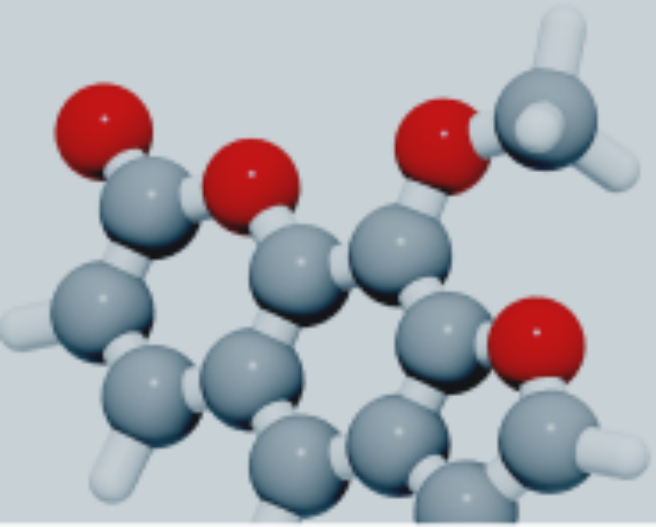
INFLAMMATION

More Than Skin Deep in Psoriasis



NEW YORK ACADEMY OF MEDICINE | HOSACK HALL | 5:15PM — 6:45PM

NOVEMBER 16TH, 2016

CME Outfitters

#SkinCME

Introductions and Overview of Systemic Inflammation

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D. Martin Carter Professor in
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Co-director, Center for
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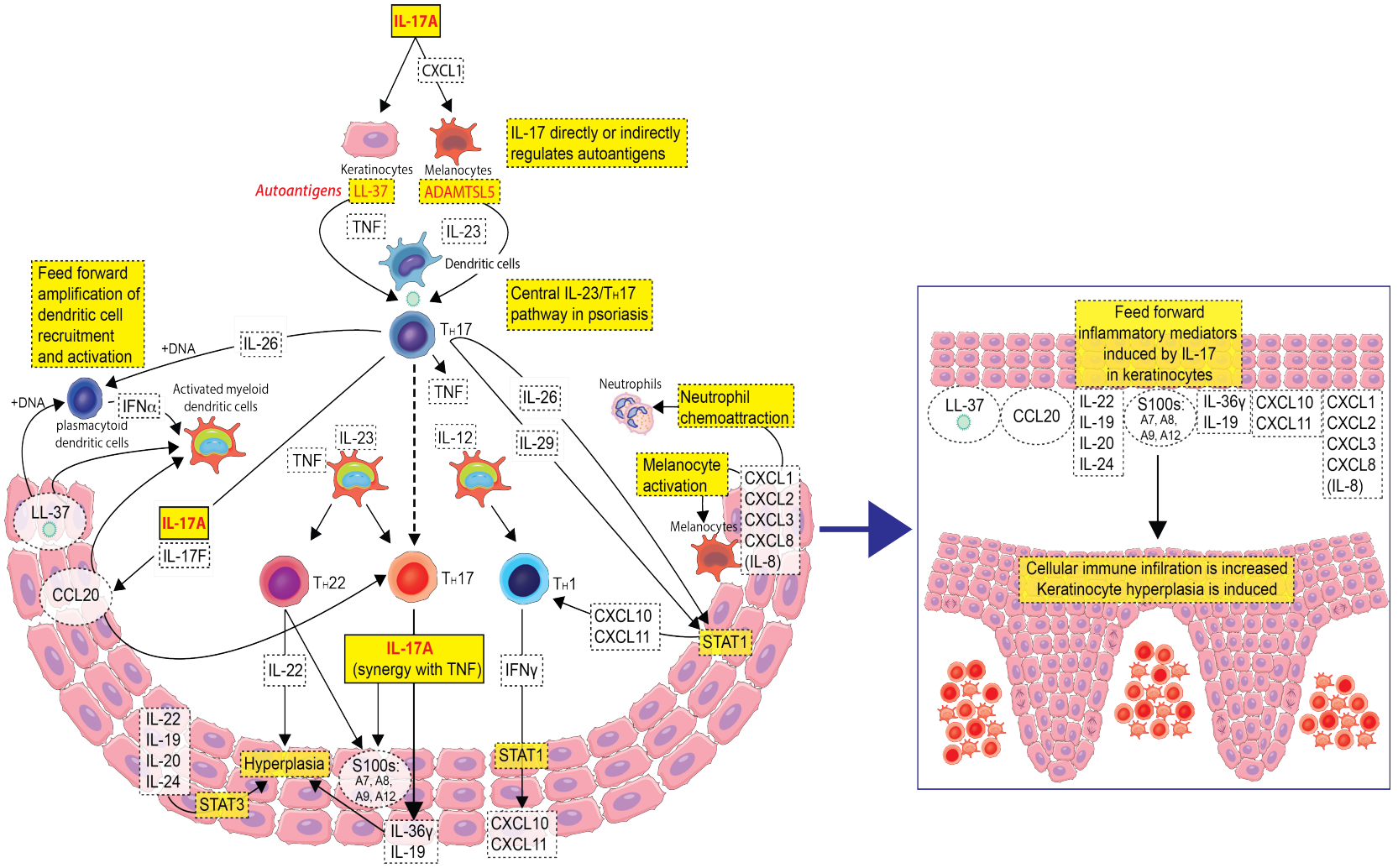
The Rockefeller University Hospital
New York, NY

Psoriasis: The Feed-Forward IL-17 Pathway Model that Includes New Auto-Antigens

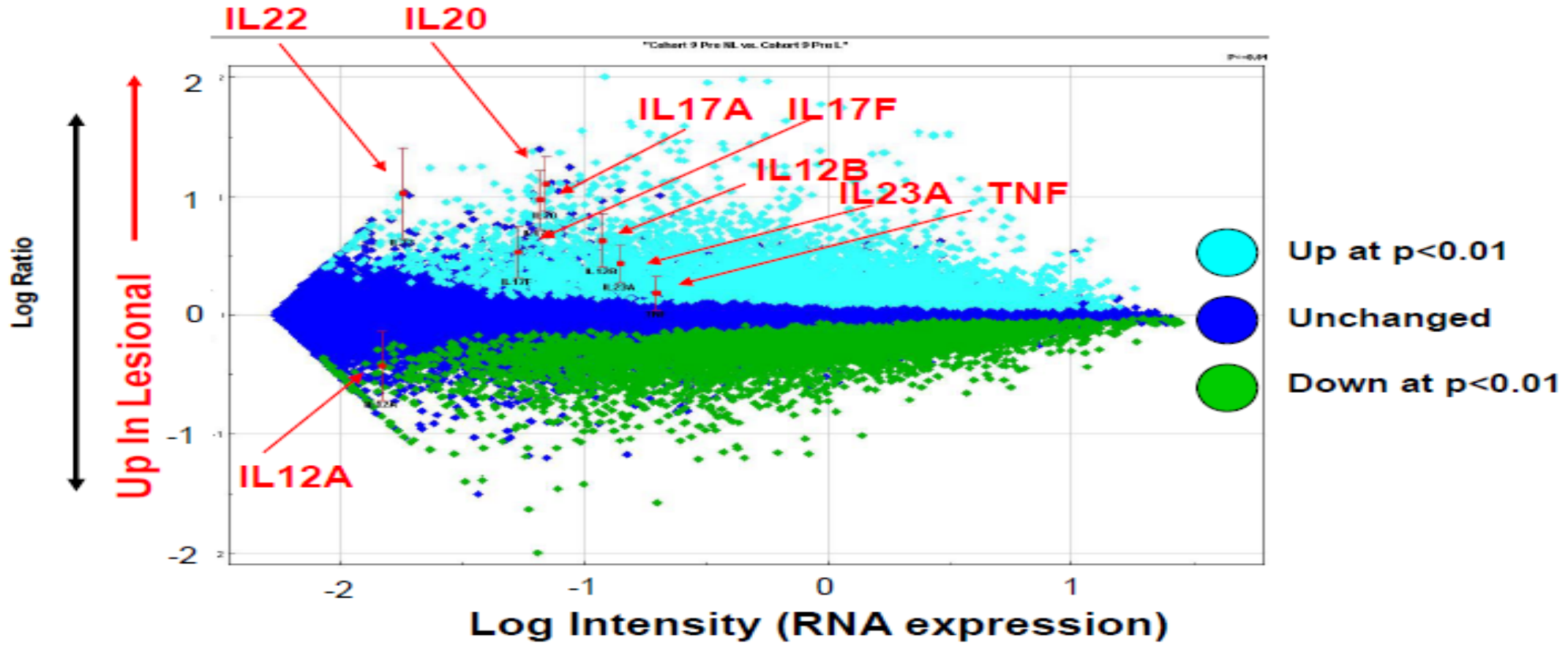


CXCL = chemokine ligand; IFN = interferon; IL = interleukin; STAT = signal transducer and activator of transcription.

Kim J, et al. *Annual Reviews.* Available at: http://www.annualreviews.org/doi/pdf/10.1146/annurev-med-042915-103905.

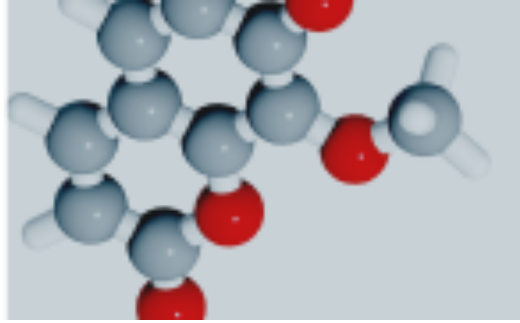
Differences in Lesional vs. Non-Lesional Psoriasis Skin

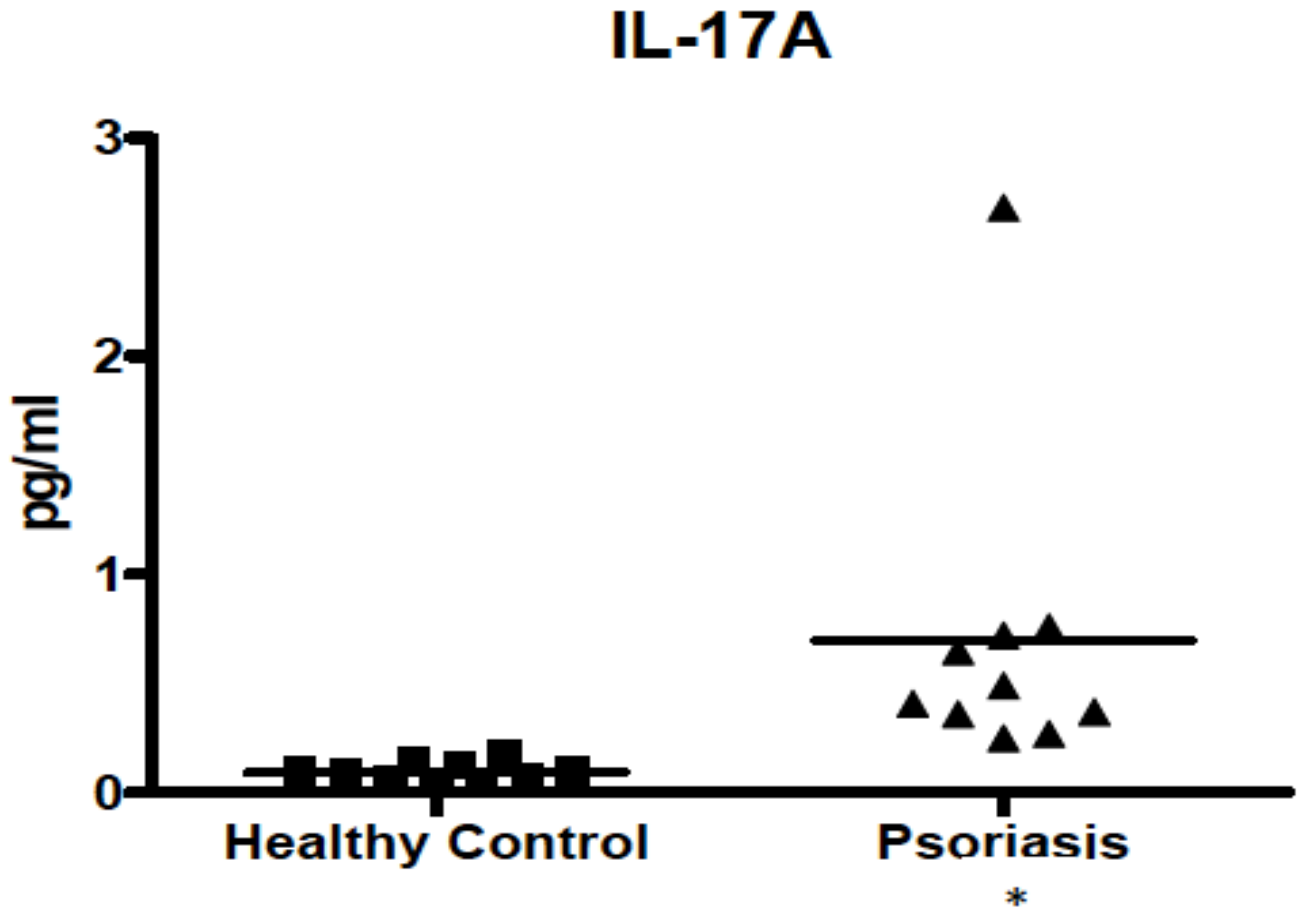
mRNA Array Reveals Major Differences in Lesional vs Non-Lesional Psoriasis Skin: Pre-dose Samples



Russell CB, et al. *J Immunol*. 2014;192(8):3828-3836.

IL-17 Serum Levels in Patients With Psoriasis





*Psoriasis vs. Healthy control, $p < .0001$, Mann-Whitney test.

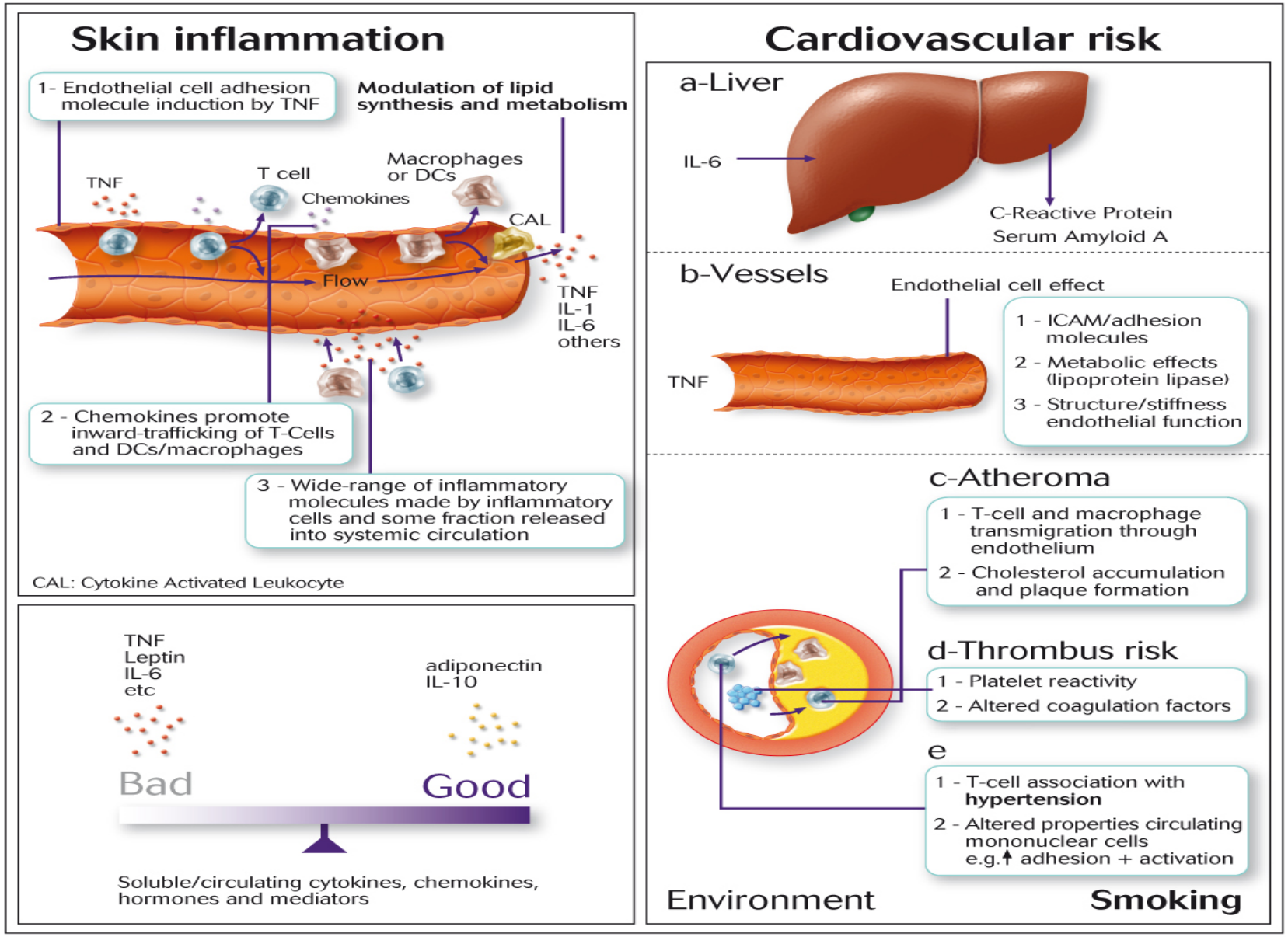
Suárez-Fariñas M, et al. *J Invest Dermatol*. 2012;132:2552-2264.

Increased Expression of 12 Proteins as Detected by Serum and Gene Microarray Assessments

Symbol	Name	Serum Measurements						Gene Array	
		P value[1]	FCH (psoriasis vs. healthy)	Healthy (n=162)	Psoriasis (n=146)	Psoriasis BMI<30 [2] (n=75)	Psoriasis BMI >30[2] (n=73)	FCH (LS vs. NL)	FDR
S100A12	ENRAGE	4.06×10^{-26}	2.30	25.46	58.55	55.94	60.22	889.1	$<10^{-20}$
ACPP	Prostatic acid phosphatase	1.17×10^{-35}	2.50	0.20	0.49	0.46	0.51	8.3	$<10^{-20}$
CCL22	MDC	$<10^{-50}$	3.03	409.31	1240.06	1227.13	1211.61	3.91	1.18×10^{-15}
IL1RN	IL1RA	5.67×10^{-32}	2.65	68.97	182.84	138.65	223.63	3.03	1.65×10^{-10}
TNPO1	MIP1β	1.52×10^{-39}	2.34	131.53	307.87	299.36	314.43	2.82	$<10^{-20}$
CCL2	MCP1	$<10^{-40}$	3.55	141.20	501.78	491.29	509.71	2.47	$<10^{-20}$
VEGFA	VEGF	1.74×10^{-29}	1.83	449.19	821.76	859.10	794.82	1.99	6.61×10^{-12}
ICAM1	ICAM1	1.67×10^{-05}	1.26	134.07	169.41	153.51	184.43	1.84	3.17×10^{-07}
IL15	IL-15	8.80×10^{-06}	1.25	0.65	0.81	0.80	0.81	1.84	8.86×10^{-09}
TNFRSF1B	TNF-RII	7.32×10^{18}	1.40	3.50	4.91	4.60	5.21	1.53	2.26×10^{-07}
TNF	TNFα	$<10^{-50}$	2.50	3.54	8.85	8.37	9.31	1.45[3]	5.51×10^{-08}
CXCL5	ENA78	1.40×10^{-45}	3.04	0.75	2.29	2.08	2.48	1.14[4]	6.28×10^{-02}

Suárez-Fariñas M, et al. *J Invest Dermatol*. 2012;132:2552-2264.

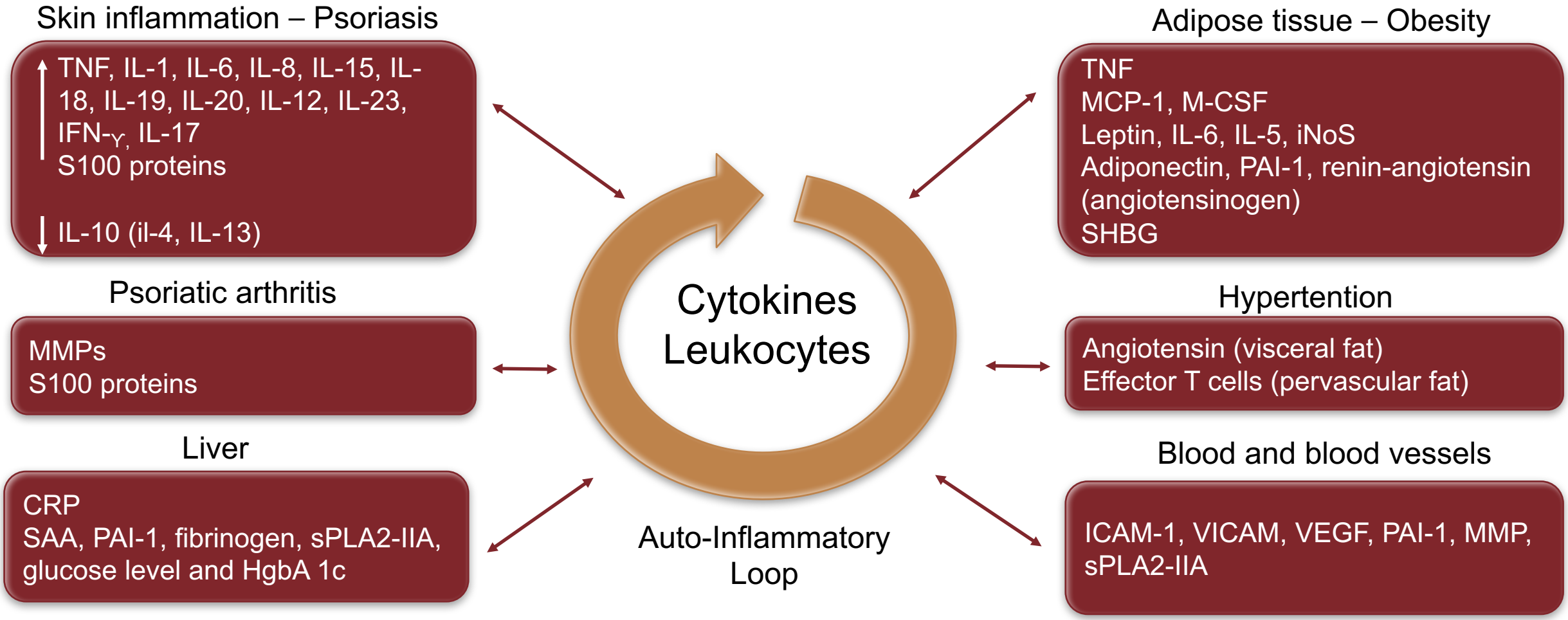
A New Model for the Relationship Between Skin Inflammation and CVD



CVD = cardiovascular disease; DC = dendritic cell; TNF-α= tumor necrosis factor α.

Davidovici BB, et al. *J Invest Dermatol*. 2010;130:1785-1796.

Vicious Circle of Inflammation

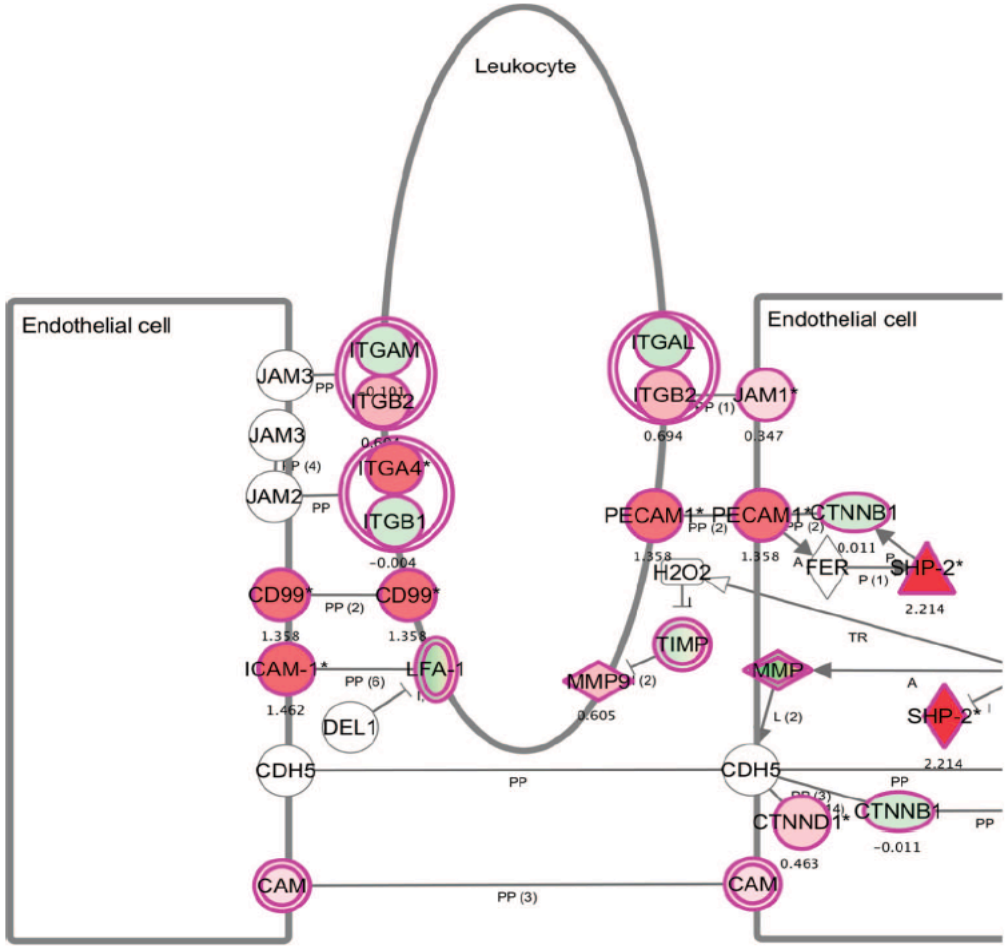


"Vicious circle of inflammation": mediators of inflammation produced in different organs or tissues are released into the systematic circulation and thus may contribute to the increased risk of inflammation in additional organs or tissues…

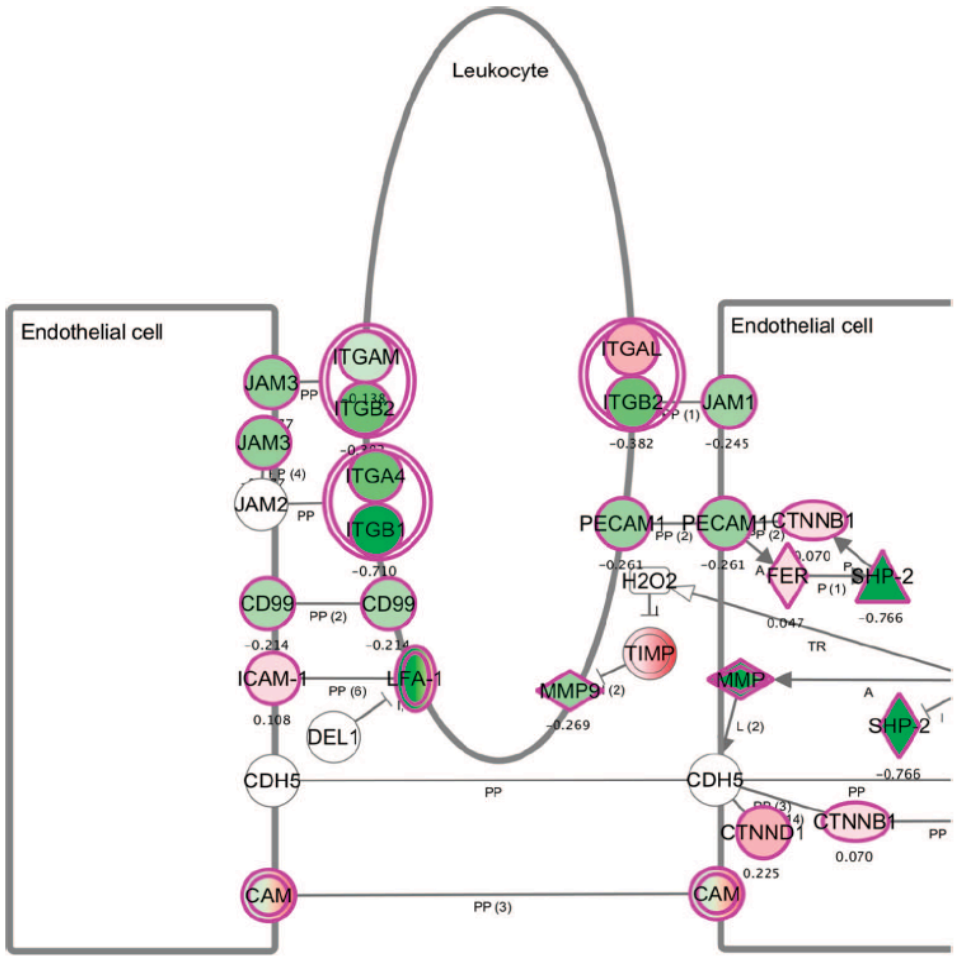
CRP = C-reactive protein; HgbA 1c = hemoglobin A1C; iNOS = inducible nitric oxide synthase; ICAM-1 = intracellular adhesion moleacule-1; MCP-1= monocyte chemoattractant protein-1; MMP = matrix metalloproteinases; M-CSF = macrophage colony stimulating factor; PAI-1 = plasminogen activator inhibitor; SAA = serum amyloid A; SHGB = sex hormone-binding globulin; sPLA2-IIA = secretory phospholipase A2 group Ia; VICAM = vascular intercellular adhesion molecule.

Davidovici BB, et al. *J Invest Dermatol*. 2010;130:1785-1796.

Genes Up-regulated in Blood Monocytes in Vitro in Response to IL-17

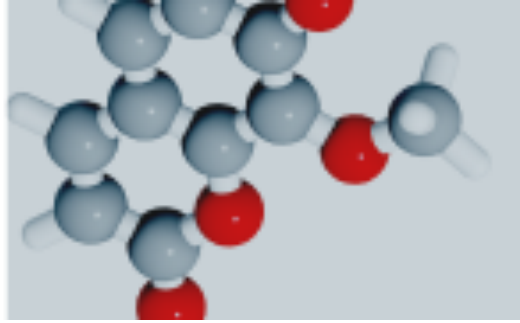


Genes Down-regulated in Blood of Psoriasis Patients 2 Weeks after Starting Ixekizumab (anti-IL-17)



Wang et al. *J Invest Dermatol*. 2014;134:2990-2993.

Summary



- Inflammation is more than skin deep in psoriasis and is a likely driver of systemic co-morbid diseases
- Today an in-depth discussion of
  - Pathologic spectrum of psoriatic disease
  - Cardiovascular disease risk
  - Treatment implications

#SkinCME

Tissue Heterogeneity

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University of Glasgow, Glasgow, Scotland
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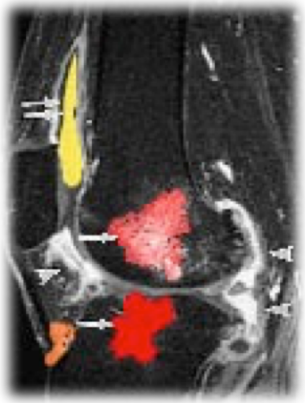
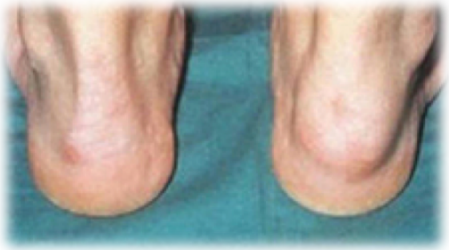
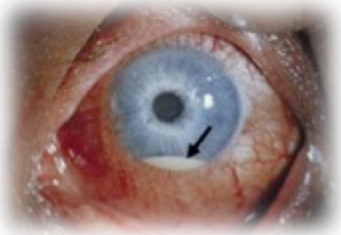
The Wider SpA Spectrum: Target Tissue Heterogeneity...

