Servicio de Enfermedades del Sistema Inmune y Oncología

Unidad Asociada I+D al Consejo Superior de Investigaciones Científicas

Departamento de Medicina Interna

Hospital Universitario "Príncipe de Asturias"

Universidad de Alcalá

Tratamientos biológicos en enfermedades autoinmunes

- Estrategias de tratamiento sobre dianas patogénicas en enfermedades autoinmunes
- Modelo de aplicación: La artritis reumatoide

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Madrid

FUNDAMENTOS Y CONSEDERACIONES INICIALES

CSIC
Hospital Universitario Príncipe de Asturias
Madrid

ENFERMEDADES INFLAMATORIAS IDIOPÁTICAS Y AUTOINMUNES

CSIC

HETEROGENEIDAD EN LOS MECANISMOS PATOGÉNICOS SUBYACENTES Y EN LA EXPRESIÓN CLÍNICA EN "ENFERMEDADES" Y EN "ENFERMOS"

CRISIS DE LA NOSOLOGIA

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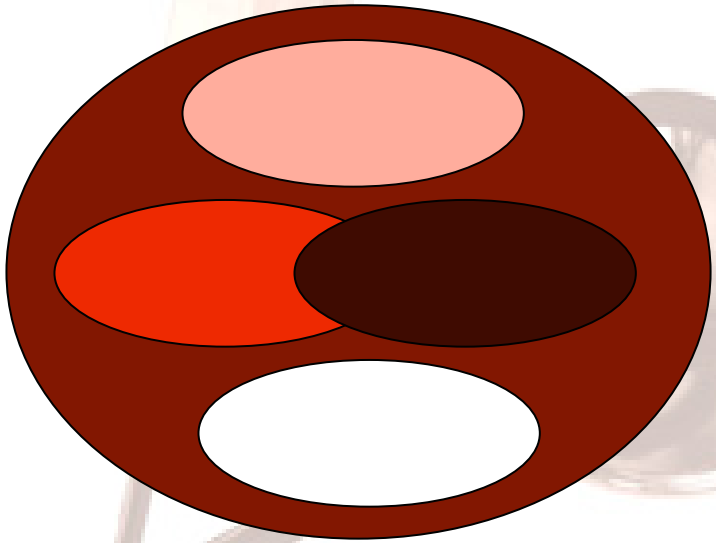
Investigación biomédica etiopatogénica, diagnóstica, terapéutica y reparativa

SIMILITUD CLÍNICA DIAGNÓSTICO DE ENFERMEDAD ÚNICA



SUPERAR LIMITACIONES EN:
·LA REALIZACIÓN DE ENSAYOS CLÍNICOS
·LA OPTIMIZACIÓN Y EL DESARROLLO TERAPÉUTICO Y REPARATIVO

IDENTIFICACION DE MECANISMOS ETIOPATOGÉNICOS ESPECÍFICOS Y COMUNES

Medicina traslacional

Medicina individualizada

No existen enfermedades sino enfermos

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Tratamientos biológicos en enfermedades autoinmunes

Estrategias de tratamiento sobre dianas etiológicas (óptimo) y patogénicas (alternativo) en enfermedades autoinmunes

Estrategias terapéuticas

¿Cual es la etiología de las enfermedades inflamatorias mediadas por el sistema inmunitario y de las clasificadas como autoinmunes?

Respuesta inmune frente a agresiones microbiológicas o tumorales

Reconocimiento antigénico y fase efectora **eficientes**

↓

Supresión funcional y/o lisis del agente infeccioso o de las células neoplásicas

↙ ↘

Asintomático — Manifestaciones clínicas

↘ ↙

RECUPERACIÓN DE LA SALUD

Respuesta inmune frente a agresiones microbiológicas o tumorales

Reconocimiento antigénico y fase efectora <u>ineficientes</u>

↓

consecuencias patológicas

↙ Deficiente respuesta

↓

Progresión de la infección o del tumor

↘ Inadecuado control de la respuesta

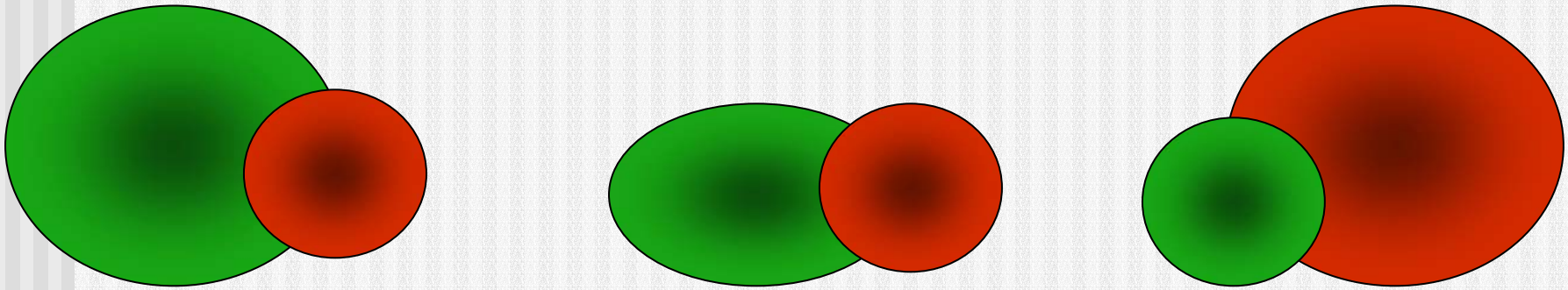
↙

- Sepsis
- Shock
- Síndrome inflamatorio sistémico

↘

- Enfermedades inflamatorias
- Enfermedades autoinmunes

ETIOPATOGENIA DE ENFERMEDADES DEL SISTEMA INMUNOLÓGICO/INFLAMATORIO

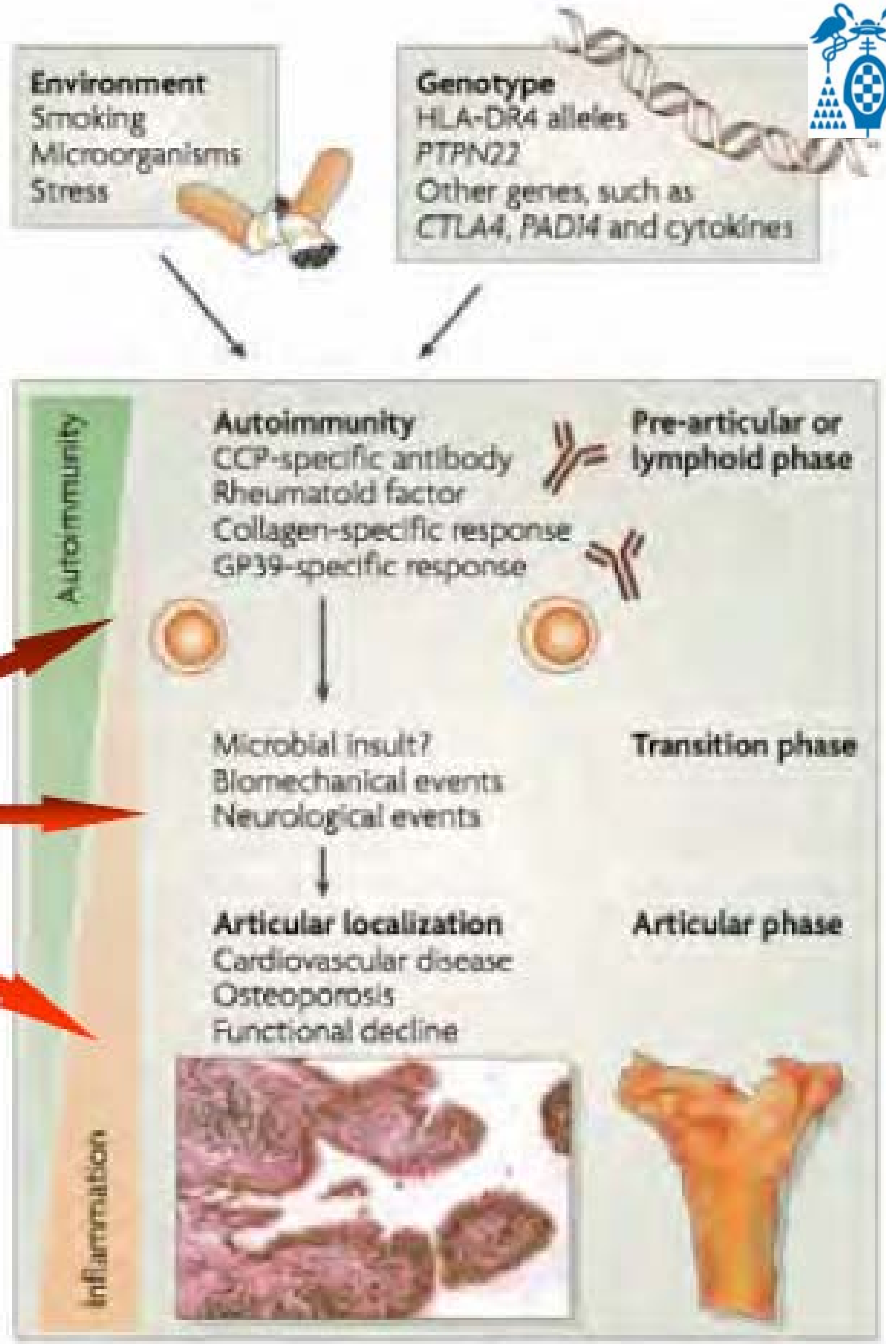


BASES GENÉTICAS

INTERACCIÓN CON EL MEDIO EXTERNO E INTERNO

HETEROGENEIDAD INDIVIDUAL Y TEMPORAL

Pathogenesis of RA?



McInnes IB & Schett G *Nature Reviews Imm.* 2007

Genome wide studies - implicate immunity!

Association of *STAT4* with Rheumatoid Arthritis in the Korean Population

Re-evaluation of putative rheumatoid arthritis susceptibility genes in the post-genome wide association study era and hypothesis of a key pathway underlying susceptibility

Anne Barton[1,*], Wendy Thomson[1], Xiayi Ke[1], Steve Eyre[1], Anne Hinks[1], John Bowes[1], Laura Gibbons[1], Darren Plant[1], Wellcome Trust Case Control Consortium[2], Anthony G. Wilson[3], consortium[4], Sophia Steer[5], Pille Harrison[6] and Jane Worthington[1]

Association of *STAT4* With Susceptibility to Rheumatoid Arthritis and Systemic Lupus Erythematosus in the Japanese Population

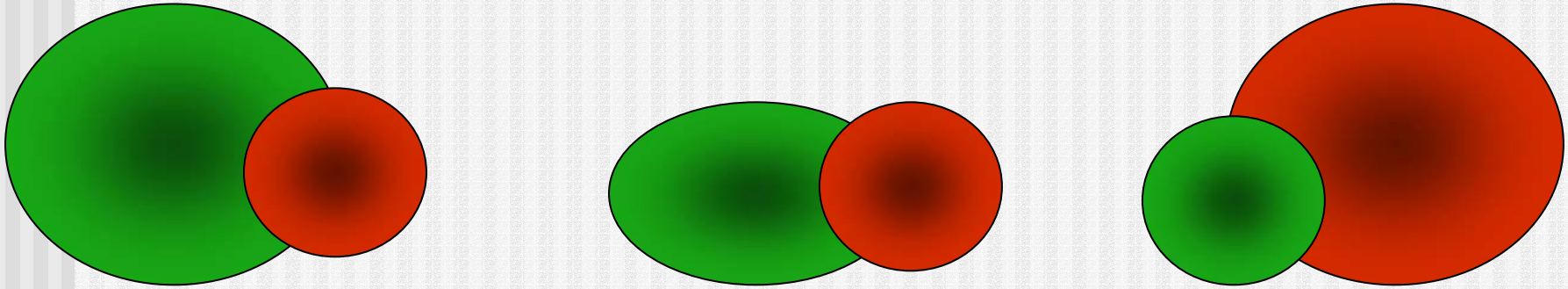
A Large-Scale Rheumatoid Arthritis Genetic Study Identifies Association at Chromosome 9q33.2

Monica Chang[1], Charles M. Rowland[1], Veronica E. Garcia[1], Steven J. Schrodi[1], Joseph J. Catanese[1], Annette H. M. van der Heim-van Mil[2], Kristin G. Andlie[1,3], Christopher I. Amos[4], Lindsey A. Criswell[5], Daniel L. Kastner[6], Peter K. Gregersen[7], Fina A. S. Kurreeman[2], Rene E. M. Toes[2], Tom W. J. Huizinga[2], Michael F. Seldin[8], Ann B. Begovich[1,9]*

Abstract

Rheumatoid arthritis (RA) is a chronic, systemic autoimmune disease affecting both joints and extra-articular tissues. Although some genetic risk factors for RA are well-established, most notably *HLA-DRB1* and *PTPN22*, these markers do not fully account for the observed heritability. To identify additional susceptibility loci, we carried out a multi-tiered, case-control association study, genotyping 25,996 putative functional SNPs in 475 white North American RA patients and 475 matched controls. Significant markers were genotyped in two additional, independent, white case-control sample sets (867

ETIOPATOGENIA DE ENFERMEDADES DEL SISTEMA INMUNOLÓGICO/INFLAMATORIO



BASES GENÉTICAS

INTERACCIÓN CON EL MEDIO EXTERNO E INTERNO

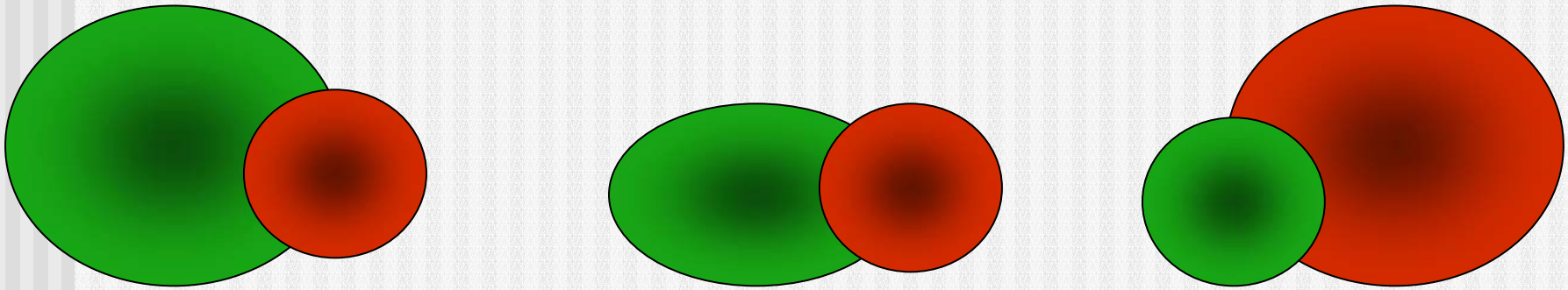
HETEROGENEIDAD INDIVIDUAL Y TEMPORAL

Environmental matters…?

- Deprivation, life style and inflammatory diseases

- **Disease activity**
  - **Endogenous Mechanisms**
    - e.g. PsoBid study
- **Health care access**
  - Compliance
- **Environmental challenge**
  - **Hygiene hypothesis**
    - microbial triggers
  - **Smoking & *HLADR* gene**

ETIOPATOGENIA DE ENFERMEDADES DEL SISTEMA INMUNOLÓGICO/INFLAMATORIO



BASES GENÉTICAS

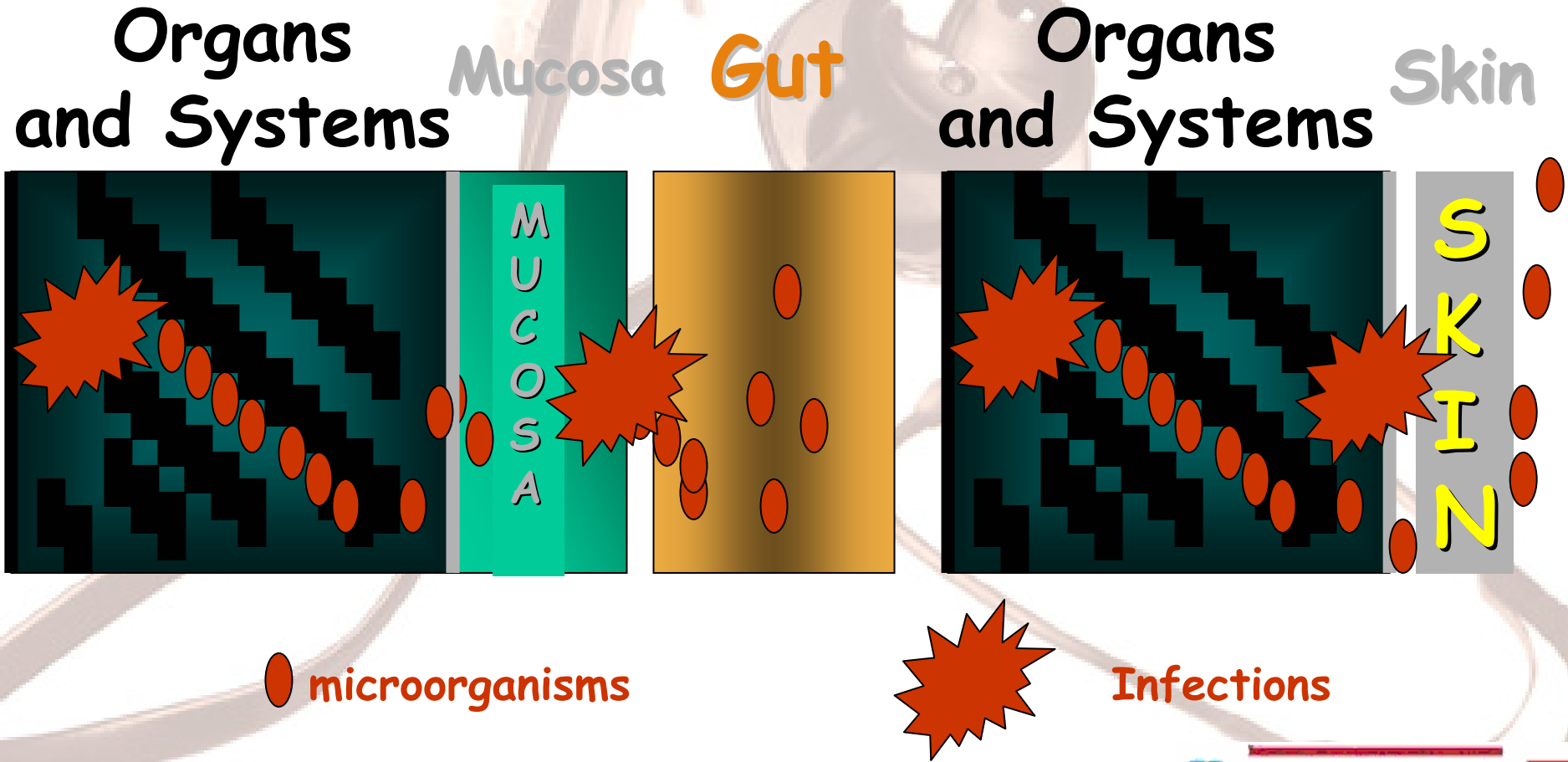
INTERACCIÓN CON EL MEDIO EXTERNO E INTERNO

