



**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



TRATAMIENTO BIOLÓGICO DE LAS ENFERMEDADES AUTOINMUNES



FUNDAMENTOS Y CONSIDERACIONES INICIALES



Hospital Universitario
Príncipe de Asturias





ENFERMEDADES INFLAMATORIAS IDIOPÁTICAS Y AUTOINMUNES



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

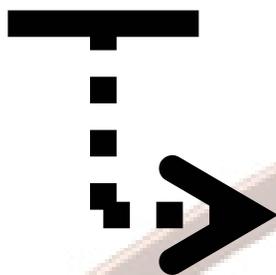
CRISIS DE LA NOSOLOGÍA



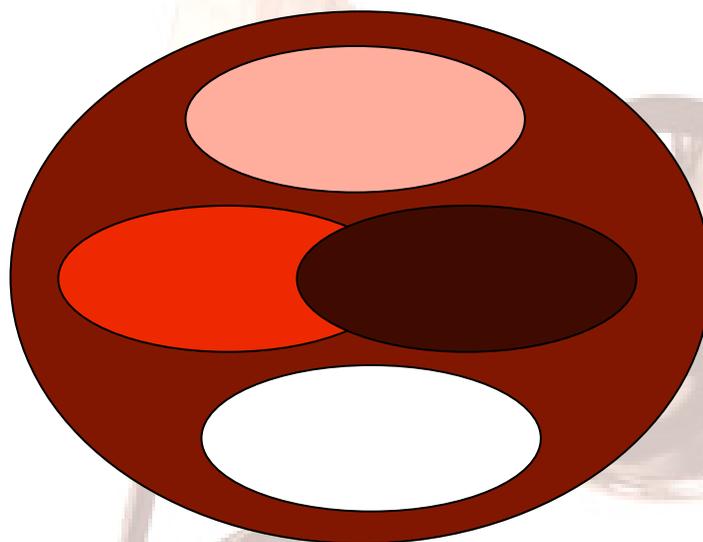
Investigación biomédica etiopatogénica, diagnóstica, terapéutica y reparativa



**SIMILITUD
CLÍNICA
DIAGNÓSTICO
DE
ENFERMEDAD
ÚNICA**

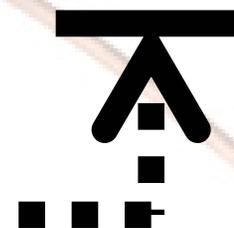


**Medicina
traslacional**



**IDENTIFICACION
DE MECANISMOS
ETIOPATOGÉNICOS
ESPECÍFICOS
Y COMUNES**

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



**Medicina
individualizada**

No existen enfermedades sino enfermos



Tratamientos biológicos en enfermedades autoinmunes



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



Estrategias terapéuticas



¿Cuál 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 ineficientes

consecuencias patológicas

Deficiente respuesta

Inadecuado control de la respuesta

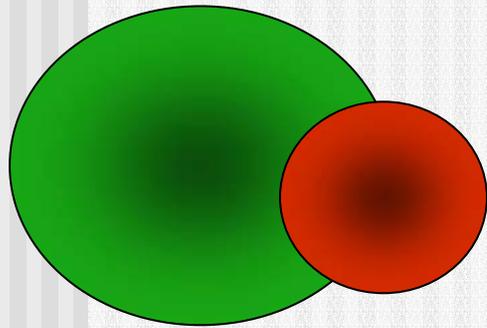
Progresión de la infección o del tumor

- Sepsis
- Shock
- Síndrome inflamatorio sistémico

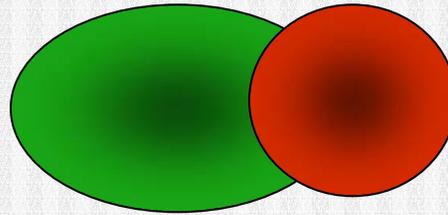
- Enfermedades inflamatorias
- Enfermedades autoinmunes



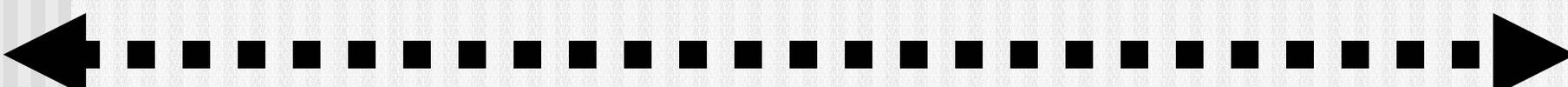
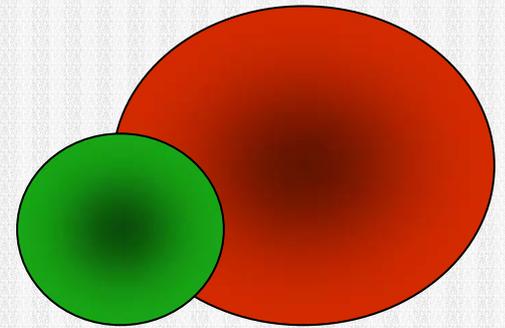
ETIOPATOGENIA DE ENFERMEDADES DEL SISTEMA INMUNOLÓGICO/INFLAMATORIO



BASES GENÉTICAS



**INTERACCIÓN
CON EL MEDIO
EXTERNO E INTERNO**

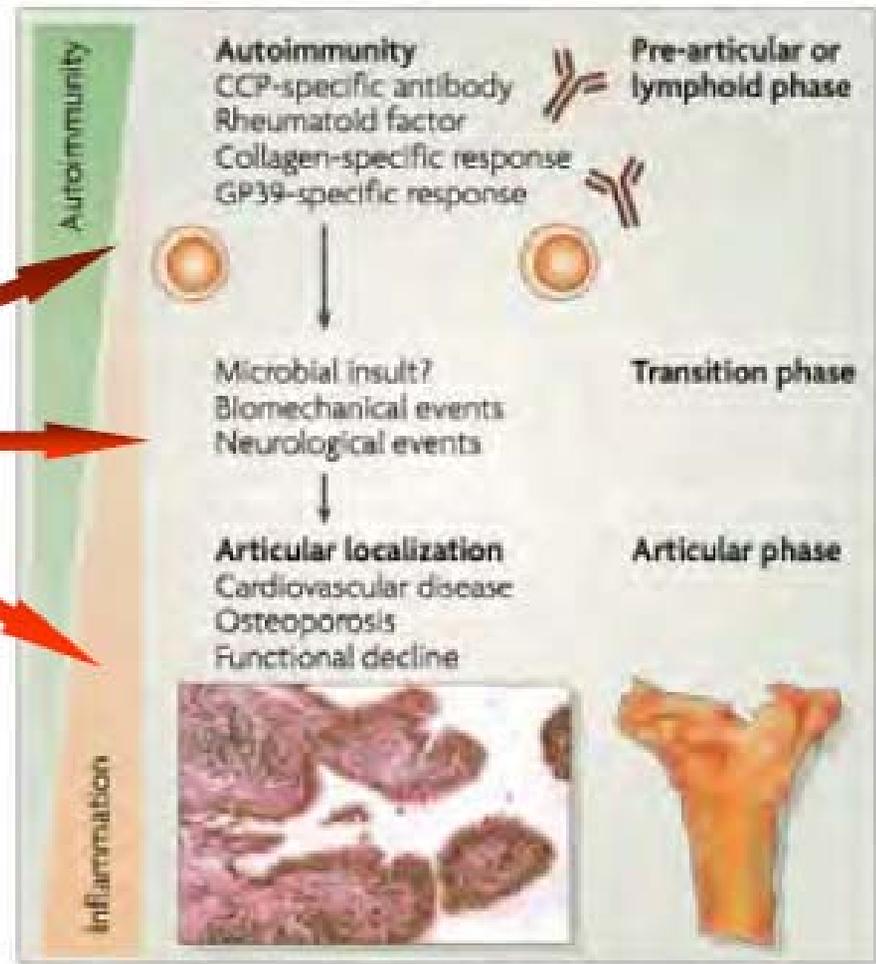
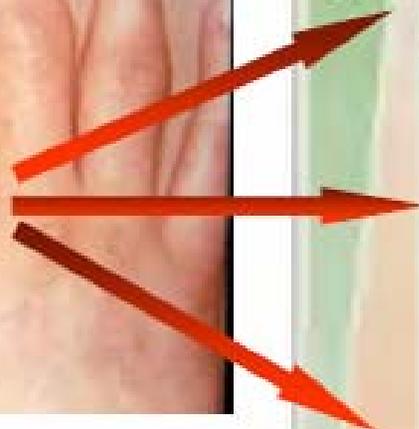


**HETEROGENEIDAD
INDIVIDUAL Y TEMPORAL**

Pathogenesis of RA?



Immune mediated dysfunction



Genome wide studies - implicate immunity!

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

Hyeon-Seon Lee^{1,2}, Eunsoo P. Kim³, Julie M. Lee⁴, David L. Rothman⁵, Sang-Chul Bae⁶, and Peter K. Gregersen¹

¹The Feinstein Institute for Medical Research, North Shore Long Island Jewish Health System, Manhasset, New York, USA, ²Seoul National University College of Medicine and the Hospital for Rheumatic Diseases, Seoul, South Korea, ³The National Institute of Arthritis and Musculoskeletal and Skin Diseases, Bethesda, Maryland, USA

A recent study in the North American white population has documented the association of a common SNP in *STAT4* with RA in rheumatoid arthritis (RA) and systemic lupus erythematosus. To evaluate the link in this population, we performed a case-control association study. We genotyped single nucleotide polymorphisms within the *STAT4* gene in 1122 Korean patients with RA and 1025 ethnicity-matched controls. The most significant SNP (rs1044388, rs1044388, rs1044388) was associated with the first onset of RA at a *P* value of 1.2 × 10⁻⁶. A common allele defined by this marker (T) is associated with RA in Koreans (84 percent vs 78 percent). T is also associated with RA in the Korean population (70.5 percent vs 64.5 percent) (84 percent vs 78 percent). T is also associated with RA in the Korean population (70.5 percent vs 64.5 percent) (84 percent vs 78 percent).

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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^{1,2}, Wendy Thomson¹, Xiyi Ke¹, Steve Eyrse¹, Anne Hinks¹, John Bowes¹, Laura Gibbons¹, Darren Plant¹, Wellcome Trust Case Control Consortium², Anthony G. Wilson¹, Simon Hingorani¹, Alan Kingsley¹, Yiyi Li¹, HLA Consortium³, Soren Kristiansen⁴

¹Academic Unit of Rheumatology, University of Manchester, Oxford Road, Manchester, UK, ²Wellcome Trust Case Control Consortium, 400 Brookings Drive, Cambridge, UK, ³HLA Consortium, University of Oxford, Oxford, UK, ⁴Department of Medical Genetics, University of Copenhagen, Copenhagen, Denmark

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

Wu Ballewally¹, Katsunori Inoue¹, Hiroko Kawanishi¹, Yuki Kato¹, Susumu Yamamoto¹, Yumiko Mitsuoka¹, Yumiko Takahashi¹, Yoshiko Teramae¹, Takashi Mochizuki¹, Masahiro Yamada¹, Yumiko Kawanishi¹, Chikako Inoue¹, Masako Hara¹, Takako Tomiyama¹, Hiroaki Yamamoto¹, Takahiko Inoue¹, Kazuo Tani¹, Koji Yamamoto¹, Daikoku Hamada¹, Kazuo Yano¹, Hiroko Kawanishi¹, Mitsuo Nakamura¹, Hiroaki Kawanishi¹, Kazuo Kawanishi¹, and Yiyi Li¹

STAT4 encodes a transcription factor highly induced in several key cytokines in a key pathway in the development of human immunity. A *STAT4* haplotype was associated with rheumatoid arthritis in the Japanese population. We performed a case-control association study in 1,122 Japanese RA patients and 1,025 ethnicity-matched controls. The most significant SNP (rs1044388, rs1044388, rs1044388) was associated with the first onset of RA at a *P* value of 1.2 × 10⁻⁶. A common allele defined by this marker (T) is associated with RA in Koreans (84 percent vs 78 percent). T is also associated with RA in the Korean population (70.5 percent vs 64.5 percent) (84 percent vs 78 percent).

We will evaluate gene-environment (GxE) in the Japanese population. This was replicated in a Korean RA population. Genotyping the region of RA susceptibility with the *STAT4* haplotype was similar in the Korean and Japanese populations. The present study was undertaken to investigate the effect of *STAT4* in susceptibility to RA and SLE in the Japanese population. We performed an association study using 1,122 Japanese RA patients and 1,025 ethnicity-matched controls. The most significant SNP (rs1044388, rs1044388, rs1044388) was associated with the first onset of RA at a *P* value of 1.2 × 10⁻⁶. A common allele defined by this marker (T) is associated with RA in Koreans (84 percent vs 78 percent). T is also associated with RA in the Korean population (70.5 percent vs 64.5 percent) (84 percent vs 78 percent).

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

Monica Chang¹, Charles M. Rowland¹, Veronica E. Garcia¹, Steven J. Schrod¹, Joseph J. Catanese¹, Annette H. M. van der Helm-van Mil², Kristin G. Ardlie^{3,4}, Christopher I. Amos⁵, Lindsey A. Criswell⁶, Daniel L. Kastner⁷, Peter K. Gregersen⁷, Fina A. S. Kurreeman⁸, Rene E. M. Toes⁹, Tom W. J. Huizinga¹⁰, Michael F. Seldin¹¹, Ann B. Begovich^{12,13}

¹Patton, Nevada California United States of America, ²Erasmus University Medical Center, Leiden, The Netherlands, ³GeneDavid Lab Sciences, Cambridge, Massachusetts, United States of America, ⁴University of Texas Health Science Center, United States of America, ⁵Stanford Research Center for Asthma, Department of Medicine, University of California San Francisco, San Francisco, California, United States of America, ⁶National Institute of Health, Bethesda, Maryland United States of America, ⁷Feinstein Institute for Medical Research, North Shore Long Island Jewish Health System, Manhasset, New York, United States of America, ⁸University of California, Davis, California, United States of America

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-ethnic, case-control association study, genotyping 25,966 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 (M1 and M2). We identified a novel association at chromosome 9q33.2, with a lead SNP (rs1044388, rs1044388, rs1044388) associated with RA at a *P* value of 1.2 × 10⁻⁶. A common allele defined by this marker (T) is associated with RA in Koreans (84 percent vs 78 percent). T is also associated with RA in the Korean population (70.5 percent vs 64.5 percent) (84 percent vs 78 percent).

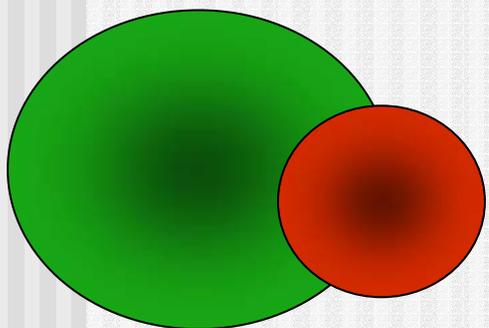
W. Ballewally¹, K. Inoue¹, H. Kawanishi¹, Y. Kato¹, S. Yamamoto¹, Y. Mitsuoka¹, Y. Takahashi¹, Y. Teramae¹, T. Mochizuki¹, M. Yamada¹, Y. Kawanishi¹, C. Inoue¹, M. Hara¹, T. Tomiyama¹, H. Yamamoto¹, T. Inoue¹, K. Tani¹, K. Yamamoto¹, D. Hamada¹, K. Yano¹, H. Kawanishi¹, M. Nakamura¹, H. Kawanishi¹, K. Kawanishi¹, and Y. Li¹

RA is a systemic autoimmune disease with both genetic and environmental risk factors. We, therefore, investigated the evidence for imputed data from the Wellcome Trust Case Control Consortium (WTCCC) genome-wide association study (GWAS) of RA. We performed a case-control association study using 1,122 Japanese RA patients and 1,025 ethnicity-matched controls. The most significant SNP (rs1044388, rs1044388, rs1044388) was associated with the first onset of RA at a *P* value of 1.2 × 10⁻⁶. A common allele defined by this marker (T) is associated with RA in Koreans (84 percent vs 78 percent). T is also associated with RA in the Korean population (70.5 percent vs 64.5 percent) (84 percent vs 78 percent).

