Axial Spondyloarthritis: A Year in Review

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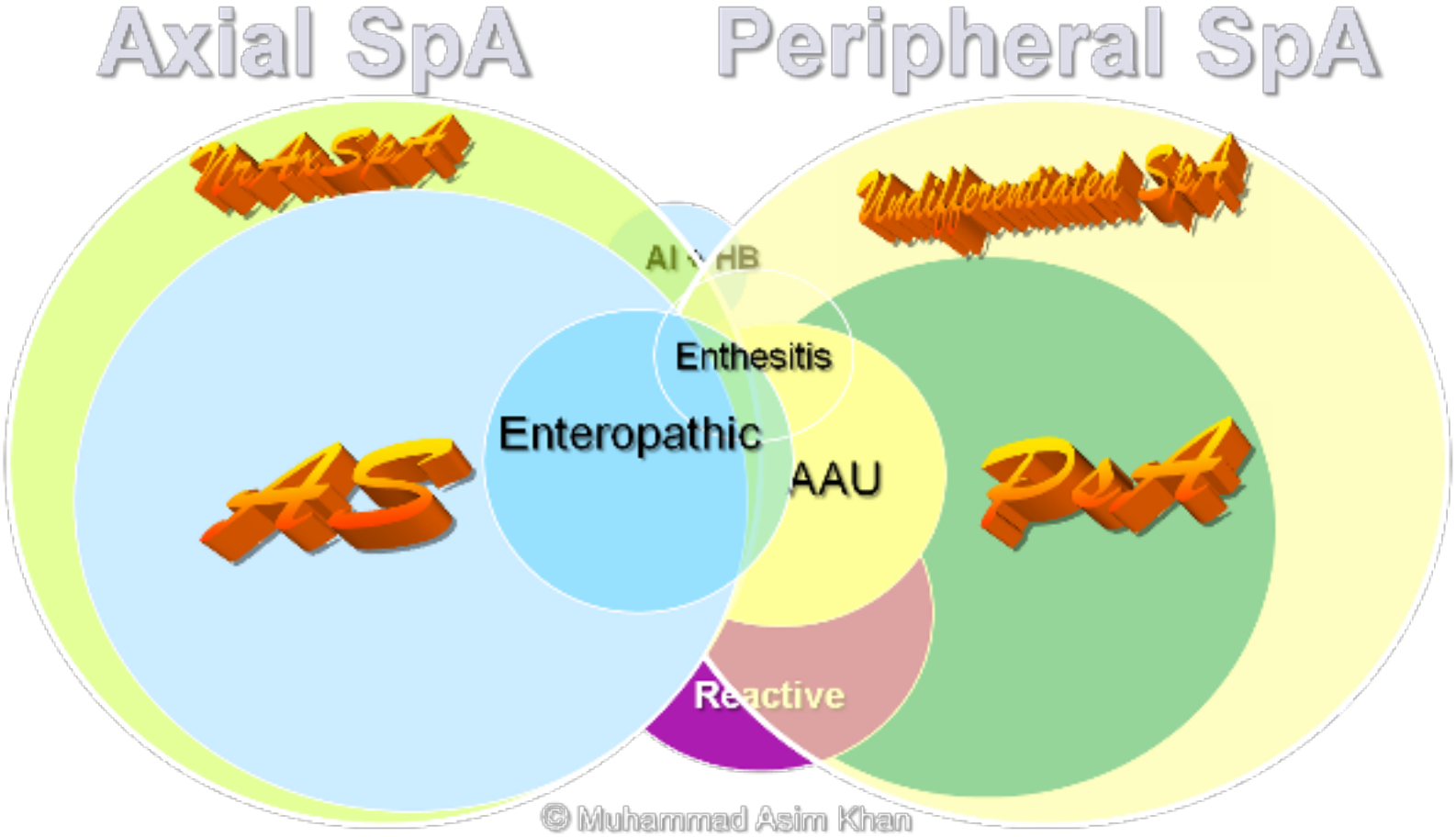
Disclosures

Consultant/Clinical Studies/Speaker

- Abbvie
- Janssen
- Novartis
- Pfizer
- Sun Pharma

Spondyloarthritis



NrAxSpA = non-radiographic axial SpA, PsA = psoriatic arthritis. AAU = acute anterior uveitis. AI+HB = aortic incompetence plus heart block. Miscellaneous entities not shown, include FMF (familial Mediterranean fever), and SAPHO and Behcet's syndrome.

Ozgocmen S, Khan MA. *Curr Rheum Report*. 2012 July

www.spondyloarthritis.com

ASAS Classification Criteria for Axial SpA

(chronic back pain >3 months, age at onset <45 years)

Imaging Arm

Sacroiliitis (x-rays or MRI)

+

At least one clinical parameter

Imaging arm:
Sensitivity: 66.2%
Specificity: 97.3%

!---------- OR ----------!

Sensitivity: 82.9%
Specificity: 84.4%

Clinical Arm

HLA-B27

+

≥ 2 other clinical parameters

Clinical arm:
Sensitivity: 56.6%
Specificity: 83.3%

These criteria were validated against expert clinical judgement in a cohort of 649 patients with chronic back pain; the same cohort that was used to develop the ASAS criteria.

Rudwaleit M, et al. ***Ann Rheum Dis***. 2009; 68(6):777-83

Estimated Prevalence of AS/SpA

USA

Older Estimate*: 0.4% to 1.3%

[0.6 to 2.4 million patients with SpA]

Among adults age ≥ 25

A More Recent Study**: Overall prevalence = **0.9%** to **1.4%**

[1.7 to 2.7 million patients with SpA]

Non-Hispanic whites: **1%** to **1.5%**

Age adjusted prevalence (adults aged 20-69)

No difference in the prevalence of SpA among males and females

Germany

Estimated Prevalence of AS & SpA in Berlin****

AS prevalence: **0.55%**

SpA prevalence: **1.73%**

* Helmick CG, Felson DT, Lawrence RC, et al *Arthritis Rheum* 2008, 58: 15-25.

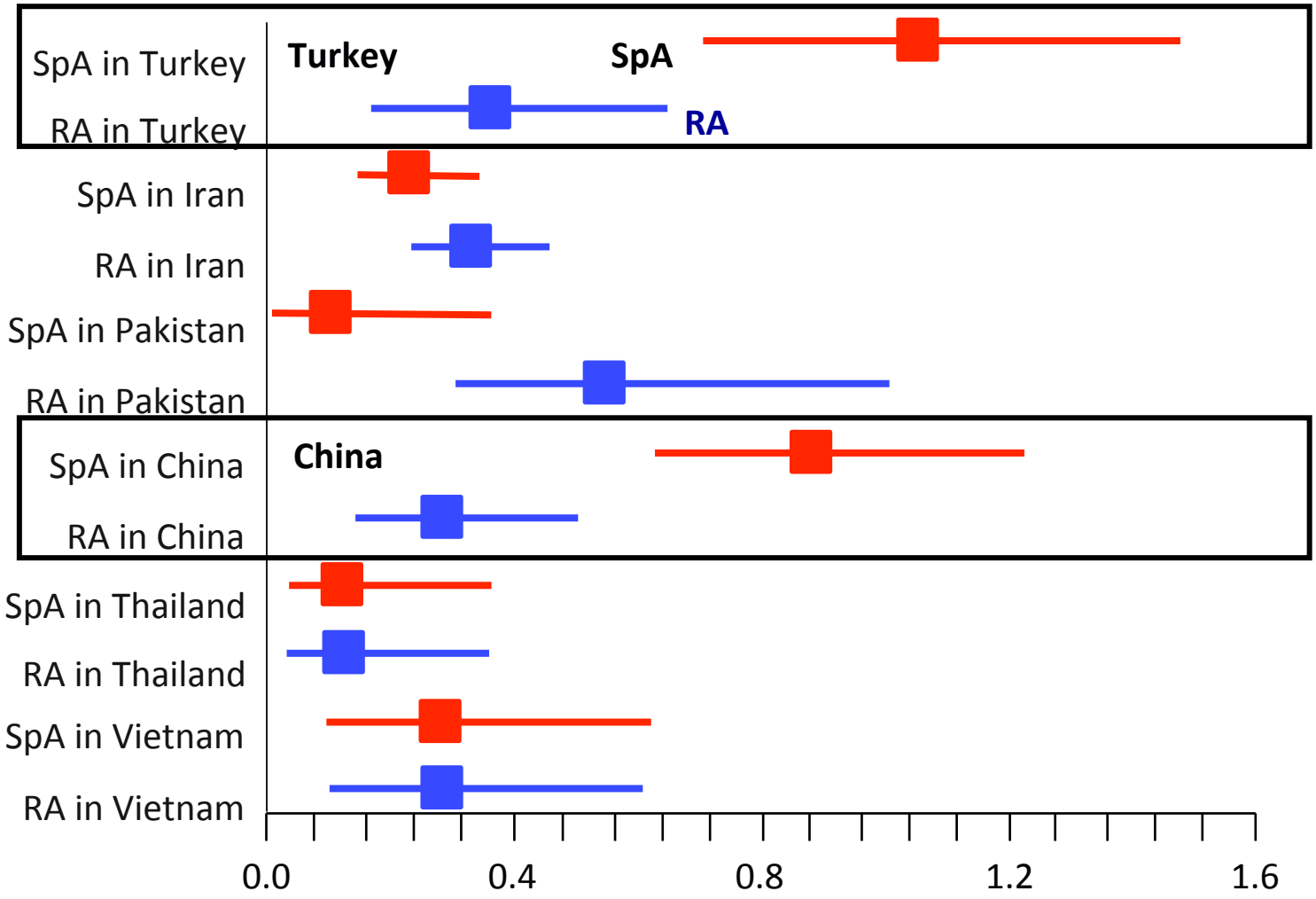
**Reveille JD, et al. *Arthritis Care Res. 2012; 64:905-10.* (NHANES 1)

***Strand V et al. *Arthritis Care Res*. 2013 Aug;65(8):1299-306

****Akkoc N, Khan MA. Overestimation of the prevalence of AS in the Berlin study: comment on the article by Braun et al. *Arthritis Rheum*. 2005. Dec;52(12): 4048-9; author reply 4049-50.

