Early Systemic Lupus Erythematosus (SLE)

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SLE has a long disease course, typically with alternating periods of activity and quiescence

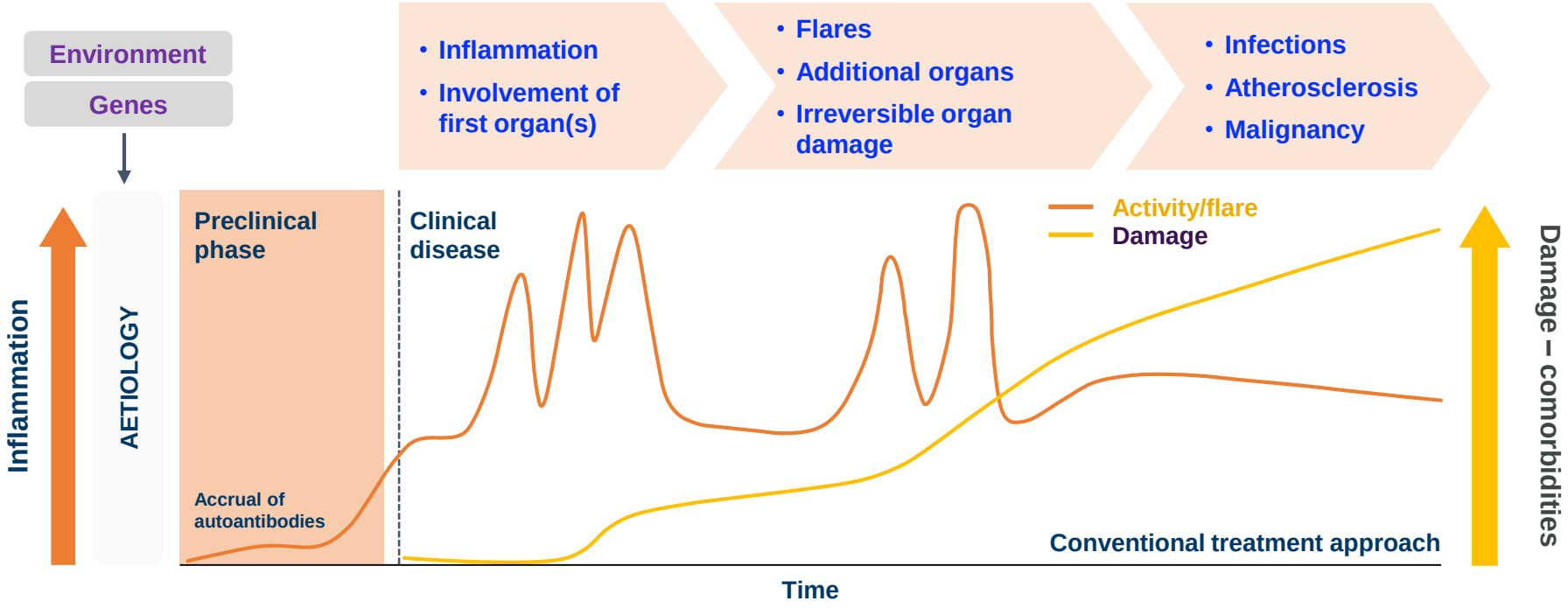


Figure developed and elaborated from Figure 1 in Bertsias GK, et al. Ann Rheum Dis 2010;69:1603–1611 and Figure 1 in Fanouriakis A, et al. Ann Rheum Dis 2021;80:14–25

Outline

- Clinical characteristics and burden of early SLE
- Why is early diagnosis and treatment of SLE important?
- What are the early pathogenic events in SLE?
- Strategies for the early identification of SLE and individuals at-risk
- Possibilities for personalised intervention

Early SLE: not always a 'full-blown' disease

Table 3 Comparison of clinical features of SLE patients at the time of diagnosis from large SLE cohorts around the world

Items *Centre based* *No. patients*	*'Attikon' cohort* *Europe* N = *555*	*Mosca et al.*[3] *Multi-centre* N = *389*	*Pons-Estel et al.*[25] *Latin America* N = *1214*	*Joo et al.*[26] *Asia* N = *996*	*Fiorot et al.*[27] *Latin America (childhood onset)* N = *1312*	*Total* N = *4466*
Malar rash	39.8%	49.5%	23.6%	44%	52.9%	41.1%
Photosensitivity	50.8%	31.6%	24.5%	35%	45.0%	36.8%
Discoid	7.4%	9.3%	5.3%	8%	5.3%	6.5%
Oral ulcers	17.7%	21.6%	10.5%	36%	32.8%	24.6%
Alopecia	22.3%	30.6%	20.3%	–	21.7%	22.3%
Arthritis	73.3%	57.6%	67.3%	65%	68.4%	67.0%
Pericarditis	7.0%	18.8%	2.7%	15%	19.1%	12.2%
Pleuritis	7.6%	22.4%	3.6%	19%	17.6%	13.3%
Renal involvement	10.3%	13.1%	5.3%	42%	40.8%	25.1%
Neuropsychiatric	11.5%	9.2%	4.1%	6%	11.0%	7.9%
Leucopaenia	23.8%	16.2%	5.1%	61%	41.8%	31.6%
Thrombocytopaenia	12.3%	6.6%	5.2%	24%	18.9%	15.5%
AIHA	2.7%	4.6%	2.4%	14%	21.4%	10.8%
Fever	25.0%	34.5%	28.6%	–	–	28.7%
Raynaud's	33.0%	22.1%	10.2%	–	–	18.2%
ANA	93.7%	99.5%	–	100%	93.4%	96.1%
Anti-dsDNA	36.6%	71.7%	–	79%	59.4%	62.1%

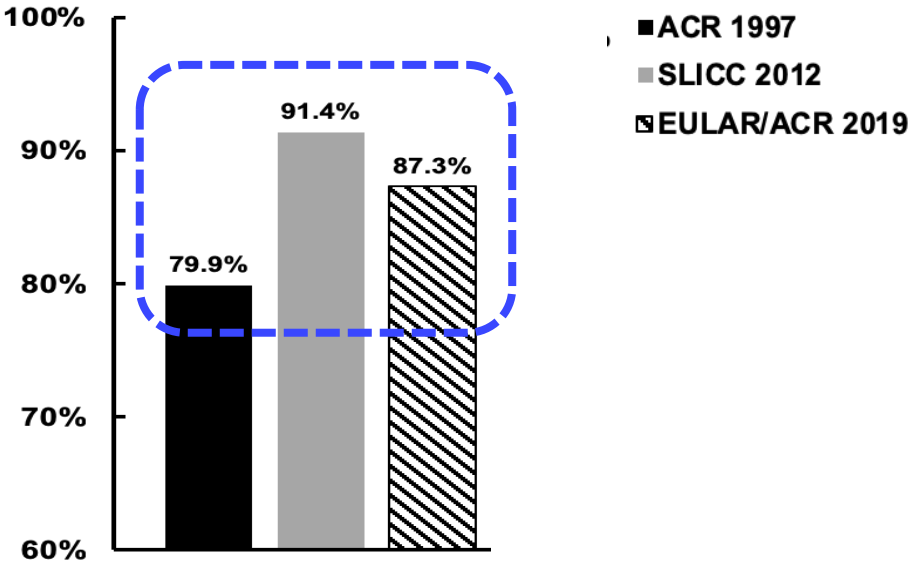
ANA: antinuclear antibodies; AIHA; Autoimmune hemolytic anemia; Anti-dsDNA; antidouble-strand DNA.

Nikolopoulos D, et al. *Lupus*. 2020; 29(5): 514-22; Mosca M, et al. Arthritis Rheumatol. 2019; 71(1): 91–98

Classification criteria have suboptimal diagnostic performance at early disease (<3 years)

sensitivity

Patients diagnosed with SLE (n=690) or control diseases (n=401), ascertained by experienced physicians through follow-up



Adamichou C, et al. *Ann Rheum Dis*. 2020; 79(2): 232-241

Classification criteria can miss or delay the diagnosis of SLE in a fraction of patients with major/severe disease

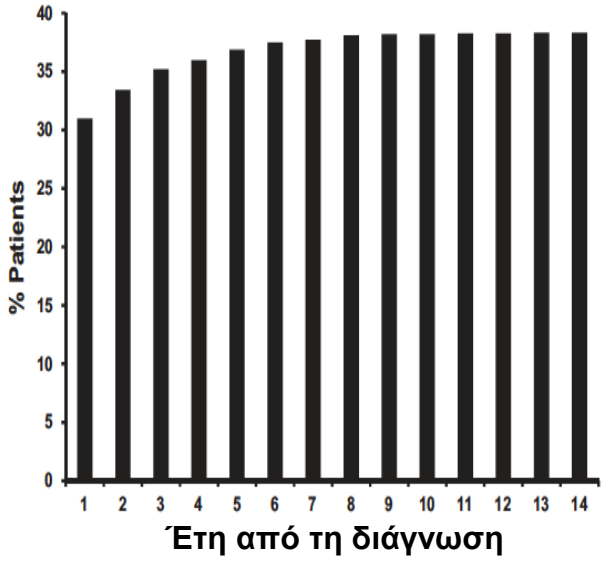
	Sensitivity of the criteria		
	ACR 1997	SLICC 2012	EULAR/ACR 2019
Neurological SLE			
Moderate or severe (n=60)	81.7%	91.7%	90.0%
Renal SLE			
Moderate or severe (n=59)	96.6%	98.3%	93.2%
Hematological SLE			
Moderate or severe (n=80)	81.3%	95.0%	87.5%
Severe SLE (according to BILAG)			
≥1 A (n=127)	82.7%	92.9%	88.2%

Physician (rheumatologist) **diagnosis predated classification by >3 months in 17.3%–19.9% of cases**

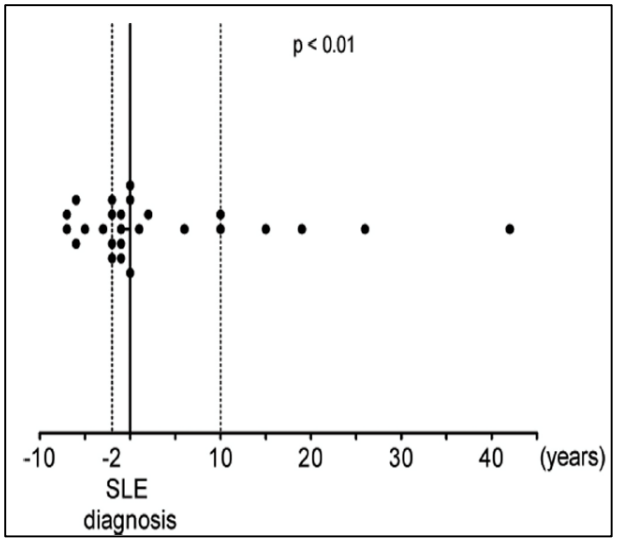
Adamichou C, et al. *Ann Rheum Dis*. 2020; 79(2): 232-241

Οι μείζονες εκδηλώσεις του ΣΕΛ εμφανίζονται συνηθέστερα κοντά στη διάγνωση ή εντός των πρώτων 5-10 ετών

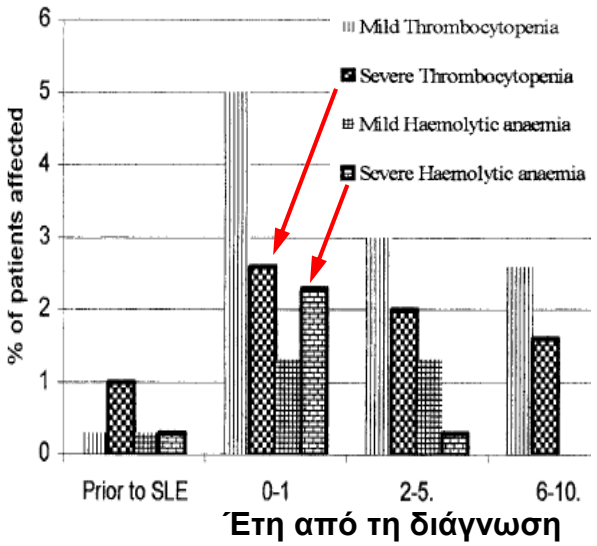
Νεφρίτιδα (SLICC cohort)



