Con il patrocinio di

Associazione Italiana Pneumologi Ospedalieri

Ospedale San Giuseppe
MultiMedica S.p.A.

PNEUMOLOGIA 2016

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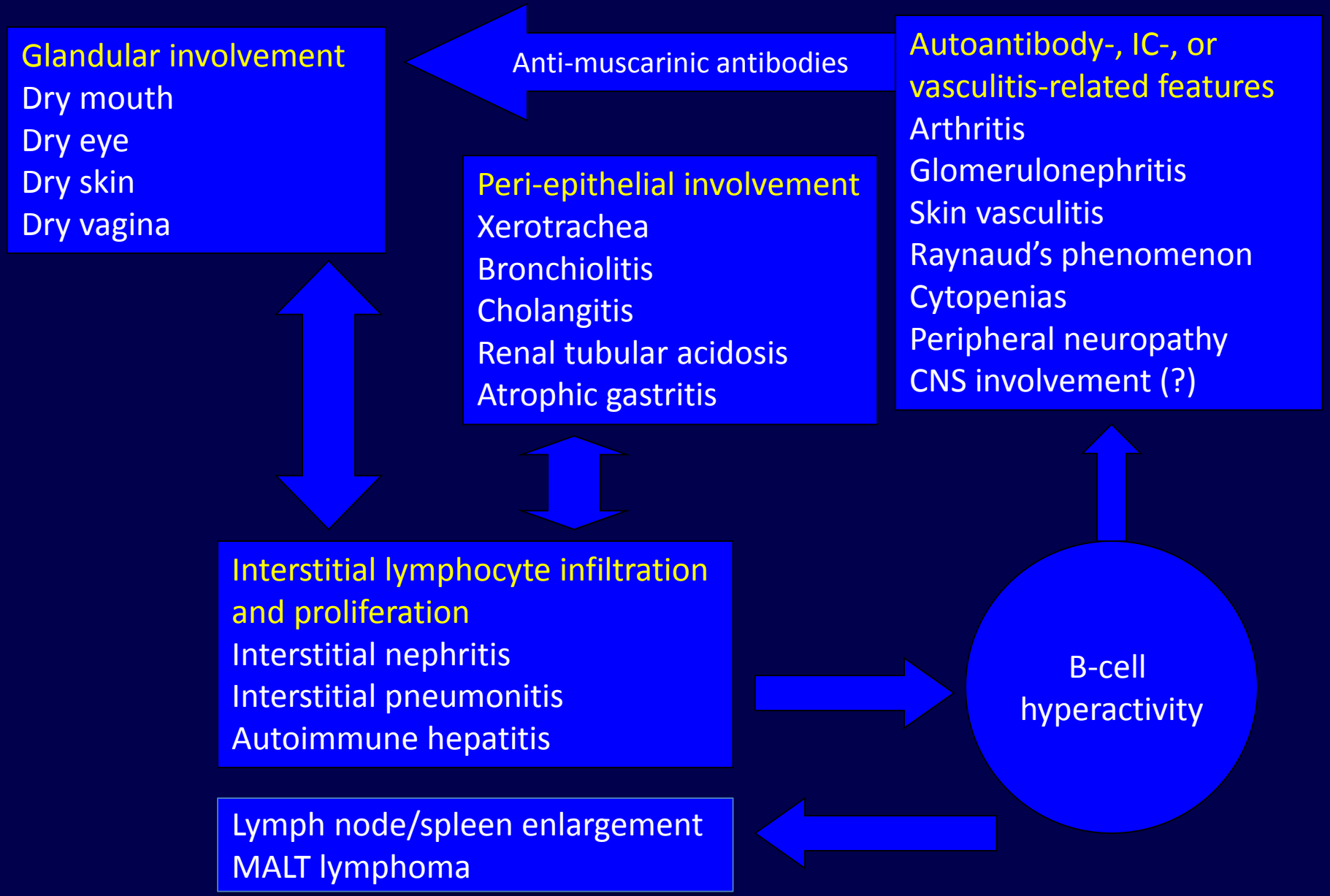
New Therapeutic Perspectives in Sjögren's Syndrome

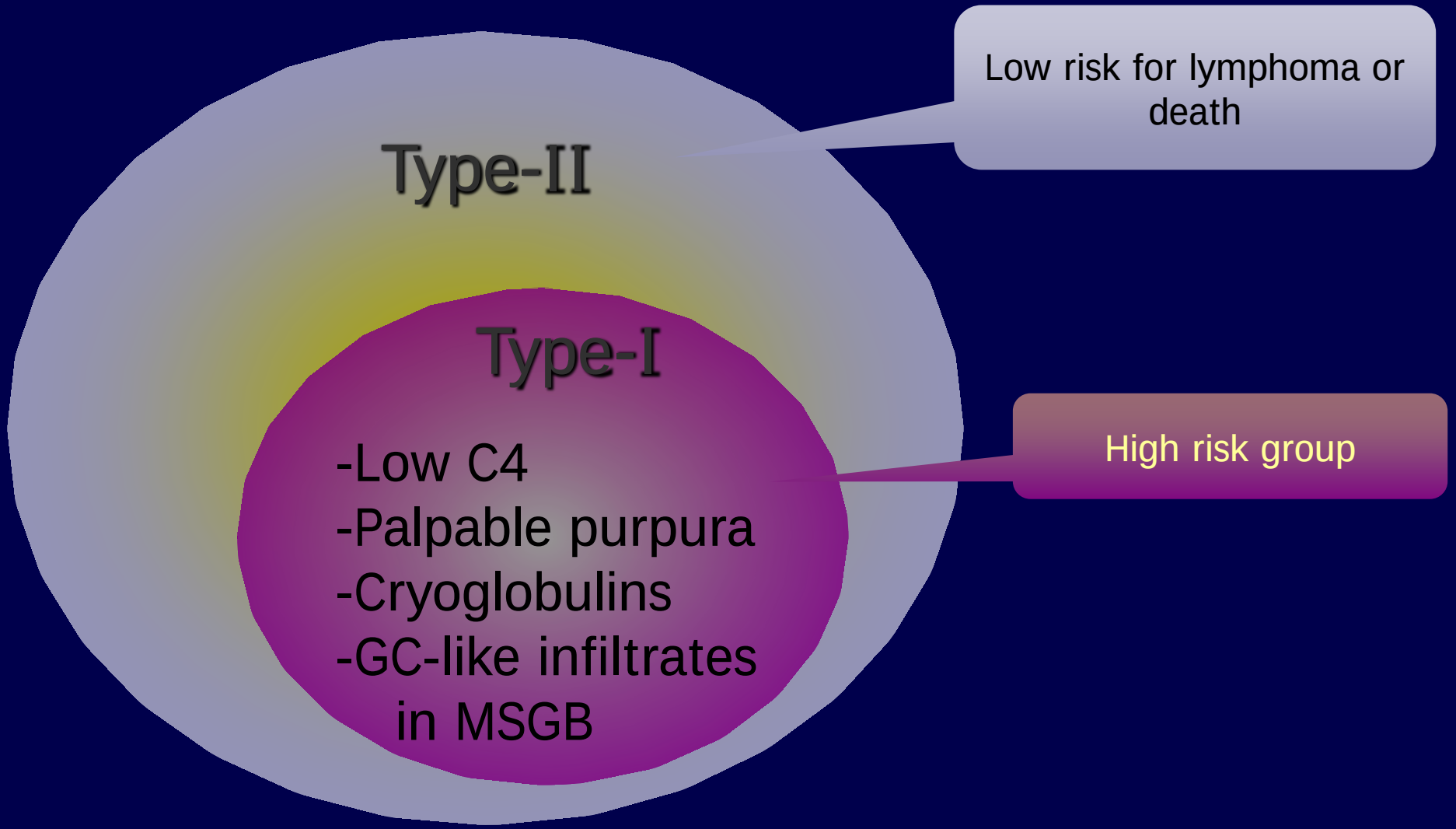
Claudio Vitali

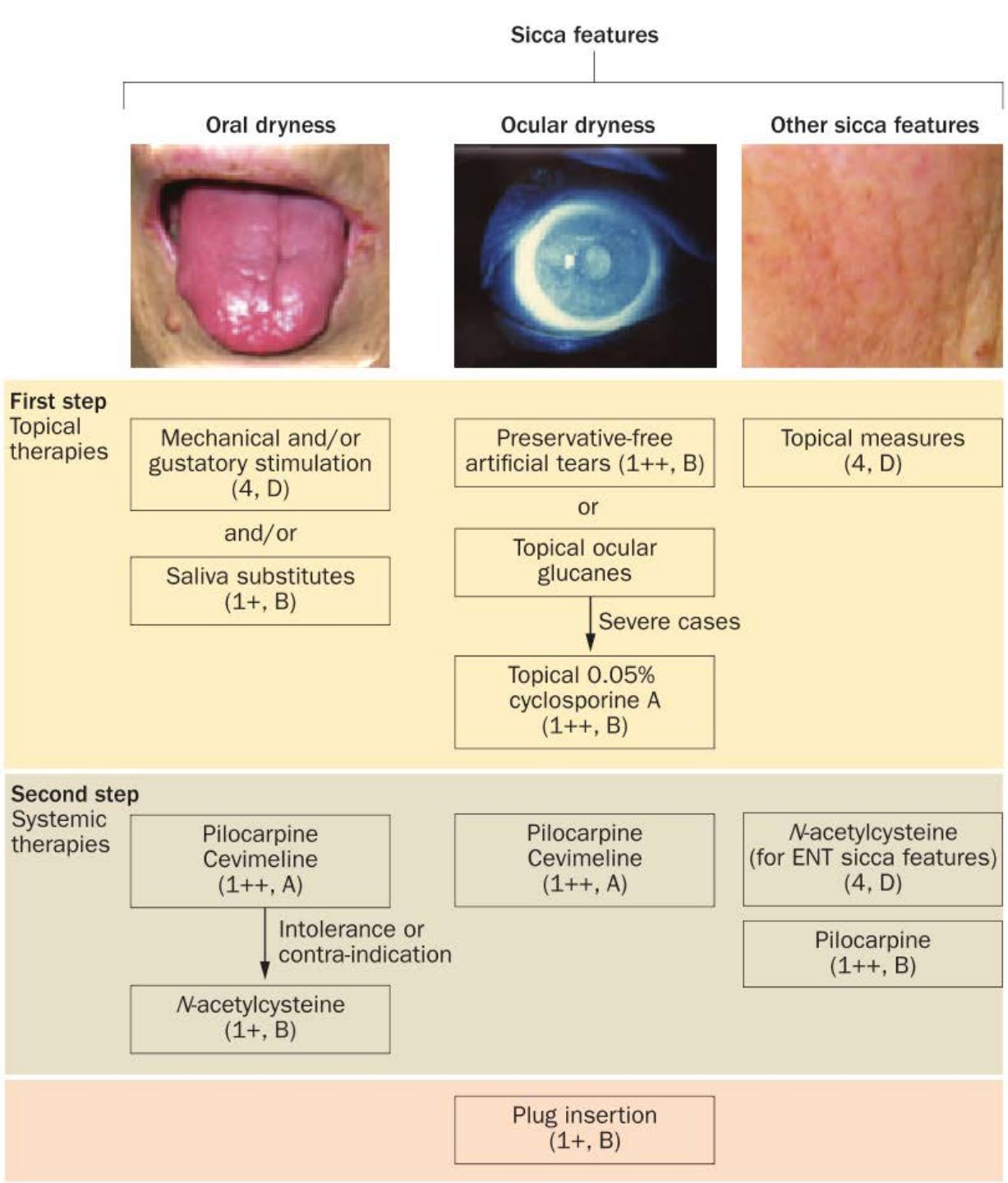
- Chairman of the EULAR Task Force for Disease Activity Criteria in Sjögren's Syndrome.
- Member of the Steering Committee for the ACR-EULAR Sjögren's Syndrome Working Group on Classification Criteria.

