Rheumatology in the 21st century

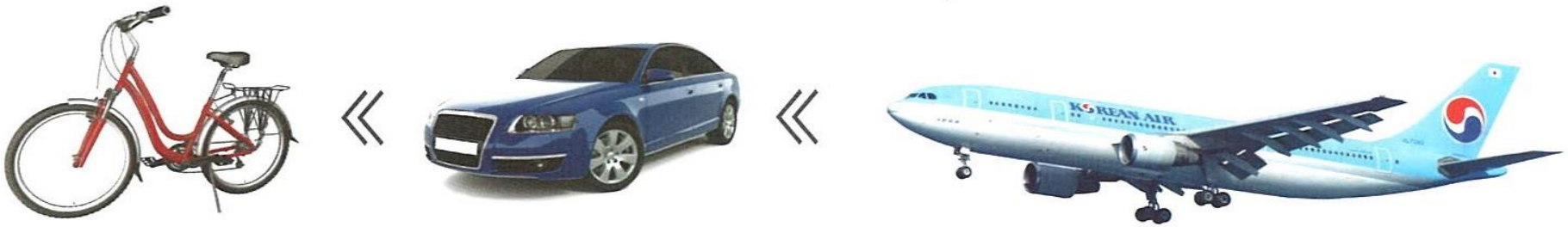
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The author has no conflicts of interest to disclose

Rheumatology in the 21st century

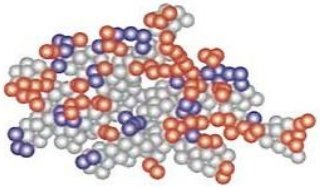
Rheumatology in the 21st century uses current cellular, biochemical and immunologic techniques to explain the etiology of rheumatic diseases. While it is unlikely that molecular biology will differentiate rheumatic diseases into subsets based on their etiology, the genome revolution does provide us with new diagnostic tools, which are already beginning to have an impact.

Molecular Weight Comparison

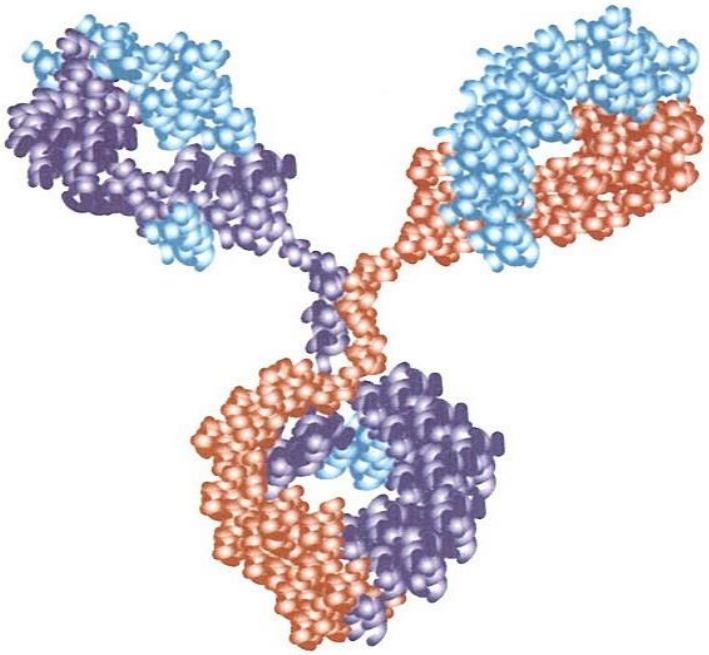




Aspirin
180 Daltons



Insulin
5,700 Daltons



mAb
150,000 Daltons

Rheumatology in the 21st century

For many years, polymorphisms in drug metabolizing enzymes have been associated with both reduced clinical response and adverse effects of treatment. Proteomics and genomics offer new opportunities to identify biomarkers that provide surrogates of disease activity and response to therapy.

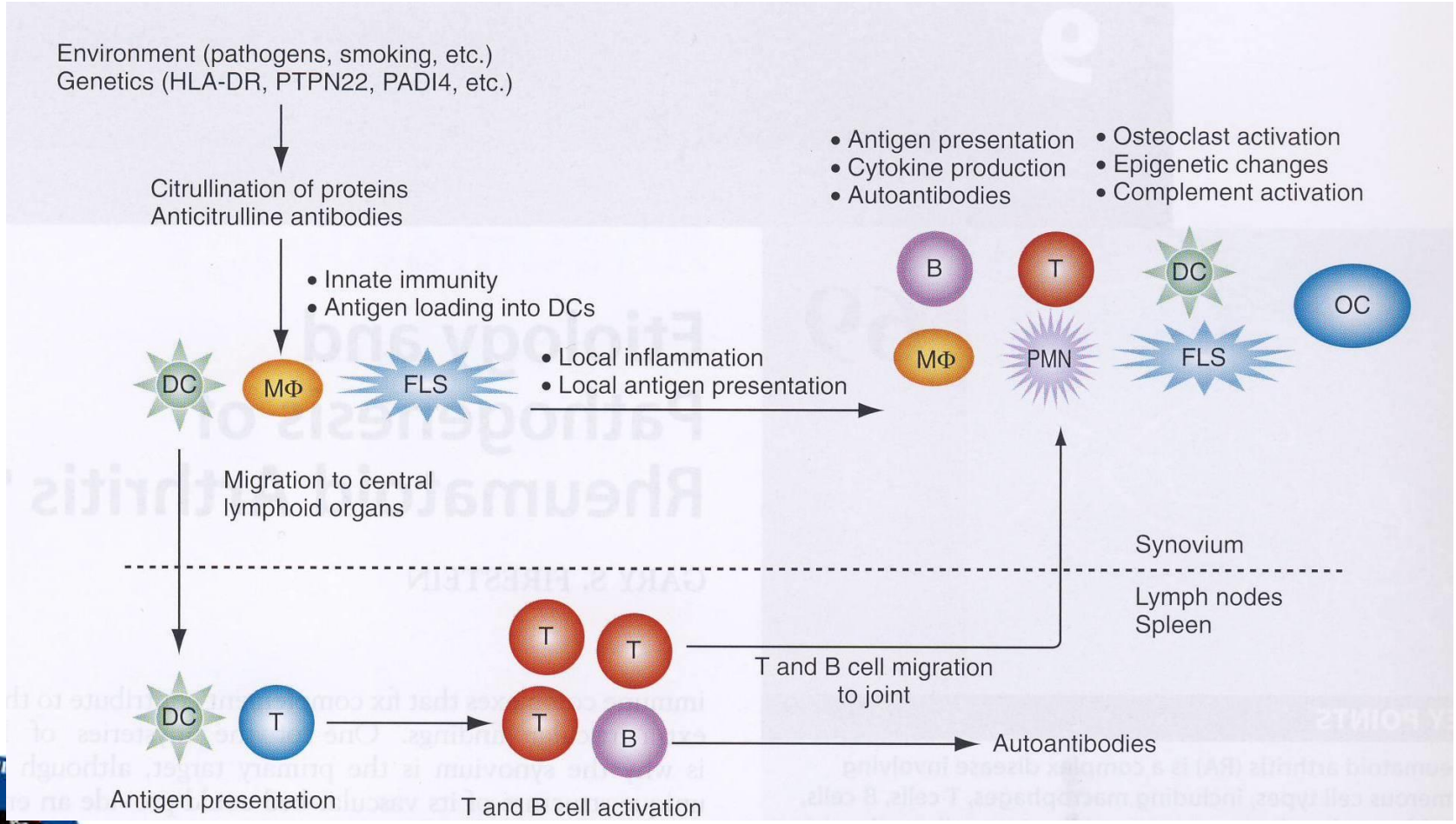
Rheumatology in the 21st century

Micro RNAs are small, imperfectly paired, double-stranded RNAs expressed in all cells regulating the expression of hundreds of genes by inhibiting the translation and promoting the degradation of messenger RNAs. MicroRNAs act as master regulators of how a cell respons to changes in its environment, including growth factors and enviromental stressors.

Rheumatology in the 21st century

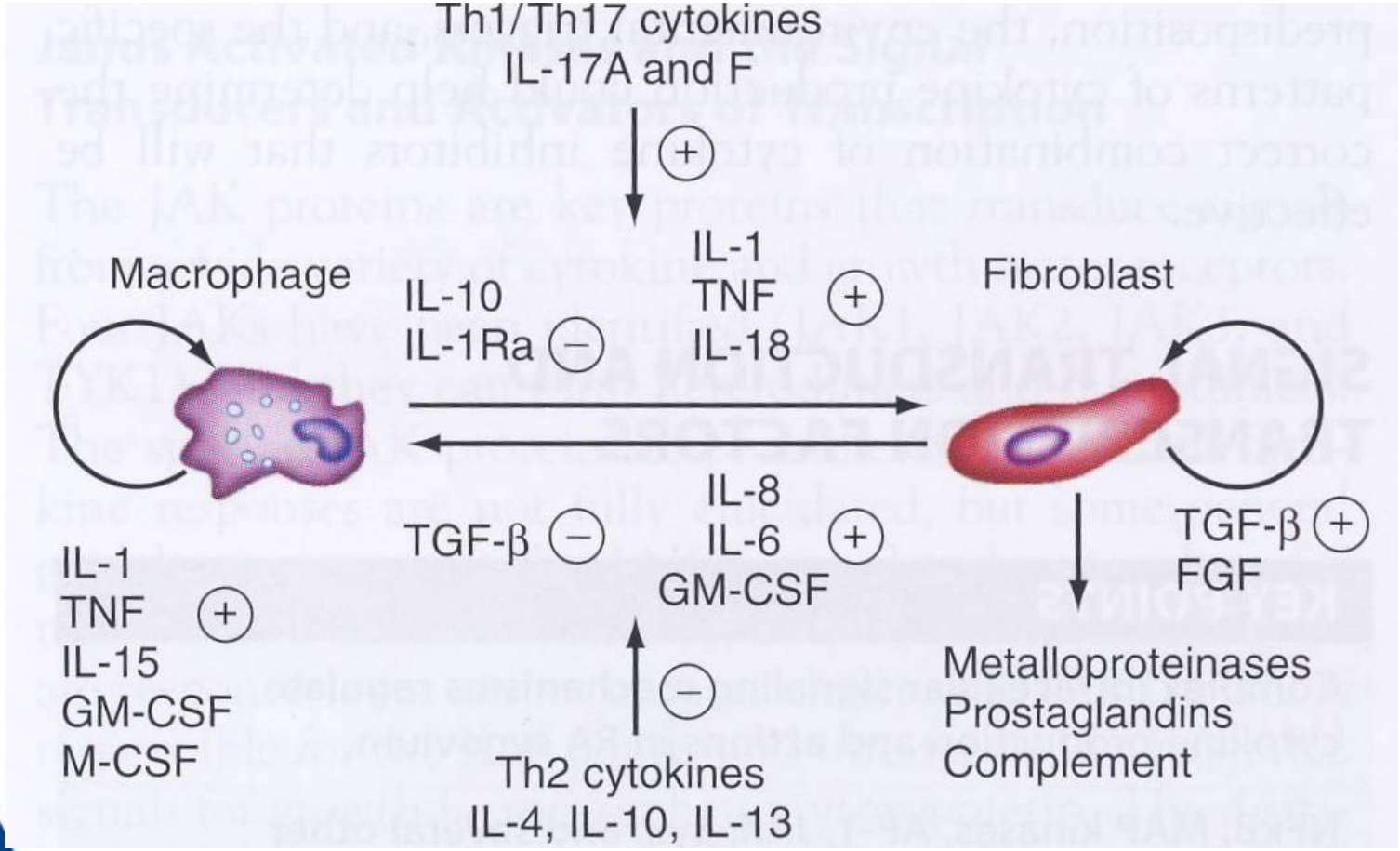
There have been substantial advances in the field of rheumatology in the past 20 years in the management of rheumatoid arthritis (RA), spondyloarthritis (SpA), psoriatic arthritis (PsA), systemic lupus erythematosus (SLE) and vasculitis.

