Lupus on the Horizon

Νέα Δεδομένα Νέες Ελπίδες

ΣΤΑΜΑΤΗΣ-ΝΙΚΟΣ ΛΙΟΣΗΣ

Καθηγητής

Πανεπιστήμιο Πατρών

Σύγκρουση συμφερόντων

Καμμιά

Νέα Δεδομένα

Δεδομένα που **ΔΕΝ** θα ακούσετε

- Για τη Διάγνωση (κλινική και συνήθως εύκολη)
- Για τις Κλινικές Εκδηλώσεις (….)
- Για τα Εργαστηριακά
- Για τα Αυτοαντισώματα
- Για τα metrics (SLICC, SLAC, SLAM, SLEDAI, BILAG, κλπ)
- Για το “T2T”

2024 **Albert Lasker** Award

LASKER FOUNDATION

Zhijian "James" Chen

Basic Research

cGAS enzyme that senses self and foreign DNA

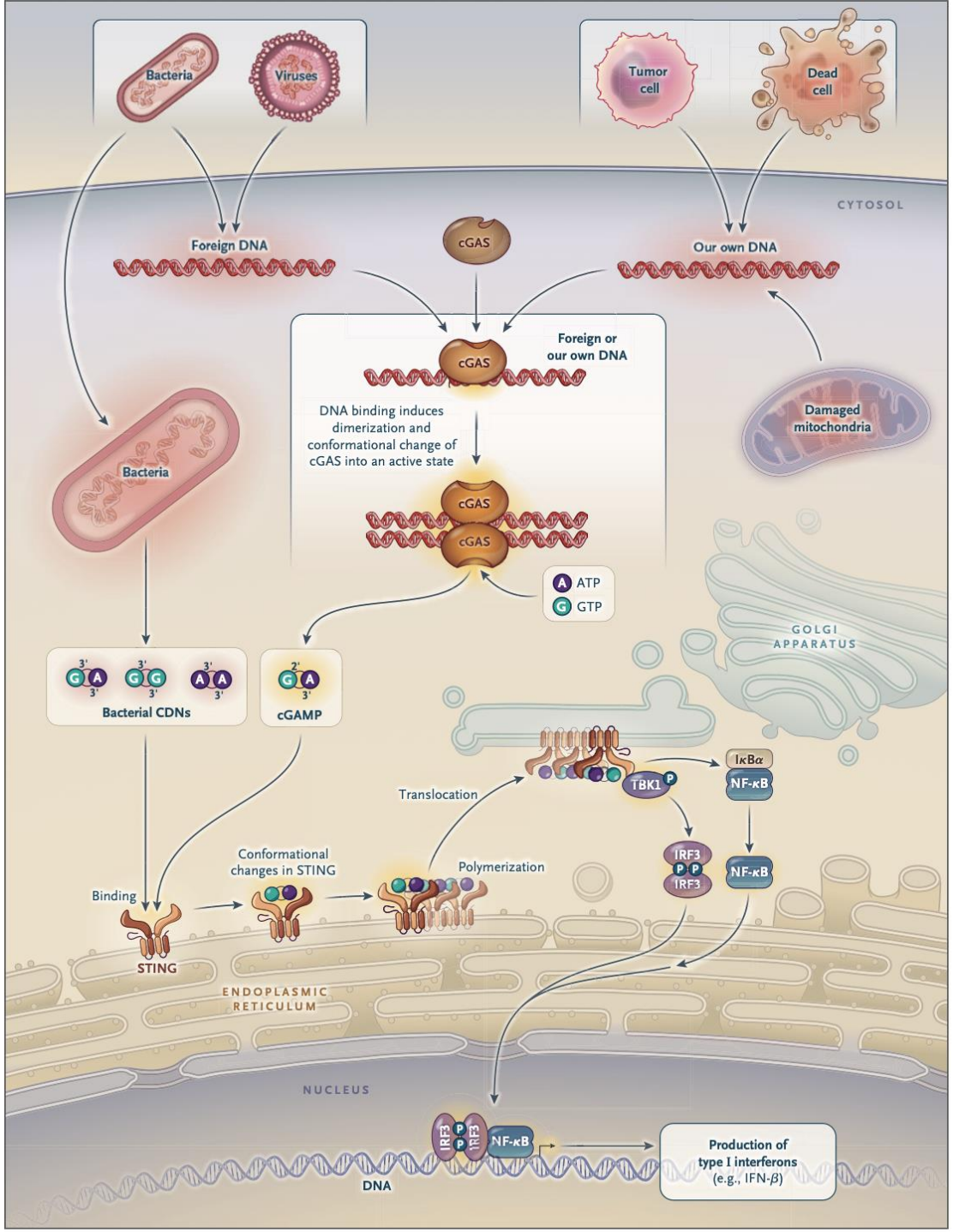
Learn More >

Cyclic GMP-AMP Synthase Is a Cytosolic DNA Sensor That Activates the Type I Interferon Pathway

Lijun Sun,[1,2]* Jiaxi Wu,[1]* Fenghe Du,[1,2] Xiang Chen,[1,2] Zhijian J. Chen[1,2]†

Cyclic GMP-AMP Is an Endogenous Second Messenger in Innate Immune Signaling by Cytosolic DNA

Jiaxi Wu,[1]* Lijun Sun,[1,2]* Xiang Chen,[1] Fenghe Du,[1] Heping Shi,[3] Chuo Chen,[3] Zhijian J. Chen[1,2]†



