Immunology Bootcamp – Pathways in SLE: - IFN, IL-17, CD40L, BAFF, CNI…

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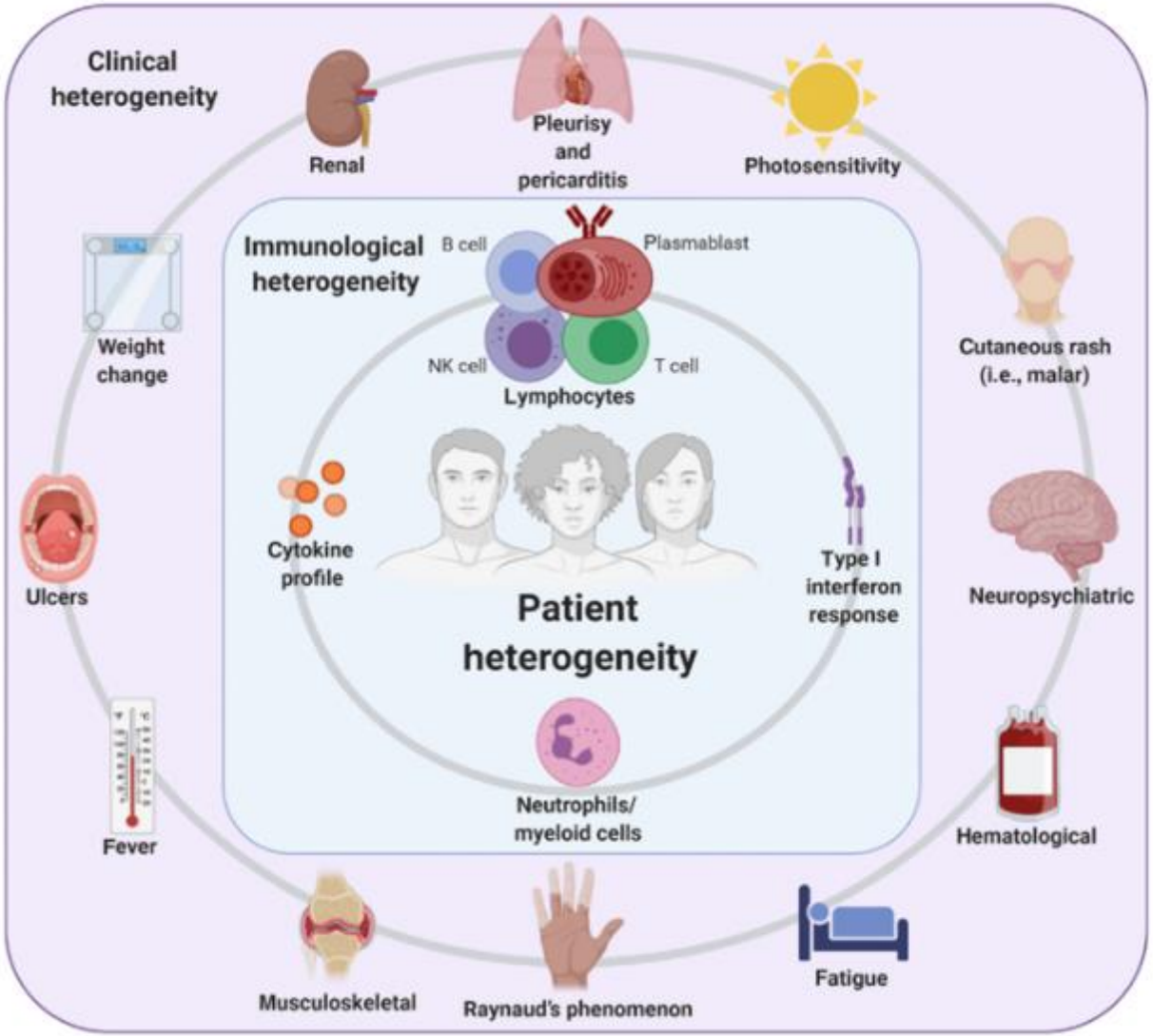
Conflict(s) of interest disclosure…

- I have received honoraria and research funding from Abbvie, Astra Zeneca, BMS, Causeway Therapeutics, Celgene, Evelo, Cabaletta, Janssen, Novartis, Lilly, Pfizer, BI, Roche and UCB
- I have received academic funding from Versus Arthritis, Wellcome Trust and MRC

Learning Objectives

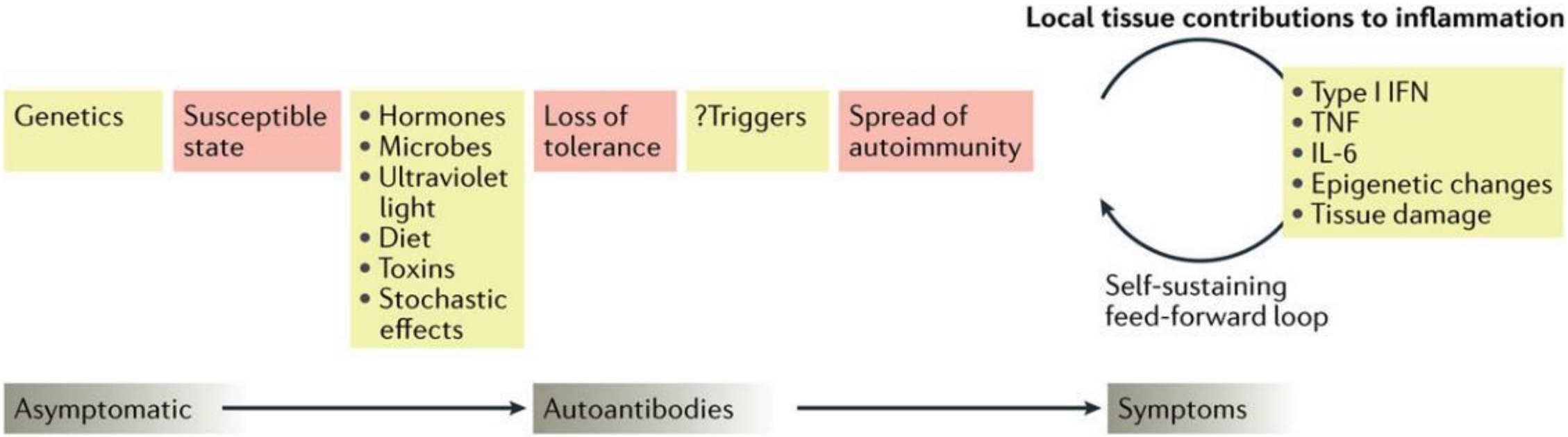
- Explore and be able to explain the basic properties and effector biology of the major pathways currently implicated in SLE pathogenesis

SLE is clinically heterogeneous – so too its immunology?



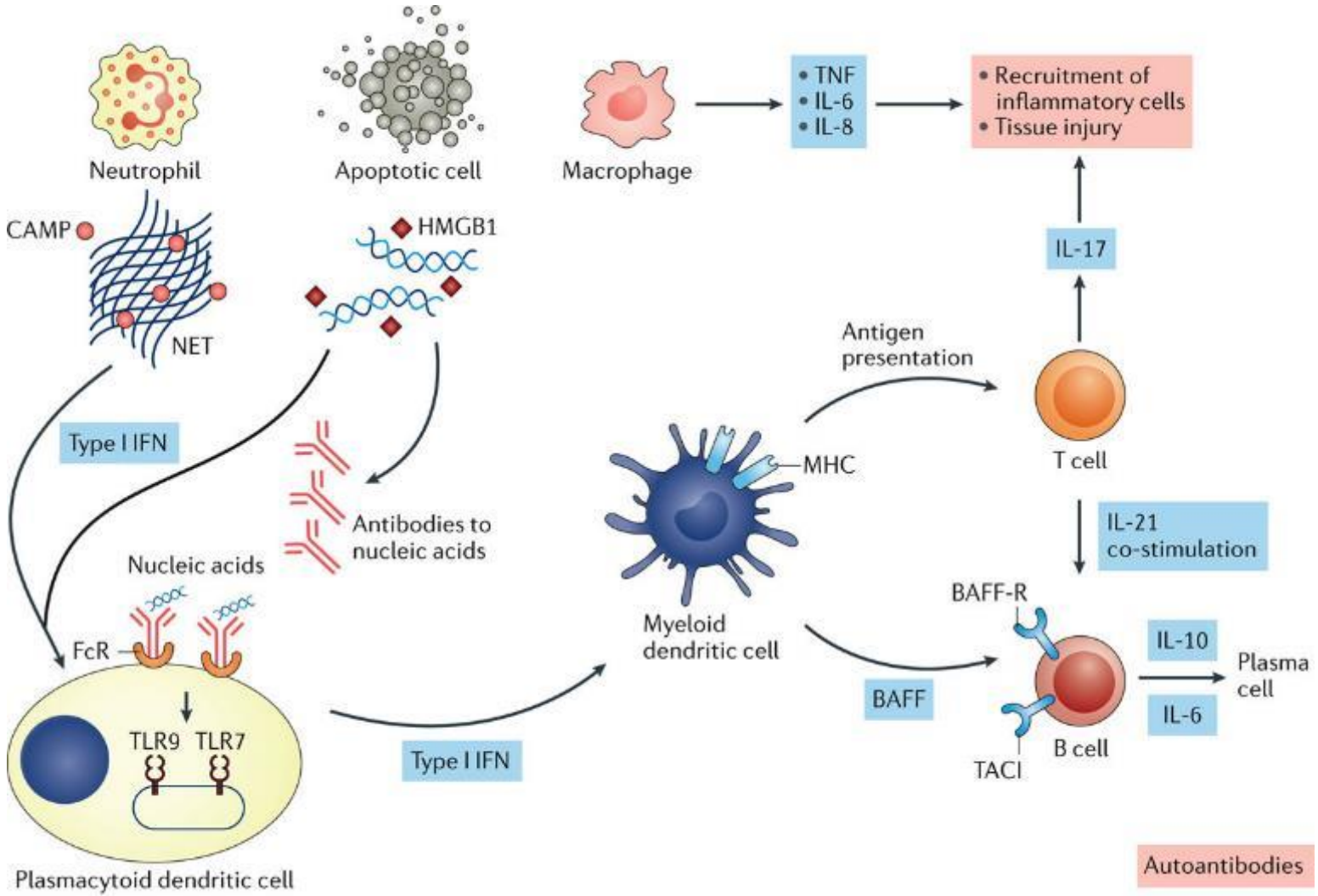
Allen M et al Trends in Molecular Medicine, February 2021, https://doi.org/10.1016/j.molmed.2020.09.009