Pathogenesis of rheumatoid arthritis



Kelley's Textbook of Rheumatology, 2012, p. 1060

Pathogenesis of rheumatoid arthritis



Kelley's Textbook of Rheumatology, 2012, p. 1093

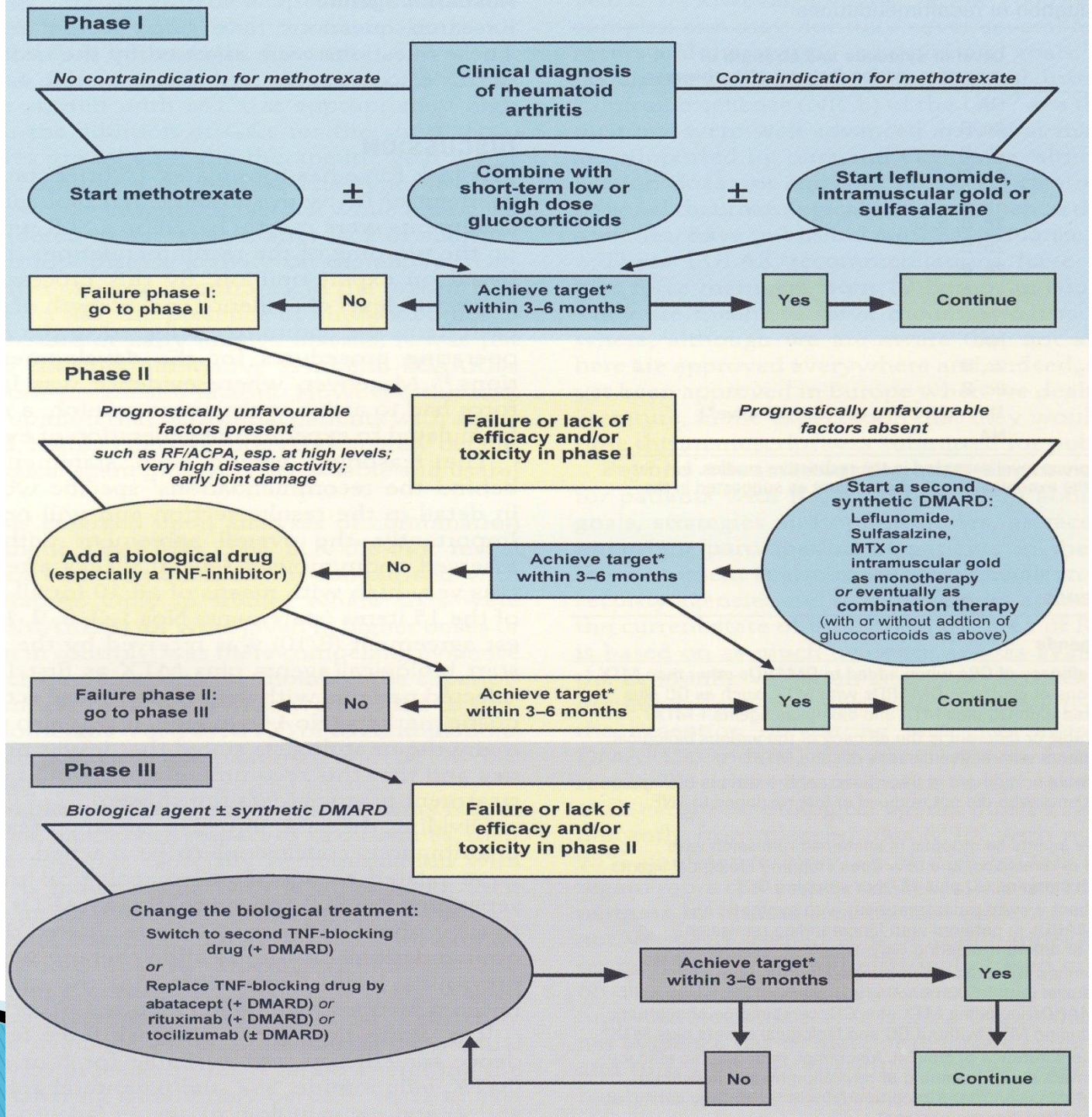
2010 ACR/EULAR Classification criteria for Rheumatoid arthritis

Joint Involvement*	**(0-5)**
1 medium to large[†] joint	0
2-10 medium to large joints	1
1-3 small[‡] joints (with or without involvement of large joints)	2
4-10 small joints (with or without involvement of large joints)	3
>10 joints[§] (at least one small joint)	5
Serology[‖¶]	**(0-3)**
Negative RF **AND** negative ACPA	0
Low-positive RF **OR** low-positive ACPA	2
High-positive RF **OR** high-positive ACPA	3
Acute Phase Reactants[‖#]	**1**
Normal CRP **AND** normal ESR	0
Abnormal CRP **OR** abnormal ESR	1
Duration of Symptoms**	**(0-1)**
<6 weeks	0
≥6 weeks	1

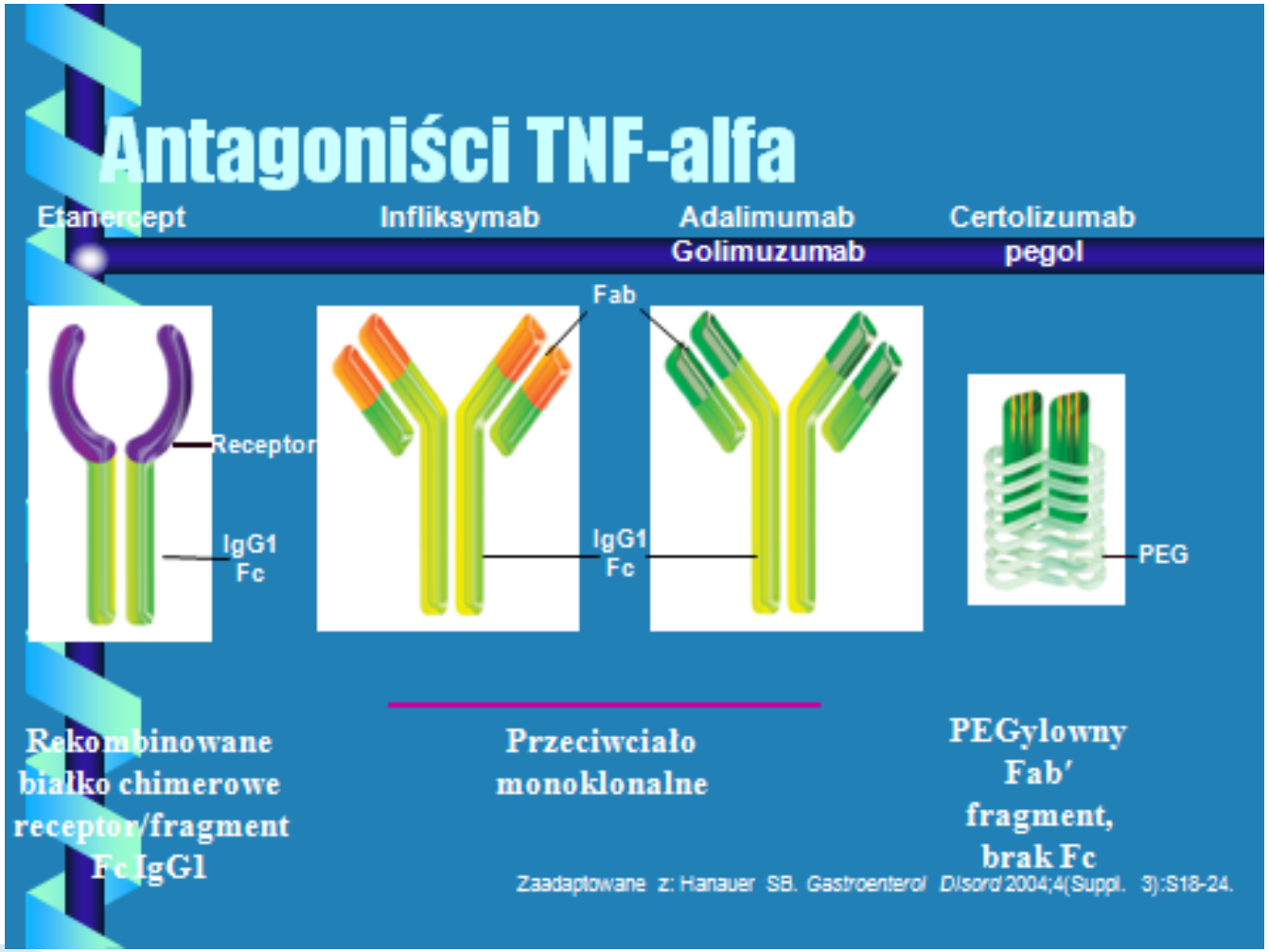
Kelley's Textbook of Rheumatology, 2012, p. 1127