The cGAS-STING Pathway

N ENGL J MED 391;15 NEJM.ORG OCTOBER 17, 2024

Published March 27, 2015, doi:10.4049/jimmunol.1402793

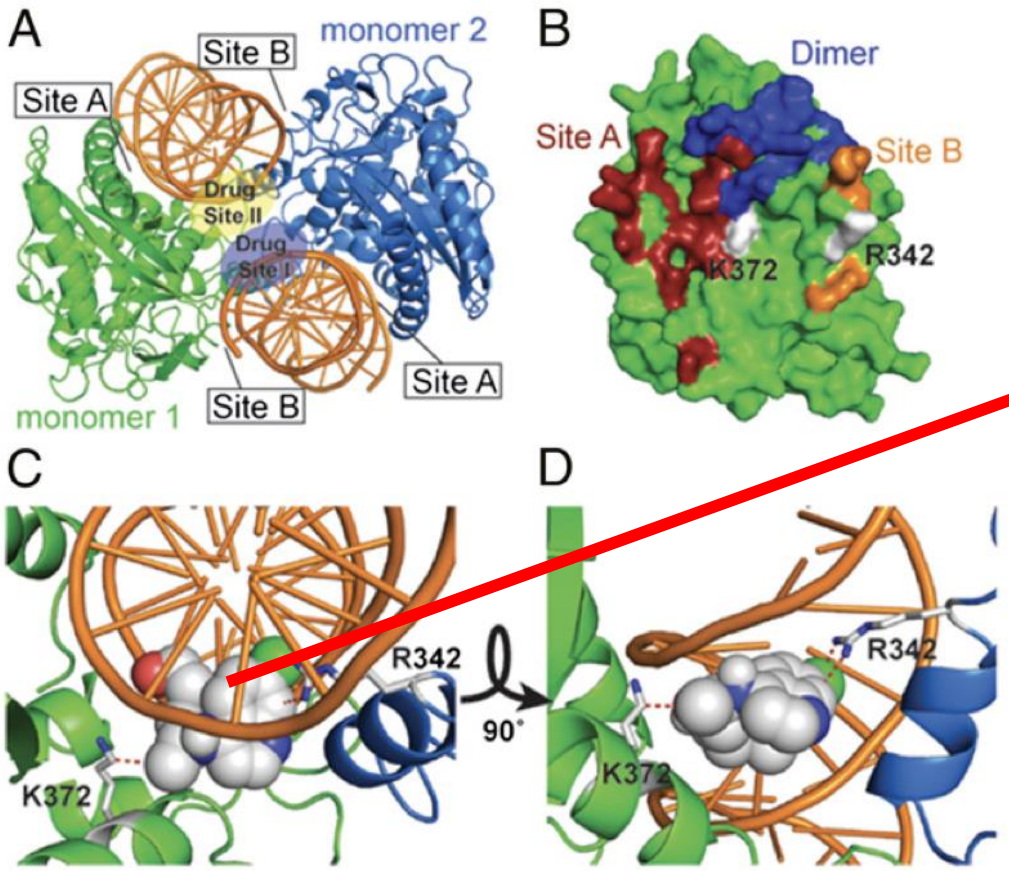
Cutting Edge

The Journal of Immunology

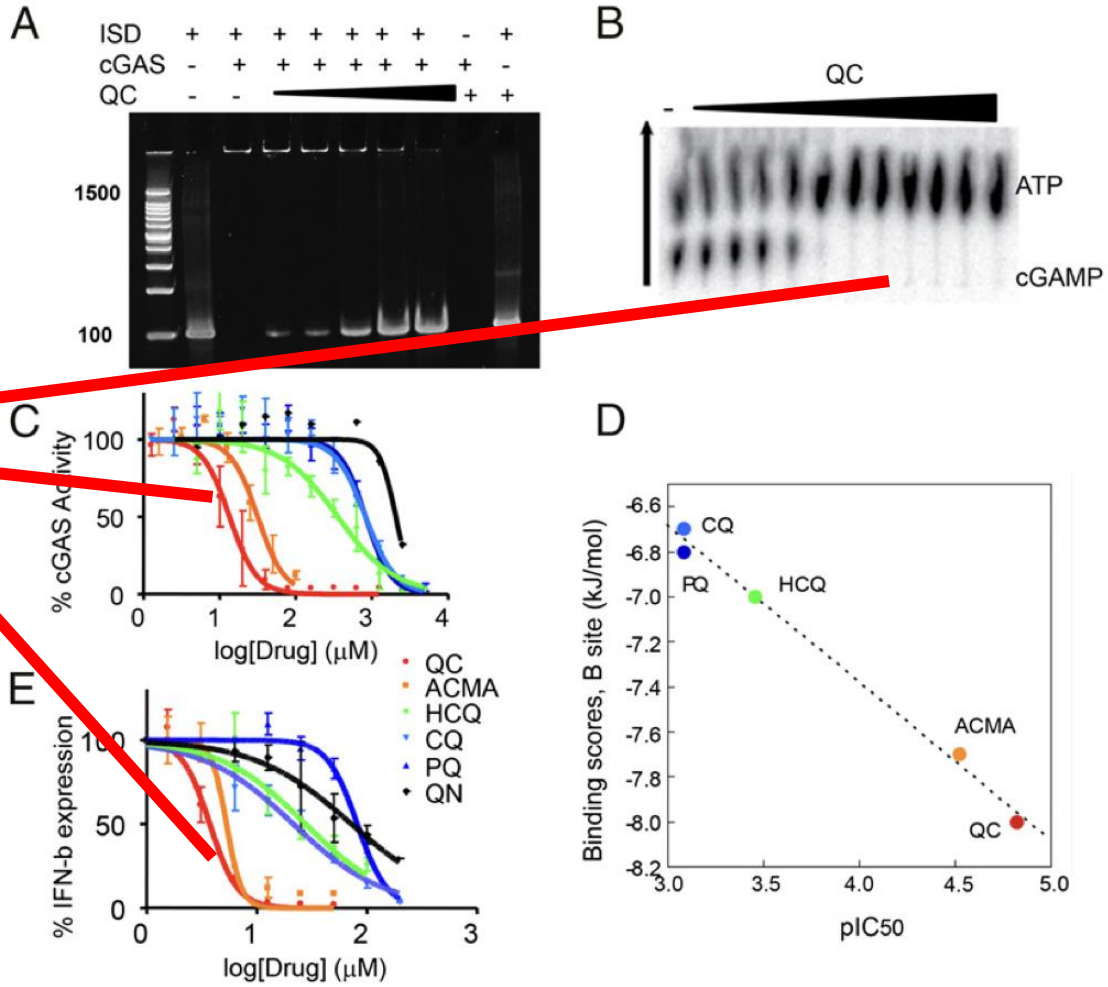
Cutting Edge: Antimalarial Drugs Inhibit IFN-β Production through Blockade of Cyclic GMP-AMP Synthase–DNA Interaction

Jie An,* Joshua J. Woodward,† Tomikazu Sasaki,§ Mark Minie,†,‡ and Keith B. Elkon*,¶