HETEROGENEIDAD INDIVIDUAL Y TEMPORAL

PATHOGENIC INTERACTIONS OF THE IMMUNE SYSTEM

- **INTERACTIONS WITH MICROORGANISMS**
- NUTRITIONAL INTERACTIONS
- HORMONAL INTERACTIONS
- NEUROLOGICAL INTERACTIONS
- INTERACTIONS WITH DRUGS
- CUTANEOUS AND MUCUS BARRIERS
- CHANGES IN THE INTERNAL ENVIRONEMENT

Humans and microorganisms



Interactions can become infections

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PATHOGENIC INTERACTIONS OF THE IMMUNE SYSTEM

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El mal de quien la causa no se sabe, milagro es acertar la medicina

OVI-XOTE
IV CENTENARIO

Cervantes, 1605

Estrategias terapéuticas

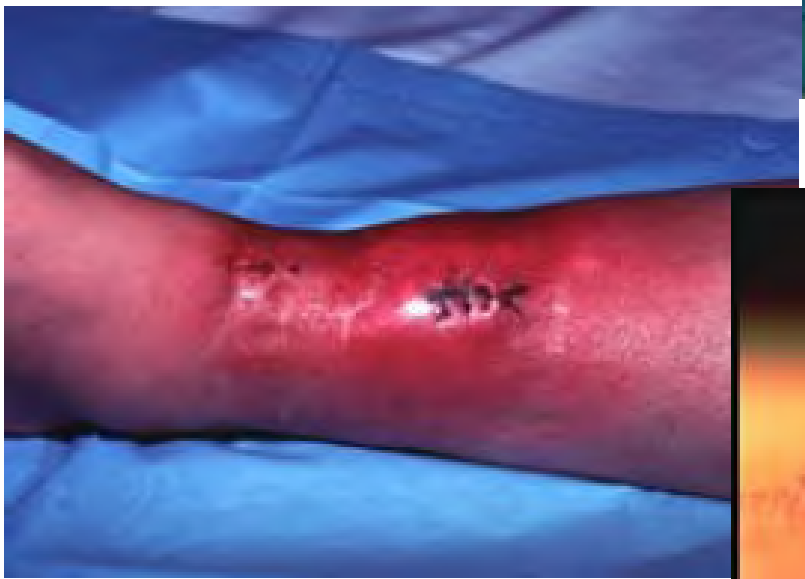
¿cuales son los mecanismos patogénicos del sistema inmunitario implicados en la patogenia de las enfermedades inflamatorias de etiología desconocida y autoinmunes?

Innate immunity - inflammation that is beneficial…normally!

- immediate & effective
- inefficient
- amnesic

- toll-like receptors

heat erythema swelling pain functional loss

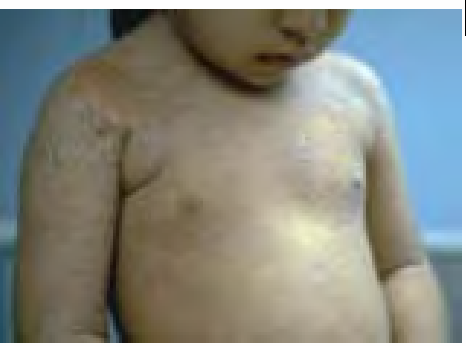


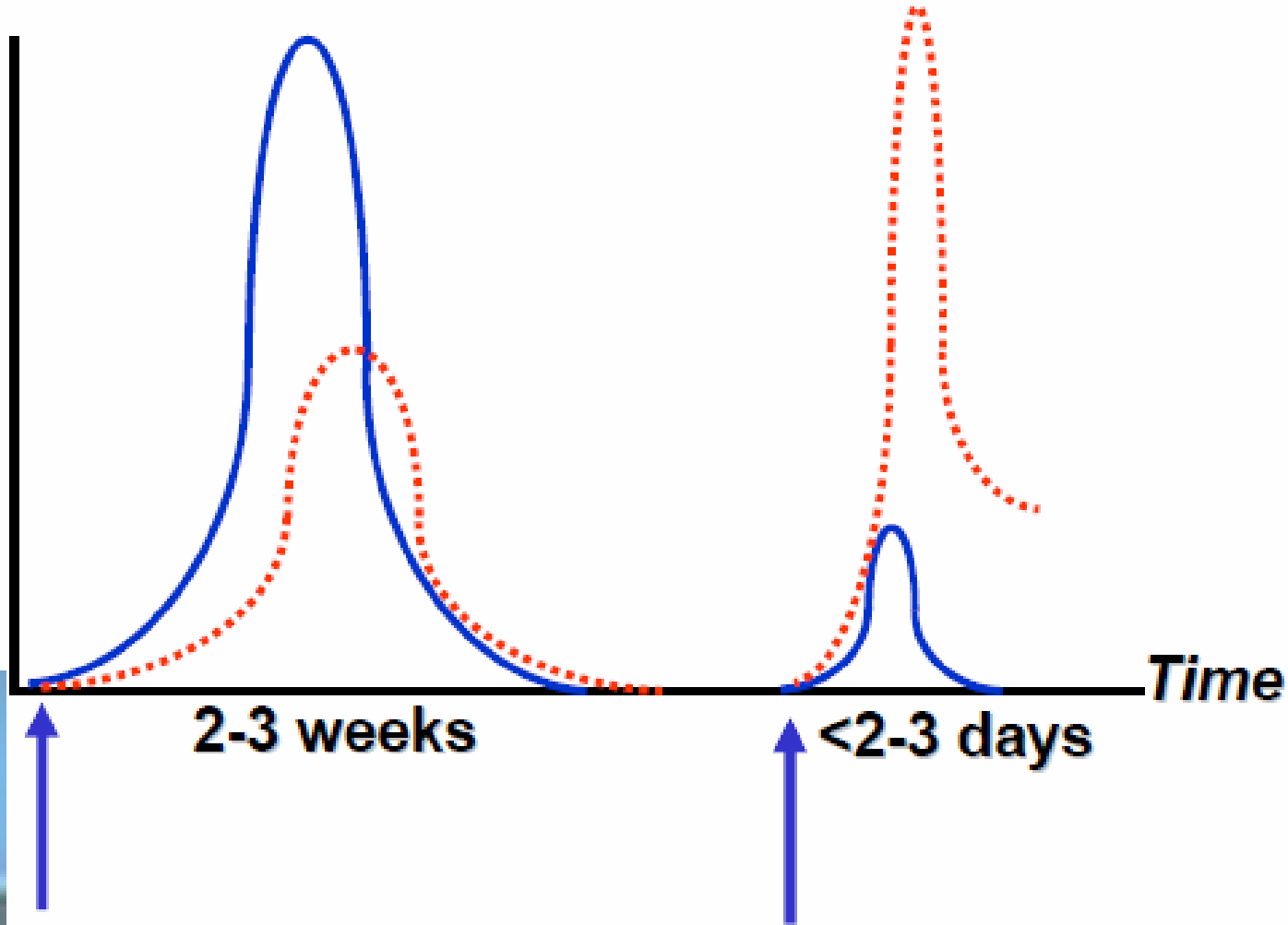
Adaptive immunity:

Overcoming immunologic amnesia!

clinical severity

protective antibody





Análisis estratégico del sistema inmunológico

- **Respuesta inmune innata**
  - Células fagocíticas y presentadoras de antígeno (APC)
    - Células monocitarias. Receptores Toll
  - Células citotóxicas espontáneas (NK)
  - Citoquinas y quimioquinas
- **Respuesta inmune adaptativa**
  - APC
  - Linfocitos T y B
  - Citoquinas, inmunoglobulinas, sistema principal de histocompatabilidad

Dianas patogénicas en enfermedades inflamtorias crónicas / autoinmunes

- **Dianas terapéuticas**
- **Diversidad**
- **Selección eficiente**

Muchos interpretes… ¿Quién es el director?

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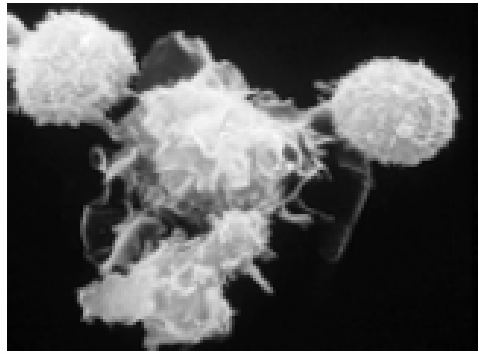
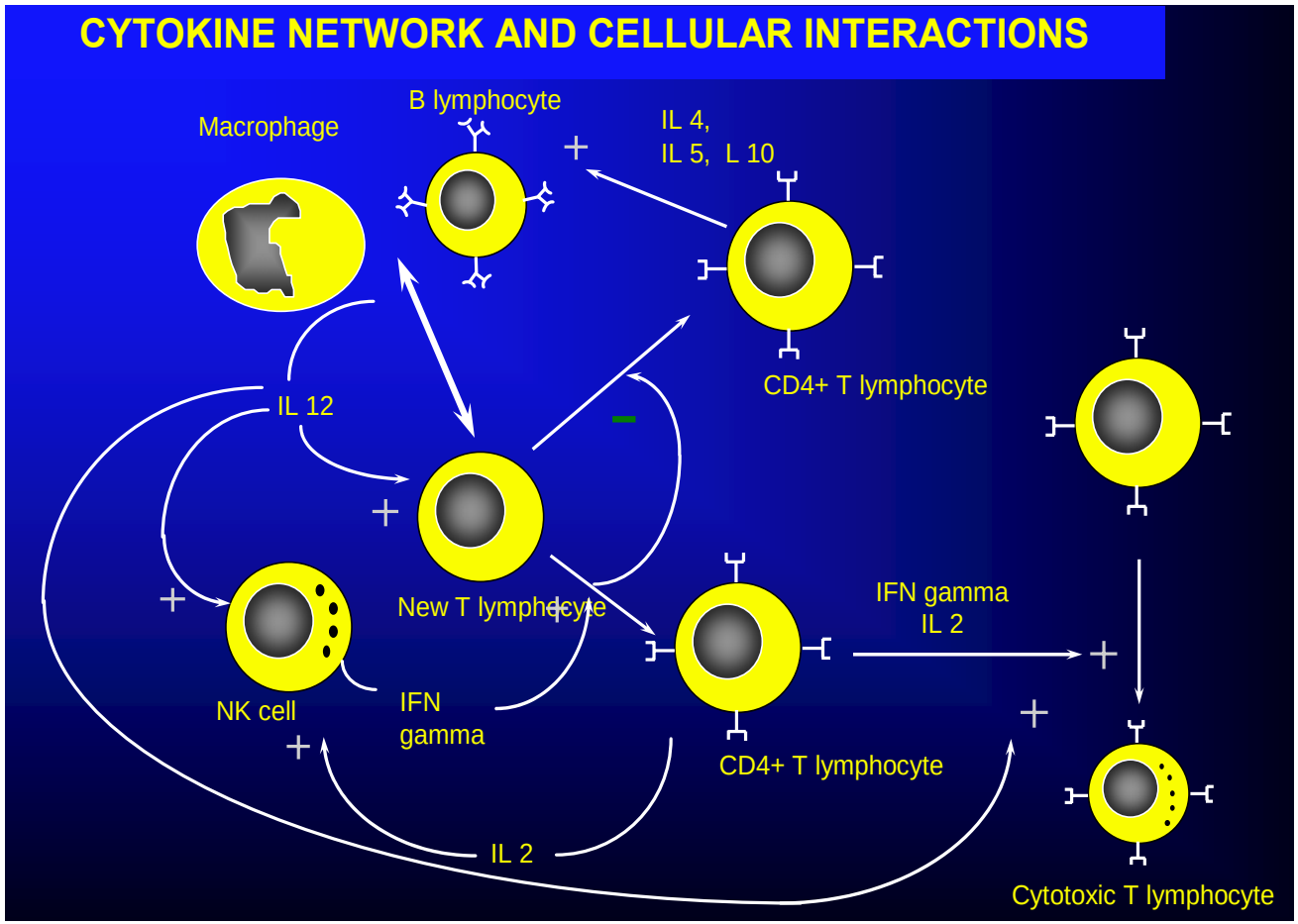
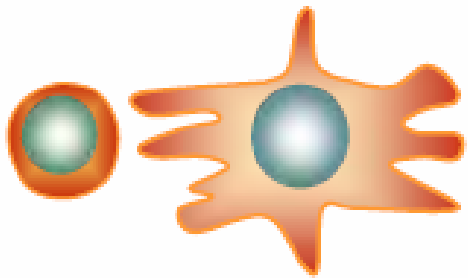
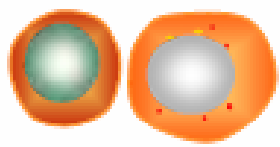
Adaptive immunity









Immunity is a dynamic process!

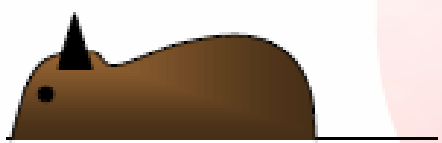
- driven primarily by cytokines & chemokines

Dianas patogénicas en artritis reumatoide

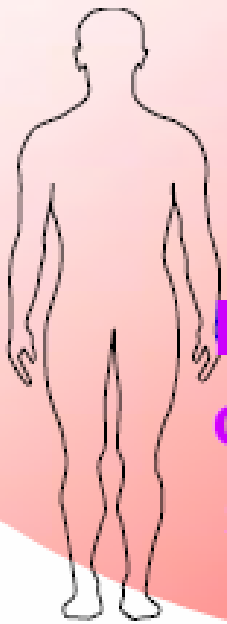
- Espectro de mecanismos patogénicos con relevancia variable entre pacientes y a lo largo de evolución
- Selección eficientes de mecanismos celulares y moleculares en el proceso patogénico del sistema inmunitario/inflamatorio

Which target to choose - immunologic approach?

1. Is target present in tissue?
2. Does it possess a plausible biologic profile?
2. Can it be effectively inhibited:
   - ex vivo?
   - in vivo?



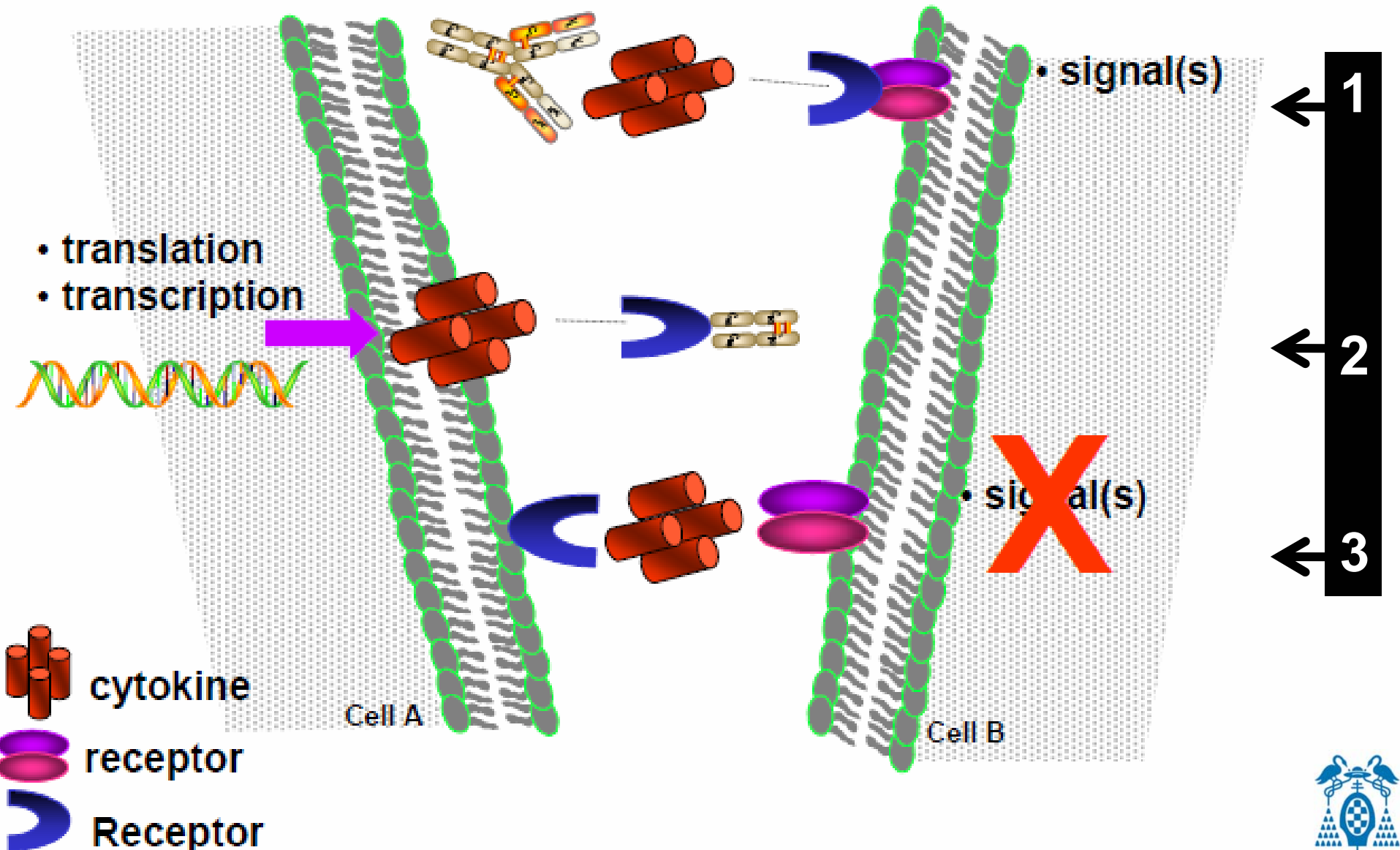
Animal models



Proof of concept studies

In vitro model systems

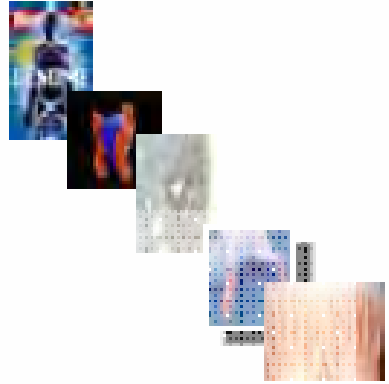
How: to target your chosen molecule…?



