Pharmacogenomics and Molecular Medicine in Application to Rheumatoid Arthritis

Carl K. Edwards, PhD

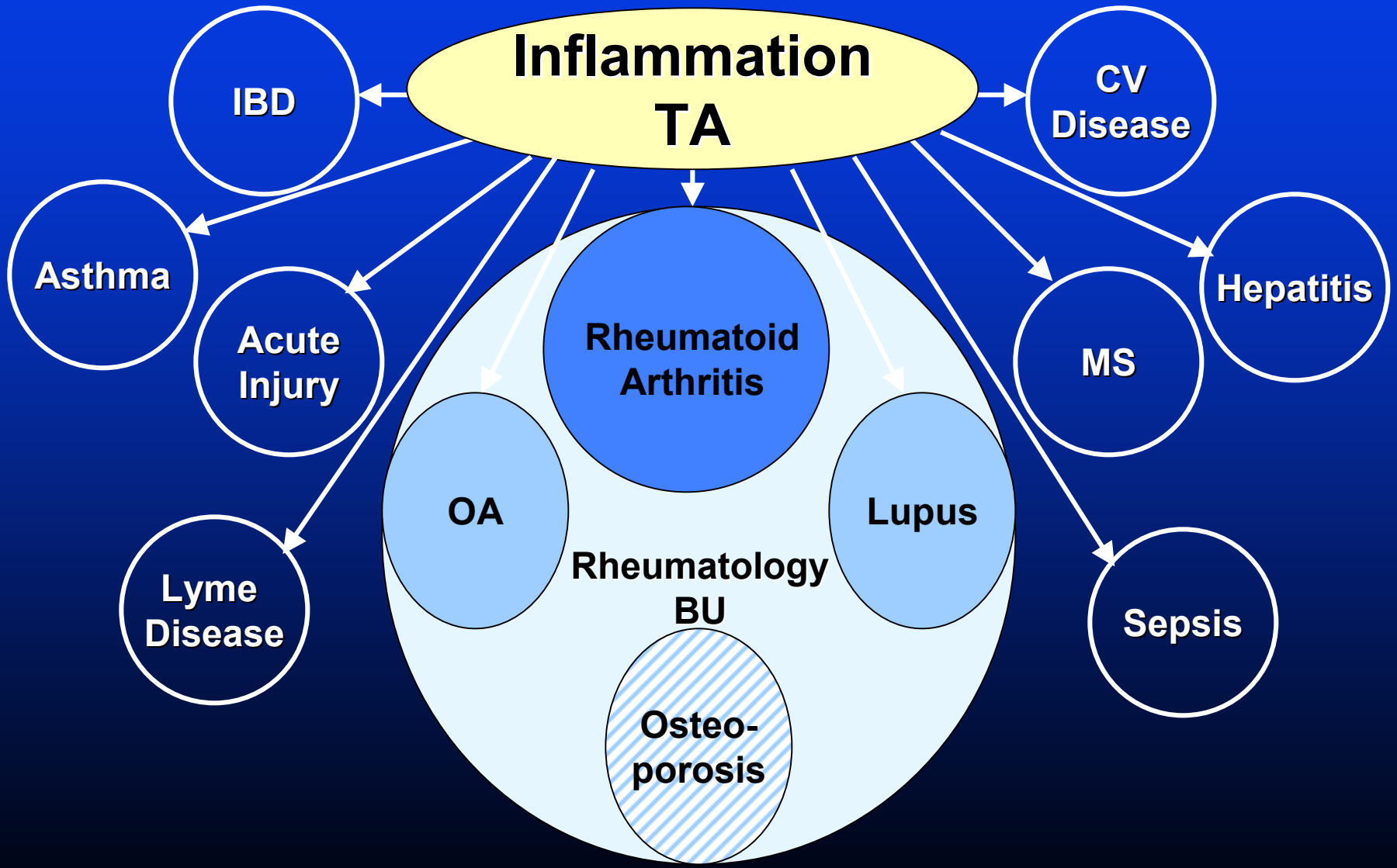
Inflammation Drug Discovery

Research Department

February 12, 2001

NISS Conference on Pharmacogenomics

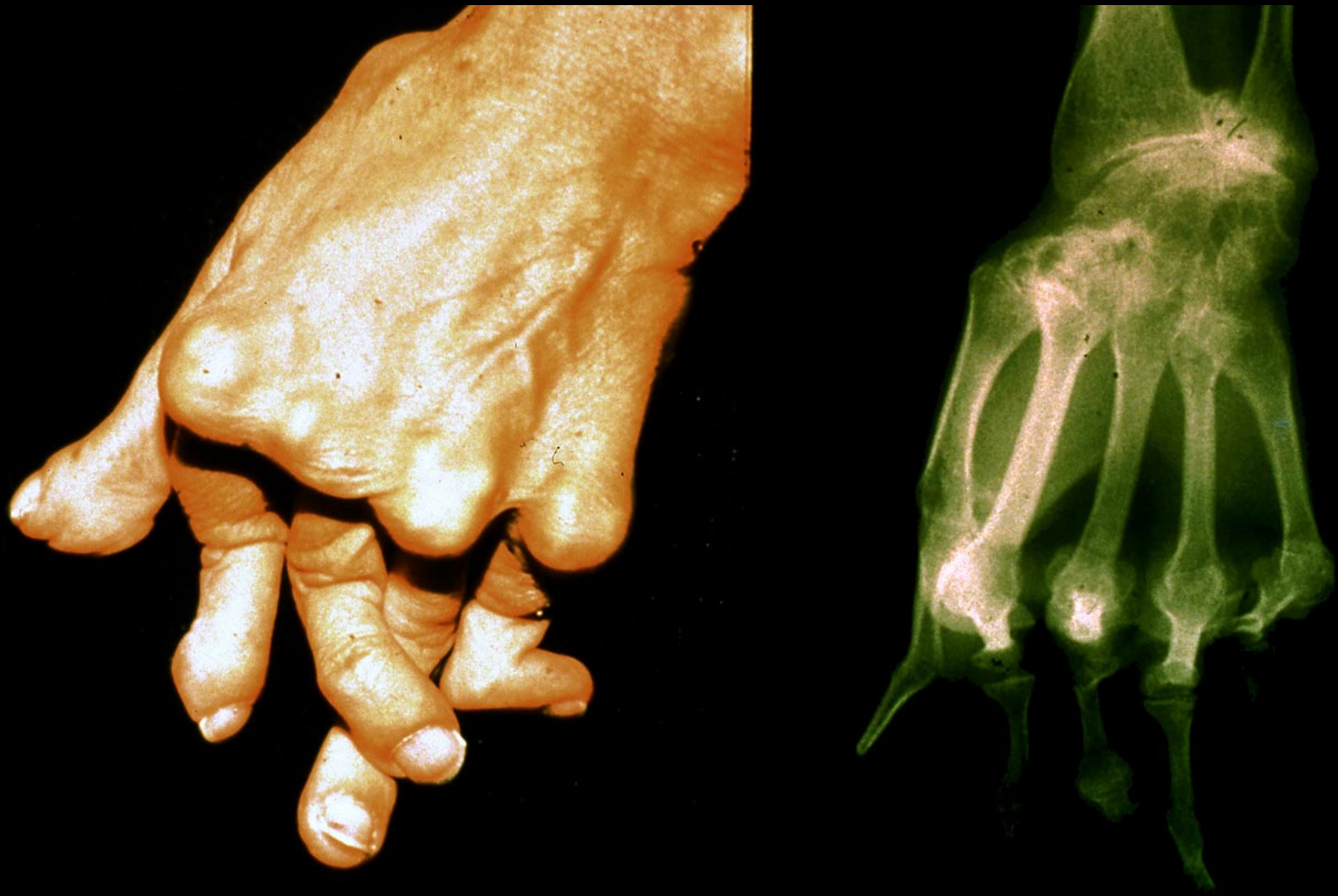
TA Focused on Specific Target Diseases



The Etiology of RA

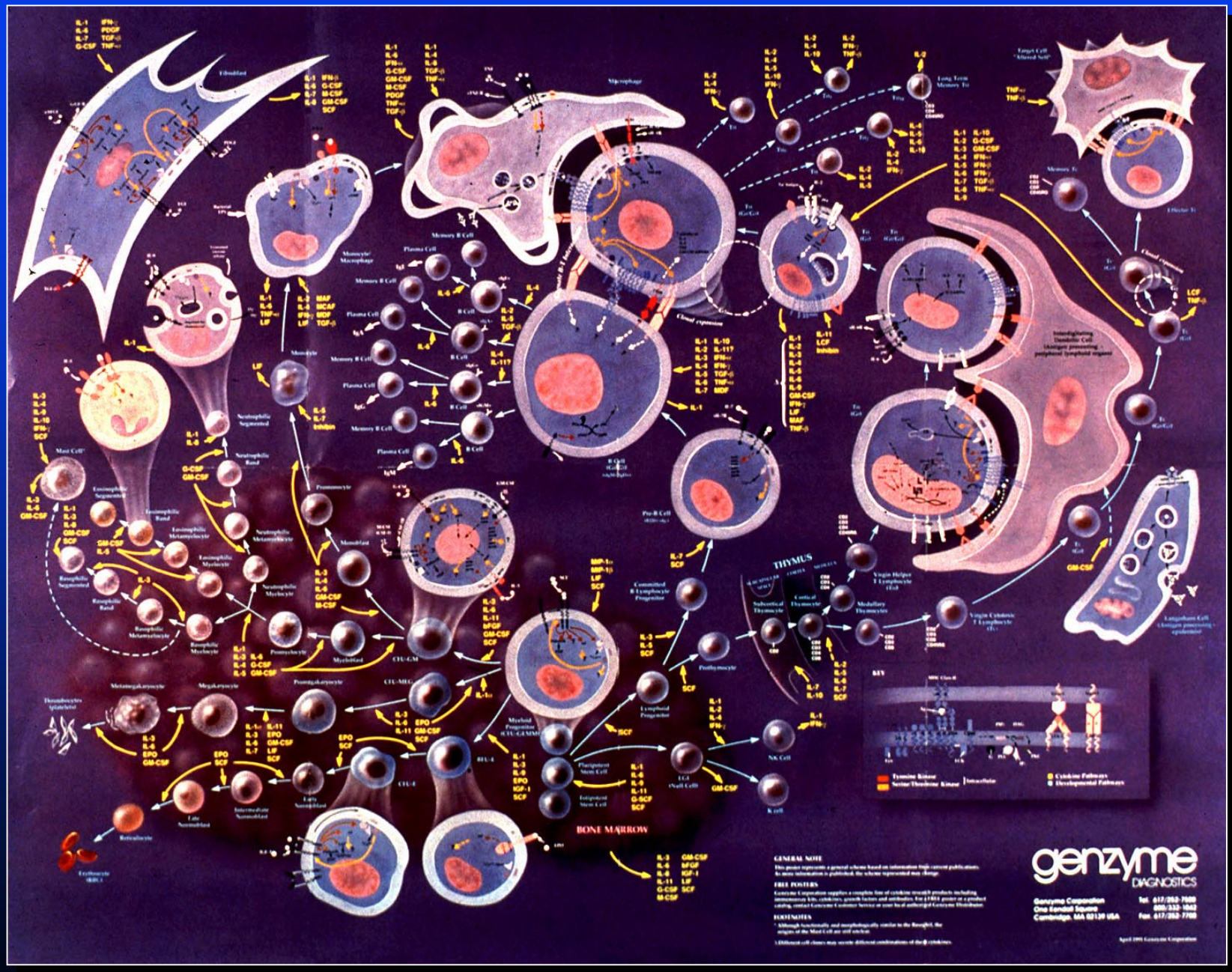
- Is RA an infectious disease?
- Is RA a disease of hypersensitivity?
- Is RA a nutritional or metabolic disease:
- Is RA an endocrine disease?
- Is the initial synovial lesion of RA a clue to etiology?
- Is RA a psychosomatic disease?
- Is RA a hereditary disease?

Robinson, WD, Ch.12 in Arthritis **and Allied Conditions, ed.*JL Hollander*, 7th edition, 1966.**

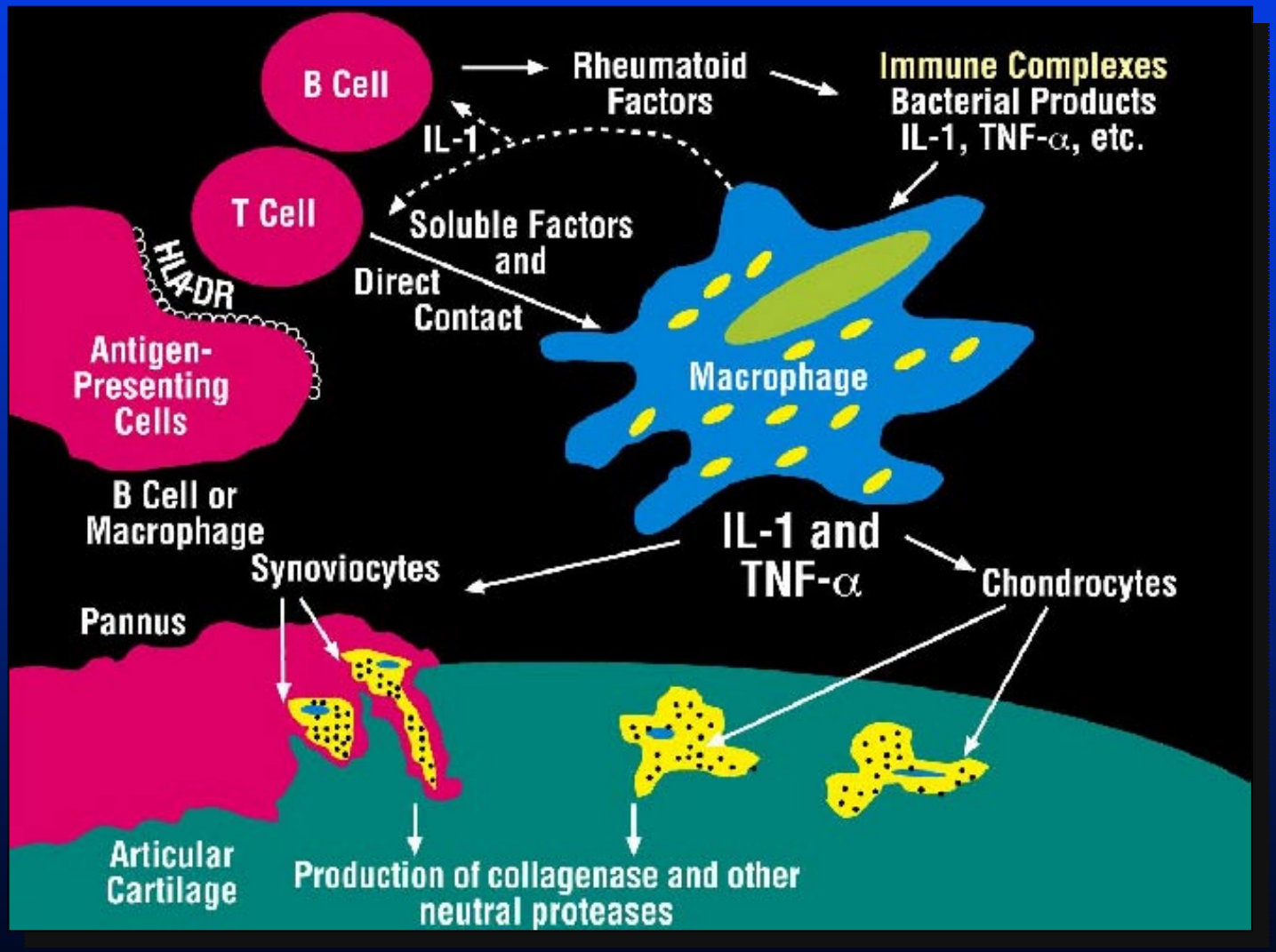


Emerging Trends in Rheumatoid Arthritis

- Identification of cells in the rheumatoid joint
- Characterization of cytokines, molecules that communicate between cells
- Distinction between inflammation and joint destruction
- Development of new treatments that prevent joint destruction