The Spectrum of Clinical Manifestations in SjS



Sjögren's Syndrome
Autoimmune Epithelitis





Ramos.Casals M et al.
Nat Rev Rheumatol; 2012: 399-411

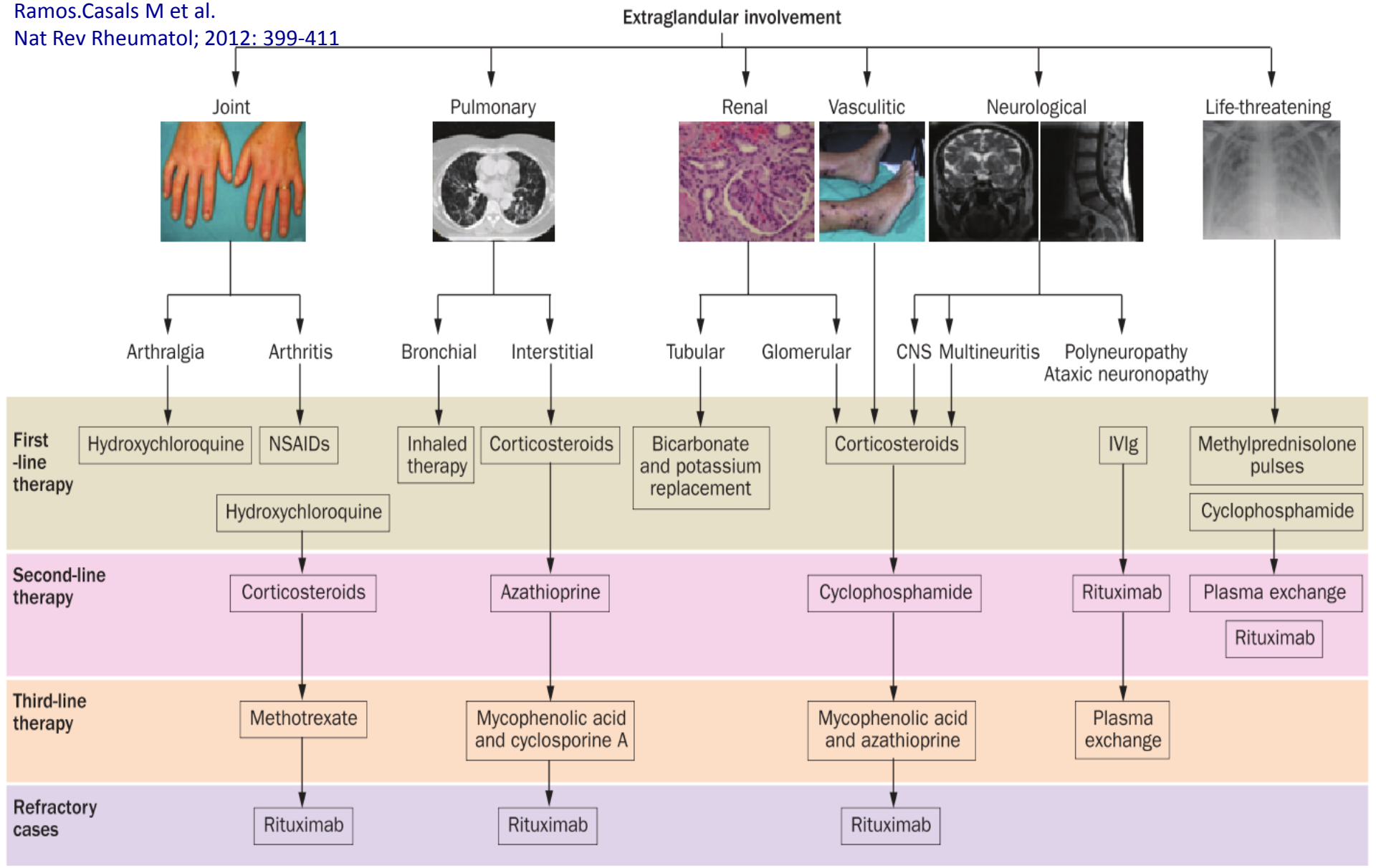
Level of evidence (1-4).

+ patients with sicca symptoms;
++ patients with SS.

Strengh of recommendation (A-D).

ENT: ear, nose, and throat.

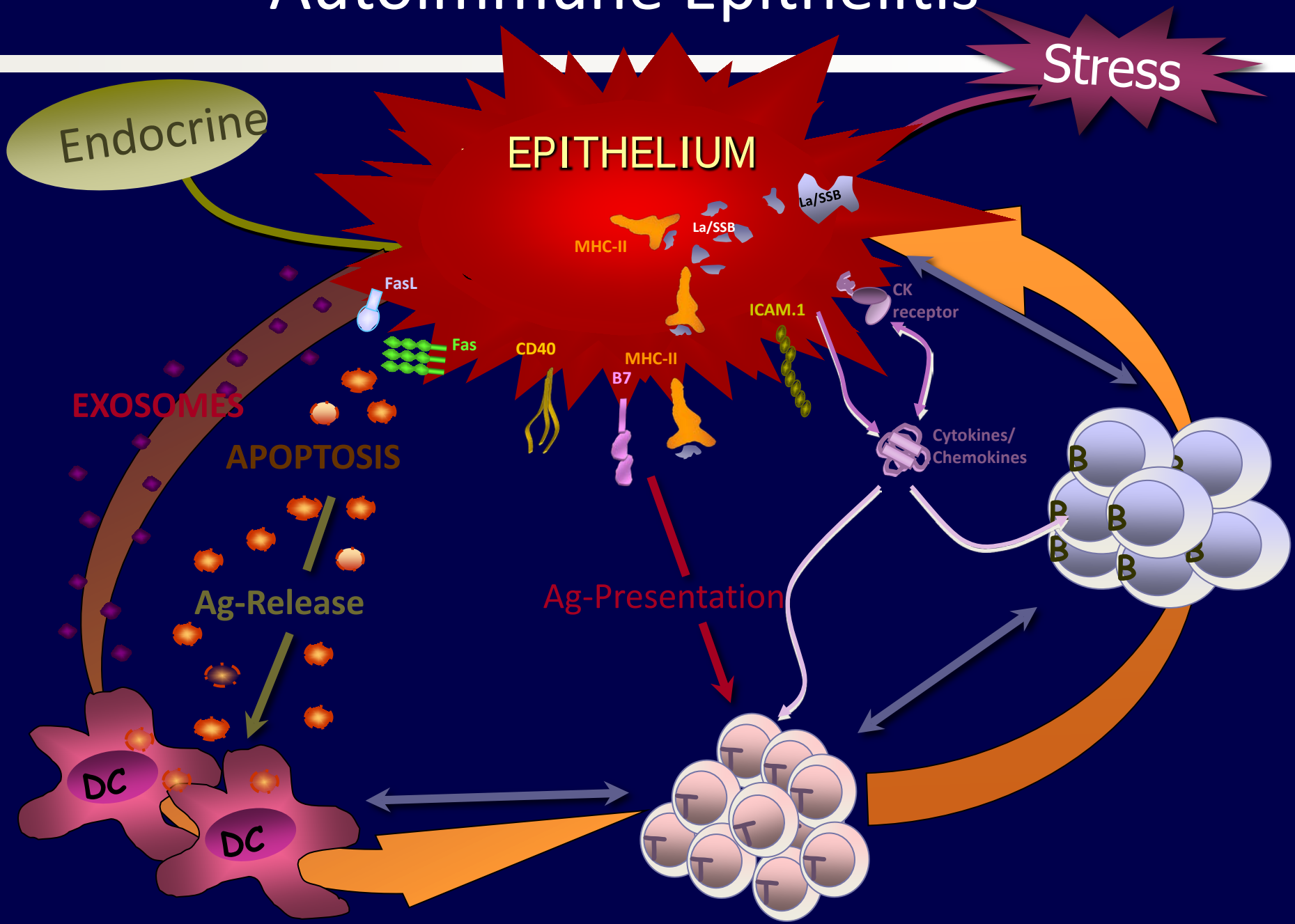
Ramos.Casals M et al.
Nat Rev Rheumatol; 2012: 399-411

