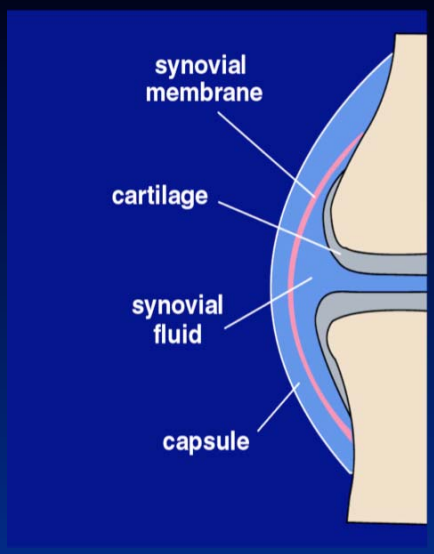
Rheumatoid Arthritis

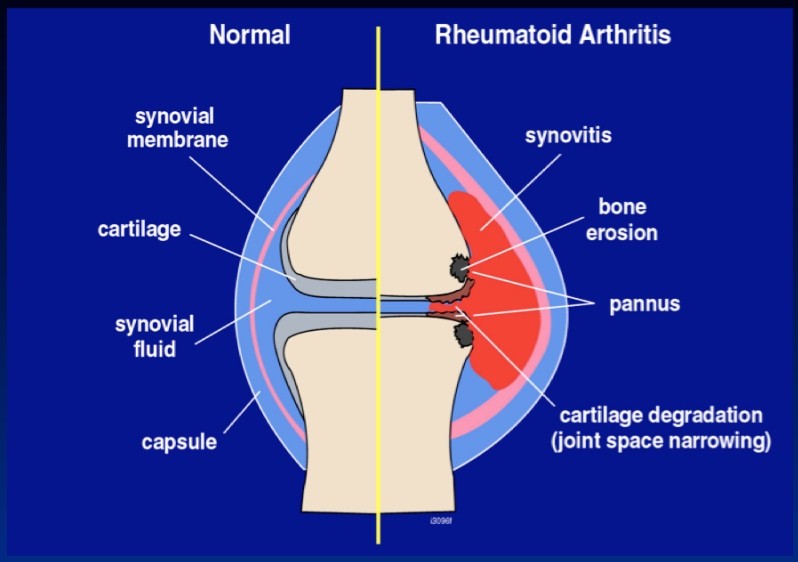
Edward Dwyer, M. D.

Division of Rheumatology

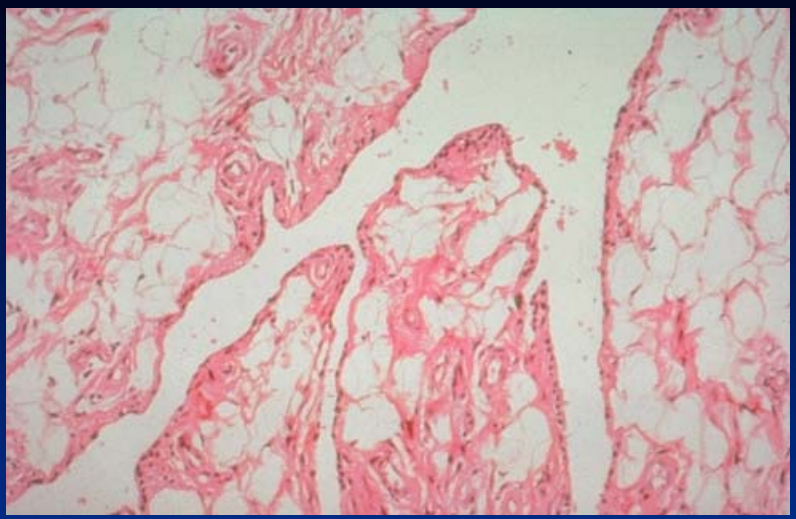
Diarthroidal Joint



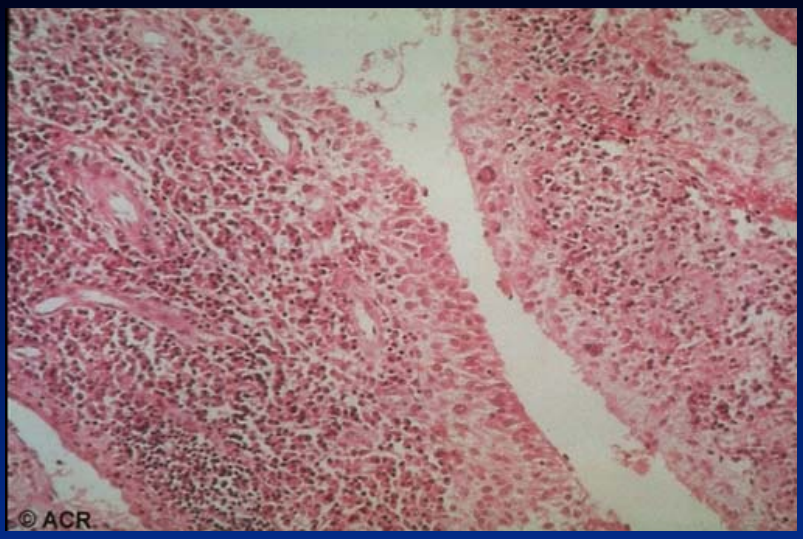
Diarthroidal Joint in Rheumatoid Arthritis