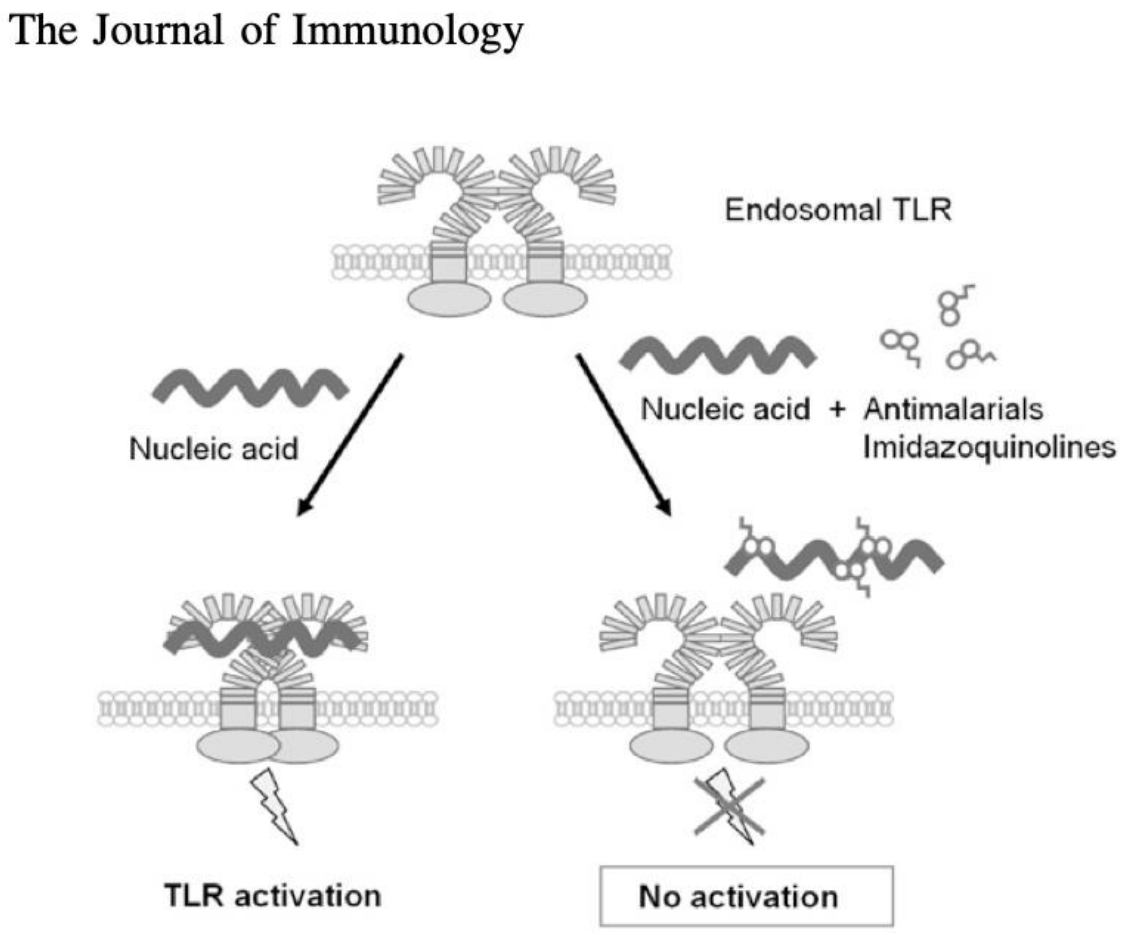
CUTTING EDGE: ANTIMALARIAL DRUGS INHIBIT cGAS



?



? = Plaquenil (!)



Kuznik A et al: J Immunol. 2011; 186:4794.

Plaquenil

Στη θεραπεία του ΣΕΛ: 1894

Αναστέλλει τον TLR7
Αναστέλλει τον TLR9

Κυρίως όμως:
Αναστέλλει το μονοπάτι cGAS-STI

Το cGAS-STING είναι άκρως σημαν
(ηλικίας δις ετών)

Το cGAS-STING είναι **νέος αγαπη**
στόχος της φαρμακοβιομηχανίας.

Νέες Ελπίδες

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Efficacy and Safety of Obinutuzumab in Active Lupus Nephritis

R.A. Furie,[1] B.H. Rovin,[2] J.P. Garg,[3] M.B. Santiago,[4,5,6] G. Aroca-Martínez,[7,8] A.E. Zuta Santillán,[9] D. Alvarez,[11] C. Navarro Sandoval,[10] A.M. Lila,[13] J.A. Tumlin,[14] A. Saxena,[15] F. Irazoque Palazuelos,[16] H. Raghu,[3] B. Yoo,[3] I. Hassan,[17] E. Martins,[18] H. Sehgal,[18] P. Kirchner,[18] J. Ross Terres,[3] T.A. Omachi,[3] T. Schindler,[18] W.F. Pendergraft III,[3] and A. Malvar,[12] for the REGENCY Trial Investigators*

What is this?

- Το Obinutuzumab είναι ένα **anti-hCD20 mAb.**
- Συνδέεται με το επιφανειακό μόριο CD20 κυττάρων και τα σκοτώνει.
- Τα μόνα κύτταρα που φέρουν το CD20 είναι τα B cells.
- **Σε τί διαφέρει από το RTX?? Είναι πολύ πιο ΑΠΟΤΕΛΕΣΜΑΤΙΚΟ.**
- Δοσολογικό σχήμα: όπως το RTX στην RA

ΑΠΟΤΕΛΕΣΜΑΤΑ

Table 2. Primary and Secondary End Point Results in the Intention-to-Treat Population.*

End Point	Obinutuzumab (N=135)	Placebo (N=136)	Adjusted Difference (95% CI)†	P Value‡
Primary end point				
Complete renal response at wk 76 — % (95% CI)§¶‖	46.4 (38.0 to 54.9)	33.1 (25.2 to 41.0)	13.4 (2.0 to 24.8)	0.02
Key secondary end points				
Complete renal response at wk 76 with prednisone taper to ≤7.5 mg/day between wks 64 and 76 — % (95% CI)§¶‖**	42.7 (34.3 to 51.1)	30.9 (23.1 to 38.7)	11.9 (0.6 to 23.2)	0.04
UPCR <0.8 at week 76 with no intercurrent event — % (95% CI)¶‖††	55.5 (47.1 to 64.0)	41.9 (33.6 to 50.2)	13.7 (2.0 to 25.4)	0.02
Change in the eGFR from baseline to wk 76 — ml/min/1.73 m^2‡‡	2.31±2.71	−1.54±2.71	3.84 (−1.83 to 9.51)	
Death or renal-related event through wk 76 — % (95% CI)¶§§	18.9 (12.1 to 25.6)	35.6 (27.5 to 43.8)	−16.8 (−27.4 to −6.2)	
Overall renal response at wk 50 — % (95% CI)¶‖¶¶	59.1 (50.8 to 67.4)	50.7 (42.2 to 59.2)	8.4 (−3.4 to 20.1)	
Change in FACIT-F score from baseline to wk 76 — points‡‡	1.8±1.2	3.1±1.2	−1.4 (−3.9 to 1.2)	