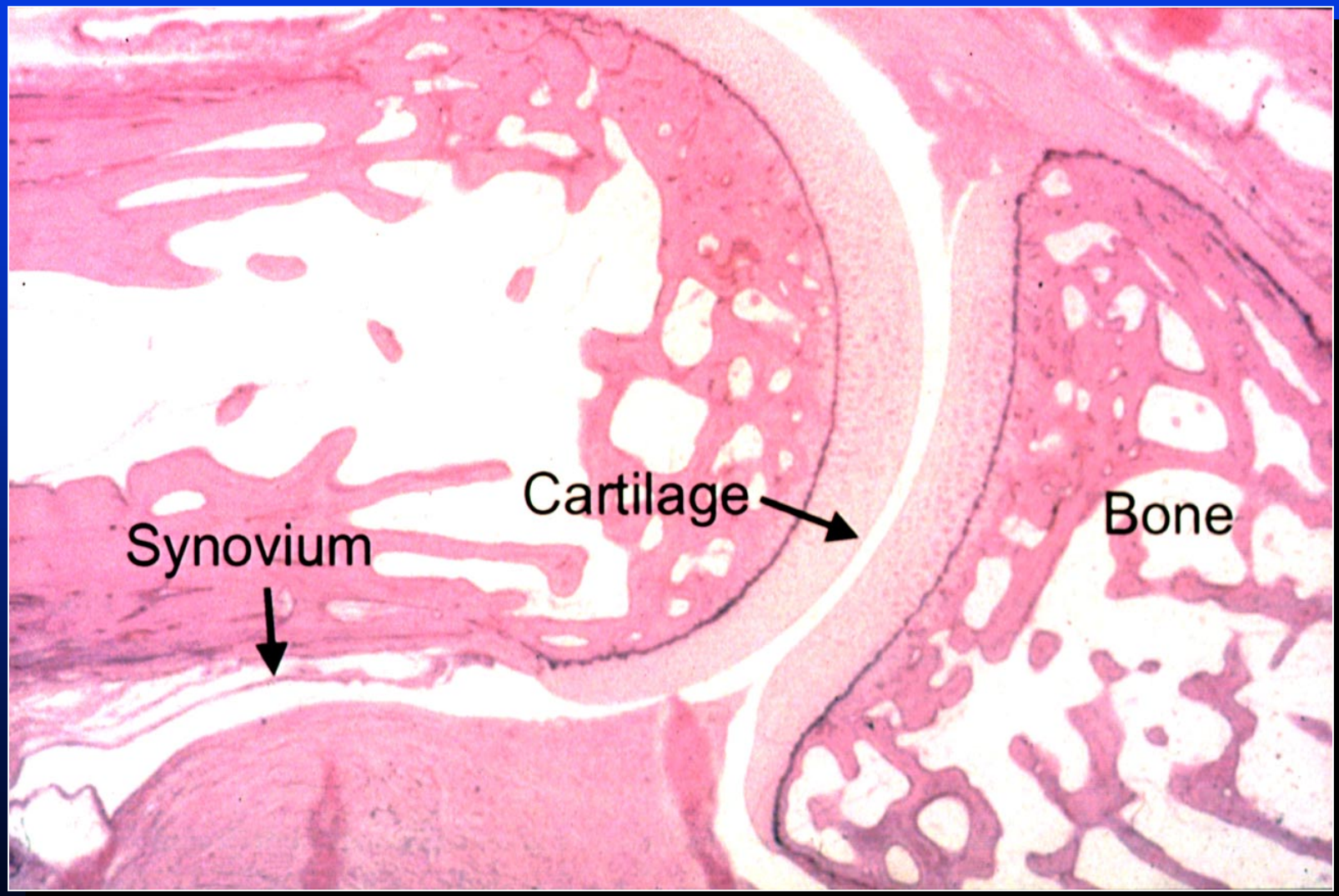

THYMUS
BONE MARROW
genzyme
DIAGNOSTICS

Pathophysiology of RA

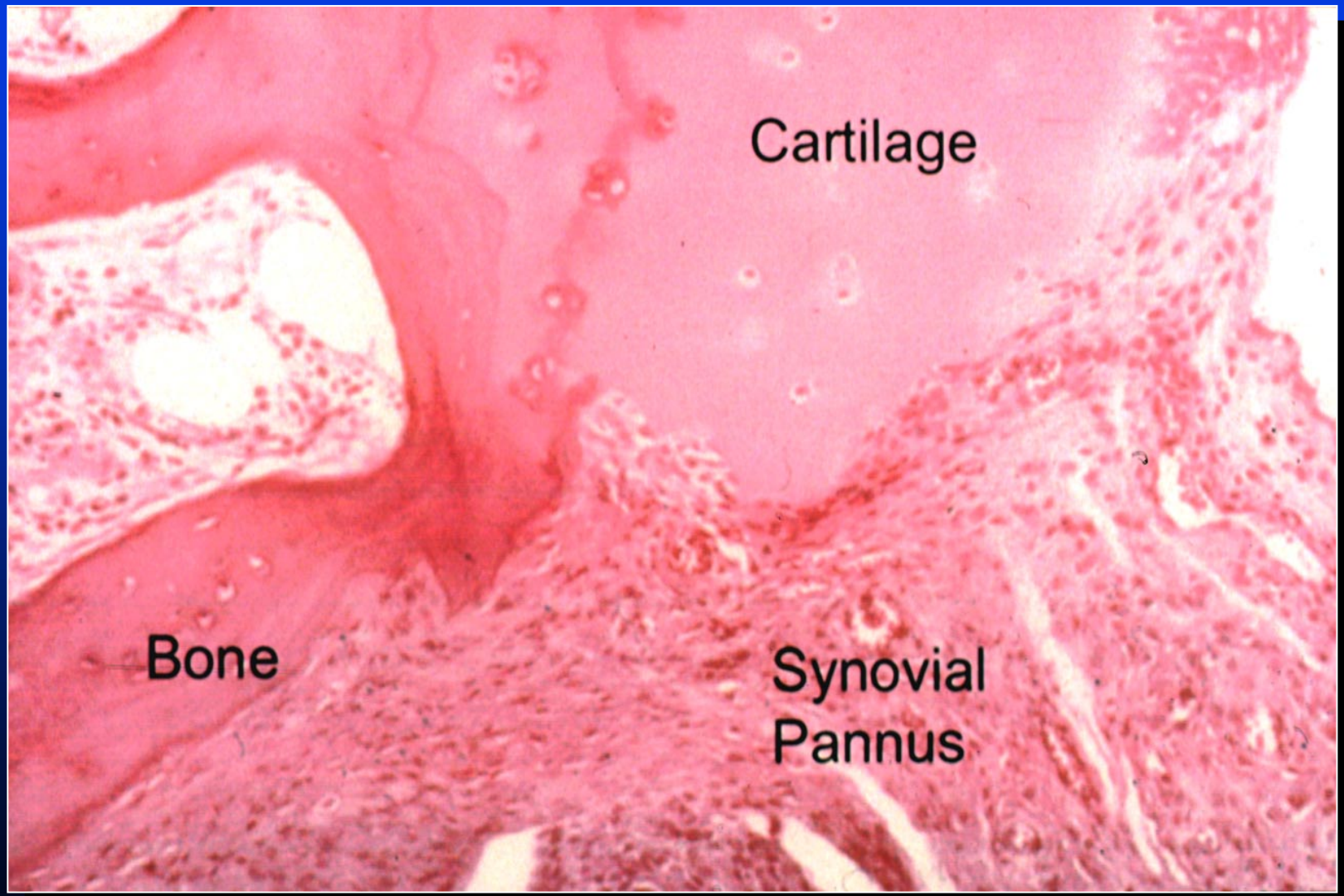


Arend & Dayer, *Arthritis Rheum* 1995

Normal Finger Joint



Finger Joint in RA



Rheumatoid Arthritis 2000

- The initial cause remains unknown
- Multiple genetic factors predispose to developing the disease or to increase severity
- Perpetuation of the chronic joint disease may involve different mechanisms

Rheumatoid Arthritis 2000: Treatment

- Inflammation: Swelling, redness, warmth and pain
  - NSAIDs (COX-2 inhibitors) traditional treatment
    - May improve symptoms but have no effect on long-term outcome
- Tissue Destruction: Loss of articular cartilage and erosion of adjacent bone
  - DMARDs (Disease Modifying Anti-Rheumatic Drugs)
  - Use early to arrest the disease process and prevent further joint destruction
  - Lead to improved function and less disability

Arthritis is now a disease that is fought with many drugs. On the whole, these drugs treat inflammation as a symptom, but do not address the actual cause of the disease.

Nature Biotechnology, 2000; 18, IT12/IT14

Selected Companies with Arthritis R&D Programs

Company	Program	Status
Abgenix (Fremont, CA)	Human Mab against IL-8	Phase I/II, 11/98
Aeterna Laboratories (Québec, PQ, Canada)	Angiogenesis inhibitor (AE-941) derivative for osteoarthritis and rheumatoid arthritis	Preclinical
Agouron (La Jolla, CA)	Selective matrix metalloprotease (MMP) inhibitor	Phase I, 9/96
Alexion (New Haven, CT)	Human Mab C5 inhibitor of the complement cascade	Phase II, 8/99
Amgen (Thousand Oaks, CA)	Oral tumor necrosis factor binding protein	Phase II, 1999
Anergen (Redwood City, CA)	MHC peptide compound	Phase I, 7/98
AnorMed (Langley, BC, Canada)	Azaspirane immunomodulators (Atiprimod)	Phase I
AutoImmune (Lexington, MA)	Synthetic type II collagen peptide (second-generation Colloral)	Preclinical
Axys Pharmaceuticals (S. San Francisco, CA)	Cathepsin as arthritis target	Lead
BASF Bioresearch (Worcester, MA)	Anti-tumor necrosis factor α (TNFα) Mab	Phase III, 2/2000
Bayer (Leverkusen, Germany)	Humanized anti-TNF antibody	Phase I
Biogen (Cambridge, MA)	Recombinant human γ-interferon	Phase III
Biomatrix (Ridgefield, NJ)	Elastoviscous hylan biopolymer for osteoarthritis of the knee (Synvisc)	Market, 8/97
Boehringer Ingelheim (Ingelheim, Germany)	Gene therapy to neutralize IL-1 and IL-10	Phase I, 1999
Boston Life Sciences (Boston, MA)	Oral amiprilose HCl (a modified hexose, Therafectin)	PLA or NDA Filed, 6/98
Cambridge Antibody Technology (Cambridge, UK)	Anti-TNFα Mab	Phase III, 2/2000
Celgene (Warren, NJ)	Thalidomide (Thalomid, formally Synovir)	Phase II, 8/99
Cell Genesys (Foster City, CA)	Human anti-IL-8 antibody from mouse transgenics	Preclinical
Centocor (Malvern, PA)	Chimeric anti-TNF Mab (Remicade)	Market, 11/99
Chiron (Emeryville, CA)	Insulin-like growth factor (IGF)-1 and IL-2	Lead
Cortech (Denver, CO)	Orally bioavailable (neutrophil) elastase inhibitor	Lead
Cypress Bioscience (San Diego, CA)	Protein-A matrix plasma apheresis column (Prosorba)	Market, 4/99
DepoTech (San Diego,CA)	IGF-1 and IL-2 DepoFoam formulations	Lead
G.D. Searle & Co. (Skokie, IL)	OX-2 inhibitor celecoxib (Celebrex)	Market
Genta (San Diego,CA)	Oral controlled-release formulation of diclofenac (Voltaren)	IND Filed
IDEC Pharmaceuticals (San Diego,CA)	Second-generation anti-CD4 Mab	Phase I/II, 1997
Immune Response Corp. (Carlsbad, CA)	Vb3, 14 and 17 T-cell receptor therapeutic vaccine for RA	Phase I, 9/92
Immunex (Seattle, WA)	Soluble TNF receptor (Enbrel)	Market, 11/98
Inflazyme (Vancouver, BC, Canada)	Inflammatory cell activation inhibitor (Bispan)	Preclinical, 1999
Isis Pharmaceuticals (Carlsbad, CA)	Antisense intercellular cell adhesion molecule-1 inhibitor	Terminated
Kissei Pharmaceutical (Tokyo)	Oral small molecule inhibitor of p38 MAP Kinase	Phase II
Ono Pharmaceutical (Osaka, Japan)	Orally bioavailable neutrophil elastase inhibitor	Lead
Peptide Therapeutics (Cambridge, UK)	HSP-tetrapeptide to split IgA and α-antitrypsin	Phase II, 9/97
SmithKline Beecham (Philadelphia, PA)	Second-generation anti-CD4 Mab	Phase I/II, 1997
Supergen (San Ramon, CA)	IV pentostatin (small-molecule purine analog, Nipent)	Phase II

Source: Biovista (www.biovista.com)

Nature Biotechnology, 2000; 18, IT12/IT14

Increasing understanding of the molecular cascades involved are already producing significantly better drugs than in the past with increased selectivity and fewer side effects.

Nature Biotechnology, 2000; 18, IT12/IT14

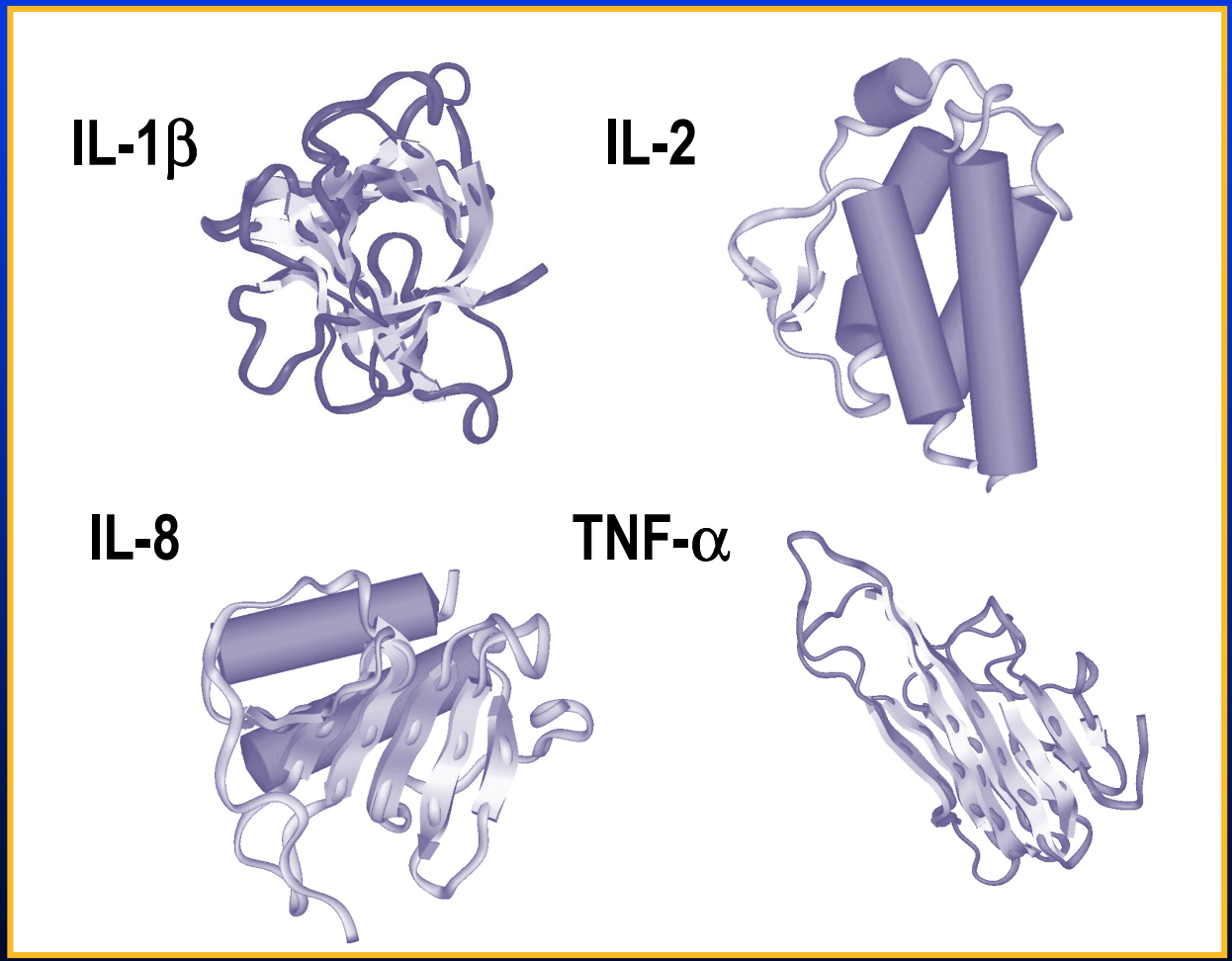
New Therapeutic Directions in RA

- Cytokine inhibitors or anti-inflammatory cytokines
- Enzyme inhibitors
- Block inflammation pathways inside cells
- Inhibit fibroblast growth

What is Interleukin-1 and Why is it Important in RA?

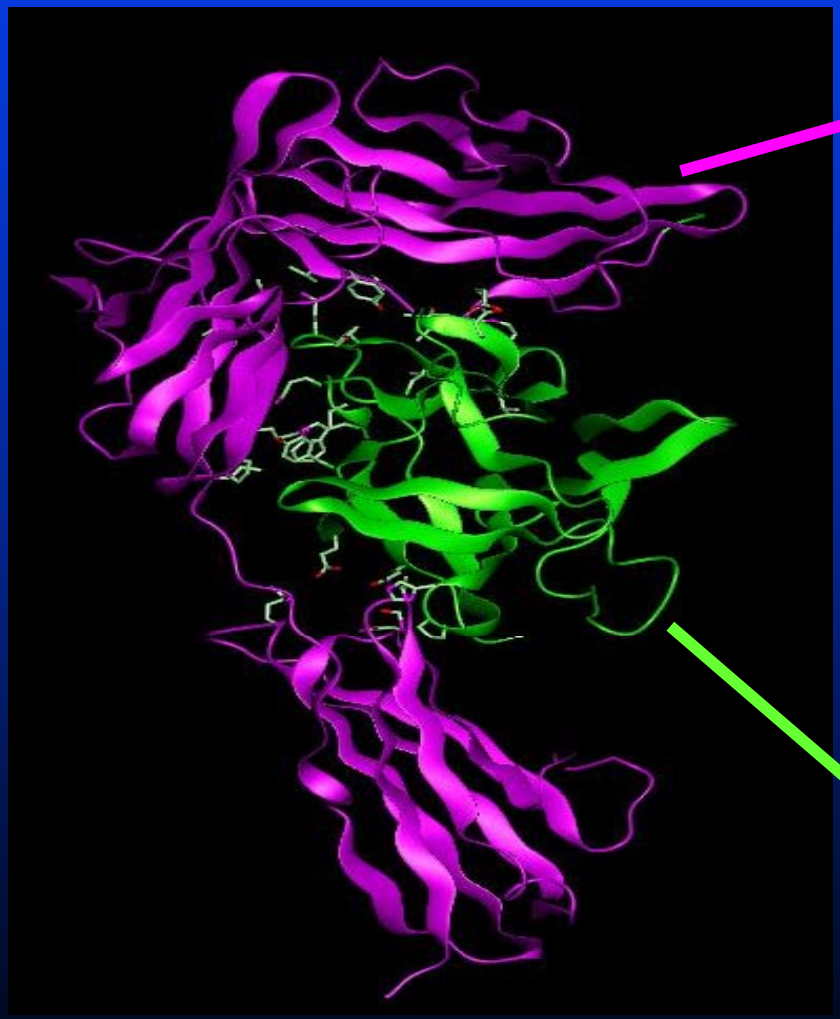
- Chemical nature
  - Small protein, non-structural but active
- Class
  - Cytokine, often associated with infection, inflammation and various disease, not health
- Subclass
  - Proinflammatory

Prototypical Structure of Several Cytokine Classes



ANAKINRA

Interleukin-1 Receptor Antagonist (IL-1Ra)



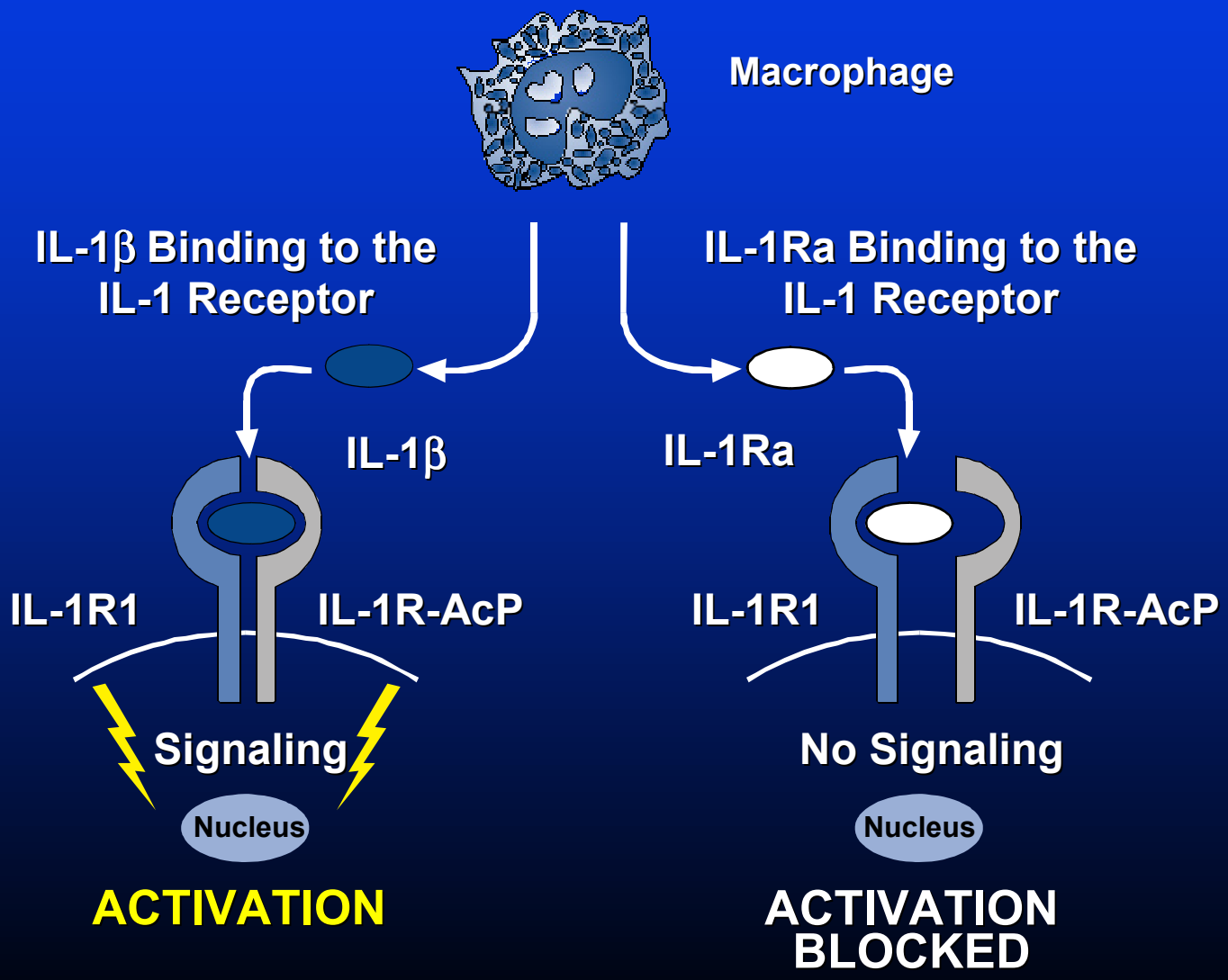
IL-1 Receptor Type I

- 153 amino acids
- MW 17.3 kd
- Binding Affinity Kd = 205 pM
- IL-1R Type I ~3300 sites/cell*