Rheumatology in the 21st century

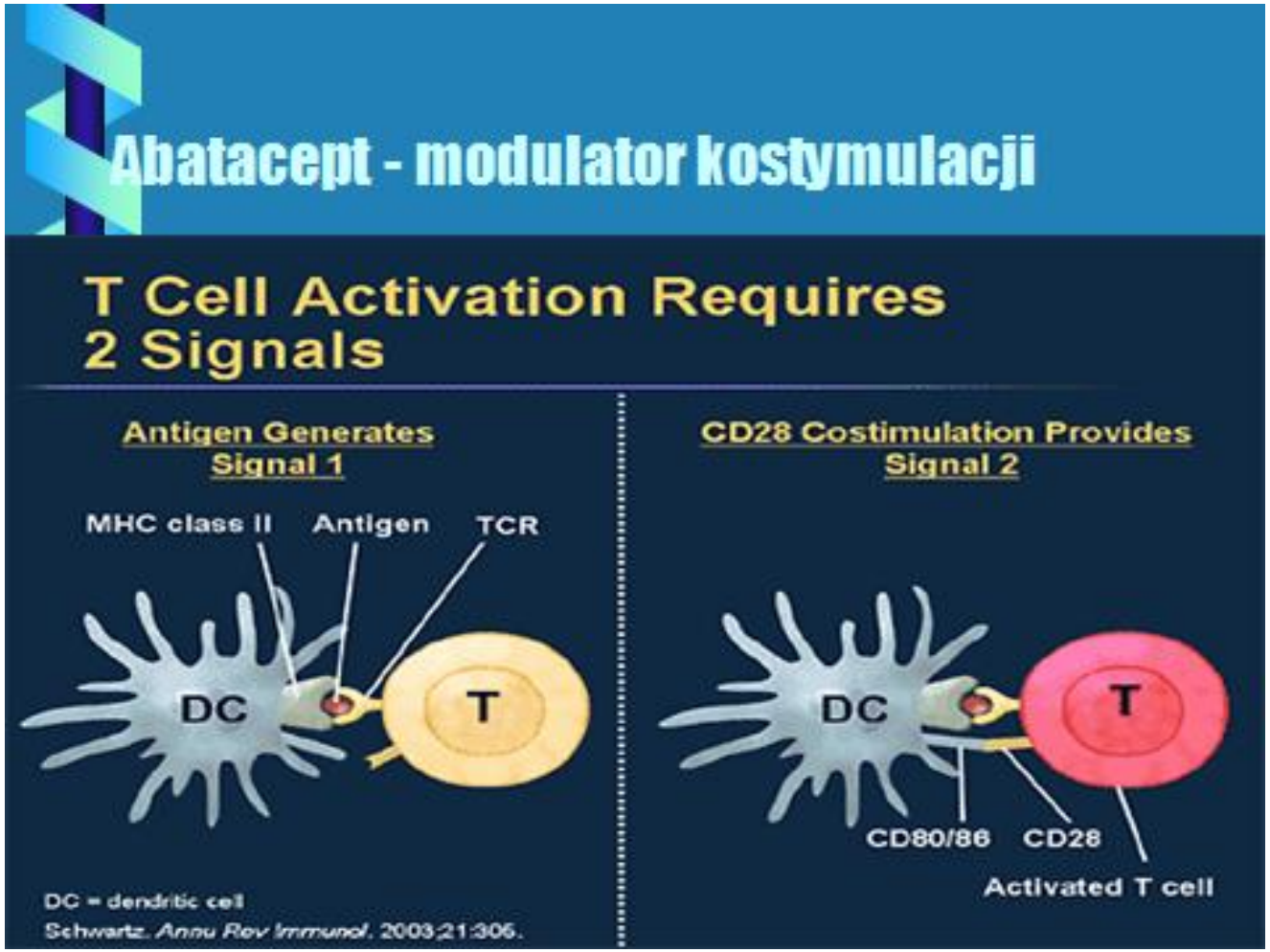
Following the introduction of the treatment recomendations for RA in 2013 by the European League Against Rheumatism (EULAR) and the introduction of biological agents in the management of RA, there is a need to consider the selection of the most appropriate therapy for an individual patient and to review how and when to switch treatment in those patients who do not show an optimal response. On 6 November 2012 FDA approved inhibitor of kinases to RA treatment.


Phase I
No contraindication for methotrexate
Clinical diagnosis of rheumatoid arthritis
Contraindication for methotrexate
Start methotrexate
±
Combine with short-term low or high dose glucocorticoids
±
Start leflunomide, intramuscular gold or sulfasalazine
Failure phase I: go to phase II
No
Achieve target* within 3–6 months
Yes
Continue
Phase II
Prognostically unfavourable factors present
such as RF/ACPA, esp. at high levels; very high disease activity; early joint damage
Failure or lack of efficacy and/or toxicity in phase I
Prognostically unfavourable factors absent
Add a biological drug (especially a TNF-inhibitor)
No
Achieve target* within 3–6 months
Start a second synthetic DMARD: Leflunomide, Sulfasalzine, MTX or intramuscular gold as monotherapy or eventually as combination therapy (with or without addtion of glucocorticoids as above)
Failure phase II: go to phase III
No
Achieve target* within 3–6 months
Yes
Continue
Phase III
Biological agent ± synthetic DMARD
Failure or lack of efficacy and/or toxicity in phase II
Change the biological treatment:
Switch to second TNF-blocking drug (+ DMARD)
or
Replace TNF-blocking drug by abatacept (+ DMARD) or rituximab (+ DMARD) or tocilizumab (± DMARD)
Achieve target* within 3–6 months
Yes
No
Continue

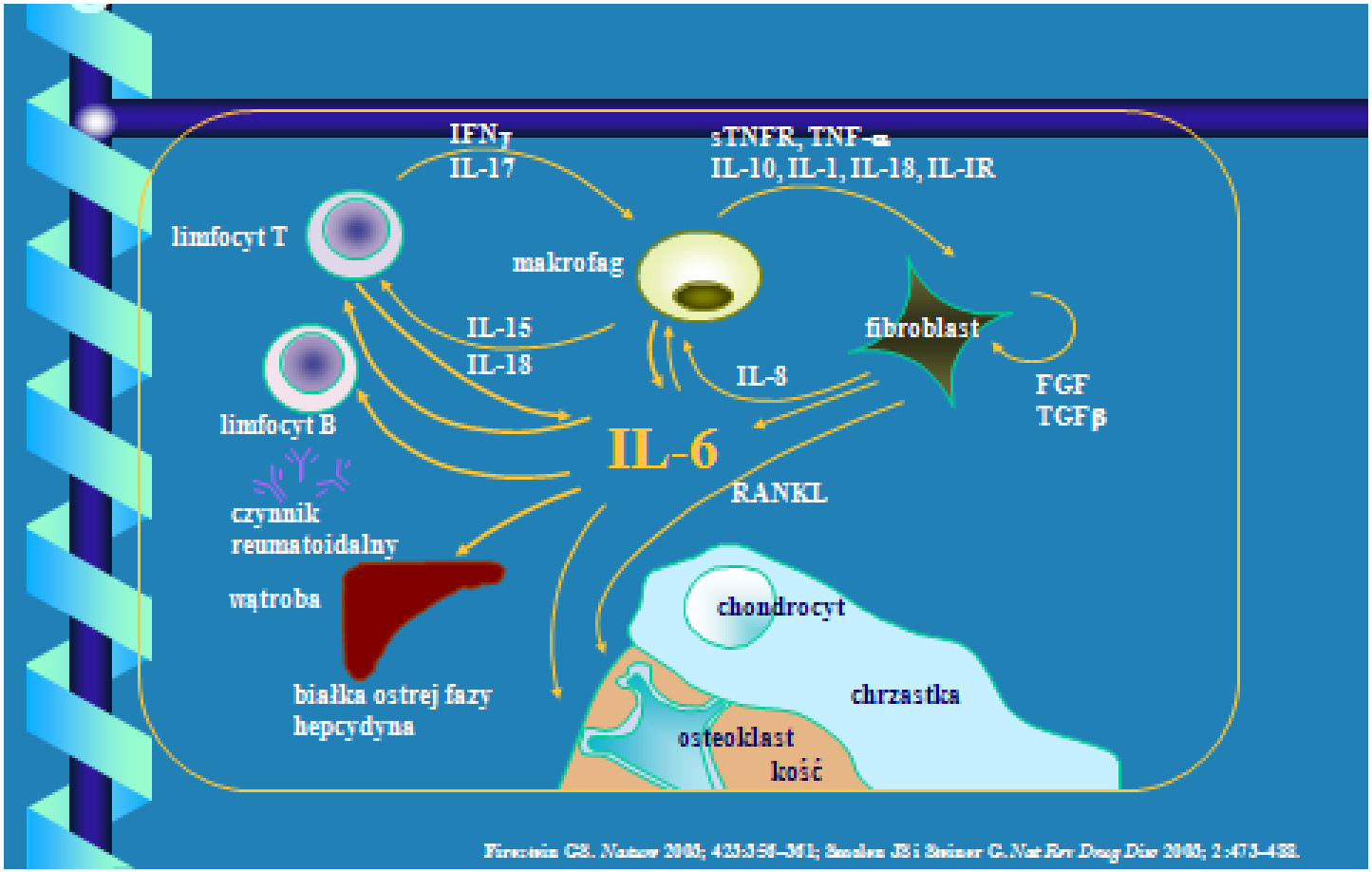
Inhibitors of TNF alpha are the standard therapy in RA, PsA and SpA



