

Rheumatoid Arthritis and the Role of Tumor Necrosis Factor Inhibitors

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Mary K. Crow, MD

**Benjamin M. Rosen Chair in Immunology and Inflammation Research
Mary Kirkland Center for Lupus Research, Hospital for Special Surgery
Professor of Medicine**

**Weill Medical College of Cornell University
New York, NY**

Rheumatoid Arthritis: Systemic autoimmune disease targeting joints

Clinical Symptoms – symmetrical pain, swelling, deformities of joints; morning stiffness; fatigue; extra-articular disease: nodules; pulmonary

Epidemiology – female:male = 2-3:1; prevalence 1%

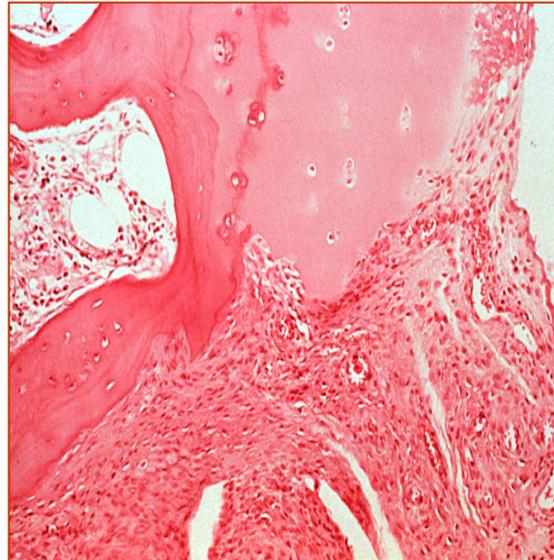
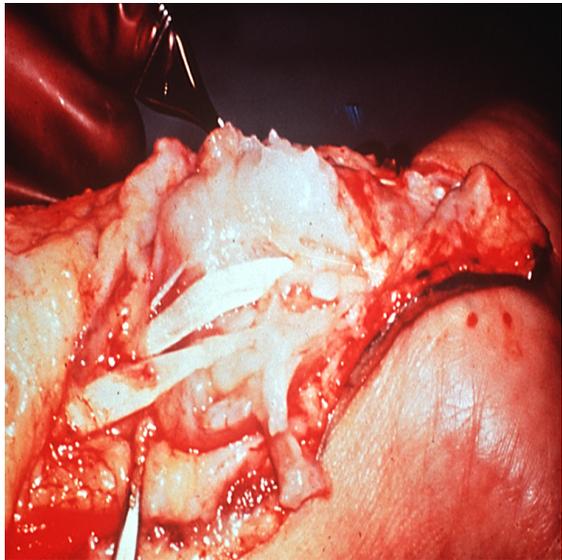
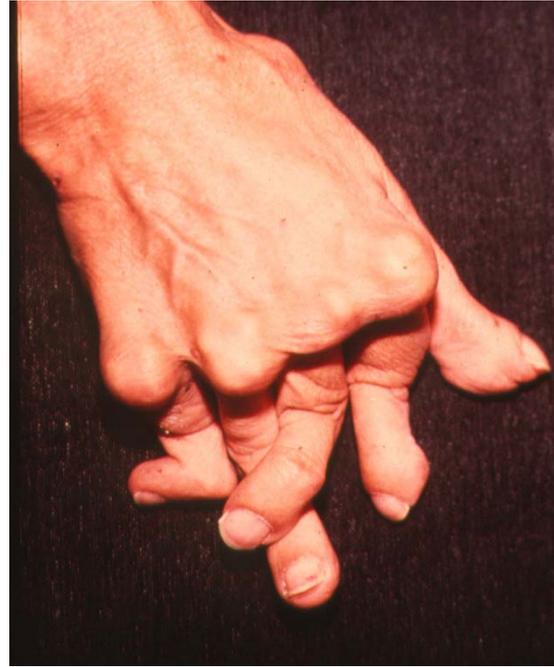
Triggers – environment + genetics