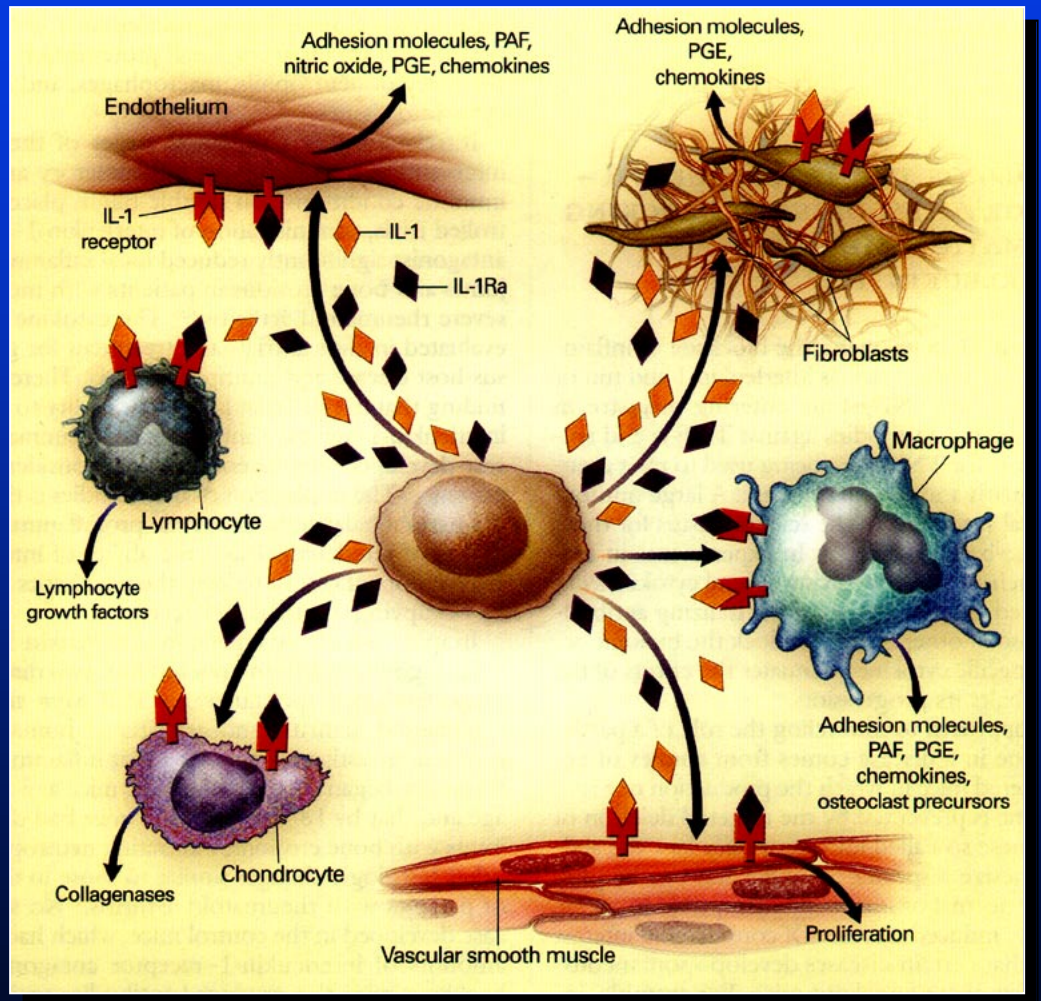
IL-1 Ra

*Dripps et al, *J. Biol. Chemistry* 1991

IL-1Ra Blocks Cellular Activation by Binding to IL-1 Receptor

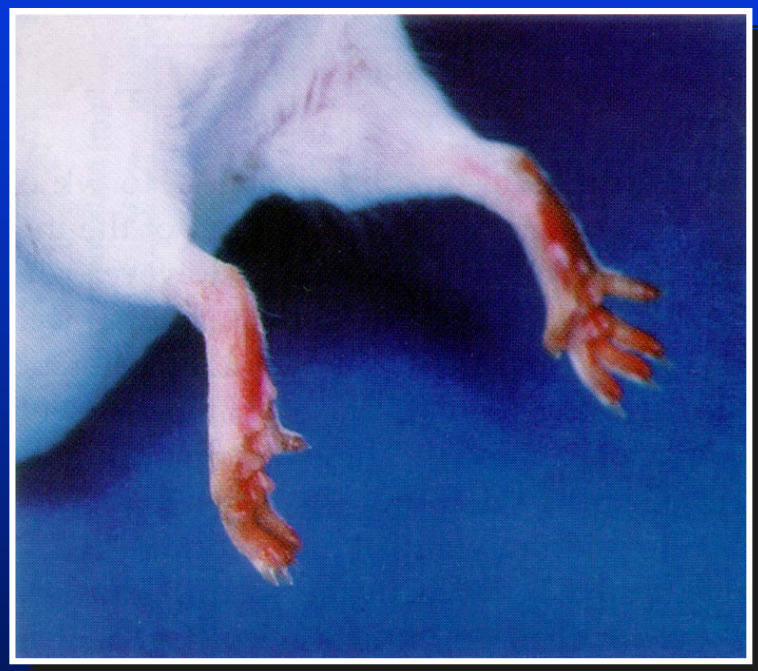


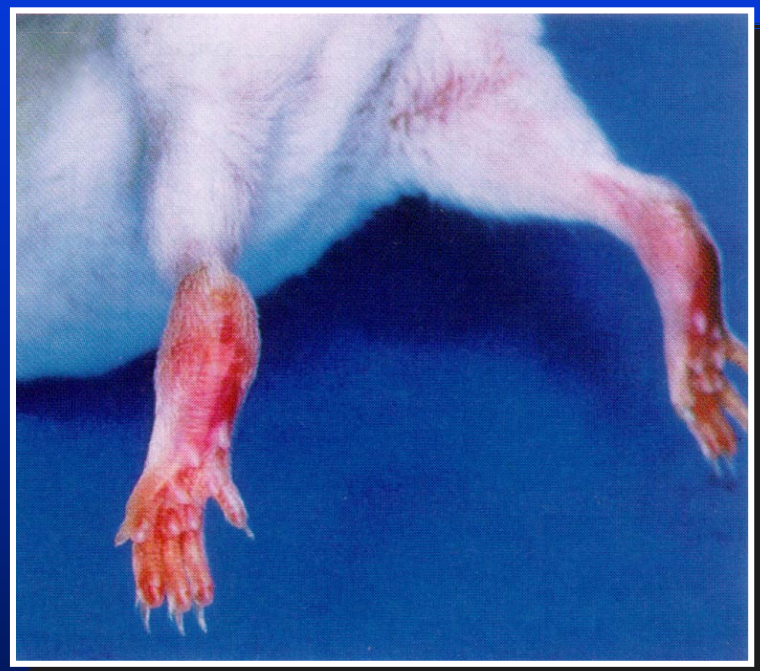
The Actions of Interleukin-1 (IL-1) and Interleukin-1-Receptor Antagonist (IL-1Ra)



Dinarello. NEJM, 343:728-730. 2000

Animals Without IL-1Ra Get Arthritis

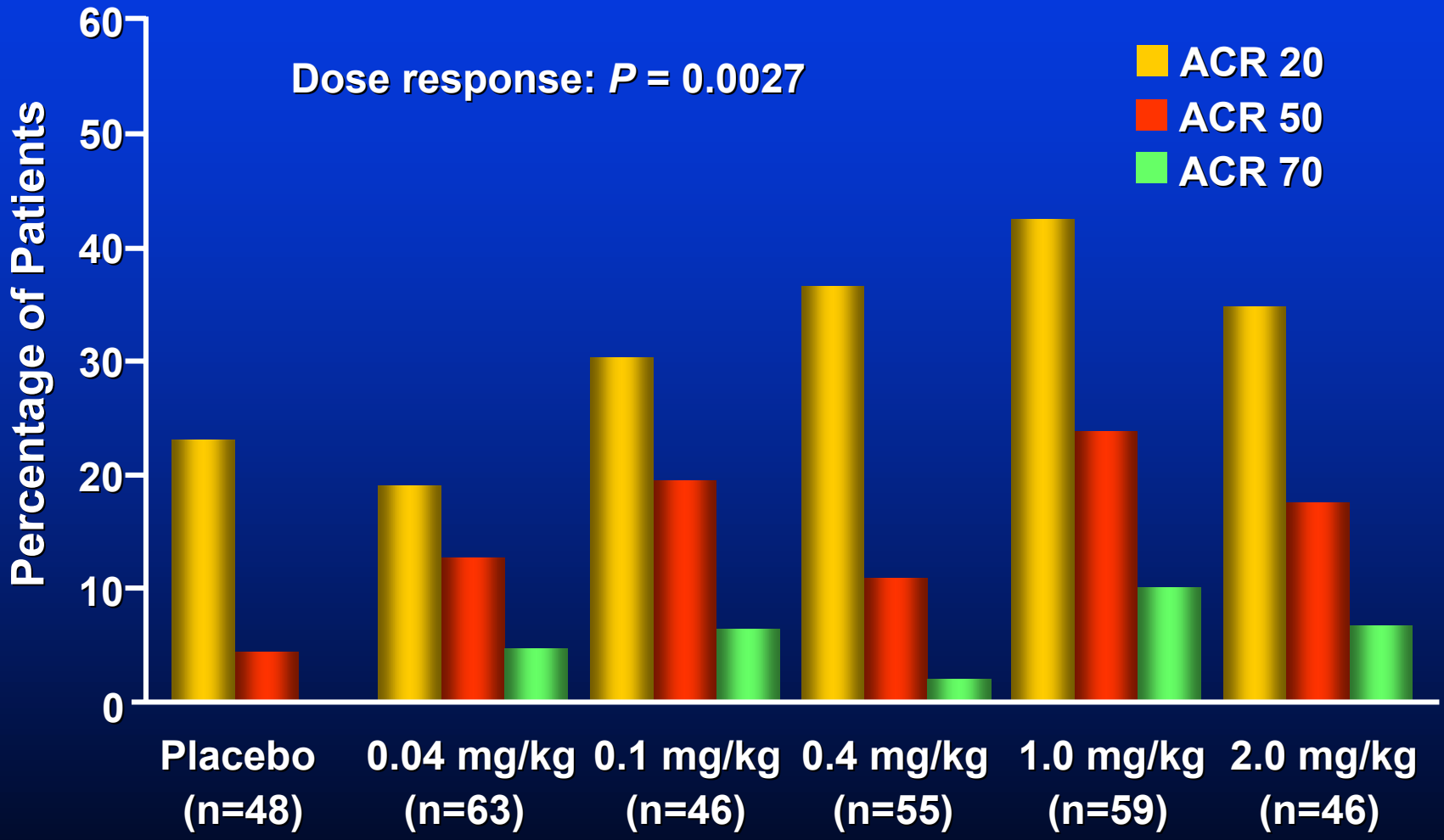




Balb/cA IL-1Ra$^{+/+}$ Normal **Balb/cA IL-1Ra$^{-/-}$ Affected**

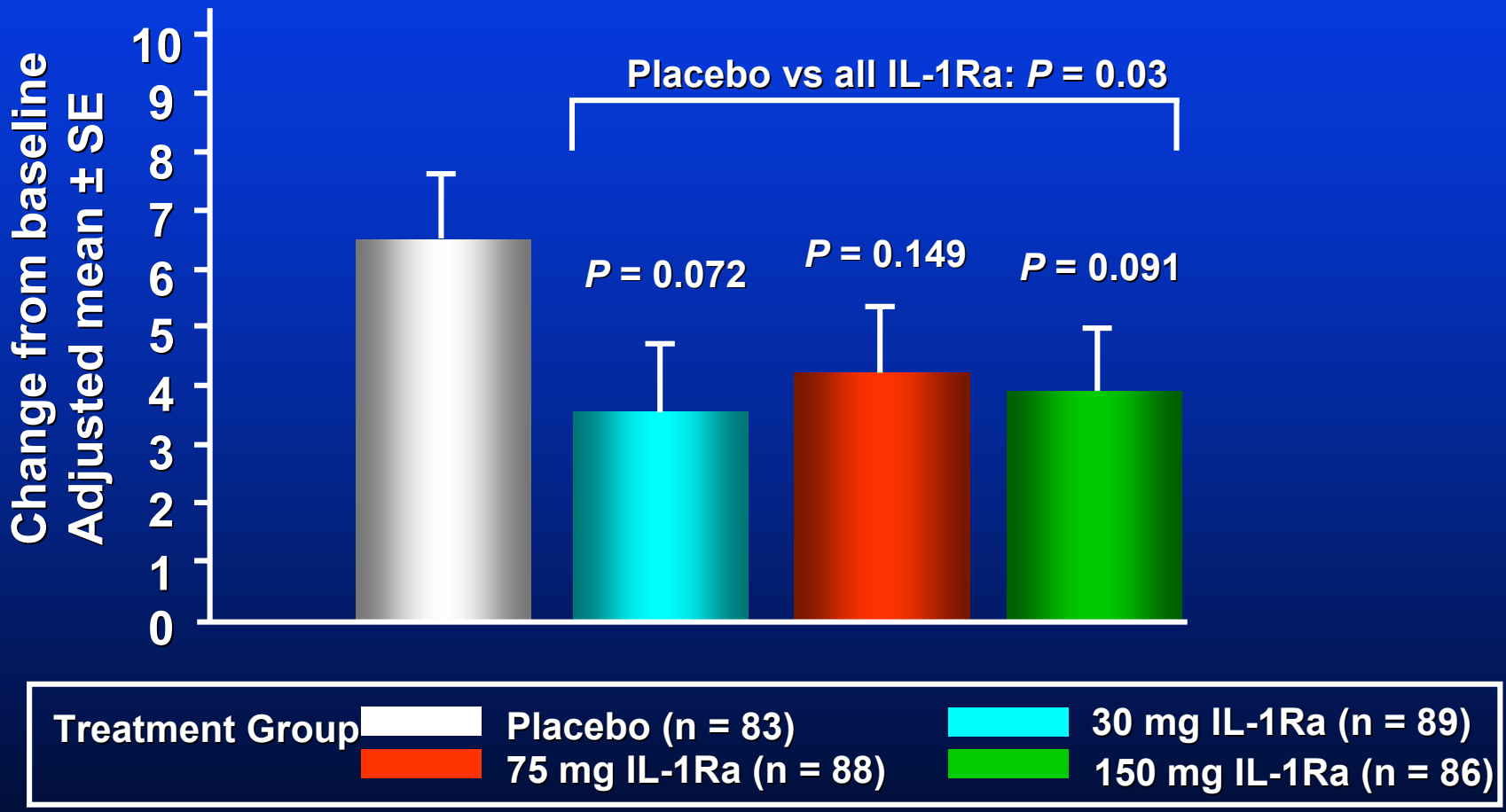
Horai et al., *J. Exp. Med*. 2000 313-320

Effect of IL-1Ra and MTX Treatment: ACR Responses at 24 Weeks



MTX Combination Therapy Study

Effect of IL-1Ra Treatment: Larsen Score



European Monotherapy Study

Pharmacogenomics

Correlating drug response to biological markers

Biological Markers

Germ Line (DNA)

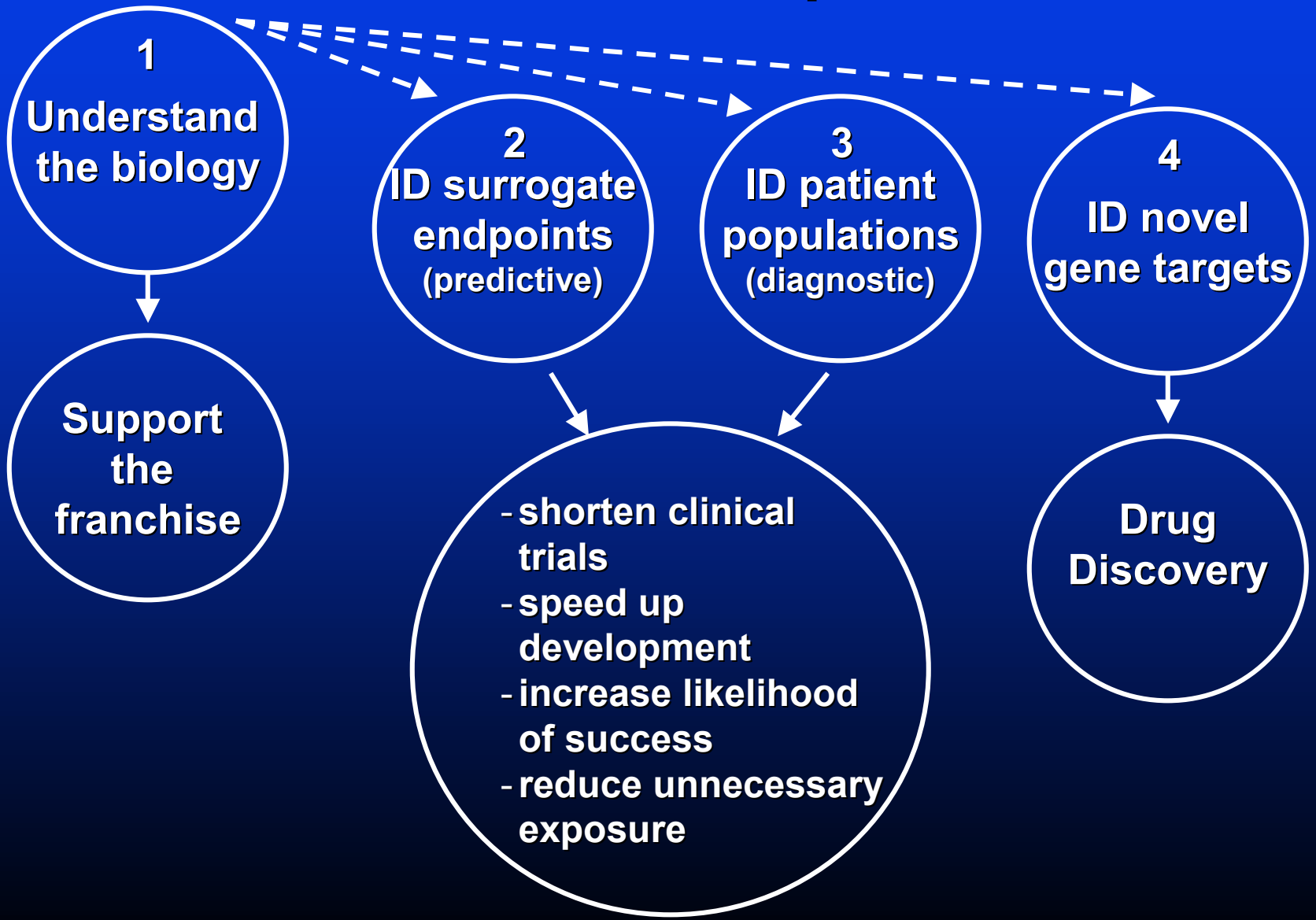
Somatic (DNA/RNA/Protein)

Drug Response

Efficacy

Safety

Why pharmacogenomics, how can it help us?



Selected Companies with Pharmacogenomics Programs

Company	Area
Aeiveos Sciences Group (Seattle, WA)	Aging-related genes and gene responses
AstraZeneca (Cheshire, UK)	Population genomic variability studies
CuraGen (New Haven, CT)	Integrated genomic and pharmacogenomic platform
diaDexus (Palo Alto, CA). Joint venture of Incyte (Palo Alto, CA), and SmithKline Beecham (Philadelphia, PA)	Diagnostic and pharmacogenomic kits based on leads from Incyte's, SmithKline Beecham's and Human Genome Science's (Rockville, MD), databases
Epidauros Biotechnologie (Bernied, Germany)	Targeted genomic variability analysis
Eurona Medical (Upsala, Sweden)	CRO–Retrospective correlations of drug response and genetic profiling
Gemini Research (Cambridge, UK)	Phenotype-based gene discovery; dizygotic twin studies
Genaissance Pharmaceuticals (New Haven, CT)	Genetic polymorphism correlations; isogene discovery; breast cancer; vascular lesions
Genome Therapeutics (Waltham, MA)	Human high-resolution polymorphism database
Genostic Pharma (Cambridge, UK)	Polymorphisms and allele frequency analysis
Genset (Paris, France)	High-density biallelic maps, 60,000 markers
Hexagen (Cambridge, UK; acquired by Incyte Genomics in 1998)	Single-strand conformational polymorphism detection methodology
Janssen Pharmaceutica (Beerse, Belgium)	Cytochrome variation analysis
Lion Bioscience (Heidelberg, Germany)	Proprietary sequencing and analysis software for drug target identification and gene expression data under varying conditions
Millennium Predictive Medicine (Cambridge, MA, re-acquired by Millennium)	SNP use in pharmacogenomics
MitoKor (San Diego, CA)	Mitochondrial genome analysis
Nova Molecular (Montreal, Canada)	CNS disease genetic profiling
Rosetta Inpharmatics (Kirkland, WA)	"Ink-jet" technology–based oligonucleotide array studies
Sequana Therapeutics (La Jolla, CA)	High-throughput genotyping
Variagenics (Cambridge, MA)	Genotyping assays based on haplotypes or SNPs for use in clinical trials.

