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# Immunosuppressive Therapies for Rheumatic Diseases (and extra-articular manifestations of RA)

## M2 Musculoskeletal Sequence

Fall 2008

David A. Fox, M.D.



## **Reading Assignment**

Primer on the Rheumatic Diseases, 13<sup>th</sup> Edition

Chapter 6C, pp. 133-141

## **Learning Objectives**

1. Identify manifestations of rheumatoid arthritis that occur in organs and tissues other than the joints.
2. Understand the main classes of medications used to treat arthritis and rheumatic diseases.
3. Learn the most common toxicities of these agents.
4. Understand the principles that underlie use of various classes of medications in the treatment of rheumatoid arthritis.

**Note:** A patient with RA will provide input during the lecture about the benefits and drawbacks of specific treatments of RA.

NB is a 71-year old woman who was diagnosed with rheumatoid arthritis in 1977, involving the hands, wrists, elbows, shoulders, feet and eventually cervical spine. Family history is notable for autoimmune disease affecting both of the patient's daughters, one with rheumatoid arthritis and the other with systemic lupus. During the first ten years of her illness medical treatment included salicylates, non-steroidals, intramuscular gold, oral gold and prednisone. Methotrexate was first administered in 1989 and her initial visit at the University of Michigan was in 1993. Due to the rheumatoid arthritis the patient had to retire from her position as a high school English teacher.

When first seen at the University of Michigan in 1993 rheumatoid nodules, active polyarticular synovitis, and joint deformities were all noted on physical examination and on radiography. Methotrexate was continued but subsequent difficulties with stomatitis limited the dose that could be administered. She was also treated with a non-steroidal, low-dose prednisone, hydroxychloroquine, folic acid, a bisphosphonate, and hormone replacement therapy. Methotrexate was eventually discontinued due to persistent toxicity and TNF-blocking treatment with etanercept was begun in 1999.

Deep venous thrombosis occurred in the leg and hormone replacement therapy was ultimately discontinued. The patient has developed a new career as a rheumatoid arthritis patient educator, which involves instructing medical students and practicing physicians in the evaluation of rheumatoid arthritis, both in small group sessions and in lectures. Bilateral foot deformities have been surgically corrected. Etanercept efficacy diminished in 2006 and it was replaced by adalimumab.

# Epidemiology

- Prevalence approximately 1%
- Peak incidence between 35 and 60 years of age
- Incidence 2-4x greater in women than in men
- 50-60% disability after 10 years of RA
- 50% reduction in lifetime earning power after onset
- Increased mortality (about 1.4 x)



# RA: Impact on Quality of Life

- RA has a negative impact on quality of life
  - Pain associated with functional disability
  - 81% of patients suffer fatigue, 42% with severe fatigue
  - Up to 40% of patients suffer depression that impacts personal and family life
- Loss of productivity in patients with RA is well known
  - Average of 30 lost days of work per year
  - Average earnings loss is 50%

# Extra-Articular Disease In RA

Patients with RA usually show clinical disease primarily in the joints. However, these patients are also systemically ill. A variety of problems can develop outside the joints (“extra-articular”), that can be serious and sometimes fatal.

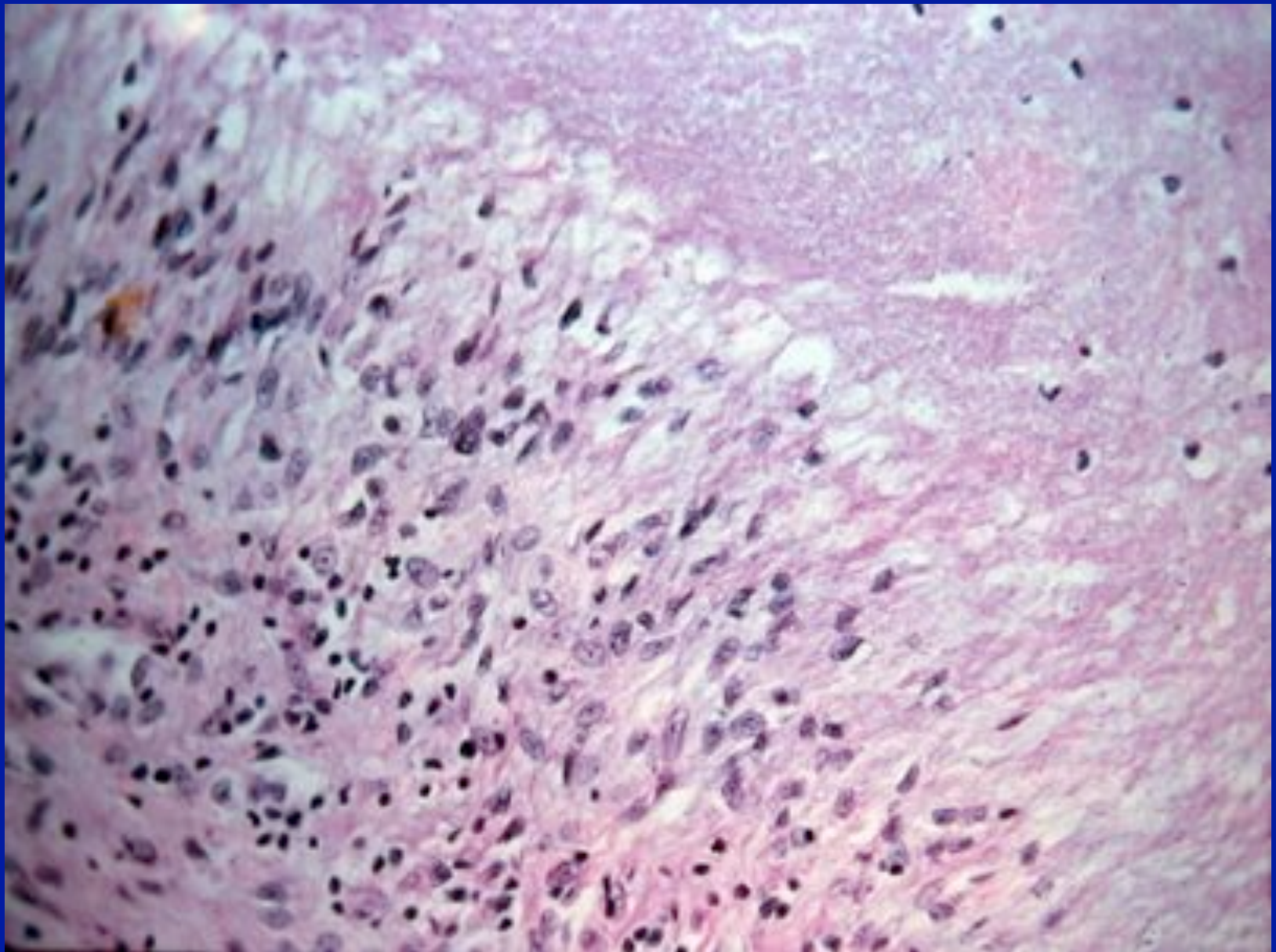
# Hematologic

- Anemia
- Thrombocytosis
- Felty's Syndrome
  - leukopenia
  - splenomegaly
  - +/- infections, leg ulcers

# Nodules

- Subcutaneous
- 20-30% of RA patients
- More common with + RF
- Histology: palisading granuloma