Stolwijk C, et al. **The global prevalence of spondyloarthritis: A systematic review and meta-regression analysis.** Arthritis Care Res. 2016. DOI: 10.1002/acr.22831

Prevalence of SpA vs RA

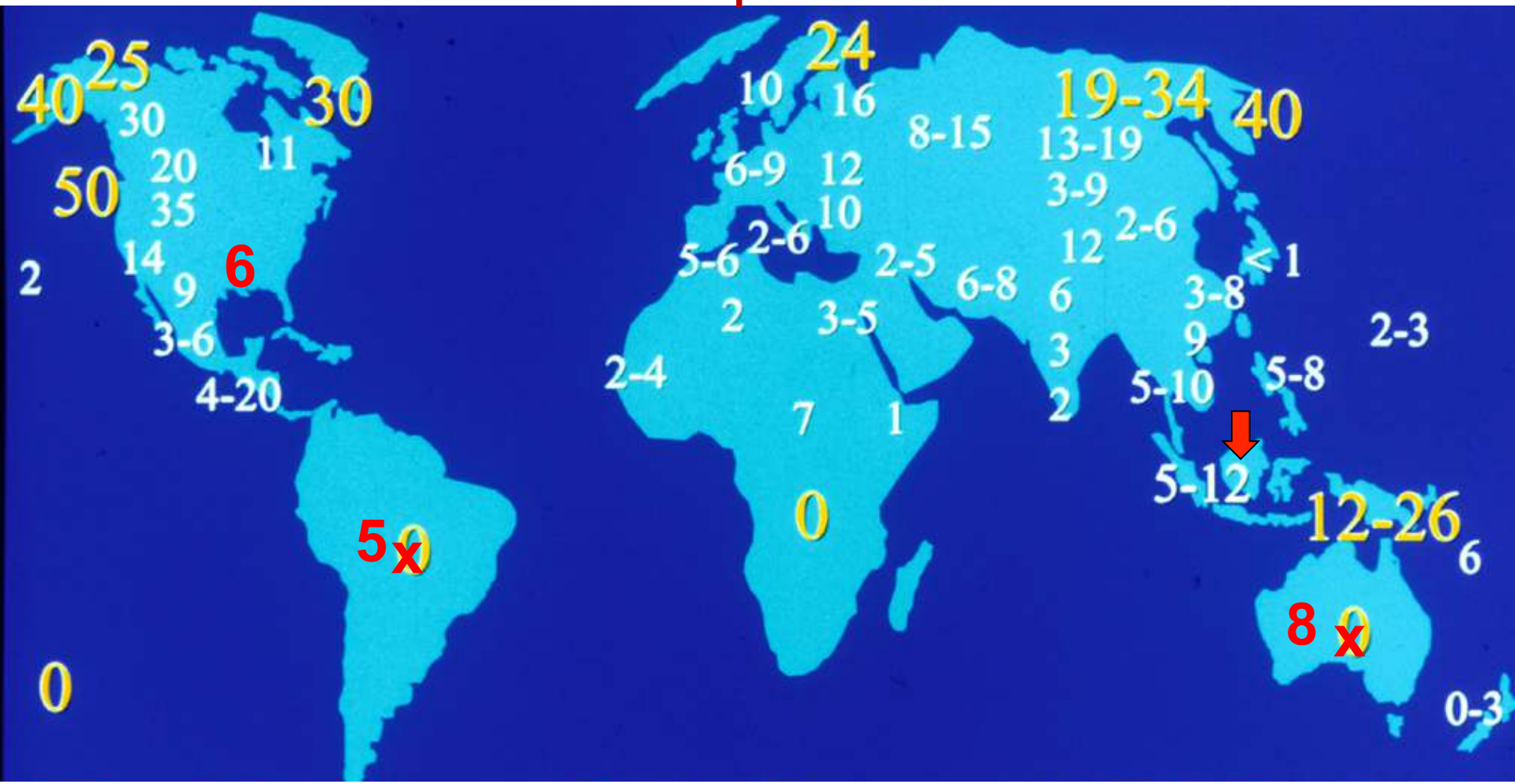


Courtesy Nurullah Akkoc.

Akkoc N. Are spondyloarthropathies as common as rheumatoid arthritis worldwide? A review. *Curr Rheumatol Rep.* 2008 Oct;*10*(5):*371-8*;
Onen F, et al. *J Rheumatol*. 2008; 35(2):305-9; Liu Y, et al. *Tisse Antigens* 2009.

HLA-B27

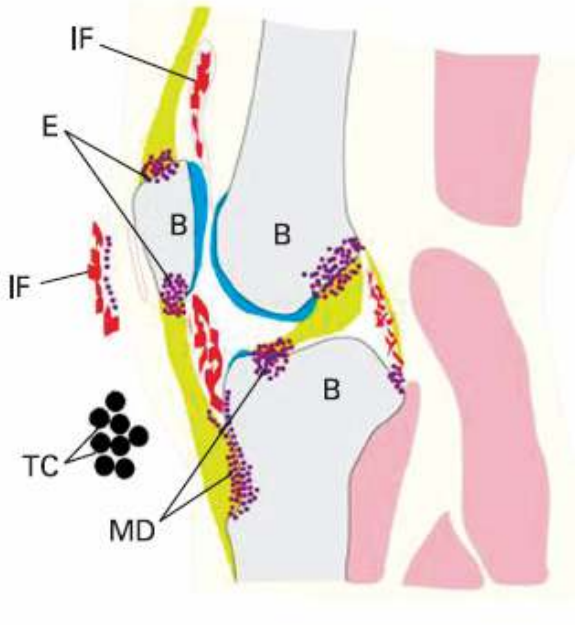
A perfectly normal gene that is widely distributed in the world but with variable prevalence



Khan MA. *Curr Opin Rheumatol*.1995; 7:263–9

Khan MA. *J Clin Rheumatol.* 2008; 14(1):50-2

Tissue specific factors (biomechanical stressing and micro-damage) related to the enthesis also play a role in joint disease in SpA, especially PsA



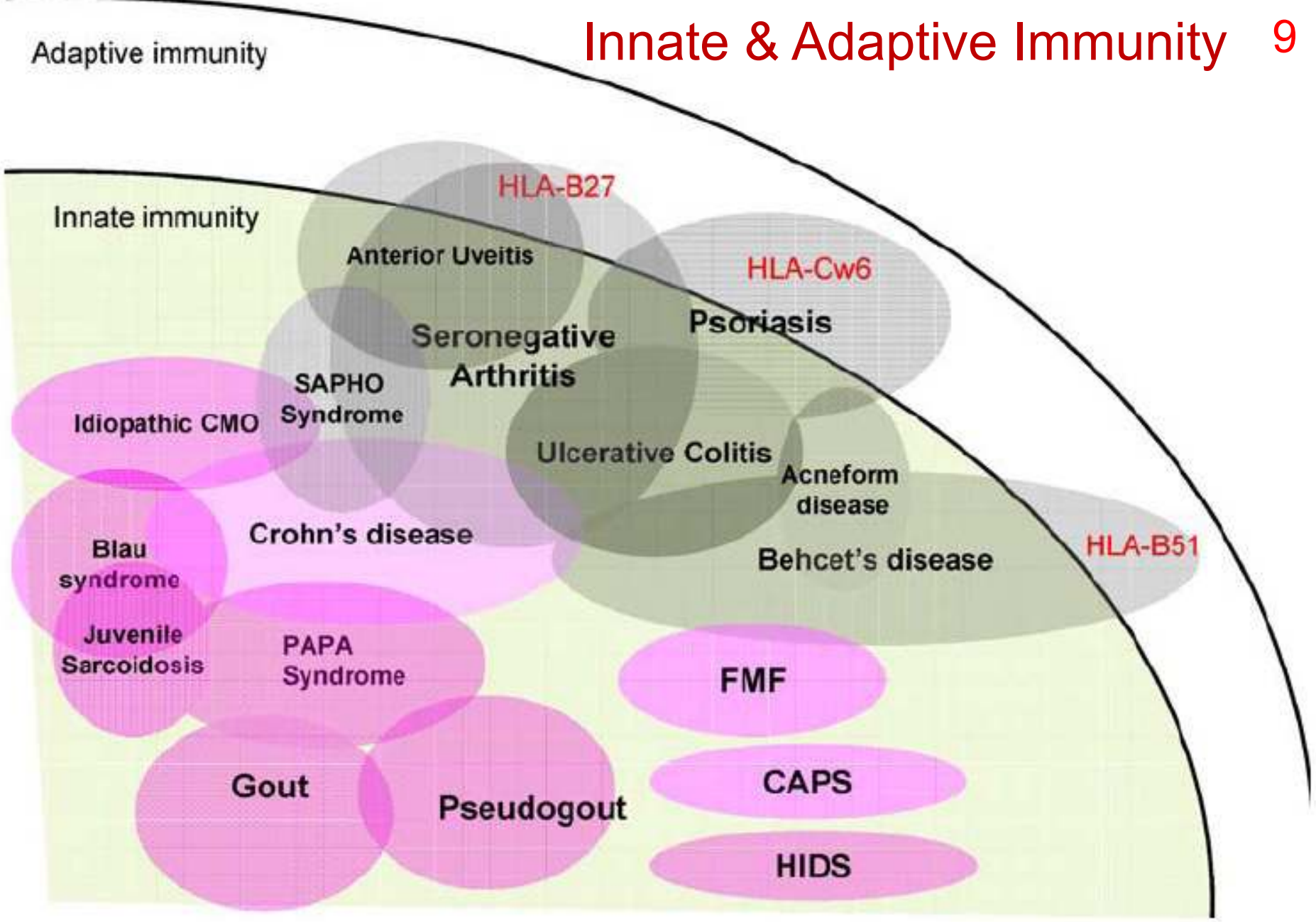
IF = Inflammation
E = Enthesis
B = Bone
MD = Micro-damage

Auto-inflammation

Self-directed inflammation, whereby local factors at sites predisposed to disease lead to activation of innate immune cells, including macrophages and neutrophils, with resultant target tissue damage. For example, disturbed homeostasis of canonical cytokine cascades (as in the periodic fevers), aberrant bacterial sensing (as in Crohn disease), and tissue microdamage predispose one to site-specific inflammation that is independent of adaptive immune responses.

McGonagle D, et al. *Ann Rheum Dis* 2007

Innate & Adaptive Immunity



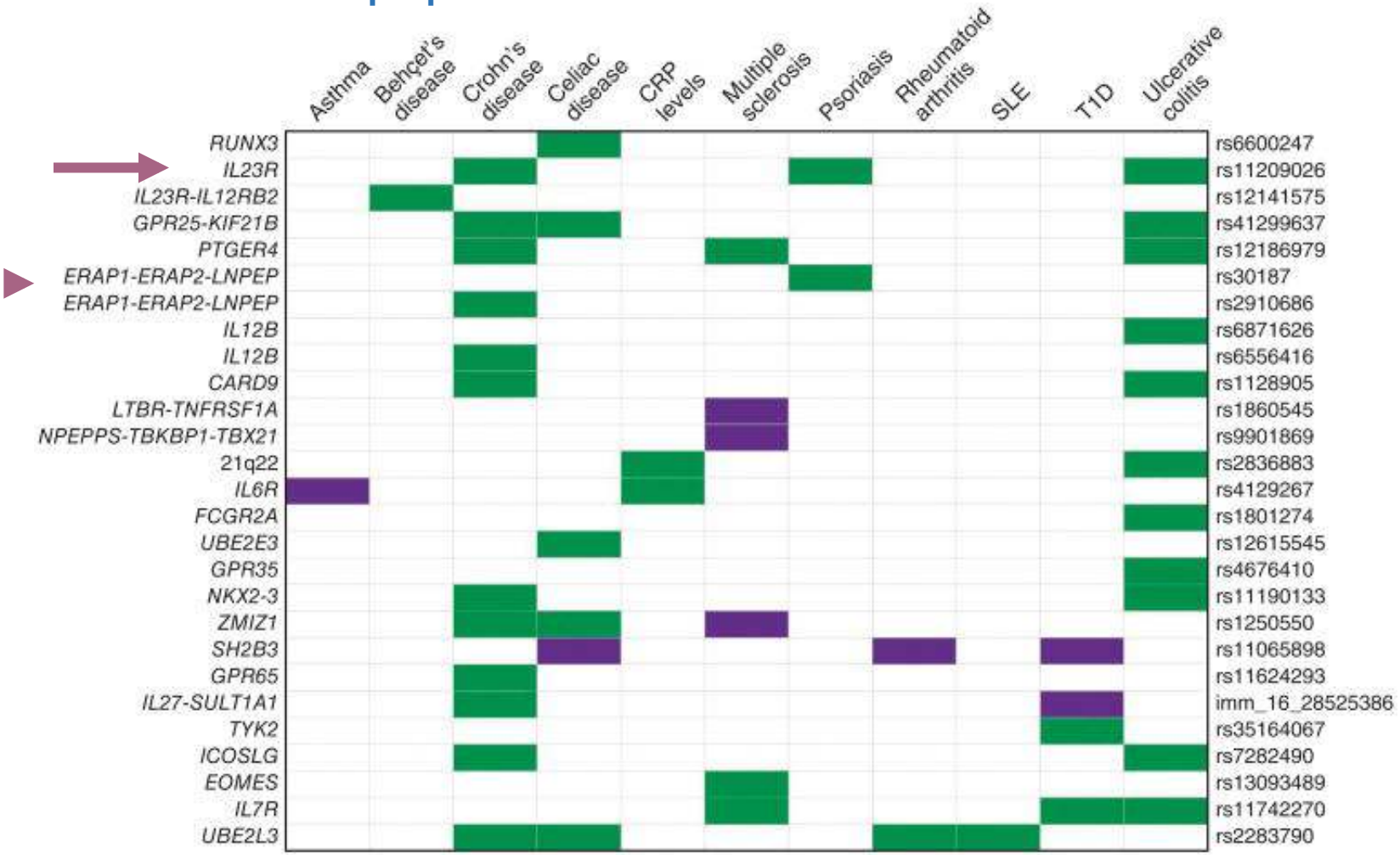
McGonagle D, McDermott MF. A proposed classification of the immunological diseases. *PLoS Med 2006 3(8): e297. (pmed 0030297)*