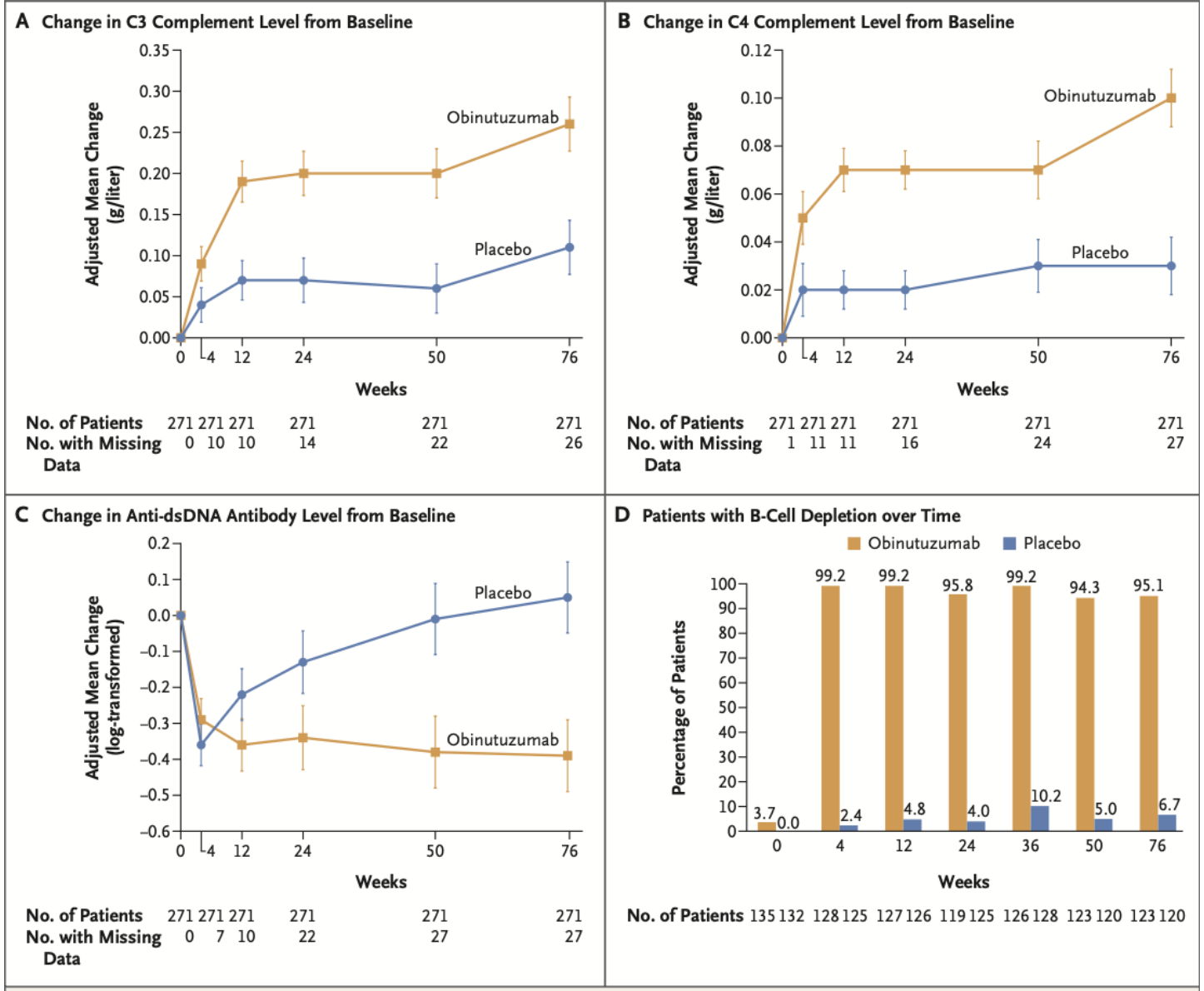
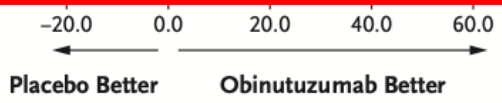


Figure 2. Serologic and Pharmacodynamic Analyses over Time.

Panel A shows the adjusted mean change in the C3 complement level from baseline in the intention-to-treat population. Panel B shows the adjusted mean change in the C4 complement level from baseline in the intention-to-treat population. Panel C shows the adjusted mean change in anti-dsDNA antibody level from baseline (log-transformed) in the intention-to-treat population. In Panels A, B, and C, an analysis-of-covariance model was used with multiple imputation for missing data; I bars indicate the standard error. Panel D shows the percentage of patients with B-cell depletion over time (T and B natural killer cells) in the safety population. B-cell depletion was defined by an absolute CD19-positive B-cell count lower than 10 cells per cubic millimeter.

Ποιοι τα πήγαν καλύτερα?