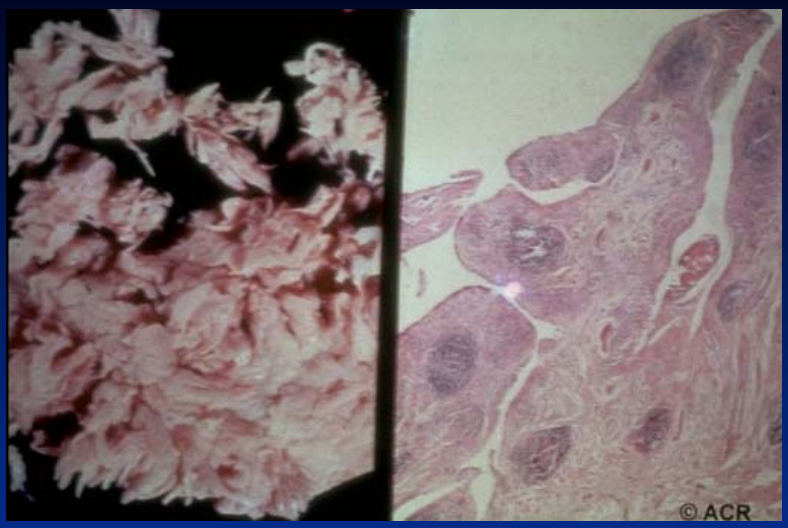
Normal Synovium



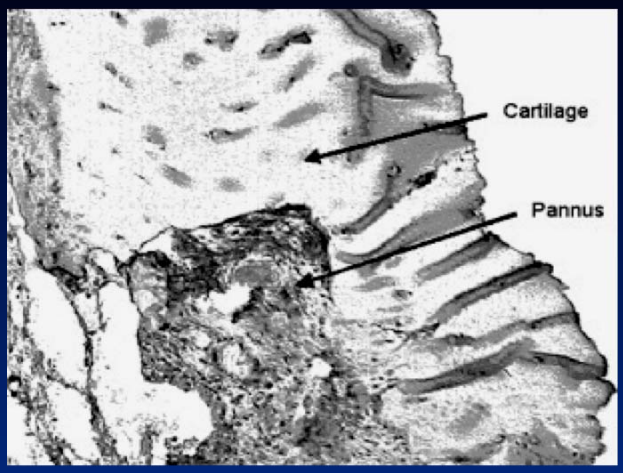
Synovium in Rheumatoid Arthritis



Synovium in Rheumatoid Arthritis



Cartilage-Pannus Interface



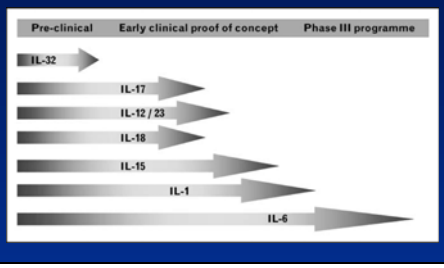
Pannus composed of macrophages and mesenchymal cells which erode into cartilage and bone

Cellular Components of Synovial Inflammation in RA

- T cells
  - CD4 TH1 phenotype (IFN-γ, IL-2)
- Macrophages
  - TNF and IL-1
- B cells
  - Rheumatoid Factor
  - Anti-Cyclic Citrullinated Peptide Ab (anti-CCP Ab)

Emerging Cytokine Targets in RA

Cytokine	Produced by	Activity
IL-1	MΦ	"TLR-like"; activates NF-κB
IL-6	MΦ, Ly, Fibr	Induces IL-17; stimulates bone resorption
IL-15	MΦ, Syn, Endo	"IL-2-like"; stimulates T_H1 polarization
IL-17	T_H17 cells	Induces TNF-α, IL-1, RANKL
IL-18	MΦ	"TLR-like"; activates NF-κB
IL-23	MΦ	IL-12 family member; induces IL-17
IL-32	MΦ, Ly	Induces TNFα, IL-1β, IL-6, and chemokines



