Physiopathologie du syndrome de Sjögren

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Sjögren's syndrome or disease

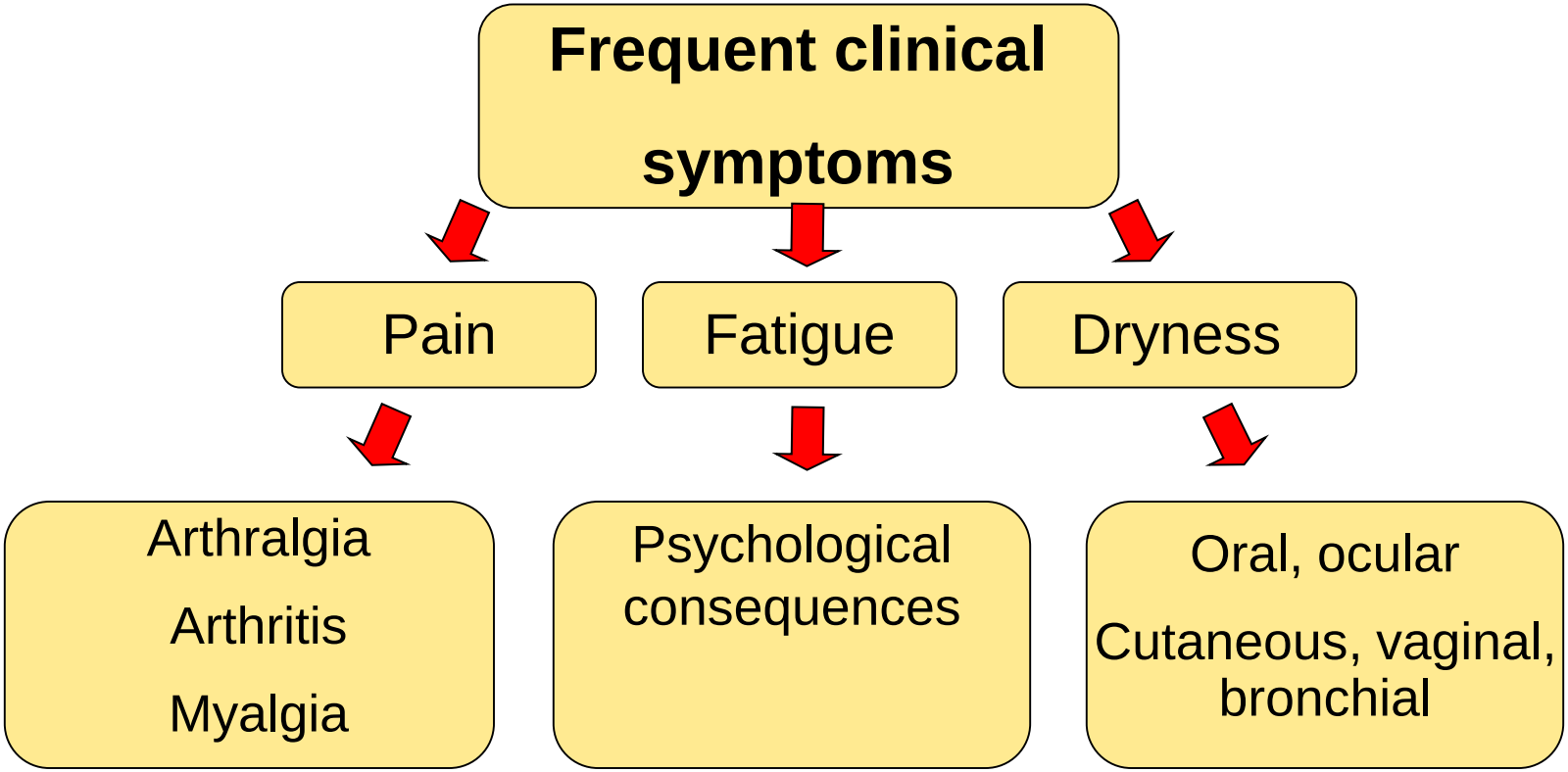
- **A systemic autoimmune disease**
  - **Auto-immune epithelitis**

- **Epidemiology :**
  - **Prevalence : 0.06 to 1/1000**
  - **Sex ratio : 9 women / 1 man**

- **Primary or associated to :**
  - **RA**
  - **Lupus**
  - **Dermatopolymyositis**
  - **scleroderma**

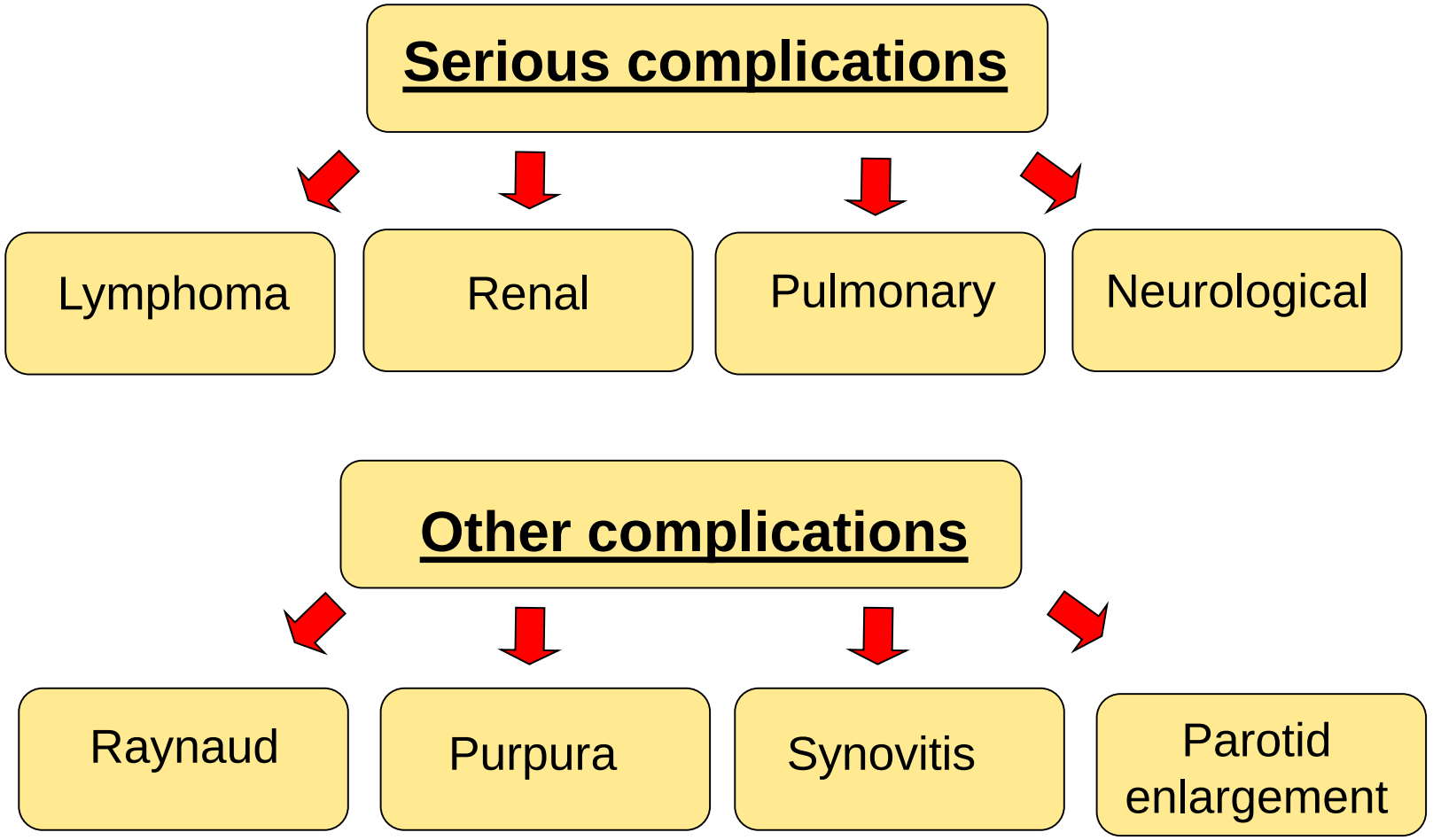
Cornec and Chiche. Ann Rheum Dis 2015.

Clinics of Sjögren's



➲ **Profound drecrease of quality of life**

Complications



The immunological mechanisms of Sjögren's

- The type 1 IFN signature and its origin
- The type 2 IFN signature and its origin
- The B-cell activation and its origin
- The cellular actors
- The mechanisms of lymphomagenesis

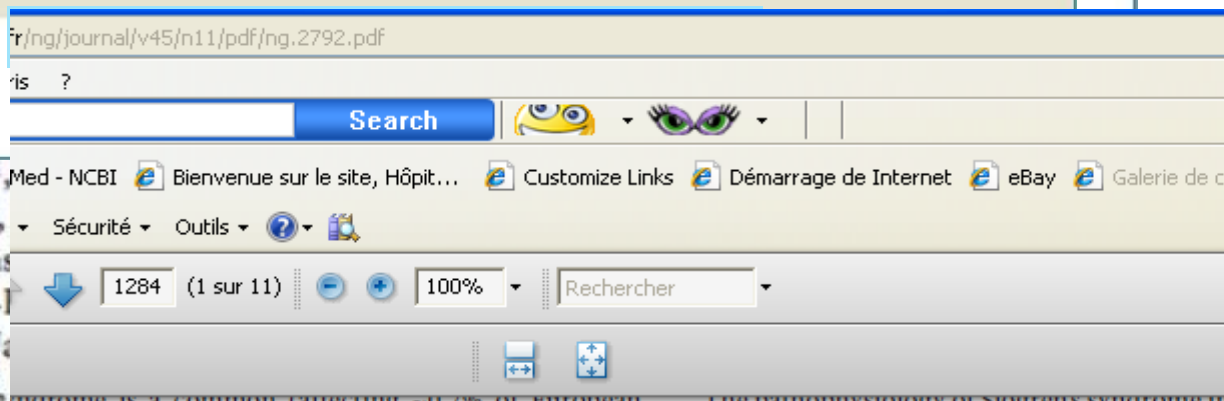
The immunological mechanisms of Sjögren's

- **The type 1 IFN signature and its origin**
- **The type 2 IFN signature and its origin**
- **The B-cell activation and its origin**
- **The cellular actors**
- **The mechanisms of lymphomagenesis**

Variants at multiple loci implicated in both innate and adaptive immune responses are associated with Sjögren's syndrome

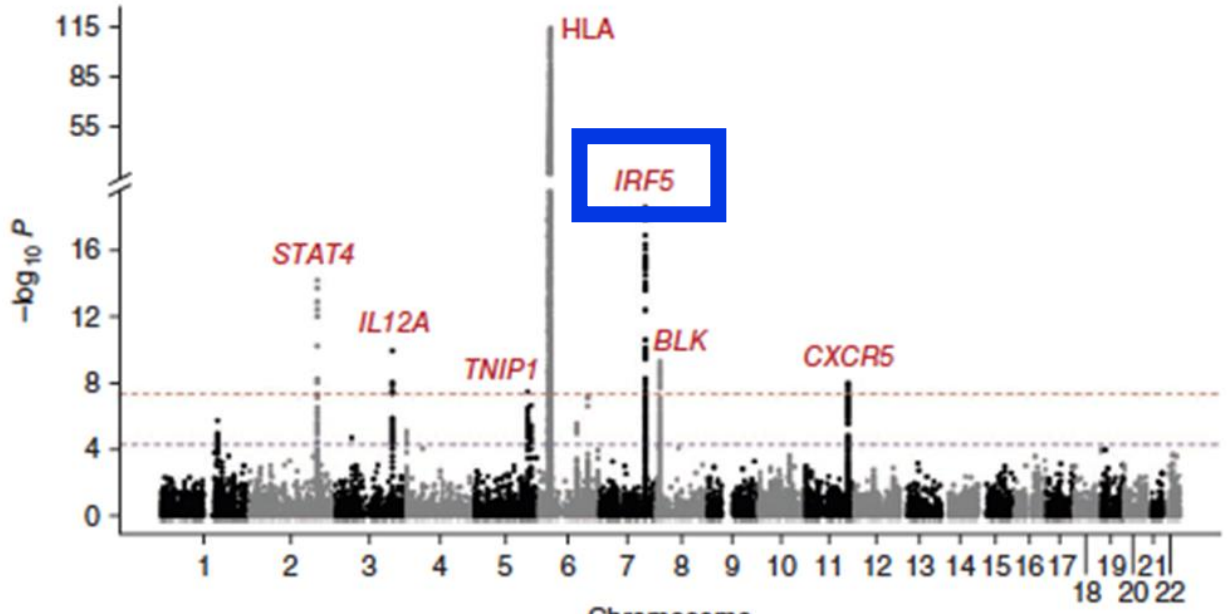
Christopher J Lessar
Jennifer A Kelly[1], Mikhail G Dozmorov[1]
Maija-Leena Eloranta[7], Johan G Brun[8,9],
Kenneth M Kaufman[11,12], Marika Kvarns
Martha E Grandits[16], Abu N M Nazmul-
A Darise Farris[1], Michael T Brennan[20], J
Kimberly S Hefner[24], Glen D Houston[25],
Lida Radfar[27], Michael D Rohrer[28], Dona
Patrick M Gaffney[1], Judith A James[1,2,19],
Torsten Witte[32], Roland Jonsson[9,33], Mau
Wan-Fai Ng[35], for UK Primary Sjögren's
Nelson L Rhodus[38], Barbara M Segal[39], R
Kathy L Sivils[1,2]

Sjögren's syndrome is

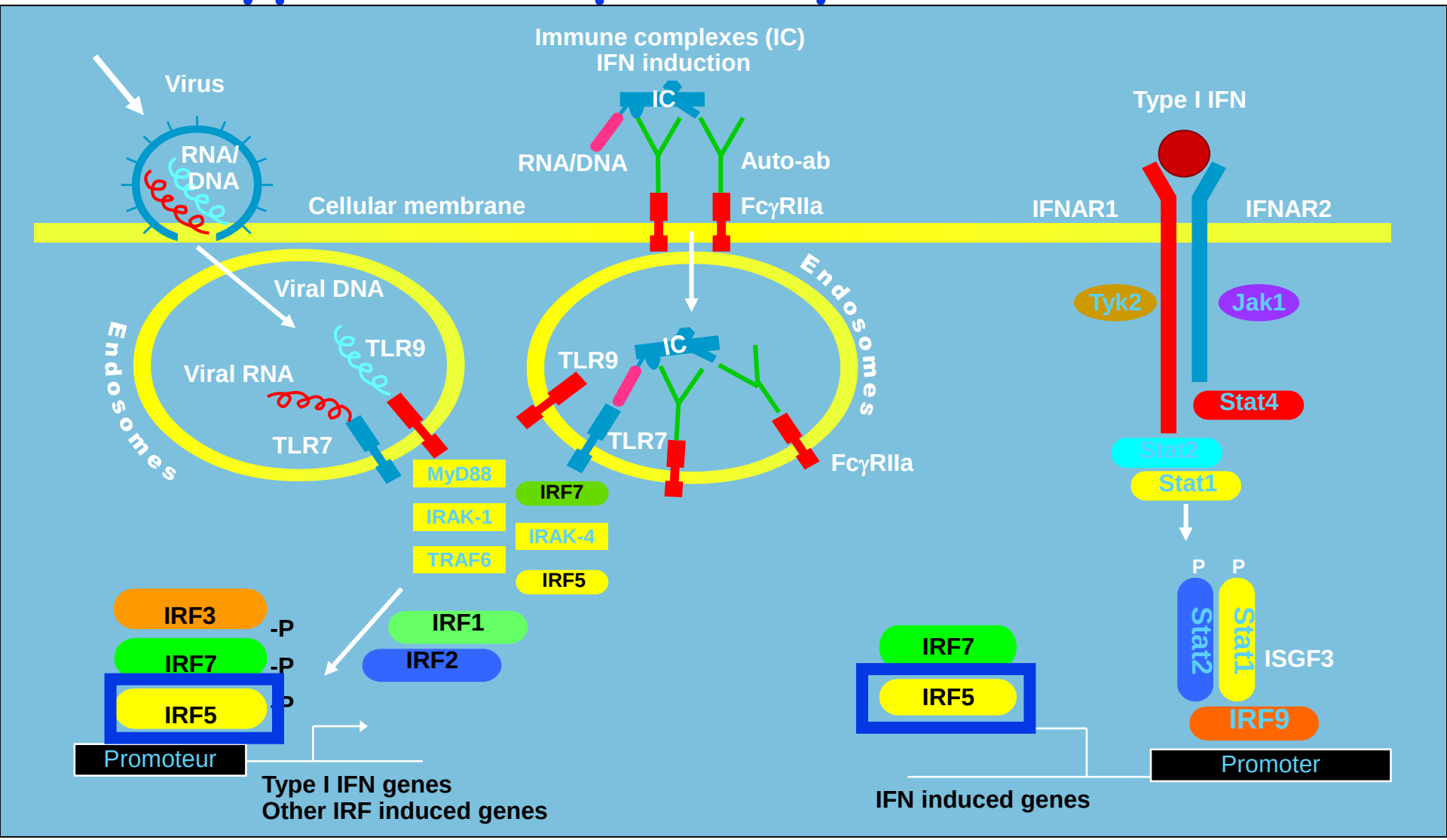


ndrome is a common (affecting ~0.7% of European
) chronic autoimmune condition that is characterized
gland dysfunction and results in substantial morbidity.
affected at a rate of approximately ten times that of
though affected individuals are identified clinically by
lar manifestations, the full disease spectrum may encom-
lex myriad of systemic features, making diagnosis clini-
ging[4]. Current American-European Consensus Group

The pathophysiology of Sjögren's syndrome i
dysregulation of innate and adaptive immune p
both cell-mediated and humoral disease process
pletely understood[7]. Labial salivary gland and
gene-expression microarray studies have demo
lation of type I interferon–inducible genes[8,9].
work in Sjögren's syndrome genetics has been
date gene studies, strong association with gene
cluding *HLA-DR*, *HL*
ed[10,11]. Several non-
isease[12–15], including
ssociations has exce
reshold of $P = 5 \times 10^{-}$
enome-wide associati



Genetic association of genes involved in the type 1 IFN pathway



Nordmark ACR 2008 (712)

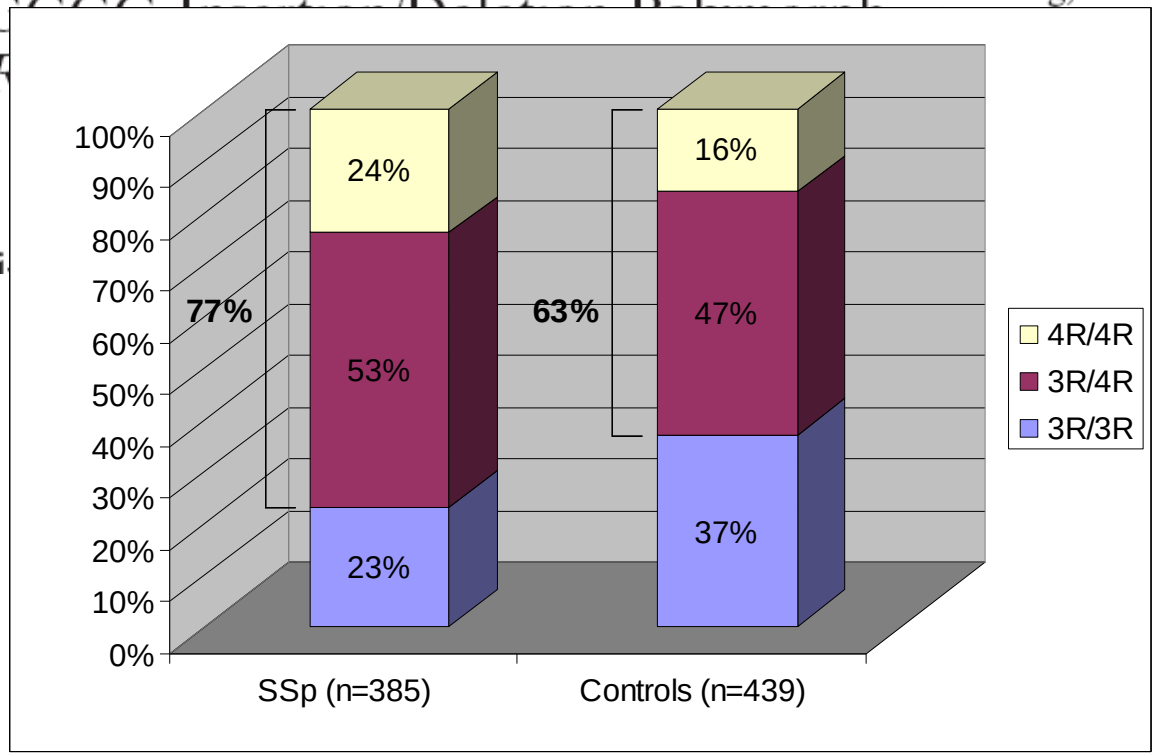
ARTHRITIS & RHEUMATISM
Vol. 60, No. 7, July 2009, pp 1991–1997
DOI 10.1002/art.24662

morphism of
Factor for
ne

Emmanuelle Comets,[2]
Gottenberg,[1] Pierre Lebon,[6]

The CG
the *IF*

Corinne Miceli

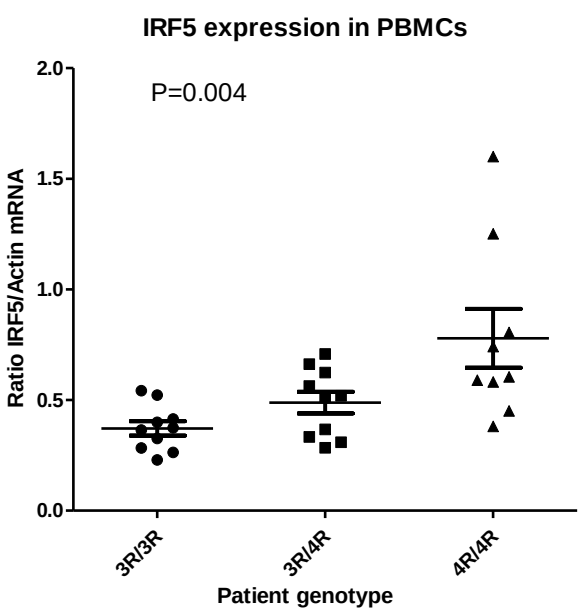


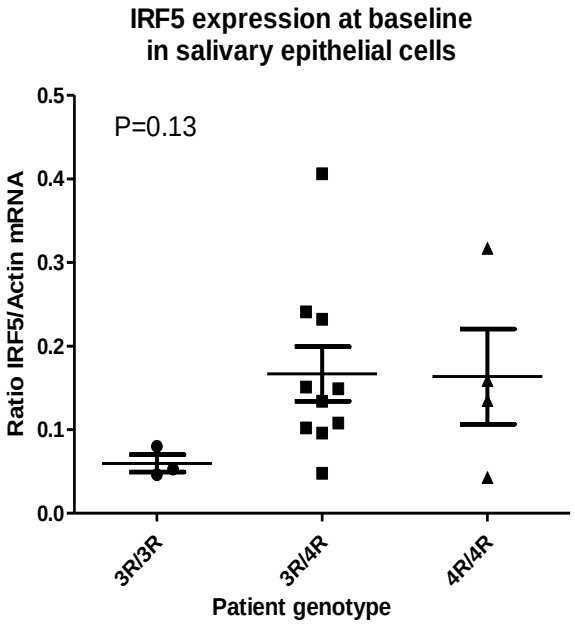
GRR 3R/3R vs 3R/4R or 4R/4R: P=6.6.10^{-6} – OR 2.0 ; CI 95% (1.5 – 2.7)

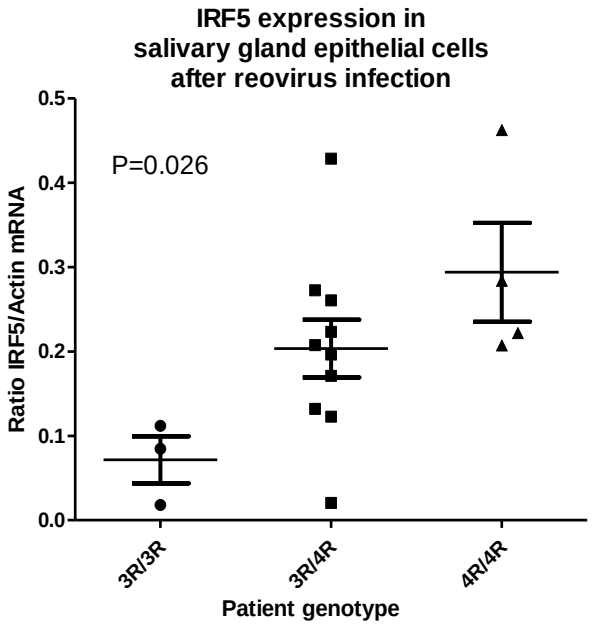
Miceli-Richard et al, Arthritis Rheum. 2009 Jul;60(7):1991-7.

