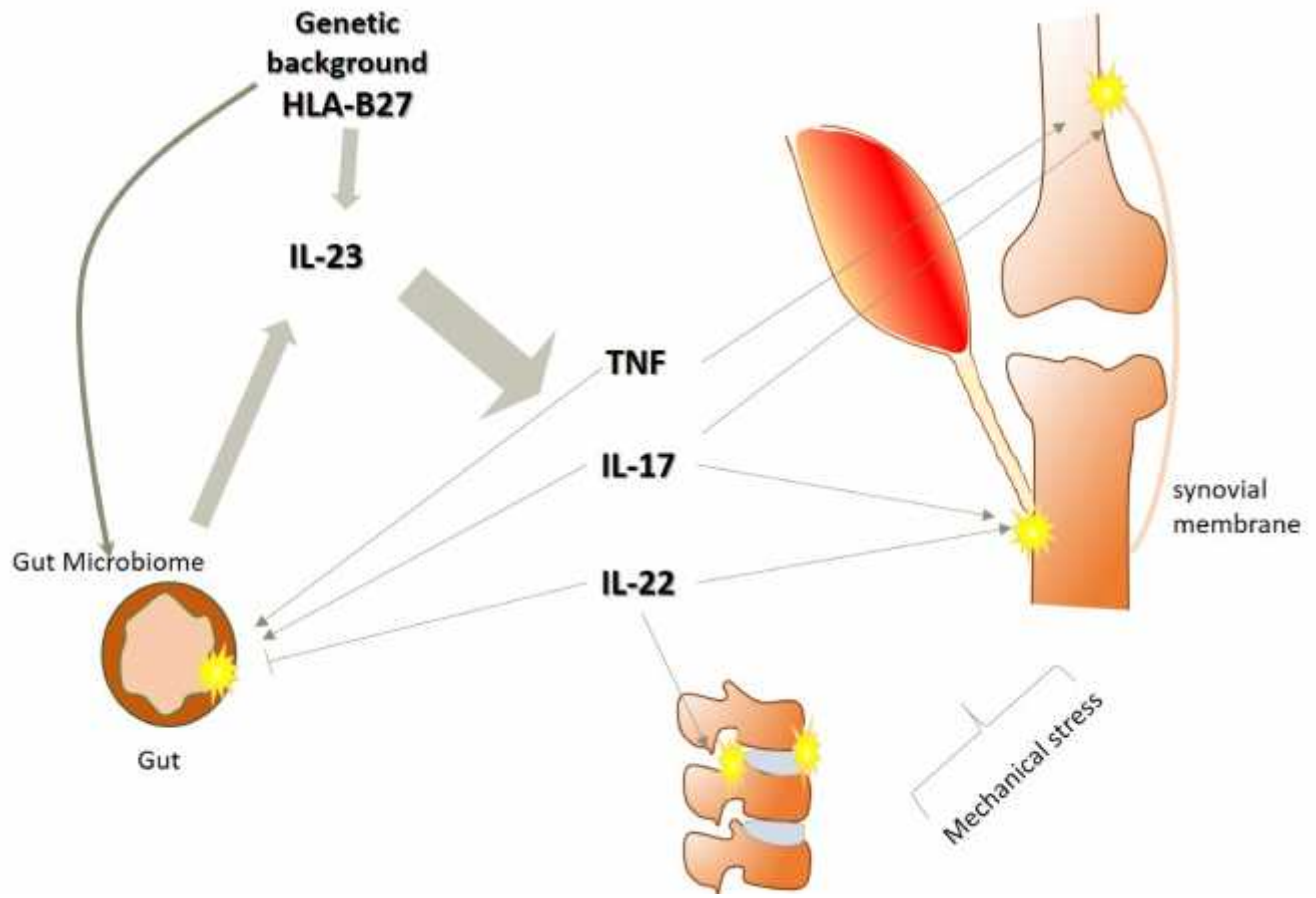
Or Psoriatic disease

- Psoriatic disease
  - ⇧ risk for IBD
  - ⇧ risk for Uveitis
  - Metabolic component
    - Diabetes
    - Obesity
      - ✓ Related to development of PsA and worsening psoriasis
    - Hypertension/CVD
      - ✓ Increased risk for CVD, not totally explained by classical risk factors
  - Psychological dysfunction
    - Inflammatory cytokines (e.g TNF) could be related to depression

Kimball AB J Am Acad Dermatol. 2008
Krishnadas R Brain Behav Immun 2016

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

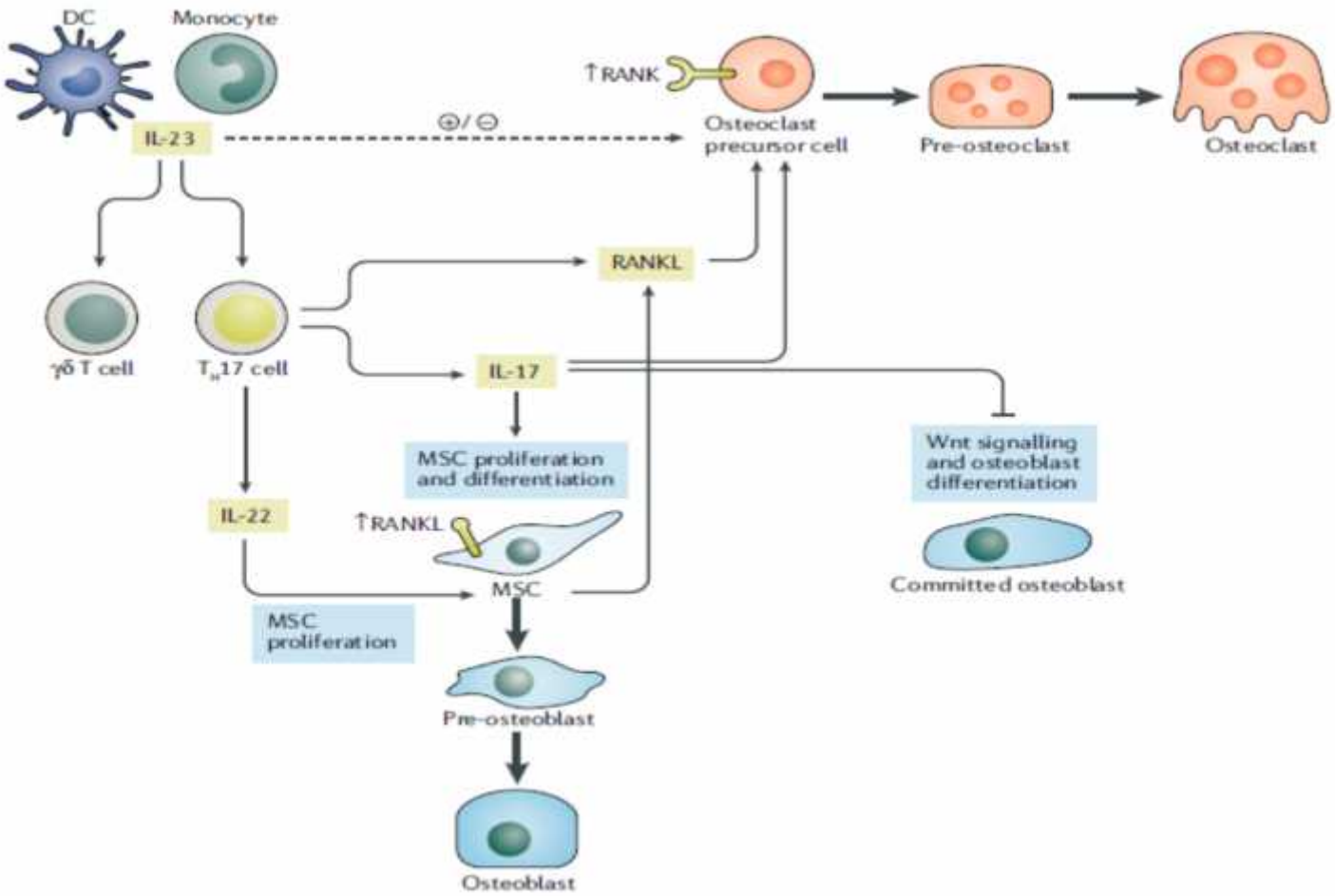
Why they work??



(modif from) Siebert S, Fragoulis GE, McInnes IB EULAR online course 2016

Psoriatic Arthritis

Pathogenesis

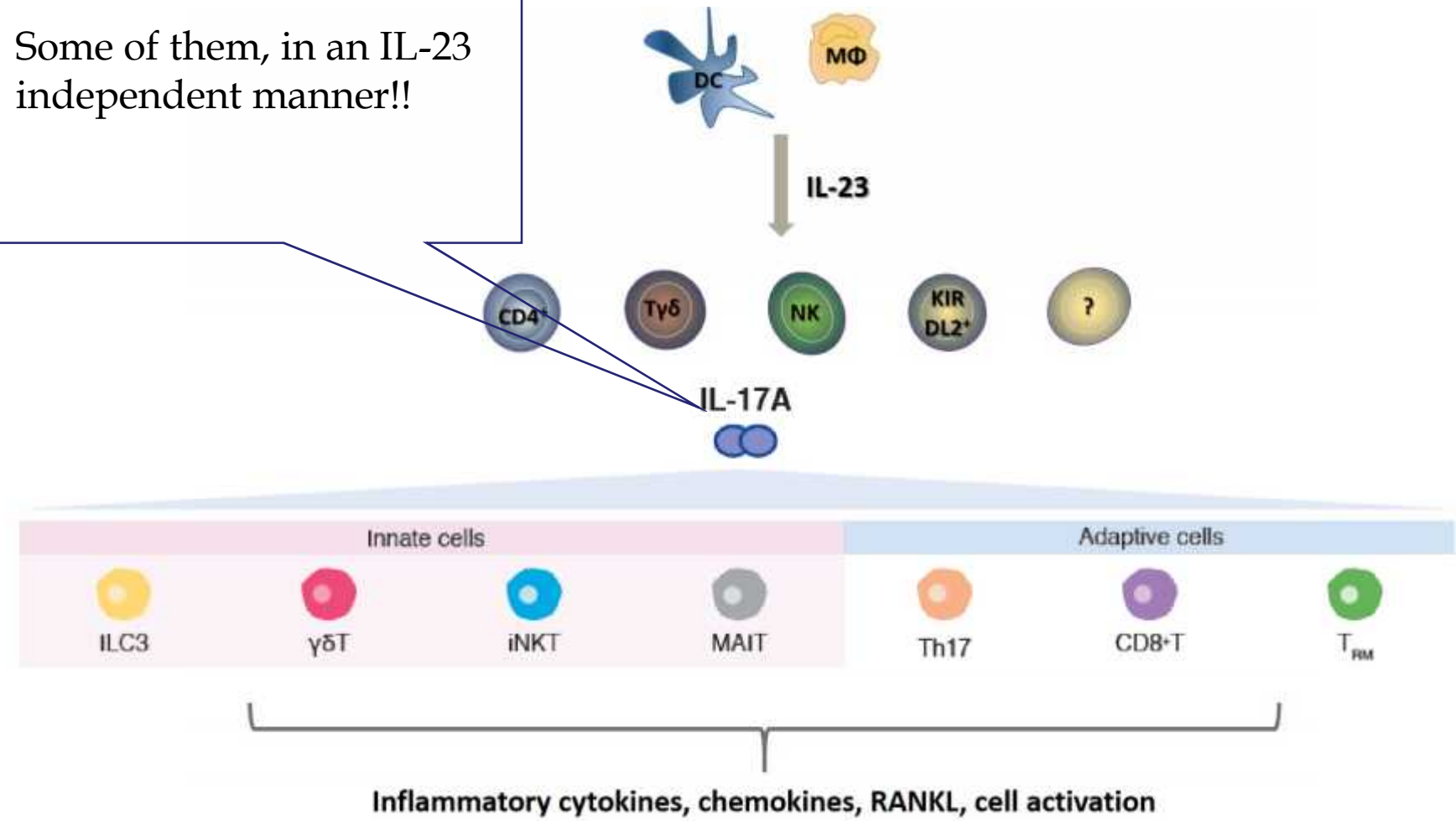


Veale D et al Lancet 2018
Gravallese E & Schett G Nat Rev Rheum 2018

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

Why they work??

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



Fragoulis GE, Siebert S, McInnes IB Ann Rev Med 2016

Treatment

Biologics

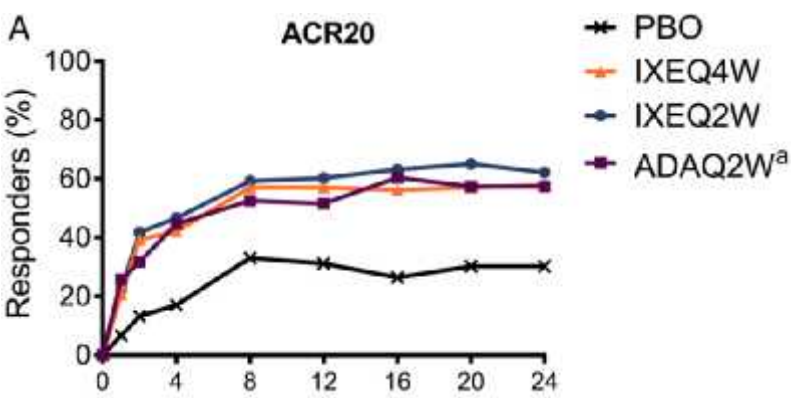
Molecule	PASI 75 (at week 24)	ACR 20 (at week 24)
Infliximab[23]	60%	54%
(5 mg/kg at weeks 0, 2, 6, 14, and 22)	(1%)	(16%)
Etanercept[26]	23%	59%*
(25 mg twice weekly)	(3%)	(15%*)
Adalimumab[29]	59%	57%
(40 mg every 2 weeks)	(1%)	(15%)
Golimumab[32]	56%	52%
(50 mg every 4 weeks)	(1%)	(12%)
Certolizumab pegol[34]	62%	64%
(400 mg at weeks 0 and 2 and then 200 mg every 4 weeks)	(15%)	(24%)
Ustekinumab[36]	57%	42%
(45 mg at weeks 0 and 4 and then every 12 weeks)	(11%)	(23%)
Secukinumab[40]	48%	51%
(150 mg at weeks 0, 1, 2, 3, and 4 and then every 4 weeks)	(16%)	(15%)

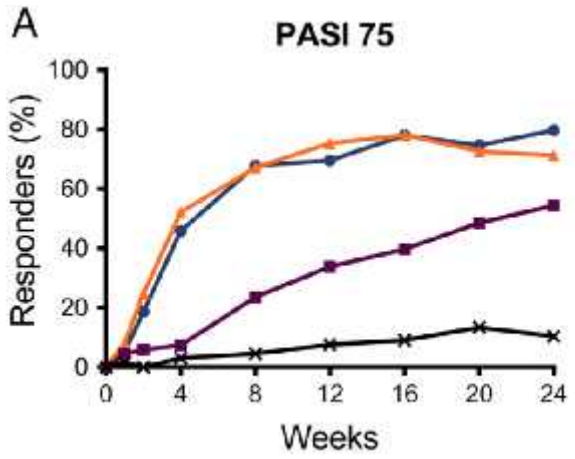
Ramiro S et al Ann Rheum Dis 2015
D'angelo S et al Open Access Rheum 2018

Θεραπεία

Anti-IL-17

- SPIRIT – 1
  - Phase III trial
  - Ixekizumab Vs Adalimumab Vs Placebo

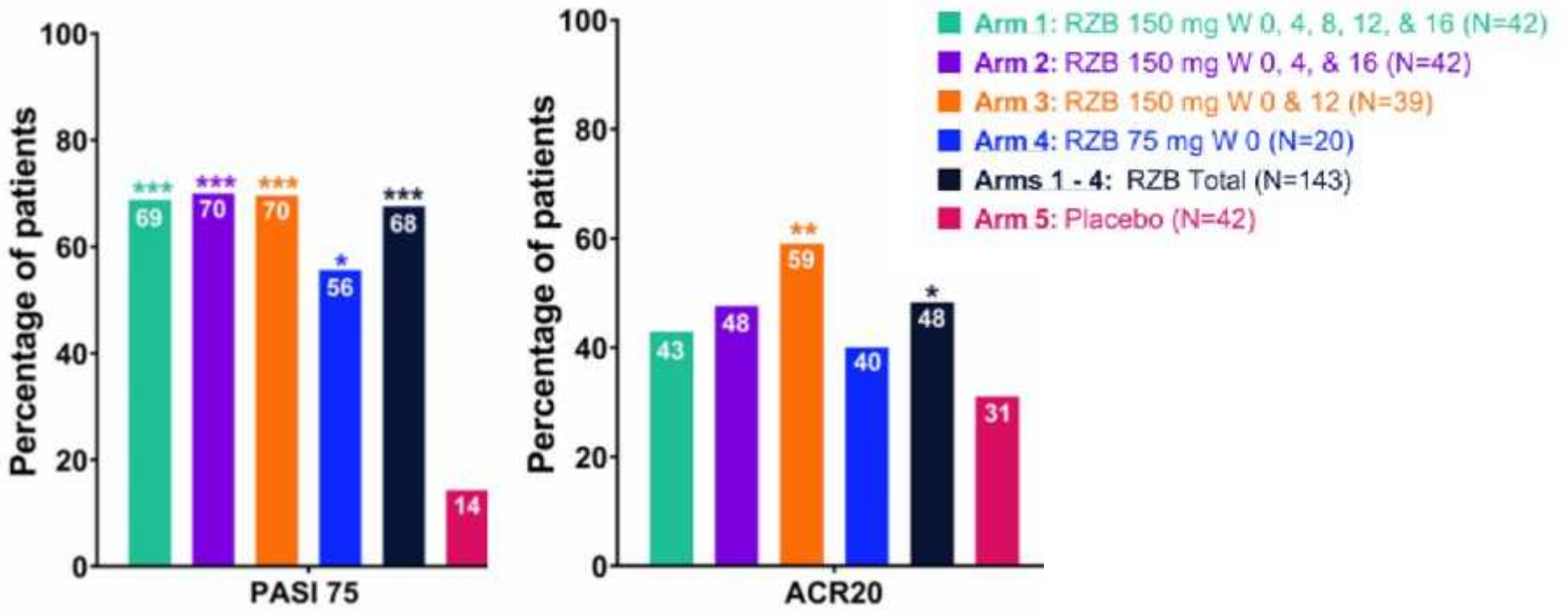




Ramiro S et al Ann Rheum Dis 2015
Noisette A Hochberg MC, Psoriasis: Target & Ther, 2018
Mease P et al Ann Rheum Dis 2018