Epidemiology of Rheumatoid Arthiritis

- Prevalence of 1% in most populations
- Age of onset: 30-50 yrs
- Sex: F:M 3:1

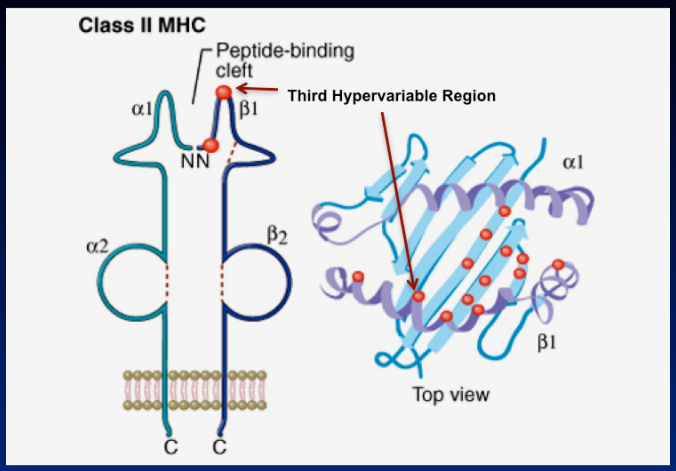
Risk Factors for Rheumatoid Arthritis

- Sex
  - F:M 3:1
- Family History:
  - Monozygotic twins: RR = 8
    - Concordance rate: 30%
  - Dizygotic twins: RR = 2-3.4
  - First degree relative: RR = 1.5

Genetics of Rheumatoid Arthritis

- MHC association accounts for 40% genetic risk
  - Alleles of the DRβ1 locus are responsible for increased risk to RA
  - Alleles of DRβ1 chain that confer increased risk exhibit a “shared epitope” of amino acid sequence in the the third hypervariable region from amino acids 70-74
    - e.g., DRβ1*0401, DRβ1*0404, DRβ1*0101
  - In some populations >95% of patients with RA exhibit this “shared epitope”

Genetics of Rheumatoid Arthritis



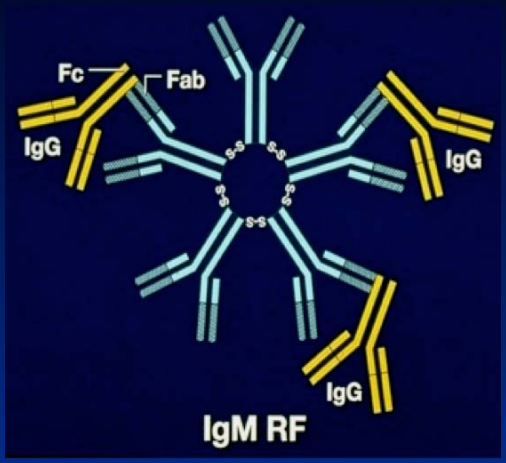
"Shared Epitope" Third Hypervariable Region Sequence:

-glutamine-lysine/arginine-arginine-alanine-alanine-

70 71 72 73 74

Rheumatoid Factor

IgM antibody with specificity for the Fc region of IgG



Diseases associated with Rheumatoid Factor

- Rheumatic Diseases
  - SLE, Sjogren's syndrome
- Viral Infections
  - HCV, HIV
- Bacterial Infections
  - SBE, TB, syphilis, leprosy
- Neoplasms
  - Lymphoproliferative diseases

- Present in 3% general population

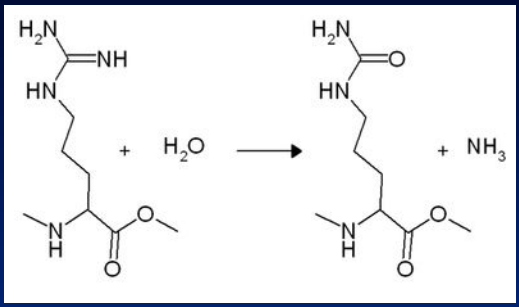
Rheumatoid Factor in RA

- Sensitivity: 70%

- Specificity: 60%

Anti-Cyclic Citrullinated Peptide Antibodies

Post-translational modification of arginine as a consequence of cell death and inflammation, i.e., oxidative stress