The IRF5 promoter CGGGG in/del association is functional in Sjögren's syndrome

- **DNA and mRNA from 30 patients included in the ASSESS cohort (French Prospective Cohort of 400 Sjögren's patients)**







Miceli-Richard et al, Arthritis Rheum. 2009 Jul;60(7):1991-7.

ARD

Overlap between differentially methylated DNA regions in blood B lym… genetic at-risk loci in primar… syndrome

Corinne Miceli-Richard, Shu-Fang Wang-Rer
Florence Busato, Céline Lallemand, Kevin Be
Gaétane Nocturne, Xavier Mariette and Jörg

Ann Rheum Dis published online July 16, 20

GRB2	cg06943385	7.56e-04
MIR21	cg04276626	1.38e-03
IL21R	cg00050618	1.12e-03
TRAF5	cg10177528	2.99e-04
CXCR5	cg04537602	4.95e-04
	cg13298528	2.93e-05
	cg19791714	7.76e-04

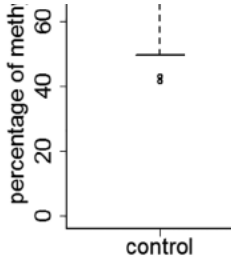
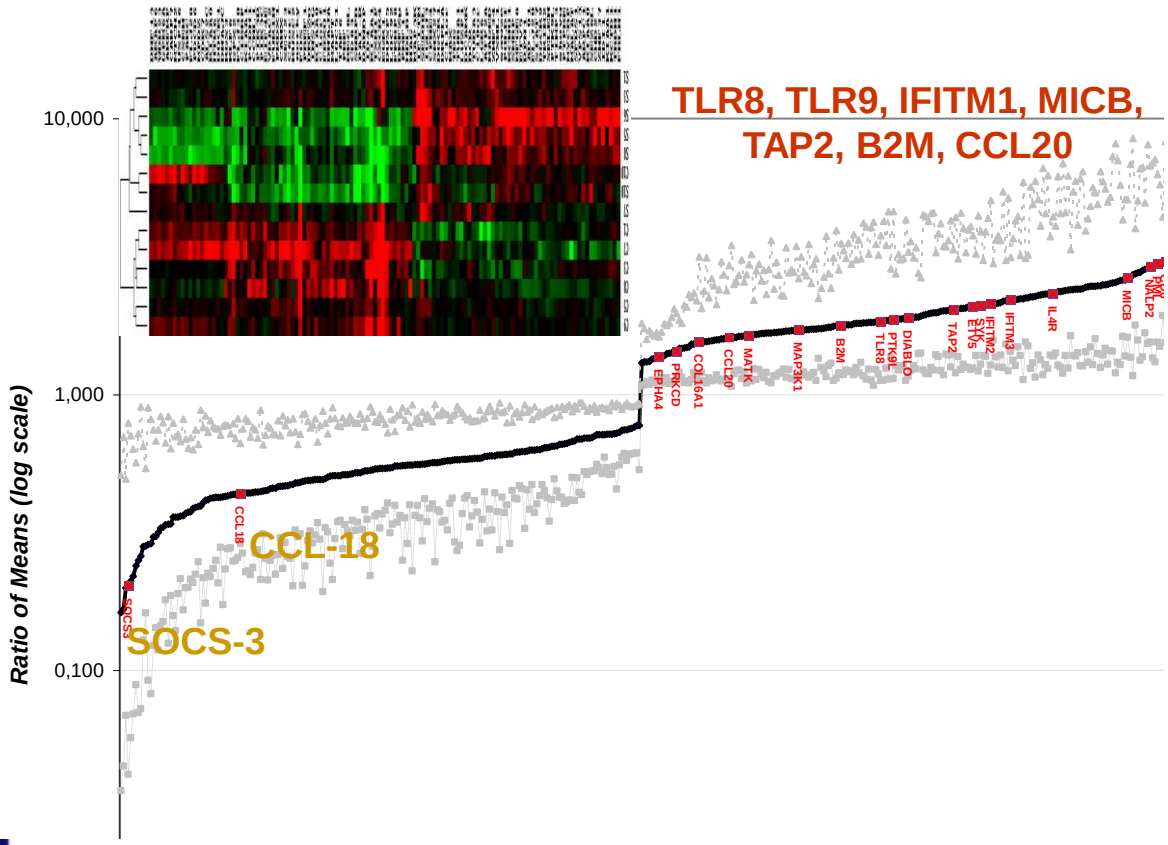
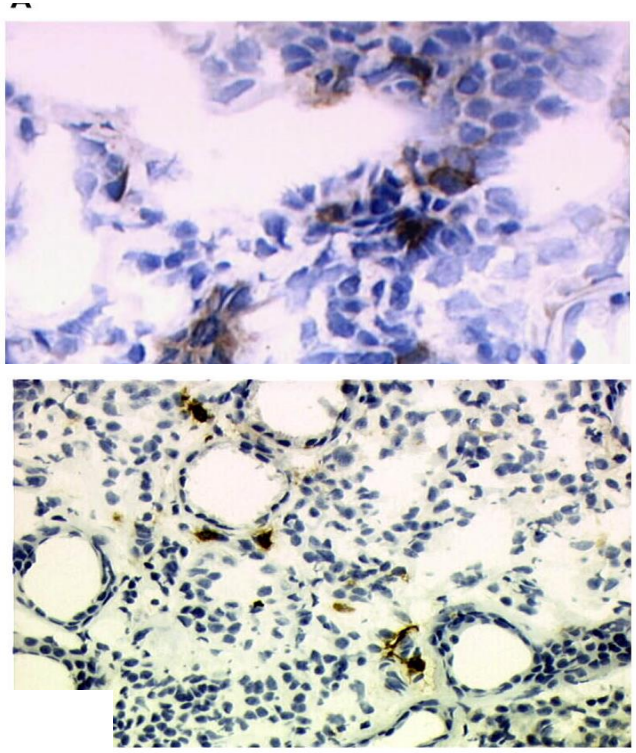


Figure 3 Validation of DNA methylation changes in different genes by pyrosequen
methylated in 450 K BeadChip and validated by pyrosequencing. (B) Boxplots of DN

Presence of an IFN signature in SS





Activation of IFN pathways and plasmacytoid dendritic cell recruitment in target organs of primary Sjögren's syndrome

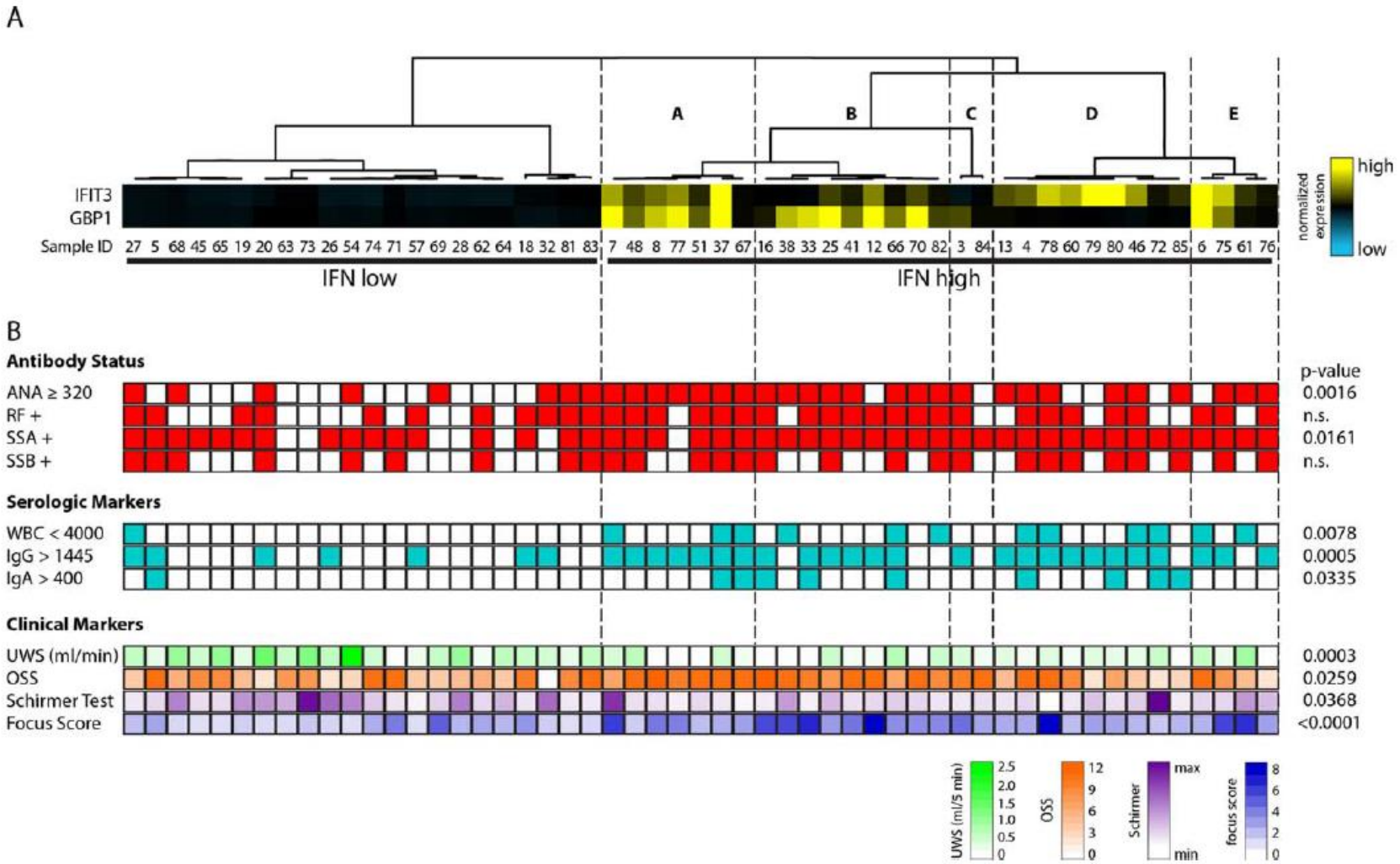
Jacques-Eric Gottenberg*†, Nicolas Cagnard†‡, Carlo Lucchesi†‡, Franck Letourneur†, Sylvie Mistou†, Thierry Lazure§, Sebastien Jacques†, Nathalie Ba§, Marc Ittah*, Christine Lepajolec¶, Marc Labetoulle‖, Marc Ardizzone†**, Jean Sibilia**, Catherine Fournier†, Gilles Chiocchia†,††, and Xavier Mariette*†††‡‡

Presence of plasmacytoid cells in salivary glands of patients

CD123 (top)

BDCA2 (bottom

IFN signature and phenotype



Hall et al. A&R 2015

What drives this interferon signature ? Viral triggers ?

- **Epstein Barr Virus:**
  - **Detection of EBV in tissue biopsies from patients with pSS**

Saito et al JEM 1989

Mariette et al, AJM 1991

- **Retrovirus: HTLV-1:**
  - **Link between HTLV-1 and pSS in Japan**

Terada et al, Lancet, 1994

- **Hepatitis C Virus:**
  - **Salivary lymphoid infiltrate in HCV-infected patients**

Haddad et al, Lancet, 1992

- **Coxsackievirus:**
  - **Controversial results**

Gottenberg et al, A&R, 2006

Triantafyllopoulou A et al, A&R, 2004

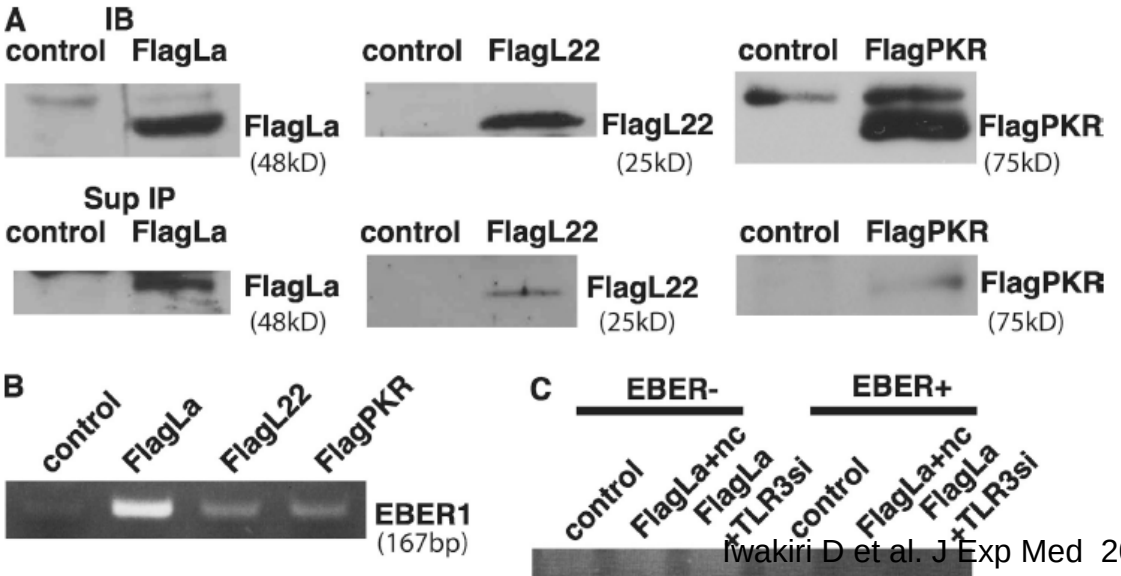
- **Abnormal expression of endogeneous retroviral sequences**
  - **i.e. LINE or ALU sequences**
  - **By epigenetic dysregulation (i.e. demethylation) ?**

Epstein-Barr virus (EBV)–encoded small RNA is released from EBV-infected cells and activates signaling from toll-like receptor 3

The majority of the released EBER RNA from EBV exists as a complex with La/SSB and the complex is stimulatory for TLR3

Dai Iwakiri,[1] Li Zhou,[1] Mitsuhiro Samanta,[1] Misako Matsumoto,[2] Takashi Ebihara,[2] Tsukasa Seya,[2] Shosuke Imai,[3] Mikiya Fujieda,[4]

and EBV-HLH. We also investigated the role of EBER on the activation of TLR3. Results from RT-PCR assays revealed that EBER1 was detected in patient sera and also in



(Fig. 4 D), expression RNAs fro proinflam PBMCs. A which con sion of IF

EBER1 ind presenting

Finally, we to clarify w induction with EBE markers of

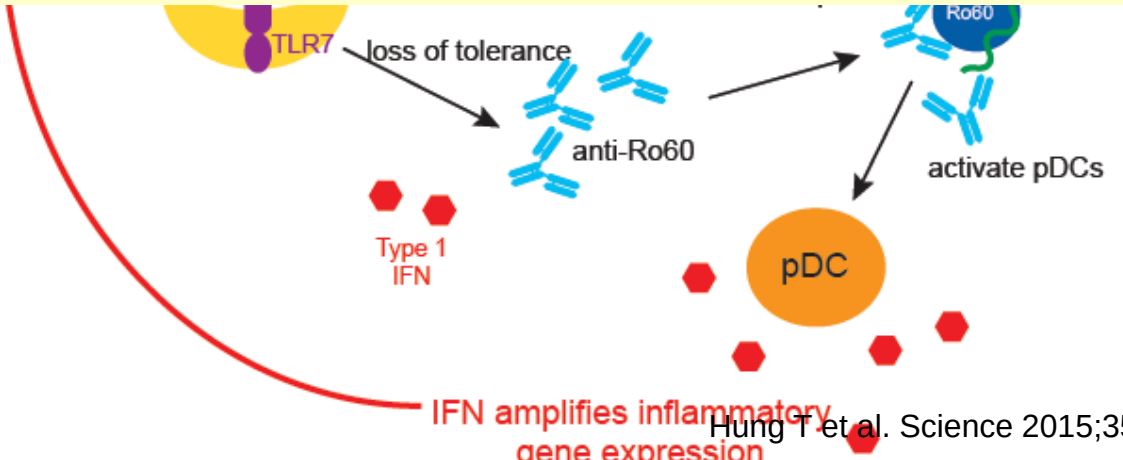
Iwakiri D et al. J Exp Med 2009;206:2091-9

Science
AAAS

The Ro60 autoantigen binds endogenous retroelements and regulates inflammatory gene expression

T. Hung *et al.*

Science **350**, 455 (2015);
DOI: 10.1126/science.aac7442



Hung T et al. Science 2015;350:455-9

cally 10^{-14} to 10^{-10} s (*4*), a
from such nonthermaliz
frared (IR) spectroscopy s
state resolution have sh

[1]Department of Chemistry, Univer
7HF, UK. [2]Central Laser Facility, R
Rutherford Appleton Laboratory, H
Campus, Science and Technology
Oxfordshire OX11 0QX, UK.
*Corresponding author. E-mail: m
julia.weinstein@sheffield.ac.uk (J.

NOTES

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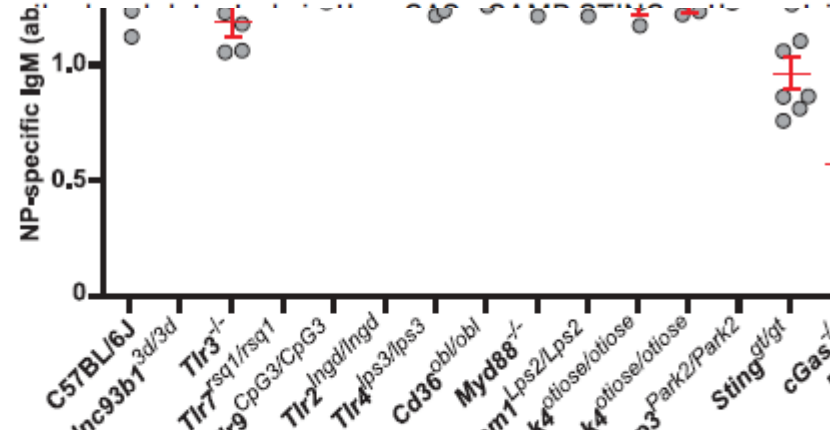
Invest. **118**, 2609–2619 (2008).
s. **71**, 1081–1091 (2011).

HUMORAL IMMUNITY

MAVS, cGAS, and endogenous retroviruses in T-independent B cell responses

Ming Zeng,[1] Zeping Hu,[2*] Xiaolei Shi,[2*] Xiaohong Li,[1*] Xiaoming Zhan,[1*] X
Jianhui Wang,[1,4] Jin Huk Choi,[1] Kuan-wen Wang,[1] Tiana Purrington,[1] Miao
Maggy Fina,[1] Ralph J. DeBerardinis,[2] Eva Marie Y. Moresco,[1] Gabriel Peder
Gerald M. McInerney,[3] Gunilla B. Karlsson Hedestam,[3] Zhijian J. Chen,[1,4]

Multivalent molecules with repetitive structures including bacterial capsul
polysaccharides and viral capsids elicit antibody responses through B cell
(BCR) crosslinking in the absence of T cell help. We report that immunizat
these T cell–independent type 2 (TI-2) antigens causes up-regulation of en
retrovirus (ERV) RNAs in antigen-specific mouse B cells. These RNAs are c
mitochondrial antiviral signaling protein (MAVS)–dependent RNA sensing



absence of IgM

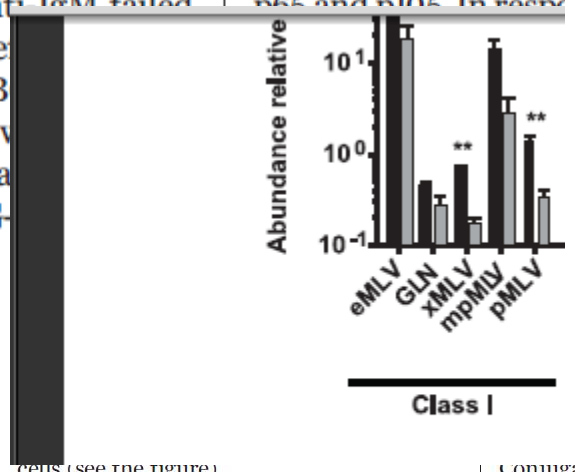
absence of:

- DNA sensor: cGAS→cGAMP→STING
- RNA sensor: RIG-I → MVAS

- **2- Hypothesis:** Since no exogenic nucleic acid is introduced, stimulation of endogenous retroviral sequences by immunization with TI-2 Ag, which is mandatory for IgM response

drive NF-κB activation needed for the TI-2 antibody response. We found that anti-IgM failed to induce ERV mRNAs in NEMO-de in vitro (Fig. 4B), suggesting that B induces ERV mRNAs via NF-κB. As v onstrated, ERV transcripts trigger a tained wave of signaling via the RIG-

vation by measuring



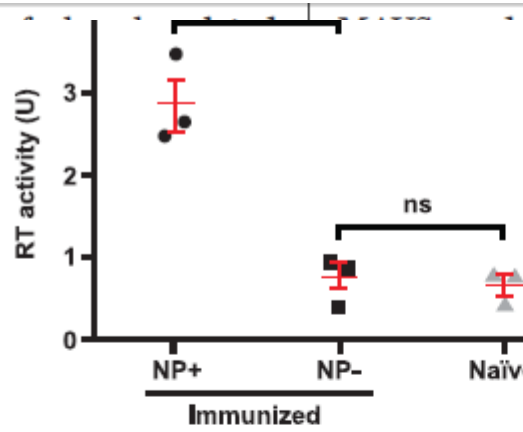
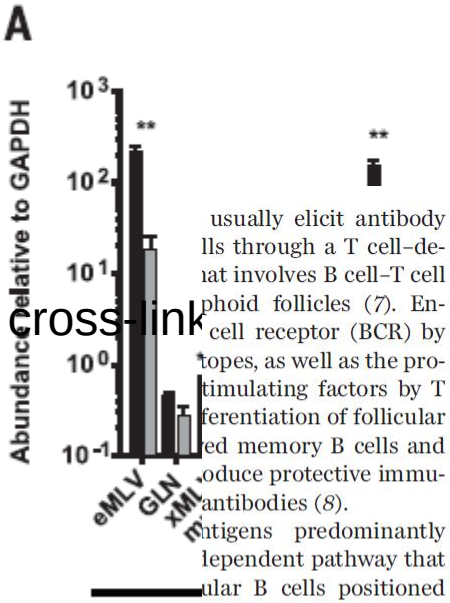


Fig. 3. TI-2 antigen immunization induce



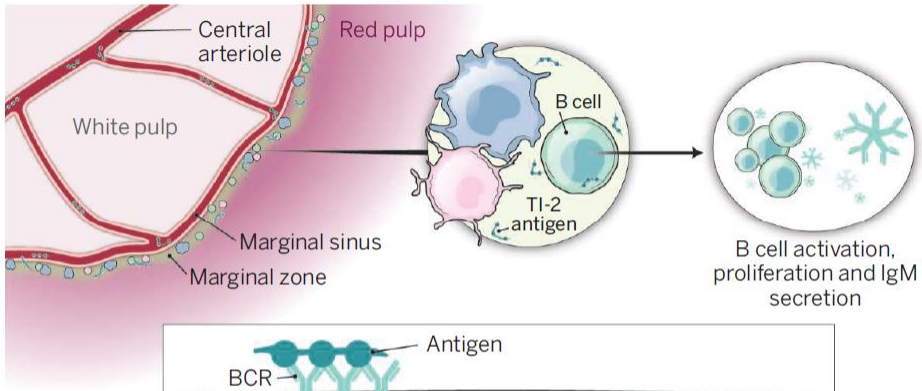
usually elicit antibody
lls through a T cell–de-
iat involves B cell–T cell
phoid follicles (*7*). En-
cell receptor (BCR) by
topes, as well as the pro-
timulating factors by T
ferentiation of follicular
ed memory B cells and
oduce protective immu-
antibodies (*8*).
ntigens predominantly
lependent pathway that
ular B cells positioned
ne of the spleen (*9*). In
nsive BCR cross-linking
arides called type-2 TI
), these B cells rapidly
hort-lived plasma cells
tive IgM and some IgG
espite recent advances
whereby TI-2 antigens
one B cells without help
s poorly understood.