Source: Biovista (www.biovista.com)

Nature Biotechnology, 2000; 18, IT40/IT42

Selected Companies with Biochip Programs

Company	Program
Affymetrix (Santa Clara, CA)	GeneChip Arrays, high-density probes per chip (64–400K spots per chip)
Amersham Pharmacia Biotech (Uppsala, Sweden)	Cy3 and Cy5 fluorescent dyes for detection by molecular array scanners
Applied Biosystems (Foster City, CA)	High throughput single nucleotide polymorphism mapping
Axys Pharmaceuticals (S. San Francisco, CA)	Variable density per chip approach
Caliper Technologies (Palo Alto, CA)	Lab-on-a-chip microfluidic technologies
Cepheid (San Jose, CA)	Microfluidics for clinical diagnostic applications
Gene Logic (Gaithersburg, MD)	READS microarray technology for expression profiles
Hewlett Packard (Palo Alto, CA)	Array scanners
Hyseq (Sunnyvale, CA)	Sequence-by-hybridization chips for sequencing, expression analysis, and diagnostics (8K per chip)
Incyte Genomics (Palo Alto, CA)	Gene expression microarrays, medium density standardized and/or customized DNA chips (10K spots per chip)
Micronics (Redmond, WA)	Microfluidics technology development
Millennium Pharmaceuticals (Cambridge, MA)	Expression analysis molecular arrays; surface plasmon resonance array chips
Molecular Dynamics (Sunnyvale, CA)	Medium density chips; confocal scanners
Mosaic Technologies (Boston, MA)	Acryite polyacrylamide gel arrays
Orchid BioSciences (Princeton, NJ)	3-D microfluidic chip for genotyping and DNA synthesis
Nanogen (San Diego, CA)	Chips use electronically mediated hybridization to move and concentrate DNA
Packard Instrument Co. (Meriden, CT)	Arrayer gel-based biochip for DNA diagnostics
ProtoGene (Palo Alto, CA)	Low density standardized and/or customized DNA chips (1K spots per chip)
Sarnoff (Princeton, NJ)	Microfluidics technology development
Sequenom (San Diego, CA)	Spectrochips for DNA diagnostics by mass spectrometry
Soane BioSciences (Hayward, CA)	Multiplexed chip for DNA sequencing and fragment analysis
Xenometrix (Boulder, CO)	Gene expression profiling by microarrays

Sources: Biovista (www.biovista.com); BioCentury.

Nature Biotechnology, 2000; 18, IT43/IT44

The great challenge faced by the pharmacogenomics industry at this point is the systematic correlation between normal versus disease patterns of gene expression in a statistically meaningful way.

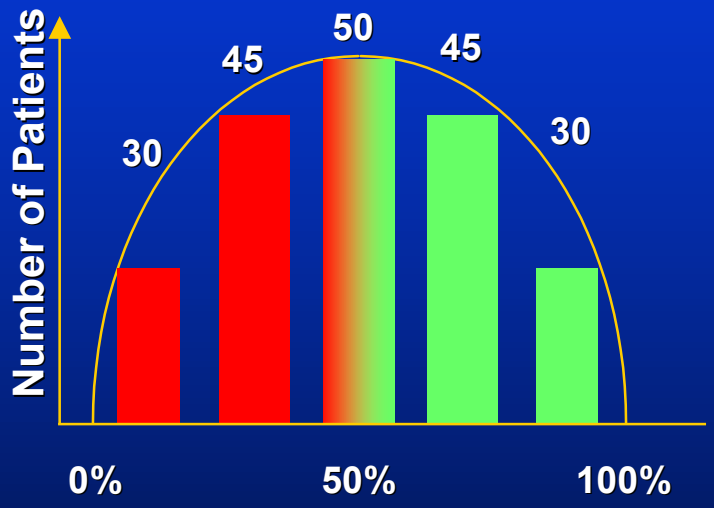
Nature Biotechnology, 2000; 18, IT40/IT42

Objectives

- Identify patient subpopulations that may be more responsive to one drug versus another
  - PEG sTNF-RI Clinical Experience
- Identify surrogate markers that can be utilized to determine if the drug is efficacious
- Identify novel gene targets that can be utilized for drug discovery

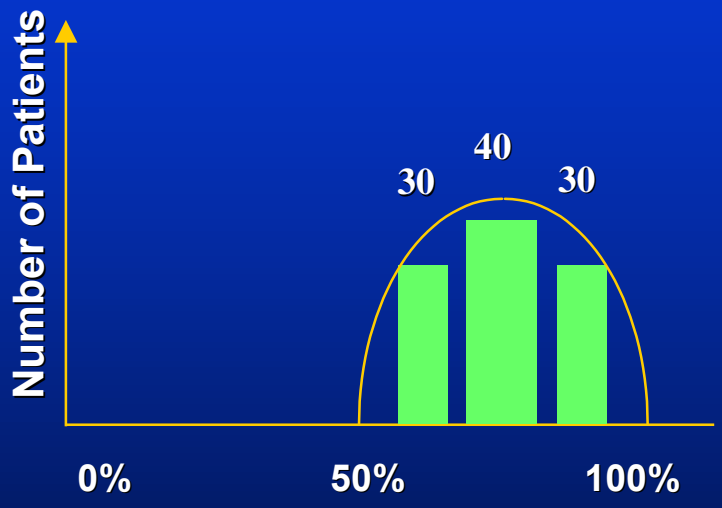
Pharmacogenomics Vision

Today



Unpredictable

Future



Predictable

Opportunities

Clinical Trials

- Reduce clinical trial size (time and cost)
- Increase likelihood of positive response
- Reduce likelihood of dangerous exposure
- Discover new surrogate markers for drug action and toxicity
- Suggest new targets and strategies for future drug development

Improve Drug Profile

- Define drug for *optimal* population
- Establish new paradigm for drug class
- Avoid toxicities / monitoring requirements

IL-1Ra Allelic Polymorphisms and Disease

- An allelic polymorphism is present in intron 2 of the IL-1Ra gene consisting of two to six copies of an 86-bp tandem repeat.
- IL-1Ra allele A2 is associated with various diseases of largely epithelial cell origin, including increased severity of SLE and Sjögren's syndrome.
- The disease associations of IL-1Ra allele A2 may be secondary to a combination of decreased production of IL-1Ra and increased production of IL-1β.

SNPs and Pharmacogenetics

What is an SNP?

Different people can have a different nucleotide or base at a given location on a chromosome

. . . G G **T** A A C T G . . .

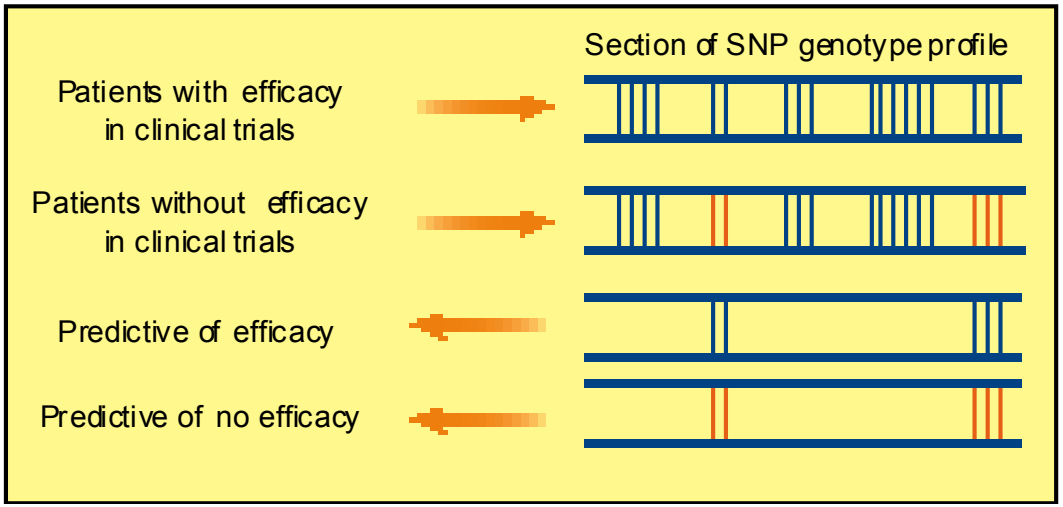
. . . G G **C** A A C T G . . .

What is an SNP map?

Location of SNPs on human DNA

Human DNA

How can an SNP map be used to predict medicine response?

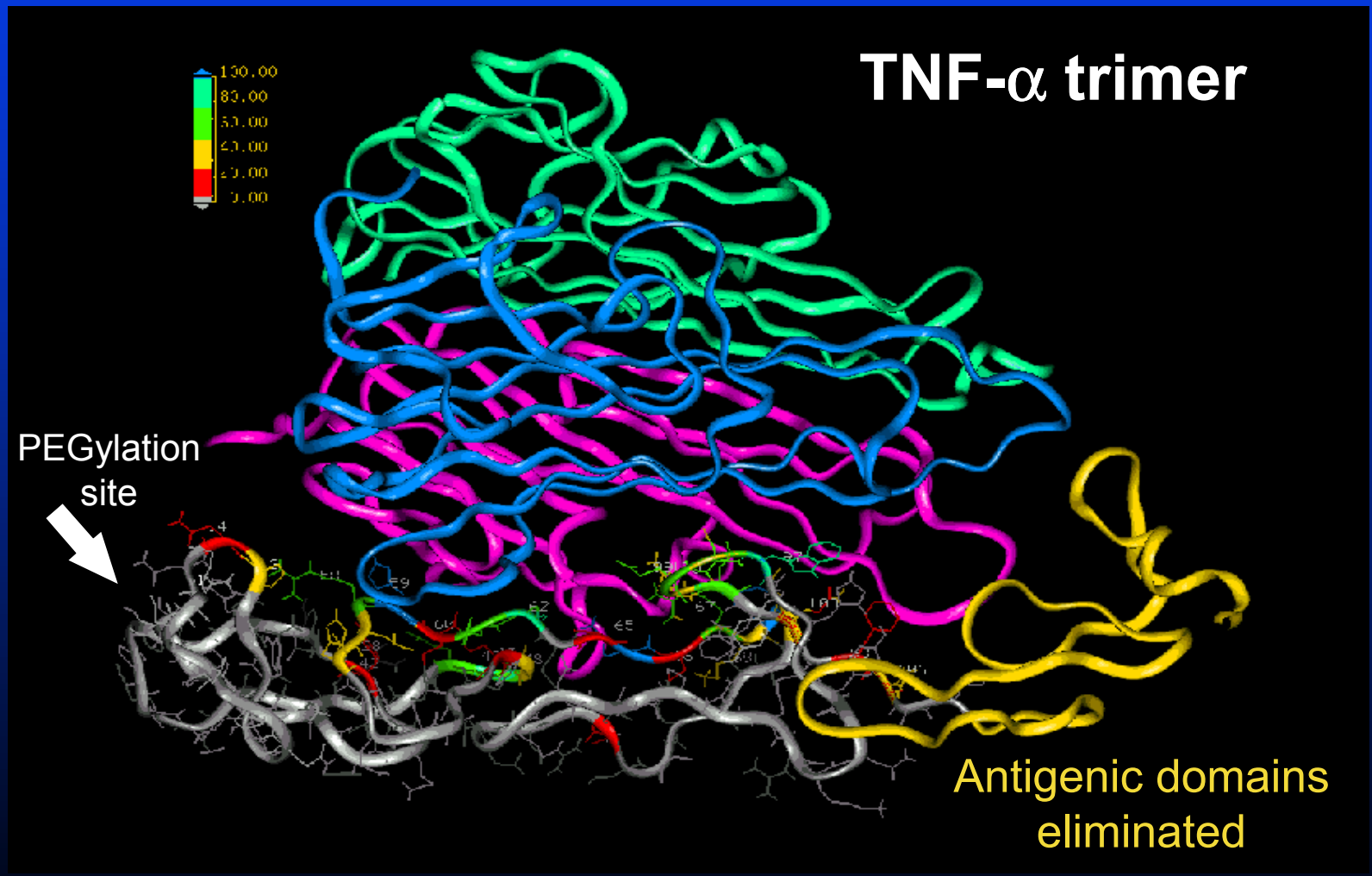


Nature 2000, 405, 857-865

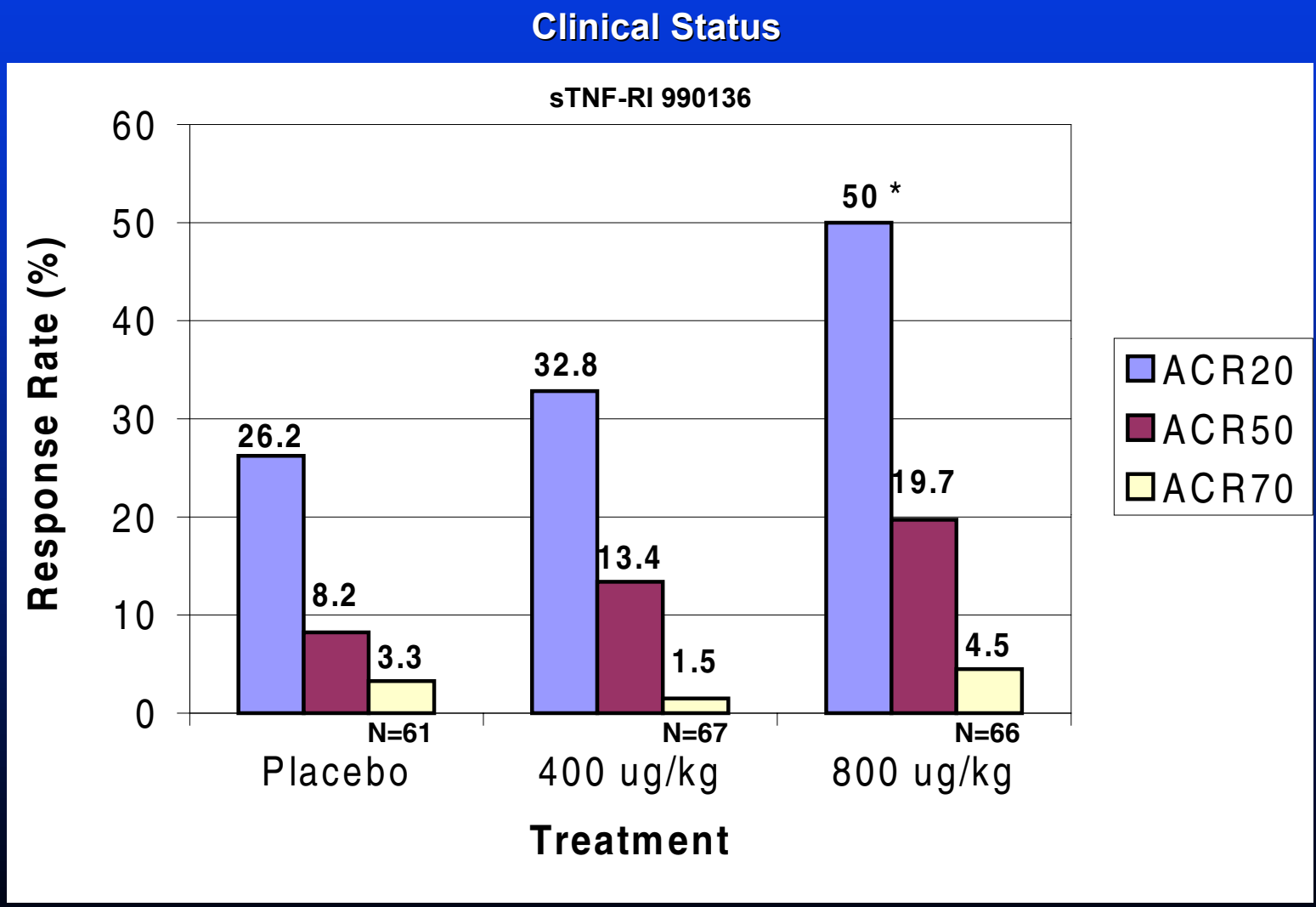
Which Genes and Which SNPs

- Genes are biologically plausible
  - Genes in the drug pathway
  - Genes in disease pathway
  - Genes in drug metabolism
- SNPs cause some biologically relevant change
  - Coding region SNPs change amino acids
  - Coding region amino acid changes alter protein structure
  - Promoter region SNPs change gene expression

sTNF-RI is a Novel, High-affinity Soluble TNF Receptor



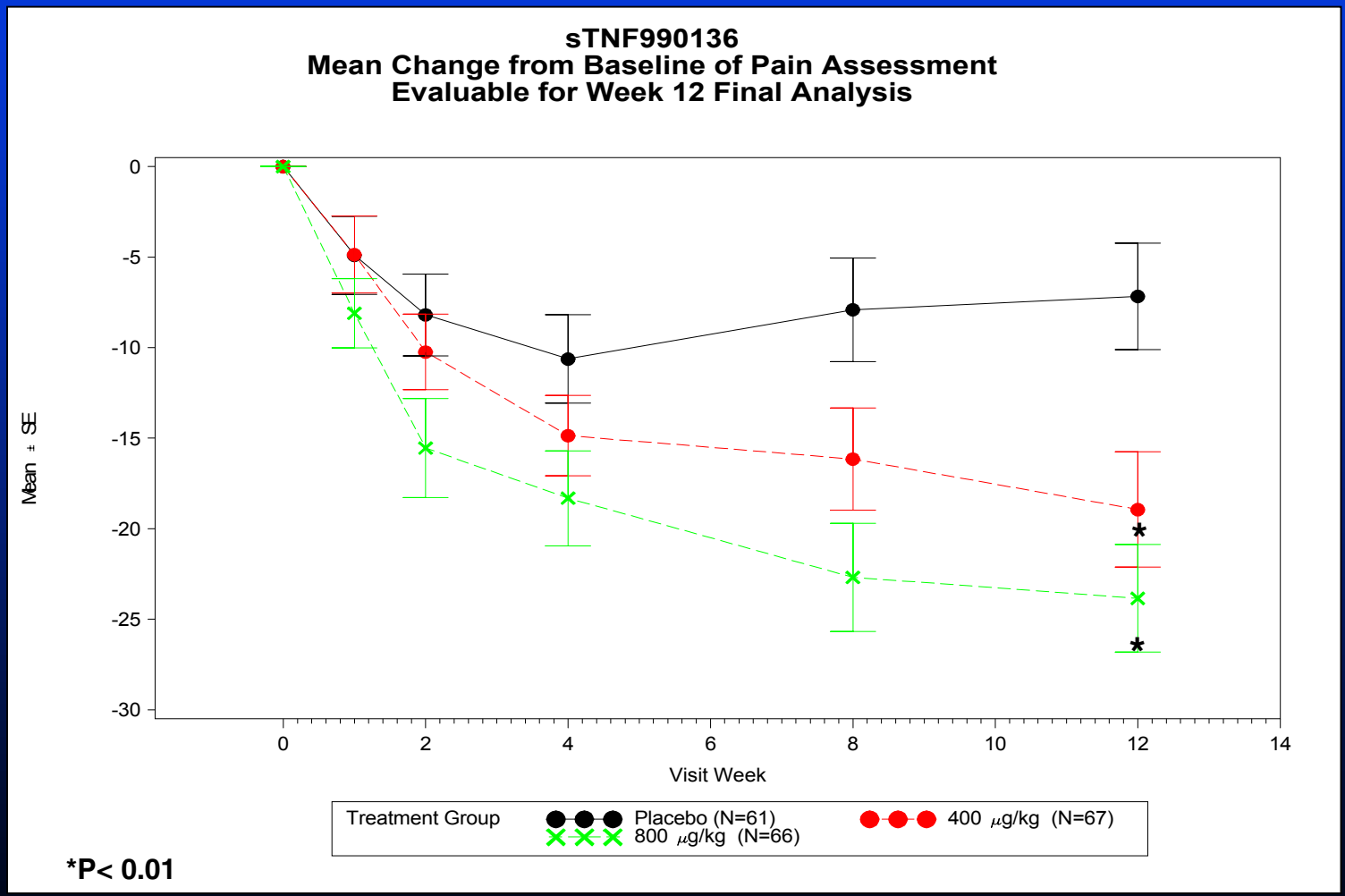
When sTNF-RI Was Delivered Weekly, There Was a Clear Dose Response in ACR 20 Scores



* P=0.022 vs. placebo (CRP or ESR for response). Dose-response (Jonckheere-Terpstra) p=0.007

