

A szisztémás autoimmun kórképek terápiája

Prof. Dr. Nagy György

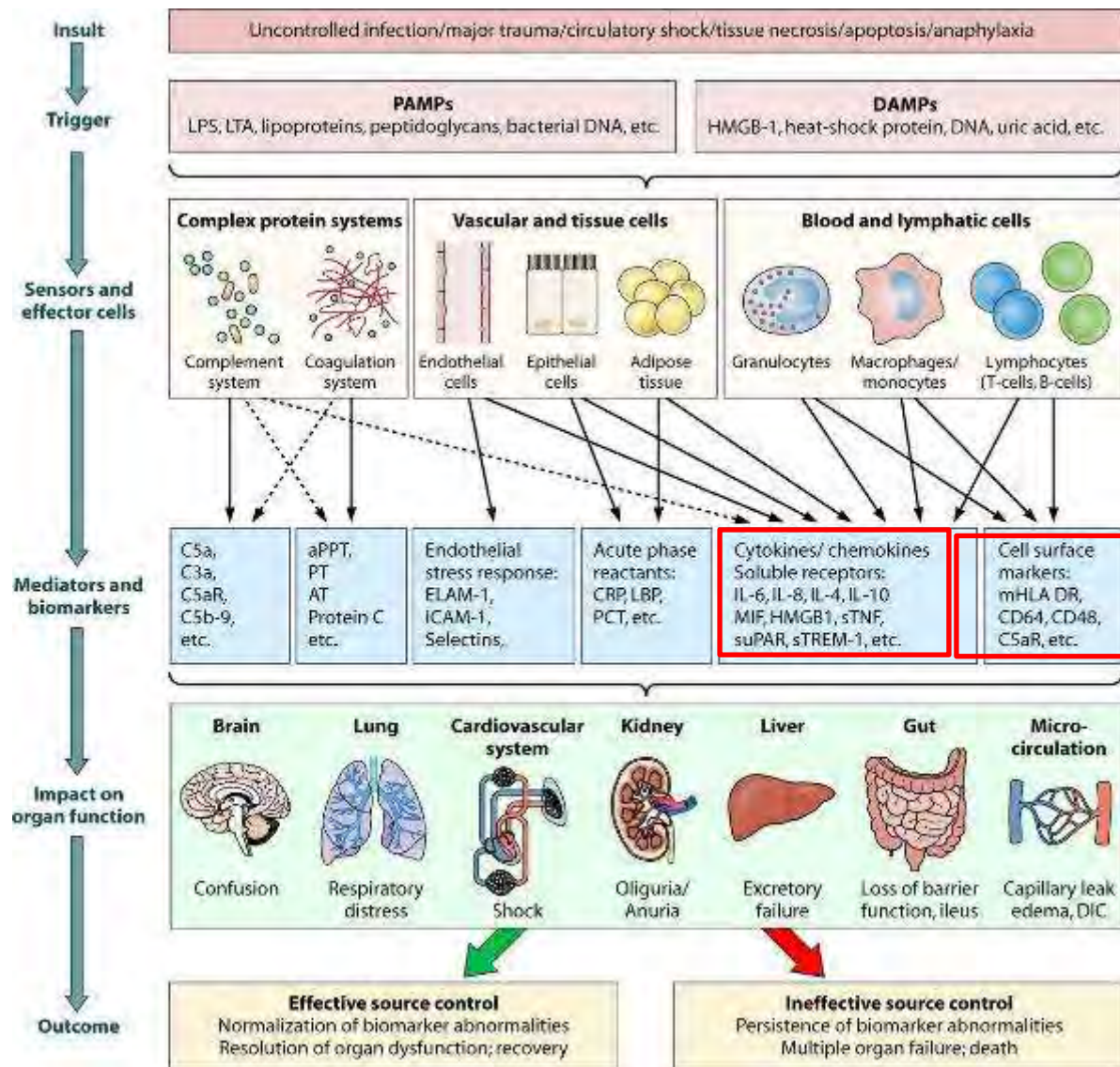
Reumatológiai és Immunológiai Klinika

2026 október 2.



SEMMELWEIS
EGYETEM 1769

A szisztémás gyulladás mediátorai



Fertőzés
Tumor

Autoimmun
Autoinflammációs
betegségek

Reinhardt K et al. Clin. Microbiol. Rev. 2012;25:609-634

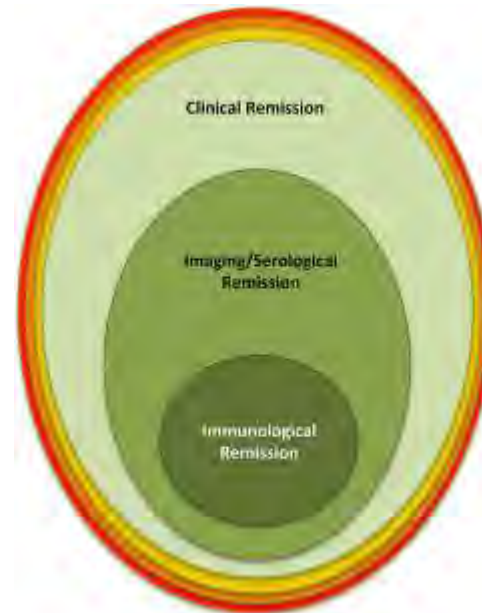
Immunválasz fertőzésekben

	Infectious agent	Disease	Humoral Immunity				Cell-mediated immunity	
			IgM	IgG	IgE	IgA	CD4 T cells (macro-phages)	CD8 killer T cells
Viruses	Herpes zoster	Chickenpox						
	Epstein-Barr virus	Mononucleosis						
	Influenza virus	Influenza						
	Polio virus	Poliomyelitis						
Intra-cellular bacteria	<i>Rickettsia prowazekii</i>	Typhus						
	Mycobacteria	Tuberculosis, leprosy						
Extra-cellular bacteria	<i>Staphylococcus aureus</i>	Boils						
	<i>Streptococcus pneumoniae</i>	Pneumonia						
	<i>Neisseria meningitidis</i>	Meningitis						
	<i>Corynebacterium diphtheriae</i>	Diphtheria						
	<i>Vibrio cholerae</i>	Cholera						
Fungi	<i>Candida albicans</i>	Candidiasis						
Protozoa	<i>Plasmodium</i> spp.	Malaria						
	<i>Trypanosoma</i> spp.	Trypanosomiasis						
Worms	Schistosome	Schistosomiasis						

Figure 10-16 Immunobiology, 7ed. (© Garland Science 2008)

A kezelés célja gyulladásos reumatológiai betegségekben

- ▶ fájdalomcsillapítás
- ▶ gyulladáscsökkentés
- ▶ mérsékelt/alacsony betegségaktivitás
- ▶ remisszió
- ▶ progresszió gátlás
- ▶ gyógyszermentes remisszió
- ▶ tolerancia indukció



- Clinical remission**
Absence or very low-level symptoms related to arthritis assessed by standardised scores and cut-offs (DAS28 <2.6, DAS44 <1.6, SDAI <3.3, CDAI <2.8, ACR/EULAR remission)
- Imaging/Serological Remission**
Clinical remission PLUS
 - No signs of ultrasound synovitis
 - No signs of MRI synovitis or osteitis
 - No serologic signs of inflammation
- Immunological Remission**
Clinical and imaging/serological remission PLUS
 - Rheumatoid factor and ACPA negative
 - Rheumatoid factor and ACPA seroconversion is documented

Schett G et al Ann Rheum Dis. 2016 Aug;75(8):1428-37.

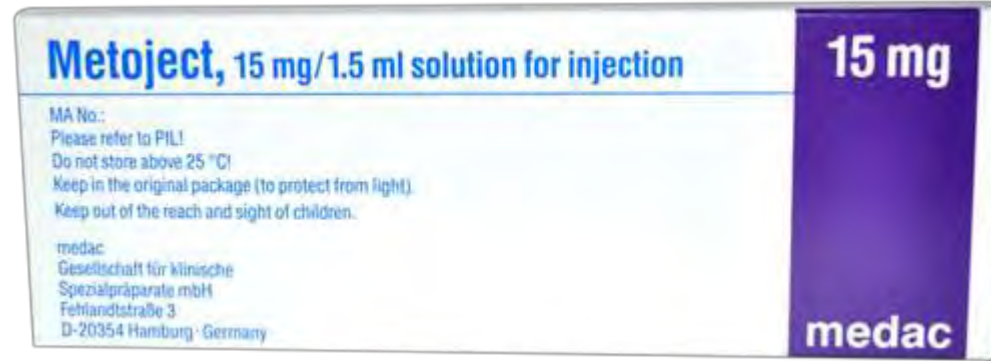
Szintetikus bázisterápiás szerek

- **methotrexate (MTX)**
- chloroquin (CHL)
- sulfasalazin (SSZ)
- leflunomid (LEF)
- azathioprin (AZA)
- cyclosporin A (CSA)
- cyclophosphamid (CPH)

Az MTX RA-ban



évtizedek óta alkalmazott
minden ajánlás központi része
biztonságos és hatékony



MTX mellékhatások

csontvelő-szuppresszió, hepatotoxicitás
intersticiális pneumonitis
nyálkahártya-károsodás, stomatitis ulcerosa
rossz közérzet, borzongás és láz, szédülés,
a fertőzésekkel szembeni ellenállóképeség
csökkenése

émelygés, hányinger

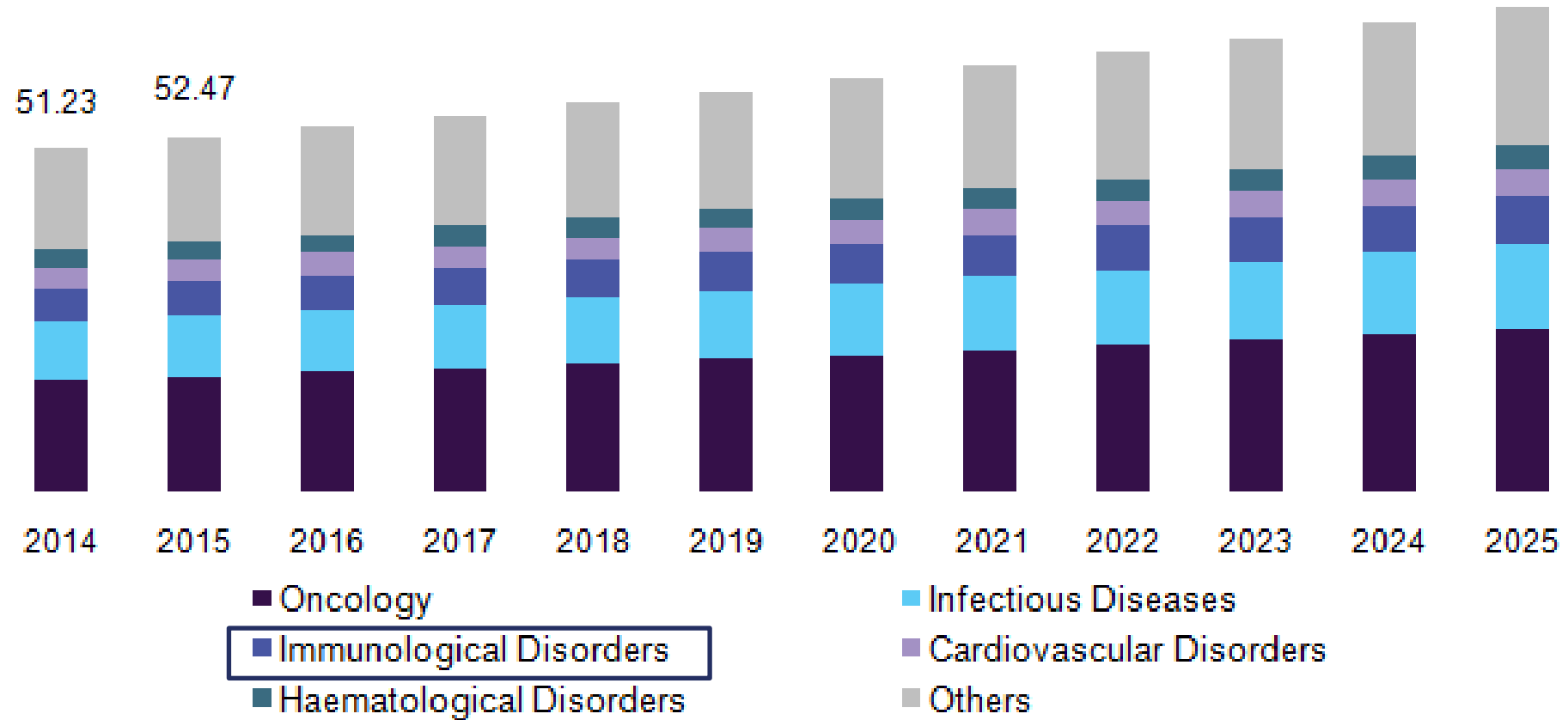
reverzibilis

***dózis csökkentés, sz.e.
elhagyás***

sc. adagolás

Biológia terápiák 2014-2025

U.S. Biologics market share, by disease category, 2014 - 2025 (USD Billion)



<https://www.grandviewresearch.com/industry-analysis/biologics-market>

Célzott terápiák a reumatológiában

- I: TNF-blokkolás
- II: IL1-blokkolás
- III: IL-6-blokkolás
- IV: IL-17-blokkolás
- V: IL12/23-blokkolás
- VI: B-sejt-gátlás
- VII: T-sejt-gátlás
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- IX: IVIG
- X: IFN gátlás
- XI: CAR-T kezelés

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FERTŐZÉS ÉS TNF

Fertőzéseket követően egyes tumorok növekedése lassul

Streptococcus pyogenes baktérium közvetlenül a tumorba

Első betege 16 éves fiú, nagy hasi tumorra, melyet négy naponta infiltrált.

A fiú esetét publikálta.

Coley WB. *Annals of Surgery* 1891;14:199-200

Roger, G.H. *Séances et Mém Soc de Biol Paris* 1890;2:573-580



1975: TNF

Carswell EA *Proc Natl Acad Sci U S A*. 1975 Sep;72(9):3666-70. An endotoxin-induced serum factor that causes necrosis of tumors.

Proc. Nat. Acad. Sci. USA
Vol. 72, No. 9, pp. 3666-3670, September 1975
Immunology

An endotoxin-induced serum factor that causes necrosis of tumors (activated macrophage)

E. A. CARSWELL, L. J. OLD, R. L. KASSEL, S. GREEN, N. FIORE, AND B. WILLIAMSON

Memorial Sloan-Kettering Cancer Center, New York, N.Y. 10021

Communicated by Lewis Thomas, June 23, 1975

ABSTRACT In studying "hemorrhagic necrosis" of tumors produced by endotoxin, it was found that the serum of bacillus Calmette-Guérin (BCG)-infected mice treated with endotoxin contains a substance (tumor necrosis factor; TNF) which mimics the tumor necrotic action of endotoxin itself. TNF-positive serum is as effective as endotoxin itself in causing necrosis of the sarcoma Meth A and other transplanted tumors. A variety of tests indicate that TNF is not residual endotoxin, but a factor released from host cells, probably macrophages, by endotoxin. Corynebacteria and zymosan, which like BCG induce hyperplasia of the reticulo-endothelial system, can substitute for BCG in priming mice for release of TNF by endotoxin. TNF is toxic *in vitro* for two neoplastic cell lines; it is not toxic for mouse embryo cultures. We propose that TNF mediates endotoxin-induced tumor necrosis, and that it may be responsible for the suppression of transformed cells by activated macrophages.

response (- to ++++) elicited in individual (BALB/c X C57BL/6JF₁) mice by administration of serum containing TNF. In the maximum (++++) response, the major part of the tumor mass is destroyed, leaving only a peripheral rim of apparently viable tumor tissue. In about 25% of mice treated with 0.5 ml of TNF-positive serum, the tumor regresses. Regression is not seen in control untreated mice under these conditions. Mice receiving TNF-positive serum show no marked signs of toxicity.

Necessity for treatment with both BCG and endotoxin for the production of TNF in the serum

In the studies summarized in Table 1, TNF was demonstrable in the serum of BCG-infected mice given endotoxin, but not in the serum of mice given either BCG alone or endotoxin

Cachectin azonosítása (RAV 264 sejt)

PURIFICATION OF CACHECTIN, A LIPOPROTEIN LIPASE- SUPPRESSING HORMONE SECRETED BY ENDOTOXIN- INDUCED RAW 264.7 CELLS

BY B. BEUTLER, J. MAHONEY, N. LE TRANG, P. PEKALA,* AND
A. CERAMI

*From the Laboratory of Medical Biochemistry, The Rockefeller University, New York 10021;
and the *Department of Biochemistry, East Carolina University School of Medicine,
Greenville, North Carolina 27834*

In the course of recent studies aimed at elucidating the biochemical mechanism of cachexia in rabbits infected with *Trypanosoma brucei*, it was noted (1) that animals with a minimal parasite burden became moribund and exhibited an extreme hypertriglyceridemia, with a marked elevation of plasma very low density lipoprotein (VLDL).¹ The hypertriglyceridemic state was remarkable in view of the severe wasting diathesis that accompanied this experimental infection. The elevation of plasma VLDL was shown to result from a clearing defect, caused by a loss of peripheral tissue lipoprotein lipase (LPL) activity.

A similar deficiency of LPL activity was noted (2) in C3H/HeN mice after

JEM 1985

lábjegyzet: igen hasonló a TNF-hez.....

TNF = cachectin

Identity of tumour necrosis factor and the macrophage-secreted factor cachectin

B. Beutler*, D. Greenwald*, J. D. Hulmes†, M. Chang†, Y.-C. E. Pant†, J. Mathison‡, R. Ulevitch‡ & A. Cerami*

* Laboratory of Medical Biochemistry, The Rockefeller University, 1230 York Avenue, New York, New York 10021, USA

† Department of Biopolymer Research, Hoffmann-La Roche, Inc., Nutley, New Jersey 07110, USA

‡ Department of Immunology, Scripps Clinic and Research Foundation, 10666 N. Torrey Pines Road, La Jolla, California 92037, USA

In mammals, several well-defined metabolic changes occur during infection, many of which are attributable to products of the reticuloendothelial system¹⁻³. Among these changes, a hypertriglyceridaemic state is frequently evident⁴⁻⁷, resulting from defective triglyceride clearance, caused by systemic suppression of the enzyme lipoprotein lipase (LPL)⁸. We have found previously that macrophages secrete the hormone cachectin, which specifically suppresses LPL activity in cultured adipocytes (3T3-L1 cells)¹⁰⁻¹². When originally purified from RAW 264.7 (mouse macrophage) cells, cachectin was shown to have a pI of 4.7, a subunit size of relative molecular mass (*M*_r) 17,000 and to form non-covalent multimers¹³. A receptor for cachectin was identified on non-tumorigenic cultured cells and on normal mouse liver membranes¹². A new high-yield purification technique has enabled us to determine further details of the structure of mouse cachectin. We now report that a high degree of homology exists between the N-terminal

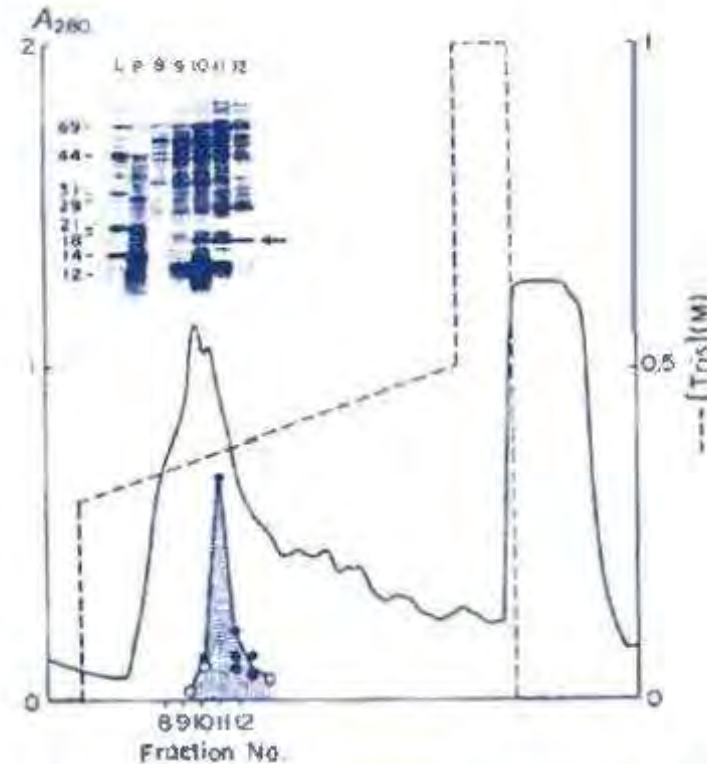


Fig. 1 Mono Q (FPLC anion exchange) chromatography. Crude concentrated RAW 264.7 medium, containing 0.1% glucoside as a dispersing agent, was applied to the column. Cachectin was eluted using a 0.1 M to 0.5 M Tris.Cl gradient, run at a flow rate 0.33 ml min⁻¹, over 34 min. Absorbance at 280 nm is indicated by the solid line. The Tris concentration is indicated by the dashed line.

Nature 1985

TNF és fertőzés

Passive Immunization Against Cachectin/Tumor Necrosis Factor Protects Mice from Lethal Effect of Endotoxin

Abstract. A highly specific polyclonal rabbit antiserum directed against murine cachectin/tumor necrosis factor (TNF) was prepared. When BALB/c mice were passively immunized with the antiserum or with purified immune globulin, they were protected against the lethal effect of the endotoxin lipopolysaccharide produced by *Escherichia coli*. The prophylactic effect was dose-dependent and was most effective when the antiserum was administered prior to the injection of the endotoxin. Antiserum to cachectin/TNF did not mitigate the febrile response of endotoxin-treated animals, and very high doses of endotoxin could overcome the protective effect. The median lethal dose of endotoxin in mice pretreated with 50 microliters of the specific antiserum was approximately 2.5 times greater the median lethal dose for controls given nonimmune serum. The data suggest that cachectin/TNF is one of the principal mediators of the lethal effect of endotoxin.