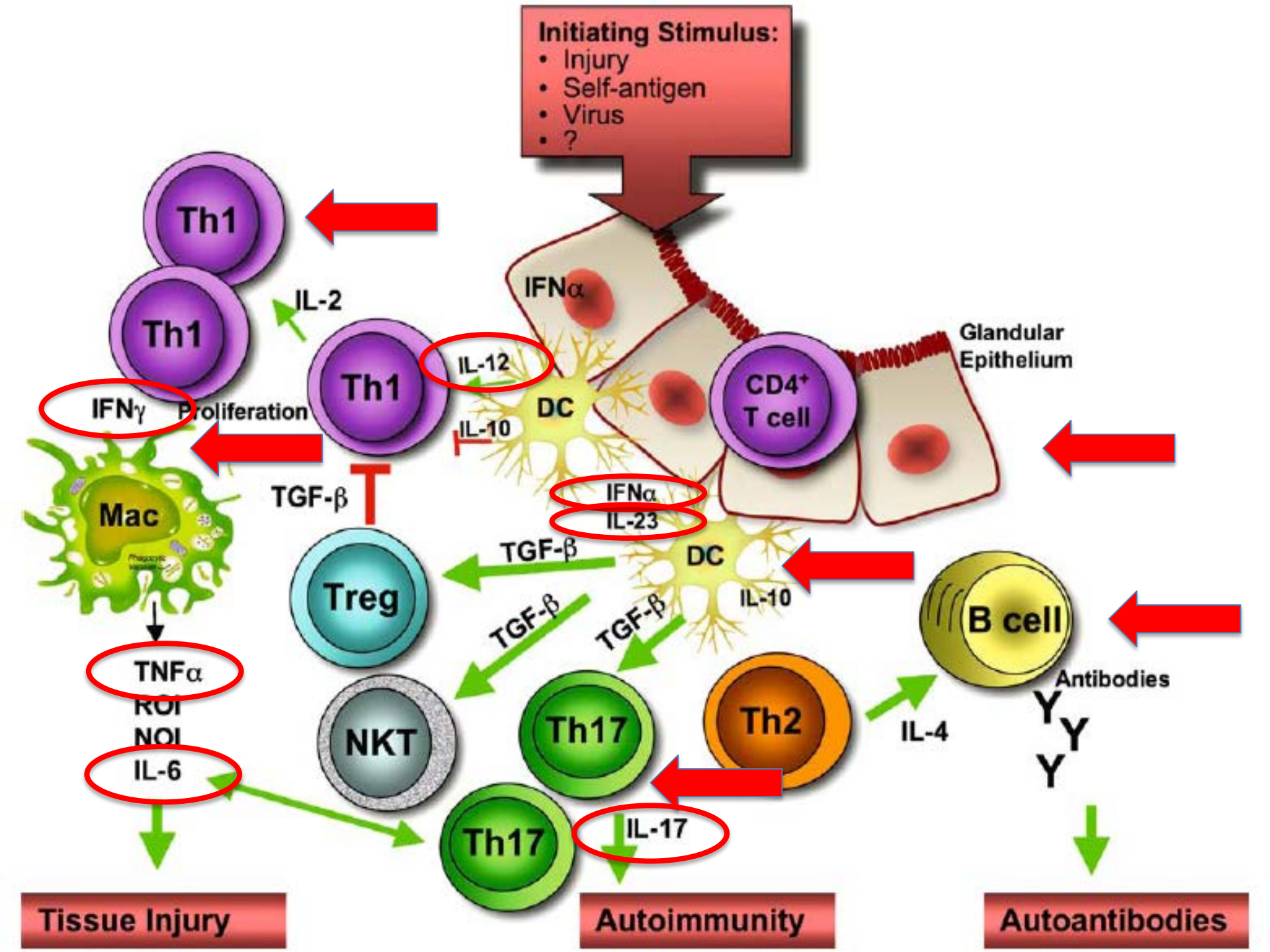


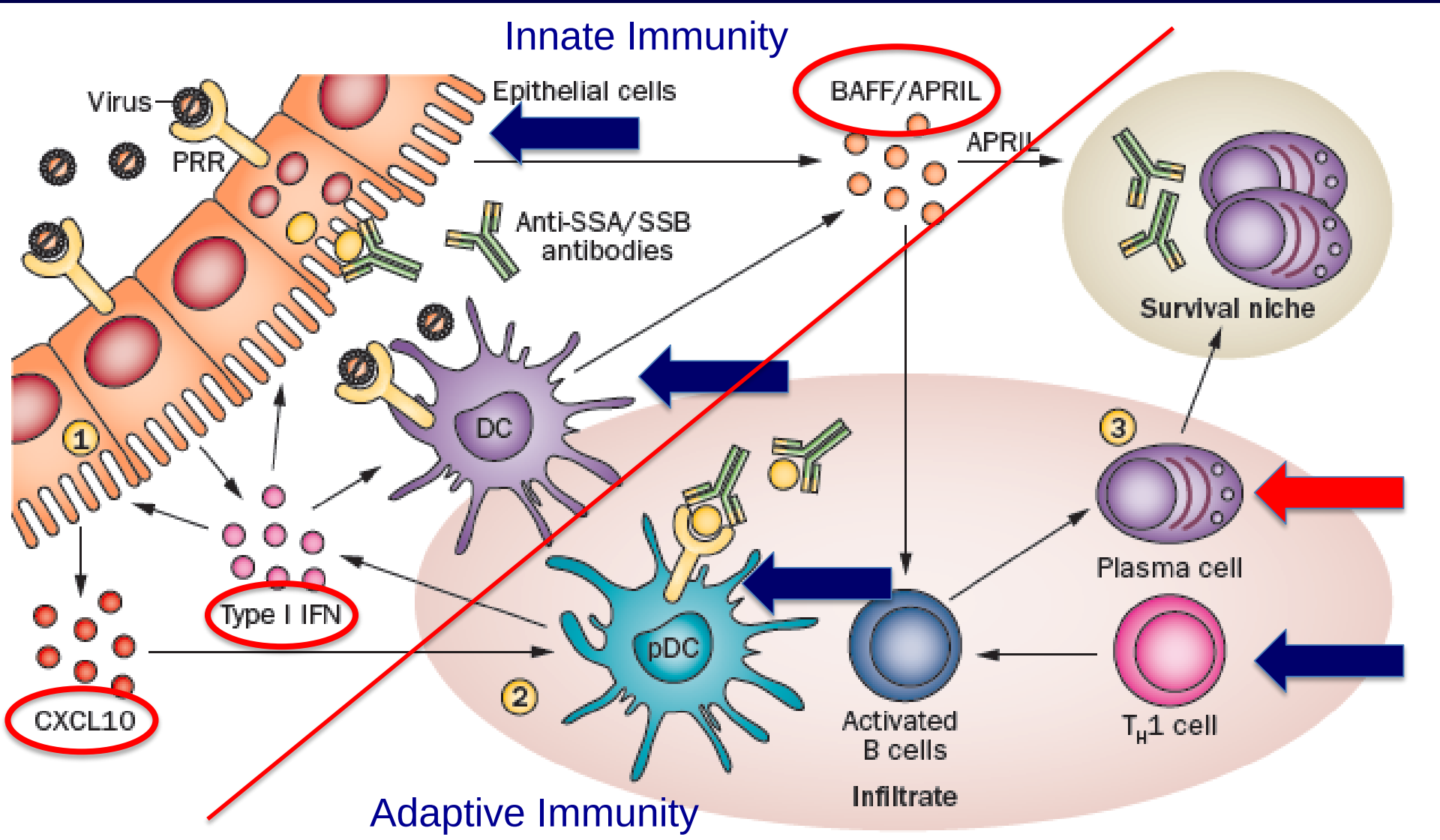
Proposed therapeutic algorithm for treatment of the main extraglandular manifestations of SS. Available data for treatment of extraglandular SS symptoms come from nonanalytical studies, such as retrospective series or case reports (evidence level 3, on a scale of 1–4) representing the lowest strength of recommendation (grade D, rated from A–D) according to the grading recommendations of Harbour and Miller.[123] The sole exception is a RCT using rituximab, which showed a reduction of the number of reported extraglandular manifestations compared with placebo

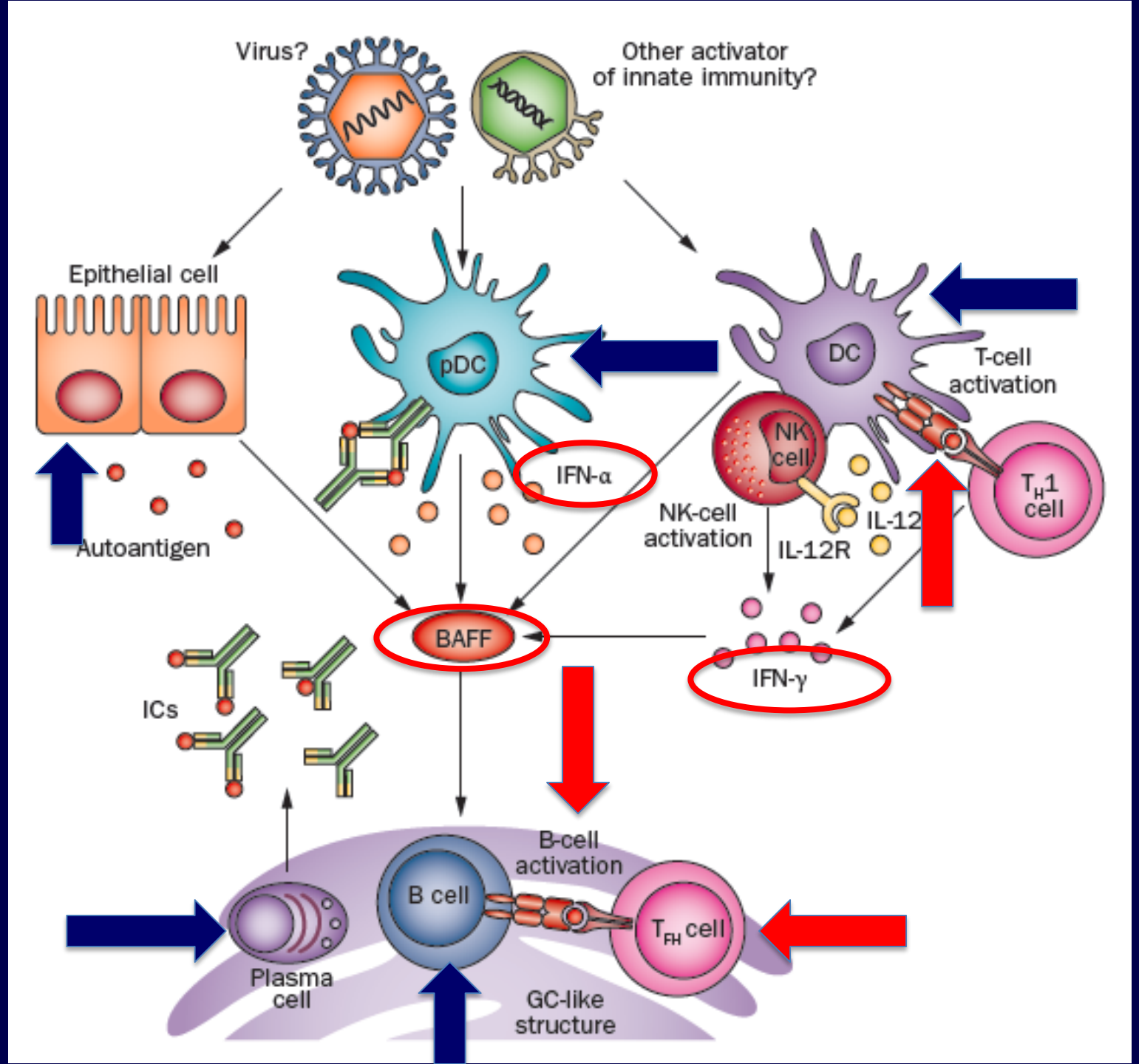
Target therapies in Sjögren's syndrome, as in all the CTDs, are a direct consequence of a better knowledge of the pathogenetic mechanisms of the disease.