Autoimmunity – anti-cyclic citrullinated peptide antibodies; rheumatoid factor

Pathology – infiltrate of immune system cells in synovial membrane lining joints; bone erosion

Complications – premature atherosclerosis; infection

Rheumatoid Arthritis



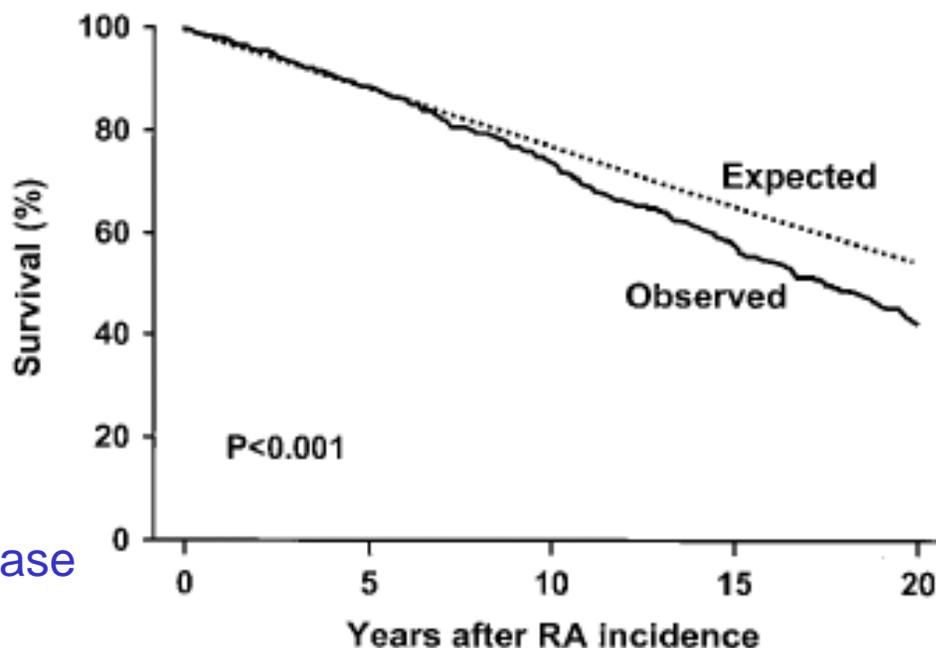
Survival in Patients with Rheumatoid Arthritis is Lower than Expected

ARTHRITIS & RHEUMATISM
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Survival in Rheumatoid Arthritis

