ACR 2017 San Diego

Highlights in SLE & APS

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251 ΓΝΑ

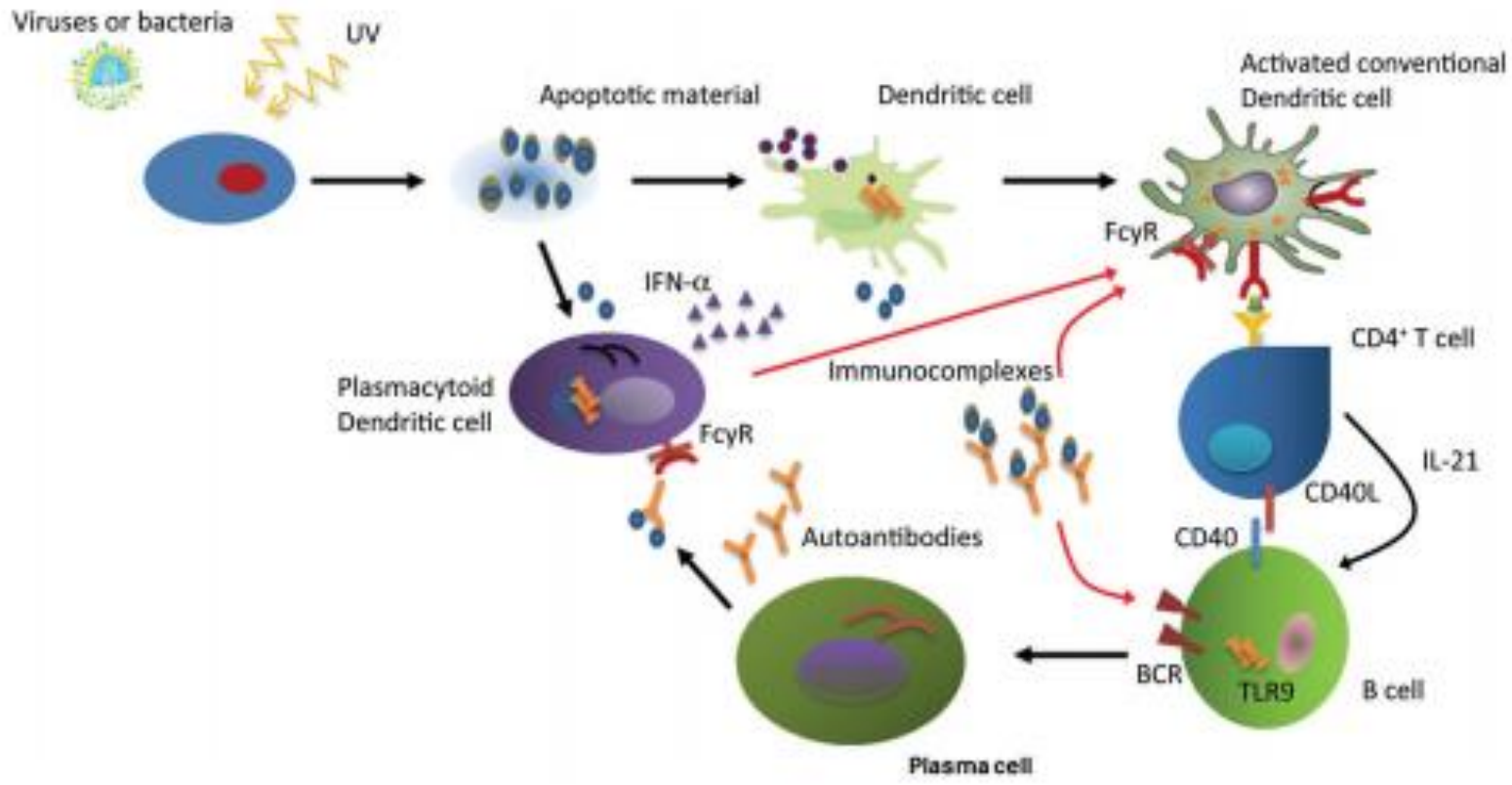
Σύγκρουση Συμφερόντων

Καμία για αυτή την παρουσίαση

Τι ειπώθηκε στο ACR meeting για τον ΣΕΛ και το ΑΦΣ;

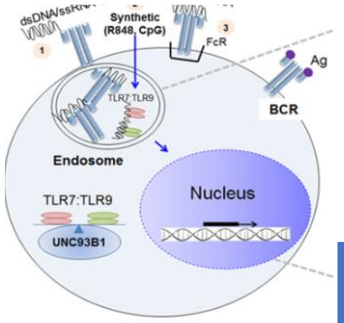
- Παθοφυσιολογία (Basic science)
- Γενετική (Genetics)
- Κλινική πρακτική (Βιοδείκτες, προτεινόμενα κριτήρια, Νεφρίτιδα)
- Θεραπεία (Treatment)
- ΑΦΣ (GAPSS, επίπτωση αντισωμάτων)
- Μελλοντικοί στόχοι (what’s next..?)

Παθοφυσιολογία στον ΣΕΛ



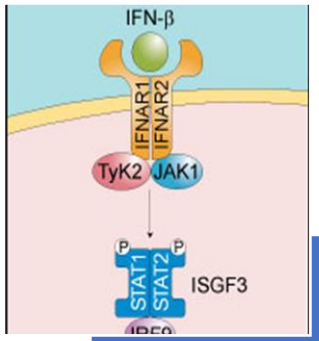
George Bertsias, Ricard Cervera, Dimitrios T Boumpas
Chapt. 20: Systemic Lupus Erythematosus: Pathogenesis and Clinical Features,
EULAR Textbook of Rheumatology

TLRs – IFNs – B-lymphocytes



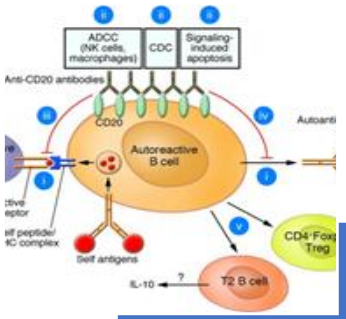
TLRs

- TLR7 ~UBE2L3
- TLR9→ B-cells only (dsdna?)
- HMGB1-TLR4 axis → NPSLE



IFNs

- TLR7/8 → IFN (NEUTROPHILS)
- IFNβ → B-cells (IFNβ ~TLR7)
- IFNB1 + IFNW1



B-cells

- IFNα→ B-cell tolerance (BAFF?)
- Transitional B-cells (BAFF req)
- Innate B1Bcells

ABSTRACTS

Γενετική

- AB2825: The indirect binding of EBNA2 to human DNA is associated with the genetic risk loci of both SLE and RA EBV, the EBV infected B cell, and EBNA2 encoded by EBV DNA participating in SLE and RA pathogenesis

- AB2818: IFNB and IFNW are likely IFN family member upstream regulators accounting for the IGS in SLE cells and tissues

- AB2648: The SLE risk variant rs10499197 is likely a causal variant that disrupts the function of a putative enhancer upstream of TNFAIP3

- AB2976: Identification of Systemic Lupus Erythematosus Causal Risk Variant Candidates Spanning the UBE2L3 Haplotype

- AB1638: High Genetic Risk Score Is Associated with Increased Organ Damage in SLE

Το συμπλήρωμα...

