Β κύτταρα: Βασικοί μηχανισμοί συμμετοχής τους στην αυτοανοσία

Ηράκλειο, 01 Νοέμβρη 2019

ΣΤΑΜΑΤΗΣ-ΝΙΚΟΣ ΛΙΟΣΗΣ
ΚΑΘΗΓΗΤΗΣ ΠΑΘΟΛΟΓΙΑΣ ΡΕΥΜΑΤΟΛΟΓΙΑΣ
ΙΑΤΡΙΚΟ ΤΜΗΜΑ ΠΑΝ/ΜΙΟΥ ΠΑΤΡΩΝ

Υπάρχει αυτοανοσία ΧΩΡΙΣ Β κύτταρα?

- Ποντίκια ΧΩΡΙΣ α/β Τ κύτταρα **παθαίνουν** lupus-like νόσημα
- Ποντίκια ΧΩΡΙΣ ούτε α/β ούτε γ/δ Τ κύτταρα **ΠΑΛΙ παθαίνουν** λύκο
- Ποντίκια ΧΩΡΙΣ Β κύτταρα **ΔΕΝ** παθαίνουν λύκο.
- Ποντίκια που έχουν Β κύτταρα που δεν εκκρίνουν ΚΑΝΕΝΑ αντίσωμα **ΠΑΛΙ παθαίνουν** λύκο.

Περίπου 5% του γενικού πληθυσμού πάσχει από κάποιο(α) αυτοάνοσο νόσημα

Σε πολλά από αυτά (αλλά ΟΧΙ σε όλα) υπάρχουν και χαρακτηριστικά αυτοαντισώματα

ΑΥΤΟΑΝΟΣΙΑ

Διαταραχές στην ανοσολογική ανοχή του Β κυττάρου

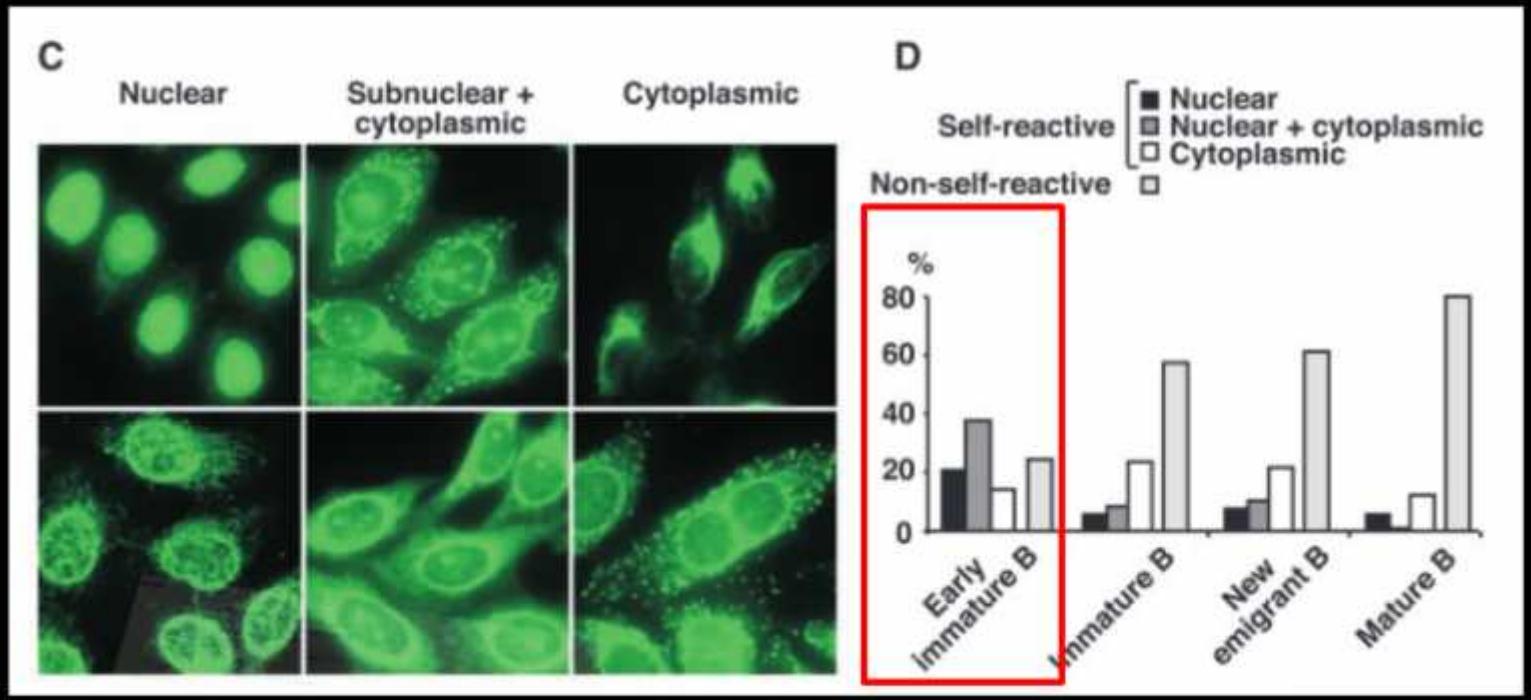
(Tolerance)

Predominant Autoantibody Production by Early Human B Cell Precursors

Hedda Wardemann,[1] Sergey Yurasov,[1,3] Anne Schaefer,[1] James W. Young,[4] Eric Meffre,[1,5*] Michel C. Nussenzweig[1,2*]

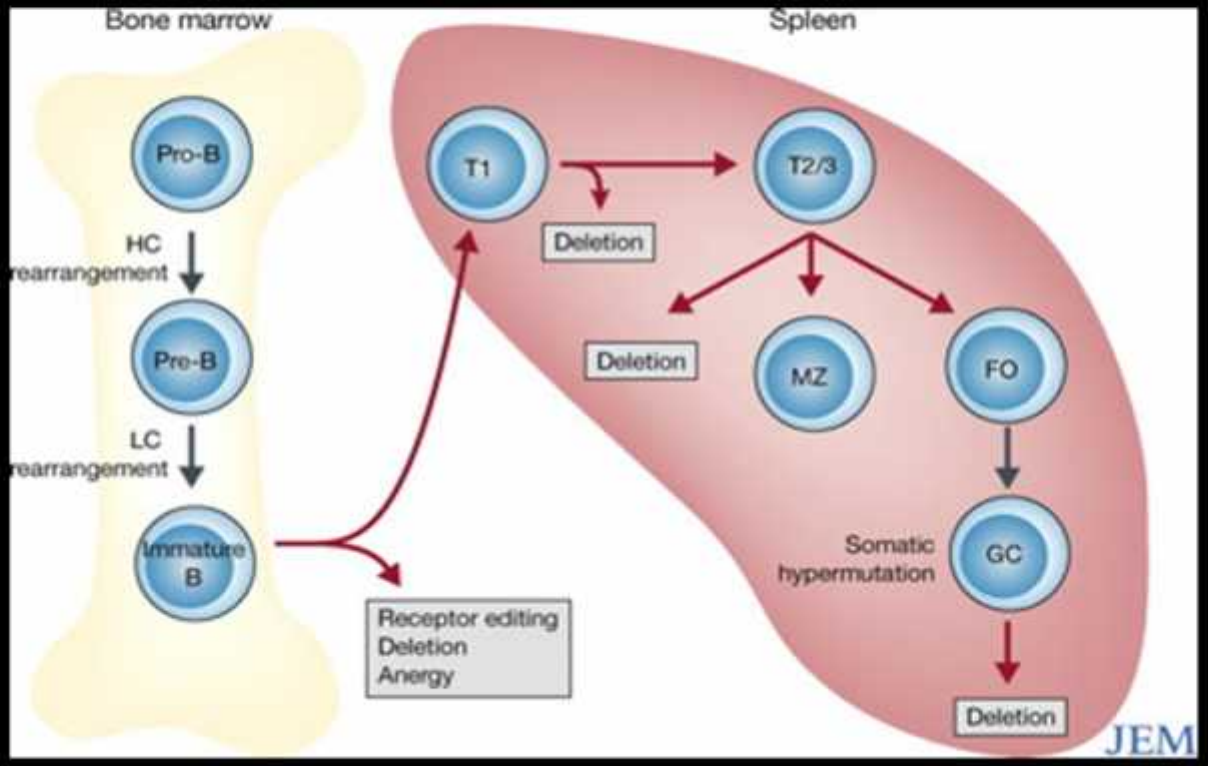
5 SEPTEMBER 2003 VOL 301 SCIENCE www.sciencemag.org

50-75% των Ab που παράγουν τα «early immature B cells» είναι αυτοαντισώματα



Όλα τα άωρα (και αυτοδραστικά) Β κύτταρα πρέπει να περάσουν από 2 checkpoints

Οντογένεση των Β λεμφοκυττάρων: Tolerance Checkpoints



Jacobi AM, Diamond B. J Exp Med 2005; 202:341.

B cells in SLE:
Dysfunctional tolerance checkpoints

- 1° checkpoint: Μέσα στον Μυελό. Newly emigrant B cells ($CD19^+CD10^+IgM^+CD27^-$).
- Normals: 40.7% autoreactive.

- 2° checkpoint: Στα δευτερογενή λεμφικά όργανα. Mature naïve B cells ($CD19^+CD10^-IgM^+CD27^-$).

- Τελικά: **5-20%** των normal mature naïve = αυτοδραστικά
- **25-50%** των lupus mature naïve = αυτοδραστικά

Yurasov S et al. J Exp Med 2005; 201:703.