DIANAS TERAPÉUTICAS

CITOQUINAS

Where? Inflamed tissue - source of targets



Adaptive immunity

- Ectopic lymphoid structure
- T cells / DC
- B cells

TNF, IL-1
IL-6, IL-15
IL-18, IL-23…

IL-10, IL-35

Lining layer

- FLS
- macrophages

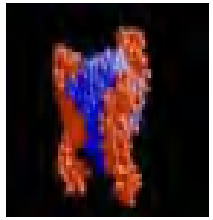
Interstitium

- mast cells
- macrophages
- neuroreceptors

Trafficking

- angiogenesis
- lymphangiogenesis

TNF in inflammatory diseases



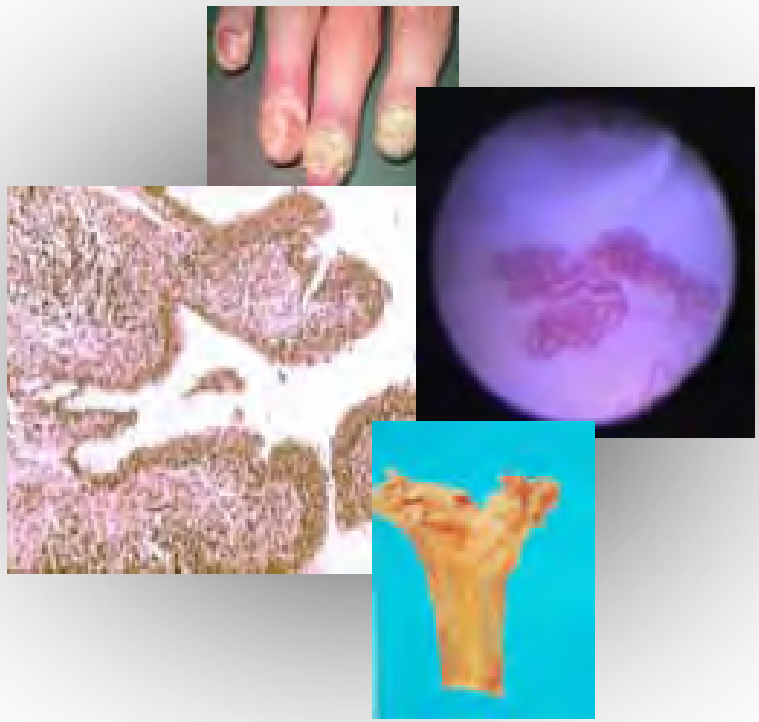
Leukocyte activation
- macrophage
- T_i cell ↑ T_r cell ↓
- NK cell

Endothelial cell activation
- pro-angiogenic

Fibroblast activation
- matrix degradation

Tissue cells
- osteoclast
- keratinocyte
- enterocyte

Nocireceptor gating

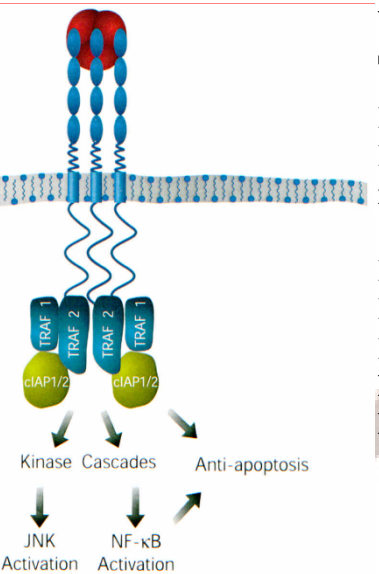


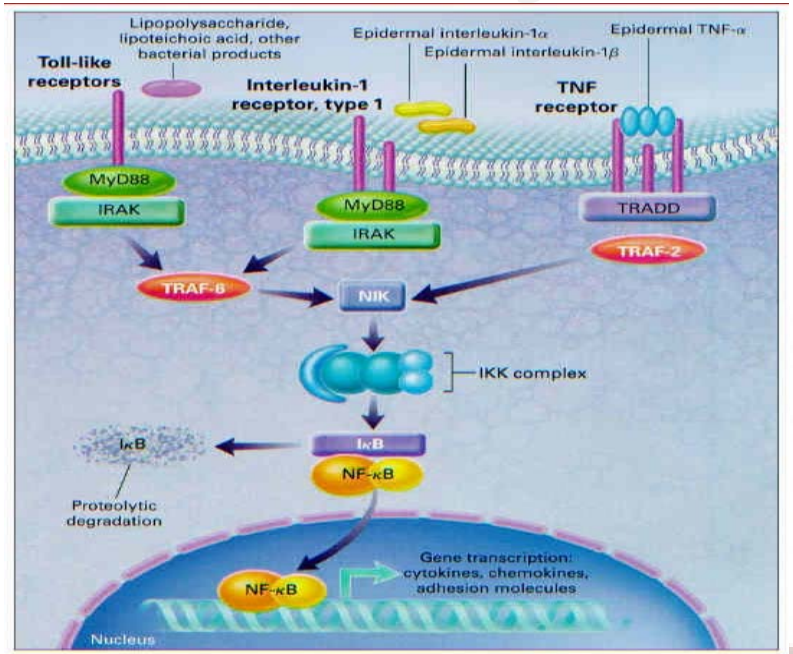
Systemic
- acute phase response (IL-6)
- atherogenesis
- cognitive function / fatigue

ESCENARIO INFLAMATORIO.
The exiciting "TNF story"

MADO

MAPKs
p42
p43
p45
p46
JNK o SAPKs





NF-kB family
NF-kB1 (p50)
NF-kB2 (p52)
p62
C-Rel
Rel B

IkB family
IkBα
IkBβ
IkBγ/p105
IkBδ/p100
IkBε

ICAM-1*
VCAM-1
TNF α
IL-1
IL-6
iNOS

IL-8
Il-12
IFNγ
LÍPIDOS DERIVADOS DE EUCOSANOIDES

IL-4
IL-10 *
TGFβ
IL-1ra
IL-11 *

TNF α
IL-1 / IL-1ra
IL-4 / IFNγ

PRO-INFLAMACIÓN

ANTI-INFLAMACIÓN

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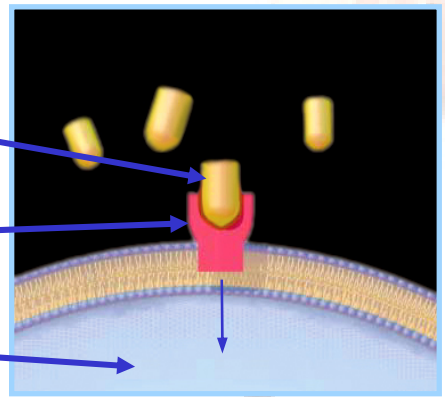
INHIBICIÓN DEL SISTEMA DEL TNFα

Interacción normal

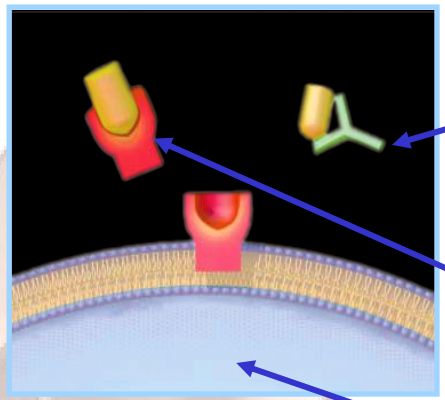


Citocina inflamatoria

Receptor de la citocina

Señal inflamatoria

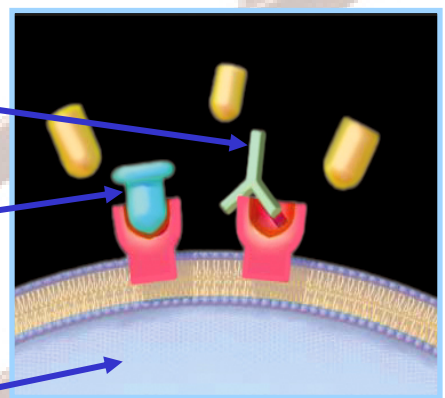
A. Neutralización de las citocinas



Anticuerpo monoclonal anti-Citoquina *(Infliximab, Adalimumab)*

Receptor soluble *(Etanercept)*

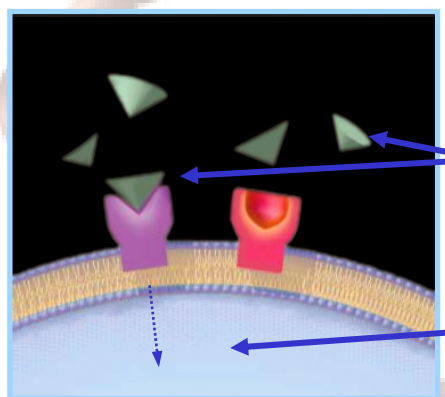
B. Bloqueo de los receptores



Anticuerpo monoclonal anti-Receptor

Antagonista del receptor

C. Activación de las vías antiinflamatorias



Citocina antiinflamatoria

Supresión de la señal inflamatoria

Biologic DMARDs: RA Disease Duration > 6 mo

"Failed" prior MTX in Comb. or With Sequential DMARDs

Disease activity

Low

Refer to Nonbiologic DMARDs algorithmes

Moderate to high

Features of poor

- Refer to Nonbiologic DMARDs Algorithms or Anti-TNF α
- Anti-TNFα OR Abatacept OR Rituximab*

* Only recommended for patients with high disease activity with features of poor prognosis

NUEVOS ANTI-TNFa

CERTOLIZUMAB
GOLIMUMAB

POTENCIALES VENTAJAS

1. COMODIDAD EN LA POSOLOGÍA
2. POTENCIALES EFECTOS BIOLÓGICOS NUEVOS

Golimumab

- **Kay et al: Arthritis Rheum 2008; 58: 964-975**
- Background MTX
- ·1º Endpoint: ACR 20 at week 16
- ·Efficacy
- Group ACR 20 (%)
  - MTX + placebo 37
  - MTX + 50 mg -2 wks 50
  - MTX + 50 mg -4 wks 60
  - MTX + 100 mg -2 wks 79
  - MTX + 100 mg -4 wks 56

Certolizumab (CDP 870)

- Humanized Fab fragment linked to PEG (no Fc fragment)
- Due to PEGylation, higher bio availability
- RAPID 1 and RAPID 2

Certolizumab

ACR	20	50	70
Placebo + MTX	14	8	3
400mg CZP + MTX	61	40	8
200mg CZP + MTX	59	21	3

Fracasos terapéuticos a anti-TNFa

- **No respondedores primarios**
  - El TNF no es un mediador patogénico crítico en todos los enfermos
  - Retraso en la respuesta
  - Dosis inadecuada o neutralización insuficiente del TNFa
- **No respondedores secundarios**
  - Desarrollo de anticuerpos bloqueates
  - Dinámica patogénica con participación de otras citoquinas que adquieren la relevancia biológica (IL-1, IL-6, IL-12, IL-15, IL-17 etc)

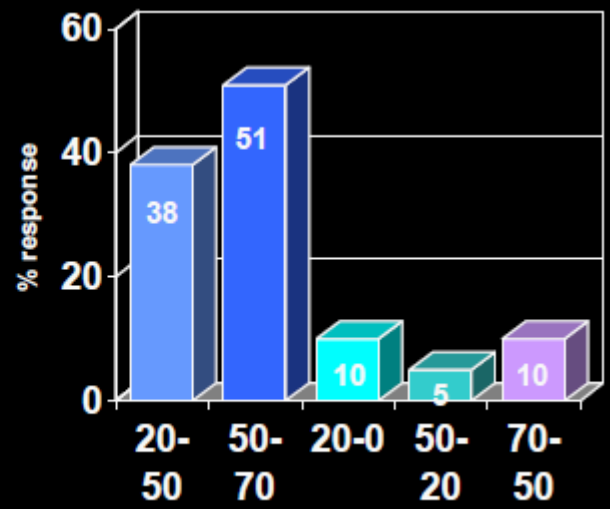
No respondedores primarios a anti-TNFa

Anti-TNF Responses May be Delayed to 24 weeks in Patients initially on MTX + Etan.

Kavanaugh et al A&R 2007; 56 (Suppl): s167

	Responders at 12 wks (%)	Non-Resp. at 12 wks (%)
ACR 20	76	24
ACR 50	42	58
ACR 70	22	78

Among Responders at Lower Levels, those changing by 24 wks



Before declaring a drug a primary non-responder—and when deciding which drug to use, consider the time to onset of action

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Onset of response

- Beginning of Mean Response:
  - TNFi:2 days;
  - Abatacept: 2 - 12 wks;
  - Rituximab: 4 - 12 wks
- WHEN THINKING ABOUT WHAT TO DO NEXT , CONSIDER ONSET OF ACTION— FASTER IS BETTER BUT NEED TO WAIT "LONG ENOUGH" ONCE STARTED ON A BIOLOGIC

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MURPHY WAS AN OPTIMIST

MURPHY´S LAW

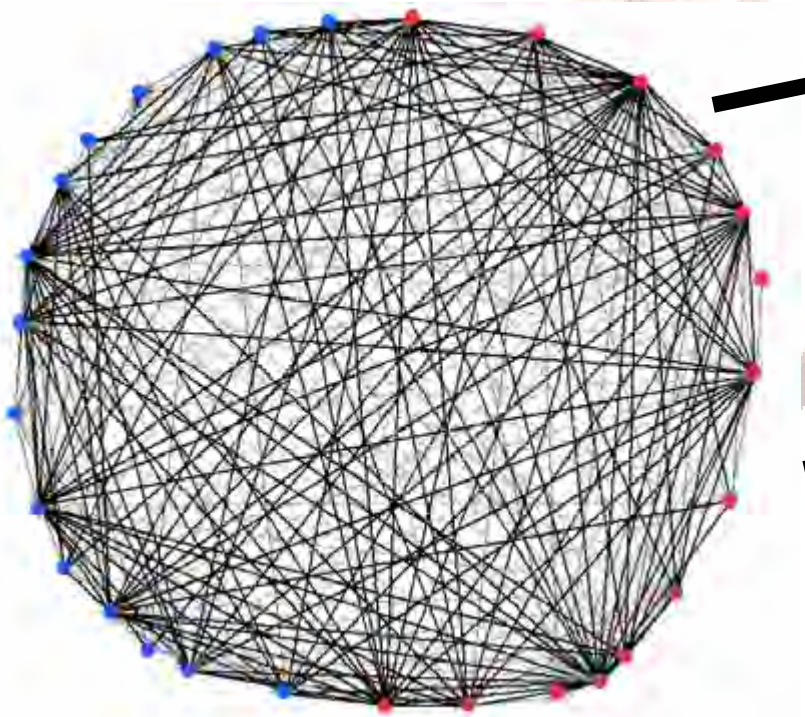
FRIENDS COME AND GO

BUT

ENEMIES ACCUMULATE.

Which other targets?