- AB680: Abnormalities in Complement System Are Related to Disease Severity in Systemic Lupus Erythematosus (SLE)
- AB682: *Complement activation in peripheral blood is intimately related to SLE and APS antibodies.*
- AB673: Cell Bound Complement Activation Products Distinguish Systemic Lupus Erythematosus from Other Diseases Among Patients with High ANA Titers and Normal C3/C4
- AB1077: The Lectin Pathway of the Complement System Is Activated in Patients with Systemic Lupus Erythematosus

Τα μικρόβια και οι ιοι…

- AB901: EBV reactivation interacts with select SLE associated genetic variants to increase the risk of clinical disease transition(CD40,IL10).
- AB1786: Lupus Nephritis Is Linked to Immunity to an Intestinal Commensal Lachnospiracaea Species
- AB1832: Gut Dysbiosis Contributes to Autoimmune Pathogenesis in Lupus-Prone Mice
- AB1808: Immunogenicity of the quadrivalent HPV vaccine was retained in 79% of SLE patients at 5 year post-vaccination (GARDASIL) – CS, TAC, MMF, (Renal) Flares → Higher risk seroreversion (6,16)
- AB383 & 2583: Humoral responses to pneumococcal polysaccharides are more blunted in patients receiving MMF compared to other immunosuppressants

Νέα Κριτήρια…? - ACR/EULAR…?

1982 revised ACR criteria

- Malar Rash
- Discoid rash
- Photosensitivity
- Oral Ulcers
- Arthritis
- Serositis
- Renal disorder
- Neurologic disorder
- Hematologic disorder
- Immunologic disorder
  - LE cell preparation
  - Anti-DNA
  - Anti-Sm
  - Lues serology false positive
- Antinuclear antibodies

Tan et al, Arthritis Rheum 1982;25:1271

1997 revised ACR criteria

- Malar Rash
- Discoid rash
- Photosensitivity
- Oral Ulcers
- Arthritis
- Serositis
- Renal disorder
- Neurologic disorder
- Hematologic disorder
- Immunologic disorder
  - ~~LE cell preparation~~
  - Anti-DNA
  - Anti-Sm
  - Anti-Phospholipid
    - ACLA
    - LAC
    - False positive Lues serology
- Antinuclear antibodies

Hochberg et al, Arthritis Rheum 1997;40:1725

2012 SLICC criteria

- ACLE/ SCLE
- CCLE
- Oral/ Nasal Ulcers
- Nonscarring Alopecia
- Arthritis
- Serositis
- Renal disorder
- Neurologic disorder
- Hemolytic anemia
- Leuko/Lymphopenia
- Thrombocytopenia
- Immunologic criteria
  - Antinuclear antibodies
  - Anti-DNA
  - Anti-Sm
  - Anti-Phospholipid
  - Low complement
  - Direct Coombs test

Petri et al, Arthritis Rheum 2012;64:2677

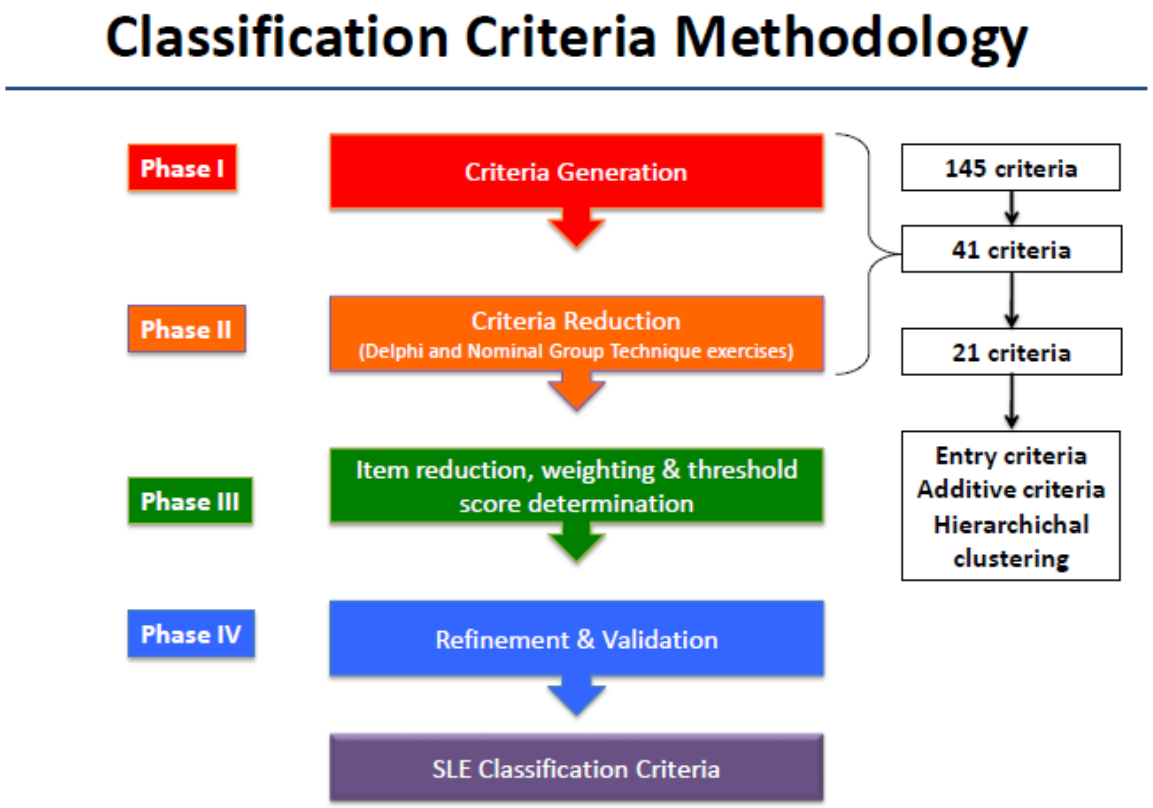
Sensitivity vs Specificity

Publication	Sens ACR	Sens SLICC	Spec ACR	Spec SLICC
Petri et al[1]	83%	97%	96%	84%
Sag et al[2]	77%	99%	93%	85%
Fonseca et al[3]	91%	96%	91%	88%
Ighe et al[4]	90%	92%	92%	74%

Τροποποιημένο από ACR 2017 handout material
Martin Aringer, Karen H. Costenbader, Sindhu Johnson (on behalf of the SLE Classification Criteria Steering Committee and Investigators and the EULAR/ACR SLE Criteria Development Subcommittee)

[1]Arthritis Rheum 2012;64:2677ff
[2]Clin Exp Rheumatol 2014;32:440
[3]Rheumatology 2015;54:241ff
[4]Arthritis Res Ther 2015;17:3

Διαδικασία επιλογής κριτηρίων…tough job!