A Population-Based Analysis of Trends Over 40 Years

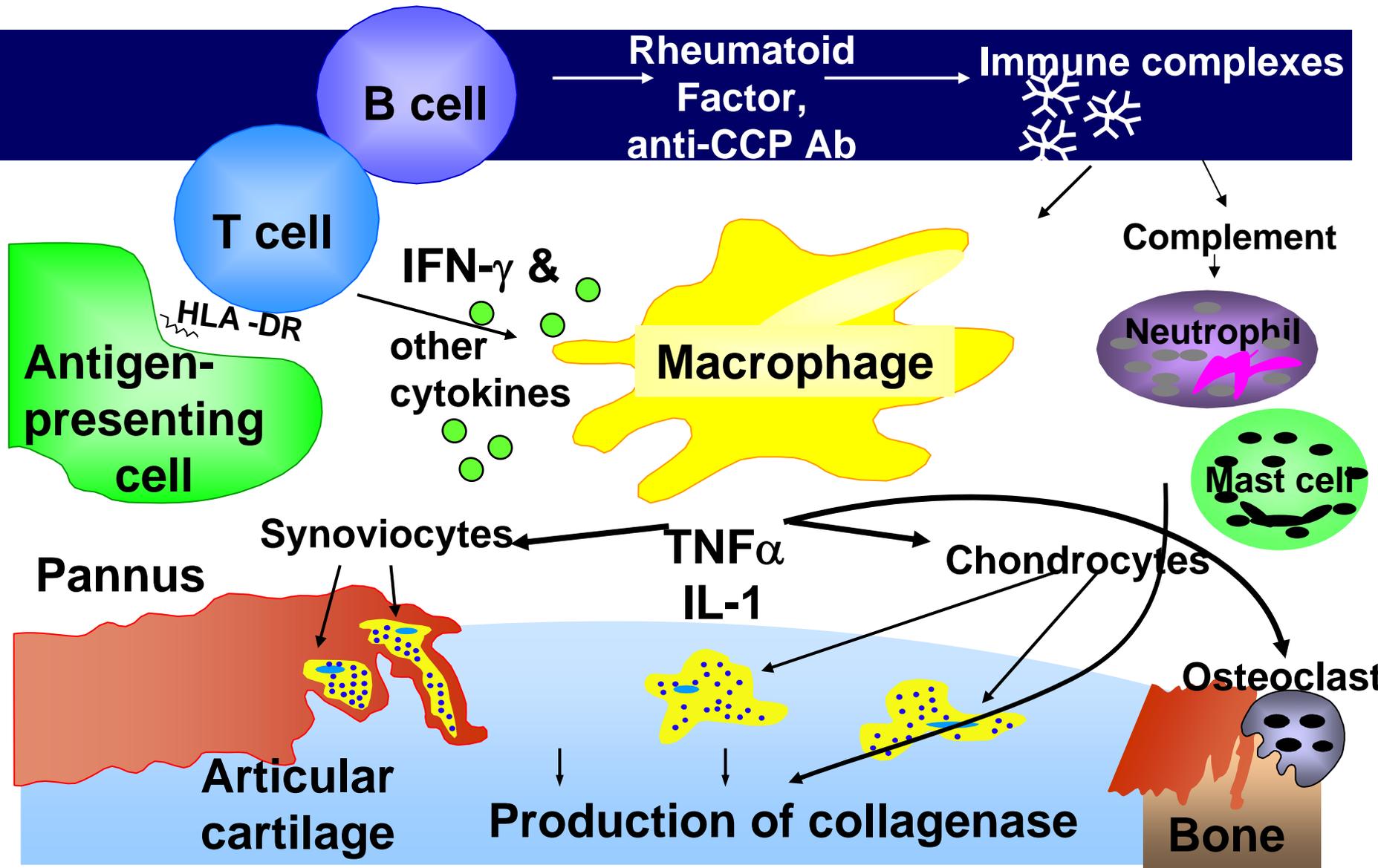
Sherine E. Gabriel,¹ Cynthia S. Crowson,¹ Hilal Maradit Kremers,¹ Michele F. Doran,²
Carl Turesson,³ W. Michael O'Fallon,¹ and Eric L. Matteson¹



Leading causes
of death:

- Cardiovascular disease
- Infection

Pathogenesis of Rheumatoid Arthritis



1988

Franchimont P, Reuter A, Vrindts-Gevaert Y et al. Production of **tumour necrosis factor-alpha**, interferon-gamma and interleukin-2 by peripheral blood mononuclear cells of subjects suffering from rheumatoid arthritis. *Scand J Rheumatol*. 1988;17(3):203-12.

Hopkins SJ, Meager A. Cytokines in synovial fluid: II. The presence of **tumour necrosis factor** and interferon. *Clin Exp Immunol*. 1988 Jul;73(1):88-92.

Husby G, Williams RC Jr. Synovial localization of **tumor necrosis factor** in patients with rheumatoid arthritis. *J Autoimmun*. 1988 Aug;1(4):363-71.

Saxne T, Palladino MA Jr., Heinegard D, et al. Detection of **tumor necrosis factor alpha** but not tumor necrosis factor beta in rheumatoid arthritis synovial fluid and serum. *Arthritis Rheum*. 1988 Aug;31(8):1041-5.