B. BEUTLER*
I. W. MILSARK

obscure, it is believed that the toxic effects are mediated by factors produced

Science 1985

Nature medicine 1997

TNF inhibition and sepsis — sounding a cautionary note

Conflicting results from anti-TNF trials in sepsis patients suggest that timely administration of TNF inhibitor drugs is crucial.

proposed in NA damage-gutathione hypothesis by plasmid-exposed species both in cell infection. In fact, by antibiotic apparent however, the of certain ing experimental cellular reactions may it is conceivable or the in particular imminent of chimera and

Sepsis, a frequent cause of death in intensive care units, remains a major public health problem. Although potent antibiotics and drugs to treat cardiovascular failure are available, new therapeutic approaches that can be taken during the early stages of sepsis regardless of the causative organism are appealing. Inhibition of tumor necrosis factor- α (TNF), a major cytokine mediator

GEORGES E. GRAU
& DANIELA N. MÄNNEL

number of clinical trials have attempted to abrogate sepsis and septic shock in patients by inhibiting TNF using either anti-TNF antibodies or fusion proteins composed of the extracellular domain of the p55 (p55-IgG) or p75 TNF receptor combined with the Fc portion of IgG (ref. 2; Fig. 1). However, data are conflicting and clinical responses disappointing. In the most encouraging anti-

RA és TNF

Tumour necrosis factor α stimulates resorption and inhibits synthesis of proteoglycan in cartilage

J. Saklatvala

Strangeways Research Laboratory, Worts' Causeway, Cambridge CB1 4RN, UK

During inflammatory reactions, activated leukocytes are thought to produce a variety of small proteins (cytokines) that influence the behaviour of other cells (including other leukocytes). Of these substances, which include the interleukins, interferons and tumour necrosis factors (TNFs), interleukin-1 (IL-1) has been considered potentially a most important inflammatory mediator because of its wide range of effects (reviewed in refs 1, 2). *In vivo* it is pyrogenic and promotes the acute phase response; *in vitro* it activates lymphocytes³ and stimulates resorption of cartilage⁴ and bone^{5,6}. Cartilage resorption is a major feature of inflammatory diseases such as rheumatoid arthritis, and IL-1 is the only cytokine hitherto known to promote it. TNFs are characterized by their effects on tumours and cytotoxicity to transformed cells⁷⁻⁹, but share some actions with IL-1. I report here that recombinant human TNF α stimulates resorption and inhibits synthesis of proteoglycan in explants of cartilage. Its action is similar to and additive with IL-1, and it is a second macrophage-derived cytokine whose production in rheumatoid arthritis, or inflammation generally, could contribute to tissue destruction.

did TNF α (Fig. 1d): results for two concentrations of each cytokine demonstrate that responses were maximal. Supramaximal doses of the two agents in combination caused a rate of release that was considerably faster than that due to TNF α alone, but was not significantly greater than that seen with IL-1 alone. The failure of TNF α to augment the maximal response to IL-1 may be because the limit of the chondrocytes' ability to degrade their matrix *in vitro* was being approached.

The enzymatic mechanism by which the proteoglycan is degraded in cartilage is not understood. Normally, cartilage proteoglycans aggregate in a specific manner with hyaluronic acid, and it is thought that the large size of these aggregates causes them to be trapped in the matrix. Cartilage stimulated by IL-1 releases fragments of proteoglycan which, as judged by gel filtration, are smaller than normal proteoglycan monomers and are unable to aggregate with hyaluronic acid¹². There is no evidence of degradation of their chondroitin sulphate chains. These changes suggest that degradation is by limited proteolysis of the protein core. The fragments of proteoglycan that were released by cartilage stimulated with TNF behaved similarly on gel filtration to those generated by stimulation with IL-1 (Fig. 2). The bulk of the fragments generated by stimulation with either agent emerged from a Sepharose 2B column at a region between the elution positions of intact proteoglycan and proteoglycan digested with papain (which consists largely of single-chain chondroitin sulphate peptides). Addition of hyaluronic acid to the proteoglycan fragments before chromatography caused little or no formation of aggregates. This suggested that the hyaluronate binding region was blocked or had been lost. When the proteoglycan fragments were chromatographed under dissoci-

TNF-nek szerepe lehet RA-ban
TNF porc lebontás
Nature 1986

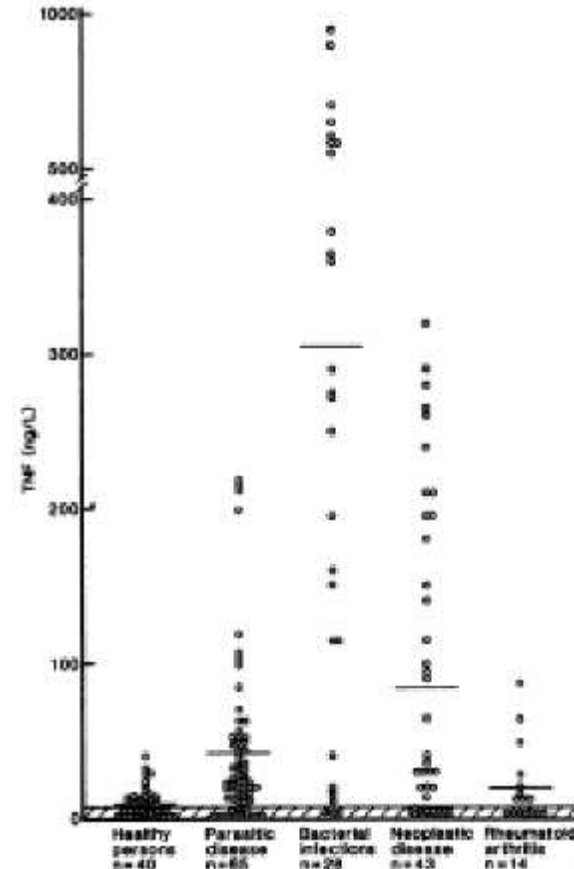
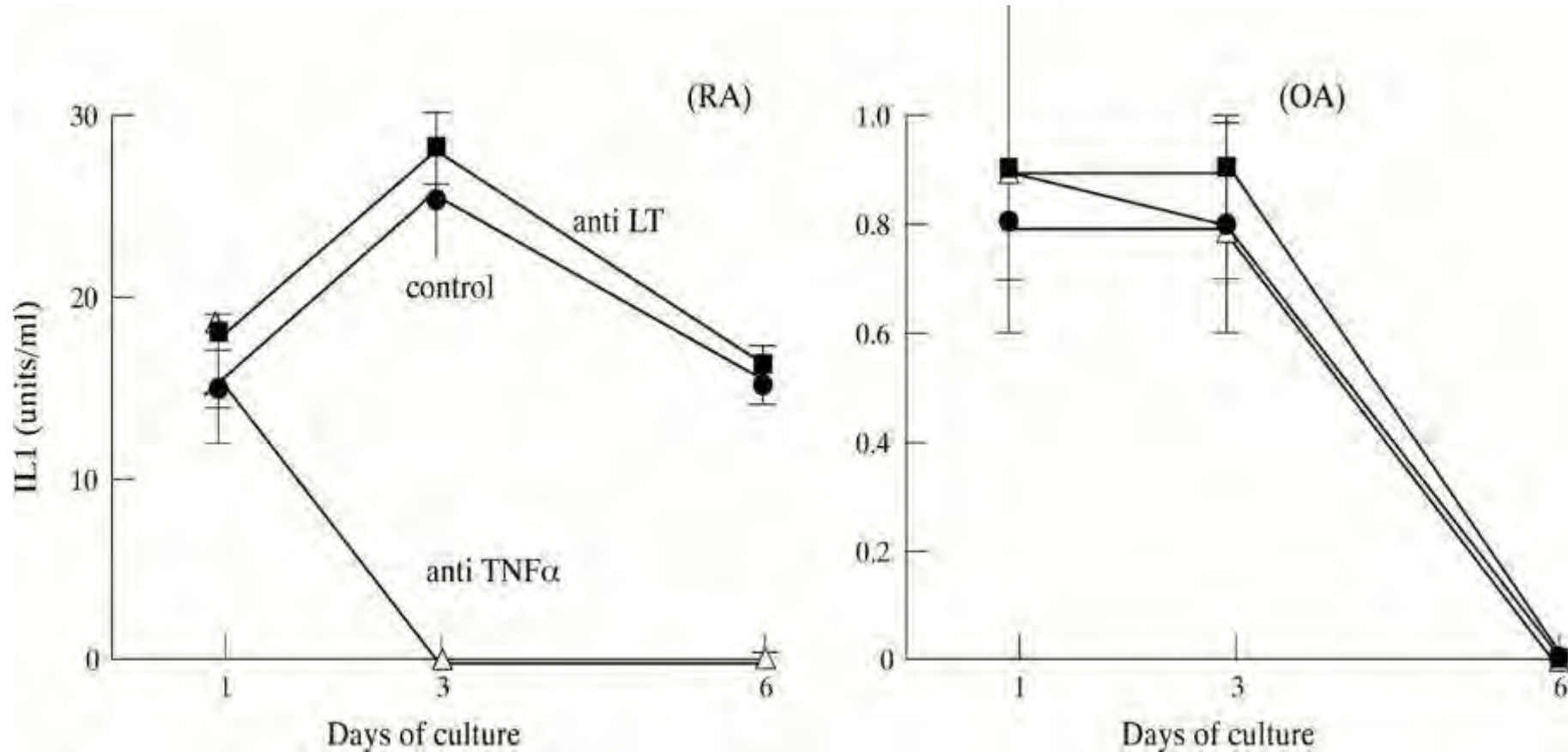


Fig. 4. Tumour necrosis factor concentrations in healthy and diseased persons. Coded area represents values below the detection limit of the method. Horizontal lines represent mean values of TNF concentrations for each group.

TNF szérumszint
Clin Chem 1987

Az első megfigyelés, mely TNF blokkolás terápiás szerepe mellett szól RA-ben

Synoviális sejtek IL1 termelése gátolható TNF blokkolással (*in vitro*)



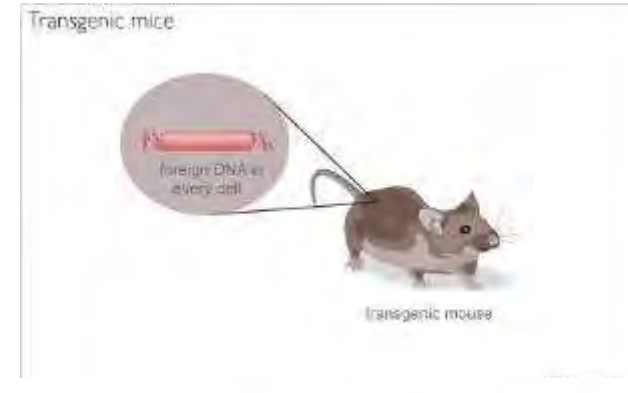
Brennan et al. Lancet 1989

Állatmodellek

TNF transzgenikus egér– súlyos destruktív arthritis

J: EMBO J. 1991

Kollias George



TNF-blokkoló kezelés- jól működik kollagén indukálta arthritisben (*in vivo*)

Proc Natl Acad Sci U S A. 1992

Maini N Ravinder



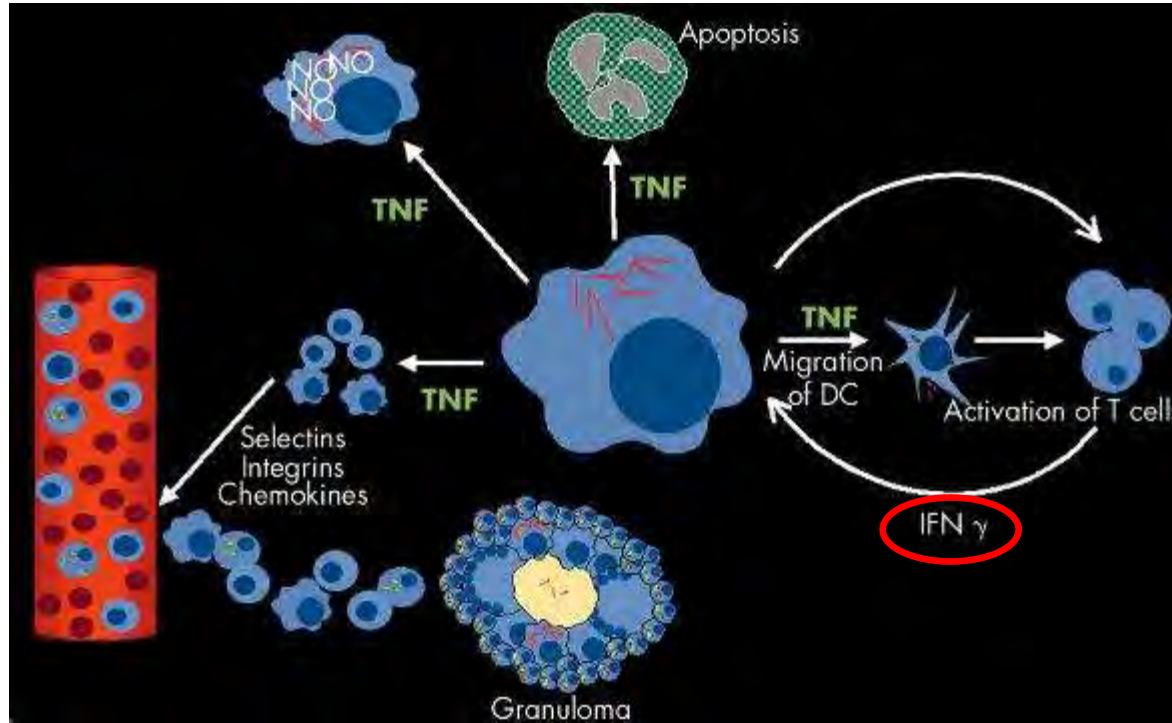
TNF deficiens egér- fokozott hajlam fertőzésekre, csökkent granuloma képződés, LPS rezisztencia

Proc Natl Acad Sci U S A. 1997

Lyoyd J Old



TNF szerepe a TBC baktérium elleni védekezésben



Stenger, S *Ann Rheum Dis* 2005;64:iv24-iv28

granuloma képződés

-a szervezet mycobactérium elleni védekezésének része

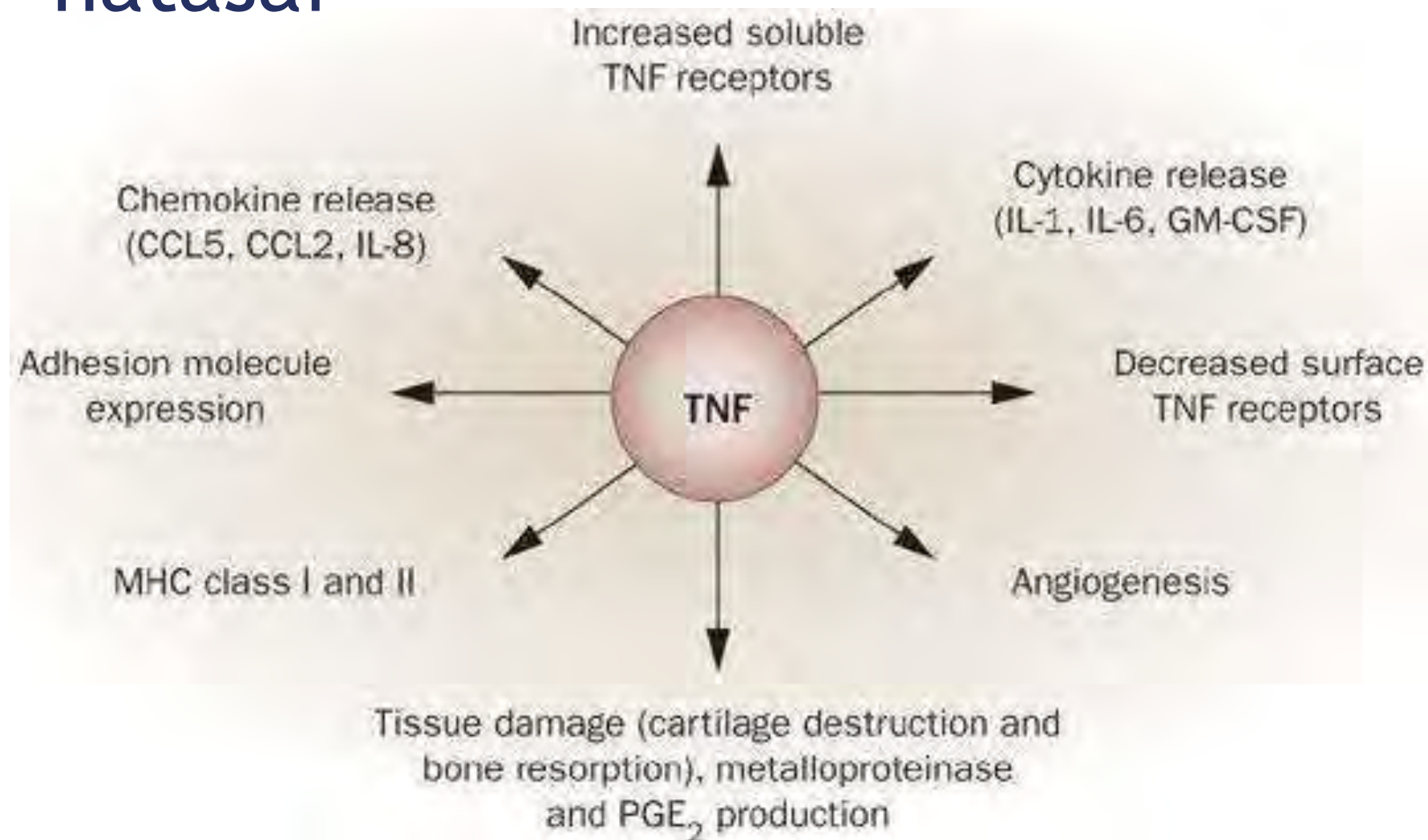
-TNF mediálja

-monocitát, limfocitát tartalmaz

TNF monocita apoptózis indít el

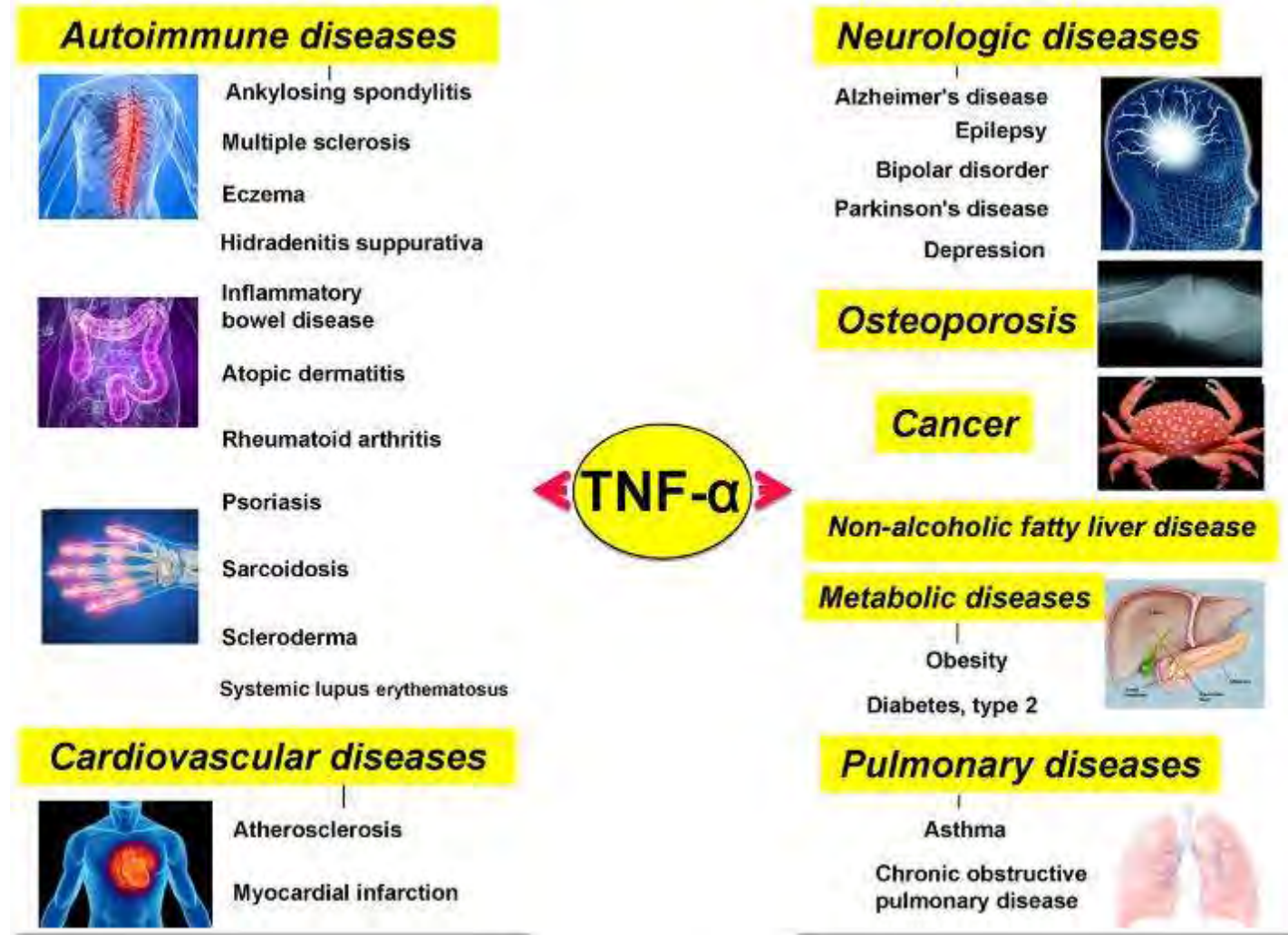
a granulomák élő baktériumokat tartalmazhatnak

A TNF-hatásai



Taylor, P. C. and Feldmann, M. (2009) Anti-TNF biologic agents: still the therapy of choice for rheumatoid arthritis Nat. Rev. Rheumatol. doi:10.1038/nrrheum.2009.181