Πώς θα διευκρινιστεί η ειδικότητα και ευαισθησία των επιλεγμένων κριτηρίων;

- Τυχαιοποίηση περιστατικών
  - 36 διεθνή κέντρα ΣΕΛ
  - Το καθένα στρατολογεί 100 ΣΕΛ - 100 μάρτυρες
  - Προτιμούνται οι νέες περιπτώσεις
  - Προτιμούνται μάρτυρες που μιμούνται ΣΕΛ

- Διασφάλιση ποιότητας δεδομένων
  - 3 ανεξάρτητοι αναθεωρητές

- Έως Νοε 2017 >2200 ΣΕΛ και μάρτυρες

- Επιλογή *κοορτής «εξαγωγής αποτελεσμάτων»*
  - 500 ΣΕΛ & 500 μάρτυρες με τυχαία επιλογή
  - Οι υπόλοιποι ασθενείς → *κοορτή «επιβεβαίωσης»*

Νέα προτεινόμενα ACR/EULAR κριτήρια ΣΕΛ

Draft SLE Classification Criteria and Weights

Entry criterion: history of a positive ANA by Hep 2 immunofluorescence ≥1:80

Opening statements:

- For each criterion, do not score if a cause *more likely* than SLE exists (such as infection, malignancy, medication, rosacea, endocrine disorder, other autoimmune disease).
- Occurrence of a criterion on at least one occasion is sufficient.
- Criteria need not occur simultaneously.
- At least one clinical criterion must be present.
- Within each domain, only the highest weighted criterion is counted toward the total score.

Clinical domains and criteria	Weight
Constitutional domain	
• Fever	2
Cutaneous domain	
• Non-scarring alopecia	2
• Oral ulcers	2
• Subacute cutaneous or discoid lupus*	4
• Acute cutaneous lupus	6
Arthritis domain	
• Synovitis in ≥2 joints or tenderness ≥2 joints and ≥30 minutes of morning stiffness	6
Neurologic domain	
• Delirium	2
• Psychosis	3
• Seizure	5
Serositis domain	
• Pleural or pericardial effusion	5
• Acute pericarditis	6
Hematologic domain	
• Leukopenia	3
• Thrombocytopenia	4
• Autoimmune hemolysis	4
Renal domain	
• Proteinuria >0.5g/24h	4
• Renal biopsy with Class II or V lupus nephritis	8
• Renal biopsy with Class III or IV lupus nephritis	10

Immunologic domains and criteria	Weight
Antiphospholipid antibodies domain	
• Anticardiolipin IgG >40 GPL units or anti-β2GP1 IgG >40 units or lupus anticoagulant positive	2
Complement proteins domain	
• Low C3 or low C4	3
• Low C3 and low C4	4
Highly specific antibodies domain	
• Anti-dsDNA antibody	6
• Anti-Smith antibody	6

Criteria	Sensitivity	Specificity
November 2017	98%	97%
ACR	85%	95%
SLICC	95%	90%

- Σημαντικά σημεία στα προτεινόμενα κριτήρια
- ✓ Point system (όπως PA)
- ✓ ANA>1/80
- ✓ Ενεργότητα>Χρονιότητα
- ✓ Όριο τιμών στα APS Ab
- ✓ Μόνο μία εκδήλωση προσμετράται από κάθε υποκατηγορία

Τροποποιημένο από ACR 2017 handout material

Martin Aringer, Karen H. Costenbader, Sindhu Johnson (on behalf of the SLE Classification Criteria Steering Committee and Investigators and te EULAR/ACR SLE Criteria Development Subcommittee

Προσωποποιημένη ή οργανοειδική ιατρική?

- Αναγνώριση «υποπληθυσμών» που θα ανταποκριθούν καλύτερα σε στοχευμένη θεραπευτική παρέμβαση
- Αυξημένη επίπτωση εξάρσεων σε ασθενείς με ορολογική ενεργότητα (anti-dsDNA(+), C3/C4 low and/or IFN high)[1,2,3,4]
- Αυξημένη πιθανότητα ανταπόκρισης σε στοχευμένη θεραπεία σε ορολογικά ενεργούς και σε όσους λαμβάνουν υψηλές δόσεις ΚΣ[5,6]

"Double Seropositivity" is More Common with Positive Interferon Signature

IFN Positive (n=1318)

DNA	+	—	+	—
↓C	+	—	—	+
	536	351	316	115

40.7%

IFN Negative (n=429)

DNA	+	—	+	—
↓C	+	—	—	+
	46	247	104	32

10.7%

Comparing Interferon Double Negative vs Other IFN Subsets

Interferon + Serology = MORE activity MORE treatment

but Double Negative was more likely to have MUSCULOSKELETAL MUCOCUTANEOUS

IFN(+) dsDNA(-) complement (-) vs.

	IFN(+)		
DNA	+	+	—
↓C	+	—	+
SLEDAI (mean)	<0.0001	<0.0001	<0.0001
SLEDAI ≥ 10	<0.0001	<0.0001	<0.0001
Corticosteroids	<0.0001	0.022	0.089
Musculoskeletal	<0.0001	0.001	0.010
Mucocutaneous	<0.0001	<0.0001	0.301

P-values shown

19

Highest SLEDAI Occurs in Double Positives in IFN Positive OR Negative

IFN Positive (n=1318)

DNA	+	—	+	—
↓C	+	—	—	+
SLEDAI (mean)	12.4	8.9	10.1	10.7
SLEDAI ≥ 10 (%)	80.2	37.3	54.4	67.8

IFN Negative (n=429)

DNA	+	—	+	—
↓C	+	—	—	+
SLEDAI (mean)	11.1	8.3	10.1	9.8
SLEDAI ≥ 10 (%)	80.4	27.9	63.5	65.6

but SLEDAI includes serologies

10

Οι ορολογικοί δείκτες αντανακλούν στην ενεργότητα του νοσήματος και άρα στην ανάγκη για θεραπεία, αλλά οι επιμέρους εκδηλώσεις όχι!