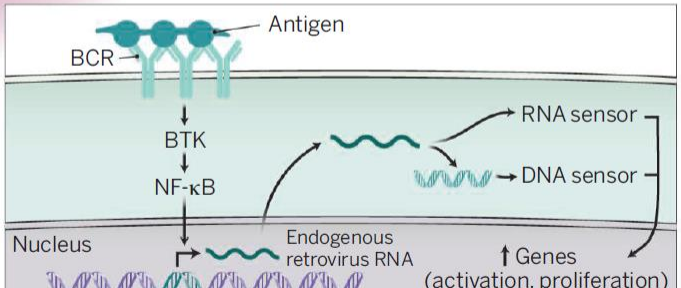
cells (see the figure).

Help from endogenous retroviruses appears to be restricted to B cell responses

Conjugation of TI-2 antigens with proteins or Toll-like receptor agonists enhances systemic but not mucosal antibody responses.

at is detected
B cells. Splen
cells were c
or *Igh*$^{B1\text{-}8+}$ tra
on with NP-Fic
ript levels of
anscription qu
from NP-speci
ormalized to g
APDH) mRNA
umber differen
erent ERVs can
(B) *Igh*$^{B1\text{-}8+}$ tra
ble region de
e of the endog
PCR of the in





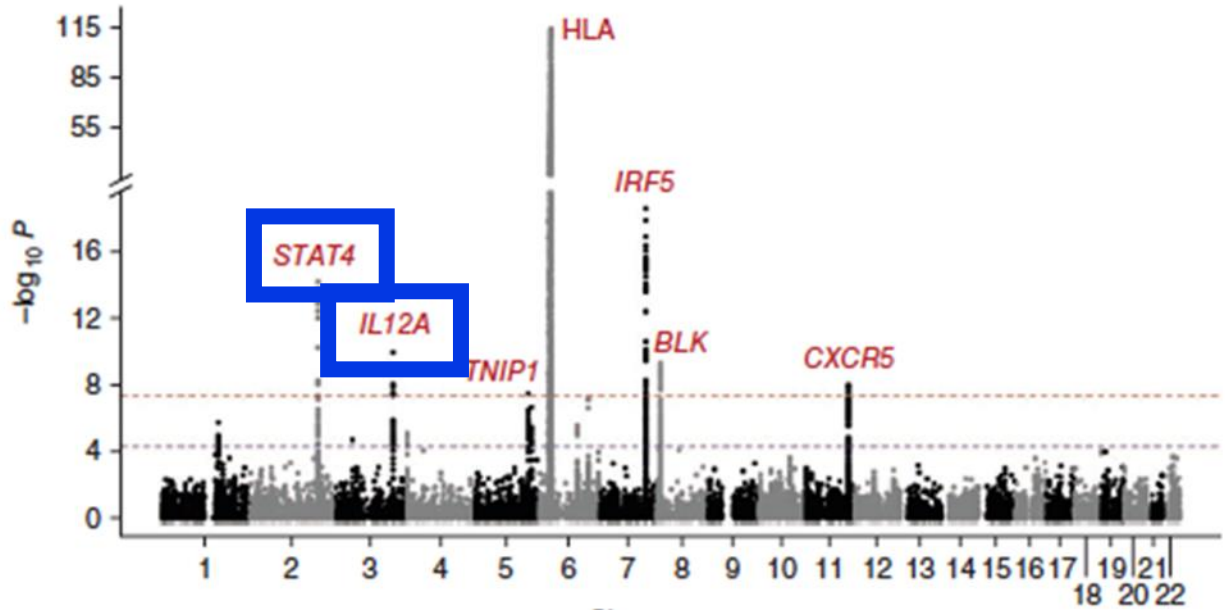
- 3- BCR cross-link

The immunological mechanisms of Sjögren's

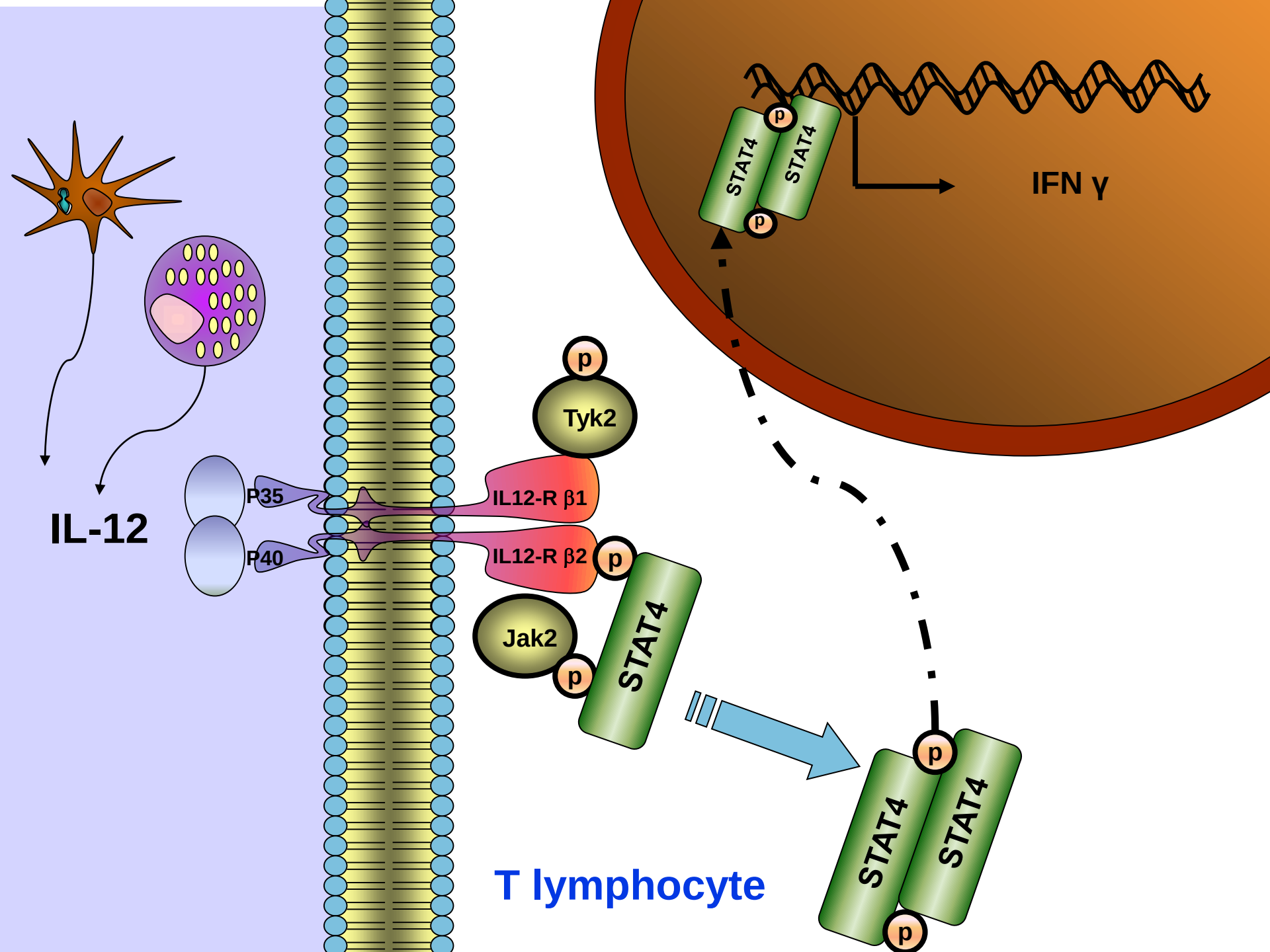
- The type 1 IFN signature and its origin
- The type 2 IFN signature and its origin
- The B-cell activation and its origin
- The cellular actors
- The mechanisms of lymphomagenesis

Type 1 but also type 2 IFN

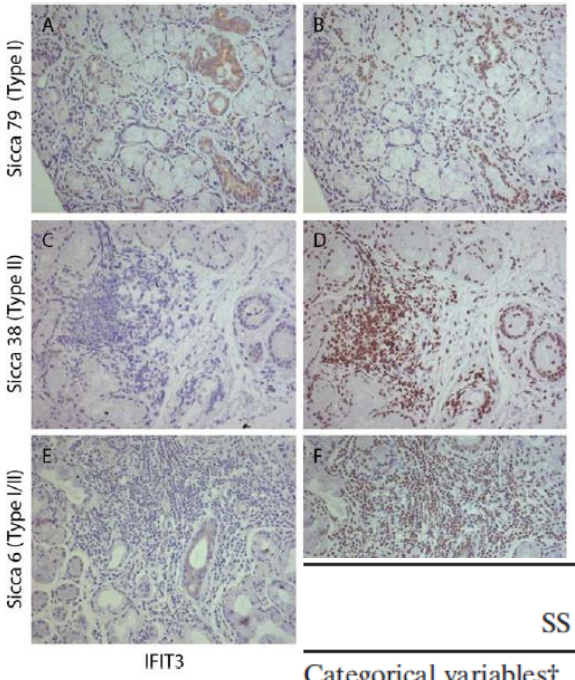
SNP Population	N(subject /controls)	Odds ratio	95%IC	Reference
rs7574865 USA	124/1112	1,46	1,09-1,97	Korman et al. Genes and Immun 2008
rs7582694 Scandinavia	368/711	1,41	1,14-1,73	Nordmark et al. Genes and Immun 2008
rs7582694 France	378/635	1,57	1,27-1,93	Miceli-Richard et al Genes and Immun 2010



Lessard et al. Nat Genet 2013


IL-12
P35
P40
IL12-R β1
IL12-R β2
Tyk2
Jak2
p
STAT4
STAT4
STAT4
STAT4
IFN γ
T lymphocyte

Type 1 but also type 2 IFN



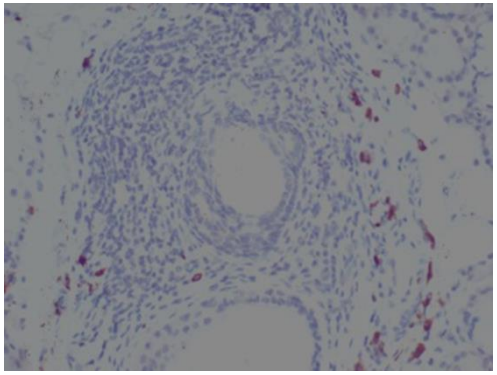
SS feature	Type I IFN (n = 9)	Type II IFN (n = 11)	Type I and type II mixed IFN (n = 11)
Categorical variables†			
Female	9 (100)	10 (91)	9 (82)
Caucasian	6 (67)	4 (36)	7 (64)
Asian/Pacific Islander	3 (33)	4 (36)	2 (18)
WBCs <4,000/μl	4 (44)	3 (27)	5 (45)
IgG >1,445 mg/dl	8 (89)	7 (64)	10 (91)
IgA >400 mg/dl	4 (44)	3 (27)	2 (18)
ANA titer ≥1:320	6 (67)	9 (82)	10 (91)
Rheumatoid factor	5 (56)	9 (82)	9 (82)
Anti-SSA	9 (100)	11 (100)	10 (91)
Anti-SSB	6 (67)	5 (45)	7 (64)
C4 <16 mg/dl	0	5 (45)	2 (18)
Dry eye symptoms	9 (100)	10 (91)	11 (100)
Dry mouth symptoms	9 (100)	10 (91)	11 (100)
Continuous variables‡			
Age, years	52 (45–69.5)	58 (52–64)	56 (39–63)
LSG focus score	2.6 (2.1–2.85)	4.3 (3.5–4.7)§	2.9 (2.3–5.8)
UWSF rate, ml/5 minutes	0.229 (0.0975–0.297)	0.114 (0–0.491)	0.164 (0–0.552)
OSS score, maximum of both eyes	5 (2.5–10)	11 (9–11)¶	11 (7–11)
Schirmer's test, ml/5 minutes, mean of both eyes	3.75 (2.625–6.25)	4 (3–6.5)	5 (3–9)

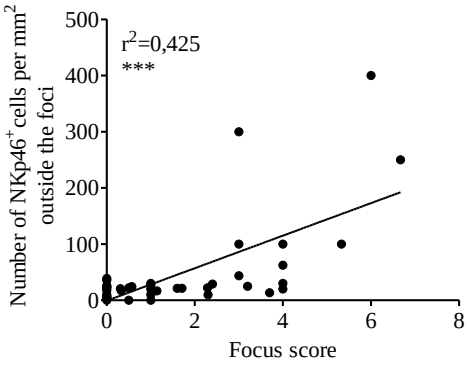
Hall et al. A&R 2015

NK cells could be the type 2 IFN-secreting cells

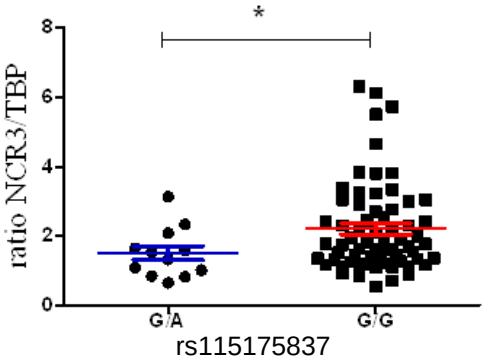
Genetic association with a SNP of NKp30 and hyperexpression and function of Nkp30

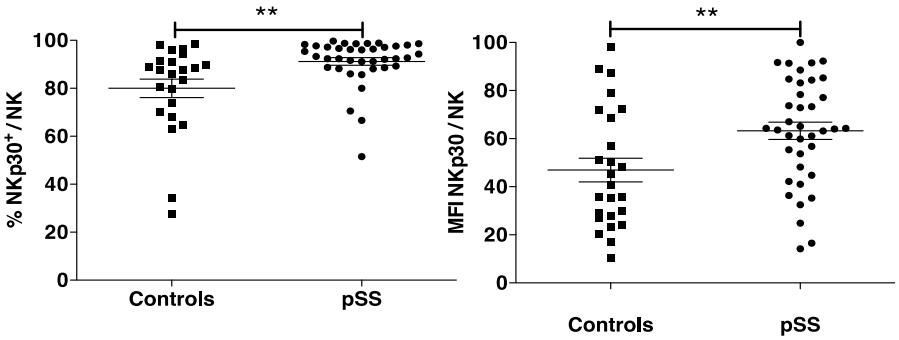
		574 pSS cases (340 SSAB+, 233 SSAB-) and 451 controls	
	SNP	OR	P
All pSS cases versus healthy controls	rs11575837	0.38	0.001
	rs2736191	0.43	0.001
	rs2187668*	2.47	2.0E-11

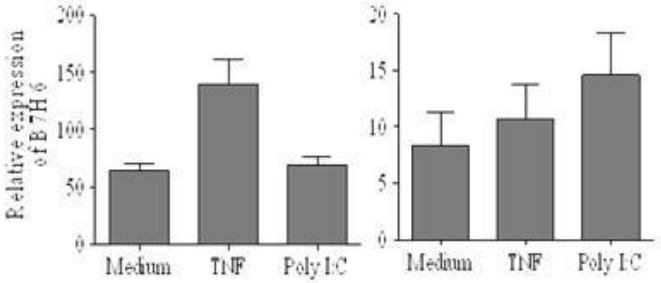




Presence of NK cells in labial salivary glands outside the foci



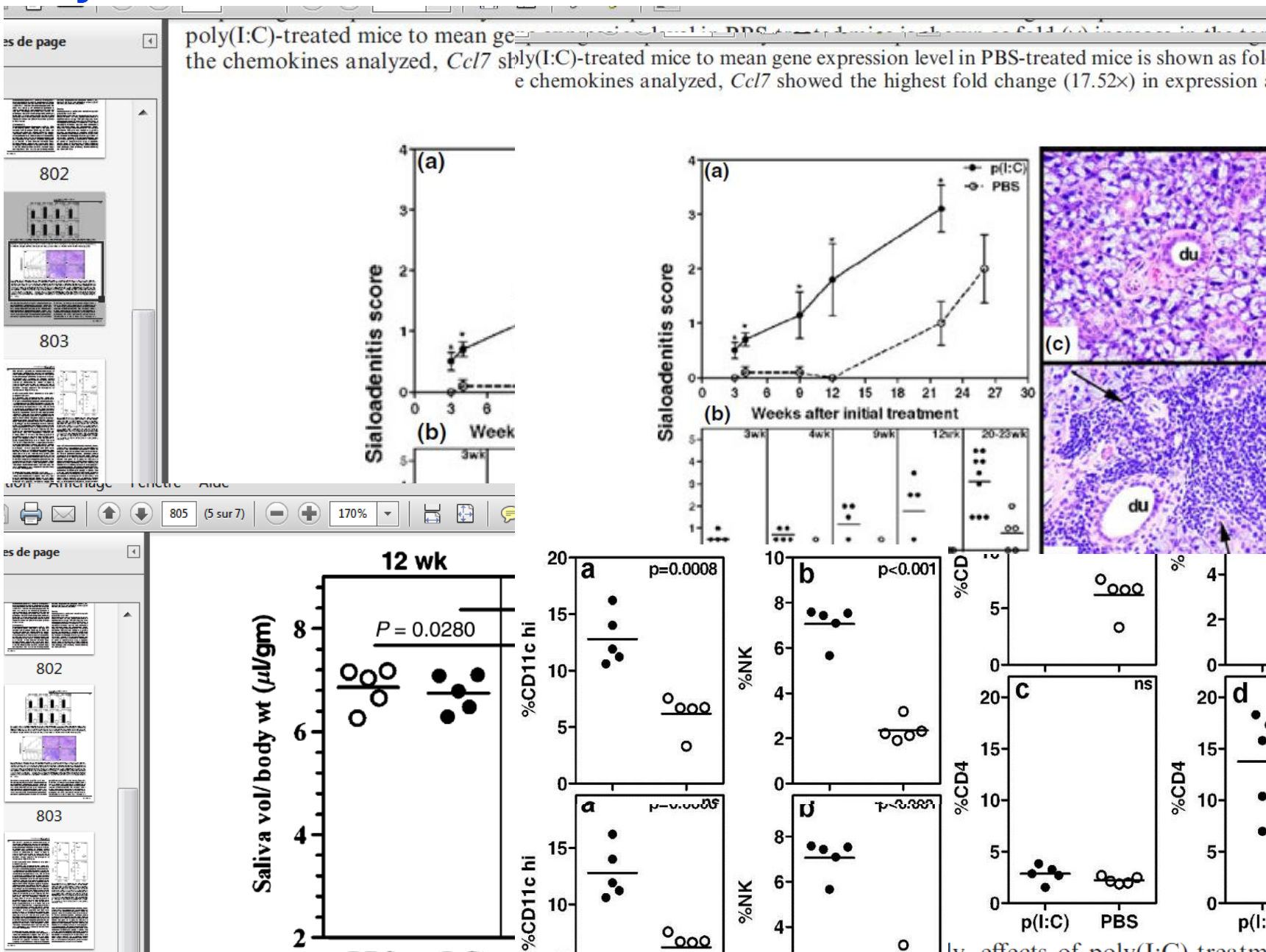




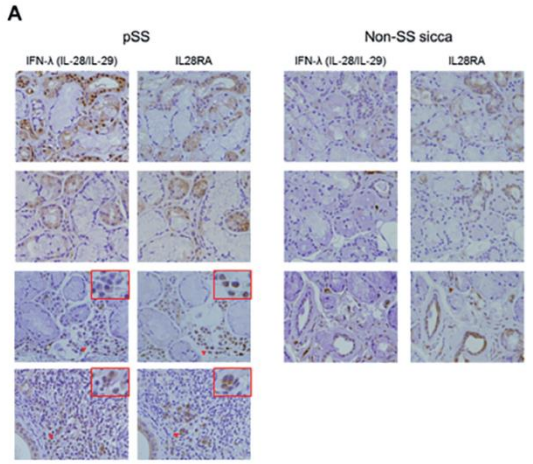
Presence of B7H6, the ligand of NKp30 on salivary glands epithelial cells

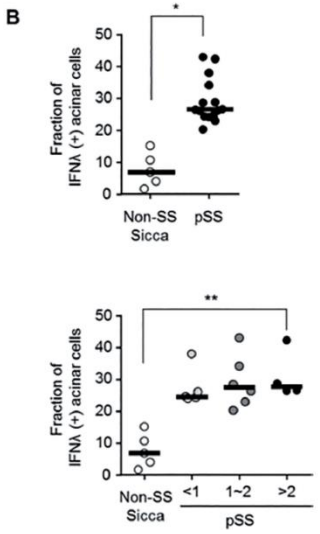
Nocturne G et al. Science Trans Medicine 2013;5:195ra96

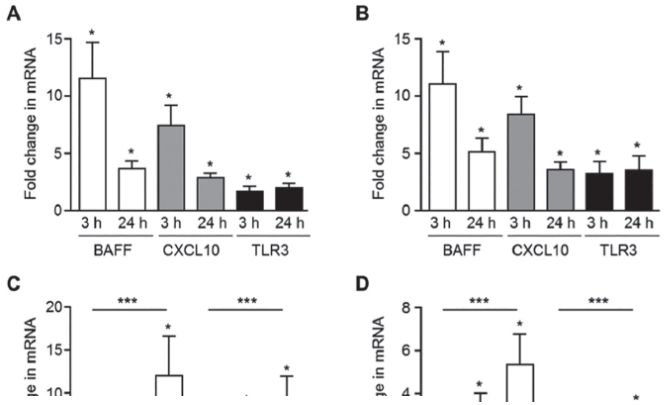
Poly (I:C) stimulation worsens mouse models of Sjögren with early NK-cell infiltration

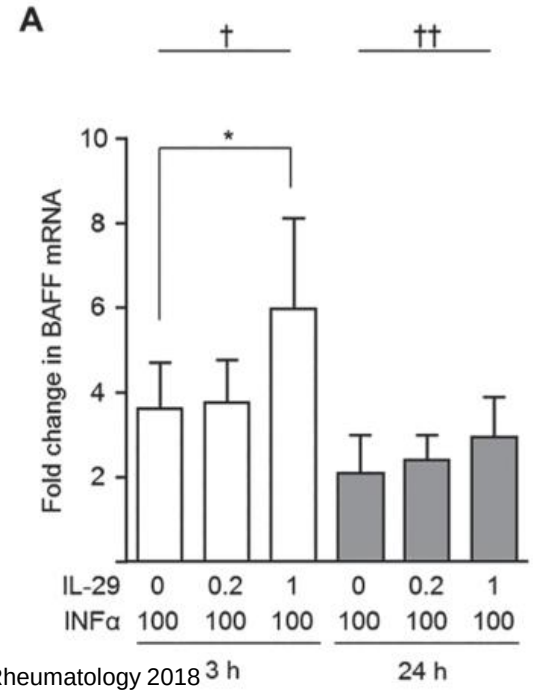


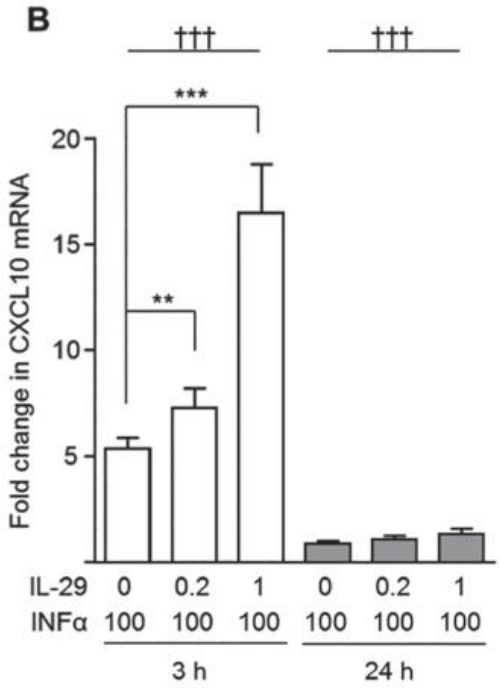
IFN type I, type II… type III











Ha et al. Clinical and Experimental Rheumatology 2018

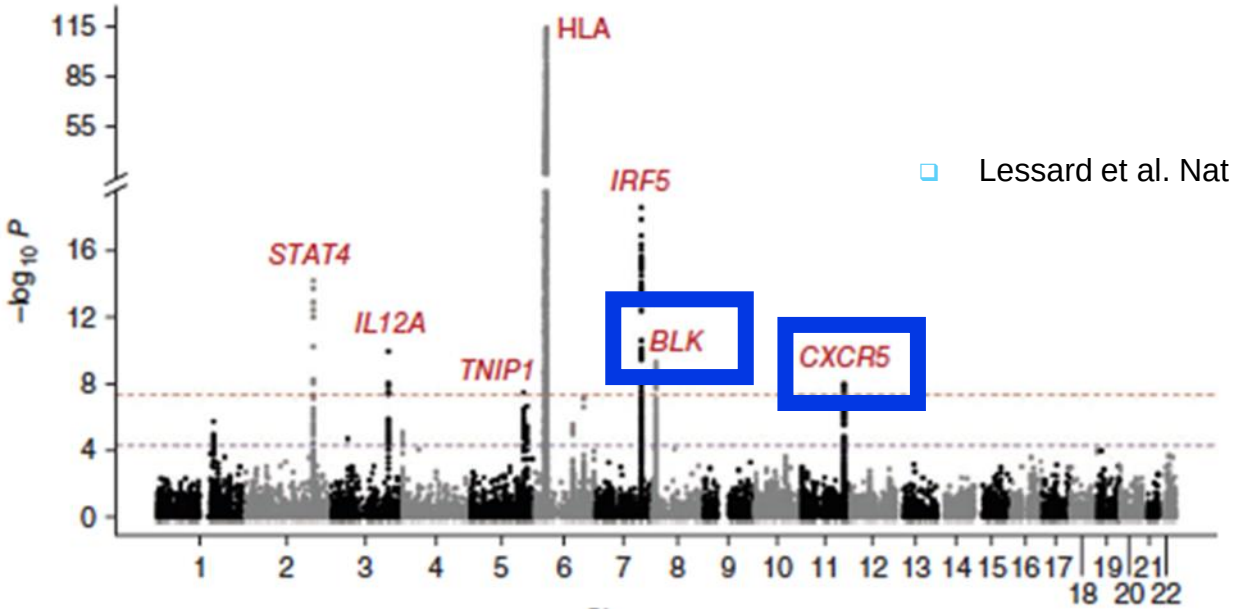
The immunological mechanisms of Sjögren's