Treatment

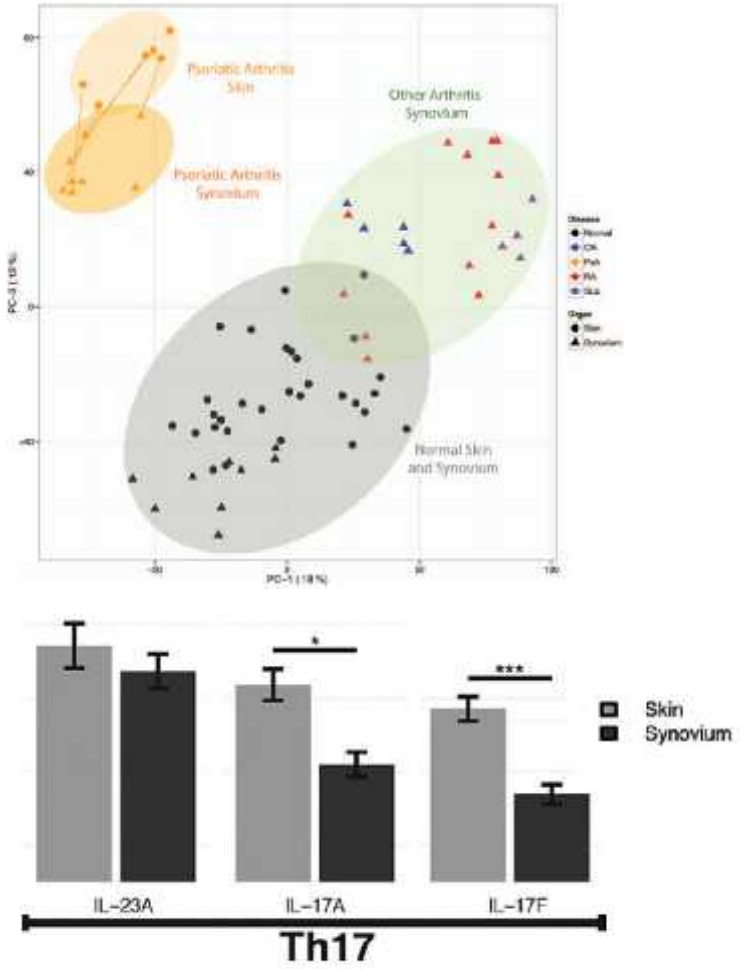
Anti-IL-23 (p19) (Risankizumab)



Mease et al EADV congress 2019 Madrid

Psoriatic Arthritis
synovial membrane Vs skin

- Δύσκολη μελέτη της ιστοπαθολογίας
- Similarities and differences
  - TNF pathway, VEGF, TGF-β1 and IL-6
    - More activated in synovial membrane
  - IL-23/-17 axis
    - More activated in skin



Belasco J et al Arthr Rheum 2015

Treatment

not one size fits all

- Skin
  - Anti-IL-23/-17 class > anti-TNF in PASI75 (network meta-analysis)
    - head-to-head in psoriasis
      - ✓ Ustekinumab, Ixekizumab >> Etanercept
      - ✓ Guselkumab > Adalimumab
      - ✓ Tildrakizumab > Etanercept
      - ✓ Secukinumab > Ustekinumab
      - ✓ Ixekizumab>Adalimumab (PsA)
      - ✓ Risankizumab > Ustekinumab ?
      - ✓ Ixekizumab >(?) Secukinumab ?

Gordon K et al Lancet 2018
Reich K et al Lancet 2017
Lin VW et al Arch Derm 2012
Griffiths CE et al NEJM 2010
Griffiths CE et al Lancet 2015
Blauvelt et al J Am Acad Dermatol 2017
Paul J et al Blauvelt et al J Am Acad Dermatol 2018

- Joints
  - Contradictory results

Strand V et al Rheumatol Ther 2017
Nash P et al Rheumatol Ther 2018
McInees IB et al J Comp Eff Res
Paul et al Br J Derm 2018
Warren et al Br J Dermat 2018

Psoriatic Arthritis

Enthesitis

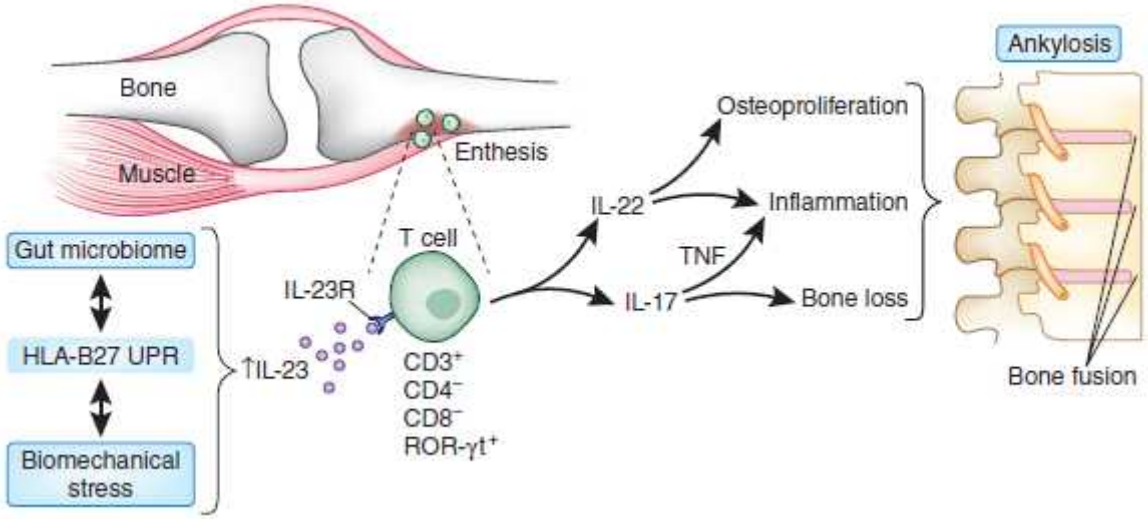
- Why enthesitis in PsA?
- Less resistance to mechanical stress? (analogy to Koebner)
- Mechanical stress
  - More often in lower limbs
  - Unloaded mice: less enthesitis

D'Agostino NA Clin Exp Rheum 2009
Schett G Nat Rev Rheum 2017
Jacques P Ann Rheum Dis 2013

Psoriatic Arthritis

Enthesitis

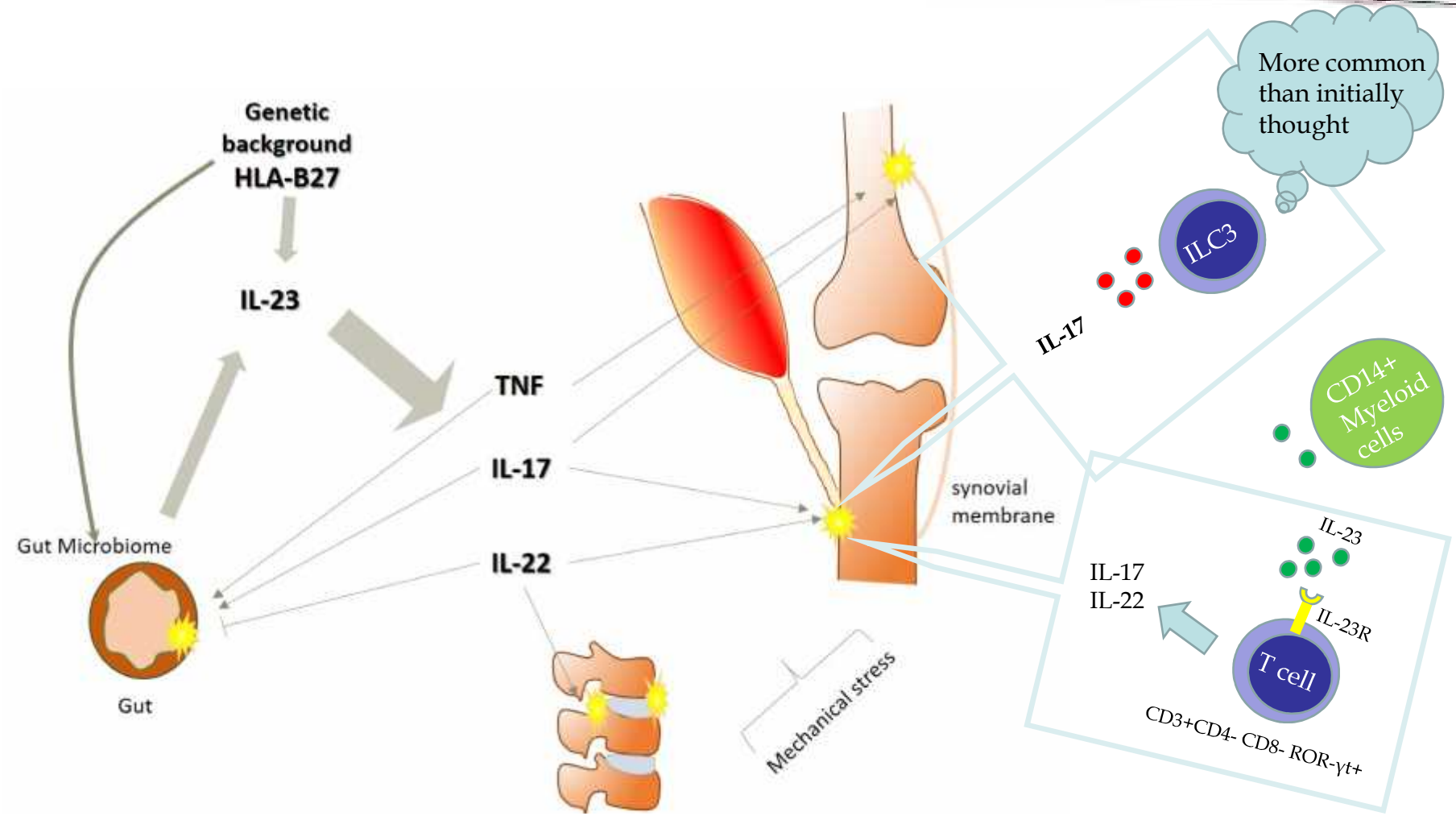
- Enthesis organ "synovio-entheseal concept"
  - bursae, tendon hseaths, fibrous tissue, fat pads, fasciae
- Can everything start from the entheses ??



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

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

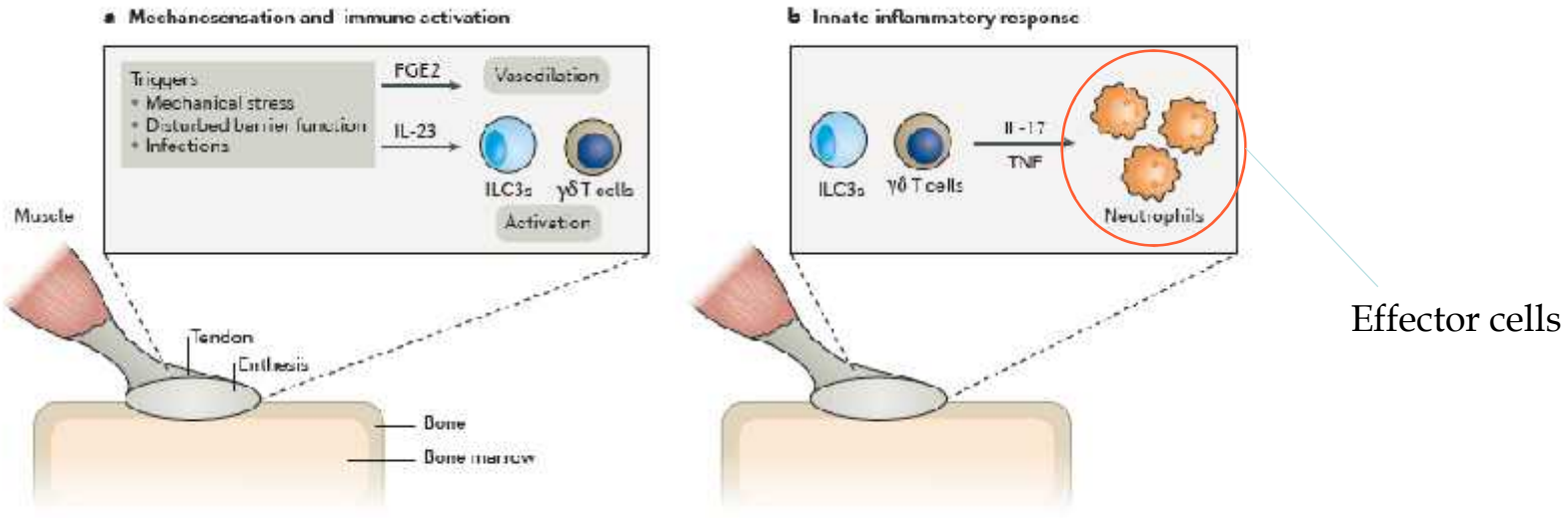
Why they work??



(modif from) Siebert S, Fragoulis GE, McInnes IB EULAR online course 2016

Psoriatic Arthritis

Enthesitis

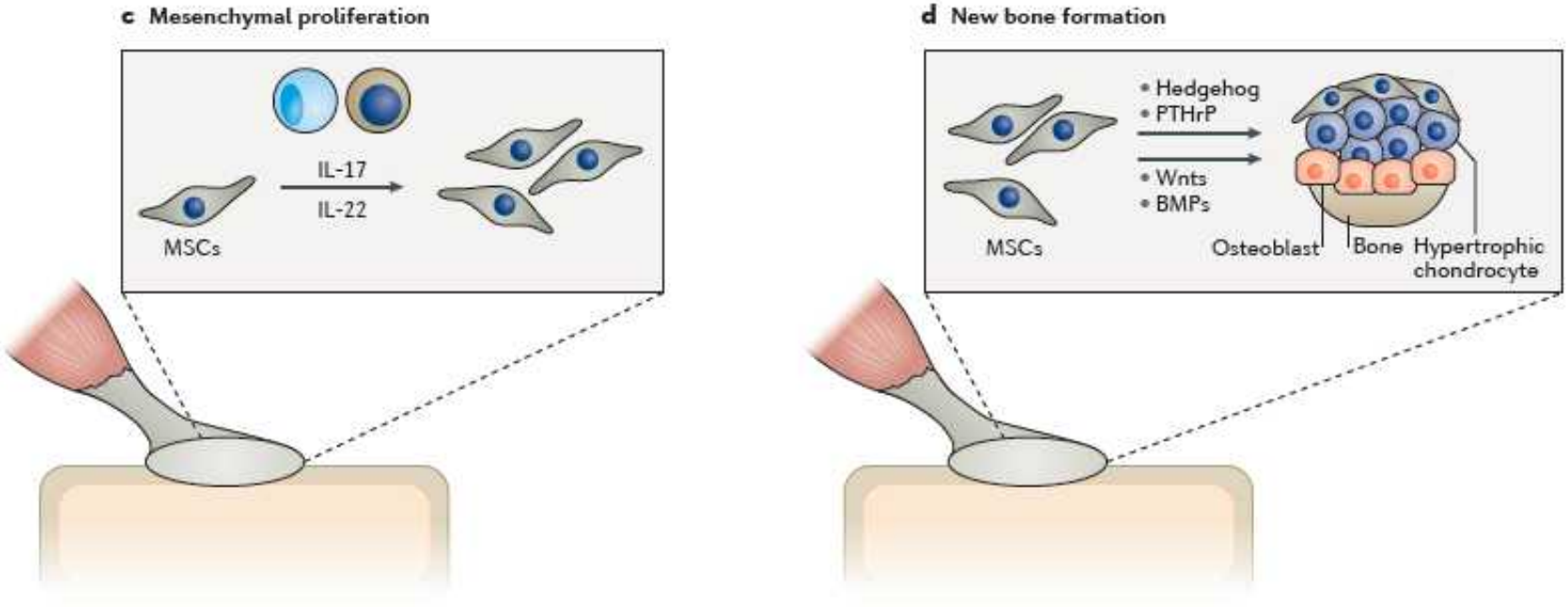


- PGE2
  - Response to mechanical stress
  - Mesenchymal cells – cox2 expression
  - Induces IL-17 production

Schett G et al Nat Rev Rheum 2017

Psoriatic Arthritis

Enthesitis



Schett G et al Nat Rev Rheum 2017
Bridgewood C et al, ARD 2019

Enthesitis

Treatment

- NSAIDs
  - Μπορεί να είναι αποτελεσματικά (> αρθρίτιδα)
    - PGE2
  - DMARDs
    - Περιορισμένα δεδομένα
    - SSA: μη αποτελεσματική
    - MTX: ενδεχομένως
- Βιολογικά
  - Anti-TNF
    - Αποτελεσματικοί
  - Anti-IL-23/ Anti-IL-17
    - Αποτελεσματικοί
    - Ustekinumab > anti-TNF (ECLIPSA)