1. Petri et al., Arthritis Rheum. 2013 Aug;65(8):2143-53.
2. Petri et al., J Rheumatol. 2009 Nov;36(11):2476-80
3. Hoffman et al., Arthritis Rheumatol. 2016 Oct 9. doi: 10.1002/art.39950.
4. Linnik et al., Arthritis Rheum. 2005 Apr;52(4):1129-37
5. van Vollenhoven et al., Ann Rheum Dis. 2012 Aug;71(8):1343-9.
6. Furie R, et al., Arthritis Rheumatol. 2017 Feb;69(2):376-386

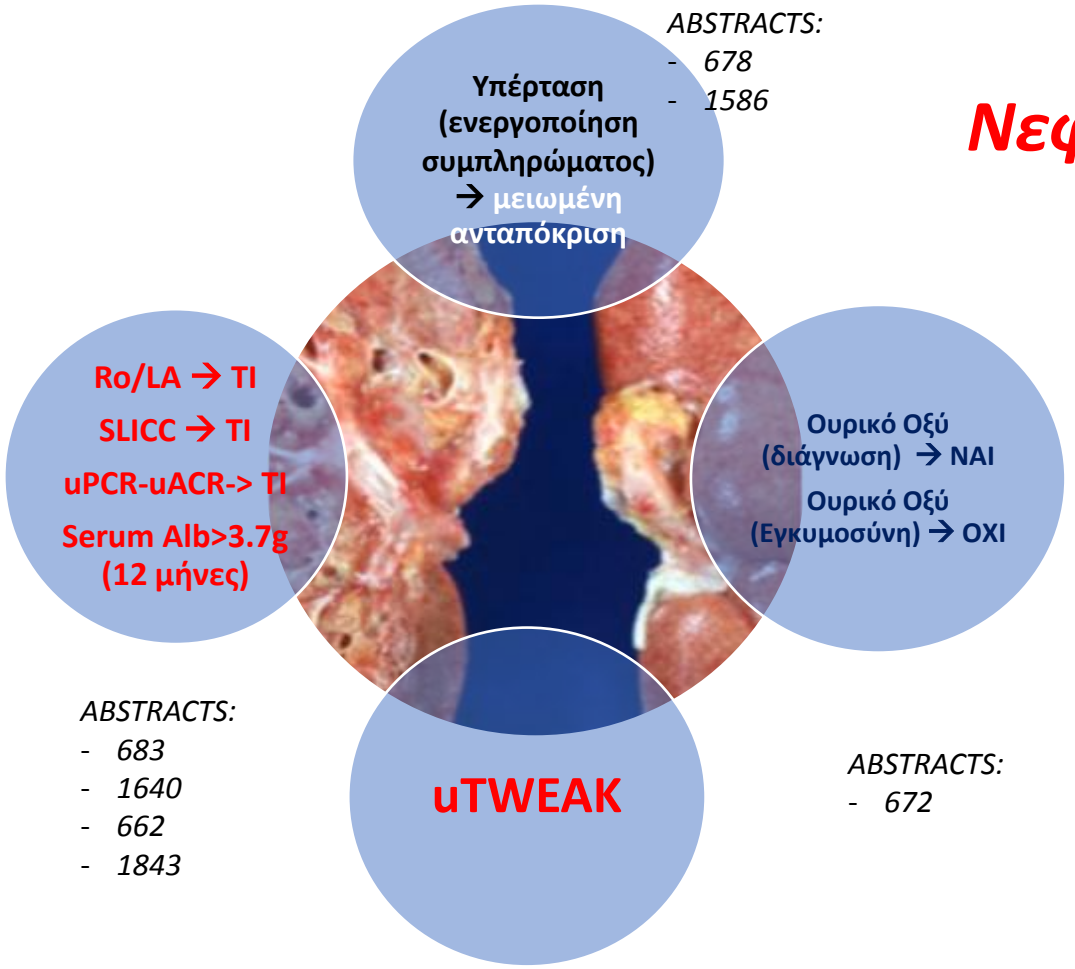
Τροποποιημένο από ACR 2017 handout material

Petri et al

Subsetting Systemic Lupus Erythematosus by Interferon Gene Signatures and Serologies (anti-dsDNA and Low Complement) Uncovers Significant Clinical Diversity - Post hoc of the ILLUMINATE trials