Autoimmune Epithelitis



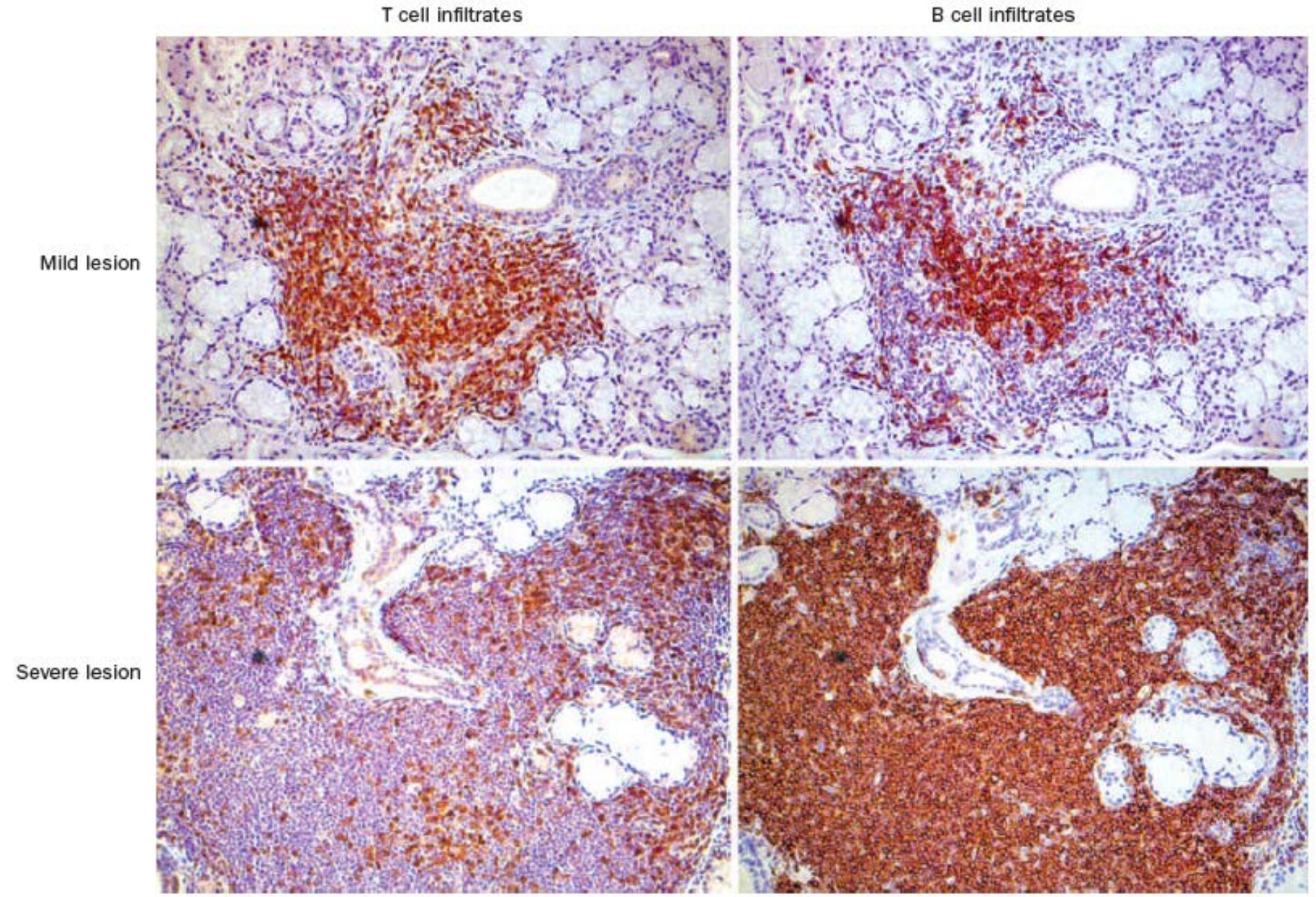

Initiating Stimulus:
• Injury
• Self-antigen
• Virus
• ?
Th1
Th1
Th1
IL-2
IFNα
IL-12
IL-10
DC
CD4+ T cell
Glandular Epithelium
IFNγ
Proliferation
Mac
TGF-β
IFNα
IL-23
DC
IL-10
TGF-β
Treg
TGF-β
TGF-β
B cell
Antibodies
TNFα
ROI
NOI
IL-6
NKT
Th17
Th2
IL-4
Th17
IL-17
Tissue Injury
Autoimmunity
Autoantibodies


Innate Immunity
Virus
PRR
Epithelial cells
BAFF/APRIL
APRIL
Anti-SSA/SSB antibodies
Survival niche
DC
1
3
Plasma cell
Type I IFN
pDC
2
CXCL10
Activated B cells
T_H1 cell
Infiltrate
Adaptive Immunity

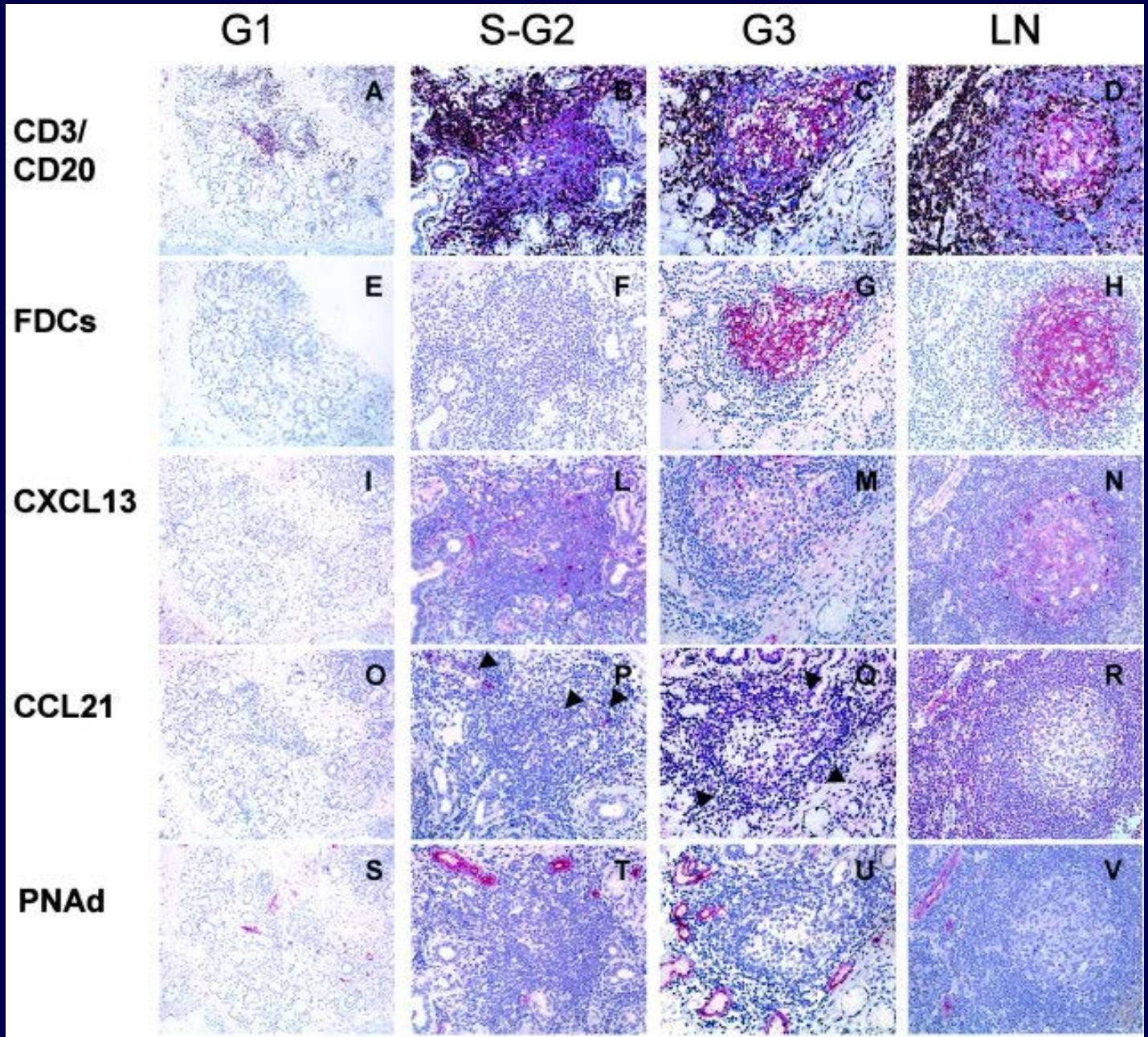

Virus?
Other activator of innate immunity?
Epithelial cell
pDC
DC
T-cell activation
NK cell
T_H1 cell
IFN-α
NK-cell activation
IL-12R
IL-12
Autoantigen
BAFF
IFN-γ
ICs
B-cell activation
B cell
T_{FH} cell
Plasma cell
GC-like structure

Are T- and B-lymphocytes possible target of therapy ?