Νευρο-ψυχιατρικός ΣΕΛ

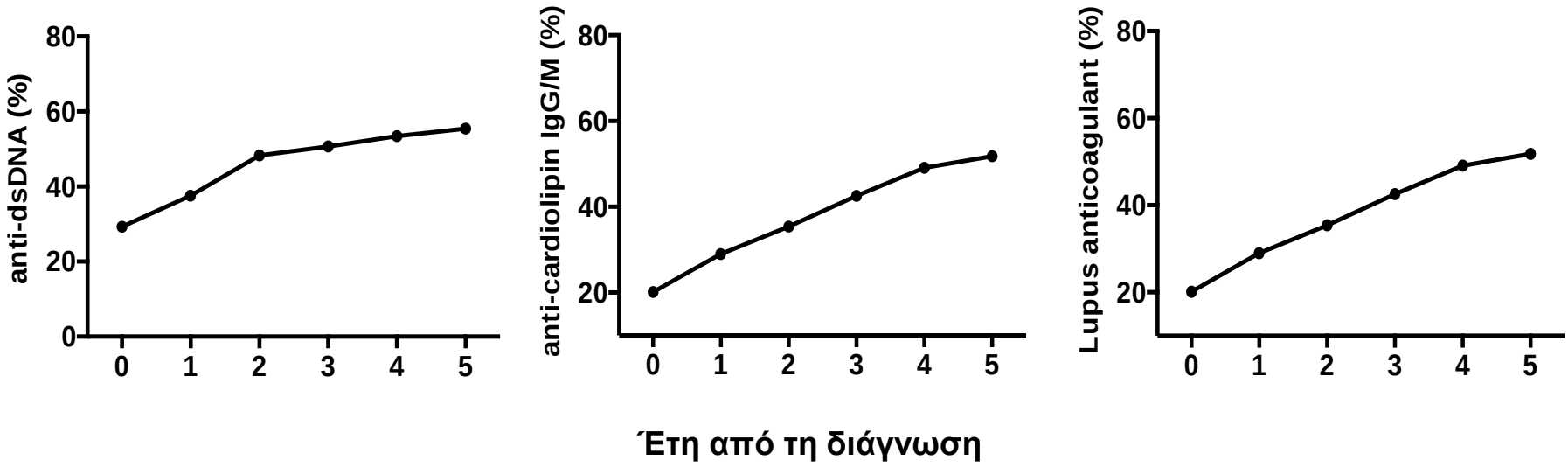


Σοβαρές κυτταροπενίες (UCL)



Hanly J, et al. *Rheumatology*. 2015 [*ahead of print*]; Hawro T, et al. *PLoS One*. 2015; 10: e0119911; Sultan SM, et al. *Rheumatology.* 2003; 42: 230–234; Joo YB, et al. *Int J Rheum Dis*. 2015; 18:117-28

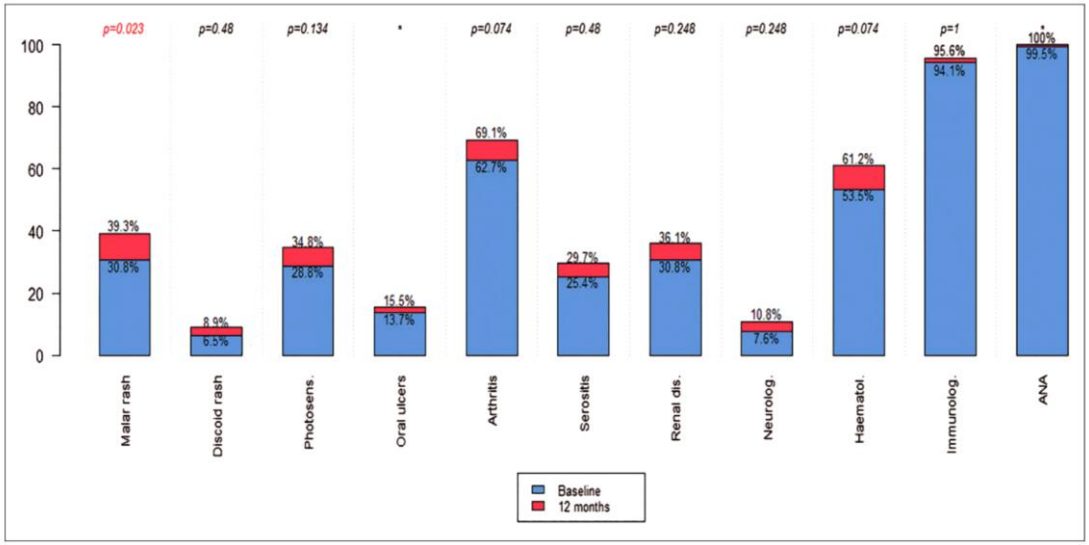
Αυξανόμενο ανοσολογικό φορτίο τα πρώτα έτη μετά τη διάγνωση του ΣΕΛ

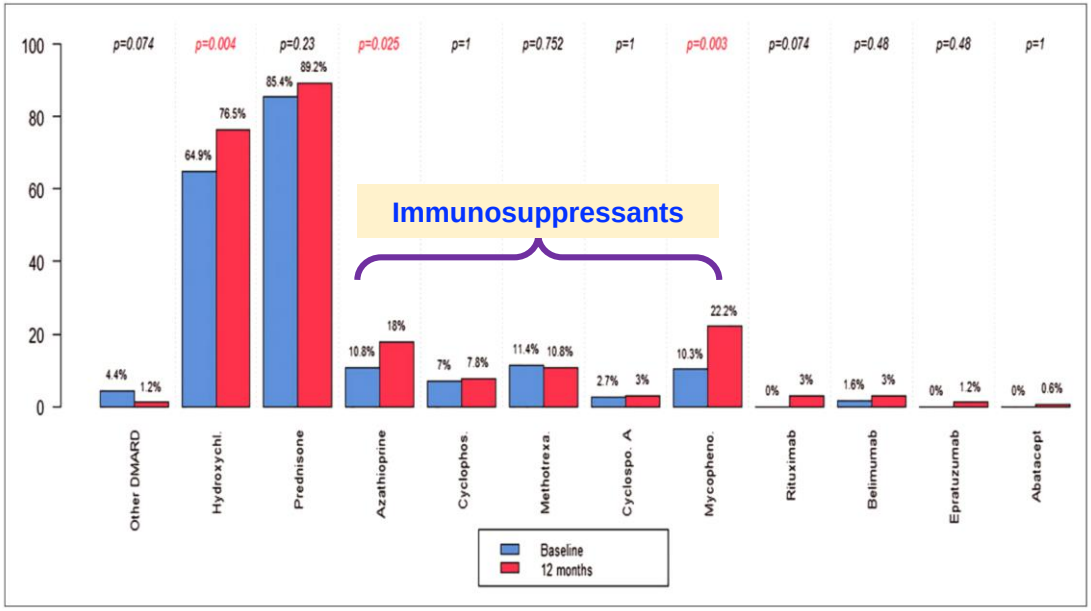


Urowitz MB, et al. *Arthritis Care Res*. 2012; 64: 132-7; Joo YB, et al. *Int J Rheum Dis*. 2015; 18:117-28; Swaak AJ, et al. *Rheumatology*. 1999; 38: 953-8; Jacobsen S, et al. *Clin Rheumatol*. 1998; 17:468-477

Early SLE progression during the first 12 months

- ❑ Accrual of new SLE manifestations/organ involvement
- ❑ Increased need for treatments (glucocorticoids, immunosuppressants)
- ❑ Only about 35% of patients achieves clinical remission
- ❑ Impaired health-related quality of life
- ❑ Accrual of comorbidities and organ damage





Sebastiani GD, et al. *Lupus*. 2018; 27: 1479-88
Piga M, et al. Rheumatology. 2020; 59: 2272–81
Segura BT, et al. Rheumatology. 2020; 59: 524–33
Koelmeyer R, et al. Lupus Sci Med. 2020; 7: e000372

Early SLE is linked to substantial disese burden

Table 3. Results of adjusted multivariate regression to determine independent effect of variables on SMR estimates*

	Adjusted SMR (95% CI)†
Female sex	1.2 (1.0–1.4)
Age, years	
<40	
40–59	
≥60	
SLE duration, years	
<1	
1–4	
5–9	
10–19	
≥20	
Calendar-year period of SLE diagnosis	
1970–1979	
1980–1989	
1990–2001	
Country	
Canada	
England	
Scotland	
Iceland	
US	
Sweden	
South Korea	0.7 (0.3–2.0)

* SMR = standardized mortality ratio; 95% CI = 95% confidence interval. SLE = systemic lupus erythematosus.
† Variables adjusted concomitantly for all others (sex, age, SLE duration, calendar-year period, and country).

Bernatsky S, et al. Arthritis Rheum. 2006; 54: 2550–7.

Highest rates of thrombosis were observed during the 2 years before till 2 years after diagnosis !!

Time since SLE diagnosis	Venous thrombosis		Arterial thrombosis	
	Rate of events per 1000 PY	Rate ratios (95% CI) adjusted for age	Rate of events per 1000 PY	Rate ratios (95% CI) adjusted for age
>5 years before SLE diagnosis	1.2	1.0 (Ref. Grp)	0.4	1.0 (Ref. Grp)
2-5 years before SLE diagnosis	2.3	1.5 (0.8, 2.7)	1.8	3.5 (1.6, 7.4)
0-2 years before SLE diagnosis	11.4	7.0 (4.7, 10.5)	8.9	15.9 (8.8, 28.8)
0-2 years after SLE diagnosis	12.5	7.4 (5.0, 11.1)	10.5	17.7 (9.9, 31.9)
2-5 years after SLE diagnosis	6.7	3.9 (2.5, 6.1)	4.5	7.2 (3.7, 13.8)
5+ years after SLE diagnosis	9.1	5.0 (3.5, 7.2)	11.8	15.8 (9.2, 27.3)

Urowitz M, et al. *Lupus Sci Med*.2016;3:e000143

Why is prompt SLE diagnosis important?