# Sjogren's Syndrome

- Dry eyes, dry mouth
- Lymphocytic infiltrate in salivary, lacrimal glands
- +/- systemic disease
- Sometimes progresses to lymphoma

# Secondary Amyloidosis (rare)

- Usually presents as proteinuria

# Rheumatoid Vasculitis

- Can be indolent or life threatening
- Severe form resembles microscopic polyarteritis





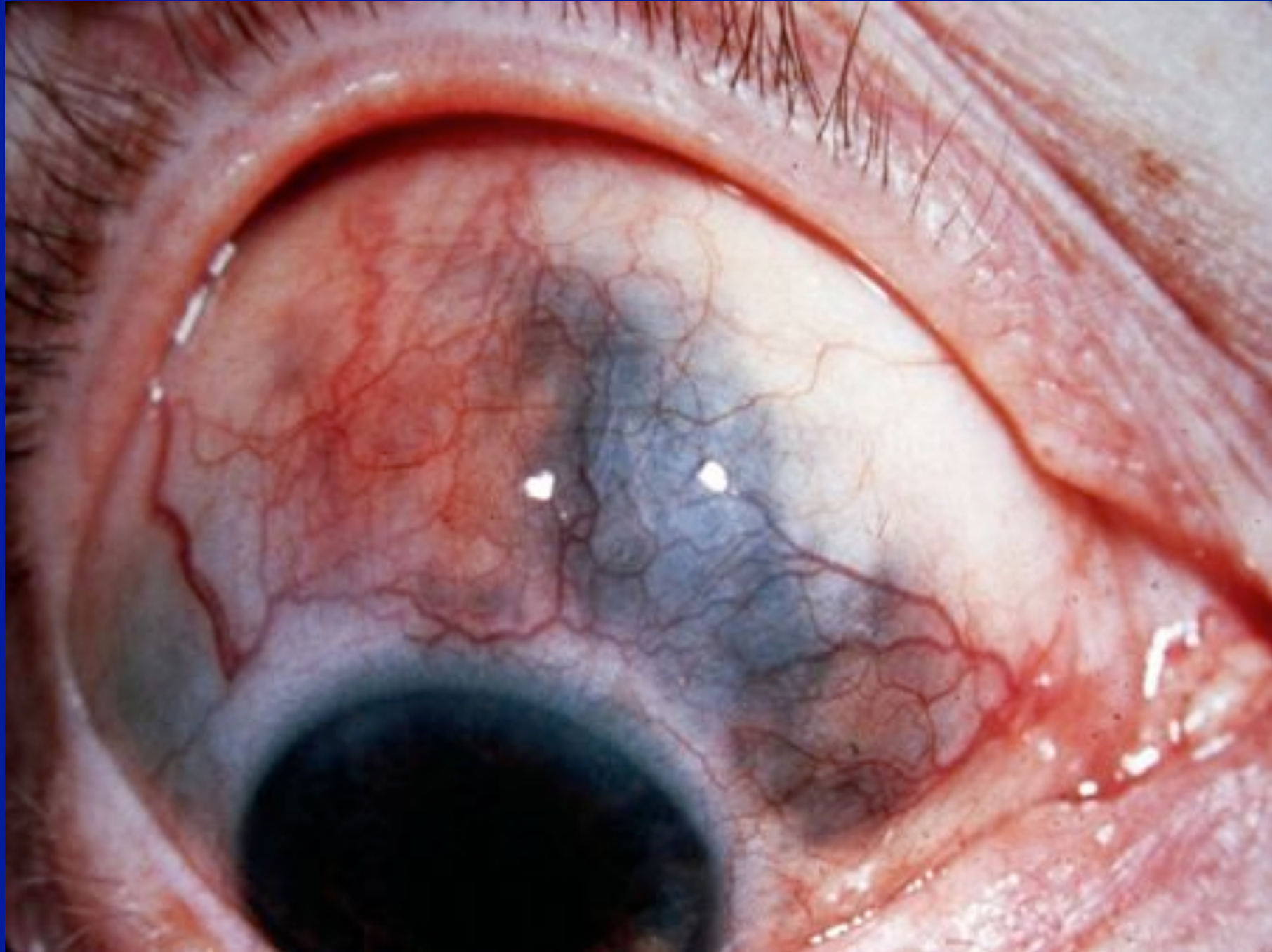


# Ocular

- Keratoconjunctivitis sicca
- Episcleritis
- Scleritis (dangerous)







# Peripheral Nervous System

- Peripheral neuropathy
- Nerve entrapments
- Mononeuritis multiplex  
(due to arteritis)