Abatacept is also a standard therapy in RA, JIA



Tocilizumab is a standard therapy in RA, JIA



Rituximab is standard therapy in RA, GPA, MPA

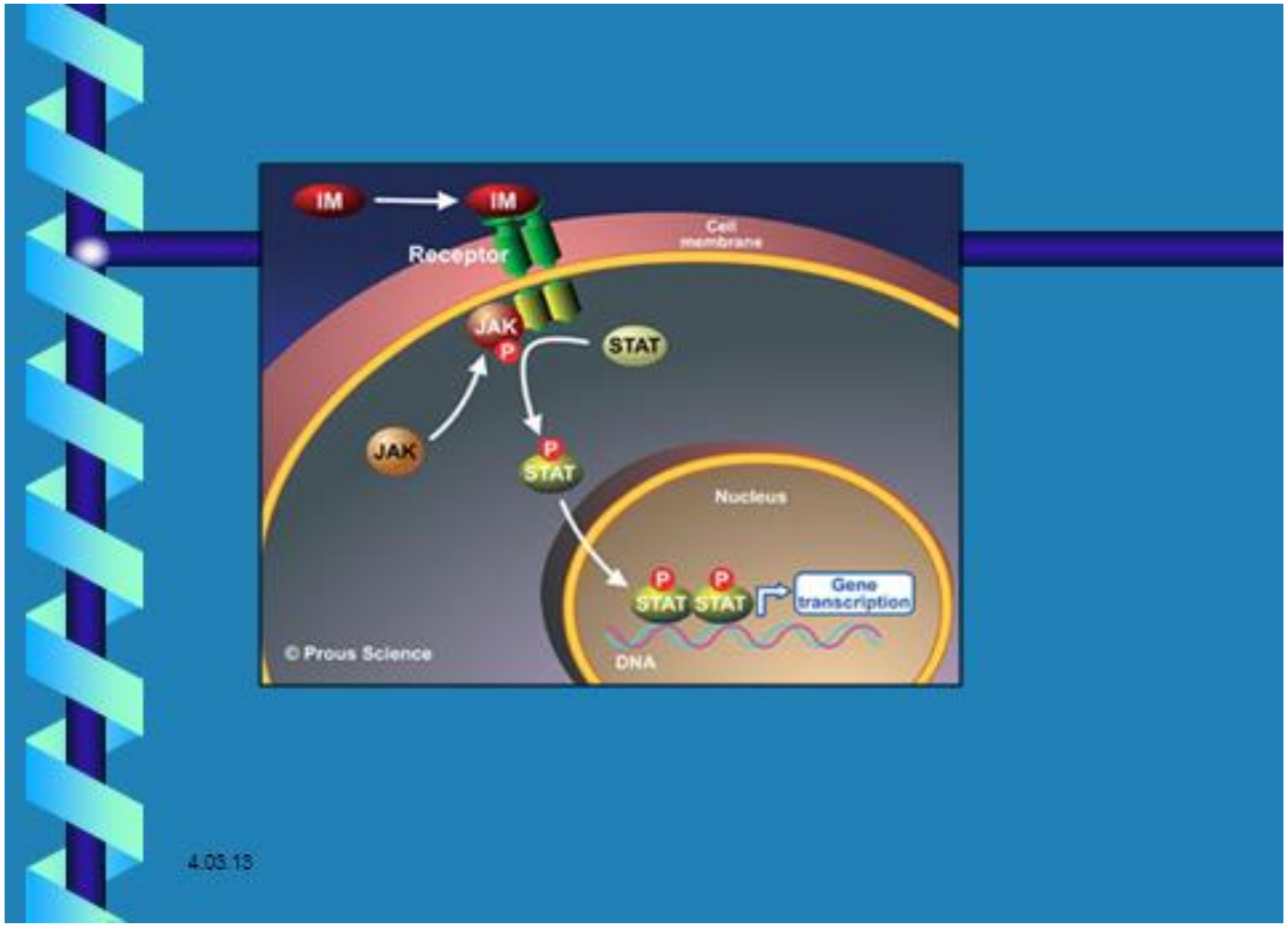


Silverman, Weisman, Arthritis Rheum 2003

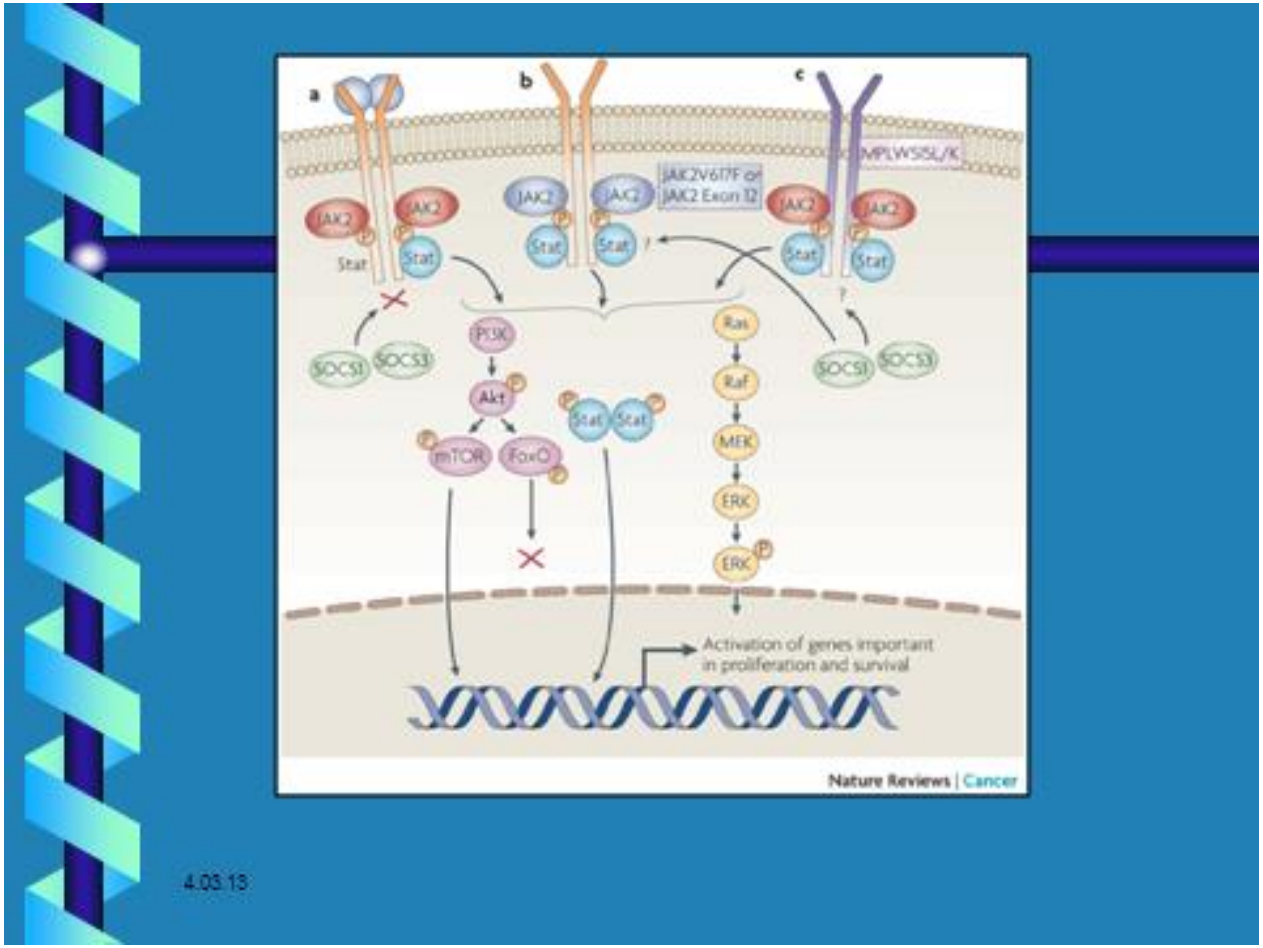
JAK-STAT

The Janus kinase, the signal transducer and activator of transduction (JAK-STAT) pathway is the signaling target of a multitude of cytokines, including INF gamma, IL-2, IL-4, IL-6, IL-7, IL-10, IL-12 and IL-15, all of which are thought to have biologically significant roles in rheumatoid synovial inflammation.

JAK inhibitors



JAK inhibitors



Assessment of SpondyloArthritis in ternational Society Classification Criteria for Axial Spondyloarthritis (SpA)

For patients with back pain for ≥3 mo and aged <45 yr:

Sacroiliitis on imaging + ≥1 SpA feature

or

HLA-B27 + ≥2 other SpA features

Sacroiliitis on imaging defined as:

- Active acute inflammation on magnetic resonance imaging highly suggestive of sacroiliitis associated with SpA
- *or*
- Definitive radiographic sacroiliitis according to the modified New York criteria

SpA features comprising:

- Arthritis
- Enthesitis (heel)
- Inflammatory back pain
- Dactylitis
- Uveitis
- Psoriasis
- Inflammatory bowel disease
- Good response to nonsteroidal anti-inflammatory drugs
- Family history of SpA
- HLA-B27
- Elevated C-reactive protein

Kelley's Textbook of Rheumatology, 2012, p. 1223

Assessment of SpondyloArthritis in ternational Society Classification Criteria for Axial Spondyloarthritis (SpA)

For patients with:
- Peripheral arthritis (usually asymmetric, lower limb)
- *or*
- Enthesitis
- *or*
- Dactylitis

+ 1 of:
- HLA-B27
- Genitourinary or gastrointestinal infection
- Psoriasis
- Inflammatory bowel disease
- Magnetic resonance imaging sacroiliitis

or

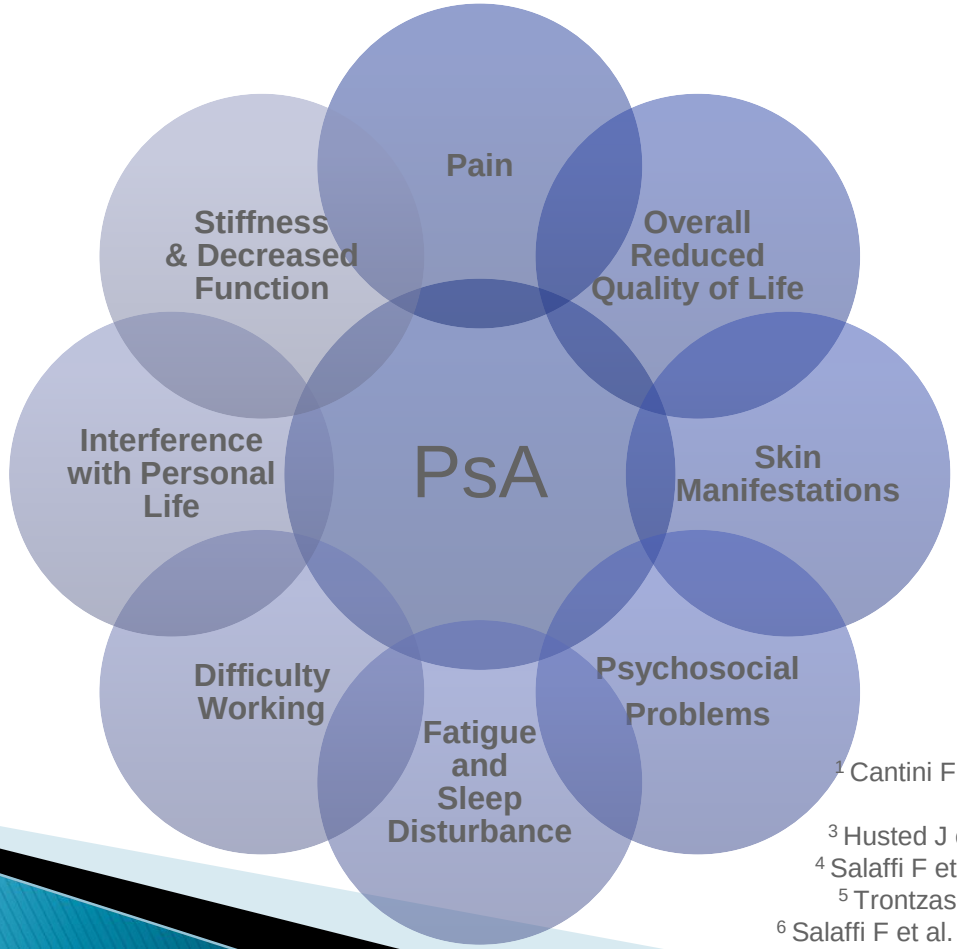
+ 2 of:
- Arthritis
- Enthesitis
- Dactylitis
- Inflammatory back pain
- Family history of spondyloarthritis

Kelley's Textbook of Rheumatology, 2012, p. 1093

Psoriatic Arthritis

Psoriatic arthritis (PsA) is a chronic inflammatory disease associated with multiple and variable clinical features.