Diagnostic delay correlates with adverse outcomes

- ❑ Worse PROs (eg, physical functioning)
- ❑ Heightened disease activity
- ❑ Increased flares
- ❑ Increased organ damage (OR 2.45 when >6 months' delay)
- ❑ Poor kidney, CNS outcomes

Kernder A, et al. *Lupus*. 2021; 30: 431-8
Faurschou M, et al. *Arthritis Care Res*. 2010; 62:873–80
Gergiannaki I, et al. *Front Med*. 2018; 5: 161
Kapsala NN, et al. *Clin Exp Rheumatol*. 2023; 41: 74-81

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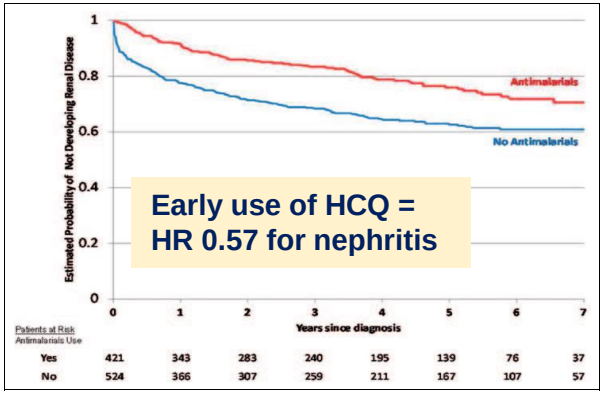
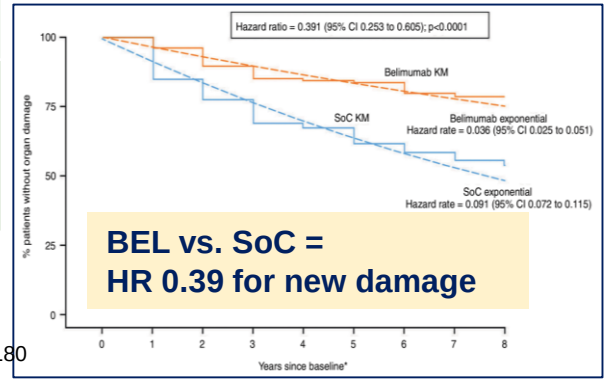
Availble drugs with favourable risk-benefit ratio

- ❑ Hydroxychloroquine (slowing of disease progression at early stages)
- ❑ Belimumab (disease modification-prevention of organ damage)
- ❑ Potent immunosuppressive or cytotoxic drugs in organ-threatening disease

Urowitz MB, et al. *Ann Rheum Dis*. 2019;78:372–9
van Vollenhoven R, et al. *Rheumatology*. 2020; 59: 281-91
Urowitz M, et al. *Lupus Sci Med*. 2020; 7: e000412
Costedoat-Chalumeau N, et al. *Presse Med.* 2014; 43:e167–180
Pons-Estel GJ, et al. *Lupus*. 2013; 22: 899–907
Kasitanon N, et al. *Rheumatology*. 2015; 54: 868-75



Early use of HCQ = HR 0.57 for nephritis

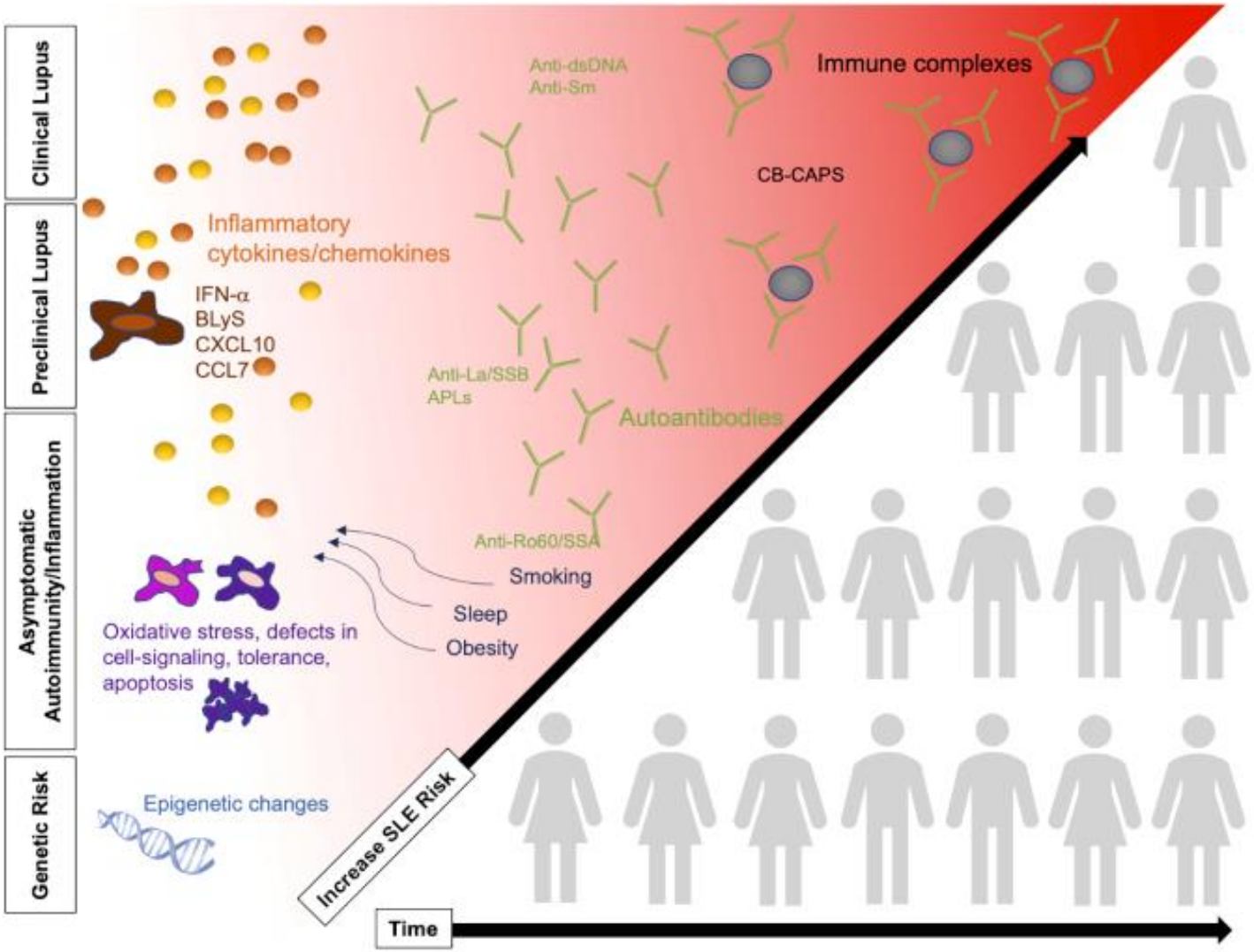


BEL vs. SoC = HR 0.39 for new damage

Outline

- Clinical characteristics and burden of early SLE
- Why is early diagnosis and treatment of SLE important?
- What are the early pathogenic events in SLE?
  - ✓ Studies before the onset of lupus
  - ✓ Studies in early, established lupus

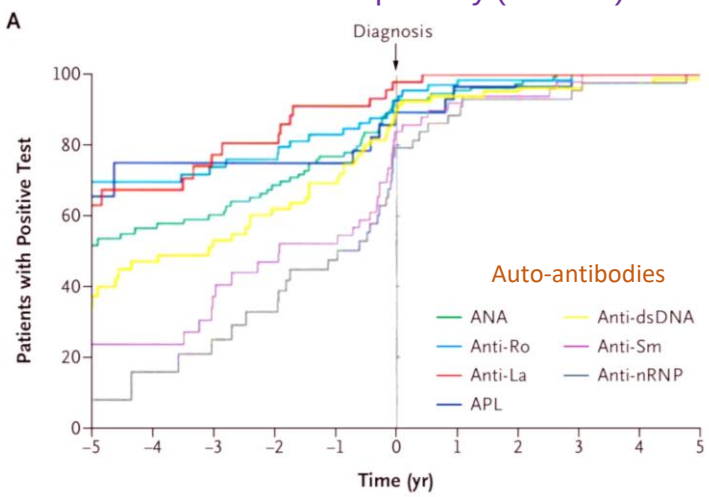
Multistep progression to clinical SLE



Choi MY, et al. *Front Immunol*. 2022; 13: 890522

Autoantibodies may precede the clinical onset of SLE

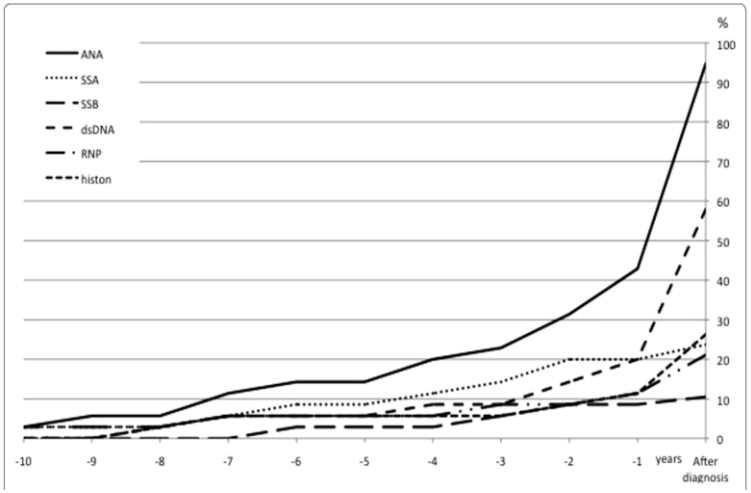
Department of Defense
Serum Repository (DoDSR)



N Engl J Med. 2003; 349: 1526-33 **

80%

Umeå (Sweden)



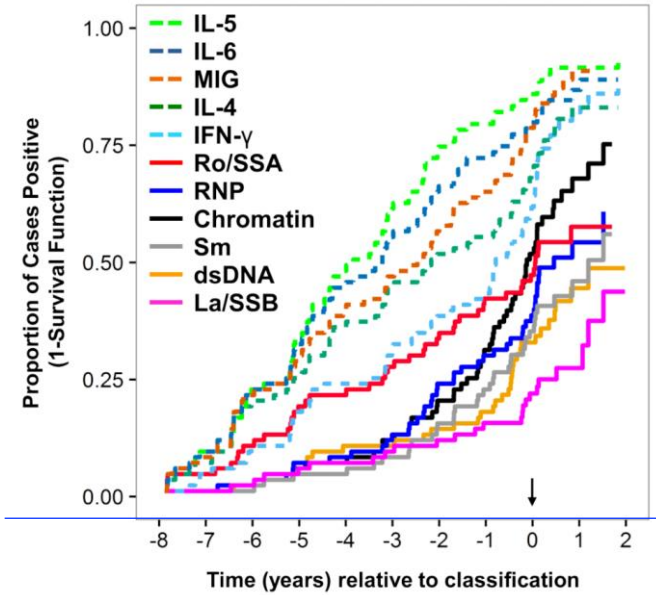
Arthritis Res Ther. 2011; 13: R30

63%

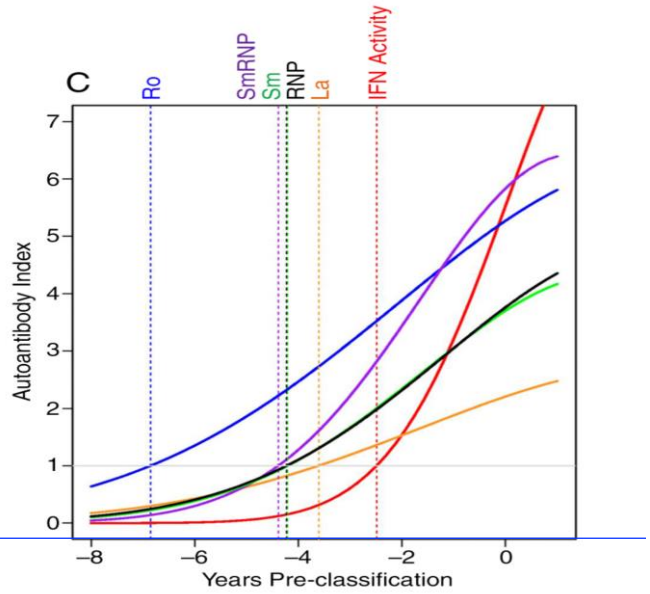
- ***Sequential appearance***: ANAs → aPL, anti-Ro/La (mean 3.2 years) → anti-dsDNA (mean 2.2 years) → anti-Sm/anti-RNP (mean 1.2 years)
- Odds ratios for SLE: 18.1 for anti-dsDNA;11.5 for ANA; 8.9 for anti-Ro/SSA
- Accumulation of autoAbs closer to diagnosis/classification (? potentially delayed by early HCQ use)
- aCL IgG/IgM (15–20%): tendency for broader clinical manifestations

Rheum Dis Clin N Am. 2014; 40: 621–35; *J Autoimmun*. 2006; 27: 153-160;
Seminars Arthritis Rheum. 2021; 51: 43-48; *Front Immunol*. 2022; 13: 890522.