Orbai AM A et al J Rheum 2014
Rose S et al J Rheum 2014
Schafer P et al Cell Sign 2014
Sakkas LI et al Semin Arthr Rheum 2013
Araujo EJ Semin Arthr Rheum 2018

Psoriatic Arthritis

Axial Disease

- cDMARDs
  - Not efficient
- Studies designed for PsA axial disease
  - are awaited
- First biologic
  - Anti-TNF
    - First choice ??
  - Secukinumab (anti-IL-17)
    - Good results
    - Approved for AS

Kavanaugh A et al Ann Rheum Dis. 2016
Gossec L et al Ann Rheum Dis 2016
Poddubny et al Ann Rheum Dis 2013

Axial spondylartropahty
IL-17 but not IL-23…

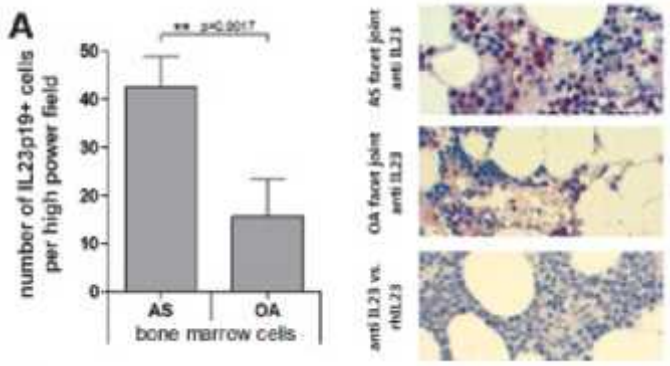
- anti-IL-17 works but not anti-IL-23 ??
- Ustekinumab
  - Good results in small open-label studies
  - phase III trials in AS & non-radiographic axSpA
    - Not achieved primary end-points
- Risankizumab
  - Did not reach primary endpoints in AS

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

Axial spondylartropahty

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**
  - Possible IL-17 production independent of IL-23

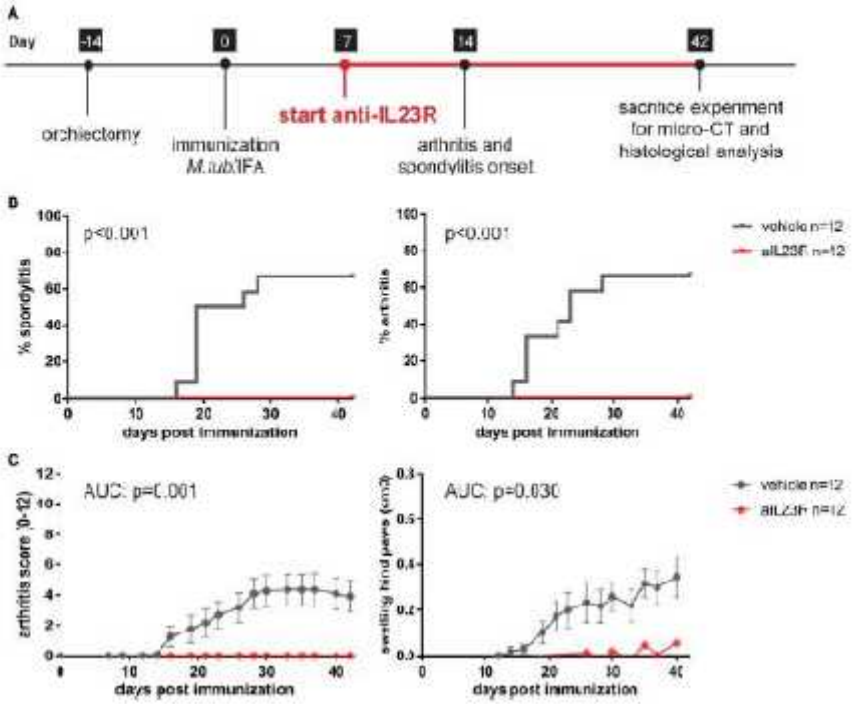


Appel H et al Arthr & Rheum 2013
Siebert S et al Ann rheum Dis 2018
DG McGonagle et al ARD 2019

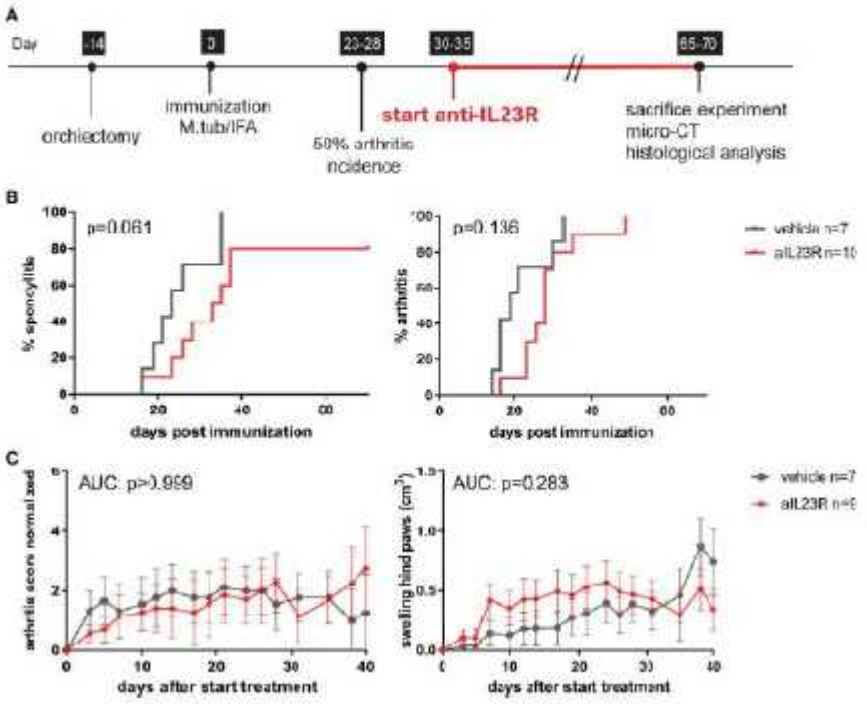
IL-23

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

Comorbidities

Inflammatory Bowel Disease and IL-17

- Anti-IL-17 negative results from Crohn's Disease clinical trials
- Possible pathogenetic mechanisms
  - Candida overgrowth (IL-17 offers fungal protection)
  - Impairment in Occludin localization (tight junction protein)
  - IL-23 blockade: retain basal levels of IL-17
    - ✓ Production of IL-17 ***independent of*** IL-23
  - New cases?? Extremely rare
    - 7355 pts with 16.226 patient-year f/u
    - 30 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
Schreiber et al ARD, 2019

Comorbidities
Hidradenitis Suppurativa

- Chronic inflammatory skin disease
  - subcutaneous painful nodules, areas rich in apocrine glands
- 0.5-2% of the general population
- Association with cardiometabolic clinical conditions
  - Diabetes, obesity, hypertension
  - ARDs: SpA and Crohn's Disease
- Pathogenesis
  - Genetic factors (30% familial cases)
  - Intrinsic activation of keratinocytes
  - Hyperkeratosis
  - Bacterial biofilm formation

Constantinou et al Ther Adv Mus Res 2019 (Under Review)
Rontags Semin Arthr Rheum 2019
Van der Zee et al Br J Dermat 2010

Comorbidities

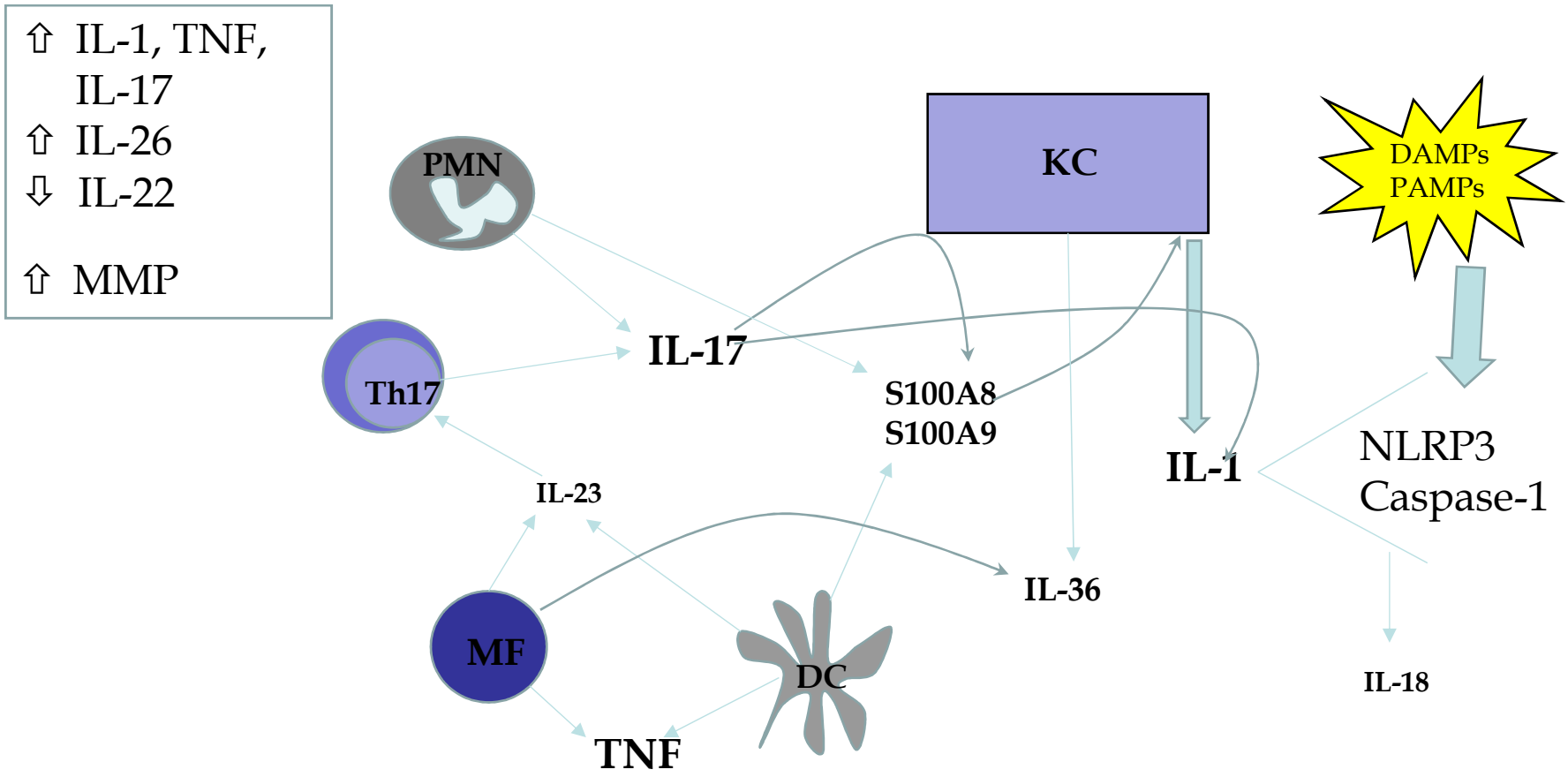
Hidradenitis Suppurativa / Tissue Level

- IL-1β, TNF, IL-17, IL-23 are ⇧ increased
- TNF
  - is produced by dendritic cells and macrophages and its levels are associated with HS severity.
- IL-17 is produced by neutrophils, Th17 cells
  - might drive production of IL1-β by KC activating NALP3
- IL-1
  - keratin fibers etc might act as PAMPs and DAMPS and activate inflammasome
  - KCs intrinsically activated

Constantinou et al Ther Adv Mus Res 2019 (Under Review)
Rontags Semin Arthr Rheum 2019
Van der Zee et al Br J Dermat 2010

Comorbidities

Hidradenitis Suppurativa



Constantinou et al Ther Adv Mus Res 2019 (Under Review)

Comorbidities

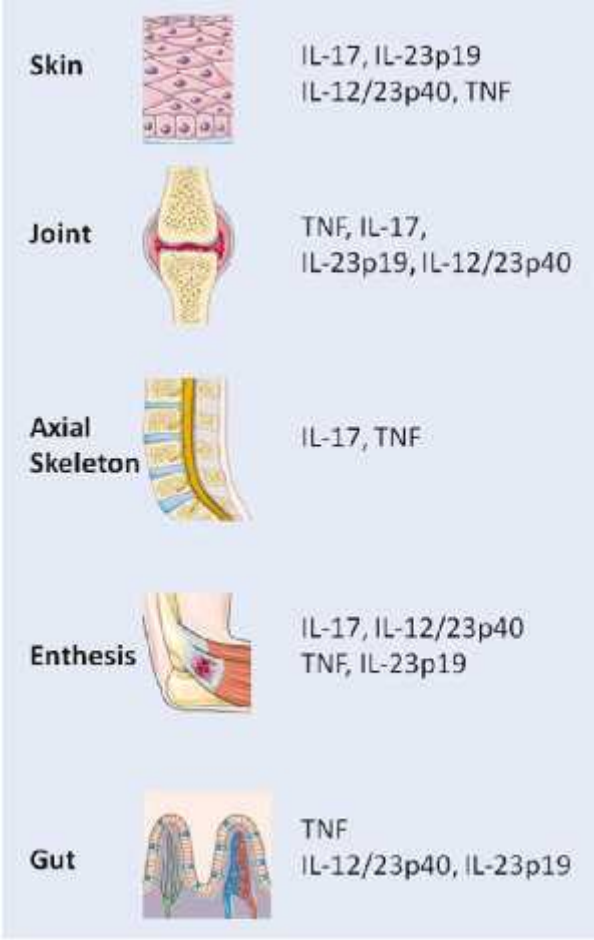
Hidradenitis Suppurativa / Treatment

- Adalimumab (approved)
  - Two largest phase-3 trials (Pioneer I and II)
    - HISCR, was achieved, at week 12 in 41.8% and 58.9% (PBO ~ 26%)
- Infliximab
  - Performed better than ADA (small study)
- Kineret
  - HISCR was achieved in 78% at week 12 compared to 30% in PBO
- Anti-IL23 (Ustekinumab/Guselkumab) & anti-IL17
  - Promising results
    - 60-80% response
  - Phase 2 trials ongoing

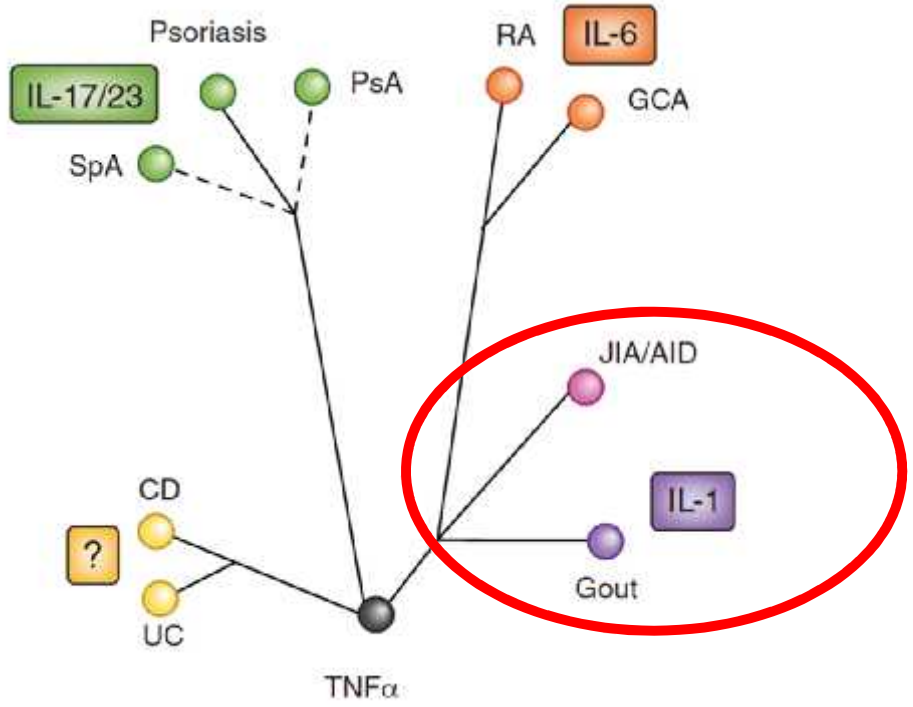
Kimball AB et al NEJM 2016
Van Rappard DC et al, J Dermatolog Treat 2012
Tzanetakou V, JAMA Dermatol 2016

Summary for PsA/SpA

- Treatment dependent on
  - Cardinal feature
    - Cytokine based classification?