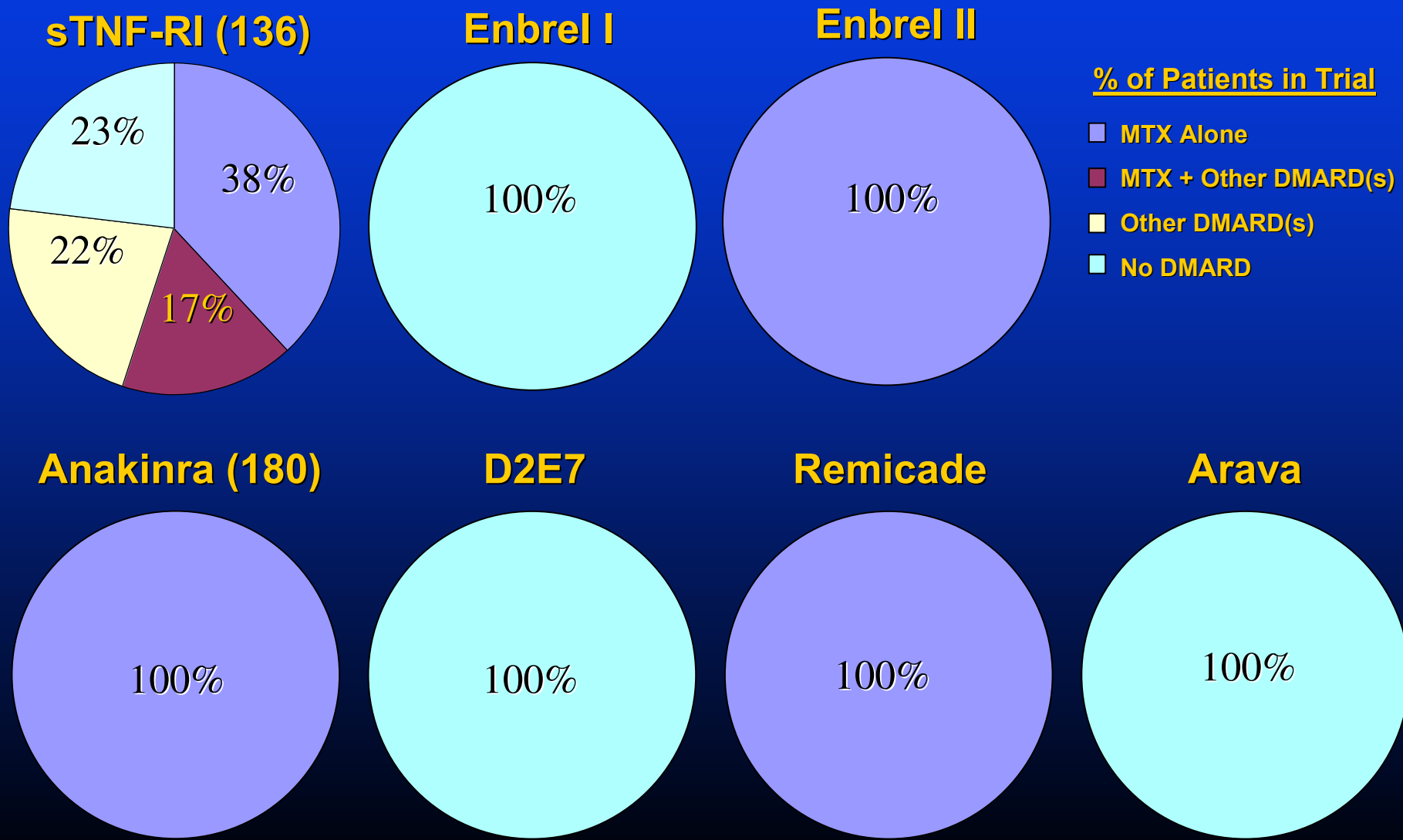
Treatment with sTNF-RI Resulted in Significant Improvement in Pain

Clinical Status



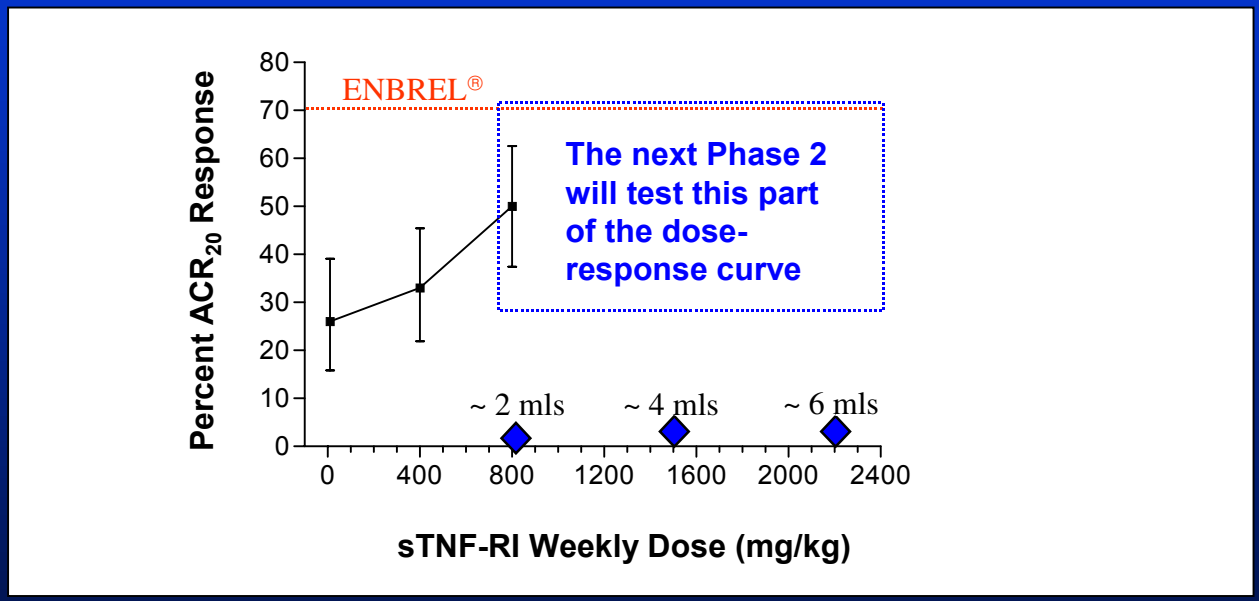
sTNF- RI was Tested and Supports Use in Real Life RA Patient Population

Clinical Status



Challenge: Get the Drug to Work Better

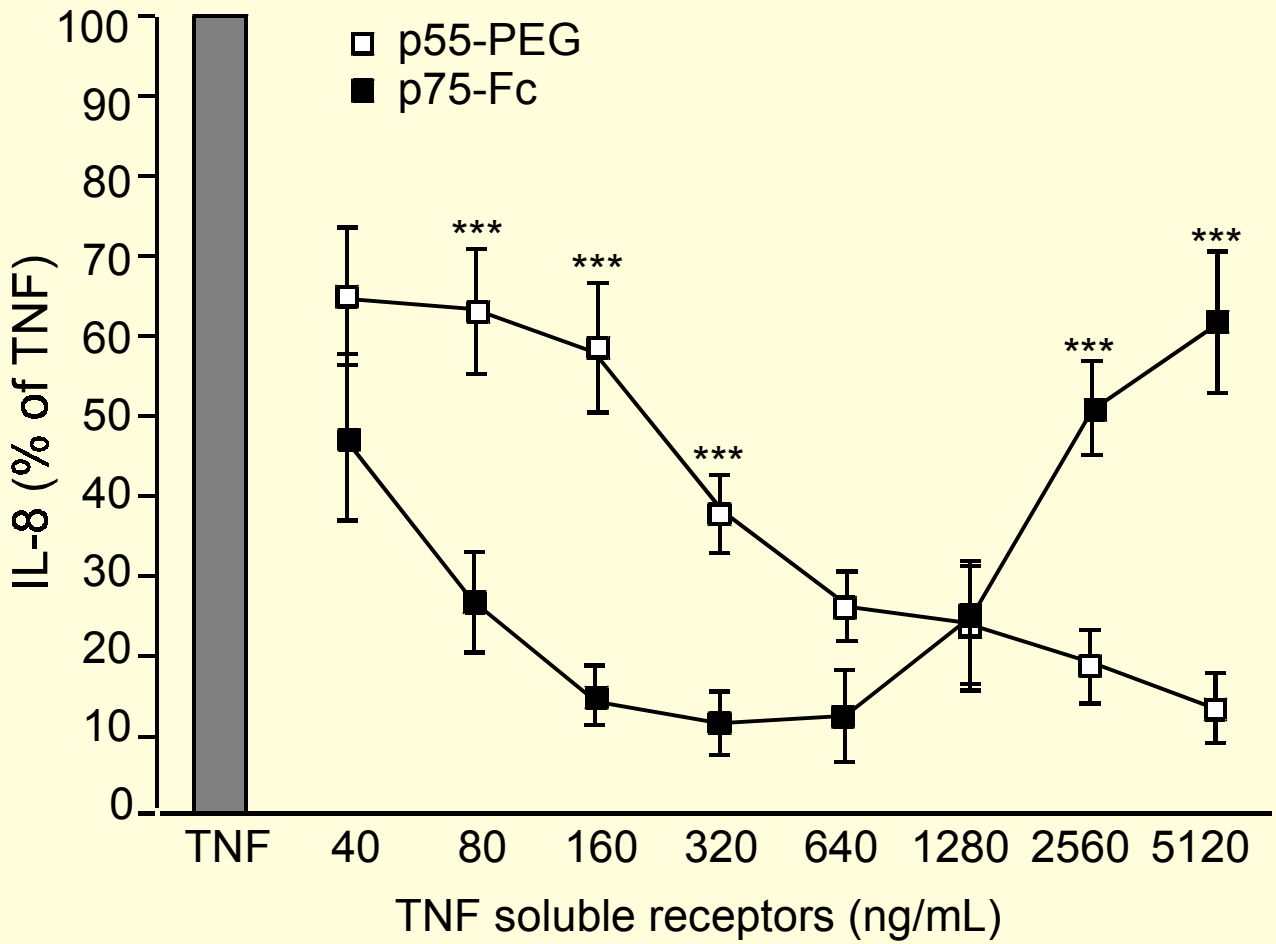
To proceed with monotherapy, we need to find an optimized dose that is equivalent to ENBREL®



To proceed with combination therapy, we need to find a combined dose that is superior to ENBREL®.


NEW
ENBREL
THE FIRST TNF-RECEPTOR
TNF binds to cell-surface receptors initiating an inflammatory response
Naturally occurring soluble TNF-receptor
TNF
Cell-surface TNF-receptor
ENBREL inhibits activation of cell-surface receptors
TNF
ENBREL
This patient is representative of responders in clinical studies. In these studies, up to 15% of patients were nonresponders.

Effect of Soluble TNF Receptors on TNF-α-induced IL-8 in Whole Blood

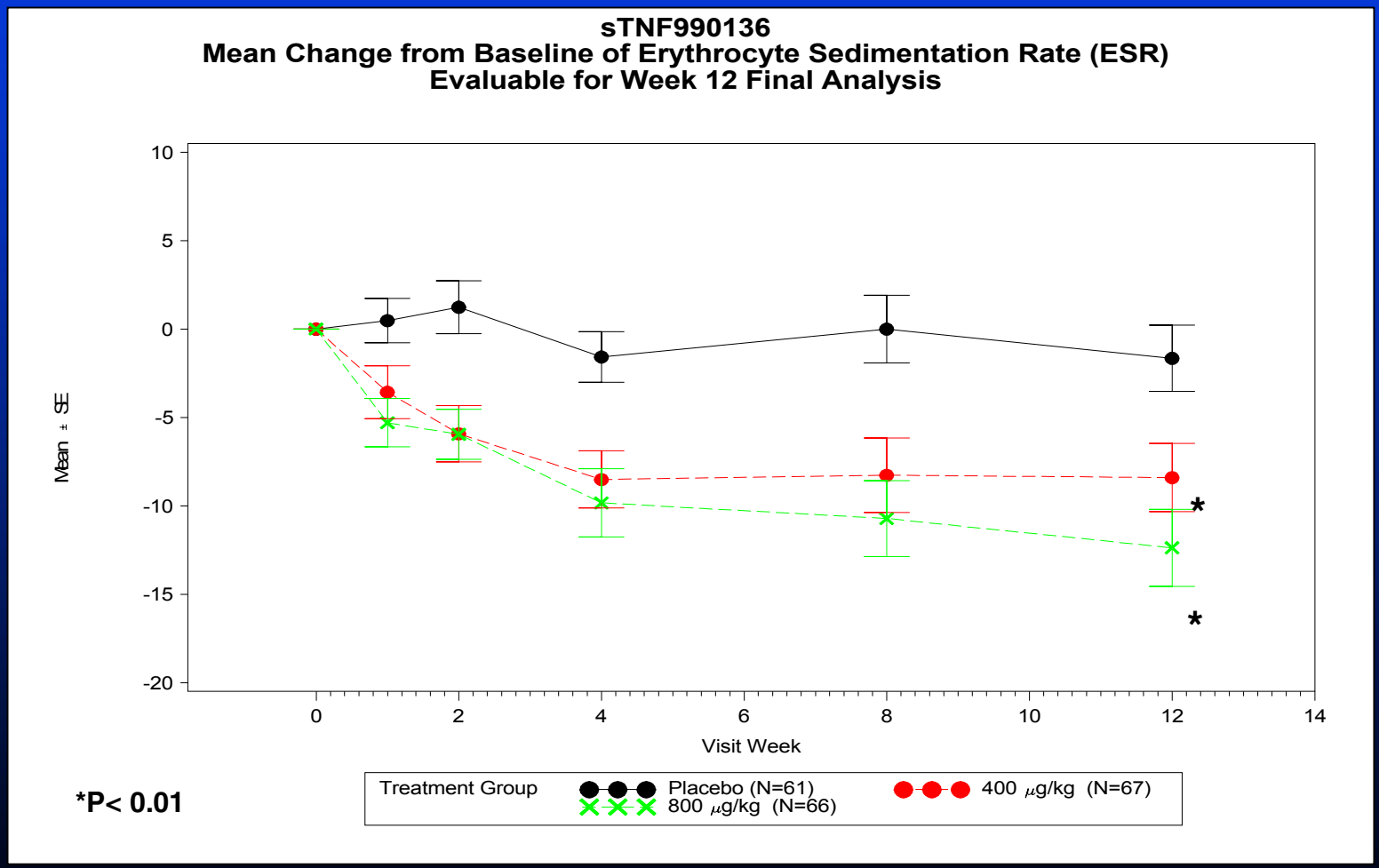


Objectives

- Identify patient subpopulations that may be more responsive to one drug versus another
- Identify surrogate markers that can be utilized to determine if the drug is efficacious
- Identify novel gene targets that can be utilized for drug discovery

Treatment with sTNF-RI Resulted in Significant Improvement in Objective Clinical Measurement (ESR)

Clinical Status



Acute Phase Reactants and Their General Functions

Acute Phase Proteins Whose Plasma Concentrations Increase

Complement System

- C3
- C4
- C9
- Factor B
- C1 inhibitor
- C4b binding protein
- Mannose binding protein (MBP)

Coagulation and Fibrinolytic System

- Fibrinogen
- Plasminogen
- Tissue plasminogen activator
- Urokinase
- Protein S
- Vitronectin
- Plasminogen-activator inhibitor 1
- Antiproteases
- α1-Protease inhibitor
- α1-Antichymotrypsin
- Pancreatic secretory trypsin inhibitor
- Inter-α-trypsin inhibitor

Transport Proteins

- Ceruloplasmin
- Haptoglobin
- Hemopexin

Participants in Inflammatory Responses

- Secreted phospholipase A_2 (PLA_2)
- Lipopolysaccharide binding protein (LBP)
- Interleukin-1 receptor antagonist (IL-1Ra)
- Granulocyte colony-stimulating factor (G-CSF)

Others

- C-reactive protein (CRP)
- Serum amyloid A
- α1-Acid glycoprotein
- Fibronectin
- Ferritin
- Angiotensinogen

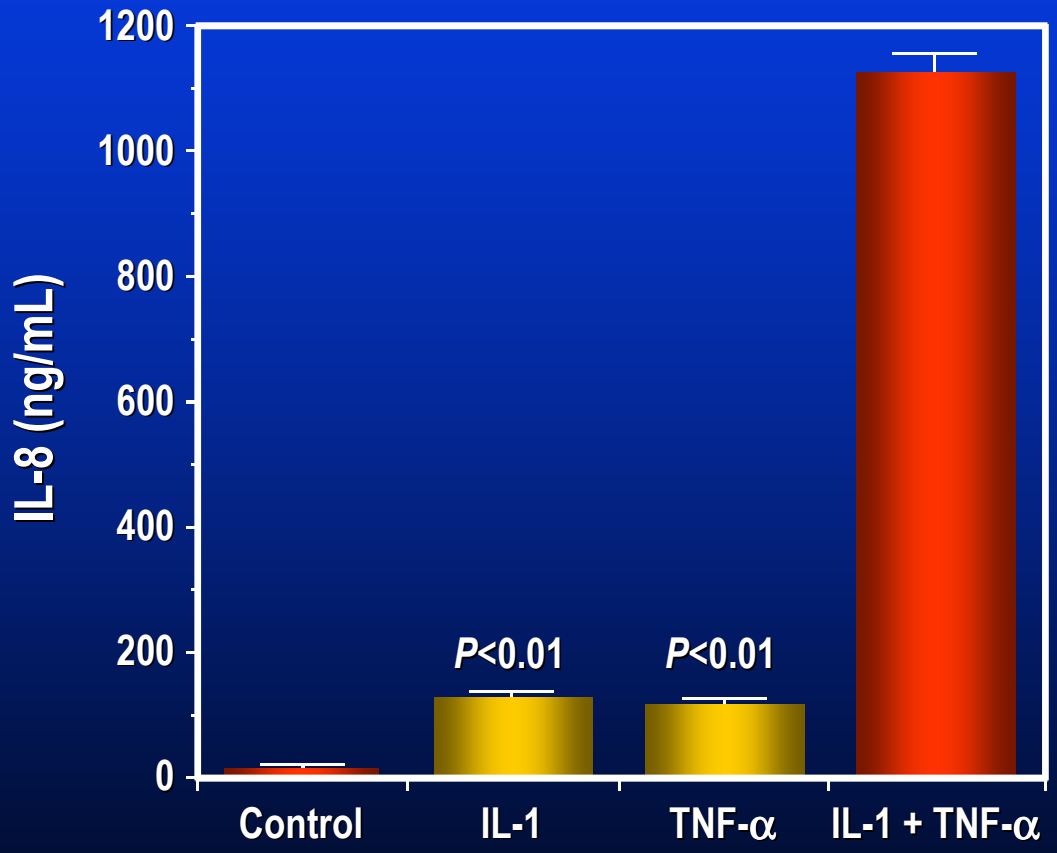
Plasma Proteins Whose Plasma Concentrations Decrease

- Albumin
- Transferrin
- Transthyretin
- α2-HS glycoprotein
- Alpha-fetoprotein
- Thyroxine-binding globulin
- Insulin-like growth factor 1 (IGF-1)
- Factor XII