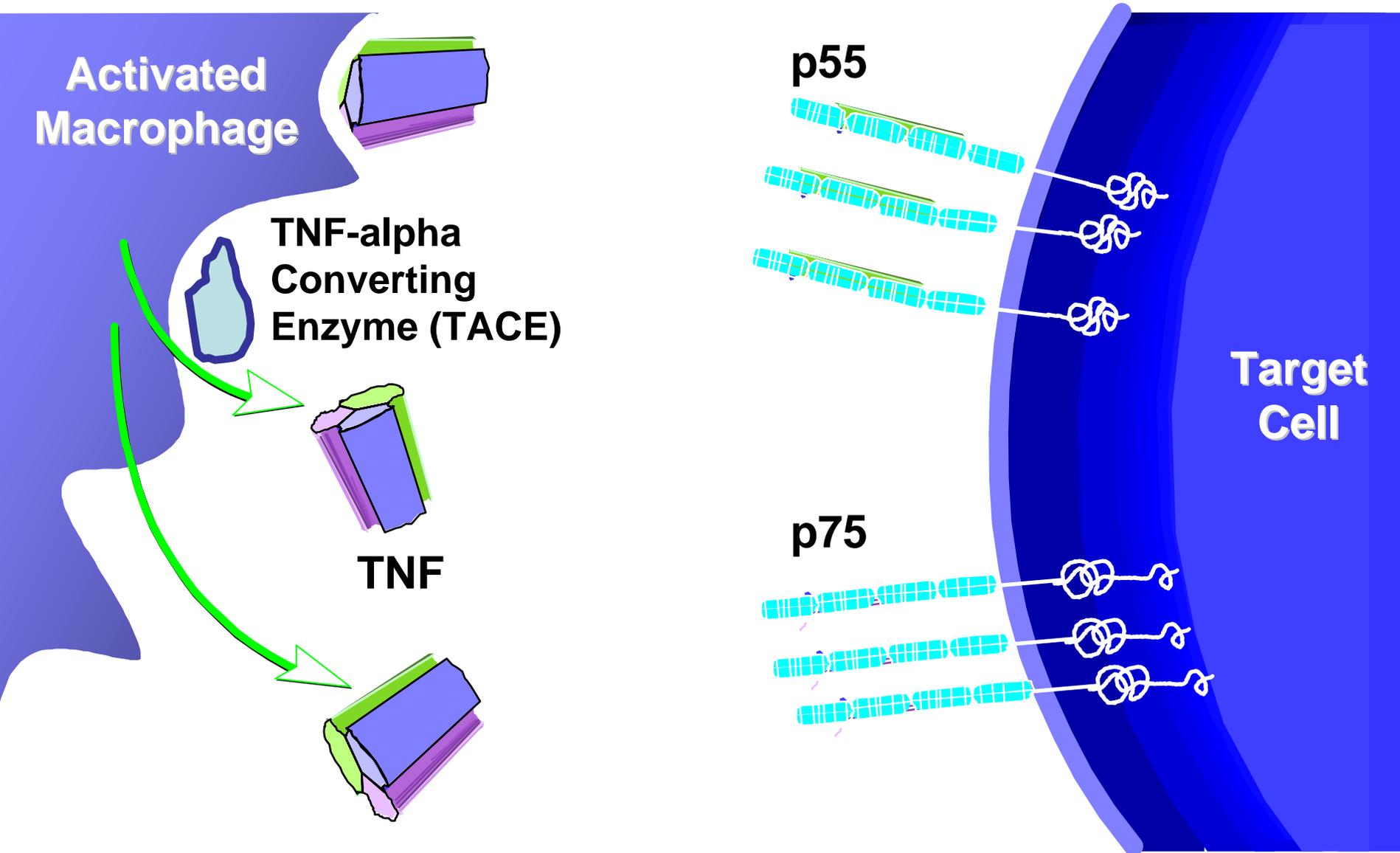
Buchan G, Barret K, Turner M, et al. Interleukin-1 and **tumour necrosis factor** mRNA expression in rheumatoid arthritis: prolonged production of IL-1 alpha. *Clin Exp Immunol*. 1988 Sep;73(3):449-55.