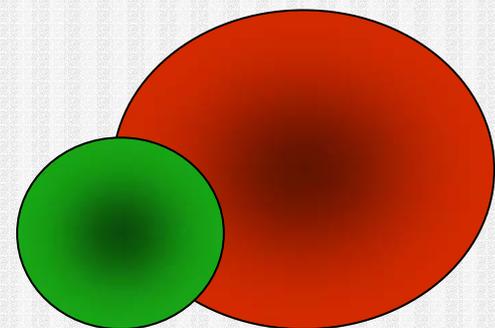
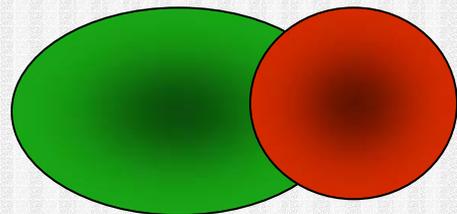




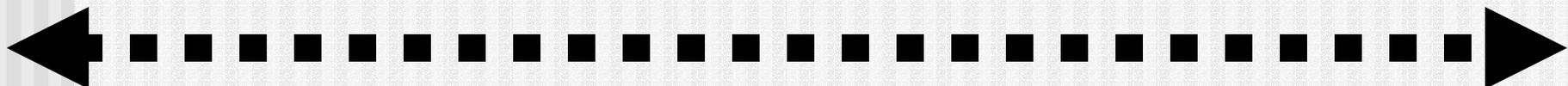
ETIOPATOGENIA DE ENFERMEDADES DEL SISTEMA INMUNOLÓGICO/INFLAMATORIO



BASES GENÉTICAS



**INTERACCIÓN
CON EL MEDIO
EXTERNO E INTERNO**



**HETEROGENEIDAD
INDIVIDUAL Y TEMPORAL**

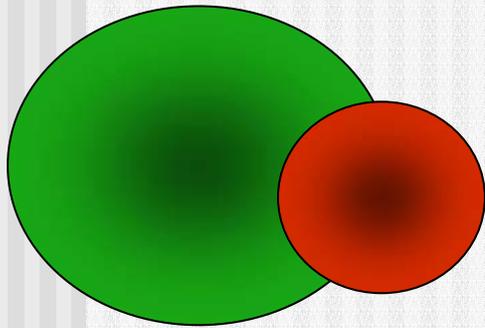
Environmental matters...?

- *Deprivation, life style and inflammatory diseases*

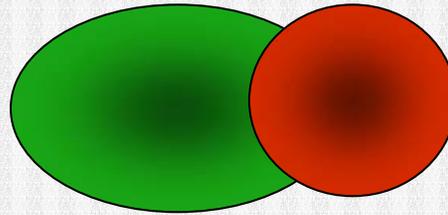
- **Disease activity**
 - Endogenous Mechanisms
 - e.g. PsoBid study
- **Health care access**
 - Compliance
- **Environmental challenge**
 - Hygiene hypothesis
 - microbial triggers
 - **Smoking & *HLADR* gene**



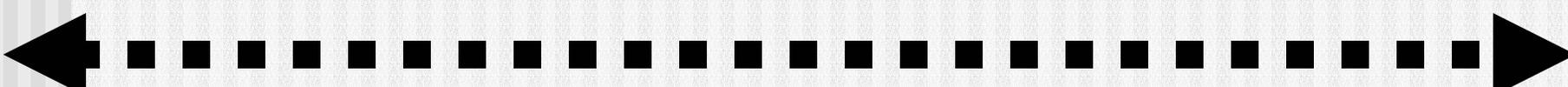
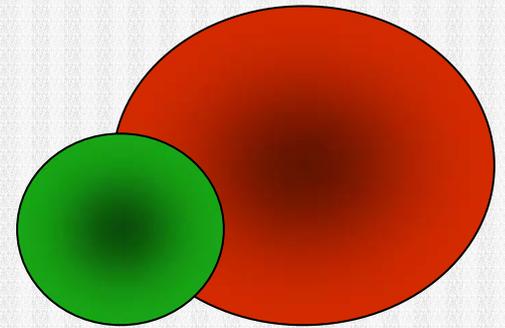
ETIOPATOGENIA DE ENFERMEDADES DEL SISTEMA INMUNOLÓGICO/INFLAMATORIO



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 ENVIRONMENT**



Humans and microorganisms

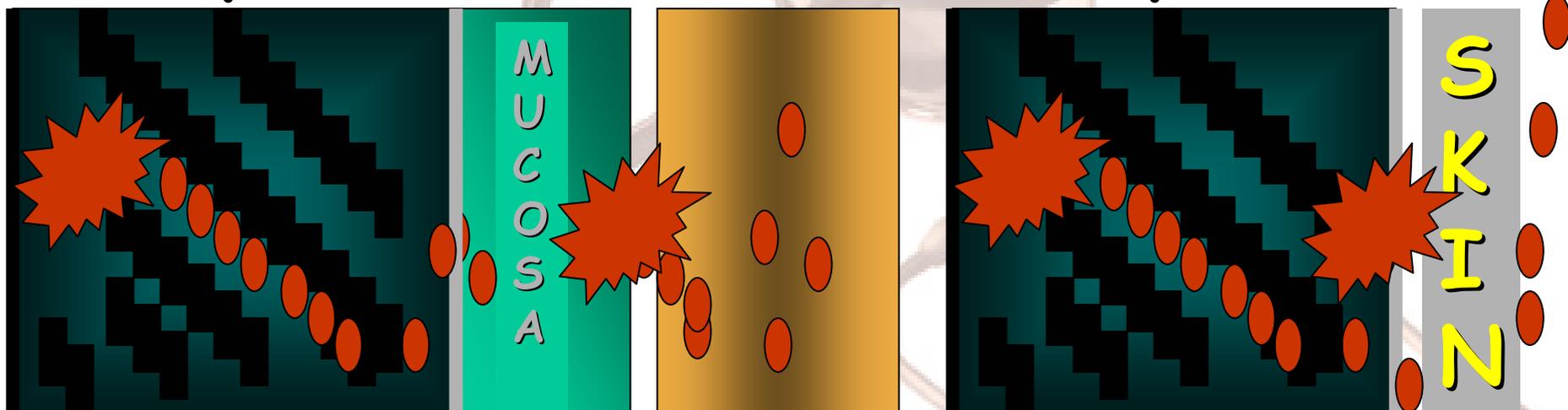


Organs
and Systems

Mucosa Gut

Organs
and Systems

Skin



● microorganisms



Infections

Interactions can become infections



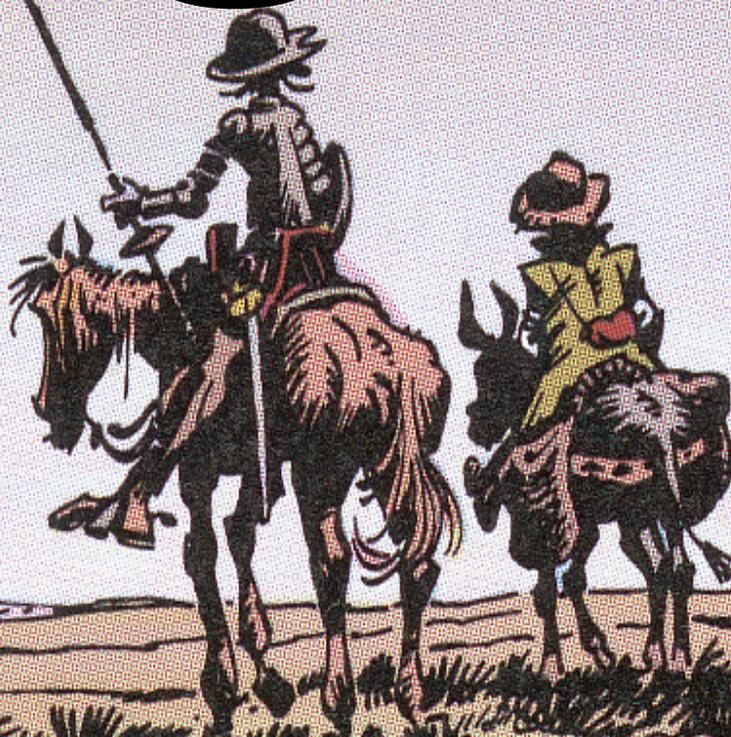
PATHOGENIC INTERACTIONS OF THE IMMUNE SYSTEM



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- CUTANEOUS AND MUCUS BARRIERS
- CHANGES IN THE INTERNAL ENVIRONMENT



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



Cervantes, 1605



Estrategias terapéuticas



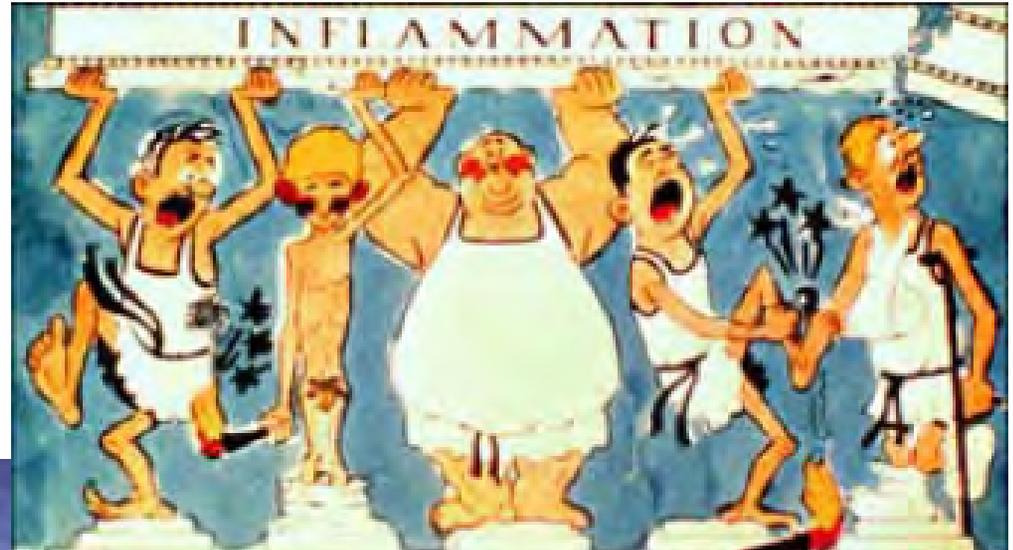
¿cuales son los mecanismos patogénicos del sistema inmunitario implicados en la patogenia de las enfermedades inflamatorias de etiología desconocida y autoinmunes?



Innate immunity - inflammation that is beneficial...normally!

- immediate & effective
- inefficient
- amnesic

- toll-like receptors



heat erythema swelling pain functional loss





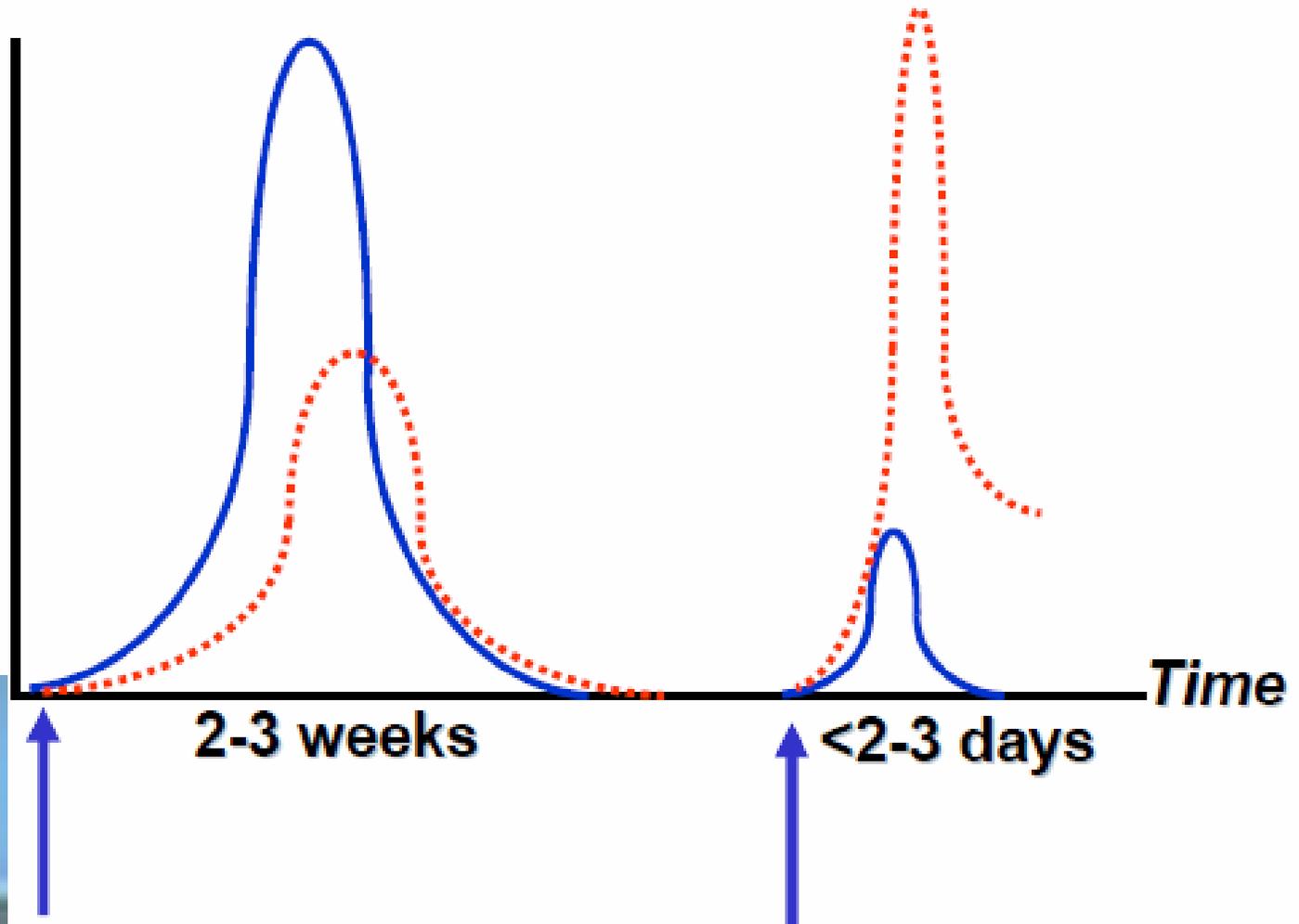
Adaptive immunity:

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 histocompatibilidad**





Dianas patogénicas en enfermedades inflamatorias crónicas / autoinmunes



■ Dianas terapéuticas

■ Diversidad

■ Selección eficiente



Muchos interpretes... ¿Quién es el director?



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

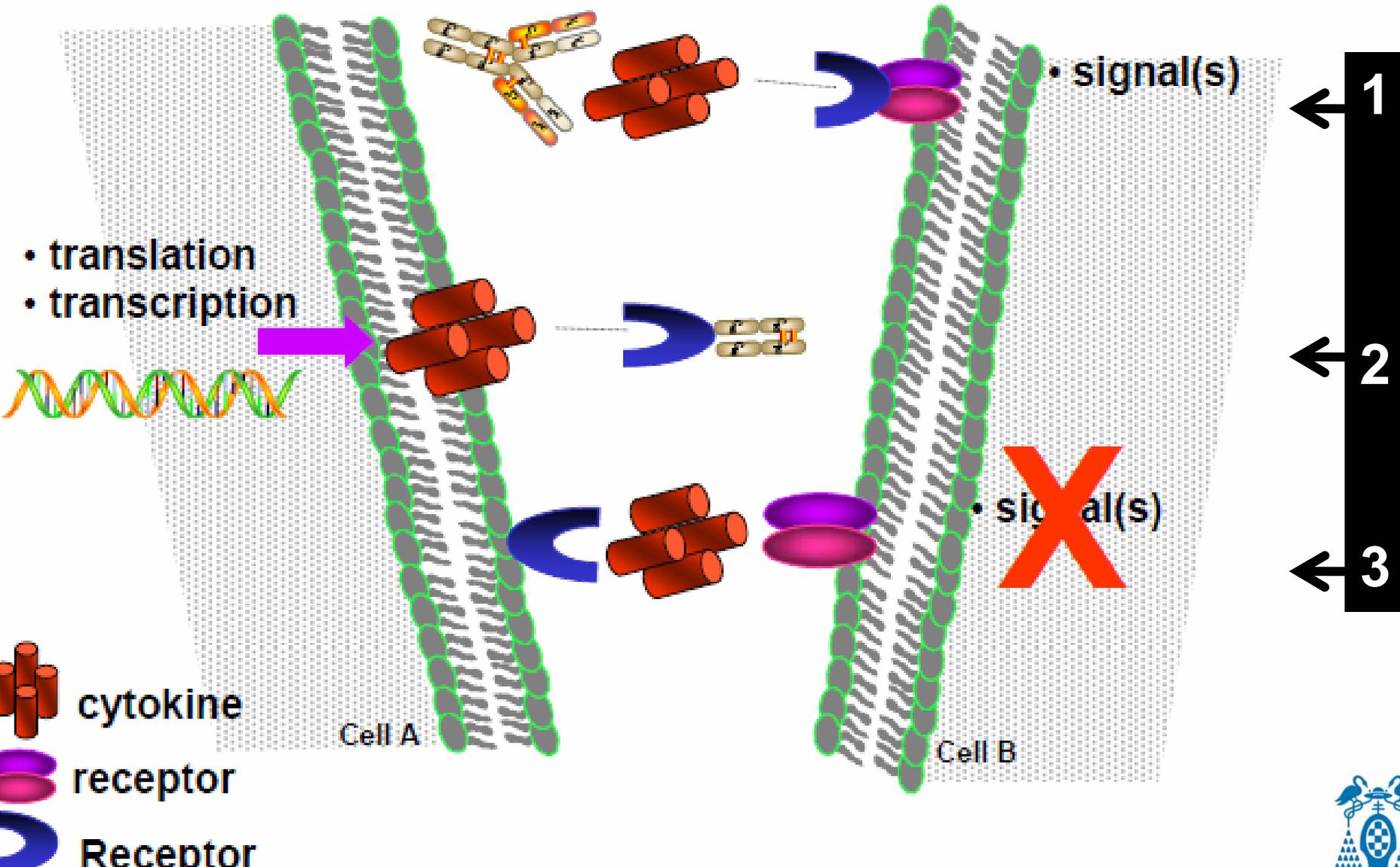


Proof of concept studies

In vitro model systems



How: to target your chosen molecule...?