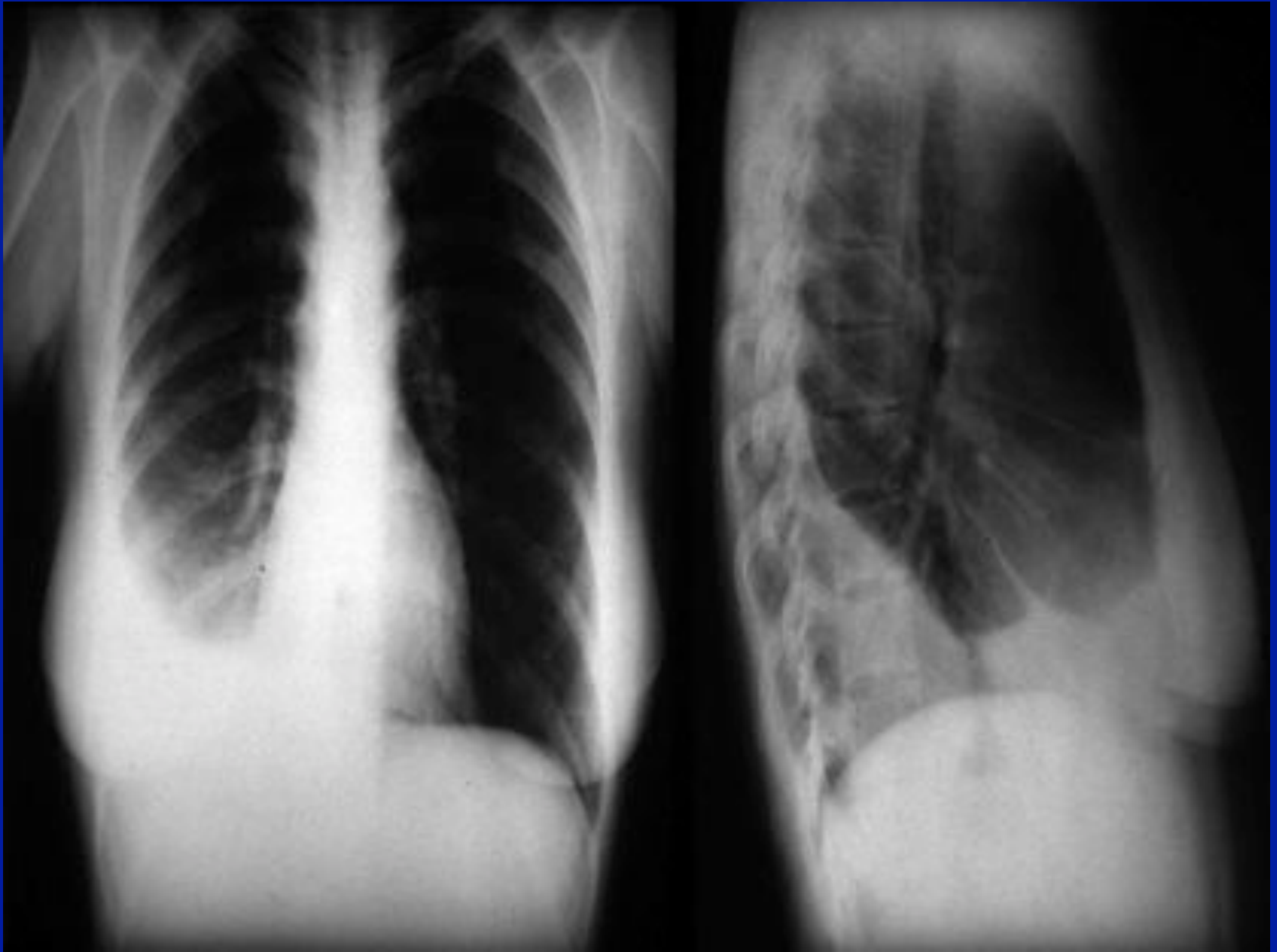
# Pulmonary

- Interstitial infiltrates
- BOOP (bronchiolitis obliterans – organizing pneumonia)
- Caplan's Syndrome (widespread small lung nodules due to coal dust + RA)

# Serositis

- Pleural effusions: **low glucose**, variable WBC, low complement, high protein
- Pericardial effusions: usually occult, occasionally → tamponade or constriction





# Medications Used to Treat RA

- NSAIDs
- Corticosteroids
- DMARDs
  - Conventional
  - biologic

# Key Abbreviations

NSAID = Non-steroidal anti-inflammatory drug

DMARD = Disease-modifying anti-rheumatic drug

# Key Concepts

1. Most rheumatic and arthritic diseases are difficult to cure, but increased potency of newer medications makes remission achievable.
2. NSAIDs, steroids, DMARDs and other anti-rheumatic medications all have the potential for severe toxicity.
3. Rheumatoid arthritis generally requires simultaneous long-term treatment with two or more medications, including anti-inflammatory and disease modifying agents.
4. Toxicities are common and patients must be closely monitored.

# NSAIDs – Mechanisms of Action

- Classic hypothesis of Vane: inhibition of prostaglandin synthesis by inhibition of cyclooxygenase.
- Alternative hypothesis of Weissman: inhibition of neutrophil aggregation/activation.
- Inhibition of activation of NF- $\kappa$ -B (a transcription factor for genes involved in inflammation).
- A second form of cyclooxygenase (COX-2) is the main COX isoform in areas of inflammation. COX-1 inhibition is responsible for most NSAID toxicity. COX-2 inhibition has anti-inflammatory effects. In 1999, more selective COX-2 inhibitors were introduced. In 2004 one of these (rofecoxib) was withdrawn due to excess MI and stroke.

# NSAIDS – Indications for Use

- Short term – for analgesic, anti-inflammatory and anti-pyretic effects in a wide variety of arthritic, soft-tissue (bursitis, tendonitis) and non-musculoskeletal conditions.
- Long term – as treatment for chronic inflammatory arthritis, (e.g., rheumatoid arthritis).
- Use of multiple concurrent NSAIDs in high doses should be avoided.

# NSAIDs – Toxicity

- Gastrointestinal: abdominal pain, ulceration, GI bleeding, diarrhea, constipation, - GI toxicity due to NSAIDs is common, can be severe, and is a leading cause of drug-induced fatalities.
- Anticoagulant: platelet dysfunction, altered warfarin kinetics.
- Hepatitis
- Renal dysfunction:
  - Transient azotemia due to decreased renal blood flow
  - Interstitial nephritis/nephrotic syndrome
  - Hyperkalemia
  - Edema
- CNS: tinnitus (especially salicylates), confusion
- Hypersensitivity reactions, including worsening of asthma.
- Vascular disease e.g. MI, especially with Cox-2 inhibitors

# NSAIDs – Cost

- Cost is a significant factor in compliance and in choice of an NSAID.
- Full-dose brand name NSAIDs typically cost >50 dollars/month in the United States. Generic salicylates can cost <\$10/month.



# STEROID USE IN RA

The optimal approach to use of corticosteroids in RA remains controversial. Whether steroids have true “disease-modifying” properties regarding joint destruction is also disputed. Options include:

1. Intra-articular injection in selected joints during flares.
2. Low-dose long-term use of Prednisone if needed at 5-7.5 mg/day (rarely 10 mg/day) in conjunction with DMARDs.
3. Higher doses for vasculitis and other severe extra-articular manifestations.

**WARNING:** Abrupt discontinuation of steroids is dangerous due to the potential for acute adrenal insufficiency. Steroid toxicities are multiple, and some can be reduced by attention to maintaining bone density and controlling blood lipid levels.

# DMARDs

DMARDs can be grouped into:

1) the “conventional DMARDs” (**gold salts, anti-malarials, tetracyclines, sulfasalazine and D-penicillamine**),

2) the cytotoxic or immunosuppressive agents that are used to treat arthritis and rheumatic diseases (**methotrexate, azathioprine, leflunomide, cyclosporin, and alkylating agents**); and

3) **cytokine inhibitors and other biologic agents.**

Many of these medications are used not only in rheumatoid arthritis, but also in other forms of severe chronic arthritis and systemic rheumatic disease. All the DMARDs have potential for serious toxicity and require regular patient monitoring. Anti-malarials and tetracyclines are least toxic and alkylating agents the most toxic.

# Conventional DMARDs:

## Hydroxychloroquine (often used in RA and SLE)

- Originally developed as an anti-malarial
- Pharmacologic action: lysosomotropic, affects APC's
- Dose: 200-400 mg/day
- Toxicity: Ocular toxicity (< 2%), rash (7%), GI (5%), rare, hemolytic anemia and neuromyopathy. Most benign of remittive agents.

# Sulfasalazine

**(often used in RA and inflammatory bowel disease)**

- Dose: initially 500 mg bid, gradually increased to 1.0-1.5 gm bid.
- Toxicity: indigestion, headache, rash, hepatitis (1%), neutropenia (rare)
- Pharmacologic action: sulfasalazine contains covalently linked sulfapyridine and 5-aminosalicylic acid, and the individual components are liberated by bacterial enzymes in the colon.
- Mechanism of action: unknown (only the sulfapyridine is absorbed).