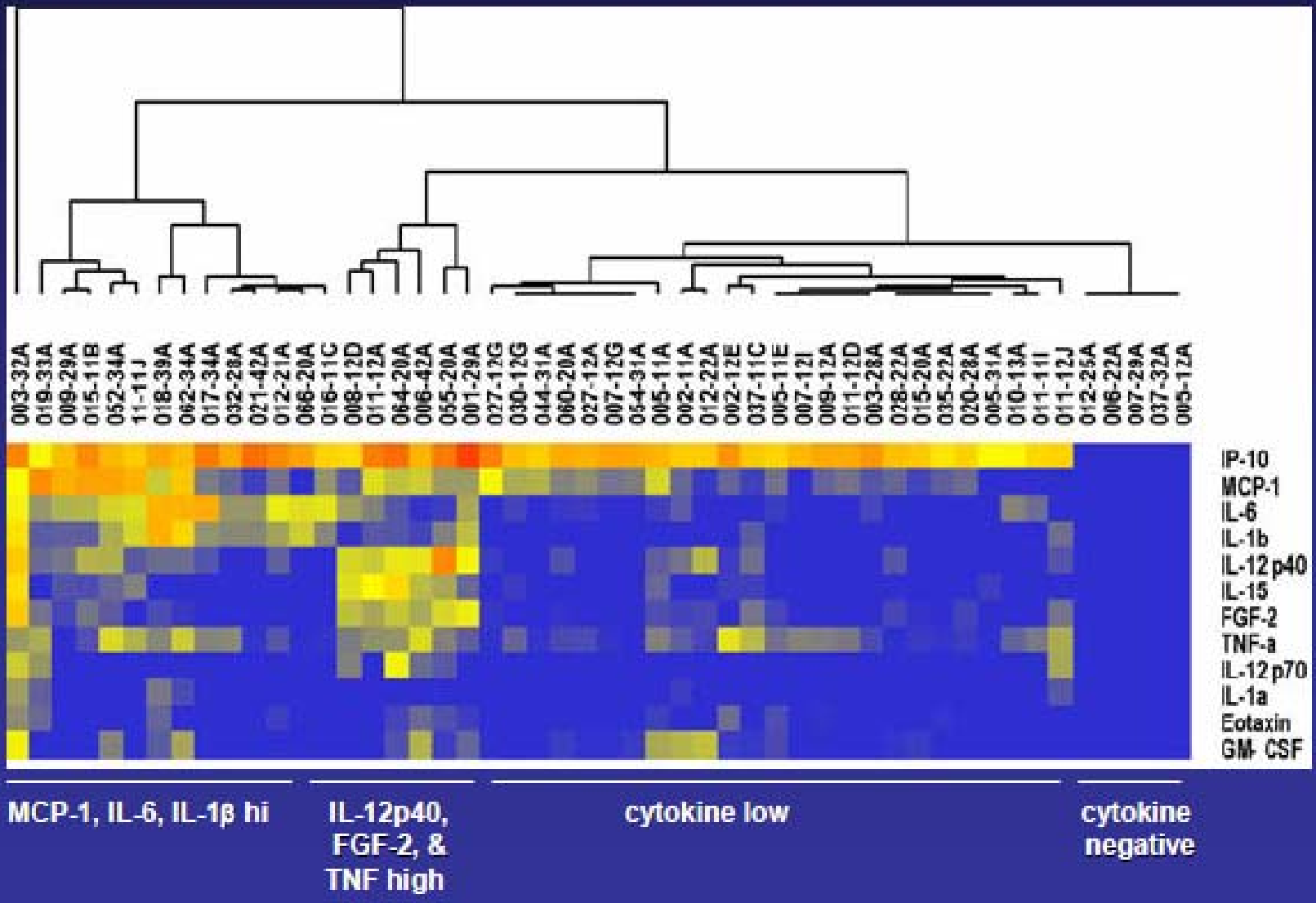
Its *quite complicated!*

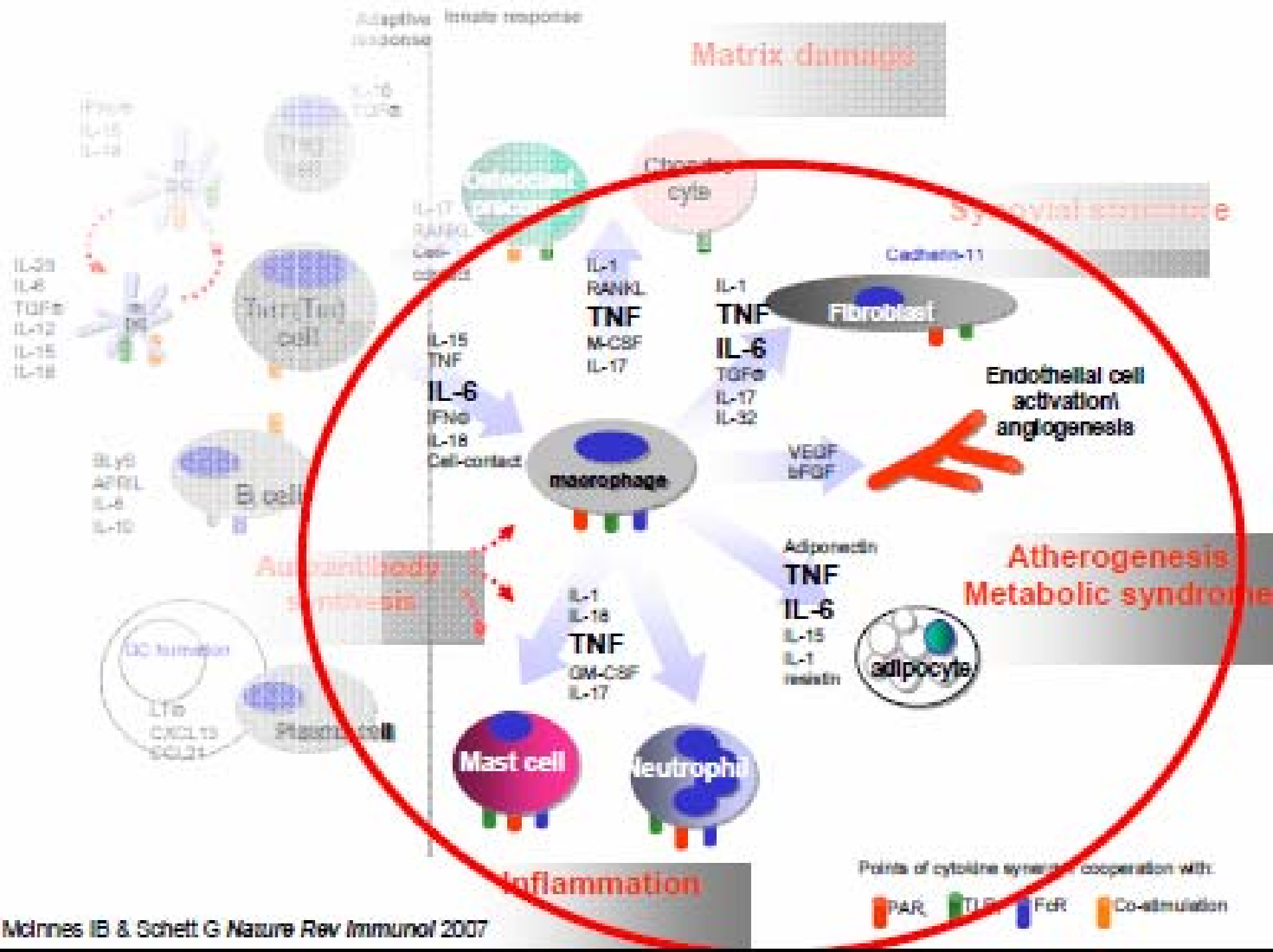


IL 1
IL 6
1L 12
IL 15
IL 17
…

Other mediator become more active with adequate inhibition of TNFa ?

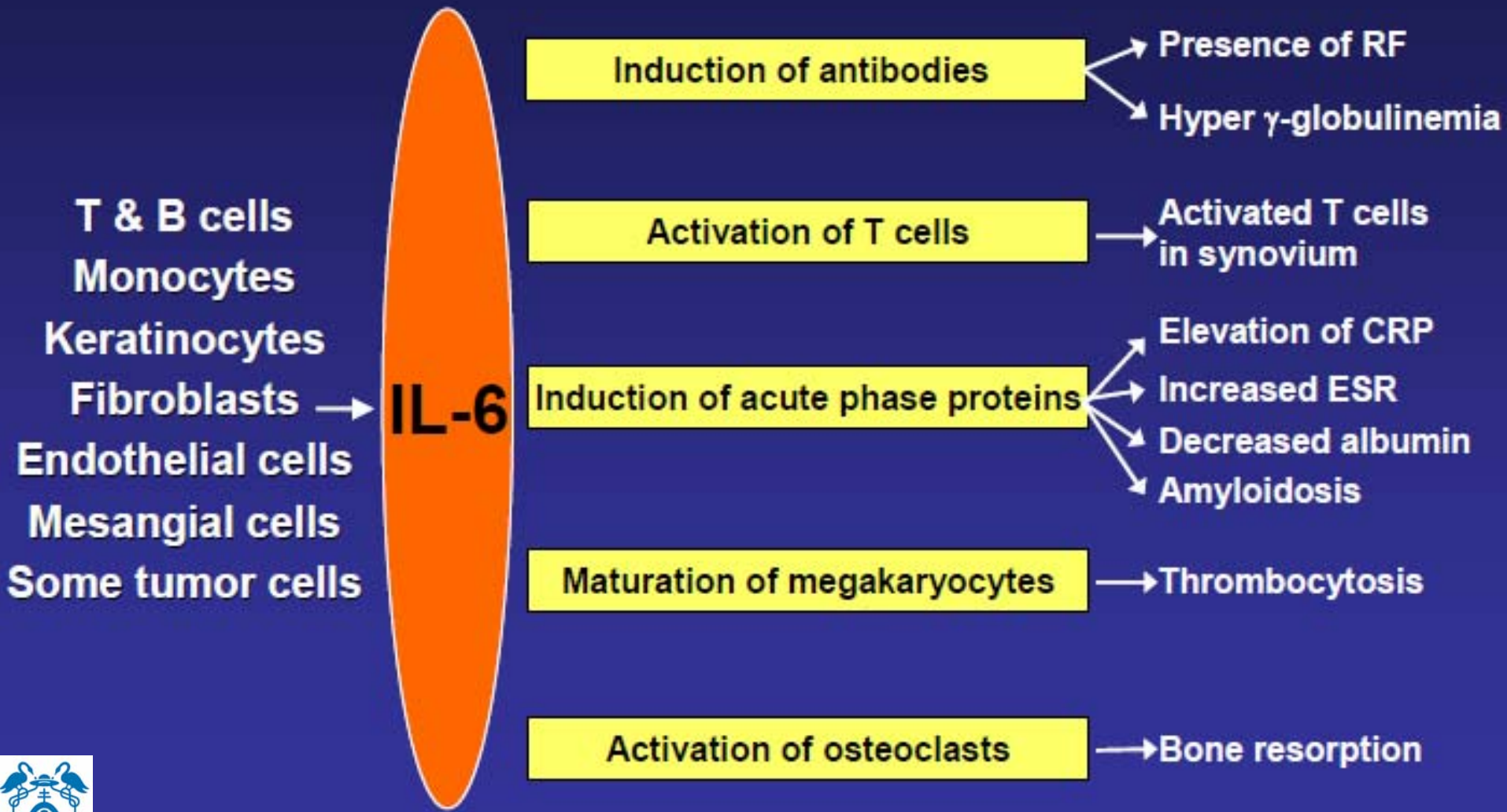
Cytokine Profiling in Early RA Patients



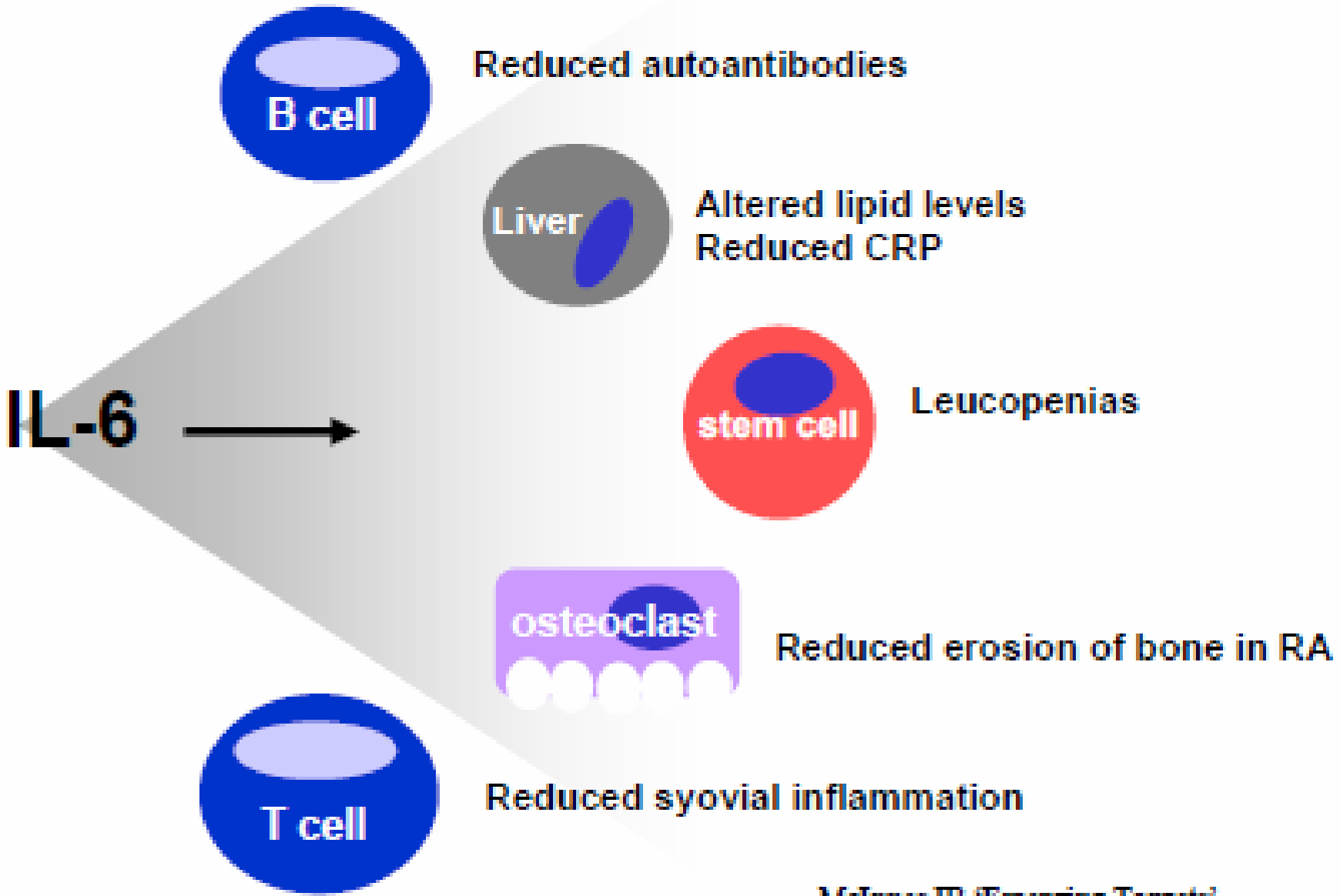


McInnes IB & Schett G *Nature Rev Immunol* 2007

IL-6 and RA Pathophysiology



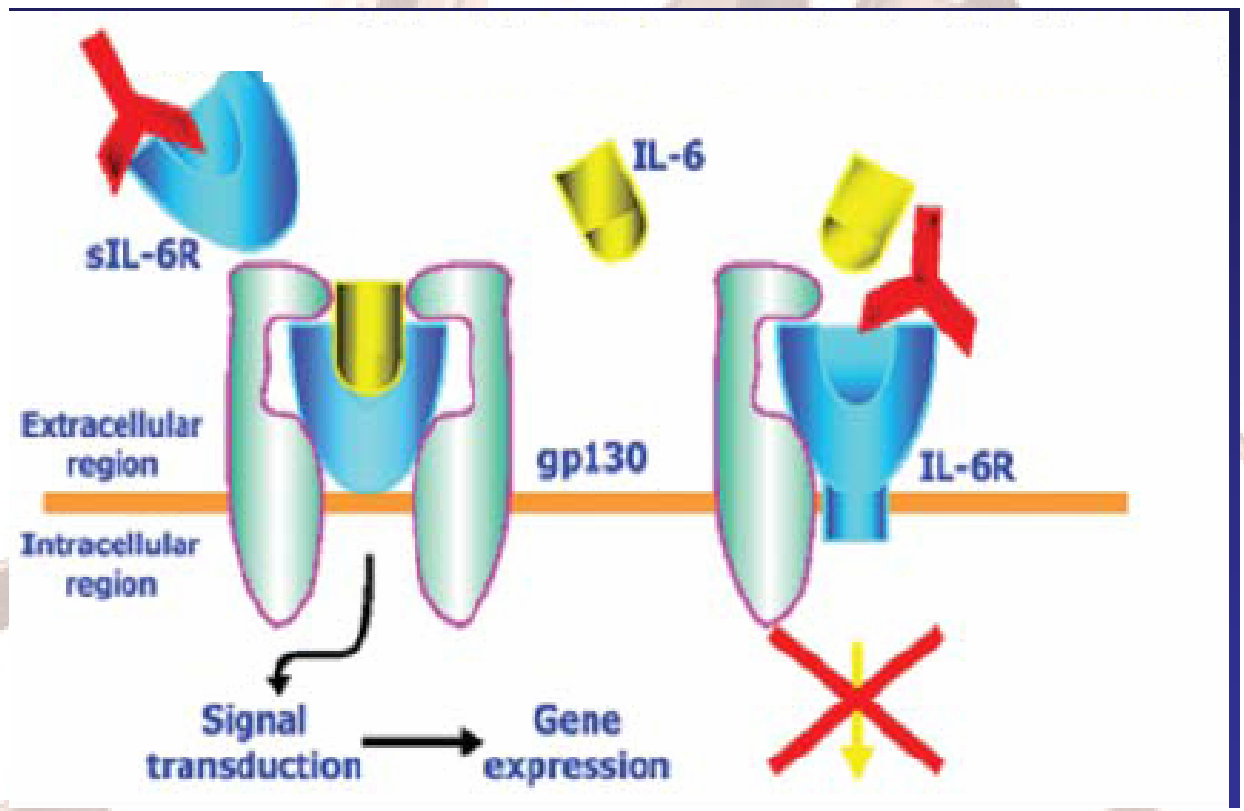
Interleukin-6 – predicted benefit of blockade?



McInnes IB 'Emerging Targets' in Hochberg et al Rheumatology, Elsevier

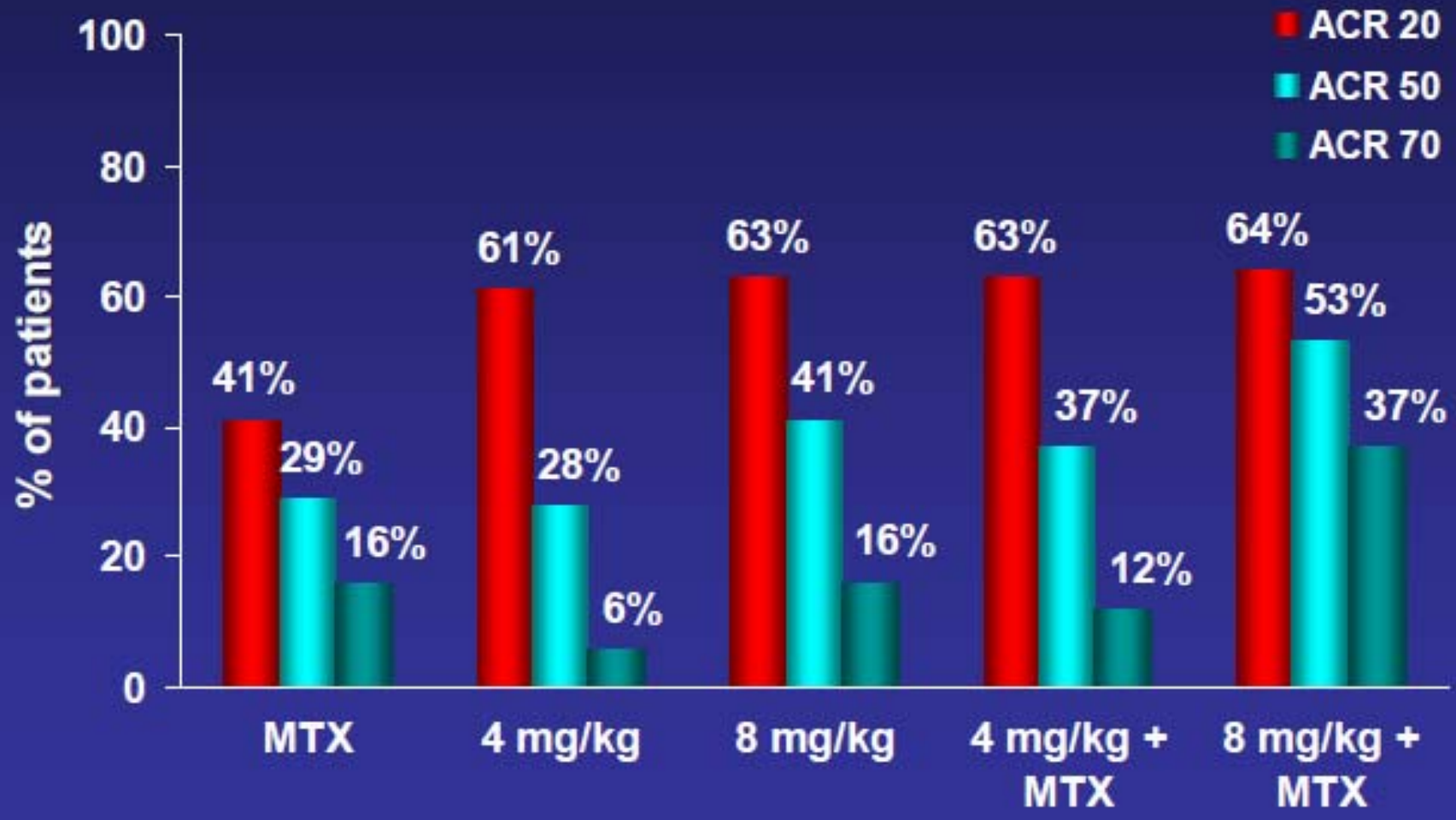
Tolcilizumab

Mecanismo de acción



Tocilizumab : CHARISMA

(Maini et al. Arthritis & Rheumatism, 2006)



Tocilizumab Option Study (phase III)

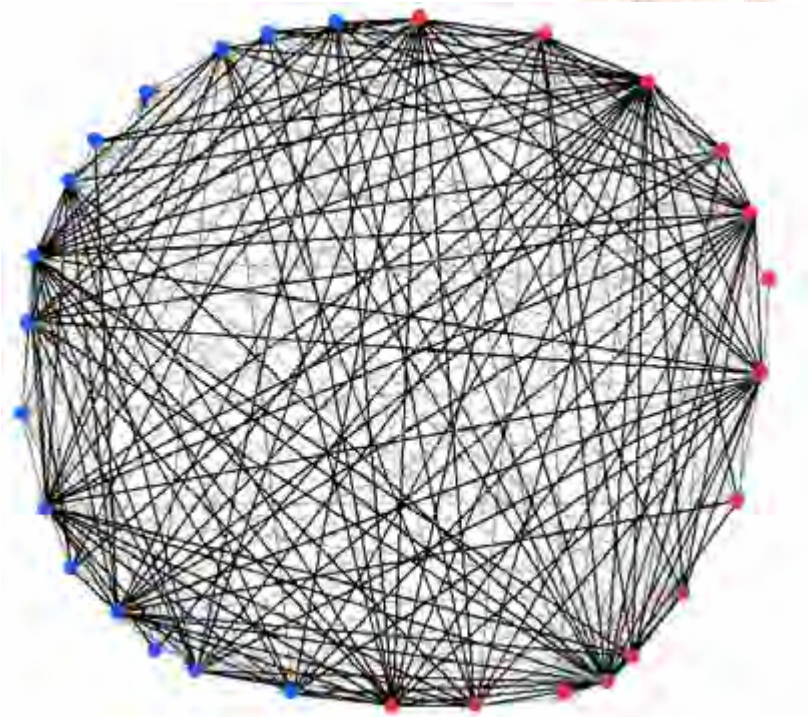
Smolen, et al Lancet, 2008; 371:987-999

- Background MTX

	Placebo	4mg/kg	8mg/kg
ACR 20%	26	48	59
50%	11	31	44
70%	2	12	22
DAS <2.6	.8	13	27

Which other targets?