DIANAS TERAPÉUTICAS



CITOQUINAS



Hospital Universitario
Príncipe de Asturias



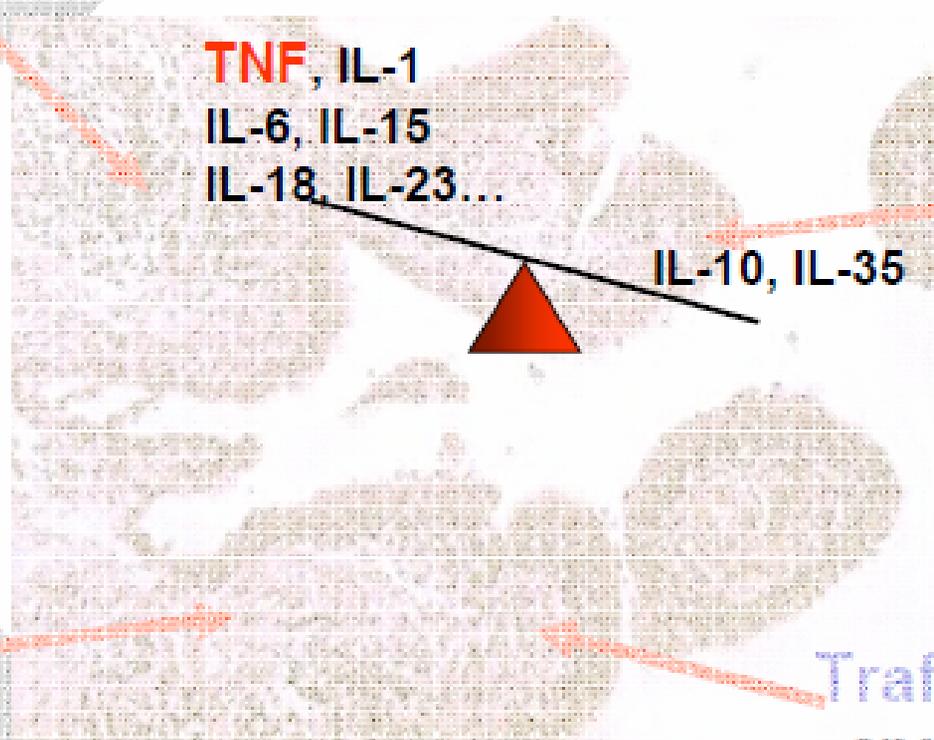
Madrid

Where? Inflamed tissue - source of targets



Adaptive immunity

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



Lining layer

- FLS
- macrophages

Interstitium

- mast cells
- macrophages
- neuroreceptors

Trafficking

- angiogenesis
- lymphangiogenesis



TNF in inflammatory diseases



Leukocyte activation

- macrophage
- T_H1 cell ↑ T_H2 cell ↓
- NK cell

Endothelial cell activation

- pro-angiogenic

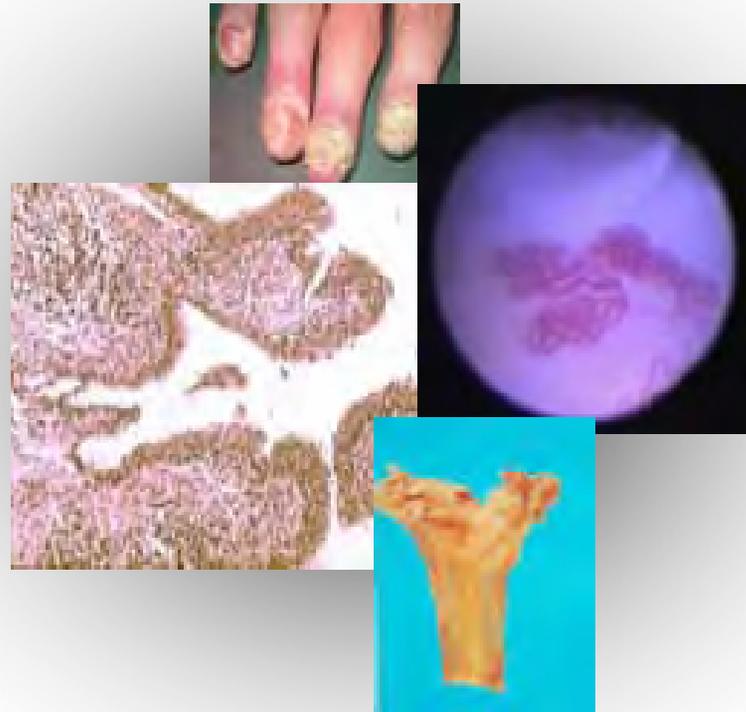
Fibroblast activation

- matrix degradation

Tissue cells

- osteoclast
- keratinocyte
- enterocyte

Nociceptor gating



Systemic

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

ESCENARIO INFLAMATORIO.

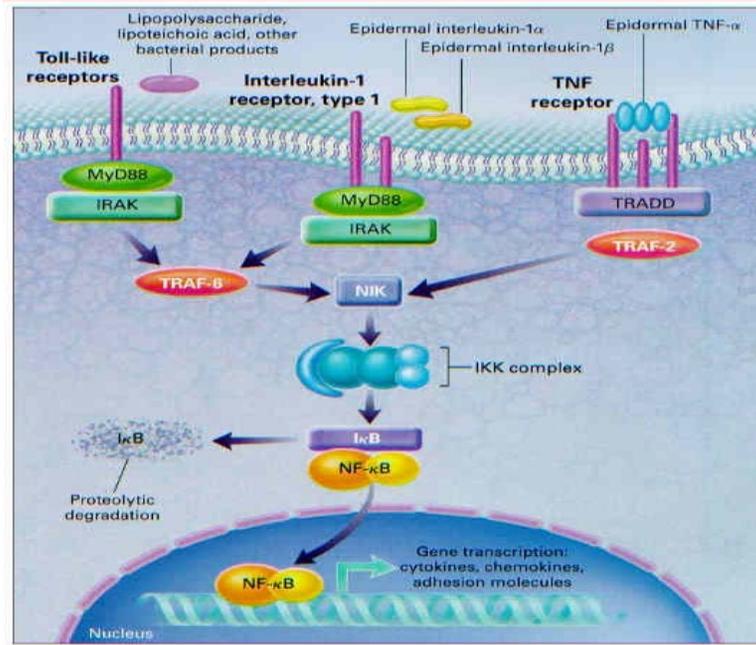
The exciting "TNF story"



MAPKs

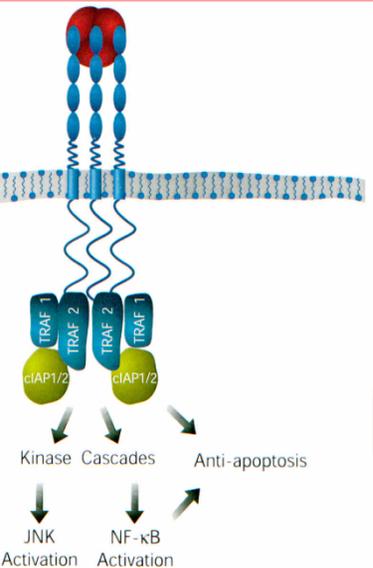
- p42
- p43
- p45
- p46
- JNK o SAPKs

MADO



- ### NF-κB family
- NF-κB1 (p50)
 - NF-κB2 (p52)
 - p62
 - C-Rel
 - Rel B

- ### IκB family
- IκBα
 - IκBβ
 - IκBγ/p105
 - IκBδ/p100
 - IκBε



- 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

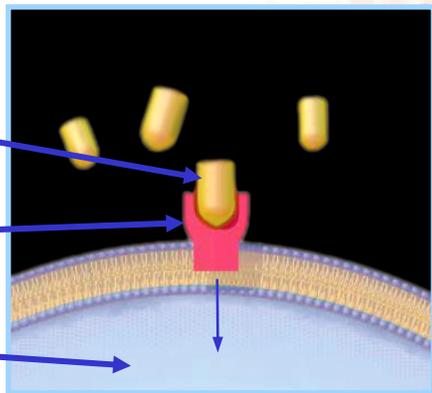


INHIBICIÓN DEL SISTEMA DEL TNF α



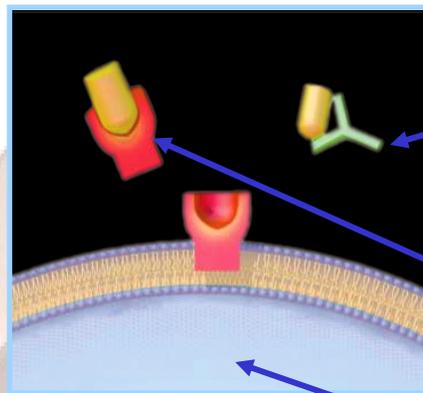
Interacción normal

Citocina inflamatoria
Receptor de la citocina
Señal inflamatoria



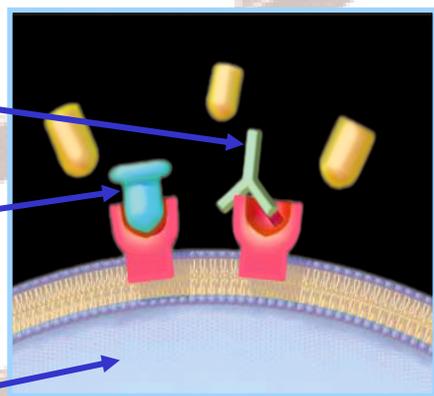
A. Neutralización de las citocinas

Anticuerpo monoclonal anti-Citoquina (*Infliximab, Adalimumab*)
Receptor soluble (*Etanercept*)



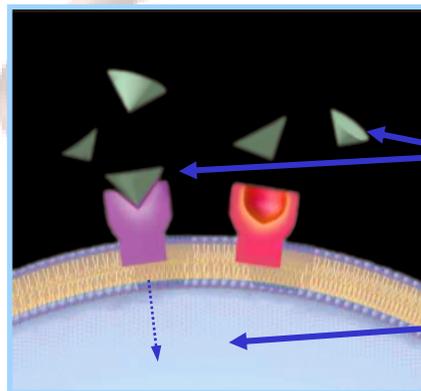
B. Bloqueo de los receptores

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 algorithms

Moderate to high

Features of poor

Refer to Nonbiologic DMARDs Algorithms or Anti-TNF α

Anti-TNF α
OR Abatacept
OR Rituximab*

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



NUEVOS ANTI-TNF α



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
- •1° 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 bioavailability
- 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-TNF α



- **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 TNF α
- **No respondedores secundarios**
 - Desarrollo de anticuerpos bloqueantes
 - 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-TNF α

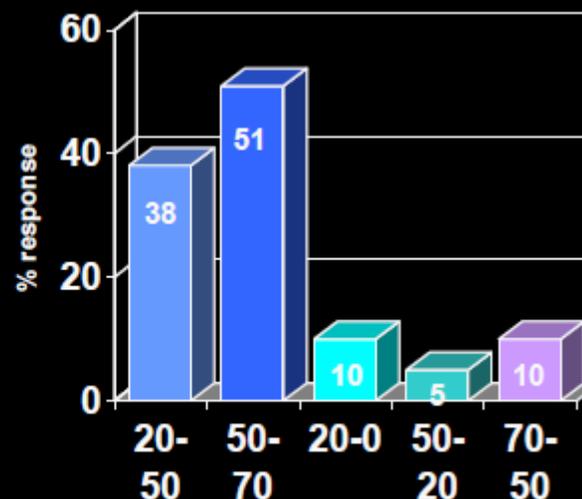


Anti-TNF Responses May be Delayed to 24 weeks in Patients initially on MTX + Etan.

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



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**



Fracasos terapéuticos a anti-TNF α



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



MURPHY
WAS
AN
OPTIMIST

MURPHY'S LAW

FRIENDS COME AND GO

BUT

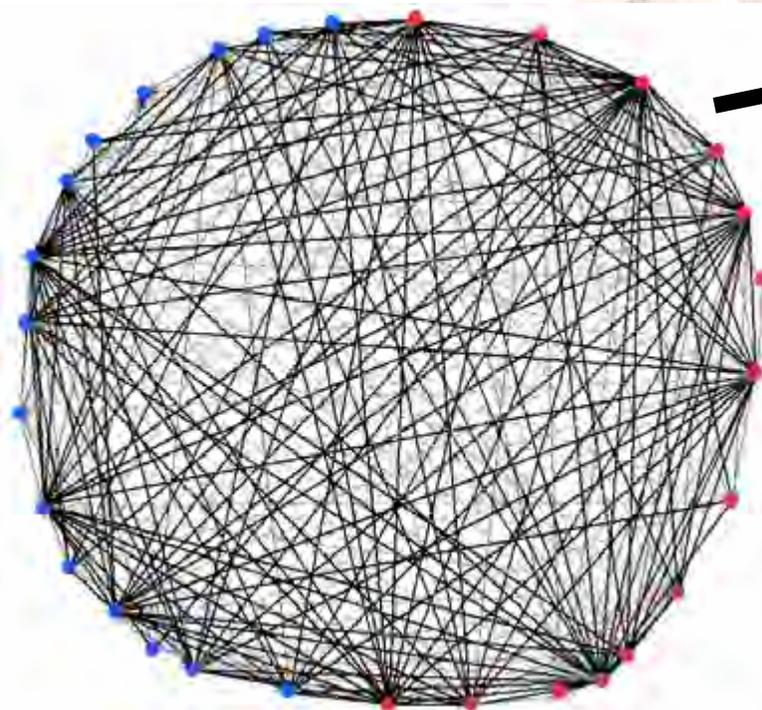
ENEMIES ACCUMULATE.



Which other targets?



Its quite complicated!



IL 1

IL 6

1L 12

IL 15

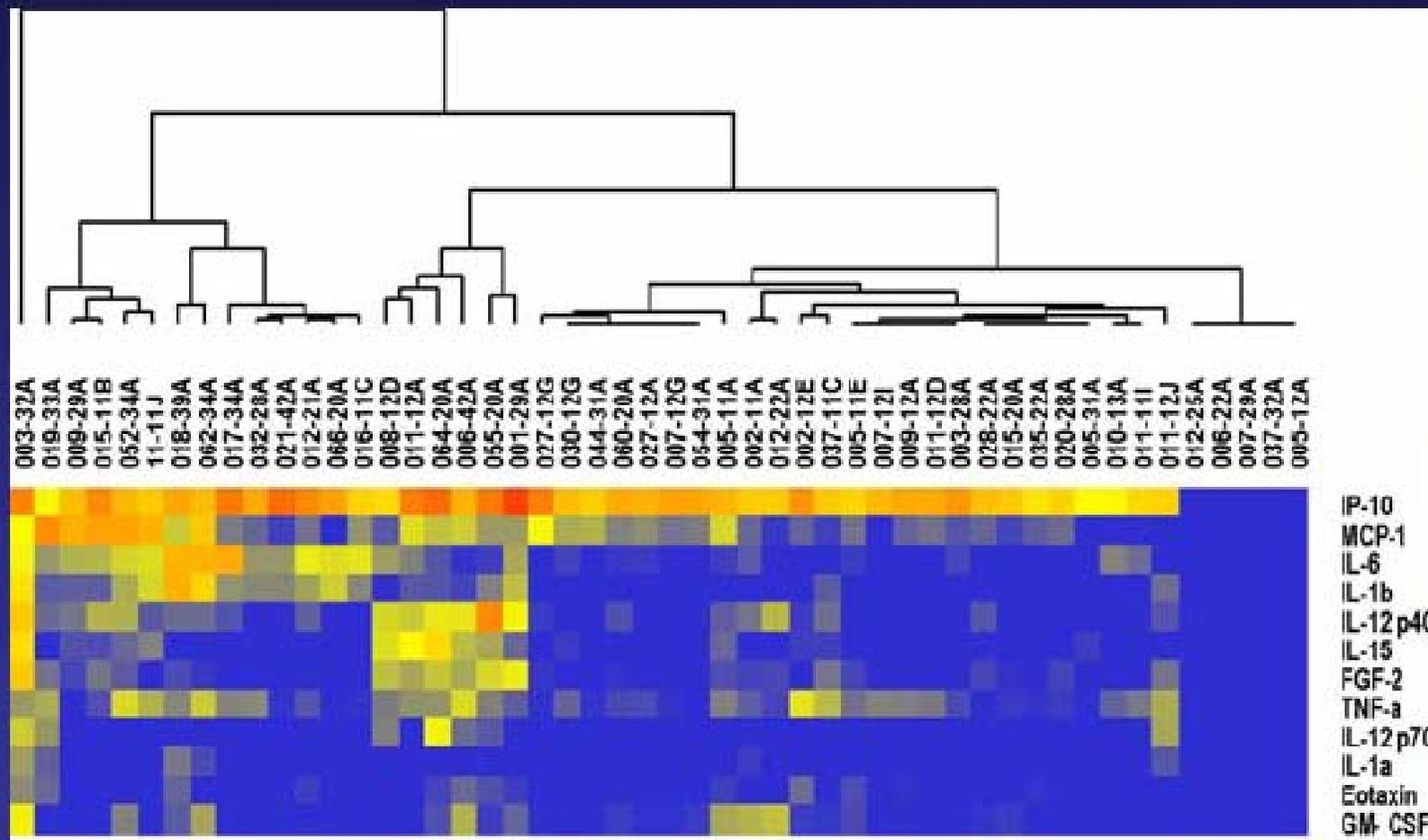
IL 17



...