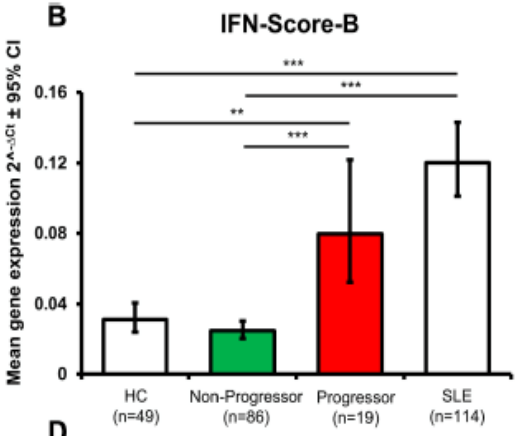
Immune aberrancies may predate SLE classification



J Autoimmun. 2016; 74: 182-93



Ann Rheum Dis. 2016; 75: 2014-21



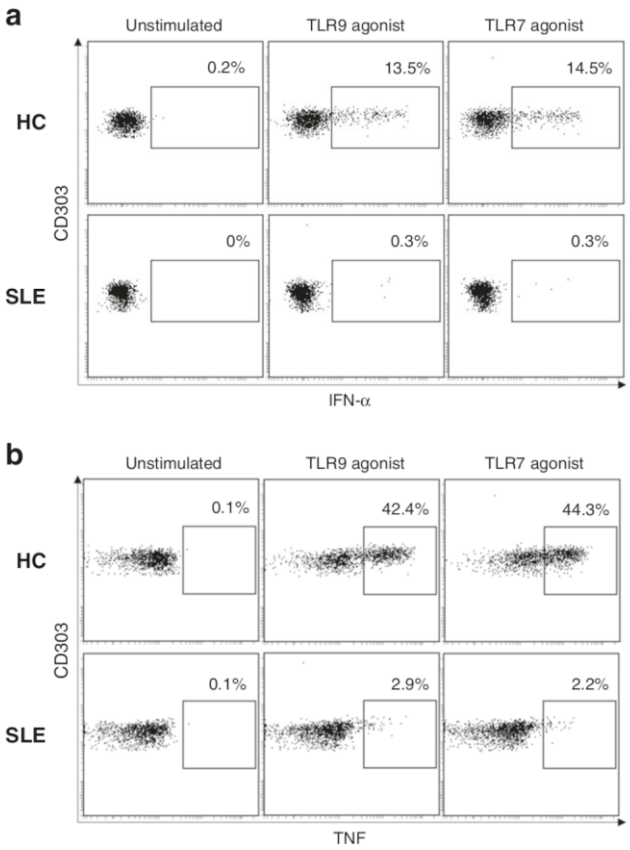
Ann Rheum Dis. 2018; 77: 1432-9

- **"IFN-B score"**: odds ratio 3.8 for SLE in ANA+ "at-risk" individuals
- *A variety of immune aberrancies may predate SLE classification*: ↑ BLyS, ↑ T_H17 cells; ↓ T_{reg}
- Combination of immune mediators and autoantibodies provides enhanced predictive power
- Small case series: HCQ might suppress IFN score and BAFF levels in iSLE or new-onset SLE

Front Immunol. 2022; 13: 890522; *Front Immunol*. 13: 866181; *Arthritis Rheumatol*. 2017; 69: 630–42; *Arthritis Res Ther*. 2019; 21(1): 260; *J Rheumatol*. 2021; 48: 847–51

Keratinocytes represent an important source of type I interferon at early lupus

Contrary to circulating SLE pDCs … (exhausted??)

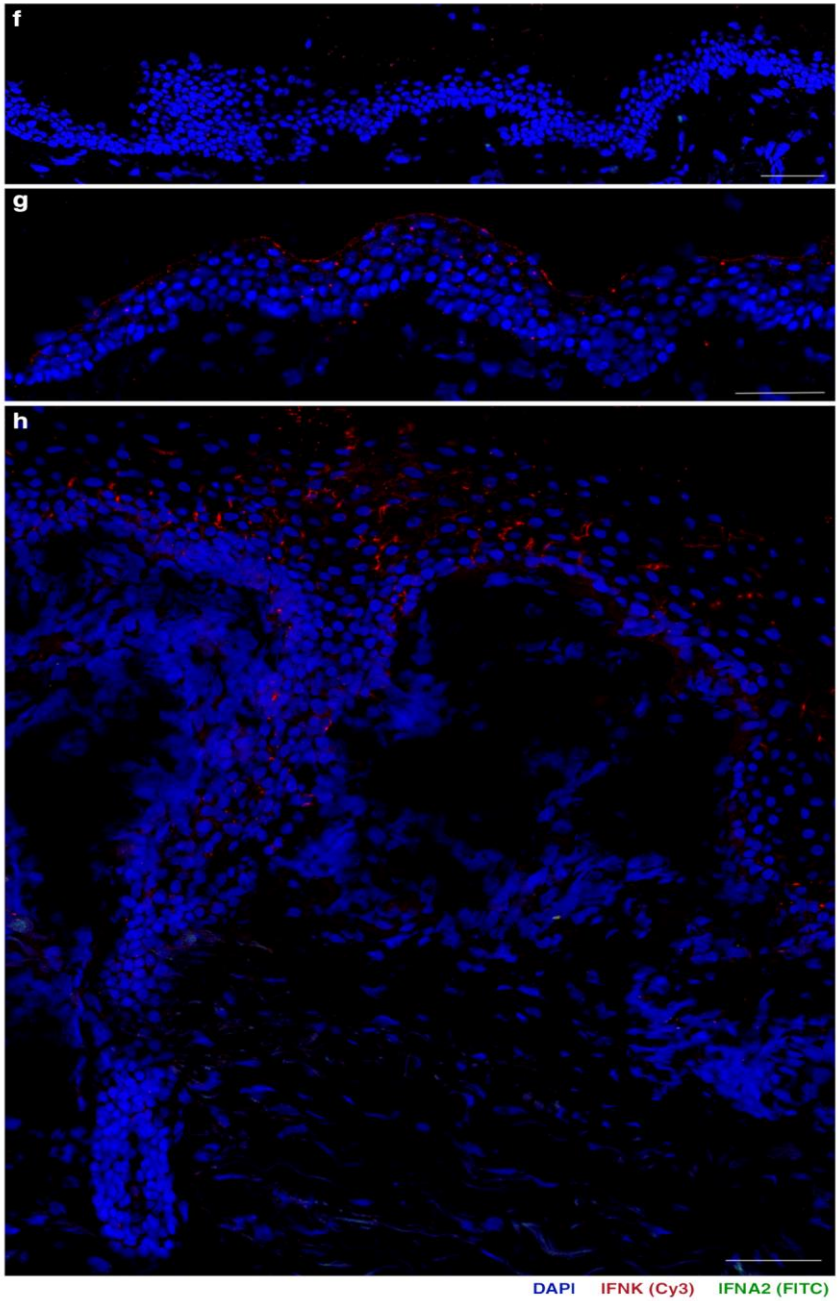


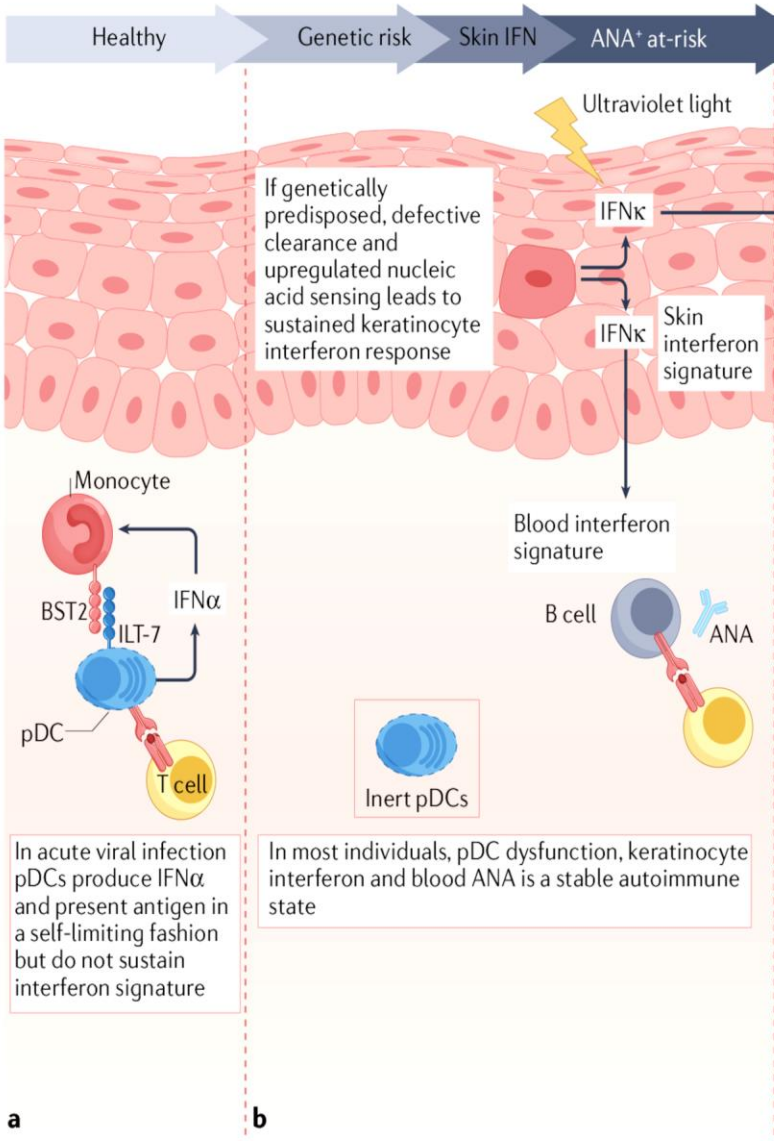
Psarras A, et al. *Nat Commun*. 2020; 11(1): 6149