- The type 1 IFN signature and its origin
- The type 2 IFN signature and its origin
- The B-cell activation and its origin
- The cellular actors
- The mechanisms of lymphomagenesis

B-cell activation in Sjögren's

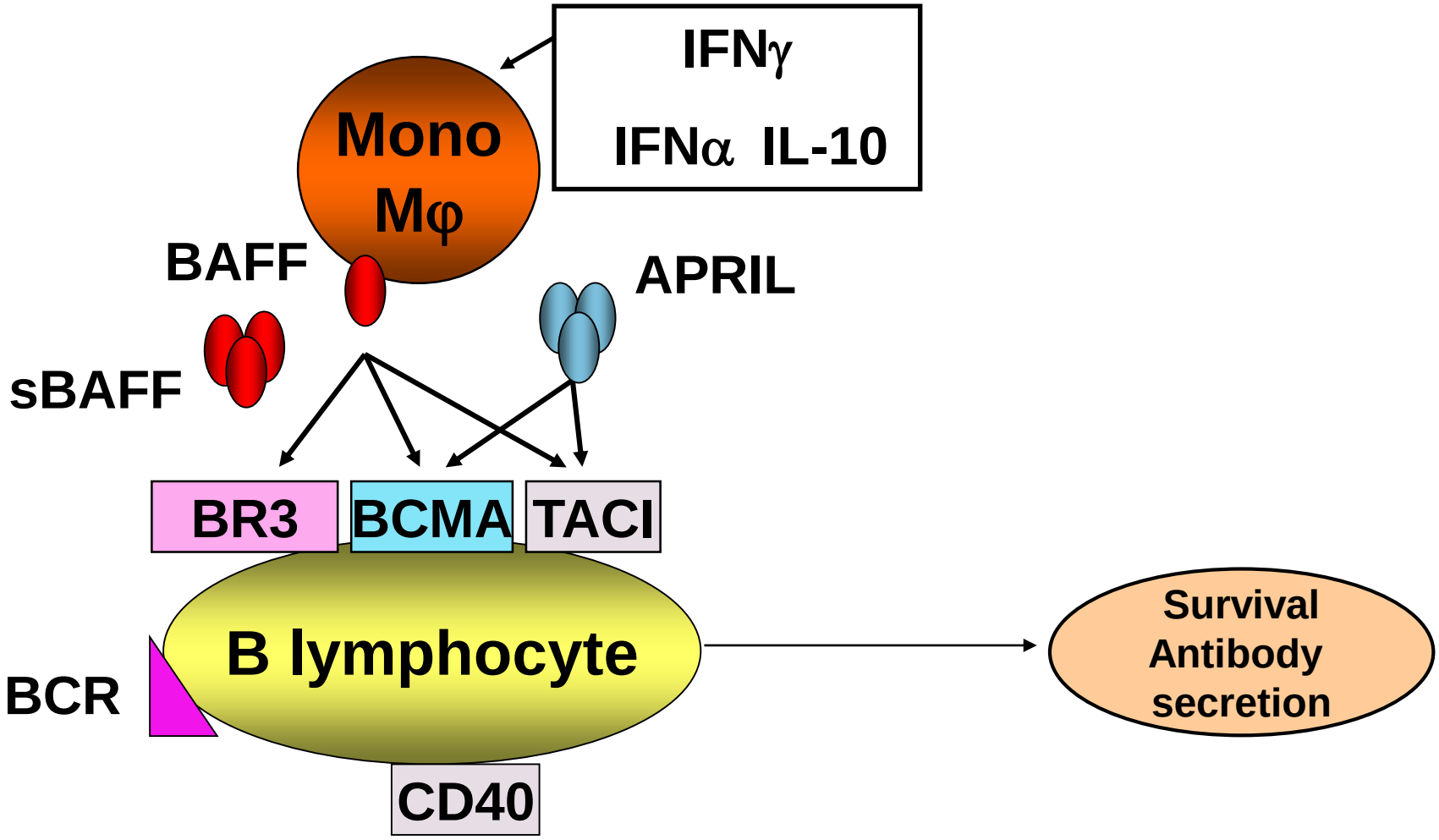
- ↗ Immunoglobulin level
- ↗ serum light chain level
- ↗ beta2 microglobulin level
- Presence of ectopic germinal centers in 20% of patients
- A 10 to 20 fold increased risk of lymphoma

- Moutsopoulos et al J Immunol 1983
- Youinou et al Clin Exp Rheumatol 1988
- Gottenberg et al Ann Rheum Dis 2006
- Michaski et al N Engl J Med 1975
- Gottenberg et al Ann Rheum Dis 2005
- Theander et al. Ann Rheum Dis. 2011
- Gottenberg et al PlosOne 2013
- Quartuccio et al Rheumatology 2013



- Lessard et al. Nat Genet 2013;45:1284-92.

The BAFF system

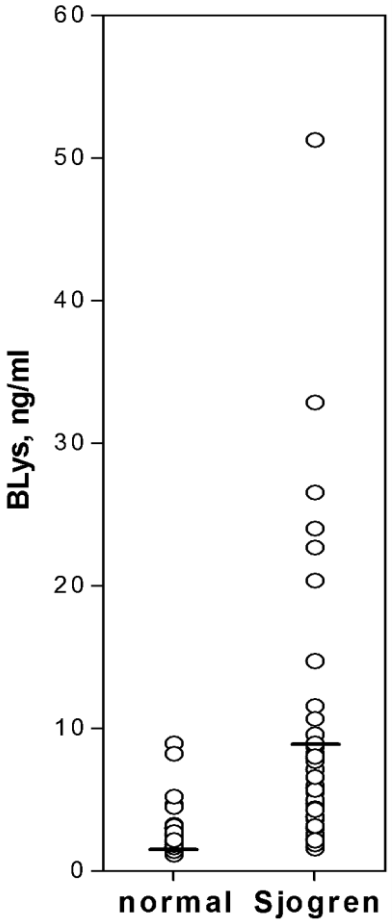


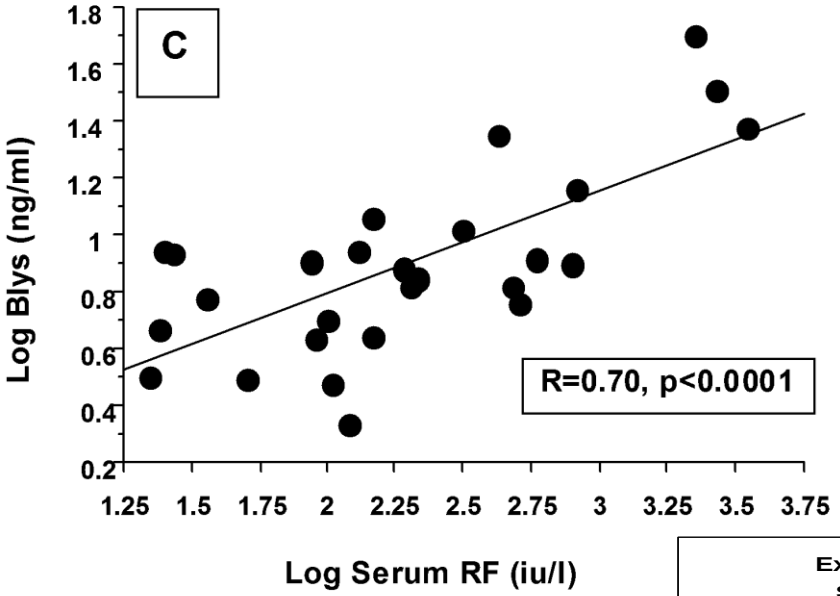
BAFF Transgenic mice

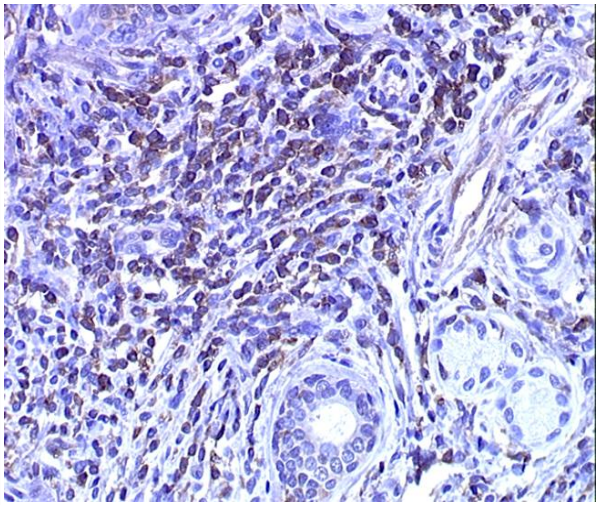
- **Biological features**
  - **Increase in peripheral B cells**
  - **Increase in serum Ig**
  - **Increase in serum auto-antibodies (RF, Anti-DNA)**
- **Clinical features**
  - **Autoimmune glomerulonephritis**
  - **Polyarthritis**
  - **Auto-immune Sialadenitis**
  - **B-cell lymphoma x2 (x30 in TNF ko mice)**

Mackay, J Exp Med 1999; Khare, PNAS 2000; Groom, JCI 2002; Batten JI 2004

Involvement of BAFF (BLyS) in pathogeny of SS and induction of BAFF in epithelial cells with type 1 IFN or viral infection

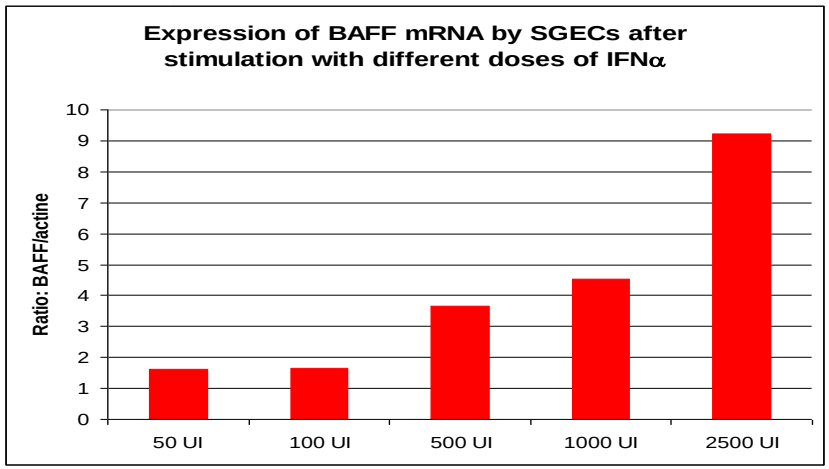






Presence of BAFF on T cells infiltrating labial salivary glands

- Mariette et al ARD 2003
- Lavie et al J Pathol 2004
- Ittah et al ART 2006
- Ittah et al Eur J Immunol 2008
- Ittah et al Eur J Immunol 2009
- Gottenberg et al PLOS One 2013



European Journal of Immunology

SHORT COMMUNICATION

Viruses induce high expression of BAFF by salivary gland epithelial cells through TLR- and type-I IFN-dependent and -independent pathways

Marc Ittah[1], Corinne Miceli-Richard[1], Jacques-Eric Gottenberg[1], Jérémie Sellam[1], Pierre Eid[2], Pierre Lebon[3], Coralie Pallier[4], Christine Lepajolec[5] and Xavier Mariette[1]

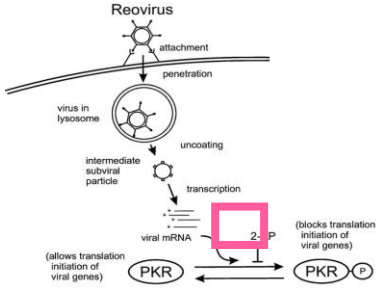
Eur J Immunol 2008; 38:1058-64

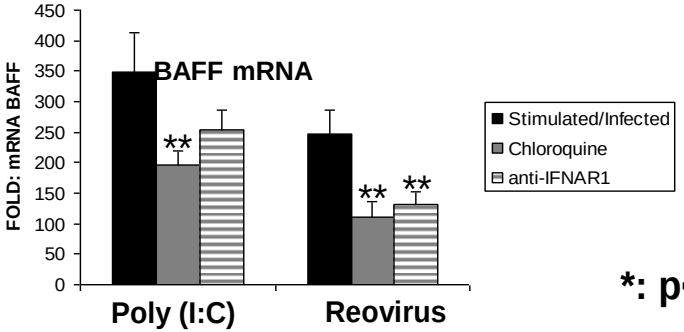
European Journal of Immunology

B-cell-activating factor expressions in salivary epithelial cells after dsRNA virus infection depends on RNA-activated protein kinase activation

Marc Ittah[1], Corinne Miceli-Richard[1], Jacques-Eric Gottenberg[1], Jérémie Sellam[1], Christine Lepajolec[2] and Xavier Mariette[1]

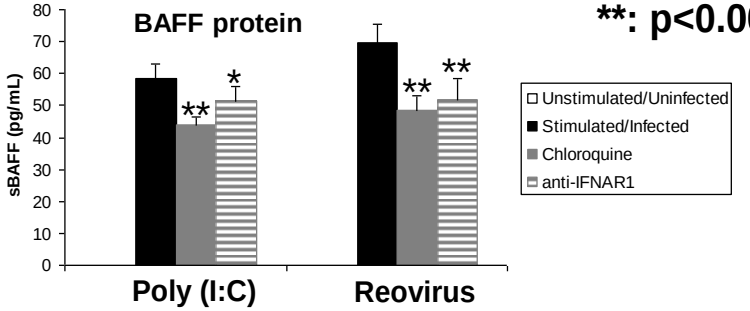
Eur J Immunol 2009; 39:1271-9



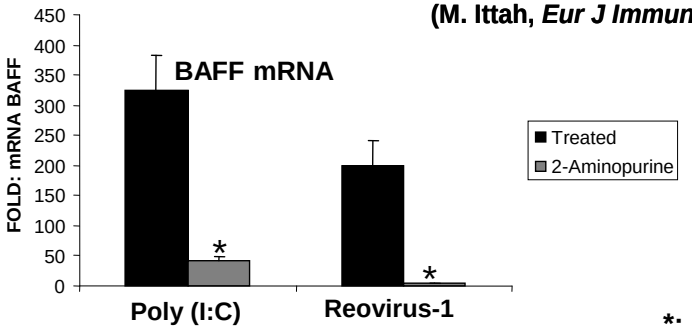


*: p<0.05

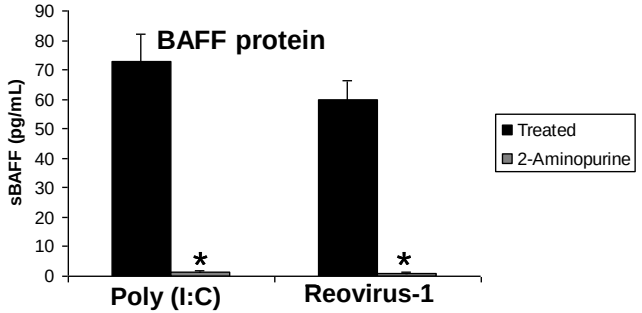
**: p<0.001

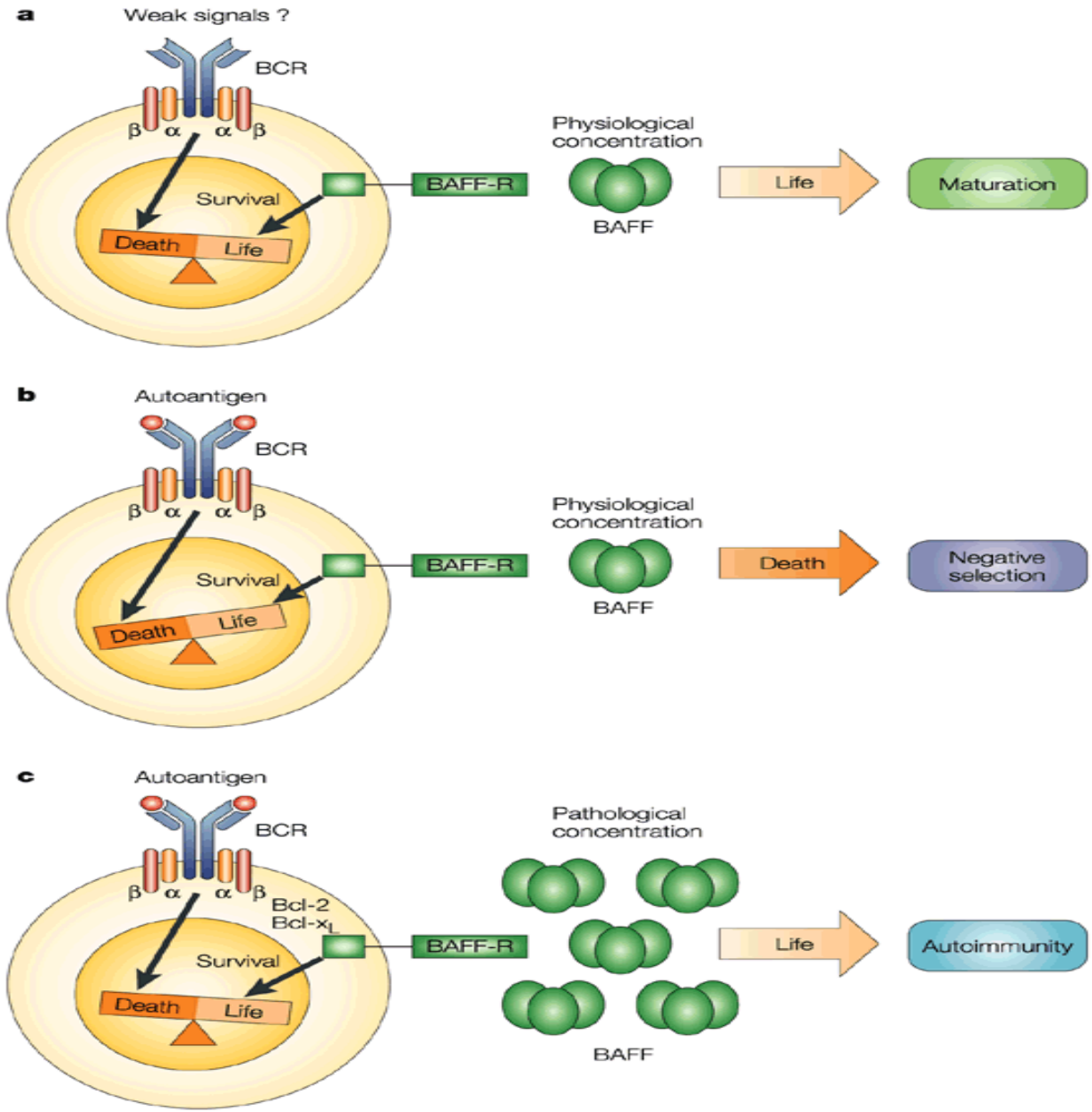


(M. Ittah, *Eur J Immunol* , 200

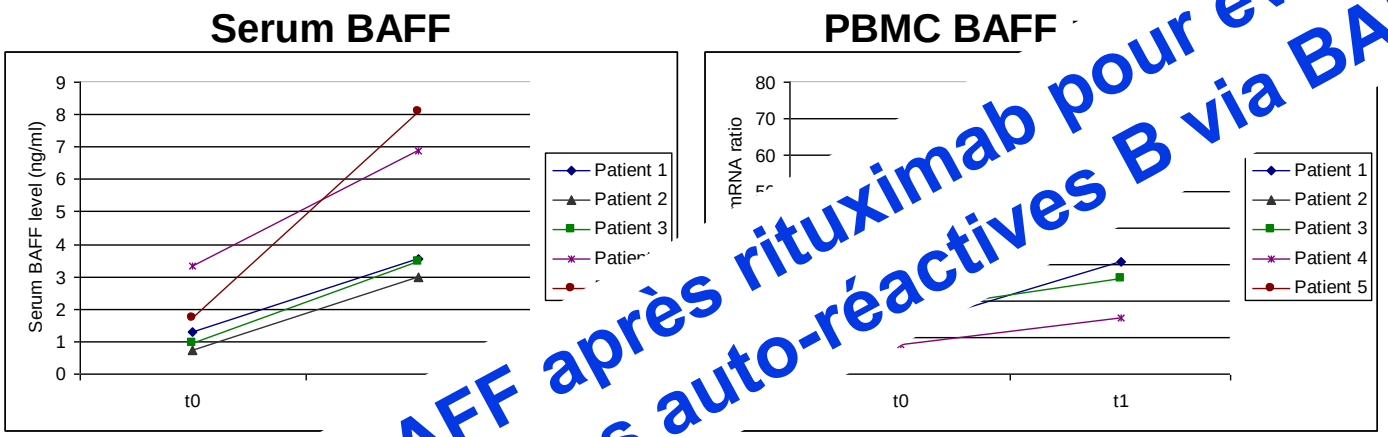


*: p<0.05



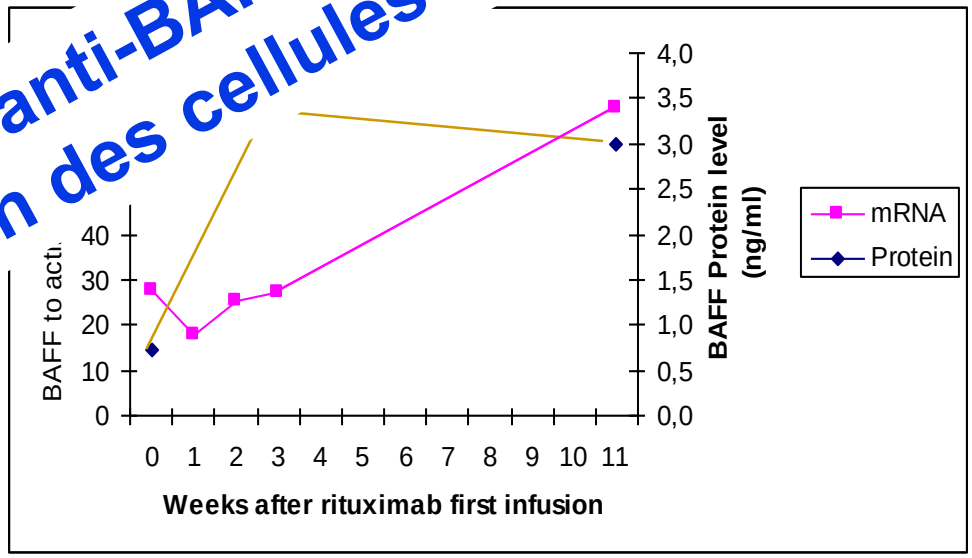

a
Weak signals ?
BCR
β α α β
Survival
Death
Life
BAFF-R
Physiological concentration
BAFF
Life
Maturation
b
Autoantigen
BCR
β α α β
Survival
Death
Life
BAFF-R
Physiological concentration
BAFF
Death
Negative selection
c
Autoantigen
BCR
β α α β
Bcl-2
Bcl-xL
Survival
Death
Life
BAFF-R
Pathological concentration
BAFF
Life
Autoimmunity

Increase of BAFF after rituximab



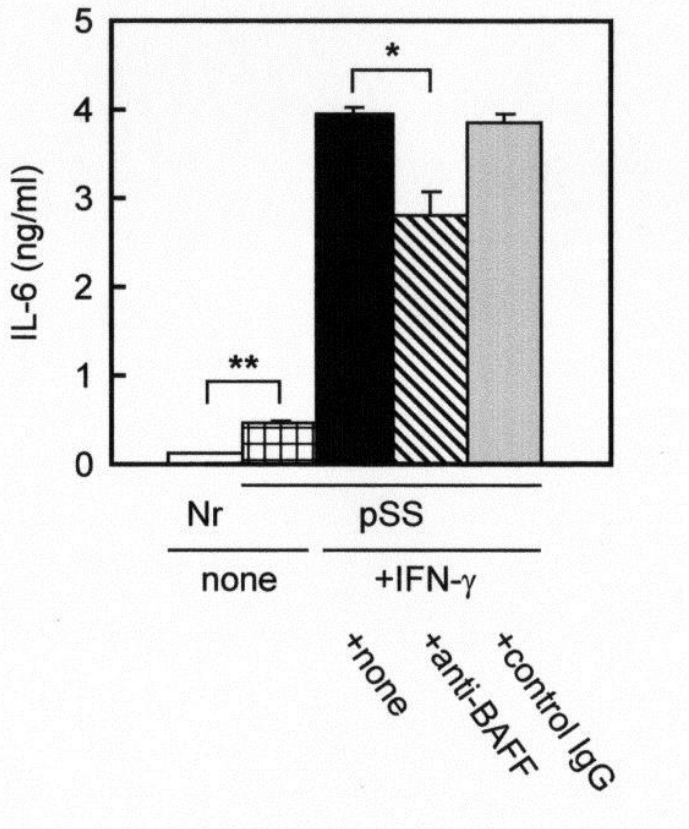
Intérêt des anti-BAFF après rituximab pour éviter la stimulation des cellules auto-réactives B via BAFF?