A focus on SLE pathogenesis



Tsokos, G. C. *et al.* (2016) New insights into the immunopathogenesis of systemic lupus erythematosus *Nat. Rev. Rheumatol.* doi:10.1038/nrrheum.2016.186

Understanding the biology of SLE…



Tsokos, G. C. *et al.* (2016)*Nat. Rev. Rheumatol.* doi:10.1038/nrrheum.2016.186

Polling Question #1

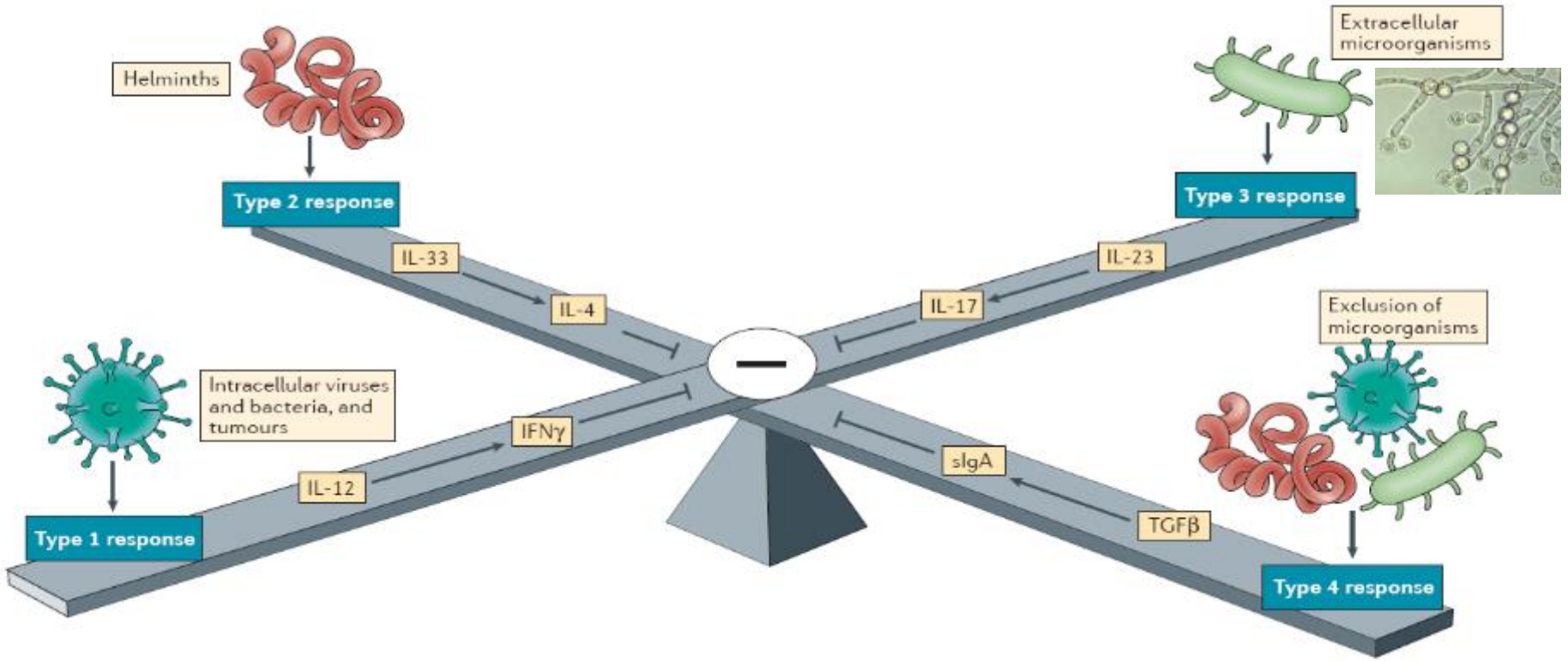
The current state of the art identifies which of the following as the dominant cytokine effector pathway in SLE?

A. BAFF
A. IL-17
B. Type 1 interferon
C. none of the above

To understand the contribution(s) of distinct mediators…

- Major mediators in the patho-immune responses (the actors)
  - Cytokines as general regulators
    - Type 1 IFN
    - IL-17 family
    - BAFF
    - JAKs???
  - Intrinsic Cellular regulators
    - Checkpoint regulation (CD40/CD40L)
    - Calcineurin dependent
- Pathogenesis in tissues (the venues & screen sets)
  - All tissues are not created identical

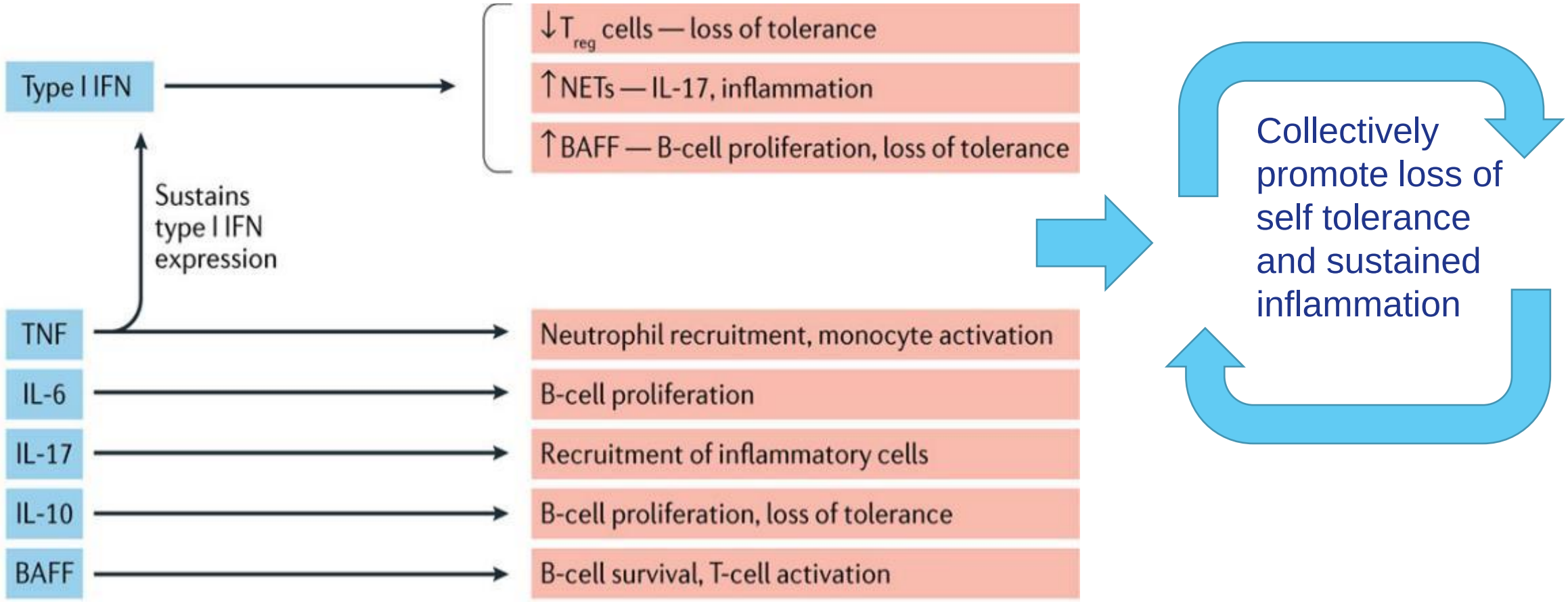
Recall a fundamental immunologic property - “Immunity by equilibrium”



- “The healthy immune system is always active and in a state of dynamic equilibrium between **antagonistic** types of response”
- “Alteration of the microbial environment leads to immune disequilibrium, which determines tolerance, protective immunity, and inflammatory pathology”