# Azathioprine (Imuran)

- Pharmacologic action: purine analogue
- Dose: 1-2.5 mg/kg/day P.O.
- Efficacy: Used in SLE, RA, Vasculitis
- Mechanism of action: Immunosuppressive effects are multiple (B cell, T cell and natural killer cell function), but the effects of significance in RA are not known.
- Toxicity:
  - Bone marrow suppression
  - Hepatotoxicity
  - Oncogenicity (rare)
  - Nausea and vomiting
  - Infections (which may not be related to neutropenia)
  - Important drug interaction: metabolism of azathioprine is blocked by allopurinol

# Methotrexate

- Pharmacologic action: folic acid antagonist
- Dose: 5 – 20 mg/wk po, im or iv
- Efficacy: Short-term improvement in multiple indices of disease activity in several controlled studies; sustained benefit in some patients; rapid flare after withdrawal
- Mechanisms of action in RA: controversial; not substantially immunosuppressive in low doses, but should be withheld if serious infection occurs

# Methotrexate

- Toxicity:**
- Nausea and vomiting
  - Oral ulcers/stomatitis
  - Bone-marrow suppression,  
especially in patients with  
renal impairment
  - Pulmonary toxicity
  - Hepatotoxicity
  - Teratogenesis
  - Infection



# Leflunomide (Arava)

- Pharmacologic action: pyrimidine synthesis inhibitor
- Dose: 10-20 mg qd
- Efficacy: similar to methotrexate in RA
- Mechanism of action: inhibits lymphocyte activation and function
- Toxicity: GI intolerance
  - alopecia
  - hepatitis
  - infection

**NOTE:** Due to long half-life, toxicity may require washout with several days of cholestyramine, which binds leflunomide in entero-hepatic circulation (primary elimination is in the bile)

# Cyclophosphamide

(used only as a last resort in RA or for associated systemic vasculitis frequently used in severe SLE or vasculitis)

- Pharmacologic action: alkylating agent
- Dose: 1-2 mg/kg/day P.O.
- Efficacy: Substantial efficacy in many autoimmune diseases
- Mechanism of action: Multiple and striking immunosuppressive effects, dependent on dose and duration of therapy; frequently causes lymphopenia and alteration of lymphocyte function.
- Toxicity: (Precludes routine use in RA)
  - Bone marrow suppression
  - Hemorrhagic cystitis
  - Oncogenicity (bladder, hematopoietic)
  - Pulmonary fibrosis
  - Gonadal suppression
  - Nausea and vomiting
  - Alopecia
  - Infection

# Indications and Prerequisites for DMARD Therapy

- Diagnosis of RA with any evidence of ongoing inflammation or joint destruction
- Reliable or adequately supervised patient
- Adequate system for monitoring toxicities
- Absence of major contraindications to specific DMARDS (e.g., pregnancy or significant renal disease prohibit use of methotrexate)
- Patient understanding and acceptance of potential risks

Note: Some RA DMARDs are also used in psoriatic arthritis, ankylosing spondylitis, Reiter's syndrome, etc.

# Management of Rheumatoid Arthritis

## Supportive Measures

Education of patient and family

Rest

Physical therapy and exercise

Occupational therapy

Rehabilitation services

## Surgery

Prophylactic procedures:

Synovectomy

Release of trapped nerve

Local excision of nodules

Fusion of cervical spine

Restorative or reconstructive procedures:

Arthrodesis

Arthroplasty

Joint Replacement

# Parameters of Disease Activity in RA

- No. of hours of morning stiffness
- No. of painful joints
- No. of swollen joints
- Erythrocyte sedimentation rate or C-reactive protein\*
- Quality of life indices / functional assessment
- Pain

\* Other than an elevated erythrocyte sedimentation rate, and/or CRP, active RA is often accompanied by anemia, hypoalbuminemia and thrombocytosis.

