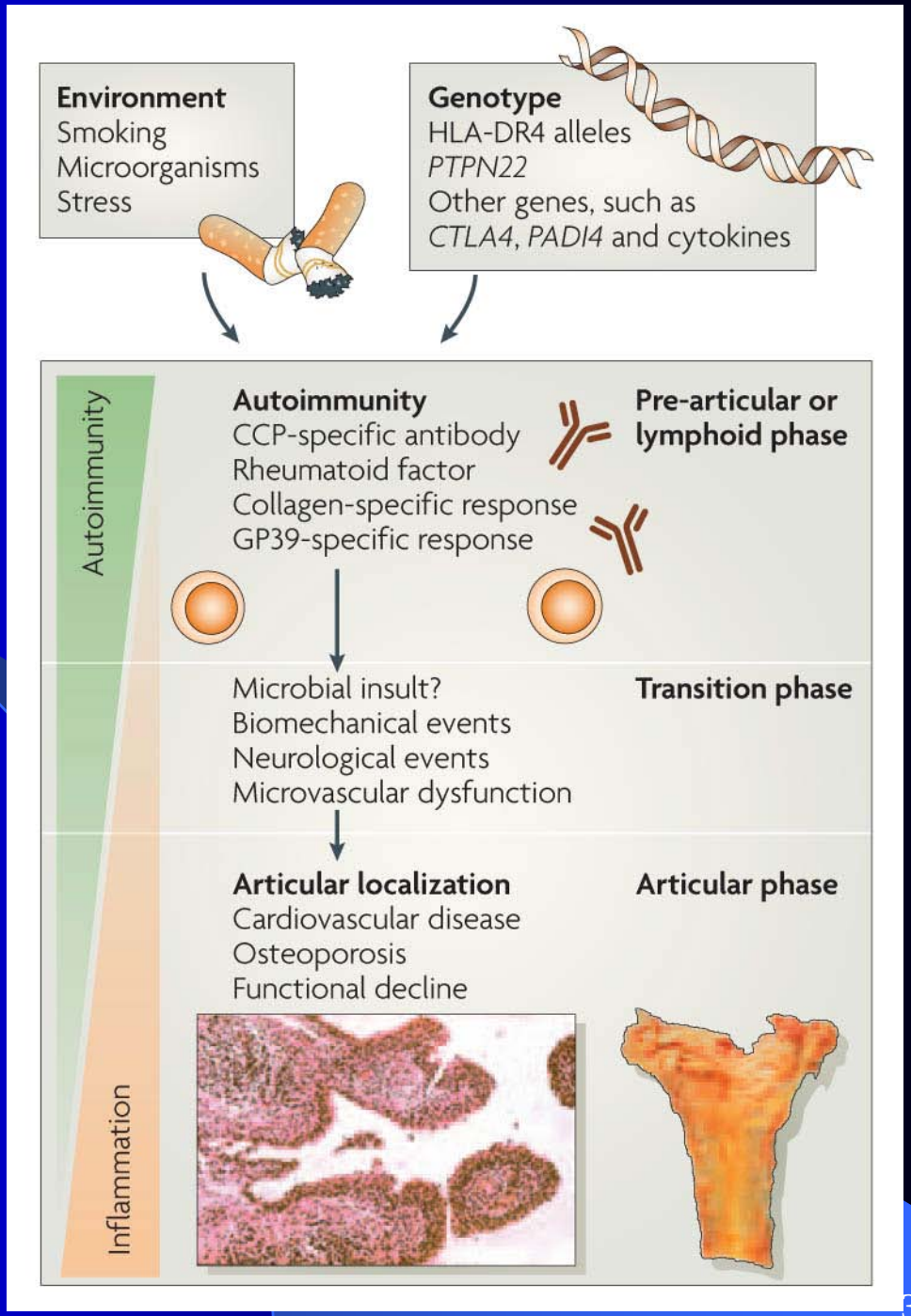
Treating Rheumatologic *Disease* in Arizona: *Good News, Bad News*

Jeffrey R. Lisse, M.D.
Ethel P. McChesney Bilby Professor of Medicine
Chief, Section of Rheumatology
University of Arizona School of Medicine

Geographic distribution of Coccidioidomycosis

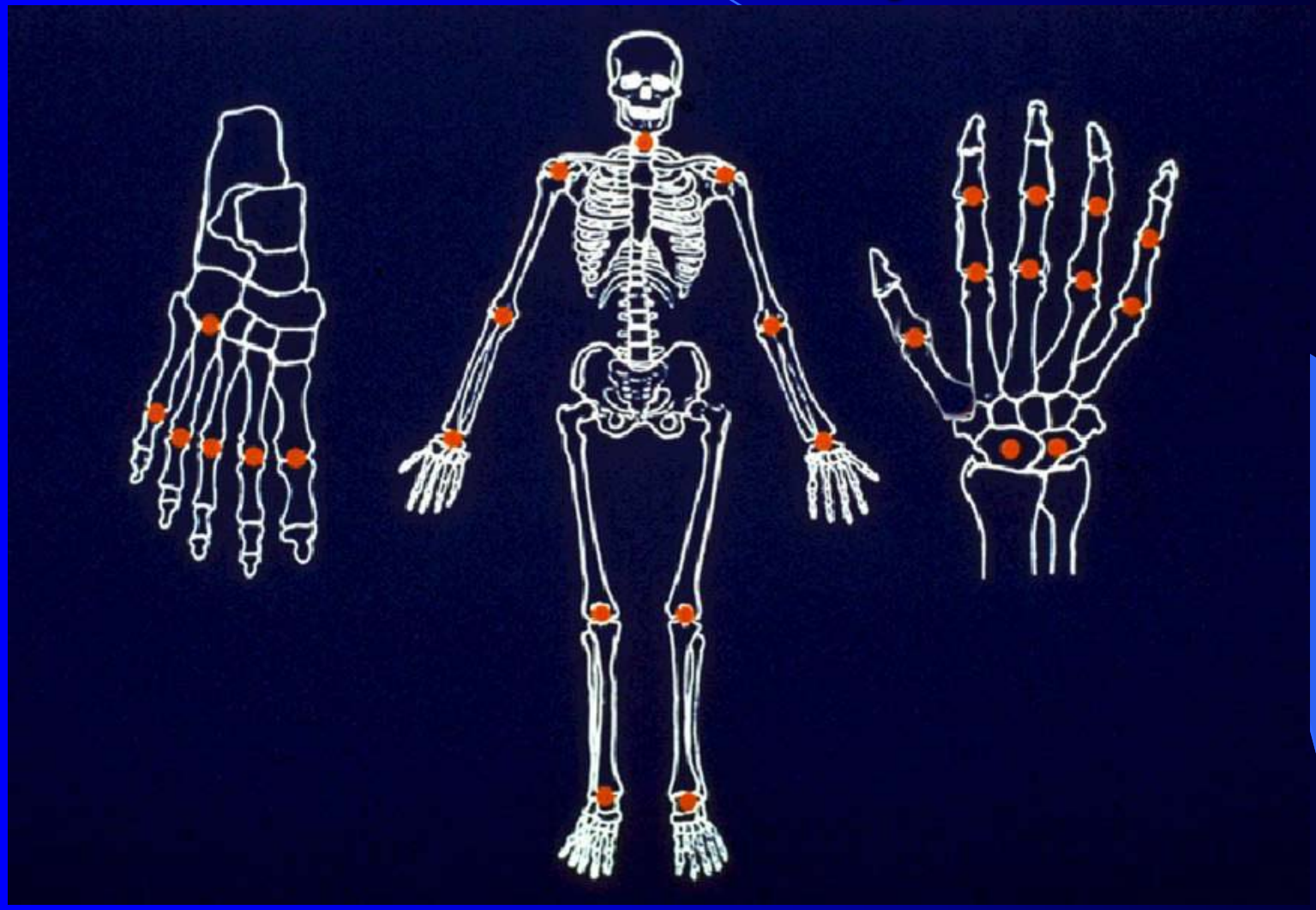
Longitudinal Course of RA



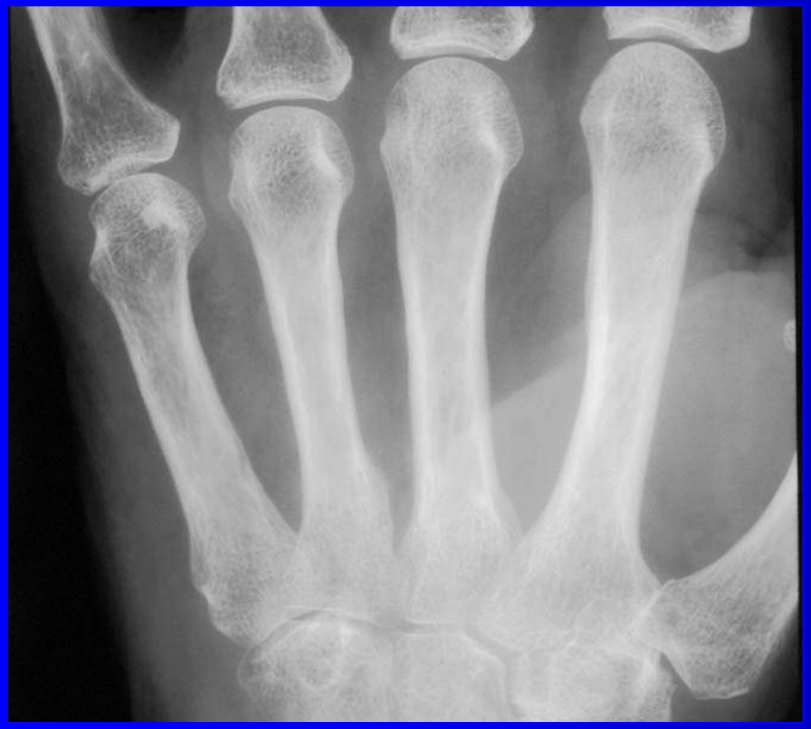
CCP, cyclic citrullinated peptide; *CTLA4*, cytotoxic T-lymphocyte antigen 4; GP39, cartilage glycoprotein 39; *PADI4*, peptidyl arginine deiminase, type IV; *PTPN22*, protein tyrosine phosphatase, non-receptor type 22.