Healthy

At-risk

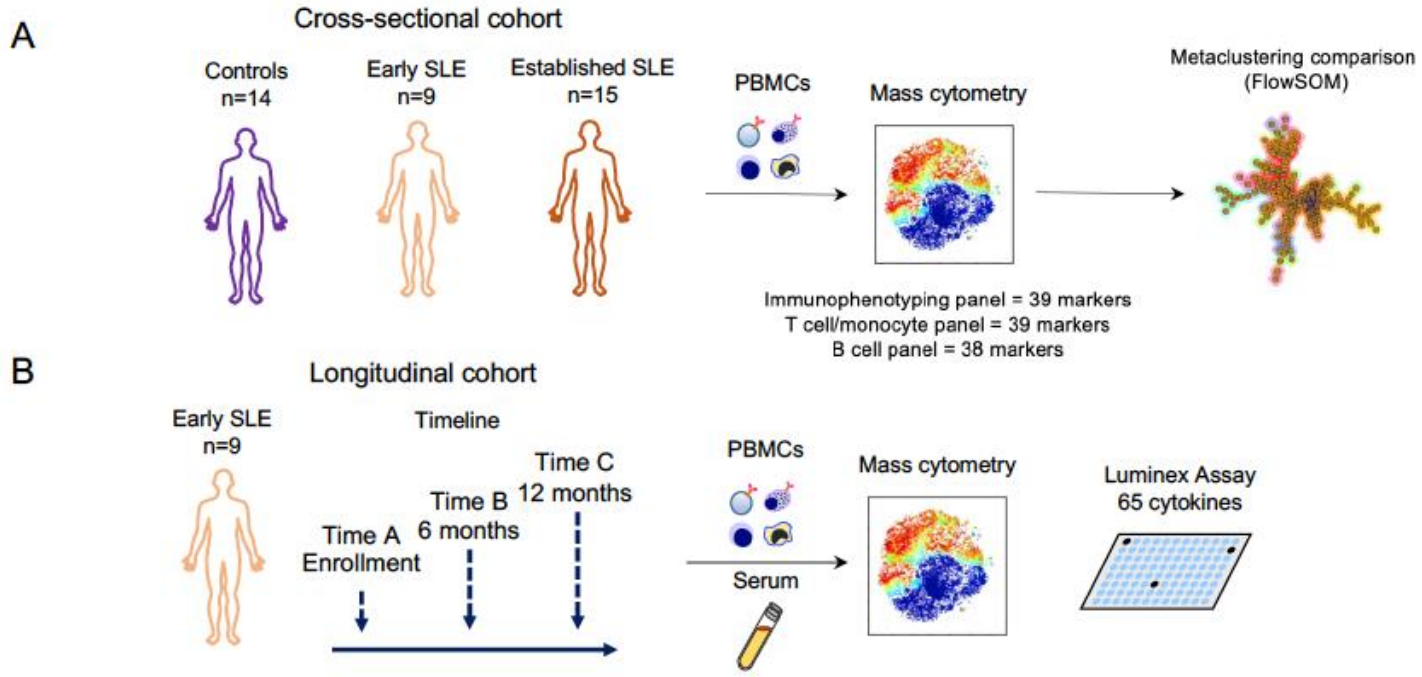
SLE





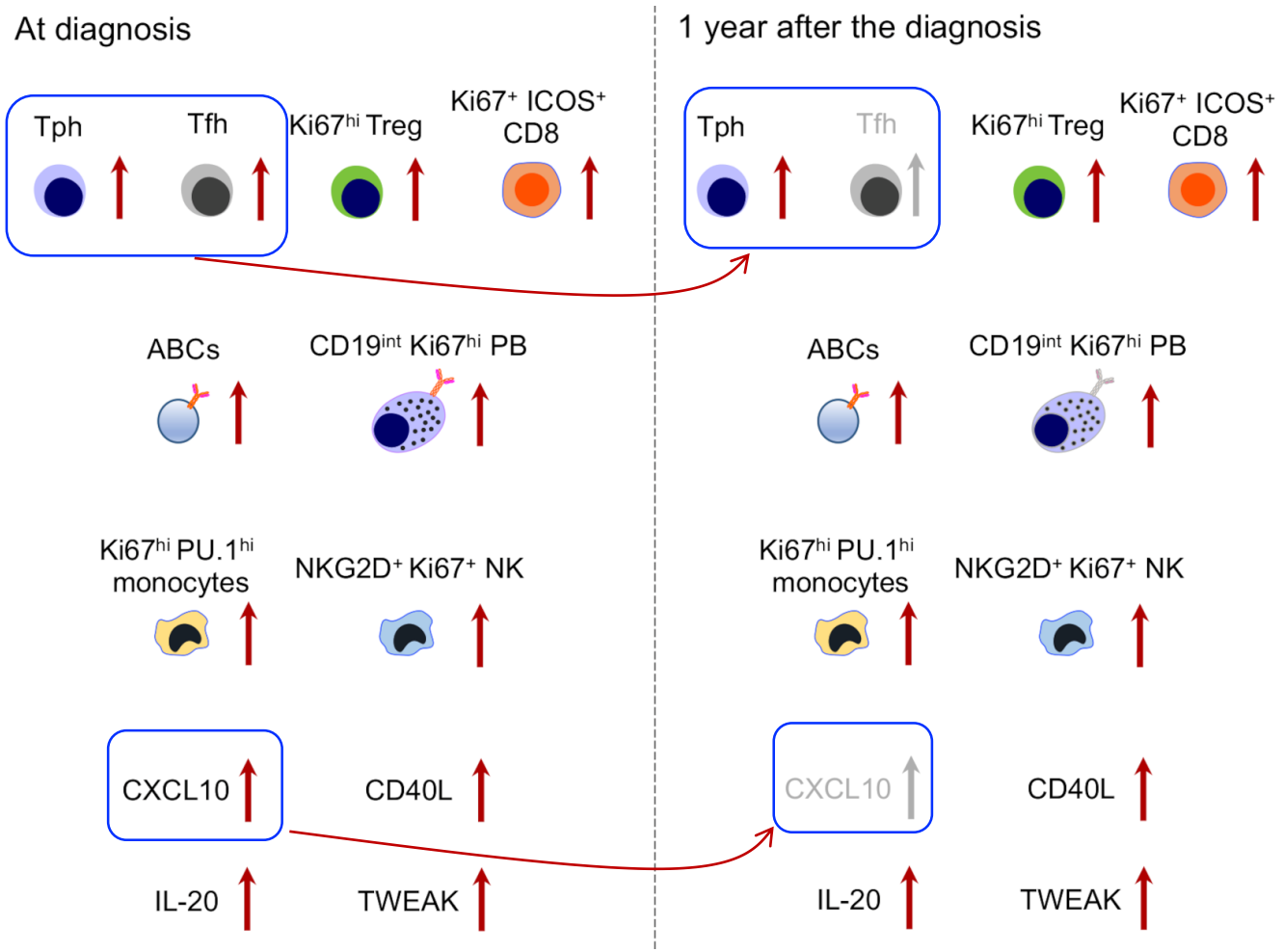
Psarras A, et al. *Nat Rev Rheumatol*. 2022; 18(10): 575-90

Immunoprofiling of early SLE patients



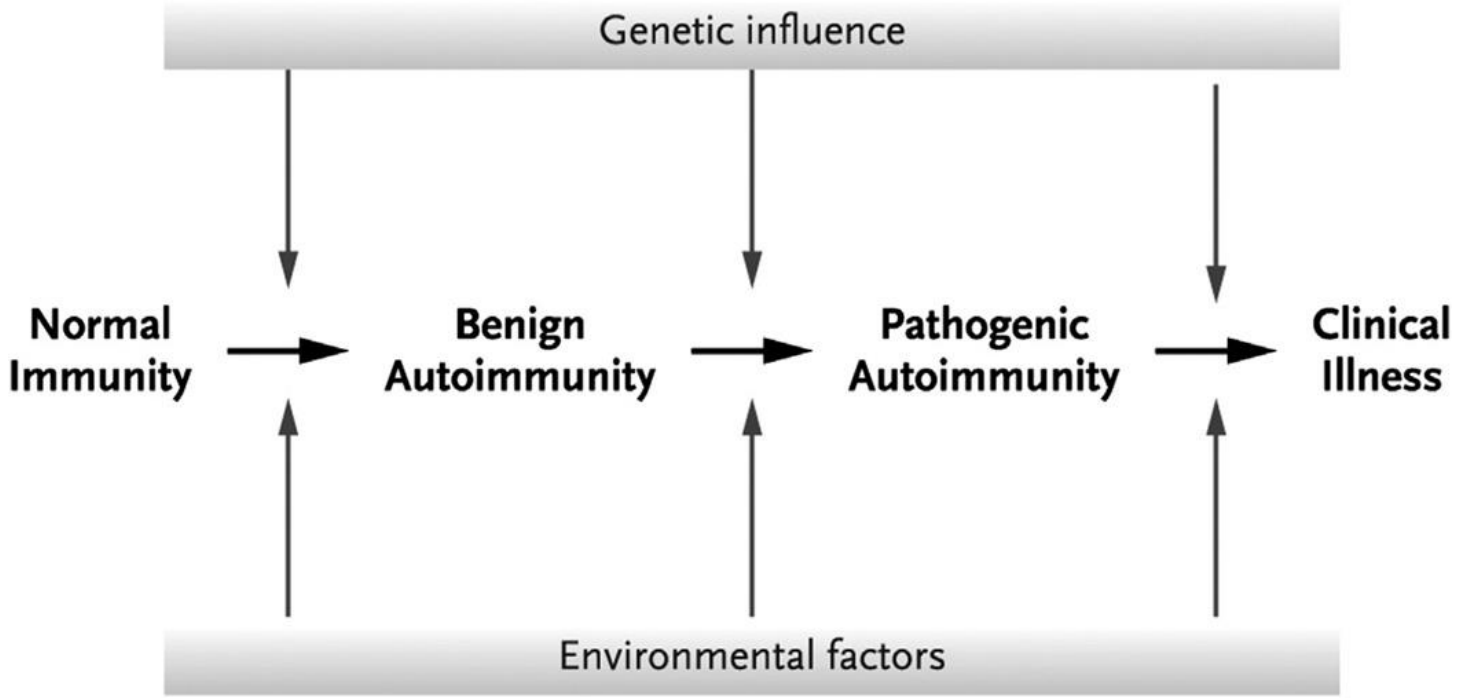
Sasaki T, et al. Arthritis Rheumatol. 2022; 74: 1808–21

Two major helper T cell subsets and unique Ki-67+ proliferating immune cell subsets are expanded in early SLE



Sasaki T, et al. Arthritis Rheumatol. 2022; 74: 1808–21

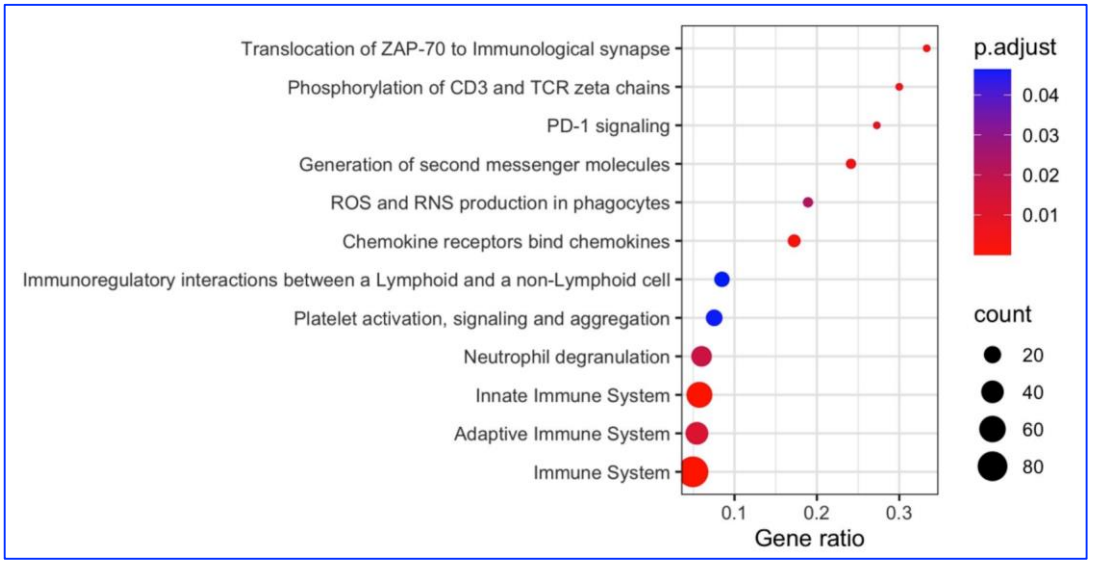
Why not all individuals with autoantibodies develop autoimmunity?