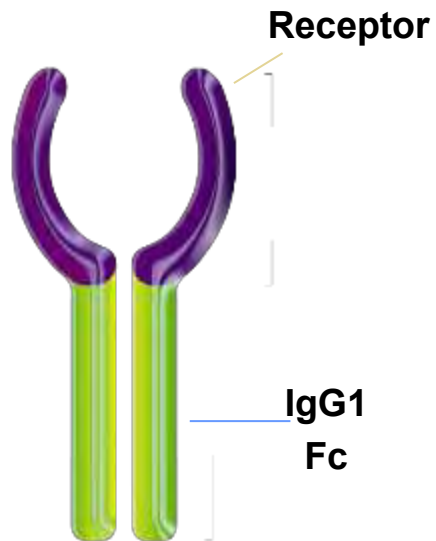
A TNF-szerepe különböző betegségekben



Bharat B. Aggarwal et al. Blood 2012;119:651-665

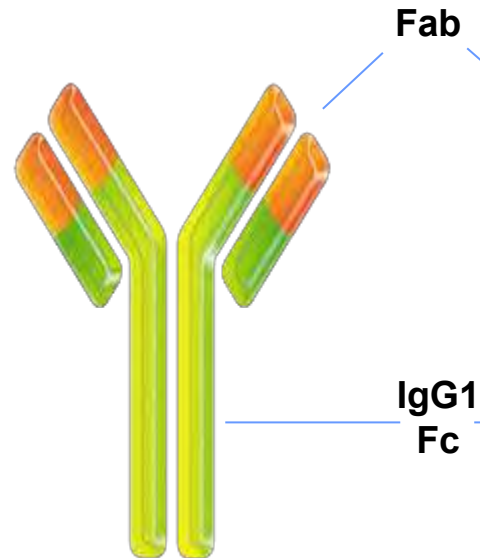
I: TNF-gátlók

**Etanercept
(Enbrel®)**



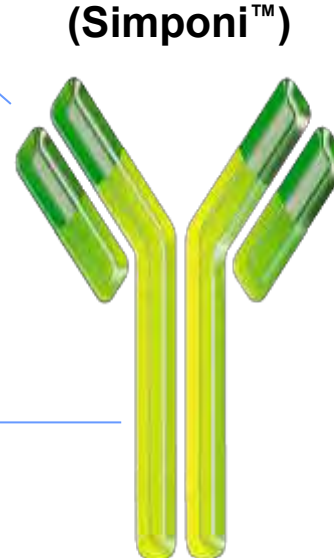
Recombinant
receptor/Fc fusion
protein

**Infliximab
(Remicade®)**

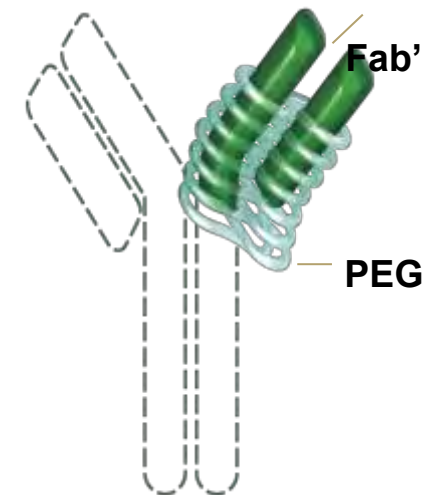


Monoclonal
antibody

**Adalimumab
(Humira®)
Golimumab
(Simponi™)**



**Certolizumab
pegol
(Cimzia®)**



PEGylated
Fab' fragment
40 kDa PEG

Weir N, Athwal D, et al. Therapy. 2006;3:535-45

I: TNF-blokkolók

Indikációk (adalimumab): RA, SPA, arthritis psoriatica, psoriasis, gyermekkori psoriasis, Crohn, gyermekkori Crohn, colitis ulcerosa, uveitis, gyermekkori uveitis, JIA, hidradenitis suppurativa

Alkalmazás: sc vagy iv (infliximab)

Eltérő affinitás TNF-hez

alkalmazás gyakorisága

Eltérő immunogenitás

másodlagos hatástalanság

Immunszuppresszió, gátolja a granulomaképződést (IFN γ)

TBC

Hepatotoxicitás

Demyelinizációs betegség

Autoimmun folyamatok

Szívelégtelenség

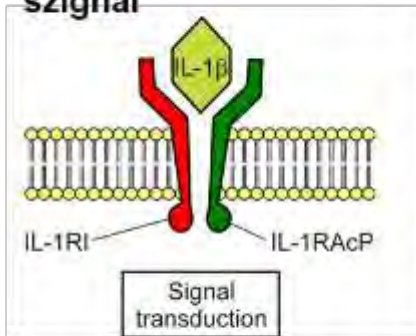
Allergia, anaphylaxiás reakció

Célzott terápiák a reumatológiában

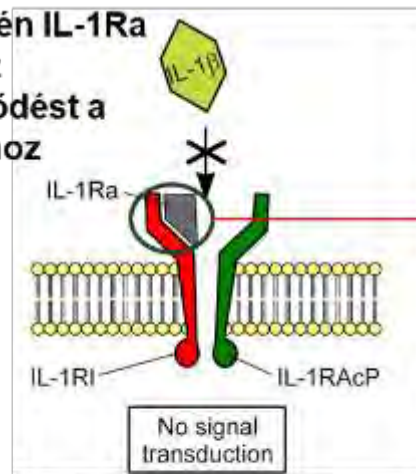
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II: IL-1 blokkolók

normál IL-1 β szignál



az endogén IL-1Ra gátolja az IL-1 β kötődést a receptorhoz

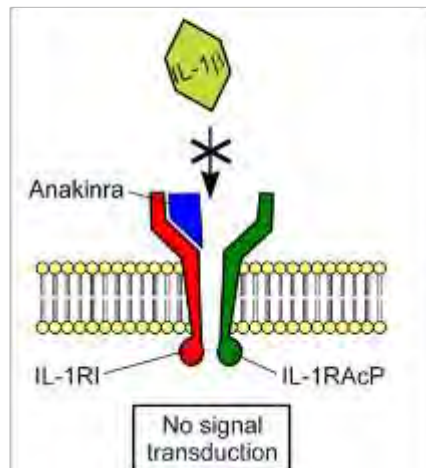


IL-1Ra – génje IL1rn mutációjában nincs IL-Ra hatás
Betegség: DIRA

Canakinumab (ILARIS):

humán monoklonális IL-1 β antitest

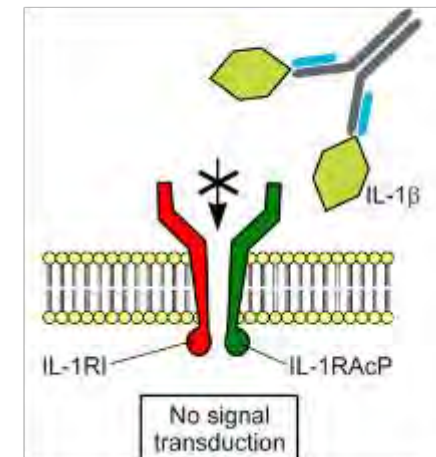
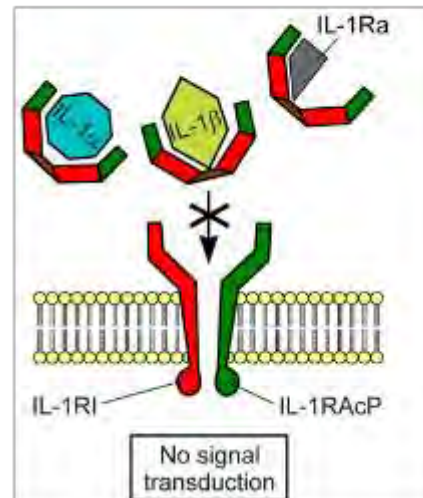
Anakinra: IL-1 receptor antagonist mimikáló



IL-1Ra, IL-1 receptor antagonist;
IL-1RAcP, IL-1 receptor accessory protein

Rilonacept: fúziós protein, köti az IL-1 α , IL-1 β és IL-1Ra

(human interleukin-1 receptor, IL-1 receptor AP, IgG1 FP)

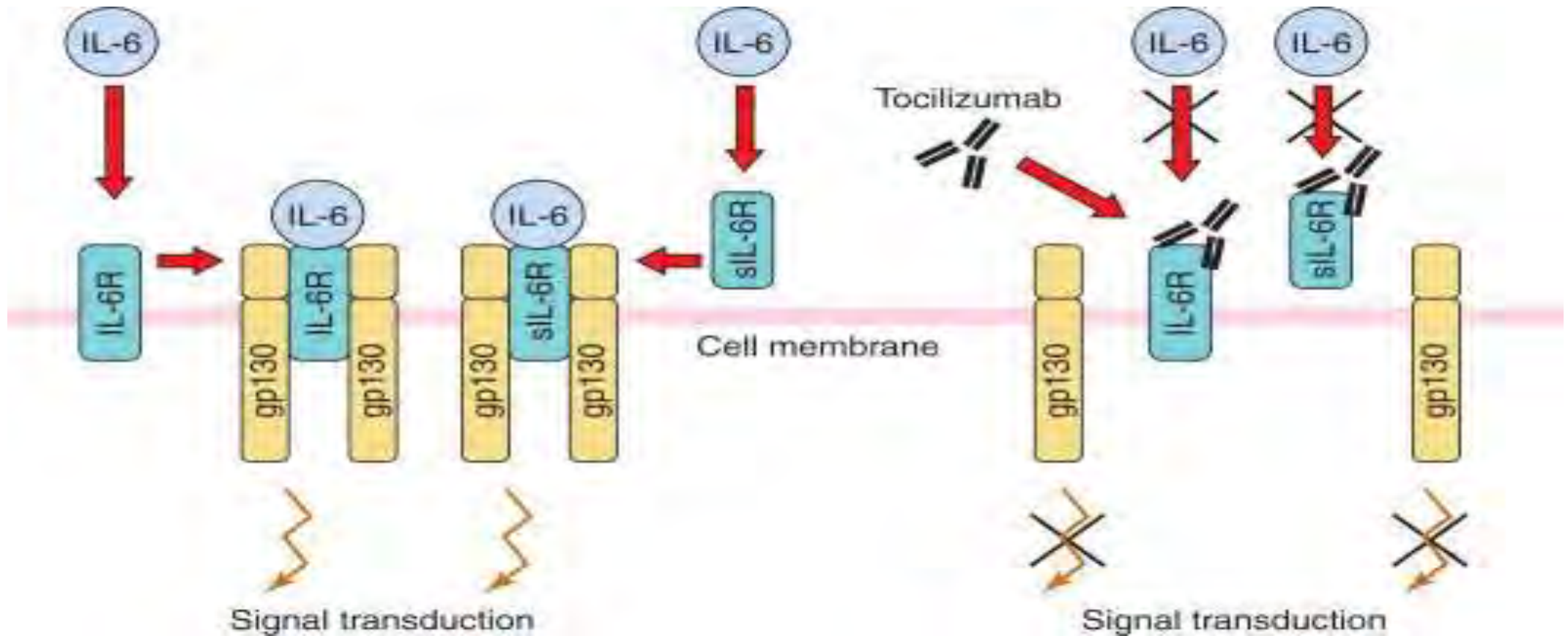


Canakinumab/ilaris indikációk: Still kór,
köszvény, CAPS, TRAPS, FMF, alkalmazás: sc. IEC-HS

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III: A tocilizumab humanizált, IL6-R elleni antitest



<https://www.sciencedirect.com/topics/neuroscience/tocilizumab>

III: Az IL-6-gátló tocilizumab/Roactemra

Indikációk:

RA, JIA, óriássejtes arteritis, GCA, kiméra antigén-receptor (CAR) T-sejt indukálta citokin felszabadulási szindróma

Alkalmazás: iv. és sc.

Közvetlenül az akut fázis válaszra hat
Fertőzések

Hepatotoxicitás
Neutropenia
Thrombocytopenia
Lipid paraméterek (CV rizikó?)
Diverticulitis
Allergia



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IV: Th17-sejtek

Gyulladásos sejtek

ROR- γ t expresszió

IL-17, IL21, IL22 termelés

IL-17 proteinek, IL-17A–F

Két, diszulfid híddal összekötött monomer



IL-17A–IL-17A
homodimer



IL-17F–IL-17F
homodimer



IL-17A–IL-17F
heterodimer



IL-17C–IL-17C
homodimer



IL-17E–IL-17E
homodimer

RA-ban a szérum és a synovialis folyadék IL-17 szintje magasabb mint arthrosisban

IL-17 szerepe ismert

Osteoclast differenciálódásban

Synovialis szövet proliferációban

Synovialis érújdonképződés

Proinflammatorikus citokin termelődés

Th17-sejt szabályozó:

Bélflóra

Magas zsírtartalmú ételek

Magas sótartalmú ételek

IL-17 gátlók

ixekizumab

brodalumab

secukinumab

1. Kolls JK & Lindén A. Immunity. 2004; 21(4):467–476
2. Miossec P & Kolls JK. Nat Rev Drug Discov. 2012; 11(10):763–776
3. Kirkham BW et al. Immunology. 2014; 141(2):133–142
4. Martin DA et al. J Invest Dermatol. 2013; 133(1):17–26

1. Alunno A Med Inflamm 2015 ID751793
2. Burkett PR et al JCI 2015; 125; 2211-2219

IV: IL-17A-gátló secukinumab/Cosentyx

- Teljesen humán IL-17A-gátló antitest, amely erősen kötődik és neutralizálja a keringő citokint.
- Gyorsan csökkenti a keringő IL-17A szintjét és az ehhez kapcsolt jelátviteli aktivitásokat



Keringő IL-17A-blokkolók

- Teljesen humán antitest
secukinumab – *indikációk: PsO, PsA, axSpA, JIA, HS*
Alkalmazás: sc.

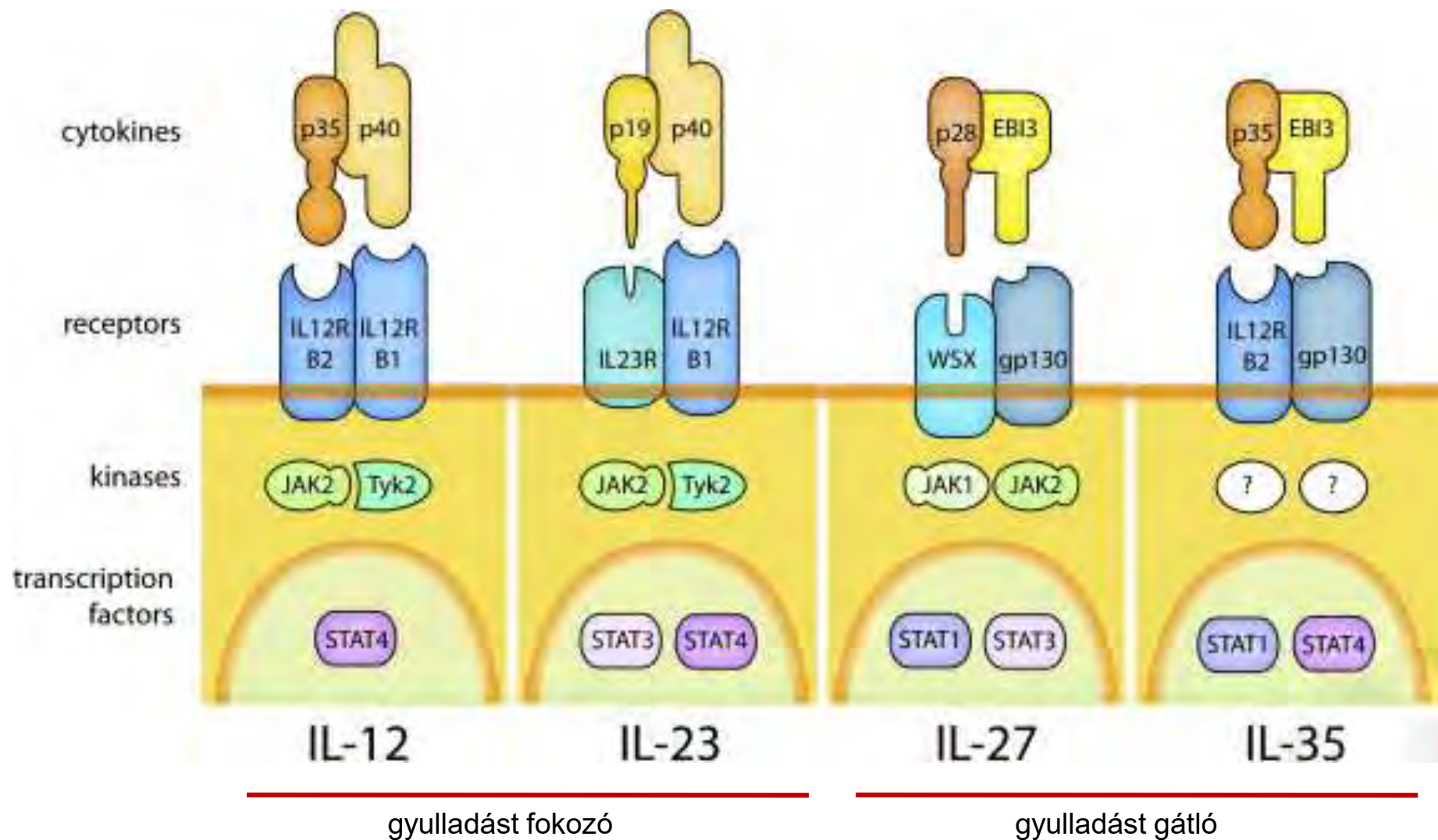
További IL-17 gátlók: brodalumab, ixekizumab, bimekizumab

Miossec P, et al. N Engl J Med. 2009;361:888–898.

Célzott terápiák a reumatológiában

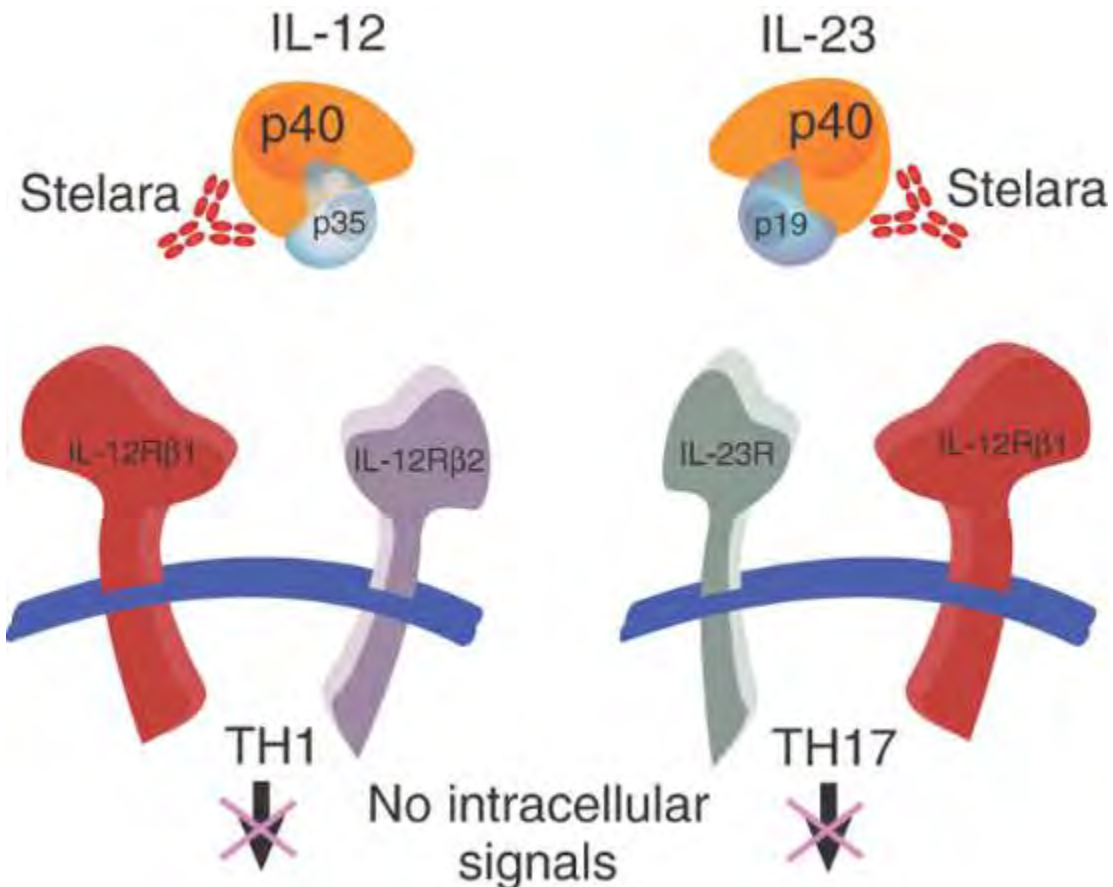
- I: TNF-blokkolás
- II: IL1-blokkolás
- III: IL-6-blokkolás
- IV: IL-17-blokkolás
- V: IL12/23-blokkolás**
- VI: B-sejt-gátlás
- VII: T-sejt-gátlás
- VIII: tsDMARD készítmények
- IX: IVIG
- X: IFN gátlás
- XI: CAR-T kezelés

V: IL-12 citokin család



van Wanrooij RL et al Genetic variations in interleukin-12 related genes in immune-mediated diseases. J Autoimmun. 2012 Jul 17.0

V: Az IL12/23-blokkoló ustekinumab/Stelara



Indikációk: *Crohn-betegség*
PsO, PsA, CB, CU
alkalmazás: *sc és iv*

Mellékhatások:
fertőzések
exfoliatív dermatitis

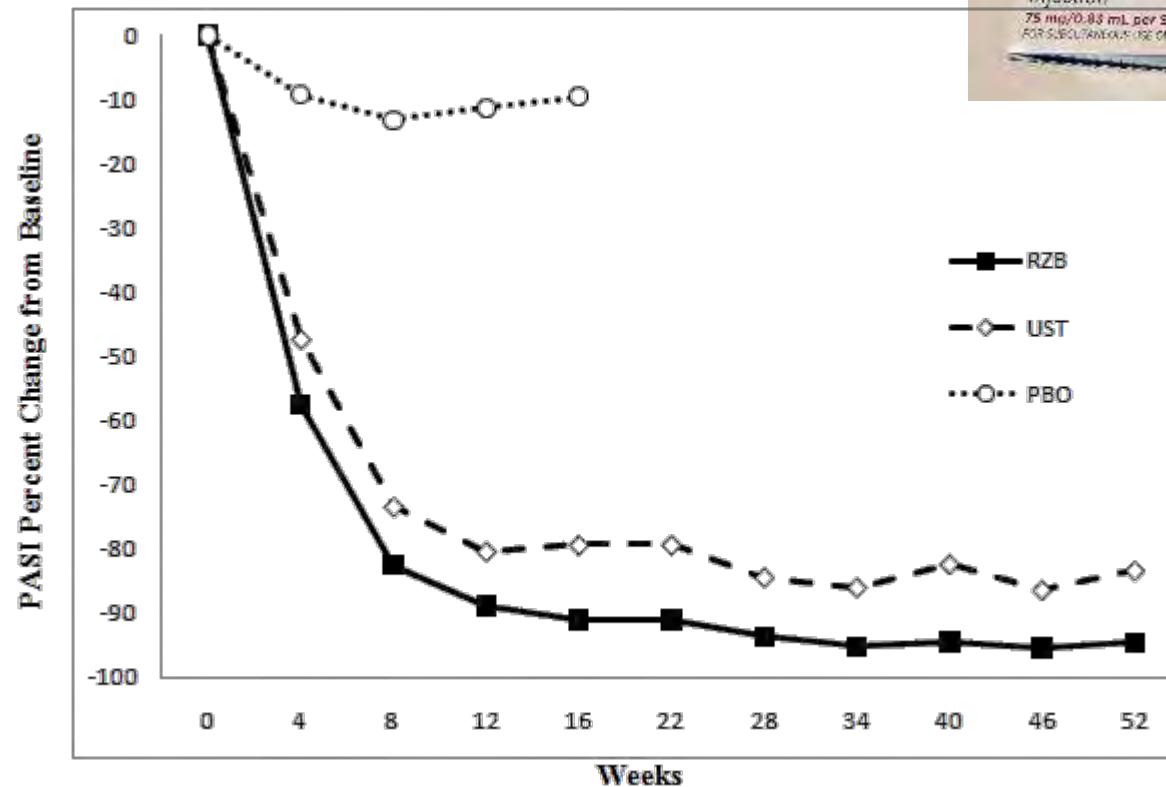
<https://www.nature.com/articles/nbt1208-1317a>

V: IL-23-blokkoló rizamkizumab/Skyrizi

Indikációk:

PsO, PsA, CU, CB

Alkalmazás: sc.