IL-1 & the inflammasome



IL-1 family

Essentials

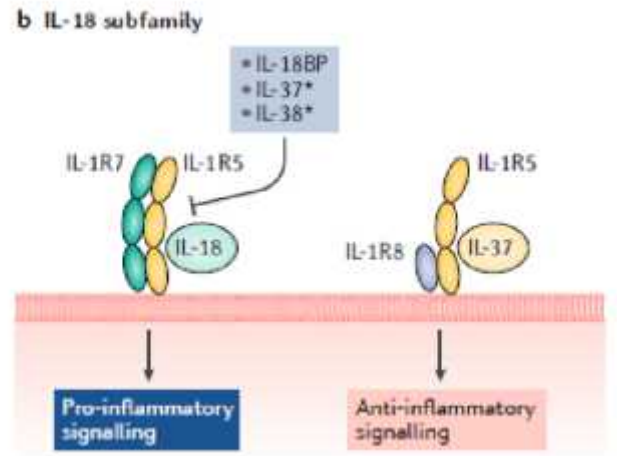
- The IL-1 family of cytokines contains 11 members that either promote inflammation or limit inflammation.
- Main functions: innate immune reactions and inflammation, rather than acquired immunity
- IL-1β has emerged as pivotal for promoting inflammation, particularly in autoinflammatory diseases
- A fundamental process in IL-1 family signaling is the formation of a heterotrimeric complex containing the ligand, receptor and co- receptor
- 3 subfamilies on the basis of shared receptor or co- receptor binding

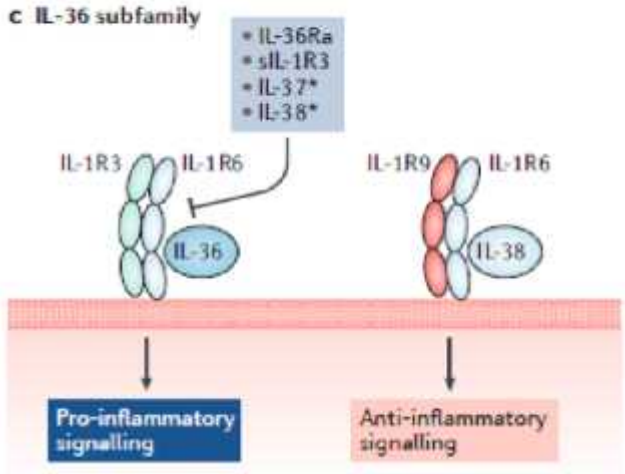
Dinarello CA et al. Nat Rev Rheum 2019

IL-1

Let's meet the family / IL-18 and IL-36 subfamilies

- IL-18 subfamily
  - IL-18 and IL-37 and bind IL-1R5 (also known as IL-18Rα)
  - IL-18 induces pro- inflammatory signaling pathways.
  - IL-18 is specifically antagonized by IL-18 binding protein (IL-18BP), which has an unusually high affinity for IL-18.
  - IL-37 promotes anti- inflammatory effects via the co-receptor IL-1R8.
- IL-36 subfamily
  - IL-36α, IL-36β, IL-36γ, IL-36Ra and IL-38 which bind IL-1R6 (also known as IL-36R)
  - IL-36 cytokines promote pro- inflammatory signalling pathways that are specifically antagonized by IL-36 receptor antagonist (IL-36Ra).
  - IL-38 is anti- inflammatory.



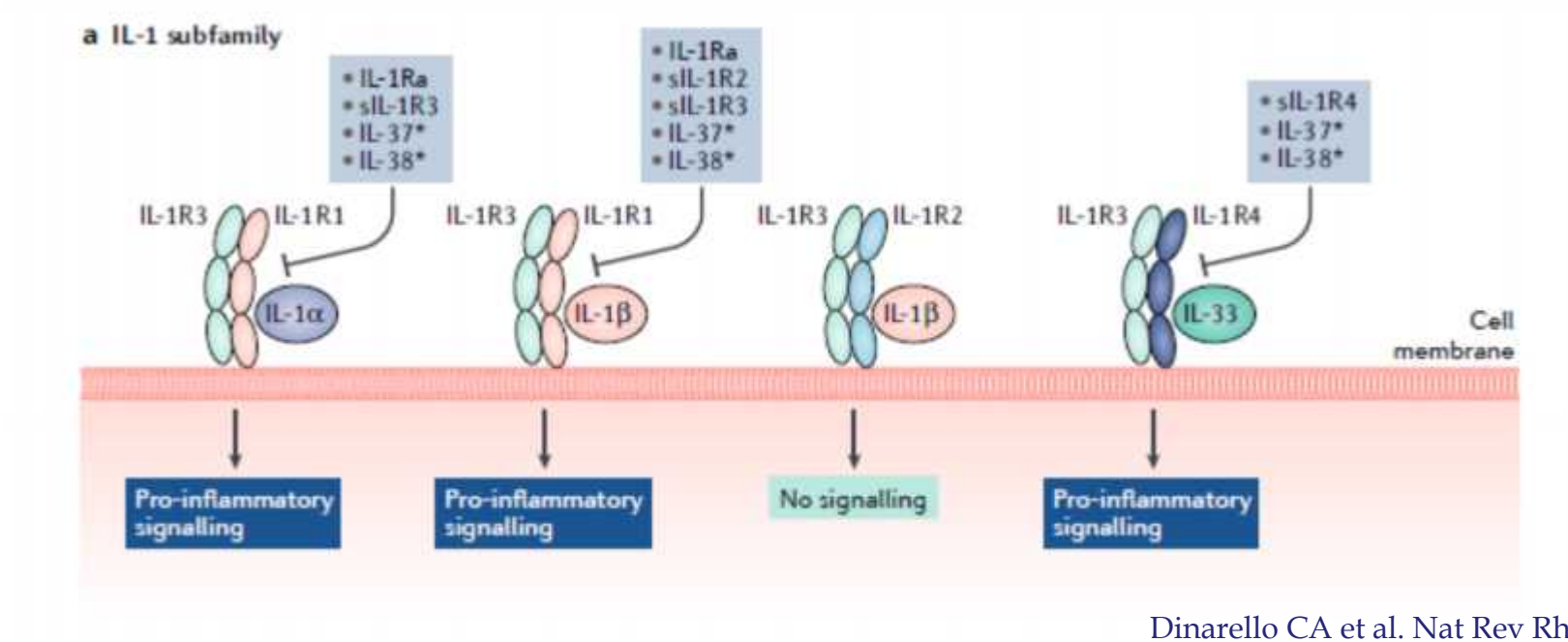


Dinarello CA et al. Nat Rev Rheum 2019

IL-1

Let's meet the family – IL-1 subfamily

- IL-1 subfamily
  - IL-1α, IL-1β and IL-33 bind the co- receptor IL-1R3
  - promote pro- inflammatory signaling pathways
  - IL-1 receptor antagonist (IL-1Ra) specifically reduces the activities of IL-1α and IL-1β
  - Soluble versions of IL-1 family receptors also exist, (e.g sIL-1R2) specifically binds and neutralizes IL-1β



Dinarello CA et al. Nat Rev Rheum 2019

IL-1 subfamily

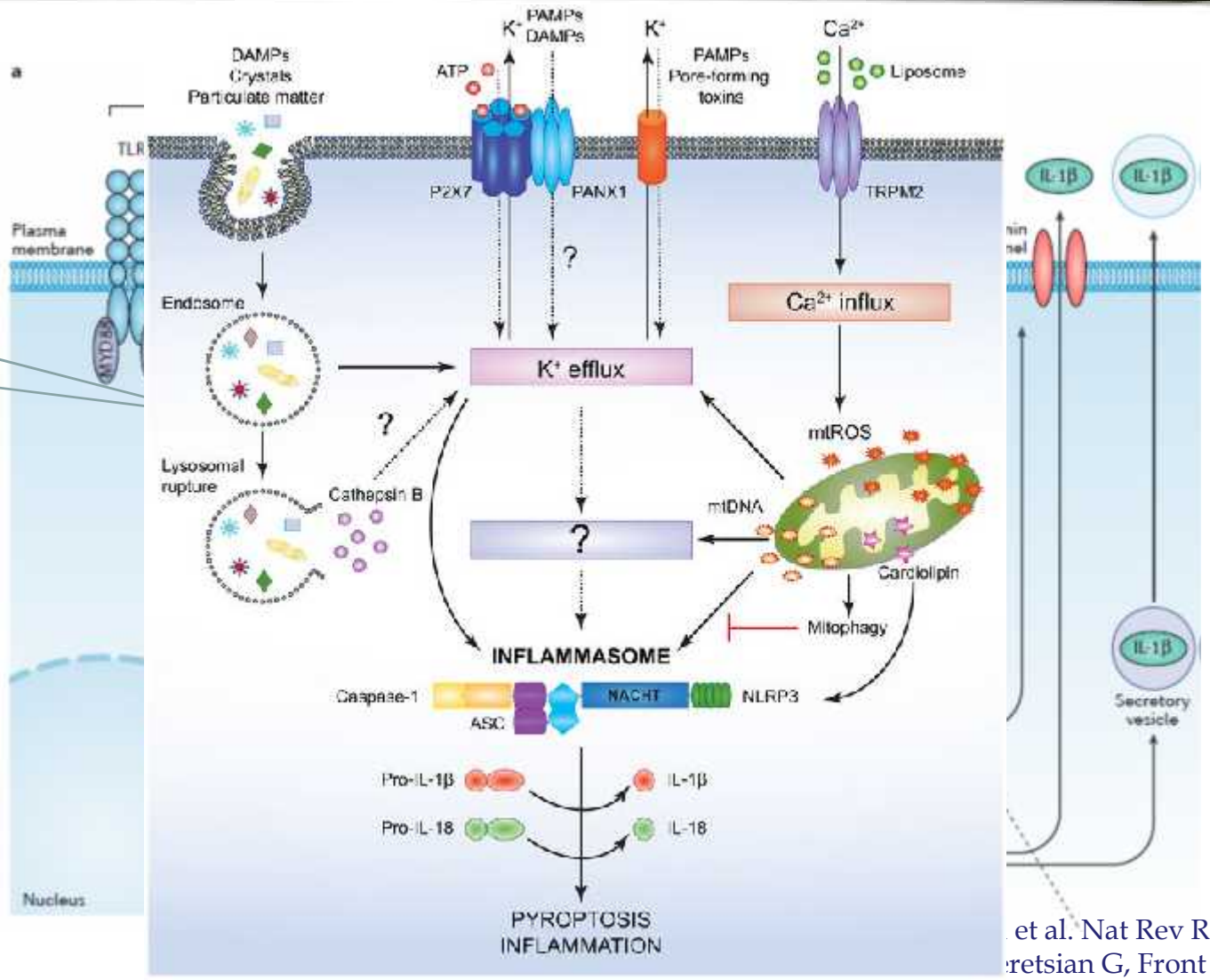
Differences?

- pro- IL-1α
  - Is constitutively present in mesenchymal cells throughout the body
  - Is active
  - Rarely in the circulation in disease states. Primary local role, not systemic
- pro- IL-1β
  - Is only constitutive in resident macrophages
  - requires processing via caspase-1 to become active protein
  - Is found in the circulation

Dinarello CA et al. Nat Rev Rheum 2019

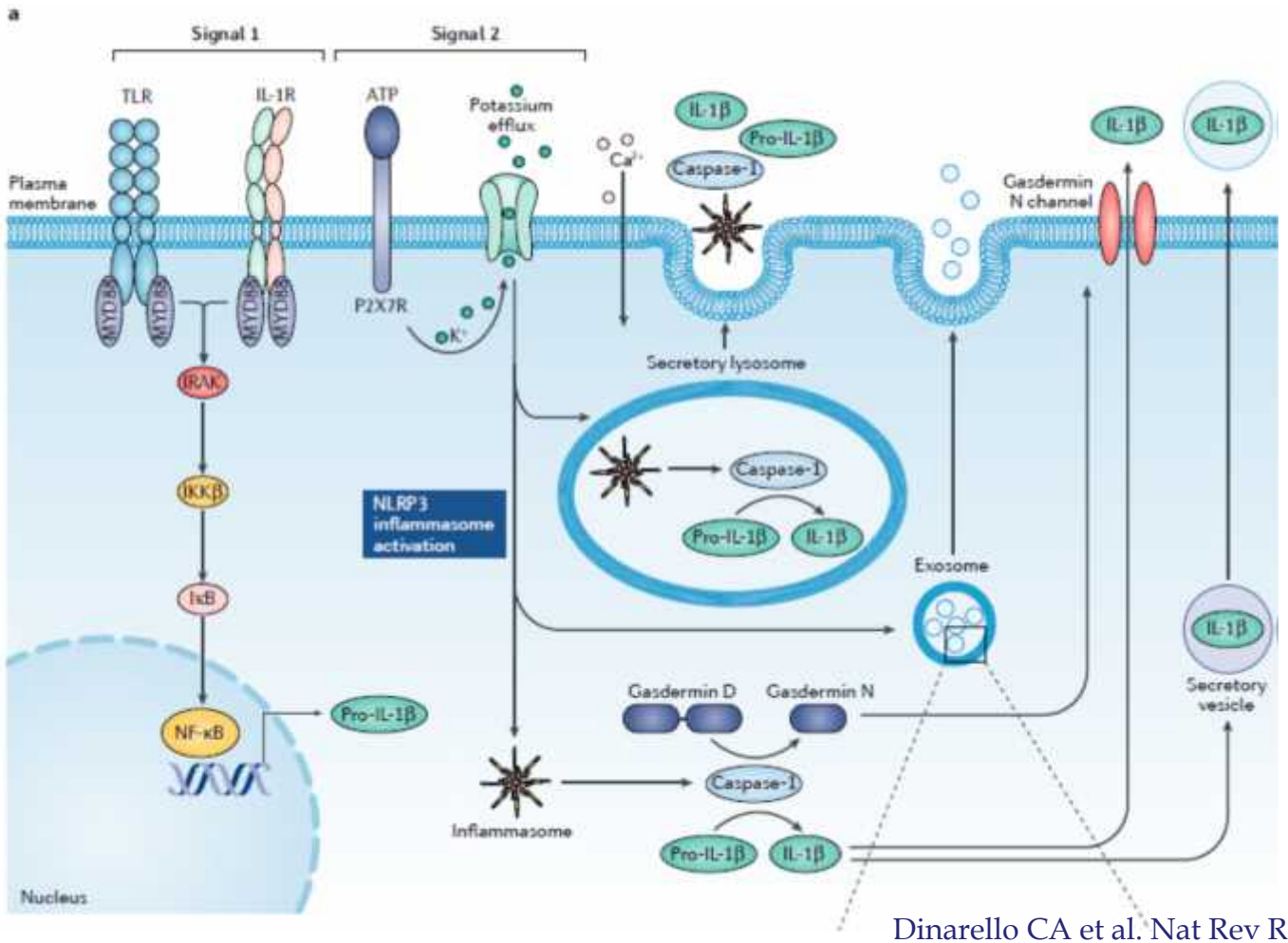
IL-1β
Production and secretion

IL-1R associated kinases



et al. Nat Rev Rheum 2019
retsian G, Front In Immun 2014

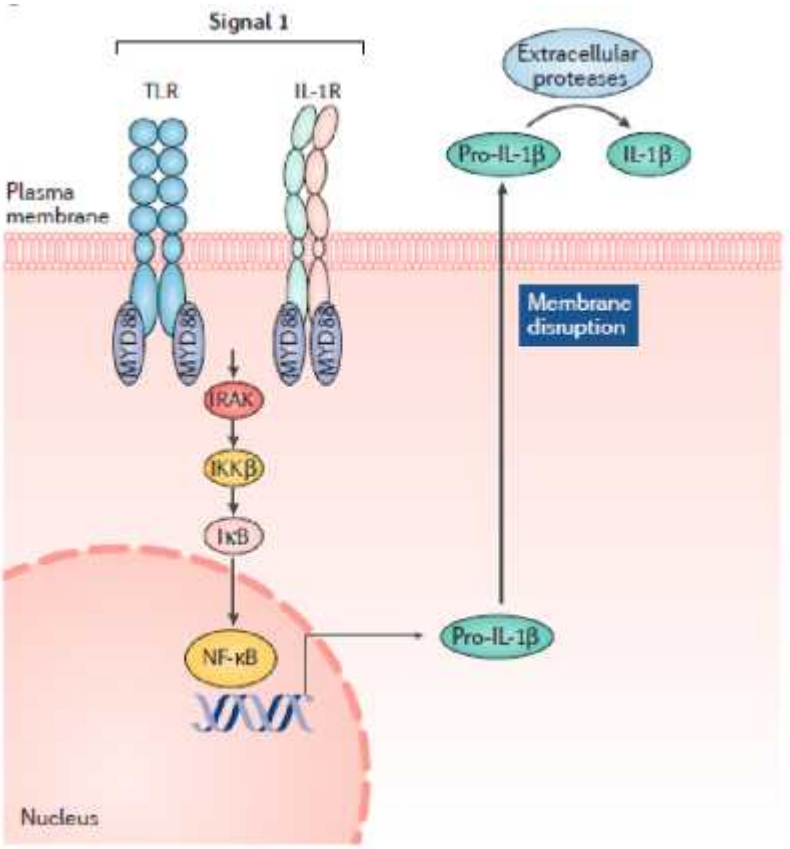
IL-1β
Production and secretion



Dinarello CA et al. Nat Rev Rheum 2019
Saxena M, Yeretsian G, Front In Immun 2014

IL-1β
Production and secretion

- Alternatively
  - Hypoxia, stress etc
  - Caspase-1 independent
  - Extracellular proteases