Other mediator become more active with adequate inhibition of TNF α ?

Cytokine Profiling in Early RA Patients



MCP-1, IL-6, IL-1 β hi

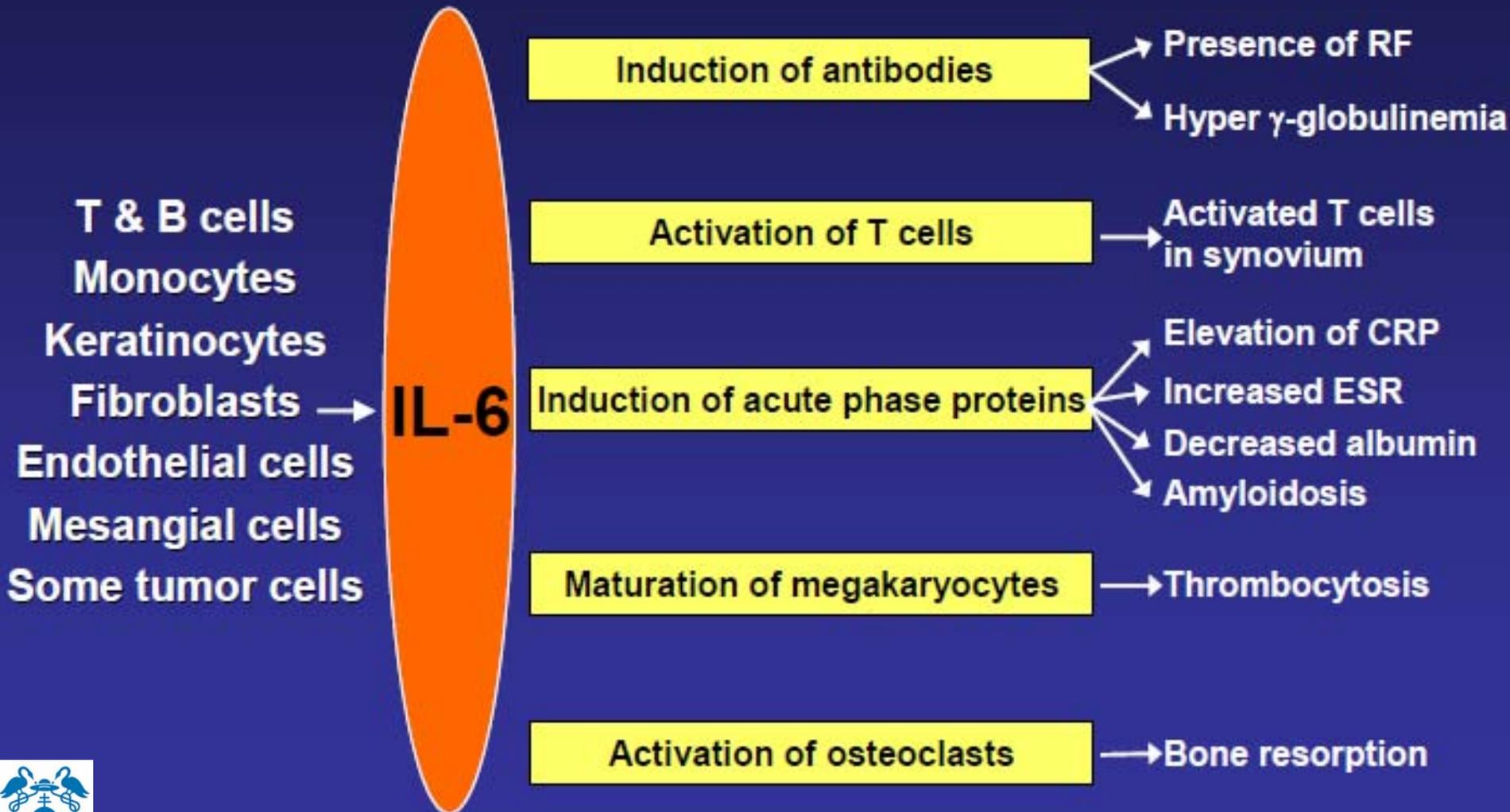
IL-12p40,
FGF-2, &
TNF high

cytokine low

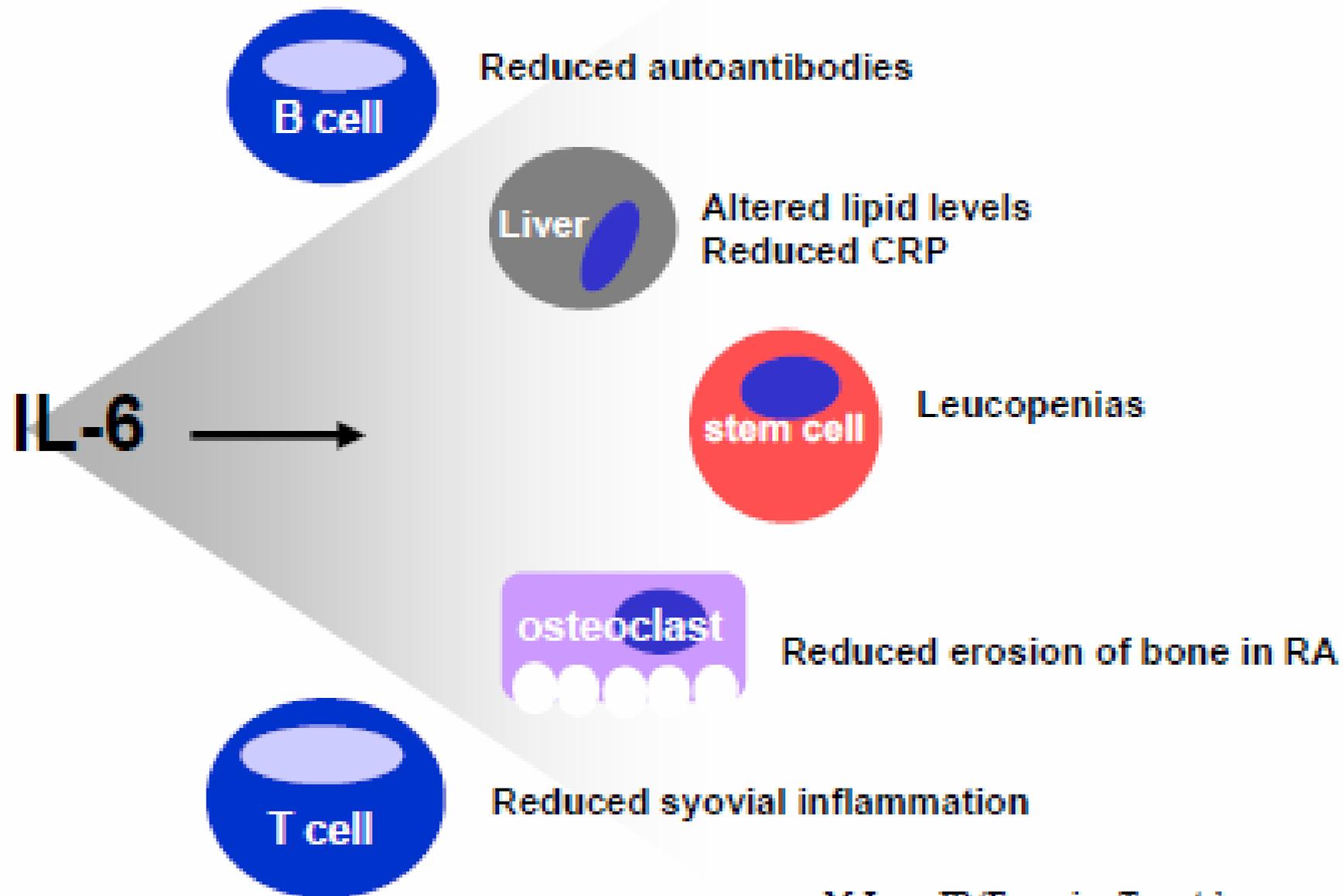
cytokine
negative



IL-6 and RA Pathophysiology



Interleukin-6 – predicted benefit of blockade?

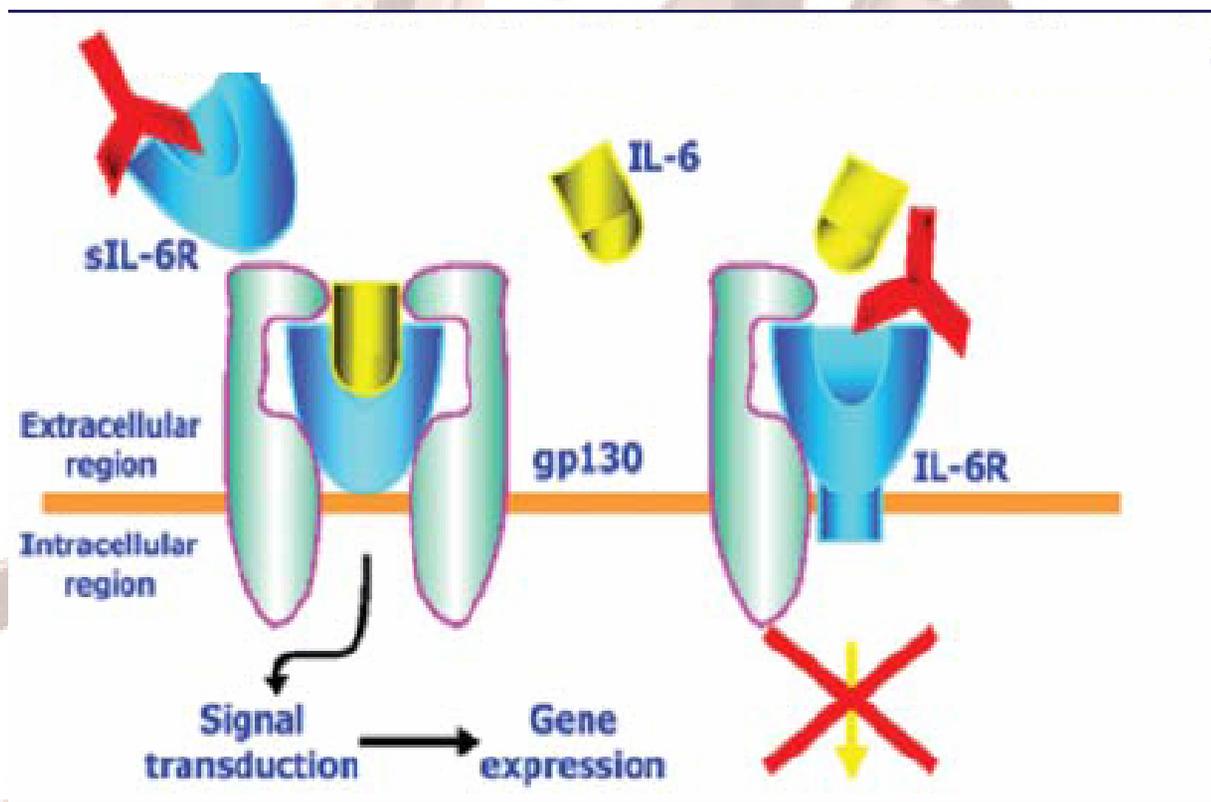




Tolcilizumab

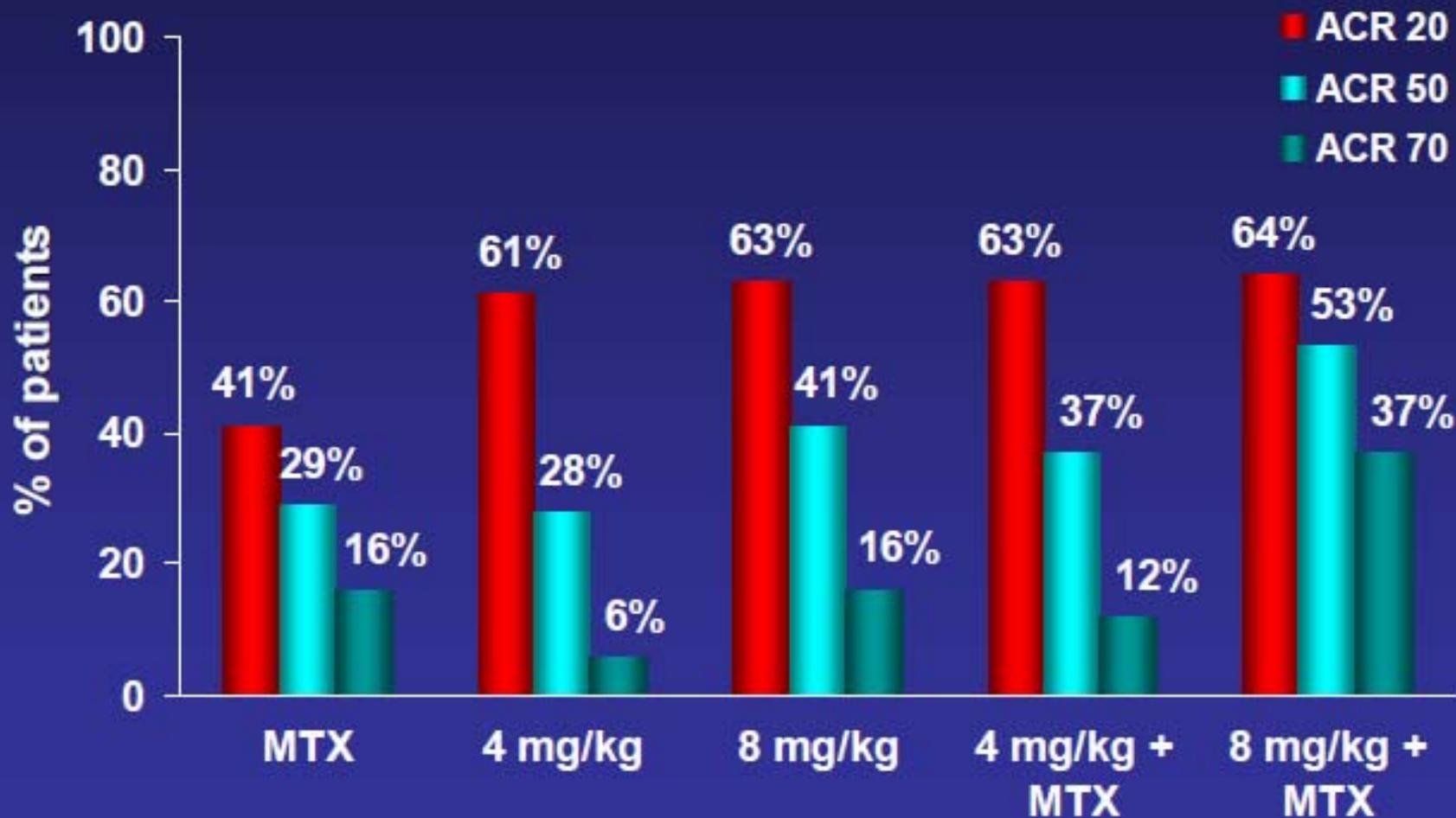


Mecanismo de acción



Tocilizumab : CHARISMA

(Maini et al. Arthritis & Rheumatism, 2006)



Tocilizumab

Option Study (phase III)