Φαίνεται ότι το πρόβλημα είναι «intrinsic», δηλ. genetic

- GWAS
- **PTPN22 (SLE, T1D, RA)**

PTPN22

- Protein-tyrosine phosphatase
- Ελαττώνει τη μετάδοση του ενδοκυττάριου σήματος από τον TCR (και ίσως από τον BCR)
- **Αλληλόμορφο R620W**
- "Gain-of-function" allele

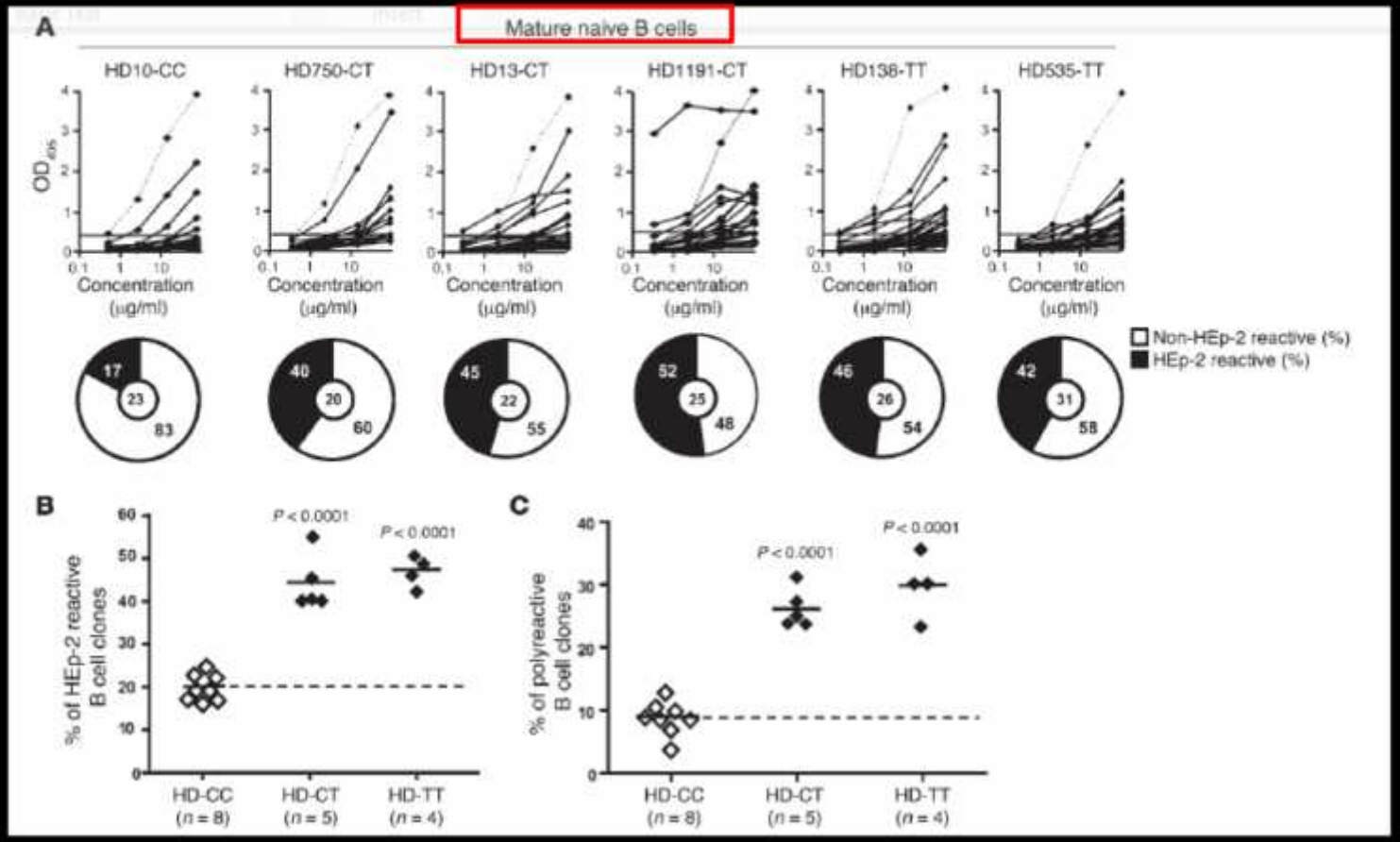
- Ανιχνεύεται στα GWAS για ΣΕΛ, RA, T1D.

The *PTPN22* allele encoding an R620W variant interferes with the removal of developing autoreactive B cells in humans

Laurence Menard,[1] David Saadoun,[1] Isabelle Isnardi,[1] Yen-Shing Ng,[1] Greta Meyers,[1] Christopher Massad,[1] Christina Price,[1] Clara Abraham,[2] Roja Motaghedi,[3] Jane H. Buckner,[4] Peter K. Gregersen,[5] and Eric Meffre[1]

[1]Department of Immunobiology and [2]Department of Medicine, Section of Digestive Diseases, Yale University School of Medicine, New Haven, Connecticut, USA. [3]Department of Pediatrics, Weill Medical College of Cornell University, New York, New York, USA. [4]Translational Research Program, Benaroya Research Institute, Seattle, Washington, USA. [5]Robert S. Boas Center for Genomics and Human Genetics, The Feinstein Institute for Medical Research, Manhasset, New York, USA.

Μόνο 1 (ή και 2) δόσεις του PTPN22 R620W αρκούν για να καταρρίψουν την ανοσολογική ανοχή



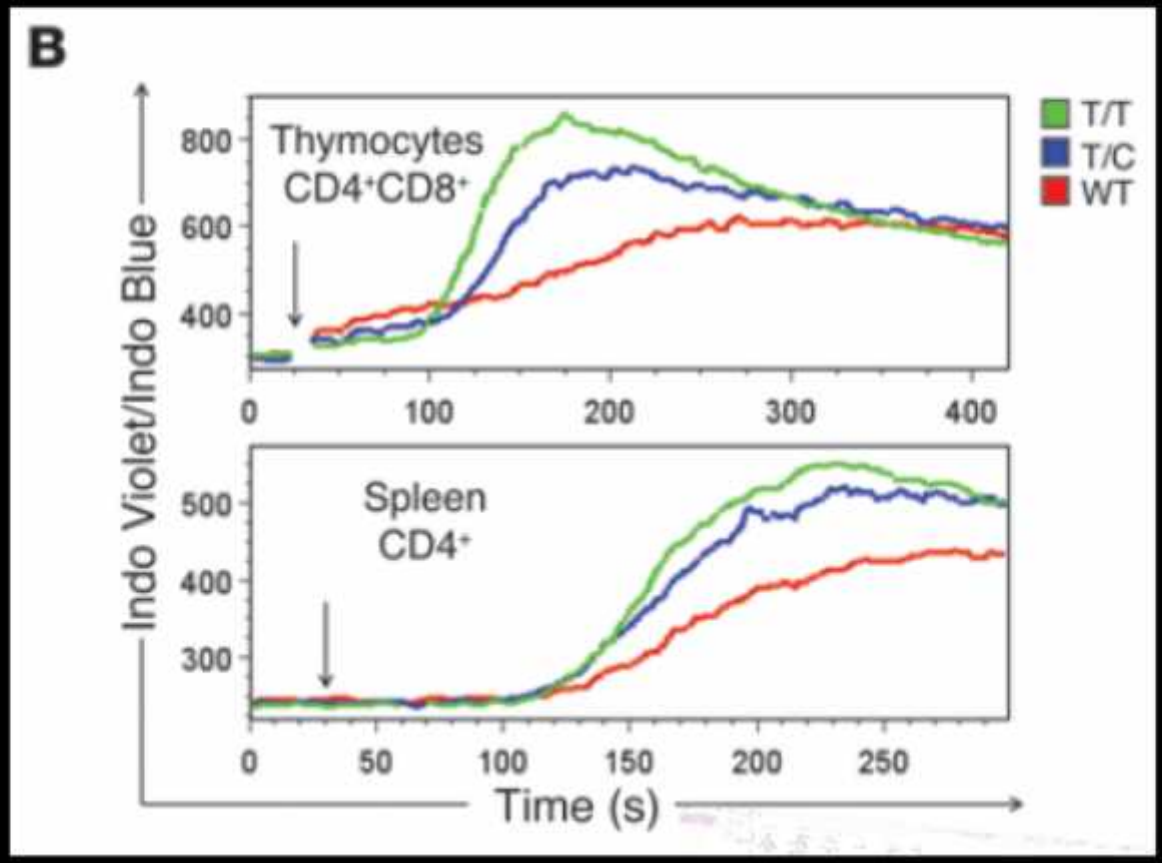
A disease-associated *PTPN22* variant promotes systemic autoimmunity in murine models

Xuezhi Dai,[1,2] Richard G. James,[3] Tania Habib,[4] Swati Singh,[1,2] Shaun Jackson,[1,2] Socheath Khim,[1,2] Randall T. Moon,[3,5] Denny Liggitt,[6] Alejandro Wolf-Yadlin,[7] Jane H. Buckner,[4] and David J. Rawlings[1,2,8]

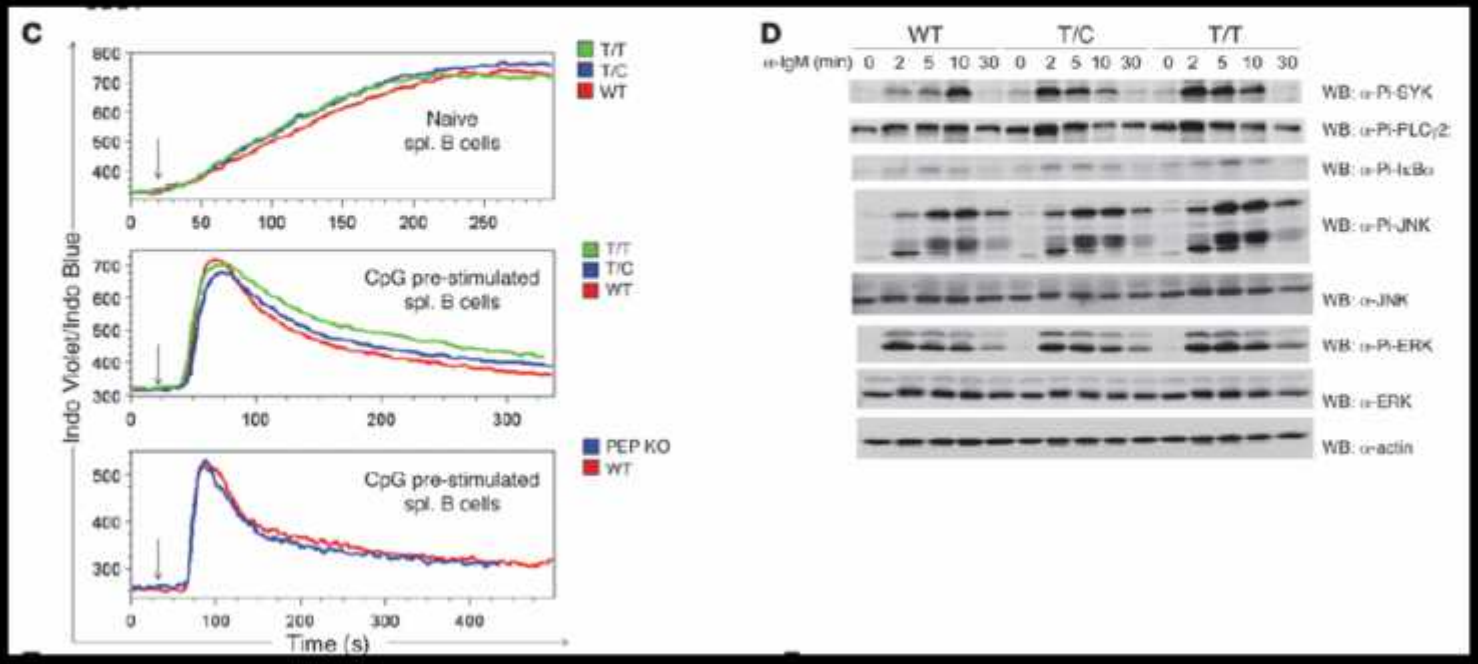
[1]Department of Pediatrics, University of Washington School of Medicine, Seattle, Washington, USA. [2]Seattle Children's Research Institute, Seattle, Washington, USA. [3]Department of Pharmacology, University of Washington School of Medicine, Seattle, Washington, USA. [4]Translational Research Program, Benaroya Research Institute, Seattle, Washington, USA. [5]Howard Hughes Medical Institute, [6]Department of Comparative Medicine, [7]Department of Genome Sciences, and [8]Department of Immunology, University of Washington School of Medicine, Seattle, Washington, USA.