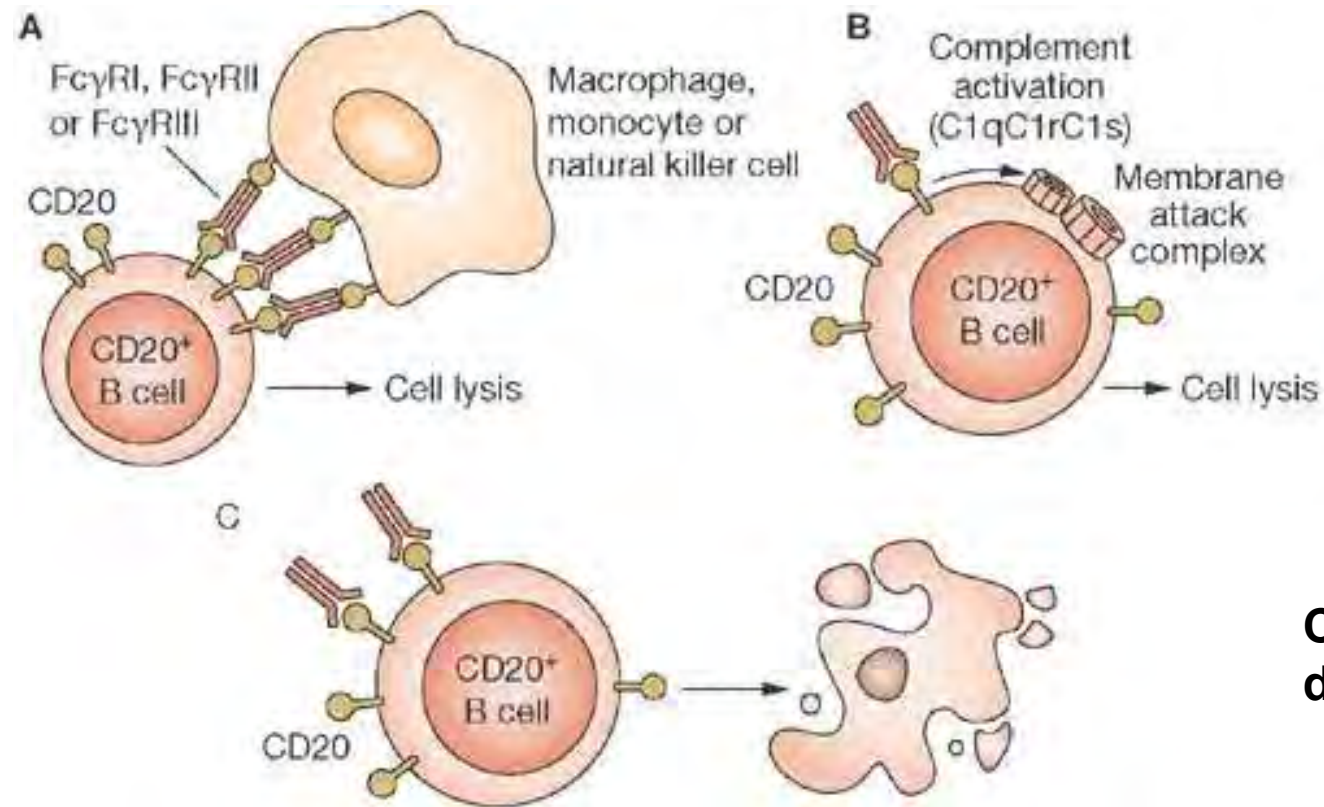
RZB = risankizumab
UST = ustekinumab
PBO = placebo

<https://www.medicines.org.uk/emc/product/10199/smpc>

Célzott terápiák a reumatológiában

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- VII: T-sejt-gátlás
- VIII: tsDMARD készítmények
- IX: IVIG
- X: IFN gátlás
- XI: CAR-T kezelés

VI: a rituximab hatásmechanizmusa



**CD20 + sejtek
depléciója**

Dalakas MC (2008) B cells as therapeutic targets in autoimmune neurological disorders
Nat Clin Pract Neurol 10.1038/ncpneuro0901

VI: rituximab indikációk, mellékhatások

indikációk: *RA, ANCA vasculitis*
Non-Hodgkin's lymphoma (NHL),
chronic lymphocytic leukaemia (CLL) , pemphigus
vulgaris
off label: *SLE, myositis, szisztémás sclerosis*
alkalmazás: *iv.*



mellékhatások

Fertőzések (progresszív multifokális
leukoencephalopathia,
hepatitis B reaktiválódás)

Neutropenia

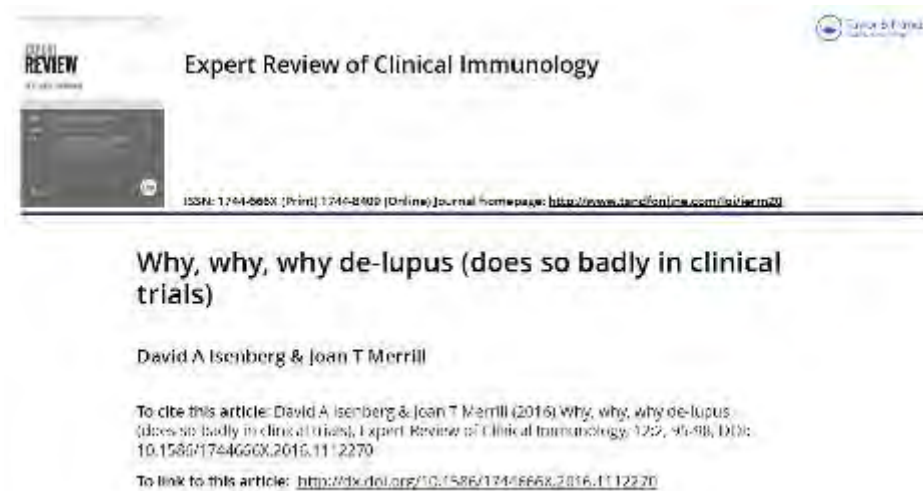
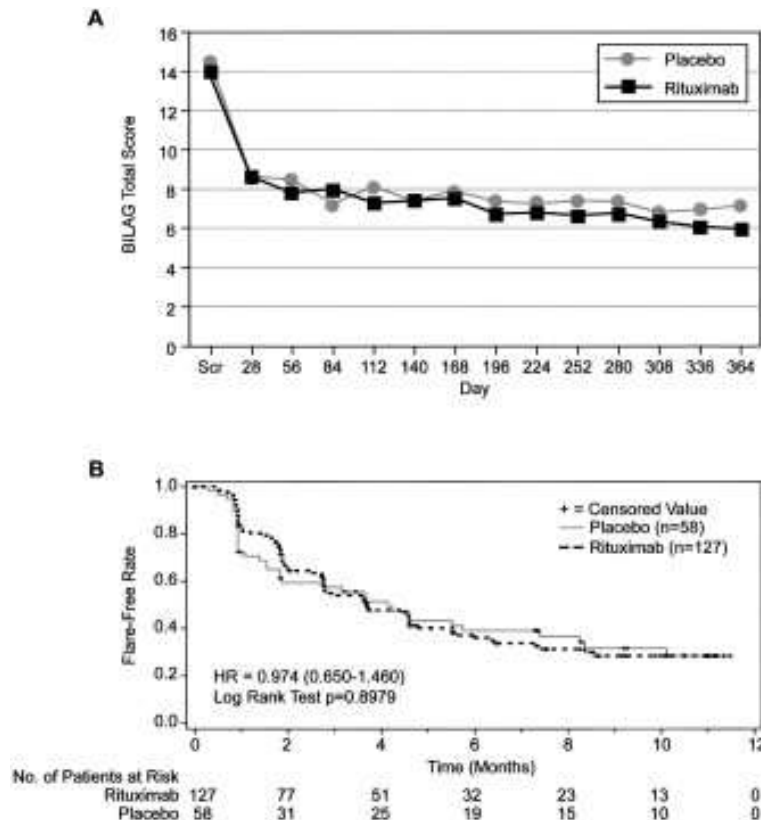
Bőrreakciók, Stevens-Johnson szindróma

Allergia, infúziós reakció



VI: rituximab indikációk, mellékhatások

Rituximab hatékonysága SLE-ben, EXPLORER (fázis II/III) vizsgálat



Arthritis & Rheumatism 222-233, 28 DEC 2009 DOI: 10.1002/art.27233

VI: obinutuzumab LN



Efficacy and Safety of Obinutuzumab in Active Lupus Nephritis

R.A. Furie,¹ B.H. Rovin,¹ J.P. Garg,¹ M.B. Santiago,^{2,3} G. Arcega-Martinez,^{2,3} A.E. Zula Santillan,⁴ D. Alvarez,⁵ C. Navarro Sandoval,^{1,6} A.M. Lila,⁷ J.A. Tumlin,^{7,8} A. Saxena,^{9,10} F. Irazoque Palacios,¹¹ H. Raghu,¹² B. Yoo,¹³ J. Hassan,¹⁴ E. Martin,¹⁵ H. Sehgal,¹⁶ P. Kirchner,¹⁷ J. Rost Torres,¹⁸ T.A. Gensler,¹⁹ T. Schindler,²⁰ W.F. Pendergraft III,¹ and A. Malvar,²¹ for the REGENCY Trial Investigators*

ABSTRACT

BACKGROUND

Obinutuzumab, a humanized type II anti-CD20 monoclonal antibody, provided significantly better renal responses than placebo in a phase 2 trial involving patients with lupus nephritis receiving standard therapy.

METHODS

In a phase 3, randomized, controlled trial, we assigned adults with biopsy-proven active lupus nephritis in a 1:1 ratio to receive obinutuzumab in one of two dose schedules (1000 mg on day 1 and at weeks 2, 24, 36, and 52, with or without a dose at week 50) or placebo. All patients received standard therapy with mycophenolate mofetil, along with oral prednisone at a target dose of 7.5 mg per day by week 12 and 5 mg per day by week 24. The primary end point was a complete renal response at week 76, defined by a urinary protein-to-creatinine ratio of less than 0.5 (with protein and creatinine both measured in milligrams), an estimated glomerular filtration rate of at least 85% of the baseline value, and no intercurrent event (i.e., rescue therapy, treatment failure, death, or early trial withdrawal). Key secondary end points at week 76 included a complete renal response with a prednisone dose of 7.5 mg per day or lower between weeks 64 and 76 and a urinary protein-to-creatinine ratio lower than 0.8 without an intercurrent event.

The authors' full names, academic degrees, and affiliations are listed at the end of the article. Dr. Furie can be contacted at rfurie@northwell.edu or at the Division of Rheumatology, Northwell Health, Donald and Barbara Zucker School of Medicine at Hofstra-Northwell, 865 Northern Blvd., Suite 107, Great Neck, NY 11021.

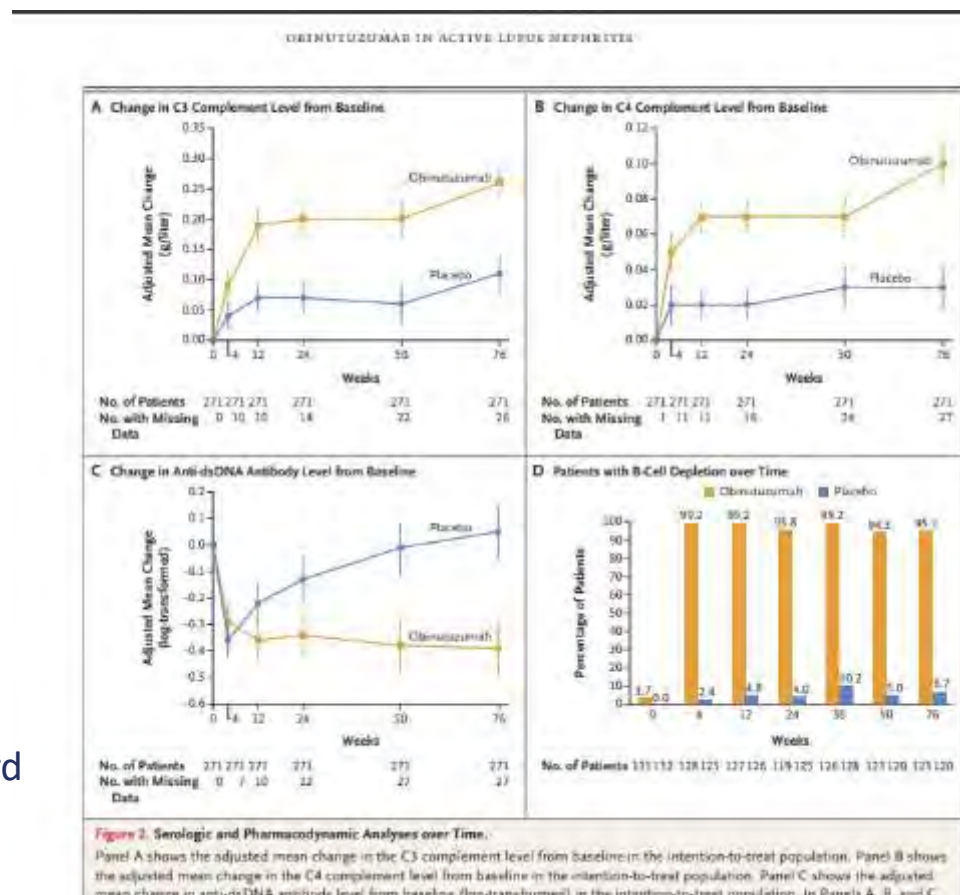
*A list of investigators in the REGENCY trial is provided in the Supplementary Appendix, available at NEJM.org.

This article was published on February 7, 2025, at NEJM.org.

N Engl J Med 2025;392:1475-89.
DOI: 10.1056/NEJMoa2410661
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CME

Among adults with active lupus nephritis, obinutuzumab plus standard therapy was more efficacious than standard therapy alone in providing a complete renal response. (Funded by F. Hoffmann–La Roche; REGENCY ClinicalTrials.gov number, NCT04221477.)



VI: obinutuzumab non-renal SLE

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Efficacy and Safety of Obinutuzumab in Active Systemic Lupus Erythematosus

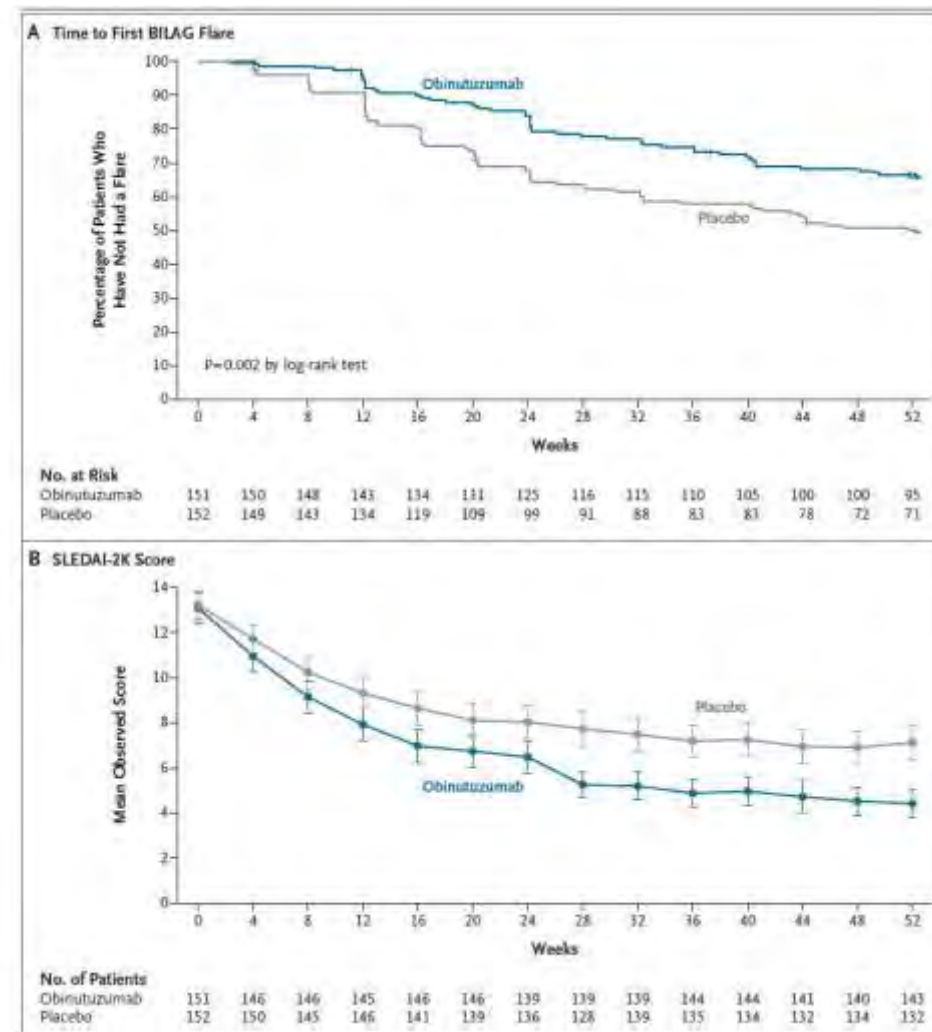
R.A. Furie,^{1,2} M. Dall'Era,³ E.M. Vital,^{4,5} J.P. Garg,⁶ F. Irazoque Palazuelos,⁷
A.E. Zuta Santillán,⁸ J. Ravelo-Hernández,⁹ M.B. Santiago,¹⁰⁻¹²
B. Zazueta Montiel,¹³ S. Botha,¹⁴ P. Leszczyński,¹⁵ V.A. de Souza,¹⁶ S.A. Sicsik,¹⁷
L. Bellatin,¹⁸ A. Naidoo,¹⁹ Z. Amoura,²⁰ M.A. D'Agostino,^{21,22} S. Kumar,²³
B. Workeneh,²⁴ J. Rae,⁶ H.A. Mao,²⁵ F. Erblang,²⁶ O. Meier,²⁶ J.C. Maller,⁶
and A.D. Askanase,²⁷ for the ALLEGORY Trial Investigators*

ABSTRACT

BACKGROUND

Obinutuzumab, a glycoengineered type II anti-CD20 monoclonal antibody, induces potent B-cell depletion and is approved for the treatment of active lupus nephritis. Its

The authors' full names, academic degrees, and affiliations are listed at the end of the article. Richard A. Furie can be



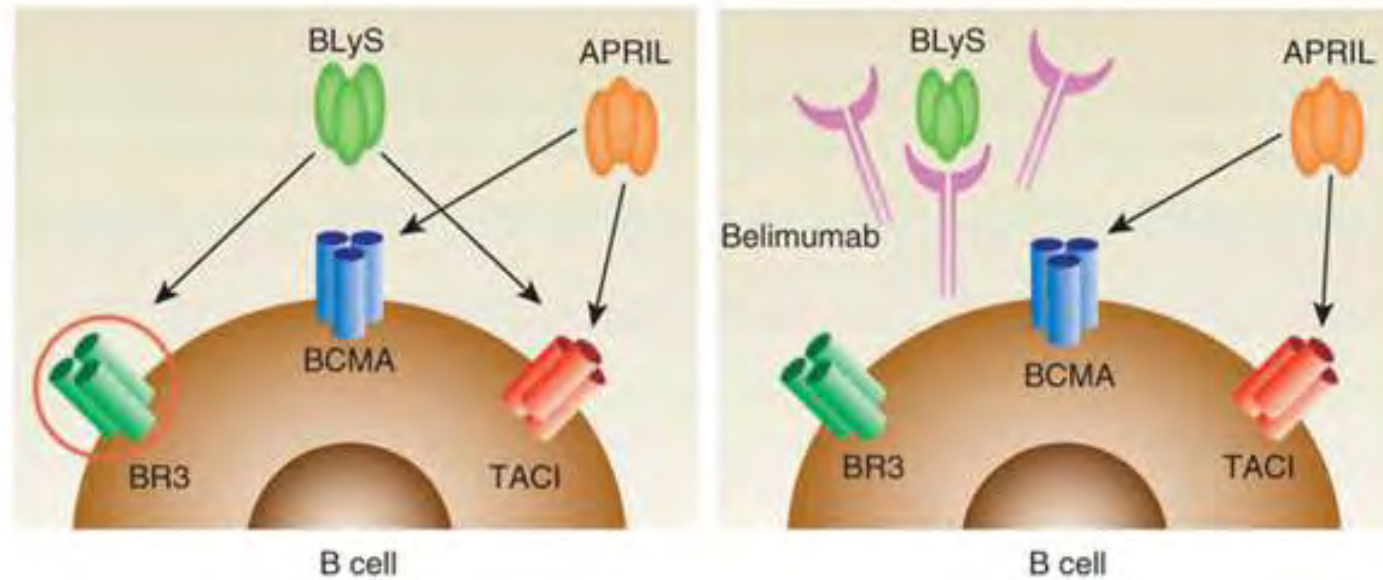
VI: Belimumab (BAFF/BLyS)

Indikáció: SLE, LN
Alkalmazás sc és iv

human monoclonal IgG1 antibody

BENLYSTA is indicated for the treatment of adult patients with active, autoantibody-positive SLE, receiving standard therapy

BUT its therapeutic effect is modest and may decrease over time.....