Data from lupus-prone mice:
both innate and adaptive immune activation underly the progression from preclinical to clinical SLE

NZBxNZW F1

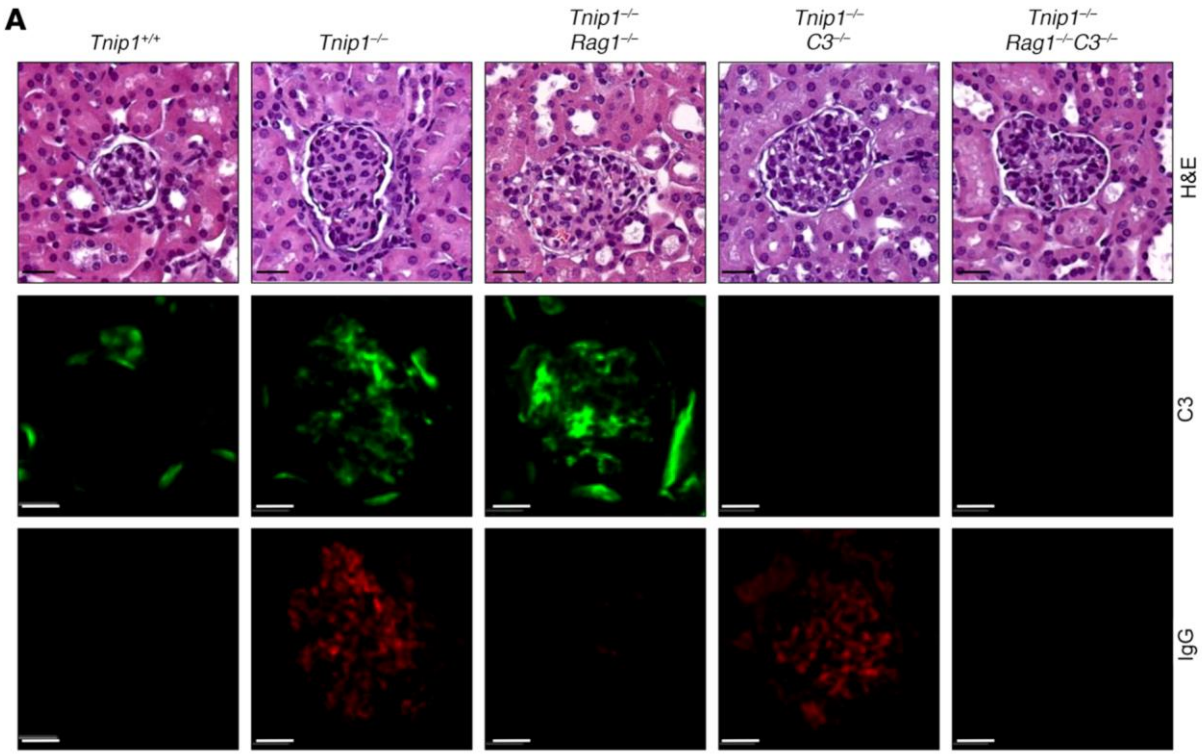
- **Neutrophil degranulation**
- **ROS production in phagocytes**
- TCR signalling
- Signal transduction by chemokine receptors
- Costimulation through PD-1 signalling

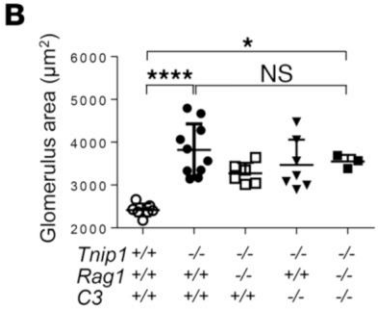


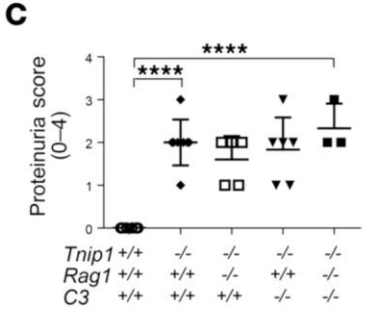
The lupus-susceptibility risk genes *PTPRC*, *IRF8*, *NCF1* and *ITGAM*, emerged as hub network genes

Frangou E, et al. Ann Rheum Dis 2022;81:1409–19

Early SLE glomerulonephritis (ABIN1-deficient mice) proceeds independently of autoreactive Abs and C3-mediated complement activation: the role of patrolling monocytes







Dissociation between humural autoimmunity & tissue inflammation-injury

Kyriakose J, et al. J Clin Invest. 2019; 129(6): 2251-65

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- Clinical characteristics and burden of early SLE
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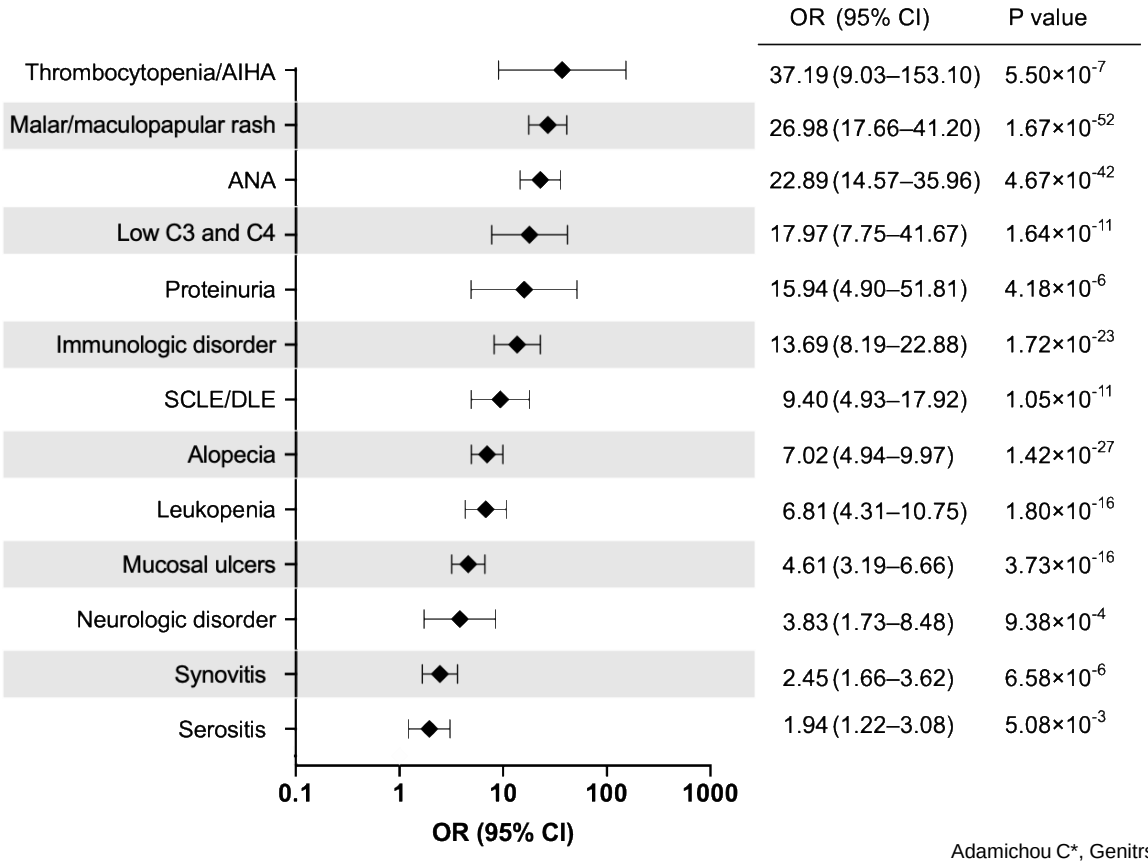
- What are the early pathogenic events in SLE?
- Strategies for the early identification of SLE and individuals at-risk
- Possibilities for personalised intervention

Development of SLERPI: a machine learning-based diagnostic index in SLE



	OR (95% CI)	P value
Thrombocytopenia/AIHA	37.19 (9.03–153.10)	5.50×10^{-7}
Malar/maculopapular rash	26.98 (17.66–41.20)	1.67×10^{-52}
ANA	22.89 (14.57–35.96)	4.67×10^{-42}
Low C3 and C4	17.97 (7.75–41.67)	1.64×10^{-11}
Proteinuria	15.94 (4.90–51.81)	4.18×10^{-6}
Immunologic disorder	13.69 (8.19–22.88)	1.72×10^{-23}
SCLE/DLE	9.40 (4.93–17.92)	1.05×10^{-11}
Alopecia	7.02 (4.94–9.97)	1.42×10^{-27}
Leukopenia	6.81 (4.31–10.75)	1.80×10^{-16}
Mucosal ulcers	4.61 (3.19–6.66)	3.73×10^{-16}
Neurologic disorder	3.83 (1.73–8.48)	9.38×10^{-4}
Synovitis	2.45 (1.66–3.62)	6.58×10^{-6}
Serositis	1.94 (1.22–3.08)	5.08×10^{-3}

Odds ratio for SLE vs. competing disease

+1 additional feature (interstitial lung disease) with negative association

Adamichou C*, Genitrsaridi I*, et al. *Ann Rheum Dis.* 2021; 80(6): 758-66

SLE Risk Probability Index (SLERPI)

Malar rash or maculopapular rash	No
Subacute cutaneous lupus erythematosus (SCLE) or discoid lupus erythematosus (DLE)	No
Alopecia	Yes
Mucosal ulcers	No
Arthritis	No
Serositis	Yes
Leukopenia <4000/μL (at least once)	No
Thrombocytopenia or autoimmune hemolytic anemia	No
Neurological disorder	No
Proteinuria ≥500 mg/g	No
ANA	Yes
Low C3 and C4	Yes
Immunological disorder (any of: anti-DNA, anti-Sm, anti-phospholipid antibodies)	No
Interstitial lung disease	No
SLE risk probability	68.97 %
SLE diagnostic certainty level	Likely/probable SLE
SLE diagnosis?	SLE

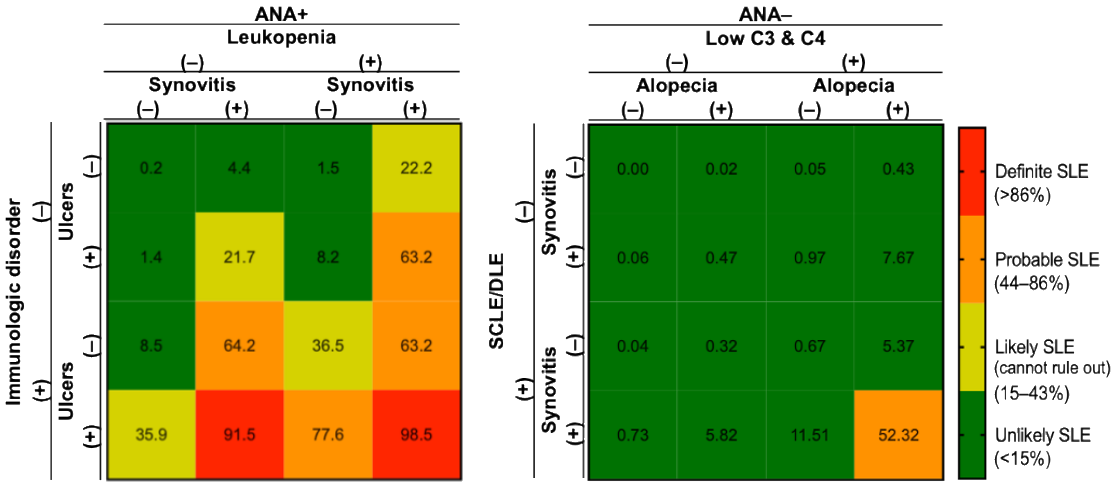
Web version: https://www.rheumatology-uoc.gr/el/slerpi

Probabilistic approach to SLE diagnosis

- ***"Definitive SLE"***
- ***"Likely SLE"***
- ***"Cannot rule-out SLE"***

} *against lupus-mimicking rheumatic diseases*

- ***"Other CTD more likely than SLE"***



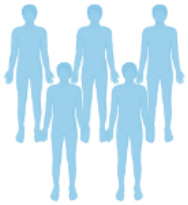
Adamichou C*, Genitrsaridi I*, et al. *Ann Rheum Dis.* 2021; 80(6): 758-66