The Journal of Clinical Investigation http://www.jci.org Volume 123 Number 5 May 2013

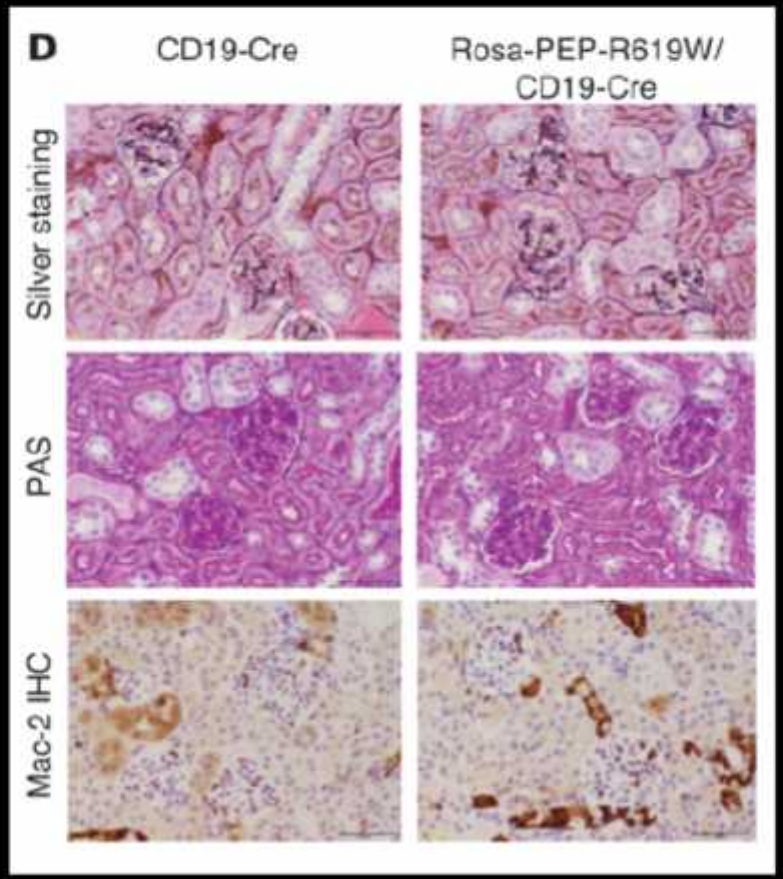
PTPN22 variant: Προκαλεί ανώμαλη διέγερση των Τ κυττάρων



PTPN22 variant: Προκαλεί ανώμαλη διέγερση των Β κυττάρων



Εκφραση του PTPN22 variant ΜΟΝΟ σε Β κύτταρα: Νεφρίτιδα!!

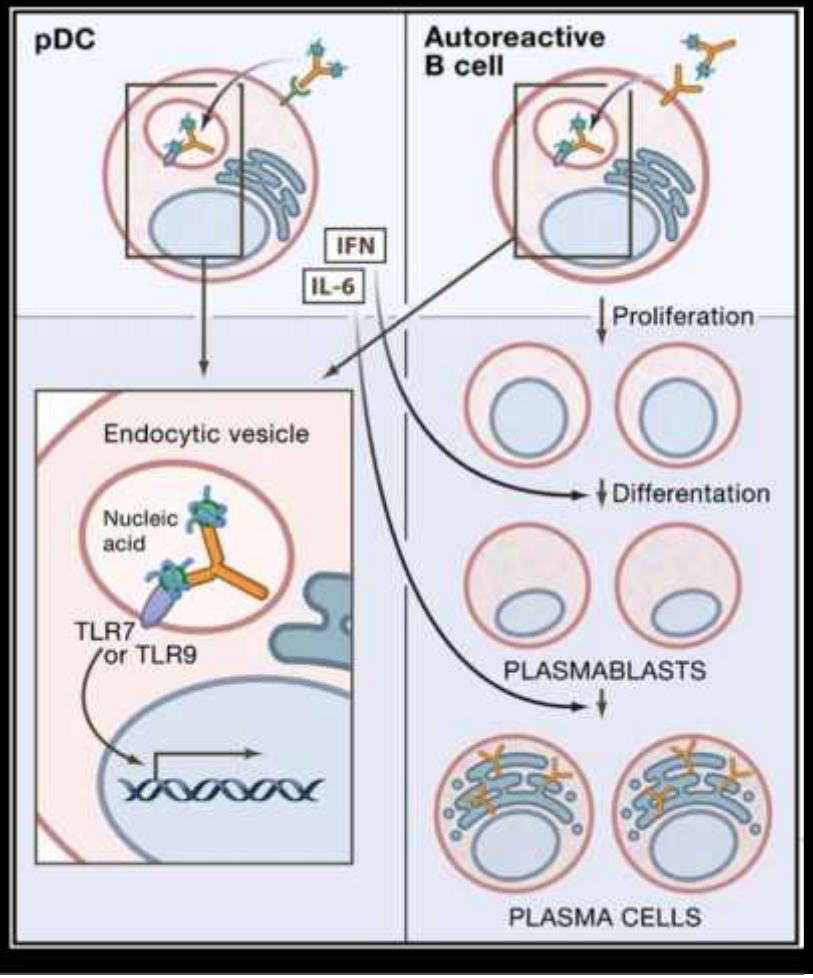


Επομένως:

- Αυτοαντιδραστικά λεμφοκύτταρα υπάρχουν πολλά.
- Αλλά, ΠΩΣ αυτά τελικά παράγουν αυτοAb?

- IFNα

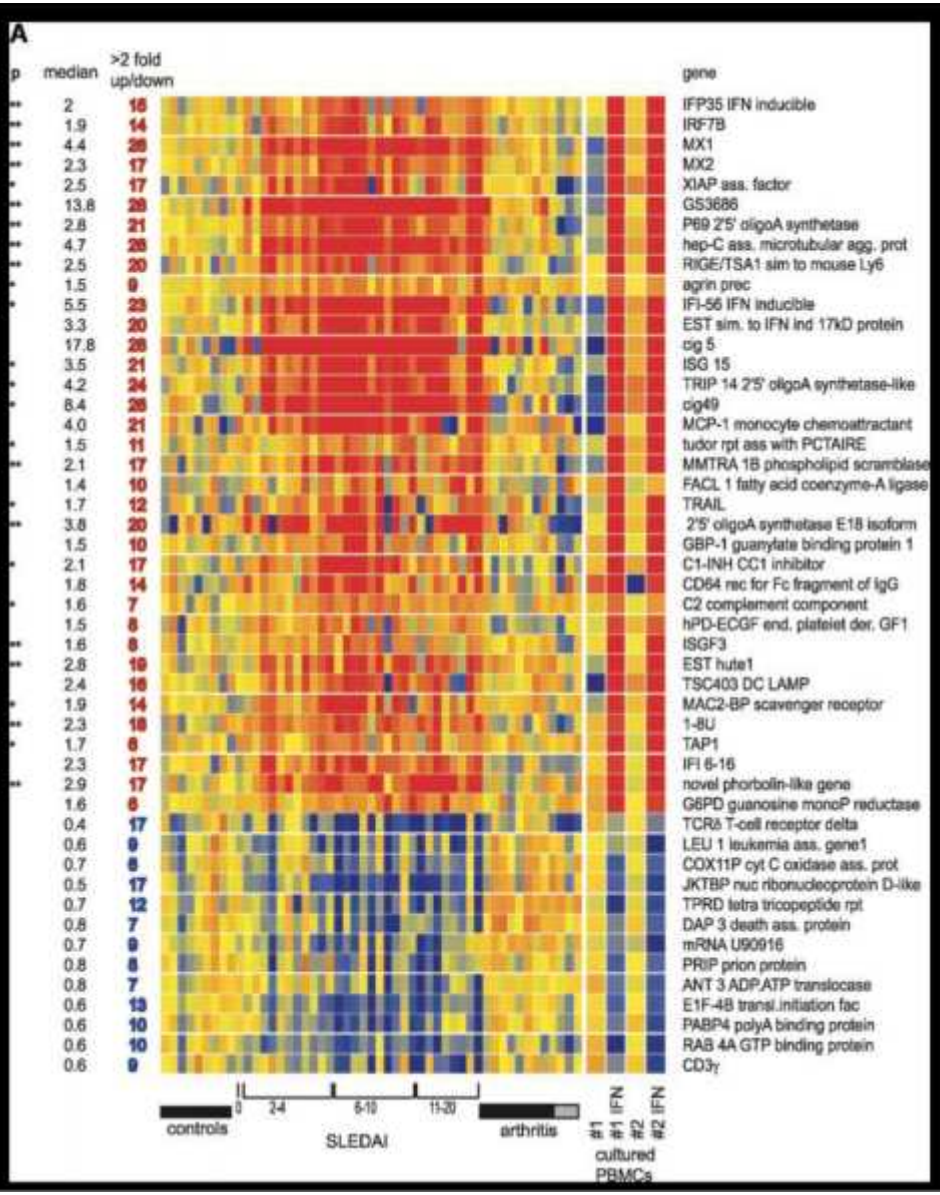
Η IFNα παράγεται κυρίως από τα pDC



Banchereau J & Pascual V.
Immunity 2006; 25:383

Normal pDC vs. Lupus pDC

- Φυσιολογικά, τα pDC διεγειρόμενα (ιοί) παράγουν πολύ IFNα για μερικές ώρες.
- Ακολούθως, εκκρίνουν TNFα.
- Ο TNFα καταστέλλει αυτοκρινώς την IFNα.
- pDC in SLE: Υπερπαραγωγή IFNα χωρίς αλλαγή σε TNFα