# DMARDs and Host Defenses

## Compromised

Cyclophosphamide

Azathioprine

Methotrexate

Mycophenolate

Leflunomide

Cytokine blockers

Other biologics

## Intact

Antimalarials

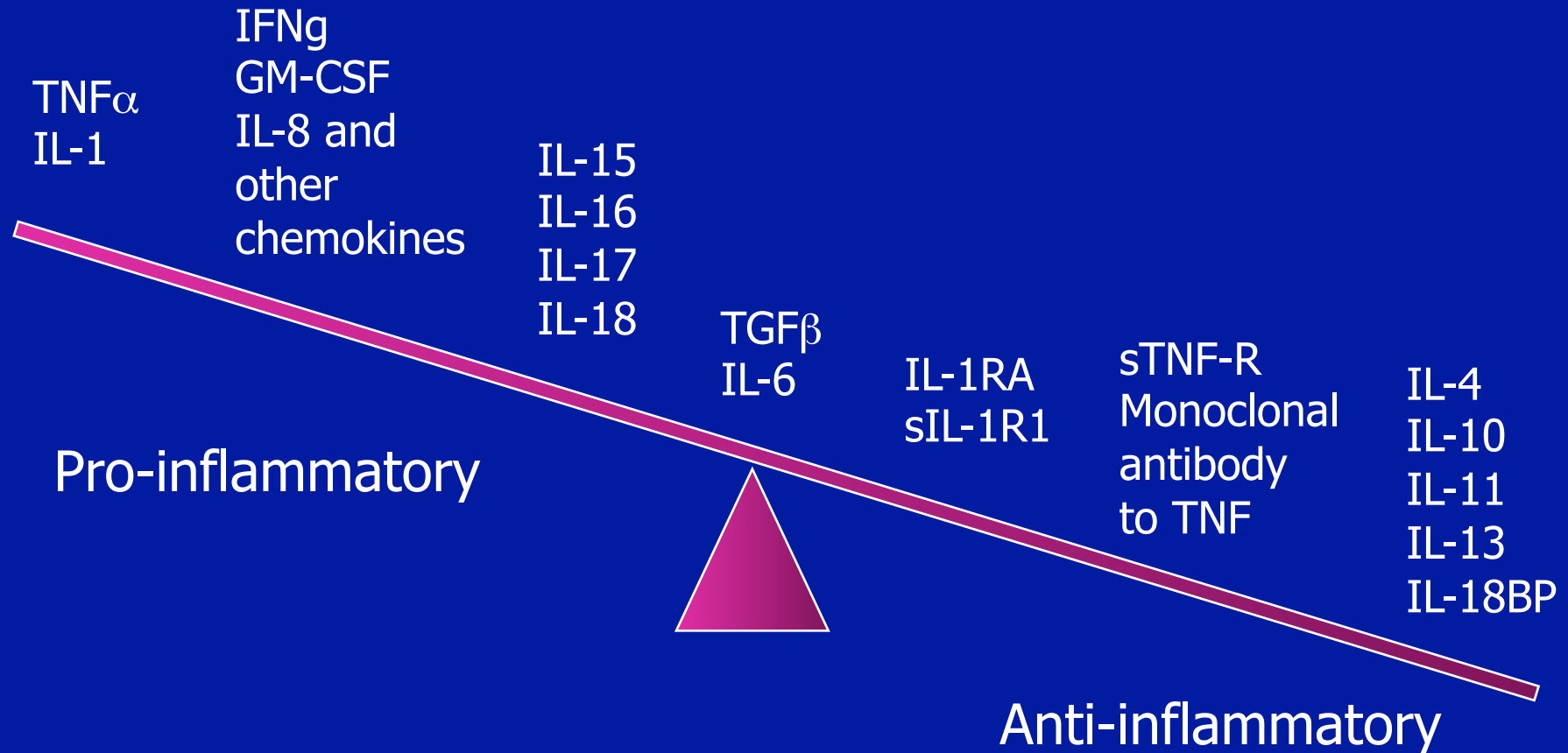
Sulfasalazine

Gold Salts

Pencillamine

Tetracyclines

# Role of Cytokines and Cytokine Inhibitors in Chronic Inflammation and Its Treatment



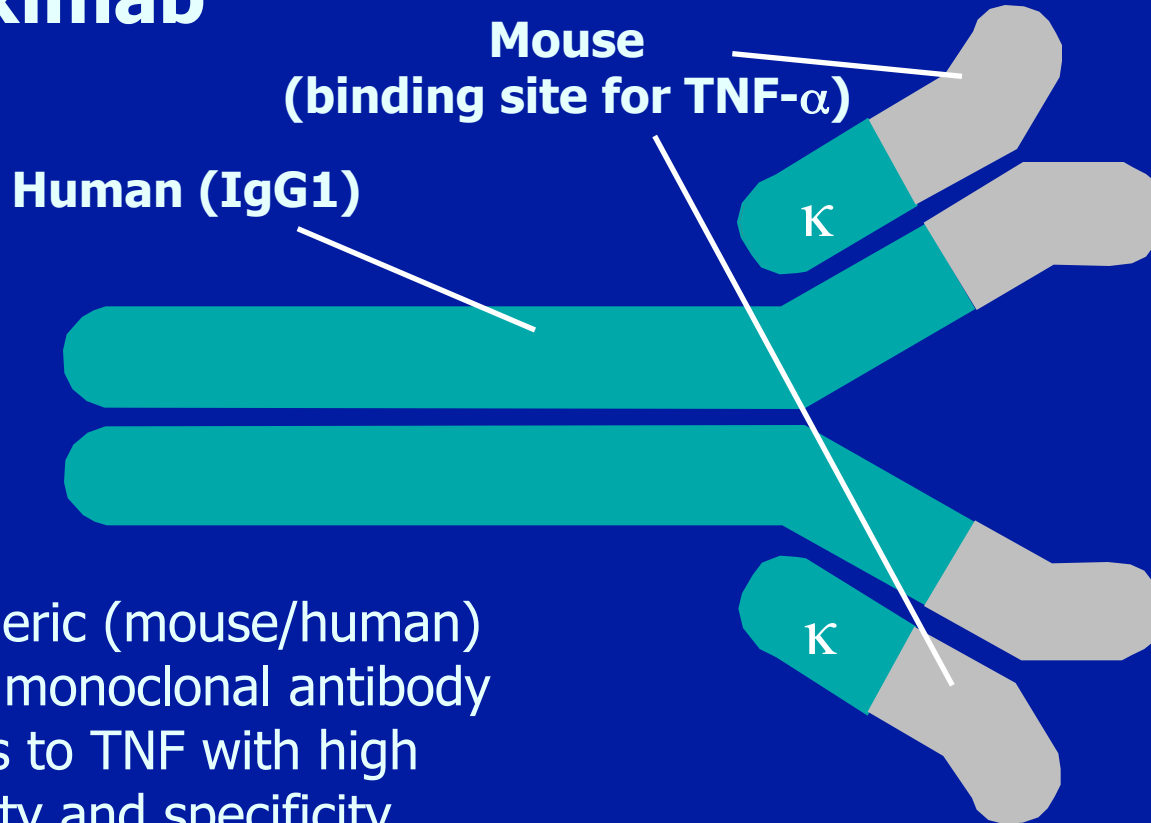
# TNF Inhibitors

- Etanercept (Enbrel) – soluble receptor – Ig dimer
- Infliximab (Remicade) – mouse-human anti-TNF
- Adalimumab (Humira) – human anti-TNF



# Chimeric Anti-TNF Monoclonal Antibody

## Infliximab



- Chimeric (mouse/human) IgG<sub>1</sub> monoclonal antibody
- Binds to TNF with high affinity and specificity

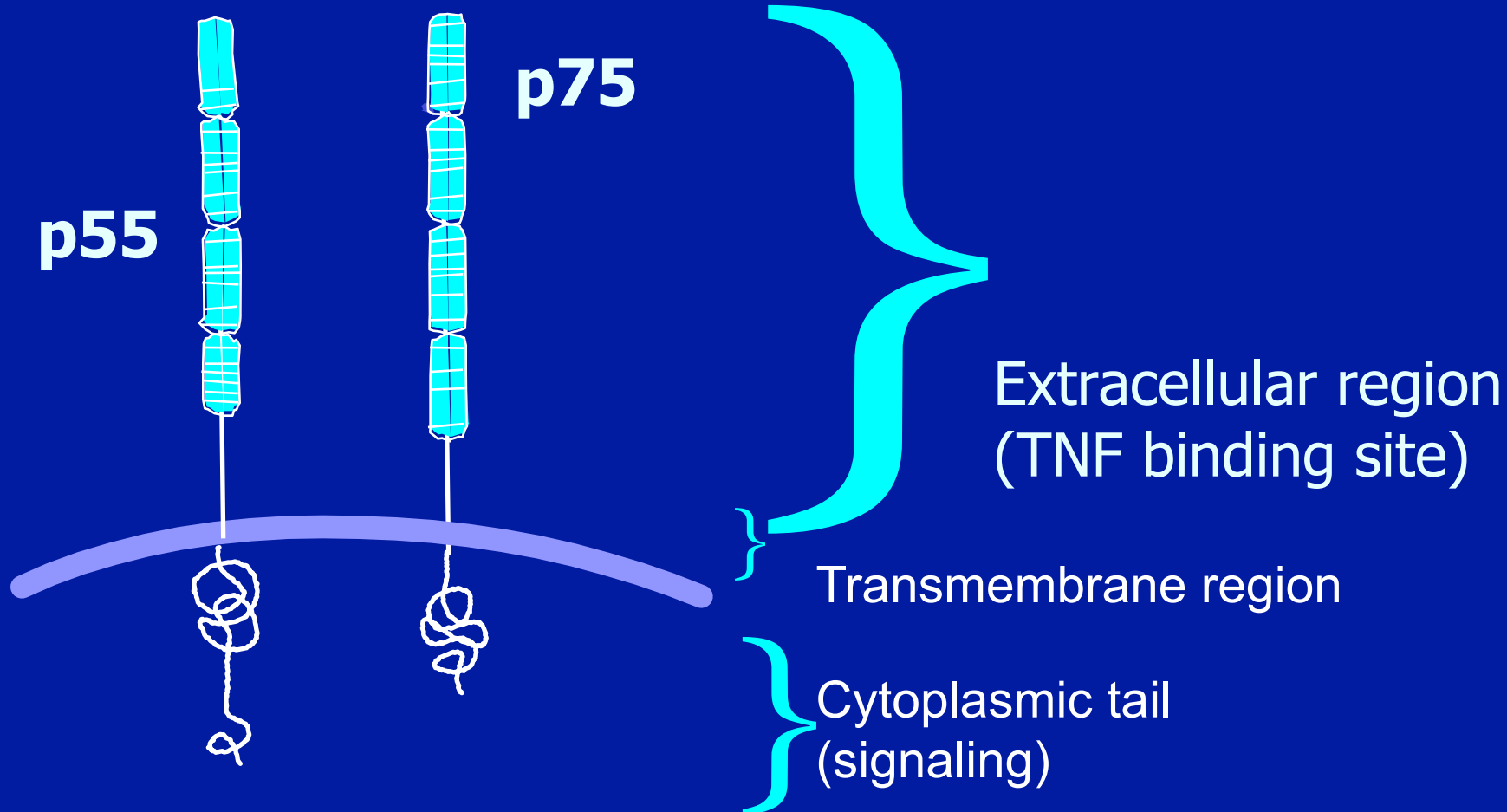
# Mechanisms for Antibody Neutralization of $\text{TNF}\alpha$