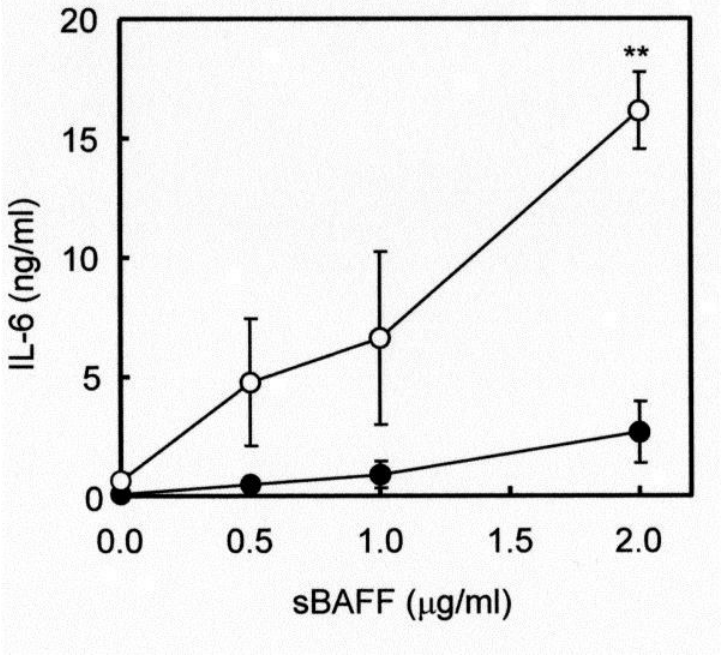
- 2 S



Lavie et al. Ann Rheum Dis 2006.

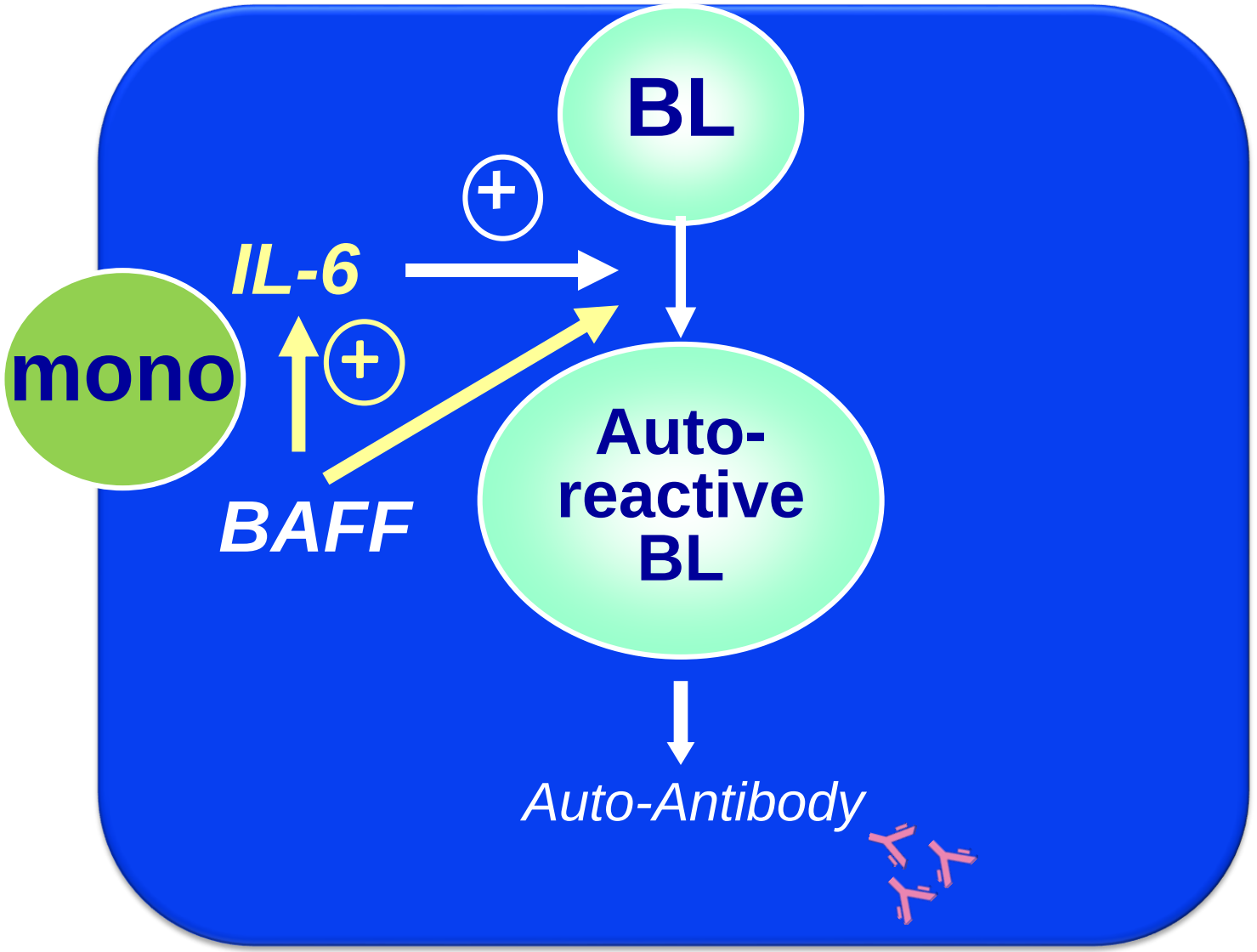
The Relationship Between BAFF and IL-6 in Sjögren's Syndrome





Yoshimoto K et al; ART, 2011

The Relationship Between BAFF and IL-6 in Sjögren's Syndrome



IL-21

ethanol. The sections were incubated for 30 minu
room temperature with blocking solution containin
mal sera and avidin block (Vector Laboratories, B
game, CA, USA), and then incubated overnight a
with either anti-IL-21 (Santa Cruz Technology
Santa Cruz, CA, USA) or anti-IL-21R, both of v
were diluted 1:100 (R&D Systems, Minneapolis, MI
USA). Mouse IgG or goat IgG served as isotype cor
The slides were washed for 5 minutes, followed by
minute incubation with biotinylated anti-rabbit I
biotinylated anti-goat IgG (Vector). Following a 15
ute wash, the slides were incubated for 1 h with h
radish peroxidase-conjugated avidin-biotin by usir
Vectastain ABC Elite (Vector). The stain was deve
by using diaminobenzidine substrate (DAKO, Ca
teria, CA, USA). Counterstaining was performed
hematoxylin. Enumeration of IL-21-positive cell
performed in the vicinity of LSG lymphocytic infilt
and in the interstitium. One lymphocytic focus per
men was randomly selected for enumerating the nu
of positively stained cells. Quantification of IL-21-p

ract
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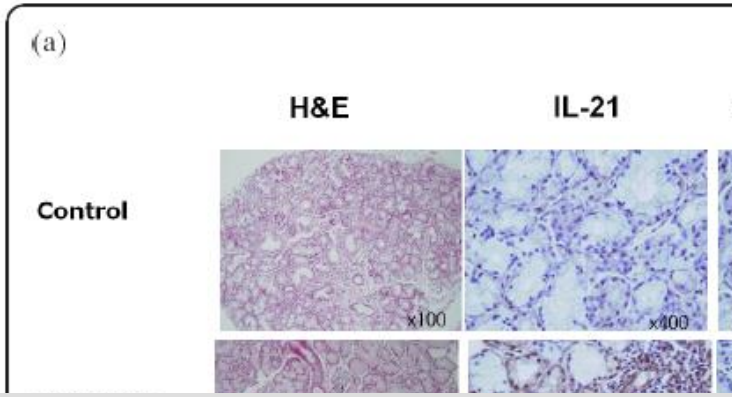
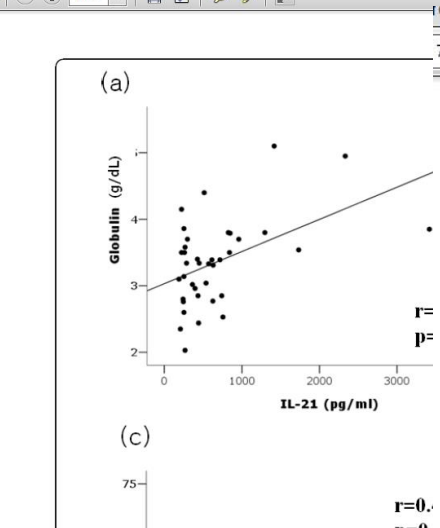
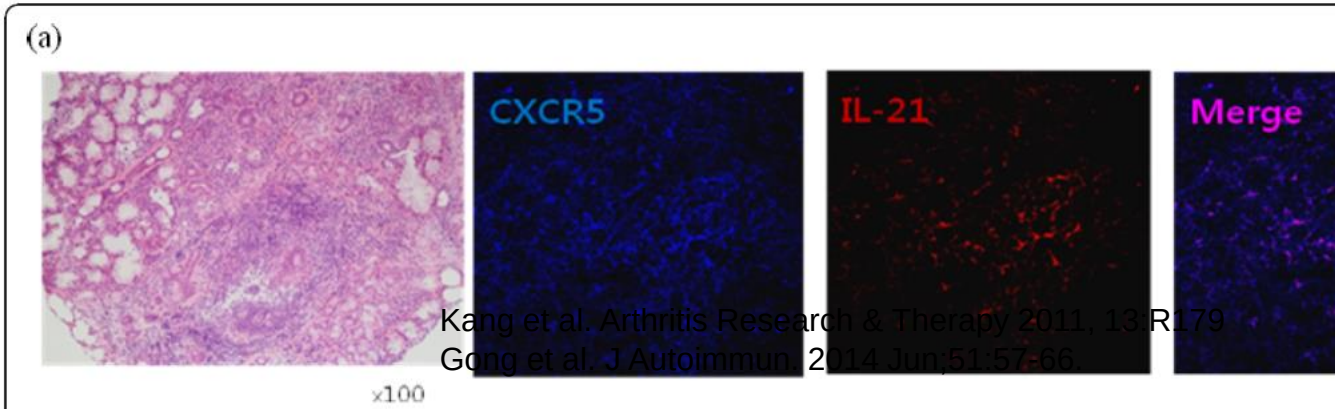
Constant	1.709	0.230	1.218 to 2.2
IL-21 (pg/ml)	0.001	0.000	0.000 to 0.0
IgG1 (ug/ml)	0.013	0.004	0.004 to 0.0

*SE: standard error.
CI: confidence interval; Ig: immunoglobin; IL: interleukin.



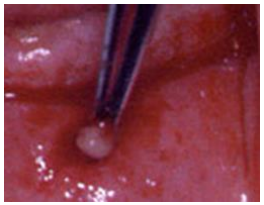




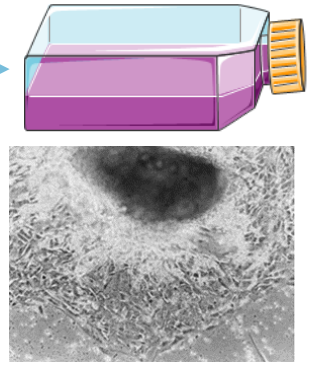
Kang et al. Arthritis Research & Therapy 2011, 13:R179
Gong et al. J Autoimmun. 2014 Jun;51:57-66.

SGEC and B cells

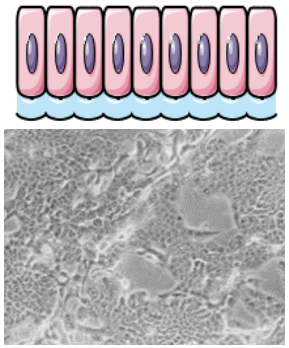
Salivary gland biopsy



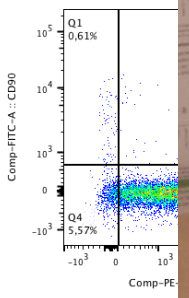
Culture 15 to 21 days

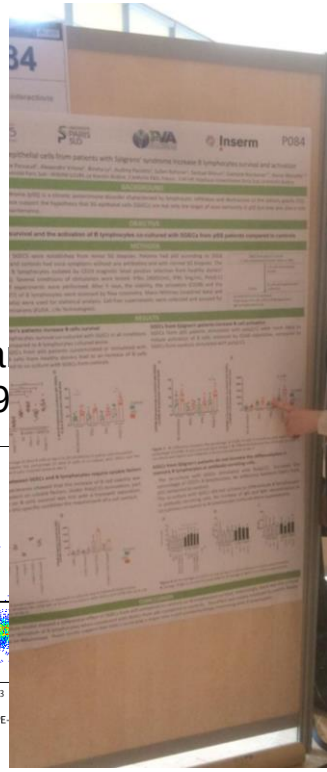


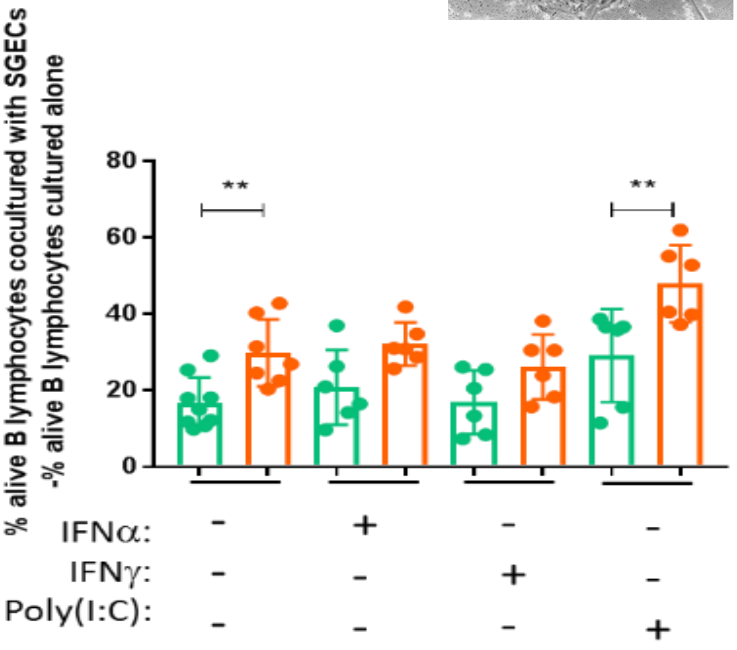
Salivary gland epithelial cells

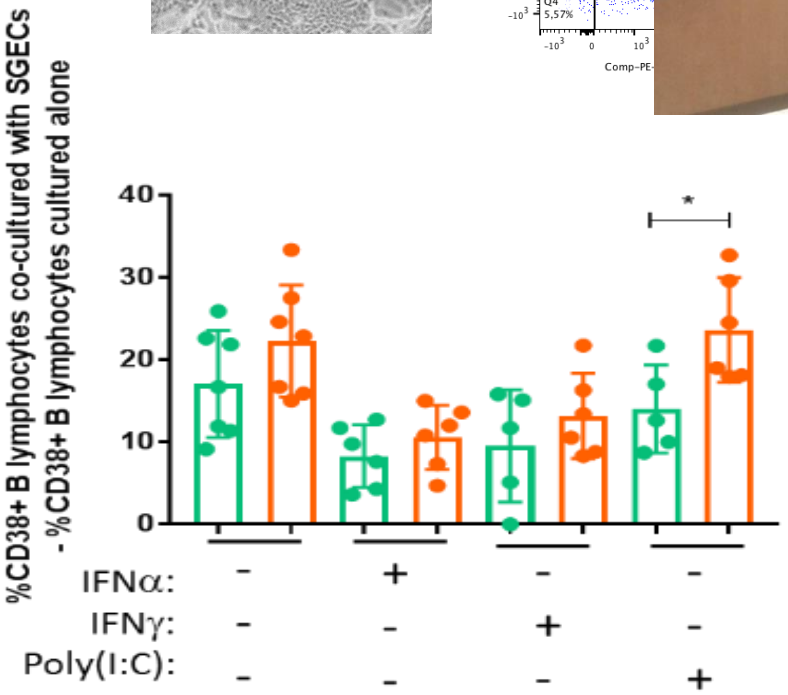


Epca… CD9…



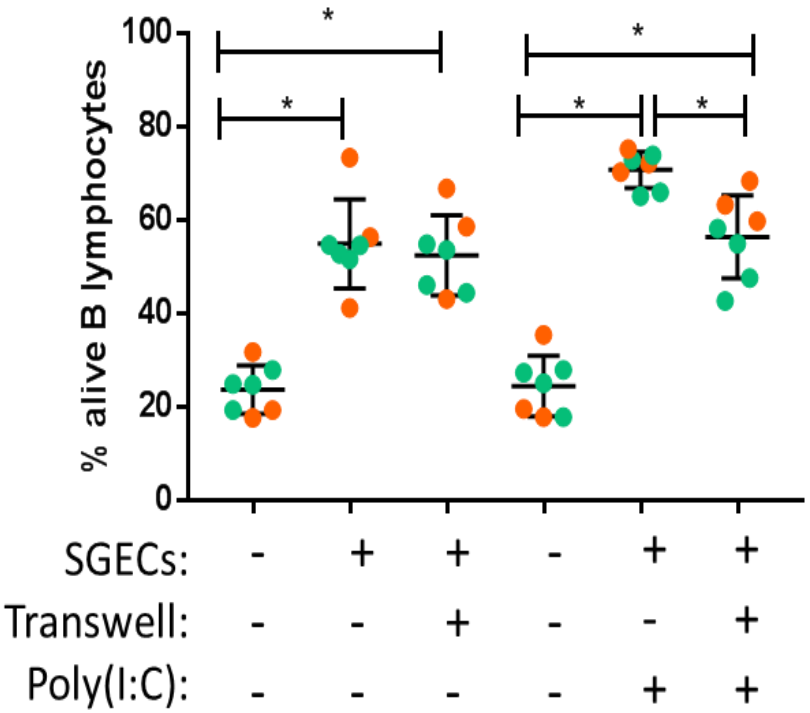


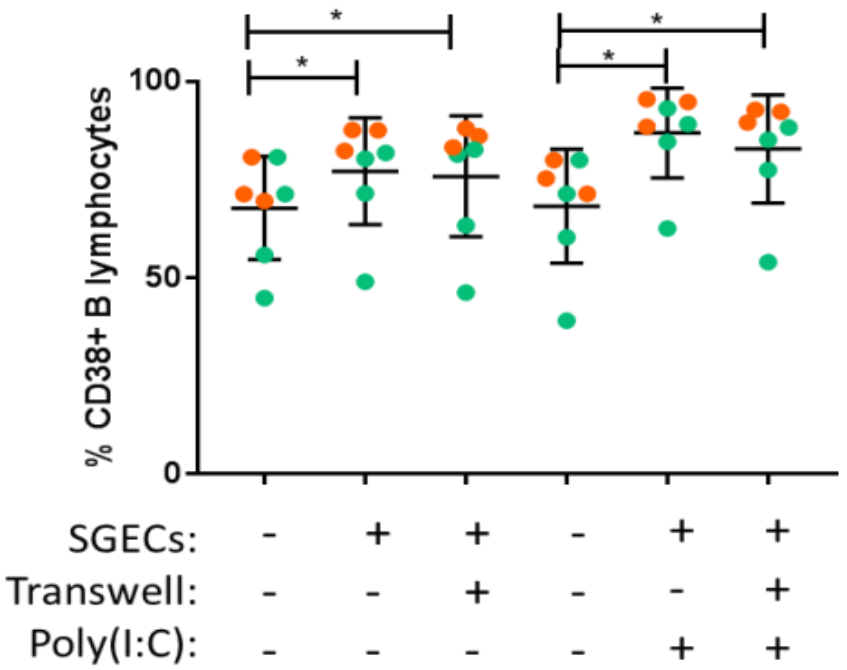




Riviere et al, EWRR 2019

SGEC and B cells





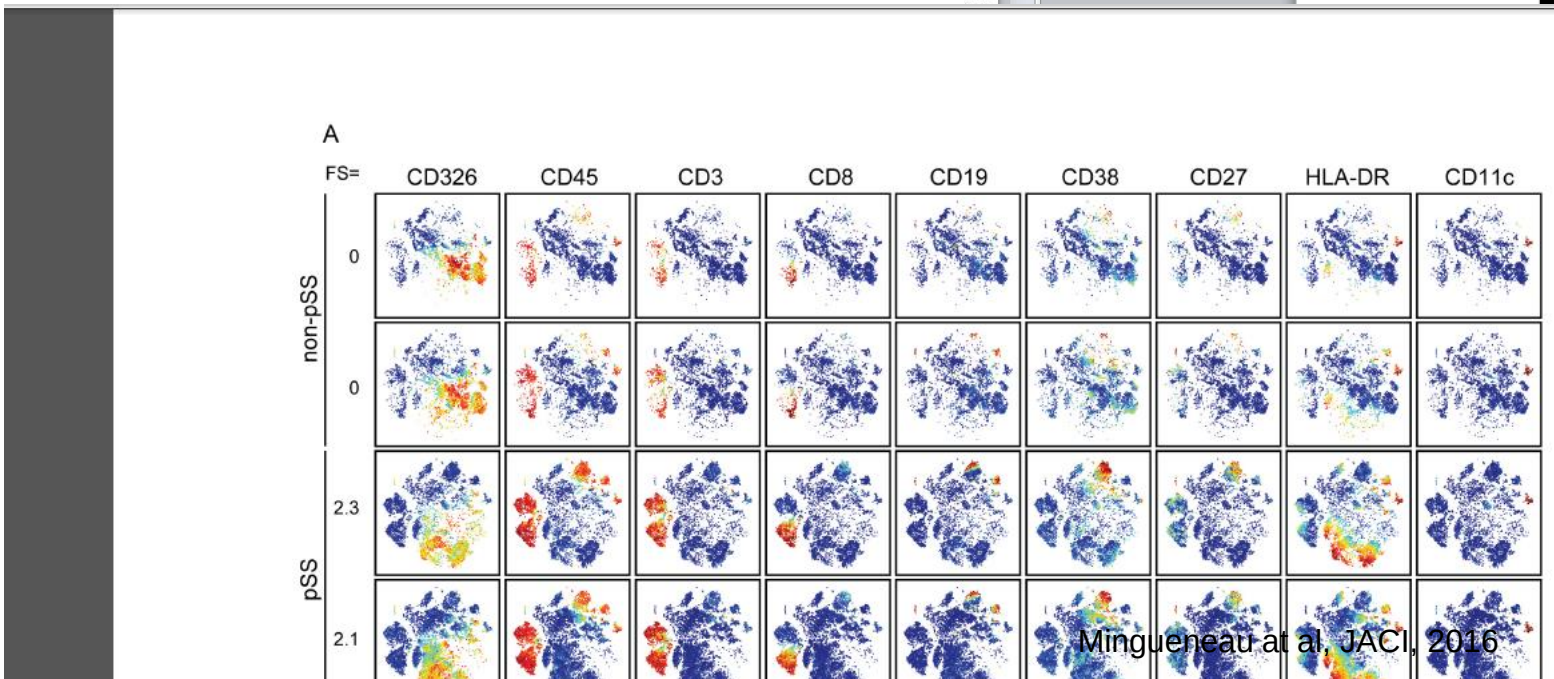
Riviere et al, EWRR 2019

The immunological mechanisms of Sjögren's

- The type 1 IFN signature and its origin
- The type 2 IFN signature and its origin
- The B-cell activation and its origin
- The cellular actors
- The mechanisms of lymphomagenesis