Reproduced with permission from McInnes IB, et al. *Nat Rev Immunol*. 2007;7(6):429-442.

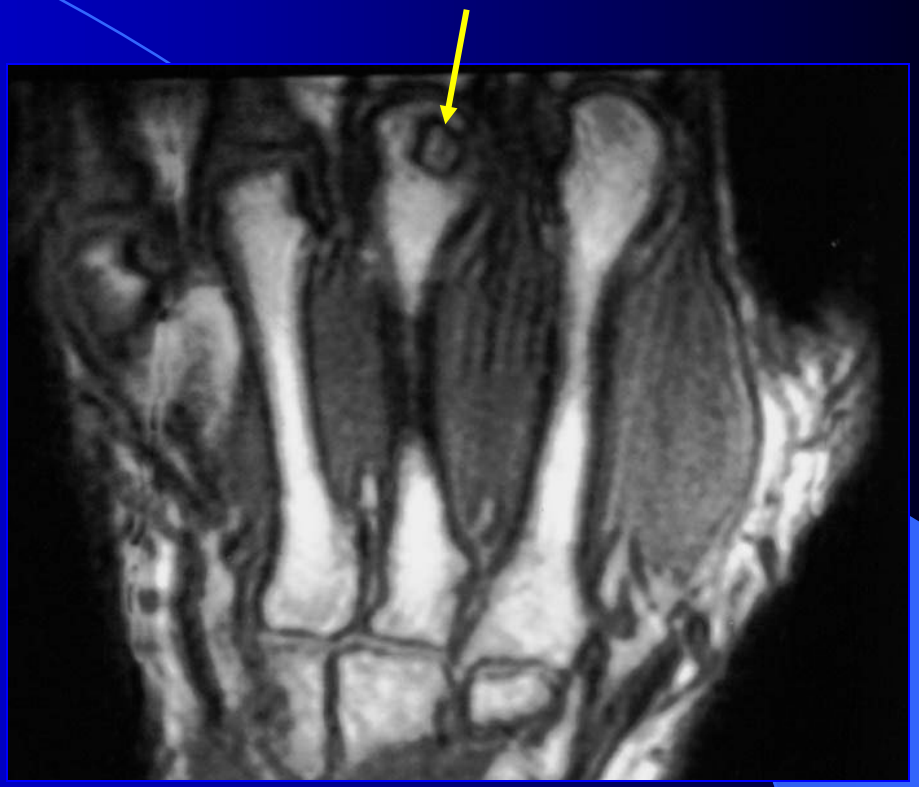
RA Joints Commonly Involved



Early RA: Radiographic Findings



High-Detail X-Ray

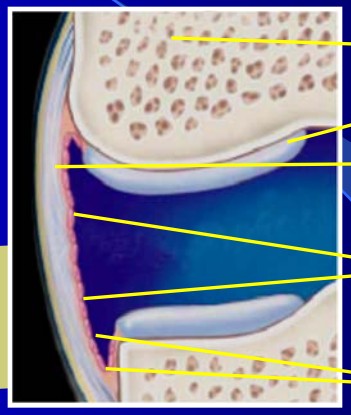


Low-Field MRI

Courtesy of Charles Peterfy, MD.

Disease Progression

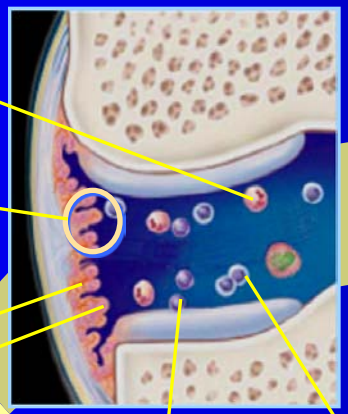
Normal Joint



Bone
Cartilage
Capsule
Synovial Membrane
Synoviocytes

Early Rheumatoid Arthritis

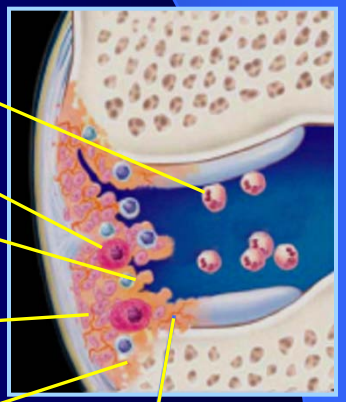
Neutrophils
Hyperplastic Synovial Membrane
Capillary Formation
Hypertrophic Synoviocyte



T Cells
B Cells

Established Rheumatoid Arthritis

Neutrophils
Plasma Cell
Synovial Villi
Extensive Angiogenesis
Eroded Bone

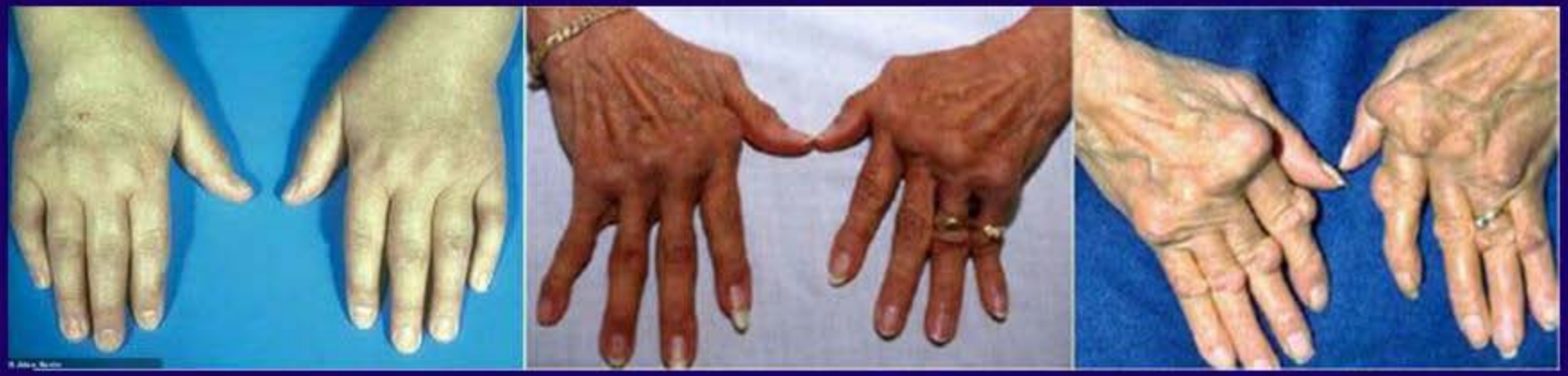


Pannus

RA—One of the Most Common Types of Inflammatory Arthritis

- Affects approximately 1% of the population[1]
- One of the most common causes of disability in the Western world[2]