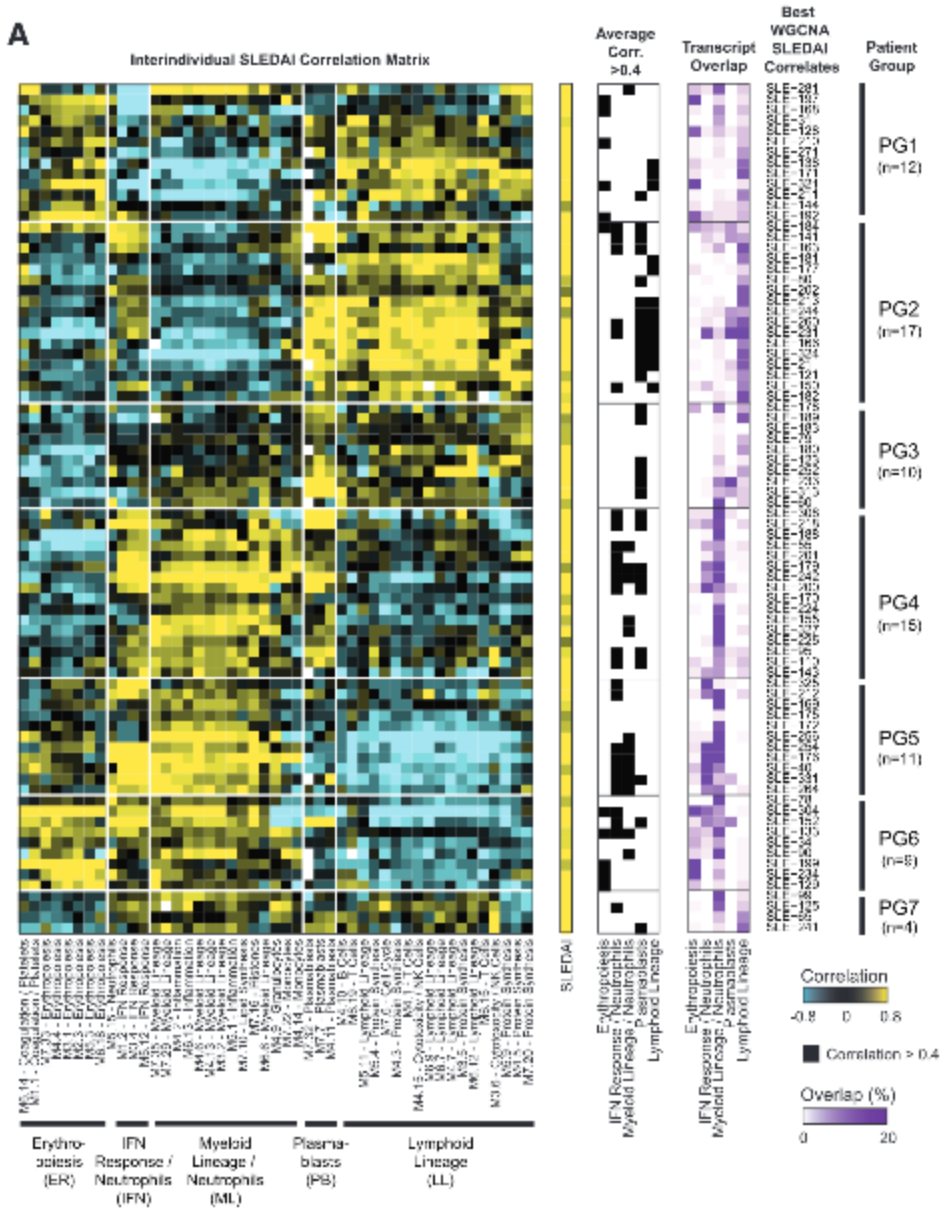
Eberl G. Nat Rev Immunol 2016;16:524–32

Recall a fundamental immunologic property - “Cytokines as hormones”



Tsokos, G. C. *et al.* (2016) *Nat. Rev. Rheumatol.* doi:10.1038/nrrheum.2016.186

Is SLE actually one disease?



‘Lupus is so diverse’…

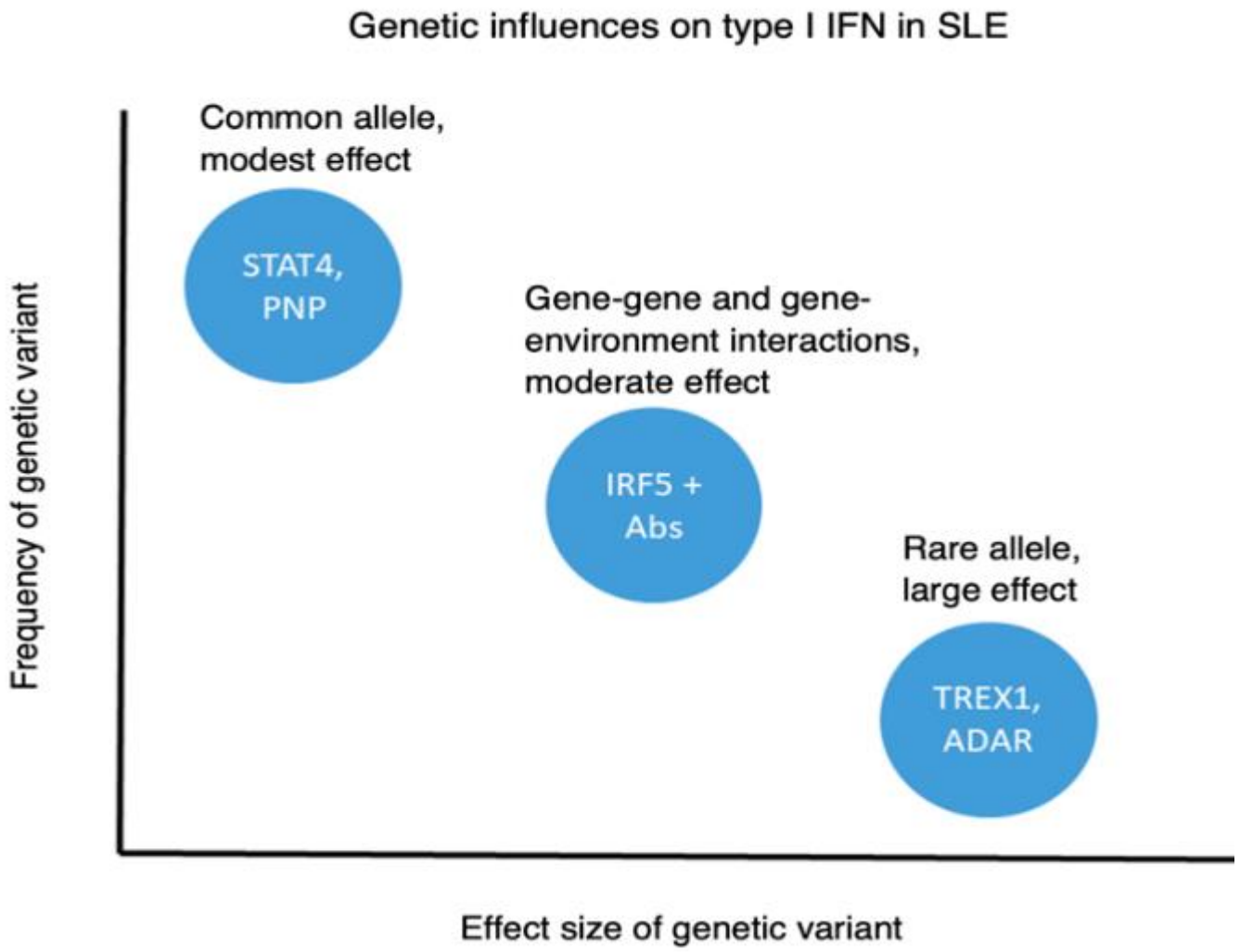
Is it?

Questions:

- Is our clinician-based classification just wrong?
- Should be we studying ‘acquired autoimmune interferonopathy’?

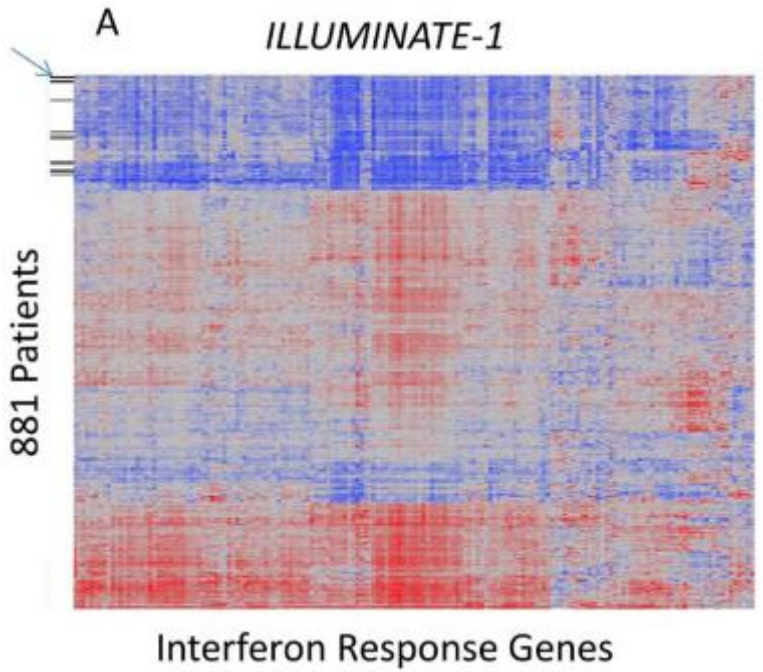
Banchereau *et al, Cell* , 2016

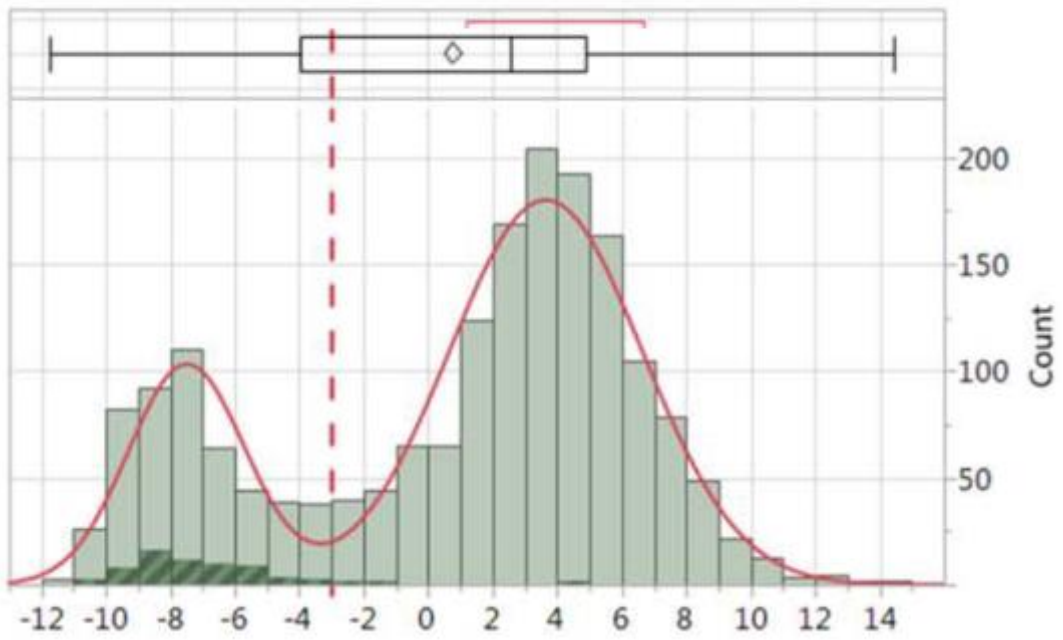
Impact of genetic variants in the IFN pathway in SLE