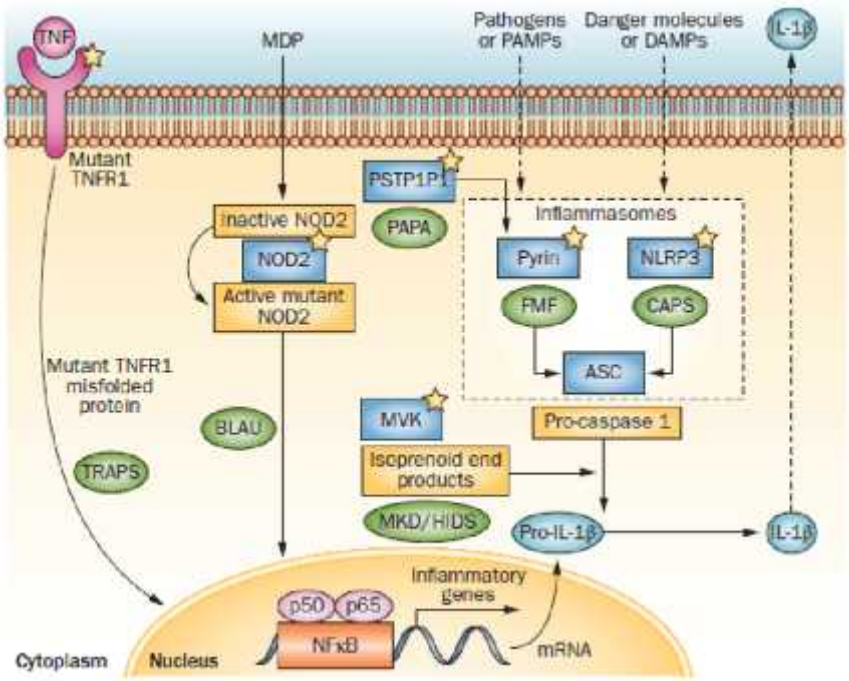


Dinarello CA et al. Nat Rev Rheum 2019

IL-1

Autoinflammatory diseases

- Cryopyrin-Associated Periodic Syndromes (CAPS)
  - Autoinflammatory diseases caused by mutations in *NLRP3 (member of the NOD-like receptor family)*
    - Gain-of-function mutations
    - Chronic, systemic and local inflammation due to active IL-1β
- FMF
  - mutant pyrin (part of the inflammasome complex)
    - associates with the inflammasome adaptor protein ASC
    - increase IL-1β processing

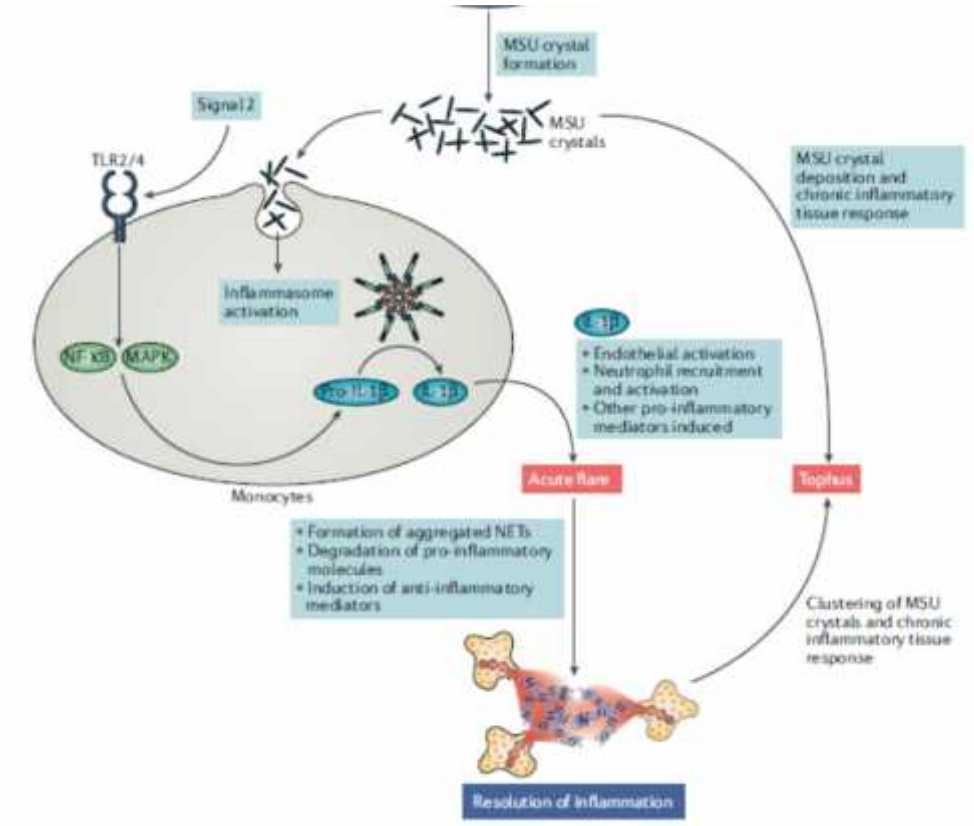


Ozen S & Bilginer Y. Nat Rev Rheum 2013

IL-1

Gout

- Fatty acids signaling via TLR2 can provide the 1st signal for the synthesis of pro- IL-1β
  - might account for the association between gout flares and dietary factors.
- MSU crystals are engulfed by synovial macrophages
  - NLRP3 is activated and caspase-1 cleaves pro- IL-1β to release mature IL-1β into the synovial space



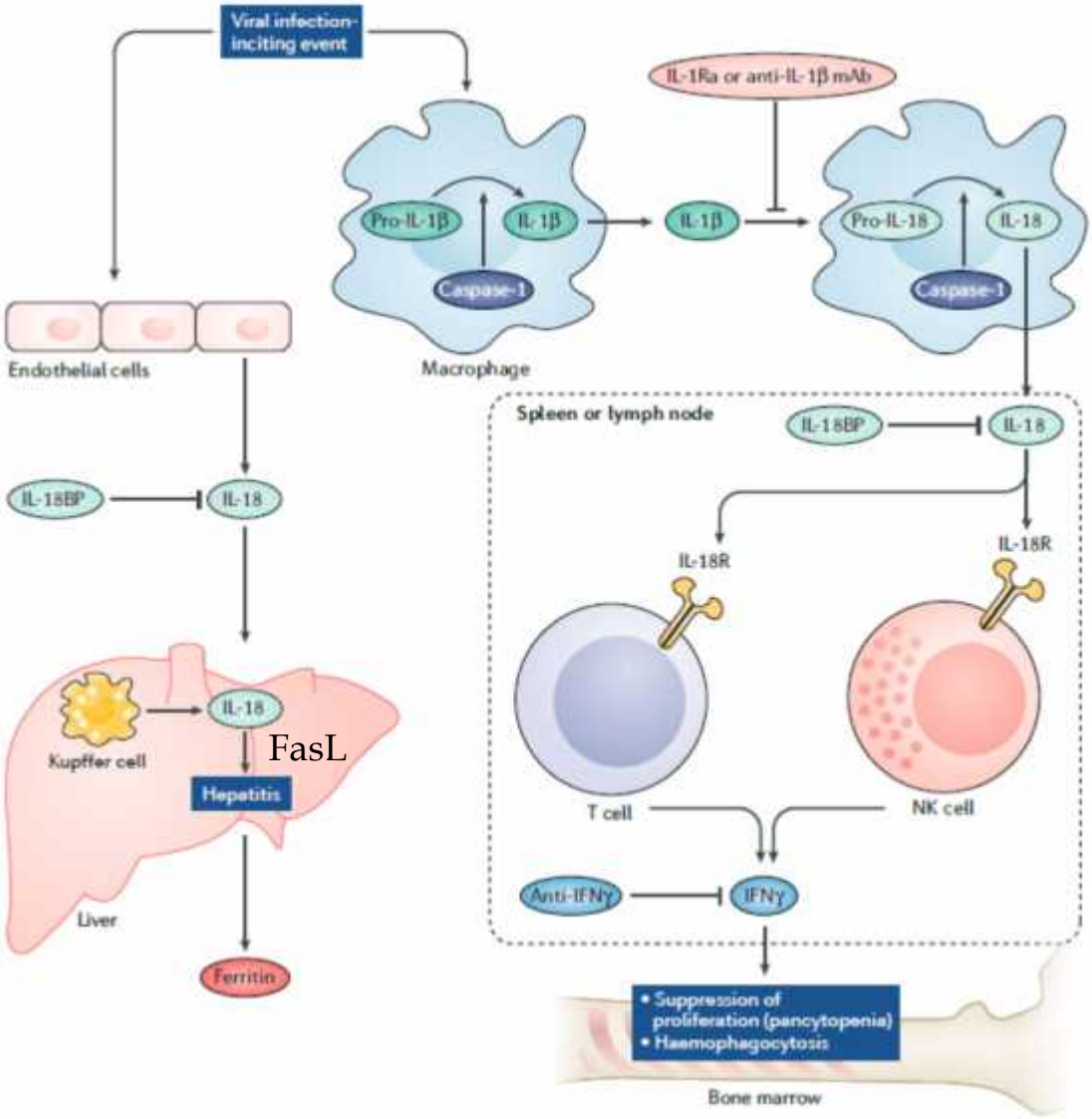
Major JJ et al Nat Rev Rheum 2018

IL-1

JIA, Still, MAS

- Not clear why IL1-b plays role
  - Is elevated in the circulation or
  - released from cultured monocytes ex vivo

- Neutralization of IL-18 with IL-18BP (Tadekinig alfa)
- might be the best treatment option for treating Still's and MAS

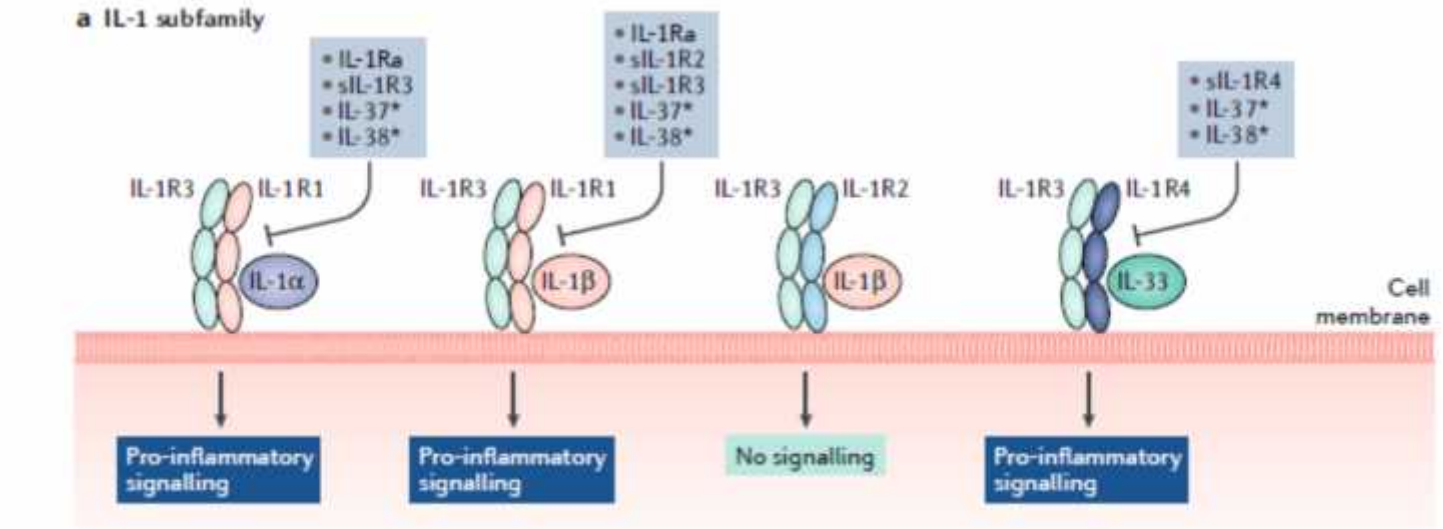


Dinarello CA et al. Nat Rev Rheum 2019
Kiltz U et al, ARD 2018
Gabay C et al, ARD 2018

IL-1

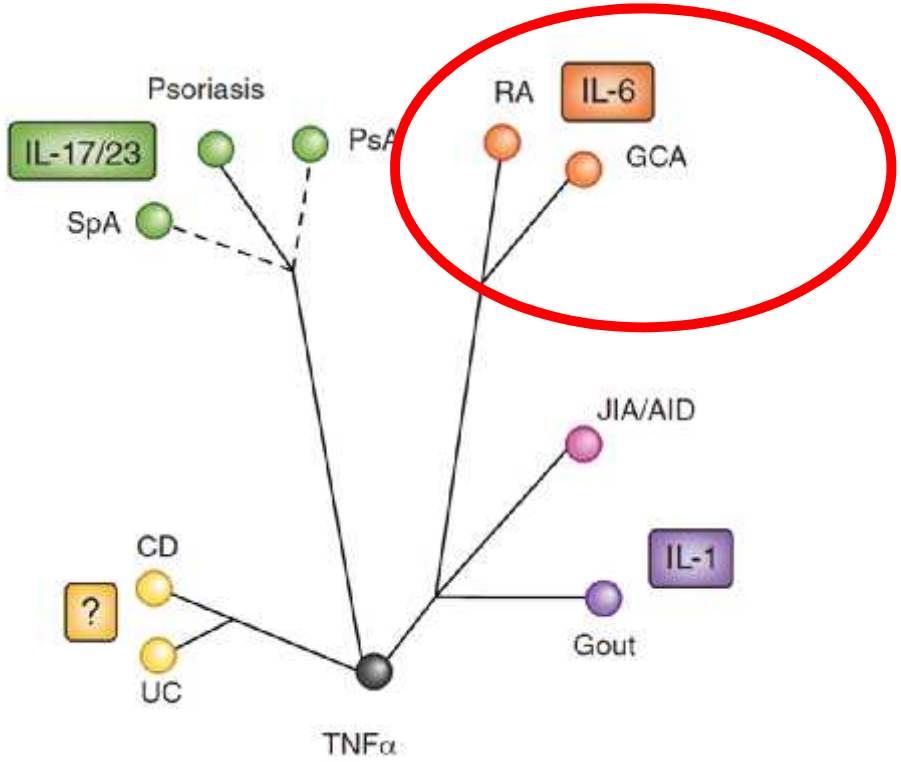
Drugs

Drug name	Target	Type of agent	Indication(s)
Approved[a]			
Anakinra	IL-1R1 (IL-1α and IL-1β)	Recombinant human IL-1Ra	CAPS[a], RA[a], AoSD, sJIA, gout and many other off-label indications
Rilonacept	IL-1β, IL-1α and IL-1Ra	IL-1R1 fusion protein	CAPS[a], AoSD
Canakinumab	IL-1β	Anti-IL-1β mAb	AoSD[a], CAPS[a], FMF[a], gout[a], sJIA[a]



Dinarello CA et al. Nat Rev Rheum 2019

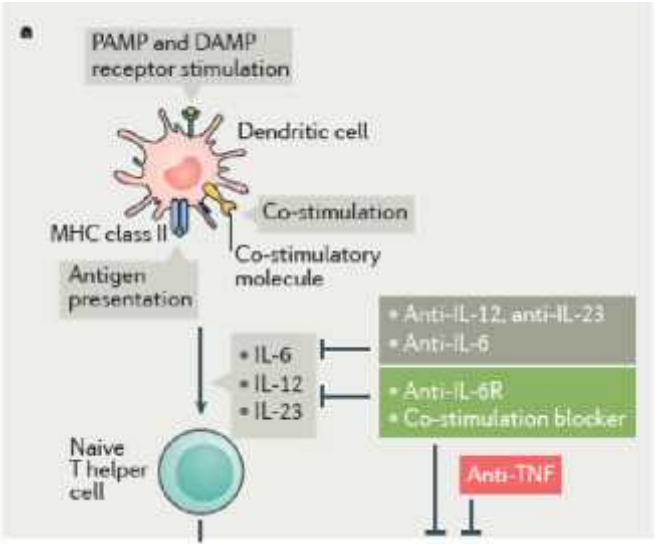
The IL-6


Psoriasis
IL-17/23
PsA
SpA
RA
IL-6
GCA
JIA/AID
IL-1
Gout
CD
?
UC
TNFα

GCA

IL-6 pathogenesis /initiation phase

- 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



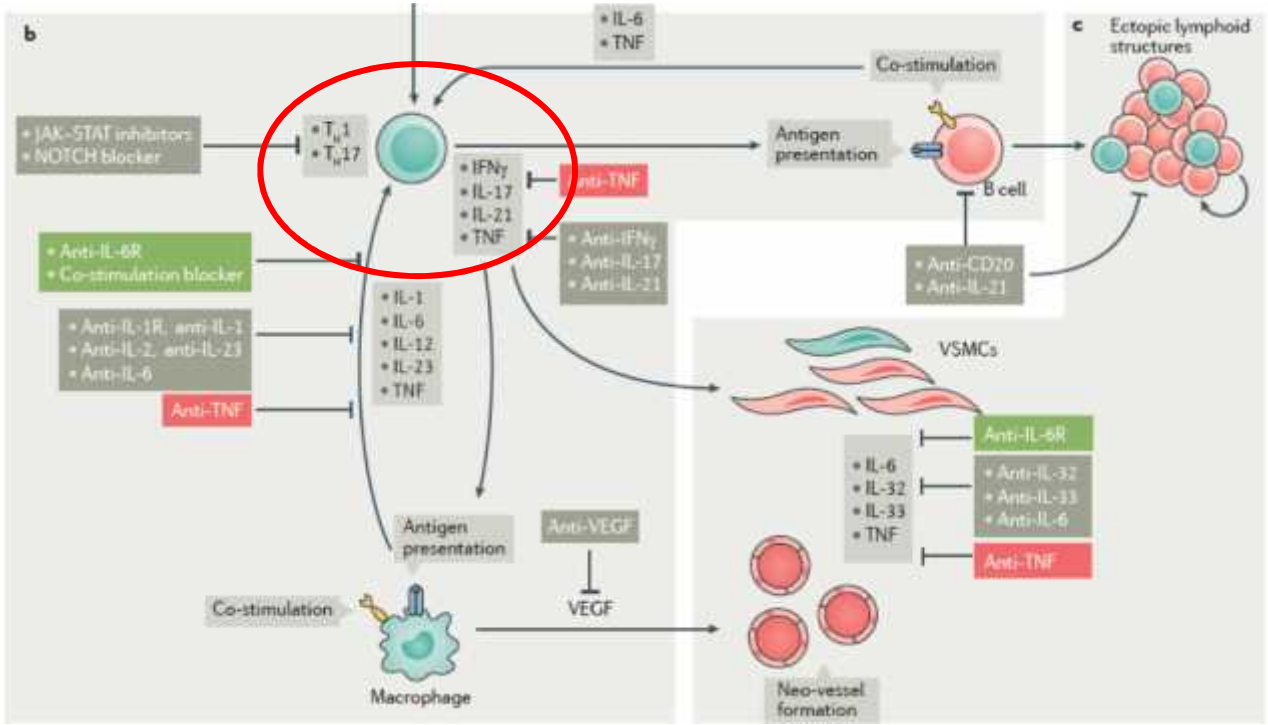
Dejaco C et al, Nat Rev Rheum 2017

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

- Tocilizumab
  - Approved for GCA
  - Trial II for PMR
- Sarilumab
  - Trial III
- Secukinumab
  - Trial II
- Abatacept
  - Increase in relapse-free survival at 12 months *Vs GC monotherapy*
  - small improvement in outcome (p=0.05 for relapse free rate)
  - planned phase III RCT has been withdrawn.