Objectives

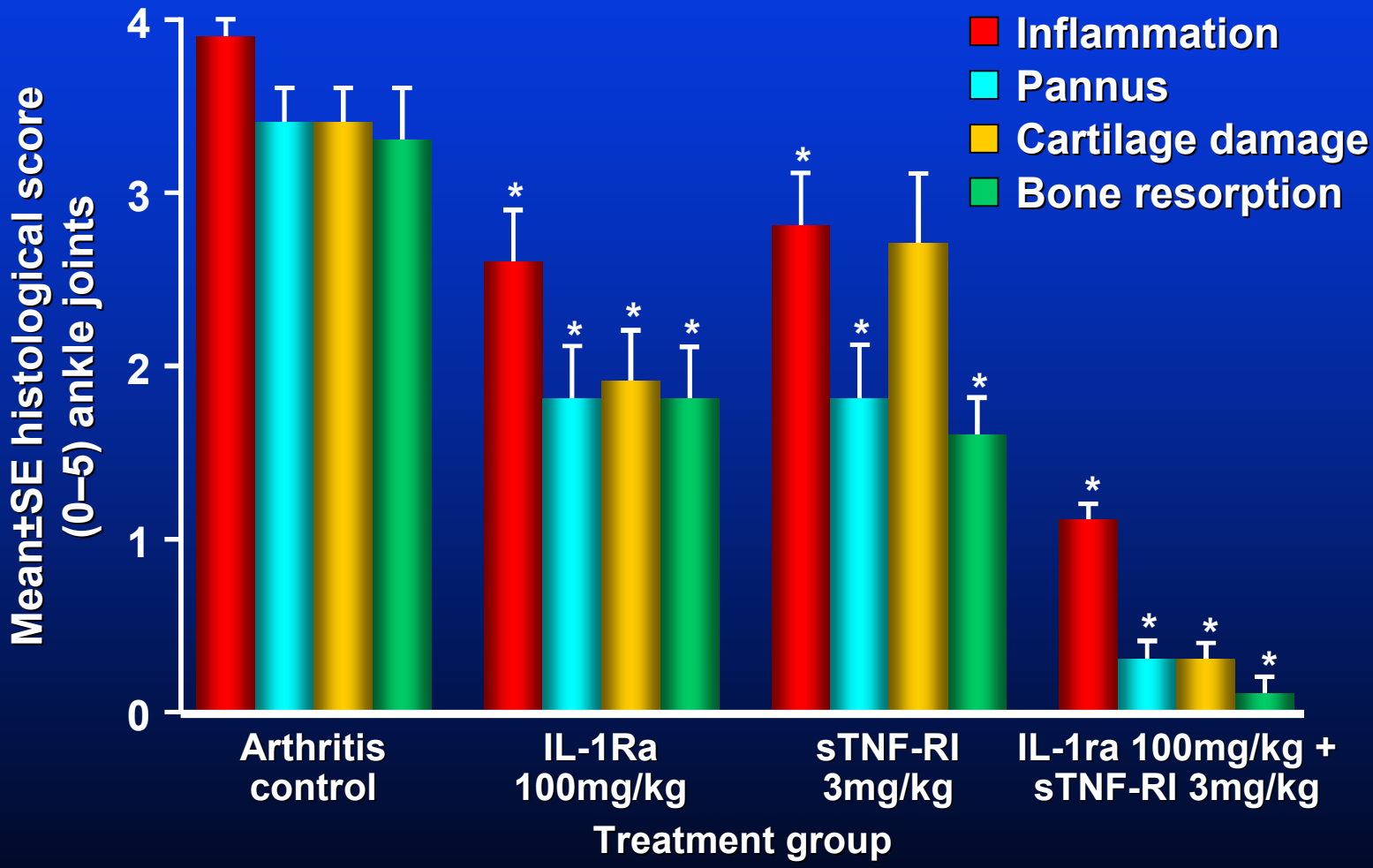
- Identify patient subpopulations that may be more responsive to one drug versus another
- Identify surrogate markers that can be utilized to determine if the drug is efficacious
  - Speed to determine this is essential!
- Identify novel gene targets that can be utilized for drug discovery

Synergistic Effect of IL-1 Plus TNF-α on Induction of IL-8 from COS Cells



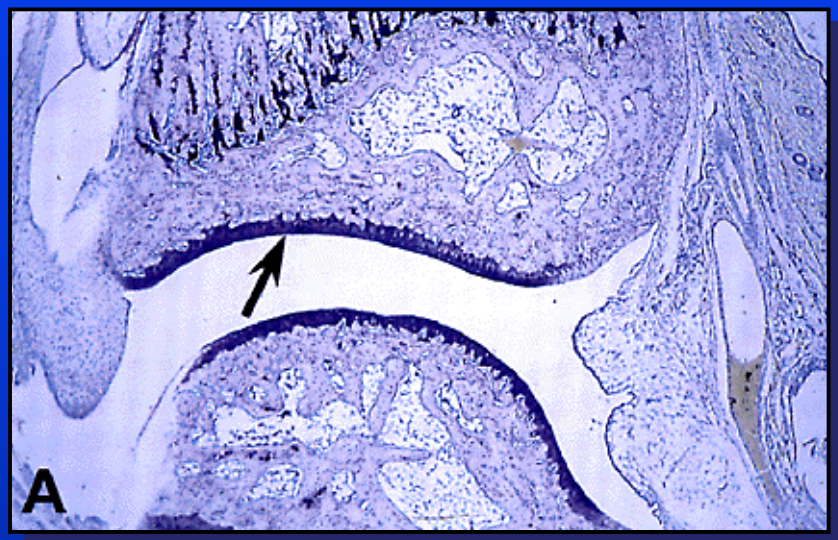
Unpublished data, Charles A. Dinarello.

IL-1Ra and PEG sTNF-RI Alone and in Combination Effects on Established Type II Collagen Arthritis in Rats

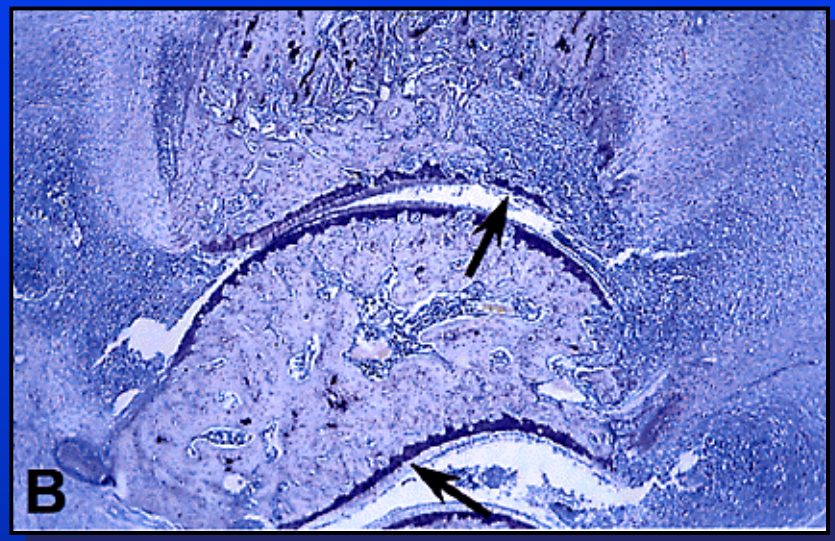


*p≤0.05, 2-tailed *t*-test to control

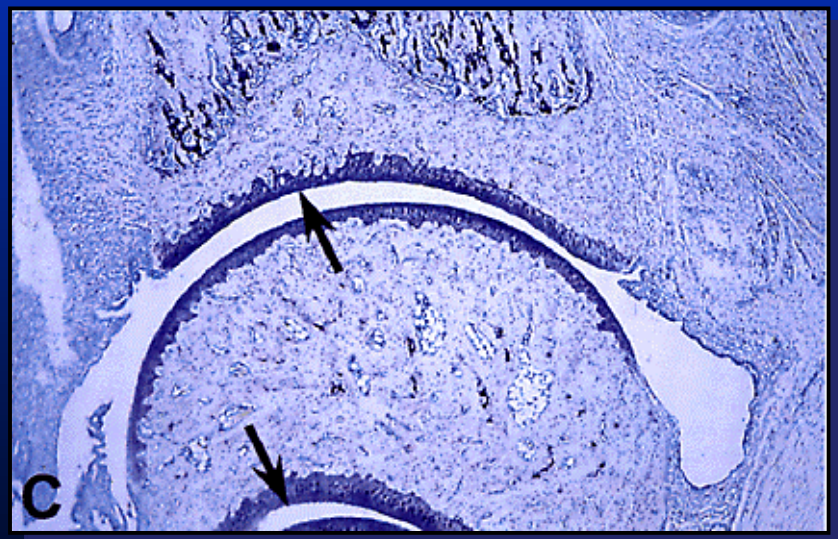
Bendele et al. Arthritis Rheum. 2000



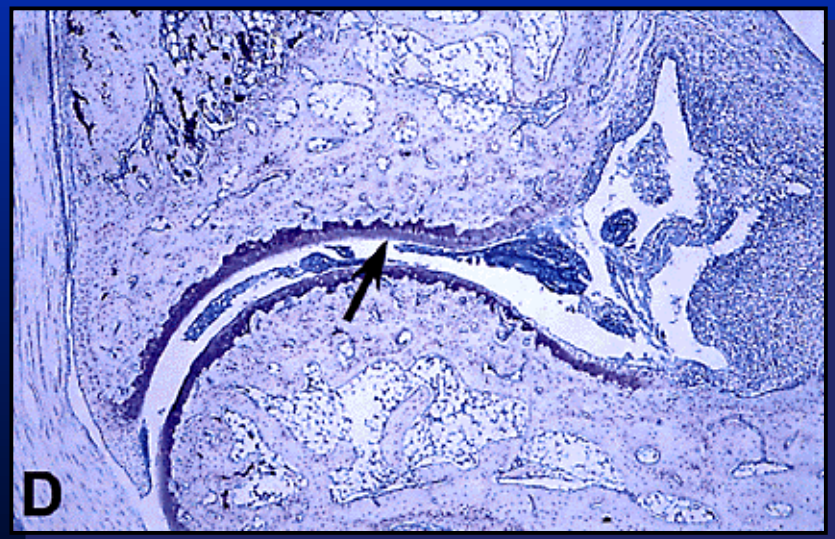
Normal control



Arthritis vehicle-treated control

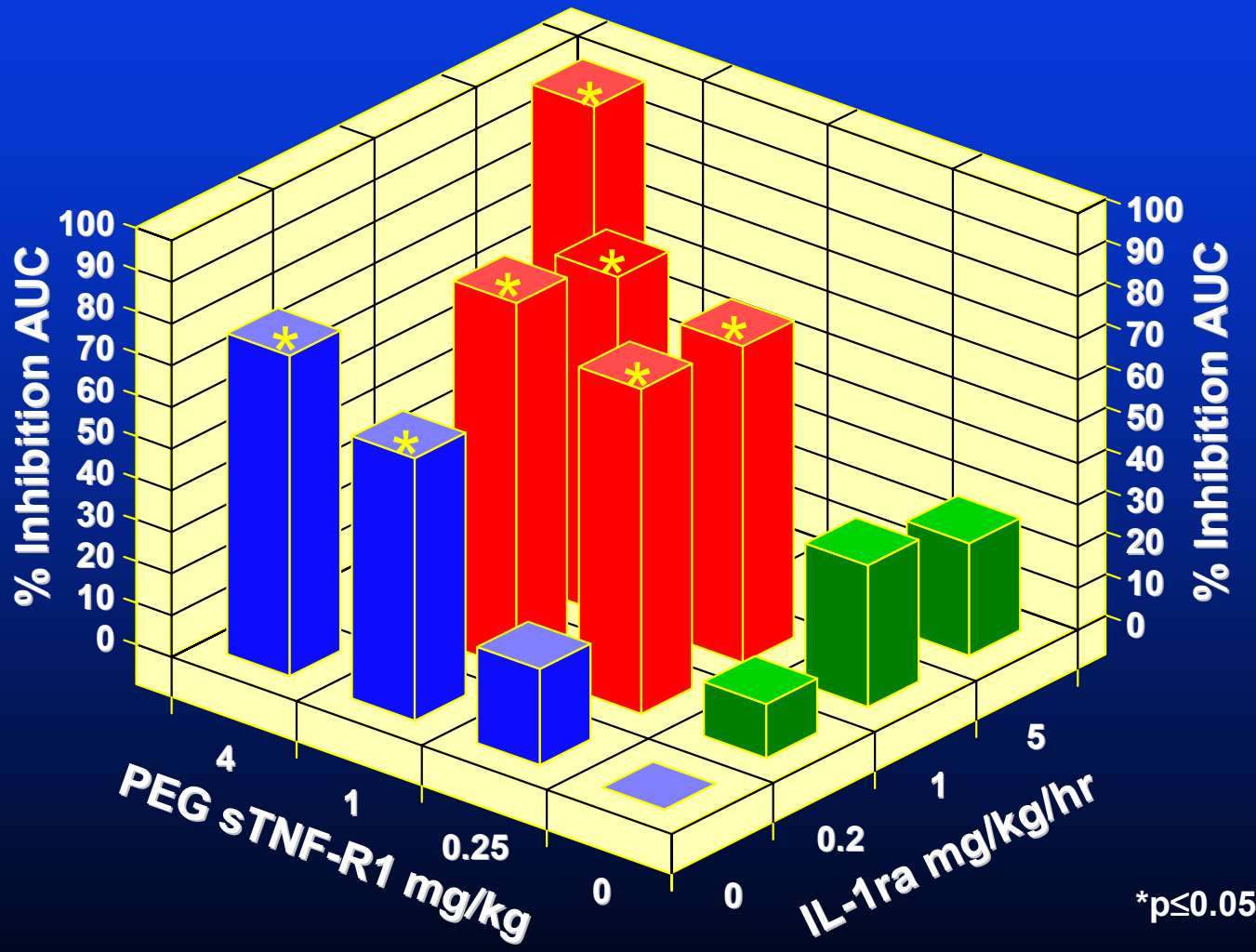


Arthritic rat treated with IL-1ra (100mg/kg) and PEG sTNF-RI (3mg/kg)



Arthritic rat treated with IL-1ra (20mg/kg) and PEG sTNF-RI (0.3mg/kg)

Inhibition of Inflammation in Adjuvant Arthritis IL-1ra/PEG sTNF-RI Combination



Feige U et al. J Mol Biol Life Sci. 2000

Arthritis & Rheumatism

Official Journal of the American College of Rheumatology

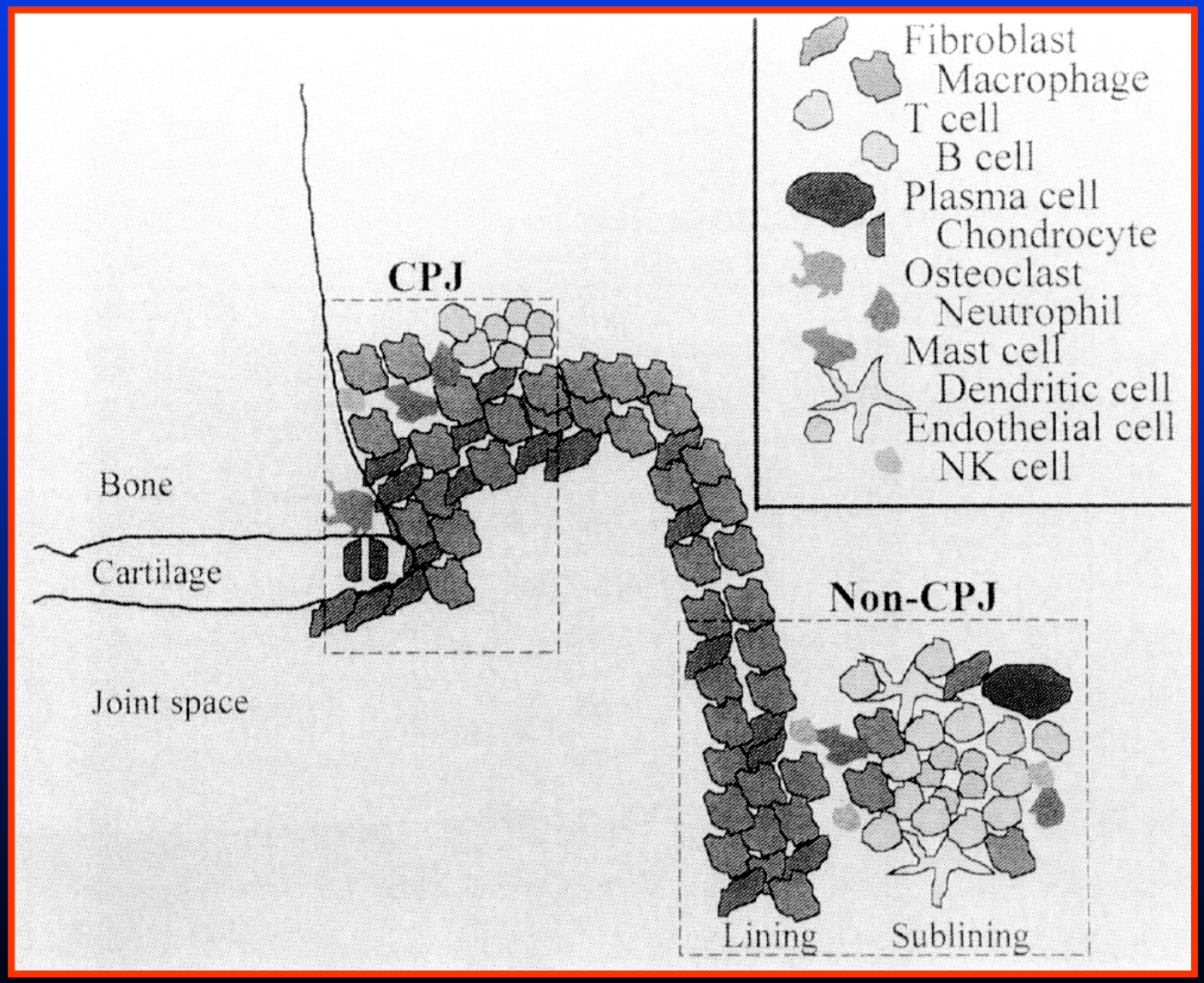
www.arthritisrheum.org

THE PATHOGENESIS AND PREVENTION OF JOINT DAMAGE IN RHEUMATOID ARTHRITIS

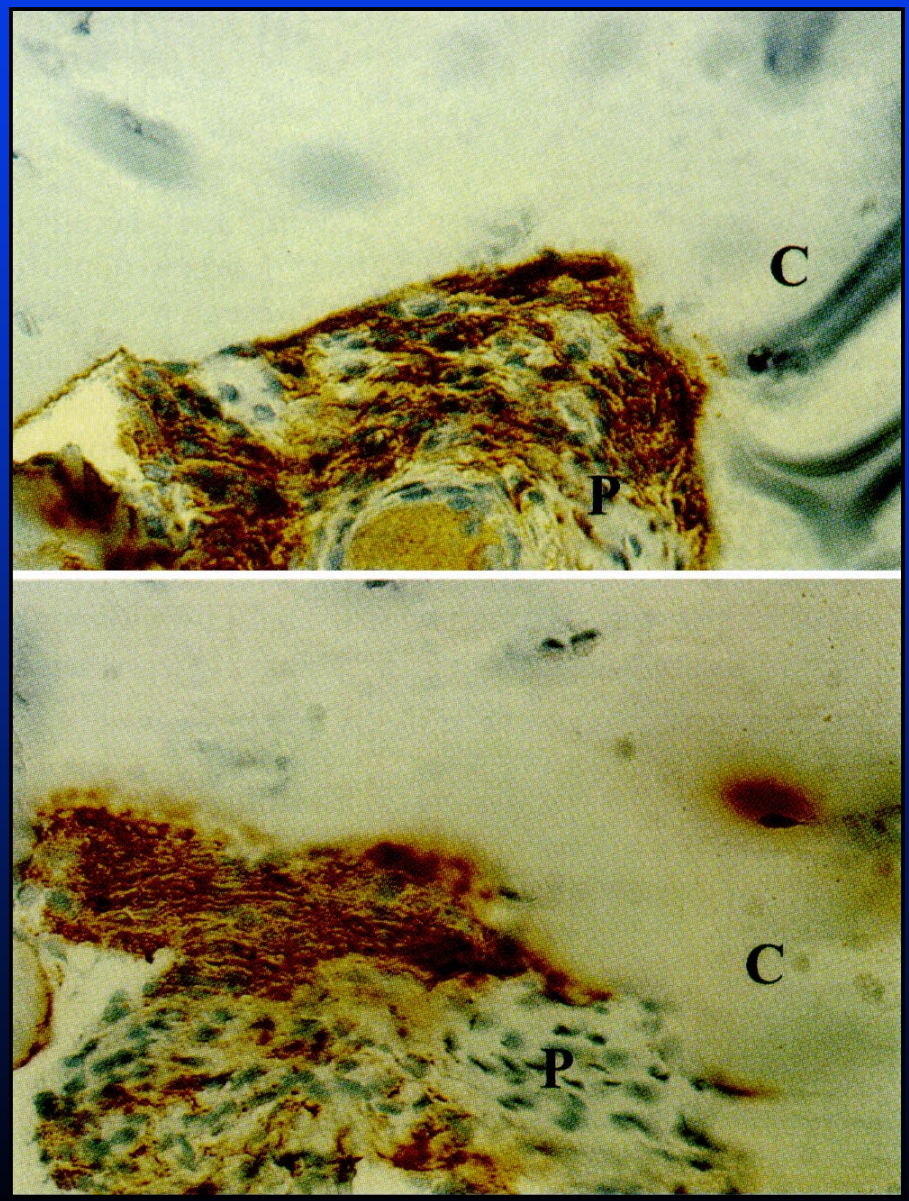
Advances from Synovial Biopsy and Tissue Analysis