ΜΟΝΟ σε ασθενείς με ΣΕΛ:
ΙΣΧΥΡΗ υπερέκφραση 15 γονιδίων

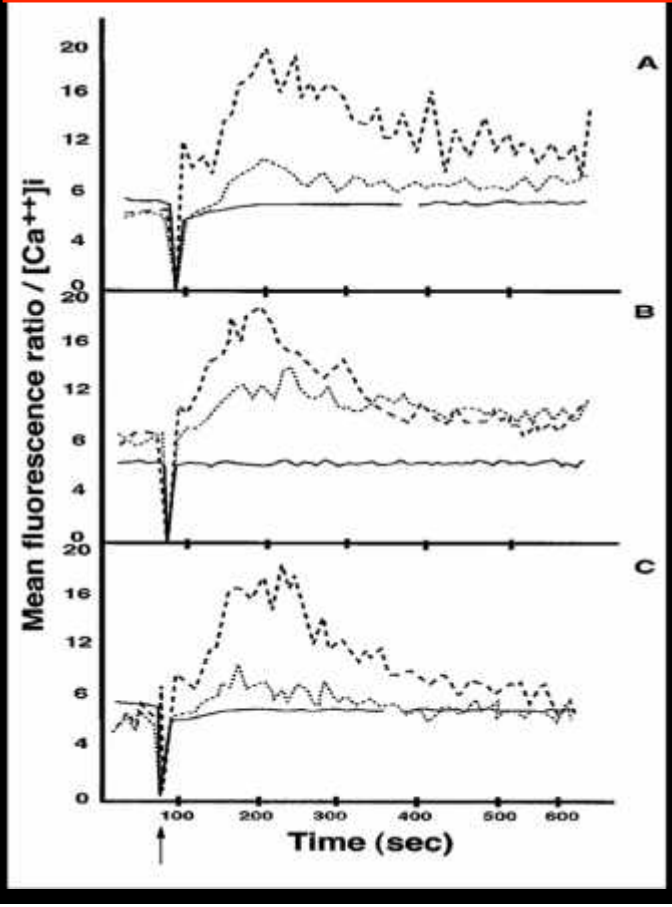
14/15 γονίδια είναι στόχοι της IFN

J. Exp. Med. © The Rockefeller University Press • 0022-1007/2003/03/711/13 $8.00
Volume 197, Number 6, March 17, 2003 711–723
http://www.jem.org/cgi/doi/10.1084/jem.20021553

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*

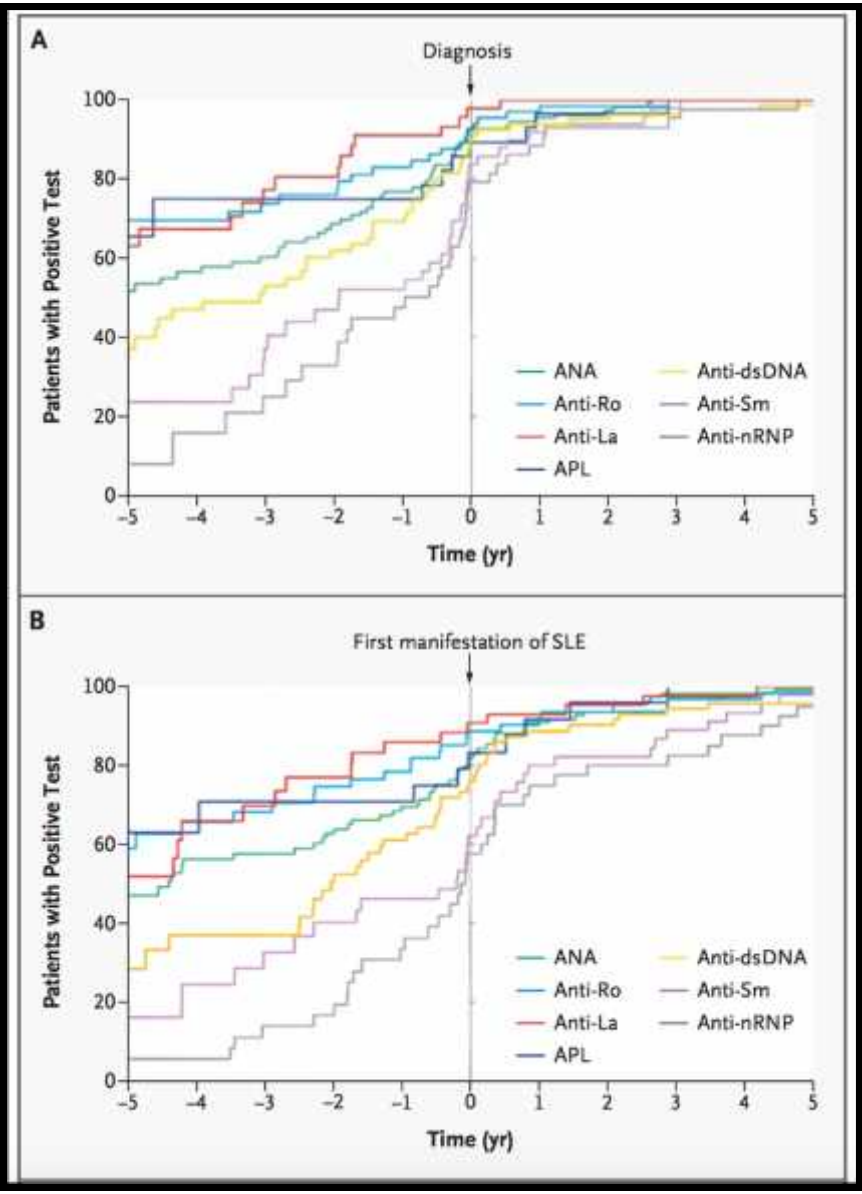


J. Clin. Invest.

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

The Lupus B cell

- Σε μεγάλο ποσοστό (έως 50%) αυτοδραστικά.
- Χαμηλός ουδός διέγερσης.
- Λαμβάνουν βοήθεια από αυτοδραστικά T cells
- Μετατρέπονται εύκολα σε πλασμαβλάστες και πλασματοκύτταρα.
- Παράγουν “ντουζίνες” απο αυτοAb.



Development of Autoantibodies before the Clinical Onset of Systemic Lupus Erythematosus

Melissa R. Arbuckle, M.D., Ph.D., Micah T. McClain, Ph.D., Mark V. Rubertone, M.D., R. Hal Scofield, M.D., Gregory J. Dennis, M.D., Judith A. James, M.D., Ph.D., and John B. Harley, M.D., Ph.D.

N ENGL J MED 349;16 WWW.NEJM.ORG OCTOBER 16, 2003

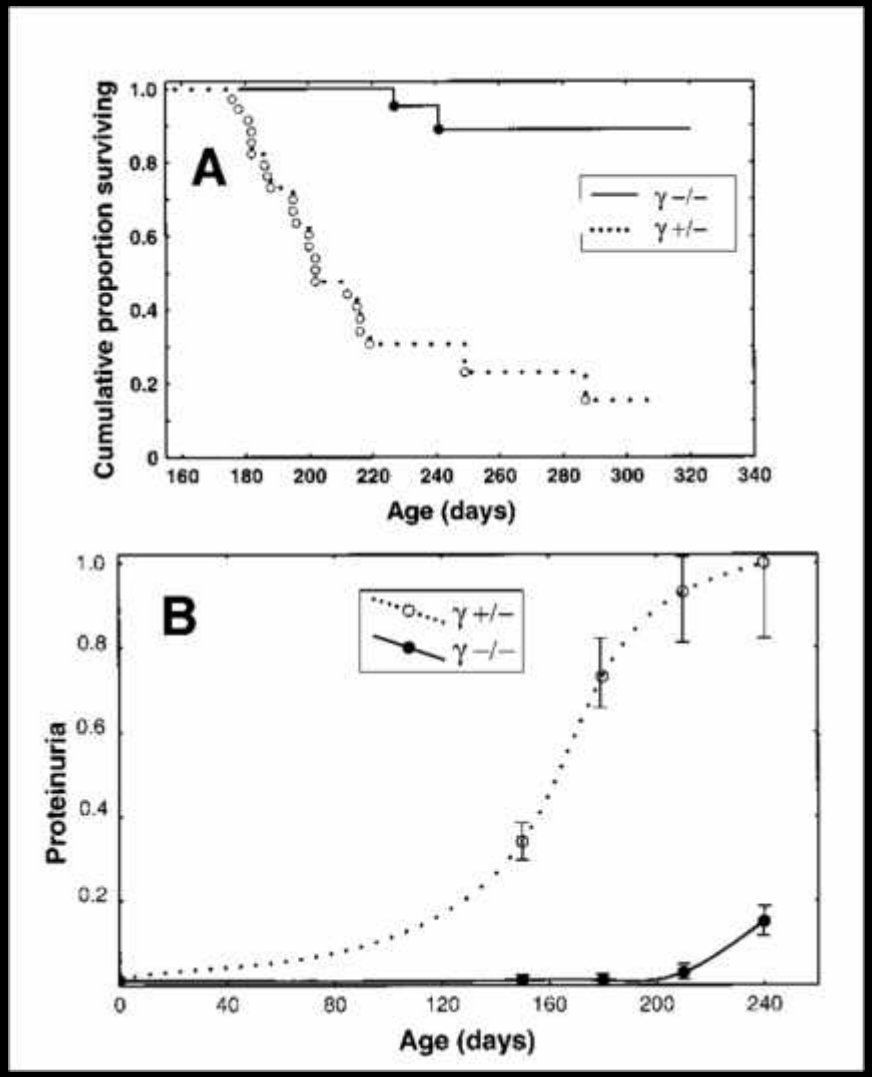
ΑυτοAb = Παθολογία?