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

- Background MTX

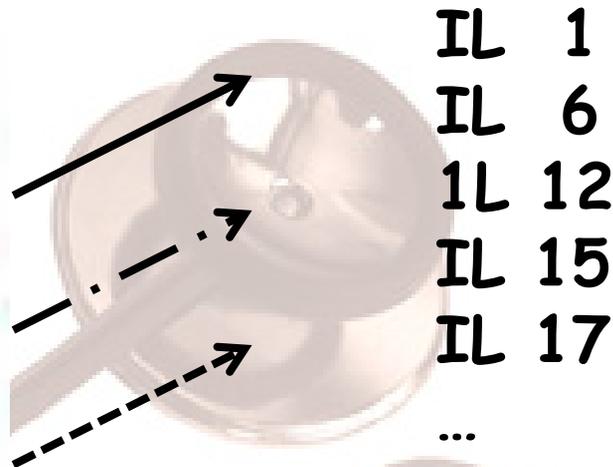
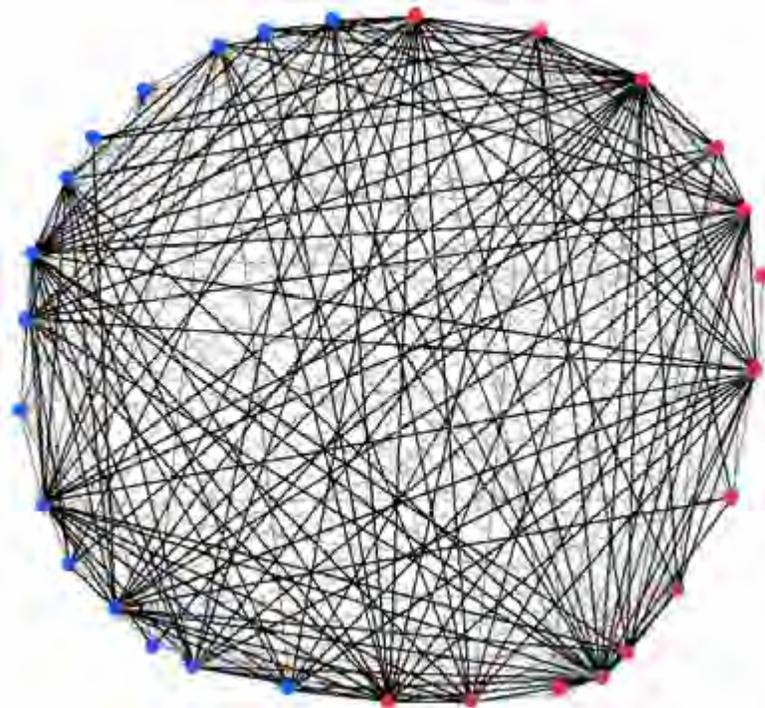
	Placebo	4mg/kg	8mg/kg
ACR 20%	26	48	59
50%	11	31	44
70%	2	12	22
DAS <2.6	.8	13	27



Which other targets?

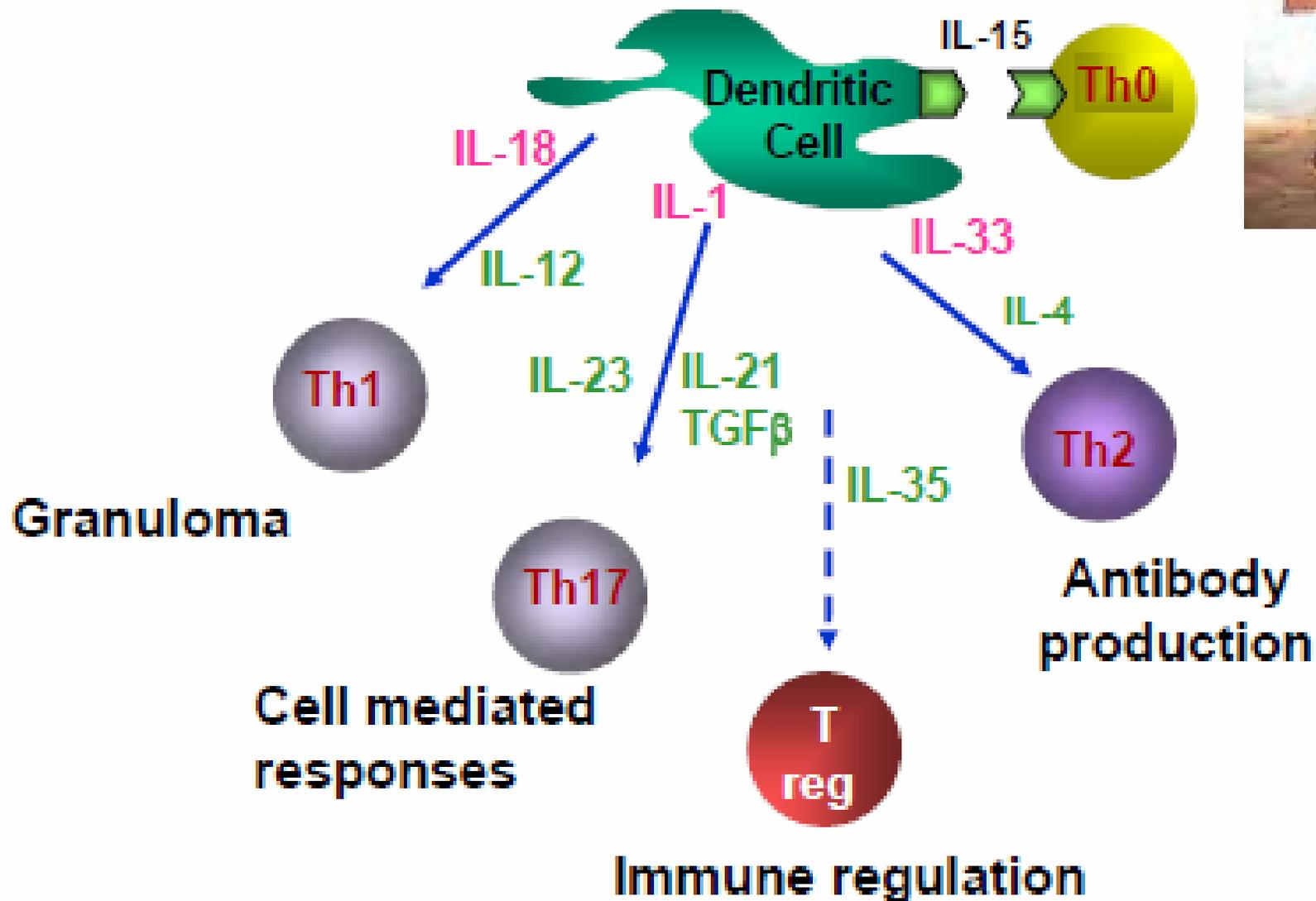


Its quite complicated!

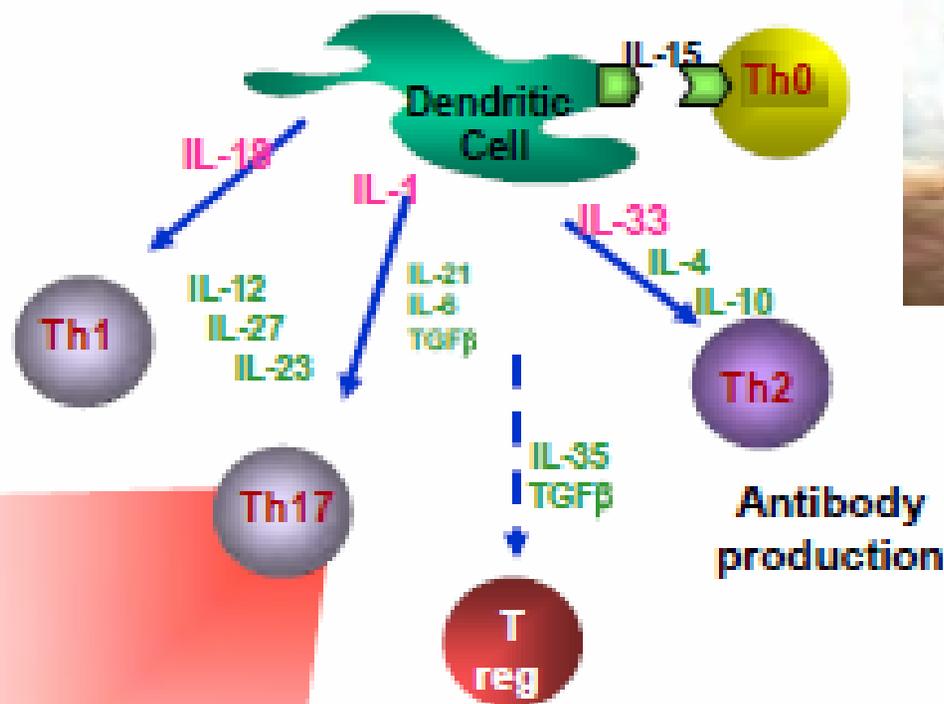
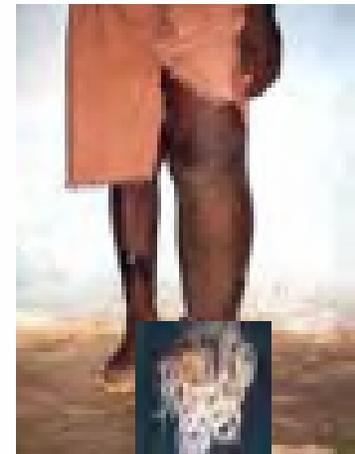


Other mediator become more active with adequate inhibition of TNF α ?

Cytokines that regulate T cells



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

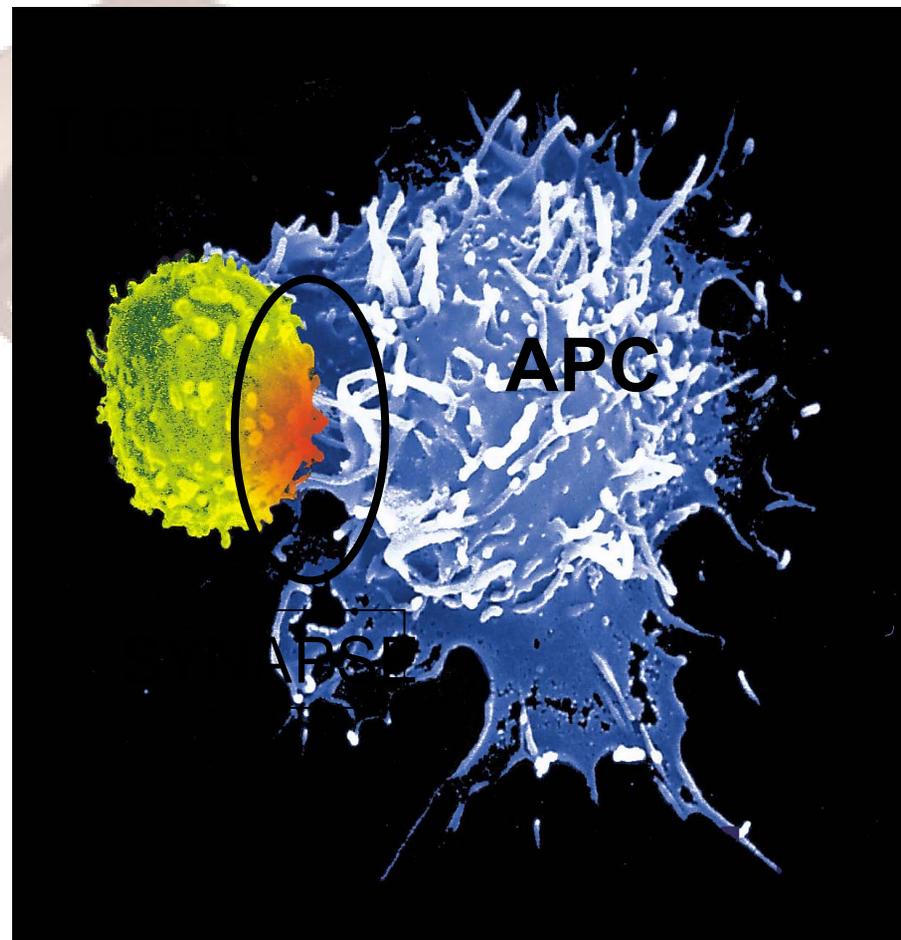


CÉLULAS DEL SISTEMA INMUNITARIO

- **SISTEMA NATURAL**
- **SISTEMA ADAPTATIVO**

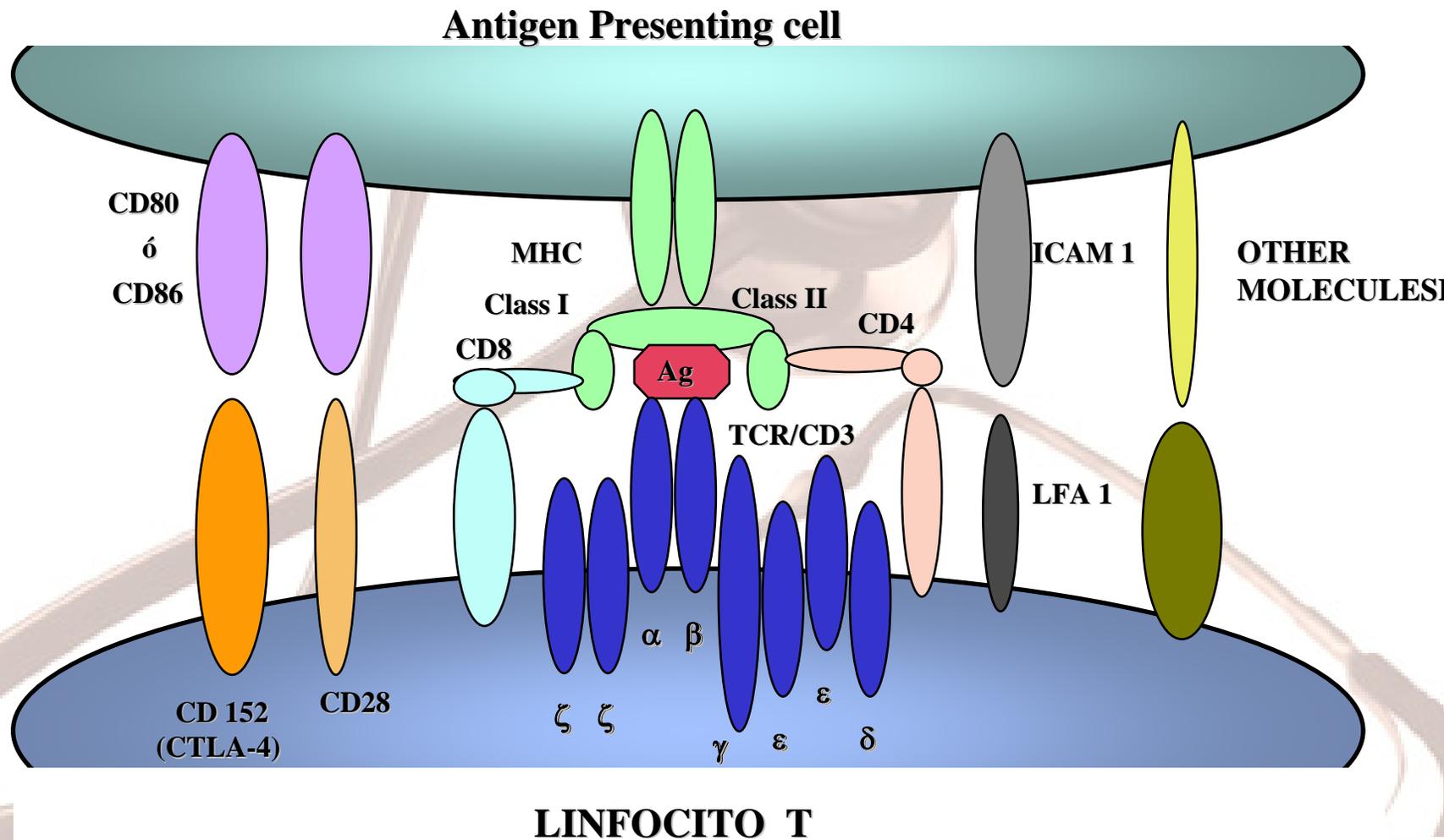


**Micrometer-sized
segregated
clusters of
proteins at the T
lymphocyte-APC
intercellular
contact**





IMMUNOLOGICAL SYNAPSE

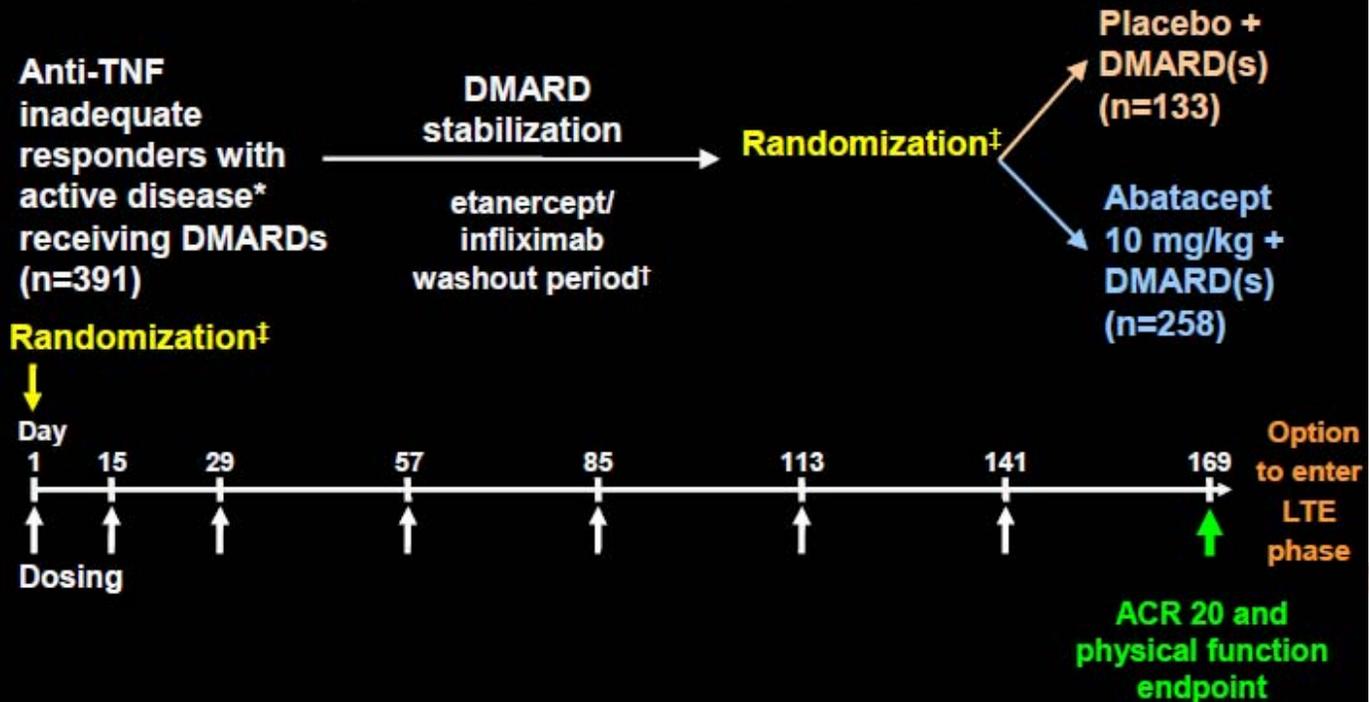




LINFOCITOS T ABATACEPT



Abatacept ATTAIN: Trial Design¹



¹Genovese M. *N Engl J Med* 2005; 353(11):1114-23.