# Infliximab

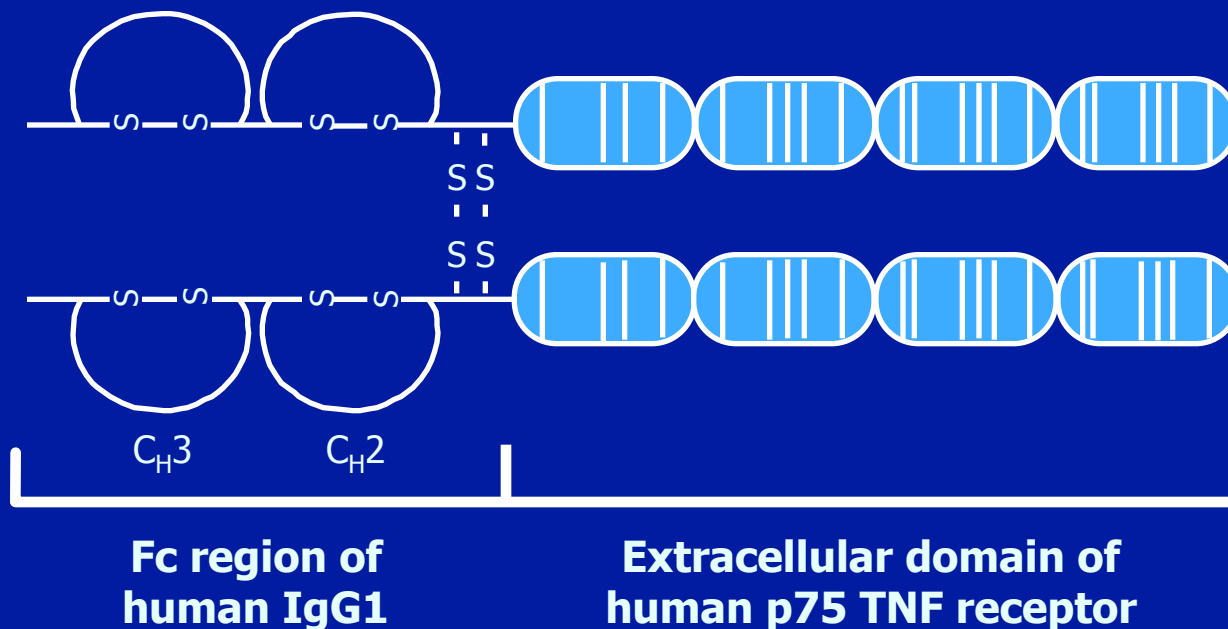
- Binds to soluble and membrane-bound TNF with high affinity
- Cells expressing membrane-bound TNF can be lysed in vitro by infliximab
- Induces neutralizing human antichimeric antibodies; requires use of MTX to maintain efficacy

# Cell-Bound TNF Receptors



# Etanercept

- Recombinant soluble TNF-receptor formed by fusion of 2 human TNF-receptors and Fc portion of human IgG1
- Inhibits TNF, preventing it from binding to cell-surface receptors and initiating proinflammatory effects



# Etanercept

- Dimeric fully human structure that binds to soluble and membrane-bound TNF with high specificity and affinity
- Neutralizes TNF without causing cell lysis in vitro
- Does not promote neutralizing antibodies
- Also binds to  $LT\alpha$ , an inflammatory cytokine

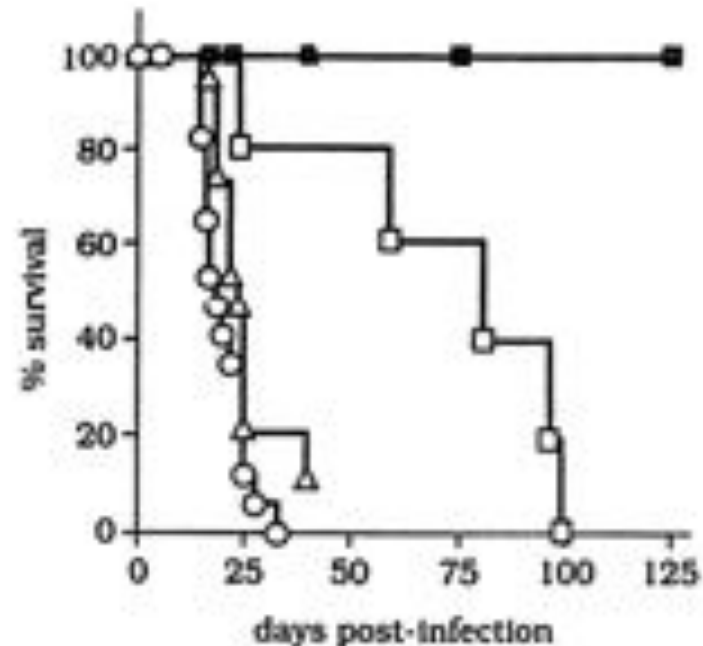
# Potential Immunologic Consequences of Administration of Anti-Cytokines

- Human Anti-Chimeric Antibody (HACA) response (with mouse-human anti-TNF antibody)
- Impairment of host defenses
  - Infection
  - Malignancy
- Shift in cytokine balance that could facilitate expression of new autoimmune phenomenon

# Tumor Necrosis Factor- $\alpha$ Is Required in the Protective Immune Response Against *Mycobacterium tuberculosis* in Mice

JoAnne L. Flynn,<sup>1</sup> Marsha M. Goldstein,<sup>2</sup>  
John Chan,<sup>3</sup> Karla J. Trieblold,<sup>4</sup>  
Klaus Pfeffer<sup>1, 5</sup>, Charles J. Lowenstein,<sup>6</sup>  
Robert Schreiber,<sup>8</sup> Tak W. Mak,<sup>9</sup>  
and Barry R. Bloom<sup>1</sup>

Understanding the immunological mechanisms of protection and pathogenesis in tuberculosis remains problematic. We have examined the extent to which tumor necrosis factor- $\alpha$  (TNF $\alpha$ ) contributes to this disease using murine models in which the action of TNF $\alpha$  is inhibited. TNF $\alpha$  was neutralized in vivo by monoclonal antibody; in addition, a mouse strain with a disruption in the gene for the 55 kDa TNF receptor was used. The data from both models established that TNF $\alpha$  and the 55 kDa TNF receptor are essential for protection against tuberculosis in mice, and for reactive nitrogen production by macrophages early in infection. Granulomas were formed in equal numbers in control and experimental mice, but necrosis was observed only in mice deficient in TNF $\alpha$  or TNF receptor. TNF $\alpha$  and the 55 kDa TNF receptor are necessary conditions for protection against murine *M. tuberculosis* infection, but are not solely responsible for the tissue damage observed.





# Granulomatous Infections and Tumor Necrosis Factor Antagonist Therapies

Atypical Mycobacteria

Aspergillosis

Burcellosis

Coccidiomycosis

Cryptococcosis

Cytomegalovirus

**Histoplasmosis**

Listeriosis

Nocardiosis

Toxoplasmosis

**Tuberculosis**

# TNF Inhibitors

## Relative Contraindications

- SLE
- CTD/Overlap patients
- Multiple sclerosis, optic neuritis
- Current active serious infections
- Chronic/recurrent infections
- Immunosuppressed
- Hx of Tbc or +PPD (untreated)
- History of cancer (?)