- **Μερικά** αυτοAb είναι παθογόνα.
- Οποιος έχει anti-dsDNA έχει και ΣΝ??
- …and vice-versa…..
- Ποιά **ΑΚΡΙΒΩΣ** παθολογία προκαλεί το anti-Sm??
- Οσοι έχουν Coombs+ έχουν και αιμόλυση??
- Το πρόσφατο παράδειγμα της RTX-treated ITP…

Το ποντίκι B6.Sle1

- Διάσπαση ανοσολογικής ανοχής του Β κυττάρου.
- Παράγει αντισώματα έναντι πυρ. αντιγόνων.
- **AυτοAb σε πολύ υψηλούς τίτλους.**

- **“ΚΛΙΝΙΚΕΣ ΕΚΔΗΛΩΣΕΙΣ”: …ΤΙΠΟΤΑ**



Αλλο τα IC
Αλλο η ΣΝ

Uncoupling of Immune Complex Formation and Kidney Damage in Autoimmune Glomerulonephritis

Raphael Clynes, Calin Dumitru, Jeffrey V. Ravetch*

SCIENCE • VOL. 279 • 13 FEBRUARY 1998 • www.sciencemag.org

Λίγα νεότερα δεδομένα

Age-associated B cells (ABC)

- Expression of CD11c
- Expression of the transcription factor T-bet
- Triggering via BCR, IFNγR, TLR7 induces HIGH LEVELS of T-bet (!!!!)

Role of ABC

- ABC appear in autoimmunity (human & murine)
- ABC produce HIGH AMOUNTS of AutoAb
- ABC are VERY POTENT APC

T-bet expressing B cells

- Increased numbers in patients with SLE (vs. controls)
- Increased numbers in patients with active Crohn's
- Increased numbers in patients with MS
- Increased numbers in patients with celiac disease

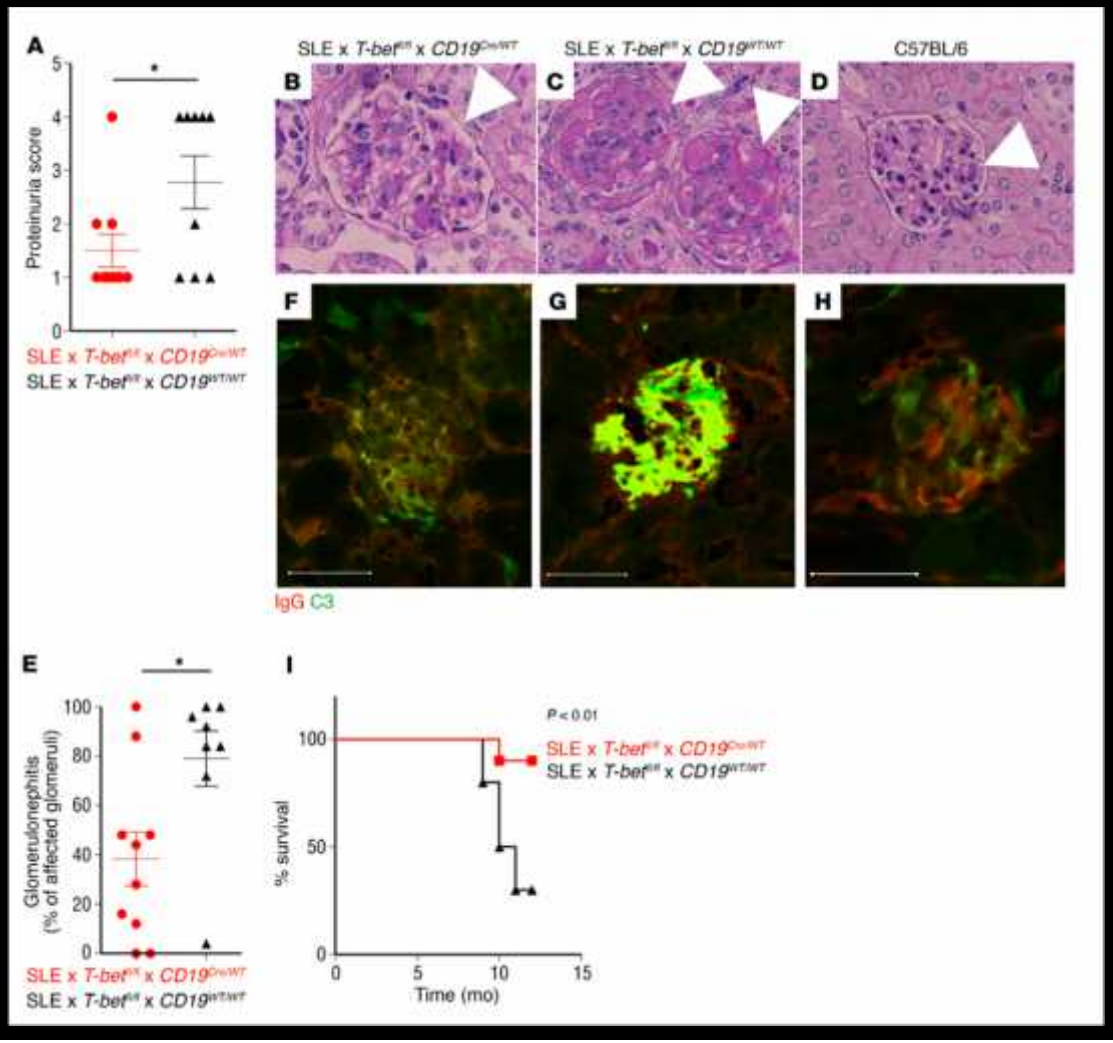
RESEARCH ARTICLE

The Journal of Clinical Investigation

B cells expressing the transcription factor T-bet drive lupus-like autoimmunity

Kira Rubtsova,[1,2] Anatoly V. Rubtsov,[1,2] Joshua M. Thurman,[3] Johanna M. Mennona,[2] John W. Kappler,[1,2,4,5] and Philippa Marrack[1,2,5,6]