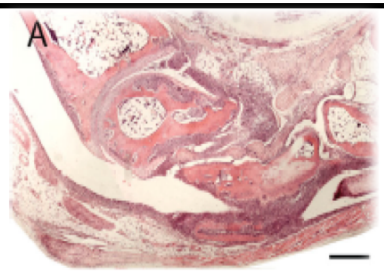
Axial SpA: bone, enthesis

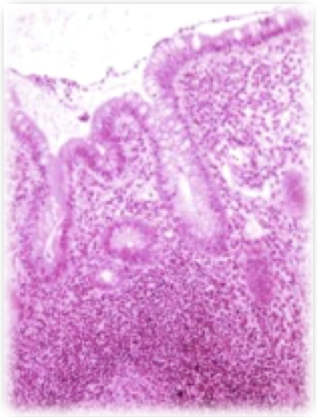


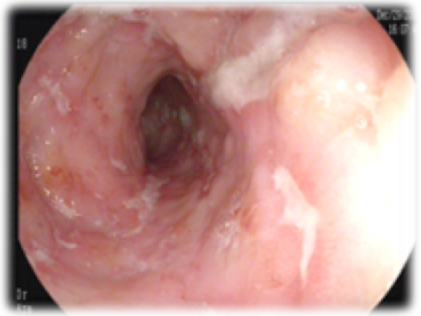
PsA: bone, enthesis, and synovium

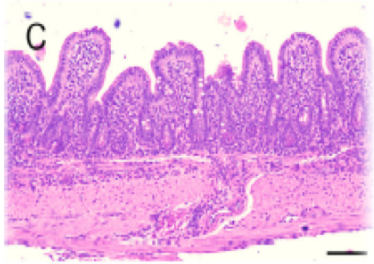


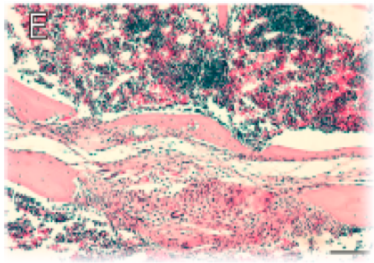


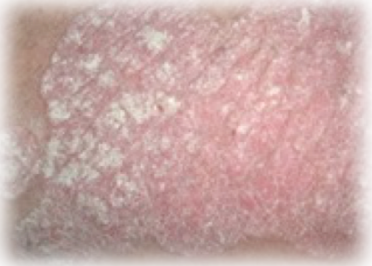


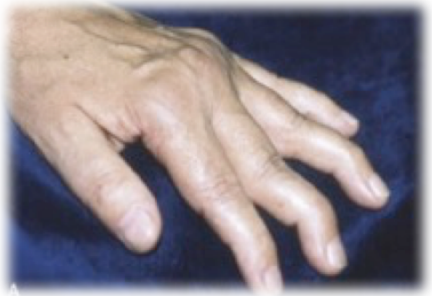


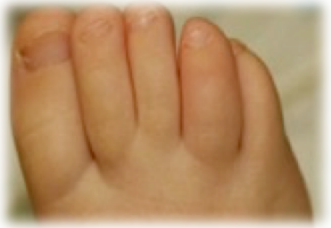






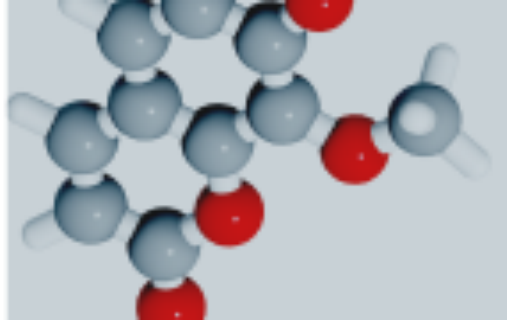




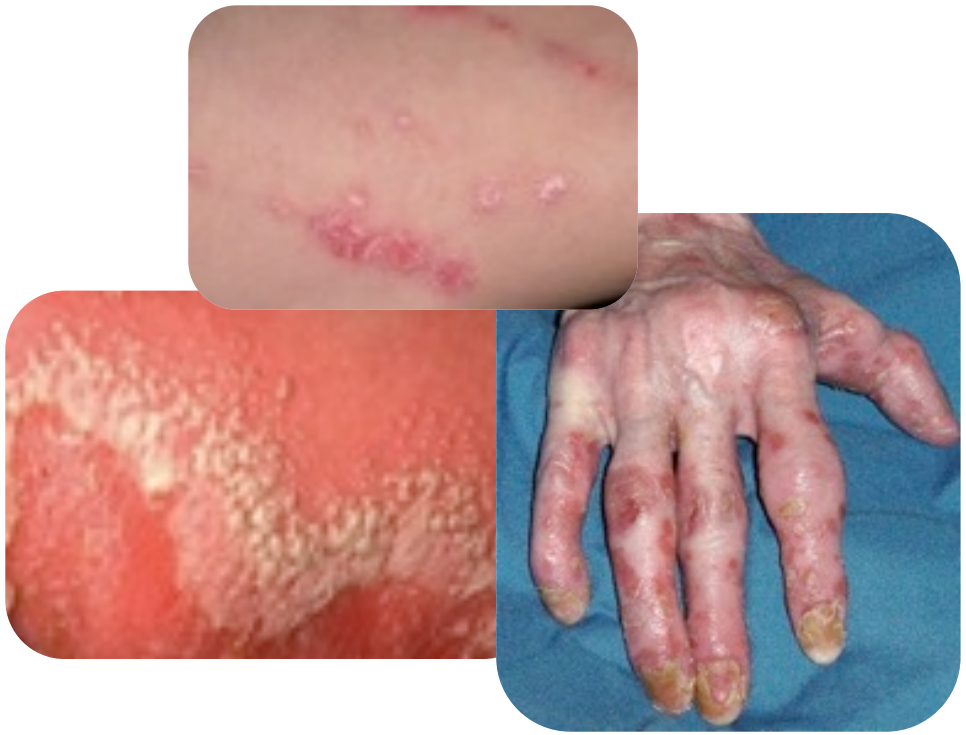


SpA = spondyloarthritis; PsA = psoriatic arthritis.

Are the Various Features of PsA Governed by the Same Pathogenetic Pathways?



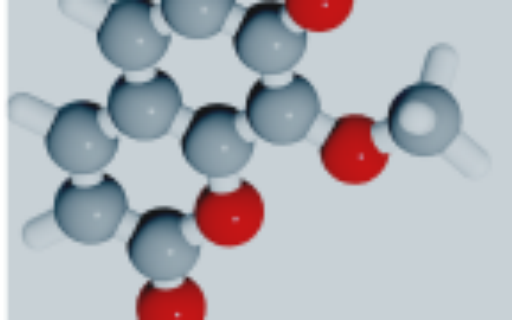
- Thoughts around pathogenesis studies
- Clinical observations
  - The ultimate molecular scalpels



Clues From the Fundaments of the Immune Response: Tissue Appropriate Responses?

Stating the obvious perhaps but…

Some Things to Think About…



- Do pathogens or host tissues determine the nature of the effector immune responses?
  - Moving beyond danger
  - Consider immune privilege (e.g. the anterior chamber of the eye)
  - Tolerance inducing sites (e.g. GI tract – oral tolerance)

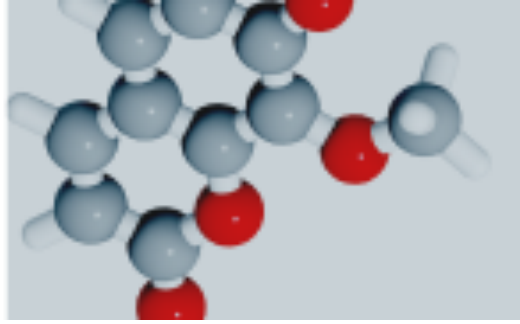
How to respond…?

- A series of decisions made with tissue (stromal) influence
- Balance of host defense versus damage to host tissue

GI = gastrointestinal.

Matzinger P, et al. *Nature Reviews Immunol. 2011;*11:221-230.

Clues From Genetics: Pathogenesis and Clinical Phenotype?



FitzGerald *et al. Arthritis Research & Therapy* (2015) 17:115
DOI 10.1186/s13075-015-0640-3

arthritis research&therapy

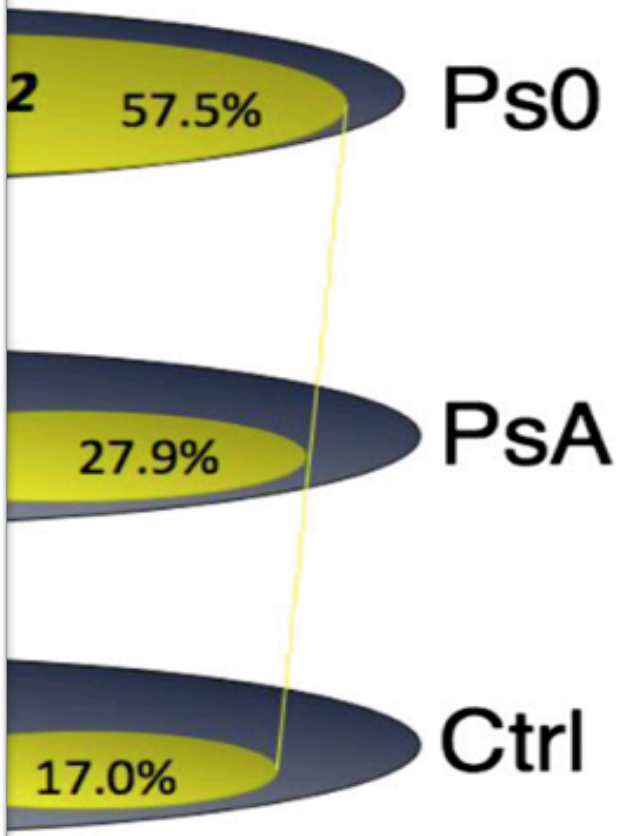
REVIEW Open Access

Concepts of pathogenesis in psoriatic arthritis: genotype determines clinical phenotype

Oliver FitzGerald[1], Muhammad Haroon[1], Jon T Giles[2] and Robert Winchester[2*]

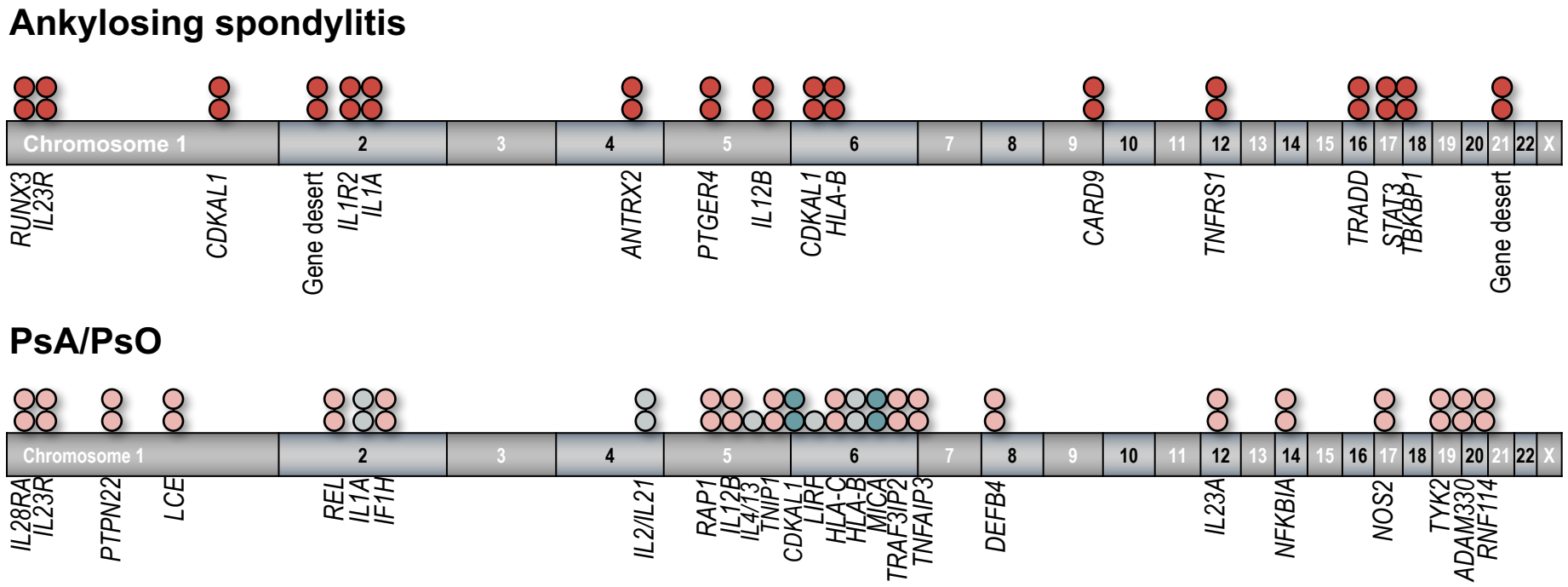
Abstract

This review focuses on the genetic features of psoriatic arthritis (PsA) and their relationship to phenotypic heterogeneity in the disease, and addresses three questions: what do the recent studies on human leukocyte antigen (HLA) tell us about the genetic relationship between cutaneous psoriasis (PsO) and PsA – that is, is PsO a unitary phenotype; is PsA a genetically heterogeneous or homogeneous entity; and do the genetic factors implicated in determining susceptibility to PsA predict clinical phenotype? We first discuss the results from comparing the HLA typing of two PsO cohorts: one cohort providing the dermatologic perspective, consisting of patients with PsO without evidence of arthritic disease; and the second cohort providing the rheumatologic perspective, consisting of patients with PsA. We show that these two cohorts differ considerably in their predominant HLA alleles, indicating the heterogeneity of the overall PsO phenotype. Moreover, the genotype of patients in the PsA cohort was shown to be heterogeneous with significant elevations in the frequency of haplotypes containing *HLA-B*08*, *HLA-C*06:02*, *HLA-B*27*, *HLA-B*38* and *HLA-B*39*. Because different genetic susceptibility genes imply different disease mechanisms, and possibly different clinical courses and therapeutic responses, we then review the evidence for a phenotypic difference among patients with PsA who have inherited different HLA alleles. We provide evidence that different alleles and, more importantly, different haplotypes implicated in determining PsA susceptibility are associated with different phenotypic characteristics that appear to be subphenotypes. The implication of these findings for the overall pathophysiologic mechanisms involved in PsA is discussed with specific reference to their bearing on the discussion of whether PsA is conceptualised as an autoimmune process or one that is based on entheseal responses.



FitzGerald O, et al. *Arth Res Therapy*. 2015;17:115.

Clues From Genome Studies?



GWAS = Genome-wide association studies.

Reveille JD. *Nat Rev Rheumatol.* 2012;8:296-304.

Clues From Genetics: Pathogenesis and Clinical Phenotype?

Table 2 | Association statistics for two novel susceptibility loci at chromosome 1q31 and 5q31.

SNP	Chr.	Position (bp)	Notable genes	Risk/non-risk allele	Stage	Sample	Phenotype	RAF (case)	RAF (control)	*P*-value	OR	Meta-analysis *P*-value
rs2477077	1	197,671,115	*DENND1B*	T/C	Discovery	Immunochip	PsA	0.26	0.22	1.20E – 6	1.23	2.36E – 7
					Validation	Erlangen	PsA	0.21	0.19	0.07	1.17	
					Validation	Erlangen	Psoriasis	0.22	0.19	6.07E – 3	1.25	2.40E – 7
					Validation	WTCCC2	Psoriasis	0.25	0.21	2.24E – 5	1.21	
rs715285	5	131,485,383	*CSF2* | *P4HA2*	G/A	Discovery	Immunochip	PsA	0.48	0.46	2.654E – 10	1.25	4.38E – 13
					Validation	Erlangen	PsA	0.49	0.43	4.04E – 4	1.27	
					Validation	Erlangen	Psoriasis	0.46	0.43	0.05	1.14	0.04
					Validation	WTCCC2	Psoriasis	0.47	0.46	0.21	1.05	

bp, base pair; Chr, chromosome; OR, odds ratio; RAF, risk allele frequency.

SNP = single nucleotide polymorphism.

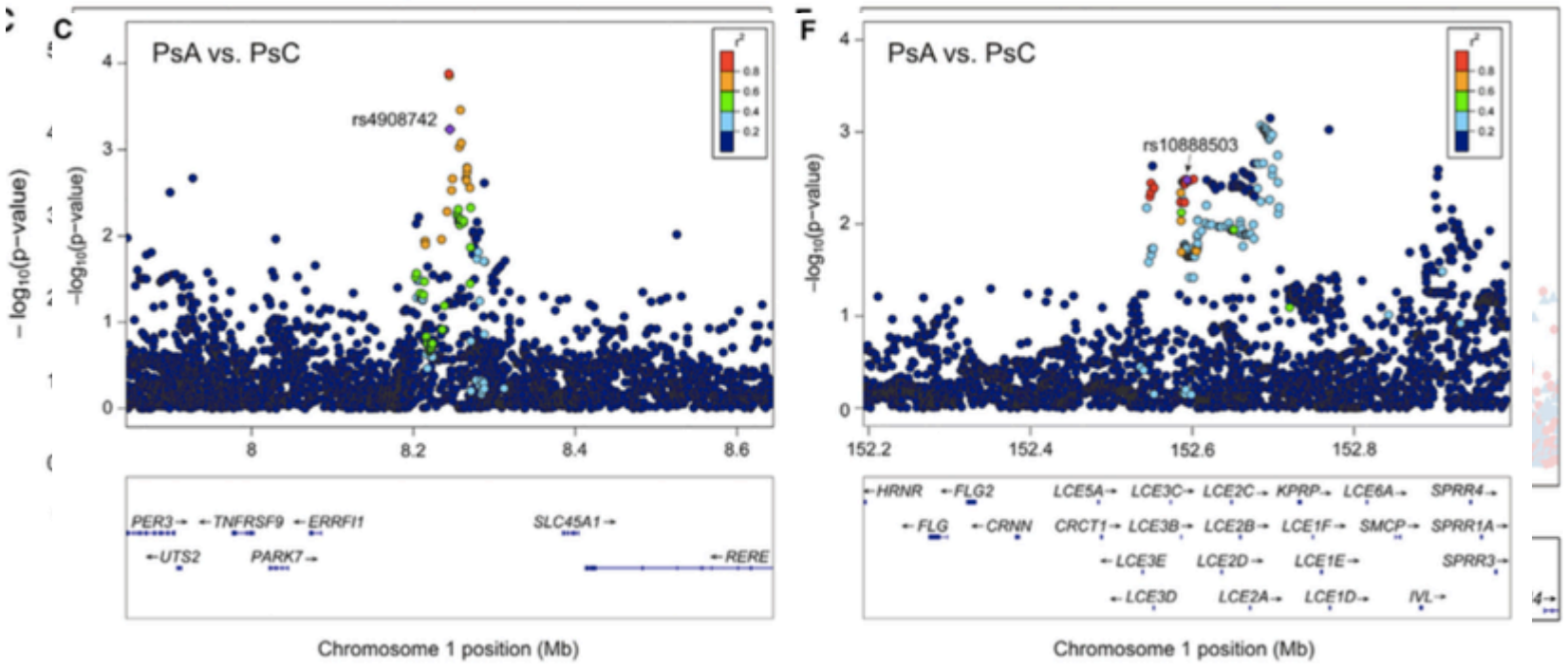
Bowes J, et al. *Nature Comm.* 2015;6:6046.

Genetic Studies Reveal Distinct Genetic Architecture in PsoC and PsA

5 Discrete Loci – 3 Associated with PsoC and 2 with PsA

TNFRSF9 region
IL-23R region

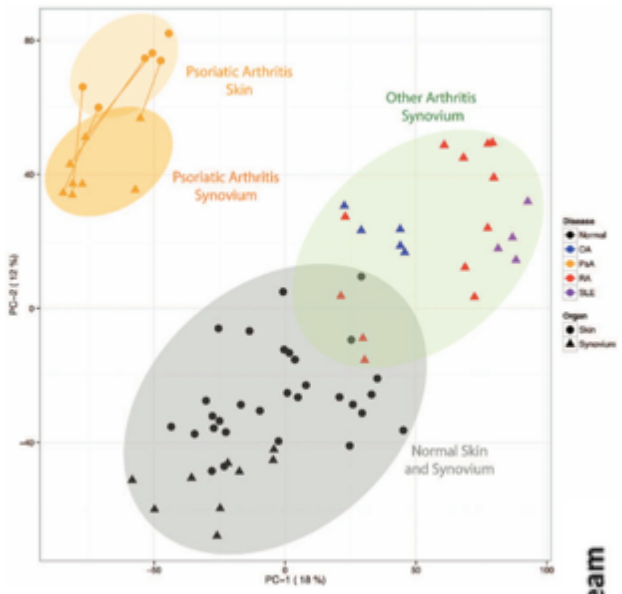
LCE3C/B region
TNFAIP3 region

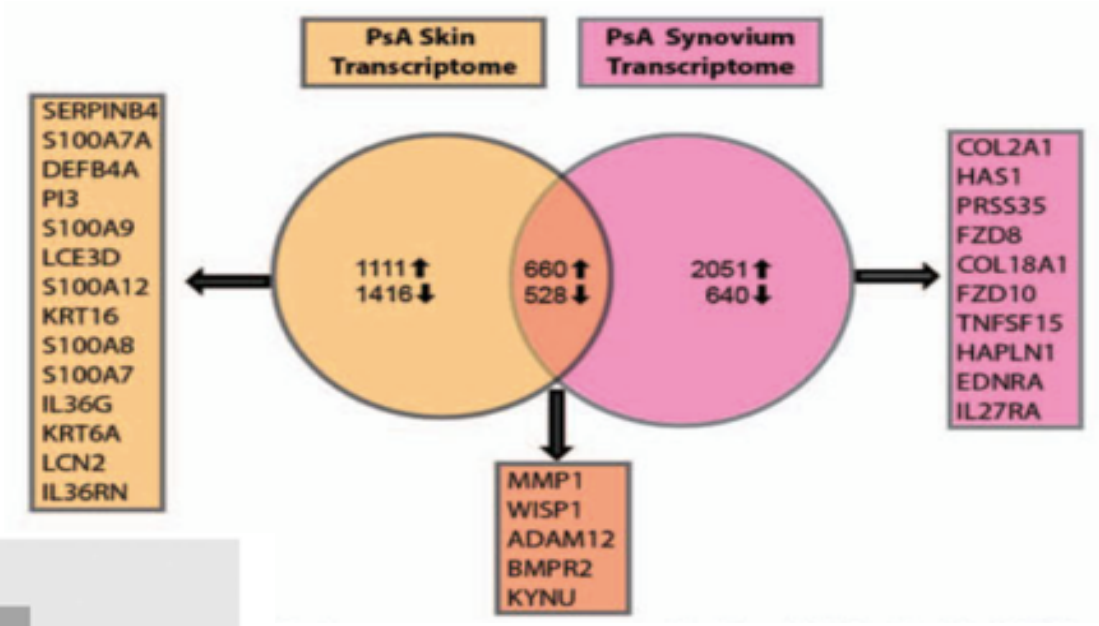


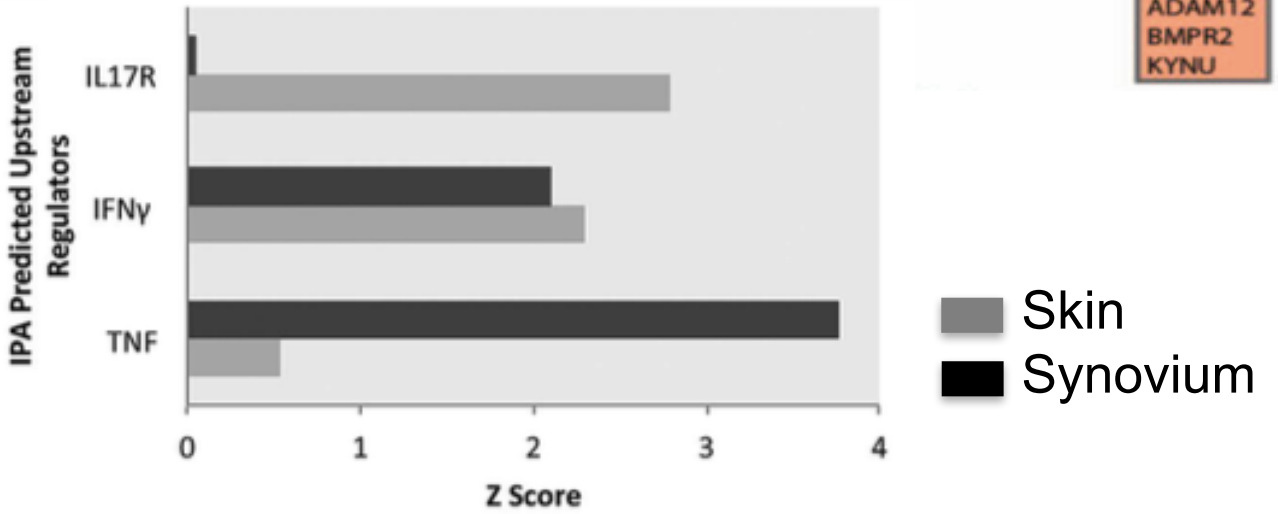
PsoC = cutaneous only psoriasis.

Stuart P, et al. *AJHG.* 2015;97:816-836.

Clues From Tissue Comparisons: Transcriptional Profiles of Skin and Joint in Patients With PsA Are Not Identical

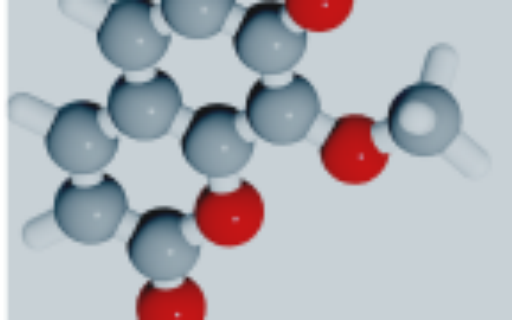






Belasco J, et al. *Arthritis Rheumatol*. 2015;67(4):934-944.

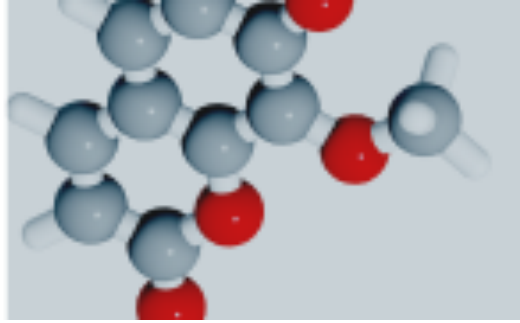
Audience Response

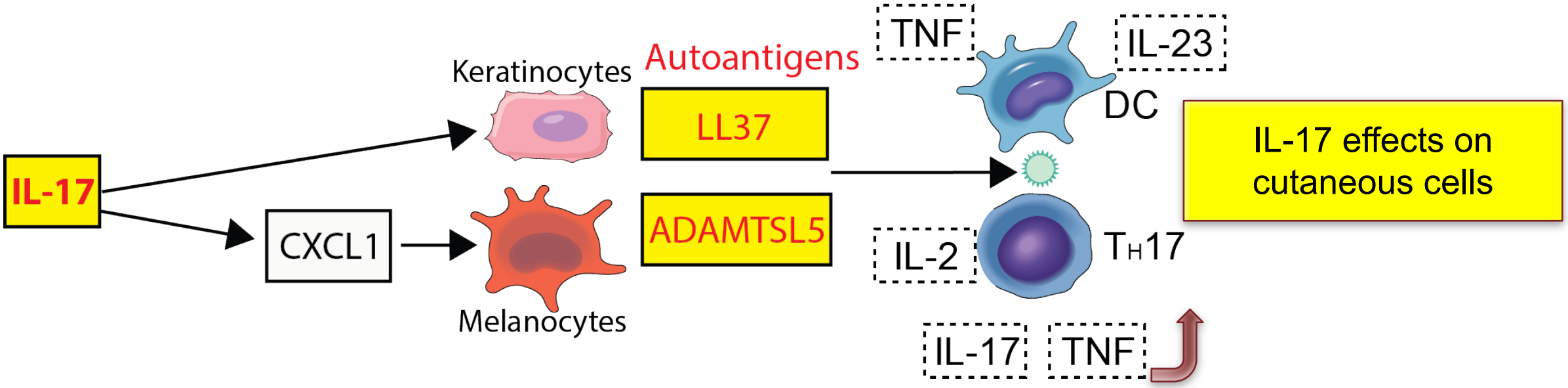


A keratinocyte-derived antigen has been identified as a potential driver of psoriasis. The class of protein of this antigen is:

A. Antimicrobial peptide
B. Cell cycle protein
C. Cholesterol ester
D. Inflammasome
E. Uric acid

Psoriasis Has New Autoantigens That Are Regulated by IL-17

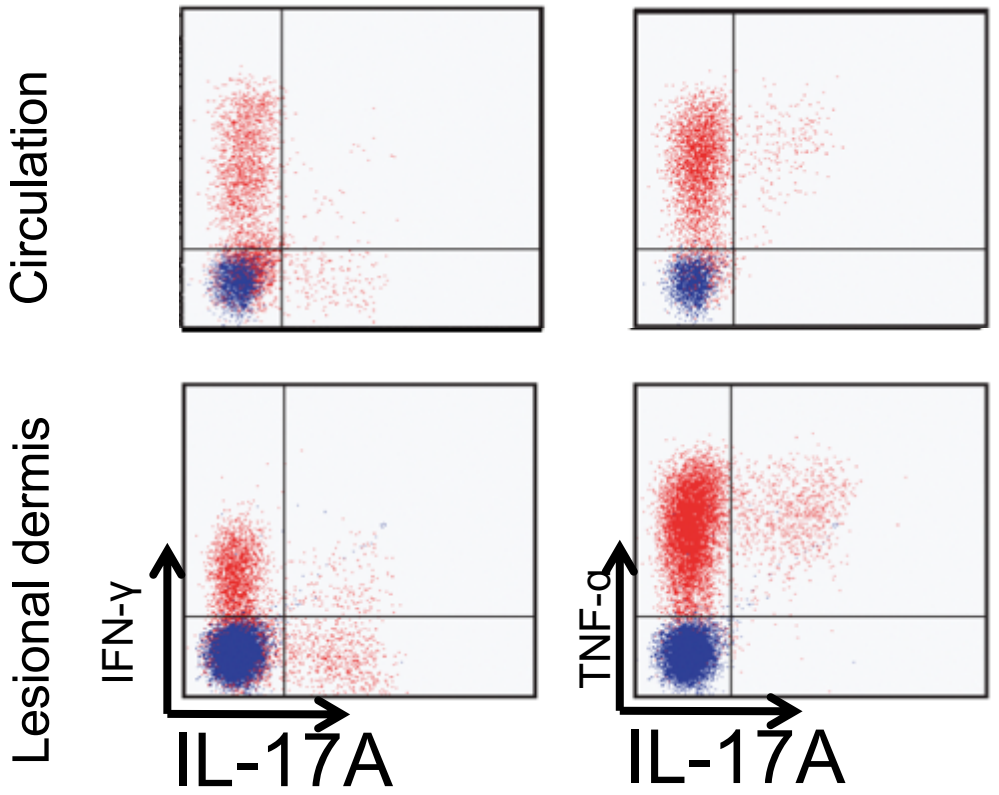




Clues From Cellular Analysis of the Lesions: Production of IL-17A by TH17 Cells, Found in Psoriatic Plaques

- Significantly more TH17 cells are present in lesional dermis (n = 4) than in normal skin (n = 4; p = .029)[2]

A subset of IL-17A–producing cells also produce IFN-γ and TNF-α[2]



Red = phorbol myristate acetate/ionomycin-activated (PMAI) cells
Blue = unactivated cells

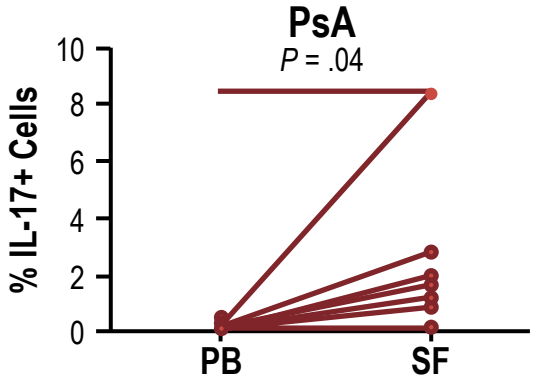
Cells activated with PMA/I and stained for intracellular IL-17A, IFN-γ, and TNF-α

Results for 1 representative subject shown (4 normal subjects and 4 subjects with psoriatic plaques analyzed).[2]

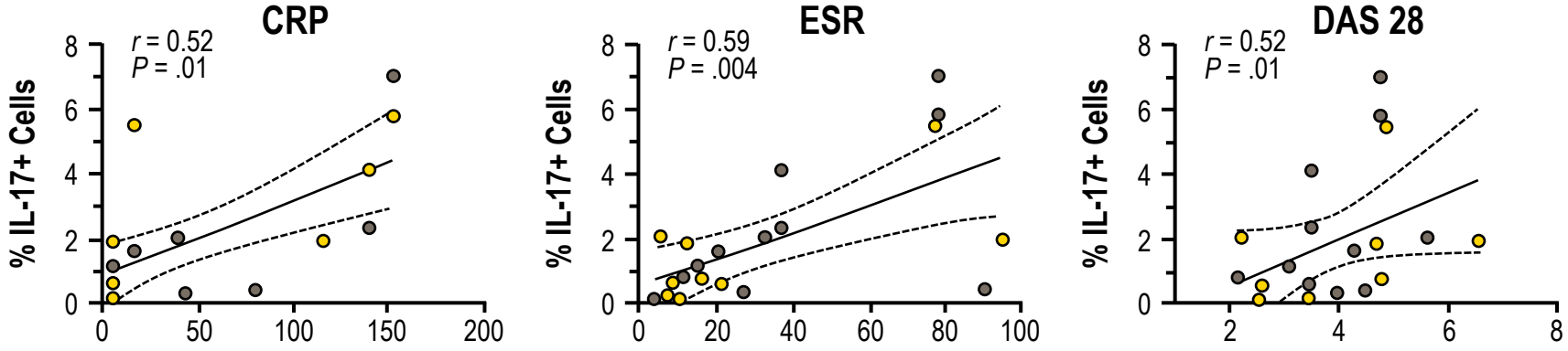
1.Lowes MA, et al. *J Invest Dermatol.* 2008;128:1207-1211.