Postal M et al Current Opinion in Immunology 2020, 67:87–94

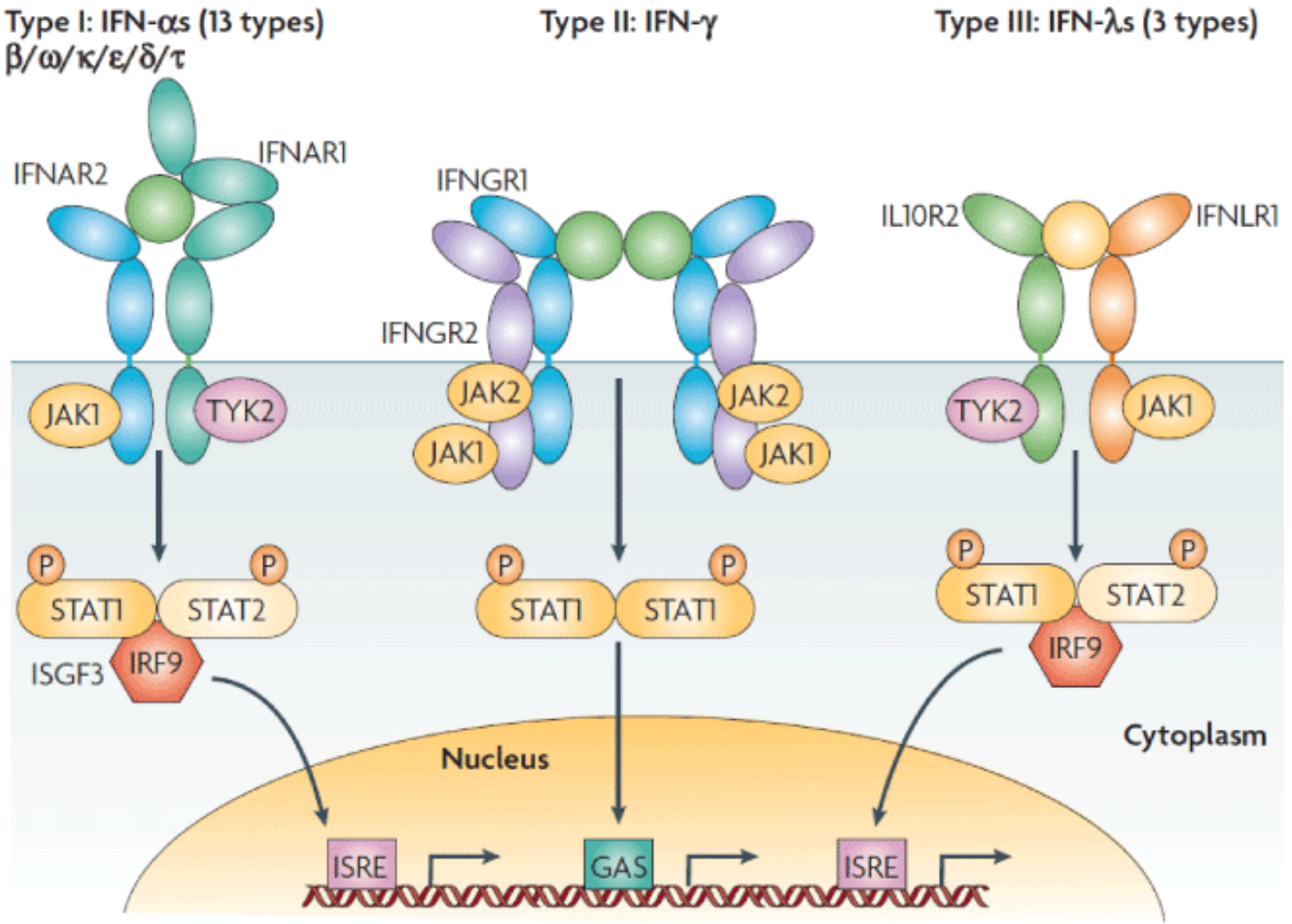
The most prevalent endotype in SLE is the Type I IFN signature





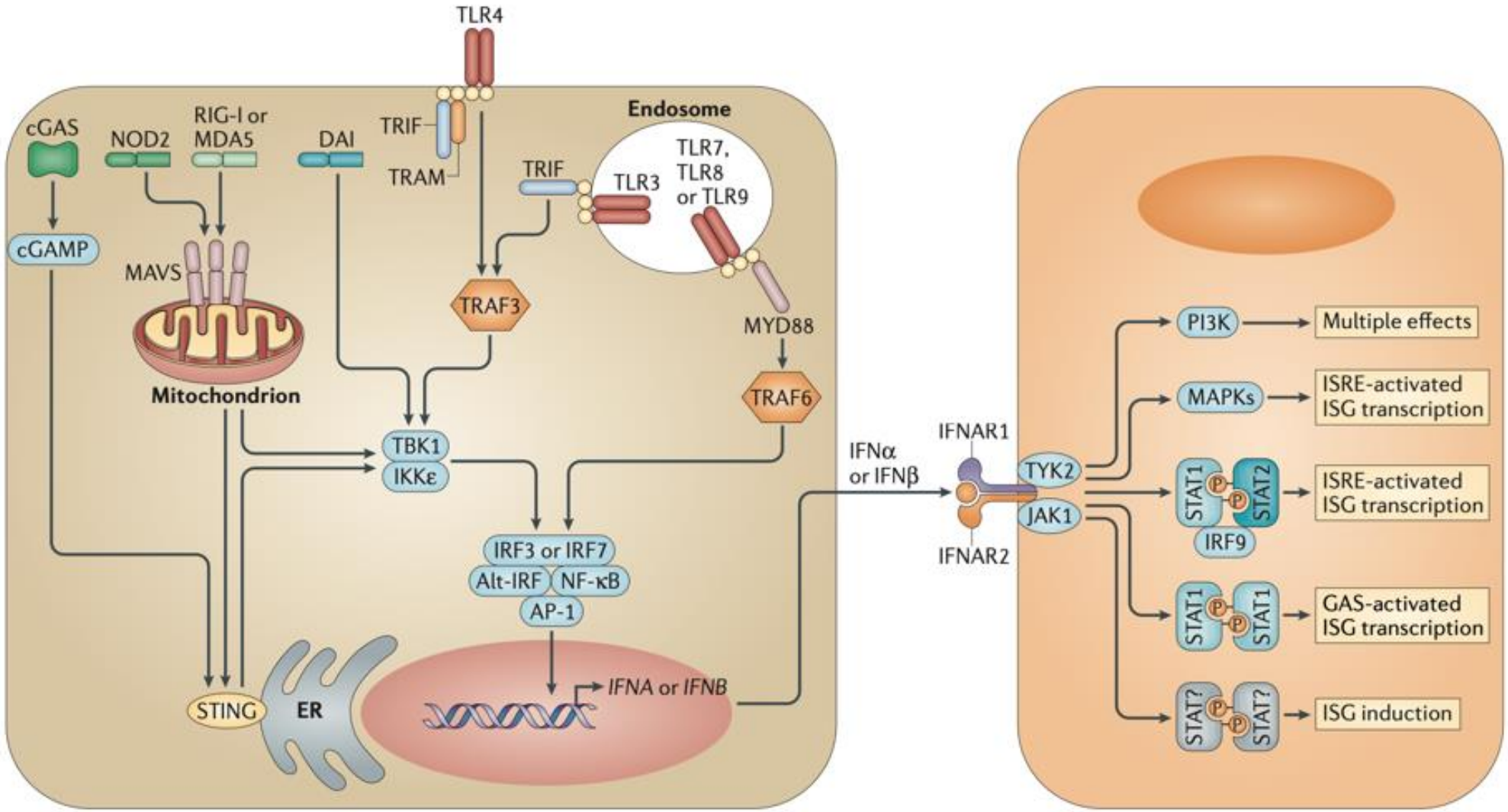
Hoffman E *et al, Arthritis Rheum* 2017 *GSE88884*