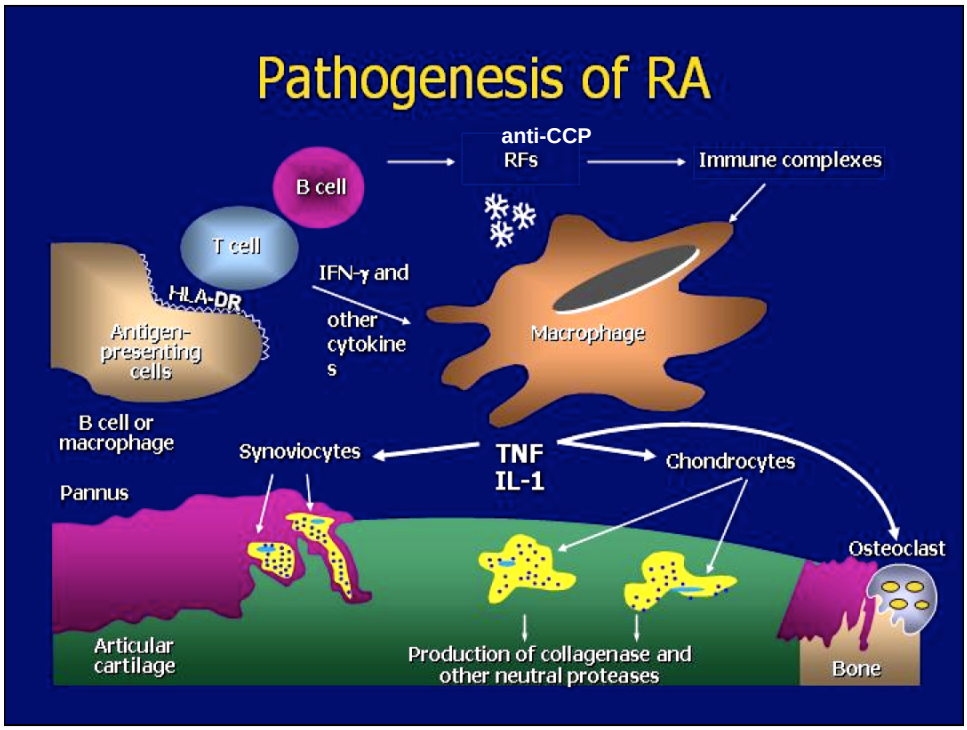
Arginine Citrulline

Anti-Cyclic Citrullinated Peptide Antibodies

- Proteins derived from synovial tissue in RA exhibit enhanced citrullination
- Patients with RA have high titers of autoantibodies directed against proteins with citrulline residues
  - e.g., anti-CCP Assay (ELISA assay)

Anti-Cyclic Citrullinated Peptide Antibodies

- Sensitivity: 70%
- Specificity: 95%



Diagnostic Criteria for Rheumatoid Arthritis*

- Morning stiffness (> 1 hour)
- Arthritis of 3 or more joint areas (polyarticular)
- Arthritis of hand joints
- Symmetric arthritis
- Rheumatoid nodules
- Rheumatoid Factor in serum
- Radiographic changes:
  - Periarticular demineralization of bone (early)
  - Marginal erosions (later)

4 of 7 criteria should be present to diagnose Rheumatoid Arthritis

*1987 American College of Rheumatology Revised Criteria for the Classification of RA

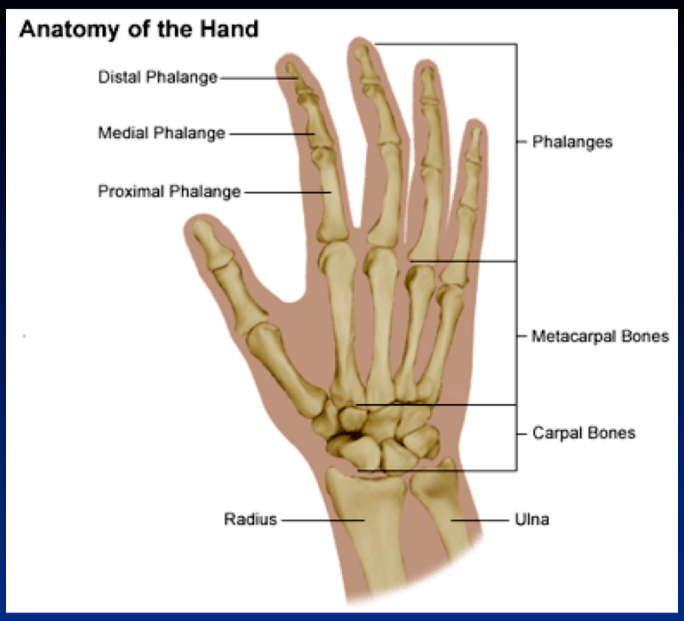
Clinical Features of Rheumatoid Arthritis

Joint involvement in Rheumatoid Arthritis

- Polyarticular
- Arthritis of hand joints most common
  - Metacarpophalangeal joints (MCPs)
  - Proximal interphalangeal joints (PIPs)
  - Never Distal interphalangeal joints (DIPs)
- Symmetric arthritis

Joint involvement in Rheumatoid Arthritis

- Less commonly involves:
  - Toes, wrists, knees
- Least commonly involves:
  - Shoulders, hips



PIP Involvement

MCP Involvement

Ulnar Deviation

Boutonierre's Deformity

Swan neck deformity

Radiographic Changes in Rheumatiod Arthritis

- Early changes
  - No abnormalities
- Initial changes
  - Periarticular osteopenia secondary to cytokine-induced bone loss
- Later changes
  - Marginal erosions at periphery of joint (cartilage-pannus interface)
- Advanced changes
  - Joint space narrowing, subluxation