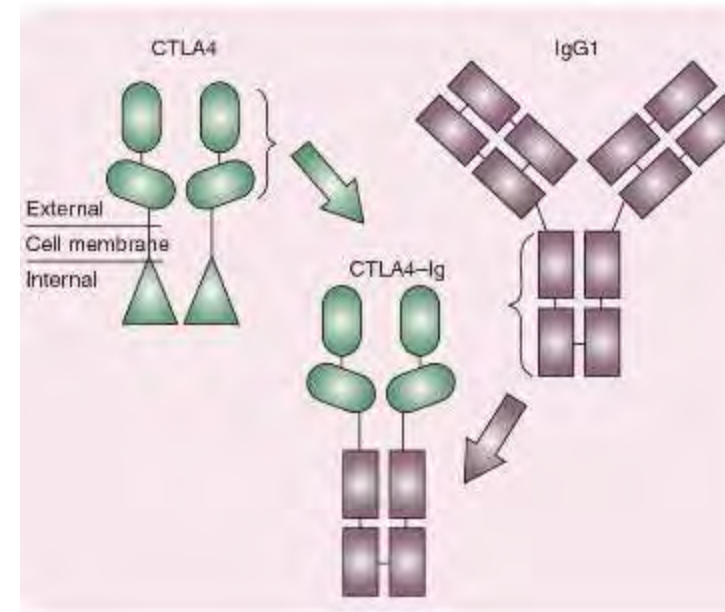
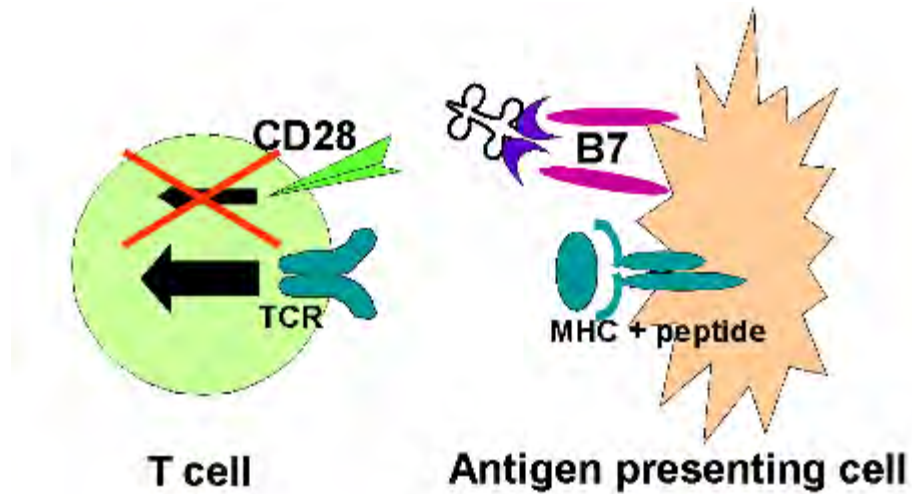


Nature Biotechnology 30, 69-77 (2012) doi:10.1038/nbt.2076

Célzott terápiák a reumatológiában

- I: TNF-blokkolás
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- VI: B-sejt-gátlás
- VII: T-sejt-gátlás**
- VIII: tsDMARD készítmények
- IX: IVIG
- X: IFN gátlás
- XI: CAR-T kezelés

VII: Abatacept, a humán CTLA4 immunoglobulin fúziós protein



**APC aktiváció gátlást is
eredményez!**

<https://www.semanticscholar.org/paper/Abatacept%3A-the-first-in-class-costimulation-blocker-Westhovens/c480b4d30fb498927cd085bf58d06f86379a3e90>

VII: Abatacept biztonságosság

Indikációk: RA, JIA, PsA
Alkalmazás sc és iv.

Sc. adalimumab és
sc. abatacept hasonló hatékonyság
A&R 2013 Weinblatt ME et al.

Fertőzések

Lokális reakció, allergia



Célzott terápiák a reumatológiában

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VIII: JAK3 gén mutációja

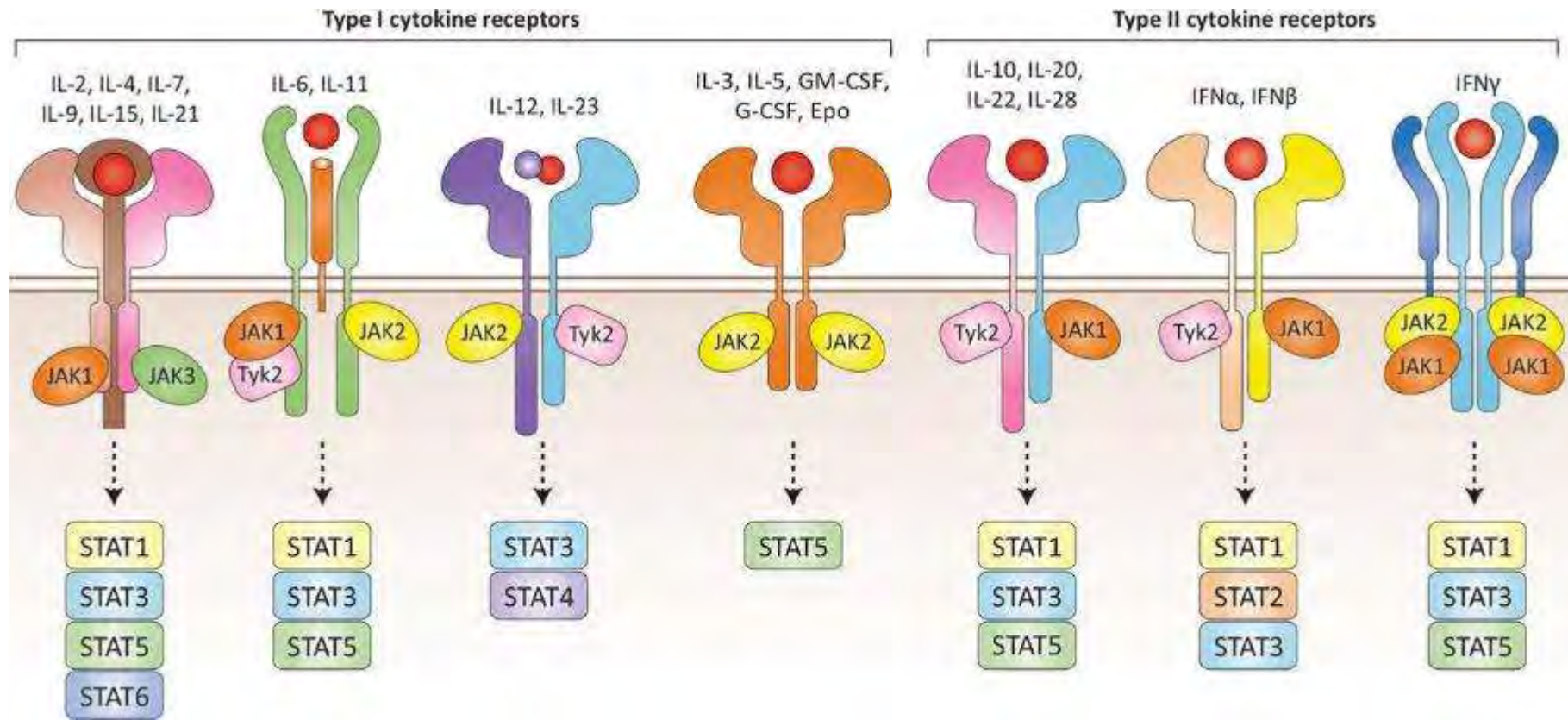
JAK3 gén mutációja a súlyos kombinált immunhiány (SCID) autoszomális recesszív formáját okozza

igen alacsony T-lymphocita szám és funkcionálisan csökkent értékű B-sejtek ú

a SCID-re súlyos fertőzések, hasmenés, atópiás dermatitis és a növekedés elmaradása jellemző



VIII: JAK gátlók



Michael Bonelli et al. Ann Rheum Dis 2024;83:139-160

VIII: JAK gátlók

	RA	PsA	Pso	AS	CD	UC
TNFi					Except etanercept	Except etanercept
IL-6Ri						
IL-1i						
Rituximab						
Abatacept						
IL-17i						
IL-12/23i						
IL-23i						
JAKinibs						

Michael Bonelli et al. Ann Rheum Dis 2024;83:139-160

VIII: JAK gátlók

Drug/JAK			Comparator (versus)								
			State of investigation	Rheumatoid arthritis	Psoriatic arthritis	Ankylosing spondylitis	Chronic plaque psoriasis	Ulcerative colitis	Crohn's disease	Atopic dermatitis	Systemic lupus erythem
Non-selective	Tofacitinib	JAK1-3	versus PLC							(topical)	
			versus TNF(R)i	ADA (NI)	ADA		ETN (NI)				
			State	Approved	Approved	Approved	Phase III ^a	Approved	Phase II	Phase II	Phase I ^c
	Peficitinib	JAK1-3	versus PLC								
			versus TNF(R)i								
			State	Appr. (JPN)			Phase II	Phase II			
	Baricitinib	JAK1,2	versus PLC				8/10 mg ^b				
			versus TNF(R)i	ADA (S)							
			State	Approved			Phase II			Approved	Phase III
Selective	Upadacitinib	JAK1,2	versus PLC								
			versus TNF(R)i	ADA (S)	ADA (NI/S)						
			State	Approved	Approved	Approved		Approved	Approved	Approved	Phase II ^d
	Filgotinib	JAK1	versus PLC								
			versus TNF(R)i	ADA (NI)							
			State	Appr. (EU)	Phase II	Phase II		Approved	Phase II		

Michael Bonelli et al. Ann Rheum Dis 2024;83:139-160

VIII: JAK gátlók

JAK			Infections		Hematologic		Liver and GIT	Thrombosis	Lipids	Others	Malignancies
			Serious	URT	NEU	LYM	TA	VTE	HDL	CREA	Malignancies
			OI	HZ	Hb	PLT	GIP	PE	LDL	CPK	NMSC
Non-selective	Tofacitinib	JAK1-3	↑	↑	↓	↑	↑	↑*	↑	↑	↑*
			↑	↑↑	↔	↑	↔(?)	↑*	↑	↑	↔(?)
	Peficitinib	JAK1-3	↑	↑	↓	↓	↑	↔(?)	↑	↑	↔(?)
			↑	↑↑	↓	↔	↔(?)	↔(?)	↑	↑	↔(?)
	Baricitinib	JAK1,2	↑	↑	↓	↔	↑	↑	↑	↑	↔(?)
			↑	↑↑	↓	↑	↔(?)	↑(?)	↑	↑	↔(?)
Selective	Upadacitinib	JAK1,2	↑	↑	↓	↓	↑	↔(?)	↑	↑	↔(?)
			↑	↑↑	↓	↓	↔(?)	↔(?)	↑	↑	↔(?)
	Filgotinib	JAK1	↑	↑	↔	↔	↔	↔(?)	↑	↔	↔(?)
			↑	↔	↑	↓	↔(?)	↔(?)	↑	↑	↔(?)

Michael Bonelli et al. Ann Rheum Dis 2024;83:139-160

Célzott terápiák a reumatológiában

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- VIII: tsDMARD készítmények
- IX: **IVIG****
- X: IFN gátlás
- XI: CAR-T kezelés

Immunglobulin kezelés alkalmazása

immunglobulin-pótló terápia

csökkent antitestképződéssel járó primer immunhiányos szindrómákban (primer immundeficienciák – PID).

Szekunder immunhiányos állapotokban (szekunder immundeficienciák – SID), olyan betegek esetében, akik súlyos vagy kiújuló fertőzésekben szenvednek és az antimikrobiális terápia hatástalan, valamint igazolt specifikus antitesthiány áll

fenn vagy **a szérum IgG-szintjük <4 g/l.**

Kanyaró elleni, expozíció

Immunglobulin kezelés alkalmazása

immunmoduláns kezelés

primer immun-thrombocytopenia (ITP)

Guillain–Barrészindróma

Kawasaki-betegség

krónikus gyulladásos demyelinisatiós polyradiculoneuropathia (CIDP)

multifocalis motoros neuropathia (MMN)

Továbbá olyan felnőtteknél, akik: immunszuppresszánsokkal, köztük kortikoszteroidokkal kezelt **aktív DM-ben szenvednek**, illetve akiknél ezekkel a gyógyszerekkel szemben intolerancia vagy ellenjavallat áll fenn

off label: SLE, myositis, szisztémás sclerosis, ANCA

Immunglobulin kezelés mellékhatások

anphalaxiás reakció (IgA hiány)

veseelégtelenség

aszéptikus meningitis

haemalytikus anaemia

tüdőoedema

thromboemboliás szövődmények



Célzott terápiák a reumatológiában

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- XI: CAR-T kezelés

Interferonok és dendritikus sejtek SLE-ben

Induction of Dendritic Cell Differentiation by IFN- α in Systemic Lupus Erythematosus

Patrick Blanco,^{1*} A. Karolina Palucka,^{1*} Michelle Gill,^{1,2} Virginia Pascual,^{1,2} Jacques Banchereau^{1†}

Dendritic cells (DCs) are important in regulating both immunity and tolerance. Hence, we hypothesized that systemic lupus erythematosus (SLE), an autoimmune disease characterized by autoreactive B and T cells, may be caused by alterations in the functions of DCs. Consistent with this, monocytes from SLE patients' blood were found to function as antigen-presenting cells, *in vitro*. Furthermore, serum from SLE patients induced normal monocytes to differentiate into DCs. These DCs could capture antigens from dying cells and present them to CD4-positive T cells. The capacity of SLE patients' serum to induce DC differentiation correlated with disease activity and depended on the actions of interferon- α (IFN- α). Thus, unabated induction of DCs by IFN- α may drive the autoimmune response in SLE.

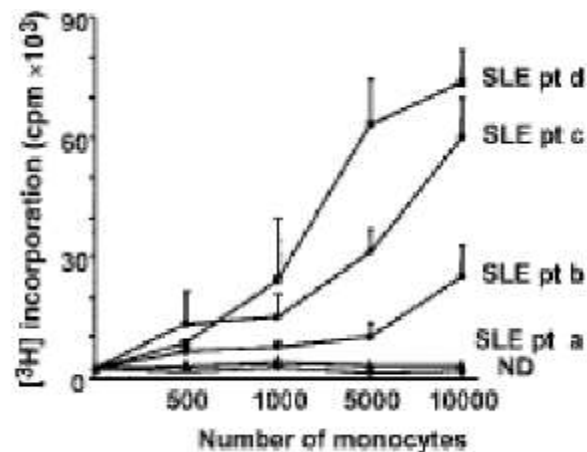
Lupus (SLE) is a systemic autoimmune disease characterized by a waxing and waning course and the involvement of multiple organs, including skin, kidneys, and central nervous system (1). Although SLE etiology is poorly understood, there is likely a role for environmental triggers, for instance viruses, acting in the context of susceptibility genes (2, 3). Now, SLE therapy is based on

nonspecific immunosuppression and symptom control, however, no cure for SLE has been found, and that is particularly needed for children, whose disease often progresses to chronic renal failure and/or death (1). Among the immunological features of SLE are high titers of autoantibodies predominantly specific for DNA and nucleosomes (4, 5). Paradoxically, polyclonal hypergammaglobulinemia, high plasma cell numbers, and an increased frequency of pre-germinal center B cells (6, 7) coincide with considerable B lymphopenia. Likewise, autoreactive T cells are found in the blood despite T lymphopenia (8, 9). The systemic autoimmune response that characterizes SLE might be explained by alter-

¹Baylor Institute for Immunology Research, Dallas, TX 75204, USA. ²The University of Texas Southwestern Medical Center at Dallas, Dallas, TX 75390, USA.

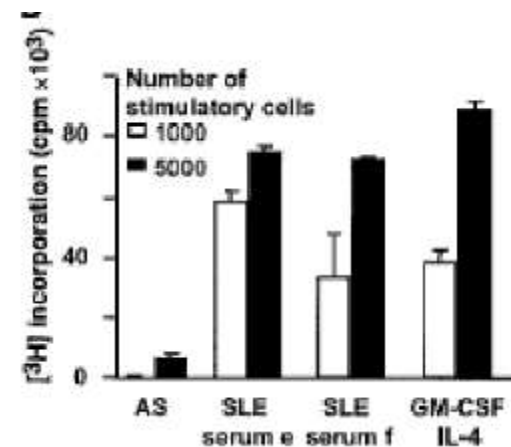
*These authors contributed equally to this work. †To whom correspondence should be addressed. E-mail: j.banchereau@bayloridallas.edu

118ER 2001 VOL 294 SCIENCE www.sciencemag.org



SLE moniciták
CD4-sejt
proliferációt
okoznak

HD moniciták SLE
szérummal
történő
inkubálást
követően CD4-
sejt
proliferációt
okoznak



Dendritikus sejtek

Nobel Prizes & Laureates | Nomination | Alfred Nobel | News & insights | Events | Educational

Medicine | The Nobel Prize In Physiology or Medicine 2011 | Ralph M. Steinman - Biographical

The Nobel Prize In Physiology or Medicine 2011

Bruce A. Beutler
Jules A. Hoffmann
Ralph M. Steinman

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Ralph M. Steinman Biographical

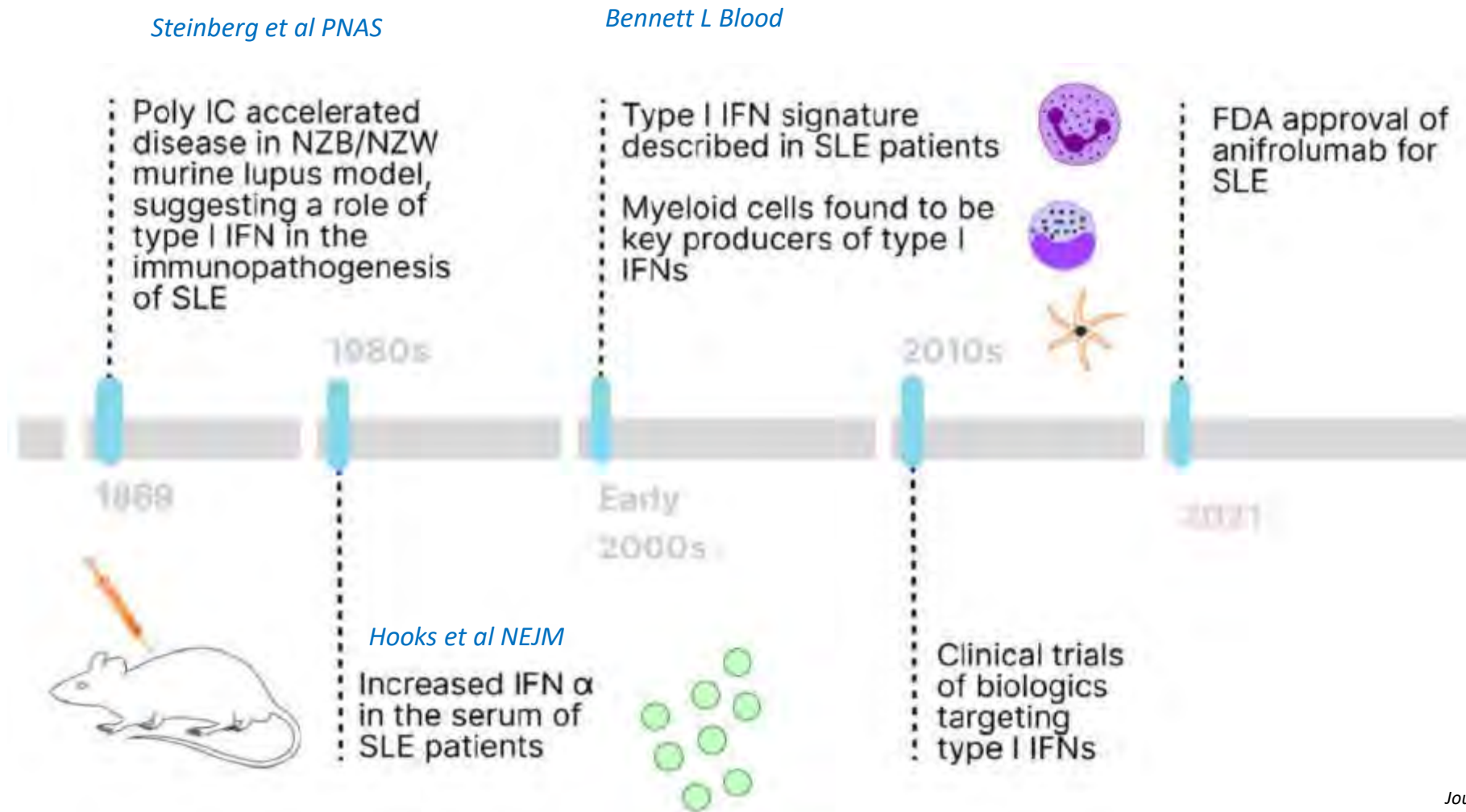


Ralph M. Steinman was born in Montreal, Canada, on 14 January 1943, the second of four children. His father Irving, a Jewish immigrant from Eastern Europe, and his mother Nettie owned a department store in Sherbrooke near Montreal. His father wanted him to continue in the family business, but in high school Ralph became interested in science. He received a B.S. with honors from McGill University in 1963, and an M.D. magna cum laude from Harvard Medical School in 1968. While at Harvard, he spent a year as a research fellow in the laboratory of Elizabeth Hay, who introduced him to cell biology and the immune system. During his internship and residency at the Massachusetts General Hospital, Steinman met Claudia Hoeffel, who was a medical social worker in the hospital. They married in 1971.

In 1973, Steinman and Cohn discovered dendritic cells, a previously unknown class of immune cells that constantly formed and retracted their processes. This discovery changed the field of immunology.

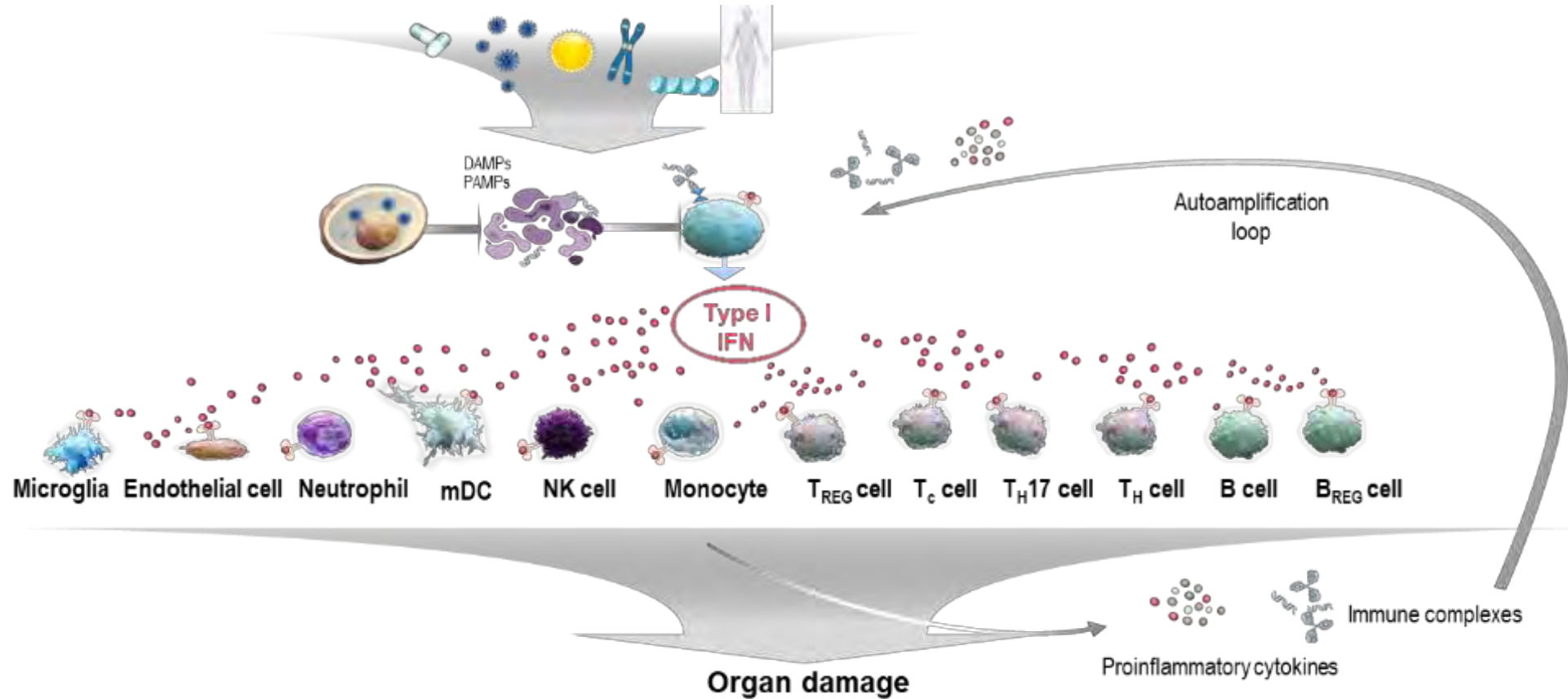
Steinman died on 30 September 2011, three days before his Nobel Prize was announced. Unaware of his death at the time of its announcement, the Nobel Committee made an unprecedented decision that his award would stand.