Clues From Cellular Analysis of the Lesions: IL-17+ CD8+ T Cells Are Present in Synovial Fluid of Patients With PsA

Frequency of IL-17–expressing cells in CD3+CD8+ T cell populations in paired PB and SF samples from patients with PsA



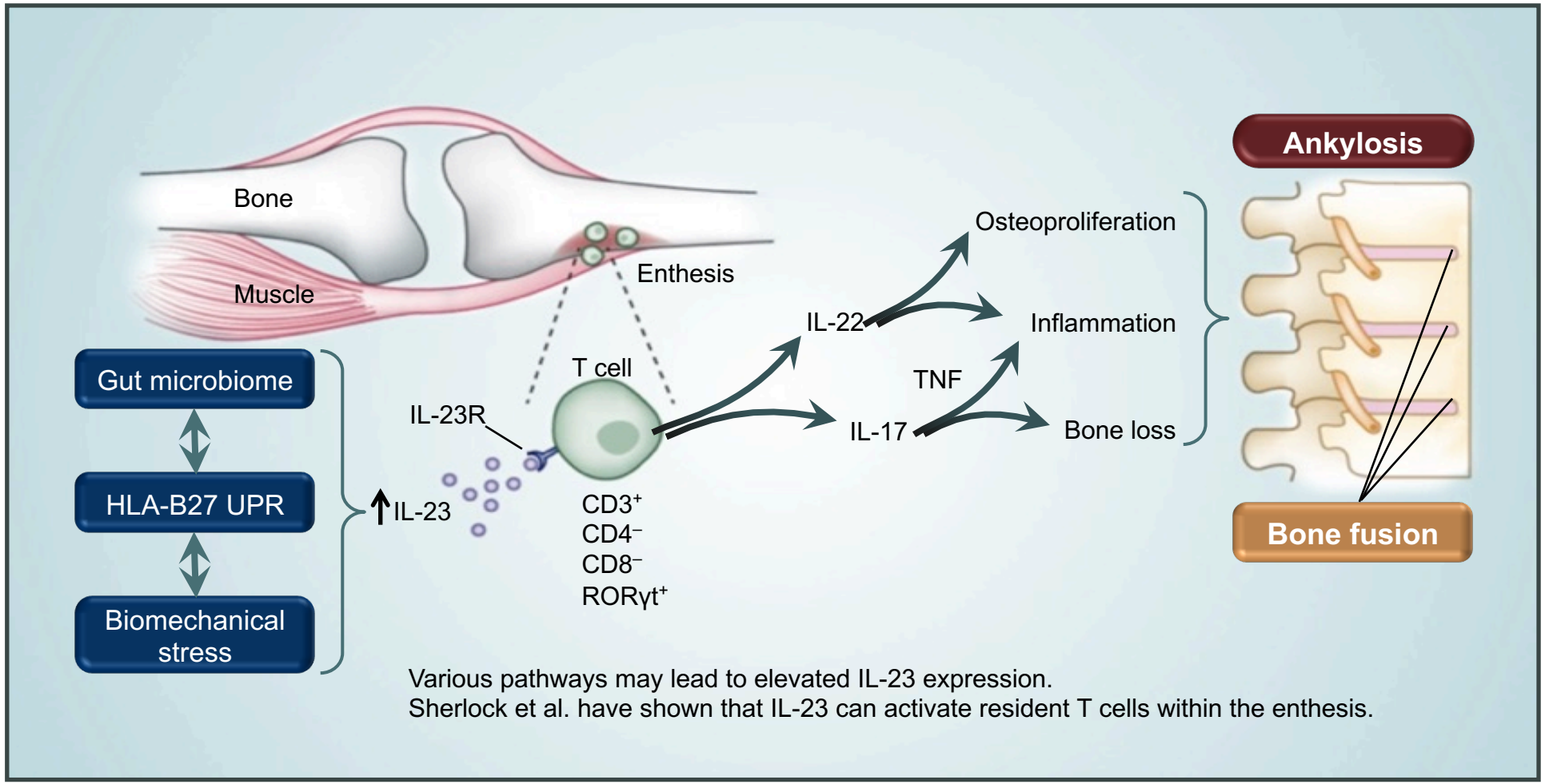
Correlation between the frequency of IL-17–expressing CD3+CD4- T cells in PsA SF and clinical parameters of disease



DAS 28 = Disease Activity Score in 28 joints; ESR = erythrocyte sedimentation rate; PB = peripheral blood; SF = synovial fluid.

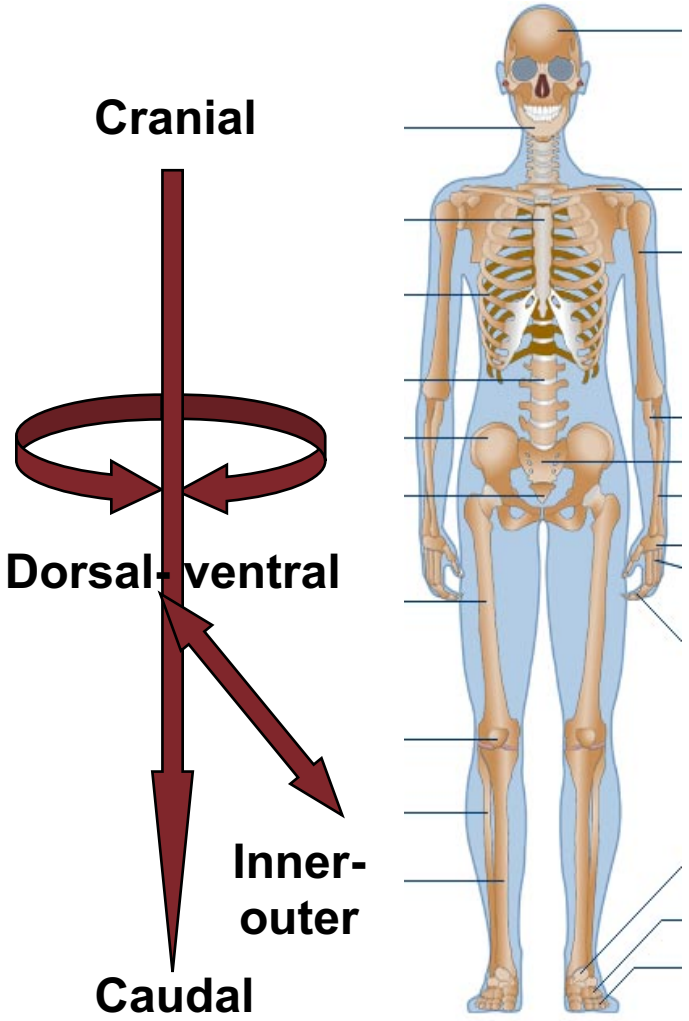
Menon B, et al. *Arthritis Rheum*. 2014;66:1272-1281.

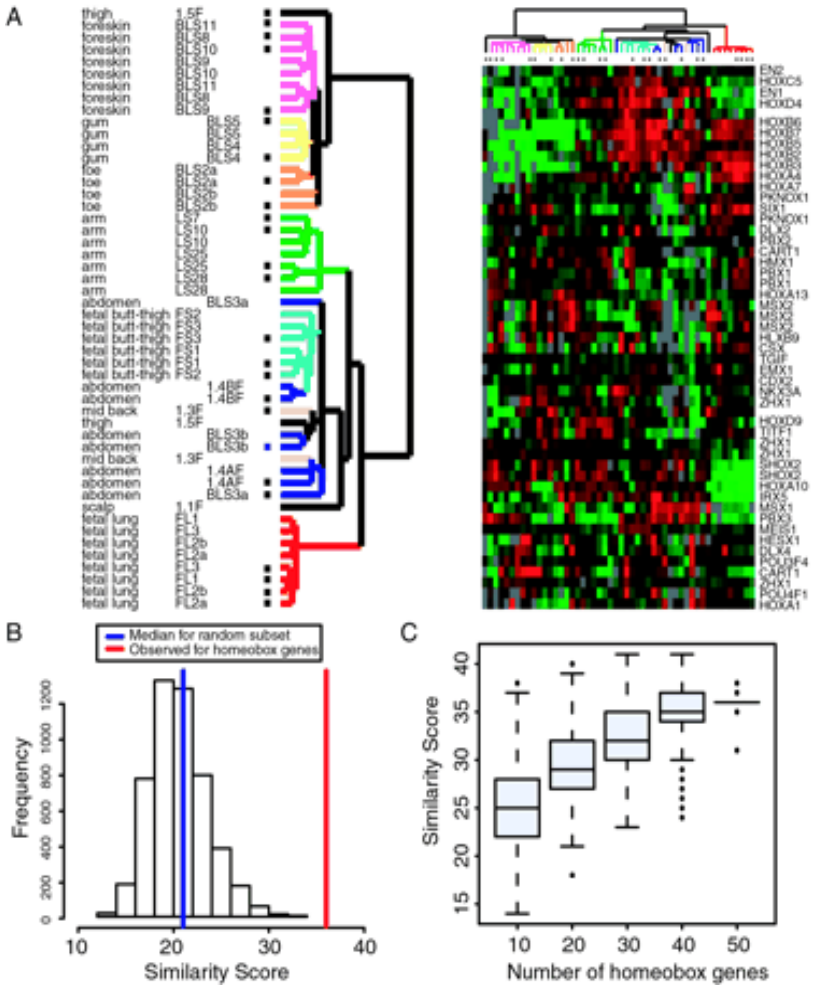
Clues From Cellular Analysis of the Lesions: Direct Cellular Activation of CD3+, CD4-, and CD48- T Cells: IL-23R and Enthesitis?



Sherlock JP, et al. *Nat Med.* 2012;18(7):1069-1076.

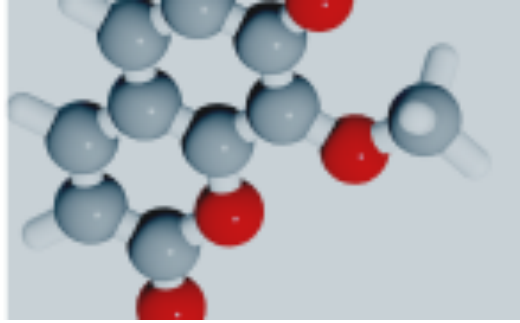
Tissues Are Different…Diversity, Topographic Differentiation, Positional Memory in Fibroblasts!

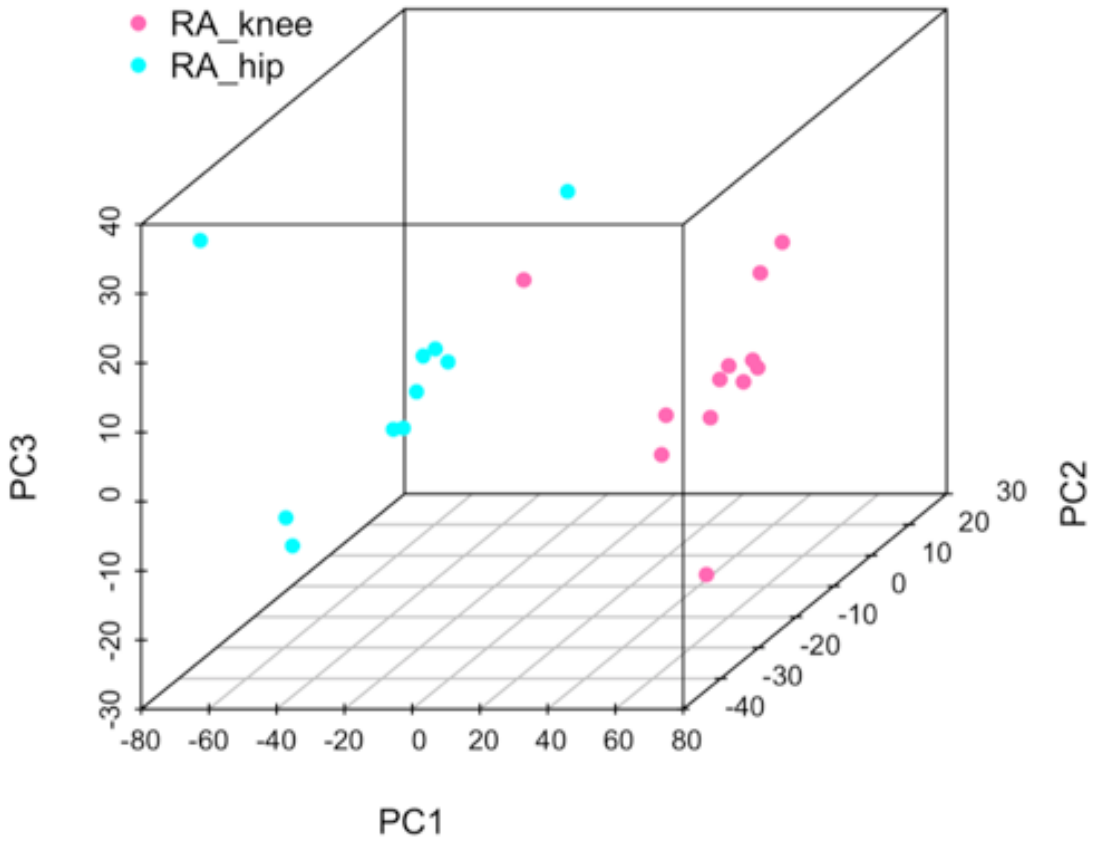




Chang HY, et al. *Proc Natl Acad Sci U S A.* 2002;99(20):12877-12882.
Rinn JL, et al. *PLoSgenetics.* 2006;2(7):e119.

Epigenetic Changes Can Define Geographically Distinct Joints: Implications for Therapeutics?





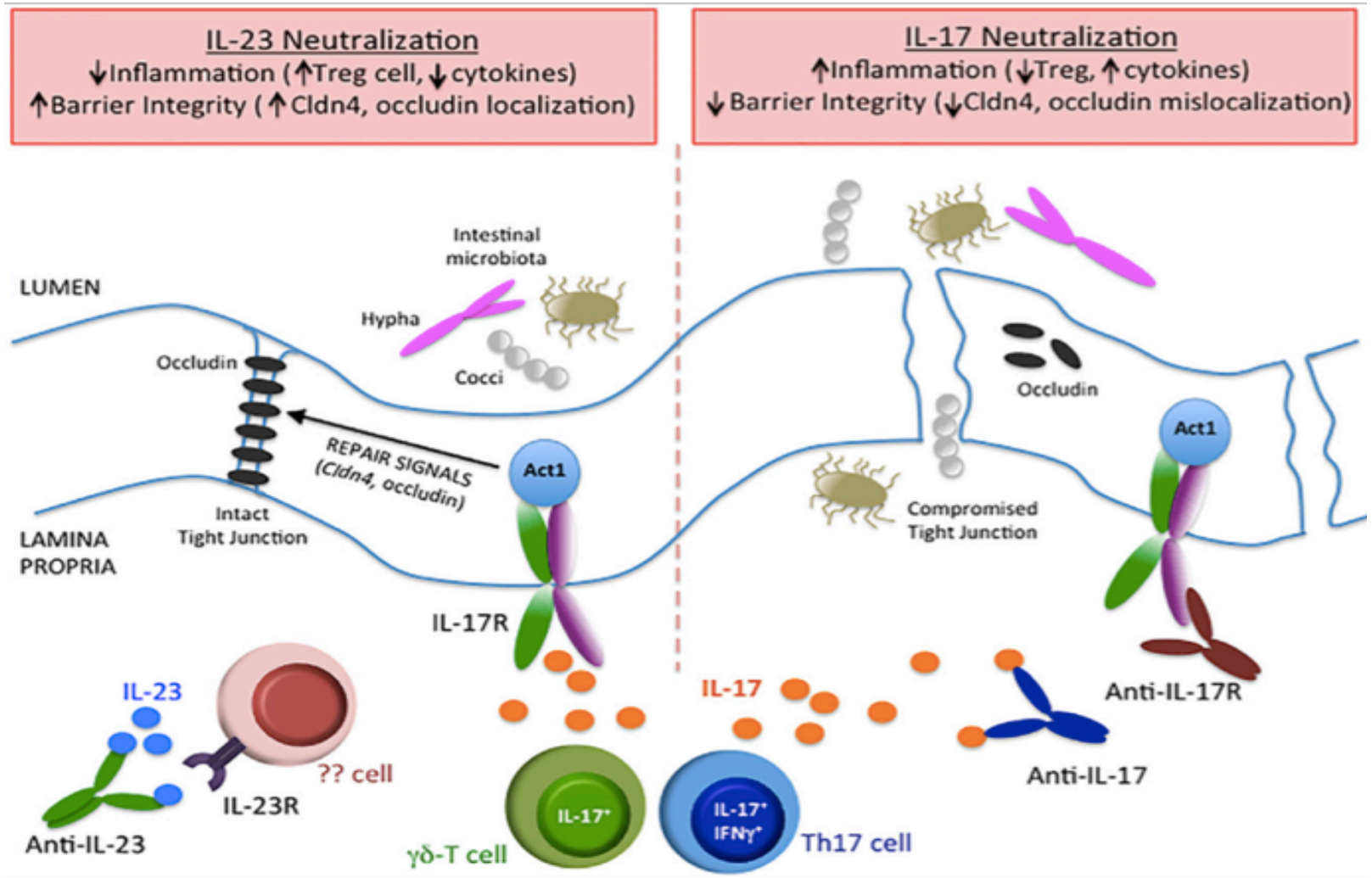
Distinct methylation patterns for RA hip and knee
Pathway differences (subtracting out OA hip/knee pathways)

- IL-6-JAK signaling
- IL-17 signaling
- IL-22 signaling
- p53 signaling

Do joints differentially respond to targeted drugs?

Data from Gary Firestein UCSD

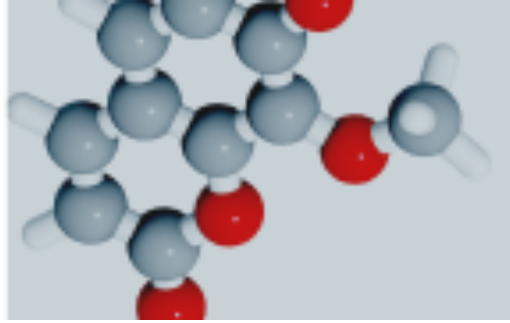
Clues From IBD: A Revised View of the Biology of IL-23/IL-17A Axis in the GI Tract



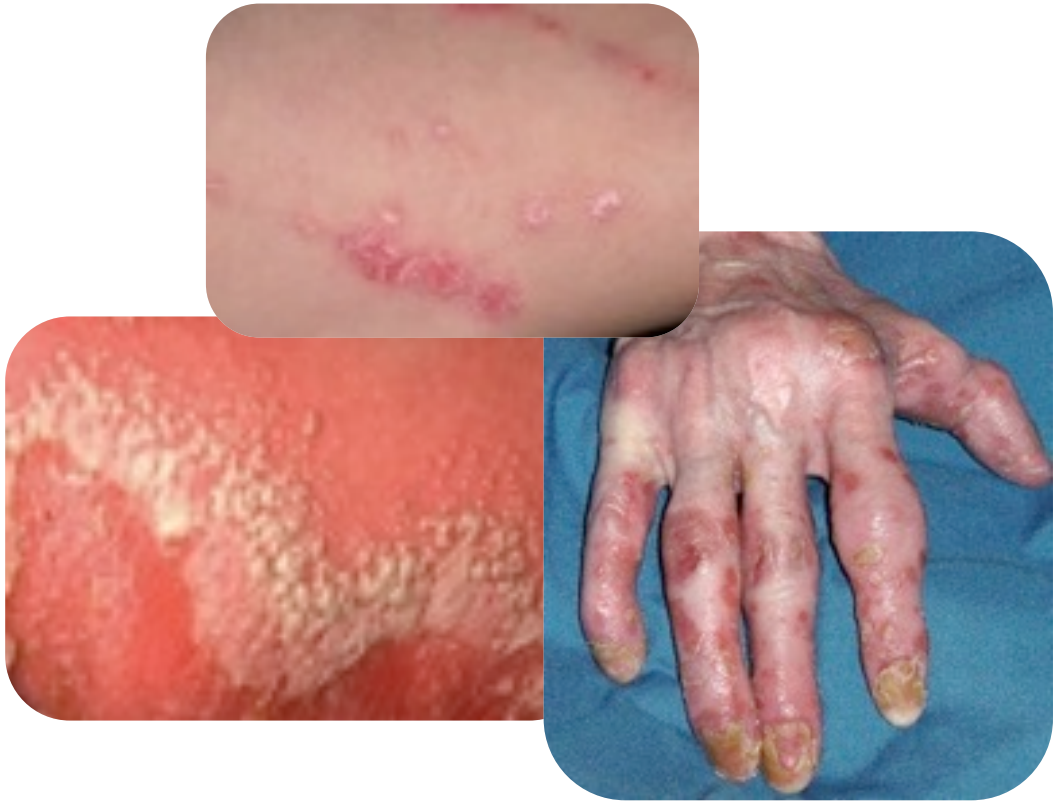
Act1 = activator 1; Cldn4 = claudin 4; IBD = Inflammatory bowel disease.

Whibley N, et al. *Immunity.* 2015;3:620-622.; Lee J, et al. *Immunity*. 2015;*4*3:727-738; Maxwell J, et al. *Immunity.* 2015;43:739-750.

Are the Various Features of PsA Governed by the Same Pathogenetic Pathways?

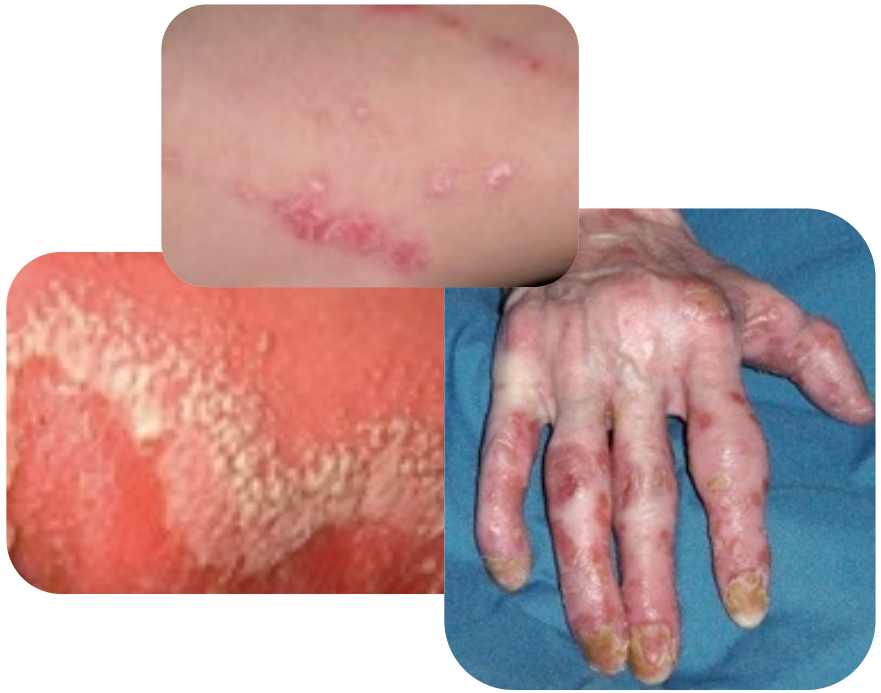


- Thoughts around pathogenesis studies
- Clinical observations
  - The ultimate molecular scalpels

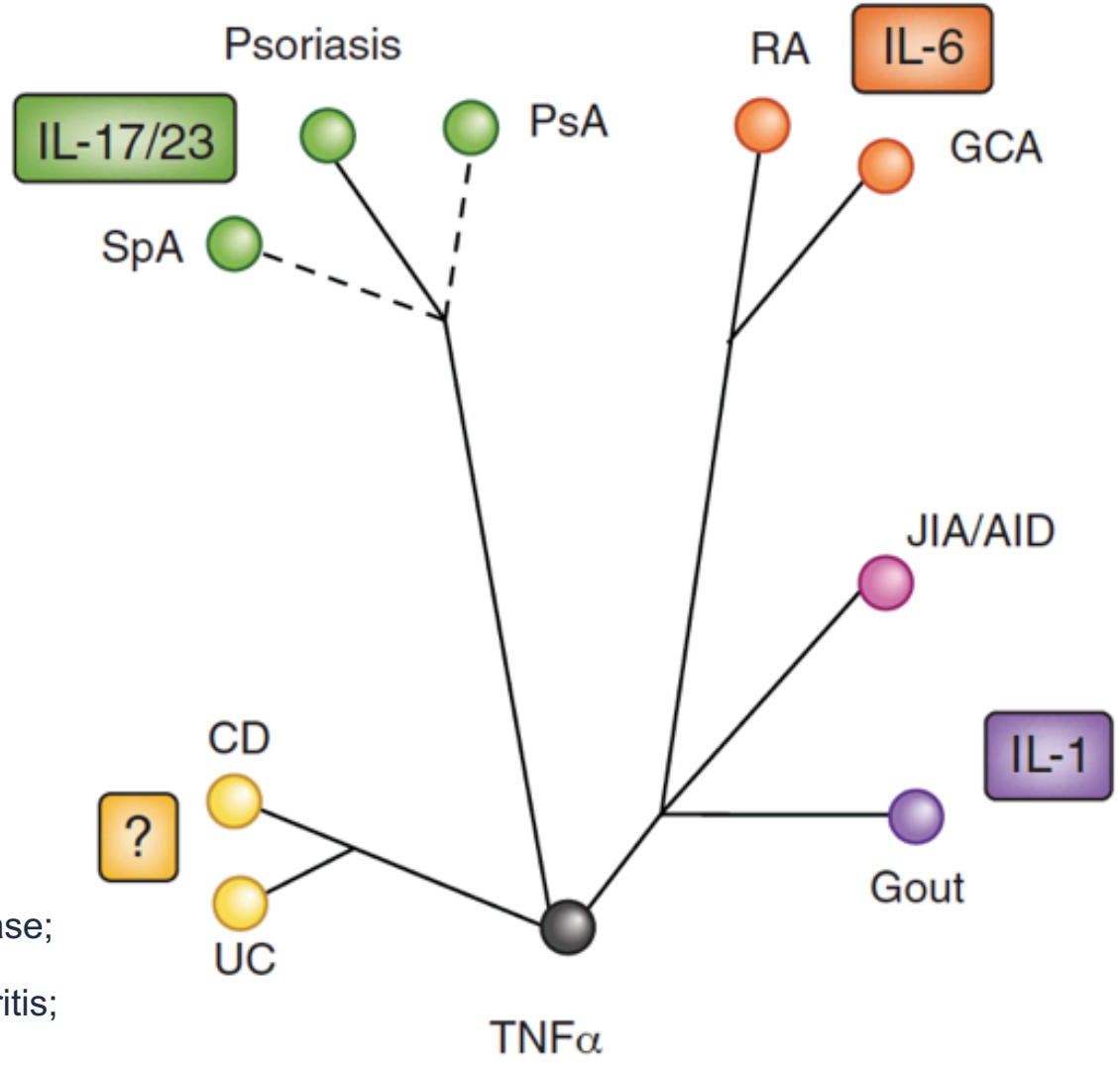


Clinical Experience Consistent With Distinct Tissue Responses?

- cDMARDS
  - Sulphasalazine (SASP)
  - Cyclosporin
- Asymetric responses
  - To biologics
- Paradoxical reactions
  - Psoriaform lesions on TNFi
  - Exacerbations/development of PsA with ustekinumab



Clues From Disease Trial Comparisons: Towards Molecular Taxonomy in Inflammation Medicine?



AID = autoinflammatory disease including Still's disease;
CD = Crohn's disease; GCA = giant cell arteritis;
JIA = juvenile idiopathic arthritis; SpA = spondyloarthritis;
UC = ulcerative colitis.

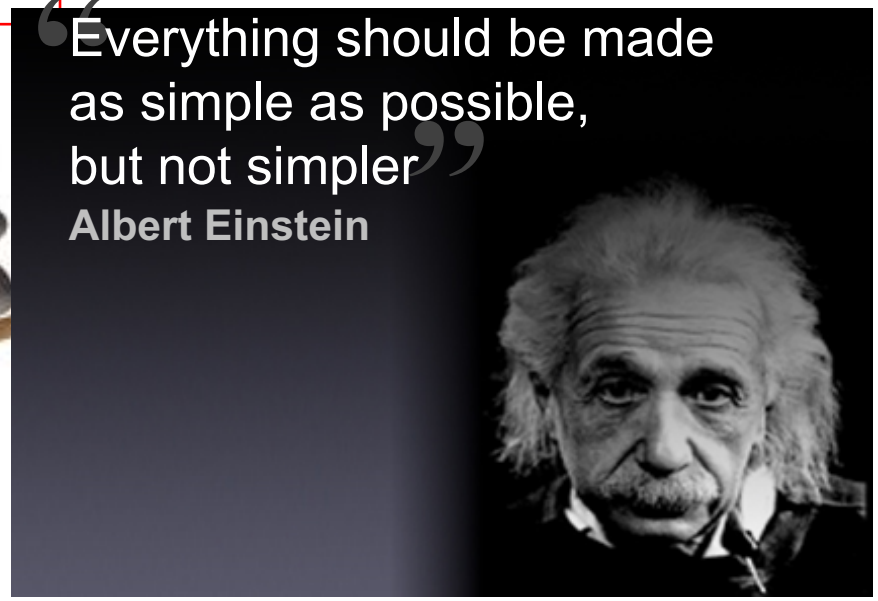
Schett G, et al. *Nat Med*. 2013;19:822-824.

Pathogenesis Lead Therapeutics in PsA?

Cutaneous psoriasis achieves PASI 100 responses in approx 50% to IL-17i

PsA achieves ACR 70 responses <20% to IL-17i, IL-23p40, TNFi

PsA achieves ACR 70 responses <20% to IL-17i, IL-23p40, TNFi



ACR = American College of Rheumatology; PASI = psoriasis area and severity index.