From Mild to Severe Lymphocytic Infiltration

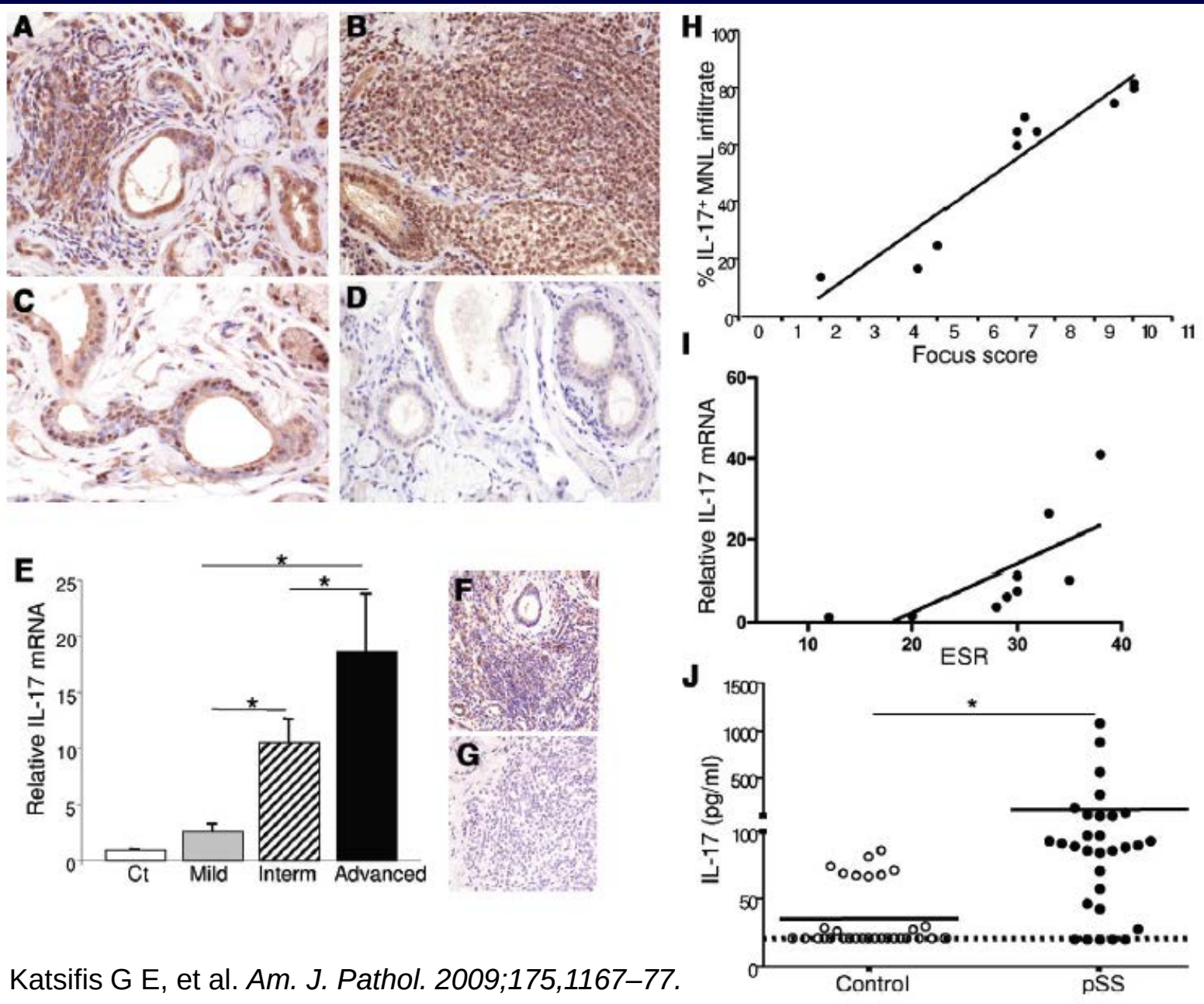


Germinal centre-like structure organization



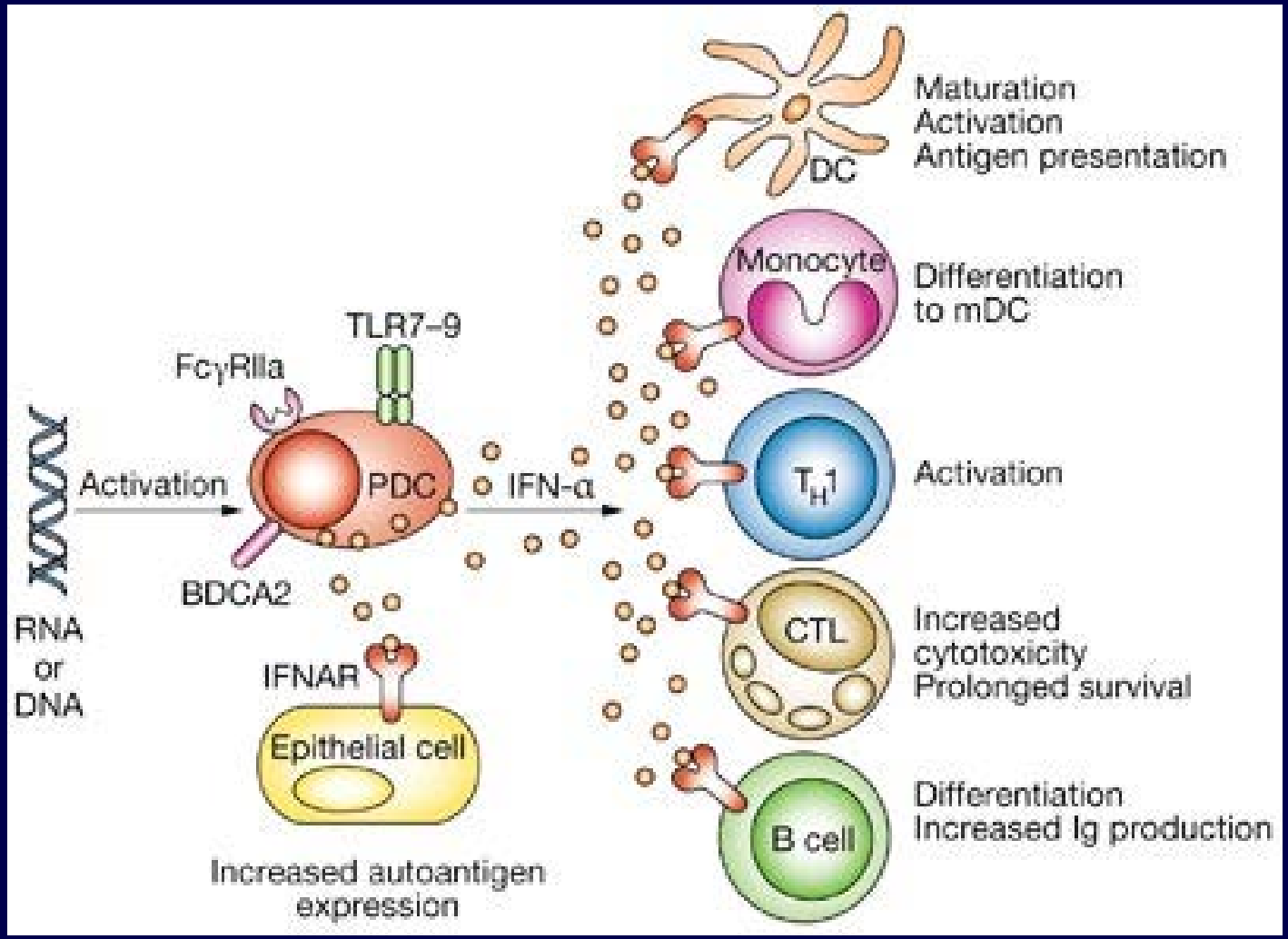
Are cytokynes possible target of therapy ?

Systemic and Local IL-17 Expression in pSS.