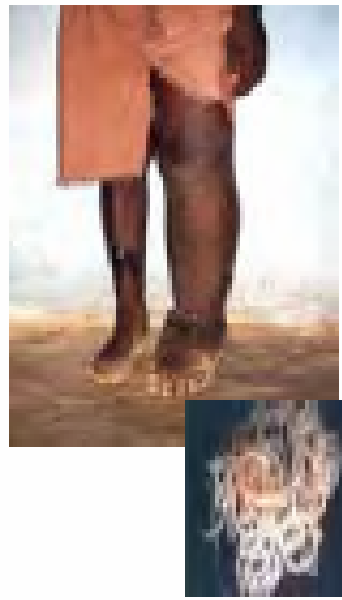
Its *quite complicated!*

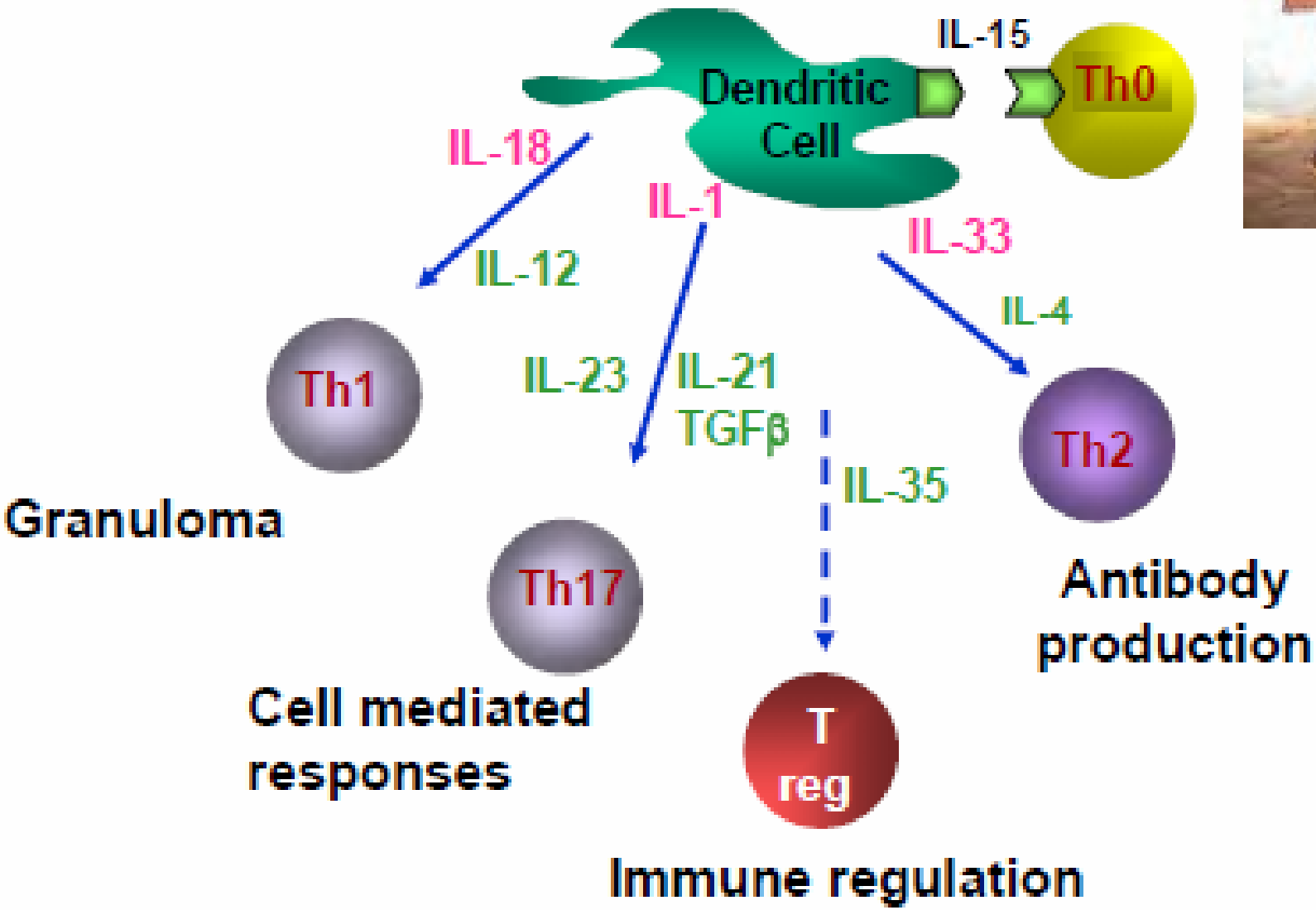


IL 1
IL 6
1L 12
IL 15
IL 17
…

Other mediator become more active with adequate inhibition of TNFa ?

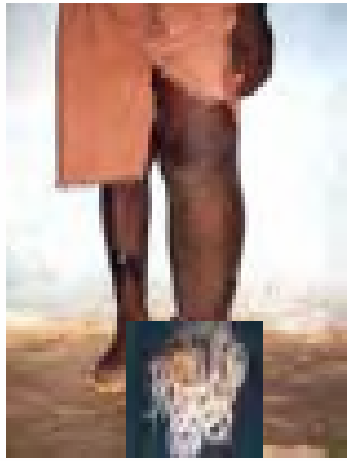
Cytokines that regulate T cells

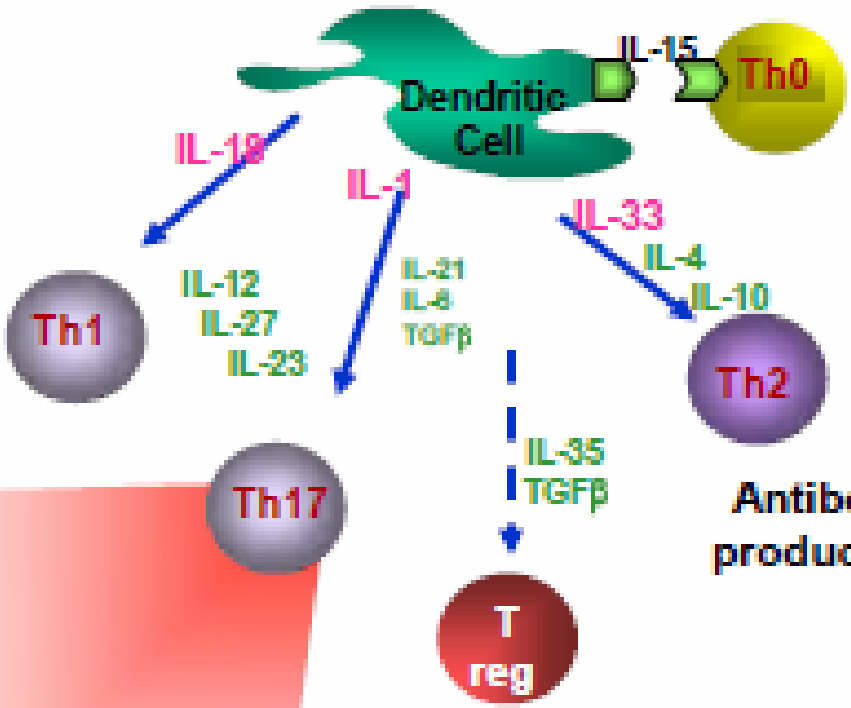




McInnes IB *Hochberg et al Textbook* 2007; Choo-Kang McInnes & Garside *Trends Immunol* 2005

IL-17A as a therapeutic target?





Inflammation:

- Leukocyte
- Fibroblast
- Chondrocyte / osteoclast

Matrix degradation

- synergistic activities

Uncertainties?

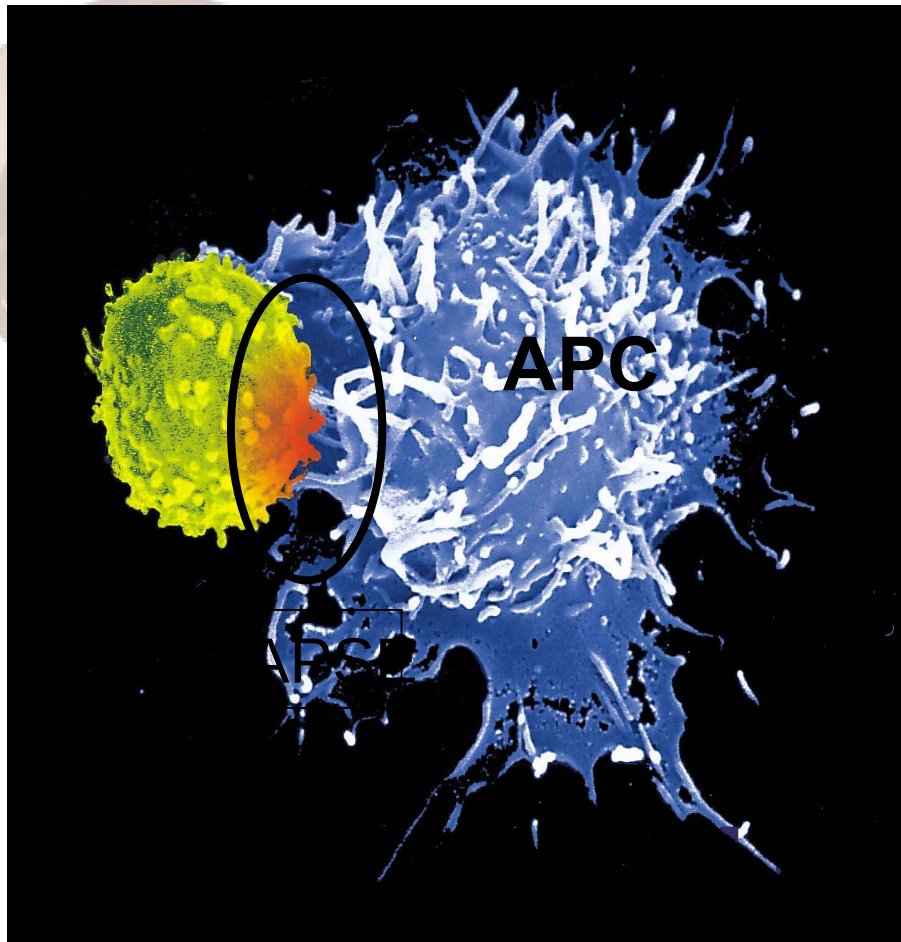
- IL-17F, IL-22, IL-26…
- role in immune defence emerging

DIANAS TERAPÉUTICAS

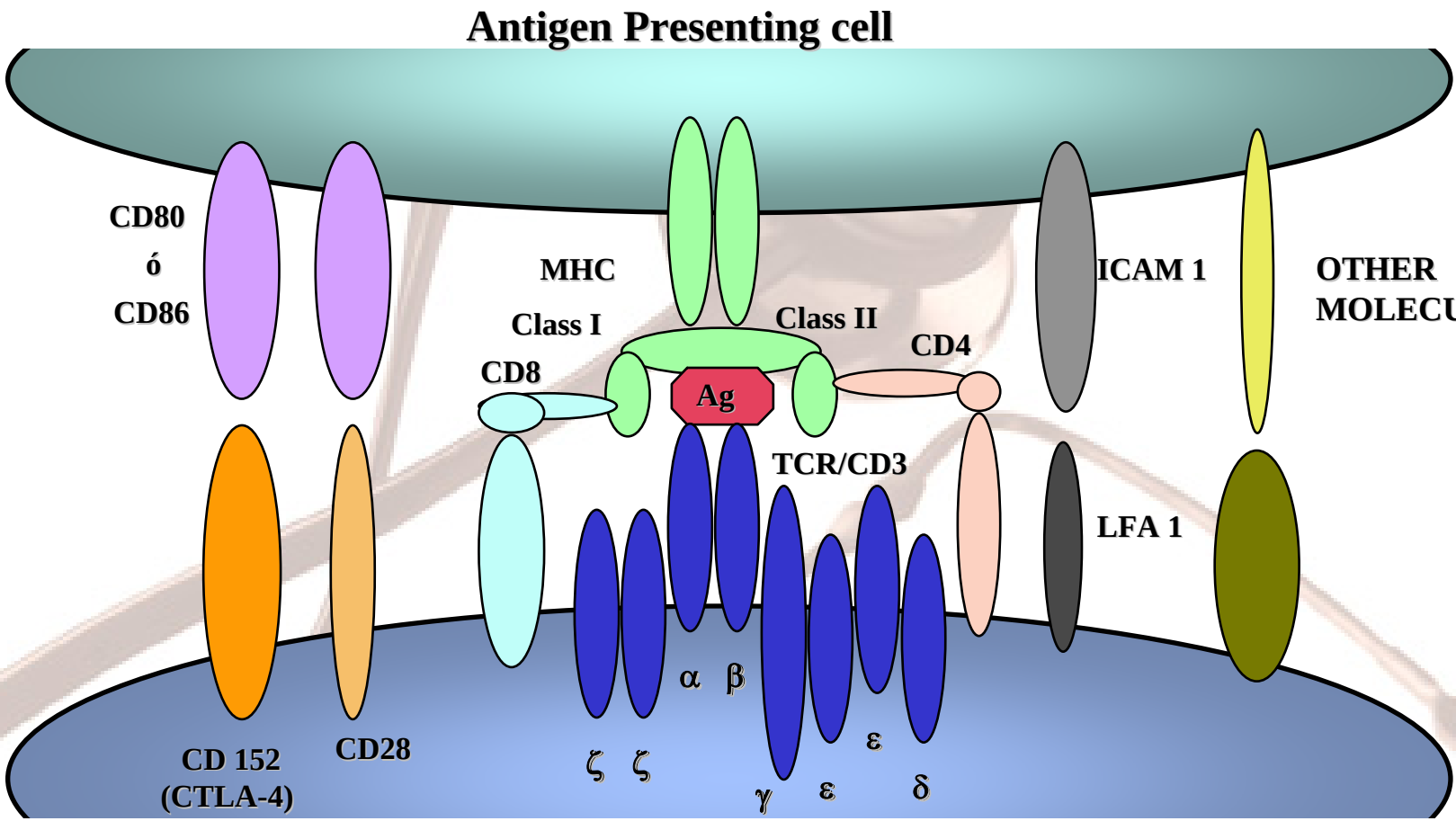
CÉLULAS DEL SISTEMA INMUNITARIO

- SISTEMA NATURAL
- SISTEMA ADAPTATIVO

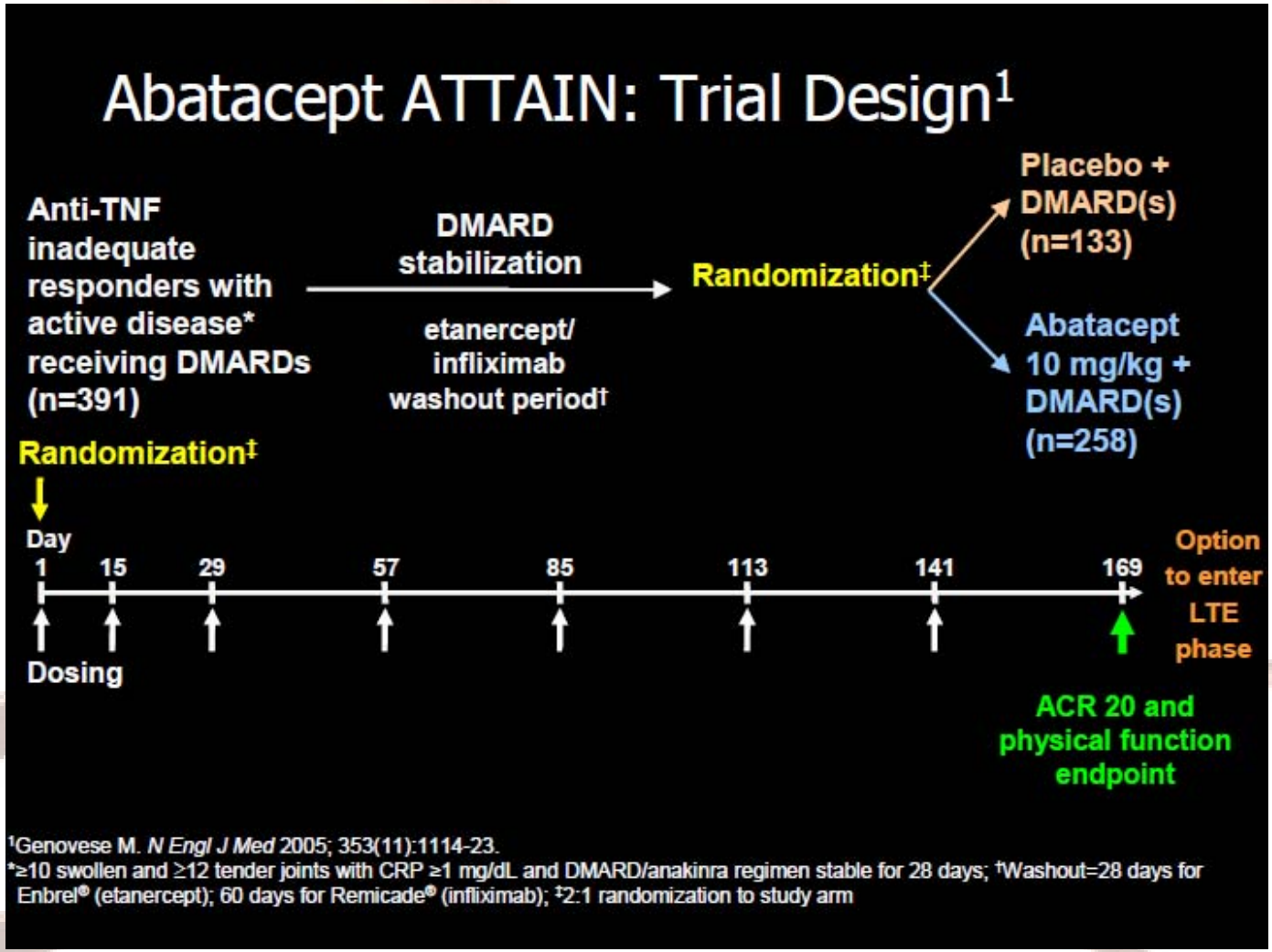
Micrometer-sized segregated clusters of proteins at the T lymphocyte-APC intercellular contact