Κλινική Πρακτική– Πρόγνωση – πιθανοί βιοδείκτες

Νεφρίτιδα



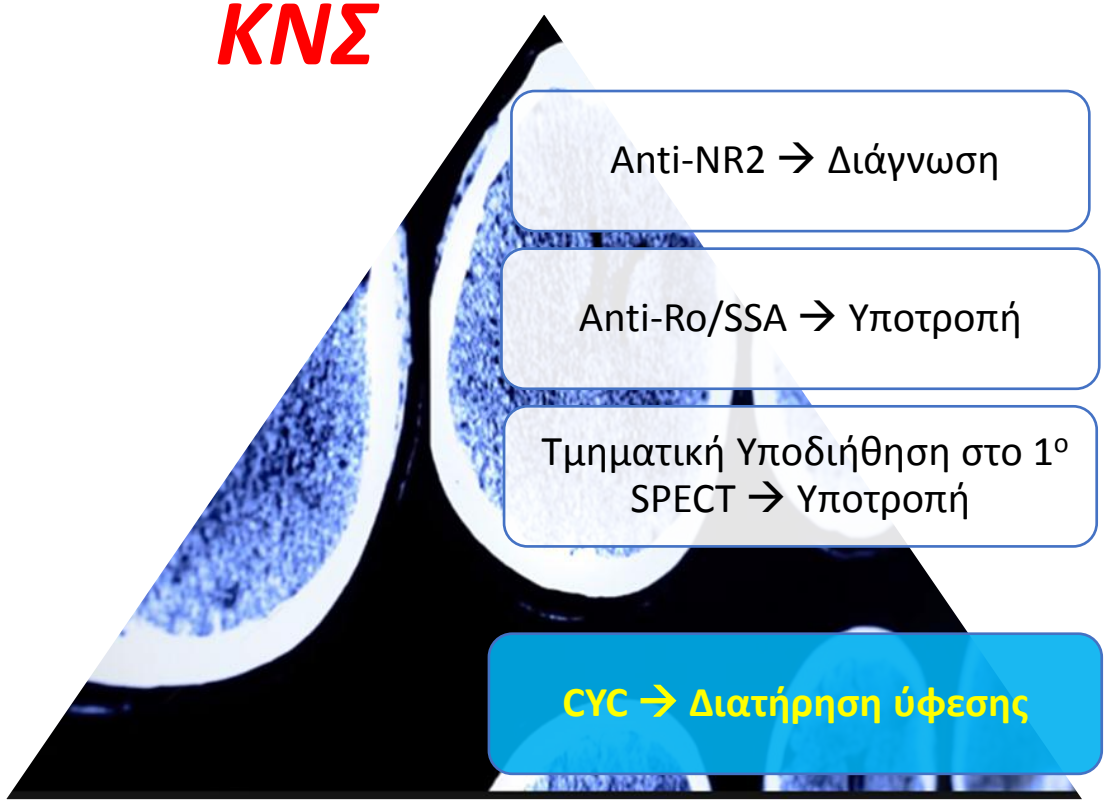
ABSTRACTS:
- *678*
- *1586*

ABSTRACTS:
- *683*
- *1640*
- *662*
- *1843*

ABSTRACTS:
- *672*

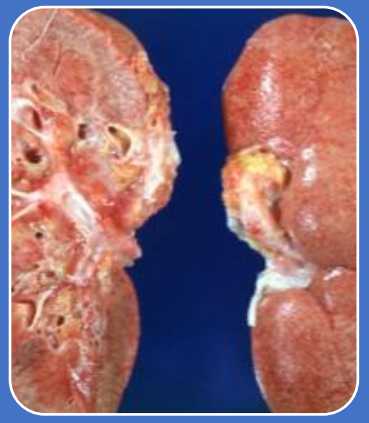
ABSTRACT:
- *662*

ΚΝΣ



ABSTRACTS:
- *691*
- *717*

Κλινική πρακτική – Θεραπεία Νεφρίτιδας



Τι νέο ειπώθηκε…

- Voclosporin (Calcineurin inhibitor, phase IIb) (προσθήκη σε MMF/ΚΣ) → υψηλά ποσοστά πλήρους ύφεσης με μικρότερη δόση ΚΣ (AURA study)
- MMF pos (μονοκεντρική, αναδρομική) → Καλή ανταπόκριση παιδιατρικών πληθυσμών με κλάσης V νεφρίτιδα
- Tacrolimus (Μη ασιατικοί πληθυσμοί, αναδρομική)→ > 75% ανταπόκριση (CR, PR) σε νεφρίτιδα [πιθανή δράση μέσω P-gp]

Abstracts No 885 – 92 - 1920, 2608

Τι ακόμα θα πρέπει ίσως να θυμάμαι…

- Ασθενείς με ΣΕΛ+νεφρίτιδα και θετικά αντισώματα ΑΦΣ → πιθανώς καλύτερη έκβαση eGFR σε κλάση III και IV νεφρίτιδα όταν λάβουν αντιπηκτική αγωγή
- Ένταξη με MMF σε ασθενείς με GFR>50ml/min σε νεφρίτιδα, ακόμα και πριν τη βιοψία (αν πρακτικοί λόγοι την καθυστερούν)
- Διατήρηση HCQ → βελτιώνει τις πιθανότητες έκβασης σε Νεφρ. Αν. Τελ. Σταδίου

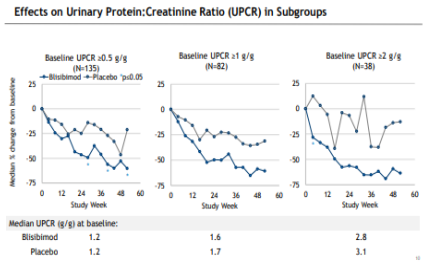
Abstracts No 9 – 2624 - 1862

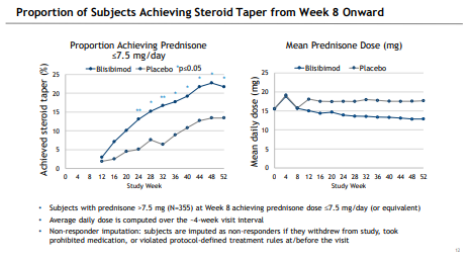
Κλινική πρακτική – B-cells

To expect…

Blisibimod

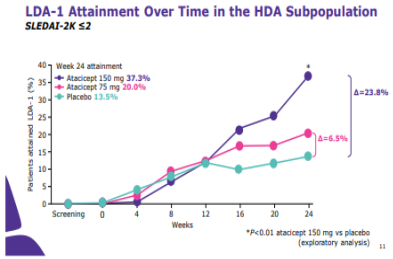
-Βελτίωση πρωτεινουρίας
-Μείωση ΚΣ

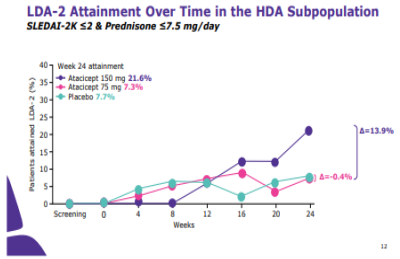


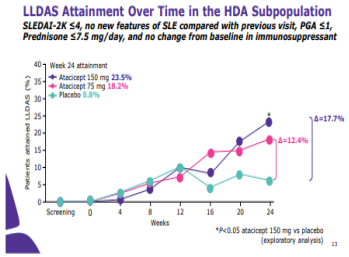


Atacicept

- 3-5 φορές πιθανότητα για επίτευξη LDA σε HDA ασθενείς







To remember…

Rituximab

- Ασθενείς με MTX → ανταπόκριση!

- Αγγειίτιδα ή Αιματολογική εκδήλωση (BILAG A/B)→ Ανταπόκριση!

ABSTRACT NUMBER: 2597

Explorer Study: Rituximab Use in Systemic Lupus Erythematosus, a New Look on Old Data

Marc Scherlinger[1,2,3], Claire Carcaud[2,4], Thomas Barnetche[1,5], Lionel Couzy[2,6], Pierre Duffau[3,7,8], Estibaliz Lazaro[2,9] and Christophe Richez[2,10,11], [1]Rheumatology, Centre hospitalier universitaire de Bordeaux - Service de Rhumatologie, Bordeaux, France, [2]FHU ACRONIM, Bordeaux, France, [3]UMR CNRS 5164 - Immunoconcept, Bordeaux, France, [4]Internal Medicine, Centre hospitalier universaire de Bordeaux, Bordeaux, France, [5]FHU ACRONIM, Pellegrin Hospital, Bordeaux University, Bordeaux, France, [6]Nephrology, Centre hospitalier universitaire de Bordeaux - Néphrologie, Bordeaux, France, [7]Internal Medecine, Centre hospitalier universitaire de Bordeaux - Médecine interne, Bordeaux, France, [8]FHU ACRONIM, bordeaux, France, [9]Department of Internal Medecine and Clinical Immunology, Bordeaux University Hospital, Pessac, France, [10]Department of Rheumatology, Bordeaux University Hospital, Bordeaux, France, [11]UMR CNRS 5164 - Immunoconcept, bordeaux, France

Meeting: 2017 ACR/ARHP Annual Meeting

Date of first publication: September 18, 2017

Belimumab (+RTX)

SynBioSe Study

ABSTRACT NUMBER: 890

Synergetic B-Cell Immunomodulation with Rituximab and Belimumab Combination Treatment in Severe, Refractory SLE

Tineke Kraaij[1], Sylvia W.A. Kamerling[1], Esther N.M. de Rooij[1], Paul L. van Daele[2], O.W. Bredewold[1], Jaap A. Bakker[3], Ingeborg Bajema[4], Hans U. Scherer[5], Rene E.M. Toes[5], Tom W.J. Huizinga[5], Ton Rabelink[1], Cees van Kooten[1] and Y.K. Onno Teng[1], [1]Nephrology, Leiden University Medical Center, Leiden, Netherlands, [2]Immunology, Erasmus Medical Center, Rotterdam, Netherlands, [3]Clinical Chemistry and Laboratory Medicine, Leiden University Medical Center, Leiden, Netherlands, [4]Pathology, Leiden University Medical Center, Leiden, Netherlands, [5]Rheumatology, Leiden University Medical Center, Leiden, Netherlands