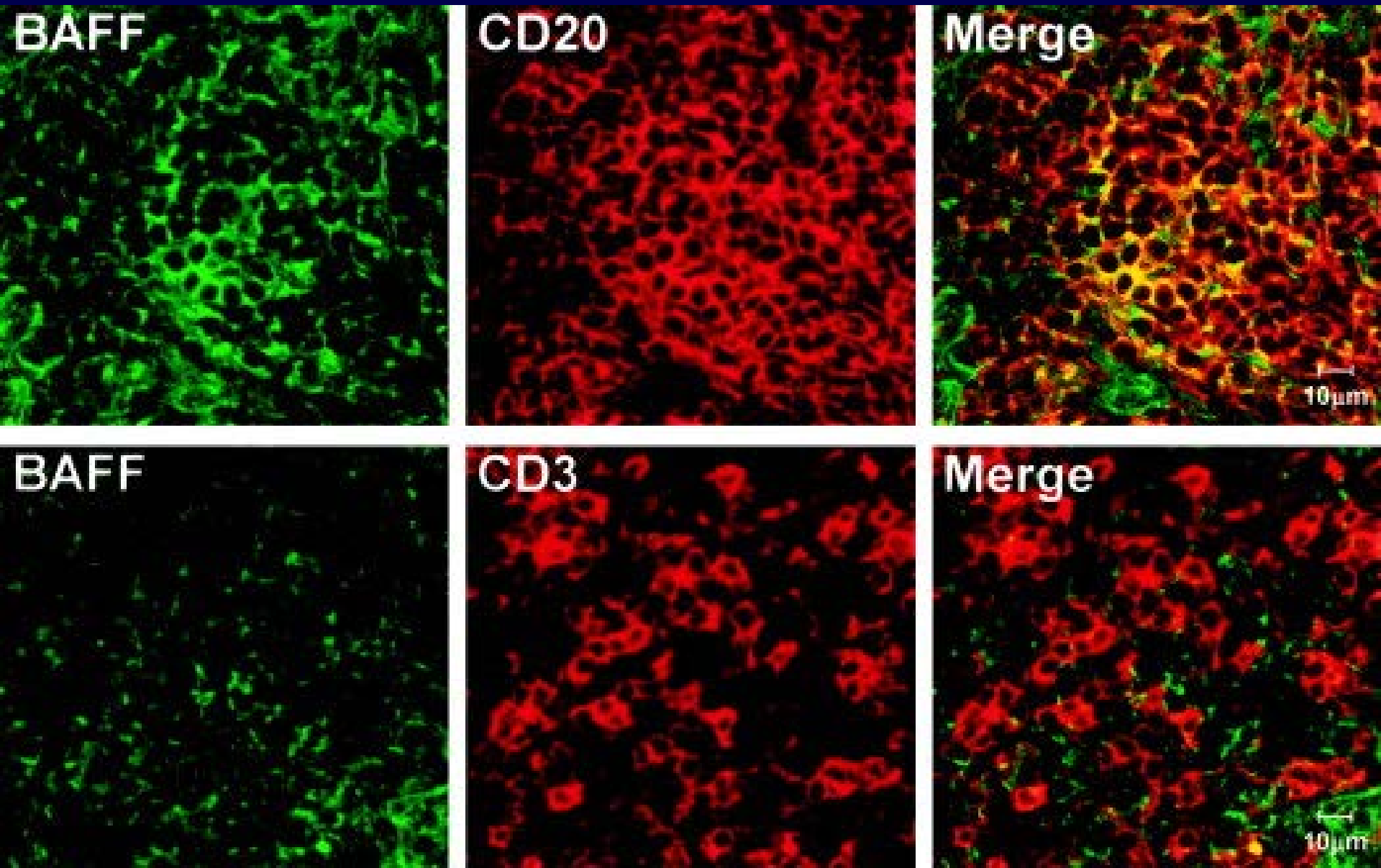


Katsifis G E, et al. *Am. J. Pathol. 2009;175,1167–77.*

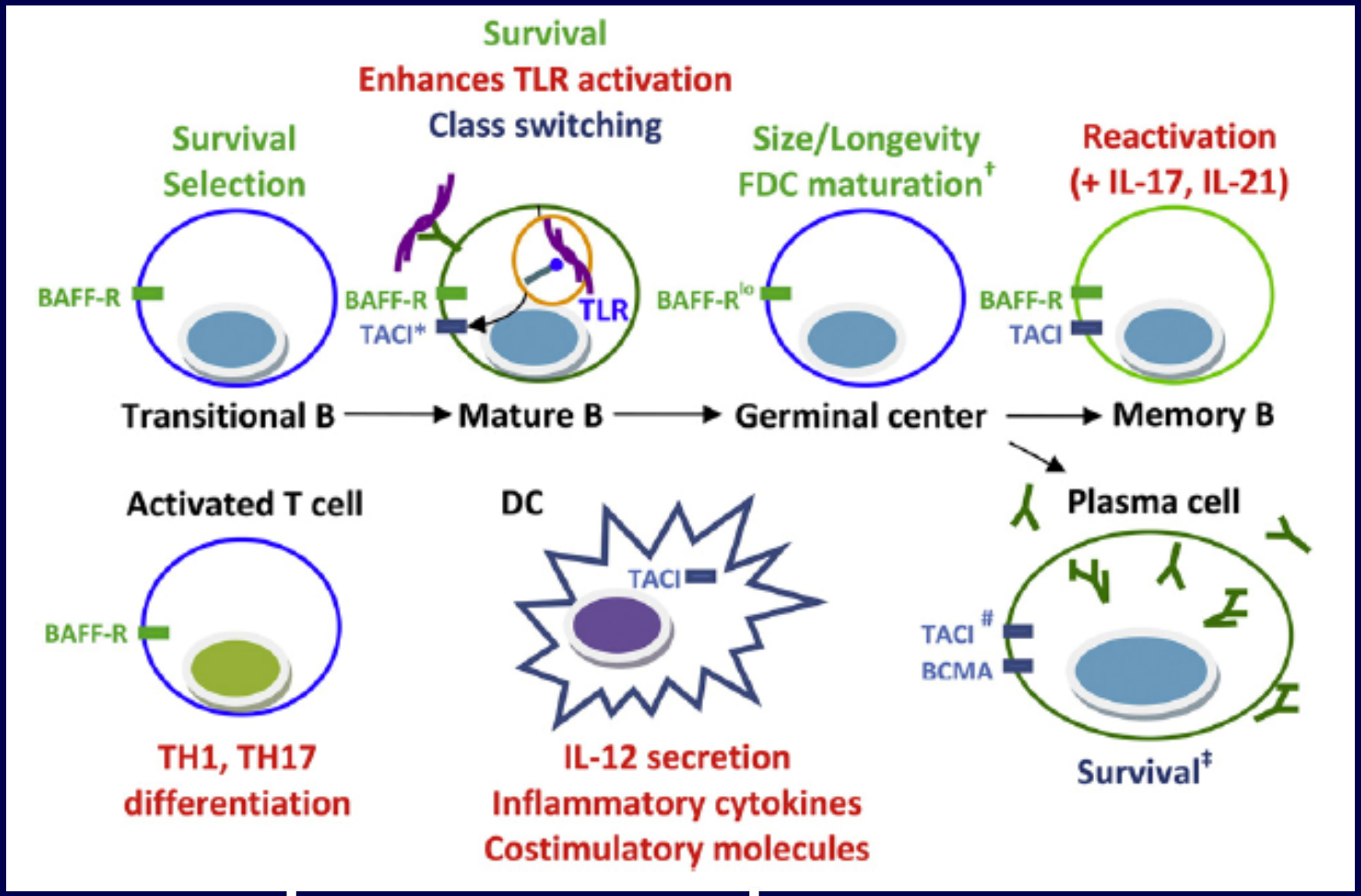
Different Actions of IFN-α in SjS



Overexpression and localizzation of BAFF in SG tissue of patients with SjS

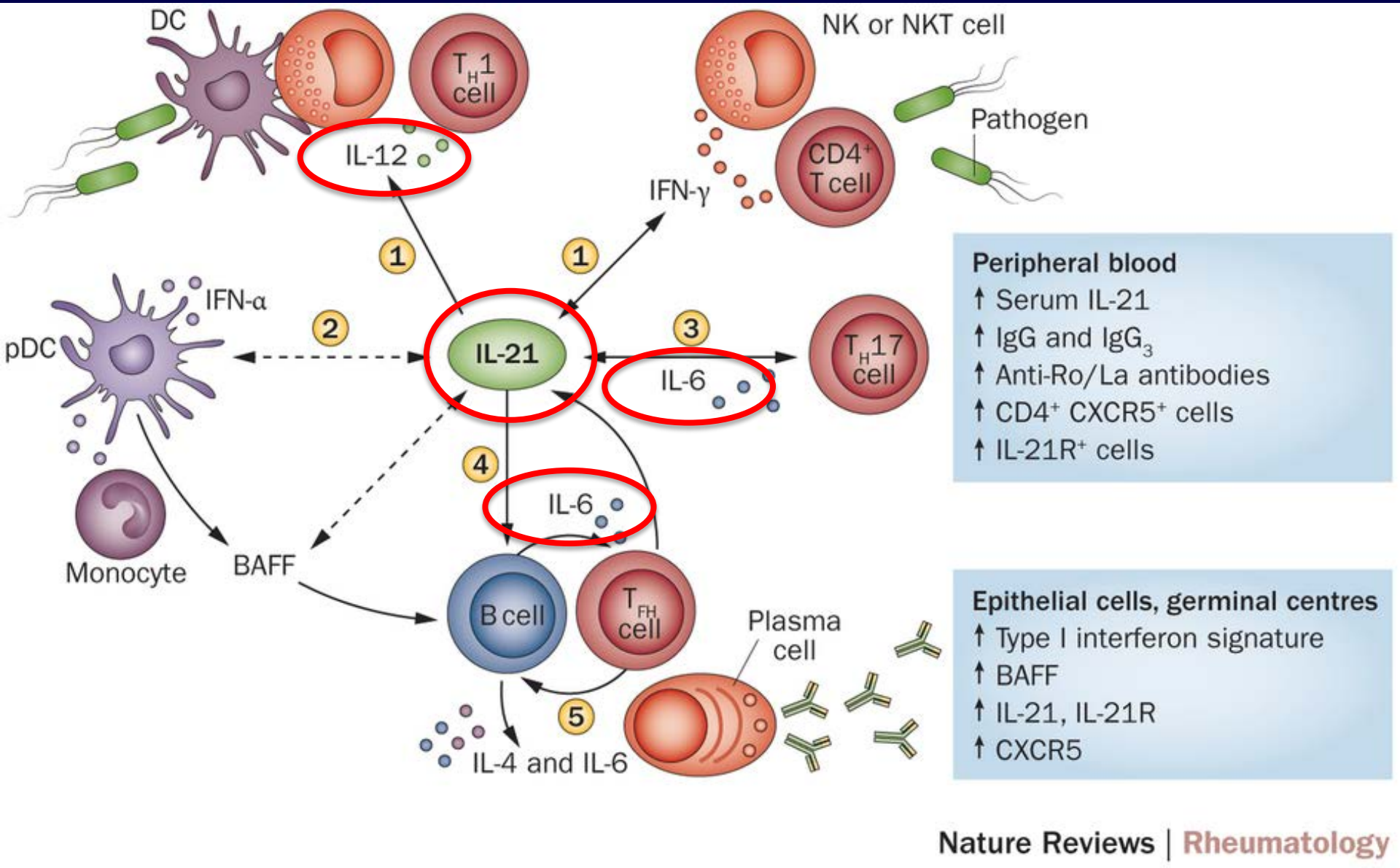


Function of BAFF and APRIL and their Receptors in Physiology and Pathology

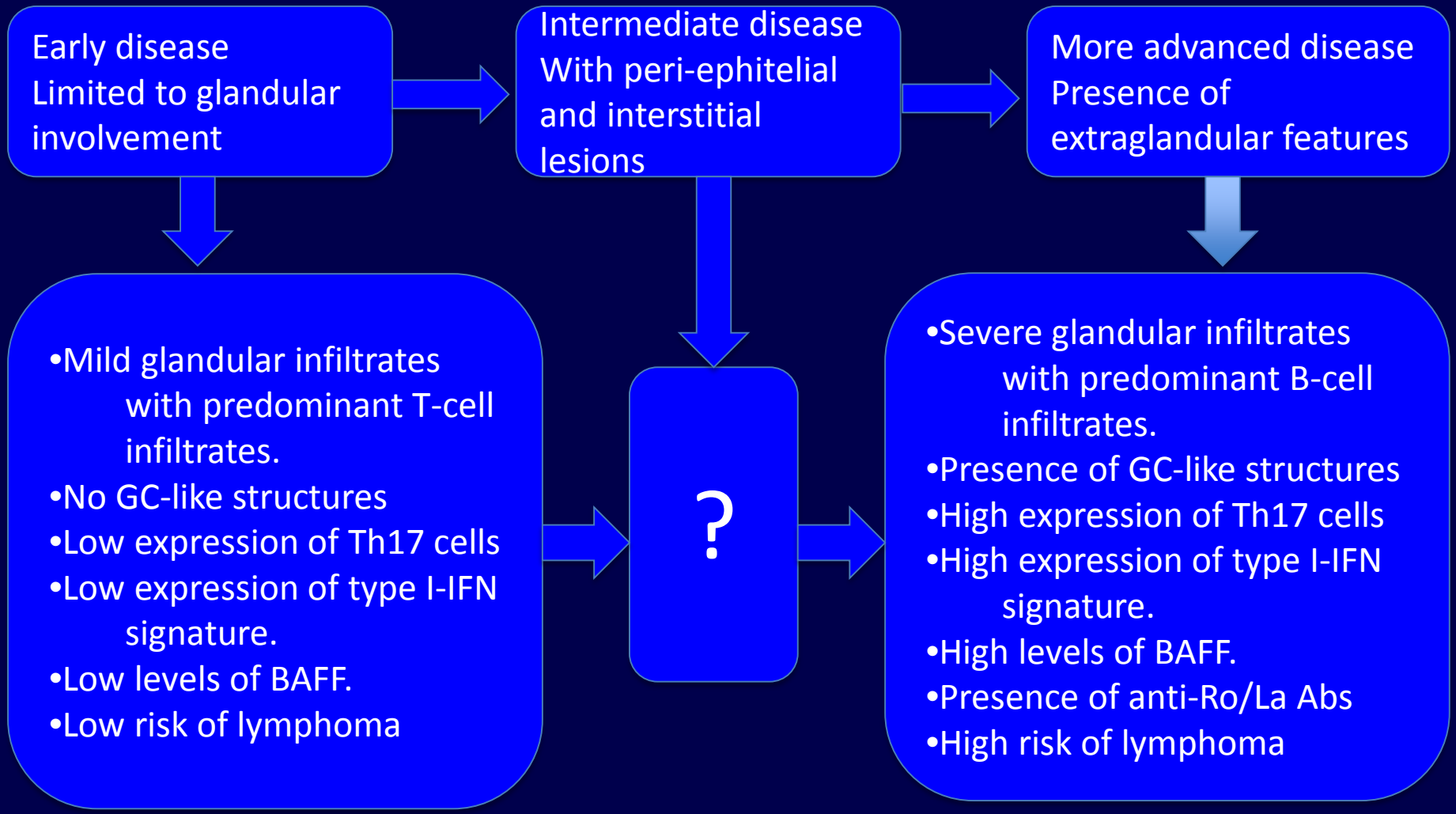


Function of BAFF | Function of BAFF/APRIL | Function of BAFF/APRIL in inflammation

IL21 e IL6


DC
T_H1 cell
IL-12
NK or NKT cell
CD4+ T cell
IFN-γ
Pathogen
1
1
IFN-α
pDC
2
IL-21
3
IL-6
T_H17 cell
4
IL-6
Monocyte
BAFF
B cell
T_{FH} cell
Plasma cell
5
IL-4 and IL-6
Peripheral blood
↑ Serum IL-21
↑ IgG and IgG_3
↑ Anti-Ro/La antibodies
↑ CD4+ CXCR5+ cells
↑ IL-21R+ cells
Epithelial cells, germinal centres
↑ Type I interferon signature
↑ BAFF
↑ IL-21, IL-21R
↑ CXCR5
Nature Reviews | Rheumatology

Sjögren's Syndrome Disease Subsetting



What about new target therapies in SjS?

Drug	Authors	Type of study	No. of patients	Treatment dose	Follow-up period	Outcome measures
Rituximab	Dass *et al.* [28]	RCT	18	1 g i.v. days 1 and 15	24 weeks	The VAS fatigue score improved significantly in the RTX group ($P < 0.001$) but not in the placebo group ($P = 0.147$). The VAS general health score also improved significantly in the RTX group ($P = 0.021$) but not in the placebo group ($P = 0.96$). Significant between-group differences were found after 6 months in the SF-36 social functioning score ($P = 0.01$).
	Meijer *et al.* [29]	RCT	30	One course (1 g i.v. days 1 and 15)	48 weeks	Improvement of the stimulated whole saliva flow rate in the RTX group *vs* placebo ($P = 0.038$).
	Devauchelle-Pensec *et al.* [30]	RCT	120	One course (1 g i.v. twice, days 1 and 15)	24 weeks	No significant difference between groups in the primary endpoint (improvement of at least 30 mm in two of the four VAS scores by week 24) was found. The proportion of patients with at least 30 mm decreases in at least two of the four VAS scores was higher in the RTX group at week 6 (22.4% *vs* 9.1%, $P = 0.036$).
	Bowman *et al.*, TRACTISS [31]	RCT	110	Two courses (1 g i.v. twice) weeks 1-3 and 24-26	48 weeks	No results currently available. ?
	Carrubi *et al.* [32]	Prospective study	41	Two courses (1 g i.v. twice) weeks 1-3 and repeated every 24 weeks *vs* standard treatment with DMARDs	120 weeks	Primary endpoint of the study: significant ESSDAI improvement in the RTX group *vs* placebo was achieved ($P < 0.05$). Superiority of RTX was generally observed after two courses of therapy and continued throughout the study period.
	William *et al.* [33]	Open label	12	One course (1 g i.v. twice) pretreated with 50 mg of oral diphenhydramine, 650 mg of oral acetaminophen and 100 mg of i.v. methylprednisolone	52 weeks	Effective depletion of blood B cells. RTX therapy was not associated with striking clinical benefits but only modest levels of improvement between week 0 and 26 in both the physician's (median decrease = 26 mm, $P = 0.012$) and patient's (median decrease = 8.5 mm, $P = 0.009$) global rating of disease activity.
	Meiners *et al.* [34]	Open label	28	One course (1 g i.v. twice)	60 weeks	ESSPRI and ESSDAI scores improved significantly ($P < 0.01$). Standardised response mean and effect sizes values for ESSPRI and ESSDAI were $\geqslant 0.8$ at week 16 and decreased afterwards, and were larger for the ESSDAI than for the ESSPRI.