Anifrolumab, mérföldkövek SLE-ben



Sim, T.M et al A
Journey from Bench to Bedside. Int. J.
Mol. Sci. 2022, 23, 2505.

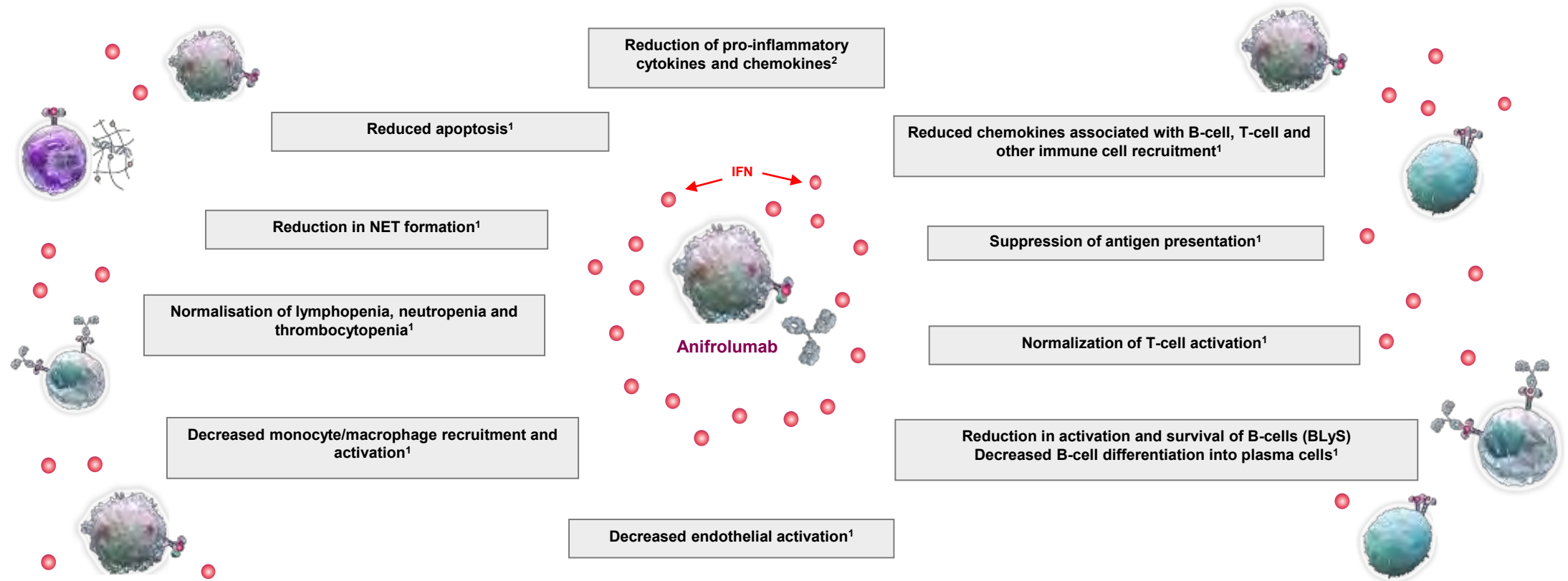
Interferonok SLE-ben



1. Rönnblom L, Leonard D. *Lupus Sci Med*. 2019;6(1):e000270. 2. West PK, et al. *Glia*. 2019;67(10):1821-1841. 3. Menon M, et al. *Immunity*. 2016;44(3):683-697. 4. Chan VS, et al. *Autoimmun Rev*. 2012;11(12):890-897. 5. Liu Z, Davison A. *Nat Med*. 2012;18(6):871-882.

Az anifrolumab hatásmechanizmusa SLE-ben

Anifrolumab-mediated changes to immune modulators may disrupt type I IFN and decrease SLE-associated inflammation and damage



1. Casey KA, et al. *Lupus Sci Med.* 2018;5(1):e000286. 2. Casey KA, et al. *Arthritis Rheumatol.* 2021;73(3):459-471.

IFN-blokkolás SLE-ben (anifrolumab/Saphnelo)

Indikációk: autoantitest pozitív SLE Alkalmazás iv.

Drugs (2021) 47:1795–1803
<https://doi.org/10.1007/s40265-021-01609-z>

ADISINSIGHT REPORT

Anifrolumab: First Approval

Emma D. Dewa¹

Published online: 23 September 2021
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Abstract

Anifrolumab (anifrolumab-tris, Saphnelo[®]) is a monoclonal antibody antagonist of the type I interferon receptor (IFNAR). It is being developed by AstraZeneca (under license from MedImmune, now Bristol-Myers Squibb) for the treatment of autoimmune disorders, including systemic lupus erythematosus (SLE) and lupus nephritis, the underlying pathogenesis of which involves type I interferon. In July 2021, intravenous anifrolumab was approved in the USA for the treatment of adult patients with moderate to severe SLE who are receiving standard therapy. Anifrolumab (intravenous or subcutaneous) continues to be assessed in clinical studies in SLE in various countries, and the intravenous formulation is under regulatory review in the EU and Japan. This article summarizes the milestones in the development of anifrolumab leading to this first approval for the treatment of moderate to severe SLE.

Digital Features for this Adisinsight Report can be found at
<https://doi.org/10.6084/m9.figshare.16564056>

Anifrolumab (Saphnelo[®]): Key Points

IFNAR antagonist being developed by AstraZeneca for the treatment of autoimmune disorders, including SLE and lupus nephritis.

Received its first approval on 30 July 2021 in the USA.

Approved for the treatment of adult patients with moderate to severe SLE who are receiving standard therapy.

Saphnelo approved in the EU for the treatment of moderate to severe systemic lupus erythematosus

Approved:
23 February 2022

EMA/CHMP/2021/0015

Saphnelo is a monoclonal type I interferon receptor antibody and the only drug available to date to be used for patients with systemic lupus erythematosus.

Anifrolumab (Saphnelo) is a monoclonal antibody that acts as an antagonist of the type I interferon receptor (IFNAR). It is being developed by AstraZeneca (under license from MedImmune, now Bristol-Myers Squibb) for the treatment of autoimmune disorders, including systemic lupus erythematosus (SLE) and lupus nephritis, the underlying pathogenesis of which involves type I interferon.

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Key milestones in the development of anifrolumab for the treatment of systemic lupus erythematosus. BLA Biological License Application

IFN-blokkolás SLE-ben (anifrolumab/Saphnelo)



OPEN ACCESS

CLINICAL SCIENCE

Anifrolumab efficacy and safety by type I interferon gene signature and clinical subgroups in patients with SLE: post hoc analysis of pooled data from two phase III trials

Edward M Vittal,^{1,2} Joan T Merrill,¹ Eric F Morand,¹ Richard A Furie,³ Ian N Bruce,^{6,7} Yoshiya Tanaka,⁸ Susan Manzi,⁹ Kenneth C Kalunian,¹⁰ Rubana N Kalyani,¹¹ Katie Streicher,¹¹ Gabriel Abreu,¹² Raj Tummala¹¹

Handling editor: Joel S. Spector

► Additional supplemental material is published on the open access journal *Open Access Rheumatology* (<http://dx.doi.org/10.1186/s13075-021-02143-1>).

For numbered affiliations see end of article.

Correspondence to: Dr Raj Tummala, Biopharmaceutical R&D, AstraZeneca US, Gaithersburg, Maryland, USA; raj.tummala@astrazeneca.com

Received: 27 August 2021
Accepted: 16 January 2022

ABSTRACT

Objectives To characterise the efficacy and safety of anifrolumab in patients with systemic lupus erythematosus (SLE) according to interferon gene signature (IFNGS), demographic and clinical subgroups.

Methods We performed post hoc analyses of pooled data from the 52-week phase III TULIP-1/TULIP-2 placebo-controlled trials of intravenous anifrolumab in moderate-to-severe SLE. Outcomes were assessed in predefined subgroups: IFNGS (high/low), age, sex, body mass index, race, geographic region, age of onset, glucocorticoid use, disease activity and serological markers.

Results In pooled data, patients received anifrolumab 300 mg (366/726) or placebo (366/726); 82.8% were IFNGS high. IFNGS high patients had greater baseline disease activity and were more likely to have abnormal serological markers versus IFNGS-low patients. In the total population, a greater proportion of patients

Key messages

What is already known about this subject?

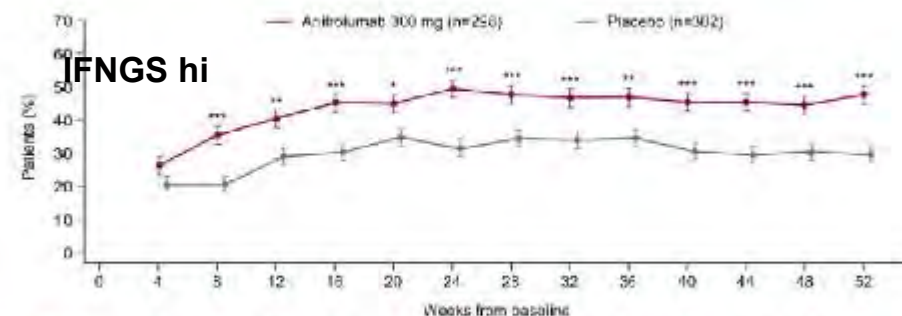
- Systemic lupus erythematosus (SLE) is a heterogeneous disease, in which aspects of patient demographics and clinical characteristics are associated with disease severity and therapeutic response.
- Anifrolumab, a human monoclonal antibody that binds the type I interferon receptor subunit 1, has demonstrated efficacy with an acceptable safety profile in patients with moderate-to-severe SLE in phase III clinical trials.

What does this study add?

- This pooled analysis of two phase III trials adds to the knowledge of the efficacy and safety of

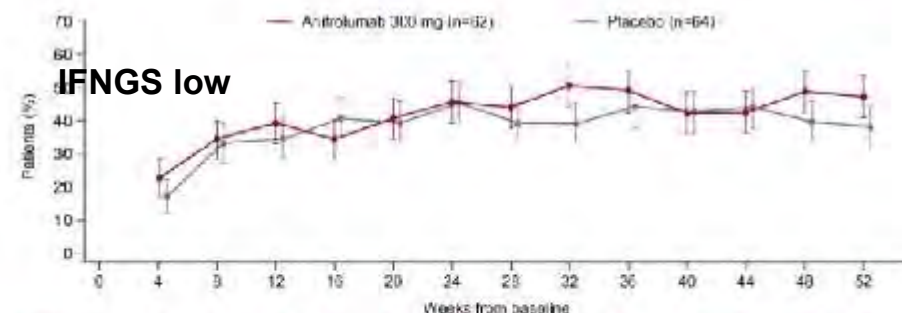
Systemic lupus erythematosus

A



Anifrolumab 300 mg n= 296 296 296 296 296 296 296 296 296 296 296 296 296
Placebo n= 302 302 302 302 302 302 302 302 302 302 302 302 302

B



Anifrolumab 300 mg n= 62 62 62 62 62 62 62 62 62 62 62 62 62
Placebo n= 64 64 64 64 64 64 64 64 64 64 64 64 64

Figure 4 BICLA response estimates and SEs from weeks 4–52 in (A) type I IFNGS-high and (B) IFNGS-low patients in pooled TULIP data. The percentage of responders was calculated using a stratified Cochran-Mantel-Haenszel approach, with stratification factors: SLEDAI-2K score at screening, baseline GC dosage and study. Points represent response estimates plotted with SE. *Nominal $p < 0.05$; **nominal $p < 0.01$; ***nominal $p < 0.001$. BICLA, British Isles Lupus Assessment Group-based Composite Lupus Assessment; GC, oral glucocorticoid; IFNGS, interferon gene signature; SLEDAI-2K, Systemic Lupus Erythematosus Disease Activity Index 2000.



SEMMEIWEIS
EGYETEM 1769

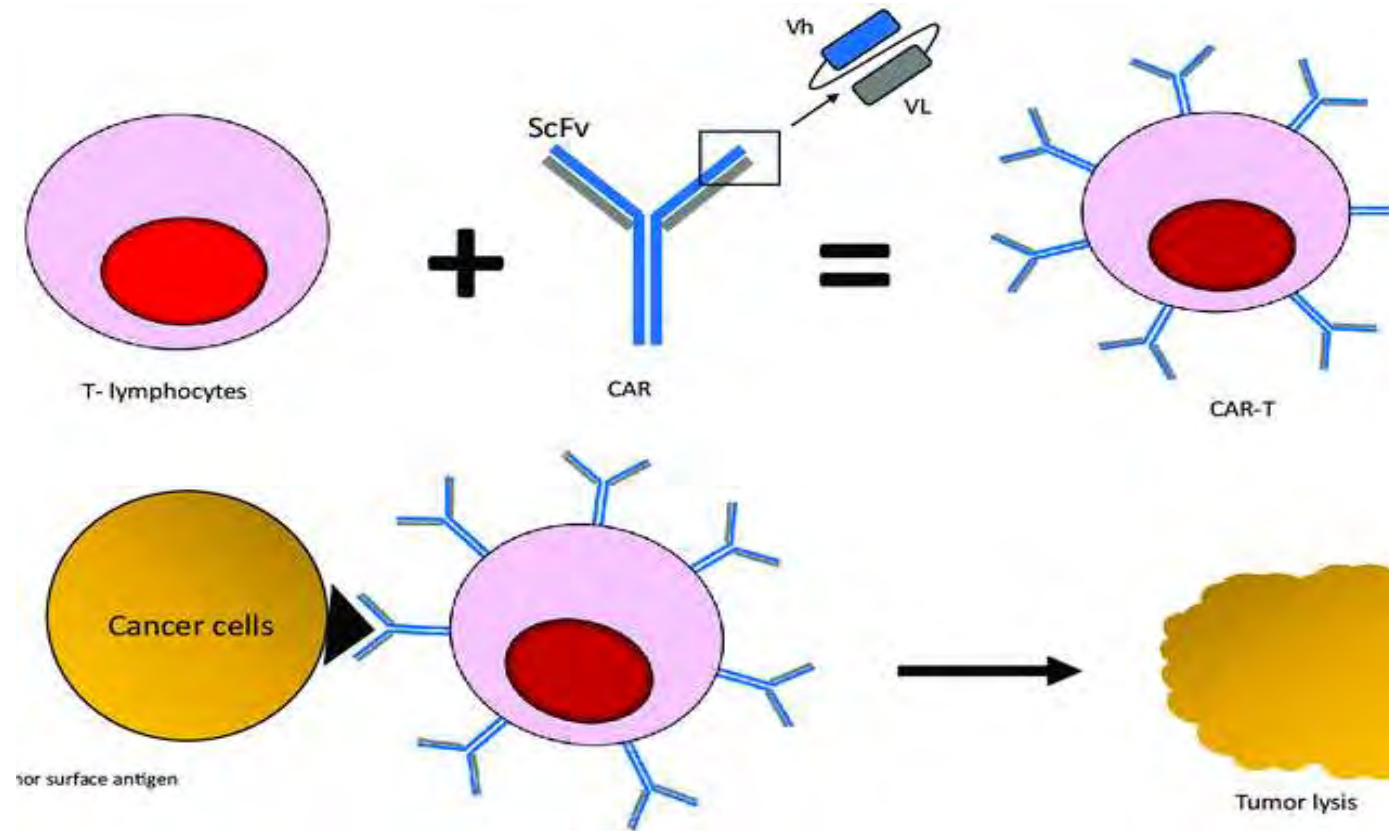
Reumatológiai és Immunológiai Klinika

Prof. Dr. Nagy György

Célzott terápiák a reumatológiában

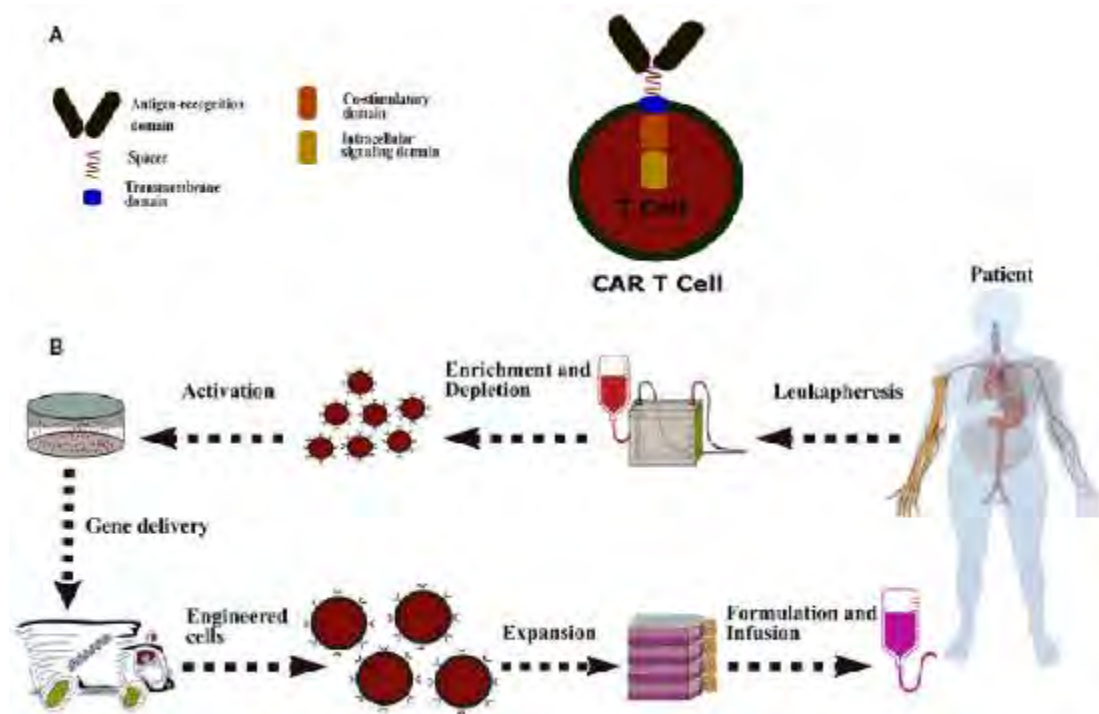
- I: TNF-blokkolás
- II: IL1-blokkolás
- III: IL-6-blokkolás
- IV: IL-17-blokkolás
- V: IL12/23-blokkolás
- VI: B-sejt-gátlás
- VII: T-sejt-gátlás
- VIII: tsDMARD készítmények
- IX: IVIG
- X: IFN gátlás
- XI: CAR-T kezelés**

CAR-T koncepció, T-sejt, B-sejt



https://www.researchgate.net/figure/The-basic-principle-of-CAR-T-cell-therapy-a-T-lymphocytes-are-genetically-modified-to_fig2_351201877

CAR-T sejt kezelés alkalmazás



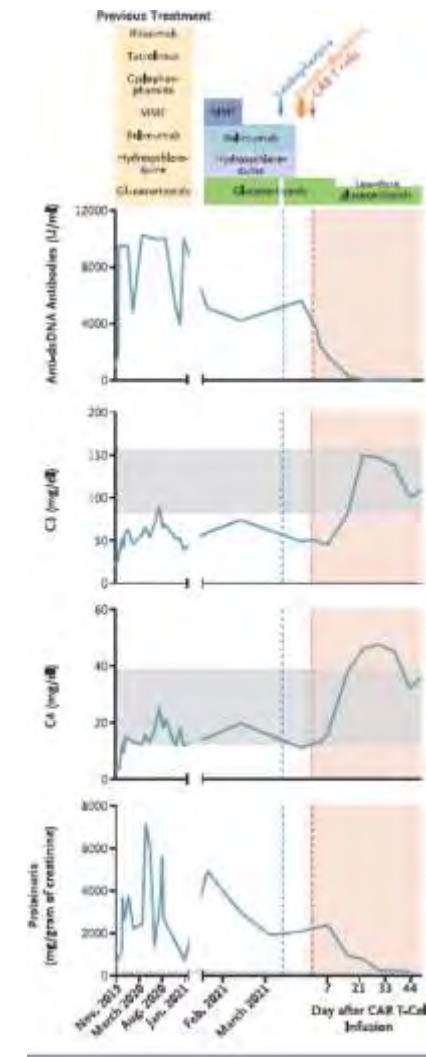
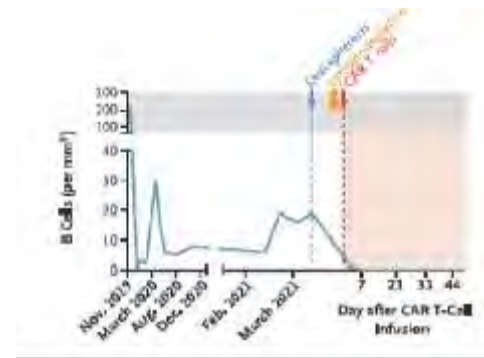
Egyesíti a B-sejt Ag-felismerő és a T-sejt effektor funkciókat

B-sejt lymphoma, ALL, MM hematológiai malignus betegségekben hatékony kezelés
MH: CRS 54-91%, terápia, szteroid, anti-IL6, anti-IL1, Solid tumorokban?