Meeting: 2017 ACR/ARHP Annual Meeting

Date of first publication: September 18, 2017

- ✓ Μείωση δόσης ανοσοκατασταλτικών
- ✓ 10/11 LN → Ανταπόκριση στις 24w
- ✓ 4/10 → CR
- ✓ Μείωση Ab
- ✓ Καλό προφίλ ασφαλείας

Μελλοντικοί Στόχοι…

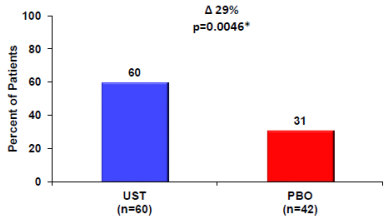
ABSTRACT NUMBER: 6L

Efficacy and Safety of Ustekinumab, an Interleukin 12/23 Inhibitor, in Patients with Active Systemic Lupus Erythematosus: Results of a Phase 2, Randomized Placebo-Controlled Study

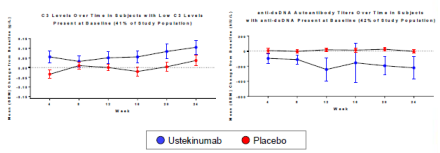
Ronald van Vollenhoven[1], Bevra H. Hahn[2], George C. Tsokos[3], Carrie Wagner[4], Peter Lipsky[5], Benjamin Hsu[4], Marc Chevrier[4], Robert Gordon[4], Manon Triebel[6] and Shawn Rose[4], [1]Amsterdam Rheumatology and Immunology Center ARC, Amsterdam, Netherlands, [2]UCLA David Geffen School of Medicine, Los Angeles, CA, [3]Division of Rheumatology, Department of Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, [4]Janssen Research & Development, LLC, Spring House, PA, [5]Ampel BioSolutions LLC, Charlottesville, VA, [6]Janssen Biologics Europe, Leiden, Netherlands

Meeting: 2017 ACR/ARHP Annual Meeting

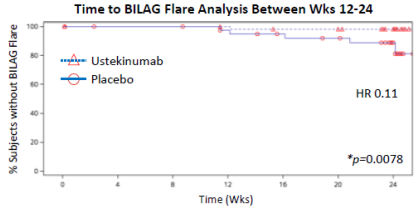
UST Exhibited a Statistically Significant Improvement in SRI-4 Response at Wk 24 Compared to PBO: Primary Endpoint Analysis



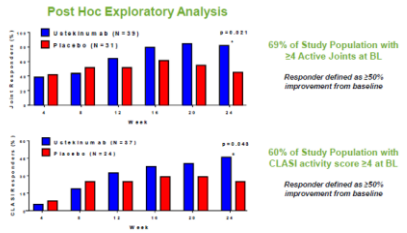
UST Improves C3 and anti-dsDNA Levels



UST Treatment Prevented SLE Flares



UST Demonstrated Greater Proportions of Patients with Improvement in Joint and Mucocutaneous Disease Compared to PBO



ABSTRACT NUMBER: 886

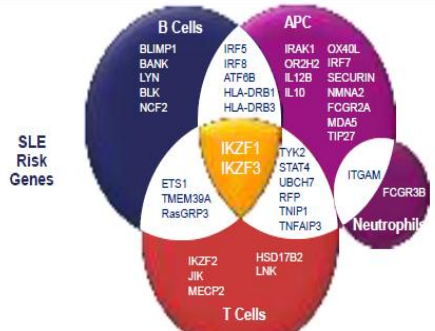
CC-220 Decreases B-Cell Subsets and Plasmacytoid Dendritic Cells in Systemic Lupus Erythematosus (SLE) Patients and Is Associated with Skin Improvement: Pharmacodynamic Results from a Phase IIa Proof of Concept Study

Victoria P Werth[1], Richard Furie[2], Allison Gaudy[3], Ying Ye[3], Shimon Korish[3], Nikolay Delev[3], Douglas Hough[3], Michael Weiswasser[3], Suktae Choi[3] and Peter Schafer[3], [1]University of Pennsylvania and the VA Medical Center, Philadelphia, PA, [2]Northwell Health, Great Neck, NY, [3]Celgene Corporation, Summit, NJ

Meeting: 2017 ACR/ARHP Annual Meeting

Date of first publication: September 18, 2017

IKZF1 (Ikaros) and IKZF3 (Aiolos) are Central Players Among SLE Risk Loci



Westra. *Nat Genet.* 2013;45(10):1238-1243; You. *Tissue Antigens.* 2015;85(3):200-203; Dang. *Tissue Antigens.* 2014;83(6):401-408; Hu. *Mod Rheumatol.* 2013;23(2):205-209; Cunninghame. *PLoS Genet.* 2011;7(10):e1002341. Cai. *PLoS One.* 2014;9(10):e108661;Han. *Nat Genet.* 2009;41(11):1234-1237. Wang. *Eur J Hum Genet.* 2013;21(9):994-999. Lessard. *Am J Hum Genet.* 2012;90(4):648-660

ABSTRACT NUMBER: 887

A Randomized, Placebo-Controlled, Double-Blind, Ascending-Dose, Safety, and Pharmacokinetics Study of CC-220 in Subjects with Systemic LUPUS Erythematosus

Richard Furie[1], Victoria P. Werth[2], Allison Gaudy[3], Ying Ye[3], Shimon Korish[3], Ada Azaryan[3], Nikolay Delev[3], Douglas Hough[3], Michael Weiswasser[3], Suktae Choi[3] and Peter Schafer[3], [1]Northwell Health, Great Neck, NY, [2]University of Pennsylvania and the VA Medical Center, Philadelphia, PA, [3]Celgene Corporation, Summit, NJ

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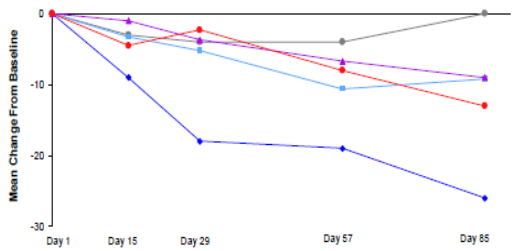
Trend Toward Improvement in the CLASI Activity Score through Day 85 in Subjects with a Baseline CLASI Score ≥10



	Baseline	
	n	Mean
Placebo	1	18.0
0.3 mg QOD	6	22.7
0.3 mg QD	1	27.0
0.3/0.6 mg QD alternating	3	18.7
0.6 mg QD	4	23.8

ITT population. Data as observed.