An inception cohort of individuals ‘at-risk’ to SLE

Age: 18 to 50 years			
Group A	**Group B**	**Group C**	**Group D**
ANA ≥ 1:640 **PLUS** ≥1 additional feature (serological or clinical)	**ANA ≥ 1:80** **PLUS** ≥2 additional features (serological or clinical)	**ANA-negative** **PLUS** ≥1 serological **AND** ≥2 clinical features	**First-degree relative of SLE** **PLUS** ≥2 additional features (serological [**including ANA**] or clinical)

- ❑ **Not fulfilling the ACR 1997 or EULAR/ACR 2019 classification criteria**
- ❑ **No physician diagnosis of SLE or other inflammatory rheumatic disease**
- ❑ **Not receiving ≥20 mg/day prednisone or csDMARD/ISTs (except HCQ)**

Methodology: evaluation at baseline and every 4 to 12 months depending on the disease status



Inception cohort

- autoAbs+ individuals or FDRs
- not satisfied SLE criteria

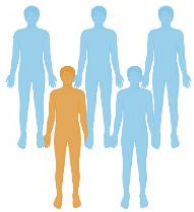
Demographics, family history, infections and other past history

Hematological, urinalysis and serological parameters

Lifestyle exposures and use of medications

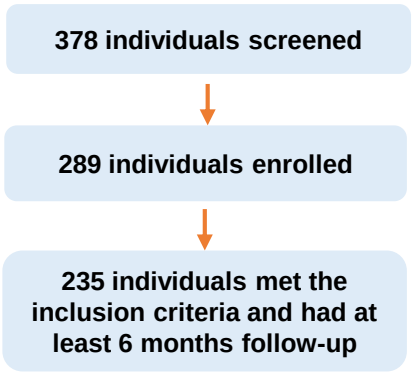
Whole blood collection

Monitored prospectively for up to 5 years



Transition to classifiable SLE

Baseline characteristics



Gender (female)	94.0%
Race (white)	97.9%
Age (years, mean ± SD)	37.0 ± 11.3
Education (<12 years)	21.7%
Residence (rural)	19.1%
First degree relative with SLE	10.6%
1997 ACR items (baseline)	
Malar rash	14.9%
Discoid rash	1.7%
Photosensitivity	24.3%
Ulcers	8.9%
Synovitis	28.1%
Serositis	1.3%
Renal	0.4%
Neurological	0.9%
Hematological	20.9%
Immunological	23.6%
ANA	80.9%

Transition to classifiable SLE (median follow-up 21 months)

SLE classified	No. (%)
by the ACR-97 and/or the EULAR/ACR-19 criteria	**52 (22.1%)**
by BOTH the ACR-97 AND the EULAR/ACR-19 criteria	19 (8.1%)
by the ACR-97 BUT NOT the EULAR/ACR-19 criteria	11 (4.7%)
by the EULAR/ACR-19 BUT NOT the ACR-97 criteria	22 (9.4%)

Classification criteria	No. new items/score
ACR 1997	1.4 ± 0.6
EULAR/ACR 2019	1.8 ± 3.3

Majority of transitions occurred within the first 18 months

New-onset features of SLE

- Predominant mucocutaneous (ACLE: 29.3%, alopecia: 17.1%, ulcers: 9.8%) and joints (56.1%), and serological abnormalities (anti-DNA: 12.2%, low C3/C4: 19.5%)

	No. (%)
Non-criteria immunol. features	
Anti-Ro/SSA	5 (12.2%)
Anti-La/SSB	2 (4.9%)
Anti-RNP	0
Treatments	
Azathioprine	2 (4.9%)
Belimumab	1 (2.4%)
Cyclophosphamide	1 (2.4%)
Ciclosporin	1 (2.4%)
Methotrexate	7 (17.1%)
Mycophenolate	1 (2.4%)

✓ ***About 25% had moderate/severe form of SLE***

Demographic and clinical features associated with the transition from 'at-risk' to classfied SLE

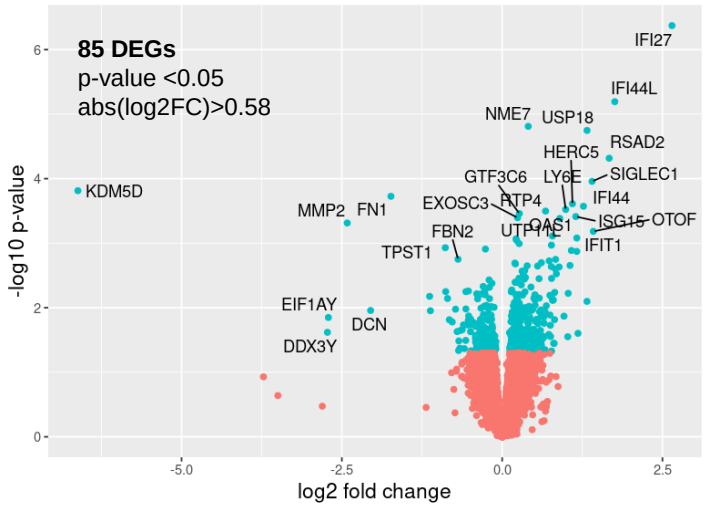
Baseline features	Progression to SLE (ACR 1997 and/or EULAR/ACR 2019 criteria)	
	Hazard ratio (95% CI)	**P value**
FDR(s) with SLE (yes)	2.21 (1.07–4.54)	**0.031**
Smoking Never smoker Smoker – active Smoker – past	 1.00 1.23 (0.56–2.72) 2.15 (1.17–3.96)	 0.610 **0.014**
Mediterranean score (0 to 8)	0.88 (0.76–1.02)	0.090
Malar rash	1.76 (0.92 – 3.36)	0.087
Photosensitivity	2.37 (1.35 – 4.17)	**0.003**
Mucosal ulcers	1.87 (0.84 – 4.16)	0.125
Serositis	4.87 (1.17 – 20.24)	**0.029**
Non-scarring alopecia	1.85 (0.92 – 3.71)	0.082
Autoimmune hemolysis	2.56 (0.62 – 10.56)	0.193
Thrombocytopenia	0.22 (0.03 – 1.61)	0.136
Low C3 and low C4)	2.13 (0.77 – 5.93)	0.148
Raynaud's	0.52 (0.27 – 1.02)	0.057

Baseline molecular signatures discriminate individuals who progress or not to SLE

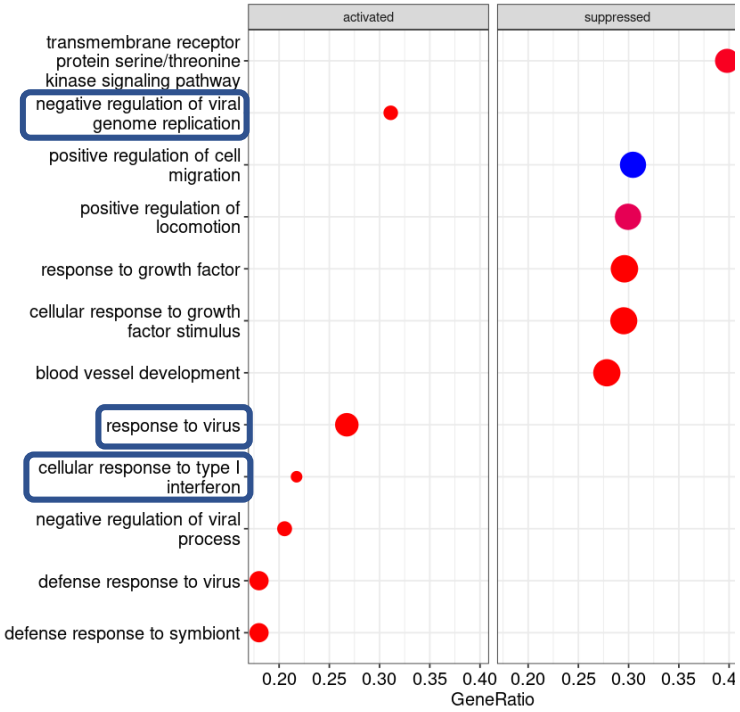
Blood RNA-seq

Status	Total
Healthy	42
Non-Progressors	**36**
Progressors	**36**

Volcano plot



Gene Set Enrichment Analysis



Transition to SLE:

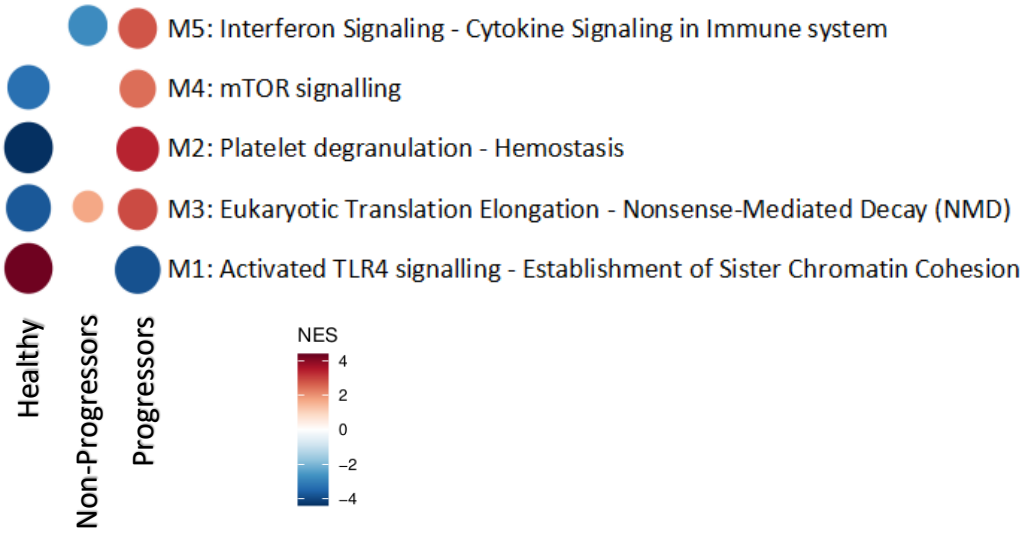
✓ Increased *IFI27*, *OTOF*, *IFI44L* expression

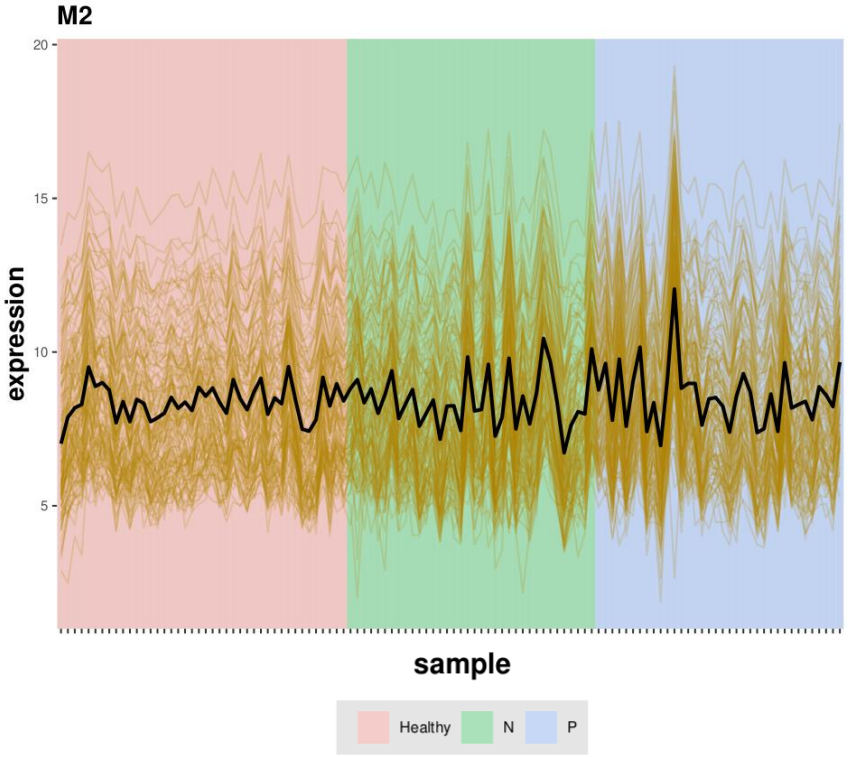
✓ Deregulation of response to type I IFN