B-sejtek jó terápiás célpont több gyulladásos reum. betegségben, CD19
targetálás jelentősebb B-sejt depletiok okozhat mint CD20

Sadeqi Nezhad M et al Front. Immunol. 11:603237.
doi: 10.3389/fimmu.2020.603237

CAR-T sejt kezelés SLE-ben



20- éves SLE-s nő autolog CD-19 CAR-T sejt sikeres kezeléséről számolnak be, LN, pericarditis, arthritis, bőrérintettség és Libman-Sacks endocarditis

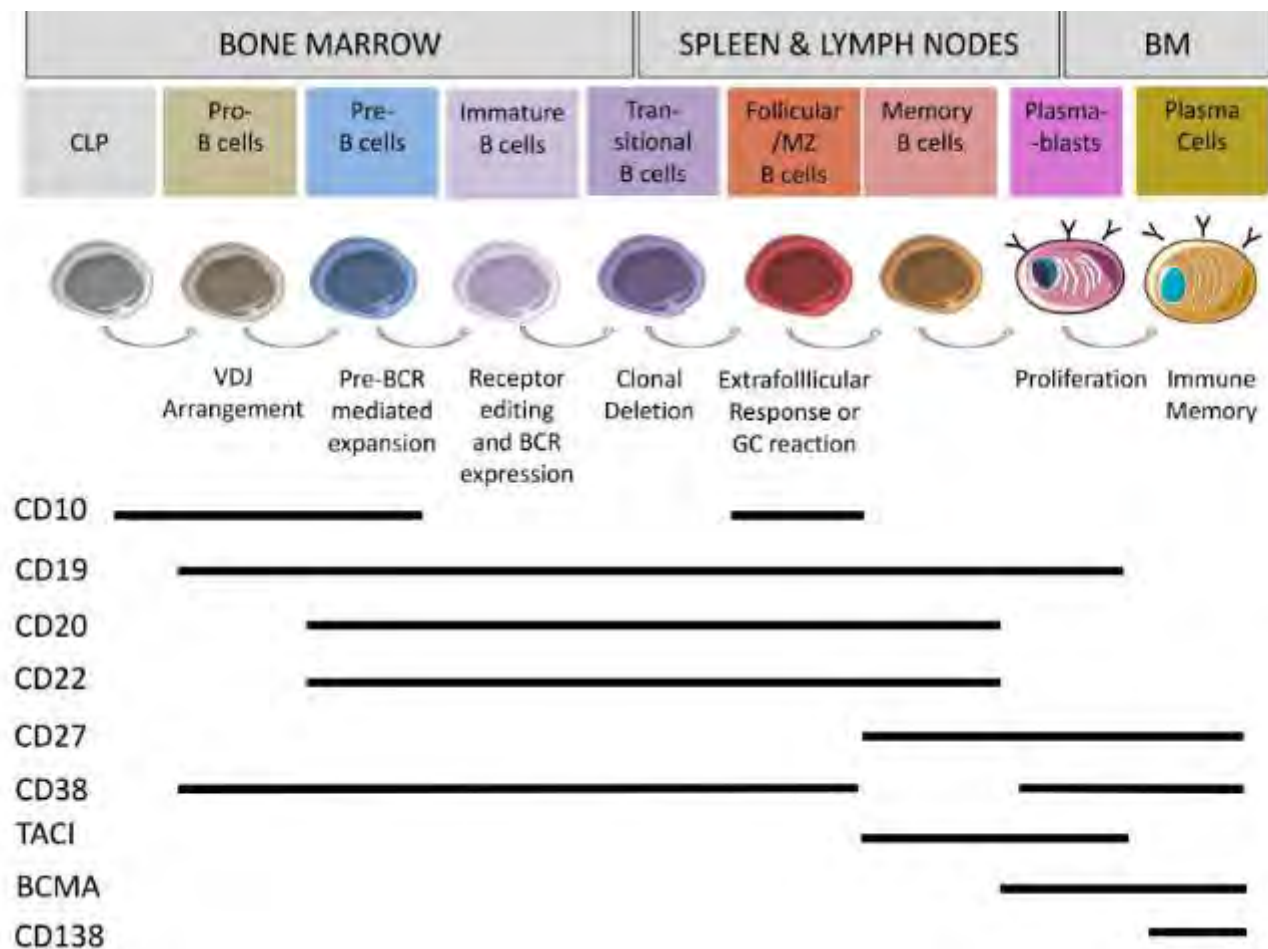
Korábbi sikertelen kezelések: hydrochloroquine, nagy dózis szteroid, cyclophosphamide, MMF, tacrolimus, belimumab, RTX

CAR-T kezelés előtt lymphodepletio fludarabin + cyclophosphamide, kis dózis szteroid $1,1 \times 10^6$ CD19 CAR-T/ttskg (CD4/CD8: 3/1)

Anti DNA 5000-4 csökkent, mh nem volt
CD19 CAR-T vs RTX

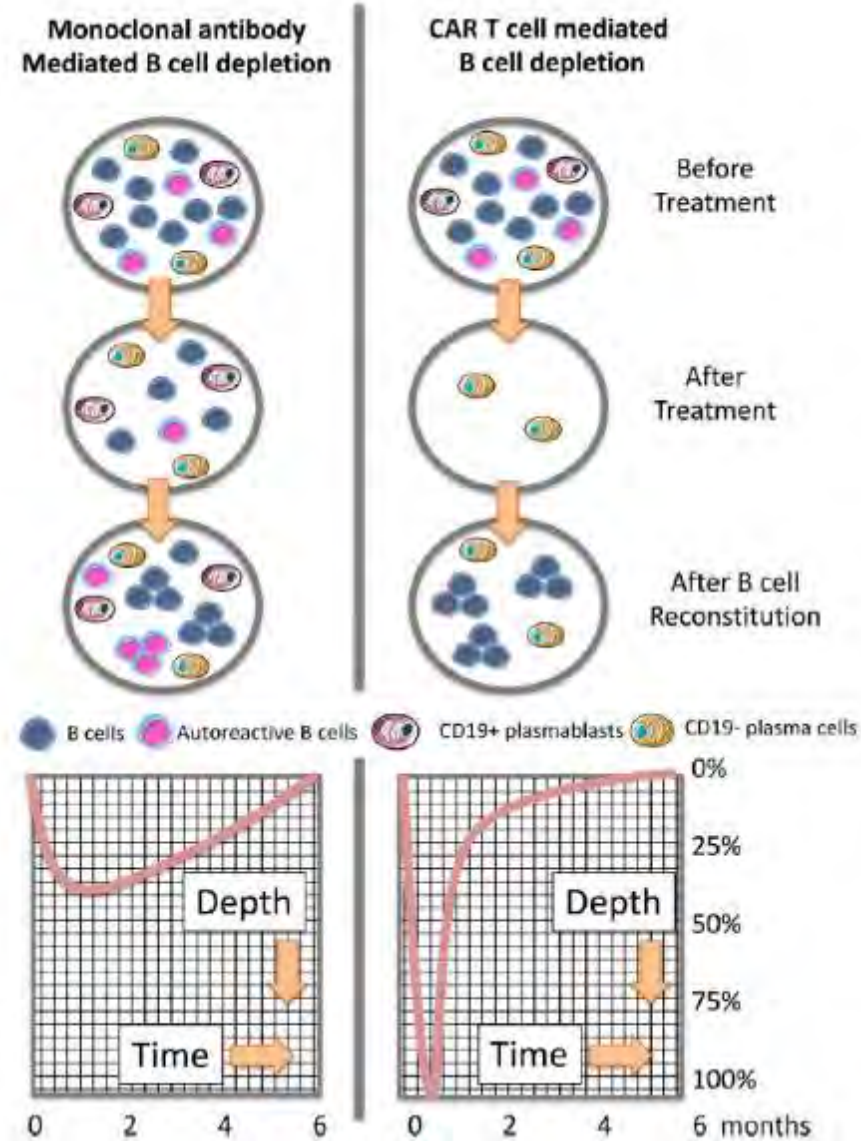
Mougiakakos D et al N Engl J Med. 2021 Aug 5;385(6):567-569. doi: 10.1056/NEJMc2107725. PMID: 34347960.

CD19/20 B sejtek



Schett G, Nagy G, Krönke G, *et al* B-cell depletion in autoimmune diseases
Annals of the Rheumatic Diseases 2024;**83**:1409-1420.

Az antitest alapú (a-CD20) és sejt alapú (a-CD19 CAR-T) sejtdepléció AIB-ben



Schett G, Nagy G, Krönke G, *et al* B-cell depletion in autoimmune diseases
Annals of the Rheumatic Diseases 2024;**83**:1409-1420.

CAR-T sejt kezelés systemás sclerosisban

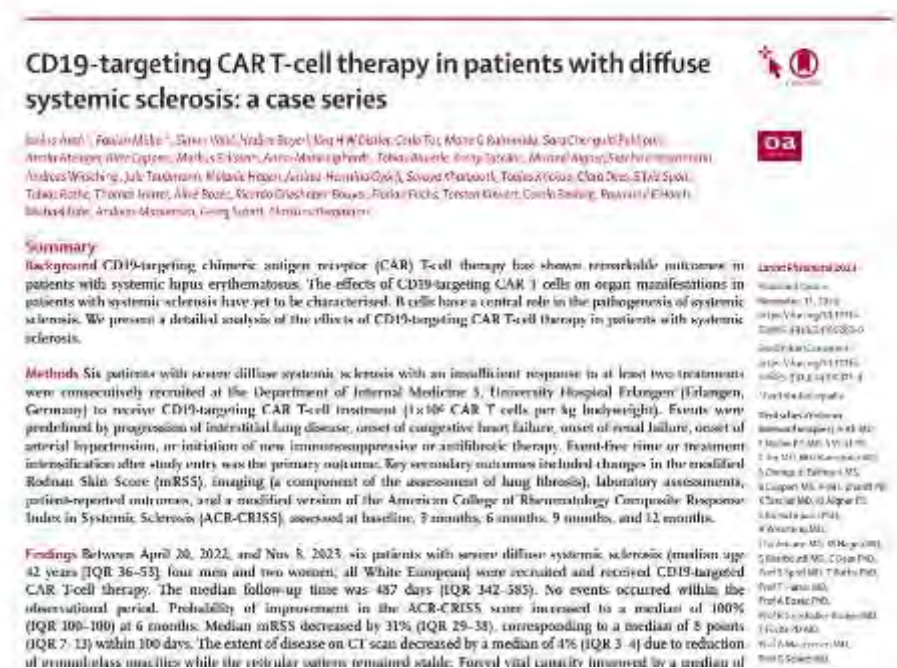
Hat súlyos diffúz szisztémás szklerózisban szenvedő beteget kezeltek, akik legalább két kezelésre nem reagáltak megfelelően.

CD19-célzó CAR T-sejt kezelés

SSc események: intersticiális tüdőbetegség progressziója, pangásos szívelégtelenség kialakulása, veseelégtelenség kialakulása, artériás magas vérnyomás kialakulása vagy új immunszuppresszív vagy antifibrotikus terápia megkezdése.

Az eseménymentes idő vagy a kezelés intenzifikálása a vizsgálatba való belépés után volt az elsődleges eredmény.

A kulcsfontosságú másodlagos eredmények a módosított Rodnan bőrpontszám (mRSS), képalkotás (tüdőfibrozis), laboratóriumi értékelések változásai voltak.



CAR-T sejt kezelés systemás sclerosisban

2022. április 20. és 2023. november 8. között hat súlyos diffúz szisztémás sclerosisban szenvedő beteget vettek be a vizsgálatba, akik CD19-célzott CAR T-sejt terápiában részesültek.

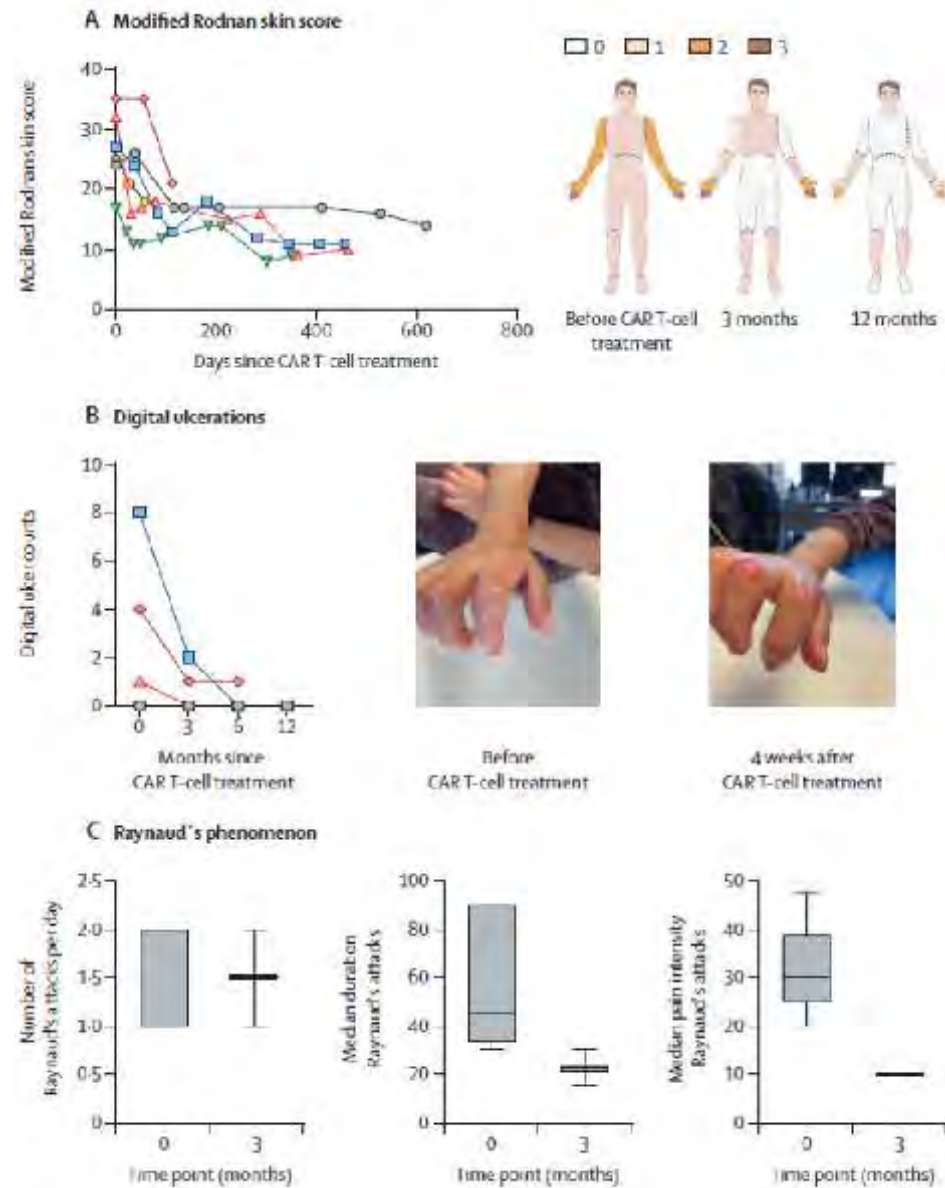
A megfigyelési időszakban semmilyen SSc esemény nem történt.

A medián mRSS 31%-kal csökkent, ami 8 pont mediánnak felel meg 100 napon belül.

A CT-vizsgálat során a fibrosis mértéke átlagosan 4%-kal csökkent (GGO)

FVC 195 ml-rel javult

CAR-T sejt kezelés systemás sclerosisban



CAR-T sejtek RA-ban

Rheumatoid arthritis

RMD Open
 Rheumatic & Musculoskeletal Diseases

CLINICAL CASE

Sustained drug-free remission in rheumatoid arthritis associated with diffuse large B-cell lymphoma following tandem CD20-CD19-directed non-cryopreserved CAR-T cell therapy using zamtocabtagene autoleucel

David Szabo^{1,2}, Alexandra Balogh², Laszlo Gopcsa², Laura Giba-Kiss², Gergely Lakatos², Melinda Paksi², Mariann Reti², Peter Takacs¹, Pearl van Heteren¹, Gregor Zadocyan¹, Silke Holtkamp¹, Toon Overstijns^{1,3}, Stefan Miltenyi^{1,3}, Peter Remenyi², György Nagy^{2,4}

ABSTRACT
 We report the case of long-term persisting rheumatoid arthritis (RA), treated with CD20-CD19 CAR-T when it became associated with diffuse large B cell lymphoma (DLBCL), resulting in a sustained drug-free remission of the preceding RA, as well as of the subsequent DLBCL, that formed the indication of the CAR-T therapy using zamtocabtagene autoleucel, with a 1-year follow-up. According to our best knowledge, this is the first published clinical case report of long-term persisting RA treated with CAR-T cell therapy.

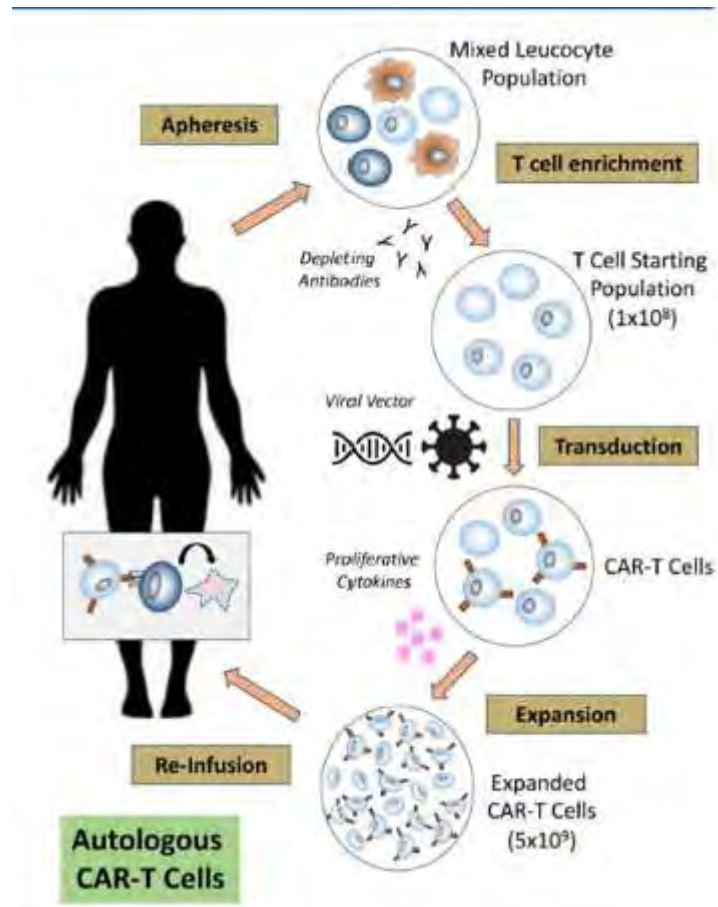
INTRODUCTION

WHAT IS ALREADY KNOWN ON THIS TOPIC
 ⇒ Rheumatoid arthritis (RA) is a B cell-driven systemic autoimmune disease characterised by synovial inflammation of joints leading to destructive complications, of which long-term persisting and difficult-to-treat forms (D2T-RA) can lead to decades-long treatment beside remaining clinically active and symptomatic, for which B cell-depleting chimeric antigen receptor T cell (CAR-T) treatment, that is applied already for the treatment of B cell malignancies, may be a treatment option.

WHAT THIS STUDY ADDS
 ⇒ This is the first published case report of long-term

To cite: Szabo D, Balogh A, Gopcsa L, et al. Sustained drug-free remission in rheumatoid arthritis associated with diffuse large B-cell lymphoma following tandem CD20-CD19-directed non-cryopreserved CAR-T cell therapy using zamtocabtagene autoleucel. RMD Open 2024;10:e004727. doi:10.1136/rmdopen-2024-004727.

Received 12 July 2024
 Accepted 23 September 2024



Schett G, Nagy G, Krönke G, et al B-cell depletion in autoimmune diseases
Annals of the Rheumatic Diseases 2024;**83**:1409-1420.

Negyedik generációs CAR-T sejtek D2T RA-ban

Az RA egy autoimmun gyulladásos betegség, amelyet szimmetrikus ízületi gyulladás jellemez, ami progresszív rokkantsághoz vezet

Az RA kezelését forradalmasította a MOA-k (pl. TNF α , IL-6, CD20) kifejllesztése, ami jobb betegségkontrollt eredményez.

Az RA-s betegek akár 30%-a azonban még mindig nem éri el a célértéket (T2T), annak ellenére, hogy számos immunmoduláló gyógyszeres ciklust alkalmaznak

Az ilyen betegeket „nehezen kezelhető (D2T)” RA-nak nevezzük

Vizsgálták egy új, autológ, negyedik generációs CD19-célzott kiméra antigén receptor (CAR) T-sejtek, amelyek IL-6 és TNF α ellen AB-eket választanak ki (CD19/aIL-6/aTNF α) a D2T RA kezelésében

Cell Res, January 09, 2025

Negyedik generációs CAR-T sejtek D2T RA-ban

Három, több hagyományos és biológiai szerre nem reagáló RA-s beteget kezeltek ezekkel az új, negyedik generációs CAR T-sejtekkel.

A vizsgálatot a Kínai Tudományos és Technológiai Egyetem Első Társult Kórházának etikai bizottsága hagyta jóvá (2023KY-379).

Valamennyi beteg írásos beleegyezését adta a Helsinki Nyilatkozat elveinek megfelelően.

A CD19/aIL-6/aTNF α CAR IL-6 és TNF α elleni antitestek IL-6 és TNF blokkoló képességét in vitro tesztelték.