Subgroup	No. of Patients		Patients with Complete Renal Response		Adjusted Difference (95% CI)
	Obinutuzumab	Placebo	Obinutuzumab	Placebo	
			percent		*percentage points*
All patients	135	136	46	33	13.4 (2.0 to 24.8)
Sex					
Female	114	115	47	27	20.6 (8.4 to 32.7)
Male	21	21	43	67	−28.2 (−53.3 to 2.3)
Race					
Black	15	17	60	41	17.7 (−15.8 to 45.4)
Other	120	119	45	32	12.8 (0.7 to 24.9)
Geographic region					
Latin America or the Caribbean	77	77	39	30	9.2 (−5.5 to 23.9)
Other	38	39	60	36	23.7 (2.8 to 44.5)
United States or Canada	20	20	50	40	10.0 (−19.3 to 37.2)
24-Hr UPCR at baseline					
<3	82	74	52	46	7.8 (−7.7 to 23.3)
≥3	52	62	37	18	17.8 (1.6 to 33.9)
Anti-dsDNA antibody level at baseline					
≤120 IU/ml	78	75	42	32	10.8 (−4.2 to 25.8)
>120 IU/ml	57	61	52	34	18.3 (1.0 to 35.7)
C3 complement at baseline					
≥0.9 g/liter	58	60	38	32	10.2 (−7.3 to 26.9)
<0.9 g/liter	77	76	53	34	16.4 (1.0 to 31.8)
C4 complement at baseline					
≥0.1 g/liter	103	93	41	31	12.0 (−1.4 to 25.3)
<0.1 g/liter	32	42	63	36	26.2 (2.4 to 46.1)
Lupus nephritis class at baseline					
Class III	56	51	50	41	7.1 (−11.5 to 25.6)
Class IV	79	85	44	28	15.2 (0.8 to 29.5)
Concomitant class V disease at baseline					
No	88	98	45	37	8.8 (−5.2 to 22.8)
Yes	47	38	49	24	25.5 (6.3 to 44.7)
History of lupus nephritis at baseline					
Previously diagnosed	81	76	43	38	6.0 (−9.2 to 21.3)
Newly diagnosed	54	60	52	27	23.8 (5.7 to 39.8)
eGFR at baseline					
≥90 ml/min/1.73 m^2	96	96	49	39	10.9 (−3.0 to 24.9)
<90 ml/min/1.73 m^2	39	40	41	20	15.1 (−6.6 to 35.0)



ΑΣΦΑΛΕΙΑ

Table 3. Adverse Events through Week 76 in the Safety Population.*

Event	Obinutuzumab (N=136)	Placebo (N=132)	Total (N=268)
Any adverse event — no. (%)	126 (92.6)	117 (88.6)	243 (90.7)
Total no. of adverse events	748	665	1413
Any serious adverse event — no. (%)	44 (32.4)	24 (18.2)	68 (25.4)
Total no. of serious adverse events	68	35	103
Deaths — no. (%)†	3 (2.2)	1 (0.8)	4 (1.5)
Adverse event leading to trial withdrawal — no. (%)	0	0	0
Serious adverse events occurring in ≥5 patients — no. (%)			
Covid-19–related pneumonia	7 (5.1)	0	7 (2.6)
Pneumonia	4 (2.9)	3 (2.3)	7 (2.6)
Urinary tract infection	4 (2.9)	2 (1.5)	6 (2.2)
Covid-19	4 (2.9)	1 (0.8)	5 (1.9)
Gastroenteritis	3 (2.2)	2 (1.5)	5 (1.9)
Acute kidney injury	3 (2.2)	2 (1.5)	5 (1.9)
Adverse events occurring in ≥1 patient — no. (%)			
Grade ≥3 adverse event	44 (32.4)	22 (16.7)	66 (24.6)
Infection	98 (72.1)	81 (61.4)	179 (66.8)
Adverse event leading to discontinuation of obinutuzumab or placebo	10 (7.4)	5 (3.8)	15 (5.6)
Adverse event with fatal outcome	3 (2.2)	2† (1.5)	5 (1.9)
Infection as a serious adverse event	23 (16.9)	10 (7.6)	33 (12.3)
Serious adverse event leading to discontinuation of obinutuzumab or placebo	8 (5.9)	4 (3.0)	12 (4.5)
Adverse events of special interest — no. (%)			
Infusion-related reaction	21 (15.4)	15 (11.4)	36 (13.4)
Grade ≥3 infection	21 (15.4)	9 (6.8)	30 (11.2)
Any hepatitis B reactivation or progressive multifocal leukoencephalopathy	0	0	0
Drug-related neutropenia	17 (12.5)	5 (3.8)	22 (8.2)
Drug-related thrombocytopenia	1 (0.7)	0	1 (0.4)
Gastrointestinal perforation	0	0	0
Worsening of preexisting cardiac condition	0	2 (1.5)	2 (0.7)
Potential drug-induced liver failure meeting Hy's law criteria	0	0	0
Suspected transmission of an infectious agent by obinutuzumab or placebo	0	0	0

Γιατί να στοχεύσουμε τα B cells στο Λύκο ???

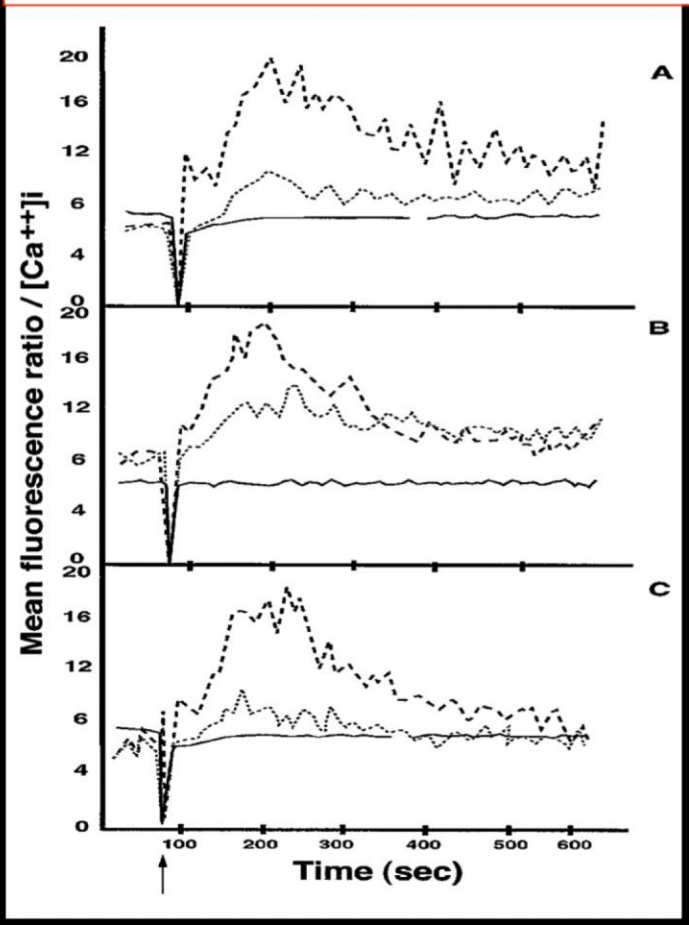
BCR-initiated signalling is abnormally increased in SLE

Lupus B cells are hyperreactive

B Cells from Patients with Systemic Lupus Erythematosus Display Abnormal Antigen Receptor–mediated Early Signal Transduction Events