SLE mice with Tbet-deficient B cells: attenuated autoimmunity



nature COMMUNICATIONS

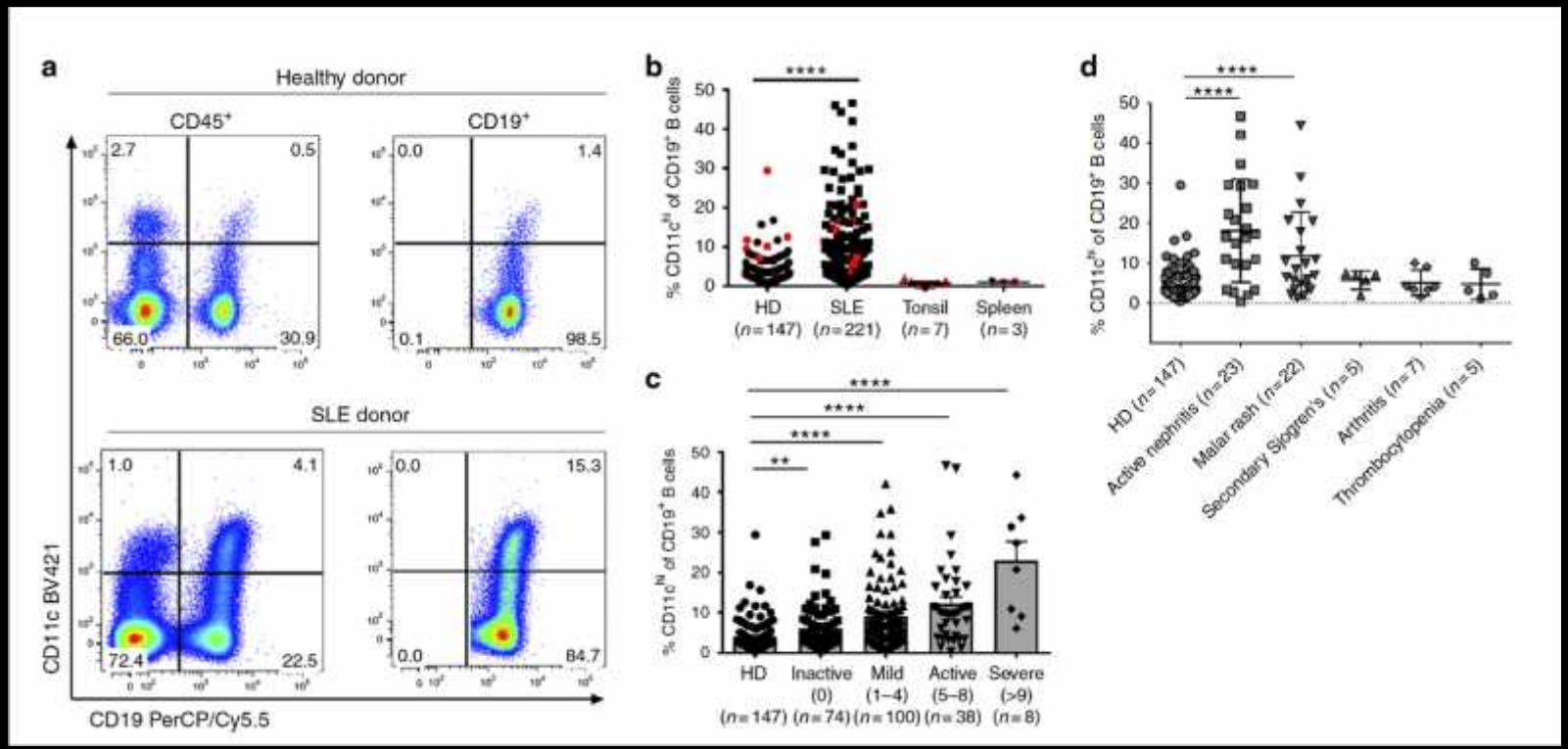
ARTICLE

DOI: 10.1038/s41467-018-03750-7 OPEN

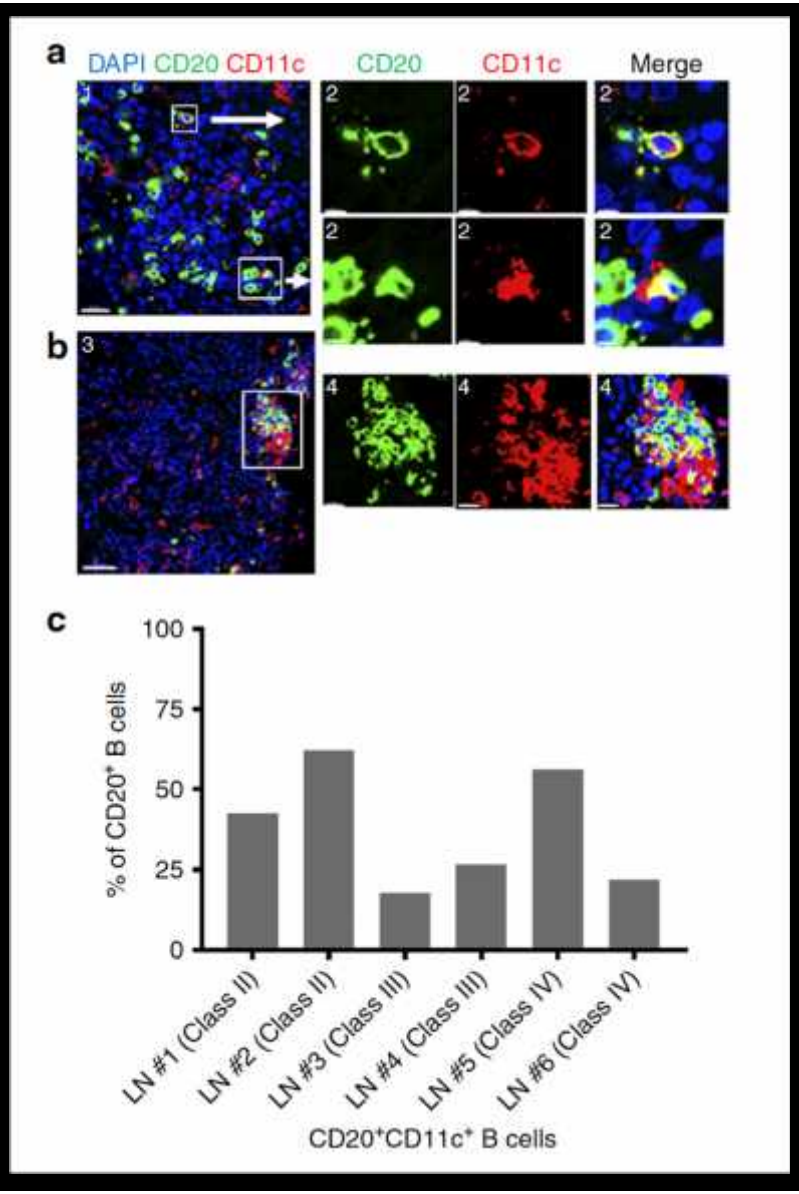
IL-21 drives expansion and plasma cell differentiation of autoreactive CD11c^{hi}T-bet^{+} B cells in SLE

Shu Wang[1], Jingya Wang[1], Varsha Kumar[1], Jodi L. Karnell[1,6], Brian Naiman[1], Phillip S. Gross[1], Saifur Rahman[1], Kamelia Zerrouki[1], Richard Hanna[1], Christopher Morehouse[2], Nicholas Holoweckyj[2], Hao Liu[2], Autoimmunity Molecular Medicine Team, Zerai Manna[3], Raphaela Goldbach-Mansky[4], Sarfaraz Hasni[3], Richard Siegel[3], Miguel Sanjuan[1,7], Katie Streicher[2], Michael P. Cancro[5], Roland Kolbeck[1] & Rachel Ettinger[1,6]

CD11c+hi B cells in patients with SLE.
Associations



Wang S et al: Nature Communications 2018;9:1758.

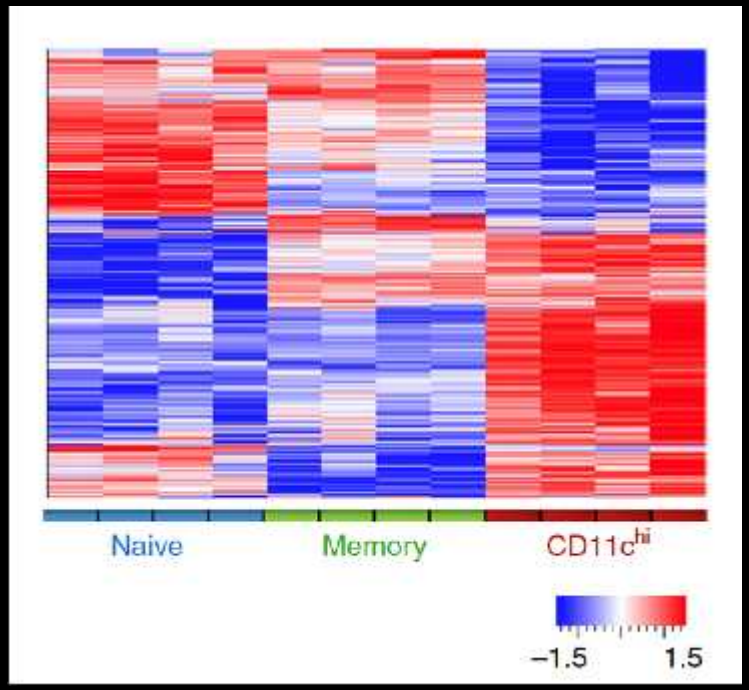


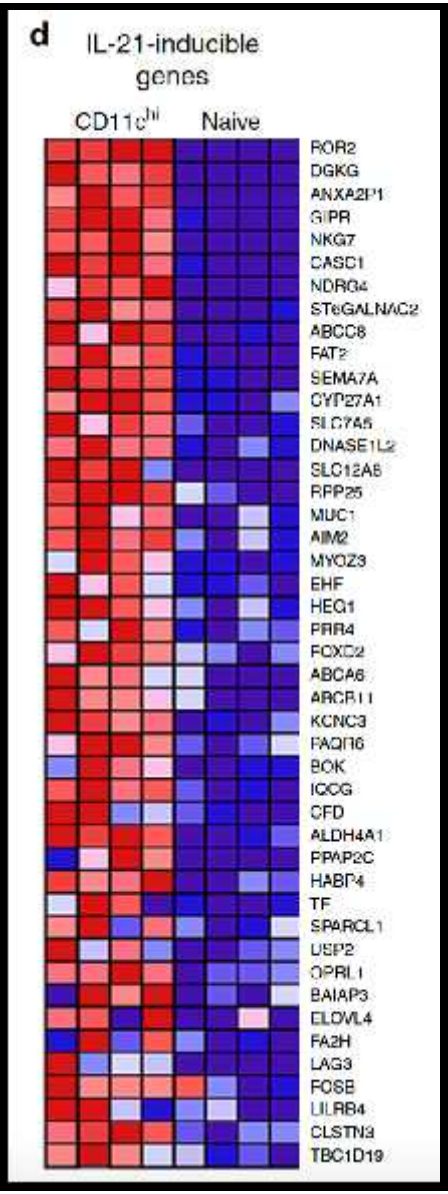
CD11c+ B cells & lupus nephritis

Υπάρχουν στο νεφρό

A unique transcriptome of CD11c+hi B cells in SLE

Clearly, an IL-21 “signature”