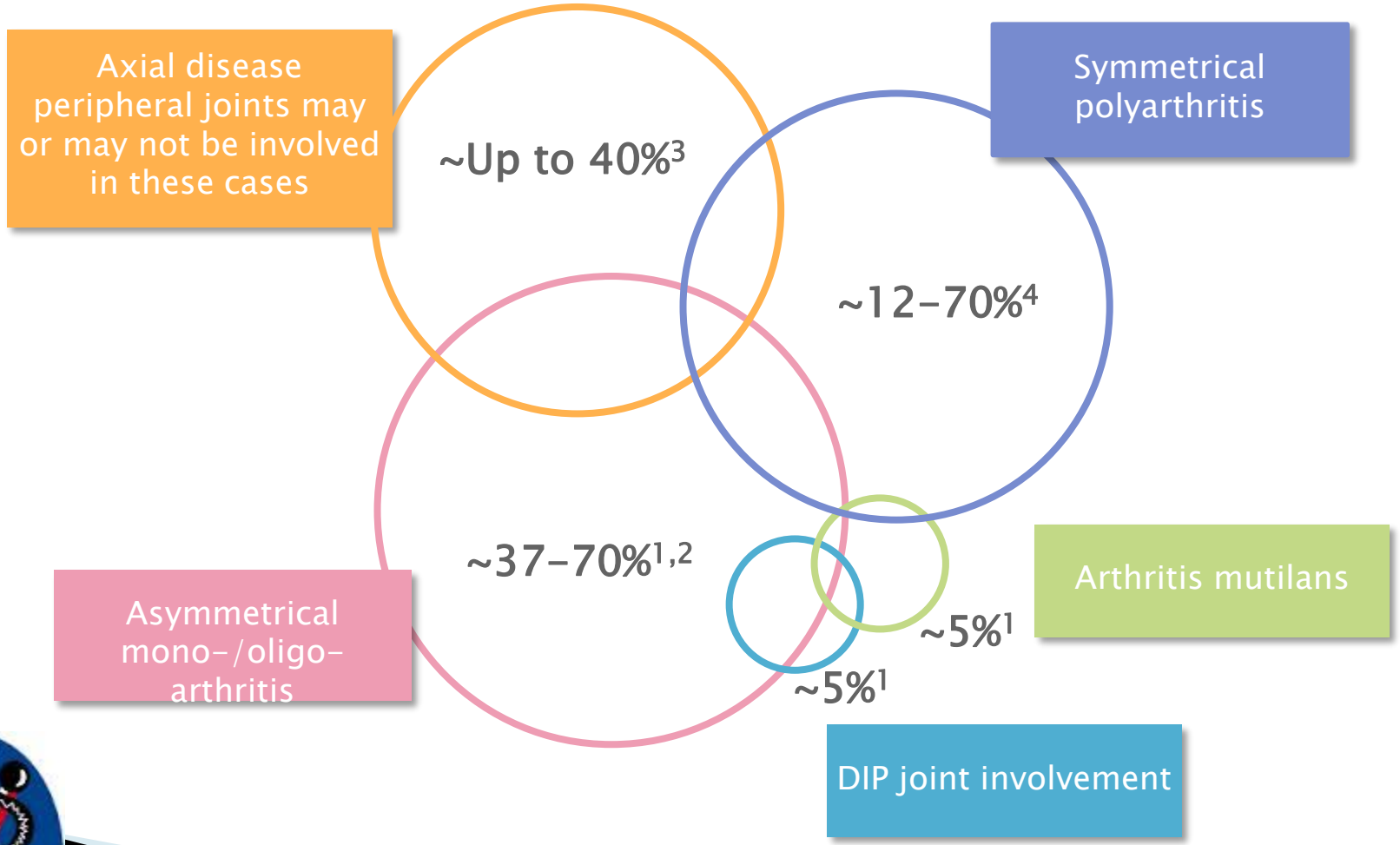
- Patients with PsA suffer from inflammatory peripheral arthritis and may also suffer from extra-articular manifestations and axial disease.[1]
- Patients with PsA have a range of disease burden.[2,3]
- Estimates of the prevalence of PsA among general adult populations range from 0.17% to 0.42%.[5,6]



[1] Cantini F et al. Int J Rheum Dis. 2010;13(4):300-17
[2] Lee et al. P & T. 2010;35:680-689
[3] Husted J et al. Ann Rheum Dis. 2009;68:1553-1558
[4] Salaffi F et al. Health Qual Life Outcomes. 2009;7:25
[5] Trontzas P et al. Clin Rheumatol. 2005;24:583-589
[6] Salaffi F et al. Clin Exp Rheumatol. 2005;23(6): 819-828

Psoriatic Arthritis

Five overlapping clinical patterns are observed in PsA[1]



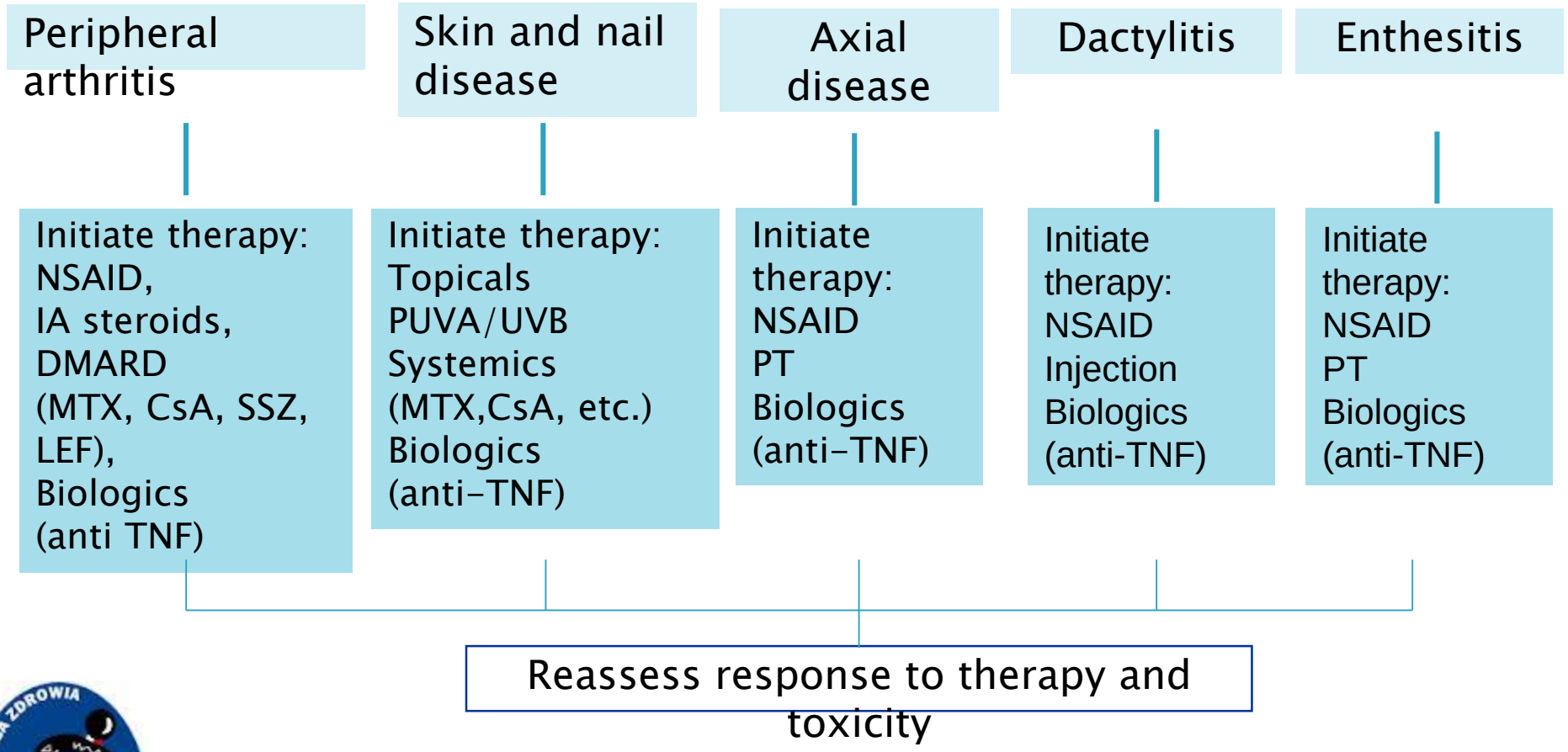
[1] Moll J and Wright V. Semin Arthritis Rheum. 1973;3:55–78
[2] Torre Alonso J et al. Br J Rheumatol. 1991;30:245–50
[3] Gladman D. Ann Rheum Dis. 2005;64(Suppl II):ii14–ii17
[4] Helliwell et al. Ann Rheum Dis. 2005;64(Suppl II):ii3–ii8

Classifiaction criteria for Psoriatic Arthritis (CASPAR)

Inflammatory articular disease (joint, spine or entheseal) with ≥3 points from the following 5 categories:		Points
Psoriasis	Current psoriasis History of psoriasis Family history of psoriasis	2 1 1
Psoriatic nail dystrophy	Onycholysis, pitting ad hyperkeratosis	1
A negative test for rheumatoid factor	By any method except latex but preferably by enzyme-linked immunosorbent assay (ELISA) or nephelometry, according to the local laboratory reference range	1
Dactylitis	Swelling of entire digit or A history of dactylitis recorded by a rheumatologist	1 1
Radiological evidence of juxta-articular new bone formation	Ill-defined ossification near joint margins (excluding osteophyte formation) on plain X-rays of hand or foot	1
Specificity 0.987, Sensitivity 0.914		