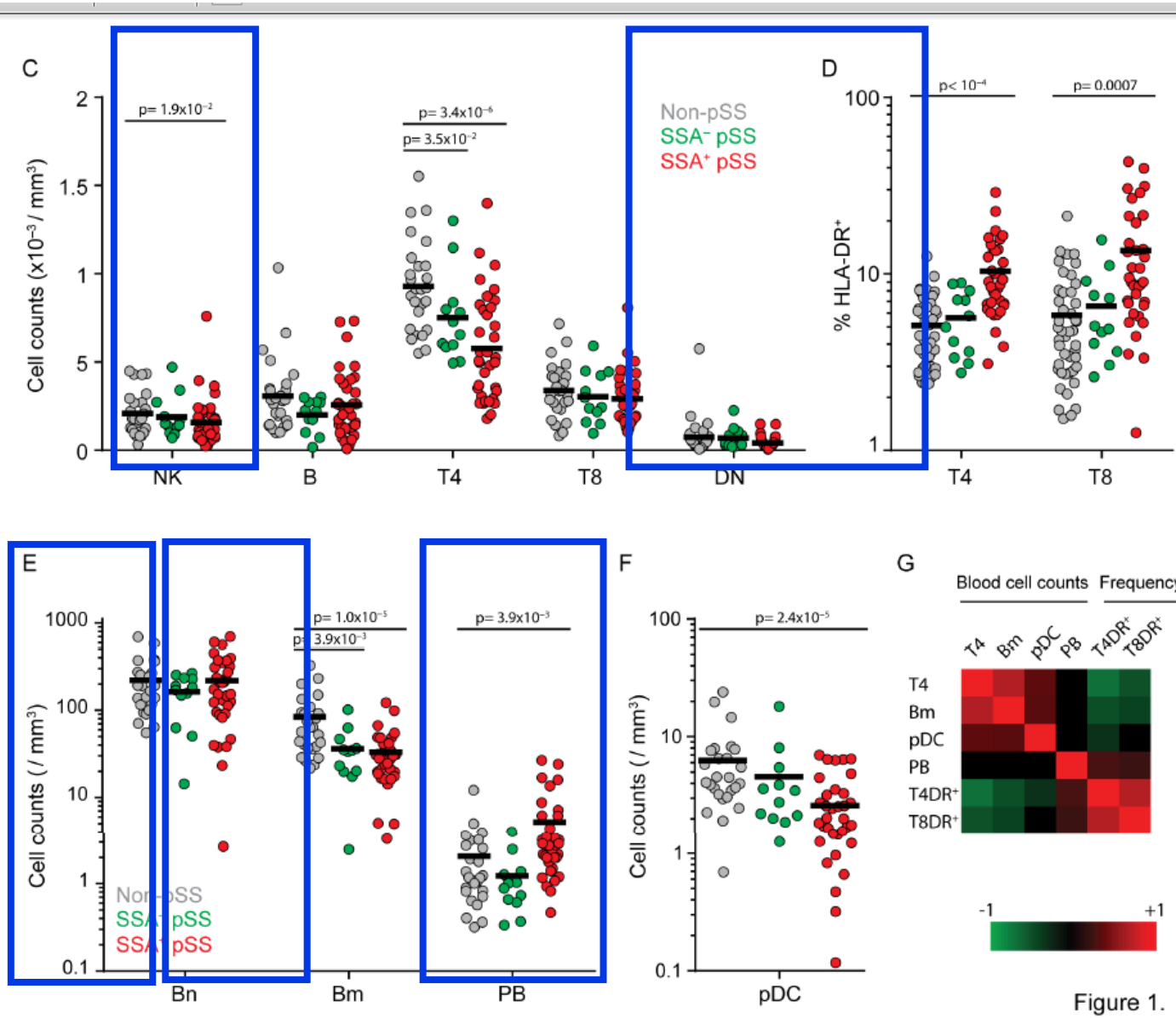
Mass spectrometry analysis of cellular subsets in blood and glands

- Blood: 49 pSS patients and 45 controls
- Salivary glands: 16 pSS patients and 13 controls



Mingueneau at al, JACI, 2016

A six-cellular subtypes signature in the blood

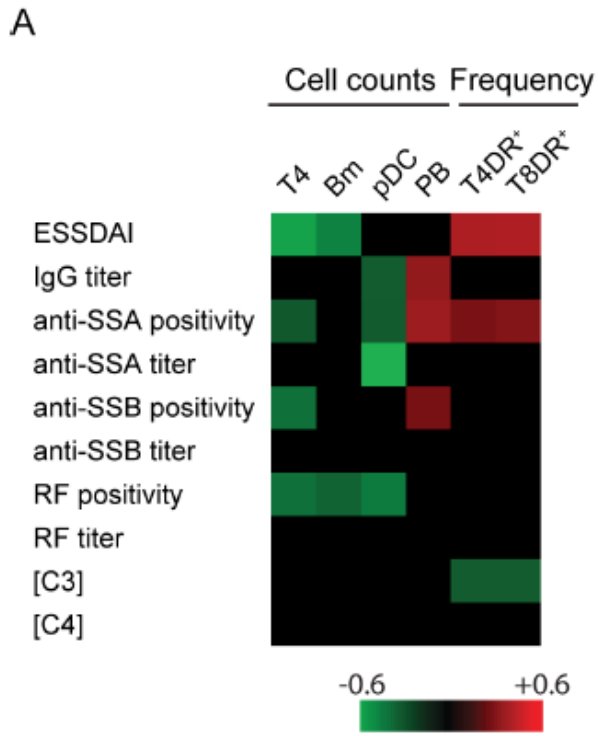


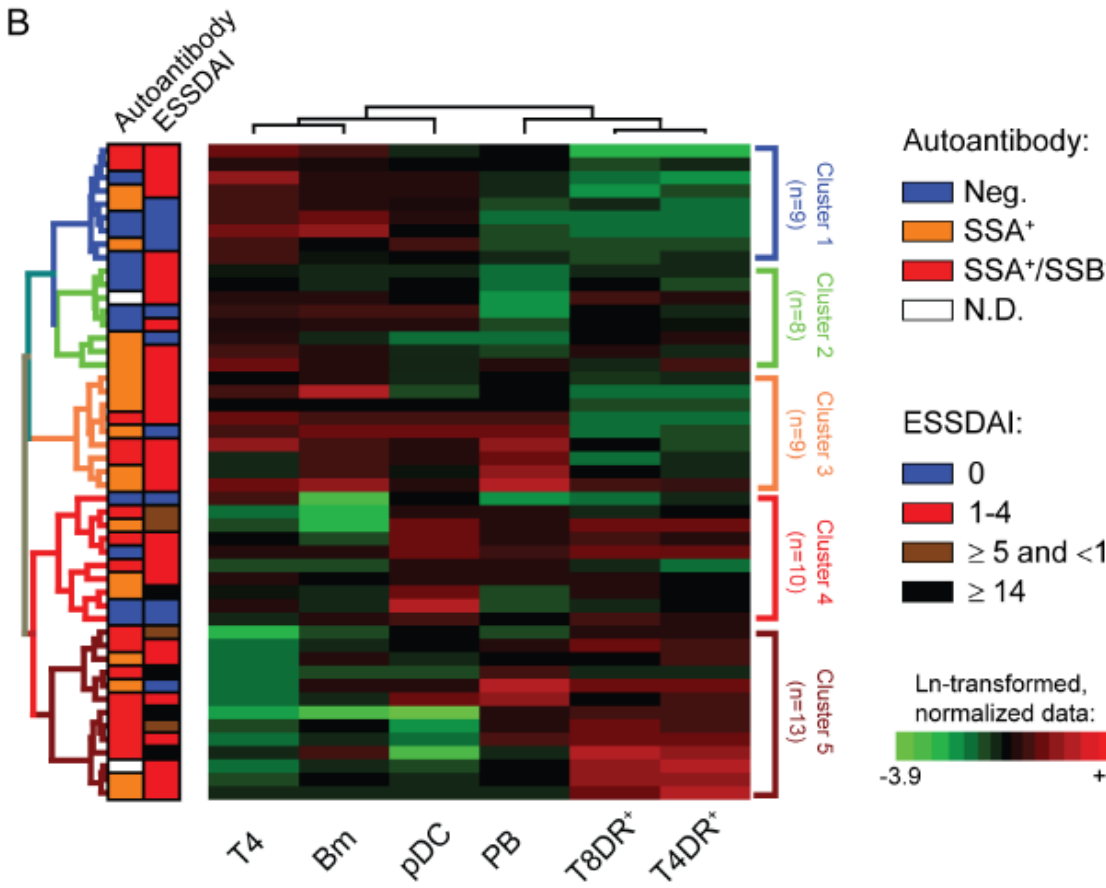
538

Figure 1.

Mingueneau at al, JACI, 2016

A six-cellular subtypes signature in the blood correlated with biomarkers and with activity



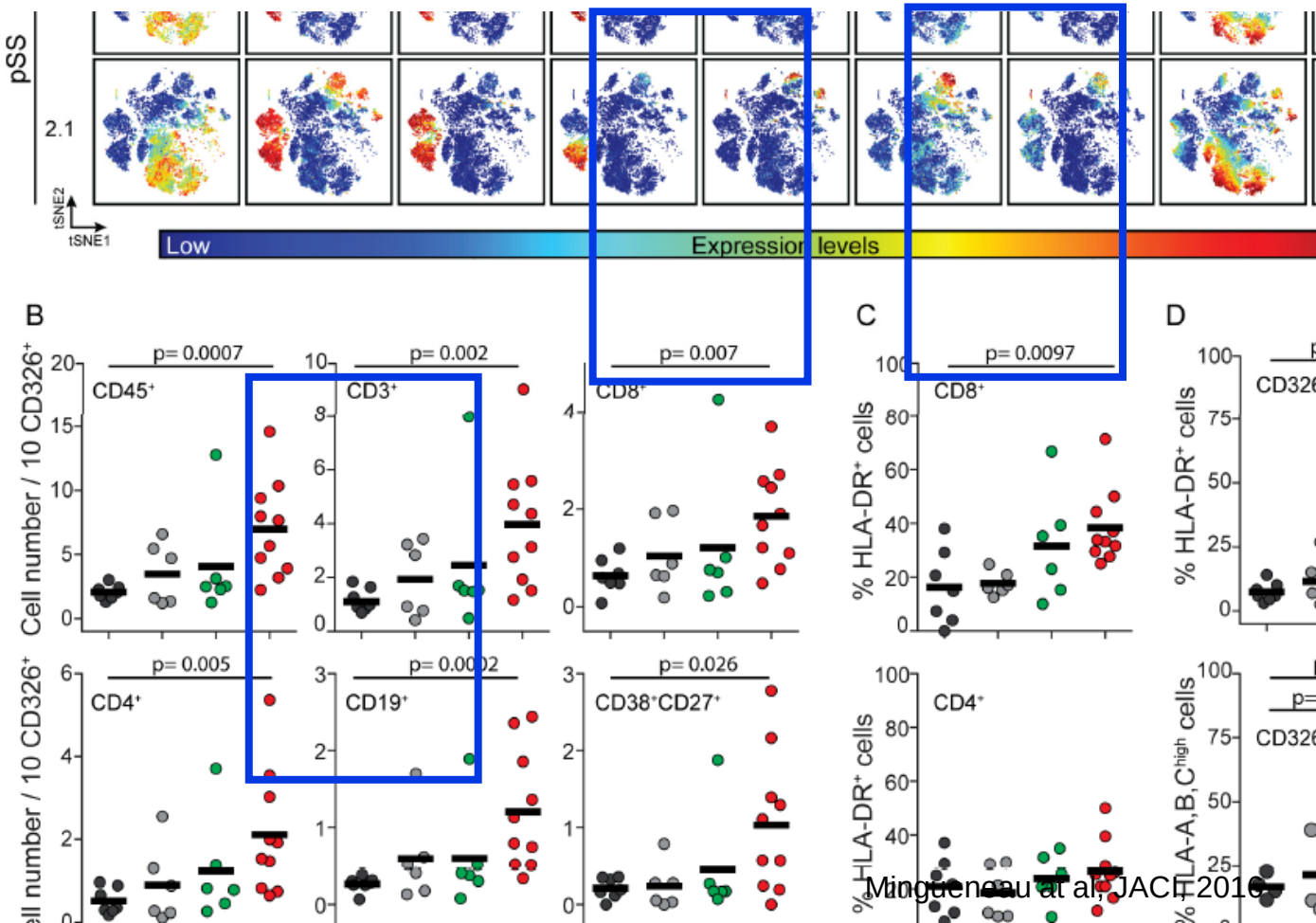


A three-cellular subtypes signature in salivary glands

Increase in: - DR+ CD8+ T cells,

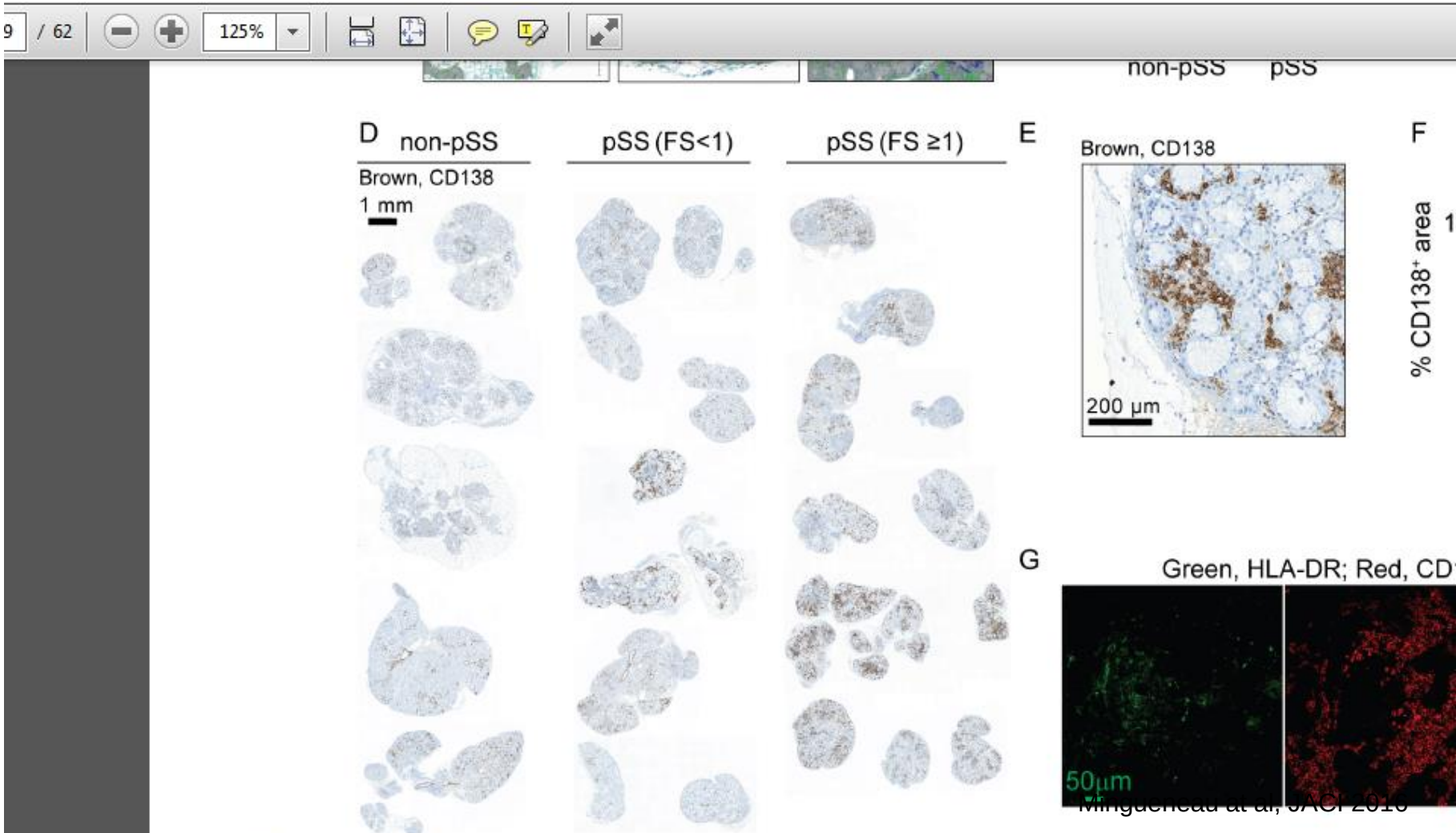
- Plasma-cells,

- DR+ Epithelial cells

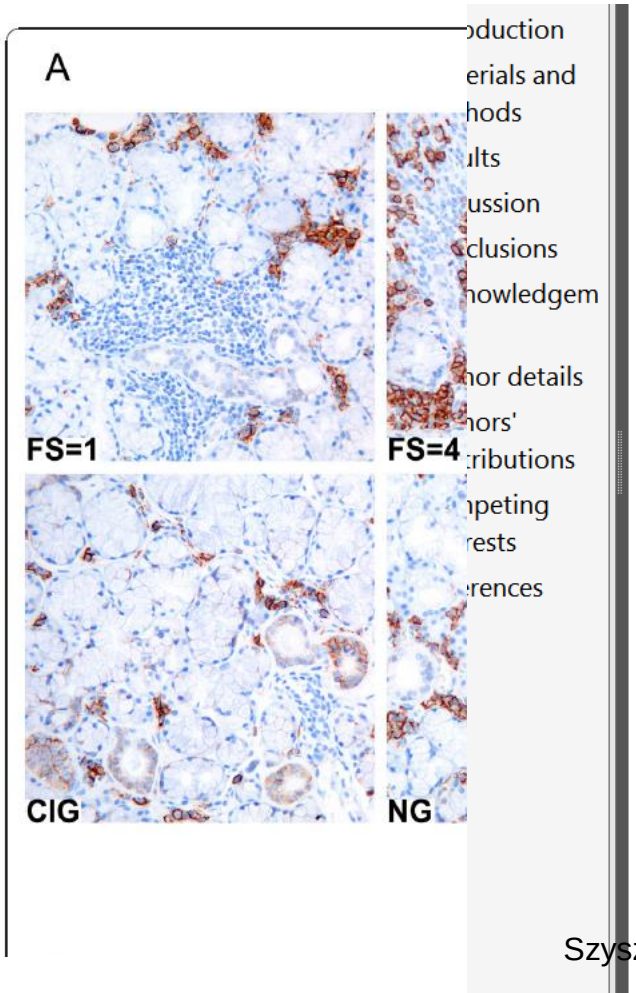


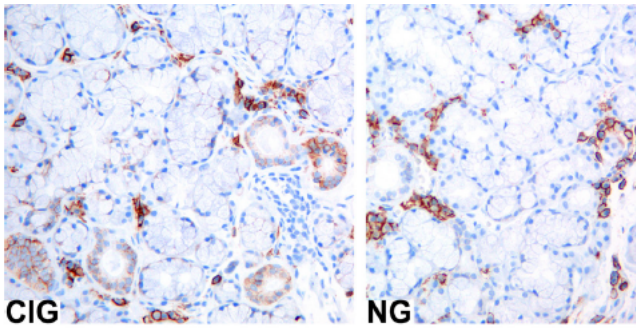
Mingueneau et al. JACI 2016

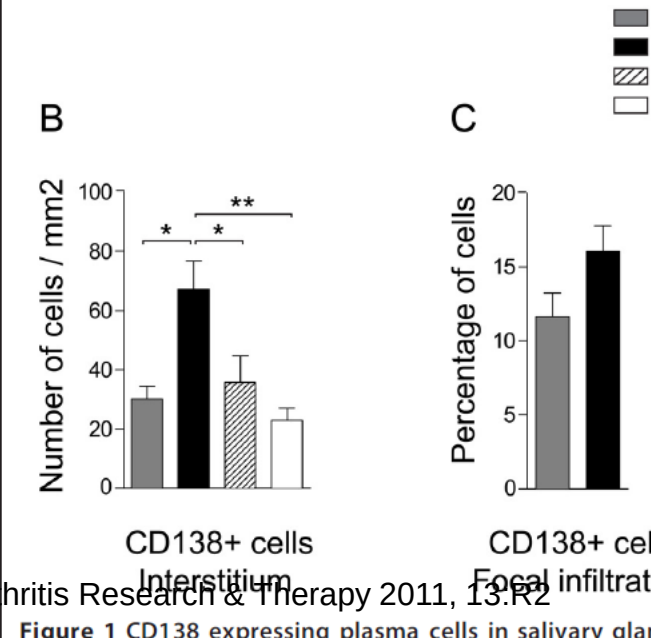
Plasma cells in the glands



Plasma cells in the glands

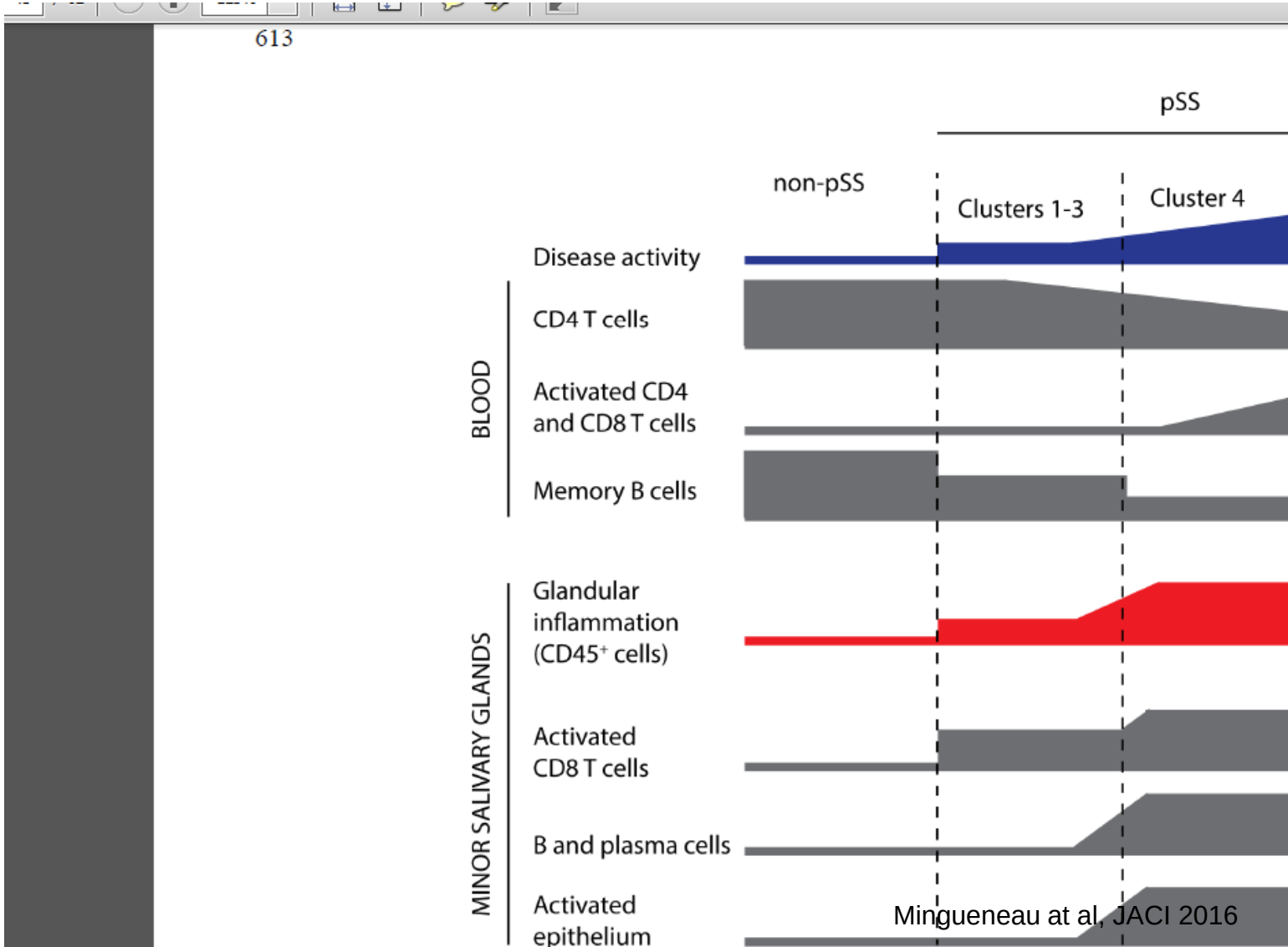






Szyszko et al. Arthritis Research & Therapy 2011, 13:R2

Correlations between blood and gland cellular subtypes and activity of the disease