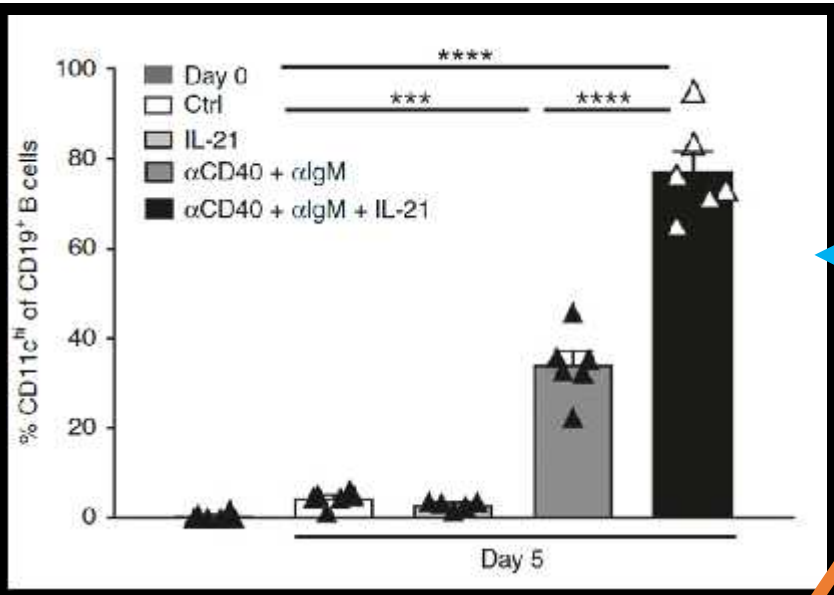


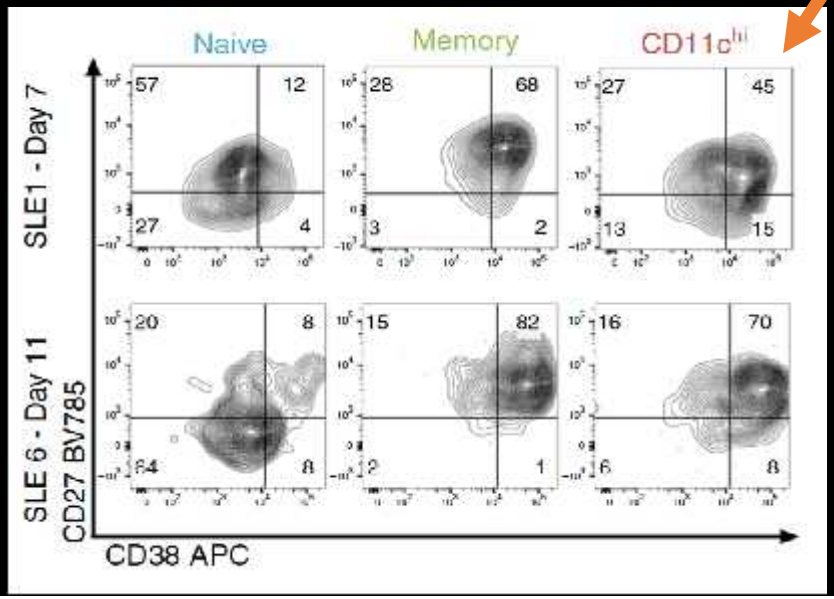
CD11c+ B cells

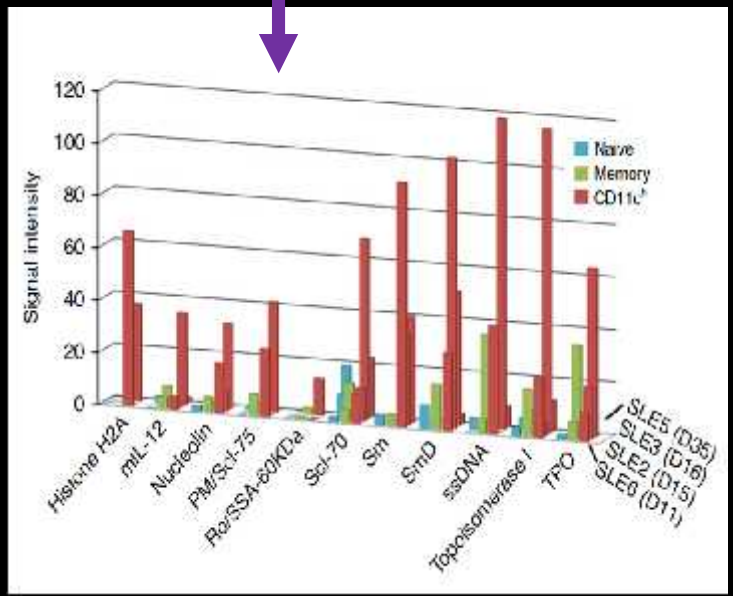
Recipe

Fate

Function







Clinical Immunology 195 (2018) 101–106

Contents lists available at ScienceDirect

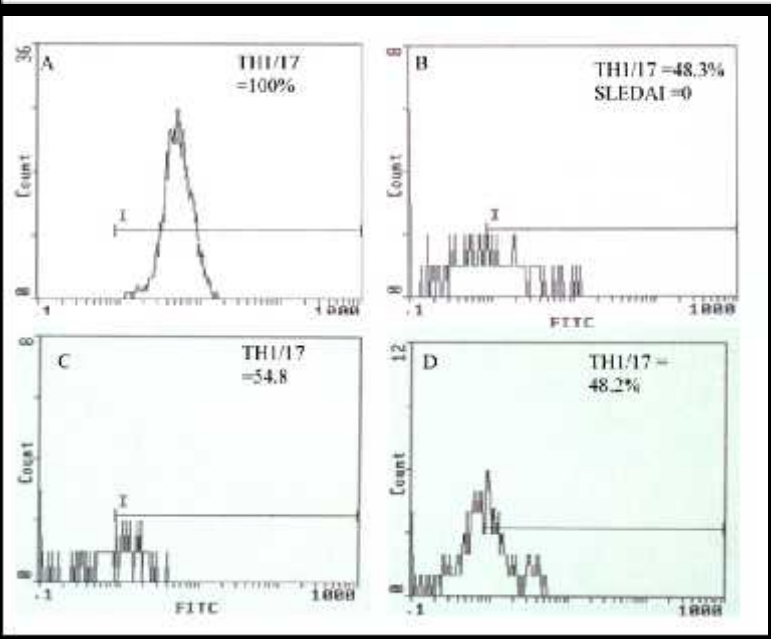
Clinical Immunology

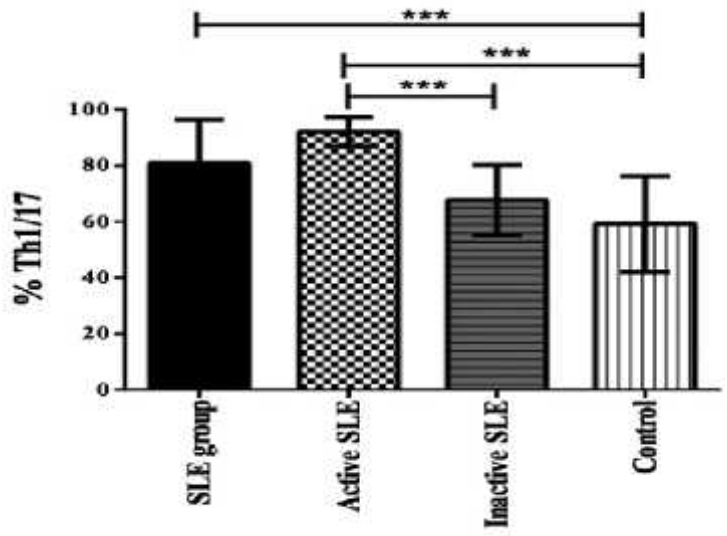
journal homepage: www.elsevier.com/locate/yclim

Th1/17 cells, a subset of Th17 cells, are expanded in patients with active systemic lupus erythematosus

Anastasia Tsanaktsi[a,1], Elena E. Solomou[b,1], Stamatis-Nick C. Liossis[a,*]

[a] Division of Rheumatology, Dept of Internal Medicine, University of Patras Medical School, Patras, Greece
[b] Dept of Internal Medicine, University of Patras Medical School, Patras, Greece





SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

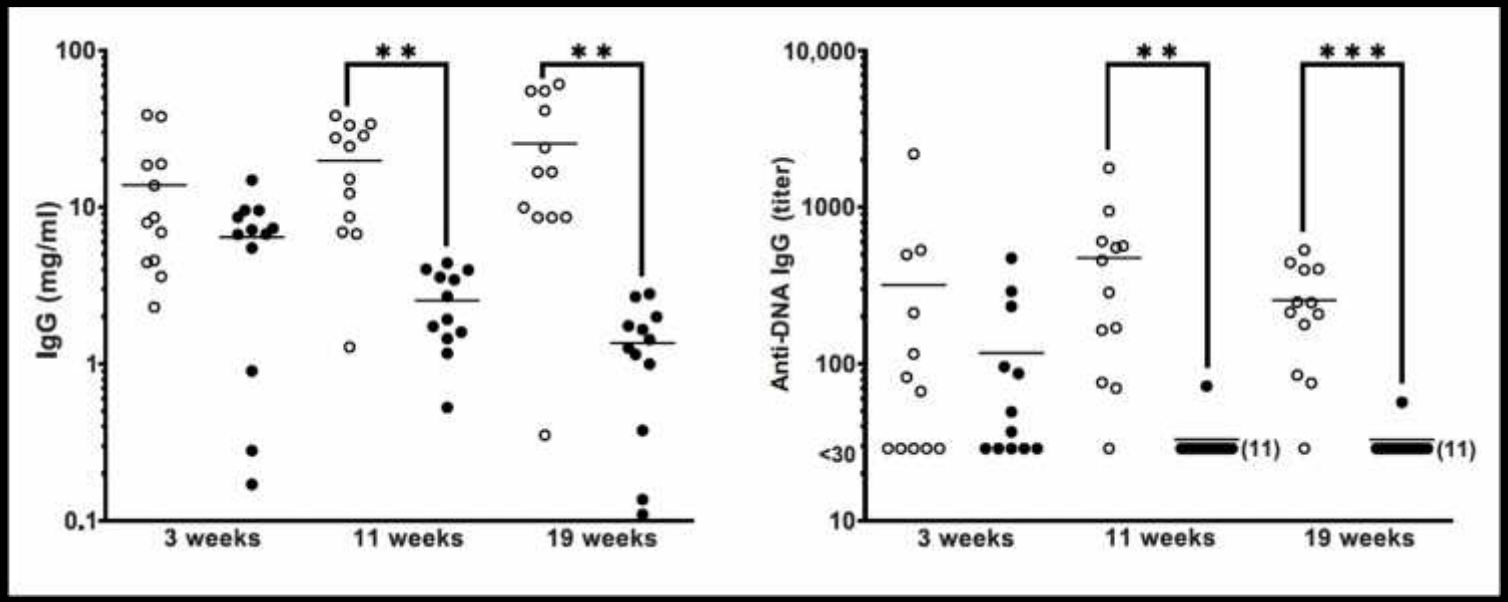
AUTOIMMUNITY

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

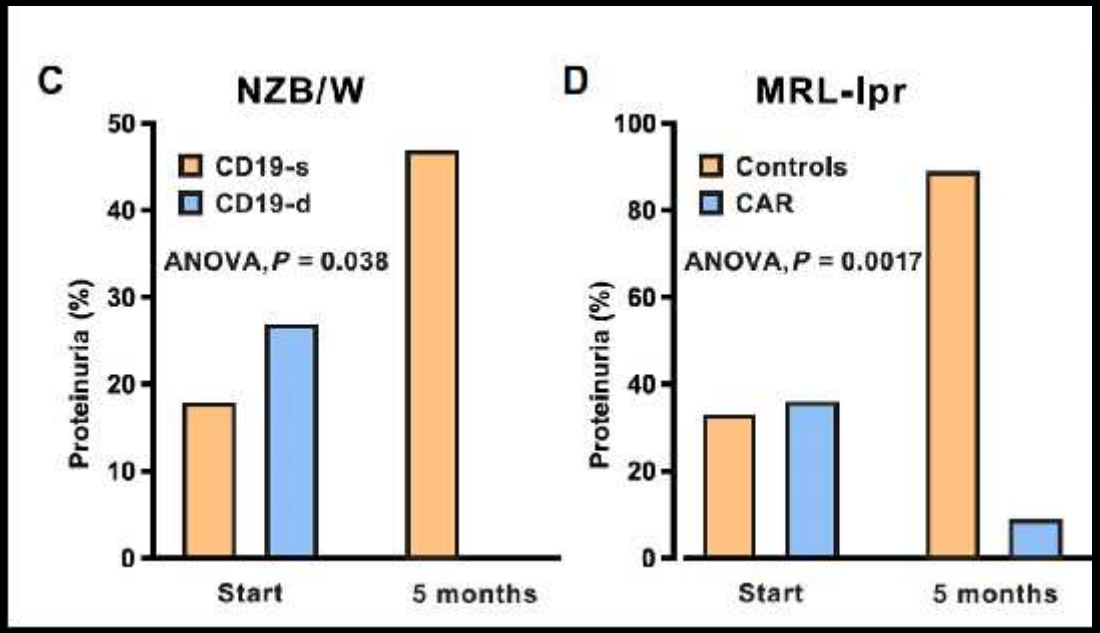
Rita Kansal[1], Noah Richardson[1], Indira Neeli[1], Saleem Khawaja[1], Damian Chamberlain[1], Marium Ghani[1], Qurat-ul-ain Ghani[1], Louisa Balazs[2], Sarka Beranova-Giorgianni[3], Francesco Giorgianni[3], James N. Kochenderfer[4], Tony Marion[1], Lorraine M. Albritton[1], Marko Radic[1]*