Dejaco C et al, Nat Rev Rheum 2017
Low C & Conway R, Ther Adv Mus Res 2019
Langford CA et al, Arthr & Rheumatol 2017

GCA

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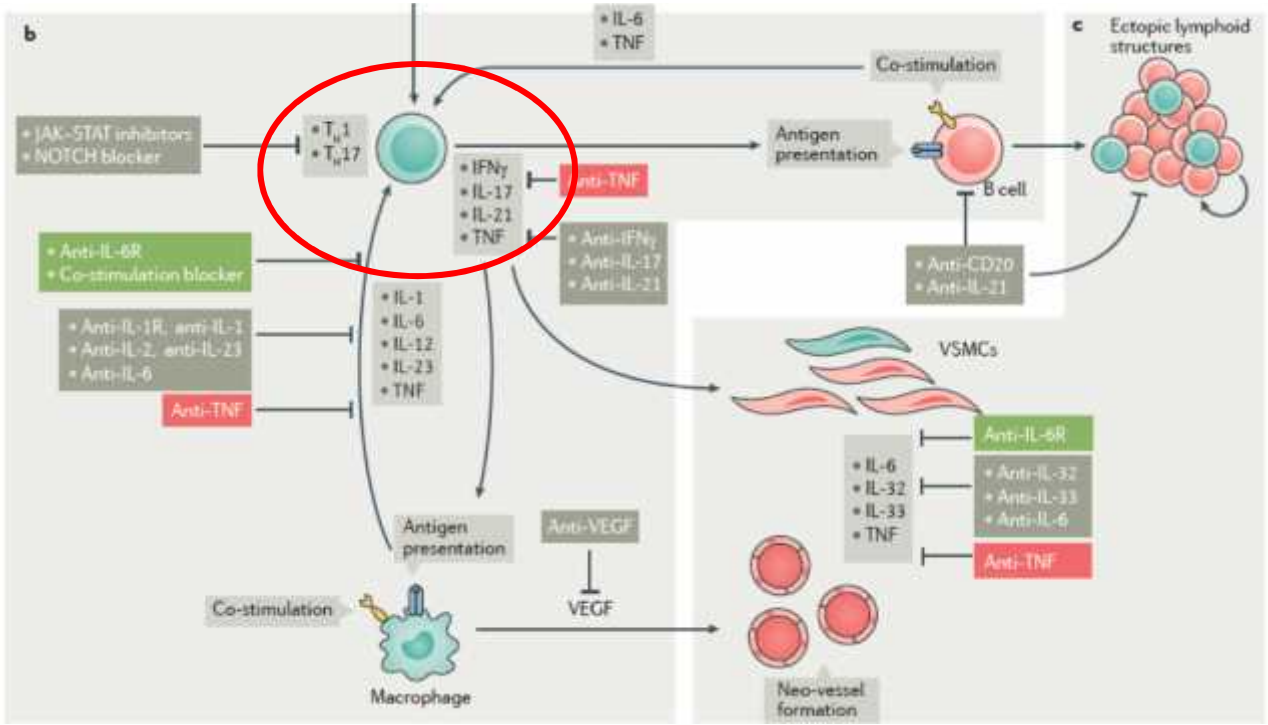


Dejaco C et al, Nat Rev Rheum 2017

GCA

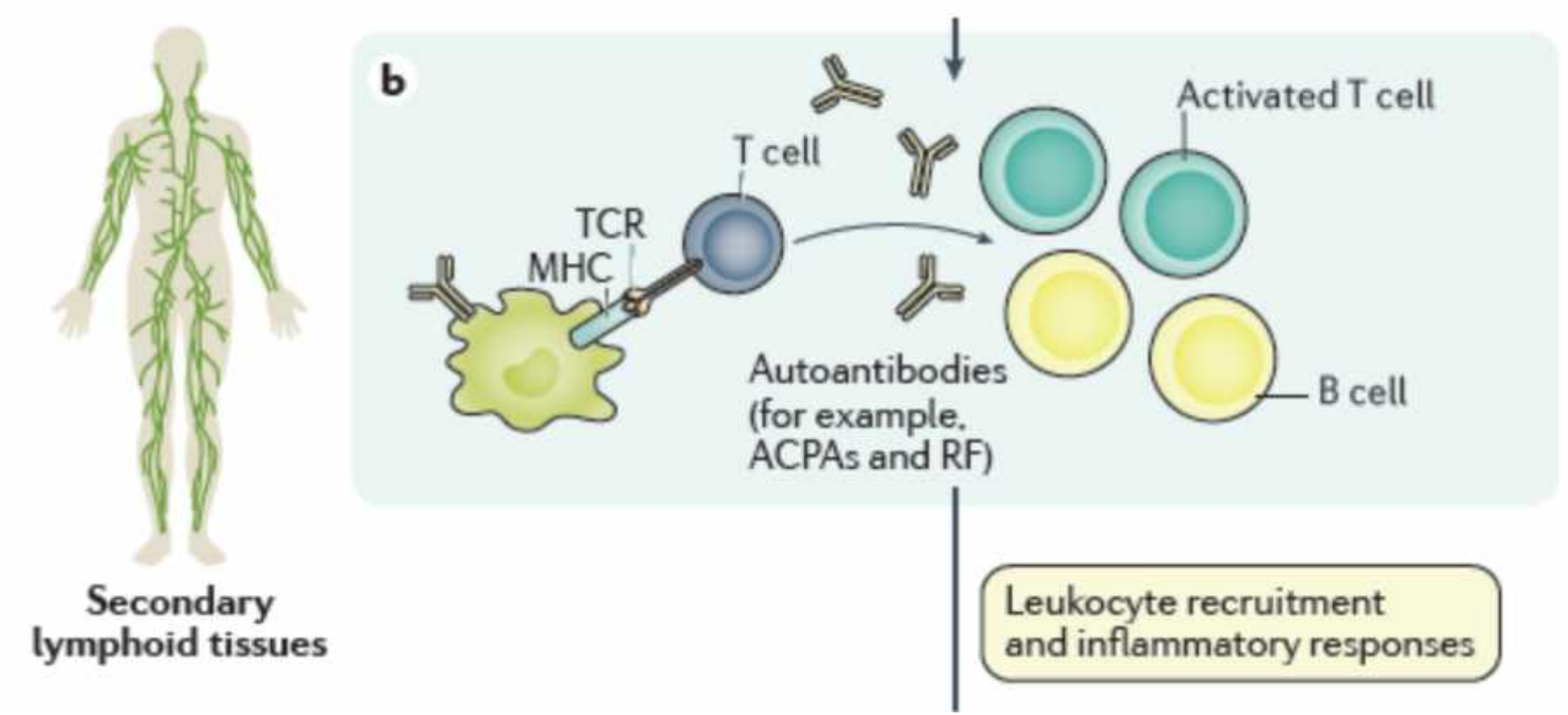
Treatment – what about Ustekinumab?

- The "dual" role (IL-12 & IL-23) makes UST a potentially attractive treatment
- Open-label/small (n=25) study
  - 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

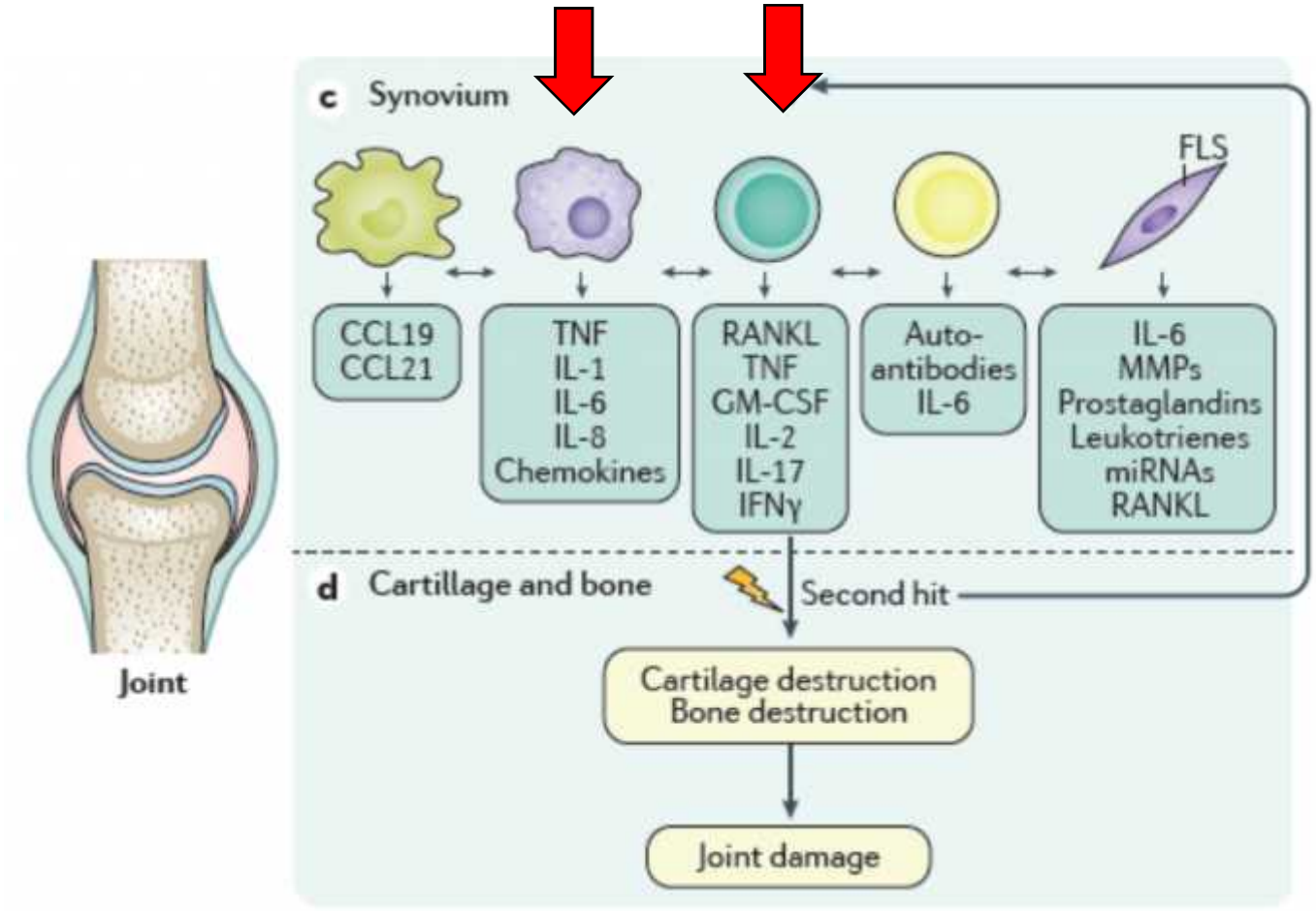
Rheumatoid Arthritis

Pathogenesis



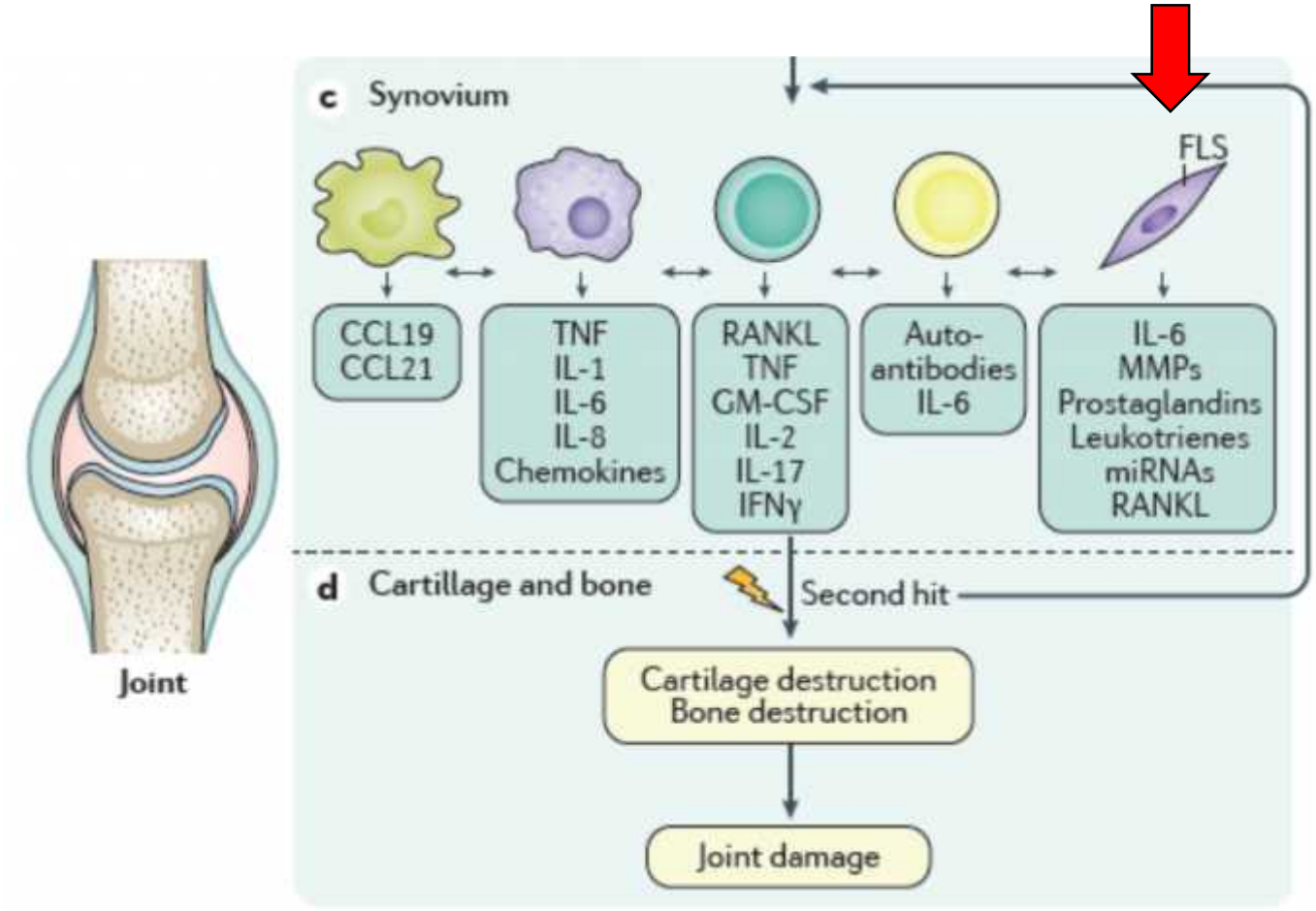
Smolen et al Nat Rev Rheum 2018

Rheumatoid Arthritis Pathogenesis



Smolen et al Nat Rev Rheum 2018

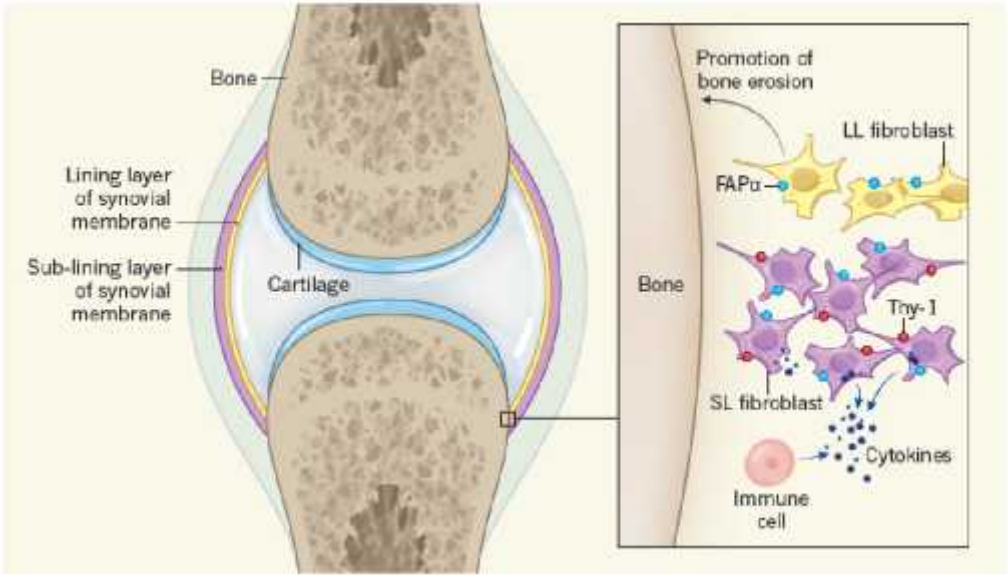
Rheumatoid Arthritis Pathogenesis



Smolen et al Nat Rev Rheum 2018

Rheumatoid Arthritis

The Fibroblasts !