Radiographic Progression of MCP Joint Destruction

MTP Subluxation

MTP Disease

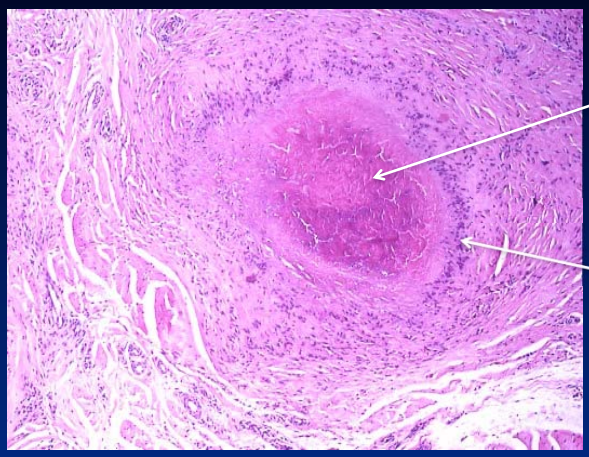
Extra-articular Manifestations of Rheumatoid Arthritis

- Extra-articular manifestations of RA are generally found in those patients who have relatively severe articular disease
- Extra-articular disease is associated with increased morbidity and mortality

Rheumatoid Nodule

Rheumatoid Nodules

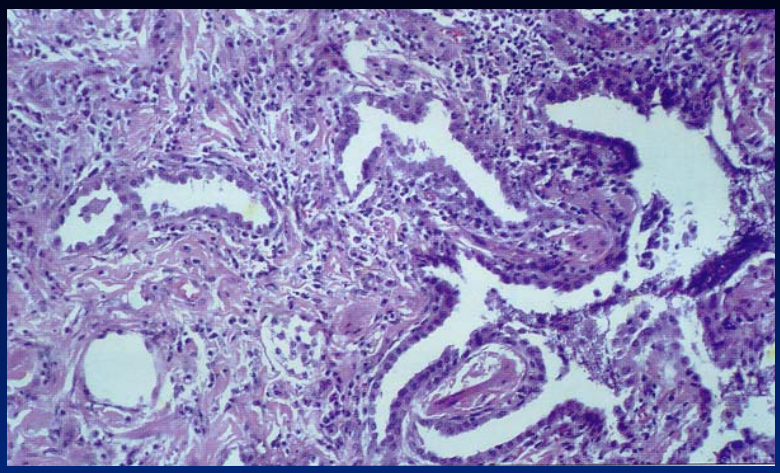
Rheumatoid Nodule Histopathology



Scleritis

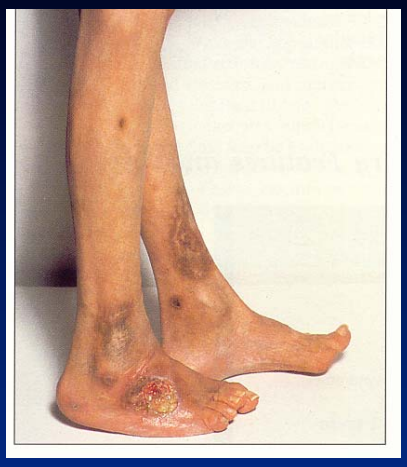
Pulmonary Nodules

“Rheumatoid Lung”



Interstitial infiltration of macrophages and T cells resulting in pulmonary fibrosis

Rheumatoid Vasculitis



Felty's Syndrome

- Rheumatoid Arthritis
- Neutropenia
- Splenomegaly

Felty's Syndrome

- 1-2% Rheumatoid Arthritis patients
- 1/3 have expansion of CD3+CD8+ Large Granular Lymphocytes in peripheral smear
- Increased risk for infections and non-Hodgkins lymphoma

Treatment of Rheumatoid Arthritis

Goals of Therapy

- Reduce or eliminate pain
- Prevent or retard joint destruction
- Maintain musculoskeletal functional status
- Prevent or retard development of extra-articular manifestations of disease

Evidence of Early Radiographic Change

- Joint-space narrowing and erosion are seen in 67% of patients within the first 2 yrs of disease
- Joint-space narrowing and erosion are seen in 77% of patients within the first 5 yrs of disease
- Progression is most rapid during the first 5 yrs of disease

Current Guidelines for the Management of Rheumatoid Arthritis

"The majority of patients with newly diagnosed RA should be started on Disease-Modifying Anti-Rheumatic Drug (DMARD) therapy within 3 months of diagnosis."