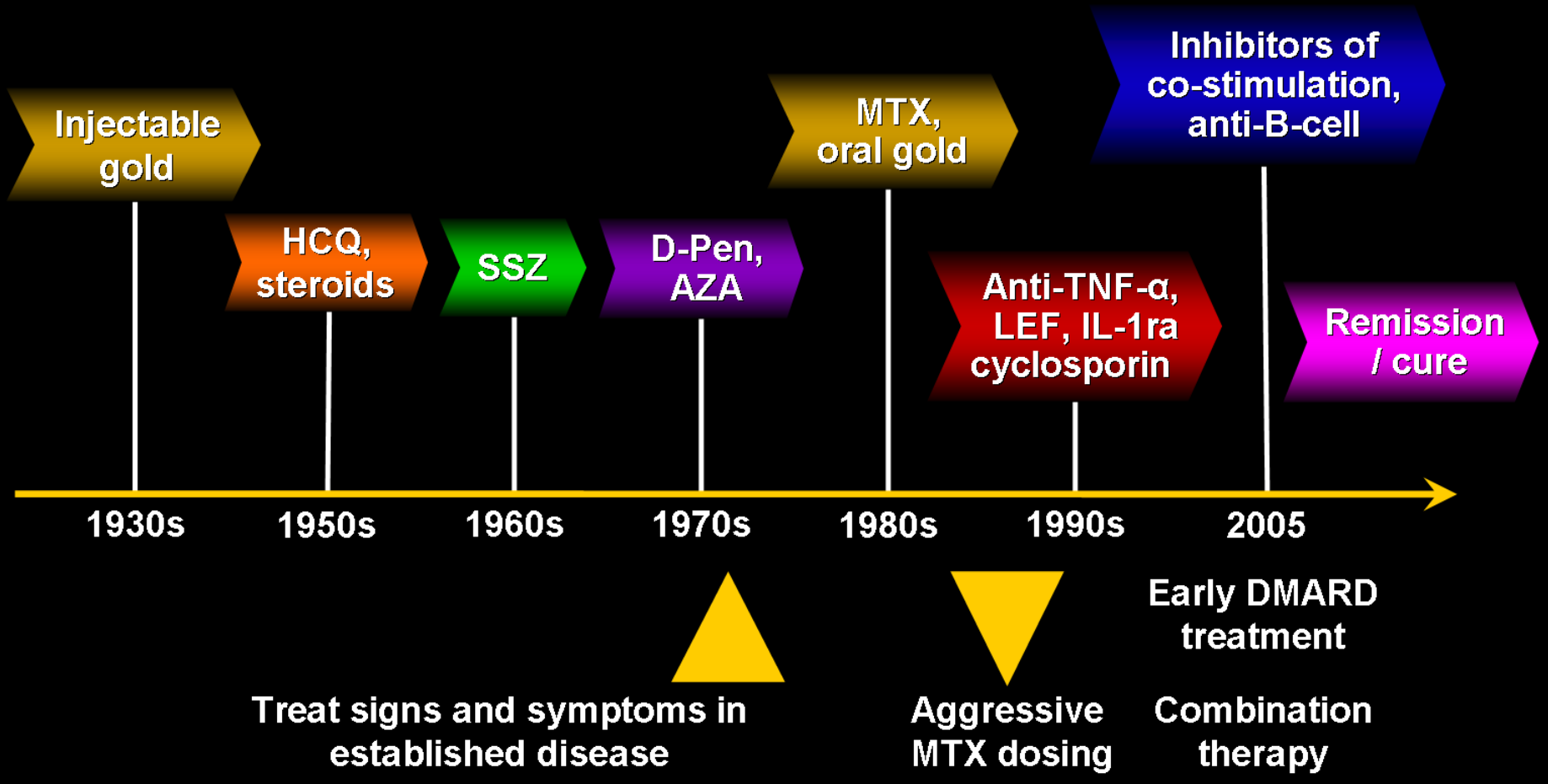
Progression Over Time



Photos courtesy Lester Miller, MD, Santa Cruz, Calif.

References: 1. Quinn MA, et al. In: Hochberg MC, et al, eds. *Rheumatology*. Vol 2. 3rd ed. New York, NY: Mosby; 2003:885-891. **2.** Emery P. *Br J Rheumatol*. 1994;33:765-768.

Evolution of RA treatment



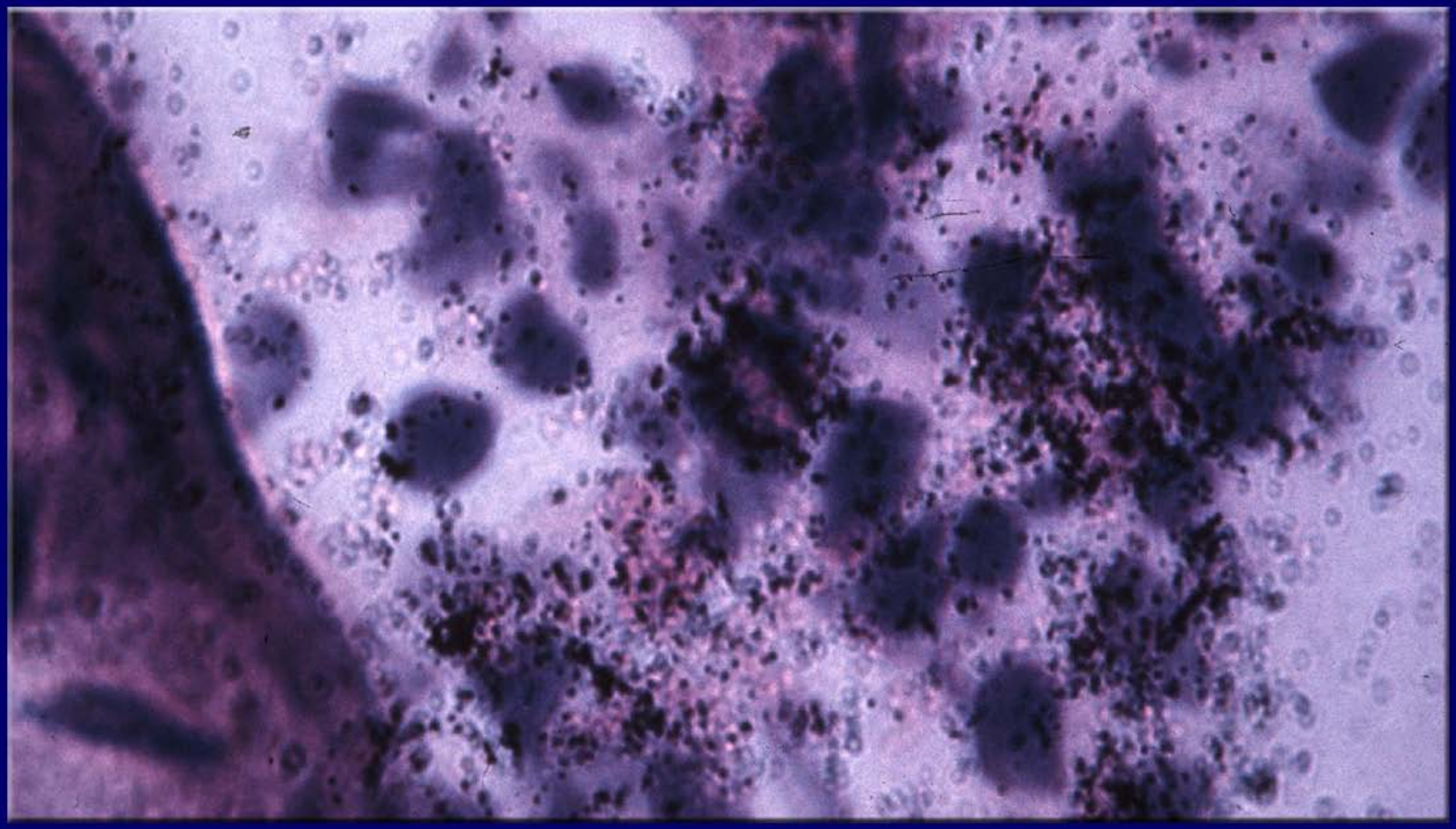
Adverse Effects of Nonbiologic DMARD Therapy

- **Corticosteroids**
  - Osteoporosis
  - Cataracts
  - Diabetes
  - HTN
- **SSZ**
  - GI
  - Rash
  - Cytopenias (G6PD deficiency)
- **Hydroxychloroquine**
  - Retinopathy (extremely rare)
  - Rash
  - Cytopenias (G6PD deficiency)
- **Leflunomide**
  - Alopecia
  - Teratogen
  - Diarrhea
  - Liver
  - Infections
- **MTX**
  - Liver
  - Mucositis/ulcers
  - Headache
  - Alopecia
  - Nausea
  - Pulmonary
  - Infections

HTN = hypertension; GI = gastrointestinal.