Αντιφωσφολιπιδικό σύνδρομο (1)

- Global APS Score (GAPSS) ή *adjusted (aGAPSS)*, χωρίς Ab aPS/PT

Factor	Point Value
Anticardiolipin IgG/IgM	5
Anti-β2-glycoprotein IgG/IgM	4
Lupus anticoagulant	4
Hyperlipidemia	3
Arterial hypertension	1

✓ Σχετίζεται με αυξημένο κίνδυνο ΑΕΕ, αρτηριακή θρόμβωση και υποτροπές[ABSTRACTS 5, 10]

✓ Η *υπέρταση* πιθανώς σχετίζεται με αρτηριακές θρομβώσεις και η παρουσία *LAC* με φλεβικές σε ασθενείς θετικούς σε aPL (χωρίς ΑΦΣ)[ABSTRACT 2]

- Αντισώματα έναντι Φωσφατιδυλσερίνης/προθρομβίνης[1]:
  - Επεισόδια θρόμβωσης (OR 6.72)
  - Αποβολές (OR 9.44)
  - Υψηλή συσχέτιση IgG/IgM aPS/PT με LAC ($p<0.001$)
  - 91.95% (80/87) με LAC(+) ανέδειξαν IgG &/ή IgM aPS/PT[ABSTRACT 1, 16]
  - Όταν και τα δύο (+) → OR 101.6 για ΑΦΣ

➢ Συσχέτιση παθολογικής εξέτασης τριχοειδοσκόπησης με α'παθές ΑΦΣ(διάταση, μικροαιμορραγίες, ατυπία)[ABSTRACT 18]

Αντιφωσφολιπιδικό σύνδρομο (2)

APS | ACTION
ANTIPHOSPHOLIPID SYNDROME
ALLIANCE FOR CLINICAL TRIALS & INTERNATIONAL NETWORKING

<u>Σύστημα καταγραφής σε ηλεκτρονική βάση δεδομένων</u>
- Δημογραφικά στοιχεία
- Ατομικό αναμνηστικό Σχετιζόμενο με aPL Ab
- Φαρμακευτική αγωγή

<u>Κριτήρια Επιλογής</u>
- Ηλικία 18-75
- Θετικά aPL Ab(LA, aCL, &/ή β2GPI) σύμφωνα με τα αναθεωρημένα κριτήρια Sapporo δύο φορές το προηγούμενο έτος

<u>Follow-up</u>
- Κάθε 12±3 μήνες κλινικά στοιχεία & αιμοληψία
- Συμβουλευτική

➢ Συμμετέχουν 26 διεθνή κέντρα

BONUS tip!

Σε ασθενείς με γνωστό ΣΕΛ, ο συνδυασμός anti-RNP/Sm + LA (OR 5.98, 95% CI 2.17-16.47, p=0.001), το SLEDAI-2K (OR 1.18, 95% CI 1.04-1.32, p=0.007) και η δόση των ΚΣ (OR 1.08, 95% CI 1.03-1.12, p<0.001) βρέθηκαν να είναι ανεξάρτητοι παράγοντες για θρόμβωση ABSTRACT 708

<u>Ετήσιος κίνδυνος για θρόμβωση:</u> ABSTRACT 2760
- 2.6% με ιστορικό θρόμβωσης
- 2.2% σε θεραπευόμενους με βαρφαρίνη και ιστορικό θρόμβωσης
- 1.7% χωρίς ιστορικό θρόμβωσης
- Υψηλή συσχέτιση με LAC και τριπλή οροθετικότητα

Αλλά…

<u>Εγκυμοσύνη:</u> ABSTRACT 12
- 50% τελειόμηνα νεογνά
- 20% πρόωρα νεογνά (φυσιολογική ανάπτυξη)
- Καμία απώλεια εμβρύου από 10η έως 20η εβδομάδα
- Μόνο μία αποβολή μετά την 20η εβδομάδα

<u>Επιδημιολογική μελέτη ΑΦΣ στο γενικό πληθυσμό (Mayo Clinic 2000-2015):</u> ABSTRACT 13
- Επίπτωση: 2/100.000
- Επιπολασμός: 50/100.000 (πολύ κοντά με ΣΕΛ?)
- Ίδια ποσοστά θνησιμότητας με γενικό πληθυσμό

ABSTRACT NUMBER: 2762

Study of 60 Patients with Intrauterine Fetal Deaths Related to Antiphospholipid Syndrome

Mériem Belhocine[1], Laetitia Coutte[2], Nicolas Martin Silva[3], Nathalie Morel[4], Gaelle Guettrot-Imbert[4], Romain Paule[4], Michel Dreyfus[5], Micaela Fredi[6], Odile Souchaud-Debouverie[7], Jean Charles Piette[8], Veronique Le Guern[4] and **Nathalie Costedoat-Chalumeau**[1], [1]Service de médecine interne Pôle médecine, Hôpital Cochin, Centre de référence maladies auto-immunes et systémiques rares de l'île de France, Paris, France, [2]Department of Internal Medicine, Department of Internal Medicine, Cochin University Hospital, paris, France, [3]Department of Internal Medicine, Department of Internal Medicine, University Hospital Center of Caen, Caen, France, [4]Department of Internal Medicine, Department of Internal Medicine, Cochin University Hospital, Paris, France, [5]Department of Gynecology and Obstetrics, Department of Gynecology and Obstetrics, University Hospital Center of Caen, Caen, France, [6]Department of Rheumatology and Clinical Immunology, Rheumatology and Clinical Immunology, Rheumatology and Clinical Immunology, Spedali Civili of Brescia, Brescia, Italy, [7]Department of Internal Medicine, Department of Internal Medicine, Poitiers University Hospital, Poitiers, France, [8]Department of Internal Medicine, Department of Internal Medicine, University Hospital Pitié-Salpétrière, Paris, France

Meeting: 2017 ACR/ARHP Annual Meeting

Date of first publication: September 18, 2017

- 1η εκδήλωση σε 74% των ασθενών
- Υψηλή συχνότητα LAC (72%) και τριπλής οροθετικότητας (35%)
- Μέση (χρονική) τιμή IUFD: 24 W [18-27]

Τι πήραμε από το ACR 2017 στο σπίτι…?