Table 3. Controlled therapeutic trials of biologics in primary Sjögren's syndrome

Author	Inclusion criteria	Treatment	N	Primary endpoint	Significance
[49]	AECG, dryness and active pSS (ESR or IgG levels)	Etanercept	14	2 of 3 domains among dry mouth, dry eyes, and IgG level or ESR	No
TRIPPS[48]	AECG and VAS (pain, fatigue, and the most disturbing dryness)	Infliximab	103	2 of 3 VASs for joint pain, fatigue, and the most disturbing dryness	No
[42]	AECG and VAS fatigue	Rituximab	17	VAS fatigue	No on primary objective but improvement
[40]	AECG and stimulated whole saliva and autoantibodies and SGB grade III or IV	Rituximab	30	Stimulated whole saliva flow rate	Yes
TEARS [50]	AECG and recent disease with biological activity or systemic manifestations and VAS (global disease, pain, fatigue, and dryness)	Rituximab	122	2 or 4 VASs	No, but slight efficacy on fatigue and sicca
[135]	AECG and fatigue	Anakinra	26	VAS fatigue	No
TRACTISS [52, 136]	AECG, fatigue, oral dryness, anti-Ro antibodies, and unstimulated salivary flow rate >0 mL/min with systemic involvement if disease duration >10 years	Rituximab	110	VAS fatigue or oral dryness score	No, but slight efficacy on sicca

TRIPPS, Trial of Remicade In Primary Sjögren's Syndrome; TEARS, Tolerance and EfficAcy of Rituximab in primary Sjögren syndrome; TRACTISS, Trial of Anti-B-Cell Therapy In primary Sjögren's Syndrome; ESR, erythrocyte sedimentation rate; Ig, immunoglobulin; pSS, primary Sjögren's syndrome; VAS, visual analogue scale (0–100 mm); RF, rheumatoid factor; SGB, salivary gland biopsy; ESSDAI, European League Against Rheumatism (EULAR) Sjögren's Syndrome Disease Activity Index; N, number of patients

EULAR collaboration

Symptomatic features	Systemic features
Dryness / Fatigue / Pain	Synovitis, vasculitis, pulmonary, PNS, CNS, renal, hematological
Disabling but benign	Severe
All	About 1/3

Evaluated by patient
ESSPRI

Evaluated by physician
ESSDAI

EULAR SS Patient Reported Index

- A specific questionnaire
- For all patients

EULAR SS Disease Activity Index

- Based on clinical, biological, radiological & histological features
- For patients with severe complications

J Autoimmun. 2012 Aug;39(1-2):97-102.

Outcome measures for primary Sjögren's syndrome.

Seror R, Bootsma H, Bowman SJ, Dorner T, Gottenberg JE, Mariette X, Ramos-Casals M, Ravaud P, Theander E, Tzioufas A, Vitali C.

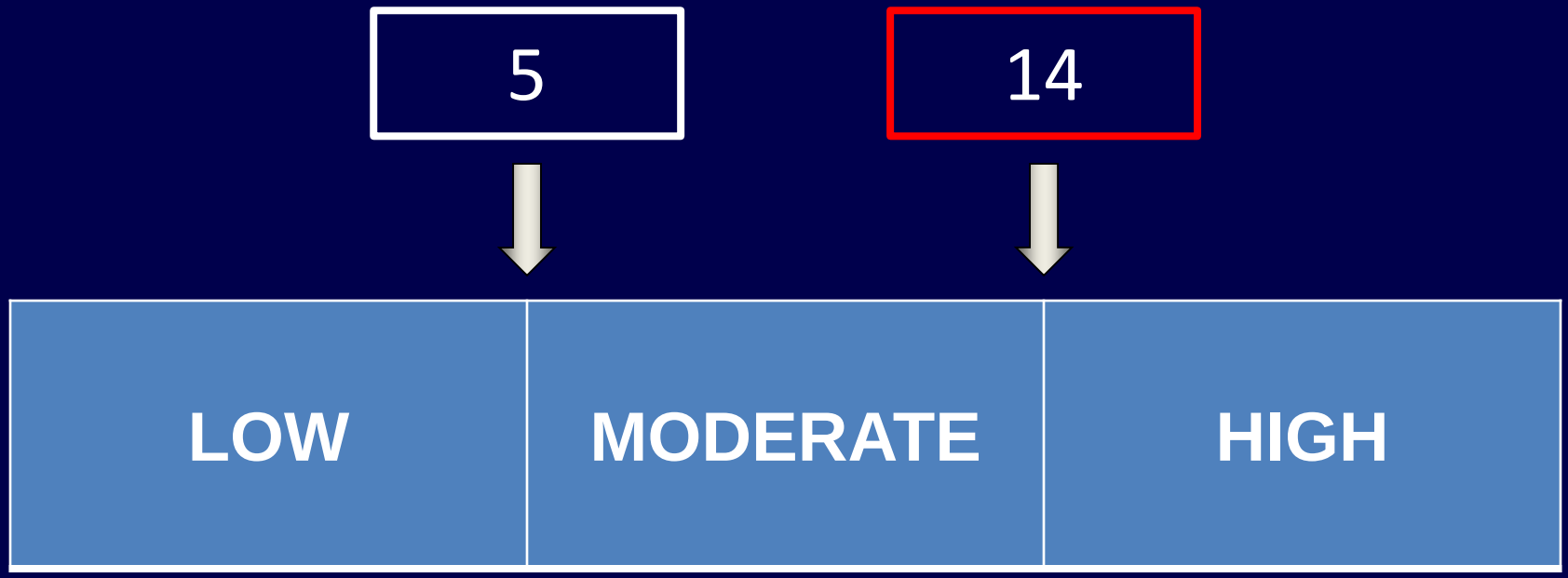
An international project was supported by EULAR, aimed at developing two consensus disease activity indexes:

The EULAR SS Patients Reported Index (ESSPRI), assessing the subjective complaints of patients;

The EULAR SS Disease Activity Index (ESSDAI), a systemic activity index assessing systemic manifestations of the disease.

Disease activity levels with ESSDAI

- Definition of reliable levels of activity



ESSDAI

- For including patient in RCT
  - To assess effect of biologic/immunosuppressant
  - Baseline ESSDAI ≥ 5
- For defining improvement
  - Minimal Clinically Important Improvement (MCII) is defined as a reduction of ESSDAI ≥ 3

ESSPRI

- The Patients Acceptable Symptom State (PASS) estimate was defined as an ESSPRI<5 points

- The Minimal Clinically Important Improvement (MCII) is defined as a decrease of at least 1 point or of 15% of baseline value.

*Ann Rheum Dis 2013;**72:1026-31***

Efficacy of rituximab in systemic manifestations of primary Sjögren's syndrome: results in 78 patients of the AutoImmune and Rituximab Registry

Gottenberg JE, et al.

Objectives.

To evaluate the efficacy and safety of rituximab in patients with primary Sjögren's syndrome (pSS).

Methods

Patients with pSS treated with rituximab followed up every 6 months for 5 years included in the Rituximab registry

Results

76 patients with pSS (11 men, 67 women), were analysed. Median age was 59.8 years (29–83), median duration of disease was 11.9 years (3–32).

Indications for treatment were systemic involvement for 74 patients and only severe glandular involvement in 4 patients.

Overall efficacy according to the treating physician was observed in 47 patients (60%) after the first cycle of rituximab.

Median ESSDAI decreased from 11 (2–31) to 7.5 (0–26) ($p<0.0001$).

Median dosage of corticosteroid decreased from 17.6 mg/day (3–60) to 10.8 mg/day ($p=0.1$).

41 patients were retreated with rituximab.

Four infusion reactions and one delayed serum sickness-like disease resulted in rituximab discontinuation.

Three serious infections (1.3/100 patient-years) and two cancer-related deaths occurred.

Conclusions

In common practice, the use of rituximab in pSS is mostly restricted to patients with systemic involvement.

This prospective study shows good efficacy and tolerance of rituximab in patients with pSS and systemic involvement.

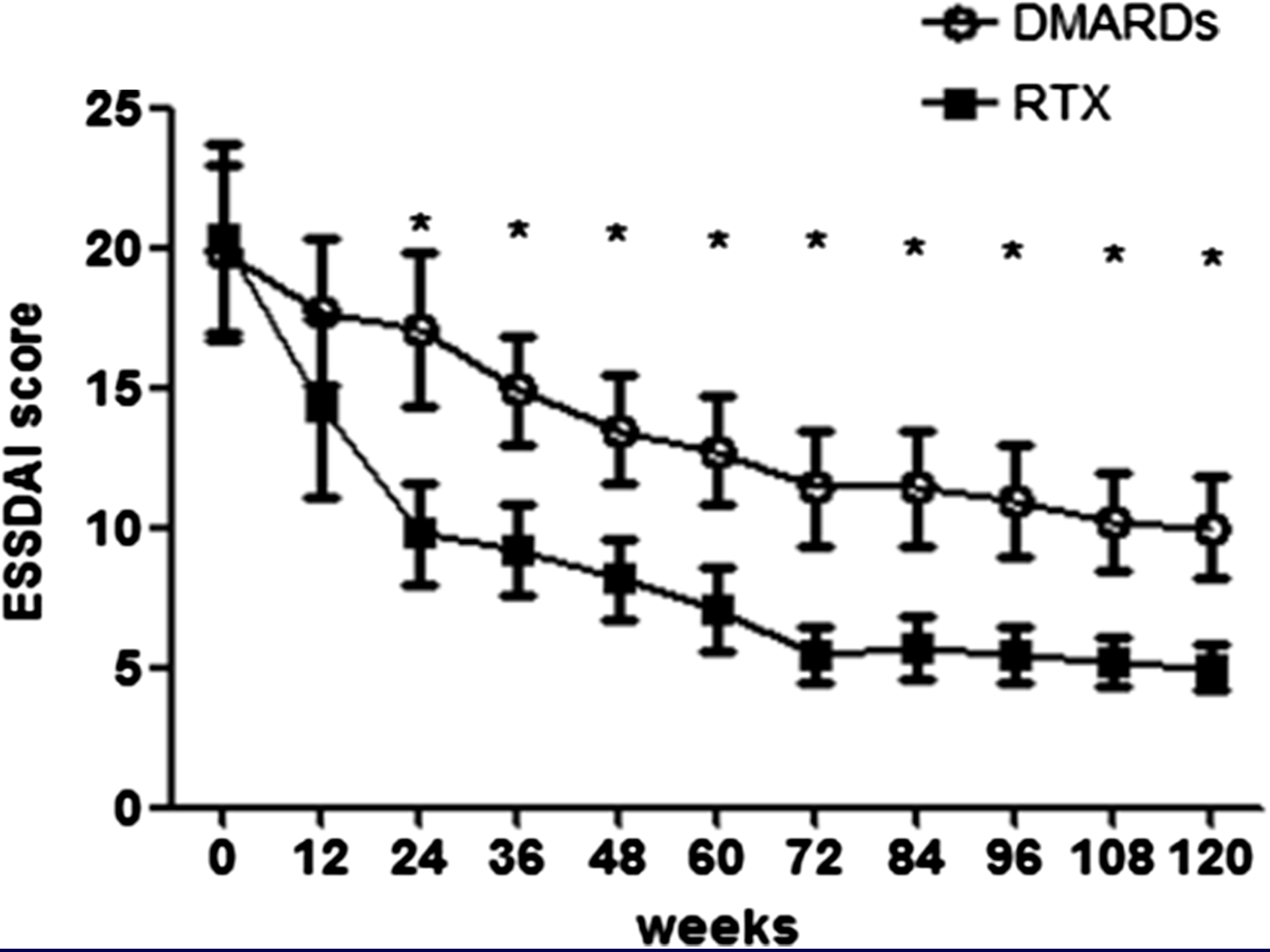
Carubbi *et al. Arthritis Research & Therapy* 2013, **15**:R172
http://arthritis-research.com/content/15/5/R172

arthritis research&therapy

RESEARCH ARTICLE Open Access

Efficacy and safety of rituximab treatment in early primary Sjögren's syndrome: a prospective, multi-center, follow-up study