#SkinCME

Clinical Significance of Cardiometabolic Co-morbidity in Psoriatic Disease

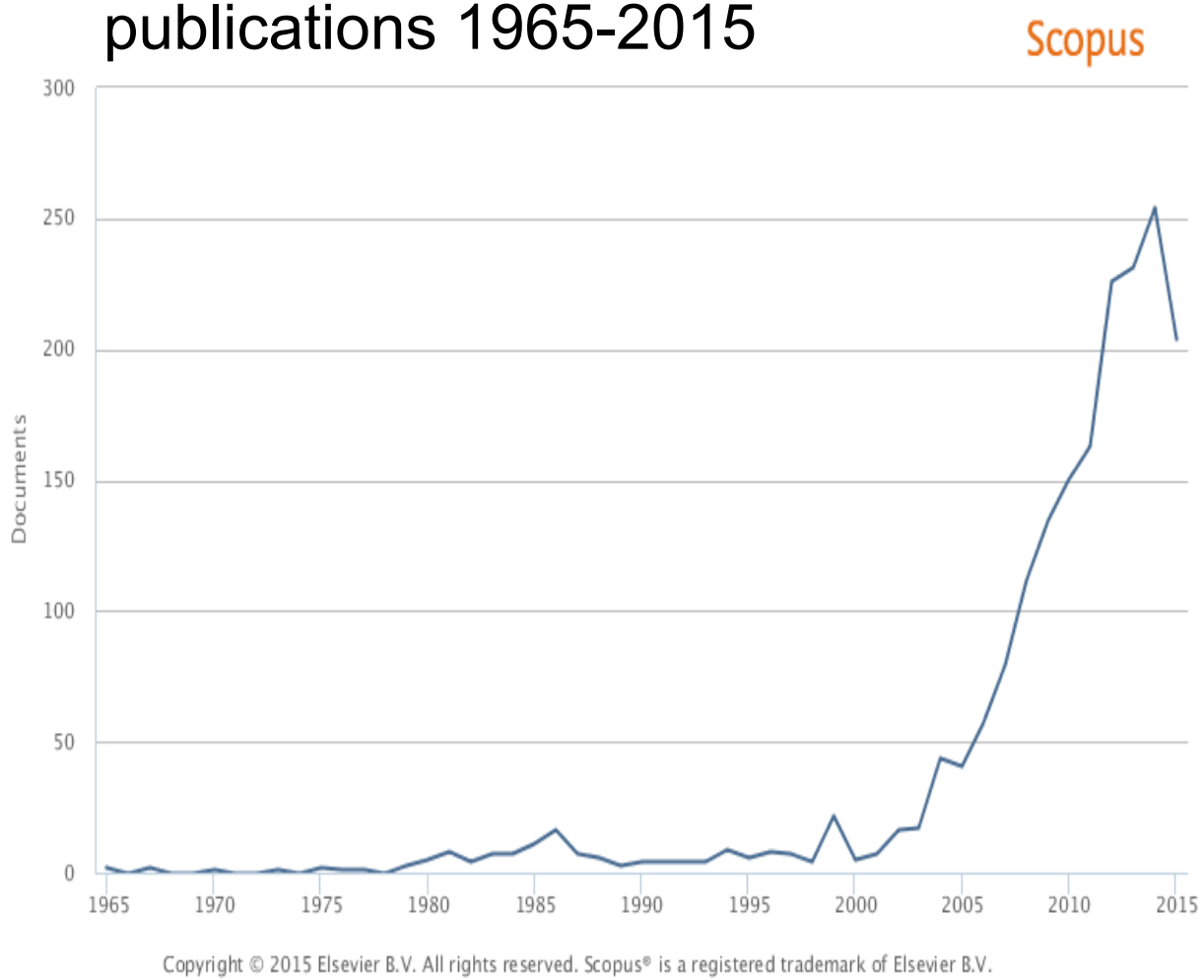
Joel M. Gelfand, MD, MSCE

Professor of Dermatology
Professor of Epidemiology
Vice Chair of Clinical Research and Medical Director
Dermatology Clinical Studies Unit
Director, Psoriasis and Phototherapy Treatment Center
University of Pennsylvania Perelman School of Medicine
Philadelphia, PA

Psoriasis and Comorbidity Knowledge Is Rapidly Expanding

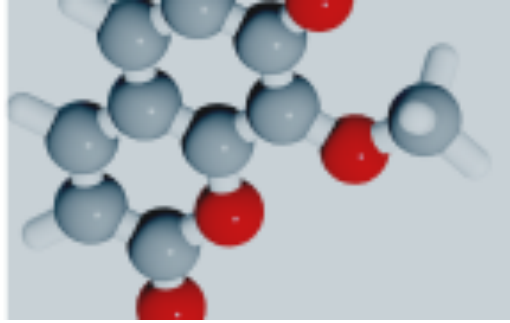
- Biologic treatment revolution targeting T cells, TNF, IL12/23, and IL-17
- Recognition of critical importance of Th17 pathway
- Identification of expanding number of susceptibility genes in psoriasis
- Application of medical informatics and modern epidemiological techniques

Psoriasis and CV Disease publications 1965-2015



CV = cardiovascular.
Graph generated 12.30.15 search terms psoriasis and cardiovascular

Psoriasis: Rapidly Changing Paradigms



Old Paradigm:

"Just a skin disease"

New Paradigm:

"A systemic disease"

Psoriasis and Co-morbidities Paradigm

Environmental Risk Factors

Smoking

Obesity

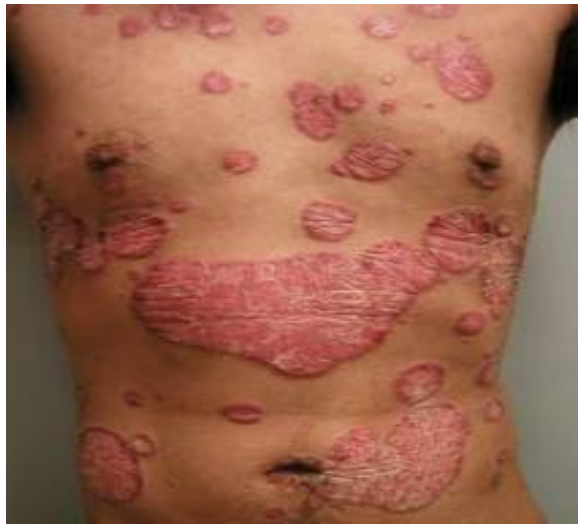
Genes and loci associated with psoriasis, diabetes and CV diseases

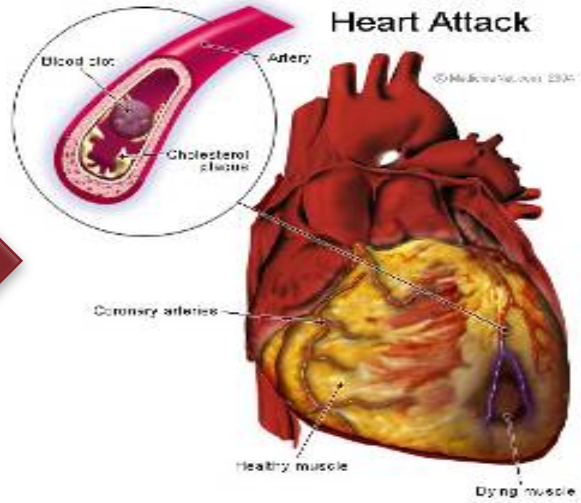
PSORS2/3/4

CDKAL1

ApoE4

TNFAIP3





Mediating Factors

Pathophysiology

- Th1/17 inflammation (atherosclerosis, thrombosis, lipid metabolism)
- Epidermal proliferation (↑uric acid, oxidative stress)
- Angiogenesis (endothelial dysfunction)

Treatment

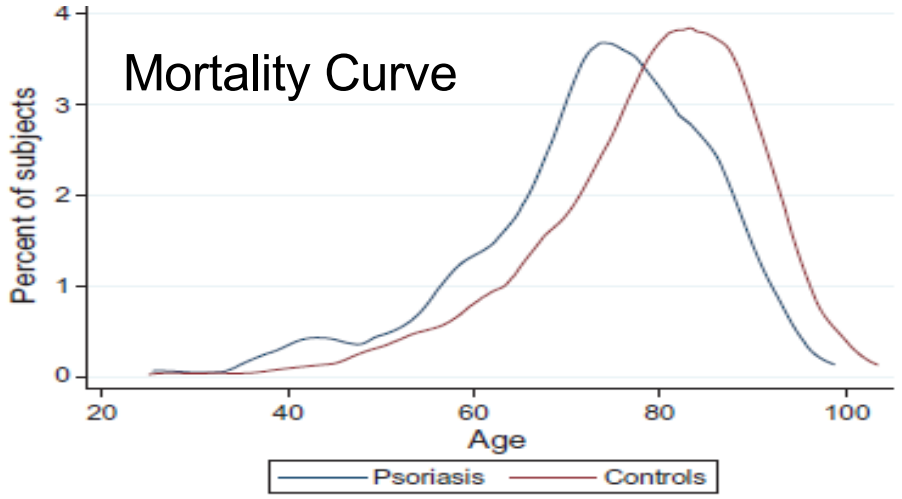
- Increase CV risk (e.g. cyclosporine, acitretin)?
- Decrease CV risk (e.g. methotrexate, TNF inhibitors)?

Psychosocial impact

- Depression, alcohol and smoking, lower socioeconomic status

Azfar RS, Gelfand JM. *Curr Opin Rheum* 2008;20:416–422.

Risk of Cardiometabolic Disease in Severe Psoriasis



Outcome	Adj. RR Mild	Adj. RR Severe
MI[1]	1.05	1.5
Stroke[2]	1.06	1.4
CV Death[3]	Not done	1.6
MACE[4]	Not done	1.5
Diabetes[5]	1.11	1.5

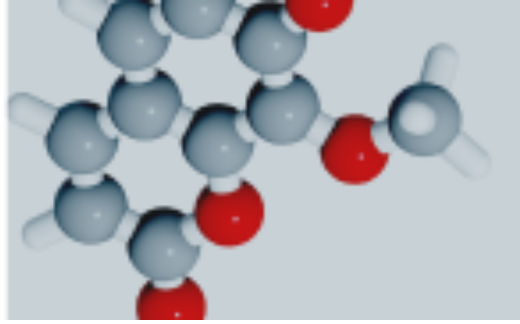
Clinical Significance:

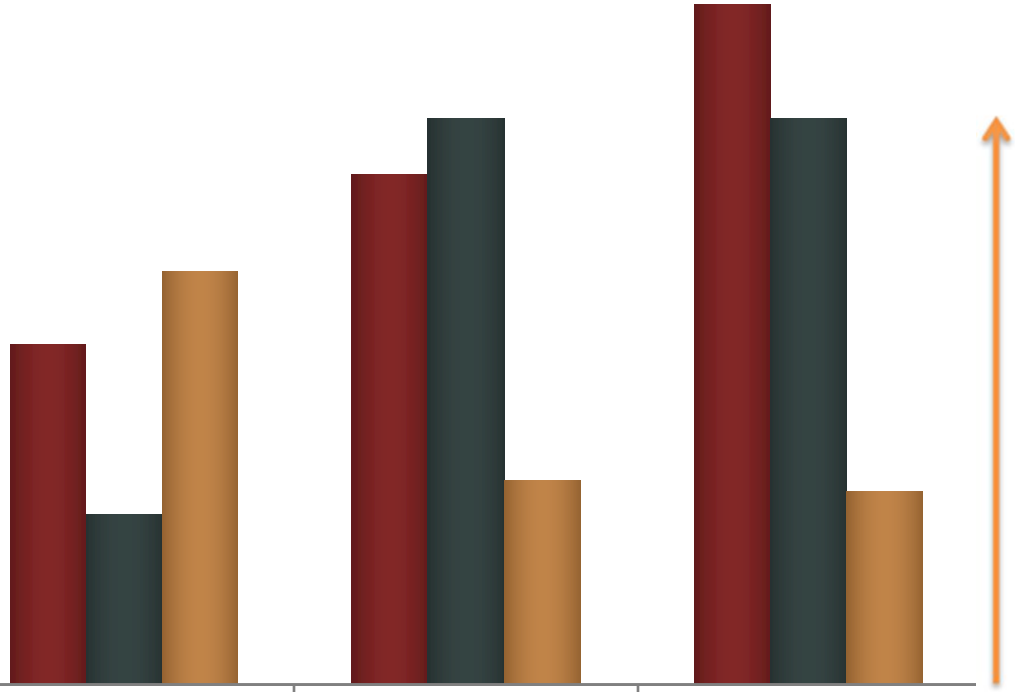
1. Increased risk of MI, stroke, CV death, diabetes
2. 5 years of life lost
3. 10 year risk of major CV event attributable to psoriasis = 6%
4. Risk of CV disease in patients with severe psoriasis similar to risk conferred by diabetes
5. Patients treated for severe psoriasis are 30X more likely to experience MACE (attributable to psoriasis) than to develop a melanoma

MACE = major adverse cardiac event

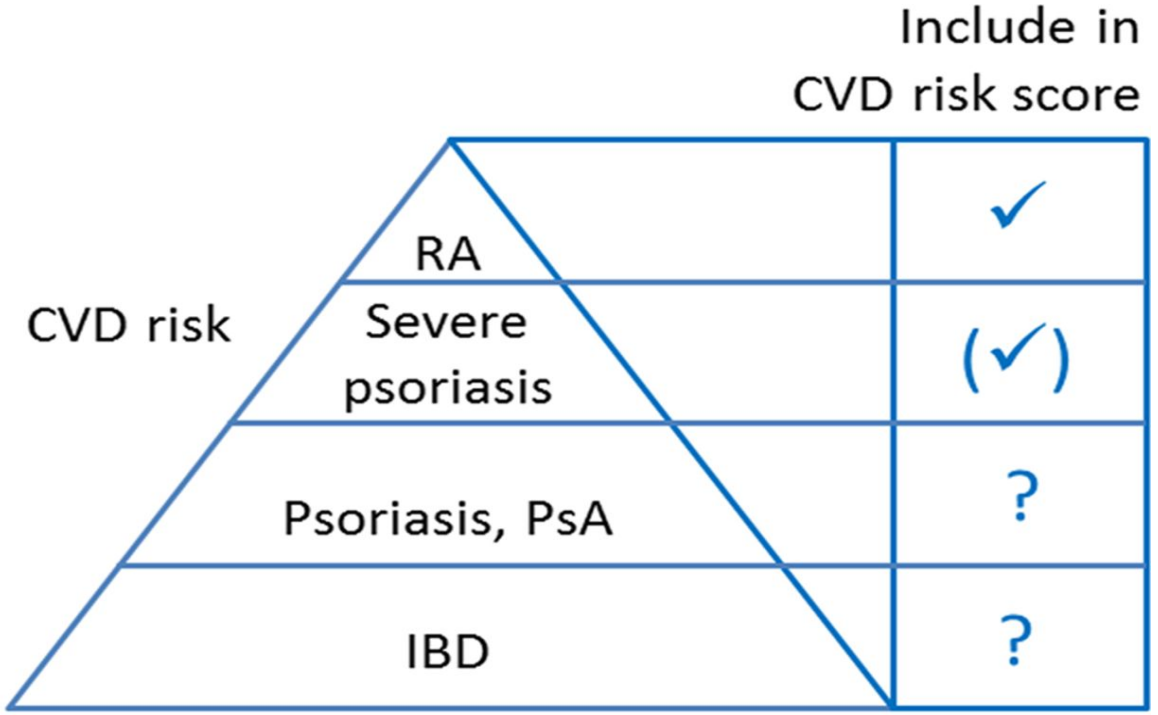
1. Gelfand JM, et al. *JAMA.* 2006; 296:1735.; 2. Gelfand, JM, et al. *J. Invest. Derm.* 2009; 129:2411.; 3. Mehta, NN, et al. *Eur Heart J.* 2010;31:1000.; 4. Mehta NN, et al. *Am. J. Med.* 2011;124:775.e1-6.; 5. Azfar R, et al. *Arch Derm* 2012;148:995-1000.

Comparison of Cardiometabolic Outcomes: Psoriasis vs. RA vs. PsA



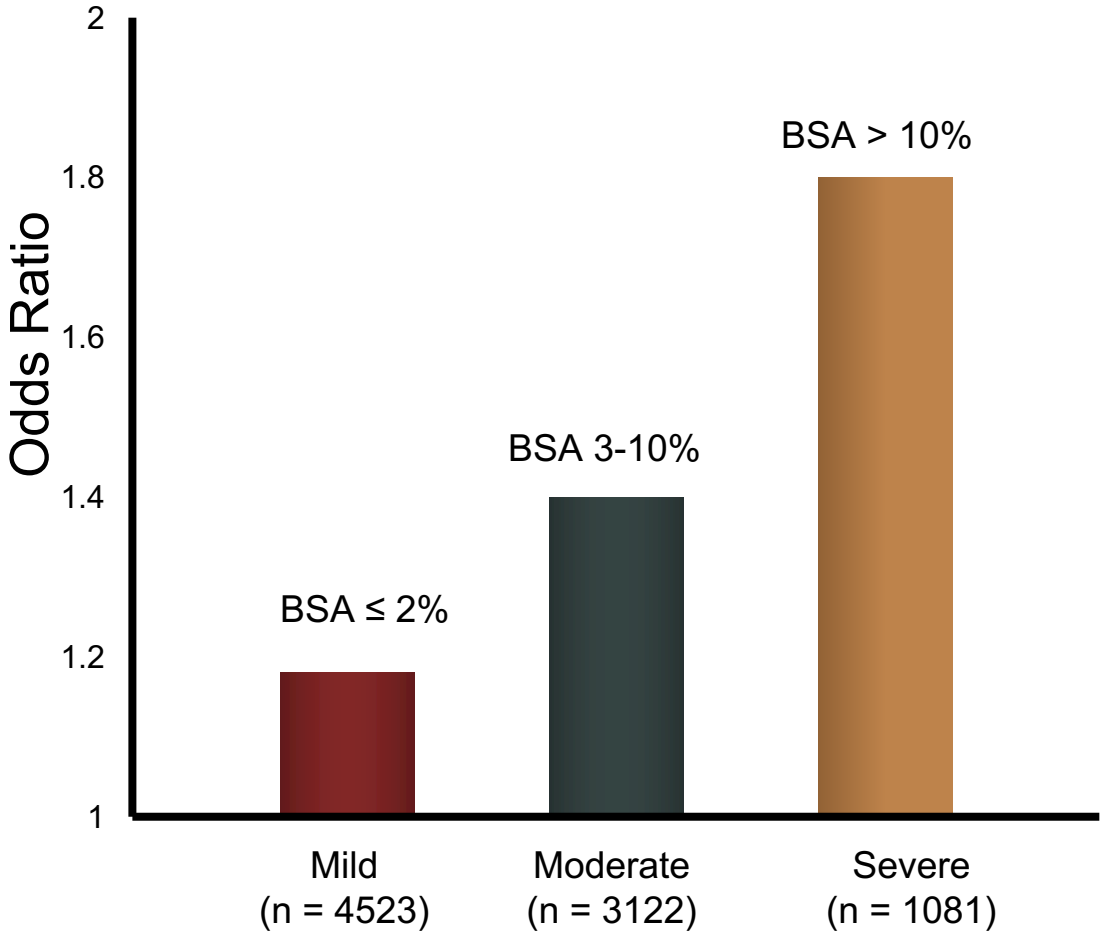


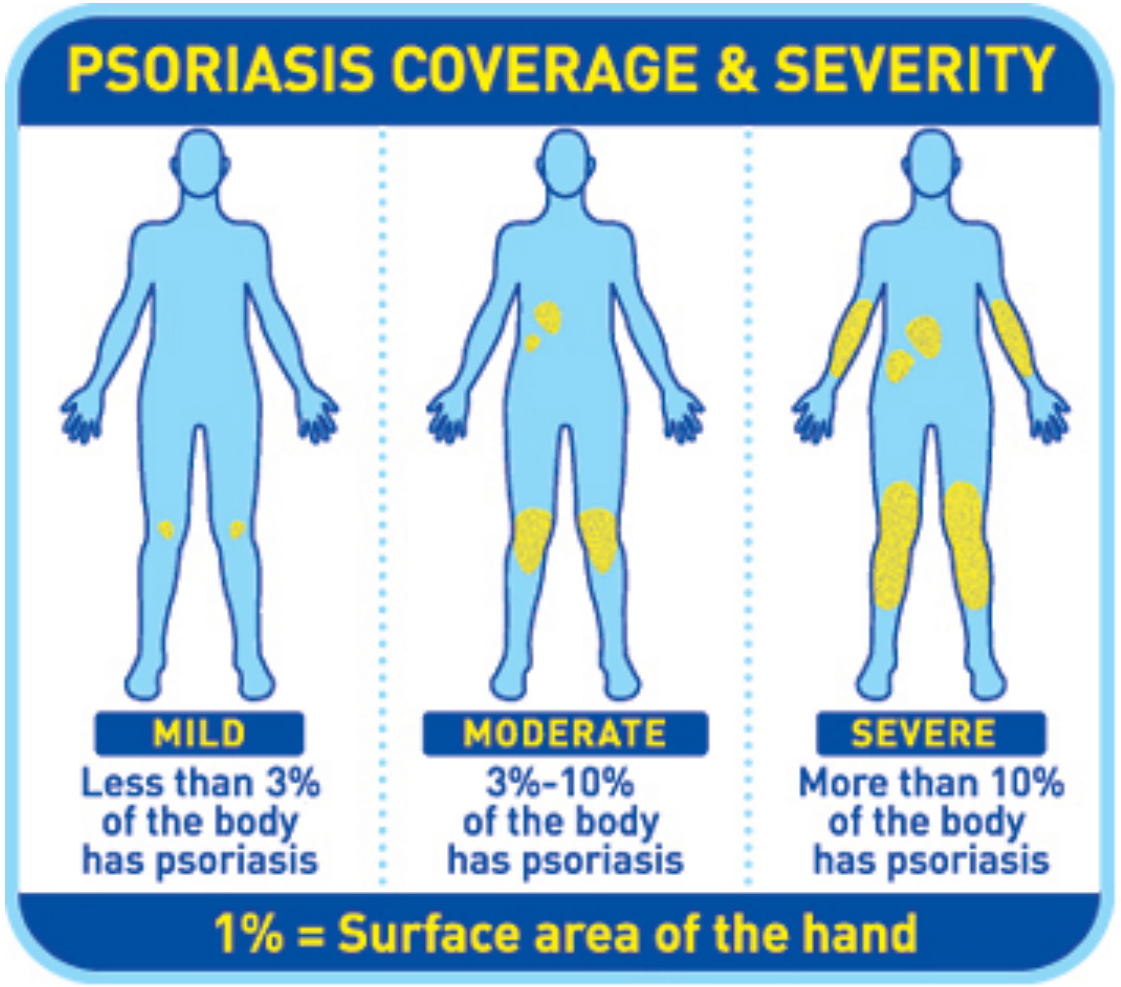
	Diabetes (all patients)	CV Death (DMARD)	All cause mortality (DMARD)
Psoriasis	1.2	1.5	1.8
RA	0.9	1.6	1.6
PsA	1.33	0.96	0.94



Ogdie A et al. *Ann Rheum Dis*. 2014;73(1):149-53; Ogdie A et al. *Ann Rheum Dis*. 2015;74: 326-32; Dubreuil M et al. *Rheumatology* 2014;53(2):346-52; Søren Lund Kristensen et al. *Ann Rheum Dis*. 2015;74:321-322.

Prevalence of CVD Increases With BSA Affected by Psoriasis (iHOPE N = 9000)

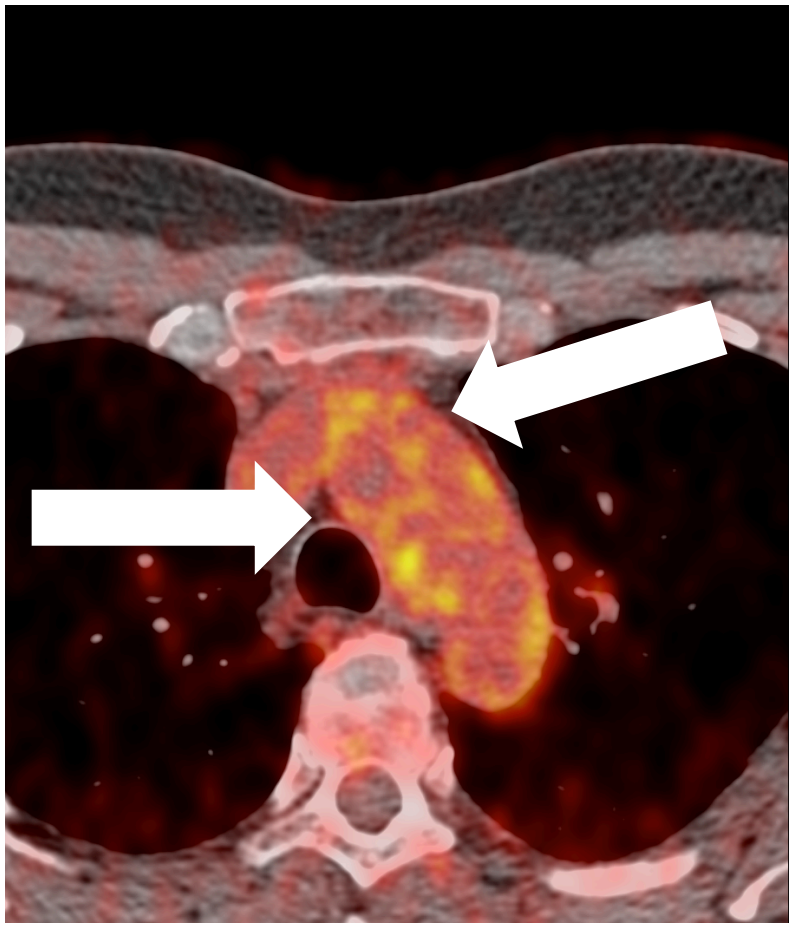




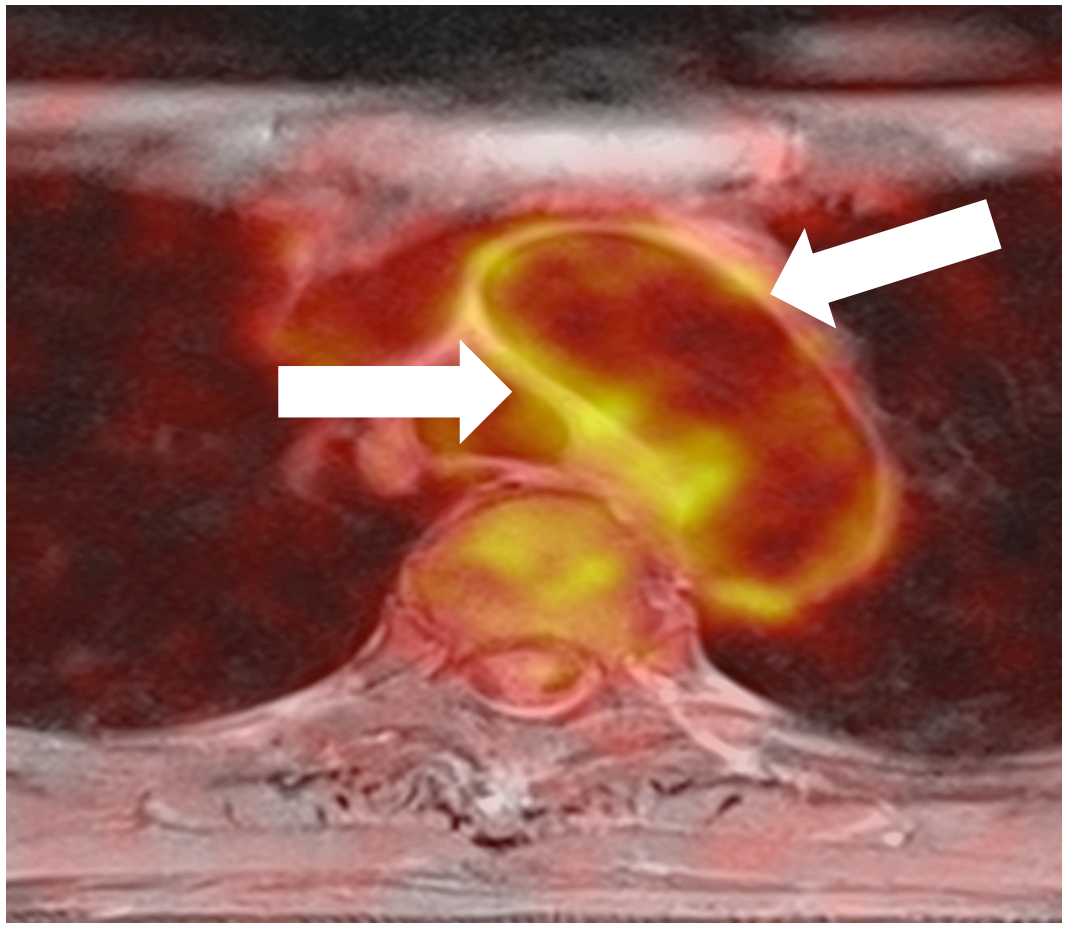
BSA = body surface area.

Yeung H, et al. *JAMA Dermatol*. 2013;149:1173-1179.

Inflammation Localizes to the Arterial Wall Using PET MRI: Severe 'Flared' Psoriasis



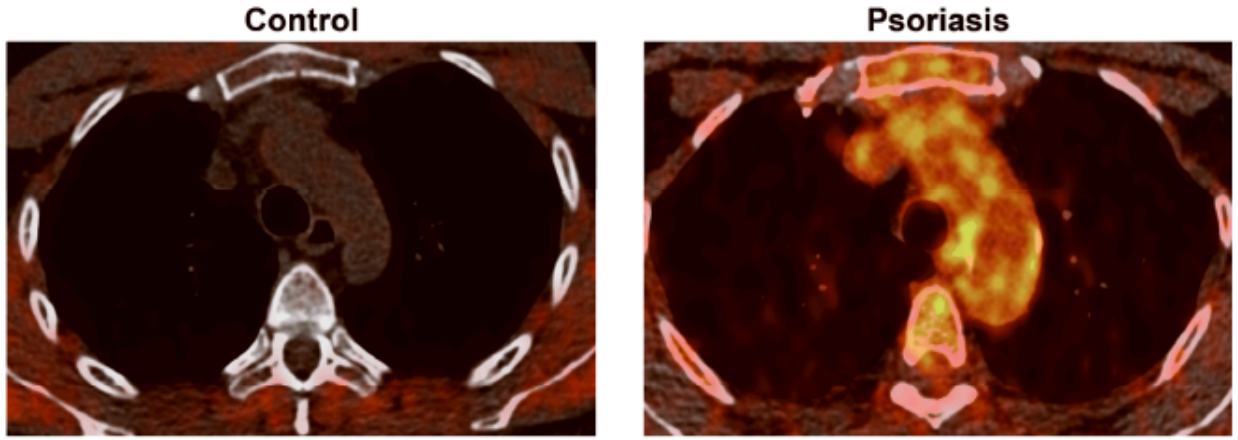
PET/CT Tissue: background of 2.0 (aortic arch)
60min imaging time

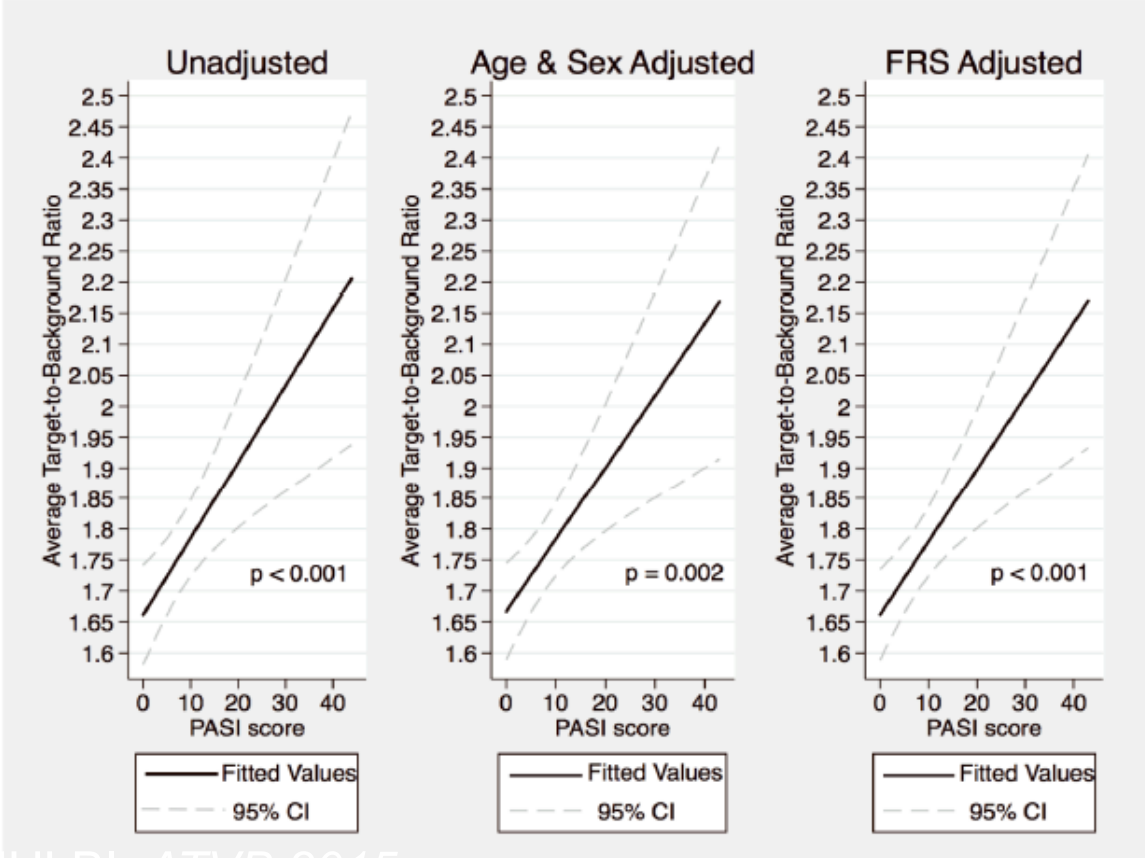


PET/MRI Tissue: background of 3.1 (aortic arch)
120min imaging time

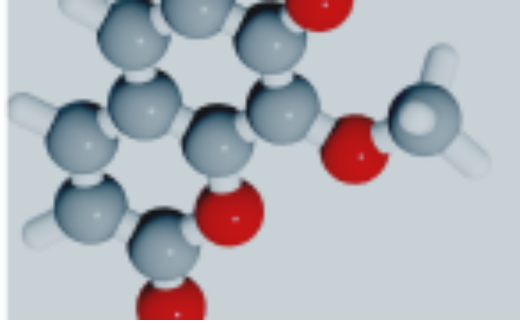
Slide courtesy of Nehal Mehta, MD, MSCE

Psoriasis Severity Correlates With Aortic TBR





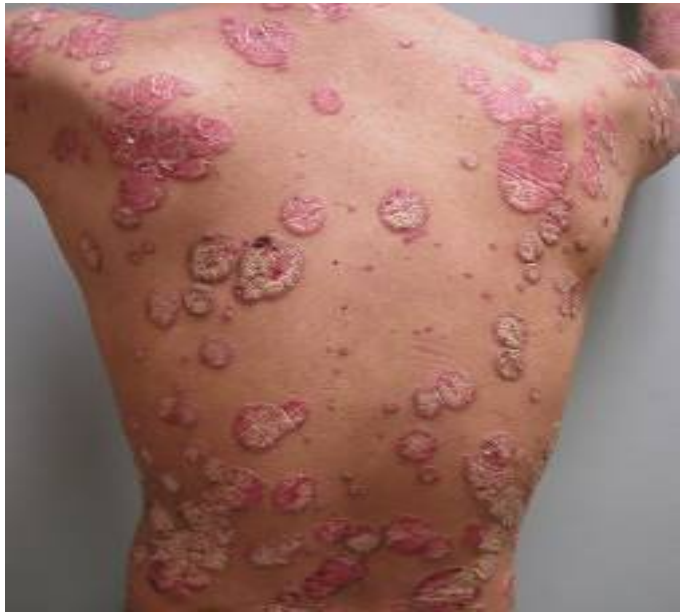
Should Psoriasis Be Aggressively Treated to Lower the Risk of CV Disease?