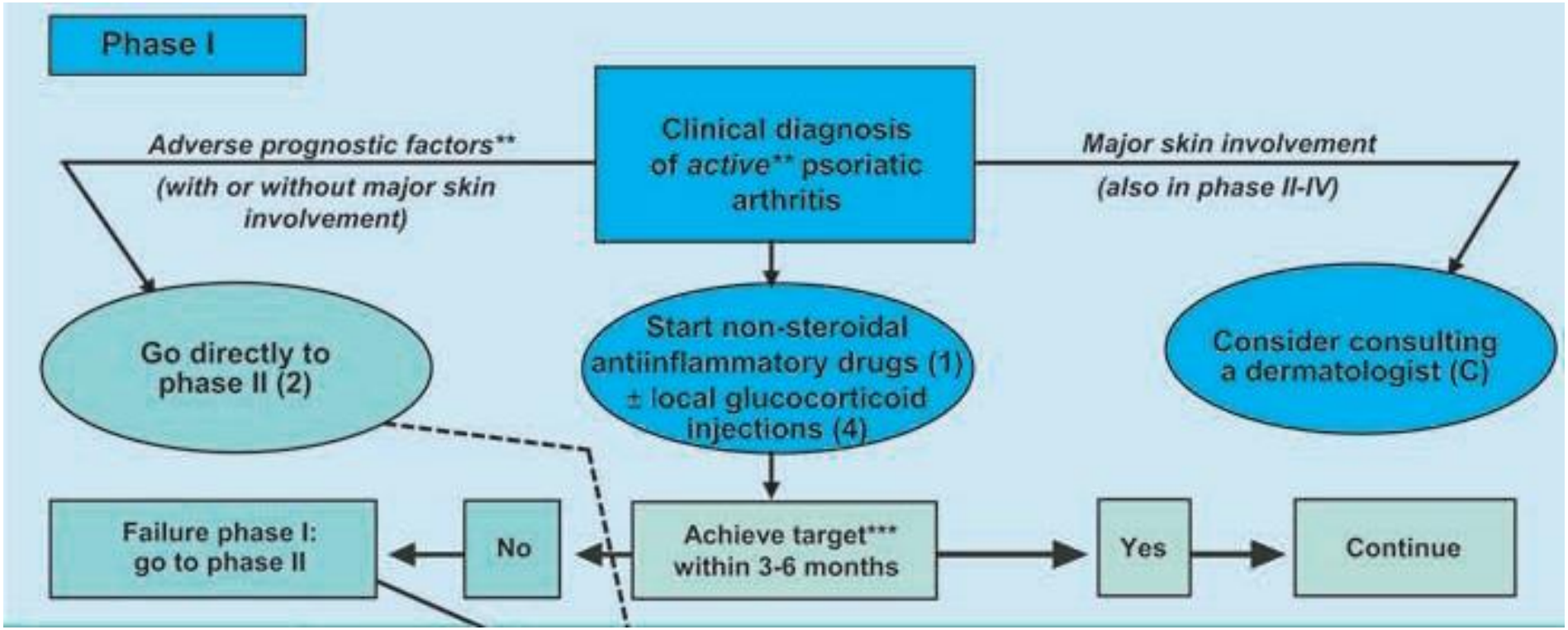
Taylor et al. Arthritis Rheum. 2006;54(8):2665-2673

GRAPPA recommendations for the management of PsA



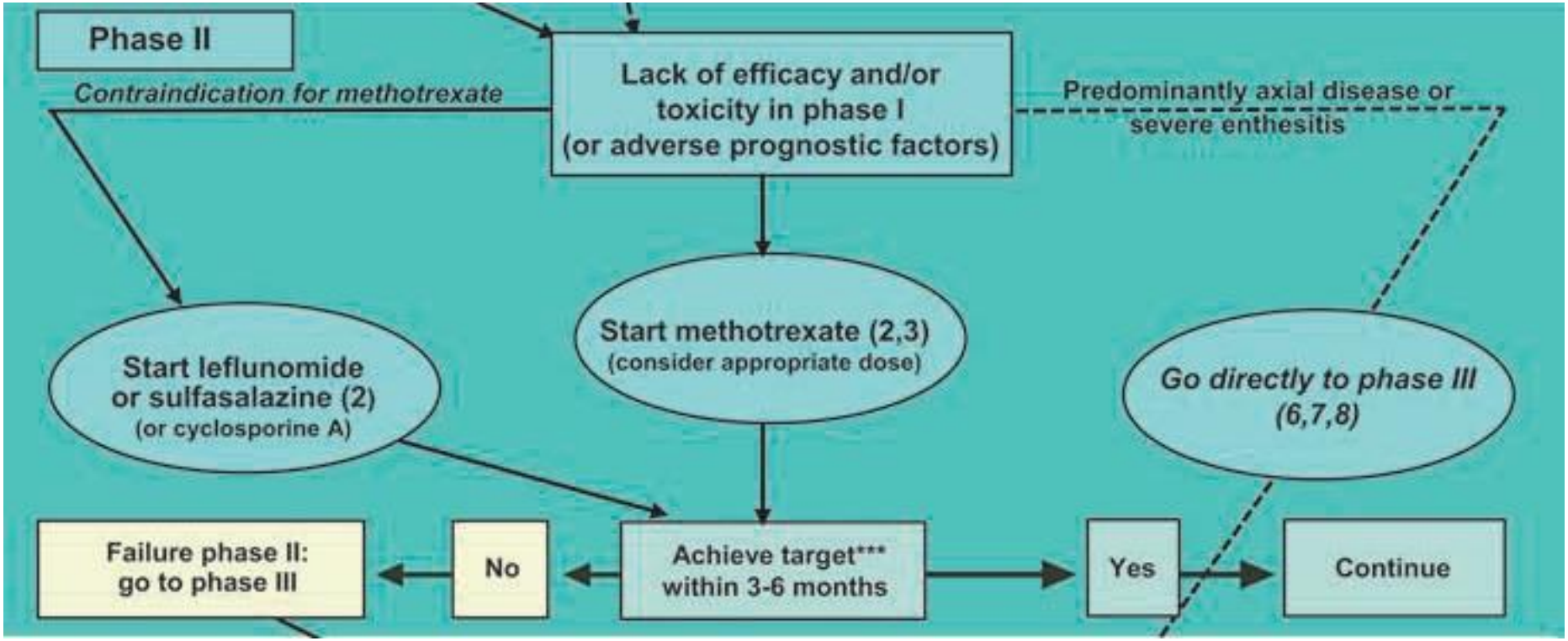
Ritchlin CT, et al. *Ann Rheum Dis.* 2009;68:1387–1394

EULAR recommendations for the management of PsA



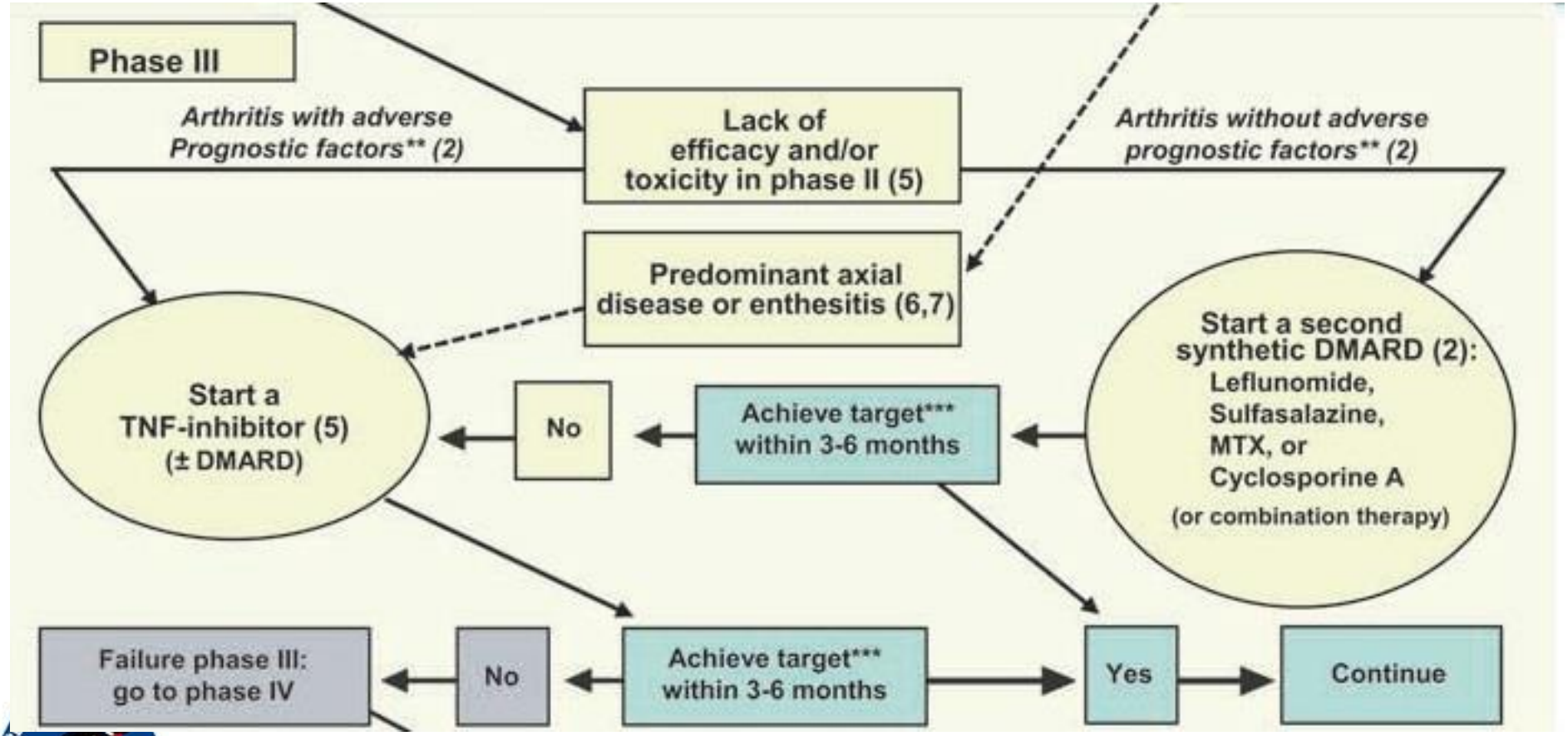
Gossec L, et al. *Ann Rheum Dis.* 2012; 71:4-12