The Link Between Gut & SpA

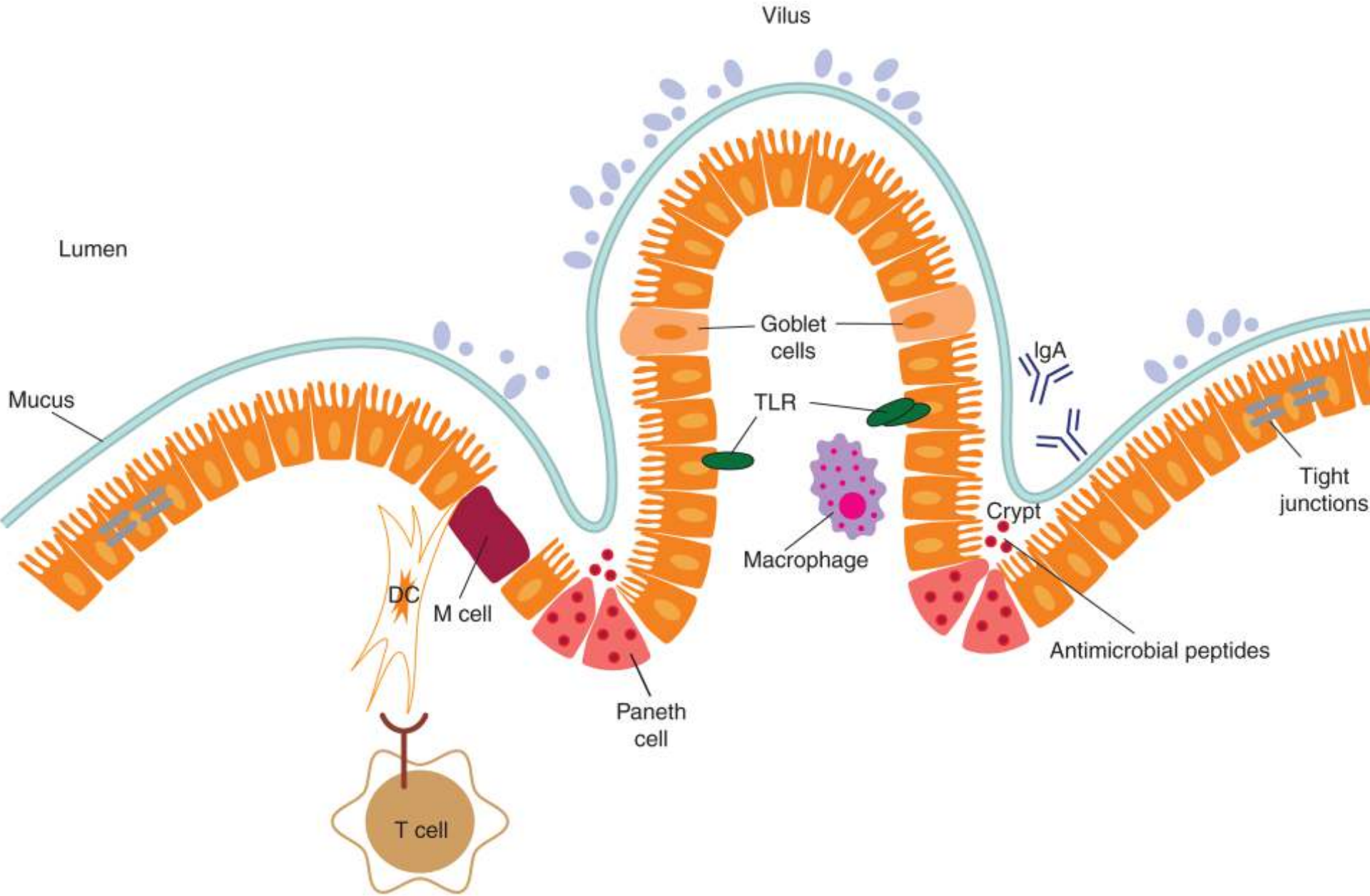
- Approximately one-half of SpA patients exhibit signs of microscopic gut inflammation.
- Chronic gut inflammation predicts a higher risk of evolving to AS.
- Remission of joint disease is associated with reduced bowel inflammation and vice versa. Therapies targeting inflammation at both sites may, therefore, be beneficial in SpA patients with bowel inflammation.

AS genetic susceptibility loci overlap with those of other autoimmune diseases

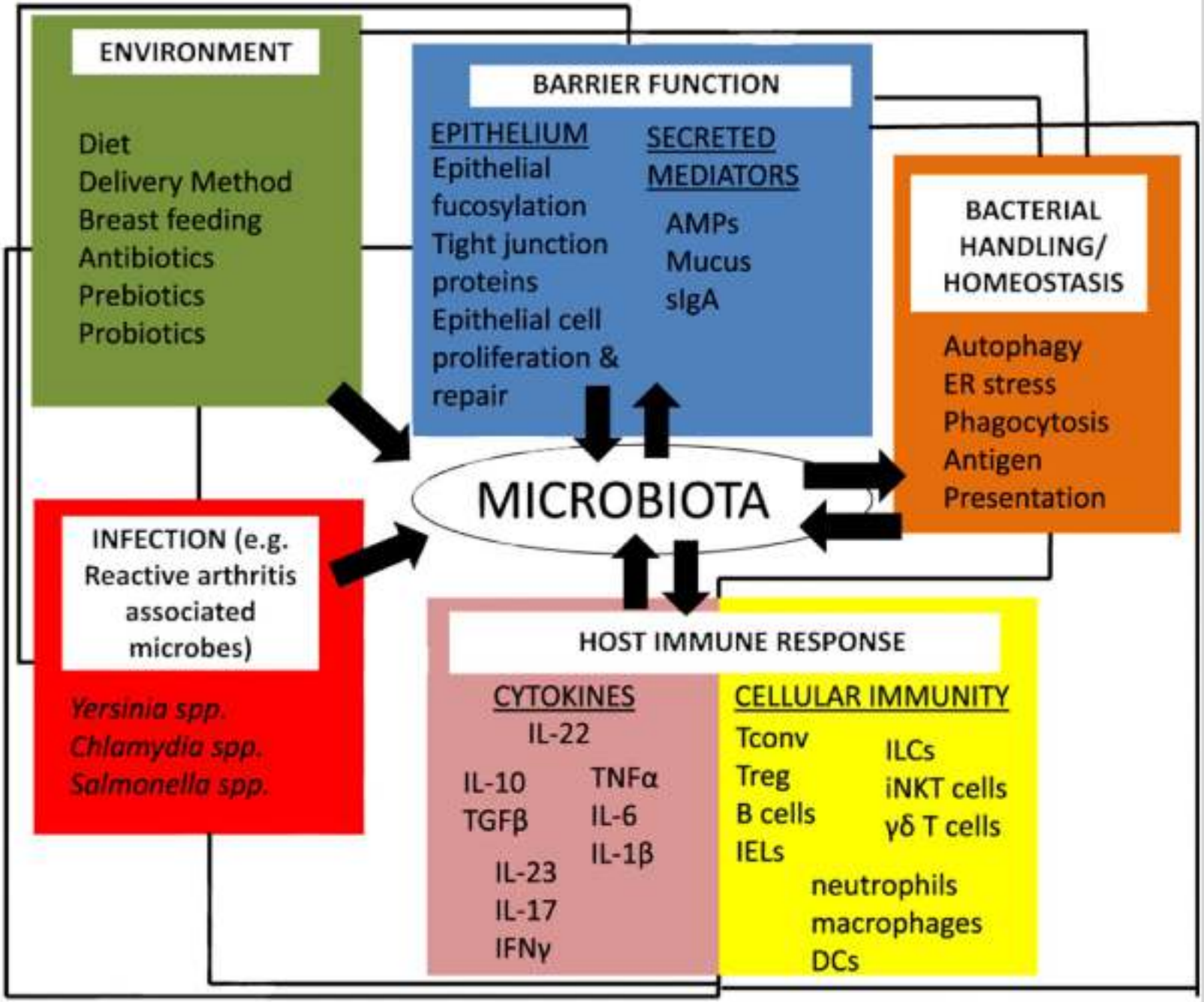
Diseases are represented in **columns**, and 27 of the >40 AS susceptibility loci are represented in **rows**. Shared susceptibility loci are colored **green** if effect size is concordant and **purple** if effect size is discordant.