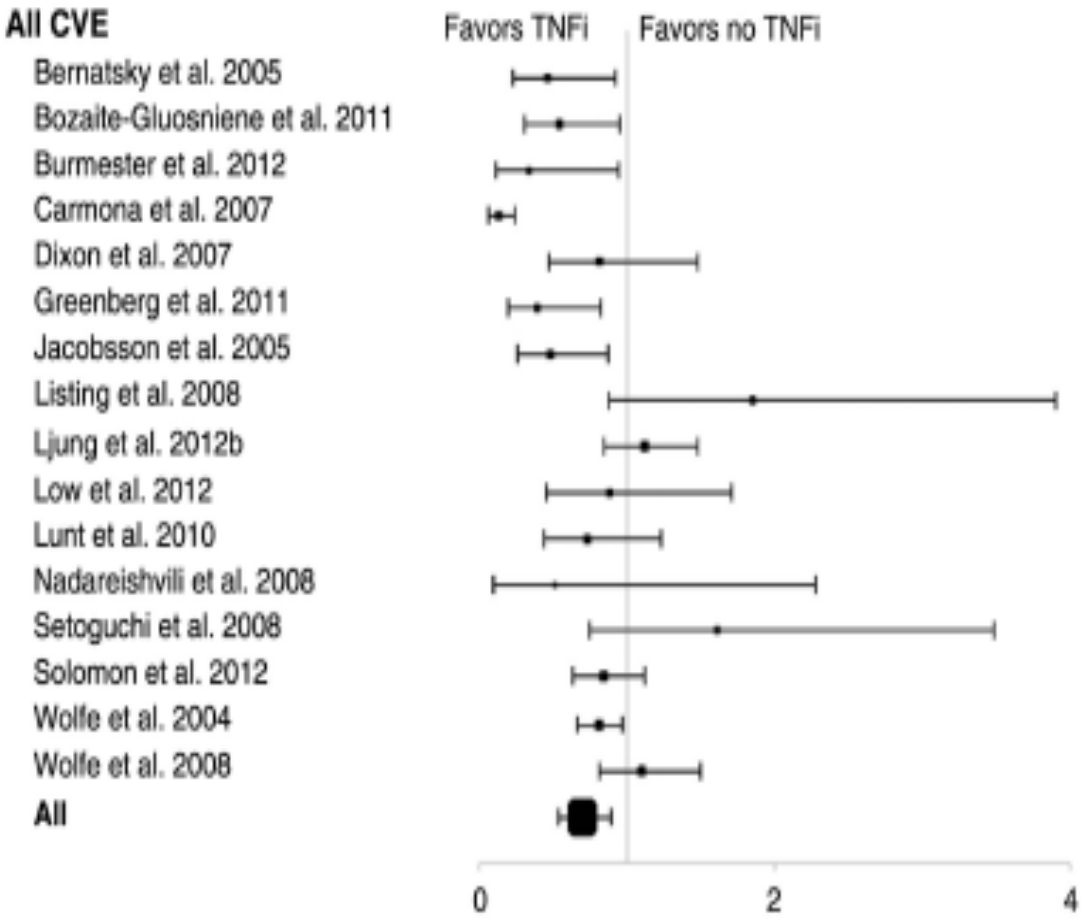
1970: Silent Killer

2004: Secret Killer

2016: Visible Killer?



TNF Inhibitors and Methotrexate Are Cardioprotective in RA Meta-Analysis

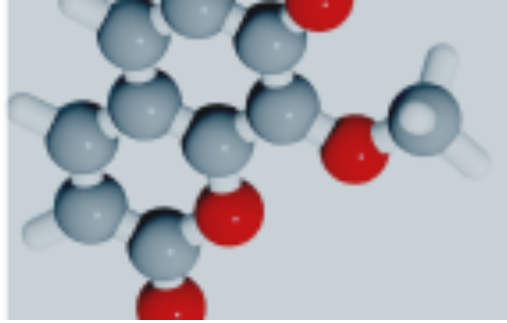


Outcome	TNF (RR)	MTX (RR)
CV all	0.70	0.72
MI	0.59	0.81
CHF	0.75 (NS)	0.8
Stroke	0.57	0.78 (NS)
MACE	0.30	0.38 (NS)

MTX = methotrexate.
Heterogeneity: $Tau^2 = 0.17$; $Chi^2 = 65.48$; df = 15 ($p < .00001$); $I^2 = 77\%$
Test for overall effect: $Z = 2.81$ ($p = .05$)
Roubille C, et al. *Ann Rheum Dis*. 2015;74:480-489.

Q: Should Psoriasis Be Aggressively Treated to Lower the Risk of CV Disease?

A: We Don't Know (For Certain)



- Observational data suggest methotrexate and TNF inhibitors lower the risk of CV events
- Data do not yet exist to demonstrate a protective effect of phototherapy, apremilast, ustekinumab, secukinumab, and ixekizumab on CV events

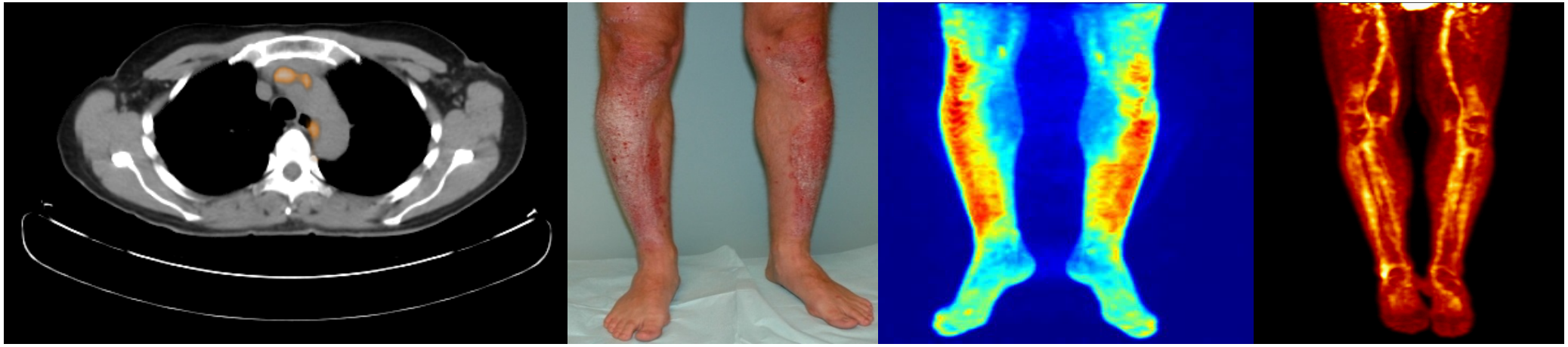
Micha R, et al. *Am J Cardiol.* 2011;108:1362–1370.; Barnabe C, et al. *Arthritis Care Res.* (Hoboken) 2011;63:522–529.; Prodanovich S, et al. J *Am Acad Dermatol.* 2005;52:262–267.; Wu JJ, et al. *Arch Dermatol*. 2012;148:1244-1250.; Ahlehoff O, et al. *J Int Med*. 2013;273:197-204.

Hierarchy of Evidence: Prevention Requires Strongest Level!

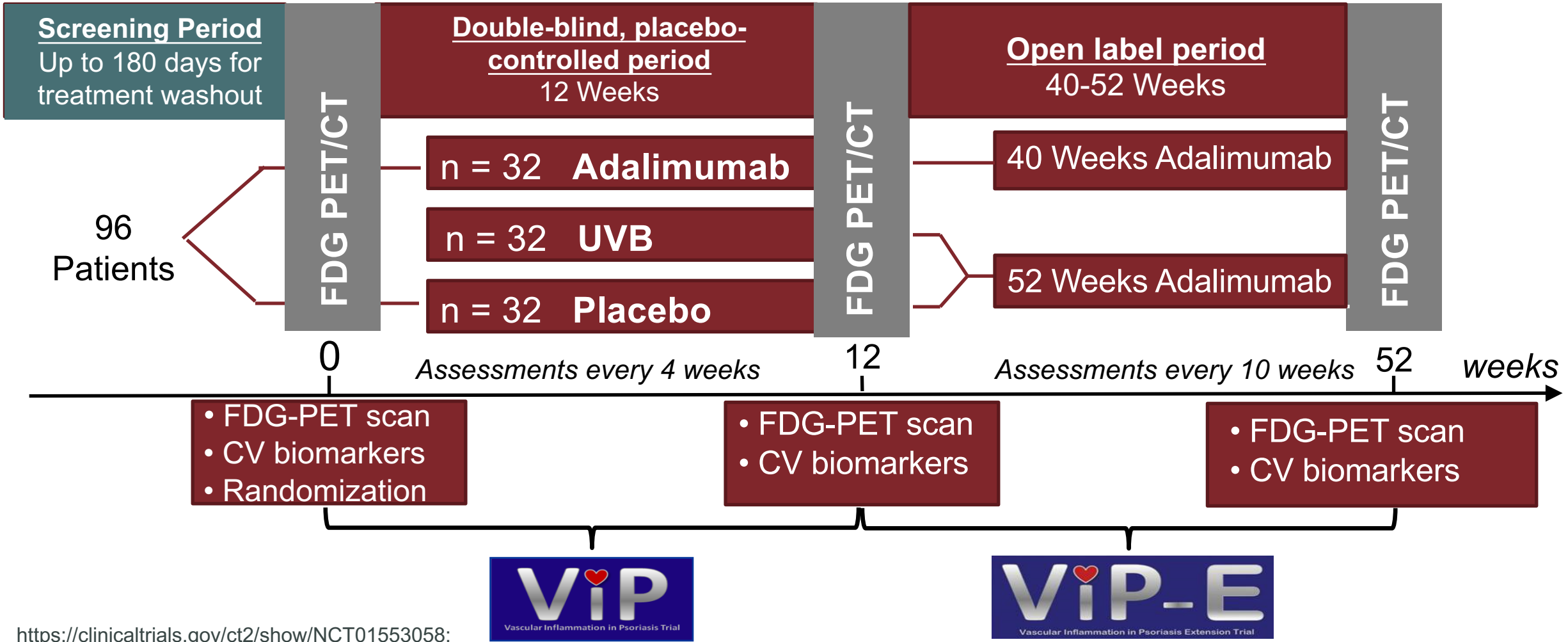
PHP Partners. Available at: http://phpartners.org/tutorial/04-ebph/2-keyConcepts/4.2.7.html. Accessed October 27, 20116.

RCTs Evaluating Impact of Psoriasis Treatment on CV Risk

- **Vascular Inflammation in Psoriasis Trials (VIP)**
  - Does treatment with adalimumab or phototherapy lower vascular inflammation and improve lipid metabolism in patients with moderate to severe psoriasis? (NCT01553058)
  - Does treatment with ustekinumab lower vascular inflammation and improve lipid metabolism in patients with moderate to severe psoriasis (NCT02187172)
  - Does treatment with secukinumab lower vascular inflammation and improve lipid metabolism in patients with moderate to severe psoriasis (NCT02690701)
- **Events based trials in patients without chronic inflammatory disease**
  - CIRT: Does methotrexate lower the risk of major vascular events in patients with a history of MI and diabetes or metabolic syndrome? (NCT01594333)
  - CANTOS: Does canakinumab treatment of patients with MI at least 1 month prior to study entry and elevated hsCRP prevent recurrent CV events? (NCT01327846)



Vascular Inflammation in Psoriasis (VIP & VIP-E)



https://clinicaltrials.gov/ct2/show/NCT01553058;
https://clinicaltrials.gov/ct2/show/NCT01866592.

Key inclusion criteria:

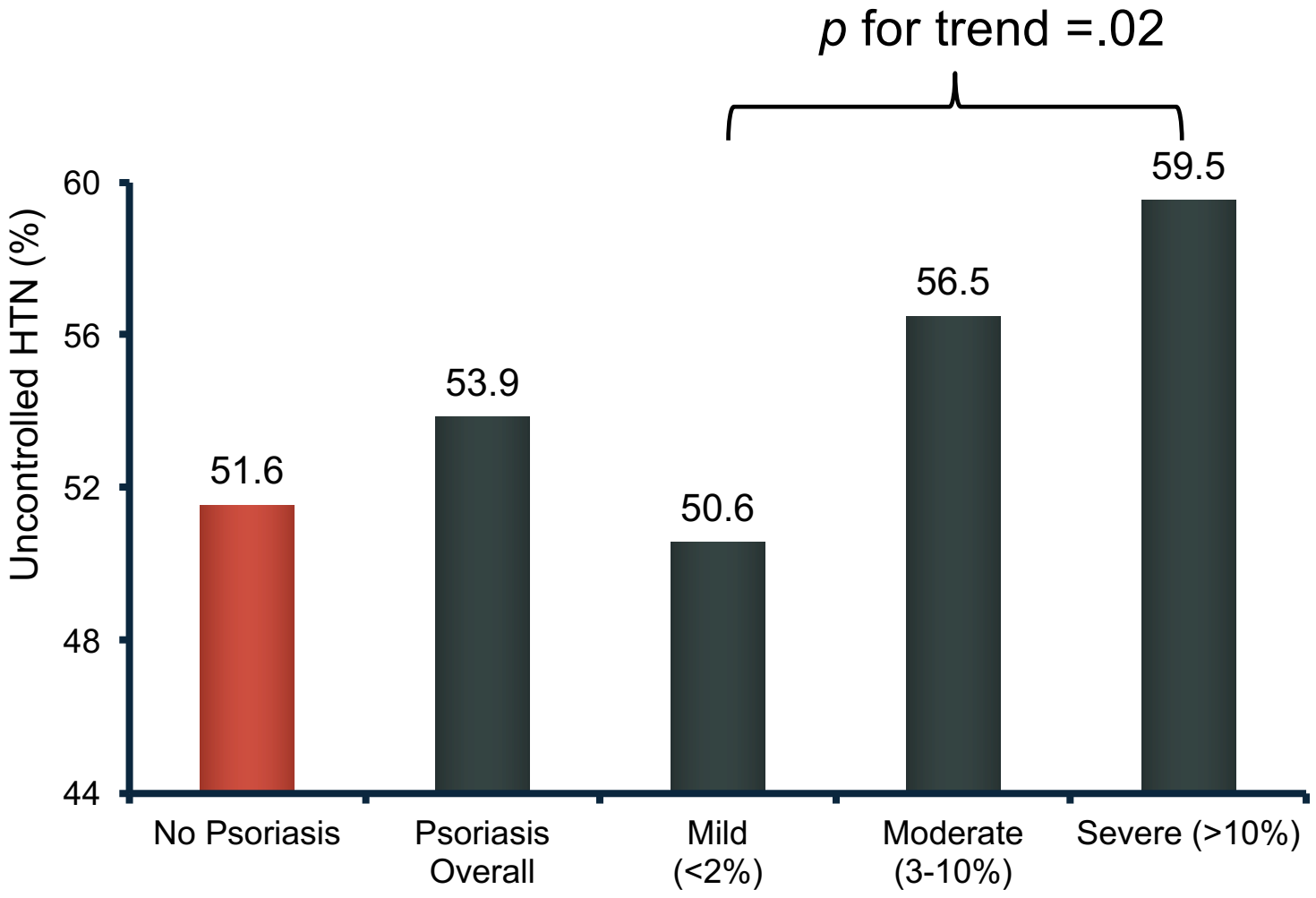
- BSA of ≥ 10%; PASI of ≥ 12%
- Diagnosis of Psoriasis > 6 months
- Candidate for systemic and phototherapy

Standard Screening Recommendations

- Hypertension[1]
  - Age 18-39, no risk factors & BP <130/85 mmHg: every 3-5 years
  - Age >40 and those at increased risk for high BP (BP 130-139/85-89 mmHg, overweight/obese, African Americans): yearly
- Diabetes (fasting plasma glucose, HbA1c, or OGTT)[2]
  - Adults 40-70 with BMI ≥25kg/m2
  - Repeat every 3 years
- Cardiovascular risk assessment[3]
  - Traditional risk factors every 4–6 years in patients 20–79
  - Estimate 10-year risk in those 40–79

Siu AL on behalf of USPSTF. *Ann Intern Med*. 2015;63(10):778-786.
Siu AL on behalf of USPSTF. *Ann Intern Med*. 2015;163(11):861-868.
Goff DC Jr. et al. *J Am Coll Cardiol*. 2014;63:2935-2959.

CV Risk Factors Are Underscreened and Undermanaged in Psoriasis Patients



- CDC US population data indicates poor screening rates for hypertension
  - Severe psoriasis dermatology: 4%
  - Non psoriasis/non dermatology: 61%
- < 50% of US dermatologists report screening for hypertension, dyslipidemia, diabetes

Takeshita J, et al. *JAMA Dermatology*. 2015;151:161-169. Alkmaar HS, et al. *J Drugs Dermatol.* 2013;12:e14-9; Manalo IF, et al. *J Am Acad Dermatol.* 2015;73:872-874; Kimball AB. *J Am Acad Dermatol*. 2012;67:76-85.

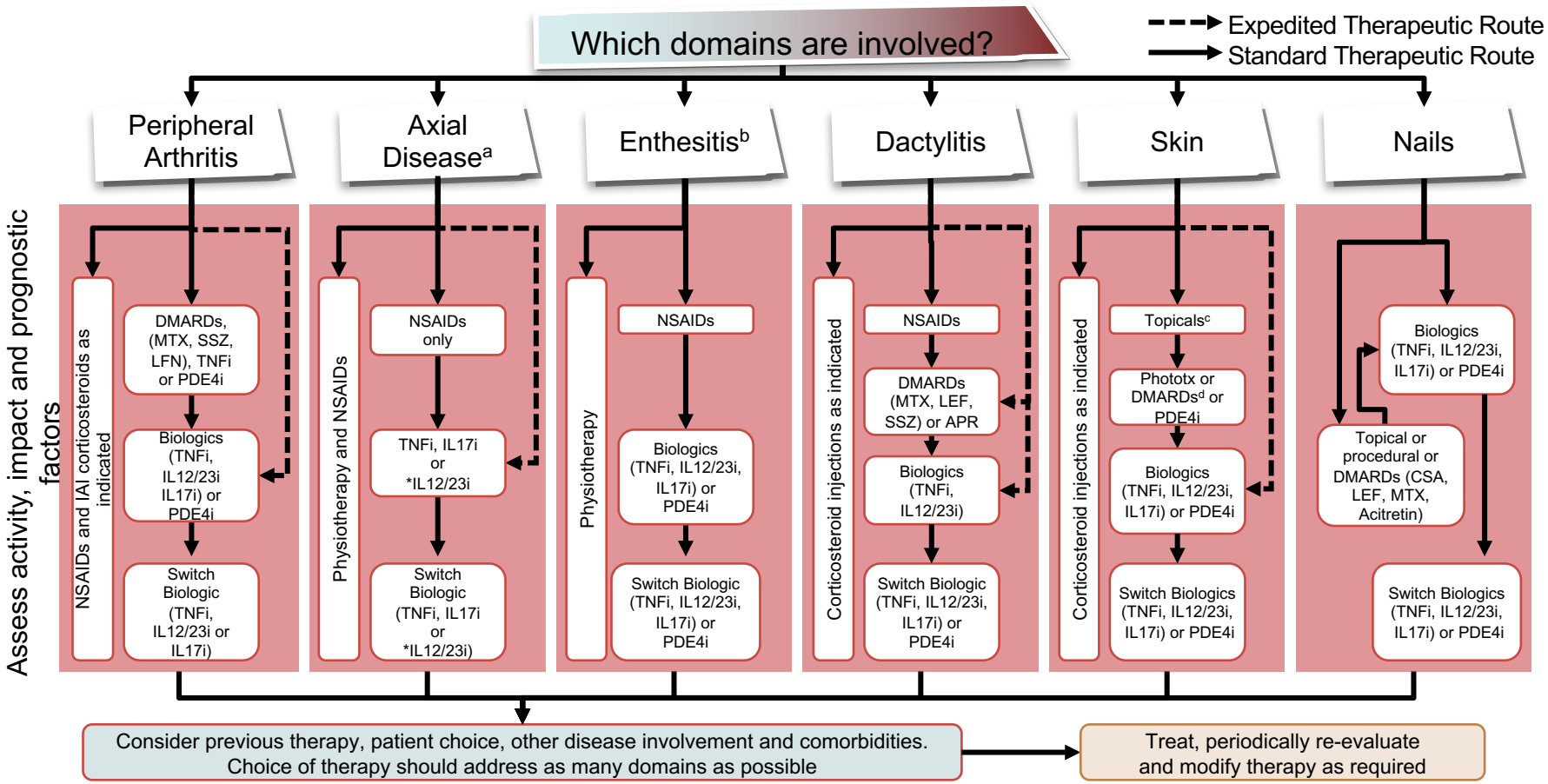
#SkinCME

Current Treatment Paradigms of Psoriatic Arthritis

Iain B. McInnes, FRCP, PhD, FRSE

Muirhead Chair of Medicine
Director, Institute of Infection, Immunity and Inflammation
Professor of Experimental Medicine
Director of Research Institute (Immunology)
College of Medical, Veterinary and Life Sciences
University of Glasgow, Glasgow, Scotland
United Kingdom

GRAPPA 2015: Treatment Recommendations



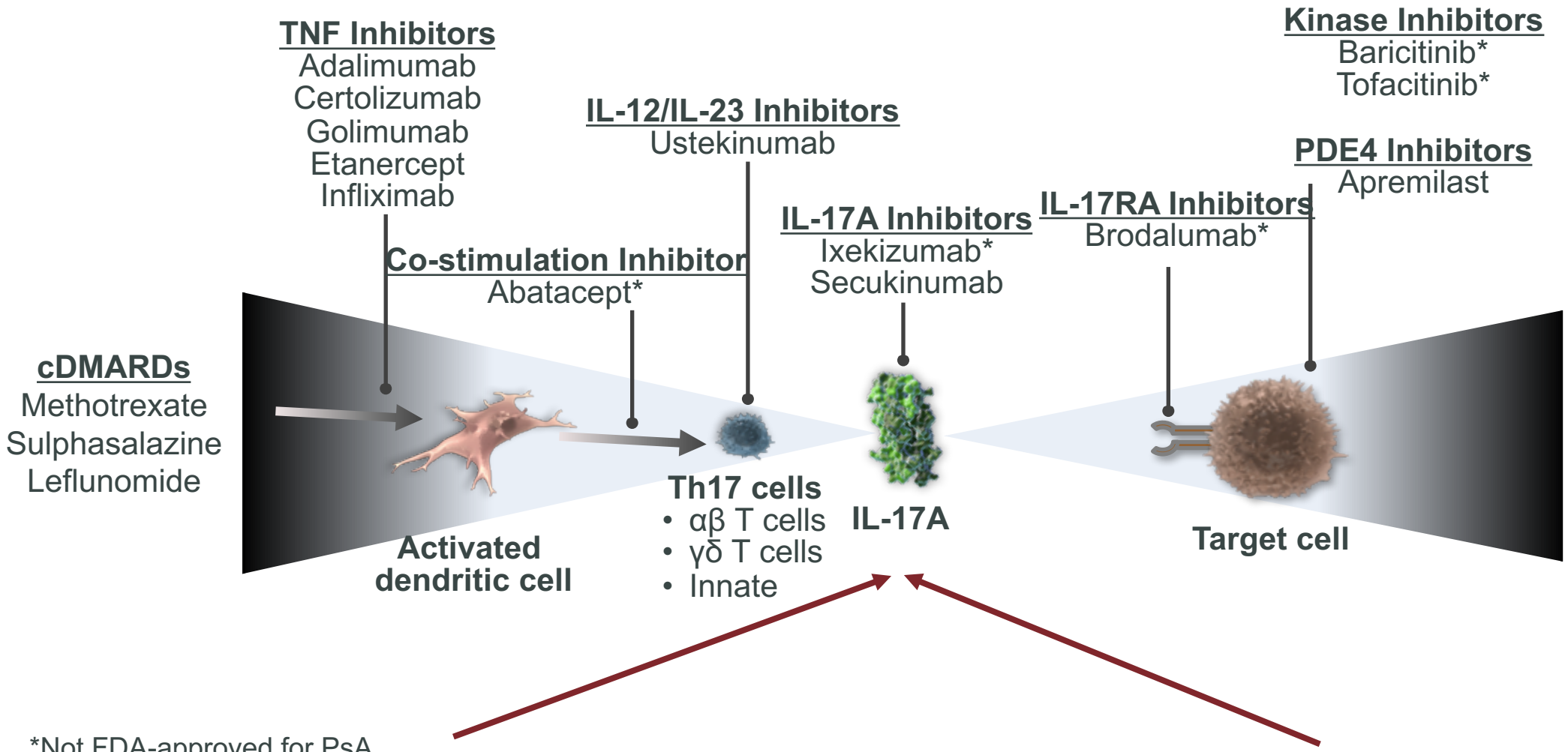
IAI = intra-articular injection.

[a]No direct evidence for therapies in axial PsA, recommendations based on axial SpA literature;

[b] Corticosteroid injections: consider on an individual basis due to potential for serious side effects; no clear evidence for efficacy; [c]Keratolytics, steroids, vitamin D analogues, emollients calcineurini; [d]MTX, CSA Acitretin, Fumaric acid esters.

Coates LC, et al. *Arthritis Rheum*. 2016;68:1060-11076.

Current and Novel Treatment Options for PsA



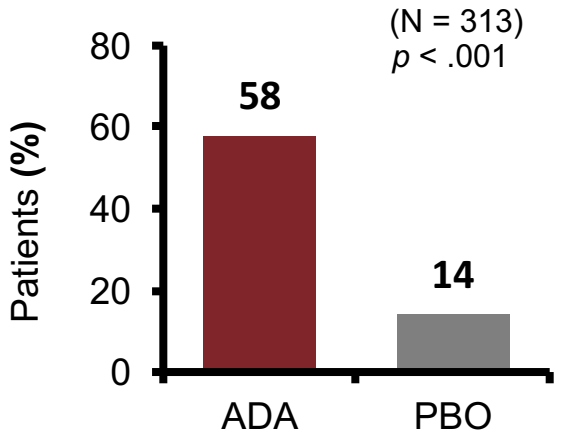
*Not FDA-approved for PsA.

PDE4 = phosphodiesterase type 4; Th17 = T helper 17 cell.

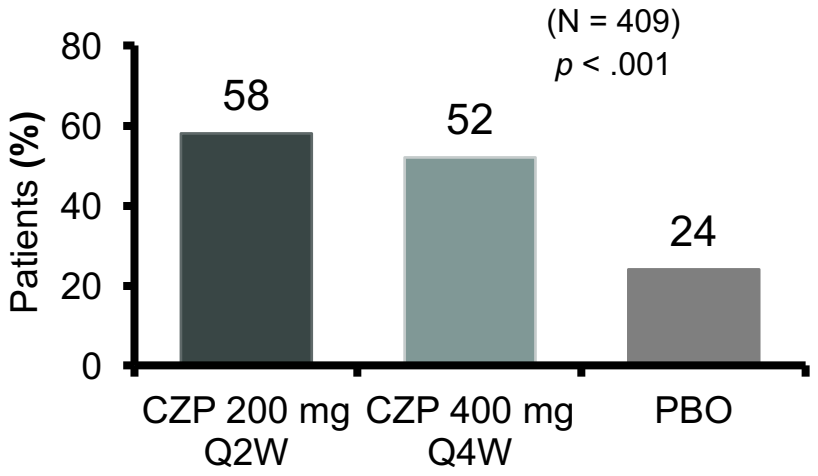
Adapted from Nestle F et al. *N Engl J Med*. 2009;361:496-509; Kopf M, et al. *Nat Rev Drug Discov*. 2010;9:703-718; Garber K. *Nat Biotechnol*. 2011;29:563-566.