EULAR recommendations for the management of PsA



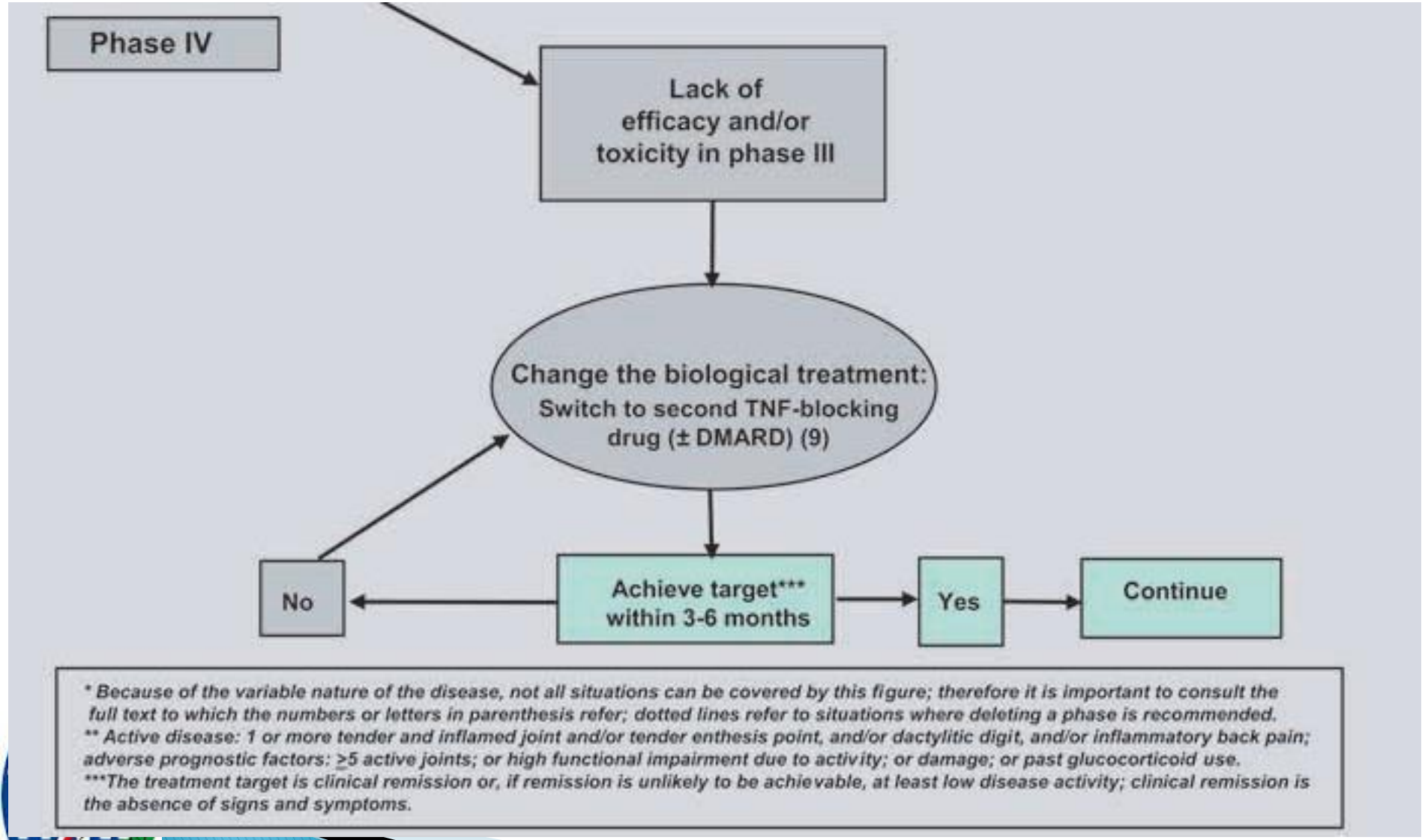
Gossec L, et al. *Ann Rheum Dis.* 2012; 71:4-12

EULAR recommendations for the management of PsA



Gossec L, et al. *Ann Rheum Dis.* 2012; 71:4-12

EULAR recommendations for the management of PsA



Gossec L, et al. *Ann Rheum Dis.* 2012; 71:4-12

Rheumatology in the 21st century

New treatment of PsA

TNF alpha inhibitors,IL-17inhibitor Ixekizumab, Ustekinumab (Stelara) –a fully human IgG 1k monoclonal antibody that binds to the common p40 subunit shared by interleukins 12 and 23

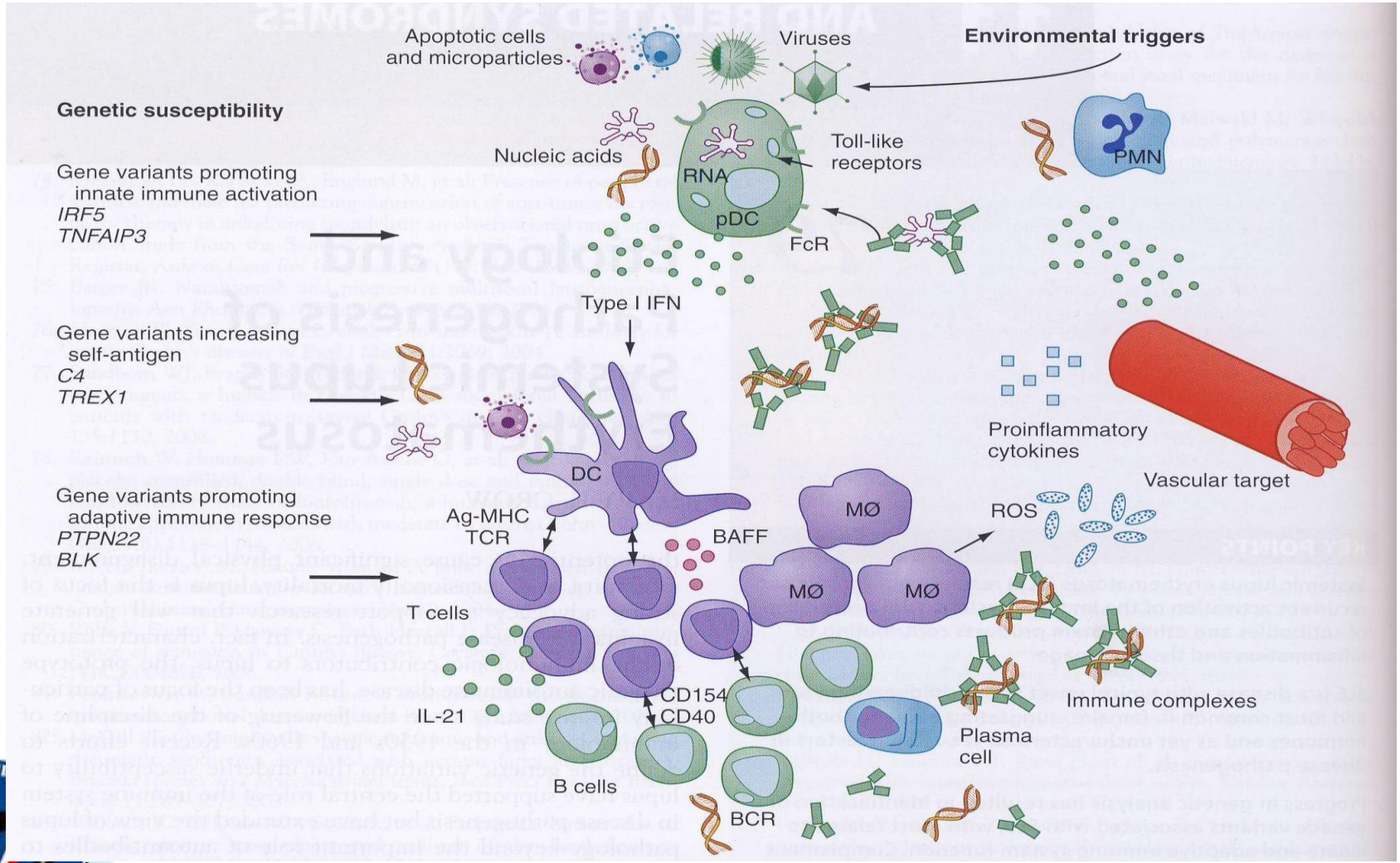
45 mg sc initially and 4 weeks later, followed by 45 mg every 12 weeks

Apremilast (Otezla) – a phosphodiesterase 4 inhibitor

Day 1 –10 mg, day – 2 x 10 mg, day 3 –10 mg + 20 mg, day 4– 2 x 20 mg, day 5– 20 mg + 30 mg, day 6 and thereafter 2 x 20 mg

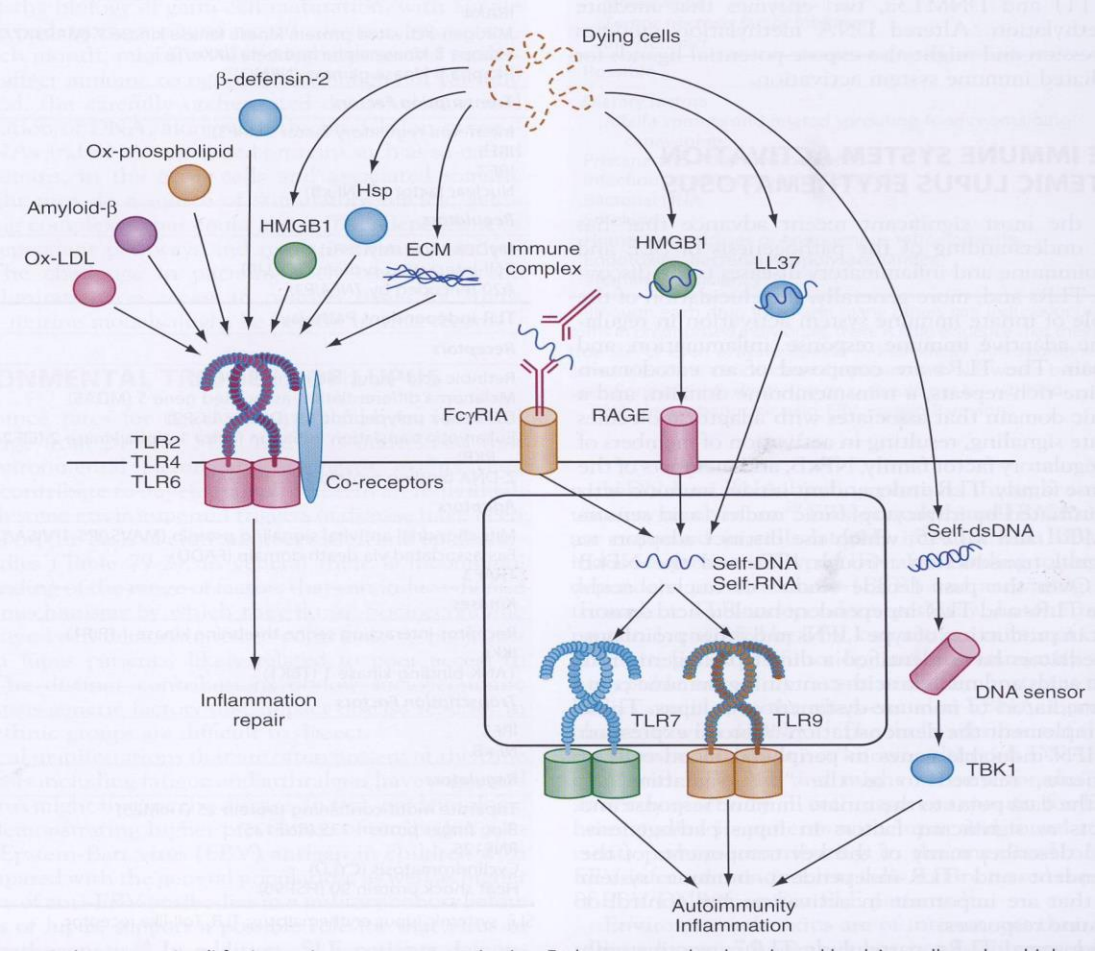
Phosphodiesteraze 4 inhibitor degrades cAMP into AMP. Elevated intracellular cAMP down-regulates the inflammatory responses through inhibition of the expression of inflammatory cytokines and increasing the expression of anti-inflammatory interleukin 10