Cortes A, et al. *Nat Genet*. 2013 July; 45(7): 730–38

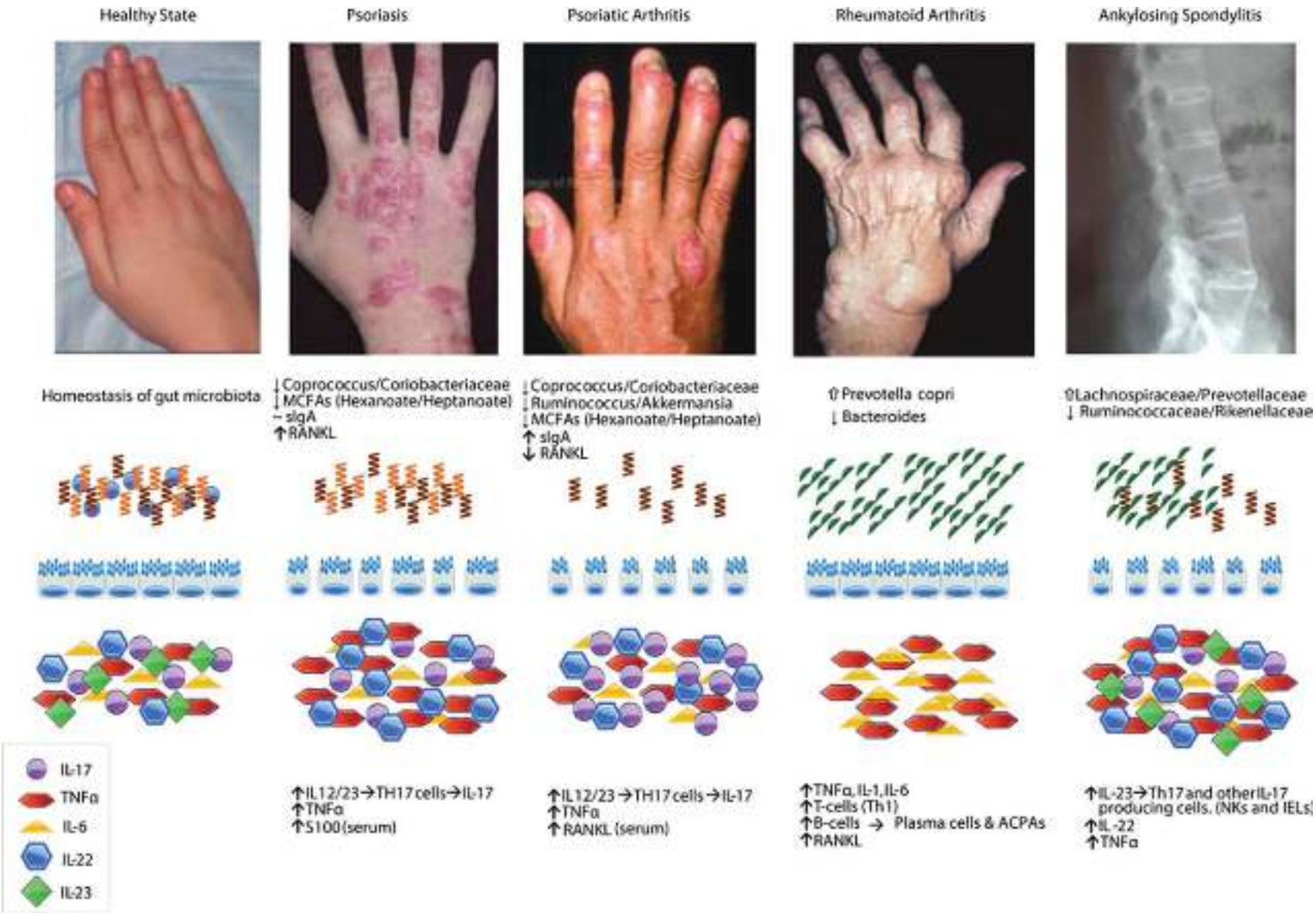


Costello *et al*. Microbes, the gut and AS. *Arthritis Research & Therapy* 2013, **15**:214



Asquith M, et al. Best Pract Res Clin Rheumatol. 2014; 28(5): 687–702.

Effect of Dysbiosis (Homeostasis Imbalance in Gut Microbiome)

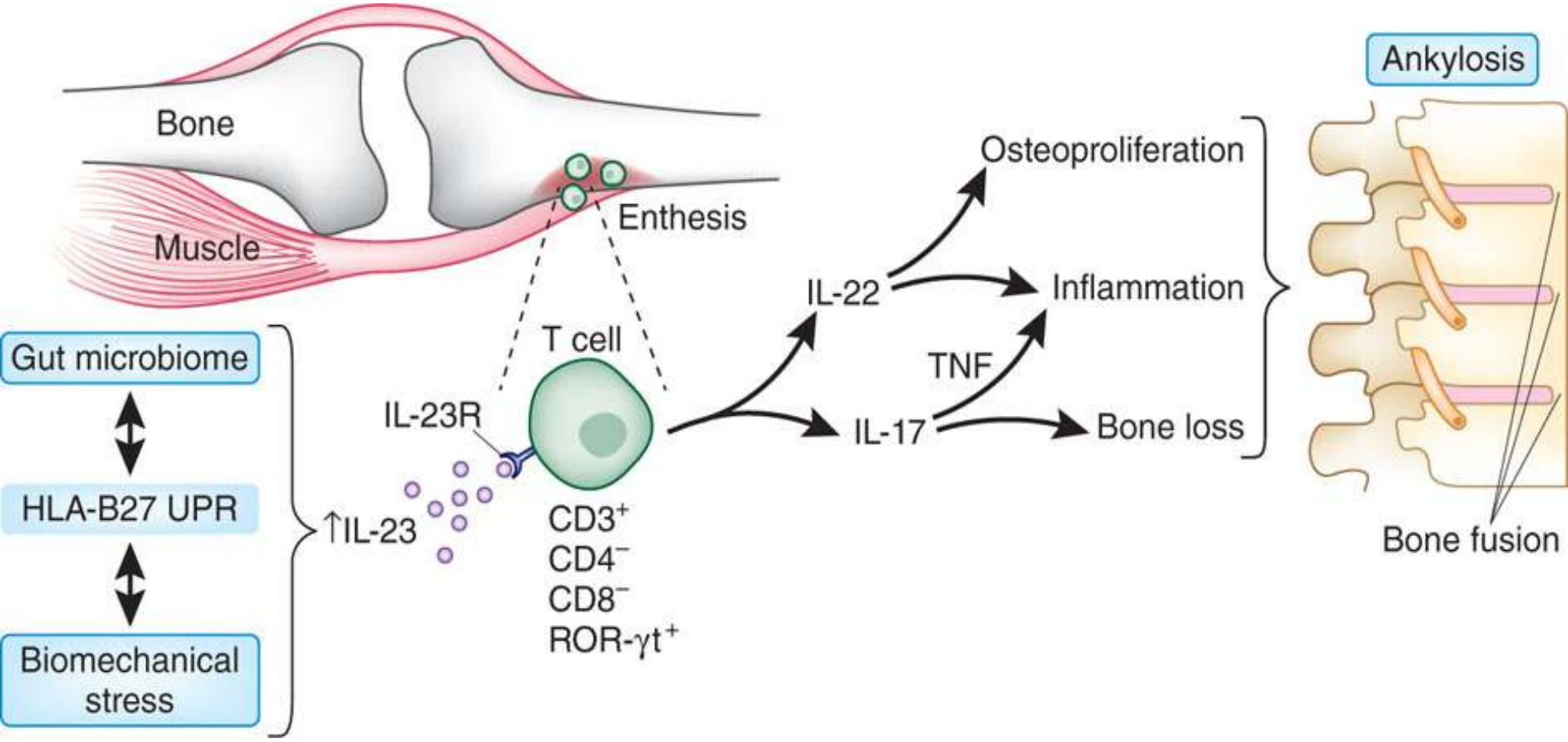


Scher JU, et al. Arthritis Rheumatology 2016;68(1):35-45

Therapeutic modulation of the microbiota

Despite compelling evidence for a major role for the microbiota in SpA and CD pathogenesis, there are **currently insufficient data from human studies** to make clinical recommendations with respect to therapeutic modulation of the microbiota by diet, probiotics, antibiotics, or other means.

Role of IL-23 and Entheseal-resident T cells in the Pathogenesis of Spondyloarthritis



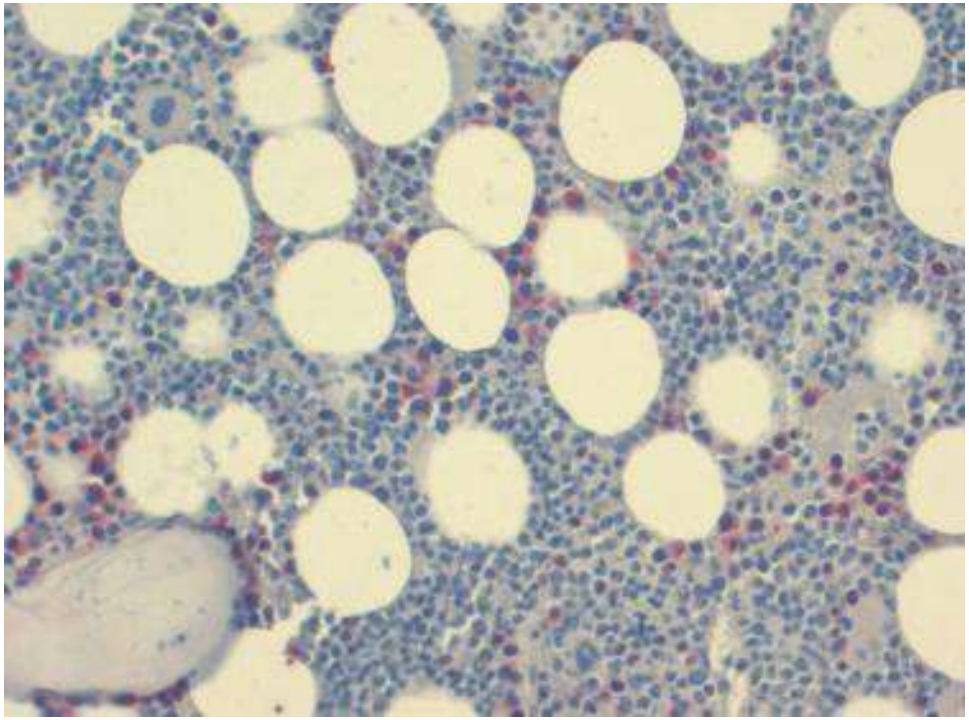
Enthesis, a key target in SpA, is now shown to contain a unique population of naïve resident T cells, which, when activated by the cytokine IL-23, can promote pathogenesis characteristic of SpA. This has provided potential for new therapeutic approaches for treatment of AS, IBD and psoriasis.

Sherlock JP, et al. IL-23 induces spondyloarthropathy by acting on ROR-γt+ CD3+CD4-CD8- entheseal resident T cells. *Nature Medicine* 2012, 18:1069-1076

Lories RJ , McInnes IB. Primed for inflammation: enthesis resident T-cells. *Nature Medicine 2012;* 18: 1018–1019

Evidence for the role of IL-23/IL-17 Axis in AS

IL-17+ cells in **facet joint** of a patient with AS.



Appel H, Maier R, Wu P, et al. *Arthritis Res Ther.* 2011; 13(3): R95.

Moreover, increased serum IL-17 and IL-23 in AS patients has also been reported.