* ≥ 10 swollen and ≥ 12 tender joints with CRP ≥ 1 mg/dL and DMARD/anakinra regimen stable for 28 days; [†]Washout=28 days for Enbrel[®] (etanercept); 60 days for Remicade[®] (infliximab); [‡]2:1 randomization to study arm

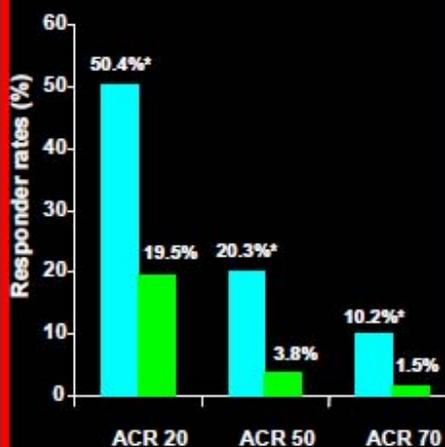


LINFOCITOS T ABATACEPT

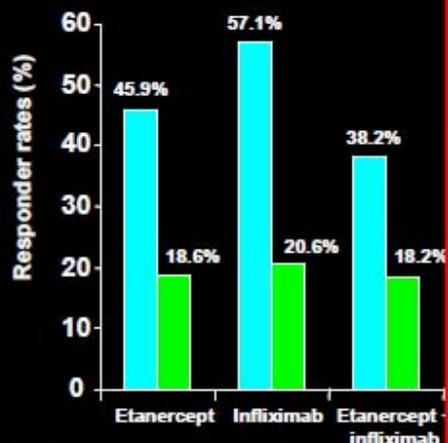


ATTAIN Trial: Results

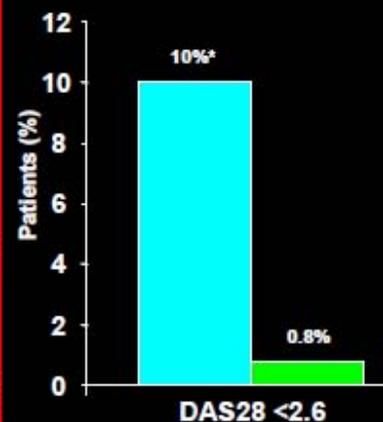
ACR Response 6 Months



ACR 20 Response by Prior Medication



DAS28 <2.6 at 6 Months (Remission)



■ Abatacept (n=258) ■ Placebo (n=133)

- Incidence of SAEs, serious infections, infections similar to placebo
- Headaches, sinusitis, and infusion reactions more frequent with abatacept
- Safe and well tolerated in RA patients previously failing anti-TNF therapy

* $P < 0.001$ vs placebo.
Genovese M, et al.

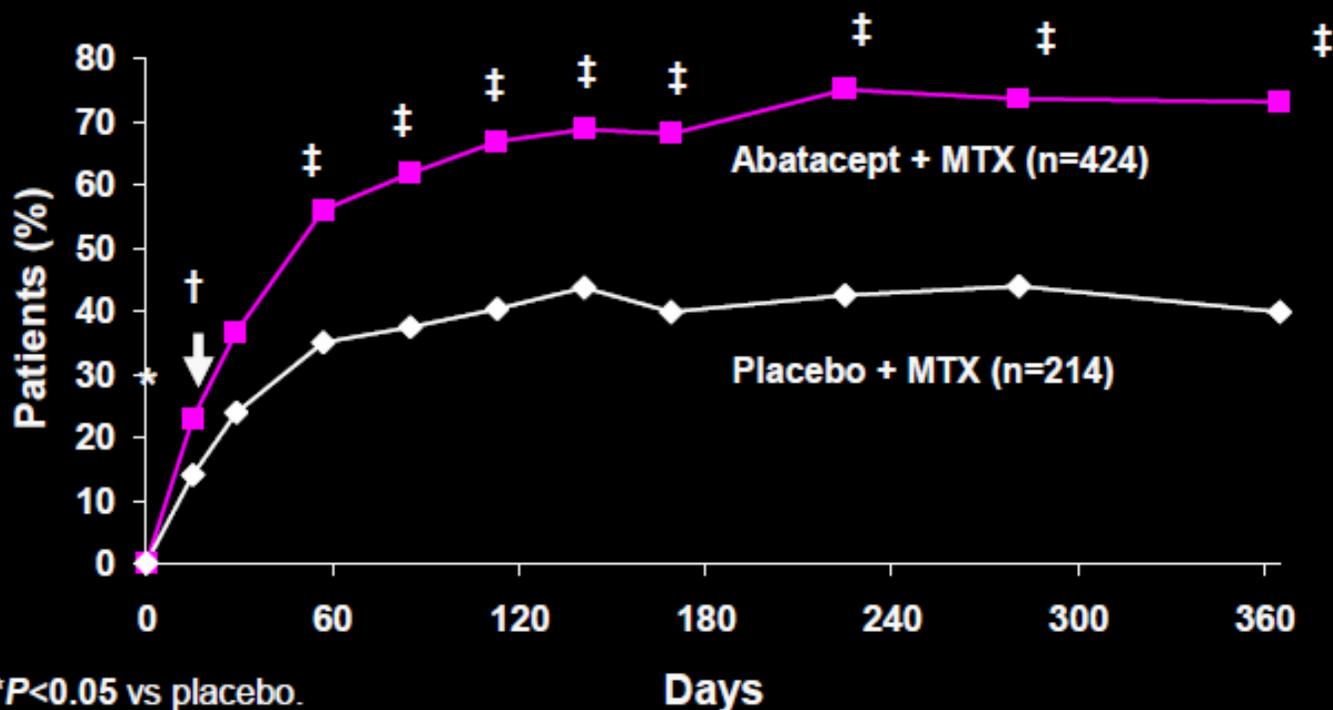




LINFOCITOS T ABATACEPT



AIM: ACR20 Responses Over 12 Months



* $P < 0.05$ vs placebo.

† $P < 0.01$ vs placebo.

‡ $P < 0.001$ vs placebo.

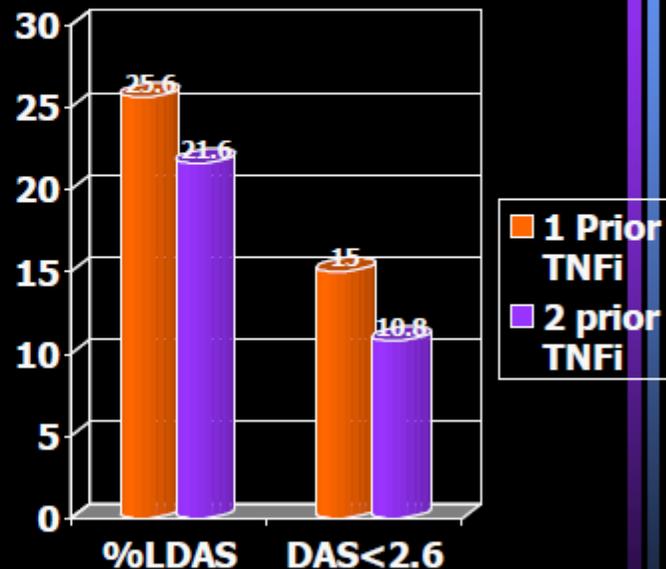
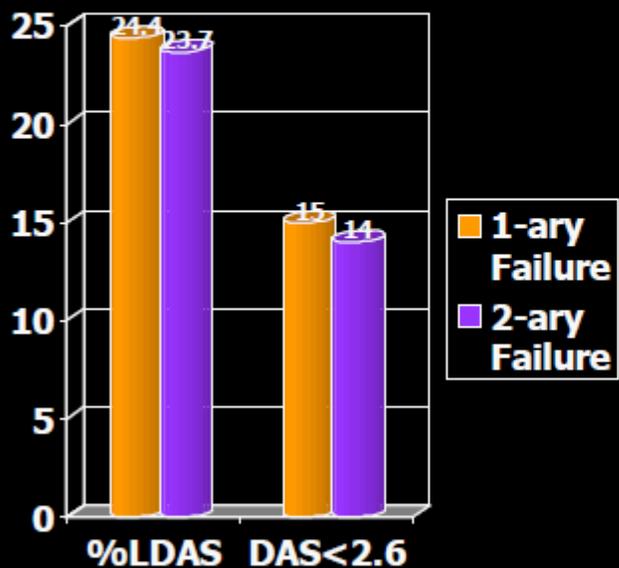




LINFOCITOS T ABATACEPT



Abatacept in anti-TNF failures: Does reason for failure affect response? Results at 1 year



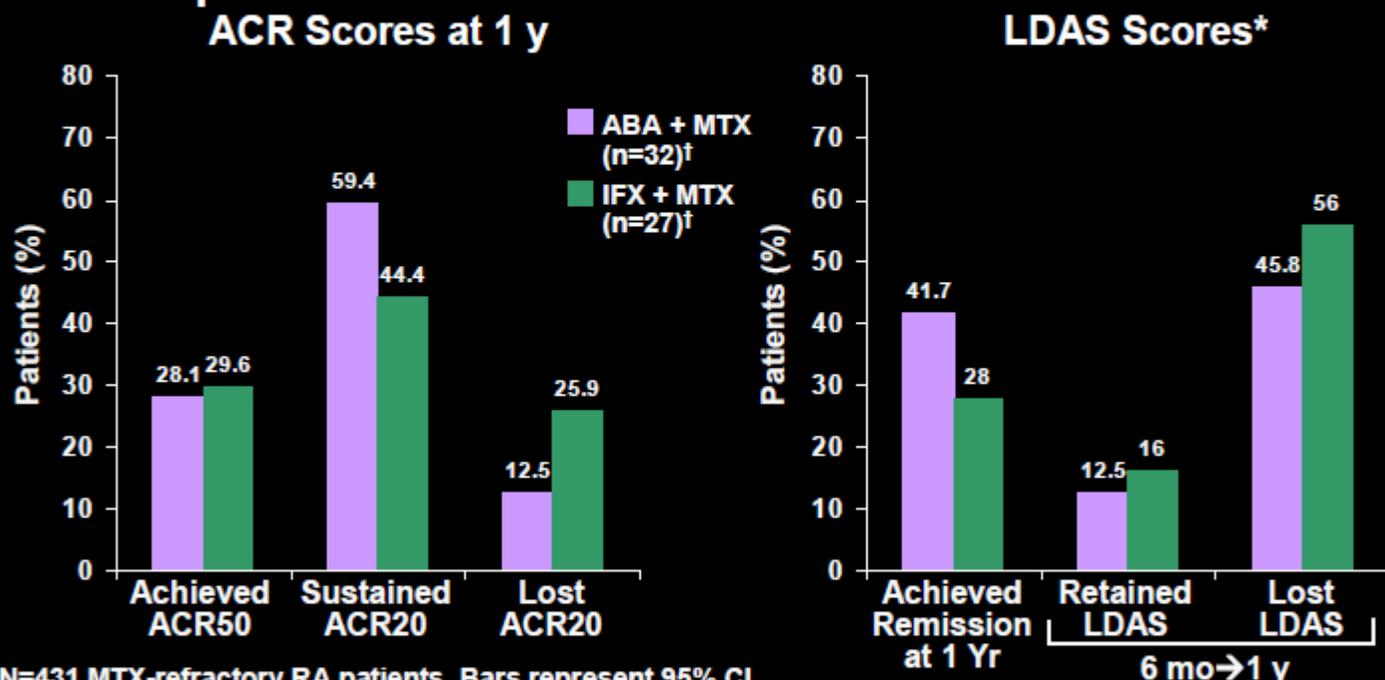
Schiff M, et al. EULAR Paris 2008, FRI0160; Keystone E, et al. ibid, THU0187



LINFOCITOS T ABATACEPT



ATTEST: ABA and IFX—Clinical Improvement From 6 to 12 Months



N=431 MTX-refractory RA patients. Bars represent 95% CI.

*LDAS = DAS28[CRP] ≥ 2.6 – ≤ 3.2 ; [†]Number of pts out of 431 who achieved ACR20/LDAS at 6 mo and were followed in this study.

LDAS = Low Disease Activity Score.

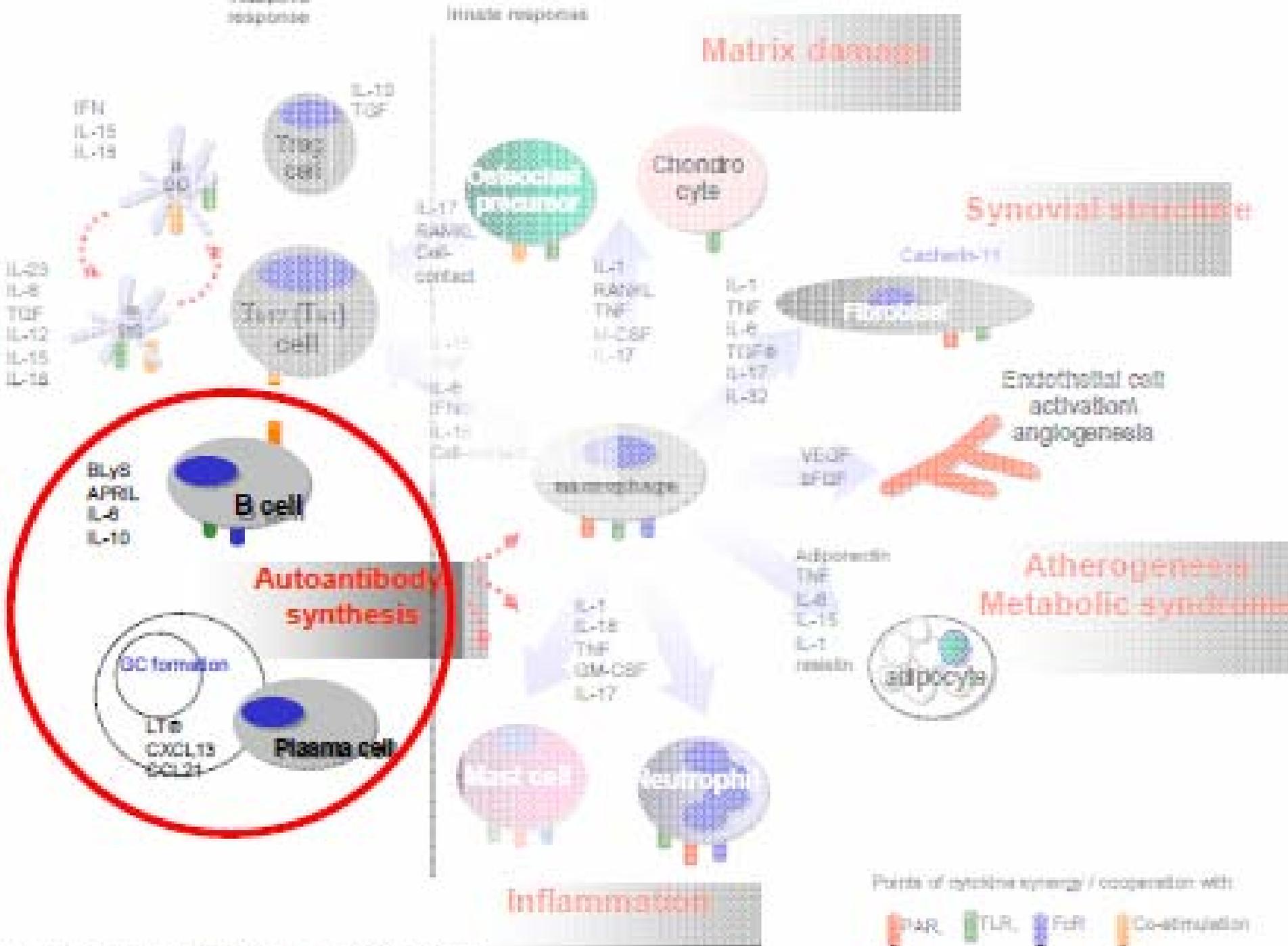
Schiff M et al. Presented at: EULAR Annual Congress; Paris, France; June 11-14, 2008. Abstract FRI0159.