IFN superfamily – some basics: classified by receptor usage



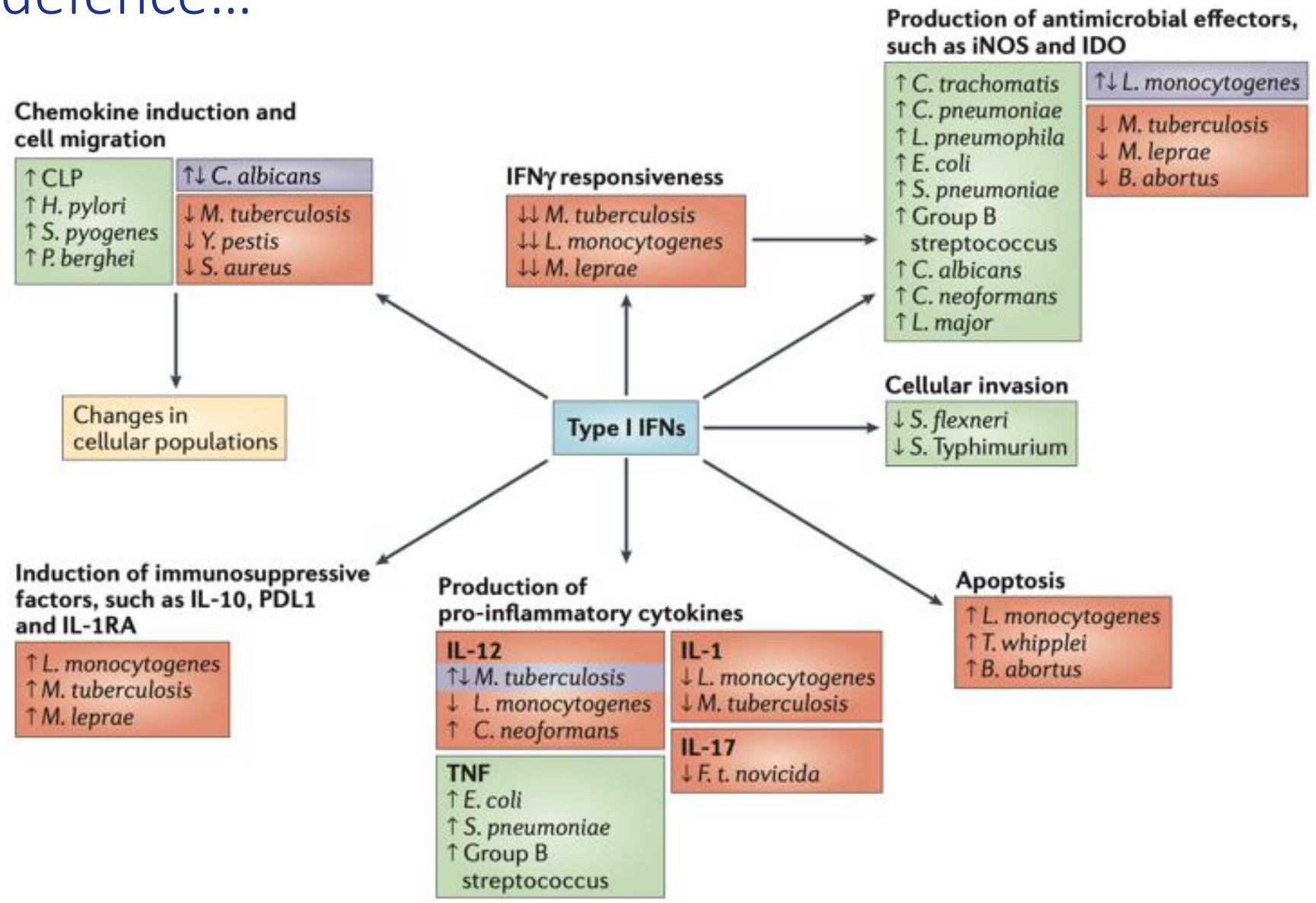
Wang H, Hu H, Zhang K. Arch Biotechnol Biomed. 2017; 1: 001-016

IFN - some basics…



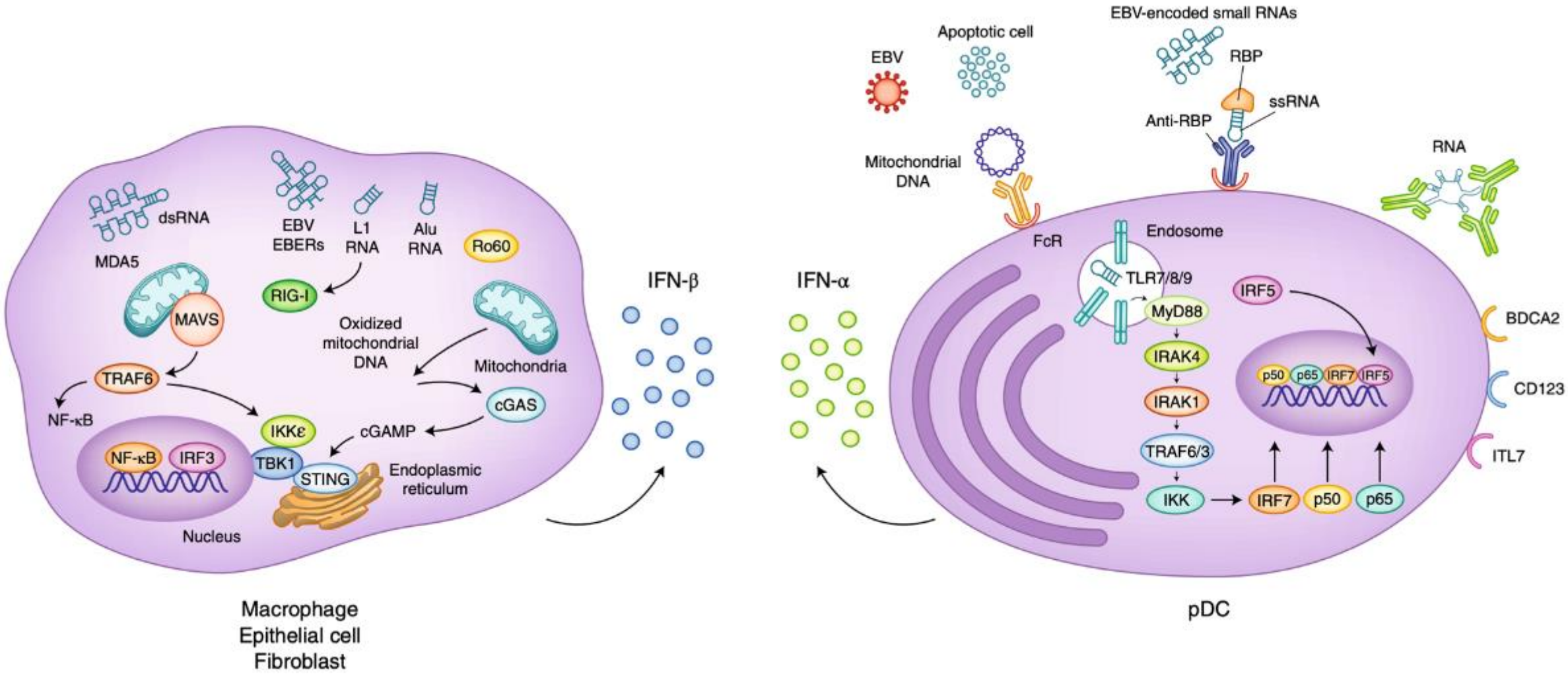
McNab F et al Nature Revs Immunol 2015 15; 89

IFN in host defence…



McNab F et al Nature Revs Immunol 2015 15; 89

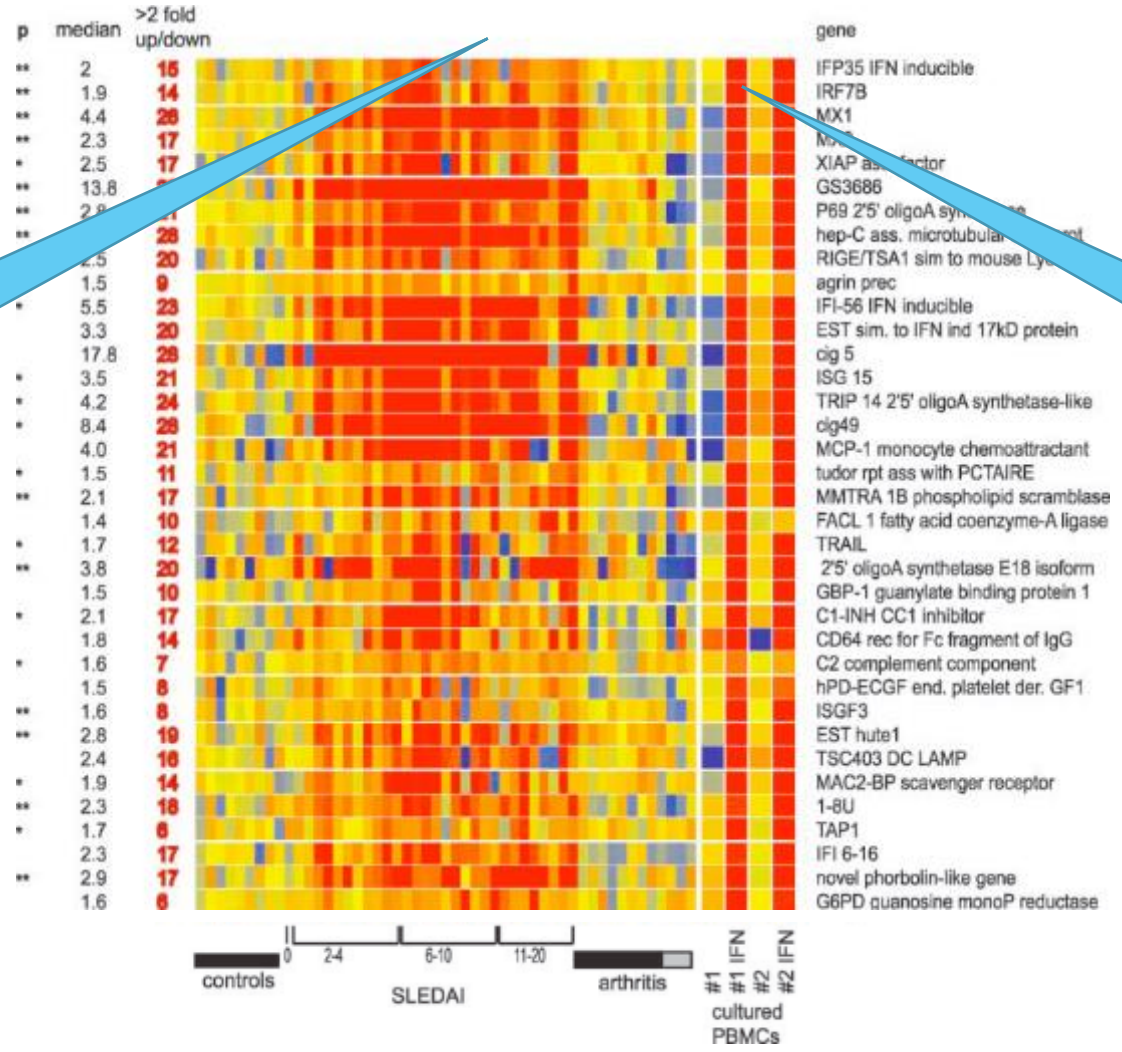
Multiple pathways to stimulate IFN



Barrat, F. J., Crow, M. K. & Ivashkiv, L. B. *Nat Immunol* **20**, 1574–1583 (2019).