PAUL PETER TAK and BARRY BRESNIHAN

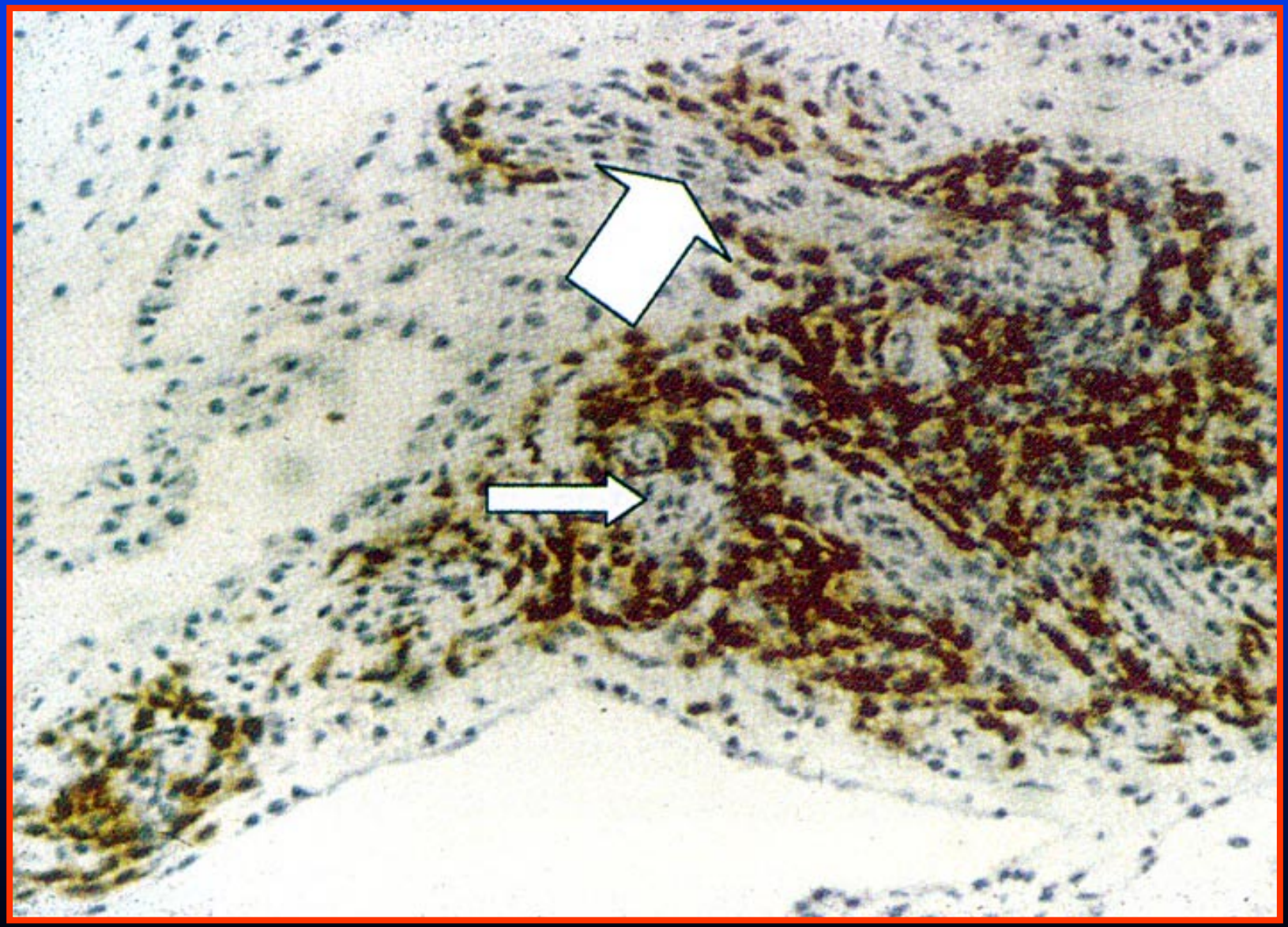
Cell Populations at the Cartilage-Pannus Junction (CPJ) and at non-CPJ Sites



Immunohistologic Analysis of Synovial Cell Population at the Cartilage-Pannus Junction



Immunohistologic Analysis of Synovial Cell Population at sites remote from the Cartilage-Pannus Junction

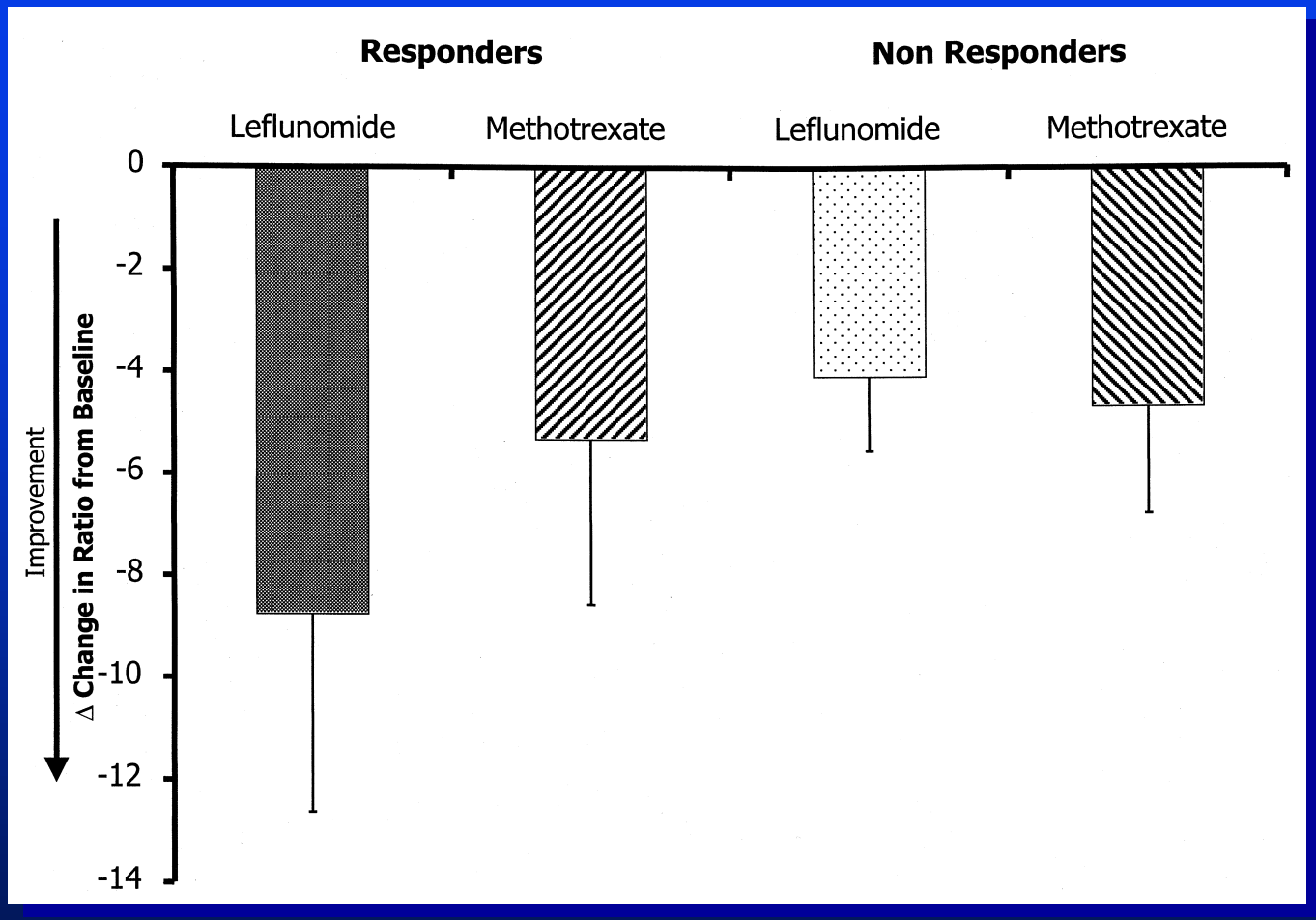


MODULATION OF INFLAMMATION AND METALLOPROTEINASE EXPRESSION IN SYNOVIAL TISSUE BY LEFLUNOMIDE AND METHOTREXATE IN PATIENTS WITH ACTIVE RHEUMATOID ARTHRITIS

Findings in a Prospective, Randomized, Double-Blind, Parallel-Design Clinical Trial in Thirty-Nine Patients at Two Centers

MAARTEN C. KRAAN, RICHARD J. REECE, ELLA C. BARG, TOM J. M. SMEETS, JACQUI FARNELL, RONALD ROSENBURG, DOUG J. VEALE, FERDINAND C. BREEDVELD, PAUL EMERY, and PAUL P. TAK

Arth. Rheum. 2000; 43, 1820-1830



Mean and SEM change in the △ matrix metalloproteinase 1 (MMP-1) to tissue inhibitor of metalloproteinases 1 (TIMP-1) ratio after 4 months of treatment in relation to the clinical response.

Arth. Rheum. 2000; 43, 1820-1830

IL-1Ra +/- PEG sTNF-RI Synovial Biopsy Study

- Provide mechanistic data on protective effects of IL-1Ra +/- PEG sTNF-RI on bone and cartilage in RA patients
  - Support commercialization efforts of IL-1Ra, ie, "bone story"
- Identify prognostic markers for future clinical research (responder vs non-responder)
- Identify potential new drug targets

Objectives

- Primary Objective: Confirm and characterize changes in synovial biopsies to changes in joint architecture in RA patients
  - Biopsies samples => CD+ markers, Cell counting
    - Similar to previous work (560) and recent Arava publication
  - X-ray, bone densitometry changes
- Secondary Objectives:
  - ACR assessments, cytokines, bone & cartilage markers
    - serum, synovial fluid, cell culture
  - Gene expression via microarray (Amgen)
    - Synovial tissue, leukocytes and/or buccal smear

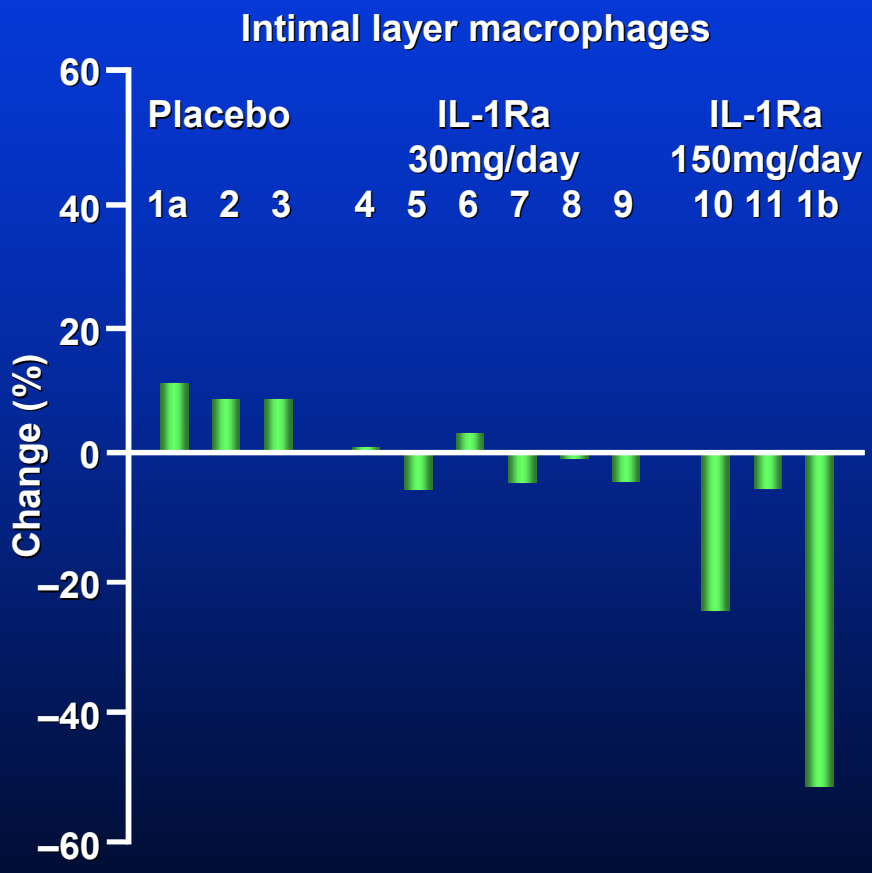
Study Logistics

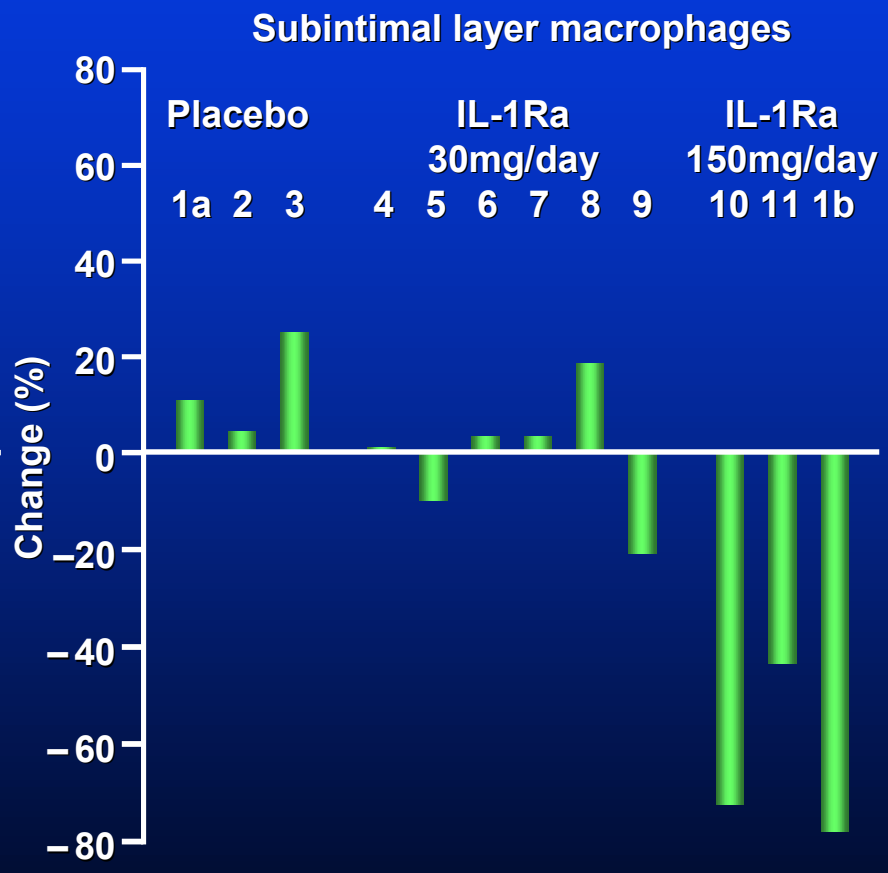
- Single center study
- Up to 3 biopsies per patient (knee) over 1 yr
- Recruit patients with early active disease (similar to patient population in 0560)

Study Design

- Two arm, open label study
  - IL-1Ra 1 mg/kg
  - IL-1Ra & PEG sTNF-RI combination
  - Estimate ~10-15 patients per arm
- Change from baseline study, with changes assessed at 1, 6, & 12 months.

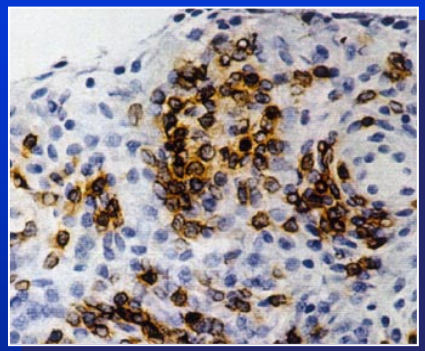
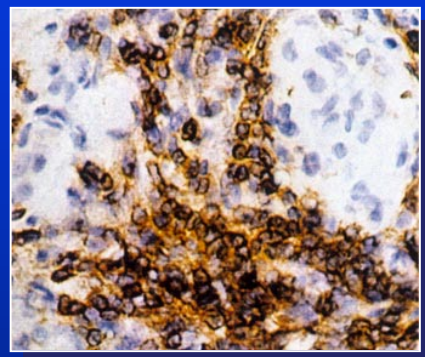
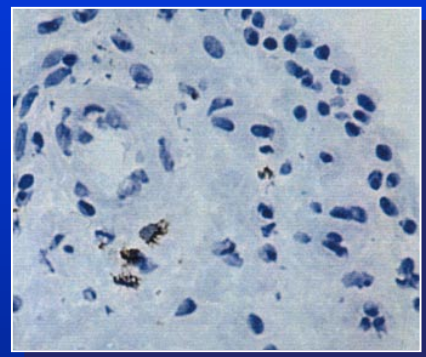
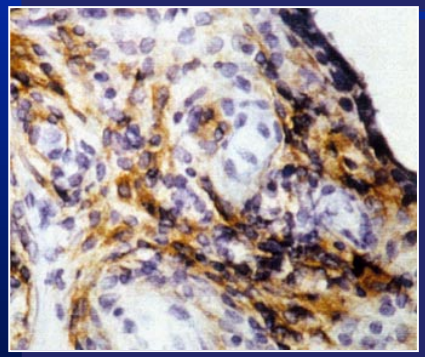
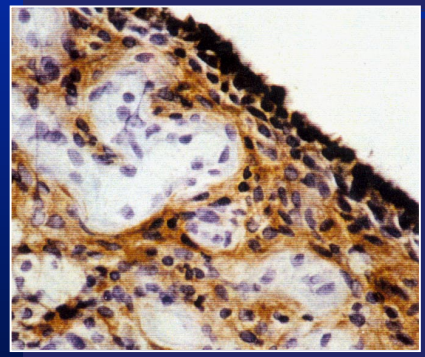
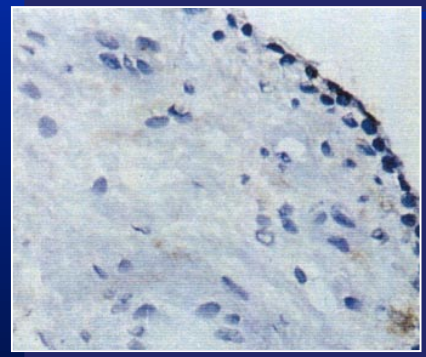
Synovial Macrophage Populations Following IL-1Ra





Cunnane G et al. Rheumatology 2000. In press

IL-1Ra Effect on Synovial Tissue

	Week 0 Pre-treatment	Week 24 Placebo treatment	Week 48 IL-1ra 150mg x 24 weeks
CD3			
CD68			

A notable reduction occurred in intimal layer macrophage accumulation and in subintimal macrophage and lymphocyte infiltration following 24 weeks of daily administration of IL-1ra 150mg subcutaneously.