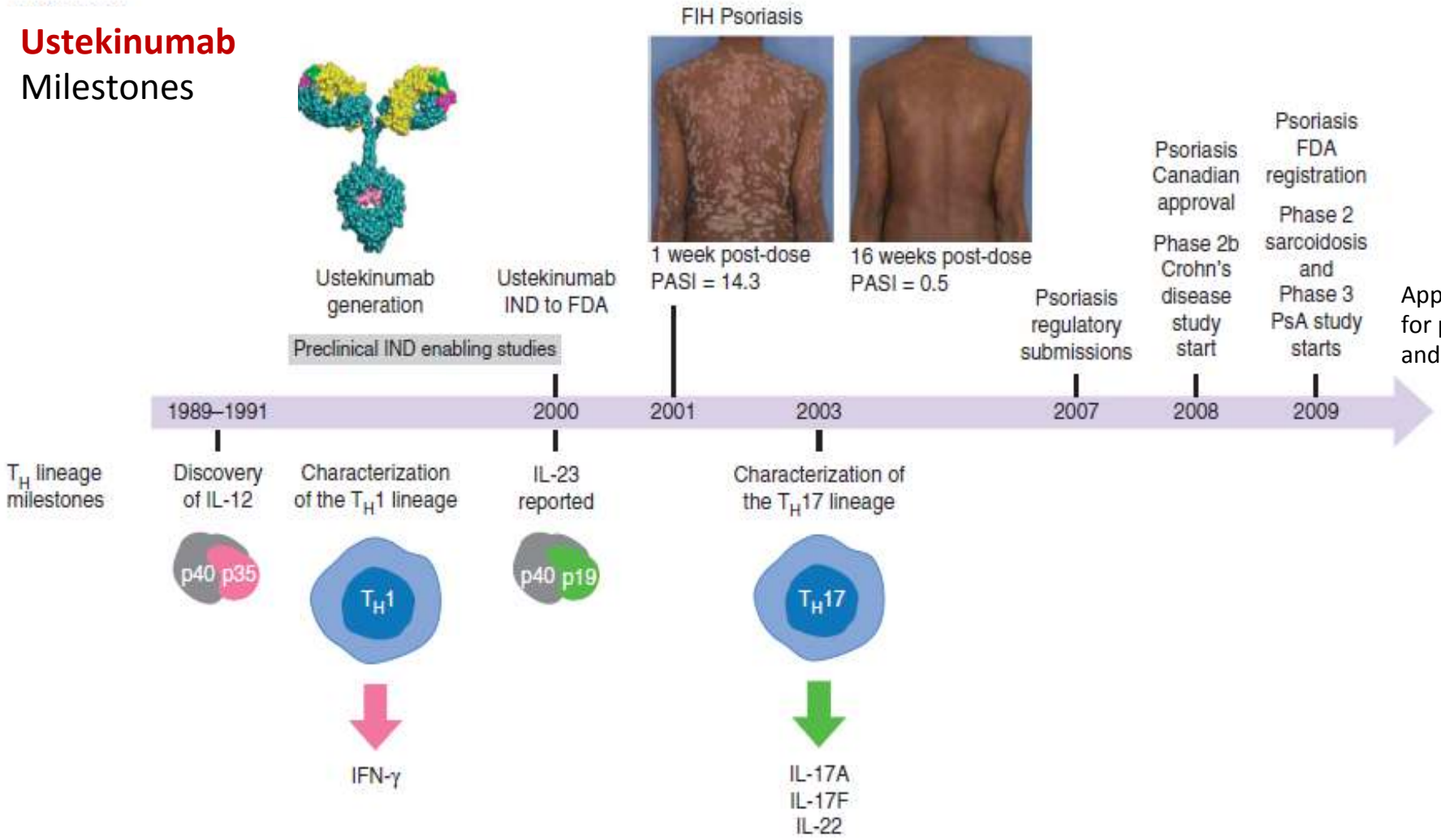
Mei Y, et al. *Clin Rheumatol*. 2011;30(2):269-73.

Genetic Associations and Treatment of AS

GENETIC ASSOCIATION WITH AS	TREATMENTS & THERAPEUTIC TRIALS IN AS	TARGET MOLECULES
IL12B, IL23R	Ustekinumab	P40 subunit of IL-12 &23
IL12B, IL23R	Secukinumab	IL-17A
IL23R	Tofacitinib	JAK
IL23R, TYK2	Fostamatinib	TYK2
TNFR1	Etanercept, infliximab, adalimumab, golimumab, certolizumab	TNF
PTGER4	NSAIDs	Prostaglandin

Adapted from: Cortes A, et al. *Nat Genet*. 2013 July; 45(7): 730–38.
Also association with *RANK* and *PTGS1*. Cortes A, et al. *Ann Rheum Dis*. 2014, March 26 {epud ahead of print}

Ustekinumab
Milestones



Ritchlin C, et al. Ann Rheum Dis 2014;73:990–999. (PSUMMIT2 Trial)
Tzellos T, et al. J Eur Acad of Dermatol & Venereol. 2013; 27(5):622-7
Baeten D, et al *Lancet*. 2013 Nov 23;382(9906):1705-13.
Poddubnyy D, et al. *Ann Rheum Dis.* 2014; Jan 3 (Epud ahead of print)
Smith JA, Colbert RA. *Arthritis Rheum*. 2014 February; 68(2): 231-41
Minyoung Her & Kavanaugh A. *Current Opin Rheumatol.*. 2013; 25(4):455-9.
Patel DD, et al. *Ann Rheum Dis*. 2013 Apr;72 Suppl 2:iii116-iii123
Papp K, et al. *Br J Dermatol*. 2013; 168(4):844-54., and AAD 2013. Abstract P6924.

Newer Treatments Being Developed for SpA

Company	Drug	Drug target	US status
Janssen (New Jersey)	**Ustekinumab (Stelara)** Human	IL-12/23 p40	• Approved: Mod-severe PsO (2009)[5] • Approved: Active PsA (2013)[1, 6] • Phase 2 completed in AS[7,8] • Phase 2 published[9],Phase 3 completed in CD[10]
Novartis (Basel)	**Secukinumab (Cosentyx)** A fully human IgG1 monoclonal antibody	IL-17A	• Approved for PsO (2015)[2] • Approved for PsA and AS (2016) • CD terminated[13,14]

1. Ratner M., *Nat Biotechnol* 2014 Jun;32(6):505-7. doi: 10.1038/nbt0614-505.
2. FDA.gov: FDA approves new psoriasis drug Cosentyx (Published 2015 Jan 21; Accessed 2015 Sept 15). http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm430969.htm
3. Novartis Press Release: Novartis announces new one-year results demonstrating sustained secukinumab efficacy in ankylosing spondylitis patients. (Published 10 June 2015; Accessed 2015 Sept 14). https://www.novartis.com/news/media-releases/novartis-announces-new-one-year-results-demonstrating-sustained-secukinumab
4. Novartis Press Release: Novartis announces publication in The Lancet showing sustained efficacy with secukinumab over one year in psoriatic arthritis patients (Published 2015 June 29; Accessed 2015 Sept 15). https://www.novartis.com/news/media-releases/novartis-announces-publication-lancet-showing-sustained-efficacy-secukinumab
5. FDA.gov: Press release -FDA Approves New Drug to Treat Psoriasis (Published 2009 25 Sept; Accessed 2015 Sept 15) http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm183851.htm
6. J&J Investor Relations: STELARA® (Ustekinumab) Receives FDA Approval To Treat Active Psoriatic Arthritis (Published 2013 Sept 23; Accessed 2015 Sept 15) http://www.investor.jnj.com/releasedetail.cfm?releaseid=792461
7. Clinicaltrials.gov: Ustekinumab for the Treatment of Patients With Active Ankylosing Spondylitis (TOPAS); https://clinicaltrials.gov/show/NCT01330901
8. Poddubnyy D, et al. *Ann Rheum Dis.* 2014 May;73(5):817-23. doi: 10.1136/annrheumdis-2013-204248. Epub 2014 Jan 3.
9. Sandborn W.J., et al. *N Engl J Med* 2012 Oct 18;367(16):1519-28. doi: 10.1056/NEJMoa1203572.
10. Clinicaltrials.gov: A Study to Evaluate the Safety and Efficacy of Ustekinumab in Patients With Moderately to Severely Active Crohn's Disease Who Have Failed or Are Intolerant to Tumor Necrosis Factor (TNF) Antagonist Therapy (UNITI-1); https://clinicaltrials.gov/ct2/show/NCT01369329
11. Clinicaltrials.gov: 16 Week Efficacy and 2 Year Long Term Safety and Efficacy of Secukinumab in Patients With Active Ankylosing Spondylitis (MEASURE 1); https://clinicaltrials.gov/ct2/show/NCT01358175
12. Clinicaltrials.gov: Extension Study up to 3 Years for Secukinumab in Psoriatic Arthritis (FUTURE 1 ext); https://clinicaltrials.gov/ct2/show/NCT01892436
13. Clinicaltrials.gov: An Open Label Safety and Tolerability Study of AIN457 in Patients With Moderate to Severe Crohn's Disease; https://clinicaltrials.gov/ct2/show/NCT01009281
14. Hueber W., et al. *Gut.* 2012 Dec;61(12):1693-700. doi: 10.1136/gutjnl-2011-301668. Epub 2012 May 17.

Secukinumab Efficacy in AS at Week 16

[MEASURE 1][3]

	Secu 75 mg§ (N=124)	Secu 150 mg§ (N=125)	Placebo (N=122)	p Value
ASAS 20%ǂ	59.7%*	60.8%*	28.7%	p<0.01[1] p<0.0001[2]
ASAS 40%	33.1%*	41.6%*	13.1%	p<0.01[1] p<0.001[2]

*all patients received 10mg/kg IV loading dose before SC maintenance dosing
ǂPrimary endpoint
*statistically significant vs. placebo

For comparison:

ASAS 40 response to TNFi vs Placebo at Wk 24

TNFi response range = 39 to 53%
Placebo response range = 12 to 16%

1. Baeten D. L. et al. Secukinumab, a monoclonal antibody to Interleukin-17A, Significantly improves Signs & Sx of AS: Results of a 52-week Phase 3 Randomized Placebo-Controlled Trial with IV Loading and S/C Maintenance Dosing; (Abstract 819). ACR Annual Meeting. November 17, 2014, Boston, MA.
2. Medscape. Secukinumab Successful in Spondylitis, Psoriatic Arthritis". [Published 2014 Nov 24; Accessed 2015 Sept 14]. http://www.medscape.com/viewarticle/835389
3. Clinicaltrials.gov: 16 Week Efficacy and 2 Year Long Term Safety and Efficacy of Secukinumab in Patients With Active AS (MEASURE 1) https://clinicaltrials.gov/ct2/show/NCT01358175?term=NCT01358175&rank=1

Secukinumab Efficacy in AS at Week 16 [MEASURE 2][3]

	Secu 150 mg§ (N=72)	Placebo (N=74)	p Value
ASAS20ǂ	61.1%*	27.0%	p<0.001[1]
ASAS20			
TNF-naïve	68.9%*	31.1%	p<0.05[1]
TNF-IR	48.1%*	20.7%	
ASAS40			
TNF-naïve	44.4%*	17.8%	p<0.05[1]
TNF-IR	22.2%*	0%	

(Secukinumab 75mg (N=73) provided numerically greater response than PBO at wk 16, but these did not reach statistical significance for any of the pre-specified primary or secondary endpoints)

UPDATE: 52 week data[4,5] – 73.8% of patients achieved ASAS20 response at 52 weeks with associated improvements in physicial function and health-related quality of life.

§all patients received weekly subcutaneous dosing for 4 weeks followed by dosing every 4 weeks
ǂPrimary endpoint
*statistically significant vs. placebo

1. Sieper J., et al. Secukinumab, a Monoclonal Antibody to Interleukin-17A, Significantly improves Signs and Symptoms of Active Ankylosing Spondylitis: Results of a Phase 3 Randomized Placebo-Controlled Trial with Subcutaneous Loading and Maintenance Dosing; (Abstract 536). ACR Annual Meeting. November 16, 2014, Boston, MA.
2. Medscape. Secukinumab Successful in Spondylitis, Psoriatic Arthritis". [Published 2014 Nov 24; Accessed 2015 Sept 14]. http://www.medscape.com/viewarticle/835389
3. Clinicaltrials.gov: 16 Week Efficacy and 5 Year Long Term Efficacy, Safety and Tolerability of Secukinumab in Patients With Active Ankylosing Spondylitis (MEASURE2) https://clinicaltrials.gov/ct2/show/NCT01649375
4. Novartis Press Release: Novartis announces new one-year results demonstrating sustained secukinumab efficacy in ankylosing spondylitis patients. [Published 10 June 2015; Accessed 2015 Sept 14]. https://www.novartis.com/news/media-releases/novartis-announces-new-one-year-results-demonstrating-sustained-secukinumab
5. Sieper et al. Secukinumab Significantly Improves Signs & Symptoms of Active Ankylosing Spondylitis: 52-week data from MEASURE 2, A Randomized, Double-Blind, Placebo-Controlled Phase 3 Trial with Subcutaneous Loading and Maintenance Dosing; (Abstract 168, Oral Presentation). EULAR Annual Meeting; 2015, Rome, Italy.