# Role of Interleukin-1 in RA

- Pro-inflammatory cytokine
- Triggers production of other proinflammatory cytokines, including TNF
- Causes T cell/neutrophil accumulation in synovium by inducing expression of endothelial adhesion molecules
- Stimulates production of collagenase and stromelysin
- Stimulates osteoclast differentiation through intermediary TNF family cytokine, RANKL

# The IL-1 Family

## Agonists

IL-1 $\alpha$

IL-1 $\beta$



## Antagonist

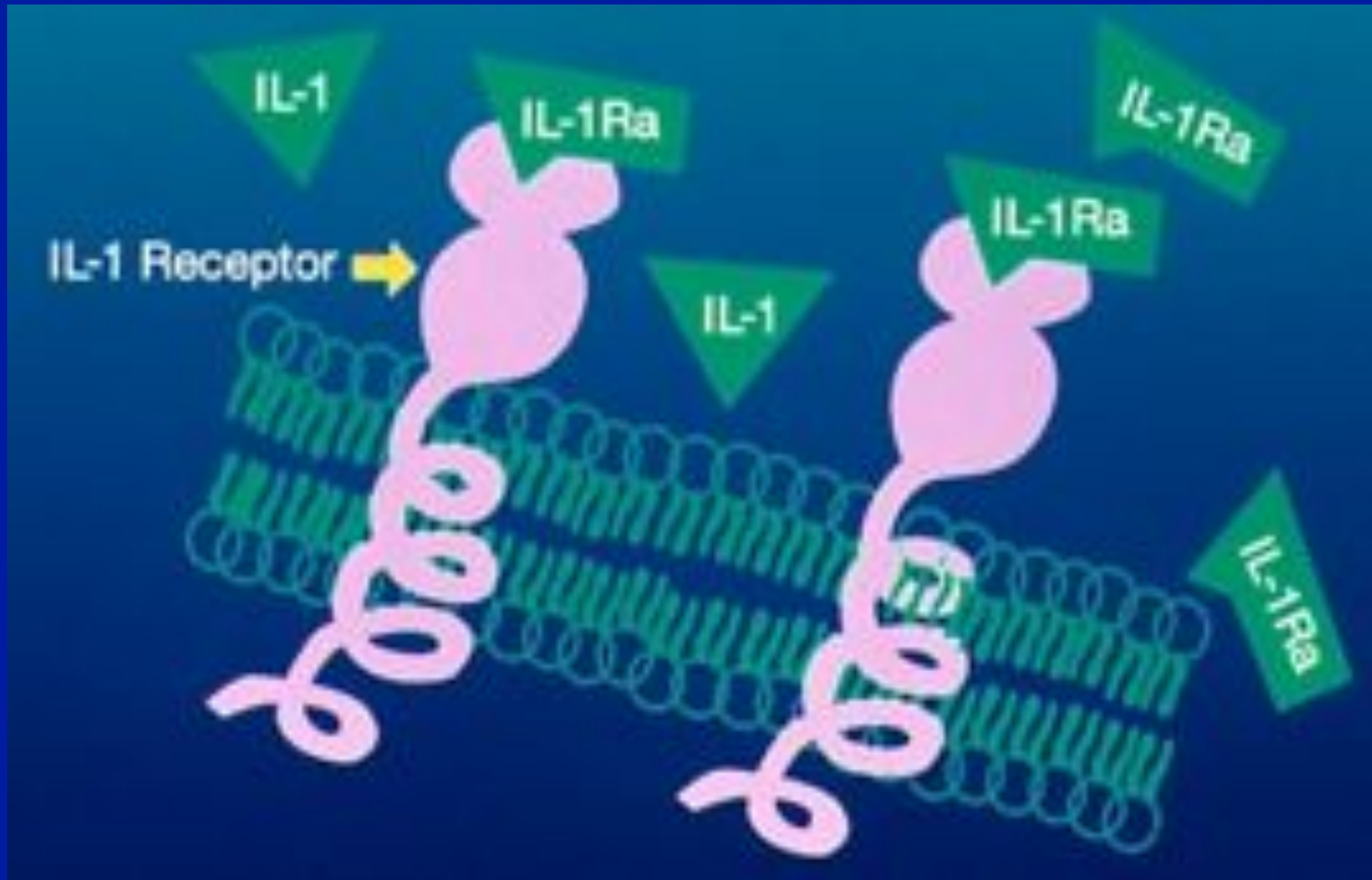
IL-1ra



# IL-1ra

- Recombinant anti-inflammatory protein
  - Differs from human IL-1ra by addition of an N-terminal methionine
  - Biologic activity identical to endogenous human IL-1ra
  - Short half-life
- Molar excess of IL-1ra is required to saturate receptors
  - Binding of IL-1b to small numbers of unoccupied IL-1 receptors can initiate signal transduction
- Efficacy weak in RA, much better in Still's Disease and periodic fever syndromes

# IL-1 Receptor Antagonist



# The IL-1R type I Is the Signaling Receptor

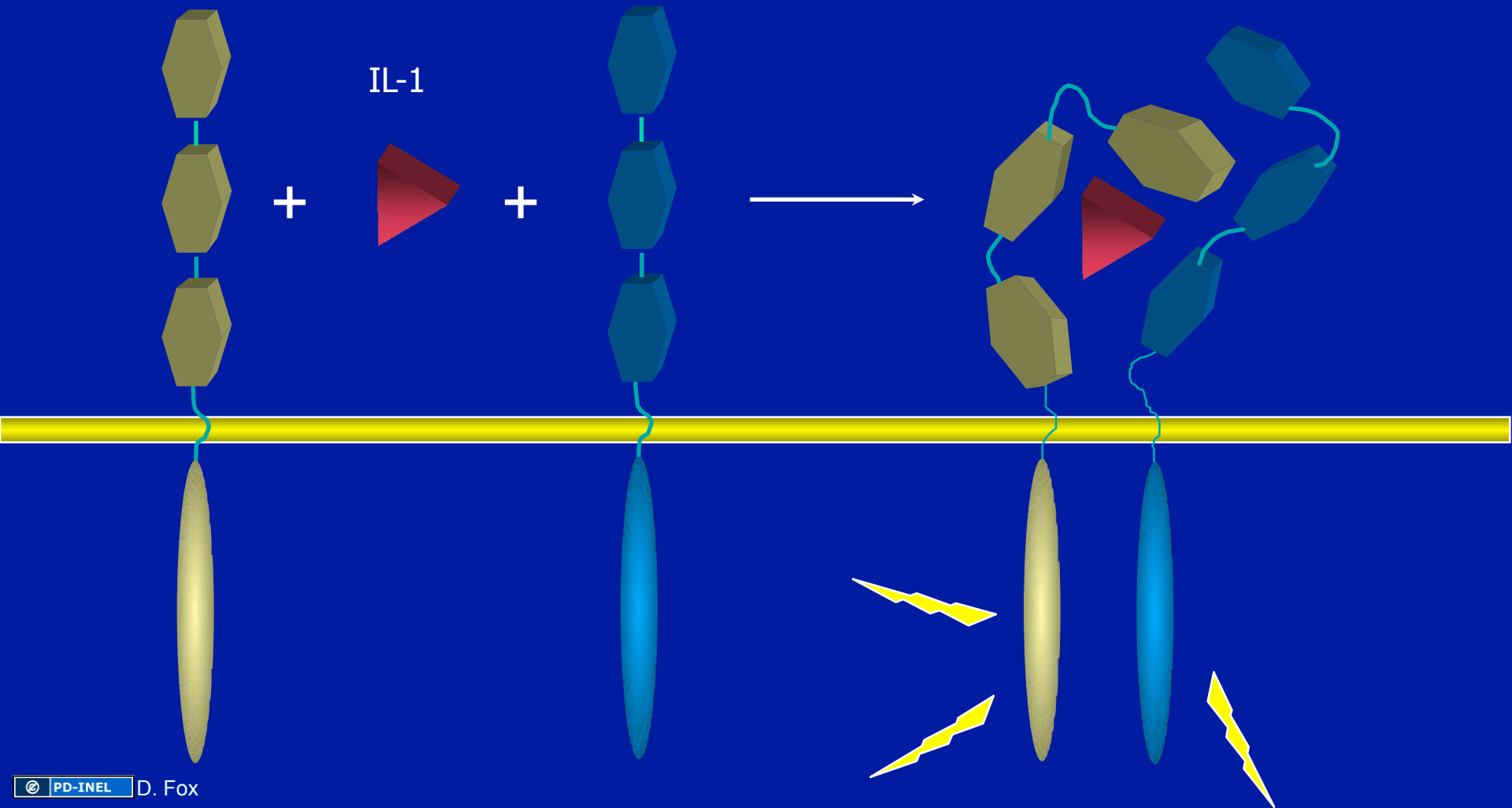
The IL-1R type I  
Is the Signaling  
Receptor