Pathogenesis of SLE



Kelley's Textbook of Rheumatology, 2012, p. 1270

Pathogenesis of SLE



Kelley's Textbook of Rheumatology, 2012, p. 1276

Treatment of SLE

Disease Severity	Induction Therapy	Maintenance Therapy
Mild	High-dose GC (0.5-1 mg/kg/day prednisone ×4-6 wk, tapered to 0.125 mg/kg every other day within 3 mo) alone or in combination with AZA (1-2 mg/kg/day)	Low-dose GC (prednisone ≤0.125 mg/kg on alternative days) alone or with AZA (1-2 mg/kg/day)
	If no remission within 3 mo, treat as moderately severe	Consider further gradual tapering at the end of each year of remission
Moderate	MMF (2 g/day) (or AZA) with GC as above; if no remission after the first 6-12 mo, treat as severe	MMF tapered to 1.5 g/day for 6-12 mo and then to 1 g/day; consider further tapering at the end of each year in remission
		Alternative: AZA (1-2 mg/kg/day)
Severe	Pulse IV-CYC alone or in combination with pulse IV-MP for the first 6 mo (background GC 0.5 mg/kg/day for 4 wk, then taper)	Quarterly pulses of IV-CYC for at least 1 year beyond remission
	If no response, consider adding RTX or switch to MMF	Alternative: AZA (1-2 mg/kg/day), MMF (1-2 g/day)

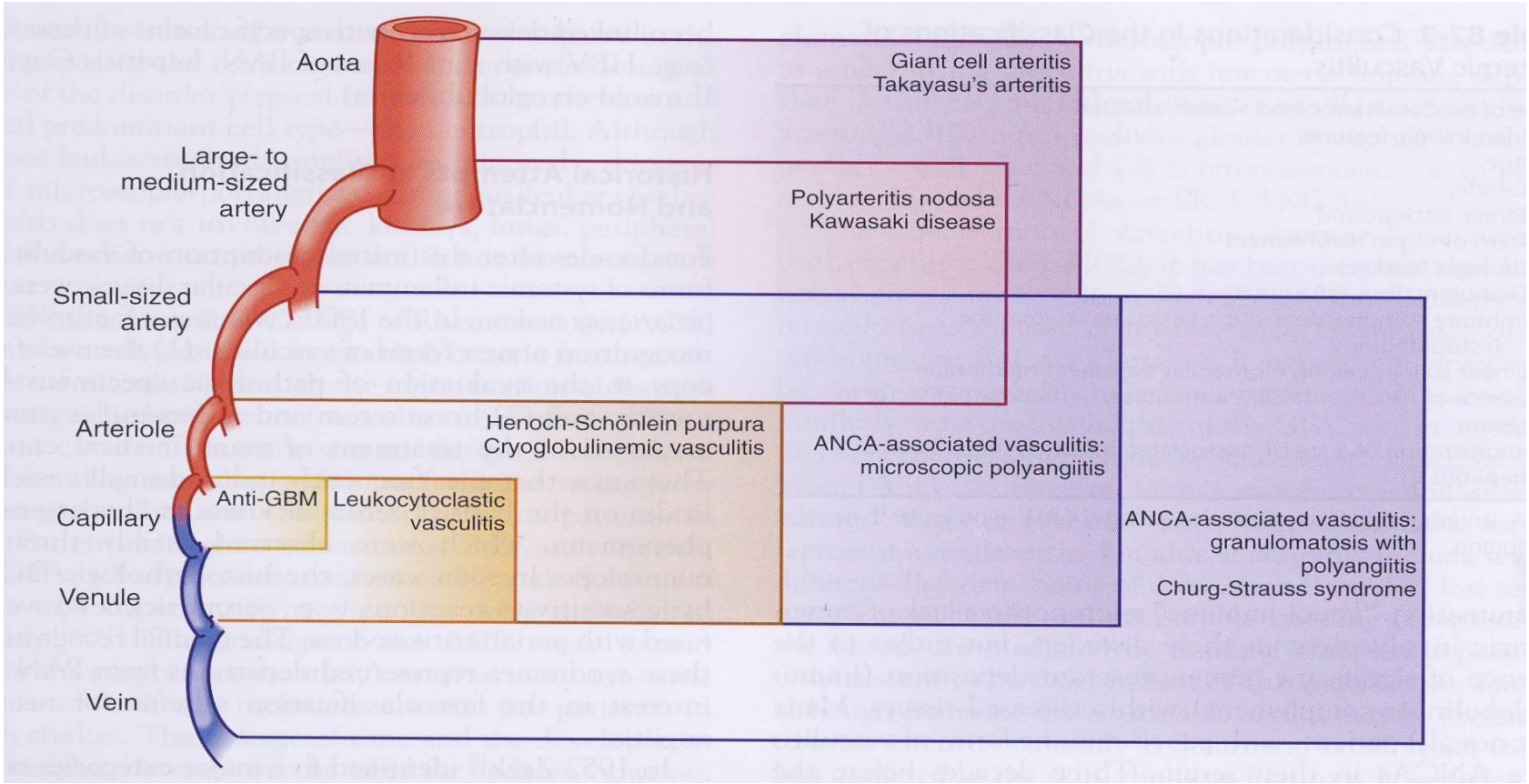
Kelley's Textbook of Rheumatology, 2012, p. 1309

Rheumatology in the 21st century

Belimumab, a fully human monoclonal antibody that inhibits B-lymphocyte stimulator BLYSS, was approved for the treatment of SLE in 2011. There is also a number of other novel therapies in development.

The clinical data for these agents and their impact on the management of lupus is an important topic.

Classification of vasculitis by blood vessel size



Kelley's Textbook of Rheumatology, 2012, p. 1455

C lassification of vasculitis by the Chapel Hill Consensus Conference

	Histopathology	Comments
Large Vessel Vasculitis		
Giant cell (temporal) arteritis	Granulomatous arteritis of the aorta and its major branches, with a predilection for the extracranial branches of the carotid artery	Often involves the temporal artery Usually occurs at >50 yr of age Often associated with polymyalgia rheumatica
Takayasu's arteritis	Granulomatous inflammation of the aorta and its major branches	Usually occurs at <50 yr of age
Medium-Sized Vessel Vasculitis		
Polyarteritis nodosa† (classic polyarteritis nodosa)	Necrotizing inflammation of medium-sized or small arteries without glomerulonephritis or vasculitis in arterioles, capillaries, or venules	
Kawasaki disease	Arteritis involving large, medium-sized, and small arteries, associated with mucocutaneous lymph node syndrome	Coronary arteries often involved Aorta and veins may be involved Usually occurs in children
Small Vessel Vasculitis		
Granulomatosis with polyangiitis‡	Granulomatous inflammation involving the respiratory tract and necrotizing vasculitis affecting small to medium-sized vessels (capillaries, venules, arterioles, arteries)	Necrotizing glomerulonephritis common
Allergic granulomatosis with polyangiitis‡	Eosinophil-rich and granulomatous inflammation involving the respiratory tract and necrotizing vasculitis affecting small to medium-sized vessels, associated with asthma and blood eosinophilia	
Microscopic polyangiitis‡	Necrotizing vasculitis with few or no immune deposits affecting small vessels (capillaries, venules, arterioles)	Necrotizing arteritis involving small and medium-sized arteries may be present Necrotizing glomerulonephritis very common Pulmonary capillaritis often occurs
Henoch-Schönlein purpura	Vasculitis with IgA-dominant immune deposits affecting small vessels (capillaries, venules, arterioles)	Typically involves skin, gut, and glomeruli Associated with arthralgia or arthritis
Essential cryoglobulinemic vasculitis	Vasculitis with cryoglobulin immune deposits affecting small vessels (capillaries, venules, arterioles) and associated with cryoglobulins in serum	Skin and glomeruli often involved
Cutaneous leukocytoclastic angiitis	Isolated cutaneous leukocytoclastic angiitis without systemic vasculitis	

Kelley's Textbook of Rheumatology, 2012, p. 1483

VASCULITIDES

BIOPSY FINDINGS IN MAJOR VASCULITIC SYNDROMES

	Vessel size	Fibrinoid	PMNs	Lymphocytes/ monocytes	Eosinophils	Giant cells	Granulomas	Comments
Takayasu's arteritis	aorta, main branches, pulmonary	–	++	++++†	±	++++†	++++†	During inactive stage lesions are primarily fibrotic
Giant cell arteritis	large arteries	+	rare	+++	±	++	+++	Giant cell granulomas seen in only 50%; 'skip' areas common
Polyarteritis	medium to small arteries, venules, arterioles	++++	+++	+++	+	–	rare*	Sectoral involvement; lesions in various stages
Churg–Strauss syndrome	small>medium arteries, veins, arterioles, venules	+++	+	++	++++	++	++++	Granulomas are extravascular; gastrointestinal and heart>kidney
Wegener's granulomatosis	medium–large arteries, small arteries, veins, capillaries	+++	+++	+++	+	++	+++	Almost always in lung; renal vasculitis in <50%; focal segmental glomerulitis
Microscopic polyangiitis	medium arteries, small arteries arterioles, venules	++	+++	+++	±	–	–	Lung and kidney common
Kawasaki disease	medium arteries, small arteries arterioles, venules	+	+++ (early)	++ (early)	–	–	+	
Behçet's syndrome	arterioles, venules>medium-sized vessels	±	+++ (early)	+++ (late)	rare	–	–	Leukocytoclasis
Hypersensitivity vasculitis	arterioles, venules> capillaries	++	+++	+++	+	–	+*	Leukocytoclasis
Henoch–Schönlein purpura	arterioles, venules> capillaries	++	++	++	rare	–	–	Leukocytoclasis

* In variants † During active phase

Kelley's Textbook of Rheumatology, 2012, p. 1483

Vasculitis

Rituximab has been found to be an alternative to cyclophosphamide in the treatment of vasculitis. The general concensus was that cyclophosphamide continues to have a role while rituximab may be considered a valid option to cyclophosphamide for remission induction in newly diagnosed patients with severe ANCA-associated vasculitis.

In 2011, the FDA approved rituximab in combination with glucocorticosteroids for the treatment of granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA), two forms of ANCA-associated vasculitis.