Primary Outcome ACR20 Responses in PsA Patients Who Received Anti-TNF Therapy

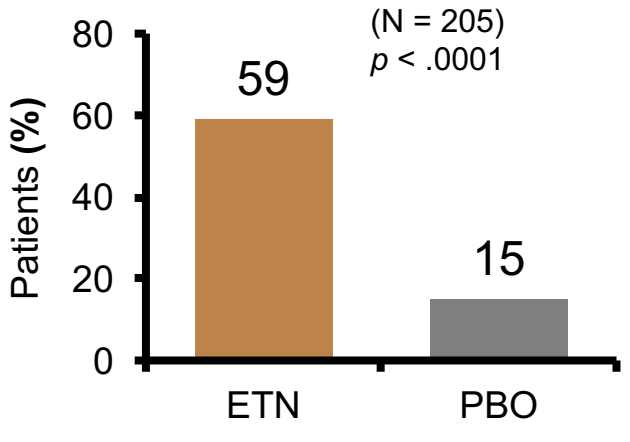
ADA (ADEPT) – Week 12[1]



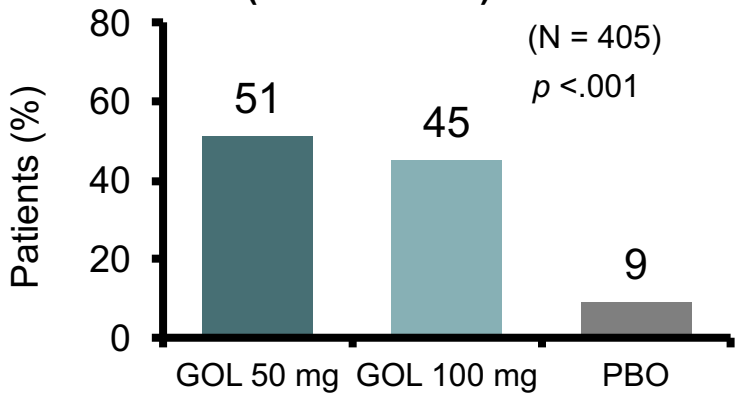
CZP (RAPID-PsA) – Week 12[2,a]



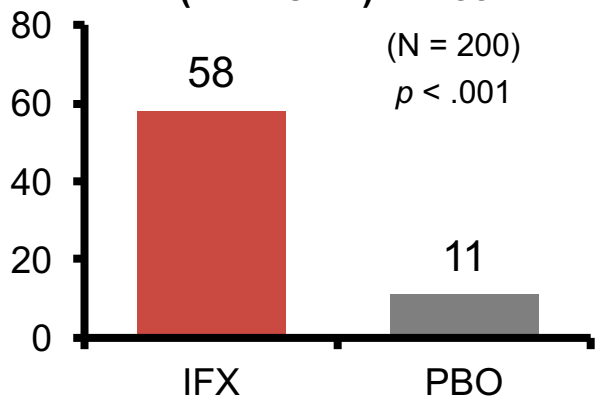
ETN – Week 12[3]



GOL (GO-REVEAL) – Week 14[4]



IFX (IMPACT-2) – Week 14[5]

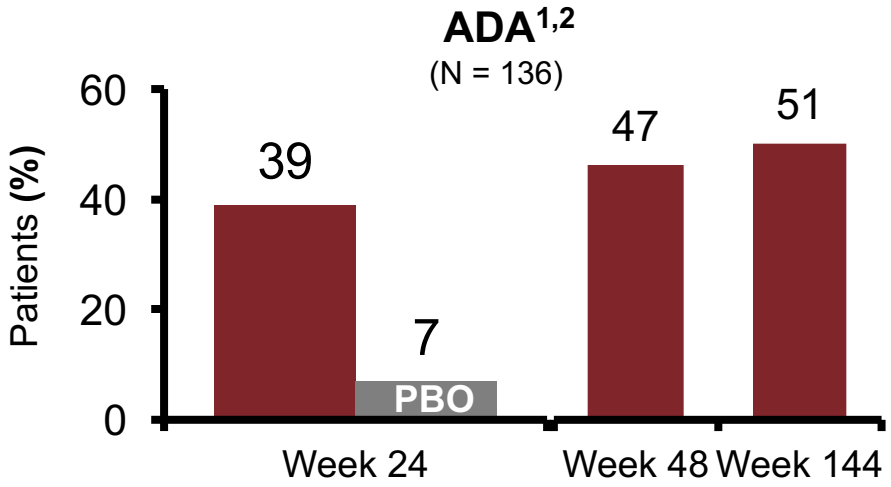


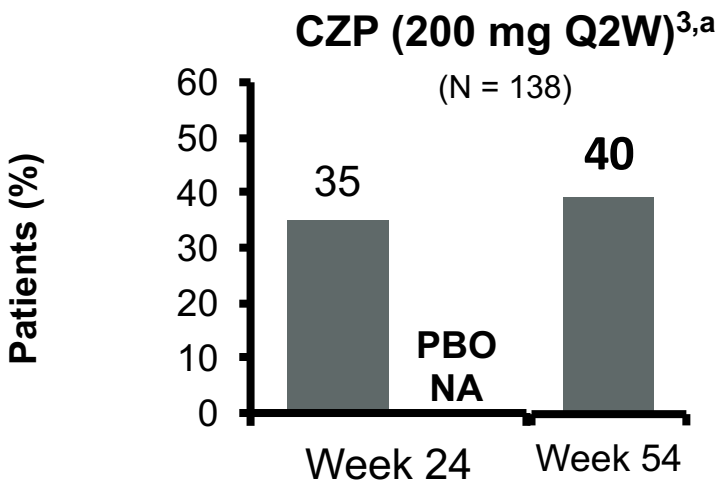
Different studies: Not head-to-head comparison. Results of individual studies cannot be directly compared

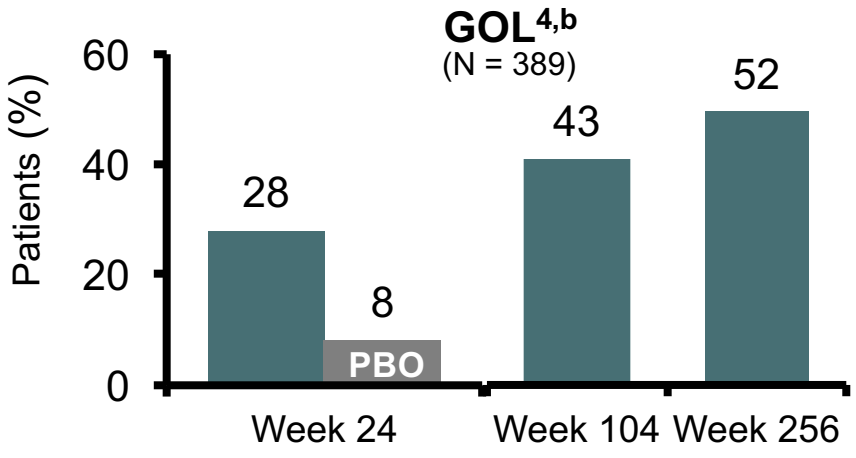
[a]The CZP population included anti-TNF-naïve and anti-TNF-experienced patients.
ADA; adalimumab, CZP; certolizumab pegol, ETN; etanercept, GOL; golimumab, IFX; infliximab

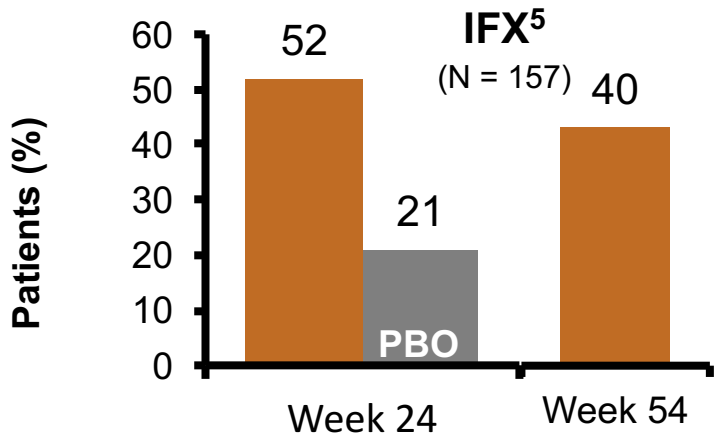
1. Mease PJ, et al. *Arthritis Rheum*. 2005;52:3279-3289; 2. Mease PJ, et al. *Ann Rheum Dis.* 2014;73:48-55; 3. Mease PJ, et al. *Arthritis Rheum.* 2004;50:2264-2272; 4. Kavanaugh A, et al. *Arthritis Rheum.* 2009;60:976-986; 5. Antoni C, et al. *Ann Rheum Dis.* 2005;64:1150-1157.

Patients With PsA Treated With Anti-TNF Therapy Achieving Minimal Disease Activity (MDA)*









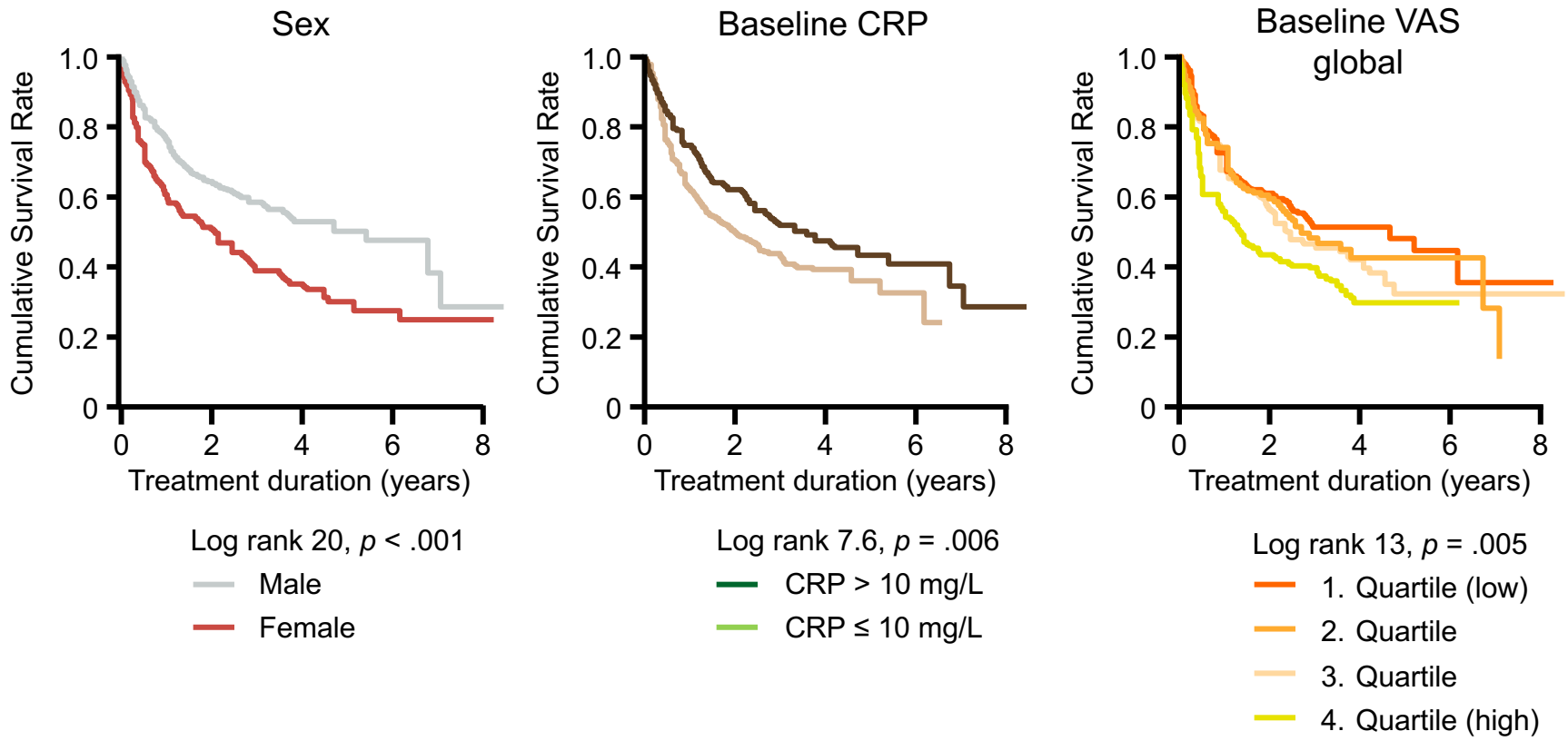
*Different studies: Not head-to-head comparison. Results of individual studies cannot be directly compared

[a]The CZP population included treatment-naïve and treatment-experienced patients; [b]Combined data from 50 and 100 mg dose groups; data for individual doses were not presented

[1]Mease P, et al. *J Rheumatol.* 2013;40:647-652; [2]Abbvie Data on file; [3]Mease P, et al. ACR 2013: Abstract 312; [4]Kavanagh A, et al. ACR 2013: Abstract 341; [5]Coates L and Helliwell PS. *Arthritis Care Res.* 2010;62:965–969

Drug Survival Rates of Anti-TNF Therapy in PsA

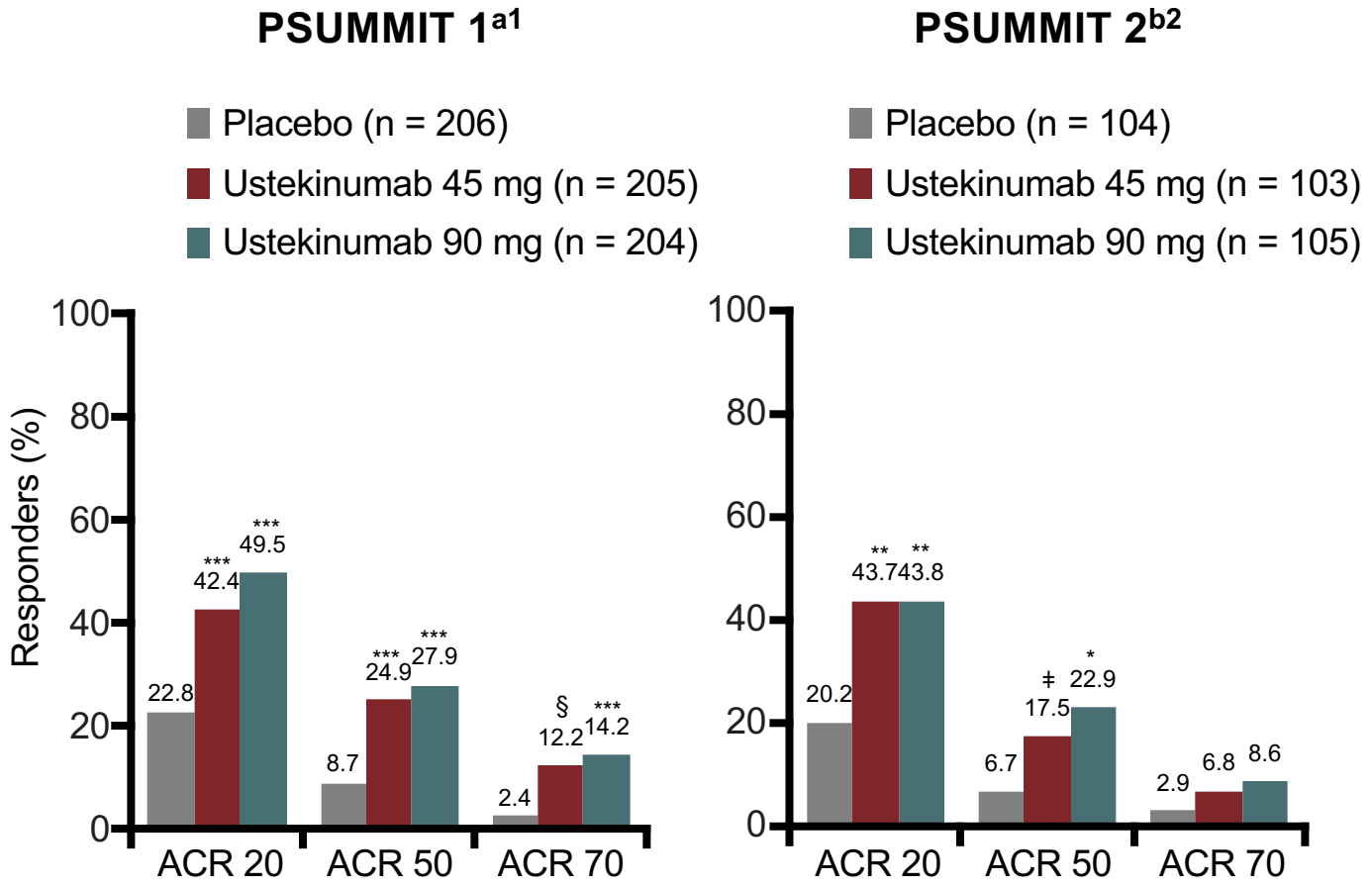
Results From the DANBIO Registry: Drug Survival in 764 Patients with PsA Treated With Anti-TNF Therapy



CRP = C-reactive protein; VAS = Visual analog scale.

Glintborg B, et al. *Arthritis Rheum*. 2011;63:382–390.

Ustekinumab in PsA: ACR Responses at Week 24



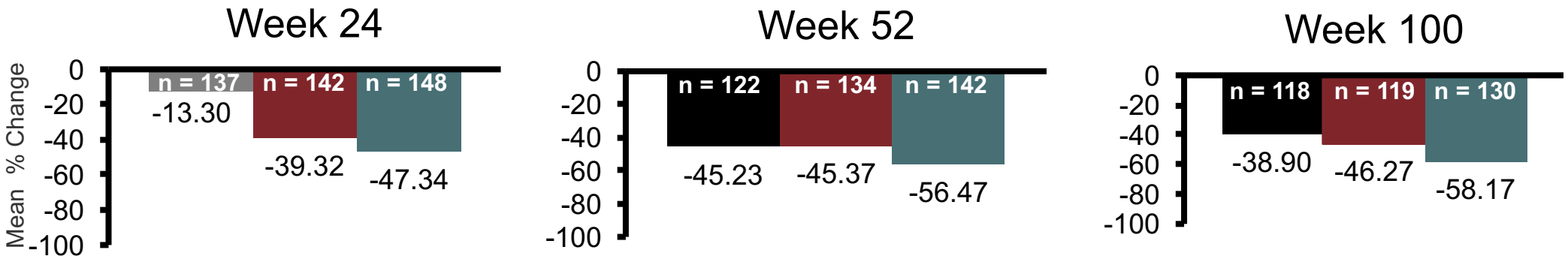
[a]Patients were biologic-naïve; [b]PSUMMIT 2 patients could have had previous anti-TNF experience

‡P < 0.05, *P < 0.01, **P < 0.001, §P = 0.0001, ***P < 0.0001 vs. placebo

1. McInnes IB, et al. *Lancet.* 2013;382:780-9.; 2. Ritchlin C, et al. *Ann Rheum Dis*. 2014;73:990-9.

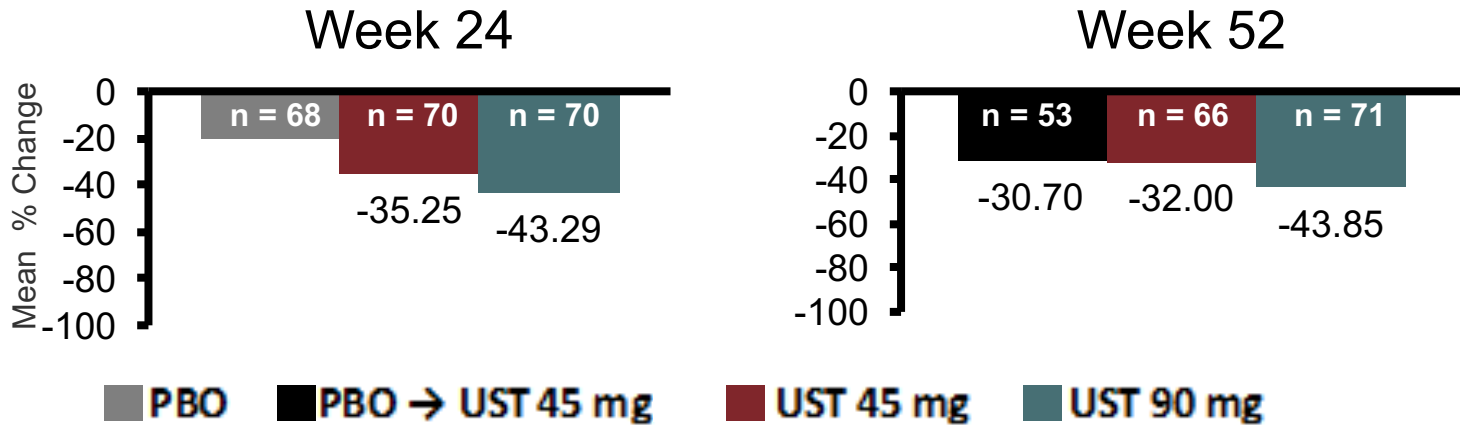
Ustekinumab in PsA: Mean Percent Change from Baseline in Enthesitis

PSUMMIT I



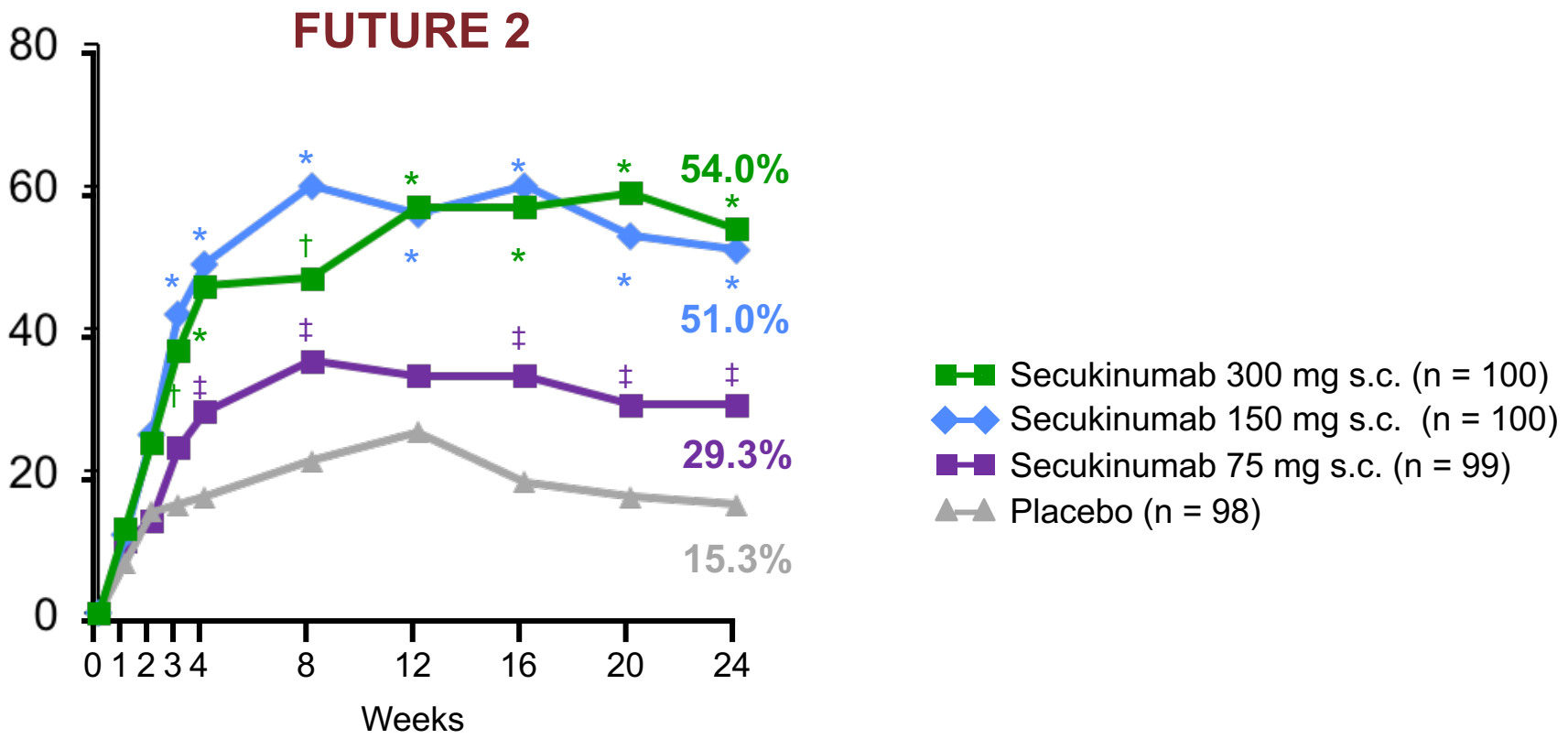
PSUMMIT 2

Enthesitis scoring based on Modified MASES Index. Includes only randomised patients with enthesitis at baseline.



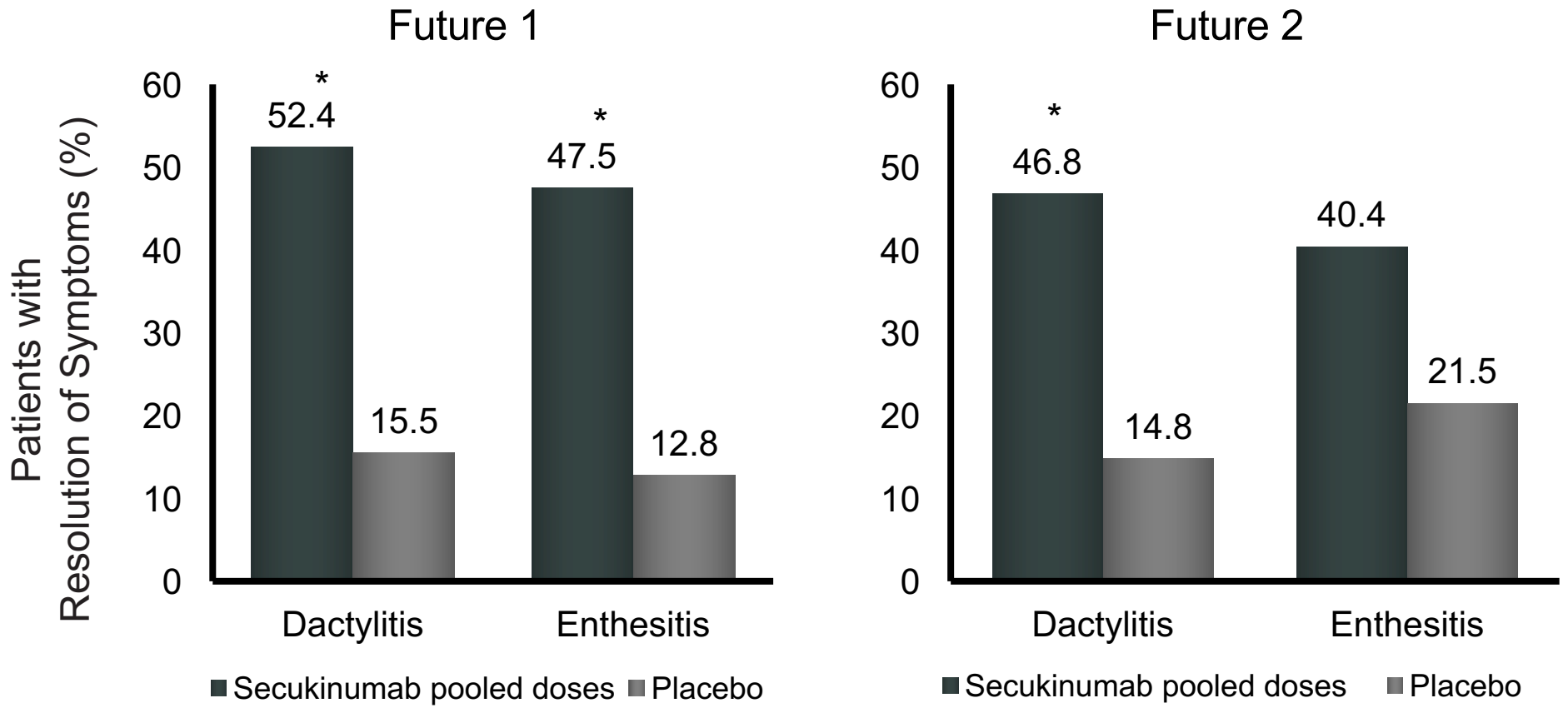
1. Kavanaugh A et al. Poster presented at EULAR 2014; SAT0396. 2. Ritchlin et al. *Ann Rheum Dis.* 2014;73(6):990-9 Supplementary data.

Secukinumab in PsA: Primary Outcome Measure



*p < .0001; †p < .001; ‡p < .05 vs. placebo (p-values at Week 24 adjusted for multiplicity).
Missing values imputed as nonresponse (nonresponder imputation).
Mease P, et al. *Rheumatol Ther*. 2016;3(1):5-29.

Secukinumab in PsA: Secondary Outcome Measures: Resolution of Dactylitis and Enthesitis at Week 24



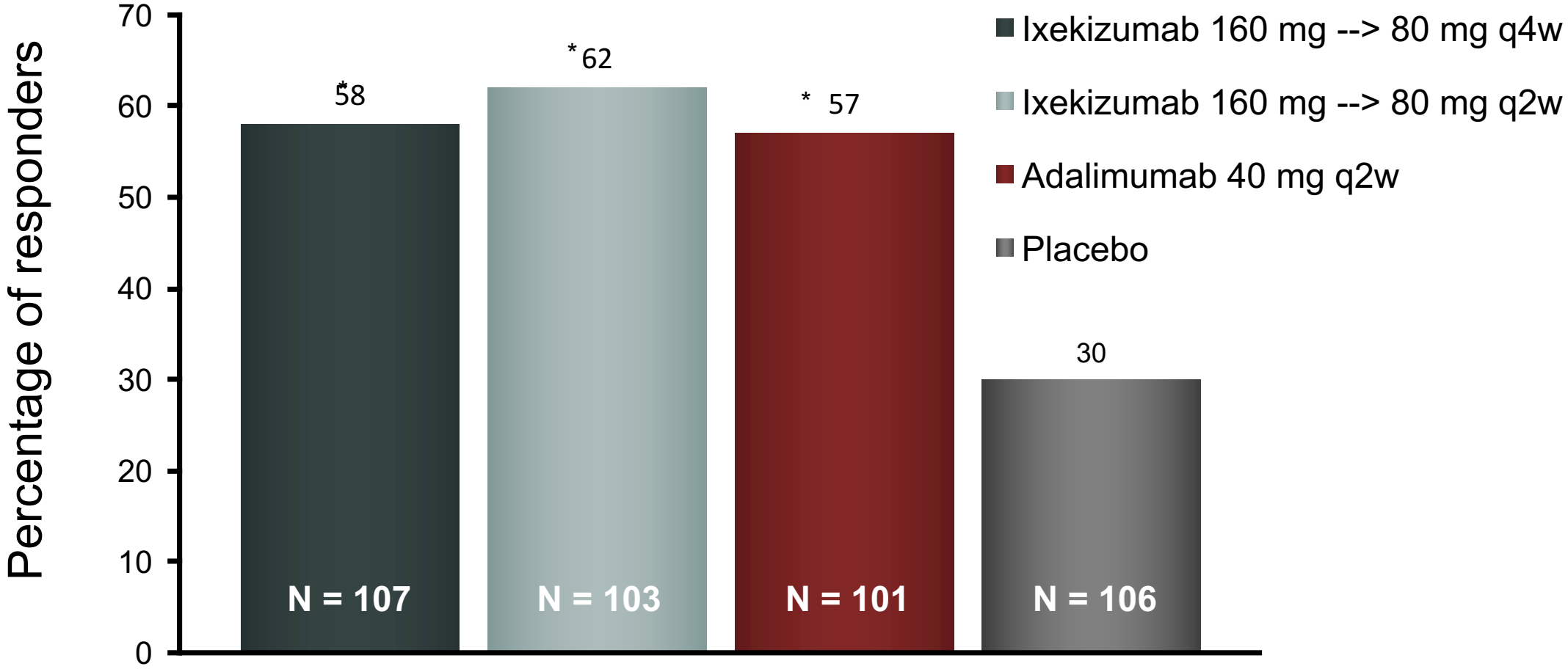
*p < .05 vs. placebo (P-values at Week 24 adjusted for multiplicity)

Resolution of dactylitis and enthesitis amongst those patients with these symptoms at baseline

Missing values were imputed as nonresponse (nonresponder imputation) at Week 24.

Mease P, et al. *Rheumatol Ther*. 2016;3:5-29; Mease P, et al. ACR (Boston 2014)

Ixekizumab: ACR 20 Responses at Week 24 (SPIRIT-P1; Primary Endpoint)

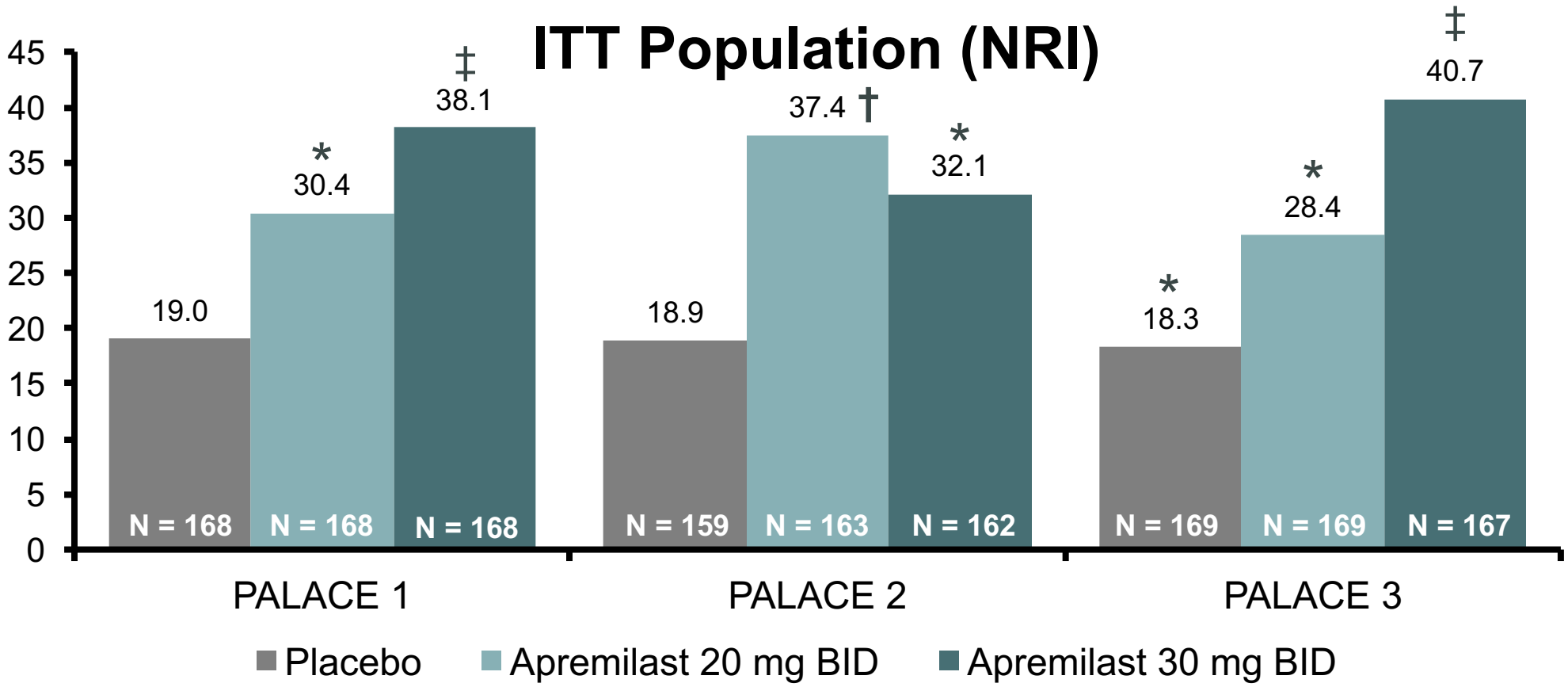


**p* <.001 vs. placebo

All patients were naïve to anti-TNF treatment; nonresponder imputation at Week 24, q2w, every two weeks; q4w, every 4 weeks

Mease PJ, et al. *Arthritis Rheumatol.* 2015;67(suppl 10):Abstract 977

Apremilast in PsA: Primary End Point Across Studies: ACR20 Response at Week 16



Apremilast 20 mg is not licensed in any indication; ACR20 = American College of Rheumatology 20; ITT = intent to treat; NRI = non-responder imputation.