1989

Brennan FM, Chantry D, Jackson A, Maini R, Feldman M. **Inhibitory effect of TNF alpha antibodies on synovial cell interleukin-1 production in rheumatoid arthritis**. *Lancet*. 1989 Jul 29;2(8657):244-7.

“In rheumatoid arthritis, TNF alpha may be the main inducer of IL-1, and anti-TNF alpha agents may be useful in treatment.”

TNF and TNF Receptors



Tumor Necrosis Factor

Essential for Host Defense against Microbes:

- Initiates the innate immune response
- Activates and differentiates macrophages
- Increases vascular permeability and adhesion
- Recruits neutrophils
- Activates dendritic cells and promotes adaptive immune responses
- Promotes granuloma formation to wall off infection

In Excess Contributes to Disease:

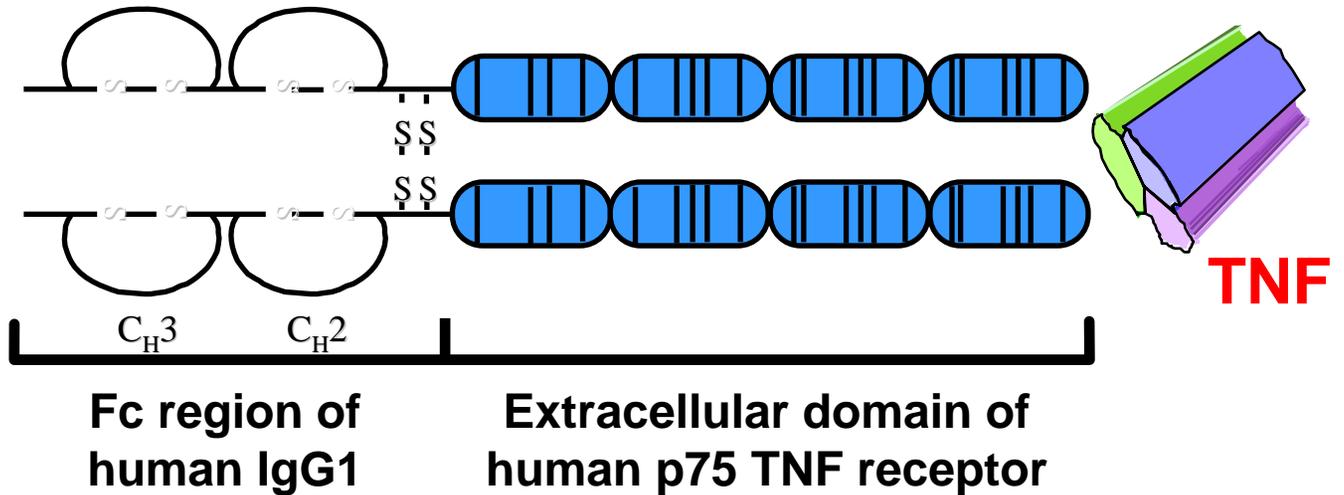
- Mediates chronic inflammation
- Contributes to bone erosions in RA
- Induces shock when systemic