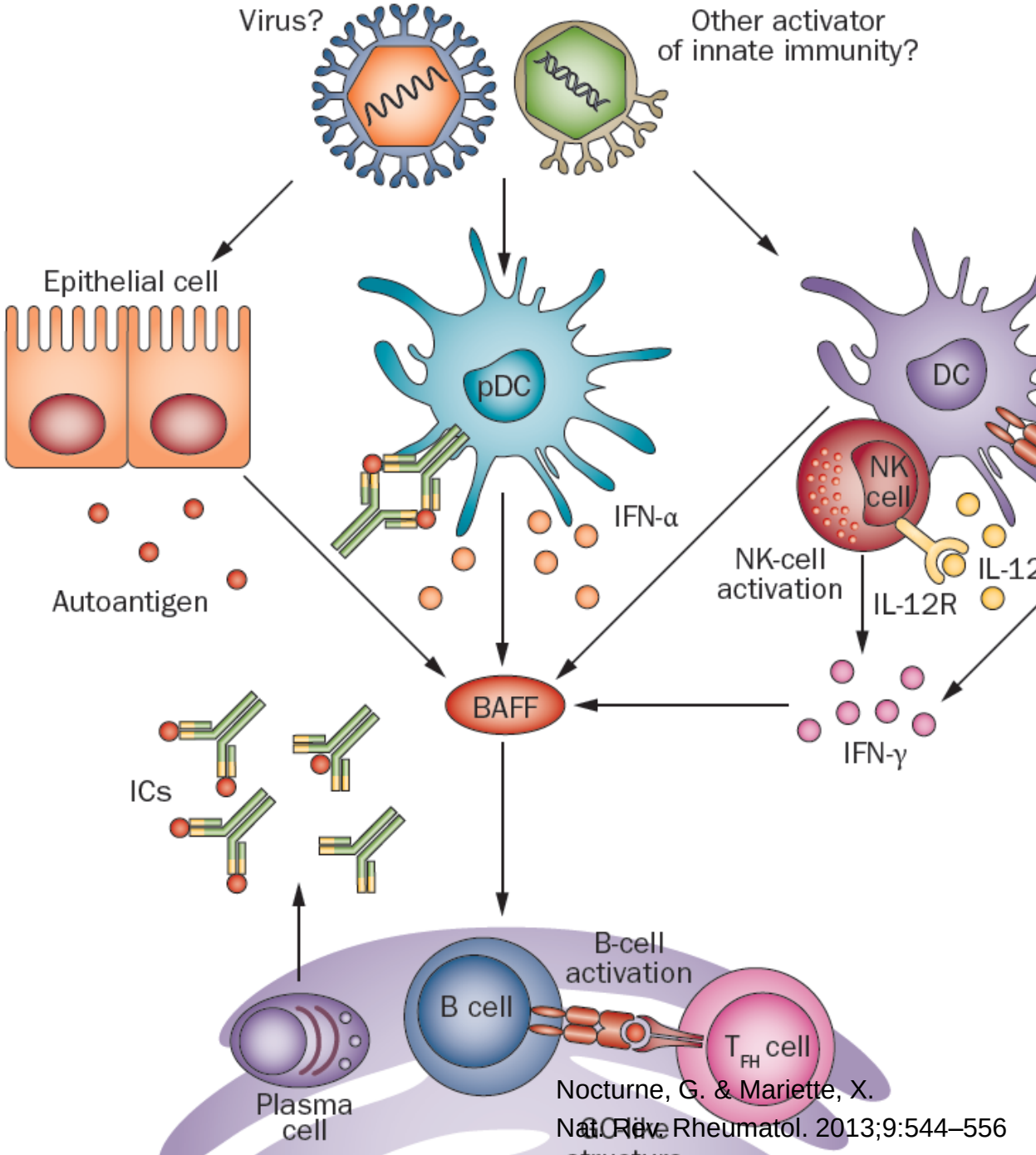


Mingueneau at al, JACI 2016

set of autoimmunity.[27]
the elusiveness of the
erexpression of some
has been overlooked,
d of searching for an
ease-associated activa-
ple, epigenetic abnor-
endogenous retroviral
activation of the type I

SS pathogenesis

stimulation of innate
lear factor κB (NFκB),
different cell types. In
om patients with pSS,
been associated with
ne regulators of NFκB
IF-α-induced protein 3
ective functioning of
k regulation of NFκB,
κBα), leads to develop-
e.[29] Furthermore, the
n association between



Nocturne, G. & Mariette, X.
Nat. Rev. Rheumatol. 2013;9:544–556

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- The type 2 IFN signature and its origin
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Lymphomas and Sjögren

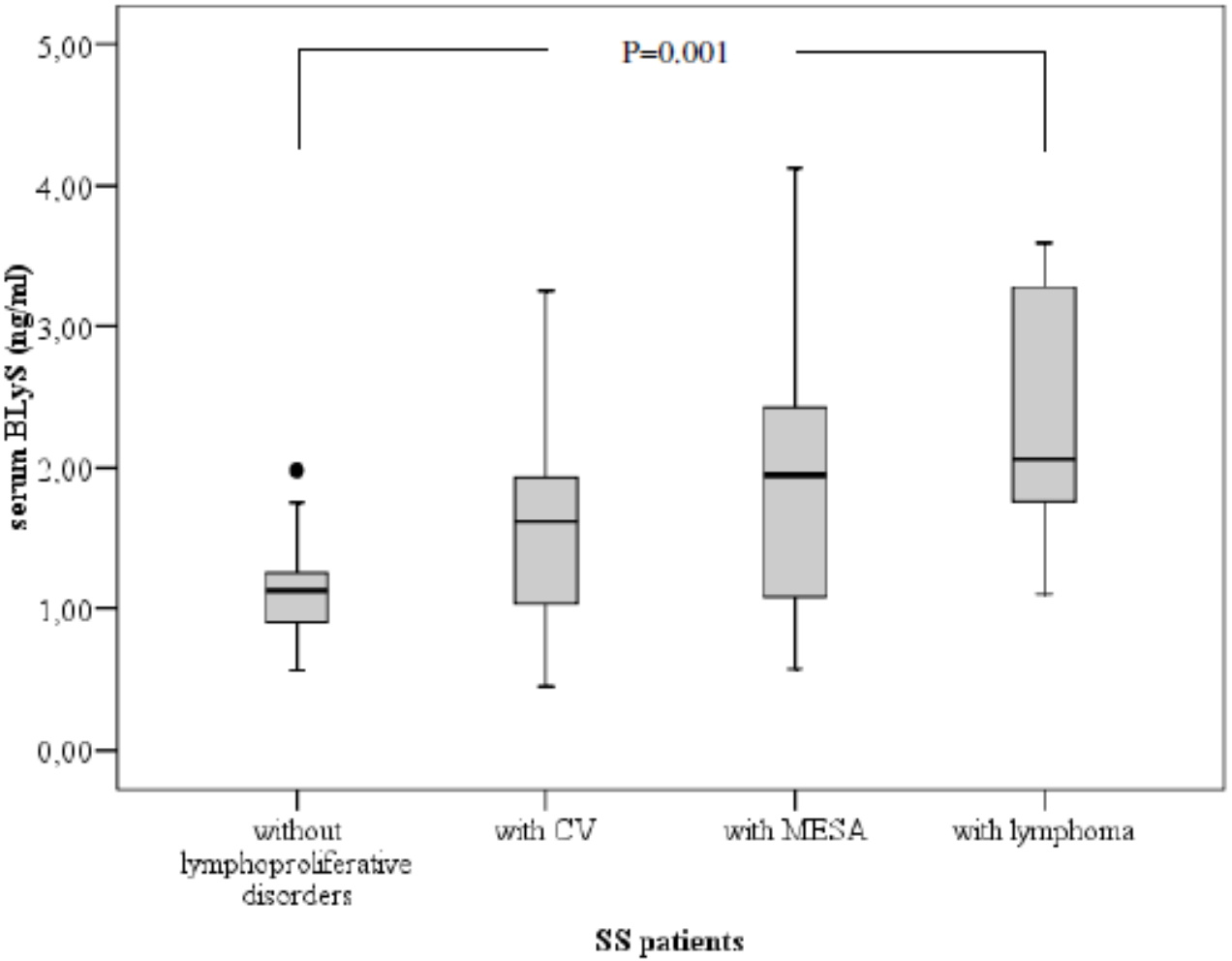
- 5% of patients with SS will develop lymphoma
- High rate of mucosal localizations
  - Kassan 1978: ?/7
  - Royer 1997: 12/16
  - Voulgarelis 1999: 27/33
  - Smedby 2006: 6/12
  - Theander 2006: 4/11
- Most frequently in salivary glands, the targets of autoimmunity
- MALT histology (marginal Zone lymphomas). Possibility of DLBCL (transformation of marginal zone lymphomas ?)
- Escape of autoimmune B cells

The classical predictive factors of lymphoma in SS

- **Parotid swelling**
- **Splenomegaly and adenopathy**
- **purpura**
- **Cryoglobulinemia**
- **Low C4**
- **CD4 T-cell lymphopenia**
- **Presence of ectopic germinal centers**
- **Focus score ≥ 3**

Review in Nocturne G, Mariette X. Br J Haematol. 2015 Feb;168(3):317-27

BAFF up-regulation in Sjögren's syndrome associated with lymphoproliferative disorders, higher ESSDAI score and B cell clonal expansion in the salivary glands



Quartuccio L, et al. Rheumatology (Oxford). 2012 Aug 9. [Epub ahead of print]

OPEN ACCESS Freely available online

PLOS ONE

Serum Levels of Beta2-Microglobulin and Free Light Chains of Immunoglobulins Are Associated with Systemic Disease Activity in Primary Sjögren's Syndrome. Data at Enrollment in the Prospective ASSESS Cohort

Jacques-Eric Gottenberg[1]*, Raphaèle Seror[2], Corinne Miceli-Richard[2], Joelle Benessiano[3], Valerie Devauchelle-Pensec[4], Philippe Dieude[5], Jean-Jacques Dubost[6], Anne-Laure Fauchais[7], Vincent Goeb[8], Eric Hachulla[9], Pierre Yves Hatron[9], Claire Larroche[10], Véronique Le Guern[11], [illegible], Alain Saraux[4], Damien Sene[15], Jean Sibilia[1], Olivier Vittecoq[16], Gaétane Nocturne[2], Philippe Ravaud[17], Xavier Mariette[2]*

1 Rheumatology Centre National de Référence des Maladies Auto-Immunes Rares, Institut National de la Santé et de la Recherche Médicale UMRS_1109, Fédération de Médecine Translationnelle de Strasbourg, Strasbourg University Hospital, Université de Strasbourg, Strasbourg, France, 2 Rheumatology, Bicetre Hospital, Institut National de la Santé et de la Recherche Médicale U-1012, Université Paris Sud, Assistance Publique des Hôpitaux de Paris, Paris, France, 3 Centre de Ressources Biologiques, Bichat Hospital, Assistance Publique des Hôpitaux de Paris, Paris, France, 4 Rheumatology, Brest University Hospital, Brest, France, 5 Rheumatology, Bichat Hospital, Assistance Publique des Hôpitaux de Paris, Paris, France, 6 Rheumatology, Clermont-Ferrand Hospital, Clermont-Ferrand, France, 7 Internal Medicine, Limoges Hospital, Limoges, France, 8 Rheumatology, Amiens University Hospital, Amiens, France, 9 Internal Medicine, Lille University Hospital, Lille, France, 10 Internal Medicine, Avicenne Hospital, Assistance Publique des Hôpitaux de Paris, Bobigny, France, 11 Internal Medicine, Cochin Hospital, Assistance Publique des Hôpitaux de Paris, Paris, France, 12 Rheumatology, Montpellier University Hospital, Montpellier, France, 13 Rheumatology, Rennes University Hospital, Rennes, France, 14 Rheumatology, Orléans Hospital, Orléans, France, 15 Internal Medicine, Lariboisière Hospital, Assistance Publique des Hôpitaux de Paris, Paris, France, 16 Rheumatology, Rouen University Hospital, Rouen, France, 17 Center of Clinical Epidemiology, Hotel Dieu Hospital, Assistance Publique des Hôpitaux de Paris, Institut National de la Santé et de la Recherche Médicale U378 University of Paris Descartes, Faculty of Medicine, Paris, France

- ASSESS: prospective cohort of 395 patients with pSS
- 18 patients with history of lymphoma (2 of them received rituximab in the past 12 months)

Table 4. Characteristics associated with a history of lymphoma.

Journal of Autoimmunity xxx (2013) 1–10

Contents lists available at SciVerse ScienceDirect

Journal of Autoimmunity

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

B-cell activating factor genetic variants in lymphomagenesis associated with primary Sjogren's syndrome

Adrianos Nezos [a,1], Aristea Papageorgiou [b,1], George Fragoulis [b], Dimitrios Ioakeimidis [c], Michael Koutsilieris [a], Athanasios G. Tzioufas [b], Haralampos M. Moutsopoulos [b], Michael Voulgarelis [b,2], Clio P. Mavragani [a,*,2]

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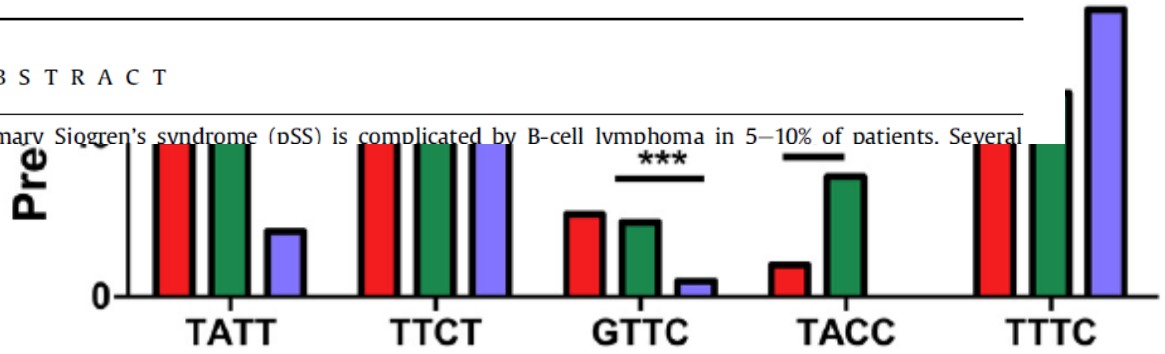
ARTICLE INFO

Article history:

ABSTRACT

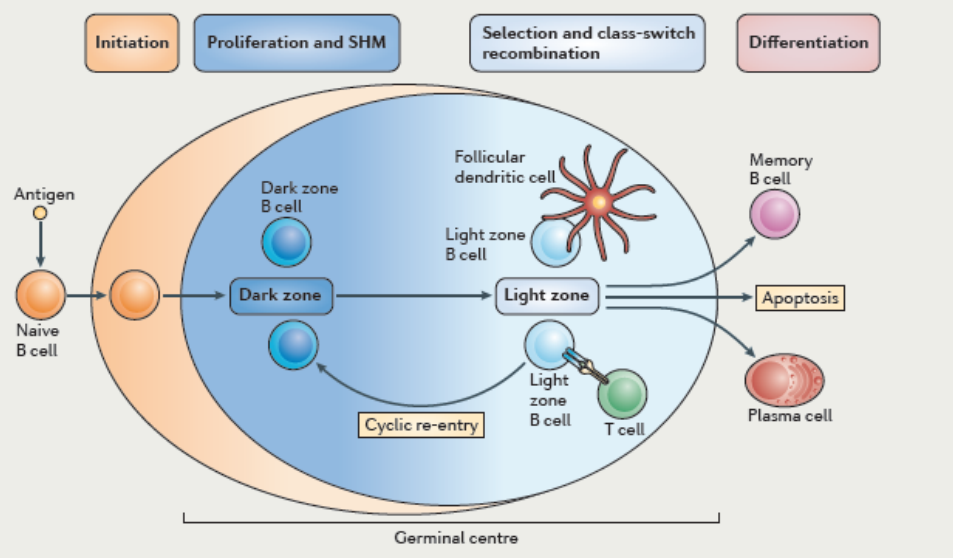
Primary Sjogren's syndrome (pSS) is complicated by B-cell lymphoma in 5–10% of patients. Several

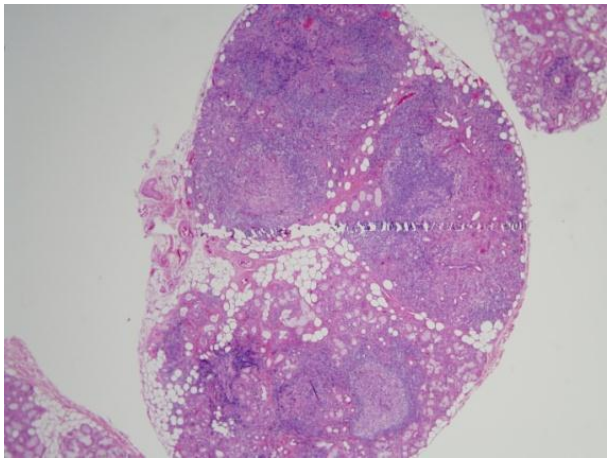


- BAFF-R polymorphism

Nezos A et al. J Autoimmunity 2013
Mavragani et al ISSS Bergen 2015, Poster #S10.10

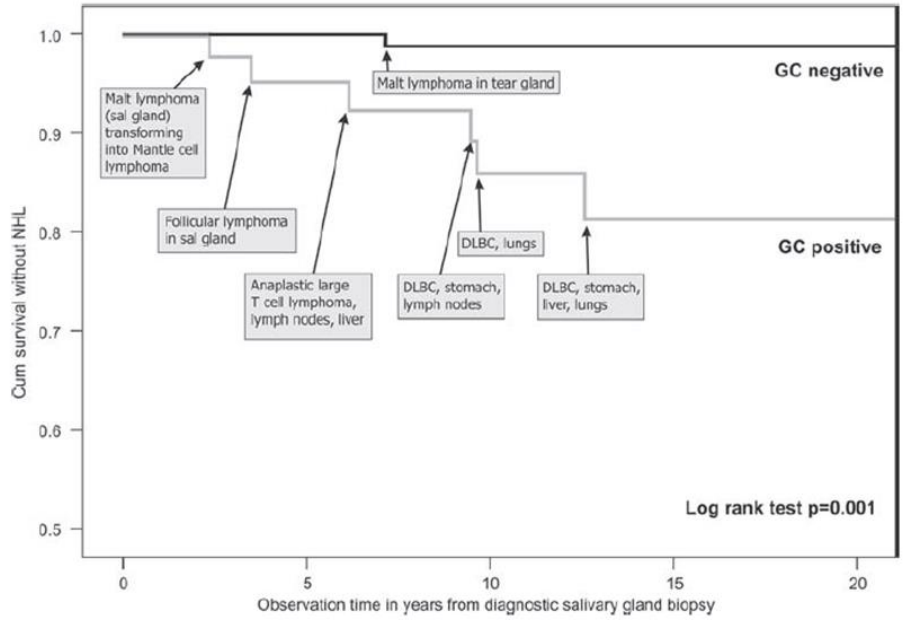
Presence of ectopic GC like structures predicts lymphoma





GC like structures in HES MSGB from a pSS patient

In salivary glands from pSS patients: ectopic GC are functional and predict lymphoma occurrence



Amft et al. A§R, 2001

Bomabardieri et al. JI, 2012

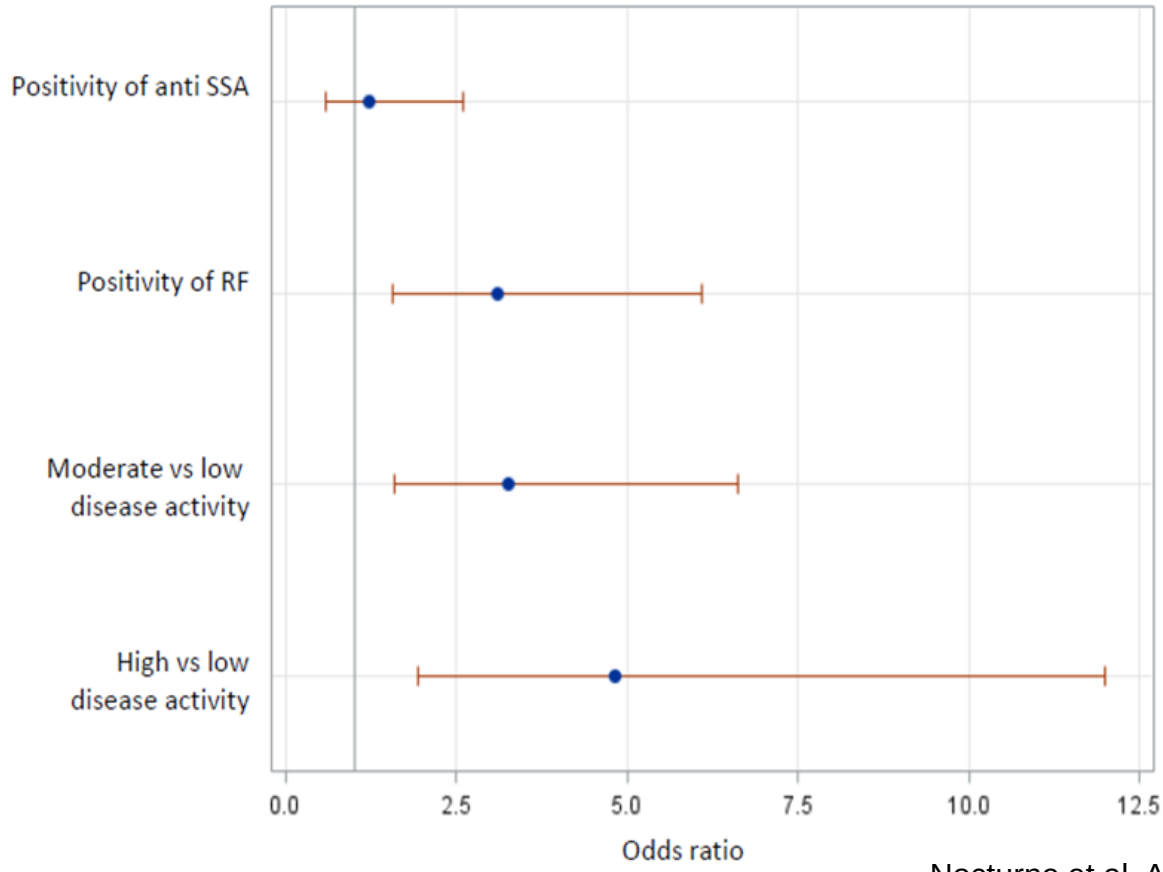
Salomonsson et al. A&R, 2003

Theander et al. Ann Rheum Dis. 2011

Basso K, Dalla-Favera R. Nat Rev Immunol 2015

Rheumatoid factor and activity of the disease are associated with lymphoma

- 77 patients with pSS and lymphoma compared to 154 patients with pSS matched on age and disease duration