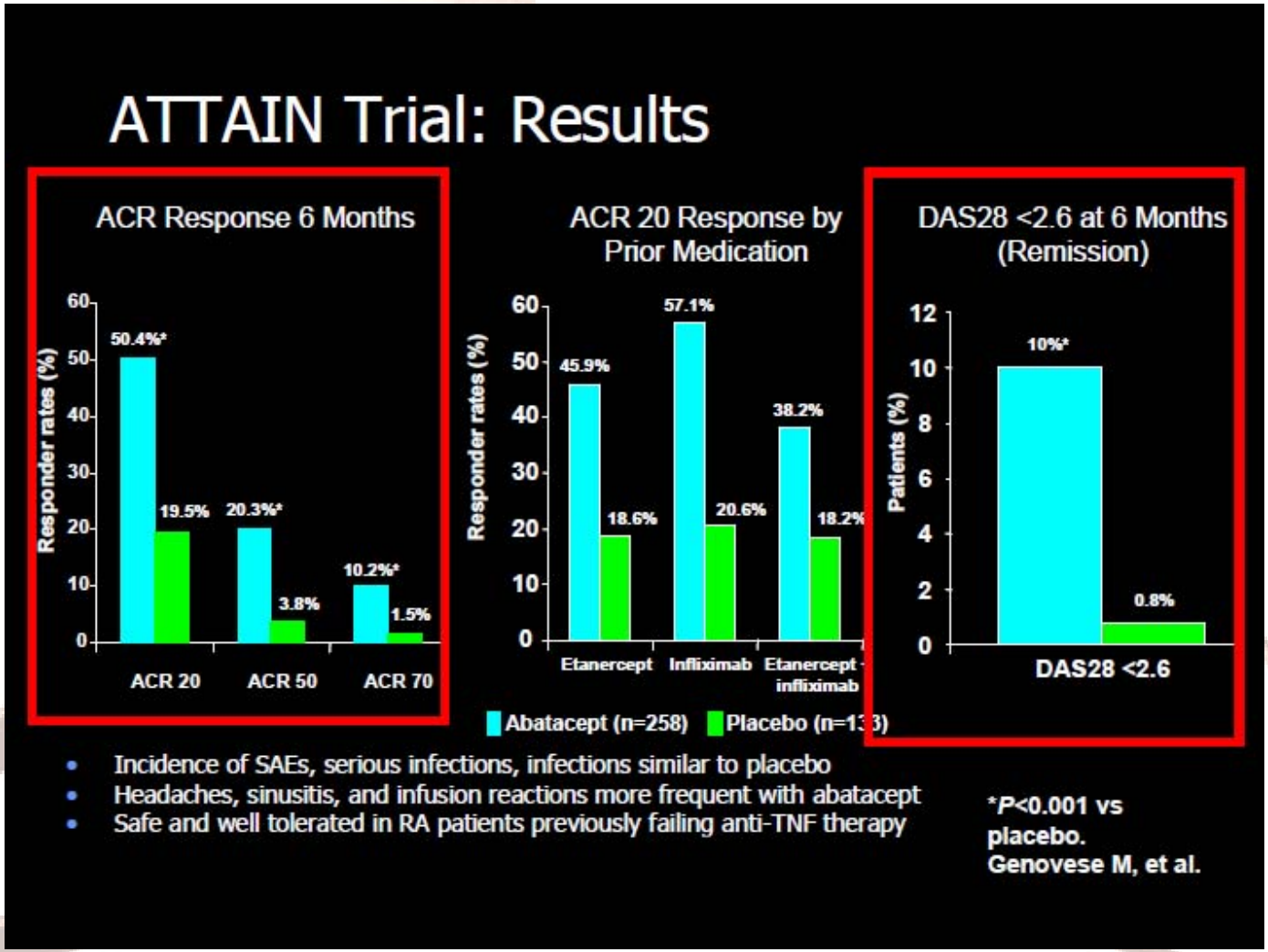
IMMUNOLOGICAL SYNAPSE



LINFOCITOS T ABATACEPT



LINFOCITOS T ABATACEPT



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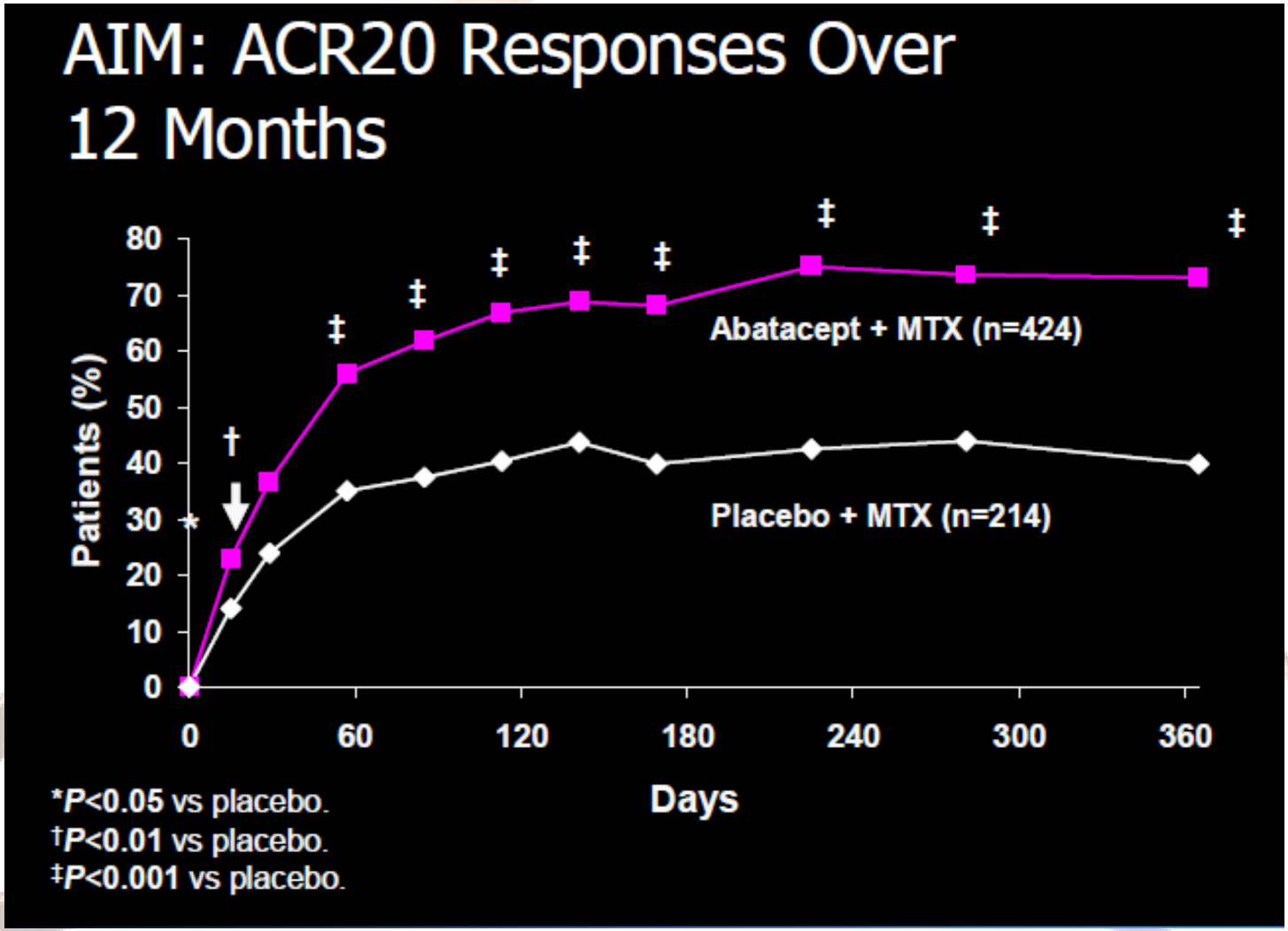

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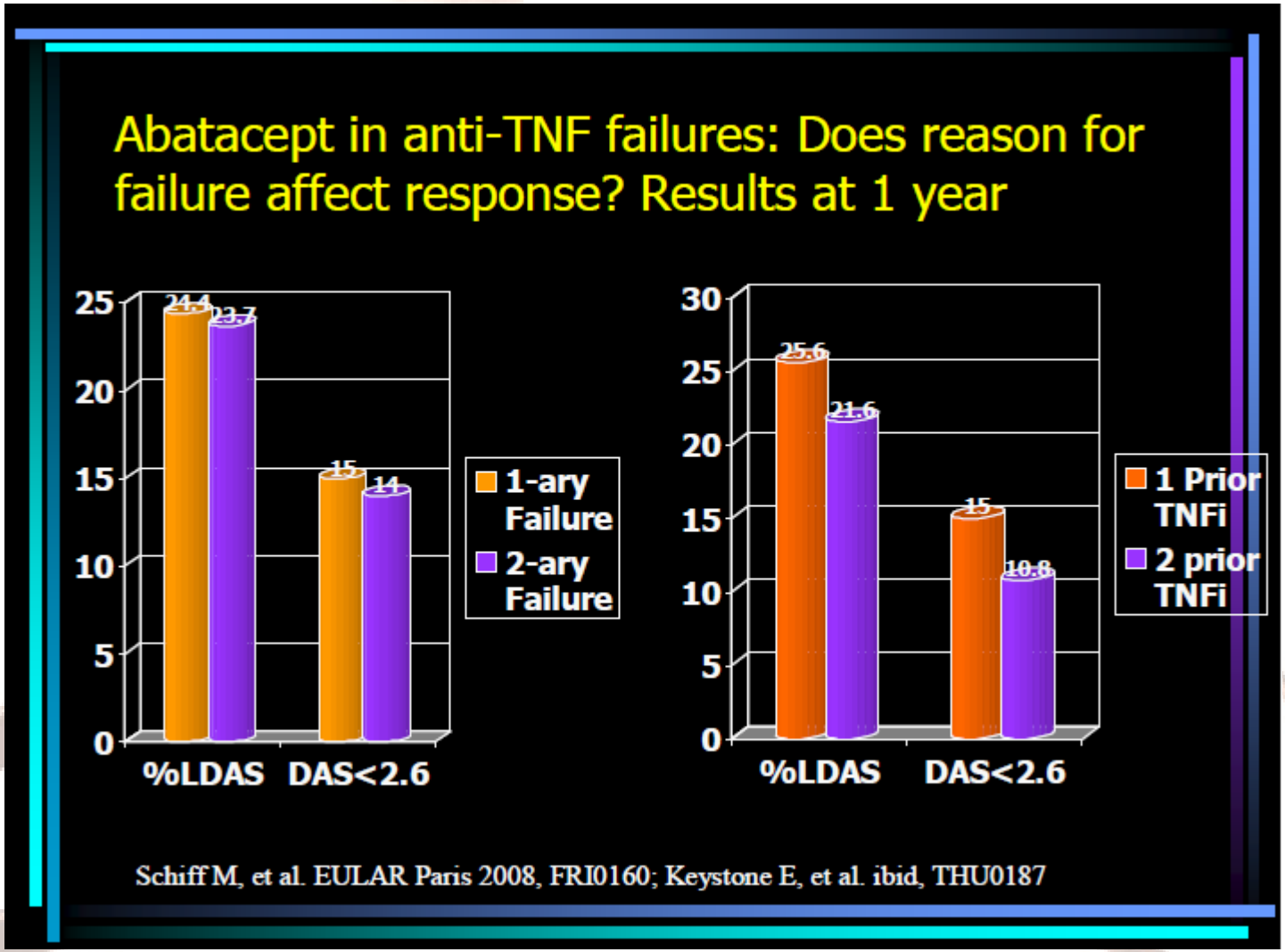
Madrid

LINFOCITOS T ABATACEPT



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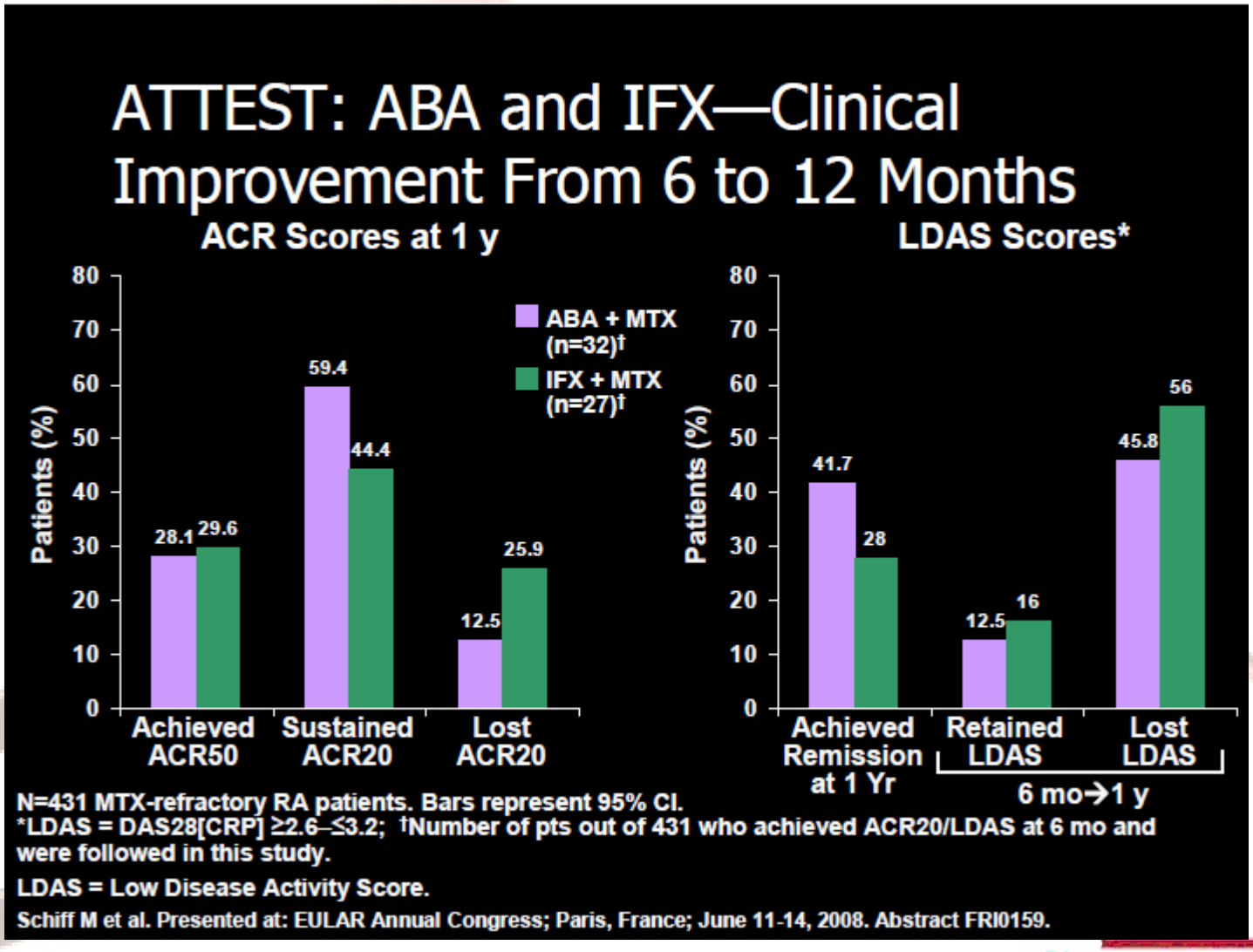
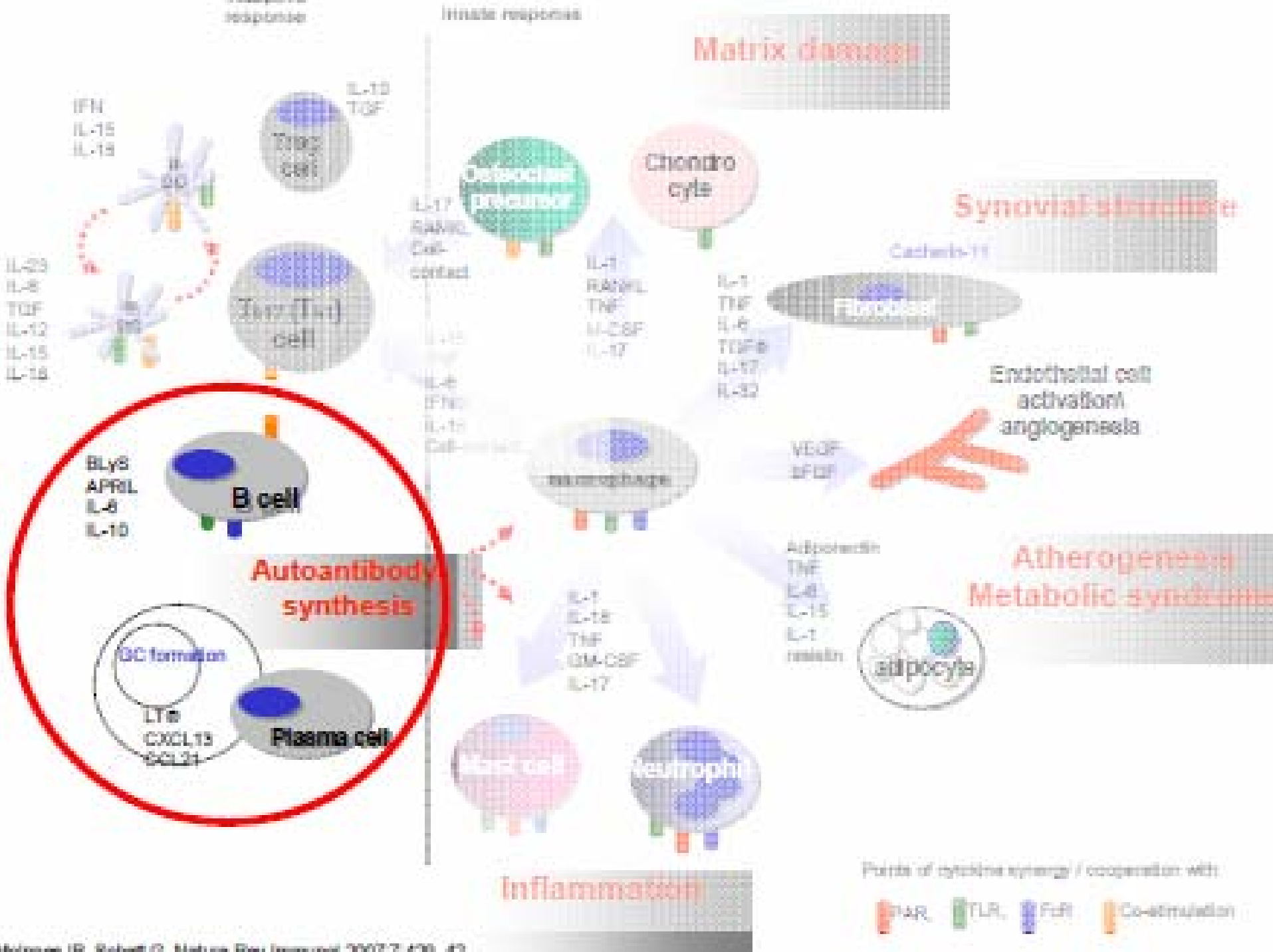