Stamatis-Nick C. Liossis,* Birgit Kovacs,* Greg Dennis,‡ Gary M. Kammer,§ and George C. Tsokos*‡

**Department of Clinical Physiology, Walter Reed Army Institute of Research, Washington, DC 20307-5100; ‡Departments of Clinical Investigation and Medicine, Walter Reed Army Medical Center, Washington, DC 20307-5001; and §Department of Medicine, Bowman Gray School of Medicine, Wake Forest University, Winston-Salem, North Carolina 27157-1058*



J. Clin. Invest.

0021-9738/96/12/2549/09 $2.00
Volume 98, Number 11, December 1996, 2549–2557

ARTICLES
https://doi.org/10.1038/s41591-022-02017-5
nature medicine

Check for updates

Anti-CD19 CAR T cell therapy for refractory systemic lupus erythematosus

Andreas Mackensen[1,2,8], Fabian Müller[1,2,8], Dimitrios Mougiakakos[1,2,3,8], Sebastian Böltz[2,4], Artur Wilhelm[2,4], Michael Aigner[1,2], Simon Völkl[1,2], David Simon[2,4], Arnd Kleyer[2,4], Luis Munoz[2,4], Sascha Kretschmann[1,2], Soraya Kharboutli[1,2], Regina Gary[1,2], Hannah Reimann[1,2], Wolf Rösler[1,2], Stefan Uderhardt[2,4], Holger Bang[5], Martin Herrmann[2,4], Arif Bülent Ekici[6], Christian Buettner[6], Katharina Marie Habenicht[7], Thomas H. Winkler[7], Gerhard Krönke[2,4,8] and Georg Schett[2,4,8] ✉

NATURE MEDICINE | VOL 28 | OCTOBER 2022 | 2124–2132 | www.nature.com/naturemedicine

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 FEBRUARY 22, 2024 VOL. 390 NO. 8

CD19 CAR T-Cell Therapy in Autoimmune Disease — A Case Series with Follow-up

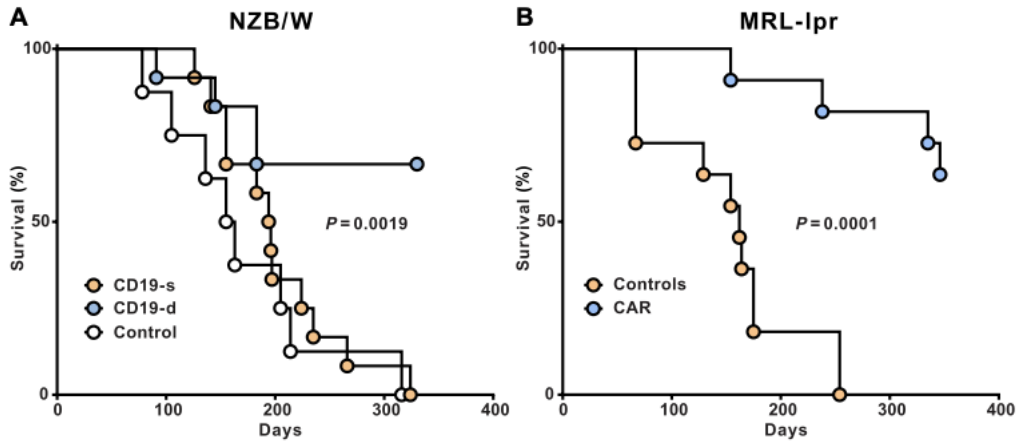
Fabian Müller, M.D., Jule Taubmann, M.D., Laura Bucci, M.D., Artur Wilhelm, Ph.D., Christina Bergmann, M.D., Simon Völkl, Ph.D., Michael Aigner, Ph.D., Tobias Rothe, Ph.D., Ioanna Minopoulou, M.D., Carlo Tur, M.D., Johannes Knitza, M.D., Soraya Kharboutli, M.D., Sascha Kretschmann, Ph.D., Ingrid Vasova, M.D., Silvia Spoerl, M.D., Hannah Reimann, Ph.D., Luis Munoz, M.D., Roman G. Gerlach, Ph.D., Simon Schäfer, Ph.D., Ricardo Grieshaber-Bouyer, M.D., Anne-Sophie Korganow, M.D., Dominique Farge-Bancel, M.D., Dimitrios Mougiakakos, M.D., Aline Bozec, Ph.D., Thomas Winkler, Ph.D., Gerhard Krönke, M.D., Andreas Mackensen, M.D., and Georg Schett, M.D.

SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

AUTOIMMUNITY

Sustained B cell depletion by CD19-targeted CAR T cells is a highly effective treatment for murine lupus

Rita Kansal[1], Noah Richardson[1], Indira Neeli[1], Saleem Khawaja[1], Damian Chamberlain[1], Marium Ghani[1], Qurat-ul-ain Ghani[1], Louisa Balazs[2], Sarka Beranova-Giorgianni[3], Francesco Giorgianni[3], James N. Kochenderfer[4], Tony Marion[1], Lorraine M. Albritton[1], Marko Radic[1]*



Kansal *et al.*, *Sci. Transl. Med.* **11**, eaav1648 (2019) 6 March 2019

CAR ΚΥΤΤΑΡΙΚΕΣ ΘΕΡΑΠΕΙΕΣ

- Οι περισσότεροι μεταμοσχευμένοι είναι ασθενείς με ΣΕΛ
- Λιγότεροι με Σκληρόδερμα και Μυοσίτιδες
- Μόνο 1 δεν ανταποκρίθηκε καθόλου (τί είχε?)