Secukinumab in AS

Conclusions

- Secukinumab 150 mg S/C provided clinically significant and sustained improvements in the signs and symptoms of AS in both anti–TNF-naïve as well as anti–TNF-IR subjects
- Responses were induced rapidly and seen as early as week 1; observed for both ASAS and BASDAI responses
- The treatment lead to reduction in inflammation and improvements in physical function and health-related QoL in both anti–TNF-naïve and anti–TNF-IR subjects
- No case of serious fungal infection was reported in any treatment group
- One case of ulcerative colitis and Crohn's disease were reported (both secukinumab 75 mg)

Treat to Target Approach for Optimal Patient Care

Many patients receive sub-optimal care

Defining targets that consider all aspects of disease and optimally managing them and the comorbidities are necessary[1]

Treating spondyloarthritis, including AS and PsA, to target: recommendations of an international task force[1]

The task force defined the treatment target as remission or, alternatively, low disease activity, being aware that the evidence base is not strong and needs to be expanded by future research. These recommendations can inform the various stakeholders about expert opinion that aims for reaching optimal outcomes of SpA.

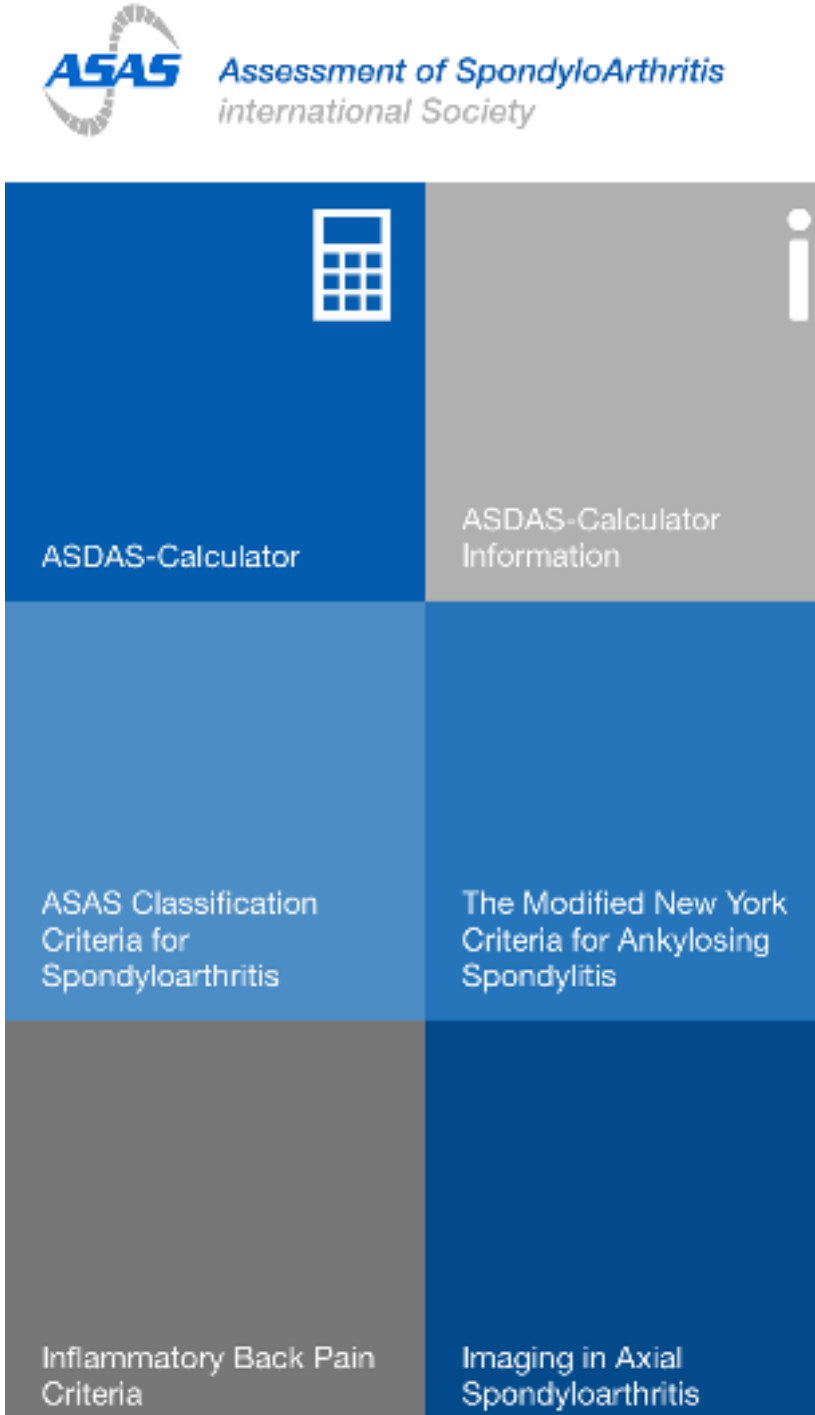
"A maximum of 6 months for reaching the treatment target of low disease activity or remission seems appropriate, but it is advisable to adapt therapy earlier if no significant reduction in disease activity is observed within 3 months"

[1] Smolen JS, et al. Ann Rheum Dis 2014:73:6-16.

AS Disease Activity Score (ASDAS) Calculator

www.asas-group.org

Sieper J et al. *Ann Rheum Dis* 2009;68;ii1-ii44

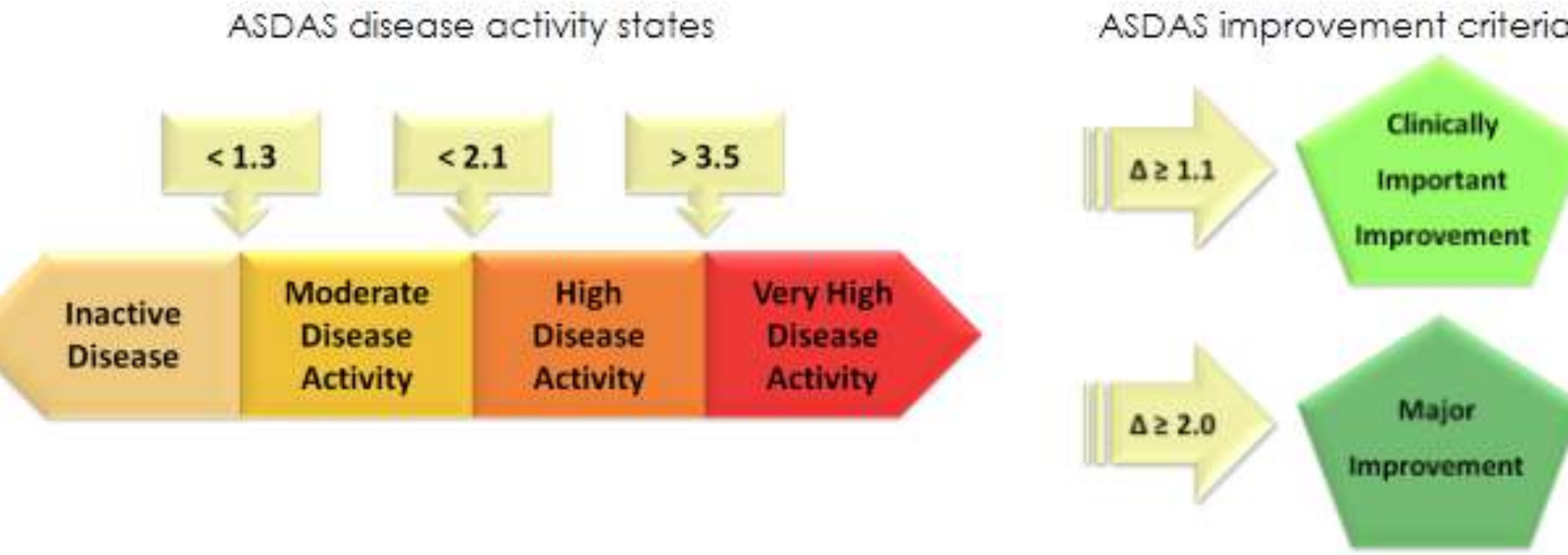


ASDAS-Calculator

Total back pain	5
Peripheral pain / swelling	5
Duration of morning stiffness	5
Patient global	5
CRP mg/dl	0.9

Clinically Important Improvement: ≥ 1.1
Major Improvement: ≥ 2

ASDAS

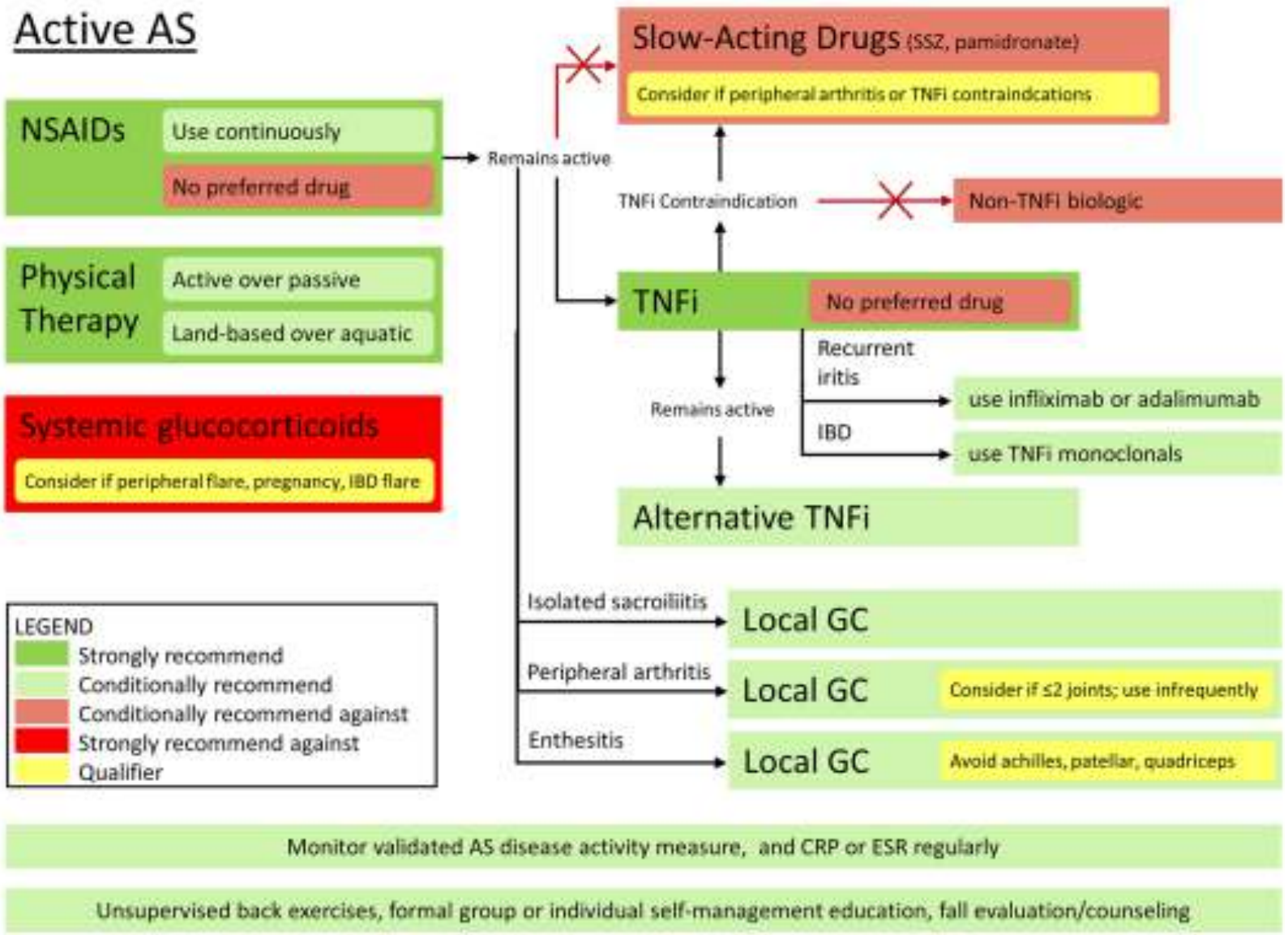


www..asas-group.org

Van der Heijde D, et al. Sensitivity and discriminatory ability of ASDAS in patients treated with etanercept or sulphasalazine in the ASCEND trial. Rheumatology (Oxford). 2012 Oct;51(10):1894-905. Epub 2012 Jul 6.