Francesco Carubbi[1*], Paola Cipriani[1], Alessandra Marrelli[1], Paola Di Benedetto[1], Piero Ruscitti[1], Onorina Berardicurti[1], Ilenia Pantano[1], Vasiliki Liakouli[1], Saverio Alvaro[1], Alessia Alunno[2], Antonio Manzo[3], Francesco Ciccia[4], Roberto Gerli[2], Giovanni Triolo[4] and Roberto Giacomelli[1]


DMARDs
RTX
ESSDAI score
25
20
15
10
5
0
0
12
24
36
48
60
72
84
96
108
120
weeks
*
*
*
*
*
*
*
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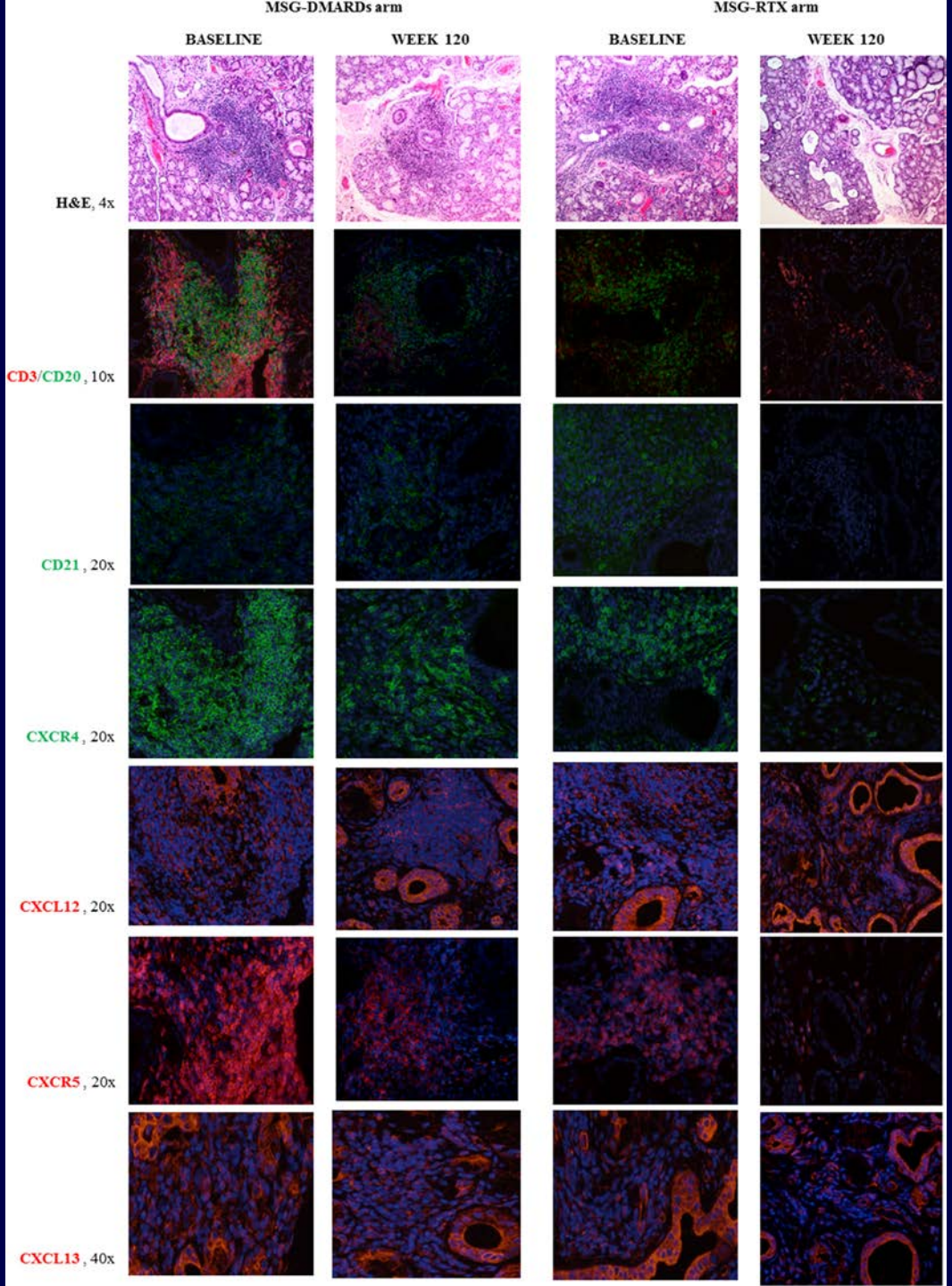
*


MSG-DMARDs arm
MSG-RTX arm
BASELINE
WEEK 120
BASELINE
WEEK 120
H&E, 4x
CD3/CD20, 10x
CD21, 20x
CXCR4, 20x
CXCL12, 20x
CXCR5, 20x
CXCL13, 40x

Drug	Authors	Type of study	No. of patients	Treatment dose	Follow-up period	Outcome measures
Belimumab	Mariette *et al.*, NCT01008982 [48]	Phase II open label	30	10 mg/kg belimumab, in solution for infusion, monthly	52 weeks	Primary endpoint achieved at week 28 in 63% of patients (reduction in two of five of the following: >33% improvement in dryness, fatigue, patient musculoskeletal pain, physician's global activity as assessed by VAS and >25% reduction of B cell activation biomarkers). Decreased ESSDAI from 8.8 (S.D. 7.39) to 5.59 (S.D. 5.49), $P < 0.0001$. Decreased ESPRI from 6.44 (S.D. 1.11) to 5.56, $P = 0.01$. Improvement in saliva production at the end of the trial ($P = 0.029$).
	De Vita *et al.*, NCT01160666 [49]	Phase II open label study	15	10 mg/kg on days 0, 14 and 28 and every 28 days for 24 weeks. There was a 24 week extension study for responders	52 weeks	No results available.

CONCLUSION: Long-term treatment with belimumab may be beneficial in SS. Randomized, double-blind, controlled studies in larger populations are encouraged.

Potential future therapies	
Being studied in SS	**Not being studied in SS**
Belimumab (mAb targeting BAFF)	Atacicept (fully human, recombinant fusion protein that inhibits B cell–stimulating factors a proliferation-inducing ligand and B lymphocyte stimulator
Abatacept (a soluble fusion protein combining the extracellular domain of human cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) linked to the modified Fc portion of human IgG1	Otelixizumab (anti-CD3 mAb)
Alefacept (fusion protein that blocks the co-stimulatory molecule leucocyte function-associated antigen-13/CD2)	Rontalizumab and sifalimumab (mAb directed against IFN-α), frontalizumab (IFN-γ blocker)
Tocilizumab (humanized mAb against the IL-6 receptor)	Briakinumab (humanized mAb against p40 subunit that is shared by IL-12 and IL-23)
	Ustekinumab (humanized mAb against p40 subunit that is shared by IL-12 and IL-23)
	Anakinra (IL-1 receptor antagonist)
	IRS-954 (synthetic oligodeoxynucleotides with immunoregulatory sequences that specifically block signalling via Toll-like receptor-7)
	Anti-chemokine (CXCL13, CXL21)

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RHEUMATOLOGY

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Original article

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Eligibility for clinical trials in primary Sjögren's syndrome: lessons from the UK Primary Sjögren's Syndrome Registry

Clare Oni[1], Sheryl Mitchell[2], Katherine James[3], Wan-Fai Ng[2,4], Bridget Griffiths[2], Victoria Hindmarsh[2], Elizabeth Price[5], Colin T. Pease[6,7], Paul Emery[6,7], Peter Lanyon[8], Adrian Jones[8], Michele Bombardieri[9], Nurhan Sutcliffe[9], Costantino Pitzalis[9], John Hunter[10], Monica Gupta[10], John McLaren[11], Annie Cooper[12], Marian Regan[13], Ian Giles[14], David Isenberg[14], Vadivelu Saravanan[15], David Coady[16], Bhaskar Dasgupta[17], Neil McHugh[18], Steven Young-Min[19], Robert Moots[20], Nagui Gendi[21], Mohammed Akil[22], Francesca Barone[23], Ben Fisher[23], Saaeha Rauz[23], Andrea Richards[24], Simon J. Bowman[1] on Behalf of the UK Primary Sjögren's Syndrome Registry*

Selection Criteria of patients with SjS for Therapeutic Trials

TABLE 3 Number of patients from the database eligible for a theoretical study

Stable therapy allowed Ro+, ESSPRI ⩾5, usf>0	Disease Duration, N (%)		
	Any	<10 years	<5 years
ESSDAI ⩾5	99 (14.4)	79 (11.5)	49 (7.1)
ESSDAI ⩾7	66 (9.6)	57 (8.3)	35 (5.1)
ESSDAI ⩾9	39 (5.7)	32 (4.7)	18 (2.6)
ESSDAI ⩾11	26 (3.8)	20 (2.9)	10 (1.5)
ESSDAI ⩾14	12 (1.7)	11 (1.6)	7 (1.0)
Ro+, ESSDAI ⩾5, usf>0 ESSPRI 2/3⩾5[a]	111 (16.1)	85 (12.4)	51 (7.4)
Ro+, ESSDAI ⩾5, usf>0, ESSPRI any	151 (21.9)	125 (18.2)	81 (11.8)
ESSDAI ⩾5, usf>0, ESSPRI ⩾5 with Ro+/-	113 (16.4)	84 (12.2)	54 (7.8)
ESSDAI ⩾5, ESSPRI ⩾5, Ro+/-, usf ⩾0	187 (27.2)	134 (19.5)	85 (12.4)
Ro+, ESSPRI ⩾5, ESSDAI ⩾5, usf > 0, no pilocarpine	90 (13.1)	73 (10.6)	46 (6.7)
Ro+, ESSDAI ⩾5, usf>0, ESSPRI ⩾5, no pilocarpine or DMARD	82 (11.9)	63 (9.2)	33 (4.8)

Data presented here according to ESSPRI >5 ([a]or 2/3 components >5 where indicated), ESSDAI score, disease duration and, where indicated, whether Ro+/-, whether usf >0 or not and/or whether current pilocarpine or DMARD therapy is allowable. DMARDs are AZA, MTX, SZP, LEF, CYA, MMF, TAC. ESSPRI: EULAR Sjögren's Syndrome Patient-Reported Index; ESSDAI: EULAR Sjögren's Syndrome Disease Activity Index; usf: unstimulated salivary flow rate; SZP: Sulfasalazine EN; TAC: Tacrolimus; CYA: Ciclosporin.

New Therapeutic Perspectives in SjS Summary

- ✓ Validated outcome measures have been developed.
- ✓ The pathogenesis of the disease is now better known but the precise sequence of the events in different disease phases and subsets has not been clarified yet.
- ✓ Immune-pathology, and molecular biology have provided new insights on disease biomarkers. Their precise role in different disease stages and patients' sub-groups should be better defined.
- ✓ New target therapies are or will be available. Treatment strategy should be tailored in any patient, according to the presence (or absence) of specific disease markers.