Cell Res, January 09, 2025

Negyedik generációs CAR-T sejtek D2T RA-ban

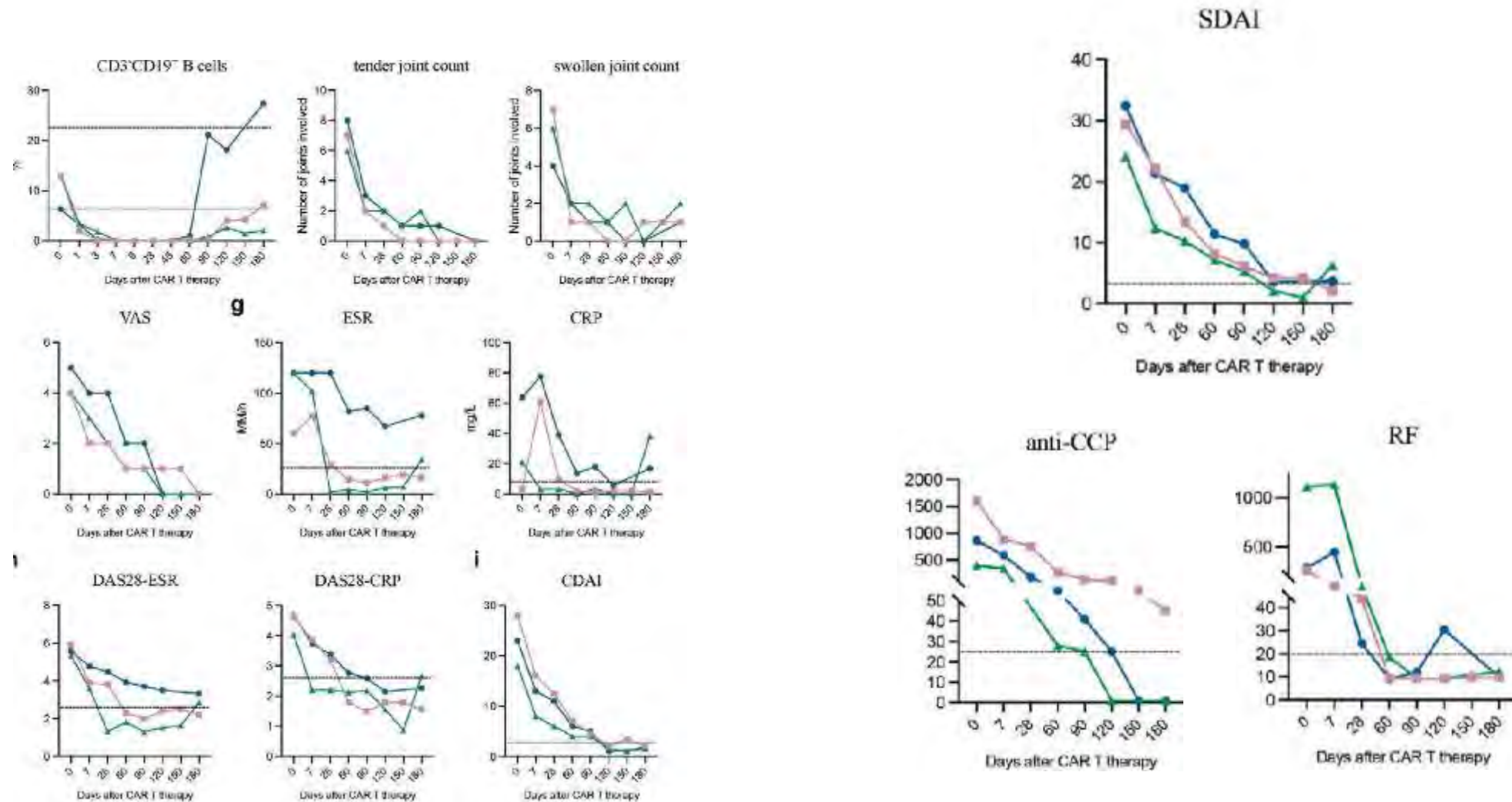
Valamennyi beteg korábban kapott glükokortikoidokat és többféle betegségmódosító DMARD-ot, beleértve a metotrexátot (3/3), a hidroxiklorokint (2/3), a leflunomidot (2/3), az iguratimodot (2/3), az etanerceptet (2/3), adalimumab (1/3), tofacitinib (1/3), baricitinib (2/3), abatacept (1/3), és etanerceptet

Az iguratimod megakadályozza az NF- κ B aktiválódását, majd szelektíven gátolja a COX-2-t és számos gyulladásos citokint

A CAR T-sejt-kezelést követően mindhárom beteg abbahagyta a biológiai DMARD-ok (bDMARD) kezelését.

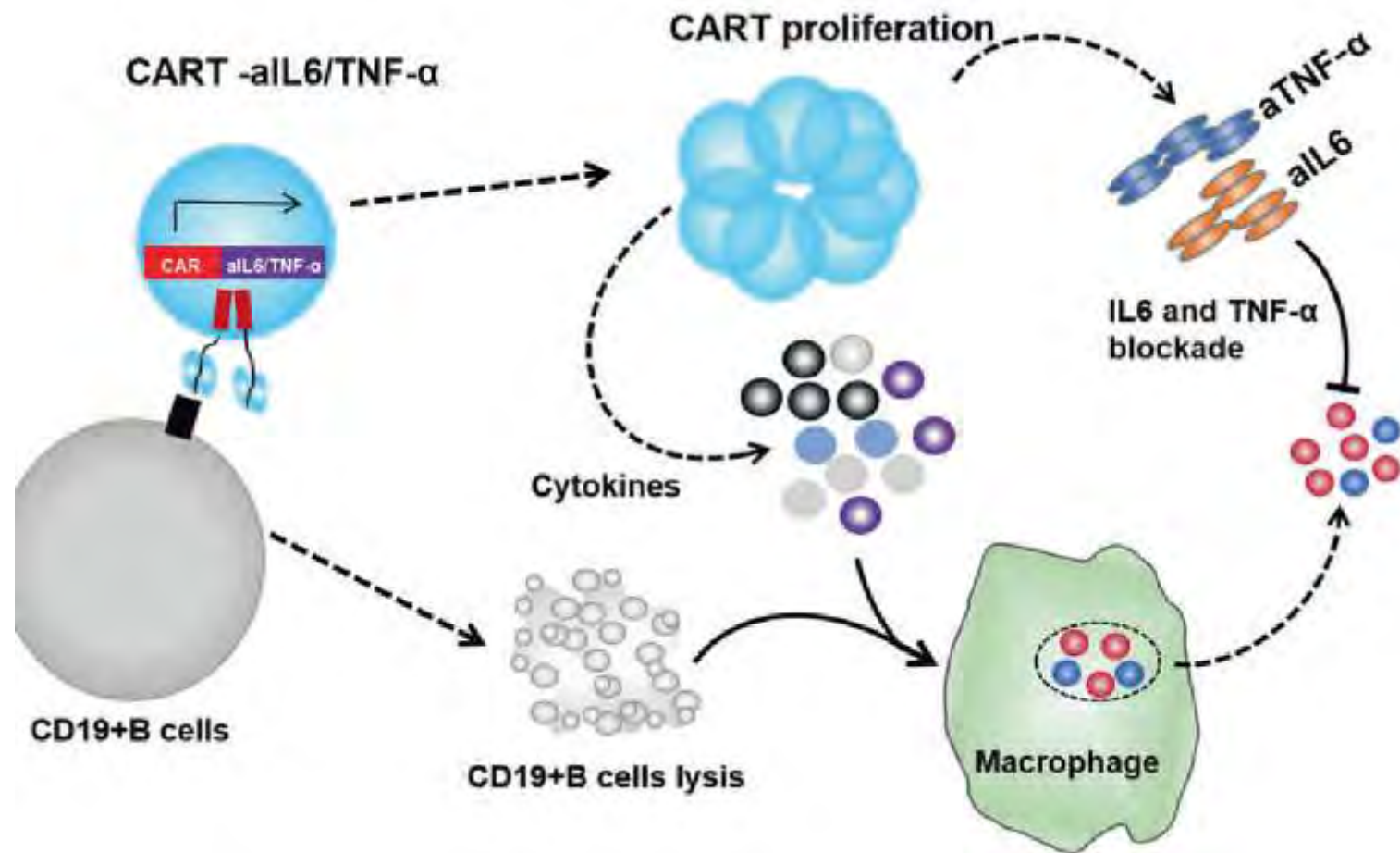
Cell Res, January 09, 2025

Negyedik generációs CAR-T sejtek D2T RA-ban



Cell Res, January 09, 2025

Negyedik generációs CAR-T sejtek D2T RA-ban



Cell Res, January 09, 2025

Negyedik generációs CAR-T sejtek D2T RA-ban

A CAR T-sejt infúziót mindhárom beteg jól tolerálta, és nem fordult elő súlyos mellékhatás

Nem fordult elő citokin felszabadulási szindróma (CRS) vagy immune effector cell-associated neurotoxicity syndrome (ICANS), nem volt láz, hipotenzió, fejfájás, légzési nehézség vagy neurológiai tünet (például zavartság, görcsrohamok, tudat- vagy viselkedésváltozások)

Az infúziót követően a CD19/aIL-6/aTNF α CAR T-sejtek gyorsan proliferáltak in vivo, a CAR kópiák csúcspontja a 9. napon az 1. betegnél, a 21. napon a 2. betegnél és a 14. napon a 3. betegnél.

Cell Res, January 09, 2025

Negyedik generációs CAR-T sejtek D2T RA-ban

Összefoglalva, a vizsgálat a CAR T-sejtek erőteljes növekedését mutatja in vivo, a CD19 B-sejtek teljes eliminációját, az RA-val kapcsolatos autoantitestek kiürülését és magas szintű tartós klinikai válaszokat RA-s betegekben.

Ez az első alkalom, hogy negyedik generációs CAR-t használnak az autoimmun betegségek kezelésére, és a citokin-gátlás és a B-sejt-kiürülés egy megközelítésben történő kombinálásának indoklása hatalmas lehetőségeket rejt magában az olyan betegségek, mint az RA, jobb kontrollálásában a jövőben.

Hosszú távú megfigyelés szükséges a kezelés tartós hatékonyságának és biztonságosságának megállapításához.

Az RA érzékeny a CD19-CAR T-sejt kezelésre, és ezzel a megközelítéssel az RA-specifikus autoimmunitás kezelhető

Cell Res, January 09, 2025

CAR-T fejlesztési irányok: in vivo CAR T sejtek

News & analysis

News

<https://doi.org/10.1038/d41573-024-00150-z>

In vivo CAR T cells move into clinical trials

By Ashor Mullard

Drug developers want to reprogramme immune cells directly in the body, opening up new gene therapy frontiers in cancer and autoimmunity.

Engineered immune cells called CAR Ts that can seek out and destroy B cells have transformed the treatment of some blood cancers, and are raising hopes for possible cures for autoimmune diseases. But these living cell therapies – made by harvesting cells from patients,

the code for a CAR selectively to a subset of immune cells. Interjus, Umoja and Kionia have embraced engineered lentiviral vectors that make permanent changes in immune cells. Capstan, Myeloid Therapeutics, Orbital and Orna have instead prioritized lipid nanoparticles (LNPs) paired with RNA molecules, to induce transient surges of CAR expression in targeted cells. Larger pharmaceutical companies are on the case as well, with Sanofi disclosing last year that it had three in vivo CAR T programmes in preclinical development.



research group at the Paul Ehrlich Institut, early inspiration struck 20 years ago. Another

“The beauty of what we’re

ing them a fraction of the cost of a living cell therapy. And they could be better, for two key reasons too. Ex vivo CAR T recipients need to be treated with harsh chemotherapy regimens ahead of cell therapy transfusions to make room for the engineered immune cells, but lymphodepletion cannot be used during the generation of in vivo CAR Ts and so patients retain intact immune systems. And because the souped up in vivo immune cells are less exhausted than their ex vivo counterparts, they could be more active too. “There’s a real, theoretical possibility that those cells will simply be better cancer fighters,” says Johnson.

These expectations are founded on emerging data from up and coming gene therapy vectors, the delivery vehicles that will carry

from cell therapies to gene therapies. “The distinctions between classes of therapies is blurring in front of our eyes,” says Bost.

“The distinctions between classes of therapies is blurring in front of our eyes”

Lentiviral reprogramming

Years before ex vivo CAR T cell therapies first entered the clinic, researchers were already hard at work retooling lentiviral vectors to enable in vivo reprogramming of immune cells.

For Christian Buchholz, who heads the molecular biotechnology and gene therapy

Buchholz, “You need to have a therapeutic strategy that will give those cells a selective advantage in vivo to finally get a readout”. With B-cell-depleting CAR Ts first entering the clinic in 2010, Buchholz saw an opportunity. A CD8-targeted CD19-CAR-loaded lentiviral vector transduced T cells in vivo in mice and wiped out B cells, he reported in 2016.

Several biotech firms have embraced this strategy, with a few tweaks along the way. Each firm has chosen a preferred cell targeting moiety, the antibody-based binder that defines which subset of cells are targeted. The glycoprotein matters too, acting as the entry key into engaged immune cells. And then there is the therapeutic payload, the CAR that enables the retrained T cells to seek out malignant foes. Layered on top of all that is manufacturing.

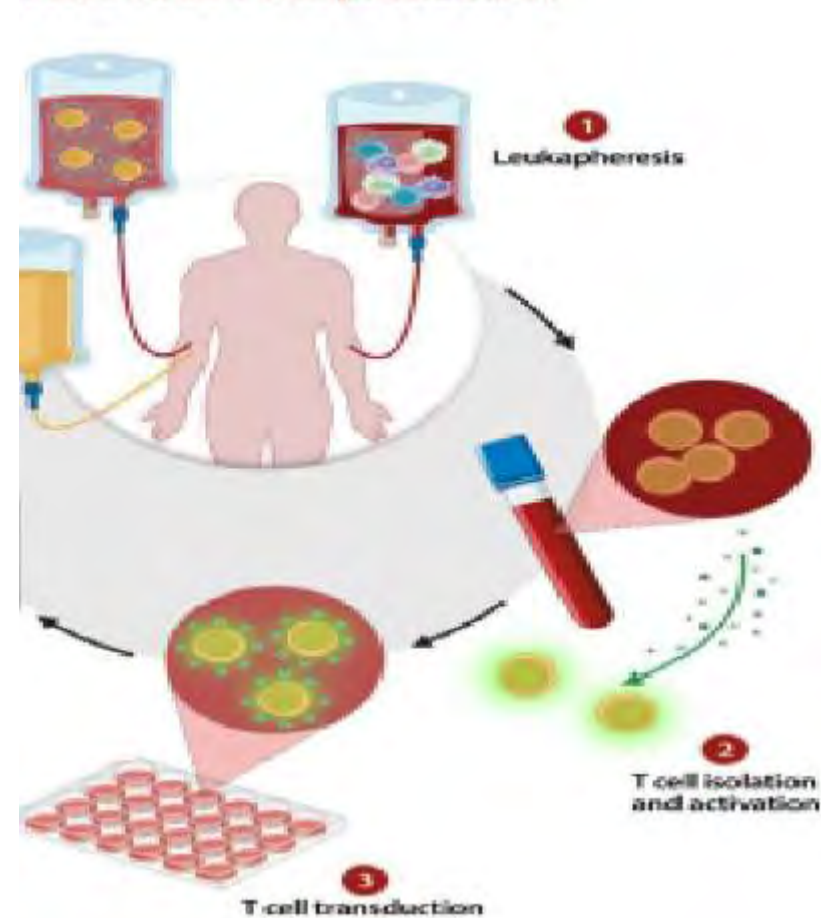
nature reviews drug discovery

Volume 23 | October 2024 | 727–730 | 727

Mullard A. In vivo CAR T cells move into clinical trials. Nat Rev Drug Discov. 2024 Oct;23(10):727-730. doi: 10.1038/d41573-024-00150-z. PMID: 39284972.

CAR-T fejlesztési irányok: in vivo CAR T sejtek

Ex vivo CAR-T cell production



In vivo CAR-T cell production



J Trans Med 2025 23:10

CAR-T fejlesztési irányok: in vivo CAR T sejtek

In vitro CAR-T: a folyamat költséges és bonyolult, a betegek sejtjeinek kinyerésével, fáradságos növesztésével és laboratóriumi tervezésével egy kiméra antigénreceptor (CAR) expresszálására, majd a betegekbe való újbóli infúzióval valósul meg.

Az in vivo CAR T generálás készen kapható újraprogramozó vektorokkal történik, így hetekkel gyorsabb, mint az ex vivo CAR T-k jelenlegi folyamatai

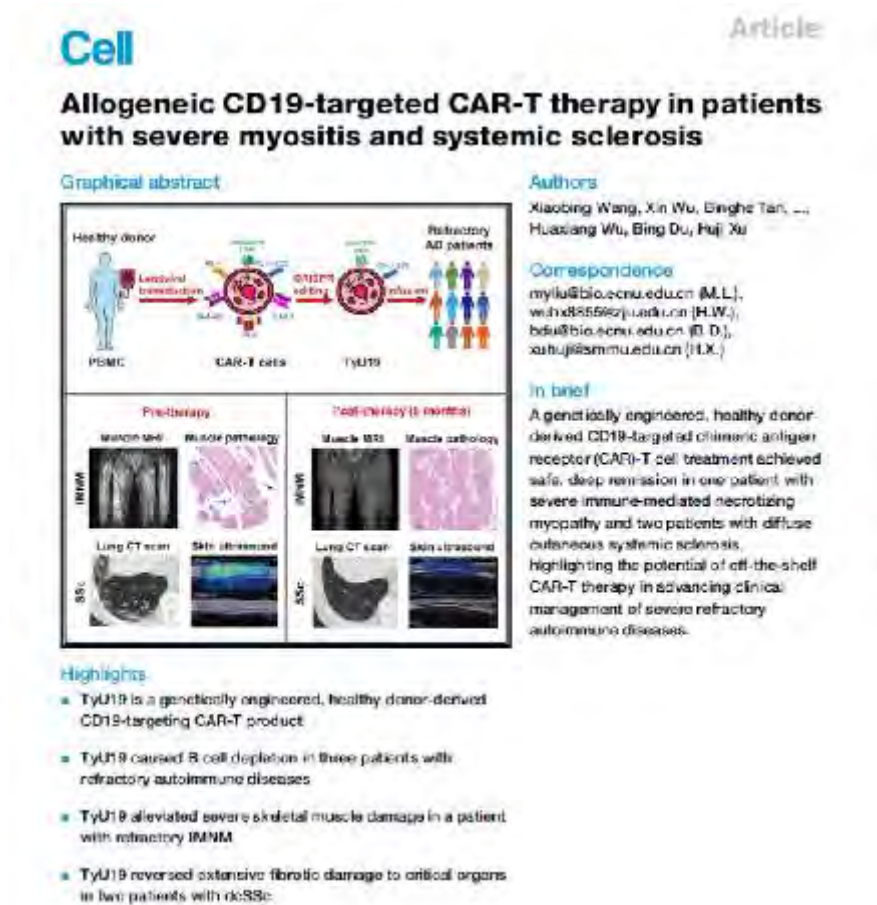
Az ex vivo CAR T recipienseket kemoterápiás kezelésekkel kell kezelni a sejterápiás transzfúzió előtt, ezzel szemben a limfodeplécia elkerülhető az in vivo CAR T-k generálásakor, így a betegek immunrendszere ép marad.

Ráadásul az in vivo immunsejtek kevésbé kimerültek, mint ex vivo társaik, lehetnének aktívabbak is

In vivo CAR T eljárás gyorsabb, jobb és olcsóbb lehet

Mullard A. In vivo CAR T cells move into clinical trials. Nat Rev Drug Discov. 2024 Oct;23(10):727-730. doi: 10.1038/d41573-024-00150-z. PMID: 39284972.

Allogén CAR-T sejt kezelés systemás sclerosisban és myositisben



A legújabb tanulmányok feltárták az autológ CD19-célzott CAR-T terápiák használatát autoimmun betegségek kezelésére, és ígéretes hatékonyságról számoltak be.

Az autológ CAR-T terápiák drágák, és a személyre szabott termék gyártása során meghibásodhatnak.

Az egészséges donorból származó késztermék nagyban javítaná a CAR-T elérhetőségét.

Allogén CAR-T termékek refrakter autoimmun betegségek kezelésére?

Allogén CAR-T sejt kezelés systemás sclerosisban és myositisben

Az allogén kiméra antigén receptor (CAR)-T sejtek nagy ígéretet hordoznak a CAR-T terápia hozzáférhetőségének bővítésében

DE az allograft kilökődés kockázata akadályozta az alkalmazását

A CRISPR-Cas9 segítségével génmanipulált, egészséges donorból származó, CD19-re célzó CAR-T sejteket használtak az immunkilökődés problémájának megoldására.

Egy refrakter immunmediált necrotizáló myopathiában és két systemás sclerosisban szenvedő beteget kezeltek

Az infundált sejtek több mint 3 hónapig fennmaradtak, és a kezelést követő 2 héten belül teljes B-sejt-kiürülést értek el.

Allogén CAR-T sejt kezelés systemás sclerosisban és myositisben

A 6 hónapos követés során mindhárom betegnél mély remissziót figyeltek meg citokin felszabadulási szindróma vagy egyéb súlyos nemkívánatos események nélkül.

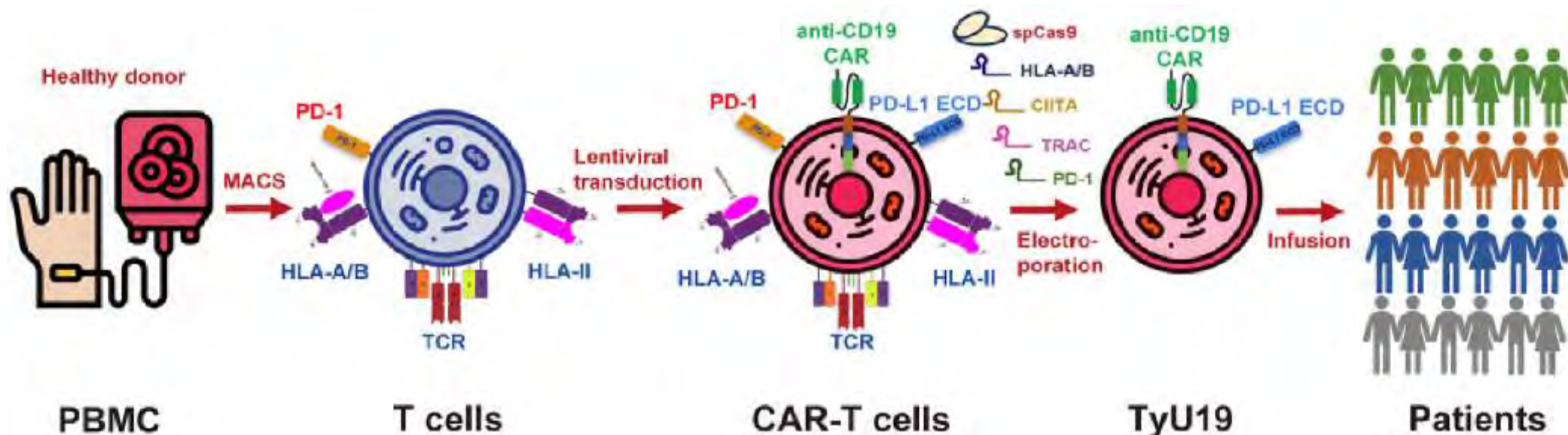
Kiváló klinikai választ figyeltek meg, a gyulladás és a fibrózis visszafordítása.

Ezek az adatok bizonyítják a készen kapható CAR-T sejtek nagy biztonságát és ígéretes immunmoduláló hatását a súlyos, refrakter autoimmun betegségek kezelésében.

Az immunközvetített necrotizáló myopathia (IMNM) súlyos szisztémás betegségautoimmun betegség

Az IMNM egyik legagresszívabb altípusa a jelfelismerő részecske (SRP)-IMNM, amelyet a vázizomzat anti-SRP autoantitest jellemez.

Allogén CAR-T sejt kezelés systemás sclerosisban és myositisben



A PBMC-ből izolált T-sejteket először lentivírus kódolással transzdukáltuk anti-CD19 CAR konstrukciót, **majd kiűtötték a (HLA)-A, HLA-B, II. osztályú fő hisztokompatibilitás komplex transzaktivátor (CIITA)**, T sejt receptor alfa állandó (TRAC) és a PD-1 elektroporáción alapuló CRISPR Cas9 génszerkesztéssel, Cas9 fehérje felhasználásával komplexben egyetlen vezető RNS-sel (sgRNS) minden egyes célponthoz

Az allogén CD-19 CAR-T kiváló klinikai hatékonysága és biztonságossága igazolódott

Összegzés

Szintetikus készítmények

Célzott terápiák

IVIG

CAR T

mellékhatások (citokin vihar)

Köszönöm
a figyelmet!



SEMMELWEIS
EGYETEM 1769