Role of TNF in Rheumatoid Arthritis

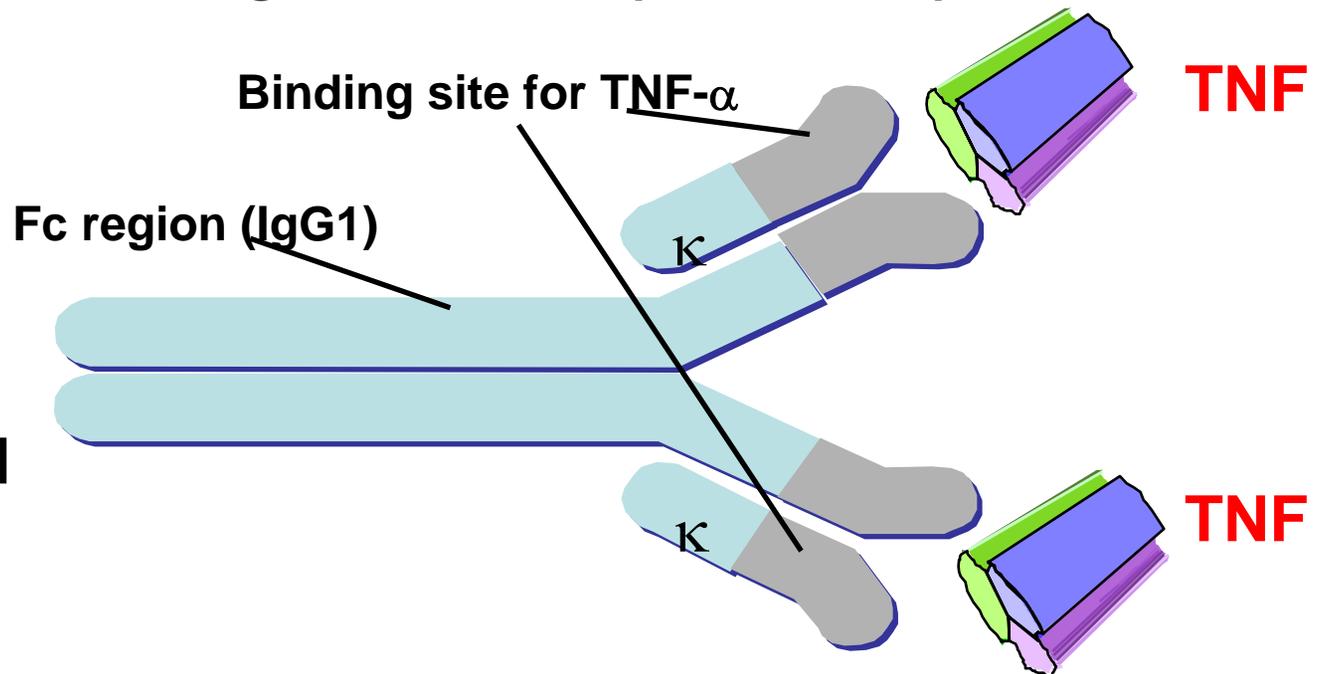
- Drives events in proinflammatory cytokine cascade
- Triggers production of other proinflammatory cytokines, including IL-1
- Facilitates activation of T lymphocytes by foreign antigens through dendritic cell maturation
- Causes T cell/neutrophil accumulation in synovial membrane by inducing expression of endothelial adhesion molecules
- Stimulates fibroblasts and macrophages to release destructive enzymes
- Stimulates osteoclastogenesis directly through differentiation of progenitor cells and through enhanced expression of RANK

TNF Inhibitors for Treatment of Rheumatoid Arthritis

**Soluble
TNF receptor
(etanercept)**



**Anti-TNF
monoclonal
antibodies
(infliximab and
adalimumab)**



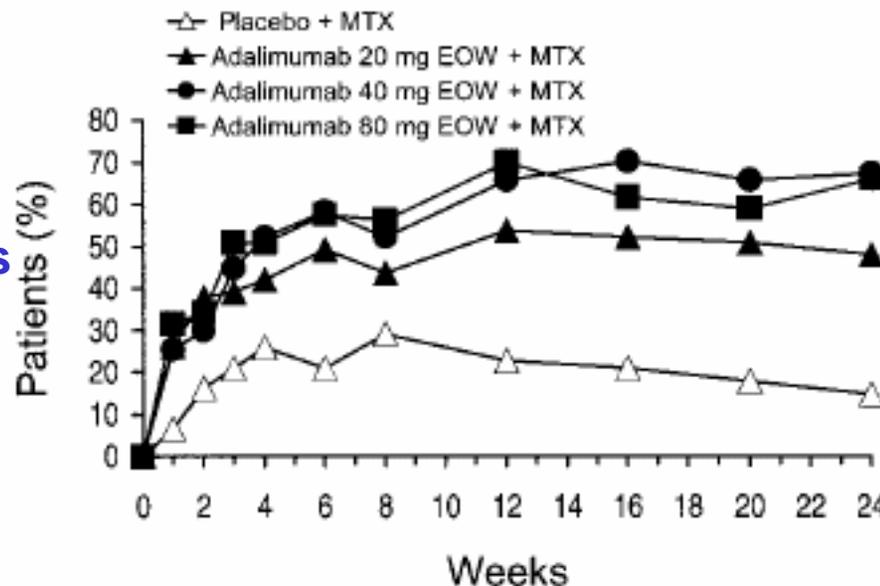
Anti-TNF Therapy Improves Disease in Rheumatoid Arthritis Patients