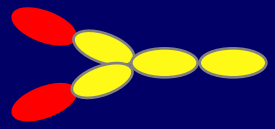
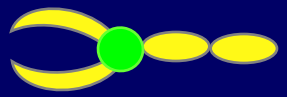
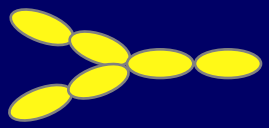
Role of TNF-α in AS

TNF-α mRNA in Sacroiliac Biopsy



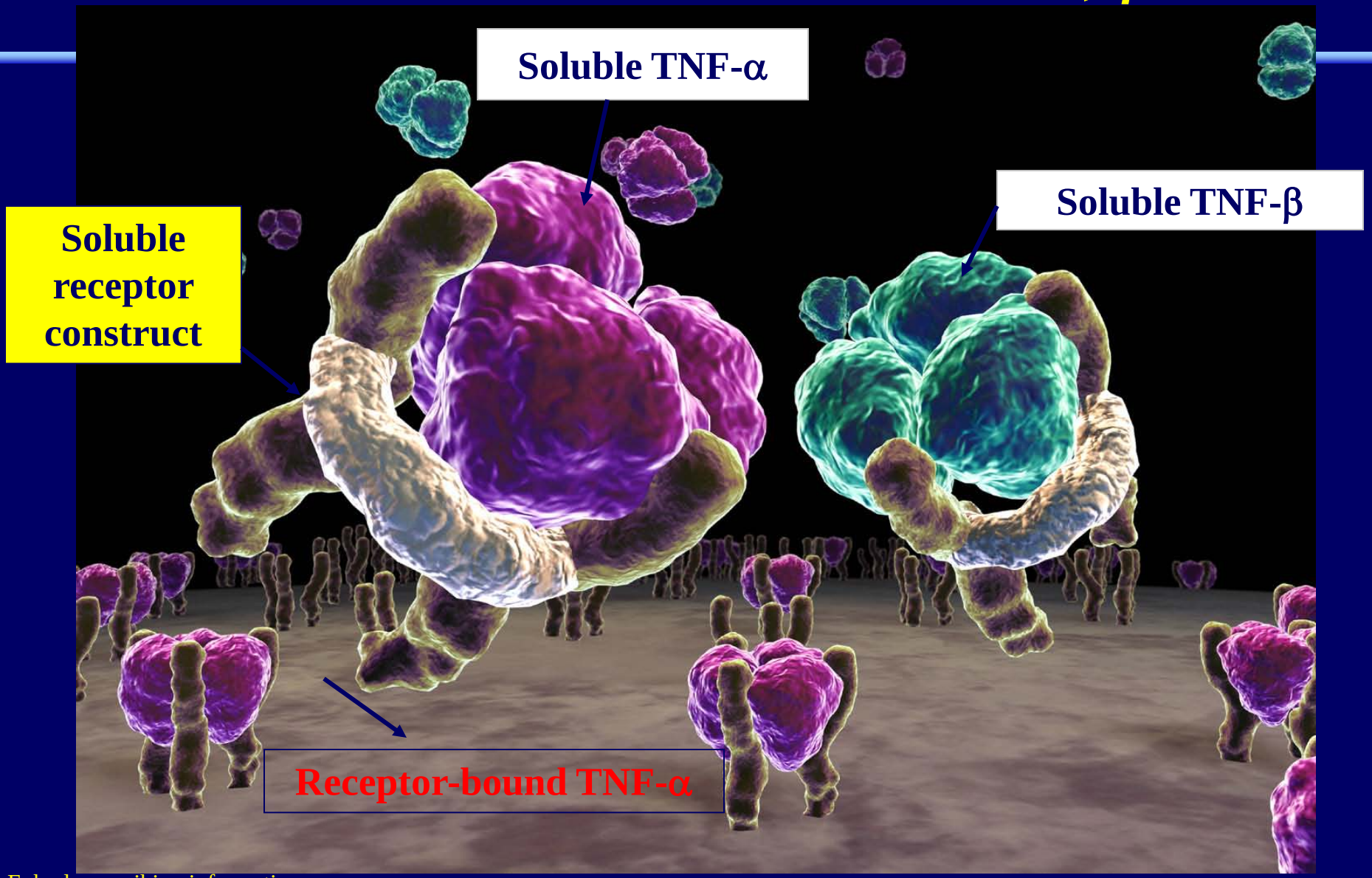
Reprinted with Permission from Braun J. et al, *Arthritis and Rheumatism* 1995;38:499-505.

Molecular Structure of Biologic Agents

Description	Structure
Chimeric anti-TNF mAb	
TNF-receptor p75 IgG_1 construct	
Fully human anti-TNF mAb	
PEGylated humanized anti-TNF Fab-fragment	
TNF-receptor p55 PEG	

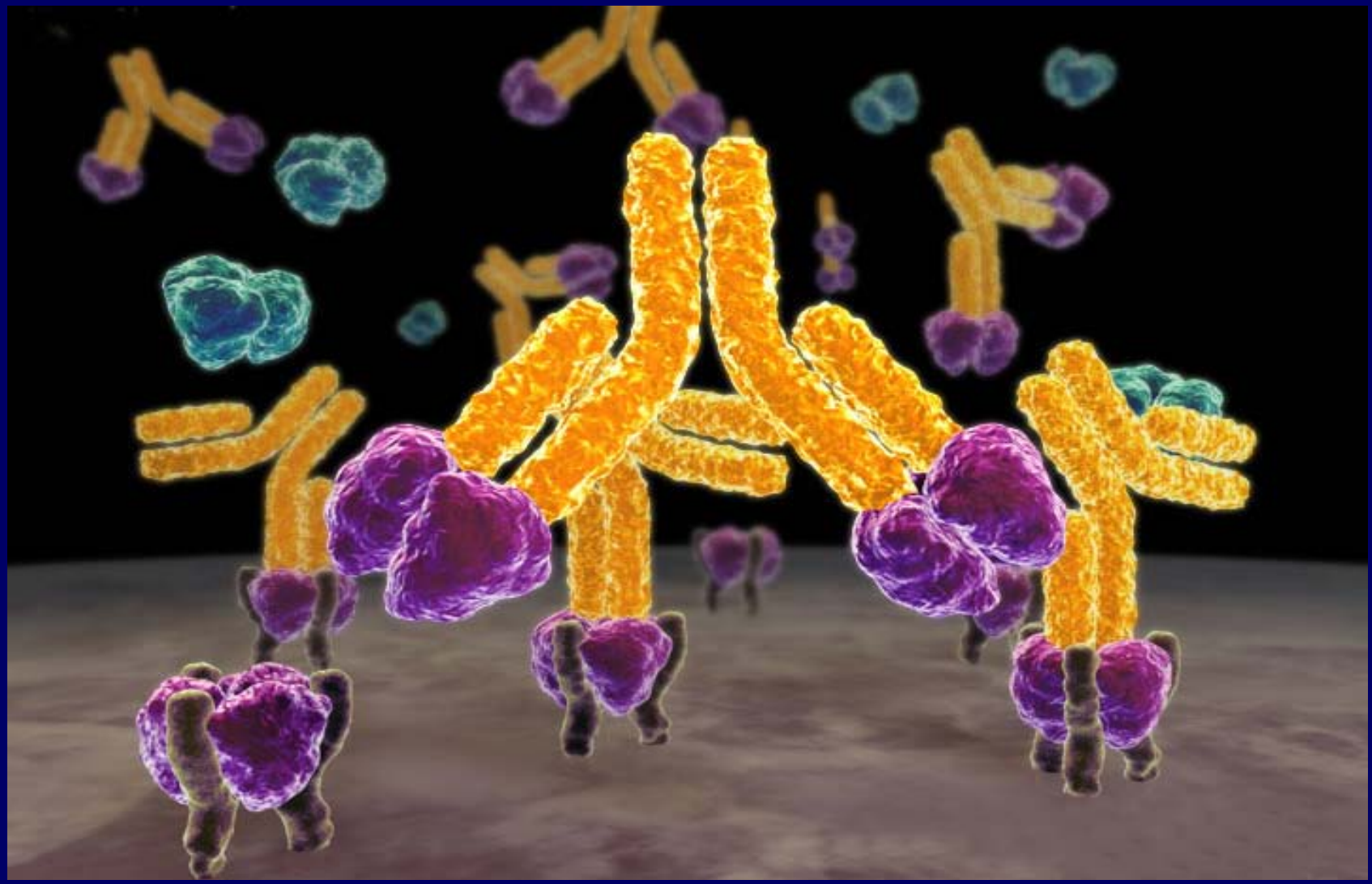
Human Mouse Synthetic element Polyethylene glycol