*$P < .05$; †$P < .005$; ‡$P \leq .0001$ vs. placebo.

Kavanaugh A, et al. ACR 2014. Abstract 548. Kavanaugh A. et al. *Ann Rheum Dis*. 2014;73:1020-1026. Cutolo M, et al. *J Rheumatol.* 2016;43;1724-1734.

Rationale for "Treat to Target" (T2T) in PsA

- RA: T2T improves clinical and radiographic outcomes versus routine approaches[1,2]
- T2T recommendations for SpA and PsA: Treatment target → remission or LDA[3]
- Availability of highly effective biologics → Minimal level of disease activity a realistic treatment target in PsA[4]

Clinical and epidemiological research

OPEN ACCESS

EXTENDED REPORT

Treating spondyloarthritis, including ankylosing spondylitis and psoriatic arthritis, to target: recommendations of an international task force

Josef S Smolen,[1,2] Jürgen Braun,[3] Maxime Dougados,[4] Paul Emery,[5] Oliver FitzGerald,[6] Philip Helliwell,[7] Arthur Kavanaugh,[7] Tore K Kvien,[8] Robert Landewé,[9,10] Thomas Lugar,[11] Philip Mease,[12] Ignazio Olivieri,[13] John Reveille,[14] Christopher Ritchlin,[15] Martin Rudwaleit,[16] Monika Schoels,[2] Joachim Sieper,[17] Martinus de Wit,[18] Xenofon Baraliakos,[3] Neil Betteridge,[19] Ruben Burgos-Vargas,[19] Eduardo Collantes-Estevez,[20] Atul Deodhar,[21] Dirk Elewaut,[22] Laure Gossec,[23] Merryn Jongkees,[18] Mara Maccarone,[18] Kurt Redlich,[1] Filip van den Bosch,[22] James Cheng-Chung Wei,[24] Kevin Winthrop,[25] Désirée van der Heijde[26]

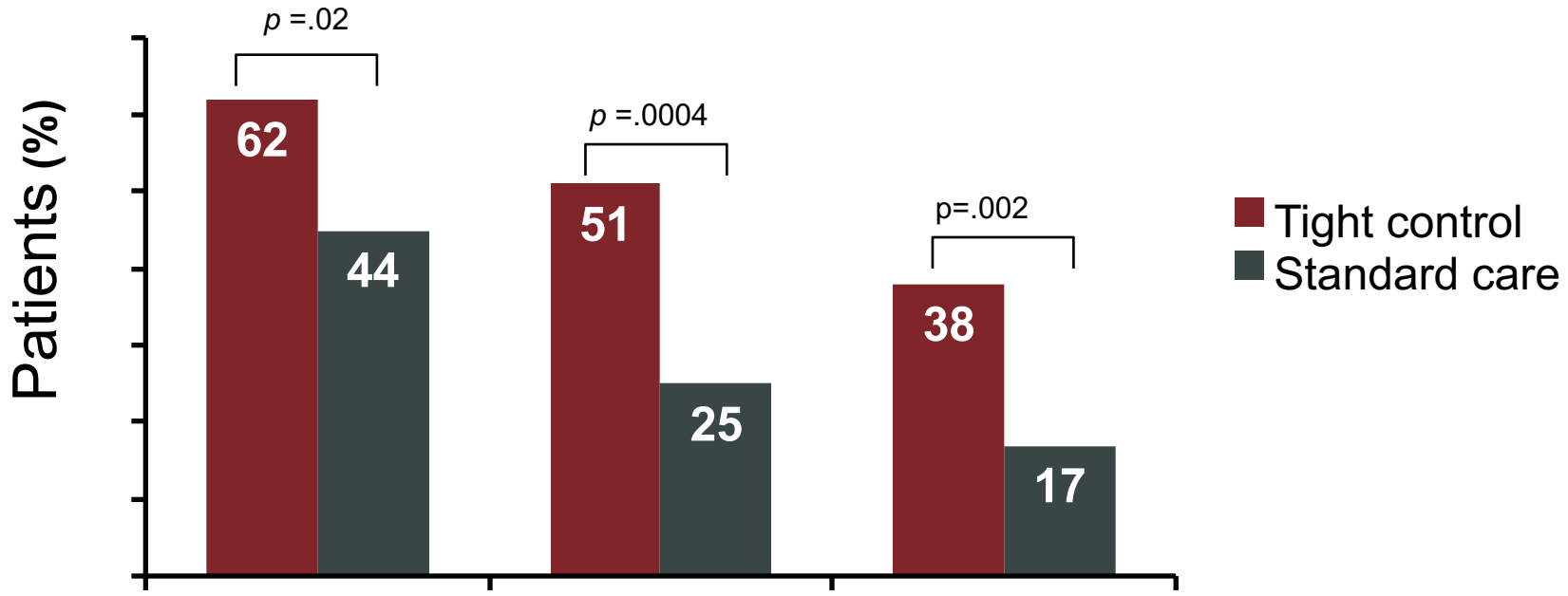
Linked

LDA = low disease activity; MDA = minimum disease activity; RA = rheumatoid arthritis; T2T = treat to target. .

1.Grigor C, et al. *Lancet*.2004;364:263–269; 2.Schoels M, et al. *Ann Rheum Dis*. 2010;69:638-643; 3. Smolen JS, et al. *Ann Rheum Dis*. 2014;73:6-16; 4.Gossec L, et al. *Ann Rheum Dis*. 2012;71:4-12;5.Coates LC, et al. *Ann Rheum Dis*. 2010;69:48-53

Tight Control Was Associated With Significantly Greater Improvements in Signs and Symptoms of Disease at Week 48

Primary Outcome: Complete Case Analysis

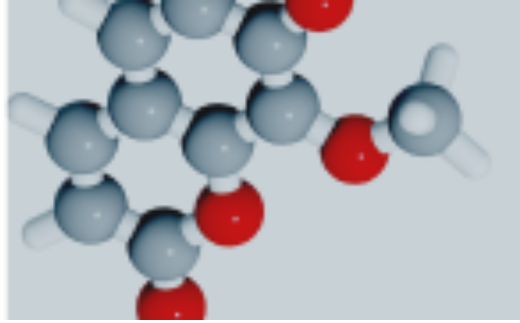


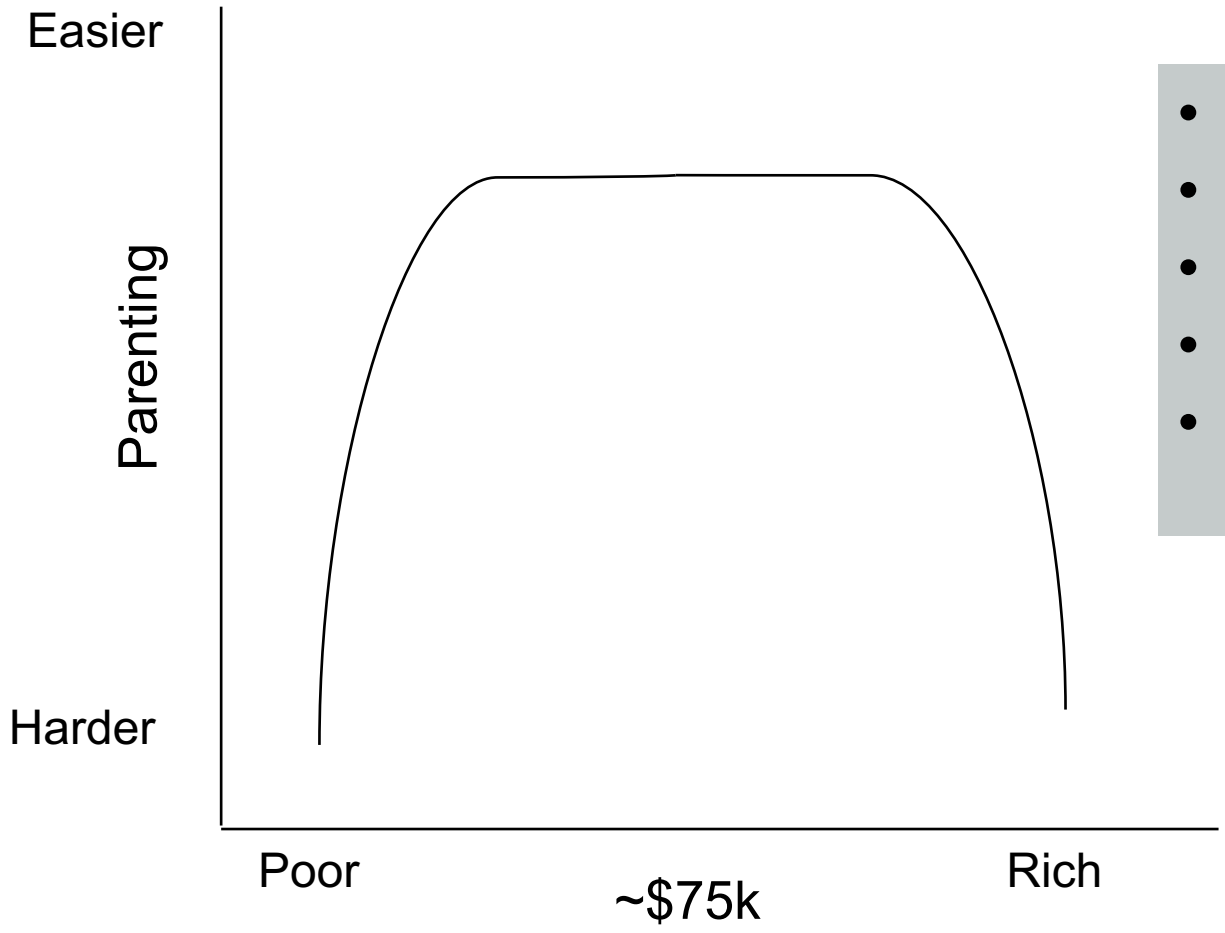
	Tight Control	Standard Care
Deaths	0	0
SAE	25	8
SAE related to drug	8	2

SAE = serious adverse event.

Coates LC, et al. *Lancet.* 2015;386(10012):2489-2498.

The Concept of ‘Disutility’



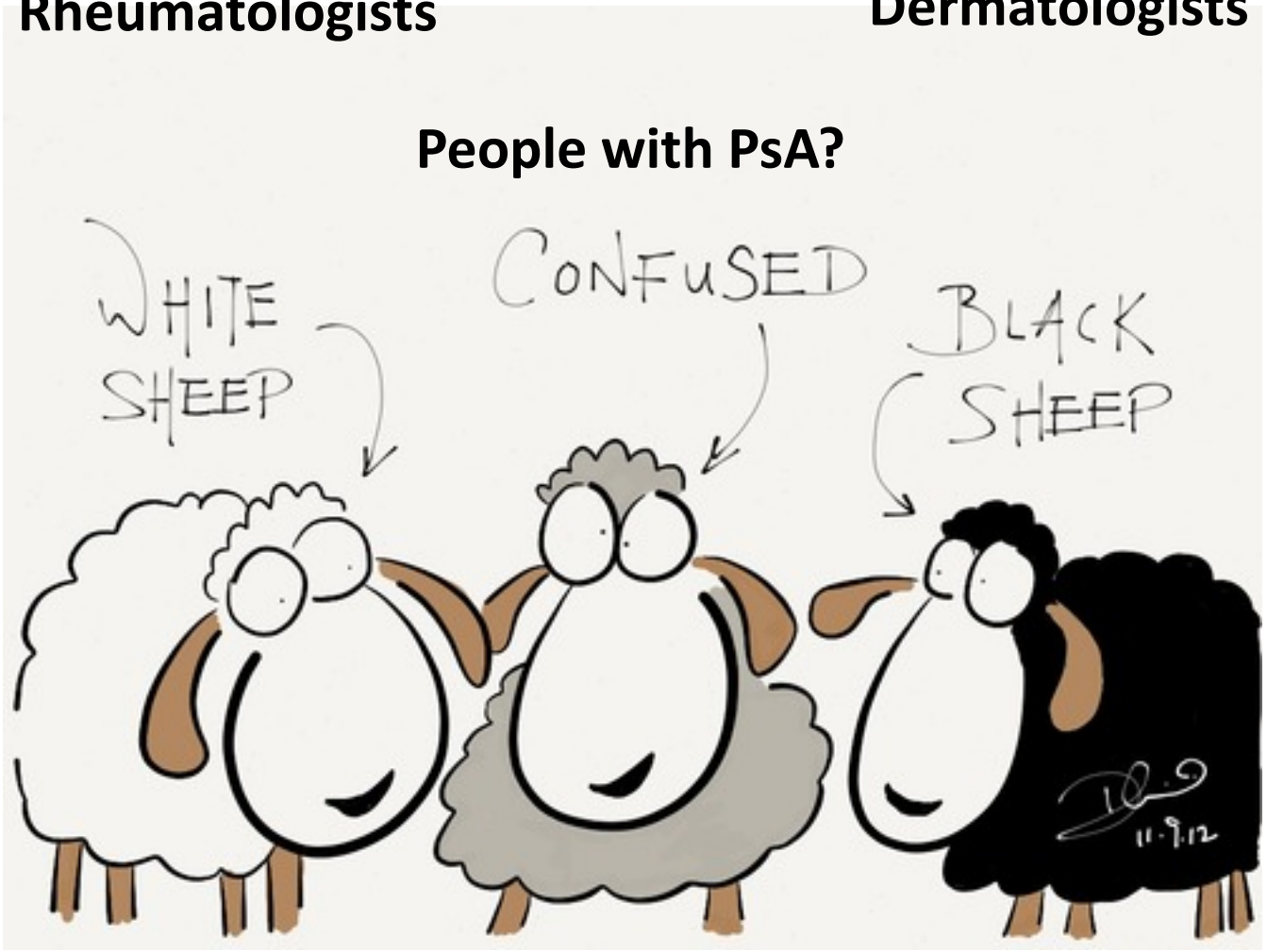


- Outcome measures?
- Surrogates for long-term harm?
- Evidence for benefit in RCTs?
- Toxicity of therapeutics?
- Disease heterogeneity…
  - Dichotomous responses

Graph from: Gladwell M. 2013 “David & Goliath’ Little, Brown and Company. See also Porter D, et al. *Ann Rheum Dis*. 2014;73(3):480-482.

Unmet Need in Treating PsA: Who is Driving?

- Recognizing the clinical syndrome
- Assessment of disease activity
- Current management
- Future treatment options



#SkinCME

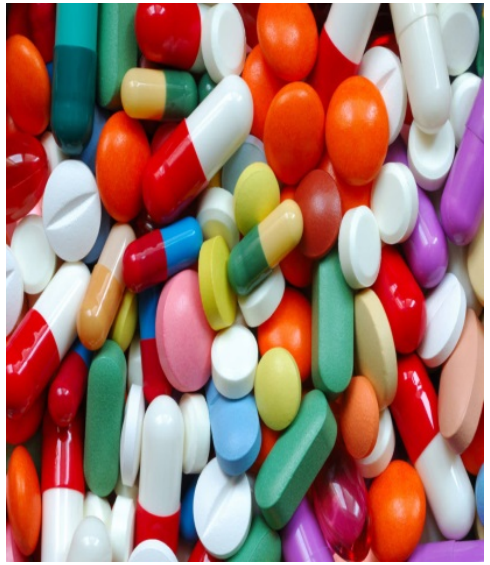
Current Treatment Paradigms of Moderate-to-Severe Psoriasis

Joel M. Gelfand, MD, MSCE

Professor of Dermatology
Professor of Epidemiology
Vice Chair of Clinical Research and Medical Director
Dermatology Clinical Studies Unit
Director, Psoriasis and Phototherapy Treatment Center
University of Pennsylvania Perelman School of Medicine
Philadelphia, PA

Psoriasis Treatment Approach

Topical
Steroids

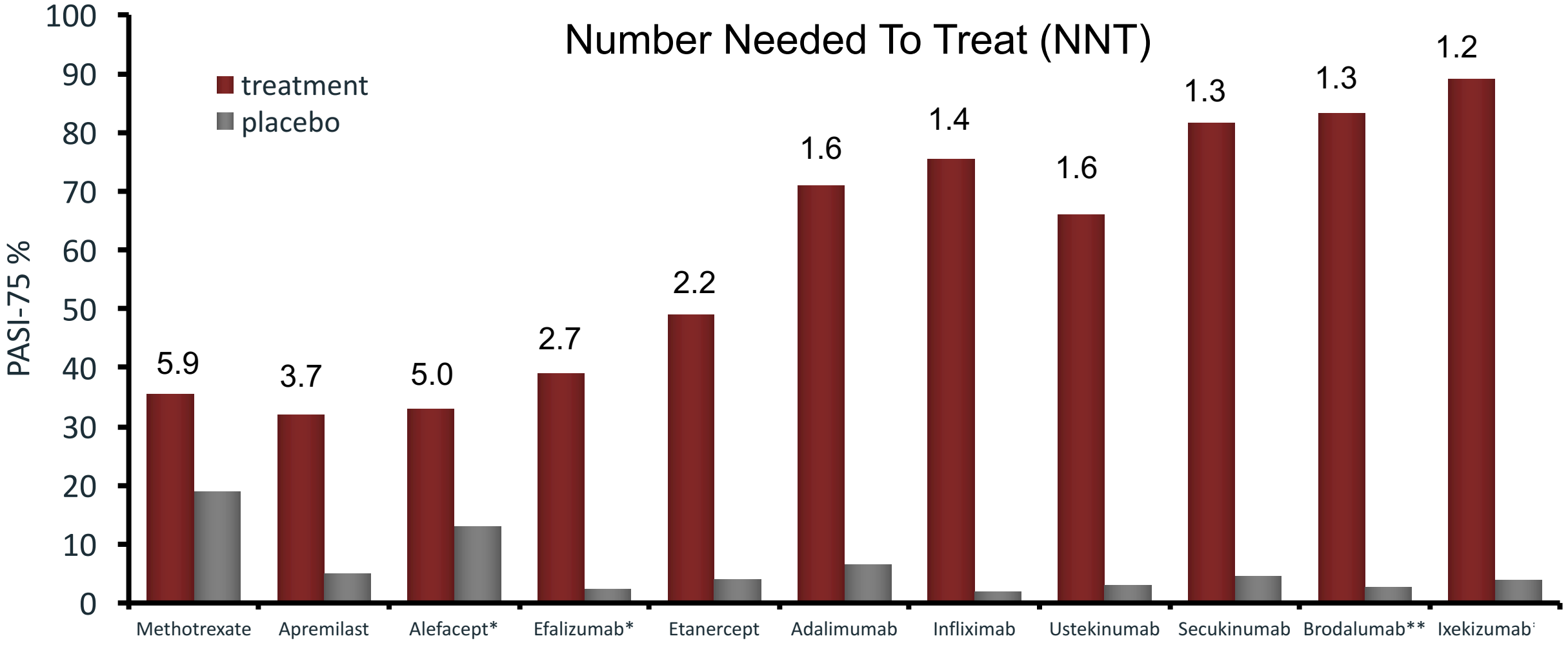


Acitretin
Apremilast
Cyclosporine
Methotrexate

Ultraviolet B
phototherapy

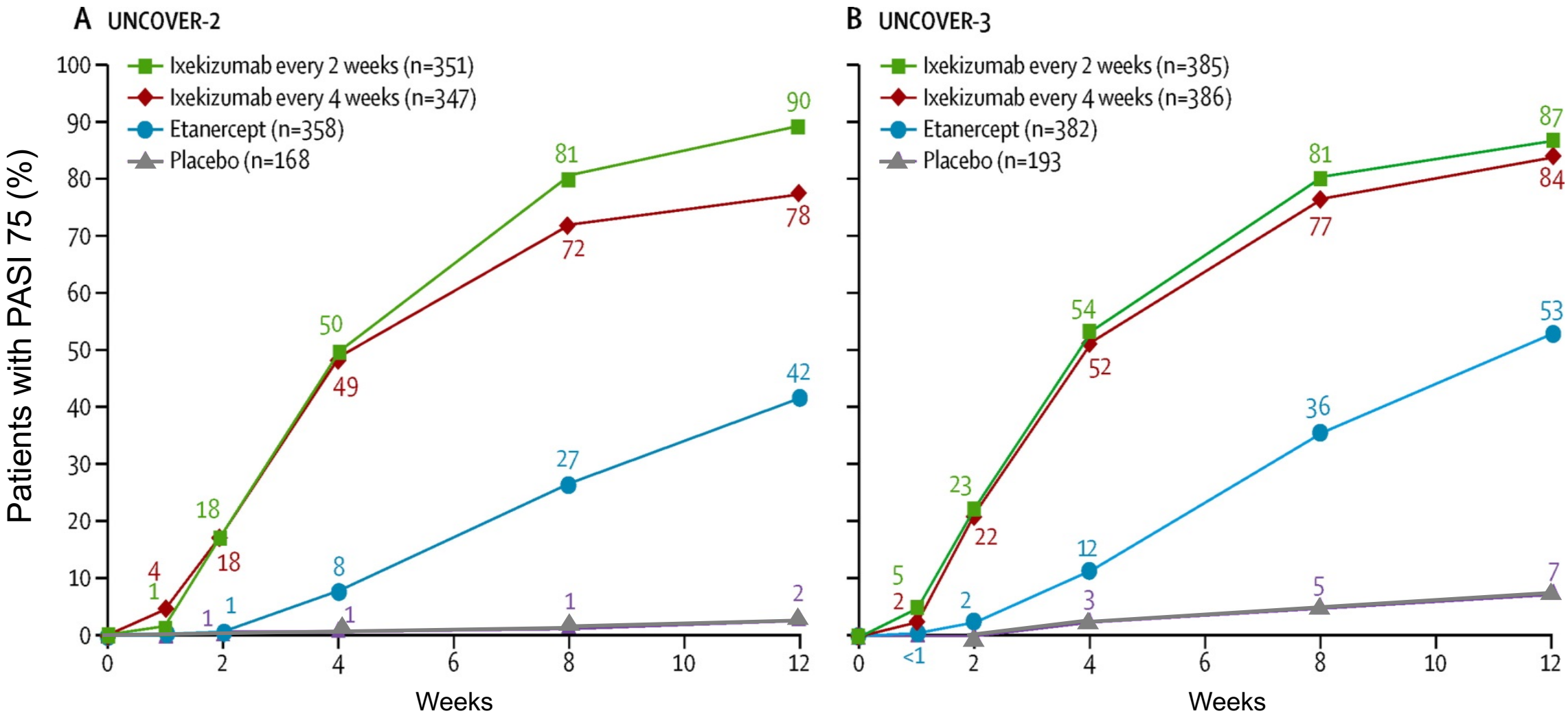
TNF
IL 12/23
IL 17

Biologics and Commonly Used Oral Treatments for Psoriasis NNT to Achieve PASI-75 at Primary Endpoint



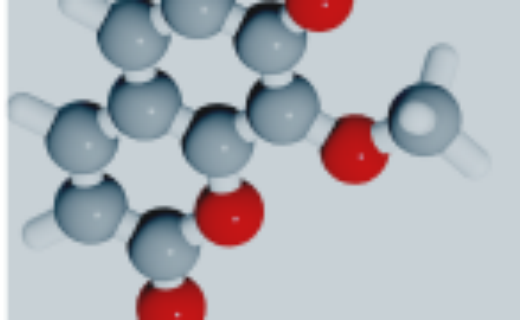
Data from Phase III RCTs: Note NOT Head to Head
*Withdrawn
**Not FDA approved

Ixekizumab vs. Etanercept

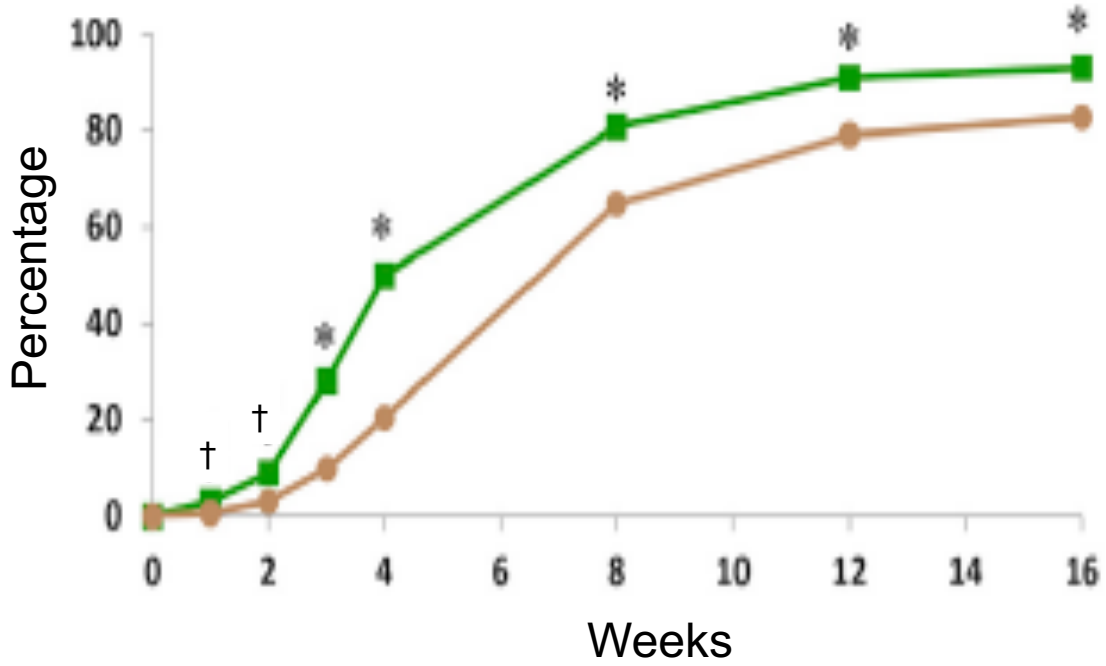


Griffiths CEM, et al. *Lancet*. 2015;386:541-551.

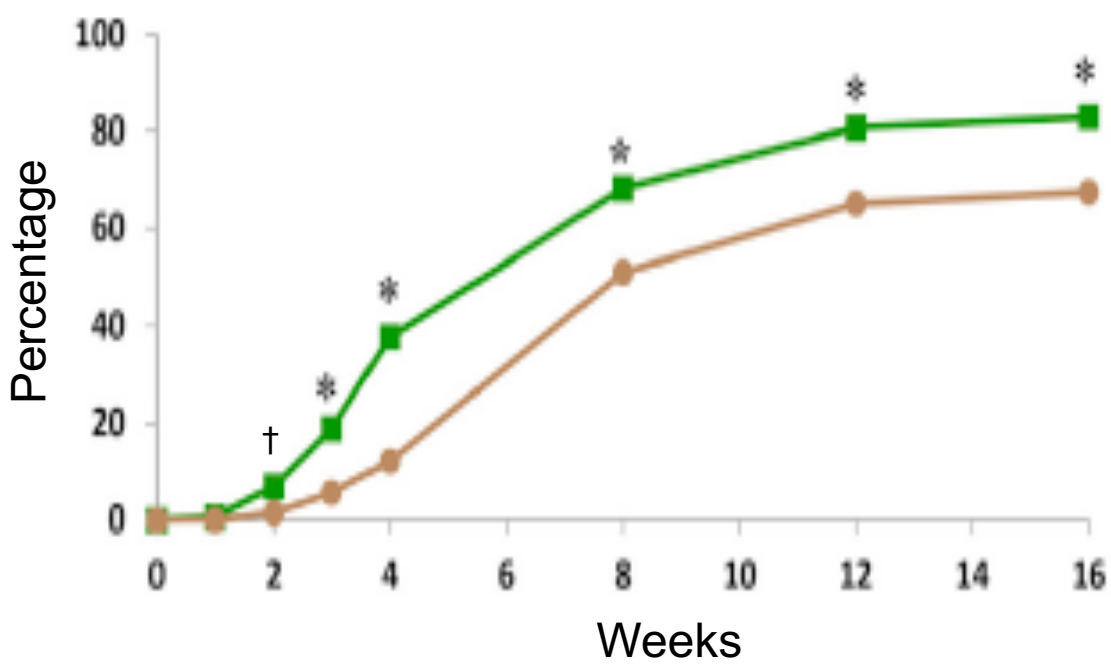
Secukinumab vs. Ustekinumab

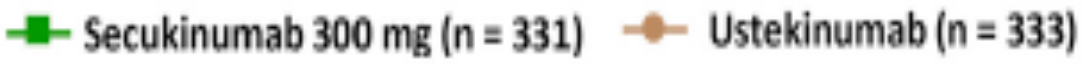


PASI 75 response



IGA mod 2011 0/1 response





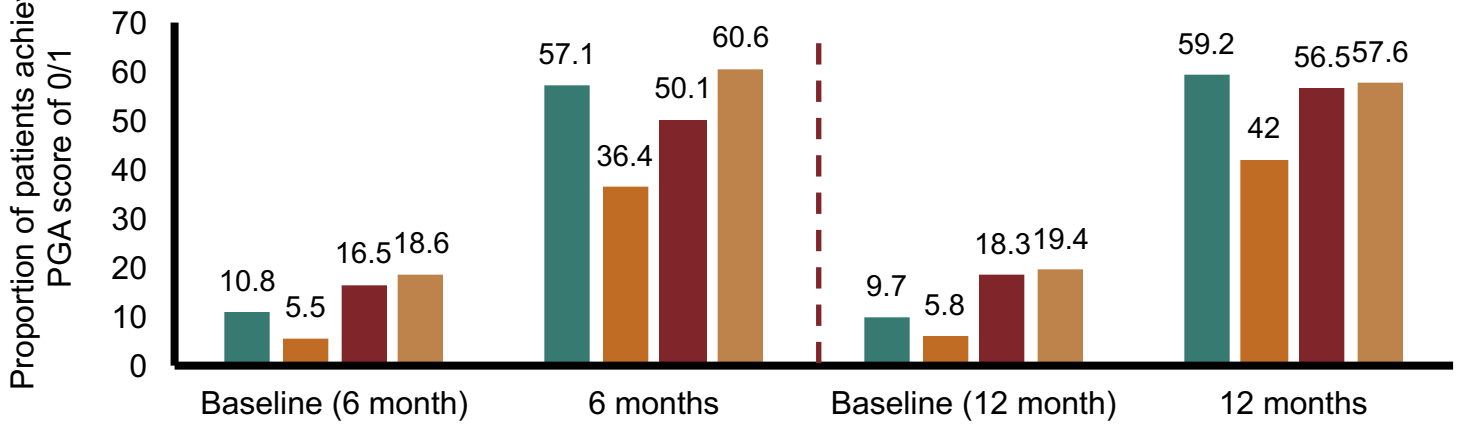
*$p \leq .0001$, †$p < .05$.

Thaçi D, et al. *J Am Acad Dermatol*. 2015;73:400-409.

Psolar Comparative Effectiveness Results

- 2541 new users, 2076 had efficacy data
- Ustekinumab generally more effective than TNFi, but not statistically significant at 12 months
- Drop out and short-term nature overestimate long-term effectiveness

Proportion of patients with PGA score of 0 (clear) or 1 (minimal) at 6 and 12 months; patients initiating ustekinumab, infliximab, adalimumab, or etanercept on registry.



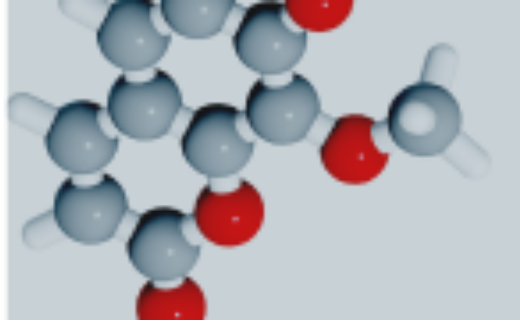
Multivariate analyses of treatment effects: logistic regression for proportion of patient achieving a PGA score of clear (0) or minimal (1) at 6 and 12 months

	6-Month Analysis		12-Month Analysis	
	Odds ratio (95% CI)	*P value*	Odds ratio (95% CI)	*P value*
IFX vs UST	0.396 (0.2555-0.617)	< .0001	0.449 (0.260-0.774)	.0040
ADA vs UST	0.686 (0.547-0.861)	.0012	0.841 (0.645-1.097)	.2025
ETA vs UST	0.554 (0.400-0.765	.0003	0.686 (-.466-1.009)	.0557

PGA = physician global assessment. CI = confidence interval; UST = ustekinumab; IFX = infliximab; ADA = adalimumab; ETA = etanercept

Strober BE, et al. *J Am Acad Dermatol.* 2016;74:(5)851–861.e4

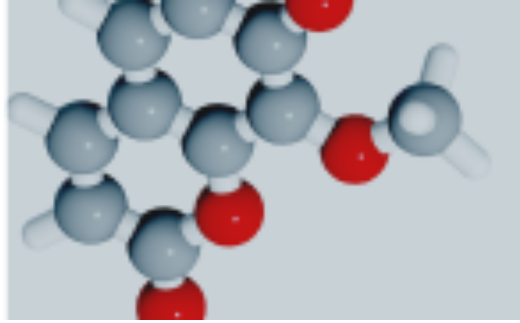
What Is Treat-to-Target?