Arthritis & Rheumatism, 46(2), 328-46, 2002

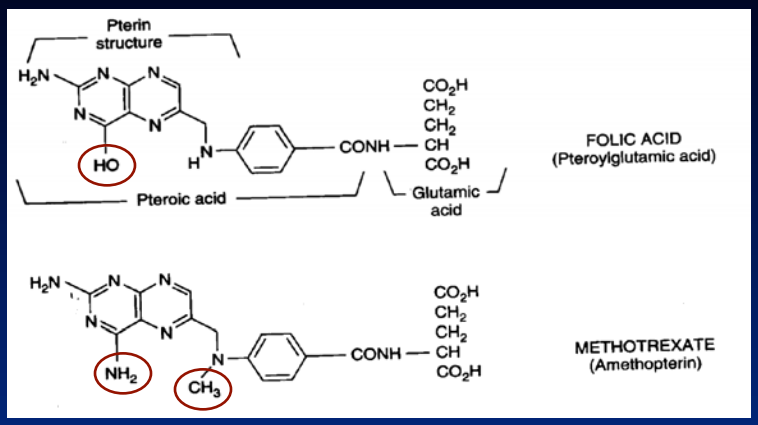
Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)

- Prostaglandin inhibitors that exhibit analgesic and anti-inflammatory effects
  - e.g., aspirin, ibuprofen, naproxen
- NSAIDS do not inhibit or retard the progression of articular destruction in Rheumatoid Arthritis
- Useful for symptom management only

Initial DMARD Therapy in Rheumatoid Arthritis

- Methotrexate: Folic acid analog that inhibits dihydrofolate reductase, an enzyme active in nucleic acid synthesis

Methotrexate



Mechanism of Action of Methotrexate in RA

1. Cytostatic agent that inhibits nucleic acid synthesis and therefore the proliferation of immune cells that mediate inflammation.

2. Inhibits pathways of purine metabolism which results in increased production of adenosine which mediates immunosuppressive and anti-inflammatory effects.

Efficacy of Methotrexate in RA

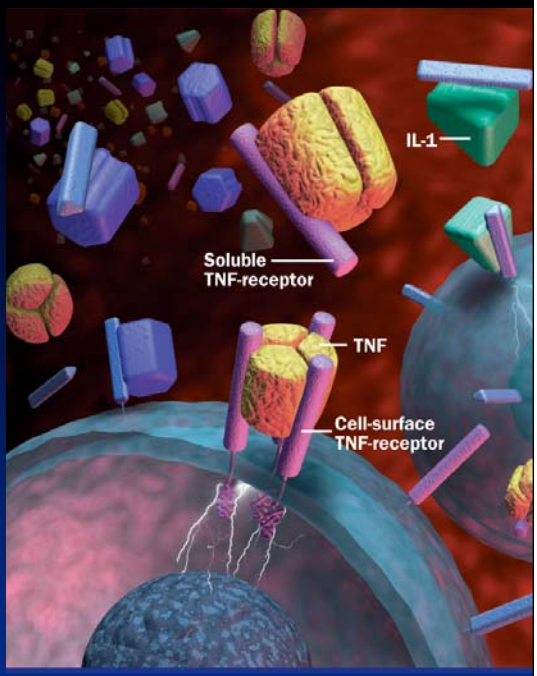
- Definitely improves symptoms and function, and retards joint destruction in a significant percentage of patients.
- However, < 50% of patients experience a sustained remission on methotrexate alone

Biologic Agents in RA Therapy

- Anticytokine agents
  - Anti-TNF agents
    - Etanercept (Enbrel)
    - Infliximab (Remicade)
    - Adalimumab (Humira)
  - Anti-IL 1
    - Anakinra (Kineret)
- B cell depleting agent
  - Anti-CD20
    - Rituximab (Rituxan)
- Costimulatory inhibitor
  - Anti-B7 (CD80)
    - Abatacept (Orencia)

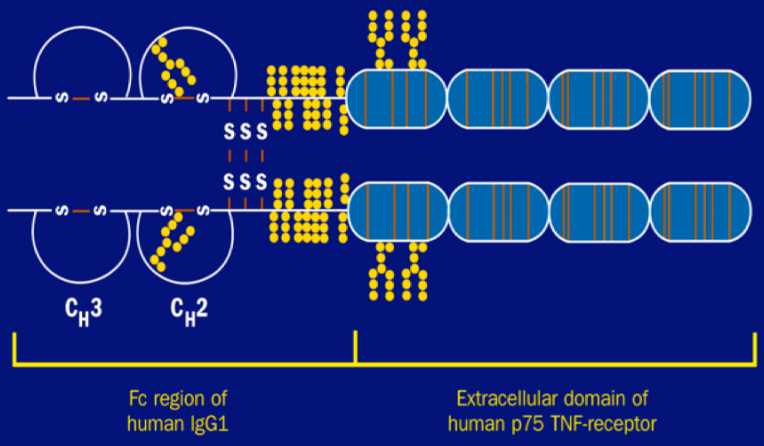
TNF-α

- Proinflammatory 17 kD protein that is composed of three identical subunits
- Produced primarily by activated macrophages
- TNF binds to 2 distinct receptors
  - TNFR1 (p55)
  - TNFR2 (p75)
- Activates fibroblasts, chondrocytes, and osteoclasts
- Promotes secretion of other pro-inflammatory cytokines, (e.g., IL-1 and IL-6) and matrix metalloproteinases