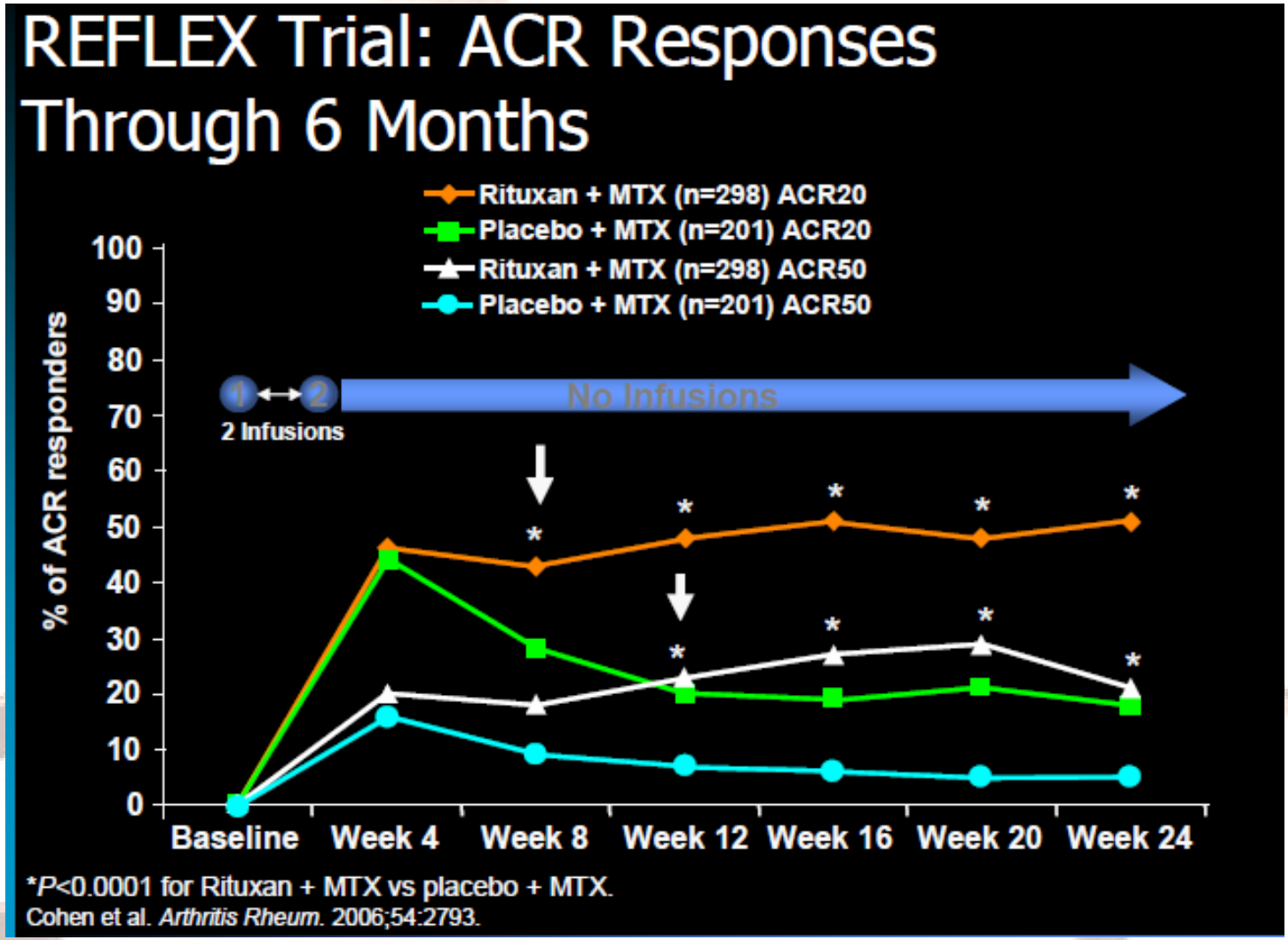
DIANAS TERAPÉUTICAS

CÉLULAS DEL SISTEMA INMUNITARIO

- SISTEMA NATURAL
- SISTEMA ADAPTATIVO


response
Innate responses
Matrix damage
IFN
IL-15
IL-18
IL-10
TGF
Th0 cell
Th1/Th2 cell
IL-23
IL-6
TGF
IL-12
IL-15
IL-18
osteoclast precursor
Chondrocyte
IL-17
RANKL
Cell-contact
IL-1
RANKL
TNF
M-CSF
IL-17
IL-1
TNF
IL-6
TGFβ
IL-17
IL-32
Synovial stromal cell
Cadherin-11
Fibroblast
Endothelial cell activation angiogenesis
VEGF
bFGF
macrophage
BLyS
APRIL
IL-6
IL-10
B cell
Autoantibody synthesis
GC formation
LTα
CXCL13
SCL21
Plasma cell
IL-1
IL-18
TNF
GM-CSF
IL-17
Adiponectin
TNF
IL-6
IL-15
IL-1
resistin
adipocyte
Atherogenesis
Metabolic syndrome
mast cell
neutrophil
Inflammation
Points of cytokine synergy / cooperation with:
PAR
TLR
FcR
Co-stimulation

LINFOCITOS B RITUXAN



B-cell Inhibitors in Development

Agent	Target	Constant
Belimumab	BAFF	human MAB
Atacicept (TACI-Ig)	BAFF & APRIL	fusion protein
Ofatumimab	CD20	human MAB
Ocrelizumab	CD20	humanized MAB
TRU015	CD20	engineered protein
Epratuzumab	CD22	humanized MAB

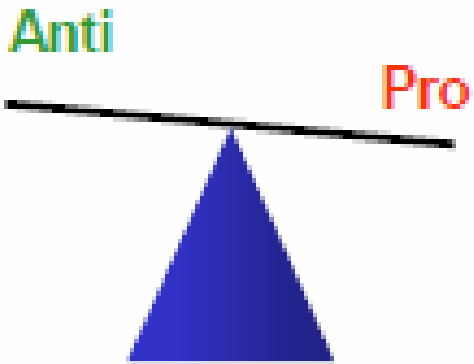
BAFF= B-cell activating factor

APRIL = A proliferation-inducing ligand

TACI-Ig = Transmembrane activator and calcium-modulating cycophilin ligand interactor -Ig

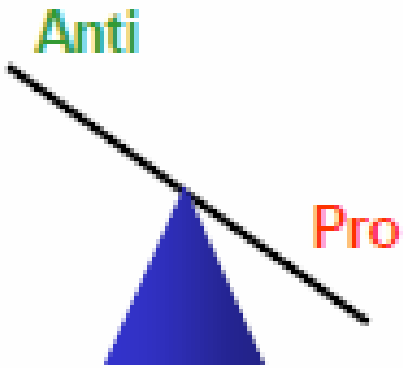
Damage sensing by innate immune response

Pre-arthritis

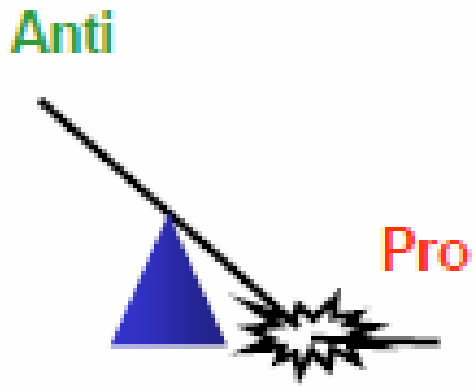


Inflammation:
- genetics
- environment

Early arthritis



Established arthritis

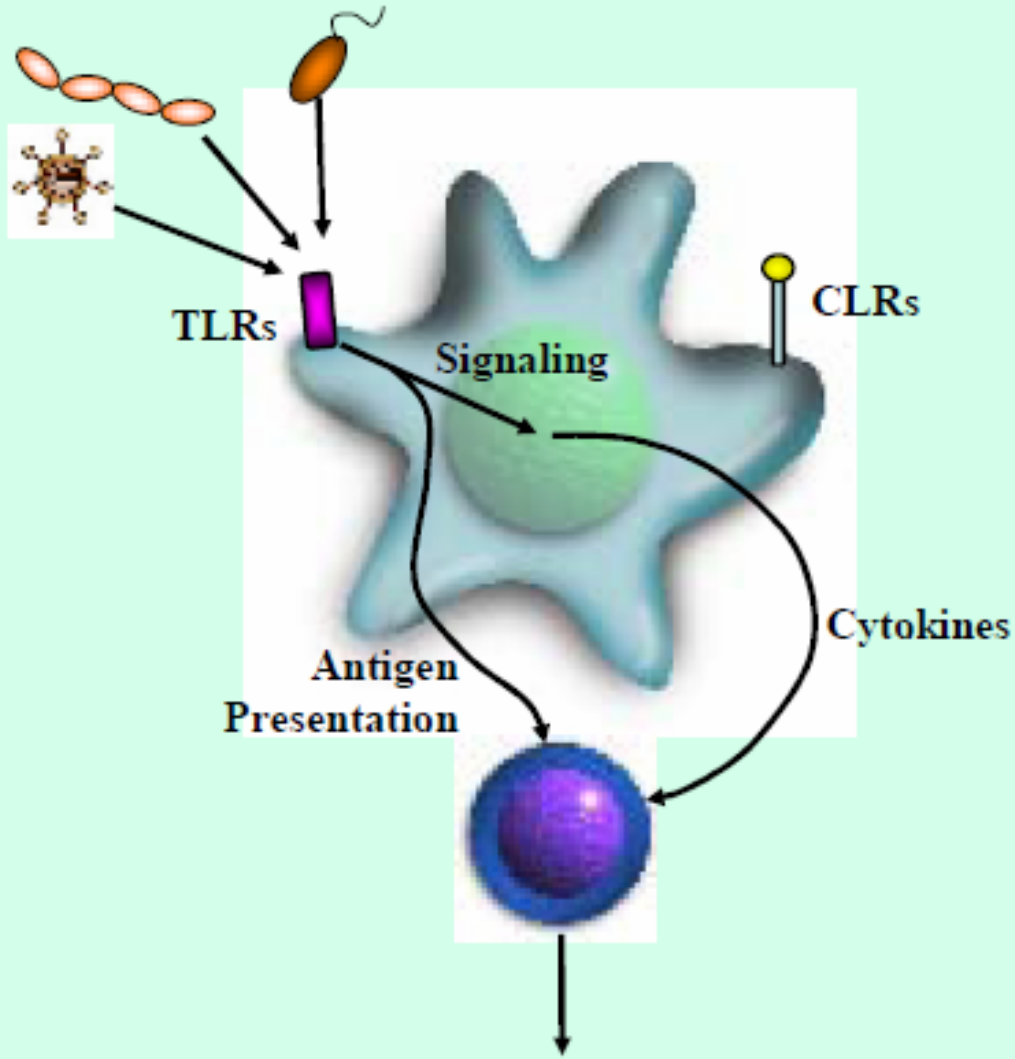


Damage / repair:
- genetics
- environment
- **TLR system**

'Drug-maintained' remission?

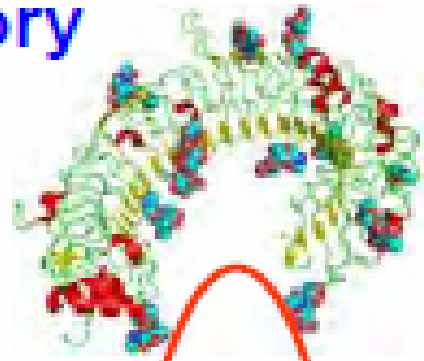
'Drug-free' remission?

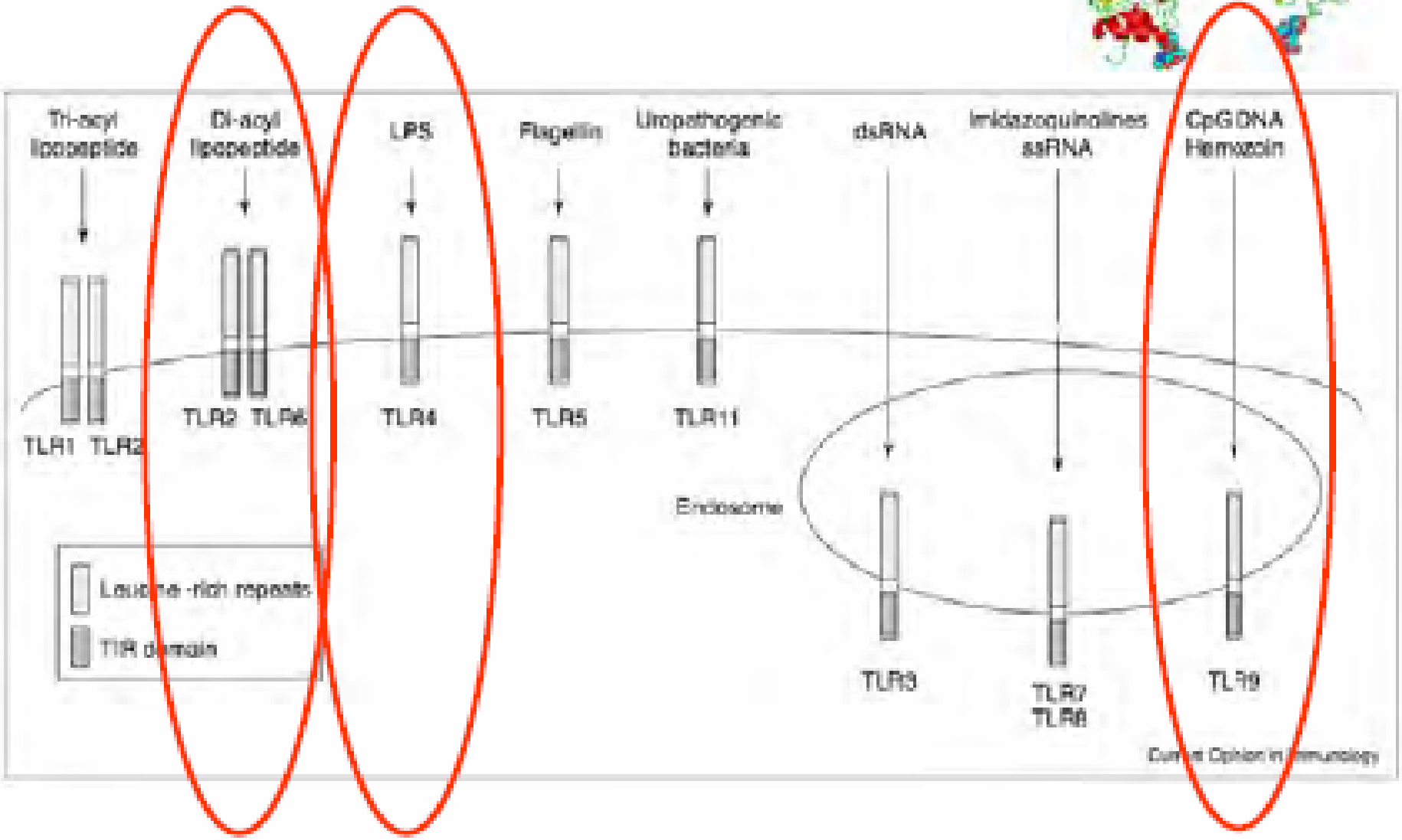
Dendritic Cell Programming through Toll-like receptors (TLRs) and C-type lectin receptors (CLRs)