- Treat disease with a variety of approaches (ideally proven effective/safe in RCTs and observational studies) until a specified objective measure is achieved (typically a biomarker)
- Goal: Better patient outcomes
- Concept largely derived from cardiovascular medicine with targets for blood pressure, glucose, and lipids

Atar D, et al. *Ann Rheum Dis*. 2010;69:629-630.

Treat-to-Target



- Hooray! It works!
  - Tight control of type 1 and type 2 diabetes associated with reductions in late diabetic complications
- #$&! It doesn't work!
  - Tight control of glucose results in increased mortality
  - Cholesterol targets largely abandoned in recent AHA/ACC guidelines

The Diabetes Control and Complications Trial Research Group. *N Engl J Med.* 1993;329:977–986.
UK Prospective Diabetes Study Group. *Lancet*.1998;352:837–853.
Gerstein HC, et al. *N Engl J Med.* 2008;358:2545–2559.

Moderate-Severe Psoriasis Outcomes: Clinical Trials

- Clinical trials primary endpoints focus on PASI75 and physician's global assessment (PGA) of clear/almost clear
- Increasingly PASI 90 and 100 reported
- Multiplying PGA x BSA correlates strongly with PASI (rho = .92; 95% CI 0.91-0.93

4. PGA: Physician's Global Assessment (Averaged over all lesions)

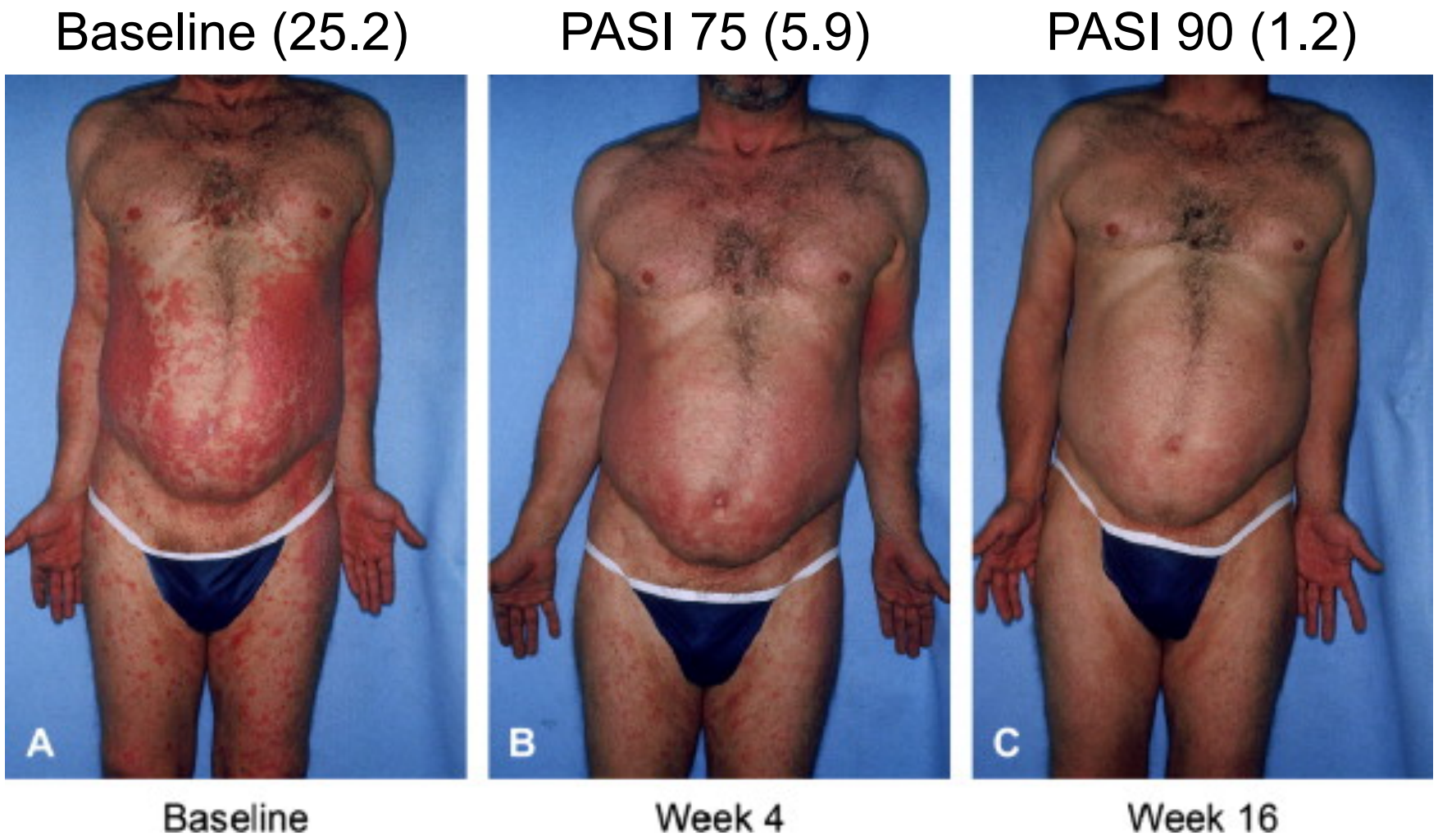
Induration (I) or Pustulation	Erythema (E)	Scaling (S)
0 = no plaque elevation 1 = minimal elevation, 0.25mm 2 = mild elevation, 0.5mm 3 = moderate elevation, 0.75mm 4 = marked elevation, 1mm 5 = severe elevation, >1.25mm	0 = no erythema or hyperpigmentation is present 1 = faint erythema 2 = light red coloration 3 = moderate red coloration 4 = bright red coloration 5 = dusky to deep red coloration	0 = no evidence of scaling 1 = minimal; fine scale on < 5% of lesion 2 = mild; fine scale predominates 3 = moderate; coarse scale predominates 4 = marked; thick, nontenacious scale predominates 5 = severe; very think tenacious scale predominates
I =	E =	S =

Physician's Static Global Assessment based upon above total average [(I + E + S)/3]

0 = Clear; except for residual discoloration
1 = Minimal; majority of lesions have individual scores for (I+E+S)/3 that average 1
2 = Mild; majority of lesions have individual scores for (I+E+S)/3 that average 2
3 = Moderate; majority of lesions have individual scores for (I+E+S)/3 that average 3
4 = Marked; majority of lesions have individual scores for (I+E+S)/3 that average 4
5 = Severe; majority of lesions have individual scores for (I+E+S)/3 that average 5

Robinson A, et al. *JAAD* 2012;66:369-75.; Revicki DA, et al. *Dermatology* 2008;216:260-270.; Torii H, et al. *J Dermatol* 2012; 39:253-259.; Chiesa Fuxench ZC, et al. *JAAD* 2015;73:868-870.

PASI Endpoints



Menter AM, et al. *JAAD*. 2008;58:106-115.

DLQI: A Generic Measure of Skin-Related Quality of Life

- DLQI asks about symptoms and feelings, daily activities, leisure, work/school, relationships, treatment
- Meaning of DLQI Scores
  0-1 = no effect at all on patient's life
  2-5 = small effect on patient's life
  6-10 = moderate effect on patient's life
  11-20 = very large effect on patient's life
  21-30 = extremely large effect on patient's life

The aim of this questionnaire is to measure how much your skin problem has affected your life OVER THE LAST WEEK. Please tick one box for each question.

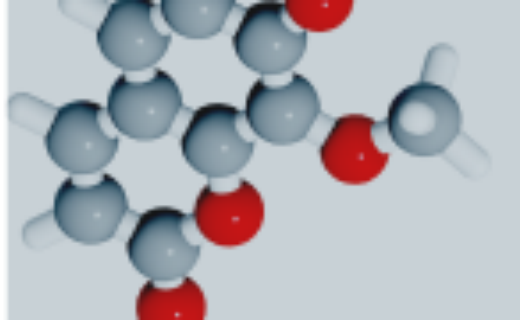
1.	Over the last week, how **itchy, sore, painful or stinging** has your skin been?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	
2.	Over the last week, how **embarrassed or self conscious** have you been because of your skin?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	
3.	Over the last week, how much has your skin interfered with you going **shopping** or looking after your **home or garden**?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	 Not relevant ☐
4.	Over the last week, how much has your skin influenced the **clothes** you wear?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	 Not relevant ☐
5.	Over the last week, how much has your skin affected any **social or leisure** activities?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	 Not relevant ☐
6.	Over the last week, how much has your skin made it difficult for you to do any **sport**?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	 Not relevant ☐
7.	Over the last week, has your skin prevented you from **working or studying**? If "No", over the last week how much has your skin been a problem at **work or studying**?	Yes No A lot A little Not at all	☐ ☐ ☐ ☐ ☐	 Not relevant ☐
8.	Over the last week, how much has your skin created problems with your **partner or any of your close friends or relatives**?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	 Not relevant ☐
9.	Over the last week, how much has your skin caused any **sexual difficulties**?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	 Not relevant ☐
10.	Over the last week, how much of a problem has the **treatment** for your skin been, for example by making your home messy, or by taking up time?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	 Not relevant ☐

Please check you have answered EVERY question. Thank you.

DLQI = dermatology quality of life index.

Hongbo Y et al *J Invest Dermatol*. 2005;125(4):659-664

Moderate-Severe Psoriasis Outcomes: Clinical Practice



- Treatment goals in clinical practice remain largely undefined
- Guideline goals:
  - European: PASI 75 and DLQI ≤1 (no effect)
  - Australasian: PASI 75 and DLQI ≤5 (small effect)
  - Canadian (expert opinion): PGA 0
- In context of PsA minimal disease activity defined as PASI ≤ 1 or BSA ≤3%
- Psoriasis non-treatment, under treatment, and treatment dissatisfaction remains a significant problem in the US

Canadian Guidelines for Management of Plaque Psoriasis 2009 Pathirana D et al JEADV 2009;23: 1-70
Smith CH, et al. *BJD*. 2009;161:987-1019; Baker C, et al. *Australasian J of Derm*. 2013;54:148-154; Gulliver W, et al. *JCMS.* 2015;19:22-7; Armstrong AW, et al. *JAMA Dermatol.* 2013;149:1180-5; Kavanaugh A. *Experimental Rheumatology.* 2012;30:s123-125.

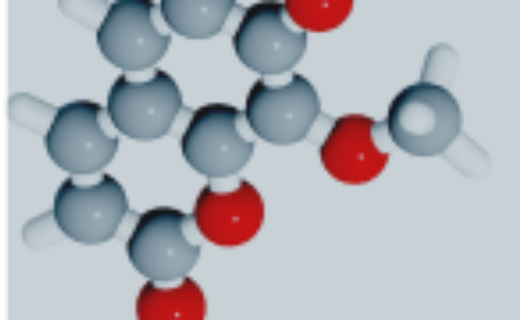
AAD Performance Measure for Psoriasis Outcomes for Medicare Incentive Program

PQRS 410	**Psoriasis:** Clinical Response to Oral Systemic or Biologic Medications	Outcome	All patients with a diagnosis of psoriasis and treated with an oral systemic or biologic medication for psoriasis for at least 6 months	Patients who have a documented physician global assessment (PGA; 6-point scale), body surface area (BSA), psoriasis area and severity index (PASI) and/or dermatology life quality index (DLQI) that meet any one of the below specified benchmarks. **Numerator Instructions:** To satisfy this measure, a patient must achieve any ONE of the following: a. PGA (6-point scale ≤ 2 (clear to mild skin disease) b. BSA < 3% (mild disease) c. PASI < 3 (no or minimal disease) d. DLQI ≤ 5 (no effect or small effect on patient's quality of life)

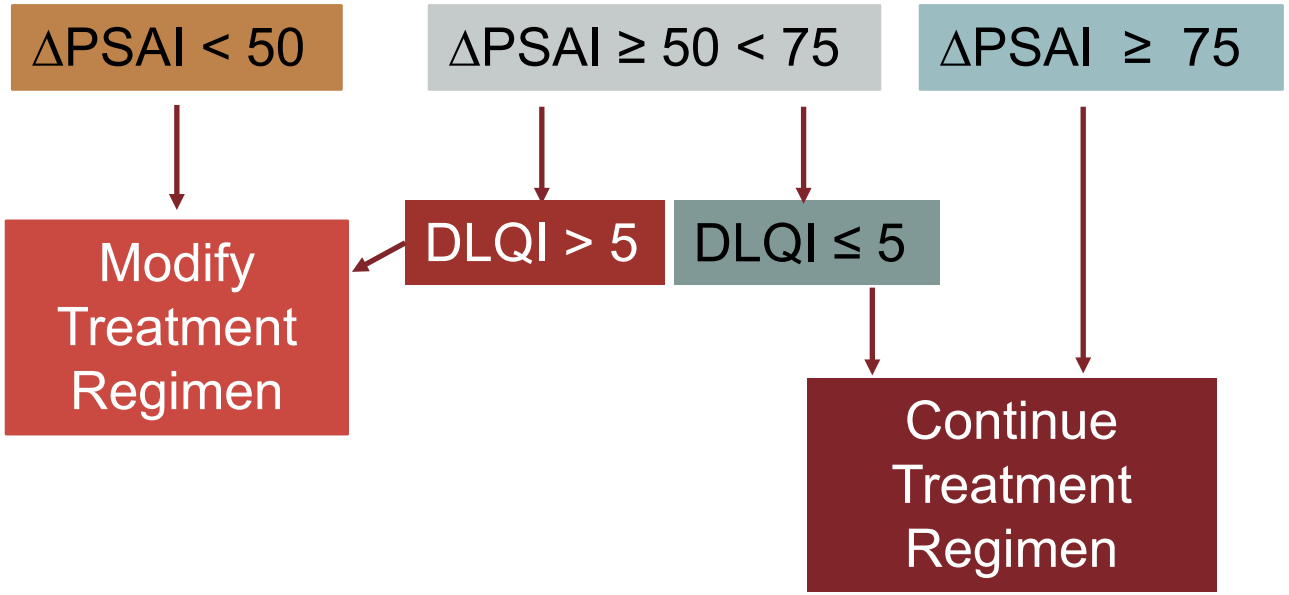
AAD = American Academy of Dermatology.

American Academy of Dermatology. Available at: https://www.aad.org/practice-tools/quality-care/quality-measures. Accessed November 4, 2016.

20% of Almost Clear Patients Meet DLQI Criteria for Treatment Change

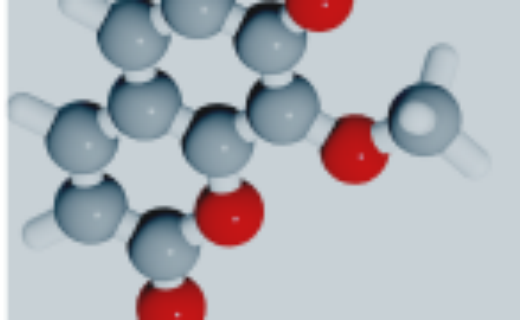


DLQI	Clear	Almost Clear	*p* value
≥ Moderate effect, N(%)	2 (2)	85 (20)	<.001



Mrowietz, U. et al. *Arch Dermatol Res*. 2011;303:1-10.

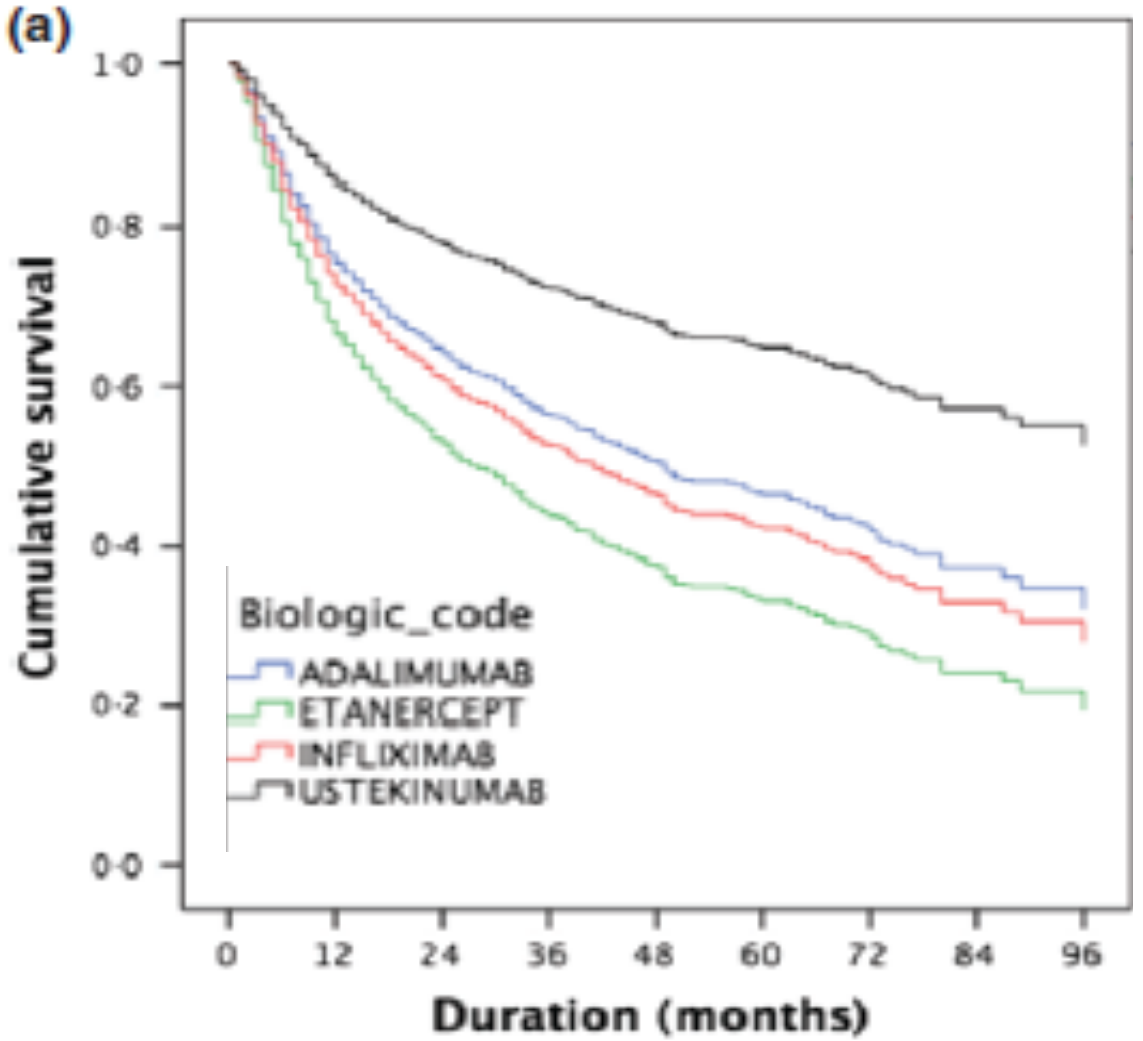
Treat-to-Target in Psoriasis



1. What should the target be?
2. Does treating to target yield clinically significant benefits on HrQOL and comorbidities compared to usual care?
3. Is safety compromised?
4. Is the approach cost-effective?
5. Can the approach be achieved in clinical practice?

Biologic Survival in Denmark: DERMBIO Database

- N = 1867 treatment sequences in 1277 patients
- Ustekinumab has longest survival
- TNF survival
  - ETN 30 months
  - ADA 59 months
  - INF 44 months
- Protective factors
  - Male sex
  - Prior biologic exposure



Gniadecki R, et al. *Br J Dermatol*. 2015;172(1):244-252.

Persistence of Biologics in US Medicare Patients

Adherence, Discontinuation, Switch, and Restart Outcomes

Outcomes	All	Adalimumab	Etanercept	Infliximab	Ustekinumab
Overall					
N	2707	1084	1025	318	280
PDC, mean (SD)	0.61 (0.31)	0.63 (0.31)	0.56 (0.31)	0.66 (0.32)	0.70 (0.28)
Adherent (PDC ≧ 0.80)	37.7%	40.7%	29.4%	49.4%	43.2%
Discontinued	45.5%	43.4%	51.7%	42.5%	35.0%
Switched	8.0%	9.0%	9.5%	5.0%	1.8%
Restarted	9.2%	6.6%	9.9%	10.4%	15.0%
With index biologic	7.6%	5.1%	8.4%	6.9%	15.0%
With different biologic	1.6%	1.5%	1.5%	3.5%	0.0%
Other discontinuer	28.4%	27.8%	32.4%	27.0%	18.2%
Discontinuation OR		1.60 (1.20-2.13)	2.18 (1.64-2.90)	1.41 (0.99-2.02)	Reference

Doshi JA, et al. *JAAD.* 2016;74(6):1057-1065.

Biologic Selection Depends on Many Factors

Scenario	TNF	IL12/23	IL-17
Long-term data	★	Emerging	No
Psoriatic arthritis	★ FDA approved		FDA approved*
Crohn's disease	★ FDA approved adalimumab and infliximab	FDA approved	Warning!
Associated with decreased MI and stroke	Yes	TBD	TBD
CHF	Warning!	No warning	No warning
Multiple sclerosis		No benefit or harm phase II	Promising phase II
Ease of administration		★	
Patient is obese	Infliximab preferred	Weight-based dosing	Flexible dosing**
Rapid onset and highest efficacy			★
Long-term persistence		★	TBD

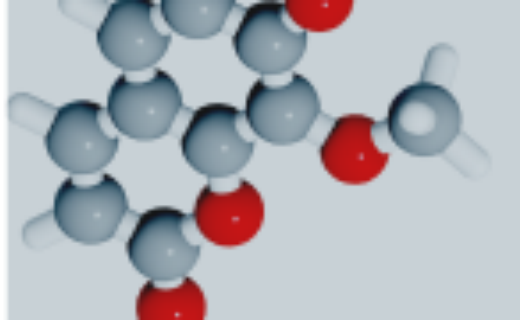
★ = gold standard

*Ixekizumab is not yet FDA-approved for psoriatic arthritis
**Flexible dosing relevant for secukinumab

#SkinCME

Translating Pathways to Clinical Cases

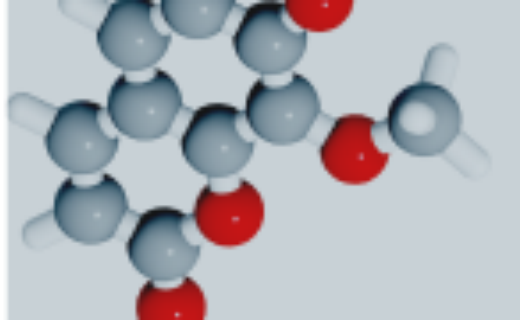
‘The Diabetic Drama Queen’



- 39-year-old former dance teacher
  - Type 1 IDDM since age 13 years
  - Psoriasis since age 14 years
  - Hypertension/GFR reduced 45
  - 3 children/supportive husband
- Upon review
  - Pain/swelling hands/fingers/toes
  - AMS 1 hr/painful eyes on occasion
  - Dactylitis several fingers & toes
  - CRP45/ESR 60
  - RF-, ANA-
  - X-rays normal
- First choice therapy?

RF- = rheumatoid factor negative; ANA- = antinuclear antibody negative; IDMM = insulin dependent diabetes mellitus; GFR = glomerular filtration rate.

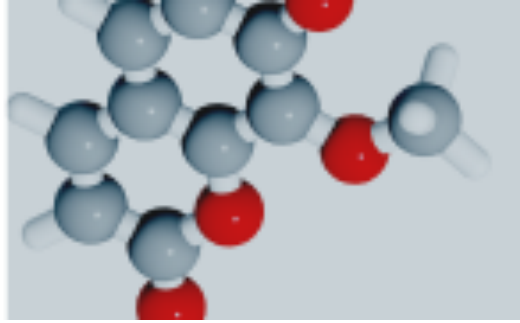
‘The Diabetic Drama Queen’



- Progress
  - Started SASP to target dose 2.5g/d
  - Well tolerated and ‘partial response’ admitted
  - Skin unchanged - moderate scalp and trunk
  - Dactylitis remains
  - At 6/12 erosive changes noted on hands and feet
- Referred to CRD
  - Pain/swelling hands/fingers/toes
  - AMS 1 hr/painful eyes on occasion
  - Dactylitis present 6 fingers/4 toes/effusions both knees and elbows
  - CRP98/ESR 110
  - RF-, ANA-
- IDDM also problematic - what next?

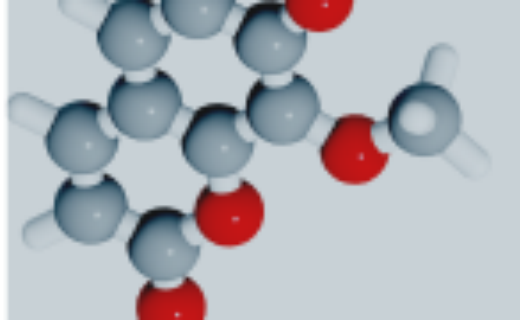
SASP = sulphasalazine.

‘The Diabetic Drama Queen’



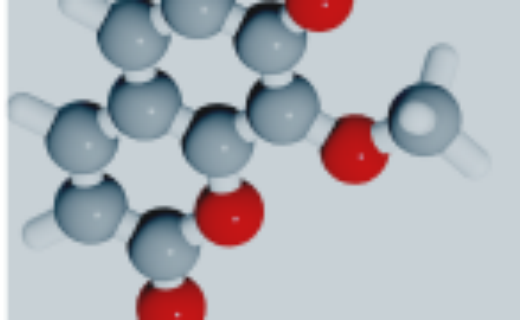
- Progress
  - Commenced low dose MTX – 10 mg/wk
  - Well tolerated and again ‘partial response’ admitted
  - Skin improved - PASI 13
  - Ongoing topical therapies
  - Dactylitis remains
  - At 6/12 further erosive progression noted
  - LFTs abnormal / refuses further MTX
- Diabetic clinic
  - Insulin pump in situ
  - Glucose control much improved
  - BP remains difficult to control
  - Feels systemically better aside from frequent UTI
- PsA flares - what next?

‘The Diabetic Drama Queen’



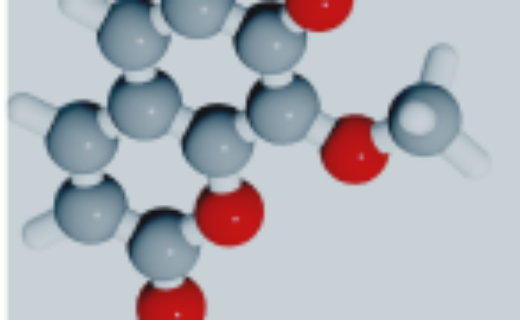
- Progress
  - DAS44 - 6.7 / PASI 13
  - Commenced etanercept 25 mg biweekly
  - Prompt improvement in joints
  - DAS44 - 3.5
  - Well being much improved
  - Insulin requirement reduced by 50%
- BUT
  - Skin no response - PASI 13
- What next?

‘The Diabetic Drama Queen’



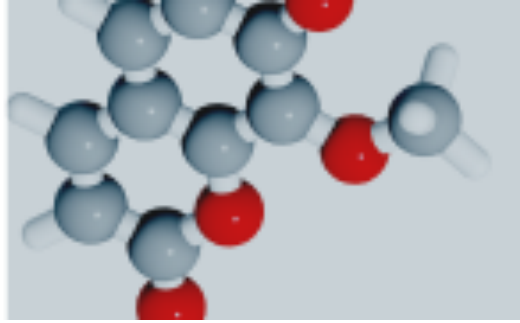
- Progress
  - Commenced adalimumab - no MTX
  - Prompt improvement in skin
  - PASI 2
  - DAS44 rises to 6.5
  - Feels ‘terrible’
  - R wrist deteriorating rapidly
  - Infection screen including biopsy all clear…Surgical fusion
- What next?

‘The Diabetic Drama Queen’



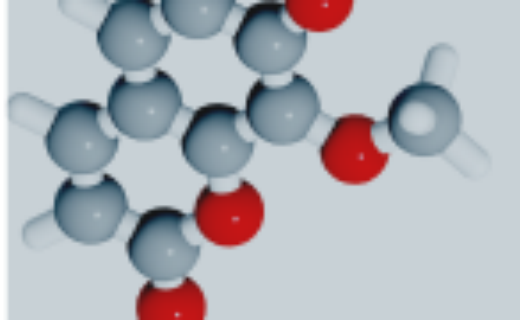
- Progress
  - Resumed etanercept 50 mg/biweekly
  - Joints responded in 3/12 - DAS44 2.8
  - PASI rises again to 16
  - Developed superficial infection at site of wrist fusion - adequately treated by orthopedic team

‘The Diabetic Drama Queen’



- Progress
  - Trial of ustekinumab – good response in skin but articular response modest
  - Currently considering secukinumab monotherapy
- Future therapeutic combinations?

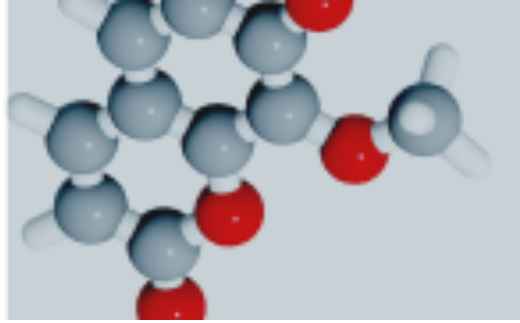
‘Cantankerous Clergy’



- 63-year-old female minister
  - Presented to dermatology, Diagnosed at age 45 with severe psoriasis
  - BMI elevated - otherwise well
  - Treated with topical agents to no benefit
  - Received UV, MTX, CyA, retinoids, fumarates
    - No response to any of the above
- What next?

UV = ultraviolet; CyA = cyclosporin A.

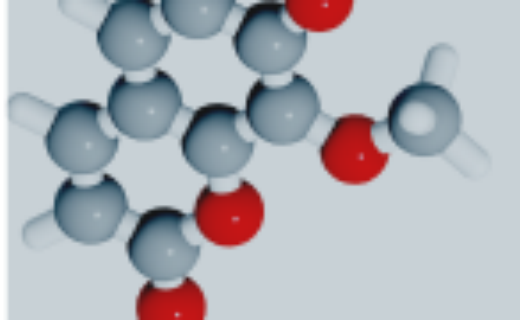
‘Cantankerous Clergy’



- Therapeutic progress:
  - Received infliximab with low dose MTX (5 mg/wk)
  - Good skin response - PASI fell from 35 to 9
  - 14 weeks into therapy developed acute inflammatory arthritis involving:
    - Wrists, MCP, PIP, DIP
    - Knees
    - Ankles
    - MTPs/hind foot

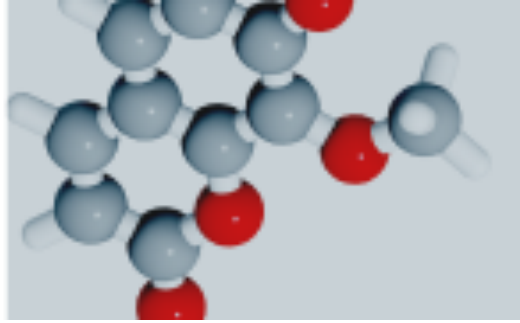
MCP = metacarpophalangeal; PIP = proximal interphalangeal; DIP = distal interphalangeal MTPs = metatarsophalangeal.

‘Cantankerous Clergy’



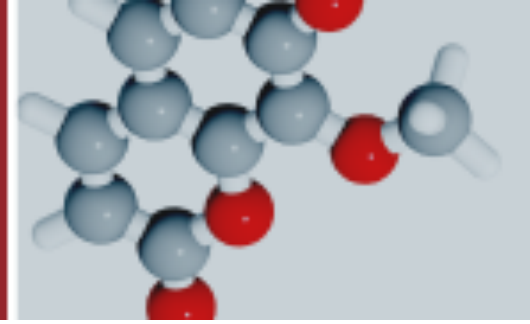
- Progress
  - Given etanercept
  - PASI rose to 28
  - Joints improved - ACR50 level response
  - Function still poor
- Not a happy clergy...

‘Cantankerous Clergy’



- Received ustekinumab
- Skin cleared for the first time in 20 years
- Joints achieved ACR70 level improvement
- Clinical fingers crossed!

Lessons



- Logical immunologic interventions do not always behave logically in the clinic
- Tissue responses are neither homogeneous nor predictable
- How can we better match pathology to the reality & complexity of complex clinical reality?

#SkinCME

Questions and Answers

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