Soluble Receptors Bind, Neutralize Soluble not Membrane-bound TNF-α,-β

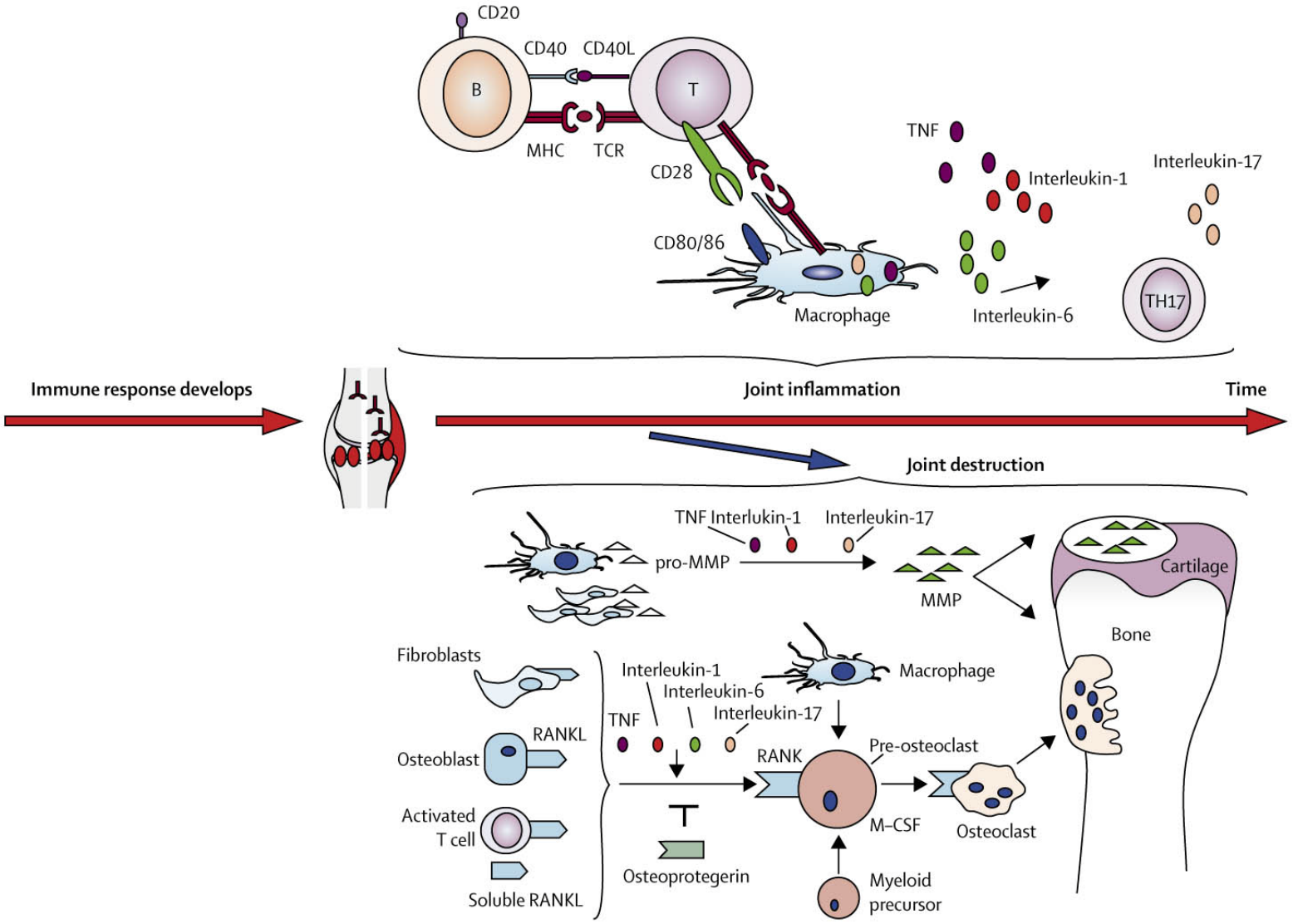


Enbrel prescribing information.

Monoclonal Antibodies Bind and Neutralize Soluble and Membrane-Bound TNF-α

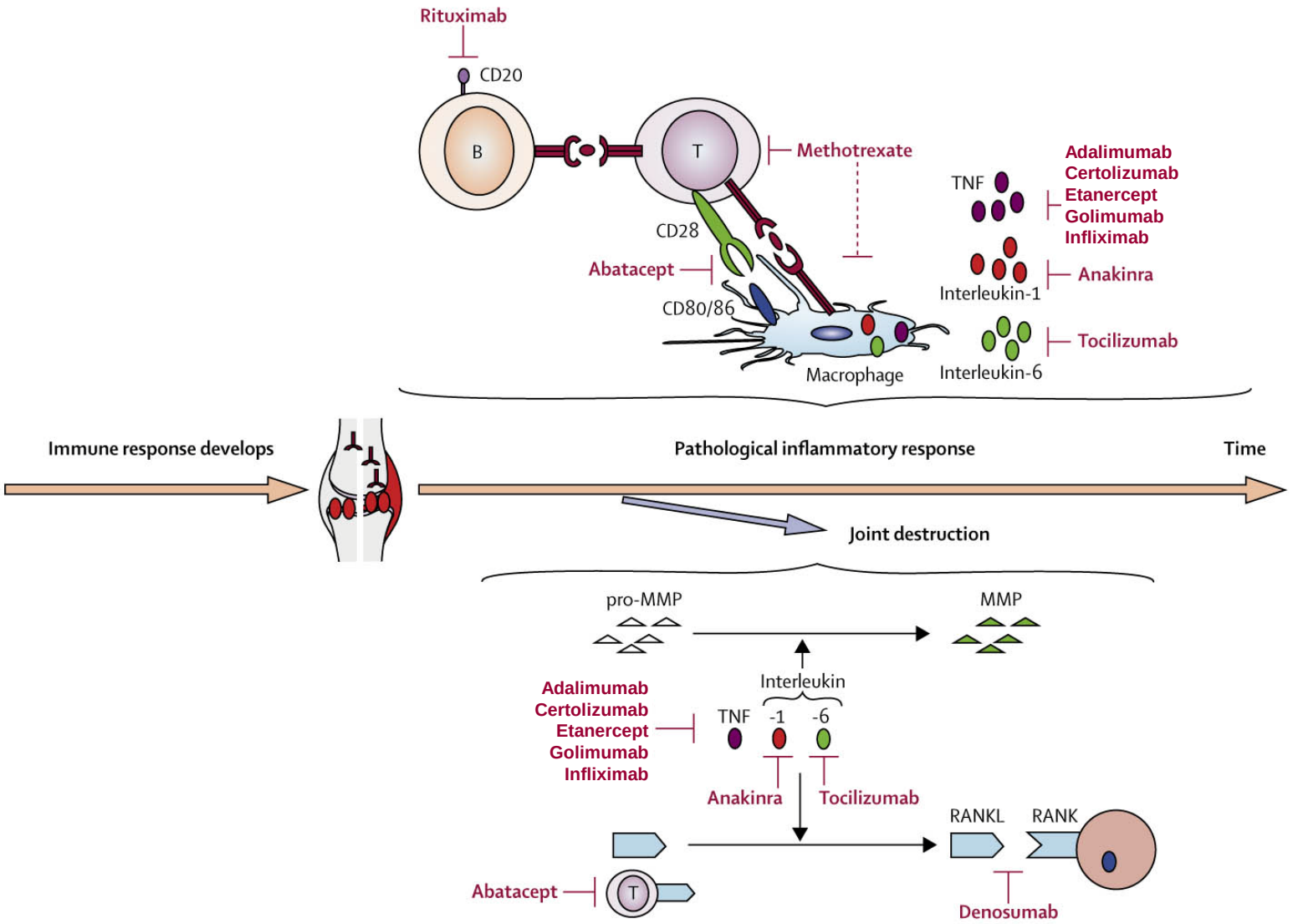


Joint Inflammation and Destruction in RA



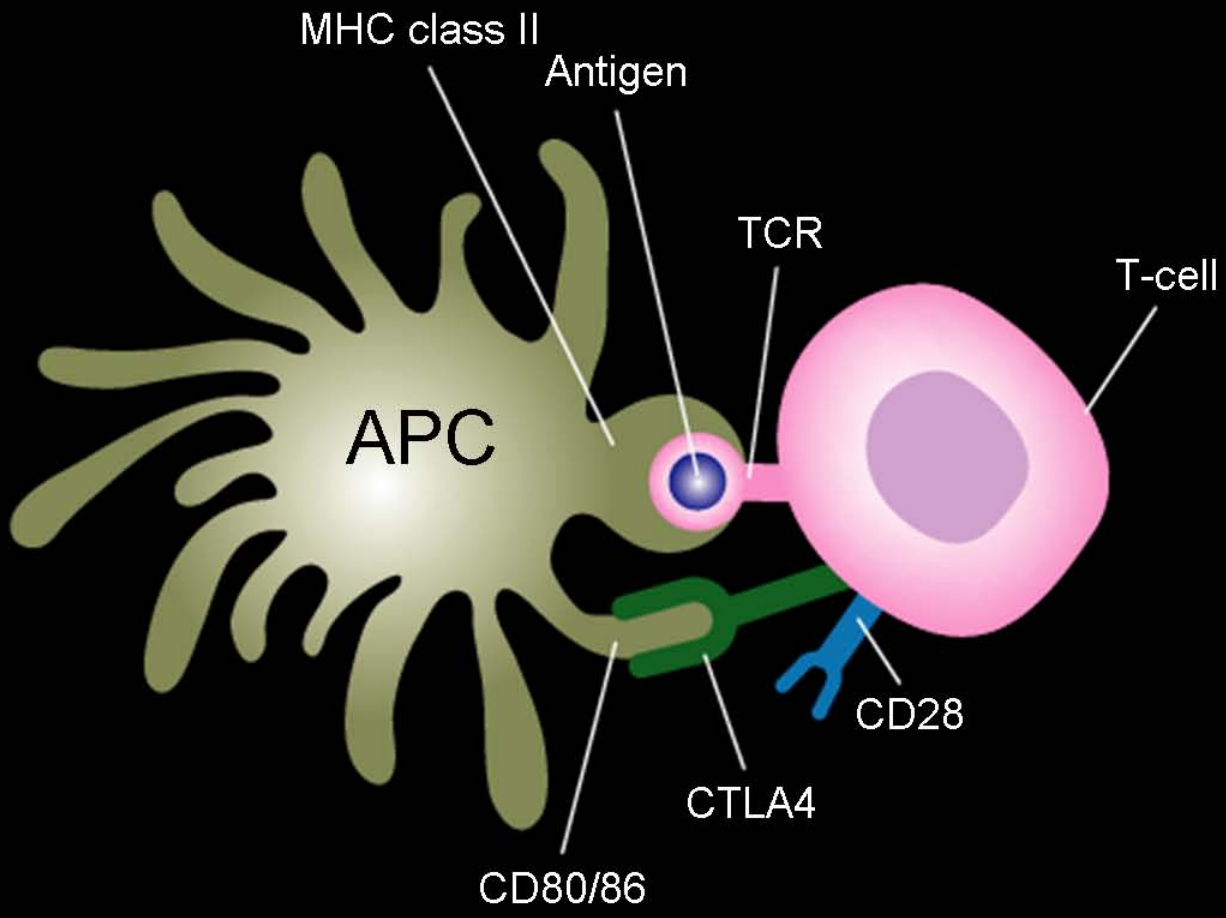
Reproduced with permission from Klareskog L, Catrina AI, Paget S. *Lancet.* 2009;373(9664):659-672.