IL-1R  
AcP

IL-1

+

+



# IL-1ra Does Not Signal

IL-1R  
Type I

IL-1R  
AcP

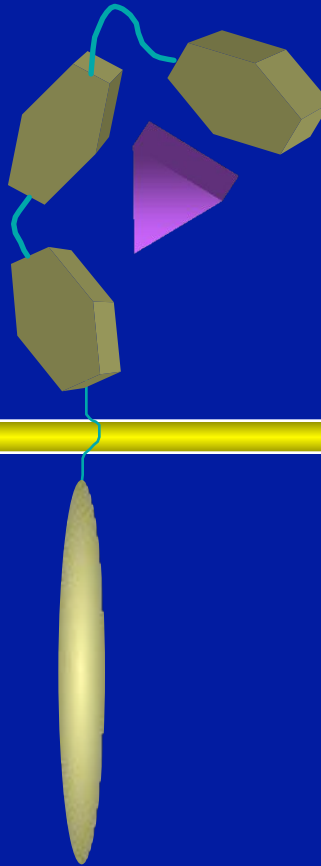
IL-1ra



+



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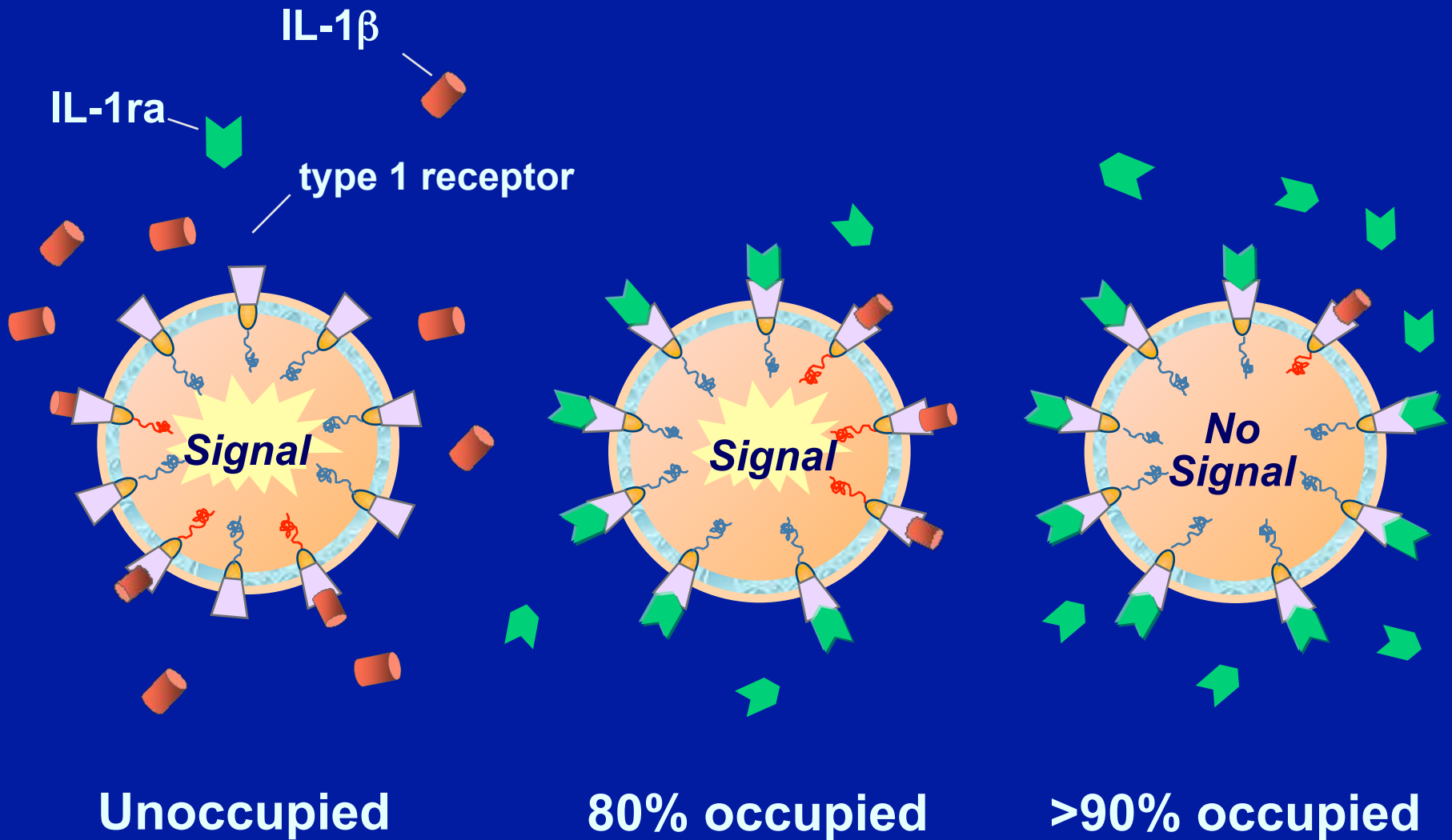


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# IL-1 Inhibition by Receptor Antagonist



# Other Targets for Treatment of RA by Biologics

## Target

B cells

## Approach

anti-CD20 (Rituximab)

T cell co-stimulation  
through CD28

CTLA-4-Ig (Abatacept)

IL-6

anti-IL-6R



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