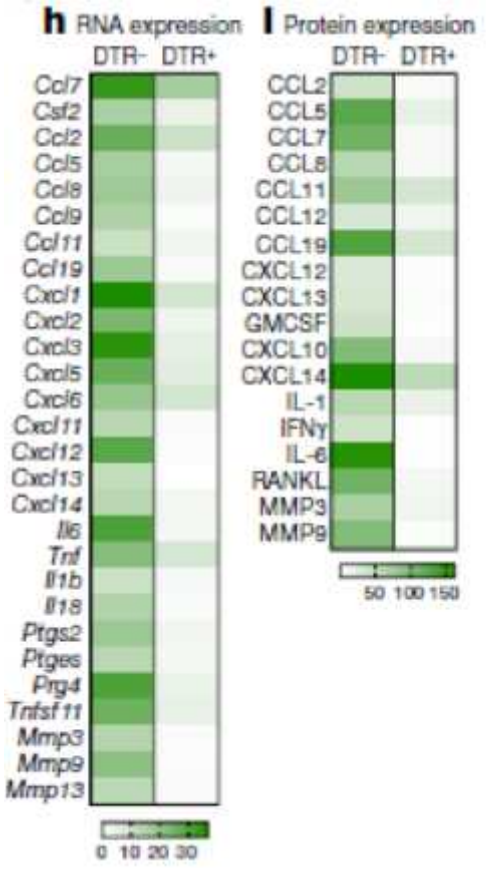
- 2 types of fibroblasts
  - FAP (fibroblast activation protein a) (+)
    - ~ inflammation
  - In different sublayers
  - SL (Thy-1 +)
    - Cytokines
  - LL
    - Cartilage damage

(comment) Wynn TA Nature 2019

Rheumatoid Arthritis

The Fibroblasts: producing cytokines (IL-6)

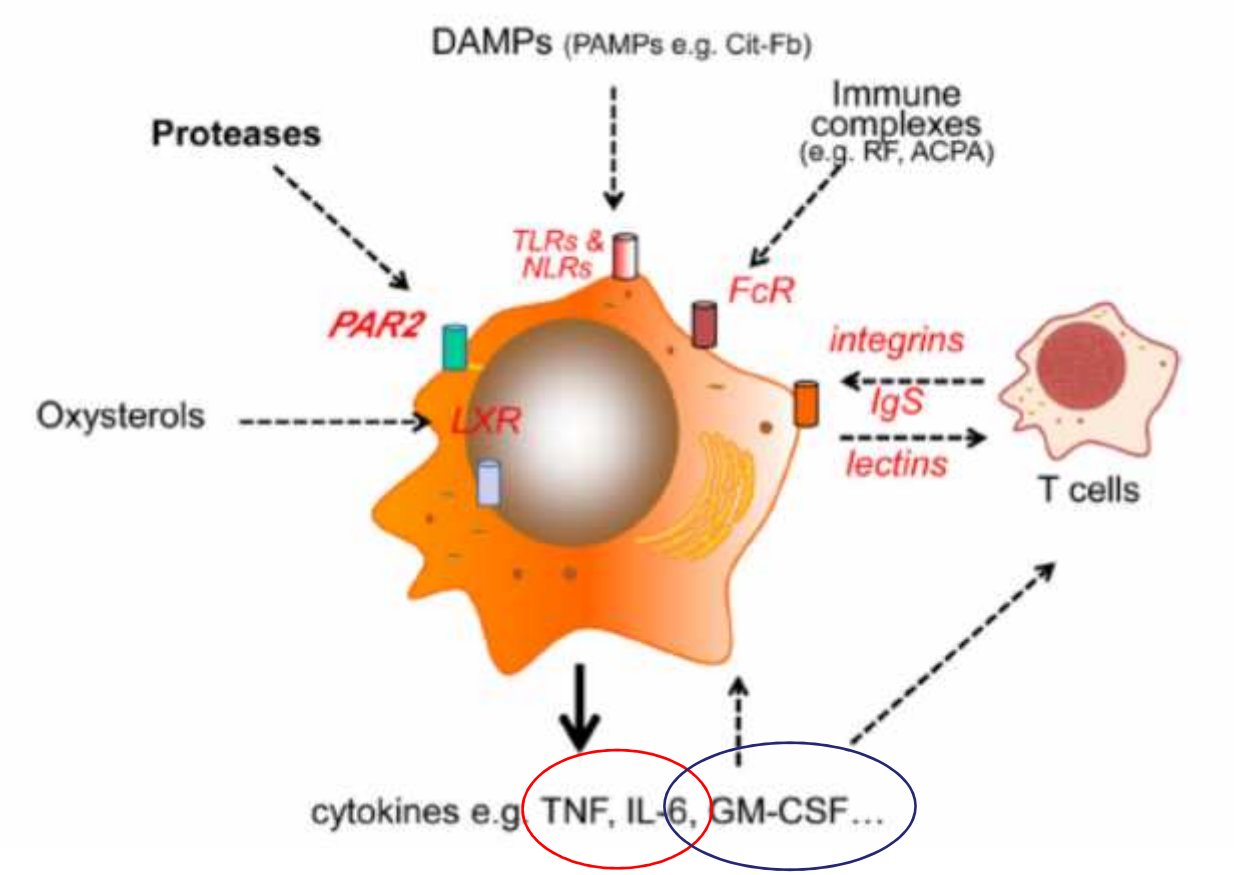
- Deletion of FAPα+ cells
  - ⇩ cartilage and bone damage, inflammatory bone remodeling, pannus formation
  - ⇩ number of synovial leukocytes, specifically neutrophils, macrophages, $CD11b^{+}$ dendritic cells and monocytes
  - ⇩pro-inflammatory chemokines, cytokines, RANKL and matrix metalloproteases (MMPs)



Croft et al. Nature 2019

Rheumatoid arthritis

Is it only TNF & IL-6

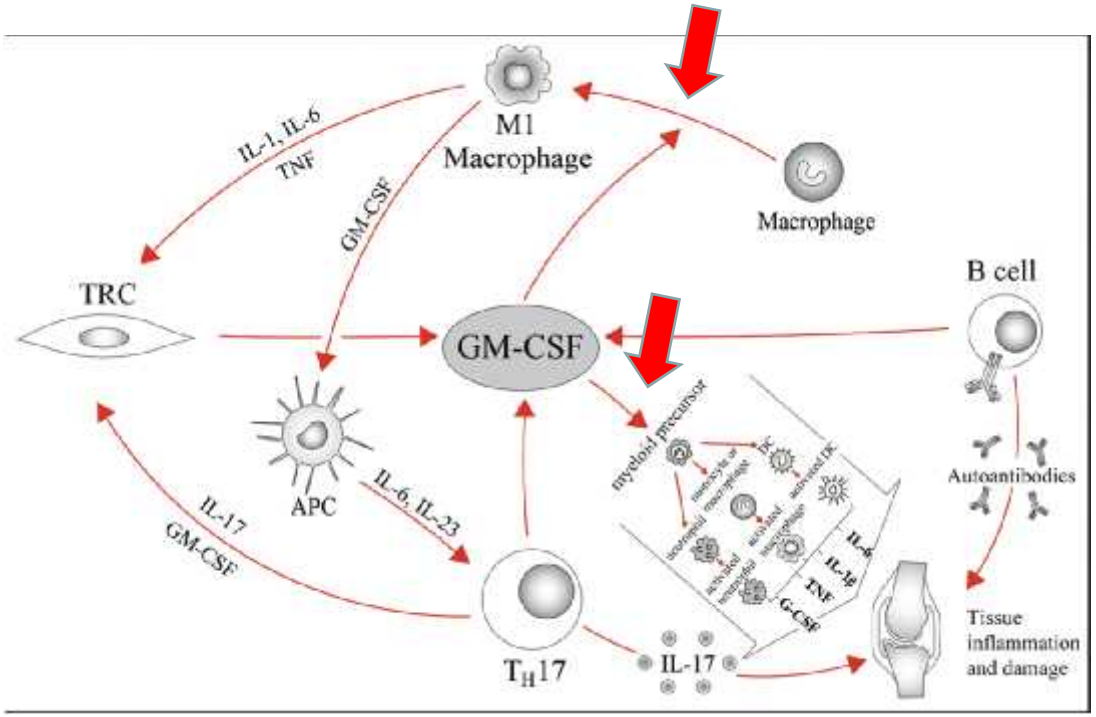


Firestein & McInnes, Immunity 2017

RA

Granulocyte macrophage colony-stimulating factor (GM-SCF)

- GM-CSF can produced by
  - haemopoietic
  - non-haemopoietic cell
- can activate/'prime'
  - Myeloid populations (e.g PMN)
    - to produce inflammatory mediators
      - ✓ TNF
      - ✓ IL-6
      - ✓ IL1-β



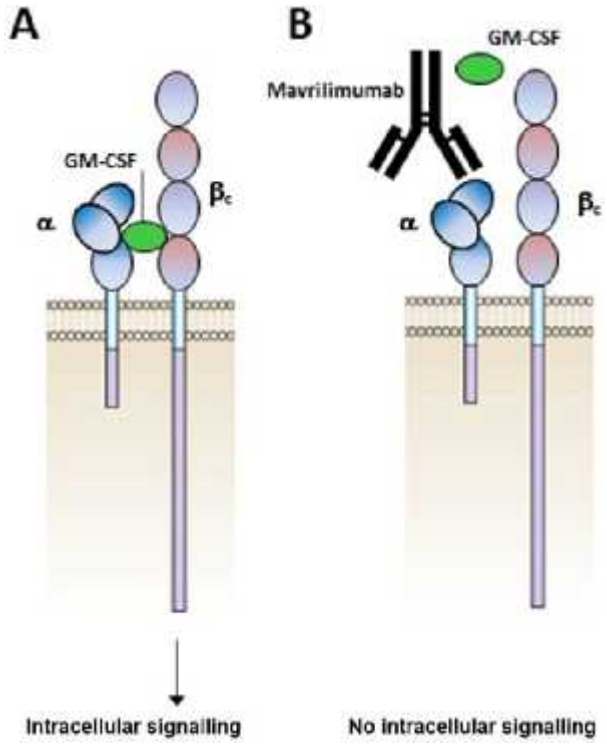
Cook A and Hamilton J, Ther Adv Mus Res 2018
Avci AB et al. Clin Exp Rheum 2016

RA

GM-CSF/Rationale

- Raised GM-CSF levels in RA
  - synovial fluid and plasma
  - overexpression of the GM-CSFR within cells of RA synovial tissue have been reported
  - Depletion of GM-CSF
    - ⇩ arthritis in a number of mouse models
  - Might be ⇧ *early* in RA

- Mavrilimumab has been developed
  - is a high-affinity, immunoglobulin against GM-CSFRα



Cook A and Hamilton J, Ther Adv Mus Res 2018
Avci AB et al. Clin Exp Rheum 2016
Deane et al ARD 2010

RA

GM-CSF/Treatment

Phase IIb, NCT01706926 EARTH EXPLORER 1	30, 100, 150 mg subcutaneously doses of mavrilimumab given every other week *versus* placebo with stable methotrexate	DAS28-CRP change from baseline at 12 weeks[a] ACR20 response (24 weeks)[a]	Mavrilimumab 30 mg, −1.37 (0.14); 100 mg, −1.64 (0.13); 150 mg, −1.90 (0.14) *versus* placebo −0.68 (0.14), $p < 0.001$ [change from baseline (SE)] Mavrilimumab 30 mg, 51%; 100 mg, 61%; 150 mg, 73% *versus* placebo 25%, $p < 0.001$
Phase IIb, NCT01715896 EARTH EXPLORER 2	100 mg mavrilimumab subcutaneously given every other week or 50 mg golimumab subcutaneously every 4 weeks, with stable methotrexate	ACR20/50/70 responses at 24 weeks[a] DAS28-CRP < 2.6 at 24 weeks[a] HAQ-DI improvement > 0.22 at 24 weeks[a]	Mavrilimumab 62.0, 34.8, 16.1% (ACR20,50,70); golimumab 65.6, 43.4, 25.9% (ACR20,50,70) Mavrilimumab 17.4%; golimumab 29.0% (DAS28-CRP < 2.6) Mavrilimumab 58.7%; golimumab 69.0% (HAQ-DI improvement > 0.22)

Despite phase II results were promising, phase III are not underway

Cook A and Hamilton J, Ther Adv Mus Res 2018
Avci AB et al. Clin Exp Rheum 2016

RA

GM-CSF/Treatment

Phase III

Name	Molecule/target	Manufacturer	Trial, ClinicalTrials.gov identifier	Ref
GSK3196165 (previously known as MOR103)	Human mAb to GM-CSF	Developed by MorphoSys AG and in-licensed by GlaxoSmithKline	Phase Ib/IIa, NCT01023256 Phase 11a, NCT02799472 Phase IIb, NCT02504671	45
KB003	High-affinity, recombinant IgG1κ mAb against GM-CSF	Kalobios Pharmaceuticals	Phase II, NCT00995449	46
Namilumab (MT203)	Human IgG1 mAb against GM-CSF	Takeda	Phase Ib, NCT01317797 Phase II, NCT02393378 Phase II, NCT02379091	47
MORAb-022	Human IgG1 mAb against GM-CSF	Morphotek/Esai	Phase I, NCT01357759	48

GM-CSF, granulocyte macrophage colony-stimulating factor; mAb, monoclonal antibody; IgG1κ, immunoglobulin G1 kappa.

Cook A and Hamilton J, Ther Adv Mus Res 2018
Avci AB et al. Clin Exp Rheum 2016

Cytokines and Comorbidities

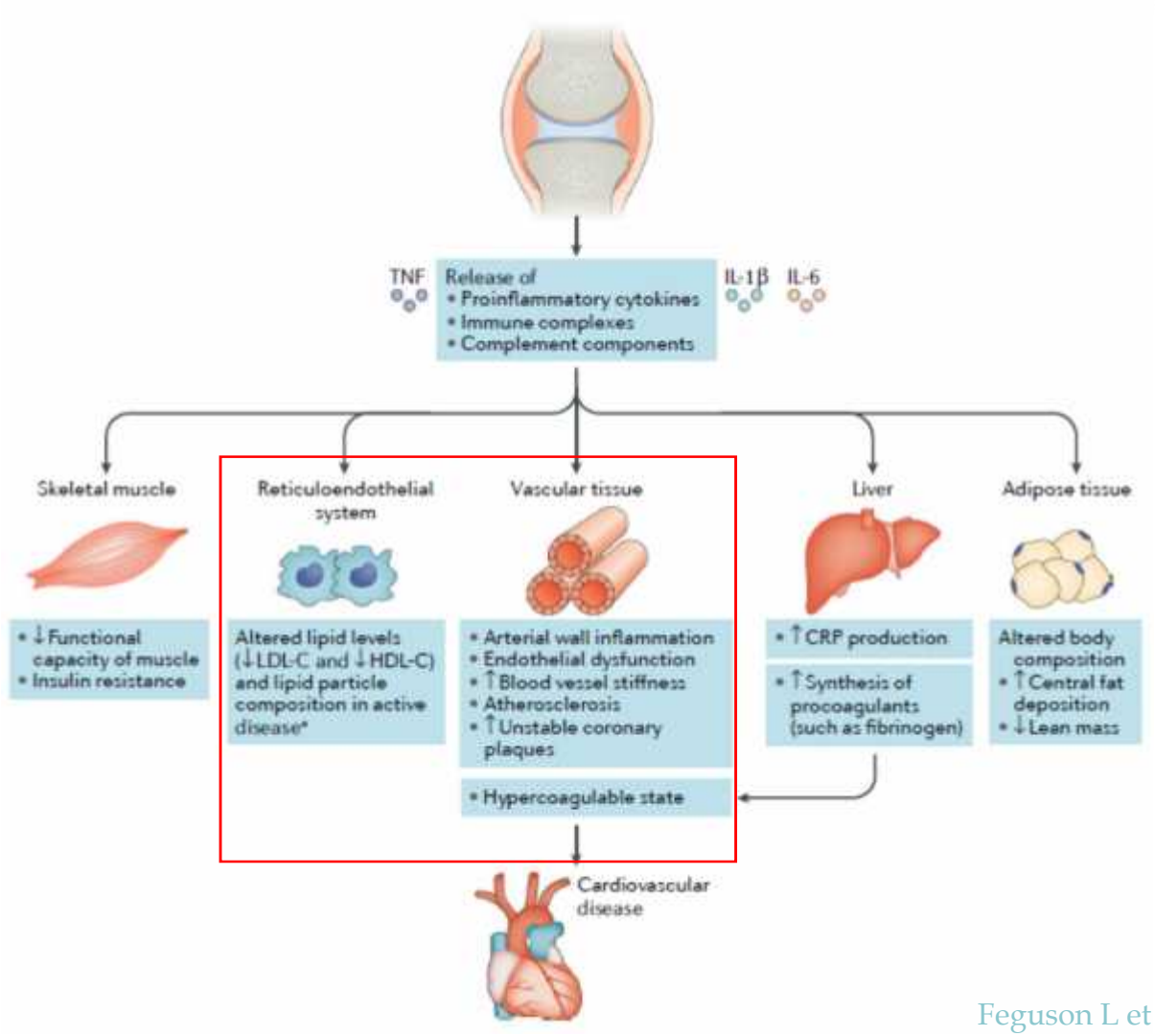
Cardiovascular risk

- We know that RA and inflammatory arthritis is general are independent risk factors for CVD
  - CVD risk ⇧ 48% in RA patients *Vs* general population
  - Inflammation is the main culprit
- IL-6
  - was associated with fatal CVD and all-cause mortality in RA women
- TNF and IL-6
  - were associated with subclinical atherosclerosis in RA, independent of Framingham score