- ✓ IFN, TLRs, Bcells → δρουν συχνά σε συνέργεια
- ✓ Η ένταξη της θεραπείας στον ΣΕΛ (*οργανοειδική)* - η διατήρηση της «ύφεσης» (*συστηματική)*
- ✓ *Αναζήτηση φαινότυπου για προσωποποιημένη θεραπεία δύσκολη (ISG, serology)*
- ✓ Αναμονή νέων κριτηρίων «κατάταξης» ΣΕΛ (point system)
- ✓ Rituximab, Belimumab = χρήσιμα στη διατήρηση της ύφεσης (συνδυασμός???)
- ✓ ΤΑC μάλλον αποτελεσματικό και σε μη Ασιατικούς πληθυσμούς
- ✓ Χρήσιμο το GAPSS και τα αντισώματα έναντι φωσφατιδυλσερίνης/προθρομβίνης

Pathophysiology

In systemic lupus erythematosus all pathways lead to endogenous nucleic acids-mediated production of interferon α (IFNα). Increased production of autoantigens during apoptosis (UV-related and/or spontaneous), decreased disposal, deregulated handling and presentation are all important for the initiation of the autoimmune response. Nucleosomes containing endogenous danger ligands that can bind to pathogen-associated molecular pattern receptors are incorporated in apoptotic blebs that promote the activation of DCs and B cells and the production of IFN and autoaantibodies, respectively. Cell surface receptors such as the BCR and FcRIIa facilitate the endocytosis of nucleic acid containing material or immune complexes and the binding to endosomal receptors of the innate immunity such as TLRs. At the early stages of disease, when autoantibodies and immune complexes may not have been formed, antimicrobial peptides released by damaged tissues such as LL37 and neutrophil extracellular traps, may bind with nucleic acids inhibiting their degradation and thus facilitating their endocytosis and stimulation of TLR-7/9 in plasmacytoid DCs. Increased amounts of apoptosis related endogenous nucleic acids stimulate the production of IFN and promote autoimmunity by breaking self-tolerance through activation and promotion of maturation of conventional (myeloid) DCs. Immature DCs promote tolerance while activated mature DCs promote autoreactivity. Production of autoantibodies by B cells in lupus is driven by the availability of endogenous antigens and is largely dependent upon T cell help, mediated by cell surface interactions (CD40L/CD40) and cytokines (IL21). Chromatin-containing immune complexes vigorously stimulate B cells due to combined BCR/TLR crosslinking. DC, dendritic cell, BCR, B cell receptor, FcR, Fc receptor, UV, ultraviolet; TLR, toll-like receptor.

Reprinted with permission from Bertsias GK, Salmon JE, Boumpas DT.
Therapeutic opportunities in systemic lupus erythematosus: state of the art and prospects for the new decade. Ann Rheum Dis 2010;69:1603–11.

Memo

- **Apoptosis:** a source of autoantigens and molecules with adjuvant/cytokine (interferon α (IFNα)) inducer activity. Apoptotic cell blebs are rich in lupus autoantigens. Increased spontaneous apoptosis, increased rates of ultraviolet-induced apoptosis in skin cells, or impaired clearance of apoptotic peripheral blood cells have been found in some lupus patients.

- **Nucleic acids (DNA and RNA):** a unique target in lupus linked to apoptosis. Their recognition in healthy individuals is prohibited by a variety of barriers which are circumvented in lupus whereby alarmins released by from stressed tissues (HMGB1), antimicrobial peptides, neutrophil extracellular traps (NETs), and immune complexes facilitate their recognition and transfer to endosomal sensors (see below TLRs, NLRs).

Innate immunity

- **Toll-like receptors (TLRs):** conserved innate immune system receptors strategically located on cell membranes, cytosol and in endosomal compartments where they survey the extracellular and intracellular space. TLRs recognising nucleic acids (TLRs-3,-7,-8 and -9) are endosomal. Autoreactive B or T lymphocytes peacefully coexisting with tissues expressing the relevant antigens may become pathogenic after engagement of TLRs. TLRs also activate APCs (dendritic, MO, B cells) enhancing autoantigen presentation. B cells from active lupus patients have increased TLR9 expression. Compared to other antigens, chromatin containing immune complexes are 100-fold more efficacious in stimulating lupus B cells because of the presence of nucleic acids and the resultant combined BCR and TLR stimulation.
- **Dendritic cells:** Two types: plasmacytoid dendritic cells (pDCs) and myeloid (CD11c+) DC (mDCs).
- **pDCs:** represent genuine 'IFNα' factories. In lupus, exogenous factors/antigens (ie, viruses) or autoantigens recognised by the innate immune system receptors activate DCs and produce IFNα. **mDCs:** involved in antigen presentation with immature conventional mDCs promoting tolerance while mature autoreactivity. In lupus, several factors (IFNα, immune complexes, TLRs) promote mDC maturation and thus autoreactivity.
- **Interferon α:** a pluripotent cytokine produced mainly by pDCs via both TLR-dependent and TLR-independent mechanisms with potent biologic effects on DCs, B and T cells, endothelial cells, neuronal cells, renal resident cells, and other tissues. Several lupus-related genes encode proteins that mediate or regulate TLR signals and are associated with increased plasma IFNα among patients with specific autoantibodies which may deliver stimulatory nucleic acids to TLR7 or TLR9 in their intracellular compartments. Activation of the IFN pathway has been associated with the presence of autoantibodies specific for RNA-associated proteins. RNA-mediated activation of TLR is an important mechanism contributing to production of IFNα and other proinflammatory cytokines. Activation of the IFN pathway is associated with renal disease and many measures of disease activity.
- **Complement:** Activation of complement shapes the immune inflammatory response and facilitates clearance of apoptotic material.
- **Neutrophils:** In lupus a distinct subset of proinflammatory neutrophils (low density granulocytes) induces vascular damage and produces IFNα. Pathogenic variants of ITAM increase the binding to ICAM and the adhesion leucocytes to activated endothelial cells.
- **Endothelial cells:** In lupus, impaired DNA degradation as a result of a defect in repair endonucleases (TREX1) increases the accumulation of ssDNA derived from endogenous retro-elements in endothelial cells and may activate production of IFNα by them. IFNα in turn propagates endothelial damage and impairs its repair.

Adaptive immunity

- **T and B cells:** Interactions between co-stimulatory ligands and receptors on T and B cells, including CD80 and CD86 with CD28, inducible costimulator (ICOS) ligand with ICOS, and CD40 ligand with CD40, contribute to B cell differentiation to antibody producing plasma cells. Autoantibodies also facilitate the delivery of stimulatory nucleic acids to TLRs. Cytokines and chemokines produced by T and B cells also shape the immune response and promote tissue damage.
- **B lymphocyte stimulator (Blys):** The soluble TNF family member BlyS is a B cell survival and differentiation. Blys is increased in serum of many lupus patients; inhibition of Blys prevents lupus flares.
- **Immune complexes:** In healthy individuals, immune complexes are cleared by FcR and complement receptors. In lupus, genetic variations in FcR genes and the C3bi receptor gene (*ITGAM*) may impair the clearing of immune complexes which then deposit and cause tissue injury at sites such as the skin and kidney.

Table 1 Key pathogenic processes, cells and molecules in systemic lupus erythematosus

LDA indexes

LDA Definitions Used in This Analysis (Assessed at Each Study Visit)

Criteria	LDA-1	LDA-2	LLDAS
SLEDAI-2K ≤2	✓	✓	
SLEDAI-2K ≤4 without major organ activity			✓
Prednisone-equivalent ≤7.5 mg/day		✓	✓
Physician's Global Assessment ≤1			✓
Stable maintenance doses of immunosuppressants			✓

- Lupus Low Disease Activity State (LLDAS) attainment is associated with reduced damage accrual[1]

1. Franklyn K, et al. *Ann Rheum Dis*. 2016;75:1615–21.