Adalimumab, a Fully Human Anti-Tumor Necrosis Factor α Monoclonal Antibody, for the Treatment of Rheumatoid Arthritis in Patients Taking Concomitant Methotrexate

The ARMADA Trial

Michael E. Weinblatt,¹ Edward C. Keystone,² Daniel E. Furst,³ Larry W. Moreland,⁴ Michael H. Weisman,⁵ Charles A. Birbara,⁶ Leah A. Teoh,⁷ Steven A. Fischkoff,⁷ and Elliot K. Chartash⁷

ACR20



% of patients achieving ACR20

Patients treated with anti-TNF Ab

Patients treated with placebo

Potential Immunologic Consequences of Administration of Anti-TNF Agents

- **Impaired host defense against microbial infection**
 - Reactivation of tuberculosis
 - Fungal infection: Histoplasmosis; Candida; Coccidioidomycosis; Aspergillus
 - Bacterial infection: Strep; Staph
- **Impaired immune surveillance against malignant cells**
- **Shift in cytokine balance that could facilitate expression of new autoimmune phenomenon**
- **Immune response to therapeutic agent**

Anti-TNF Therapy has been Associated with Reactivation of Tuberculosis

Immunity 2:561, 1995

Tumor Necrosis Factor- α Is Required in the Protective Immune Response Against *Mycobacterium tuberculosis* in Mice

JoAnne L. Flynn,¹ Marsha M. Goldstein,²
John Chan,³ Karla J. Triebold,⁴
Klaus Pfeffer^{5, 6}, Charles J. Lowenstein,⁷
Robert Schreiber,⁸ Tak W. Mak,⁸
and Barry R. Bloom⁴