CÉLULAS DEL SISTEMA INMUNITARIO

- SISTEMA NATURAL
- SISTEMA ADAPTATIVO

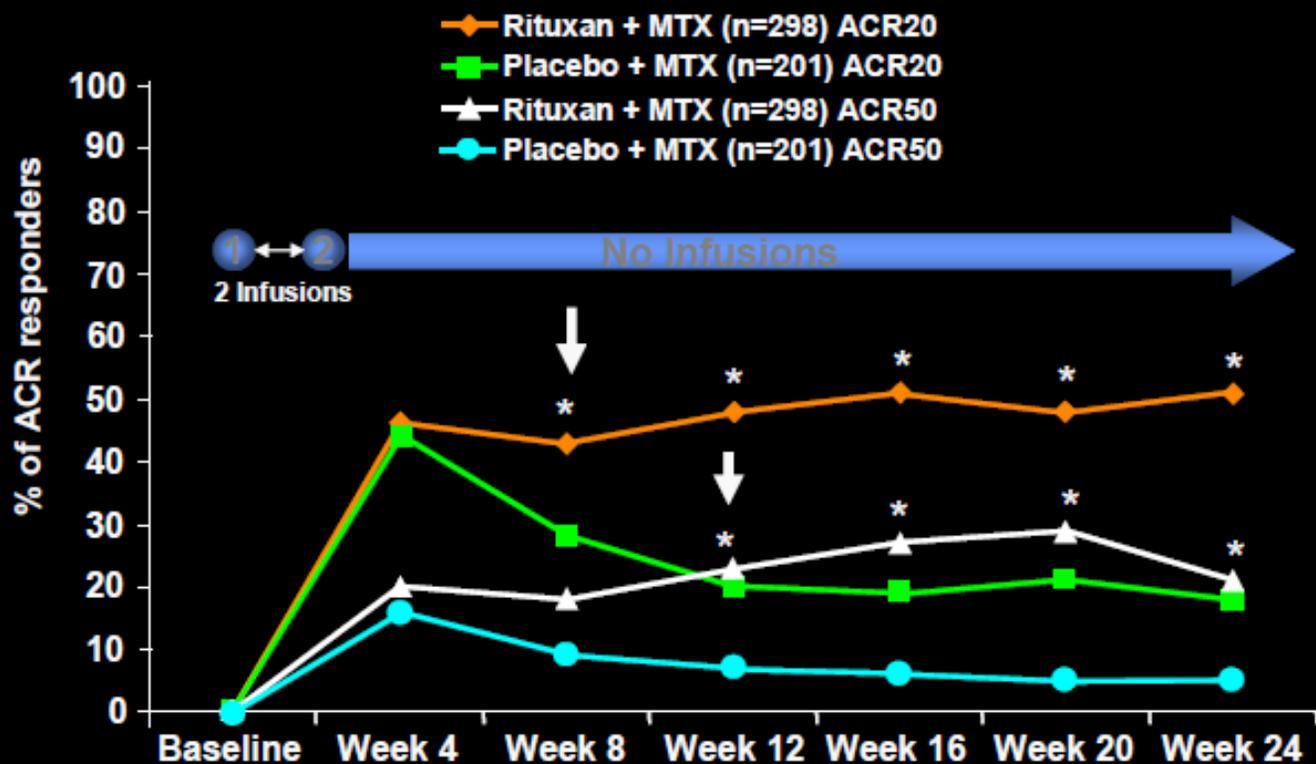




LINFOCITOS B RITUXAN



REFLEX Trial: ACR Responses Through 6 Months



* $P < 0.0001$ for Rituxan + MTX vs placebo + MTX.

Cohen et al. *Arthritis Rheum.* 2006;54:2793.



Hospital Universitario
Príncipe de Asturias



B-cell Inhibitors in Development

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

BAFF= B-cell activating factor

APRIL = A proliferation-inducing ligand

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

Damage sensing by innate immune response



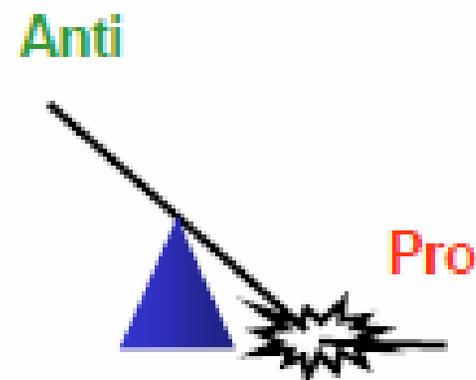
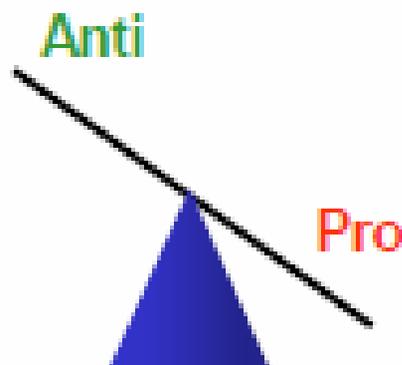
Pre-arthritis

Early arthritis

Established arthritis



Inflammation:
• genetics
• environment

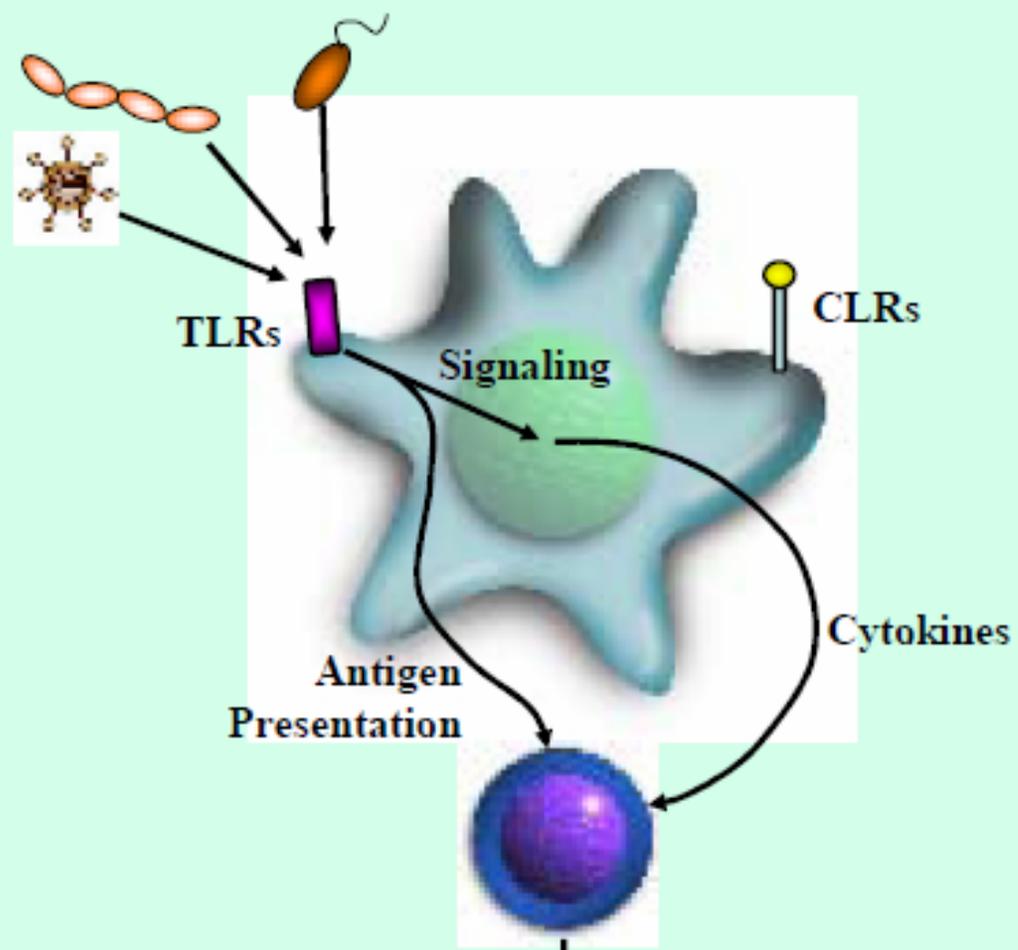


Damage / repair:
• genetics
• environment
• **TLR system**

‘Drug-maintained’ remission?

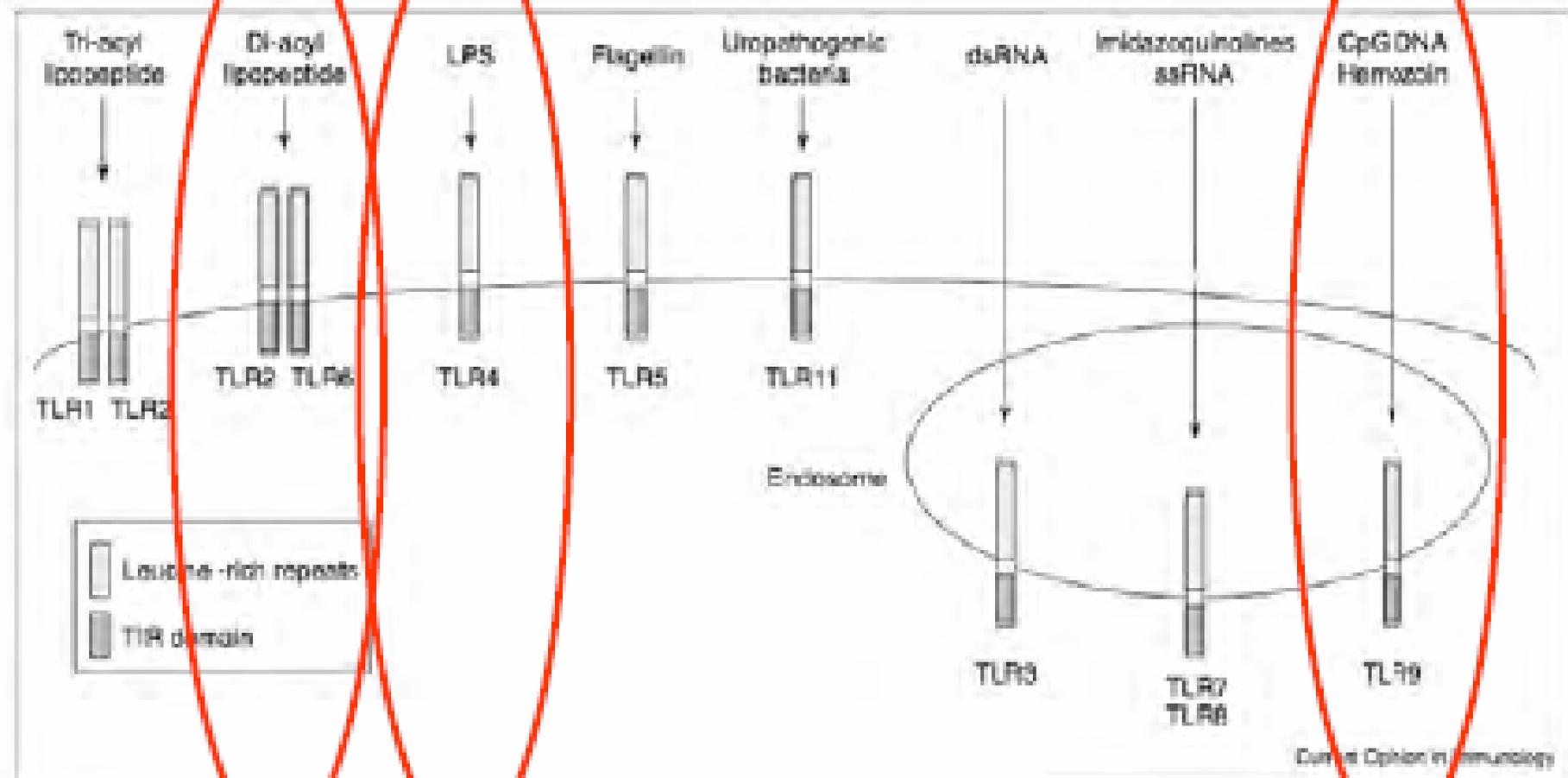
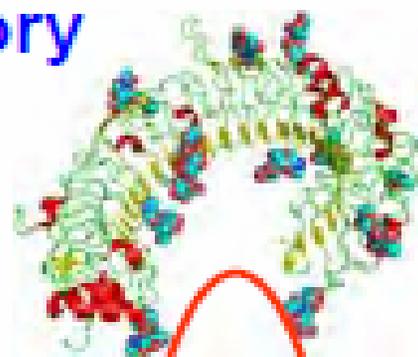
‘Drug-free’ remission?

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

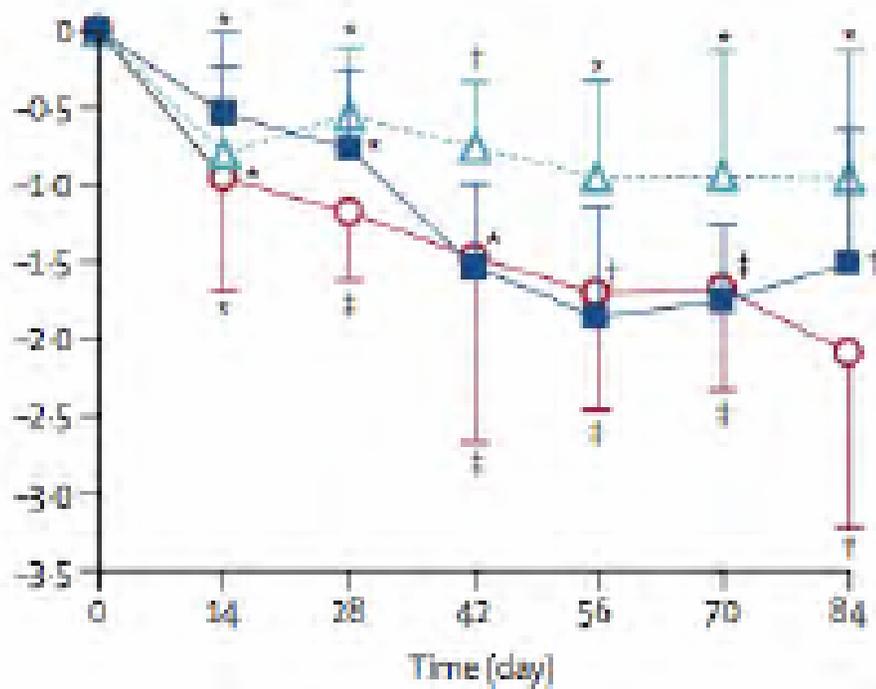


TLR antagonism: chaperonin 10 in RA

DAS28

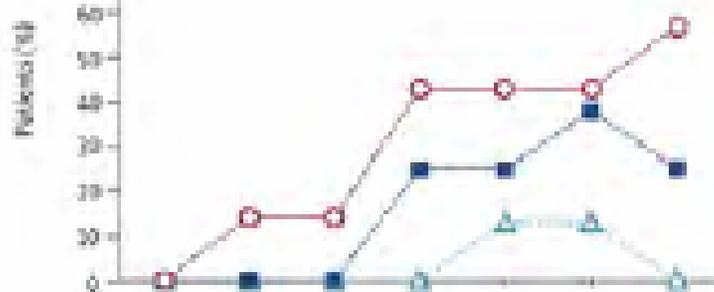
- 5 mg group
- △ 7.5 mg group
- 10 mg group