Direct the overall quality and effectiveness of immune responses

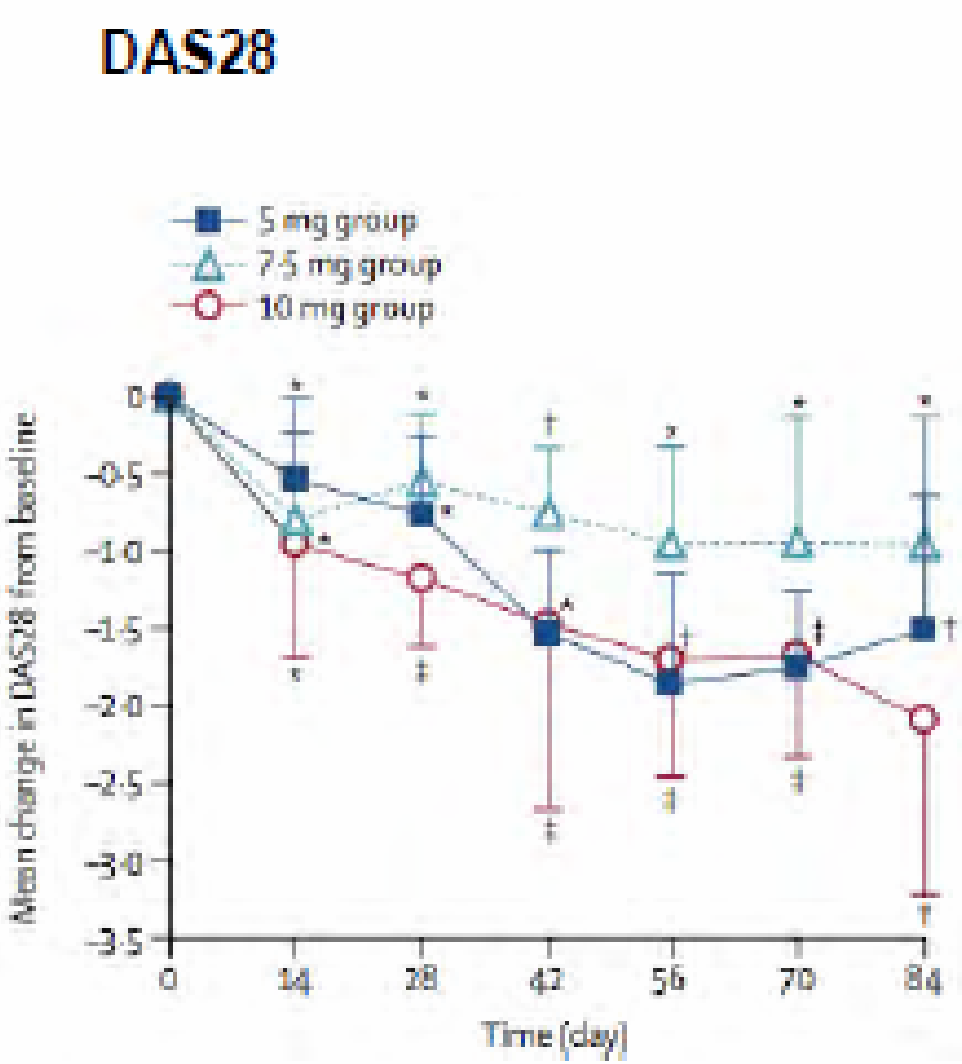
Toll-like receptors: driving inflammatory responses in rheumatic diseases

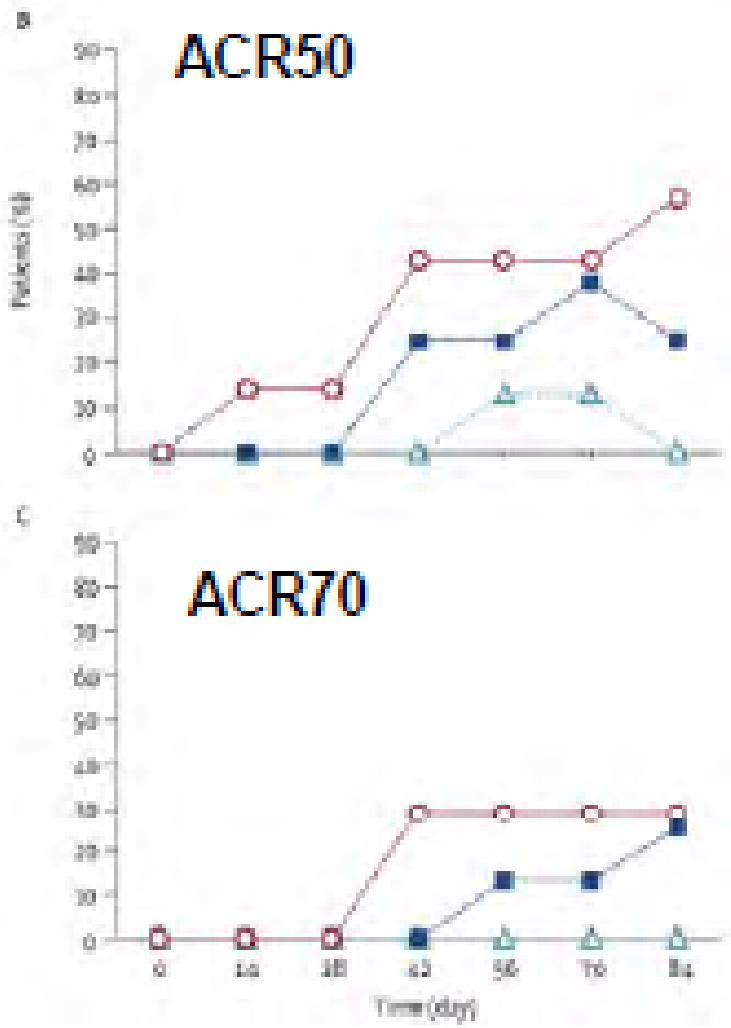




Kawai & Akira *Curr Opin Immun* 2005

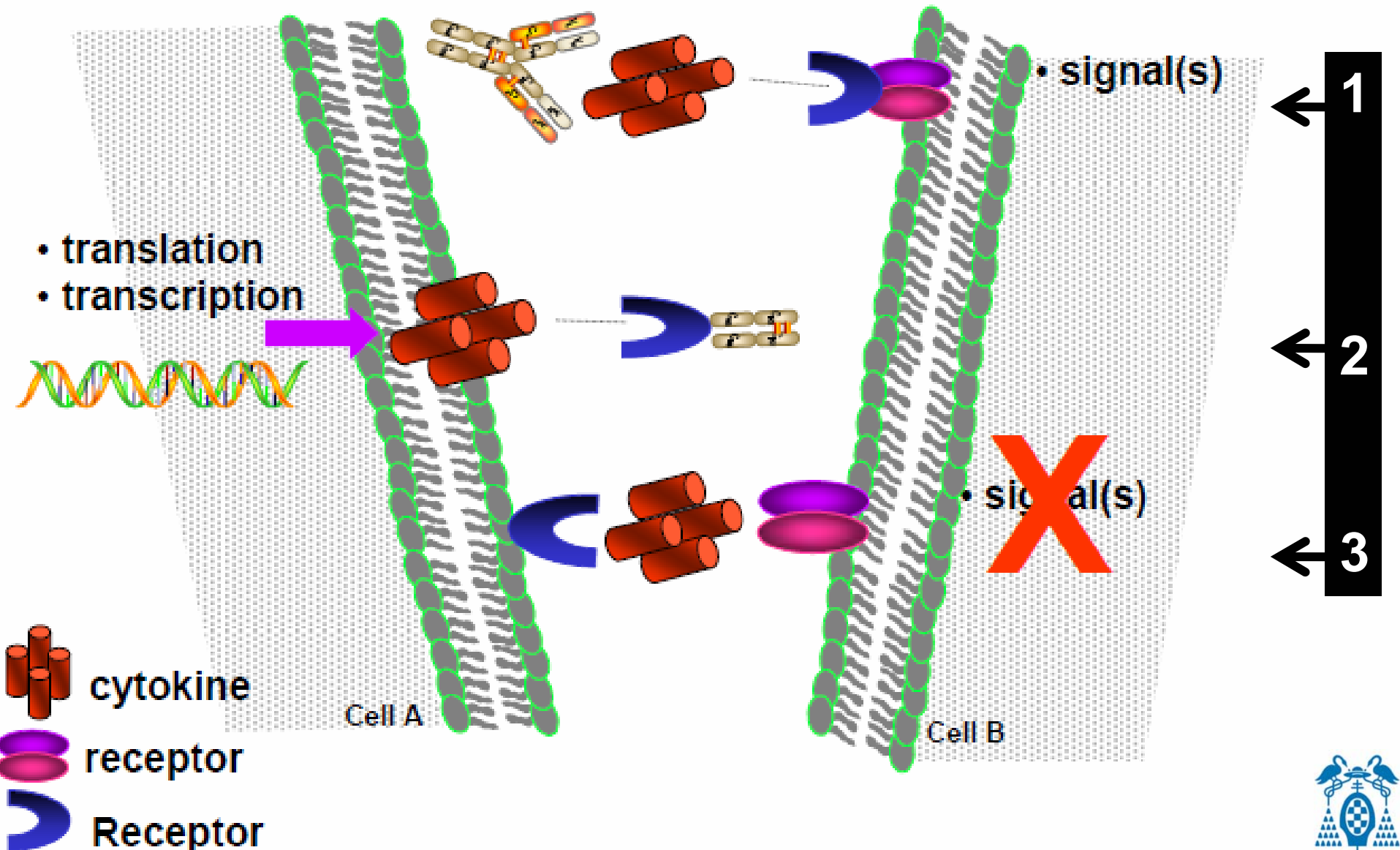
TLR antagonism: chaperonin 10 in RA





Vanags D *Lancet* (2006) 368; 855

How: to target your chosen molecule…?



Signal Transduction

Inhibitors

Signal Transduction Pathways

1.mitogen-activiated protein (MAP) kinase

2.janus-kinase/signal-transducer and

3.activator of transcription (Jak/STAT)

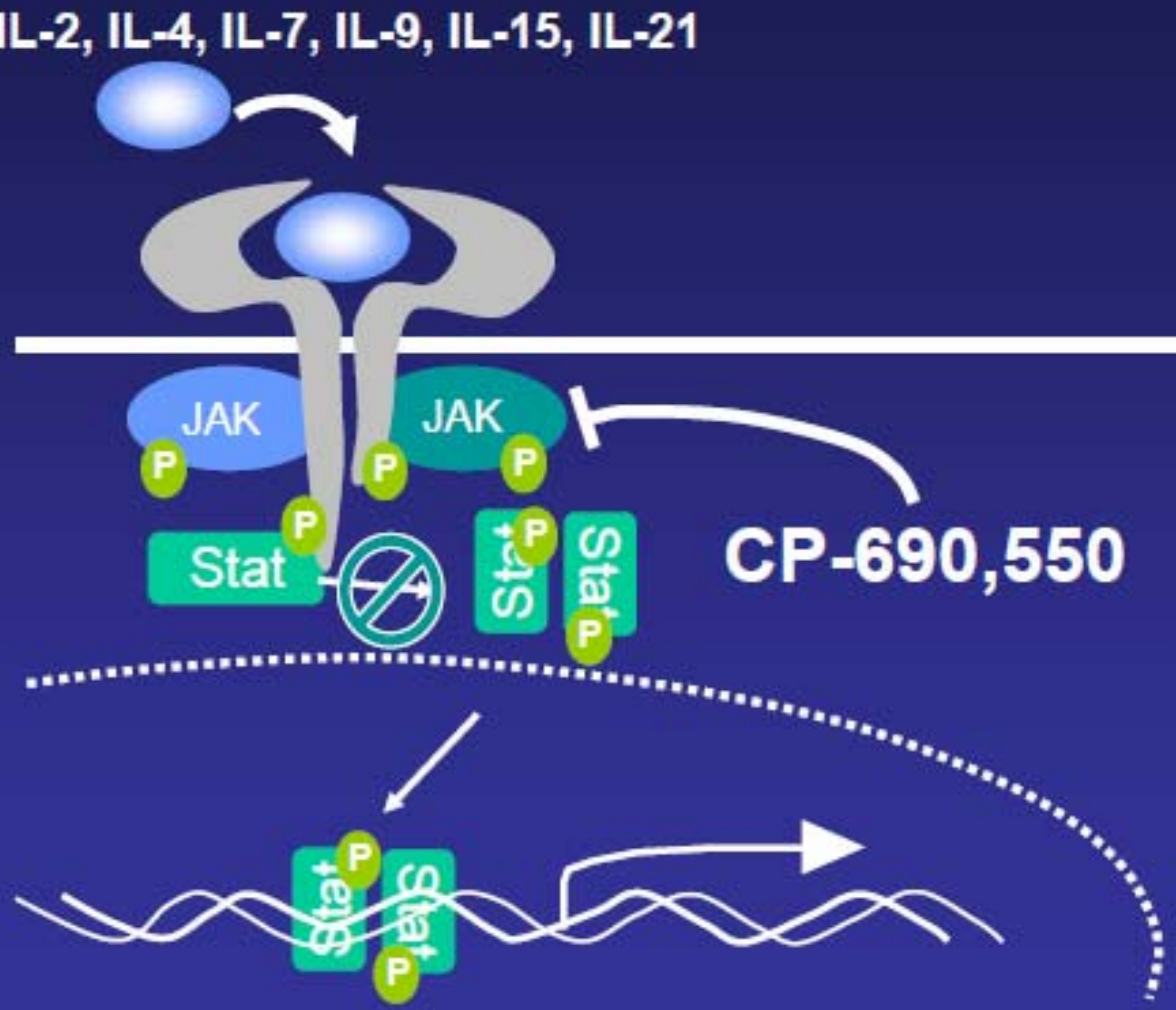
4.spleen tyrosine kinase (SYK)

5.others

Janus Kinase 3 (JAK3)

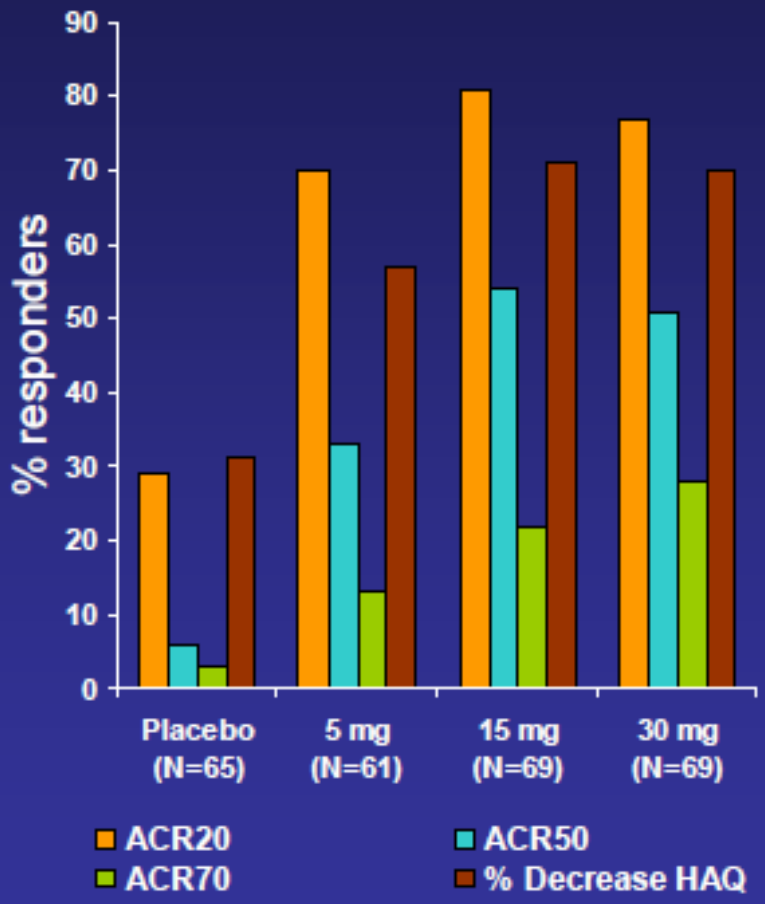
JAK3

- Most recently described member of this family
- Signaling of IL-2, 4, 7, 13, 15, and 21 in T-cells
  and myeloid cells



An Oral Inhibitor of JAK-3: CP 690, 550

- Dose-dependent increases in AEs;
  HA and nausea most common
  - ↓ neutrophil count dose dependent
  - Dose dependent↑in LDL and HDL
  - Reversible increases in mean serum creatinine in all active arms
- Infections in 15 and 30 mg: 30% each, compared with placebo (26%)
  - No opportunistic infections occurred



Kremer J, *et al. ACR,* Washington DC 2006, #L40

RHEUMATOID ARTHRITIS EMERGING THERAPIES

- **TNF inhibitors**
  - Golimumab
  - Certolizumab
- **IL-6 inhibition**
  - Tocilizumab
- **B-cell inhibitors**
  - Humanized anti-CD20
  - Belimumab (anti-BLyS)
  - Epratuzumab (anti-CD22)
  - TACI-Ig (Atacicept)
- **Cytokines**
  - Anti-IL-1
  - Anti-IL-12
  - Anti-IL-15
  - Anti-IL-17
  - Anti-IL-18
  - Anti-IL-32

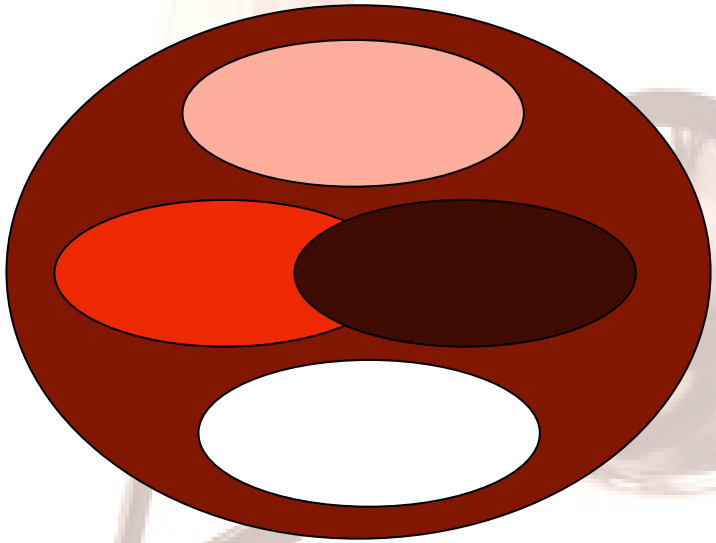
- **Chemokine inhibitors**
- **Toll-like receptor pathways**
- **Signal transduction**
  - mitogen-activated protein (MAP) kinase
  - janus-kinase/signal-transducer and activator of transcription (Jak/STAT
  - spleen tyrosine kinase (SYK)
- **Other co-stimulatory pathways**
- **Osteoclast inhibitors**
- **Adenosine agonists**
- **Cathepsin K inhibitors**
- **Wnt signaling pathway**
- **Angiogenesis inhibitors**

LA MODULACIÓN DEL SISTEMA INMUNITARIO NO ES INOCUA PERO....

...EL EMPLEO CLÍNICO DE LOS AGENTES BIOLÓGICOS Y DE NUEVAS DIANAS INDUCE TOXICIDAD CONTROLABLE

Investigación biomédica etiopatogénica, diagnóstica, terapéutica y reparativa

SIMILITUD CLÍNICA DIAGNÓSTICO DE ENFERMEDAD ÚNICA



SUPERAR LIMITACIONES EN:
·LA REALIZACIÓN DE ENSAYOS CLÍNICOS
·LA OPTIMIZACIÓN Y EL DESARROLLO TERAPÉUTICO Y REPARATIVO

IDENTIFICACION DE MECANISMOS ETIOPATOGÉNICOS ESPECÍFICOS Y COMUNES

Medicina traslacional

Medicina individualizada

No existen enfermedades sino enfermos

Hospital Universitario Príncipe de Asturias

Madrid

XXIX CONGRESO NACIONAL DE LA SOCIEDAD NACIONAL DE MEDICINA INTERNA

MUCHAS GRACIAS POR SU ATENCIÓN

A CORUÑA ,19 DE NOVIEMBRE DE 2008