IFN – some basics: ‘IFN gene signature’?

SLE patients – no IFN added



Healthy blood + IFN treatment in the test tube

Bennett, *J Exp Med* 2003

Monogenic interferonopathies

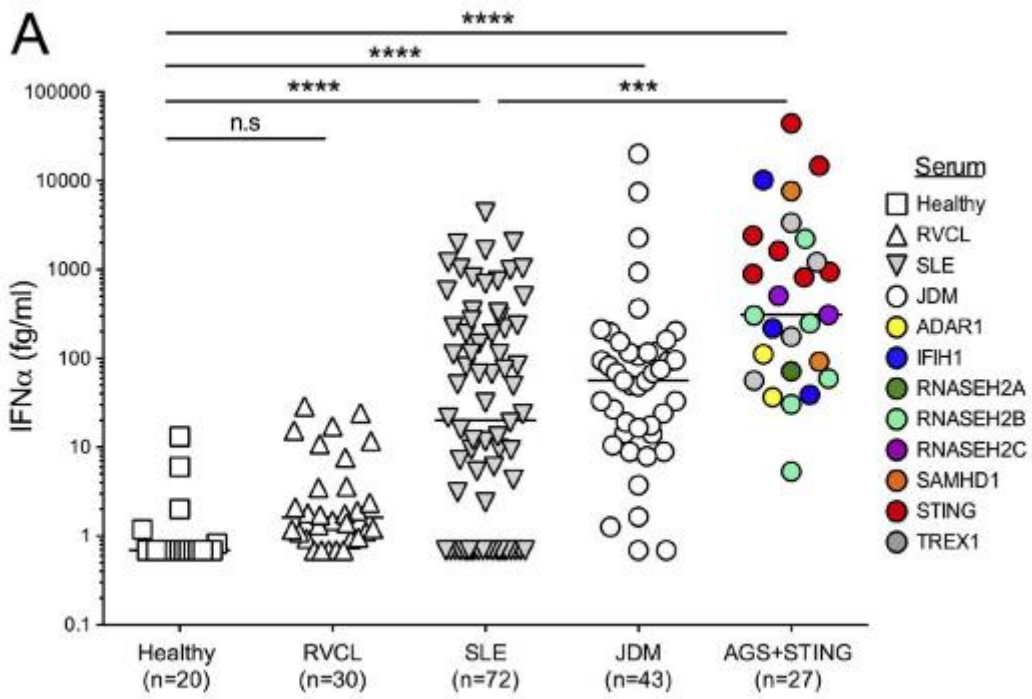
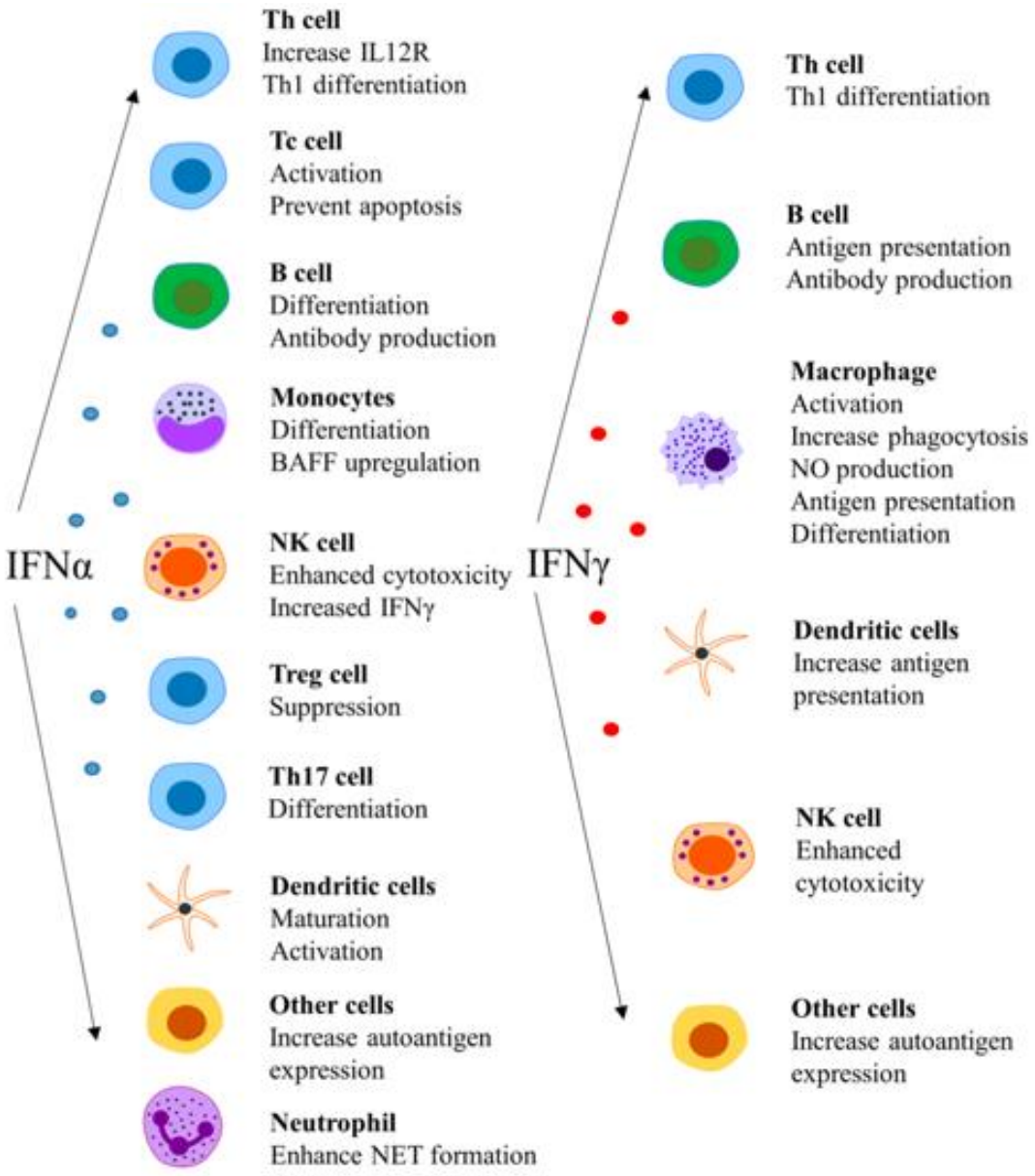


Table 1 | **Summary of recognized type I interferonopathies**

Gene name (alternative name)	Inheritance	Human phenotypes	Mouse phenotypes	Protein function
TREX1	Autosomal recessive or autosomal dominant	AGS, FCL, SLE and RVCL	Knockdown: inflammatory myocarditis with features of autoimmune activation	3′–5′ DNA exonuclease
RNASEH2A	Autosomal recessive	AGS	Not published	A catalytic component of the RNase H2 complex that acts on the RNA portion of RNA–DNA hybrids and removes ribonucleotides embedded in DNA
RNASEH2B	Autosomal recessive	AGS and spastic paraparesis	Knockdown: embryonic lethal and DNA damage response increased (not obviously IFN related)	A non-catalytic component of the RNase H2 complex
RNASEH2C	Autosomal recessive	AGS	Not published	A non-catalytic component of the RNase H2 complex
SAMHD1	Autosomal recessive	AGS, FCL and CLL	Knockdown: no obvious phenotype, but an IFN signature is observed in some tissues	dNTP triphosphohydrolase triphosphatase and ribonuclease activity
ADAR (DRADA)	Autosomal recessive or autosomal dominant	AGS, DSH, BSN and spastic paraparesis, as well as CNP	Knockdown: embryonic lethal at embryonic day 11.5, also associated with IFN signature	Hydrolytic deamination of adenosine to inosine in dsRNA
IFIH1 (MDA5)	Autosomal dominant	Various neuroimmunological and non-neurological phenotypes, including AGS, spastic paraparesis, CNP and SMS	ENU-induced gain-of-function mutant has features of type I IFN-induced lupus-like autoimmunity	Cytosolic sensor of dsRNA
DDX58 (RIG1)	Autosomal dominant	Atypical SMS	Not reported	A 5′-triphosphate and 5′-diphosphate dsRNA cytosolic sensor
TMEM173 (STING)	Autosomal dominant	SAVI (skin and lung)	Not reported	An adaptor molecule involved in transducing cytosolic DNA-induced signalling to IFN production
ISG15	Autosomal recessive	MSMD and intracranial calcification (with seizures in some cases)	Viral susceptibility	A negative regulator of type I IFN production by stabilization of USP18 (also has secreted activity in IFNγ production)
PSMB8	Autosomal recessive	JMP, NNS, JASL or CANDLE (fever, contractures, neutrophilic dermatitis, lipoatrophy and panniculitis)	Essentially normal but with reduced ability to process MHC class I-restricted antigens	Part of a multi-subunit protease complex responsible for regulating proteolysis in eukaryotic cells
ACP5 (TRAP)	Autosomal recessive	SPENCD, spastic paraparesis and various autoimmune phenotypes (particularly SLE)	Osteoclast defect and disturbance of macrophage and/or dendritic cell function	Lysosomal acid phosphatase activity

Rodero, M. P. *et al. J Exp Med* **214**, 1547–1555 (2017).