MOA of Biologic DMARDs in RA



Adapted with permission from Klareskog L, Catrina AI, Paget S. *Lancet.* 2009;373(9664):659-672.

Binding of CTLA4 to CD80/86 prevents binding of CD28 to CD80/86

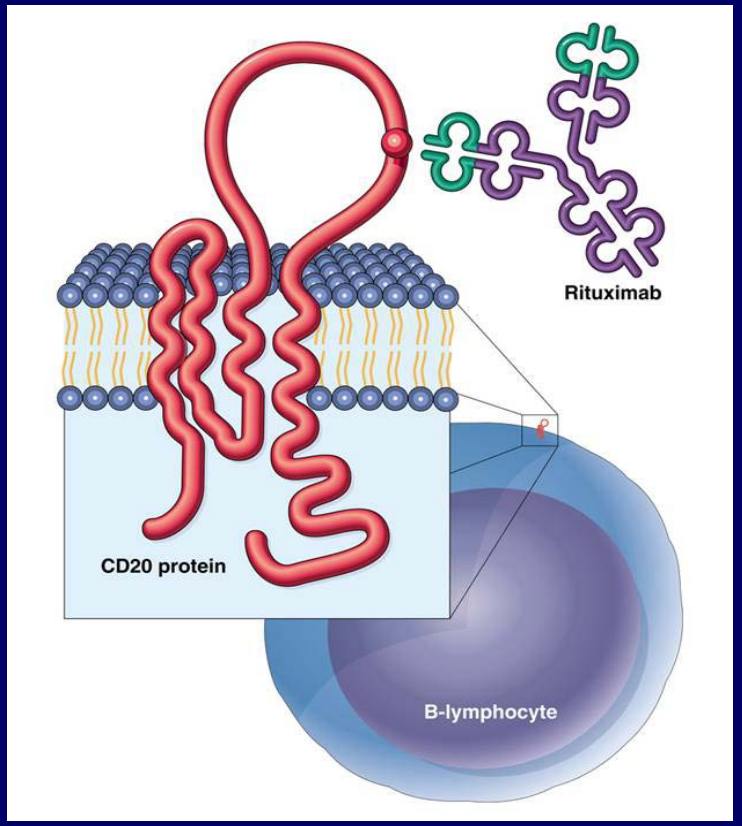


APC = Antigen-presenting cell

adapted from Emery et al, Med Gen Med 2004; 6: 4s (www.medscape.com)

Rituximab in RA: Anti-CD20 mAb

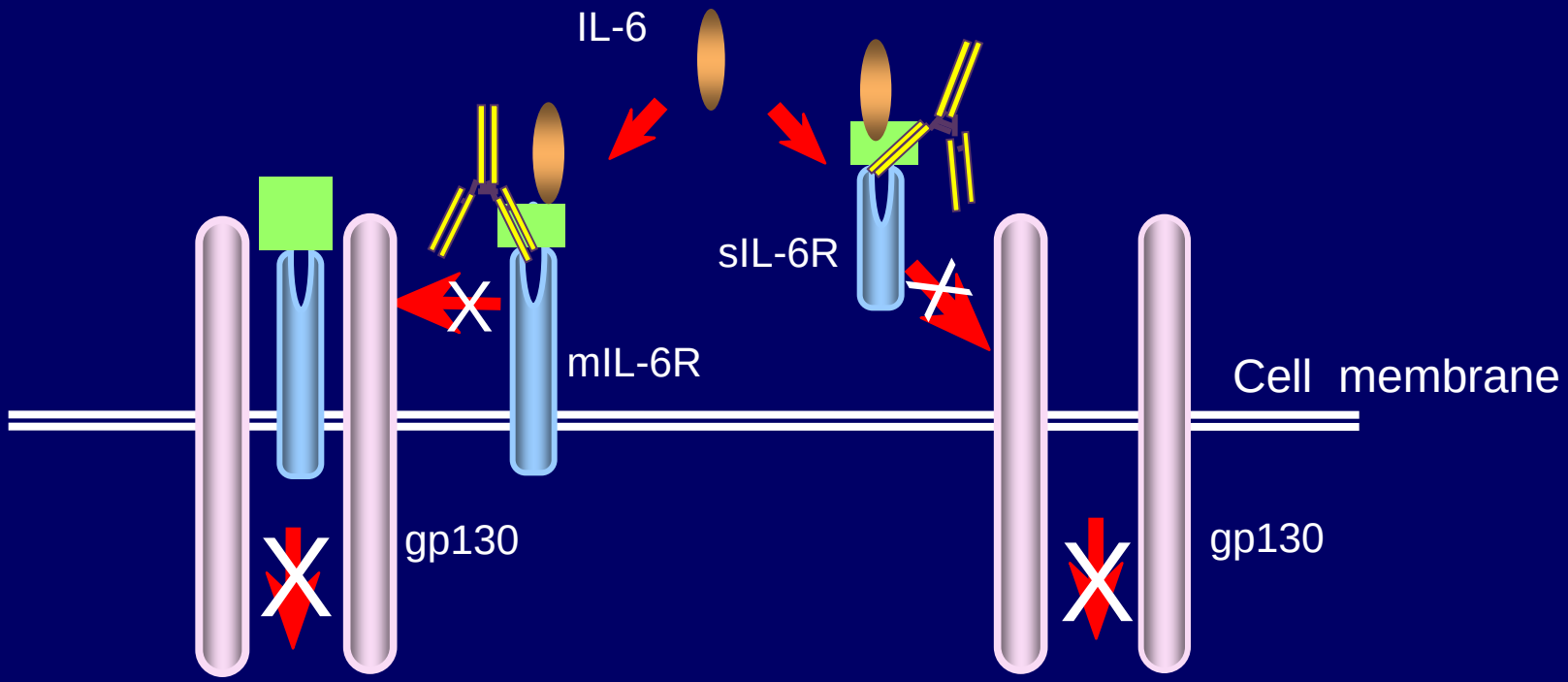
- Genetically engineered chimeric mAb
- Variable light- and heavy-chain regions from murine anti-CD20 Ab
- Human IgGk constant regions
- B-cell lineage antigen; not expressed on stem cells, early pre-B cells, dendritic cells or plasma cells
- Rapid B-cell depletion without inducing hypogamma-globulinemia



Modified from Roche slide kit

Tocilizumab: Humanized Anti–IL-6R Monoclonal Antibody

Tocilizumab binds to both the mIL-6R and the sIL-6R, preventing binding of IL-6 and association with the gp130β chain and thus IL-6–mediated signaling.