Risk stratification in individuals with preclinical lupus: gene-modular (WGCNA) analysis

Gene co-expression networks

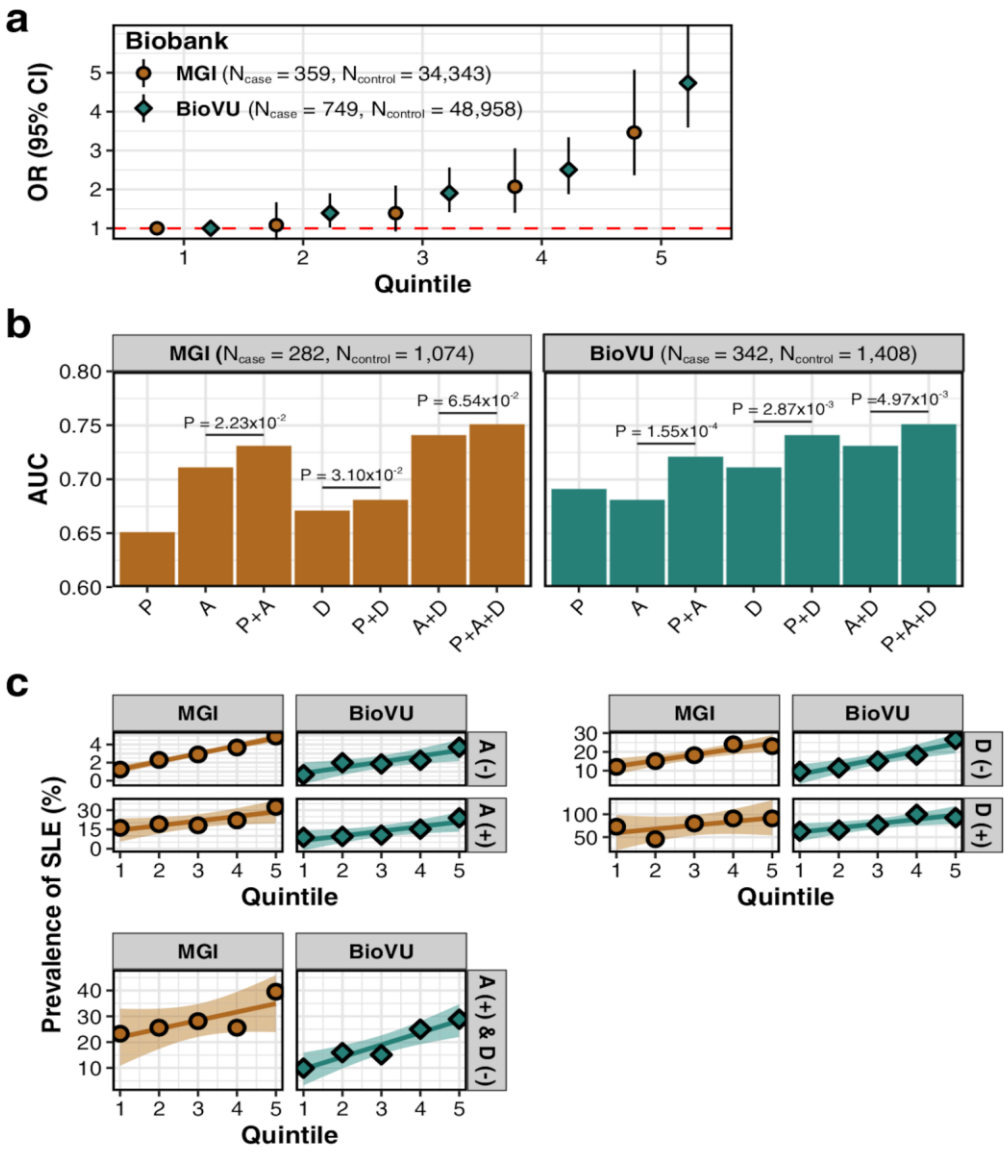
Gene Set Enrichment Analysis showing the module activity on each group of samples





Russo P.S.T., et al., BMC Bioinformatics, 2018

How can we further define individuals at-risk for SLE?



>183 risk susceptibility loci have been associated with SLE

Polygenic Risk Scores (PRS) correlate with earlier disease onset and increased burden/damage of SLE

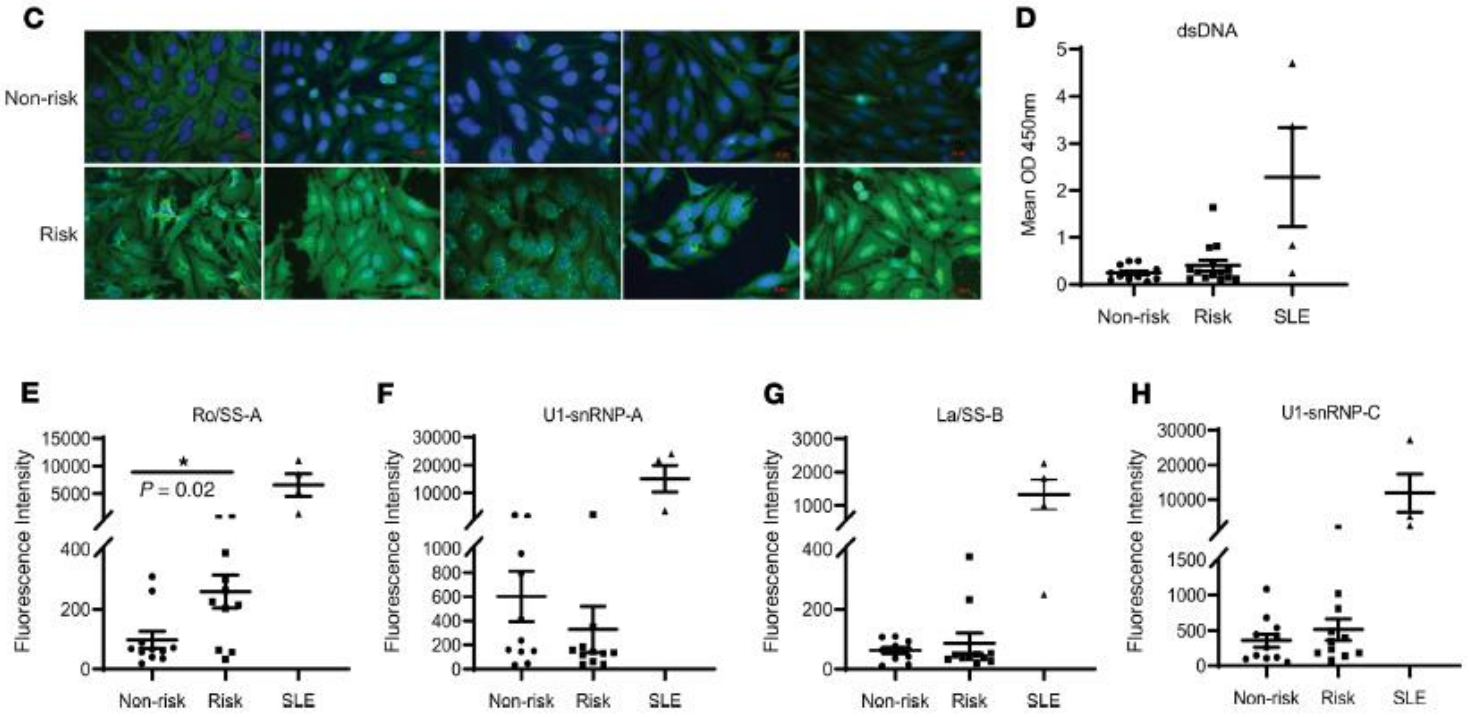
Nat Commun. 2023; 14: 668;
Front Genet. 2022; 13: 902793;
Ann Rheum Dis. 2020; 79: 363–9

The example of *IRF5* risk variant

JCI insight

RESEARCH ARTICLE

IRF5 genetic risk variants drive myeloid-specific IRF5 hyperactivation and presymptomatic SLE

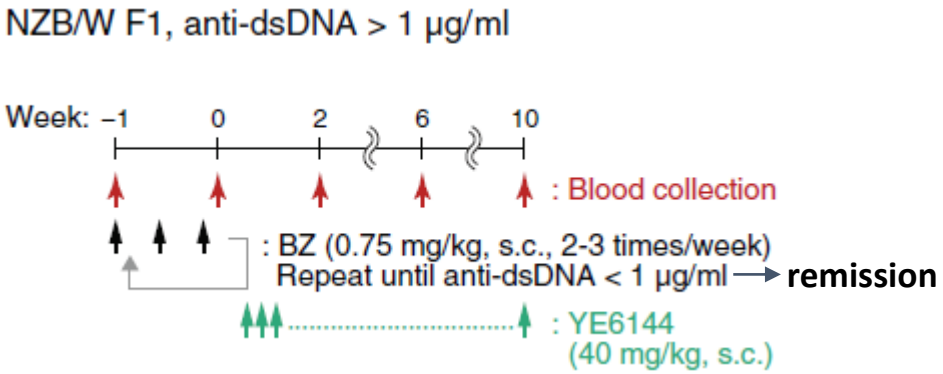


Li D, et al. *JCI Insight*. 2020; 5(2): e124020

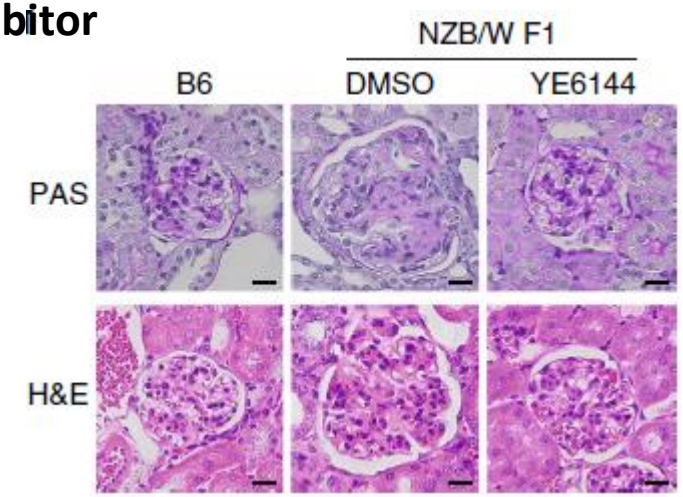
A step towards personalised intervention

IRF5

Translating into a novel targeted therapy for SLE



YE6144: IRF5 inhibitor



Hagberg N, et al. *Scand J Immunol*. 2020; 92(4):e12894
Ban T, et al. *Nat Commun*. 2021; 12(1):4379.

Take-home messages

- Early SLE has substantial clinical burden; mild cases may transit into more severe disease
- Early recognition and management of SLE is critical to ensure better outcomes
- The molecular and cellular events of early SLE remain largely unexplored and may be facilitated by preclinical/early disease cohorts
- Abberant type I inteferon is a very early event in SLE pathogenesis, possibly driving altered metabolic/functional changes in immune cells
- Still, it is uncertain whether the whole spectrum of SLE disease follows this 'progression path'. E.g., severe organ-dominant lupus?
- Possible opportunities for individualised preventative interventions

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