ΑΣΦΑΛΕΙΑ

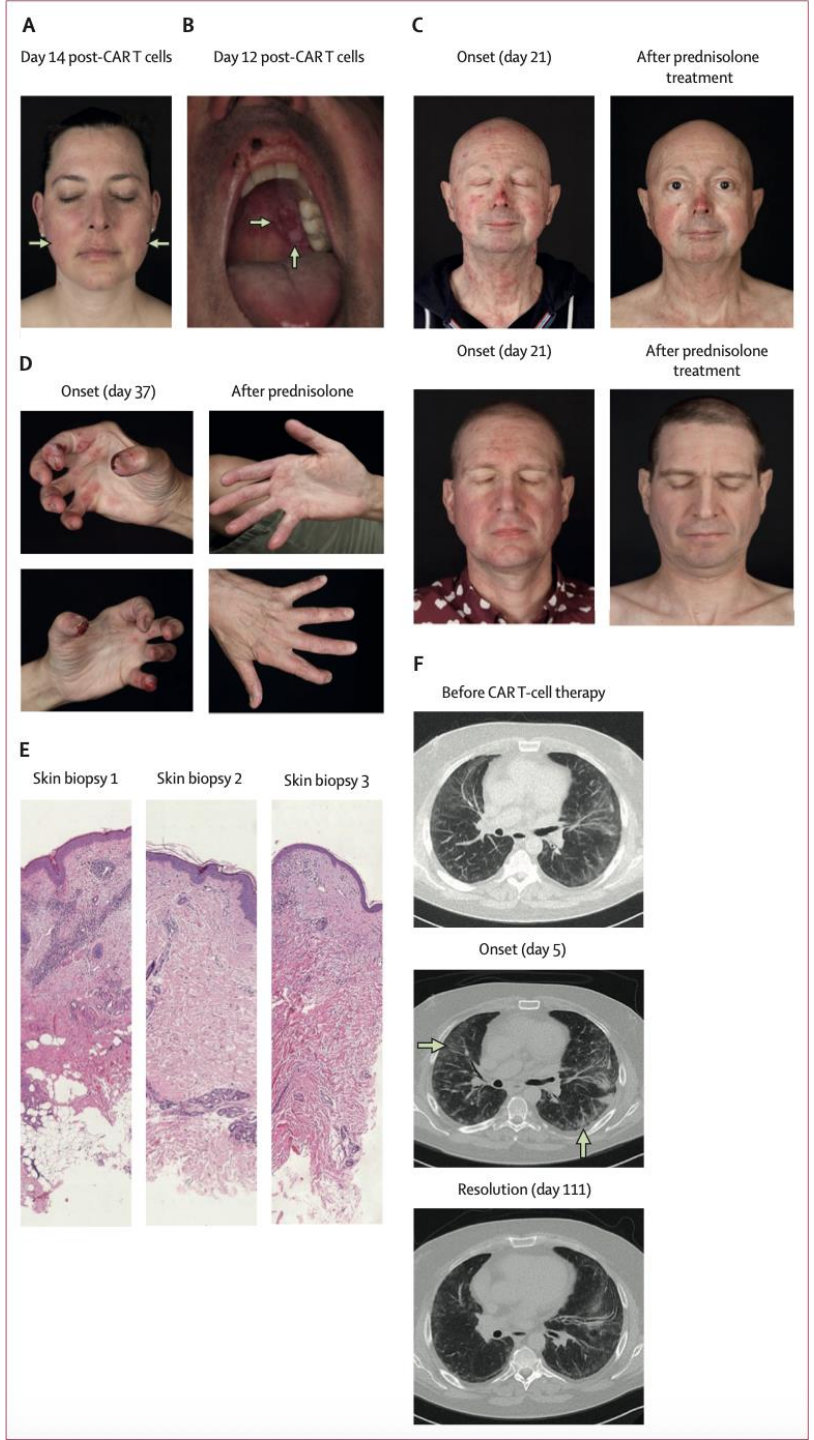
ΑΣΦΑΛΕΙΑ (?)

Local immune effector cell-associated toxicity syndrome in CAR T-cell treated patients with autoimmune disease: an observational study

Melanie Hagen, Fabian Müller*, Andreas Wirsching*, Soraya Kharboutli, Silvia Spoerl, Christina Düsing, Tobias Krickau, Markus Metzler, Simon Völkl, Michael Aigner, Sascha Kretschmann, Ingrid Vasova, Marc Saake, Stefan Schliep, Torsten Kubacki, Nicolas Hunzelmann, Laura Bucci, Jule Taubmann, Christina Bergmann, Andrea-Hermina Györfi, Sascha Dietrich, Jörg H W Distler, Ricardo Grieshaber-Bouyer, Andreas Mackensen, Georg Schett*

LICATS

www.thelancet.com/rheumatology **Published online April 30, 2025** **https://doi.org/10.1016/S2665-9913(25)00091-8**



LUPUS CARs - ΕΡΩΤΗΜΑΤΙΚΑ

- Πόσα CAR T cells χρειάζονται? Πόσα χορηγούνται? Οι μελέτες ΔΕΝ το λένε. Στα πιο έμπειρα εργαστήρια / χέρια είναι < 30% (!!).

- Τι T cells είναι τα CARs? CD4+ ? CD8+? Δεν γνωρίζουμε.

- **Στον ασθενή επαναχορηγούμε ΟΧΙ μόνο τα CAR-T cells, αλλά και τα δικά του ΑΥΤΟ-ΑΝΤΙΔΡΑΣΤΙΚΑ T cells!! Και μάλιστα expanded!**

LUPUS CARs

- Ολα τα πρωτόκολα περιλαμβάνουν **ΚΑΙ** χορήγηση "ablative" δόσης Fludara + Endoxan. **Ποιο effect βλέπουμε??** Των CARs ή της ανοσοκαταστολής?

- Οι μελέτες υποστηρίζουν ότι η διαφορά με το B cell depletion είναι η πληρέστερη εξάλειψη των B cells. Αυτό ΔΕΝ έχει τεκμηριωθεί.

- "Deep immune system reset". What is this????

LUPUS CARs
Το ΜΕΙΖΟΝ Πρόβλημα

- ΟΛΕΣ οι μέχρι σήμερα δημοσιεύσεις ΔΕΝ είναι μελέτες !!!

- Είναι case-reports ή case series.

- Απαιτούνται ΕΛΕΓΧΟΜΕΝΕΣ μελέτες (π.χ. με B cell depleting mAb)

LUPUS CARs

- Γιατί να δώσουμε CARs και όχι mAbs??

- Bispecific mAbs: anti-CD19 & anti-CD3. Πάνω στα Β λεμφοκύτταρα προσκολλάται ένα ενεργοποιημένο Τ λεμφοκύτταρο και το σκοτώνει!! **"T cell engagers"**

- **Blinatumomab**: Νέο (2025) SOC στην ΟΛΛ των παιδιών!