Nocturne et al. Arthritis Rheum, in press

Autoantibody activity of lymphomas complicating Sjögren

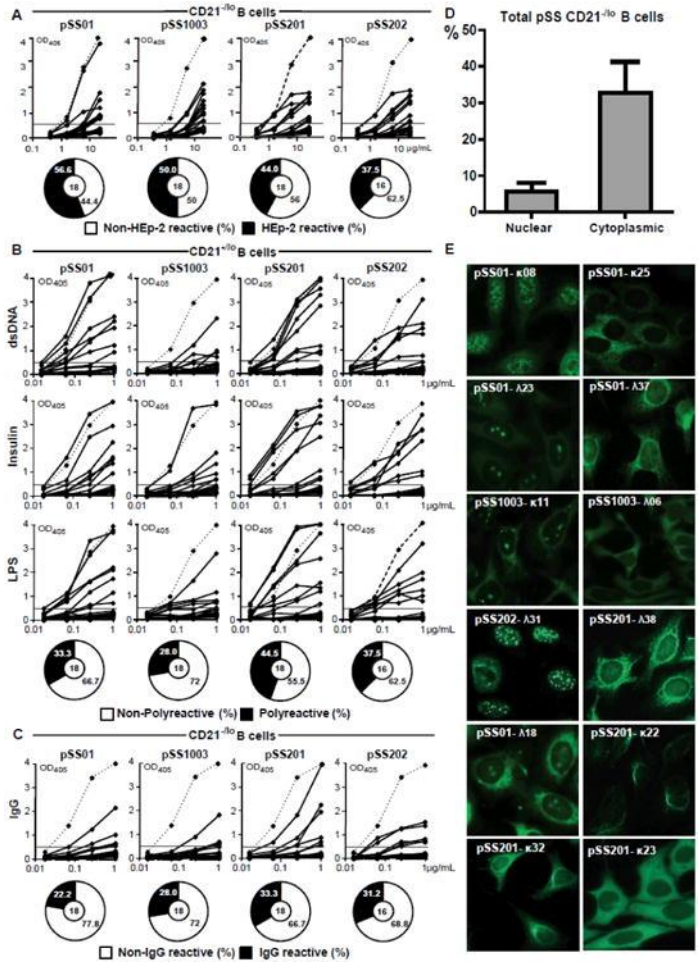
- Demonstration of a rheumatoid factor activity of membrane Ig in 2 cases of lymphoma complicating Sjögren's syndrome
- Homology of BCR from salivary MALT lymphoma with rheumatoid factor (RF)

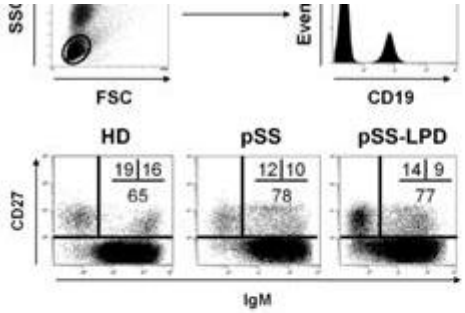
MALT localization	n	t (11, 14)	n	Homology CDR3-RF
Salivary glands	114	2 (2%)	32	13 (41%)
Stomach	209	50 (24%)	45	8 (18%)
Lung	113	47 (42%)	19	0
Others	ND	ND	4	0

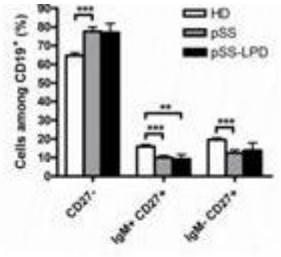
Martin, Arthritis Rheum 2000, 43, 908

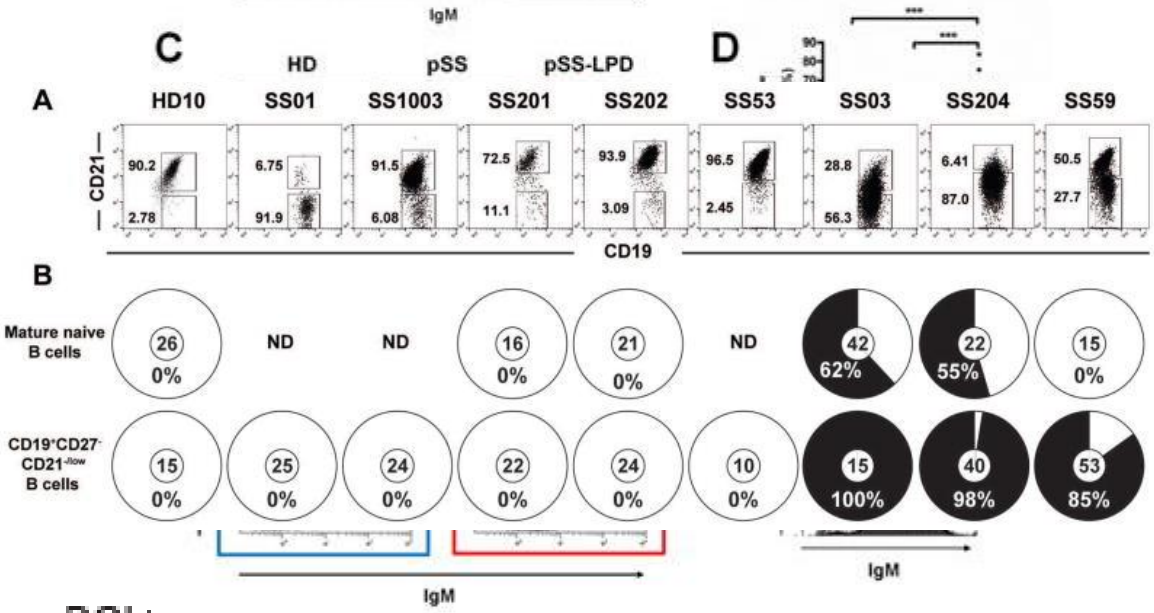
Bende et al. J Exp Med 2005

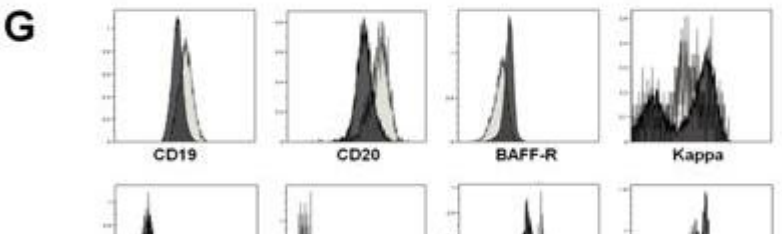
CD21 low and lymphoproliferation











Germinal and somatic genetic variations of *TNFAIP3* (A20) in lymphoma complicating primary Sjögren's syndrome

Study of 44 patients with pSS + Lymphoma

SNP	OR	95% CI	P
rs13192841	0.988	(0.52 - 1.87)	0.9703
rs2230926	**3.359**	**(1.34 - 8.42)**	**0.009763**
rs6922466	0.8597	(0.42 - 1.76)	0.6784

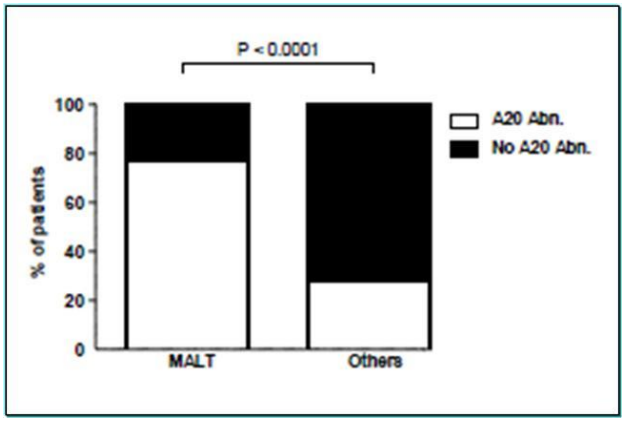
Association of A20 SNP with pSS + Lymphoma

20 patients pSS + lymphoma

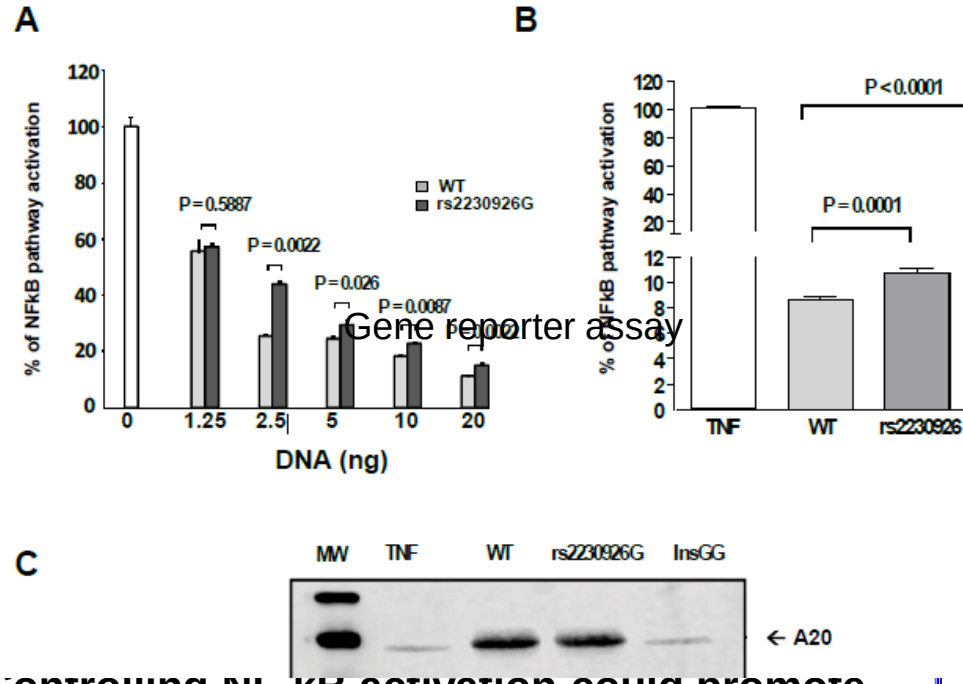
8 without any A20 mutation

6 with A20 germline mutations potentially functional

Exome sequencing of A20 in germline and lympho



A20 in MALT lymphoma

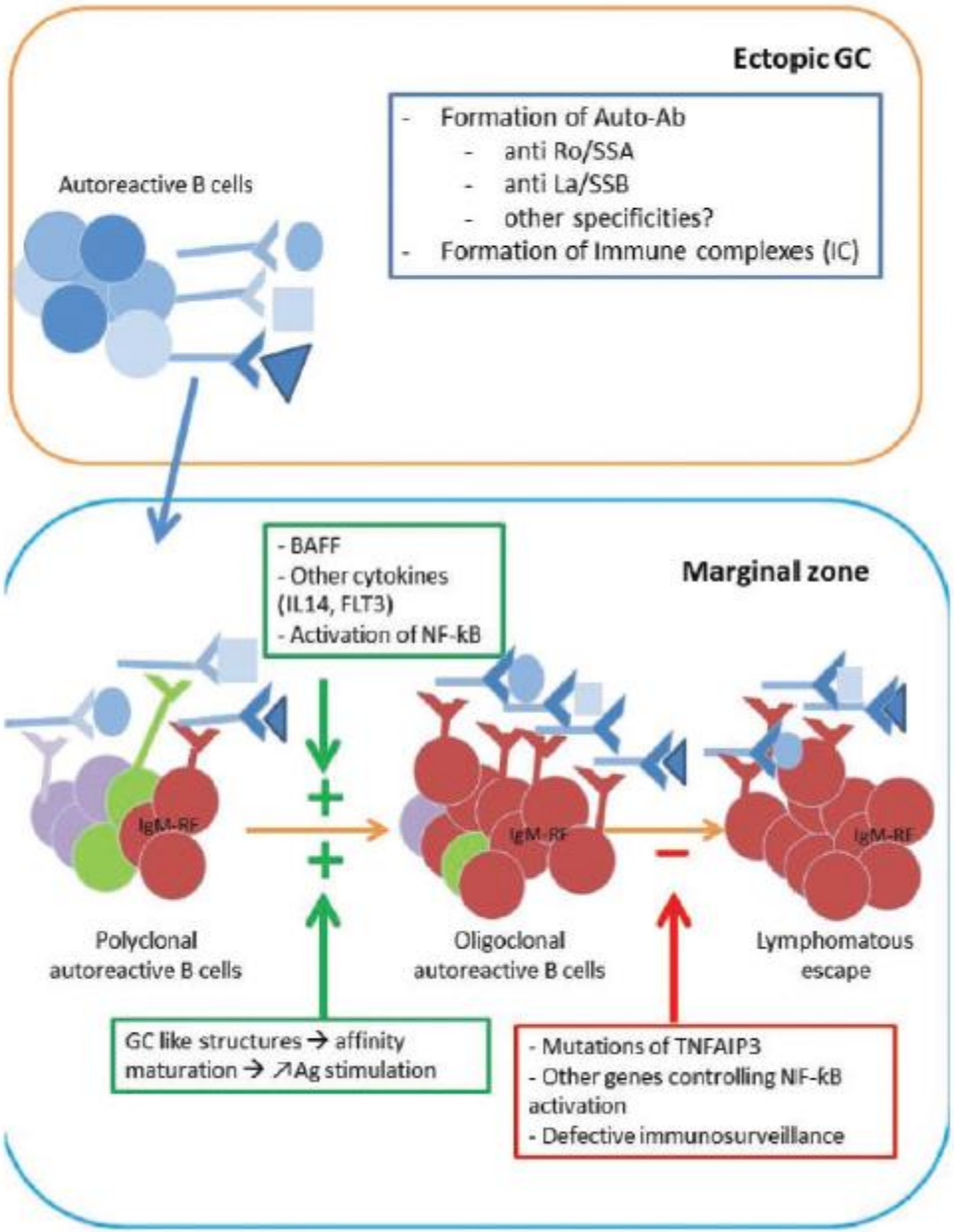


Gene reporter assay

Controlling NF-kB activation could promote lymphomagenesis in the context of auto-immunity

Nocturne al, Blood, Blood 2013 Oct 24. [Epub ahead of print]

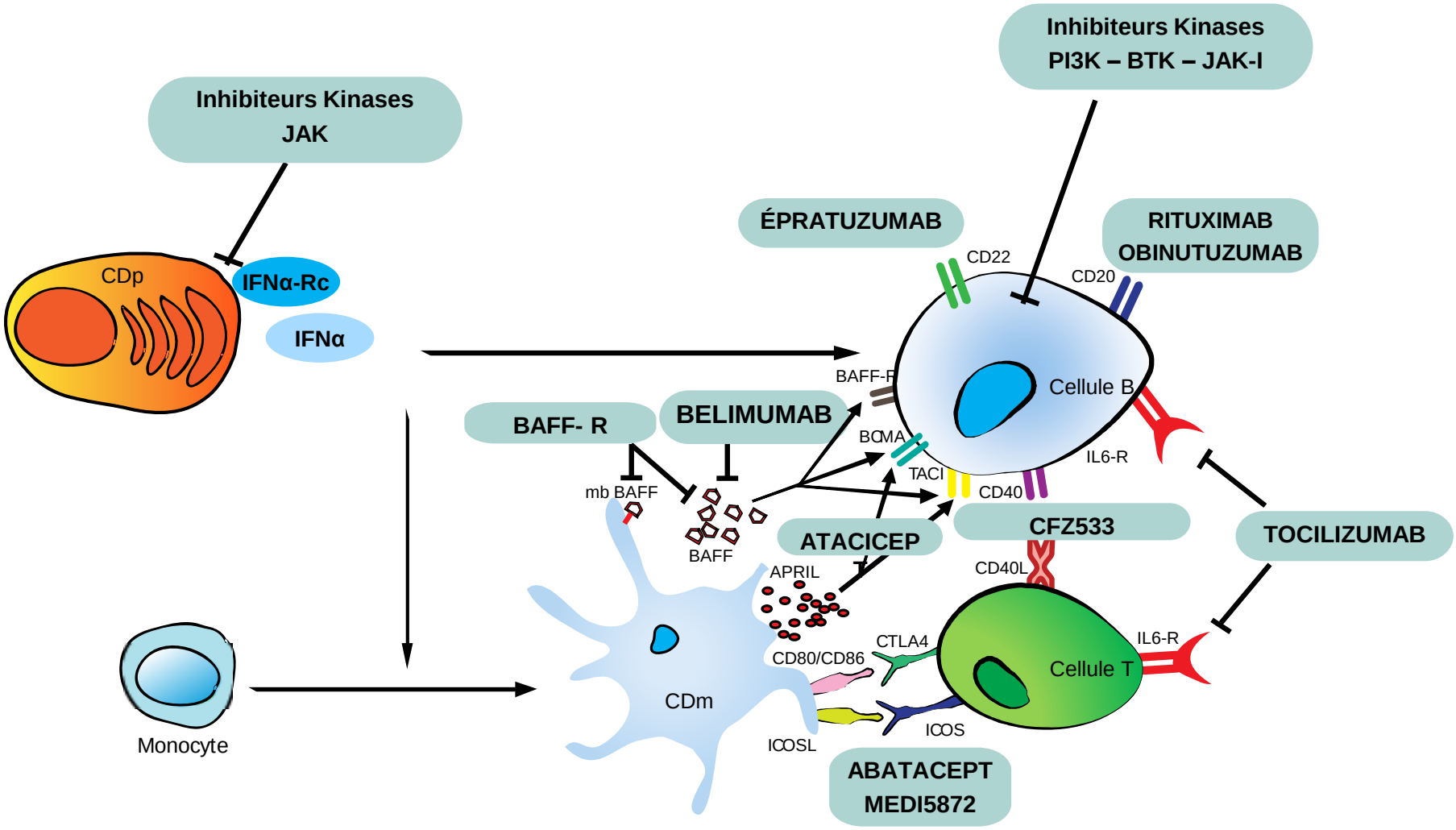
The 2019 proposed scenario for lymphomagensis in pSS



Nocturne et al. Rheumatology, 2019

THERAPEUTIC INTERVENTIONS?

Les biomédicaments : pistes



Essais en cours dans le Sjogren

Study	Drug	Inclusion criteria	Primary endpoint	Estimated completion
EUCTR2014-004523-51-GB	UCB5857 Pi3kinase inhibitor	**ESSDAI ≥ 5** Anti-SSA/SSB Sal. flow>0	**ESSDAI change W12**	Dec 2017
NCT01782235 ETAP	Tocilizumab Phase 3	**ESSDAI ≥ 5** Anti-SSA/SSB	**Improvement ESSDAI ≥3**	Jul 2018
NCT02149420	*VAY 736*, anti-BAFF-R m Ab	**ESSDAI ≥ 6** ANA (≥ 1:160) Anti-SSA/SSB Sal. flow>0	**ESSDAI change W12**	Nov 2019
NCT02067910 ASAPIII	Abatacept Phase 3	**ESSDAI ≥ 5** Disease duration ≤ 7 Positive parotid biopsy	**ESSDAI W24**	Dec 2018
NCT02334306	AMG 557/MEDI5872, anti-ICOS-L mAb	**ESSDAI ≥ 6** Anti-SSA/SSB and IgG> 16 g/L or RF +	**ESSDAI change D99**	Sept 2018
NCT03100942	Filgotinib et Tirabrutinib	**ESSDAI ≥ 5** **Anti-SSA/SSB**	**Critère composite patient et items biologiques à S12**	Dec 2019

Sjögren's syndrome: from Pathophysiology to treatment. Projects

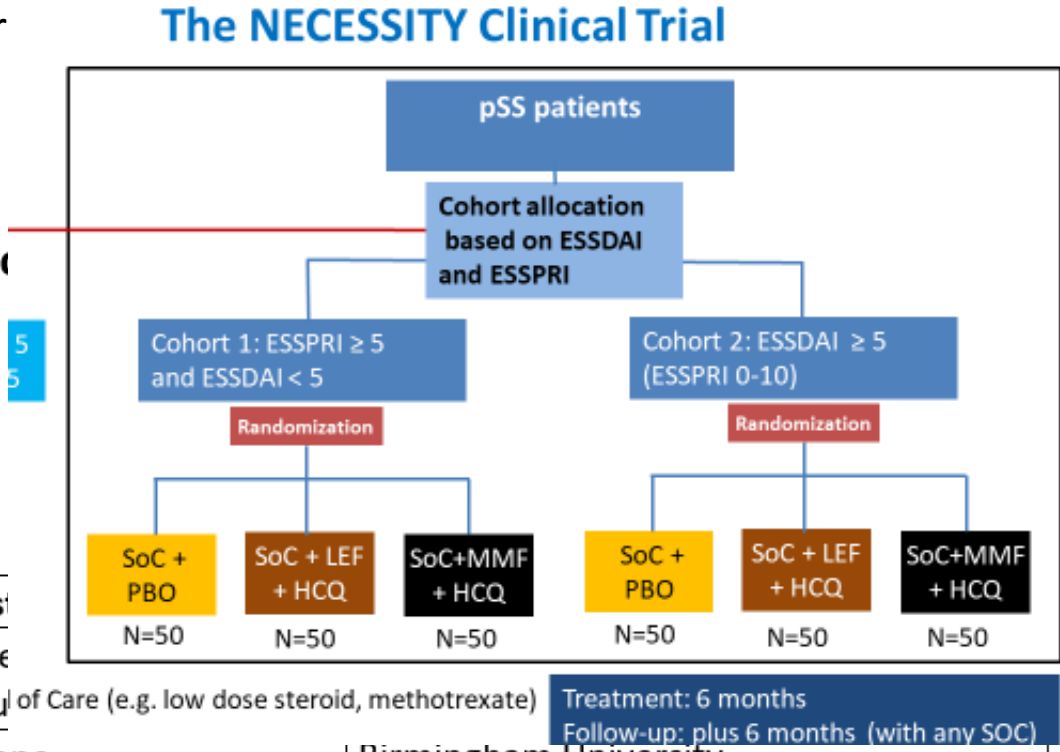
Towards a better stratification of the patients

Coordinator: X Mariette

Objectives

- To develop new clinical endpoints for use in future clinical trials
- To identify discriminative biomarkers for stratification of pSS patients
- To set-up and perform an original multi-arm multi-stage (MAMS) clinical trial to validate the newly defined pSS endpoints and the identified biomarkers.

Title: NEw Clinic



Part.	Principal Inves
1	Xavier Mariette Gaétane Noctu
2	Francesca Barone Birmingham University

Acknowledgements

- INSERM U1184, Paris-Sud university. Autoimmunity Group
  - Xavier Mariette,
  - Raphaele Seror
  - Saida Boudaoud
  - Bineta Ly
  - Elodie Riviere
  - Juliette Pascaud
  - Audrey Paoletti
  - Anastasia Dupré
  - Julien Rohmer
  - Thierry Lazure,
  - Nathalie Ba,
- Centre de Reference Paris Sud
  - Rakiba Belkhir, Julien Henry, Elisabeth Bergé, Christine Lepajolec,
- Patients from Bicêtre, Lille, Le Mans and from the ASSESS cohort (and all investigators)
- Clinical studies
  - Jean Sibilia
  - Jacques-Eric Gottenberg
  - Eric Hachulla
  - Xavier Puéchal
  - Philippe Ravaud
- Genetics and epigenetics
  - Jorg Tost (Génopole Evry – CNG)
  - Lindsey Criswell (UCSF – USA)
  - Kathy Moser Oklahoma, (USA)
- Supports:
  - INSERM Clinical Research Network
  - FRM
  - ANR 2010-2014
  - Société Française de Rhumatologie
  - Arthritis foundation
  - PHRC 2006, 2007, 2010
  - Human Genome Science
  - Biogen