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

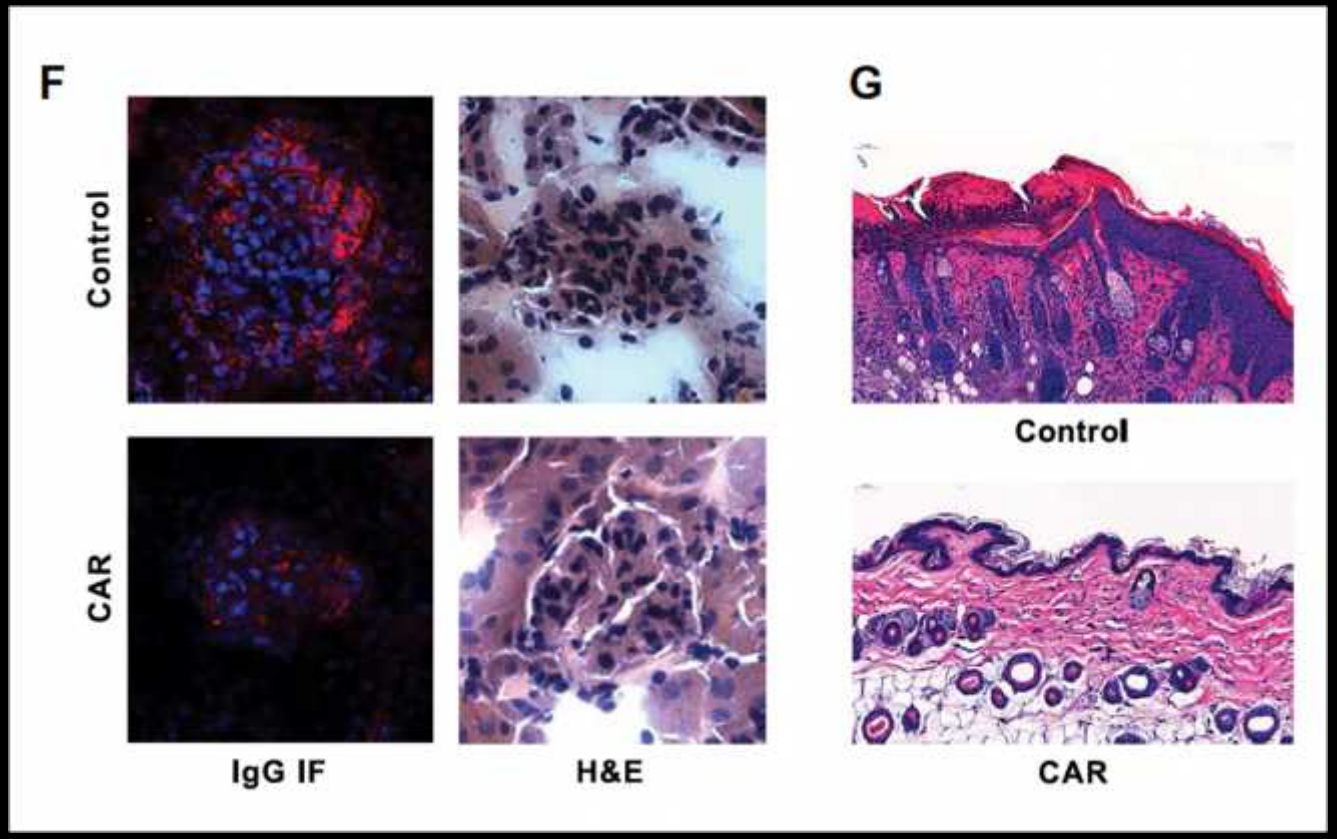
Sustained B cell depletion with CAR T cells improves autoAb titers



Sustained B cell depletion with CAR T cells improves proteinuria of lupus-prone mice

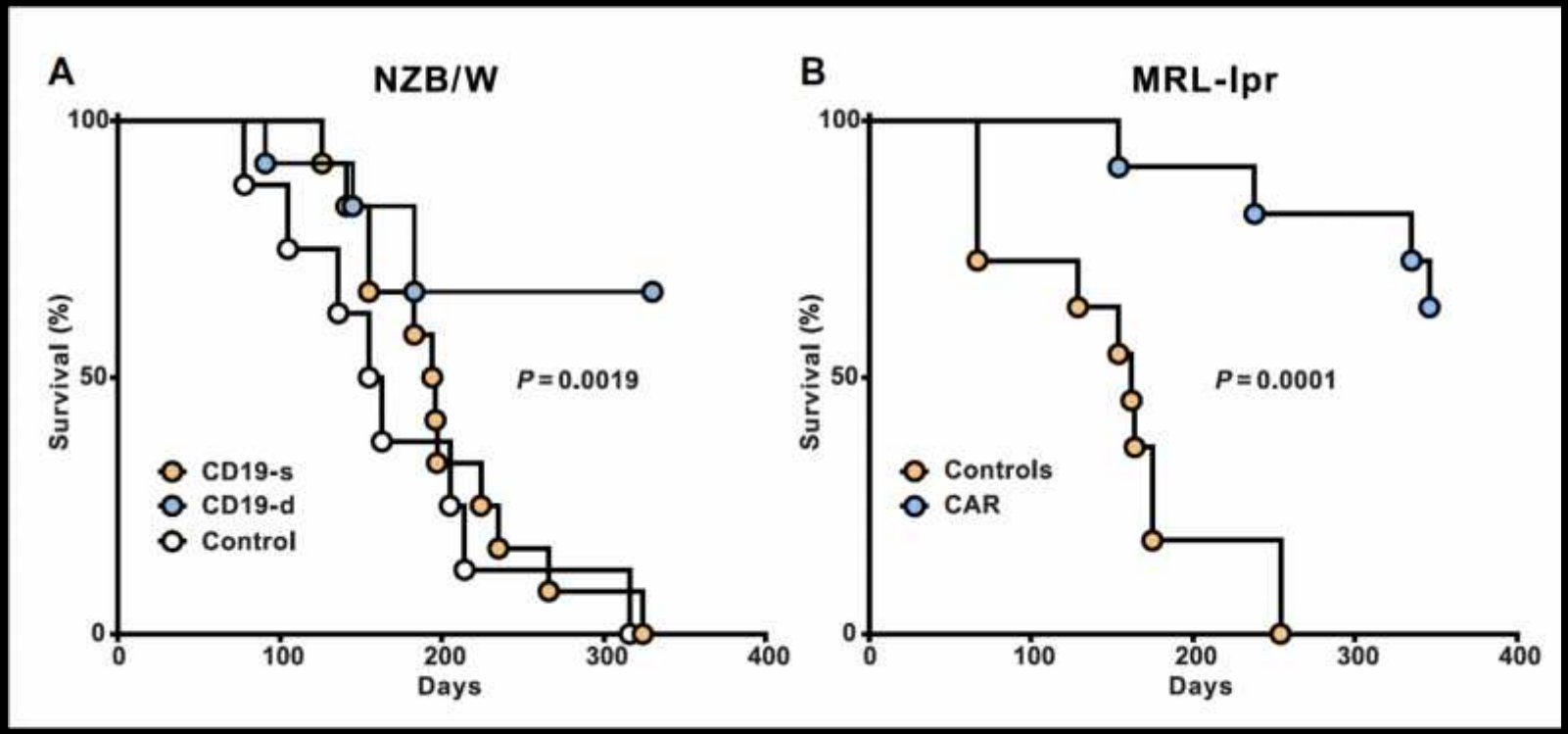


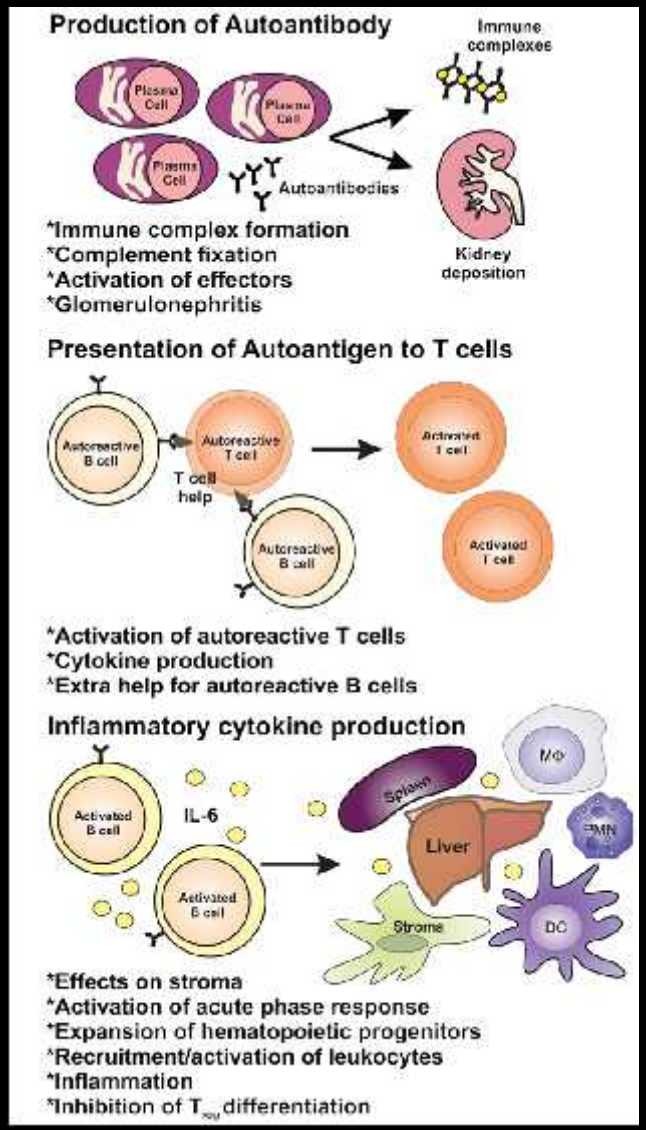
Sustained B cell depletion with CAR T cells improves renal & skin disease of lupus-prone mice



R. Kansal et al. *Science Translational Medicine*, doi:10.1126/scitranslmed.aav1648, 2019

Sustained B cell depletion with CAR T cells improves survival of lupus-prone mice





The roles of B cells in SLE

Ab / AutoAb production
Ag presentation / T cell activation
Production of cytokines