Fagerli KM et al. Selecting patients with ankylosing spondylitis for TNF inhibitor therapy: comparison of ASDAS and BASDAI eligibility criteria. Rheumatology (Oxford). 2012 Aug;51(8):1479-83

ACR/SSA/SPARTAN 2015 Recommendations for the Treatment of AS and nr-Axial SpA



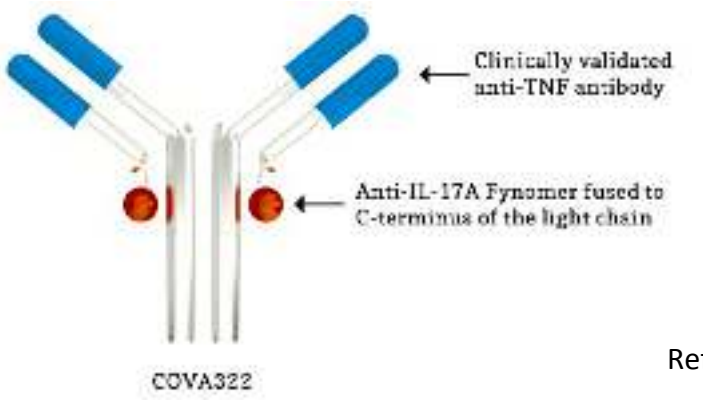
Ward MM, et al. Arthritis & Rheumatology 2016;68(2):282-98.

Newer Treatments Being Developed for SpA

Company	Drug	Drug target	US status
Merck/Sun Pharma (New Jersey)	**Tildrakizumab** (MK-322)	IL-23 p19	• Phase 2 completed in PsO • Phase 3 in PsO
Janssen (New Jersey)	**Guselkumab**	IL-23 p19	• Phase 2 in PsO completed • Phase 3 in PsO ongoing
Boehringer Ingelheim (Connecticut)	**BI-655066**	IL-23 p19	• Phase 2 ongoing in AS • Phase 2 ongoing in CD • Phase 2 completed in PsO
Amgen/ MedImmune (California/Maryland)	**AMG-139**	IL-23 p19	• Phase 1 completed in PsO • Phase 1 ongoing in CD

Newer Treatments Being Developed for SpA

Company	Drug	Drug target	US status
Janssen/ Covagen (New Jersey/Switzerland)	**COVA322 (Covagen)** Fully Humanized, Bispecific	TNF/IL-17A	• Phase 1/2 in PsO[1] • Preclinical in PsA[2] • Preclinical in AS[2]
AbbVie (Chicago)	**ABT-122** Fully Humanized, Bispecific	TNF/IL-17A	• Phase 1 completed in RA[3,4] • Phase 2 in PsA[5]



Ref6

1. Clinicaltrials.gov: Safety and Tolerability Study of COVA322 in Patients With Stable Chronic Moderate-to-severe Plaque Psoriasis; https://clinicaltrials.gov/ct2/show/NCT02243787
2. ADIS Insight: COVA322 At –A-Glance (Published 2015 Apr 23; Accessed 2015 Sept 15); http://adisinsight.springer.com/drugs/800040520
3. Gaffen S.L., et al. *Nature Reviews Immunology*. 2014 Sep;14(9):585-600. doi: 10.1038/nri3707.Clinicaltrials.gov: A Study to Evaluate the Safety, Tolerability and Pharmacokinetics of Multiple Subcutaneous Injections of ABT-122 in Subjects With Rheumatoid Arthritis; https://clinicaltrials.gov/ct2/show/NCT01853033
4. Clinicaltrials.gov: A Phase 2 Study to Investigate the Safety, Tolerability and Efficacy of ABT-122 in Subjects With Active Psoriatic Arthritis Who Have an Inadequate Response to Methotrexate; https://clinicaltrials.gov/ct2/show/NCT02349451
5. Covagen.com: COVA322 overview - http://covagen.com/pipeline/cova322/

Newer Treatments Being Developed for SpA

Company	Drug	Drug target	US status
Pfizer (New York)	**Tofacitinib** (Xeljanz)	JAK3	• Phase 3 in PsO completed[1]; FDA approval est. October 2015[7] • Phase 3 in PsA[8] • Phase 2 completed in AS[6]
Celgene (New Jersey)	**Apremilast** (Otezla)	PDE4	• Approved for PsO[12] • Approved for PsA[11] • Phase 2 AS published[10]; Phase 3 AS ongoing[1,9]
Bristol-Myers Squibb (New York)	**Abatacept** (Orencia)	Prevents T-cell activation	• Phase 2 published in PsA[3] • Phase 3 in PsA[4] • Ineffective in AS[2,5]
Alder (Washington State)	**Clazakizumab**	IL-6	• Phase 2 in PsA[13]

1. Ratner M., *Nat Biotechnol* 2014 Jun;32(6):505-7. doi: 10.1038/nbt0614-505.
2. Song I.H., et al *Ann Rheum Dis.* 2011 Jun;70(6):1108-10. doi: 10.1136/ard.2010.145946. Epub 2011 Mar 17.
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IL-23/IL-17 pathway genes associated with AS and overlap with PsA and Crohn's disease (CD)

Gene locus	Gene	OR (AS)	PsA Assoc	CD Assoc	Function
1p31	*IL23R*	0.65[a]	yes	yes	IL-23 receptor
1q21	*IL6R*	0.88	no	no	IL-6 receptor
2q11	*IL1R2-R1*	0.9, 1.11[b]	no	yes	IL-1 receptor
5p13	*PTGER4*	1.09	no	yes	Prostaglandin receptor
5q33	*IL12B*	1.11	yes	yes	Shared subunit for IL-12 and IL-23
9q34	*CARD9*	1.11	no	yes	Signaling molecule downstream of dectin-1 receptor
16p11	*IL27*	1.1, 1.24[b]	no	yes	Pro-Th1, suppresses Th17
17q21	*TBX21*	1.13	no	no[c]	Th1-directing transc factor T-bet
17q21	*STAT3*	0.84, 0.86[b]	yes	yes	Th17 differentiation
19p13	*TYK2*	0.88, 1.1[b]	yes	yes	IL-23R signaling

Judith Smith. Curr Rheumatol Repç 2016 (in press)

Association in SpA
(among "non-Hispanic whites" in US)

Ankylosing spondylitis	≥ 80 (%)
Reactive arthritis	30–70
IBD spondyloarthropathy	30–70
Psoriatic SpA	40–50
Juvenile enthesitis-related arthritis	~ 70
Undifferentiated SpA	~ 70
General Population	***~ 7***

Weaker associations among African Americans*

Brewerton DA, et al. Lancet 1973 April 28;1(7809):904-907
Schlosstein L, et al. N Eng J Med 1973 April 5;288(14):704-706
*Khan MA, et al. *J Rheumatol* 1977; 4(Suppl. 3): 39–43
*Khan MA, et al. *Ann Intern Med* 1979; 90: 202–203
Khan MA. *Ann Intern Med*. 2002;136: 896-907

Genetic Heterogeneity of HLA-B27

HLA-B*27:01 to B*27:146

- 145 subtypes (B*27:22 assignment withdrawn, it is in fact B*27:06)
- >160 alleles (based on nucleotide sequence differences)
- B*27:05 is the ancestral allele; it is the most widely distributed subtypes; B*2705 and B*2702 are the major Caucasian subtypes
- B*27:04, 5, 6 (and 11, 15, 20 & 21) are
- seen in South East Asians
- B*27:06 (and ?B*2709) NOT associated with AS

Khan MA. Polymorphism of HLA-B27: 145 subtypes currently known. (in submission)

Khan, MA. HLA and spondyloarthropathies. In Mehra N (Ed). *The HLA Complex in Biology and Medicine.* Jaypee Brothers Medical Publishers, New Delhi, India 2010; pp. 422-446

B*27:01		B*27:12
B*27:02		B*27:13
B*27:03		**B*27:14**
B*27:04		**B*27:15**
B*27:05	B*27:0502	B*27:16
	B*27:0503	B*27:17
	B*27:0504	B*27:18
	B*27:0505	**B*27:19**
	↓	B*27:20
	B*27:0513	B*27:21
B*27:06		B*27:23
B*27:07		B*27:24
B*27:08		B*27:25
B*27:09		↓
B*27:10		
B*27:11		B*27:146

HLA-B27 alpha 2 domain amino acid variations

	94	*95*	*97*	*103*	*105*	*113*	***114***	***116***	*131*	*152*	*156*	*163*	*167*	*171*
B*270502 B*2701/2/3/8	T	L	N	V	P	Y	H	D	S	V	L	E	W	Y
B*2704	-	-	-	-	-	-	-	-	-	E	-	-	-	-
B*2706	-	-	-	-	-	-	D	Y	-	E	-	-	-	-
B*2707	-	-	S	-	-	H	N	Y	R	-	-	-	-	-
B*2709	-	-	-	-	-	-	-	H	-	-	-	-	-	-