Clin Infect Dis 38:295, 2004

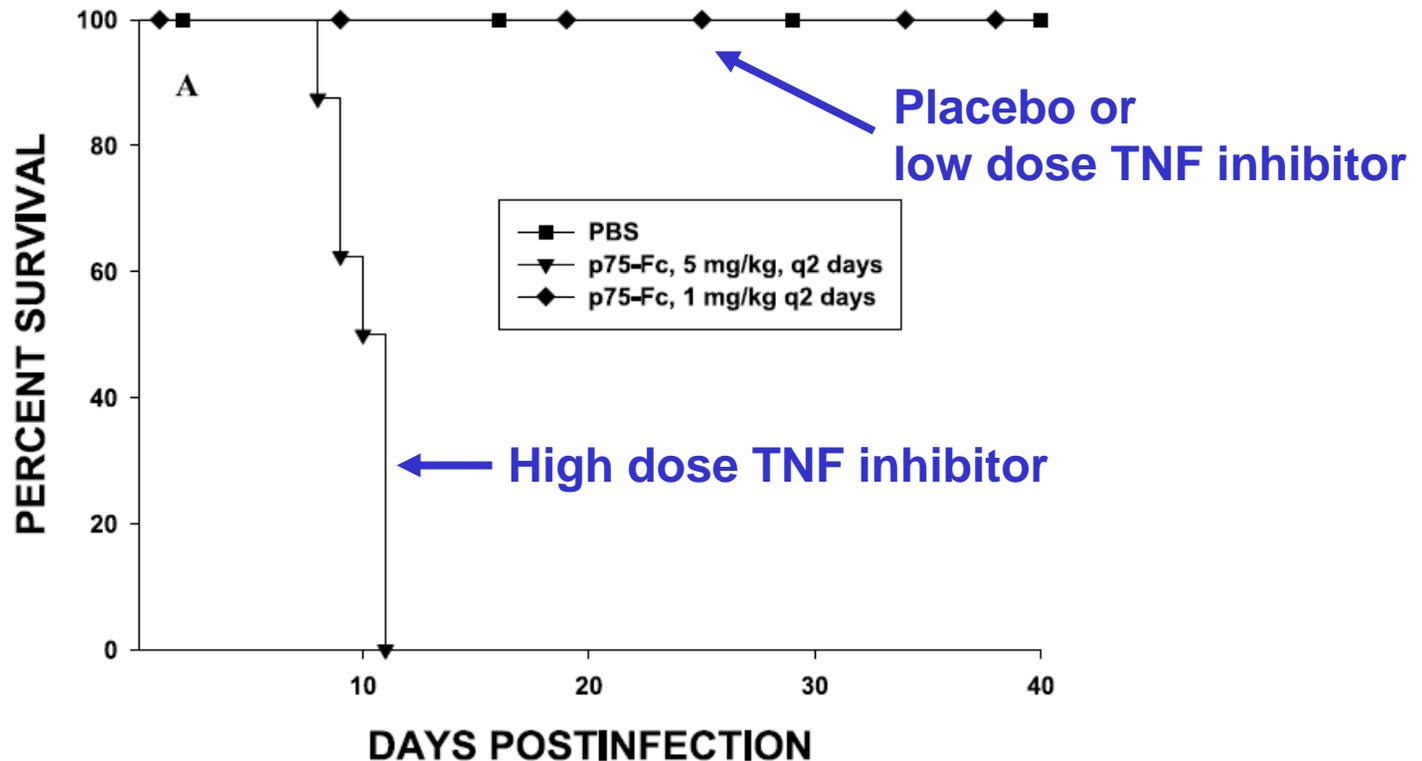
Tuberculosis following the Use of Etanercept, a Tumor Necrosis Factor Inhibitor

Aparna K. Mohan,¹ Timothy R. Coté,¹ Joel A. Block,³ Augustine M. Manadan,³ Jeffrey N. Siegel,²
and M. Miles Braun¹

Anti-TNF Therapy Associated with Poor Outcome from Histoplasmosis in a Murine Model

Tumor Necrosis Factor- α Antagonism by the Murine Tumor Necrosis Factor- α Receptor 2-Fc Fusion Protein Exacerbates Histoplasmosis in Mice

GEORGE S. DEEPE, JR.



Occurrence of Histoplasmosis in Anti-TNF-Treated Patients

Arthritis Rheum 46:2565, 2002

Life-Threatening Histoplasmosis Complicating Immunotherapy With Tumor Necrosis Factor α Antagonists Infliximab and Etanercept

Jong-Hoon Lee,¹ Nancy R. Slifman,¹ Sharon K. Gershon,¹ Evelyne T. Edwards,¹ William D. Schwieterman,¹ Jeffrey N. Siegel,¹ Robert P. Wise,¹ S. Lori Brown,¹ John N. Udall, Jr.,² and M. Miles Braun¹

Am J Respir Crit Care Med 167:1279, 2003

Histoplasmosis after Treatment with Anti-Tumor Necrosis Factor- α Therapy

Karen L. Wood, Chadi A. Hage, Kenneth S. Knox, Martin B. Kleiman, Aruna Sannuti, Richard B. Day, L. Joseph Wheat, and Homer L. Twigg III

Summary

- Rheumatoid arthritis is a significant autoimmune and inflammatory disease resulting in joint damage and decreased survival
- Tumor necrosis factor is an important mediator of chronic inflammation in rheumatoid arthritis
- Tumor necrosis factor is an important mediator of effective host defense against microbial infection
- Tumor necrosis factor blockade can result in significant improvement in disease in patients with rheumatoid arthritis
- Tumor necrosis factor blockade has been associated with opportunistic infections