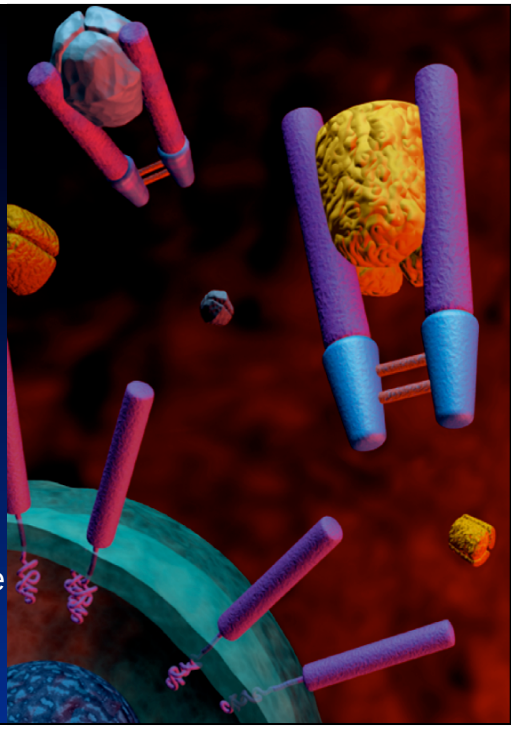
Etanercept

- Recombinant soluble TNF-receptor formed by fusion of two human TNF-receptors and the Fc portion of human IgG1[1]



Etanercept

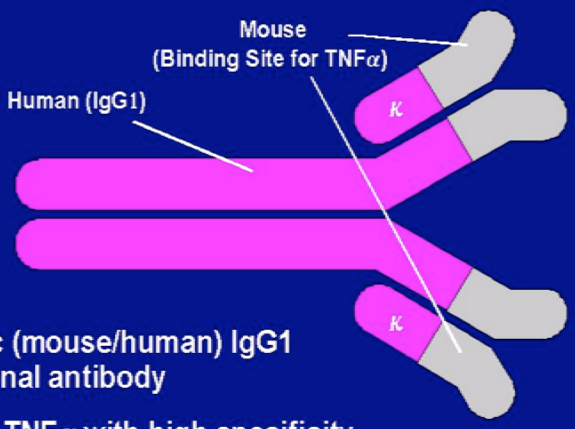
- Etanercept binds to TNF
- Antagonizes TNF receptor activation
- Dimeric structure of etanercept allows it to be 1000% times more efficient than the monomeric structure in neutralizing TNF
- Addition of Fc IgG1 portion markedly prolongs the half-life



Etanercept Administration

- Subcutaneous Injection:
  - 50 mg q. week
- Half-life of 4 days
- Generally administered in addition to methotrexate

Structure of Infliximab



- Chimeric (mouse/human) IgG1 monoclonal antibody
- Binds to TNFα with high specificity, high affinity, and high avidity

Knight DM, et al. *Mol Immunol.* 1993; 30(16):1443-53.

Infliximab Administration

- Intravenous Infusion of 3 mg/kg every 8 weeks
- Development of anti-chimeric antibodies to the murine region of the molecule is partially inhibited by the maintenance of methotrexate therapy

Adalimumab (Humira)

- IgG1κ fully “humanized” monoclonal antibody generated through application of phage display library technology
- Avoids generation of anti-chimeric antibodies

Adalimumab Administration

- Subcutaneous Injection:
  - 40 mg q. 2 wks
- Half-life: 2 weeks
- In addition to methotrexate maintenance therapy

Anti-TNF Inhibitors

- Rapid onset of action (1-2 weeks)
- Sustained clinical response
- Retards (arrests?/reverses?) joint destruction
- Well tolerated

Adverse Effects of TNF Inhibitors

- Reactivation of Latent Tuberculosis
  - TNF is an important cytokine in the immune response to *Mycobacterium tuberculosis*
  - All patients need to be screened for previous exposure to *M. tuberculosis* before initiating therapy with any anti-TNF agent
  - Those that exhibit a positive response to PPD (purified protein derivative) need to be treated with antituberculous therapy

Anti-IL 1 Therapy

- IL 1 receptor antagonist (IL-1 Ra)
  - Naturally occurring protein produced by macrophages at sites of inflammation that inhibits IL-1 induced activation
- Anakinra (Kineret)
  - Human recombinant form of IL-1 Ra produced *in vitro*

Anakinra Administration

- Subcutaneous injection
  - 100 mg per day
- Half-life: 6 hours
- **Very modest efficacy**