Cunnane G et al. Rheumatology 2000. In press

Objectives

Identification of Novel Targets to Accelerate Drug Discovery

Discovery and Analysis of Inflammatory Disease-related Genes Using cDNA Microarrays

(inflammation/human genome analysis/gene discovery)

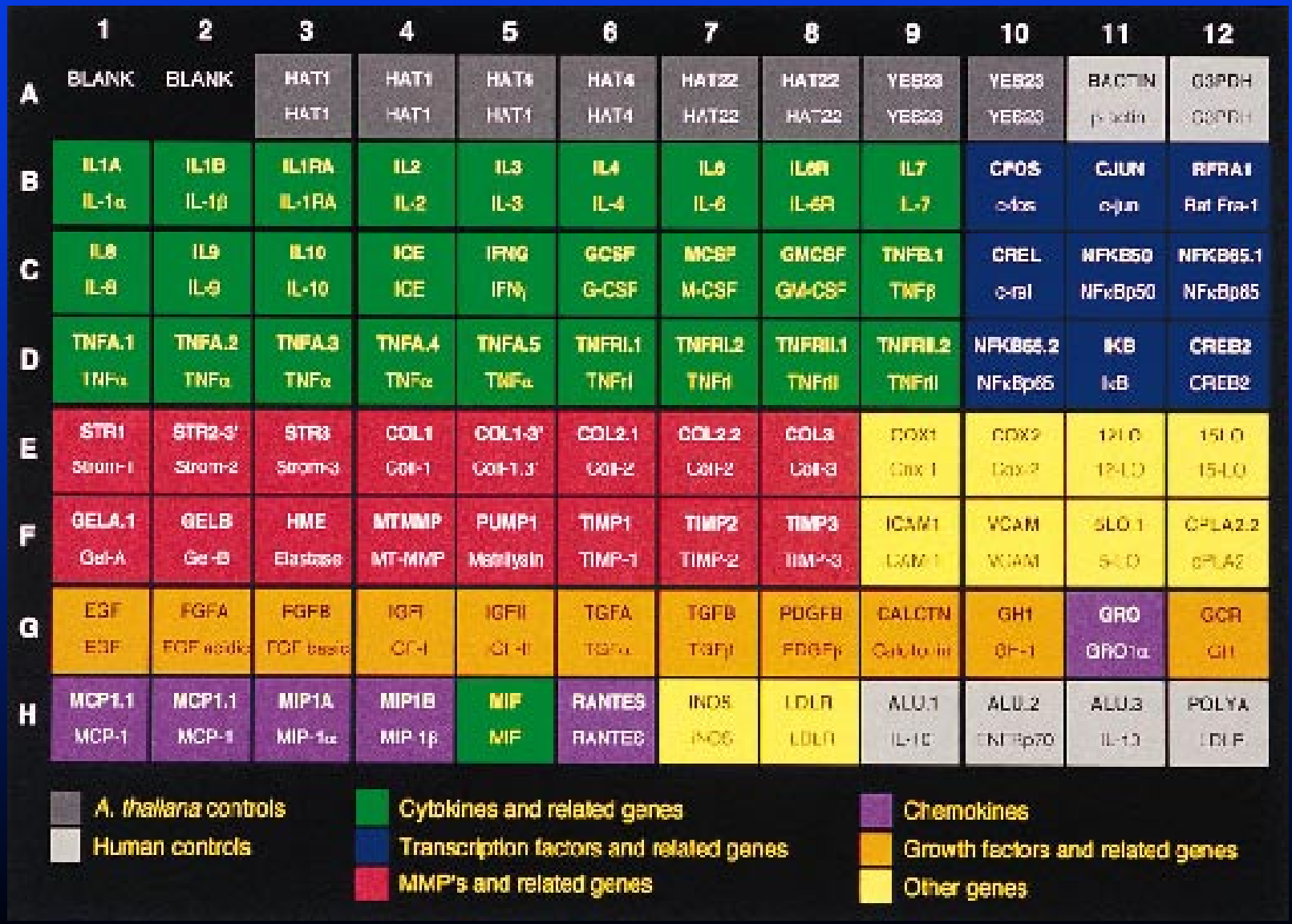
RENU A. HELLER* † ,MARK SCHENA*, ANDREW CHAI*, DARI SHALON ‡ ,TOD BEDILION ‡ , JAMES GILMORE ‡ , DAVID E. WOOLLEY § , AND RONALD W. DAVIS*

*Department of Biochemistry, Beckman Center, Stanford University Medical Center, Stanford, CA 94305; ‡ Synteni, Palo Alto, CA 94306; and § Department of Medicine, Manchester Royal Infirmary, Manchester, United Kingdom

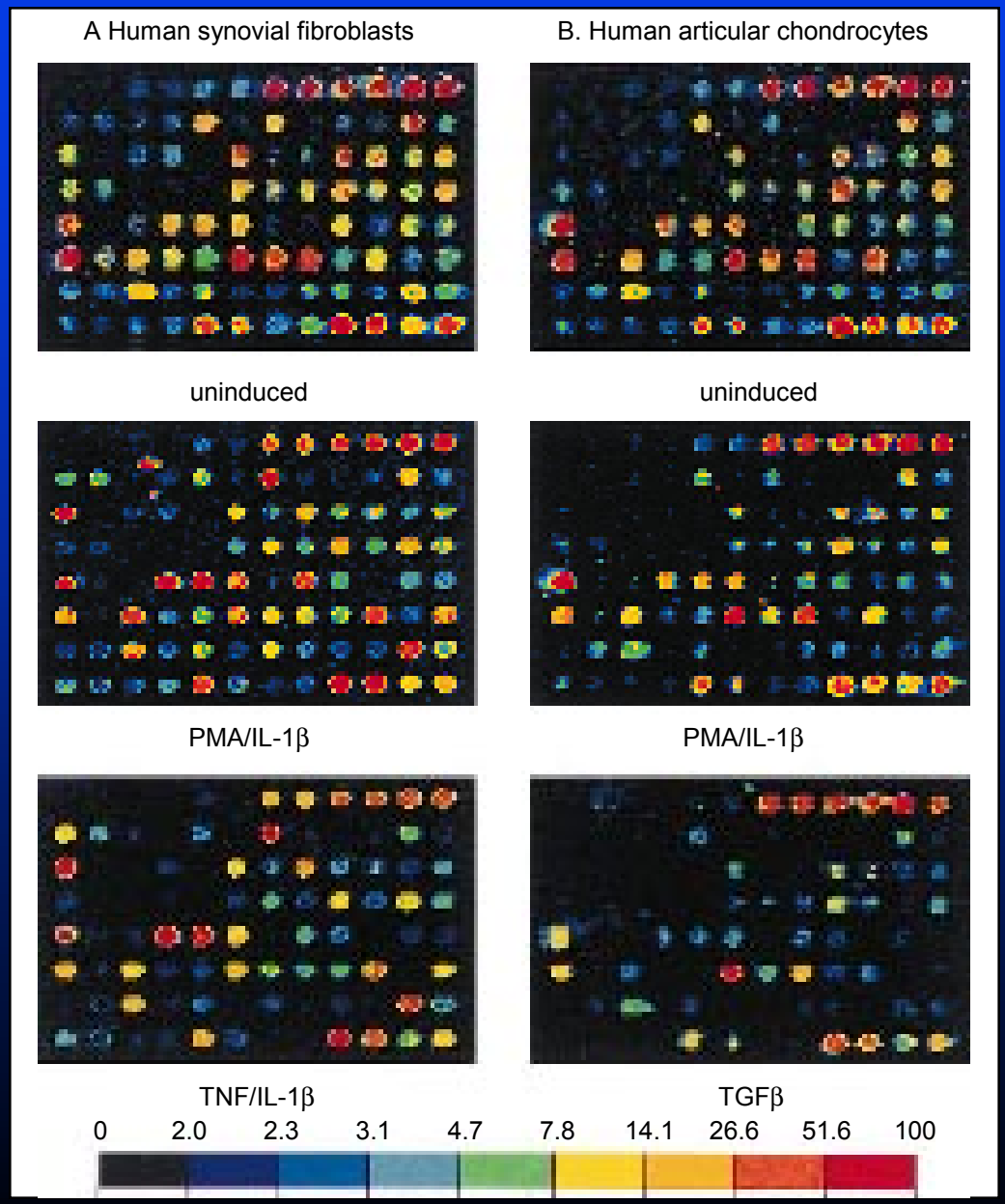
Contributed by Ronald W. Davis, December 27, 1996

Proc. Natl. Acad. Sci., 1997, 94, 2150-2155

Ninety-six-element microarray design. The target element name and the corresponding gene are shown in the layout. Some genes have more than one target element to guarantee specificity of signal. For TNF the targets represent decreasing lengths of 1, 0.8, 0.6, 0.4, and 0.2kb from left to right.

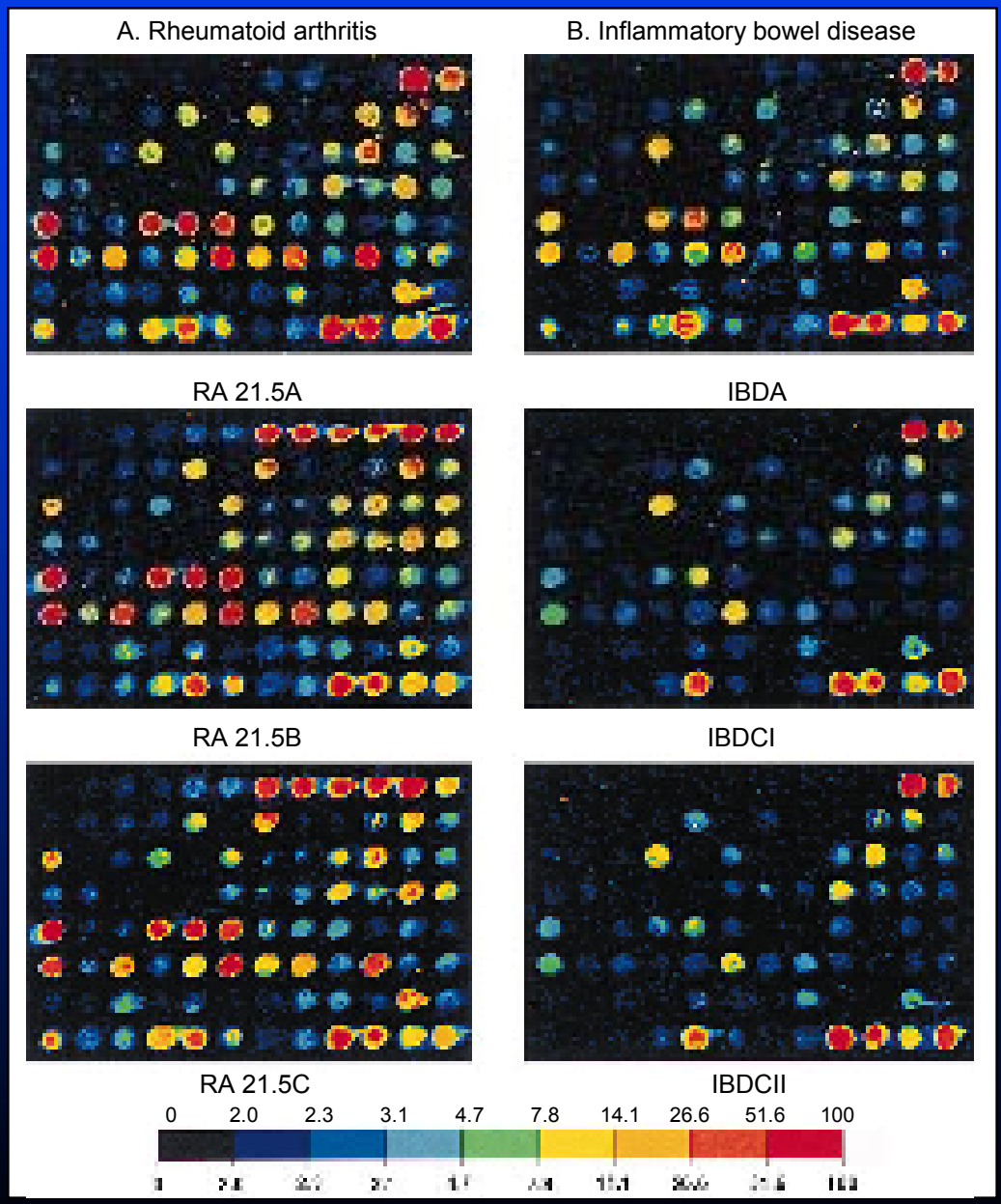


Expression profiles for early passage primary synoviocytes and chondrocytes isolated from RA tissue



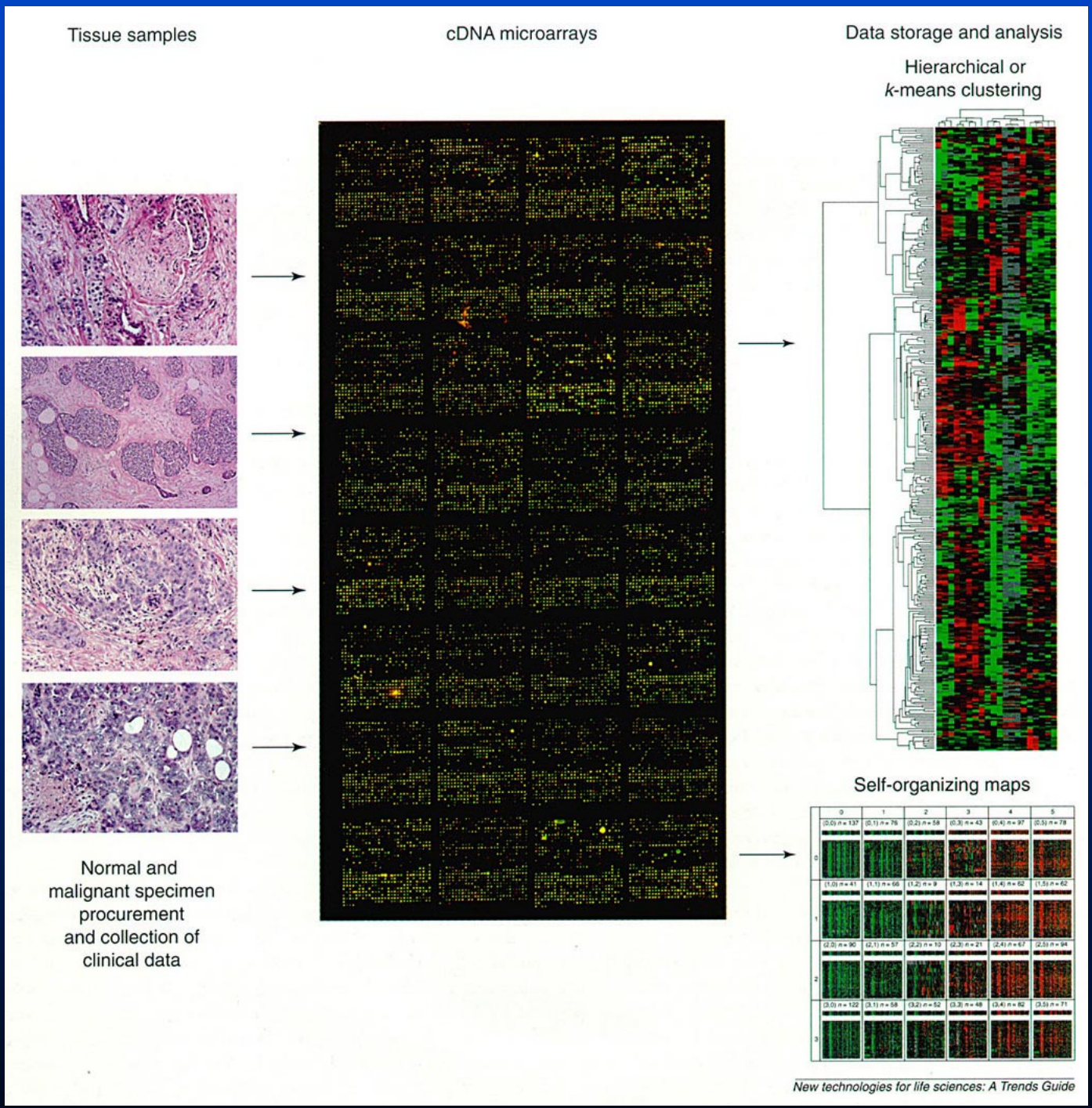
Proc. Natl. Acad. Sci., 1997, 94, 2150-2155

Expression profiles of RA tissue (*A*) and IBD tissue (*B*)



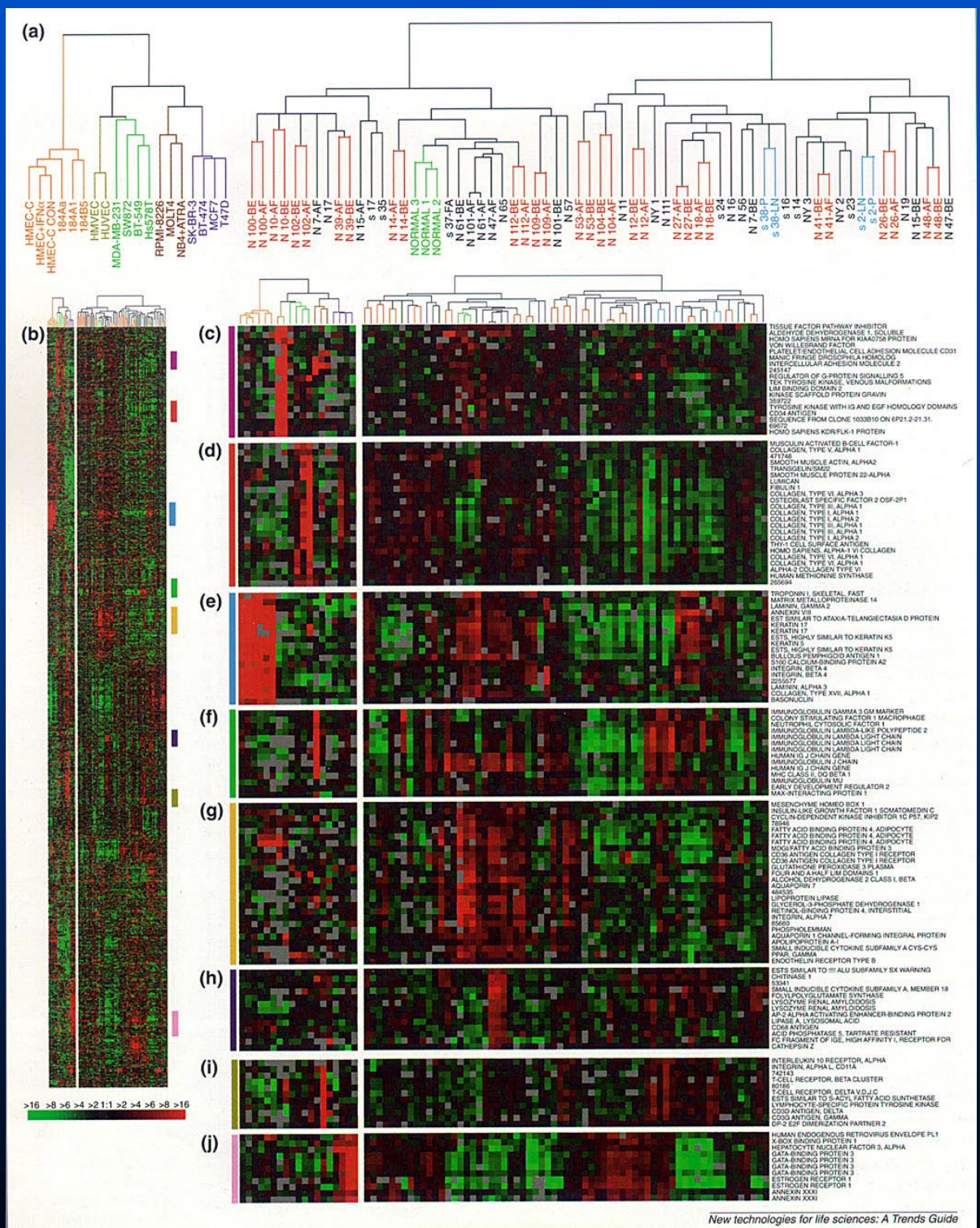
Proc. Natl. Acad. Sci., 1997, 94, 2150-2155

Flow Diagram of a DNA Microarray Tumor Profiling Project



New Technologies for Life Sciences, December 2000

Variation in Expression of 1753 Genes in 84 Experimental samples (17 cell lines and 65 breast tissue samples)



New Technologies for Life Sciences, December 2000

Family of Matrix Metalloproteases

MMP No.	Common Name
1	Collagenase-1 Fibroblast collagenase Interstitial collagenase
2	Gelatinase A 72 kDa Gelatinase
3	Stromelysin-1
4	None
5	None
6	None
7	Matrilysin
8	Collagenase-2 Neutrophil collagenase
9	Gelatinase B 92 kDa Gelatinase
10	Stromelysin-2
11	Stromelysin-3
12	Macrophage elastase
13	Collagenase-3 Rat osteoblast collagenase
14	Membrane-type matrix metalloprotease-1 (MT1-MMP)
15	Membrane-type matrix metaloprotease-2 (MT2-MMP)
16	Membrane-type matrix metalloprotease-3 (MT3-MMP)
17	Membrane type matrix metalloprotease-4 (MT4-MMP)
18	Collagenase-4
19	None
20	Enamelysin

Greenwald RA, Woessner JF Jr. Common names of matrix metalloproteinases. *Ann NY Acad Sci.* 1999;878:vi.cc

Conclusions

- These early studies using Amgen clinical candidates provide value by:
  - establishing “Proof-of-Concept” rationale for Pharmacogenomics and Pharmacogenetics
  - demonstrating platform technologies capabilities to the Drug Development process
  - accelerate drug discovery and target evaluation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Acknowledgments

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