Avina-Zubieta JA et al, ARD 2012
McKay et al Arthr Rheumatol 2015
Rho YH, Arthr Rheumatolo 2009

Cytokines and Comorbidities

Cardiovascular risk – the big picture



Feguson L et al, Nat Rev Rheum 2019

Cytokines and Comorbidities

Cardiovascular risk – data from basic science

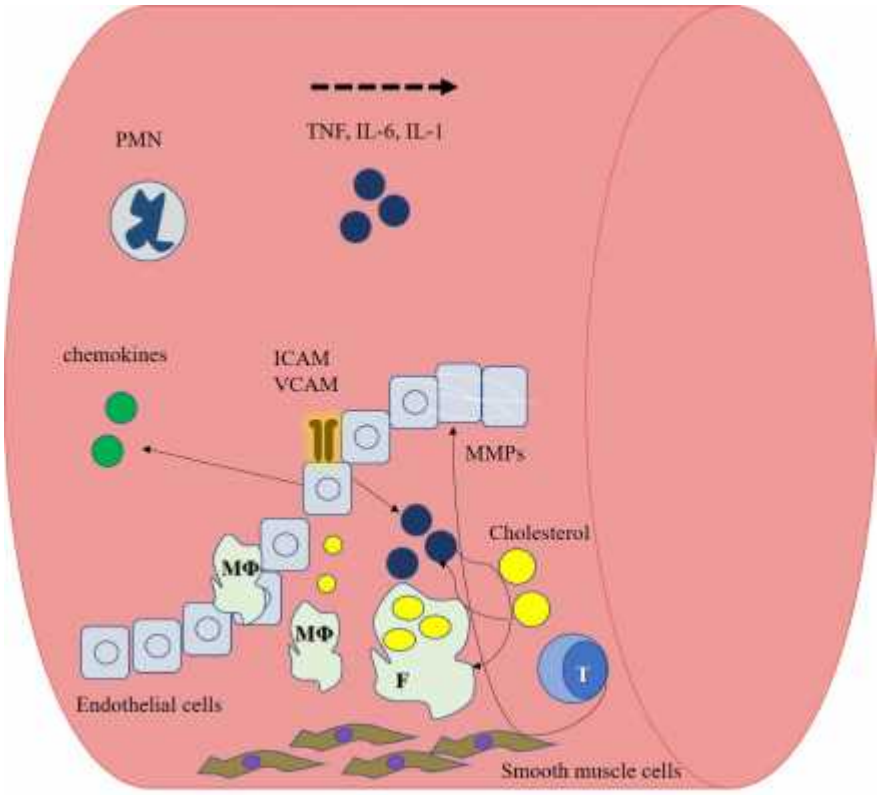
- TNF
  - promotes the expression of tissue factor by monocytes
  - Induced apoptosis in endothelial cells
  - ⇧ plasma levels of tissue plasminogen activator
  - impedes endothelium-dependent vasodilatation
- IL-6
  - Association with adhesion molecules like circulating VCAM-1, ICAM-1 and (ELAM-1) in RA patients
- IL-17
  - Enhanced genes critical for coagulation such as tissue factor and decreased thrombomodulin, leading to a pro-thrombotic state
  - ⇧ expression of adhesion molecules by monocytes
  - Induces apoptosis in endothelial cells

Sattar N et al, Circulation 2003
Zhu F et al, Clin Immunol, 2011
Dessein PH Arthr Res Ther 2005
Hot A et al, ARD 2012

Cytokines and Comorbidities

Vascular damage

- Inflammatory cytokines
  - activation of endothelial cells
    - adhesion molecules (e.g. ICAM, VCAM).
    - produce chemokines which recruit other inflammatory cells (e.g. polymorphonuclear cells)
- Inflammatory mediators promote "foam cell" formation.
  - Cholesterol further contributes to the production of pro-inflammatory cytokines by macrophages
- Plaque Destabilization
  - ⇧ MMPs



Fragoulis GE et al, Curr Vasc Pharm 2019

Cytokines and Comorbidities

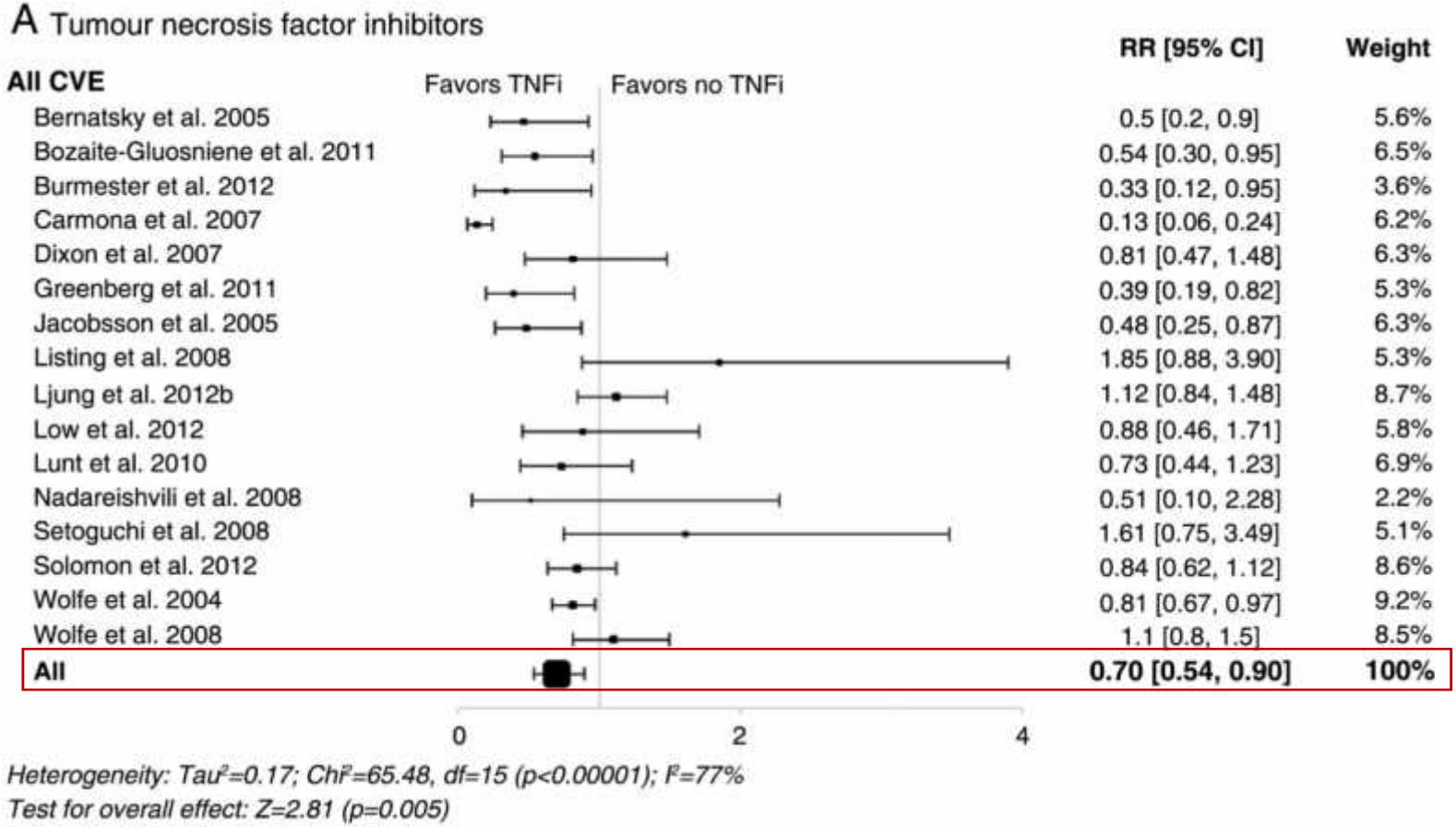
Treatment – Anti-TNF

- Several studies have demonstrated a beneficial effect of TNF inhibitors on CV outcomes.
- An advantageous effect of treatment on surrogate markers for CVD has been noted
  - Blood pressure
  - Arterial stiffness (aortic pulse wave velocity)
  - Endothelial dysfunction
  - Progression of cIMT
  - Cholesterol profile
    - Mixed results, unaffected LDL

Fragoulis GE et al, Curr Vasc Pharm 2019

Cytokines and Comorbidities

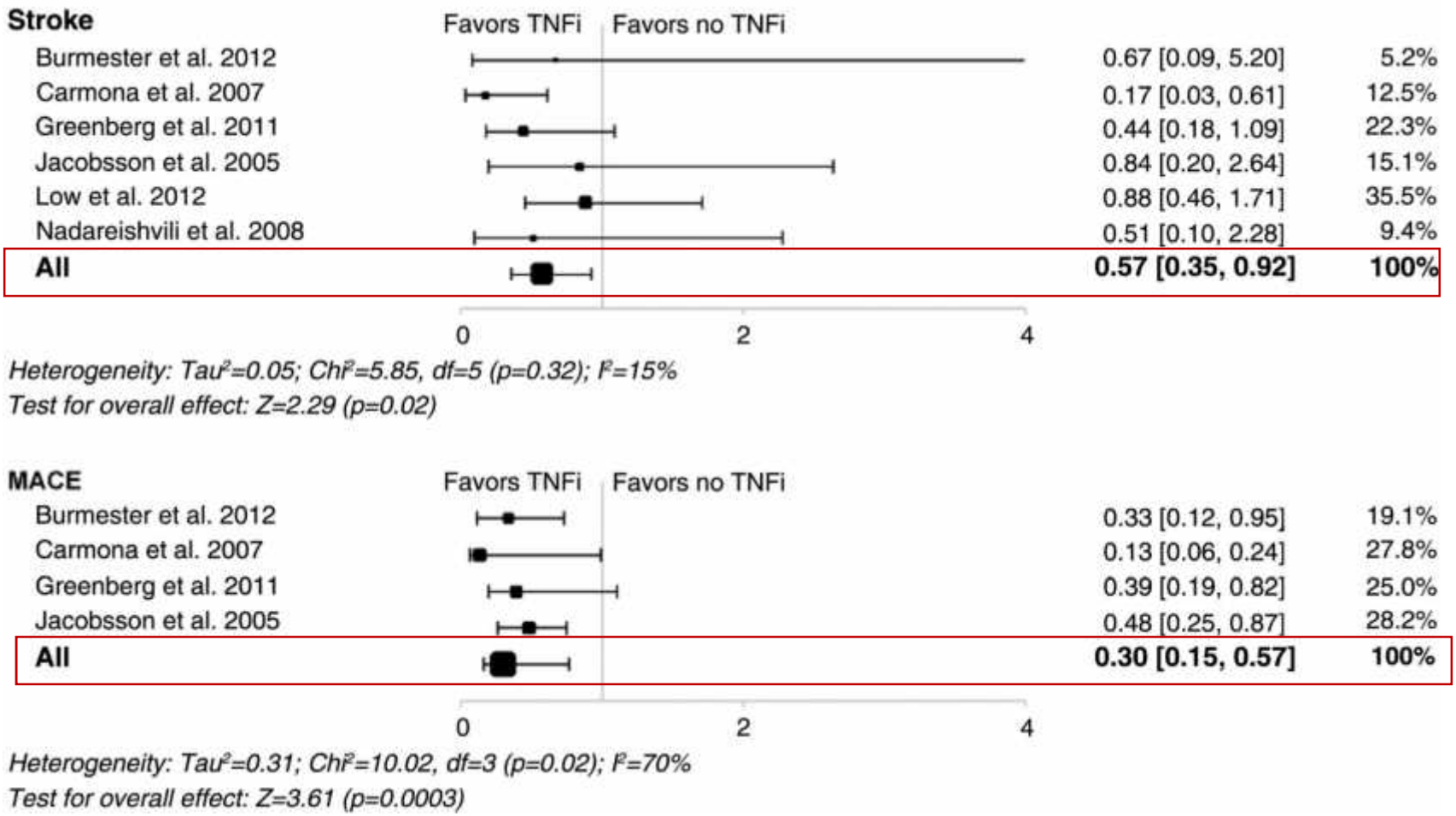
Treatment – Anti-TNF



Roubille et al. 2015 ARD

Cytokines and Comorbidities

Treatment – Anti-TNF



Roubille et al. 2015 ARD

Cytokines and Comorbidities

Treatment – Tocilizumab

- Increased levels of total cholesterol, HDL-C, LDL-C and TGs.
  - Reversal of IL-6 induced LDL clearance

BUT

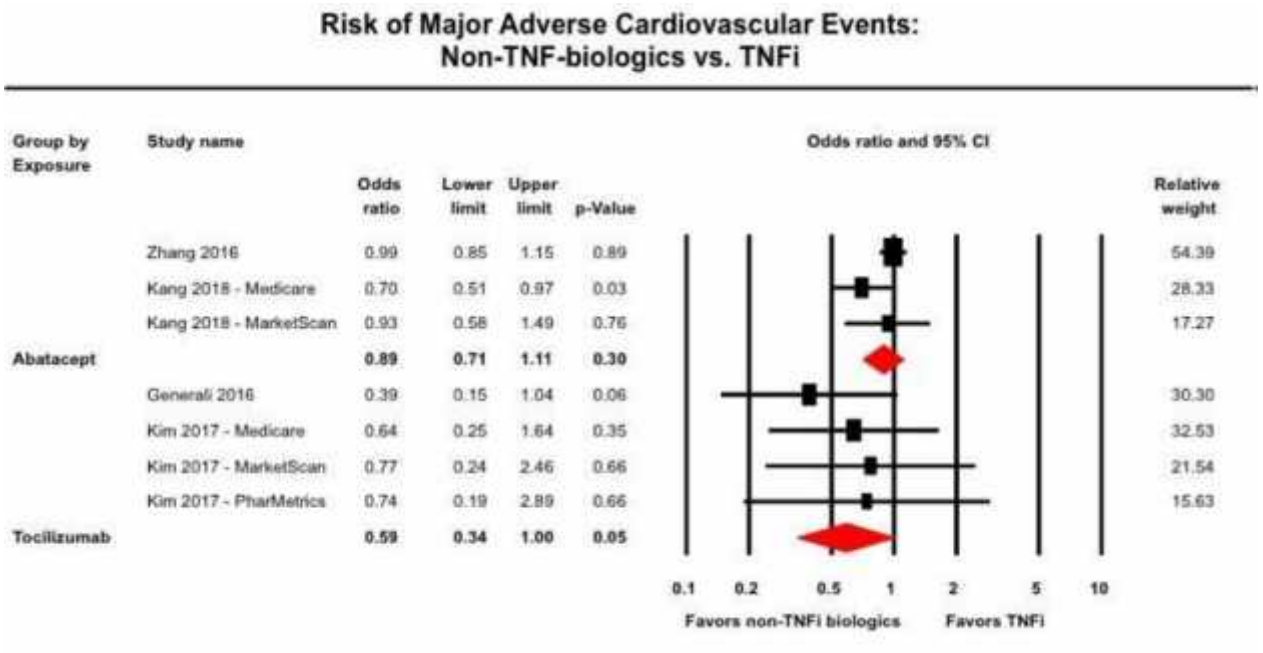
  - Alteration of HDL composition towards a more anti-inflammatory phenotype
    - Combined with improvement in CVD surrogate markers cIMT

Robertson J et al, ARD 2017
Krume K et al, J Rheum 2011
Nurmohamed M et al Drug Saf 2018

Cytokines and Comorbidities

Treatment – Tocilizumab

- In recent studies using data from MediCare and Marketscan
  - CVD risk for tocilizumab was not increased compared with abatacept, rituximab and TNF-inhibitors
- SLR and meta-analysis: Tocilizumab ⇩ reduced risk of MACE *Vs* anti-TNF.



Singh S et al, Arth C Res 2019
Xie F et al, Arth C Res 2019

Take home Messages

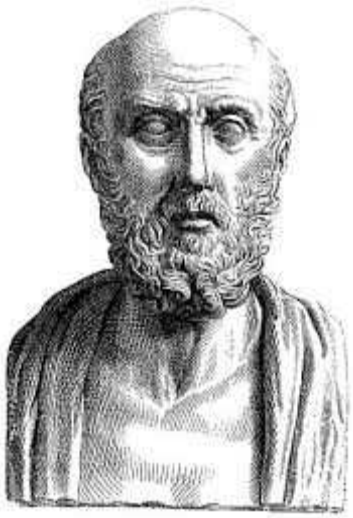
- Are we going towards cytokine-based treatment?
  - Simple but complex
- Could that be that some cytokines are involved at an earlier stage of disease than others?
- Treating inflammatory arthritis AND comorbidities
- Other (previously “innocent”) cells are contributing to the cytokine milieu.

Ευχαριστώ πολύ

Ερωτήσεις

«Ιητρική τεχνέων πασέων εστίν επιφανεστάτη»

Ιπποκράτης (Νόμος 1)



"If it were not for the great variability among individuals, medicine might as well be a science and not an art"

Sir William Osler 1892