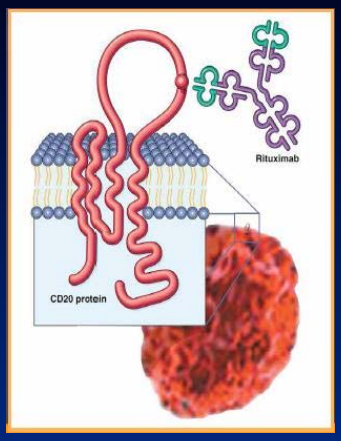
B Cell Depletion Therapy

Rituximab (Rituxan)

- Chimeric human-murine monoclonal antibody targeting CD20 expressed on B cells

- CD20 is a 35 kD B cell lineage specific cell surface molecule expressed from pre-B cells to mature B cells (not expressed on plasma cells)

- Cytolytic effect mediated by:
  - Complement activation
  - ADCC



Rituximab

- Mechanism of action in RA?

  - Does not interfere with autoantibody production (e.g., RF or anti-CCP Ab) since it does not target plasma cells

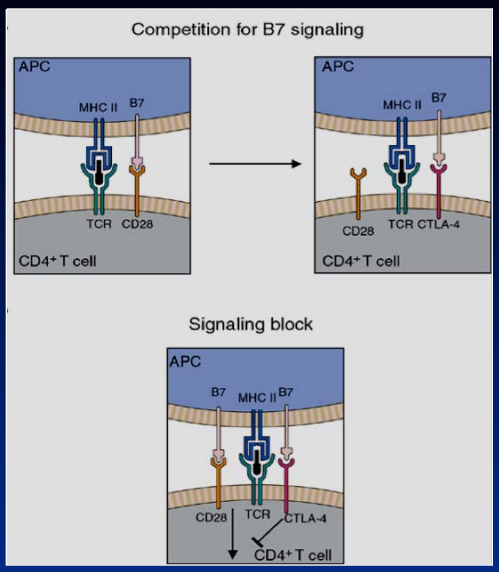
  - Hypothesis: Rituximab reduces the role of B cells that function as antigen presenting cells in presenting self-peptides to T cells in RA

Rituximab Administratiion

- Intravenous infusion of 1000 mg every 6 months
- Half-life: 2-3 weeks
- B cell depletion lasts 4-6 months

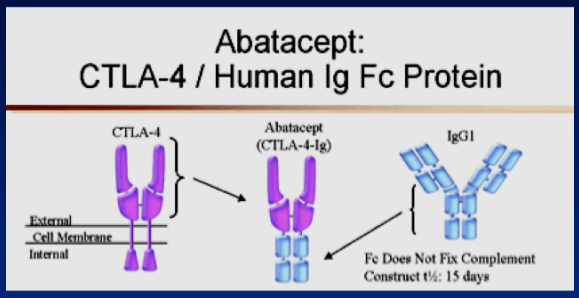
Costimulatory Blockade

Costimulation in T Cell Activation

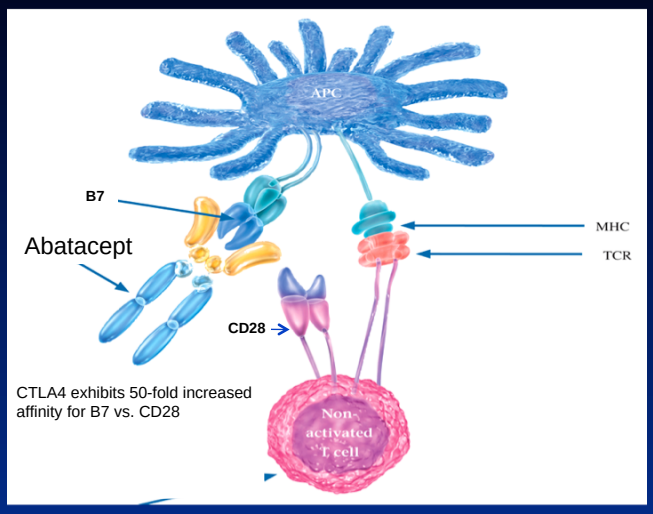


Abatacept (Orencia)

Extracellular CTLA-4 + IgG1 Constant Region



Costimulatory Blockade



Abatacept (Orencia)

- Administration: Intravenous infusion of 10 mg/kg per month
- Half-life: 15 days

Emerging Cytokine Targets in RA

Cytokine	Produced by	Activity
IL-1	MΦ	"TLR-like"; activates NF-κB
IL-6	MΦ, Ly, Fibr	Induces IL-17; stimulates bone resorption
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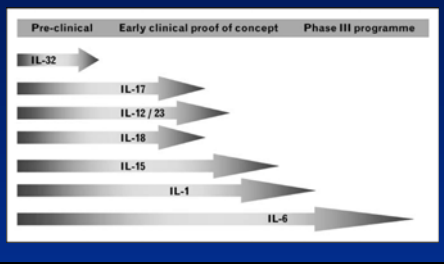

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