Mean change in DAS28 from baseline



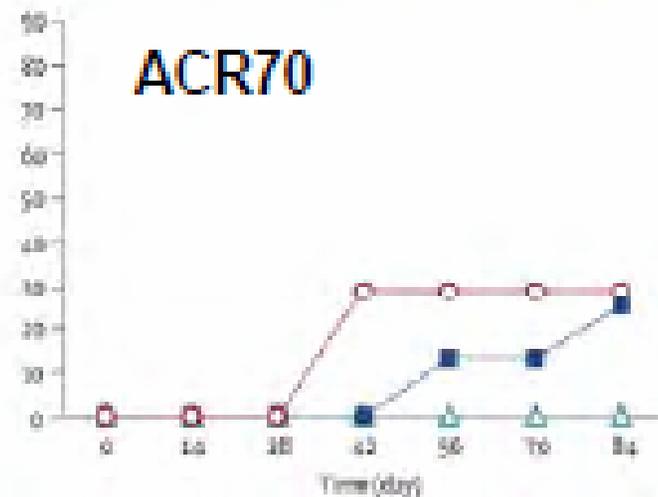
a

ACR50

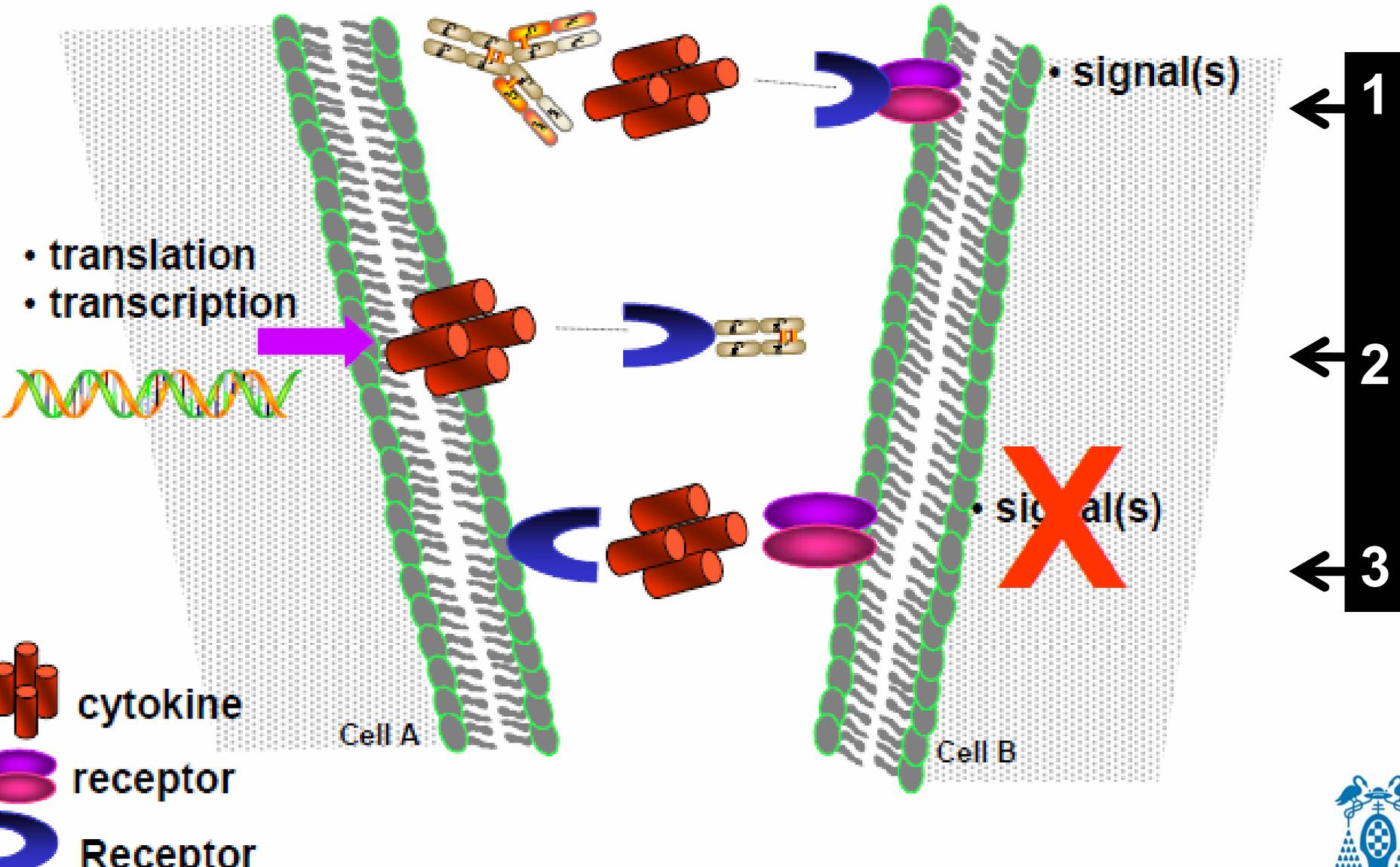


c

ACR70



How: to target your chosen molecule...?





Signal Transduction

Inhibitors



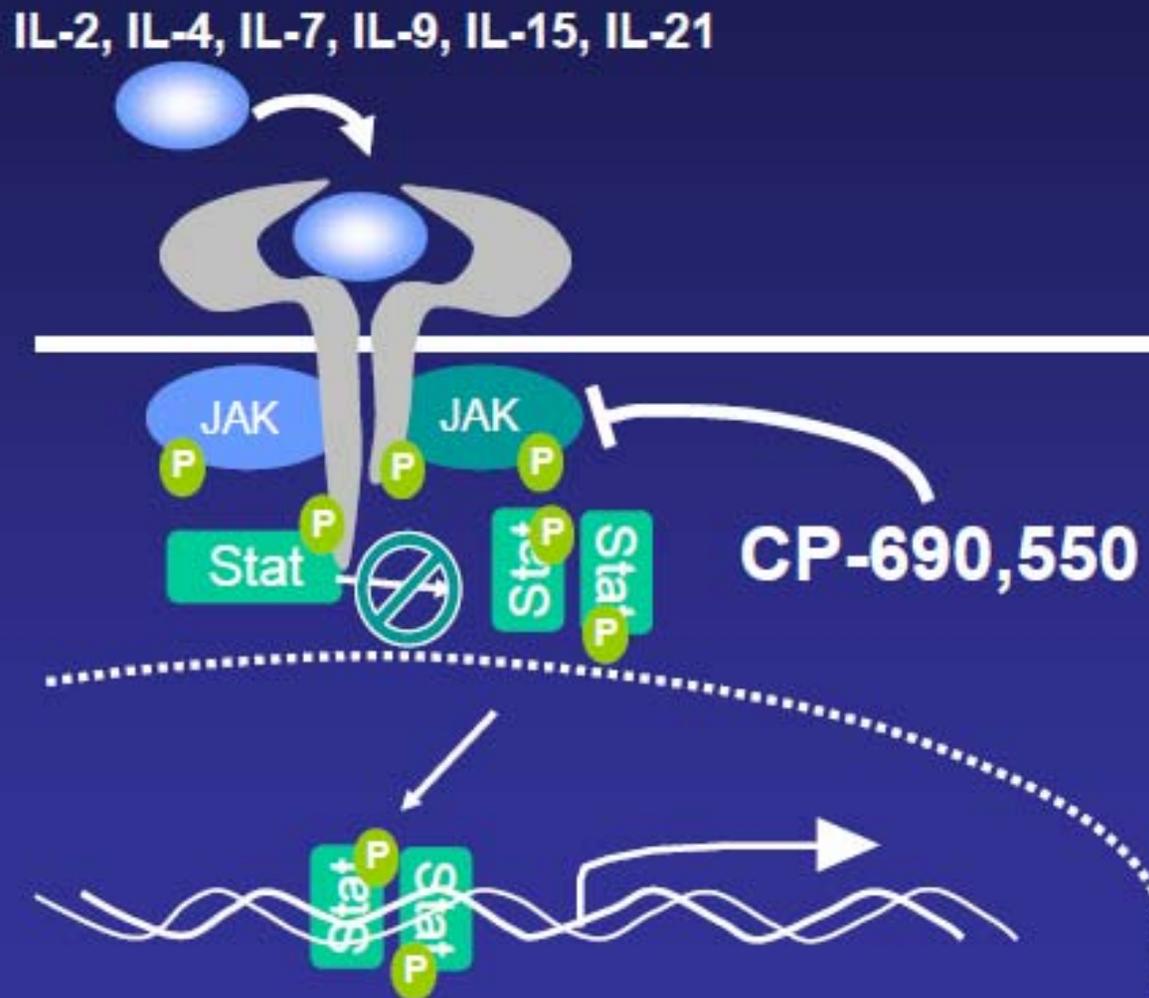
Signal Transduction Pathways

1. mitogen-activated 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)

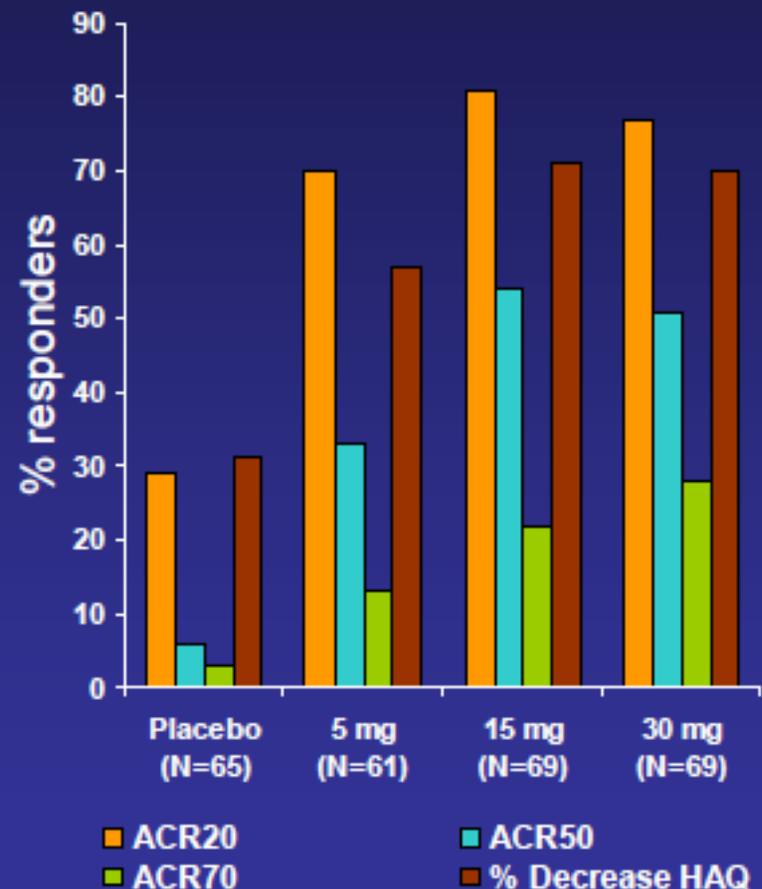
JAK3

- 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





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

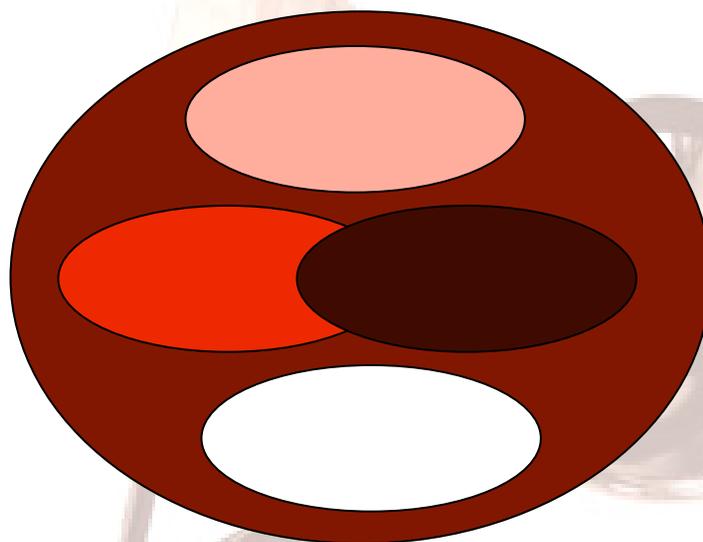




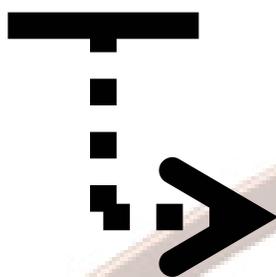
Investigación biomédica etiopatogénica, diagnóstica, terapéutica y reparativa



SIMILITUD
CLÍNICA
DIAGNÓSTICO
DE
ENFERMEDAD
ÚNICA



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



Medicina
traslacional

IDENTIFICACION
DE MECANISMOS
ETIOPATOGÉNICOS
ESPECÍFICOS
Y COMUNES

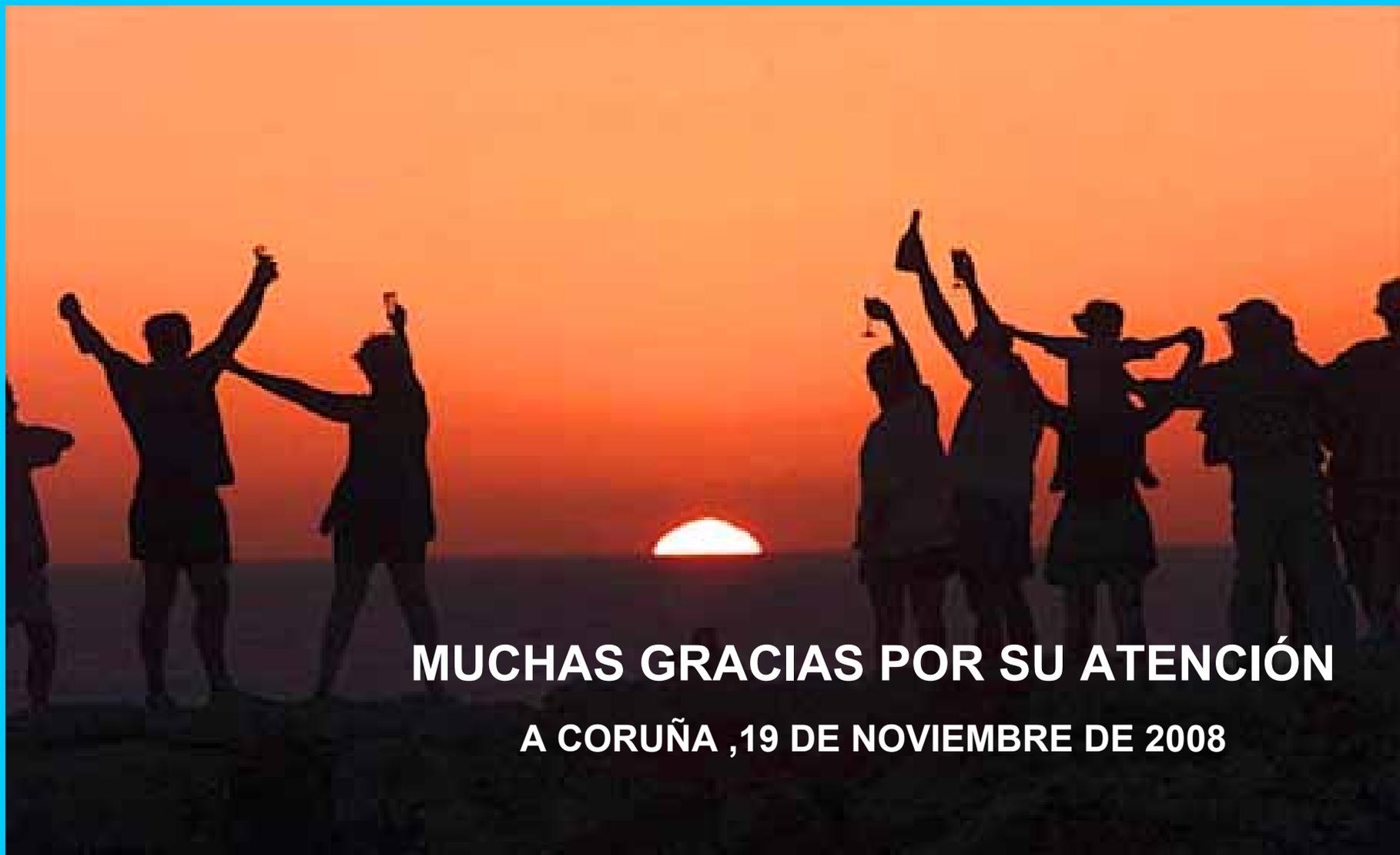


Medicina
individualizada

No existen enfermedades sino enfermos



XXIX CONGRESO NACIONAL DE LA SOCIEDAD NACIONAL DE MEDICINA INTERNA



MUCHAS GRACIAS POR SU ATENCIÓN

A CORUÑA ,19 DE NOVIEMBRE DE 2008