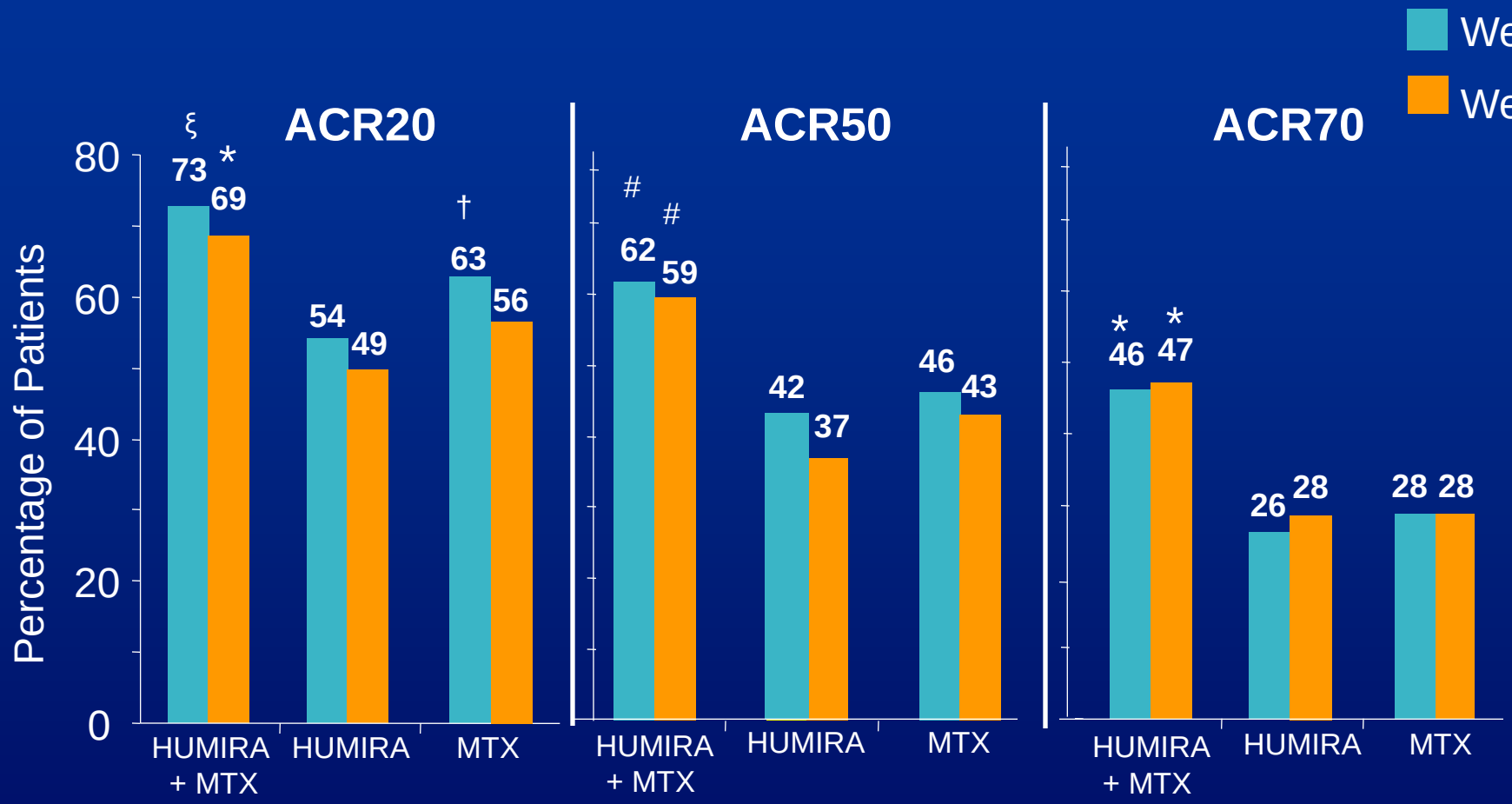
Signal Transduction Inhibited

mIL-6R = membrane-bound IL-6 receptor; sIL-6R = soluble IL-6 receptor.

Mihara M. *Int Immunopharmacol*. 2005;5(12):1731-1740; Maini RN et

ACR Responses at Years 1 and 2

Prespecified Comparison HUMIRA + MTX vs MTX Alone



Patients who withdrew or had missing values were considered nonresponders

ξ *P* <0.001 for HUMIRA + MTX vs HUMIRA alone and *P* =0.022 vs MTX alone

* *P* <0.001 vs HUMIRA alone and *P* =0.002 vs MTX alone

† *P* =0.043 vs HUMIRA alone; # *P*<0.001 vs HUMIRA alone and vs MTX alone

Adapted from Breedveld FC, et al. *Arthritis Rheum*. 2006;54(1):26-37

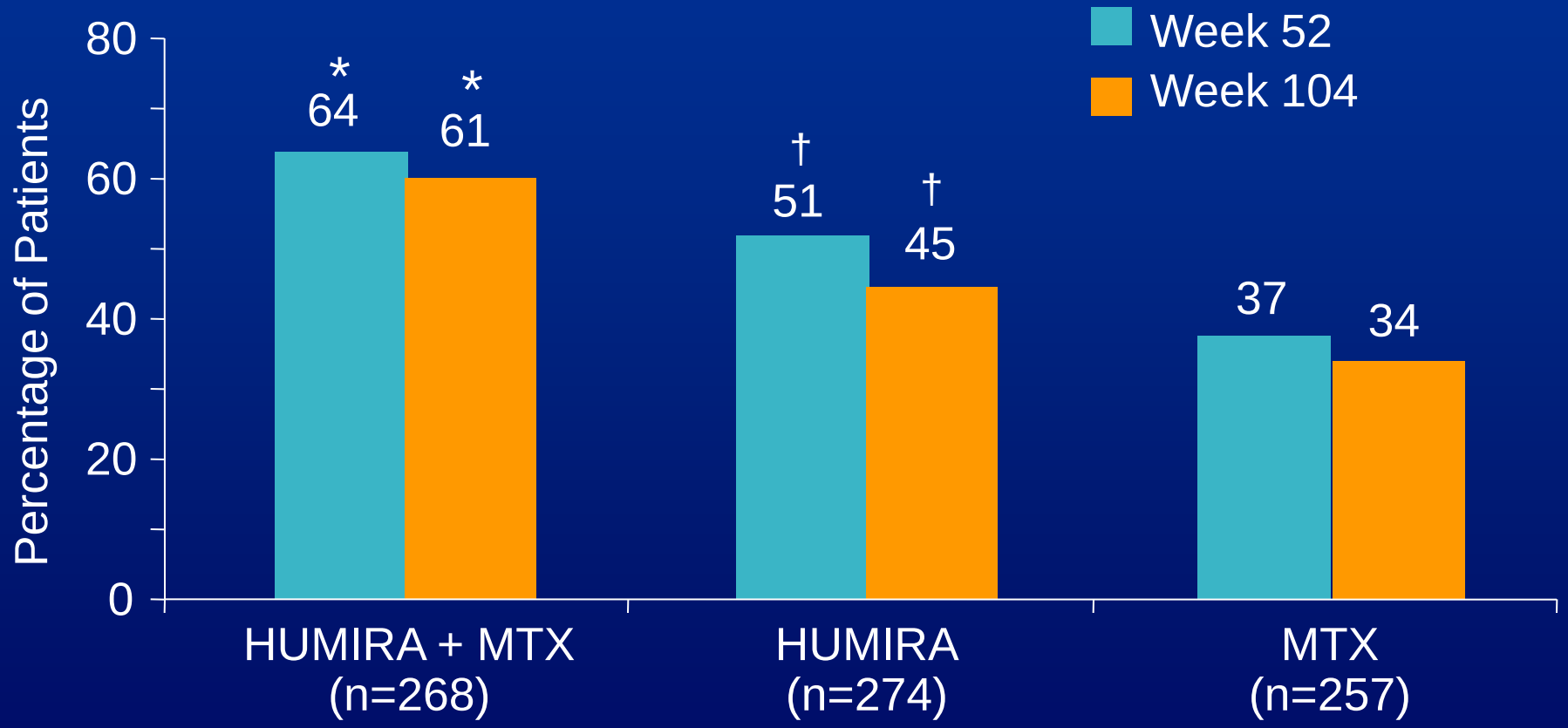
Please see full prescribing information.

No Radiographic Progression

Patients with Δ TSS ≤0.5 at Weeks 52 and 104

Prespecified Comparison HUMIRA + MTX vs MTX Alone

- Approximately twice as many patients experienced no radiographic progression on HUMIRA + MTX vs MTX monotherapy at 2 years



*P<0.01 for HUMIRA + MTX vs HUMIRA alone and MTX alone. †P<0.01 for HUMIRA alone vs MTX alone

Adapted from Breedveld FC, et al. *Arthritis Rheum*. 2006;54(1):26-37

Please see full prescribing information.