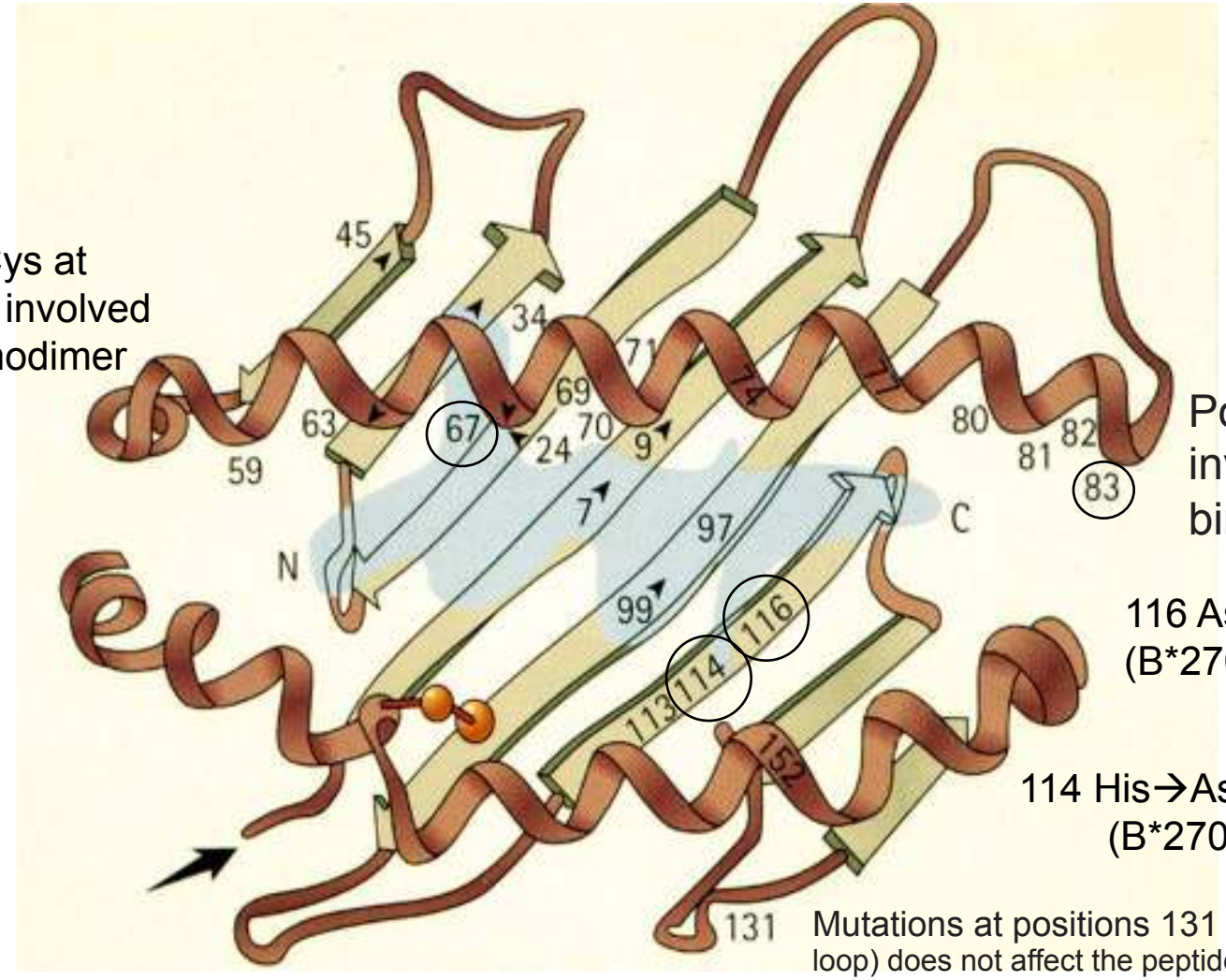
B*2704→B*2706: 114 His→Asp & 116 Asp→His

B*2705→B*2709: 116 Asp→His

Khan, MA. HLA and spondyloarthropathies. In Mehra N (Ed). *The HLA Complex in Biology and Medicine* Jaypee Brothers Medical Publishers, New Dehli, India 2010; pp. 422-446

Peptide-binding Groove of HLA-B27

Unpaired Cys at position 67 involved in B27-homodimer formation



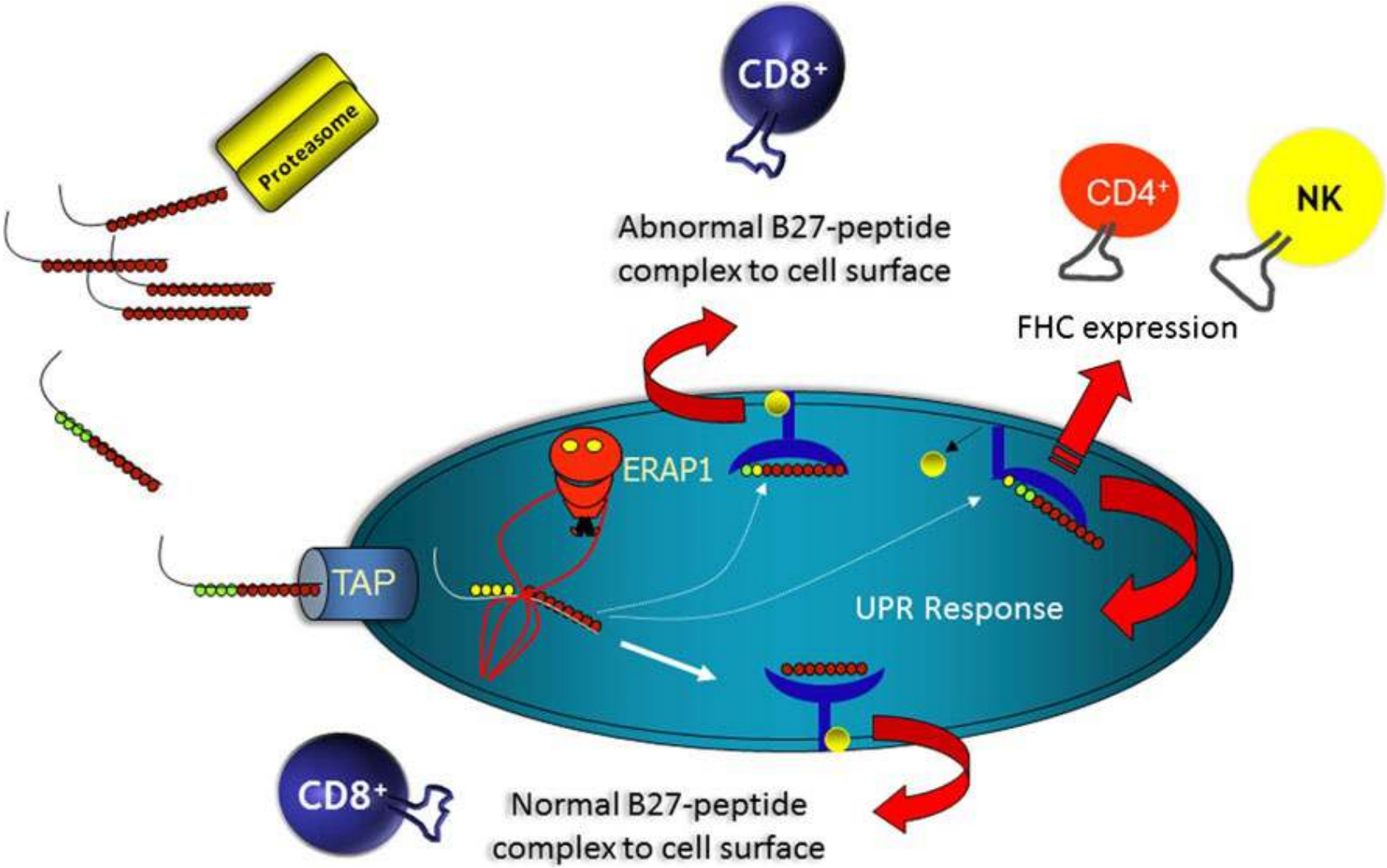
Position 83 may be involved in TCR binding

116 Asp → His
(B*2705 → B*2709)

114 His→Asp & 116 Asp→His
(B*2704→B*2706)

Mutations at positions 131 (in a non–peptide-binding loop) does not affect the peptide repertoire

Khan MA. Spondyloarthropathies. In Hunder G (Ed). ATLAS of RHEMATOLOGY. 4th Edition. Philadelphia, PA. Current Medicine;2005; pp. 151-180.

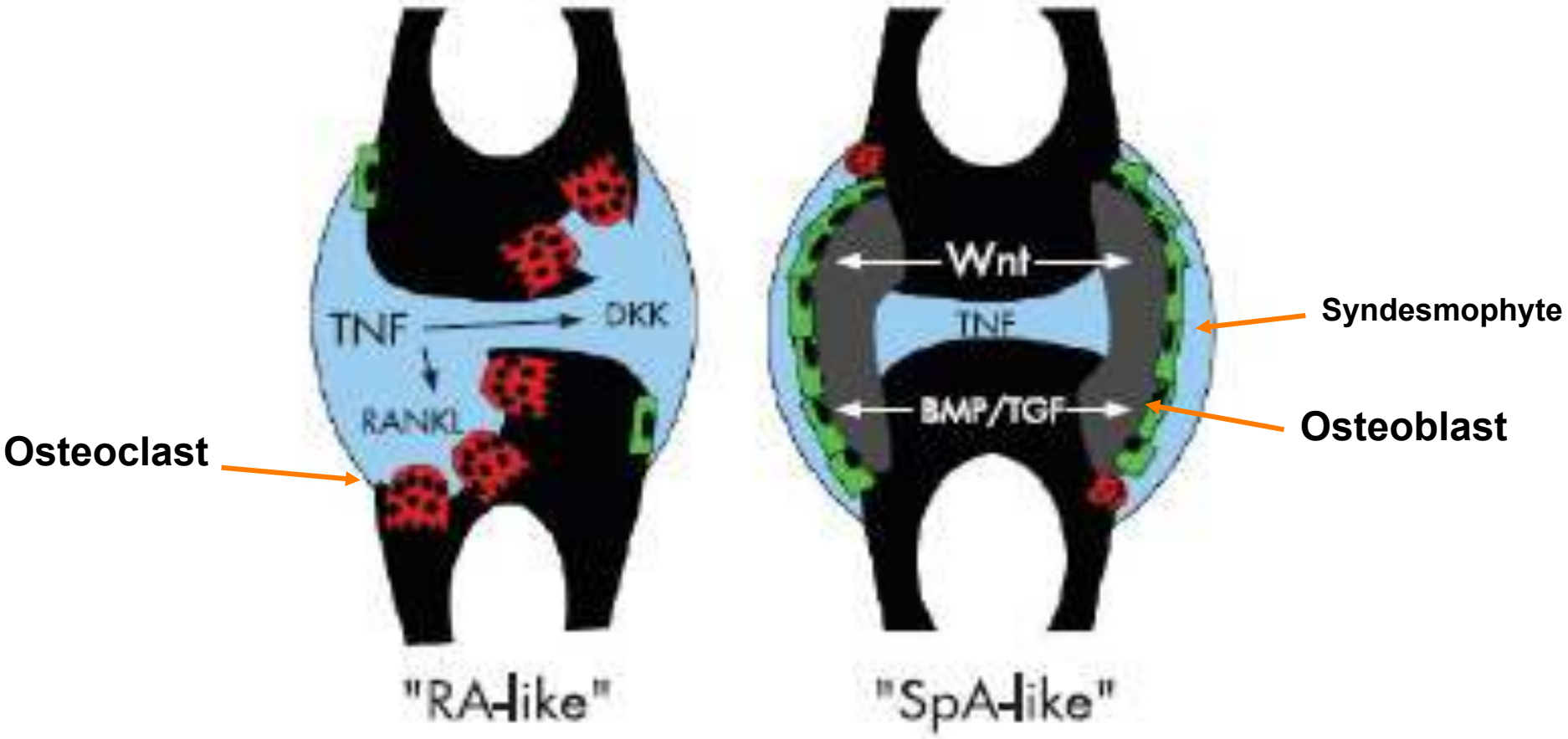


Haroon N. *Curr Rheumatol Rep.* 2012; 14:383–389

ERAP1 polymorphisms resulting in altered peptidase function can generate abnormal peptides that can be presented on MHC-I, leading to abnormal CD8 T cell immune responses. These peptides bind to MHC-I with low affinity and can trigger unfolding and, subsequently, the UPR. The free heavy chains can be presented as dimers on the cell surface that can interact with CD4+ T cells or NK cells via the killer immunoglobulin-like receptors (KIR).

Different Bone Response to Inflammation in RA and SpA

Structural damage in Axial SpA/AS has to be seen differently from that seen in RA



RANKL= RANK ligand; **DKK**= Dickkopf proteins; **BMP**=bone morphogenetic proteins;; **Wnt** = Wingless proteins; **TGF** = transforming growth factor beta

Schett et al. *Ann Rheum Dis*. 2007;66:709-11.
(Figure from the cover of the July 2007 issue.)

Concluding Remarks

- SpA form a heterogeneous group.
- They are much more common than previously thought.
- Much more effective treatments are now currently available.
- But early diagnosis is important for maximizing QoL and there is a need for more effective treatment retarding disease progression.
- Closer cooperation between relevant health care providers is crucial.