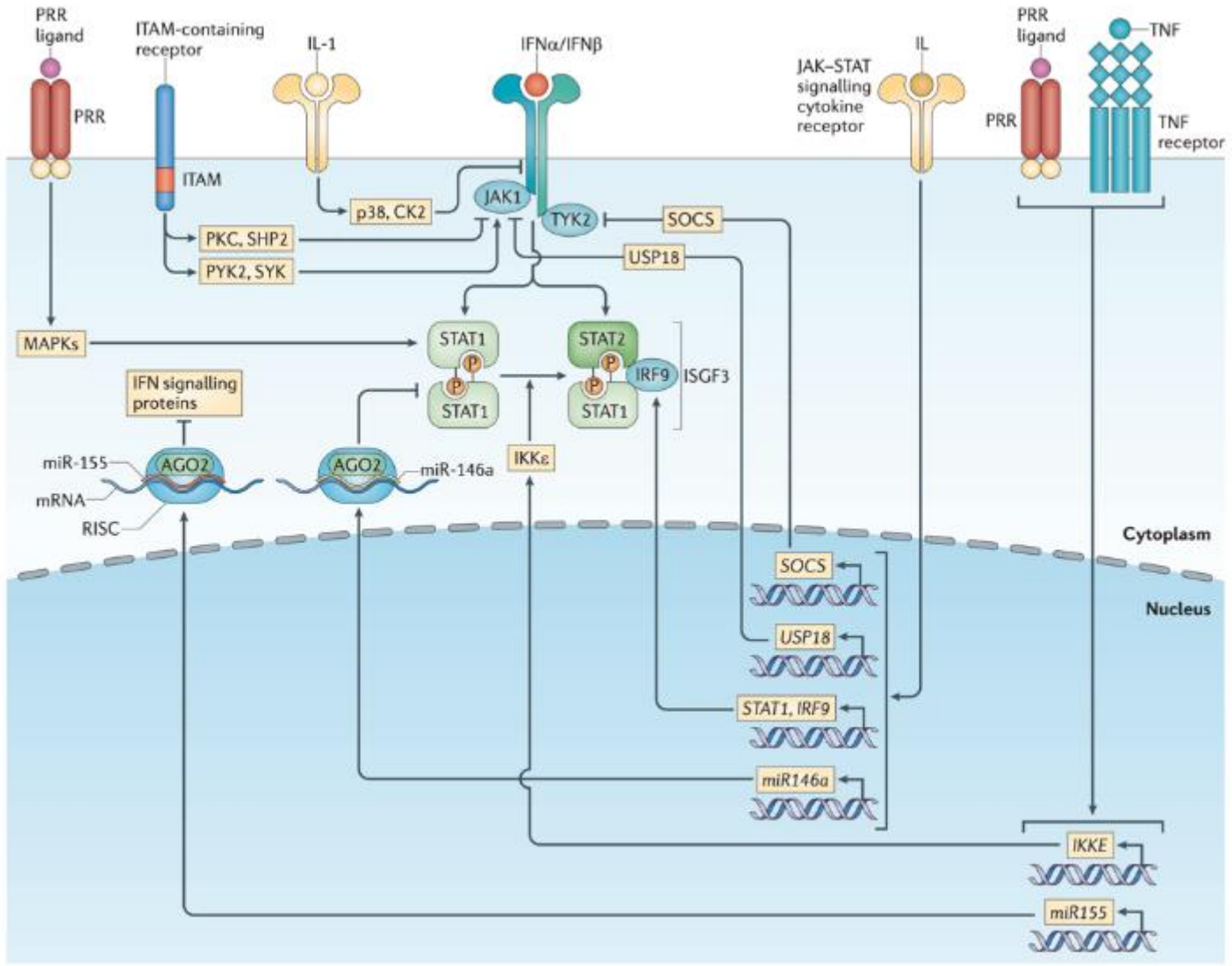
Effects of IFN across immune cells and target organs relevant to SLE



+Direct target tissue effects
- Constitutional
- Skin
- Kidney
- Brain?

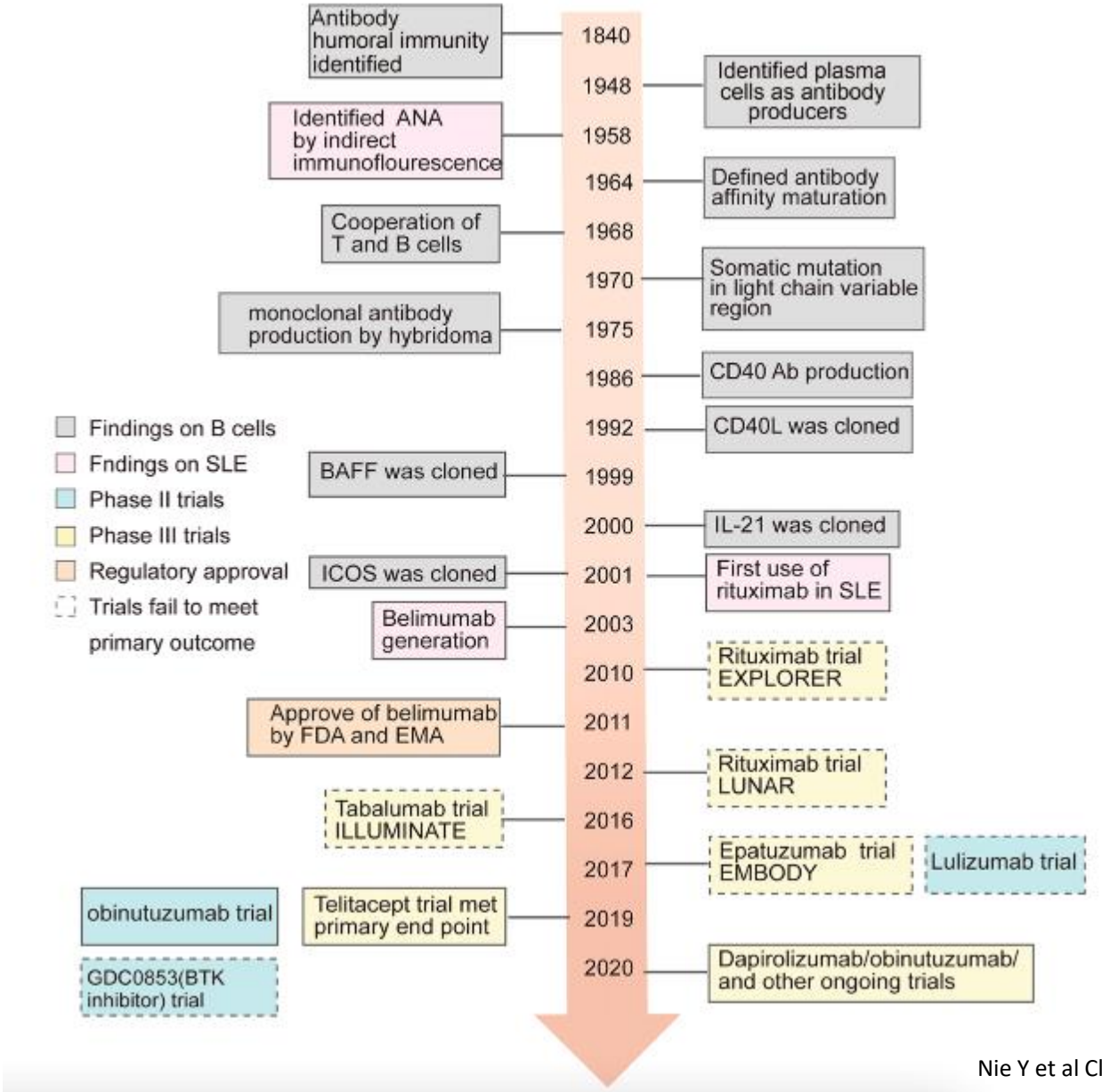
Rönnblom, L. & Leonard, D. *Lupus Sci Medicine* **6**, e000270 (2019).

IFN does not act in isolation…who are the other players?



Ivashkiv, L. B. & Donlin, L. T. *Nat Rev Immunol* 14, 36–49 (2014)

B cells: therapeutic opportunities in SLE?