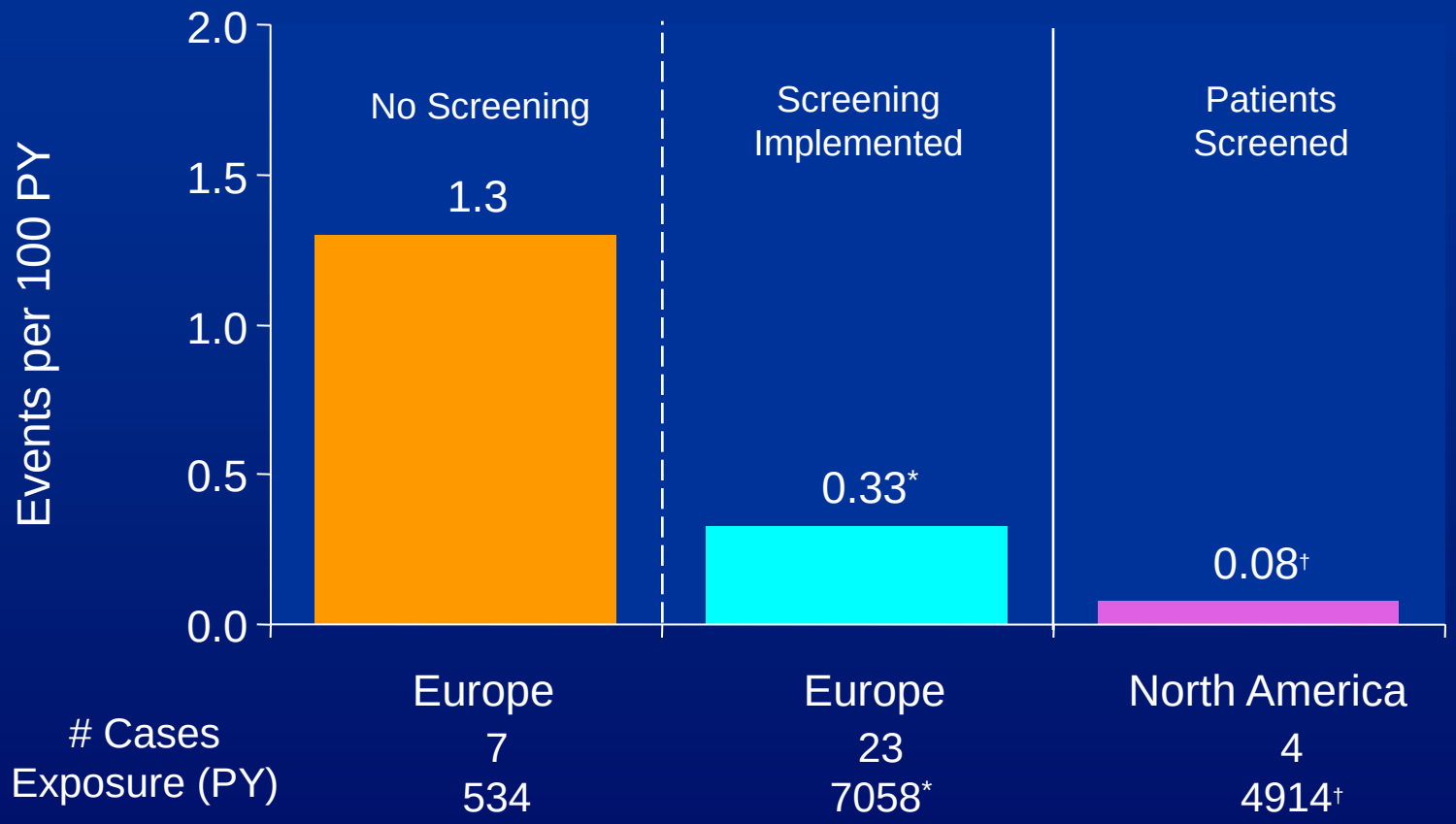
Rates of Selected Serious Adverse Events (SAEs) in HUMIRA Long-Standing Moderate to Severe RA Clinical Trials

Serious Adverse Events (SAEs)	Long-Standing RA Trials as of August 31, 2002 N=2468 4870 PY (E/100 PY)	Long-Standing RA Trials as of April 15, 2005 N=10,050 12,506 PY (E/100 PY)
Serious infections	4.90	5.10
Tuberculosis (TB)	0.27	0.27
Histoplasmosis	0.06	0.03
Demyelinating diseases	0.08	0.08
Lymphoma	0.21	0.12
SLE/Lupus-like syndrome	0.08	0.10
Congestive heart failure	0.29	0.28

Data from long-standing trials with HUMIRA, including open-label extensions and ACT and ReACT early access programs.
Values are presented as events per 100 PY.
Schiff MH, et al. *Ann Rheum Dis*. 2006;65:889-894

Please see full prescribing information.

Screening and TB Rates in HUMIRA RA Clinical Trials



Data from long-standing RA trials with HUMIRA, including open-label extensions and ACT and ReAct early access programs.

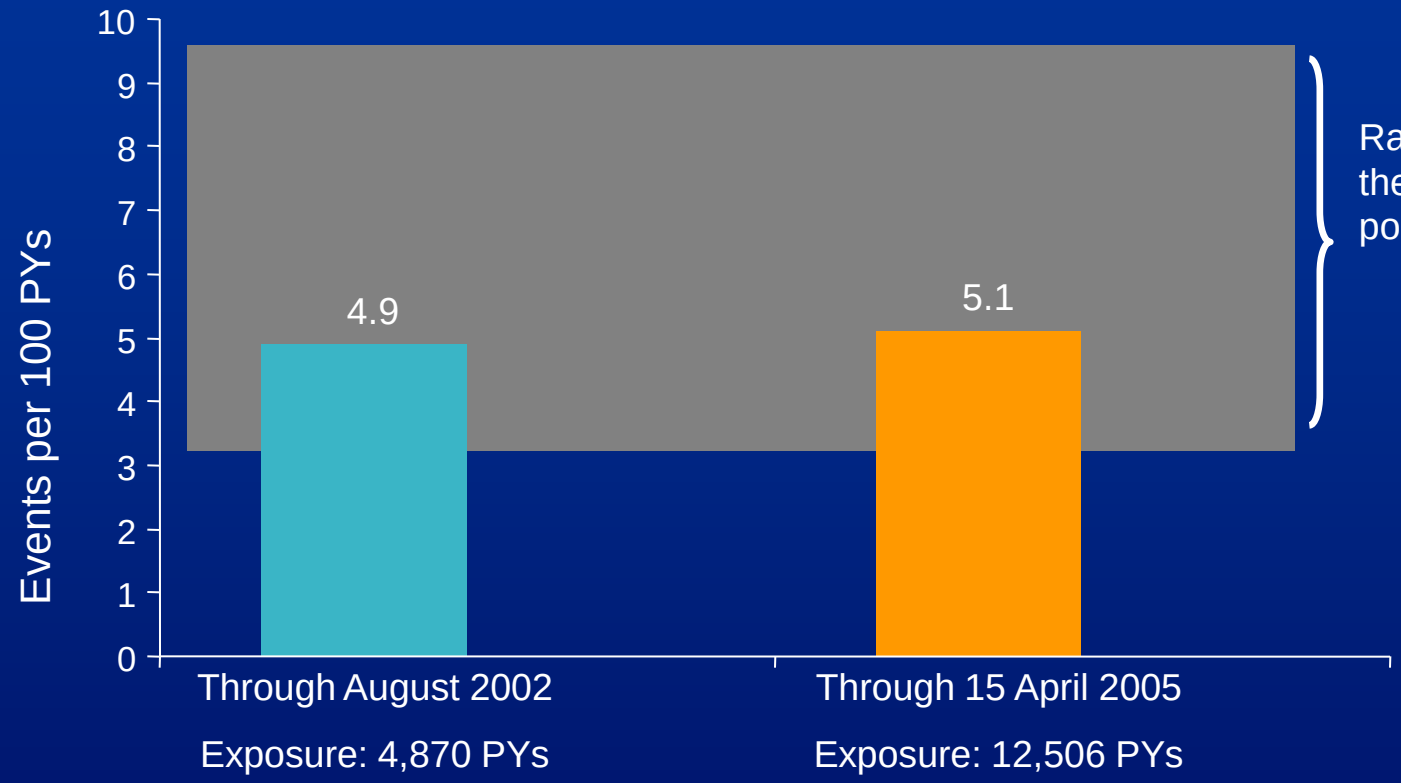
*DE018 + ReAct †DE019 + DE020 + ACT

Patients receiving HUMIRA should be monitored for signs and symptoms of active tuberculosis (TB), including patients who are TB skin test negative. Active TB has developed in patients receiving HUMIRA whose screening for latent TB infection was negative.

Schiff MH, et al. *Ann Rheum Dis*. 2006;65:889-894

Please see full prescribing information.

Serious Infection Rates in adalimumab RA Clinical Trials*



- The total infection rate (serious and nonserious) in placebo-controlled RA trials was 1 per patient year with HUMIRA vs 0.9 per patient year with placebo
- RA population serious infection rates range from 3.1 to 9.6 per 100 PY

Data from HUMIRA pivotal trials and open-label extension studies.

Range of serious infections in RA population based on rates reported in literature for RA population. One study investigating the relationship between serious infections and immunosuppressive use in RA patients reported an overall rate of 3.1 events per 100 patient years. Another population-based study reported a rate of infections requiring hospitalization of 9.57 events per 100 patient years.

*The incidence of serious infections was 0.04 per patient year in HUMIRA-treated patients and 0.02 per patient year in placebo-treated patients.

Schiff MH, et al. *Ann Rheum Dis*. 2006;65:889-894
Singh G, et al. *Arthritis Rheum.* 1999;42:S242
Doran MF, et al. *Arthritis Rheum.* 2002;46:2287-2293
HUMIRA full prescribing information

Please see full prescribing information.

- Thank you