- Για τον ΣΕΛ **ήδη έχουν σχεδιαστεί** bispecifics για **autoreactive** B cells!

nature communications

Article

https://doi.org/10.1038/s41467-024-45056-x

Smith-specific regulatory T cells halt the progression of lupus nephritis

Received: 12 March 2023

Accepted: 12 January 2024

Published online: 06 February 2024

Check for updates

Peter J. Eggenhuizen[1,8], Rachel M. Y. Cheong[1,8], Cecilia Lo[1], Janet Chang[1], Boaz H. Ng[1], Yi Tian Ting[1], Julie A. Monk[1], Khai L. Loh[1], Ashraf Broury[1], Elean S. V. Tay[1], Chanjuan Shen[2], Yong Zhong[1,3], Steven Lim[4], Jia Xi Chung[1], Rangi Kandane-Rathnayake[1], Rachel Koelmeyer[1], Alberta Hoi[1,5], Ashutosh Chaudhry[6], Paolo Manzanillo[7], Sarah L. Snelgrove[1], Eric F. Morand[1,5] & Joshua D. Ooi[1]

nature communications

Article

https://doi.org/10.1038/s41467-024-46448-9

Regulatory T cells expressing CD19-targeted chimeric antigen receptor restore homeostasis in Systemic Lupus Erythematosus

Received: 14 September 2022

Accepted: 26 February 2024

M. Doglio[1] ✉, A. Ugolini[1], C. Bercher-Brayer[1], B. Camisa[1], C. Toma[1], R. Norata[2], S. Del Rosso[3], R. Greco[4], F. Ciceri[4], F. Sanvito[2,5], M. Casucci[6], A. A. Manfredi[7] & C. Bonini[1] ✉

ΕΧΟΥΜΕ LONG-TERM DATA?

Το Obinutuzumab ακόμα δεν έχει FDA / EMA έγκριση….

Η 1η ασθενής που πήρε CAR-T cell θεραπεία συμπλήρωσε 4.5 χρόνια.

Εχουμε??

Rheumatology International (2025) 45:127
https://doi.org/10.1007/s00296-025-05879-3

Rheumatology
INTERNATIONAL

OBSERVATIONAL RESEARCH

Favorable outcomes for patients with refractory systemic lupus erythematosus treated with rituximab as evidenced with a follow-up of ≥ 10 years: a real-world evidence study

Chrysanthi Staveri[1] · Chrysa Lykoura[1] · Konstantinos Melissaropoulos[2] · Stamatis-Nick C. Liossis[1,3]

Received: 11 February 2025 / Accepted: 11 April 2025

RTX in Refractory SLE 10 Years After

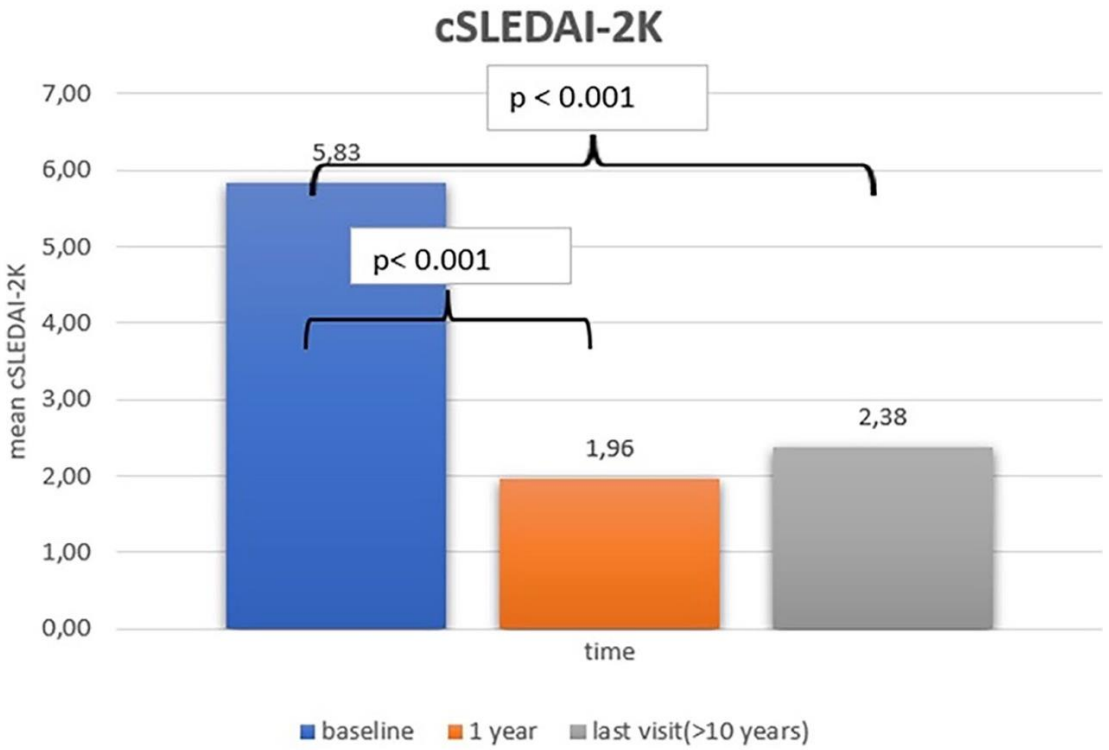


Table 5 RTX-induced clinical response at 12 months and at last visit, based on SLE manifestations

Organ involvement	% of response (12 months)	% of response (last visit)
Neuropsychiatric	100%	75%
Hematological	100%	66.67%
Vasculitis	50%	50%
Articular	66.67%	100%
Mucocutaneous	50%	75%
Pulmonary	33.33	66.67%
Miscellaneous	100%	100%
Nephritis	75%	62.5%

RTX in Refractory SLE 10 years after

Από **62** ασθενείς με ΣΕΛ που έλαβαν RTX, στρατολογήθηκαν στη μελέτη **23**.

Ολοι με ανθεκτικό ΣΕΛ και follow-up τουλάχιστον 10 χρόνια από την 1η έγχυση RTX.

Response rate: 1 έτος
68.7%

Response rate: > 10 έτη
75%

ΕΠΟΜΕΝΩΣ

Φαίνεται ότι ζούμε τη 2η επανάσταση στη Ρευματολογία

Είναι ανάγκη να «ξαναθυμηθούμε» την Ανοσολογία. Είναι η βάση για την κατανόηση των CTD και των ΘΕΡΑΠΕΙΏΝ που δίνουμε στους ασθενείς μας.

Είστε ΟΛΟΙ παραπάνω από ευπρόσδεκτοι ☺