Nie Y et al Cl*inical Reviews in Allergy & Immunology* (2022) 62:301–323

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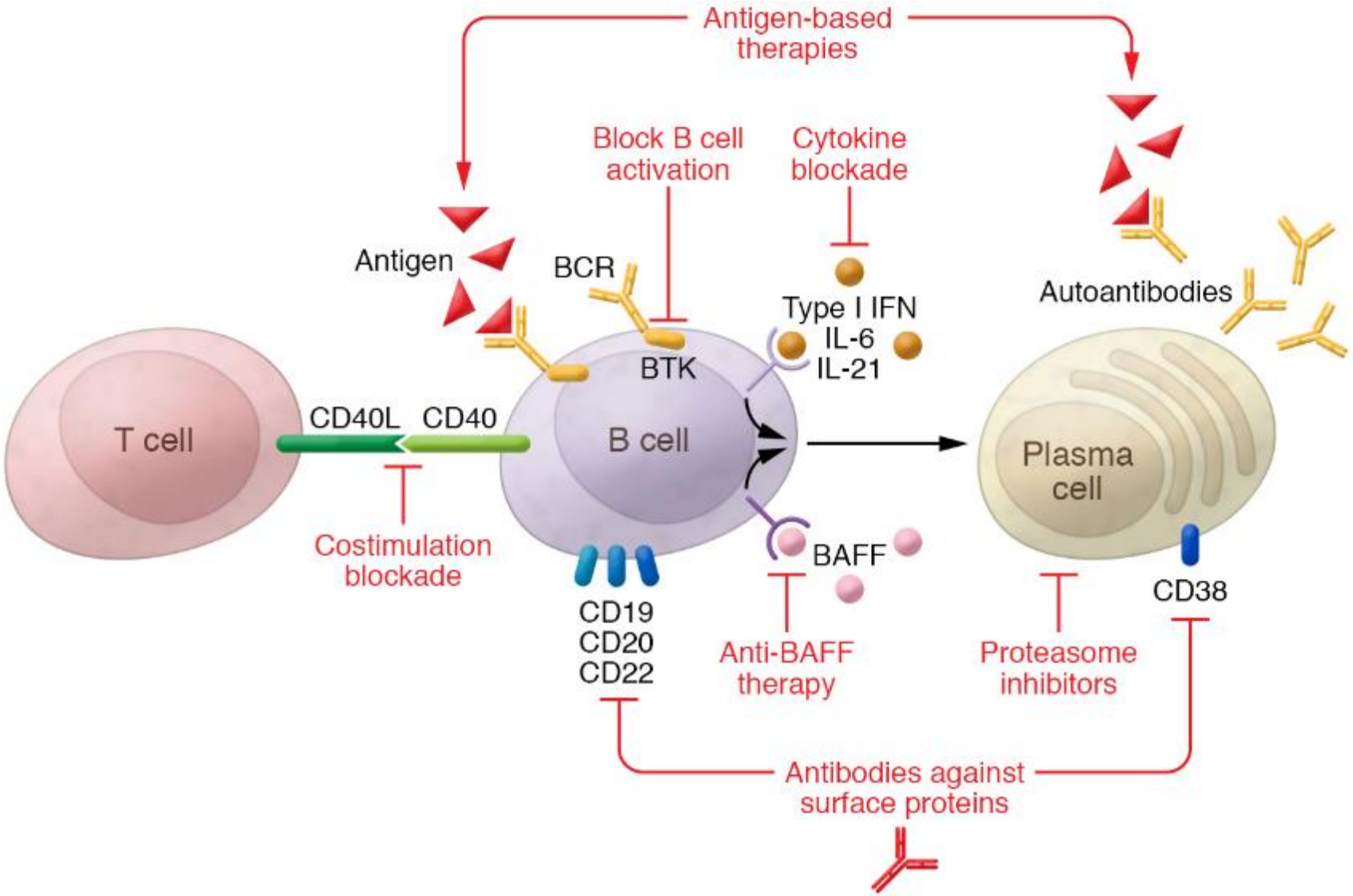
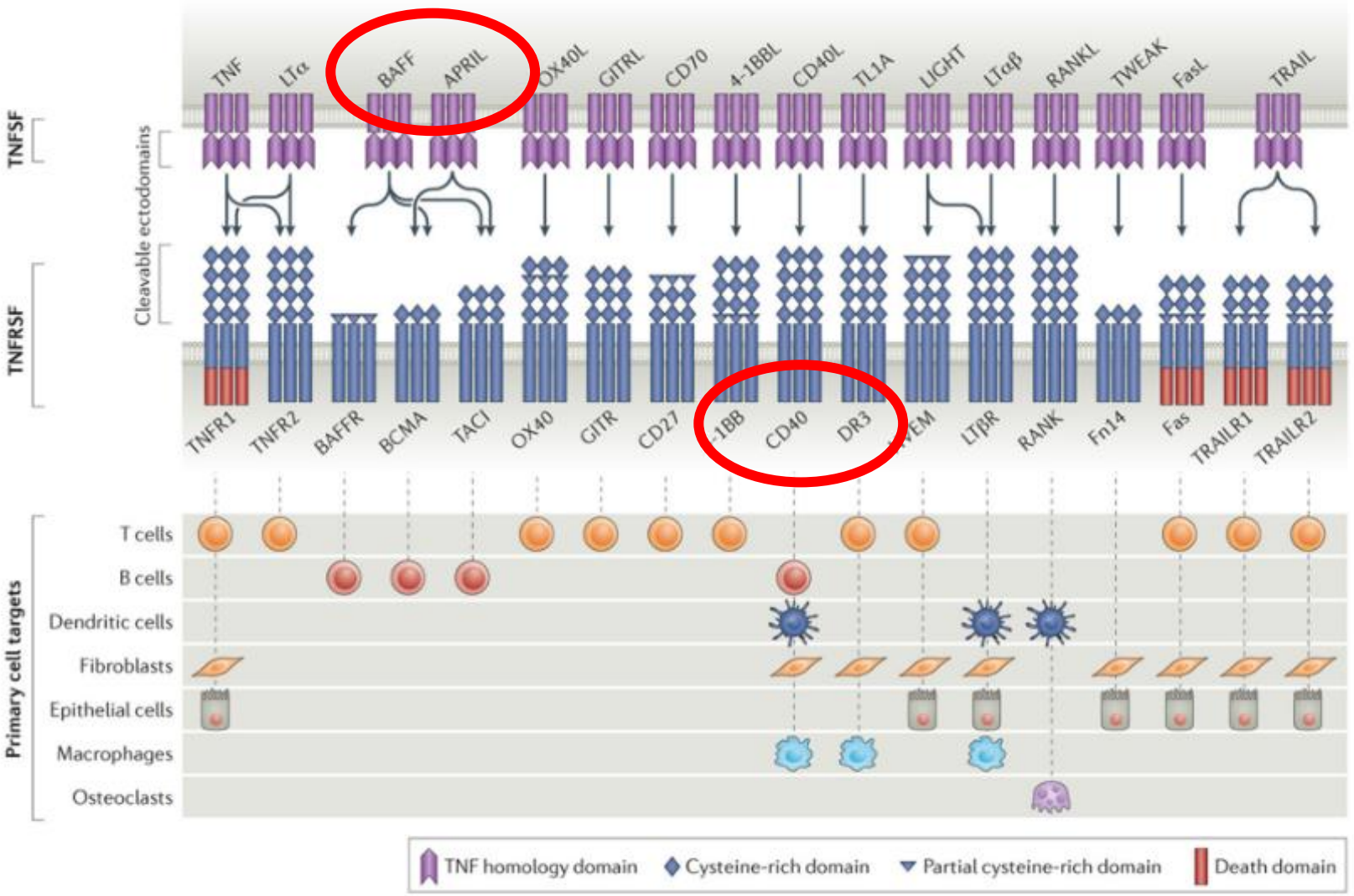


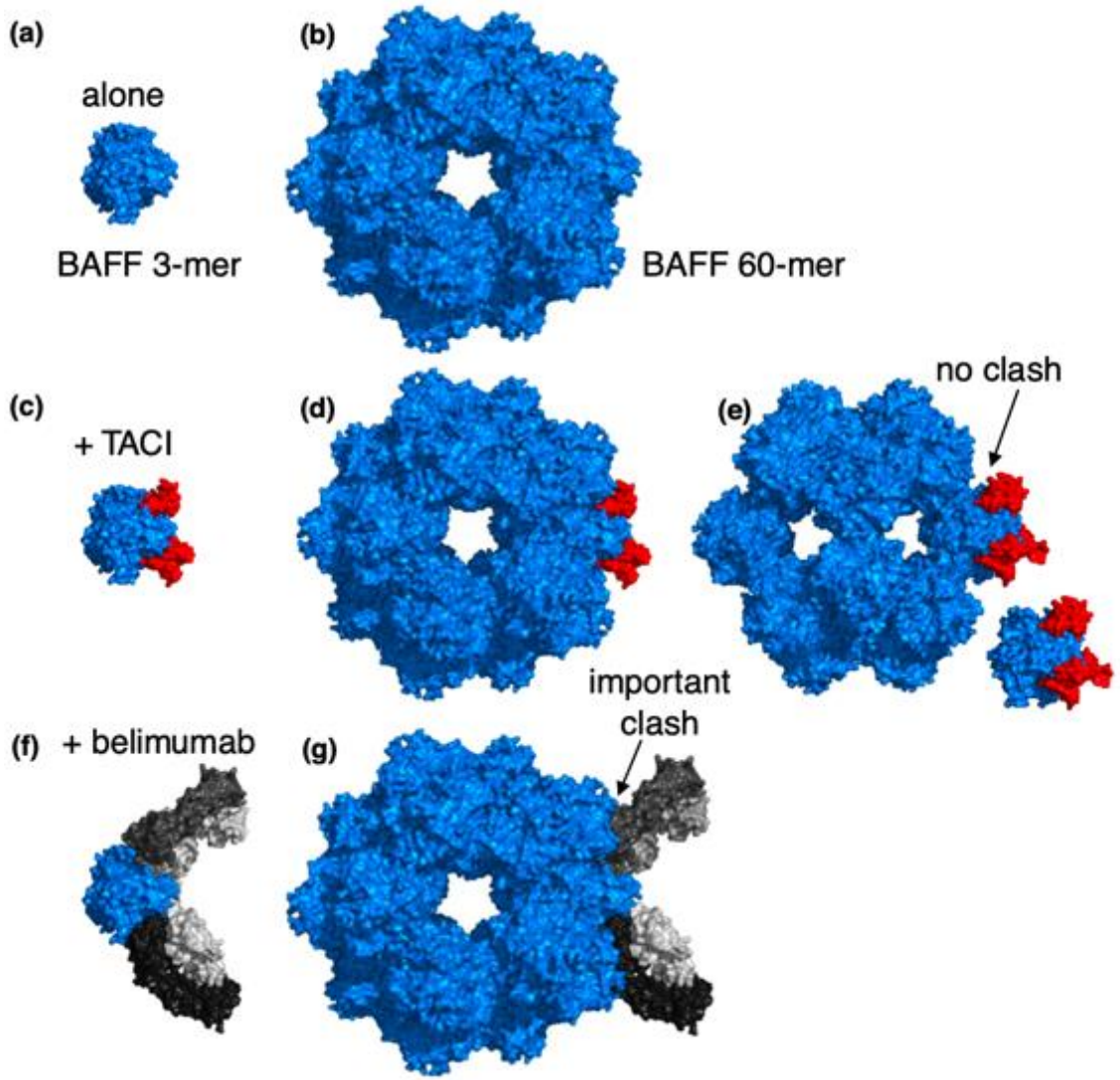
Yemil Atisha-Fregoso et al *J Clin Invest.* 2021;131(12):e149095

A familiar tale….TNF / TNF receptor superfamily.



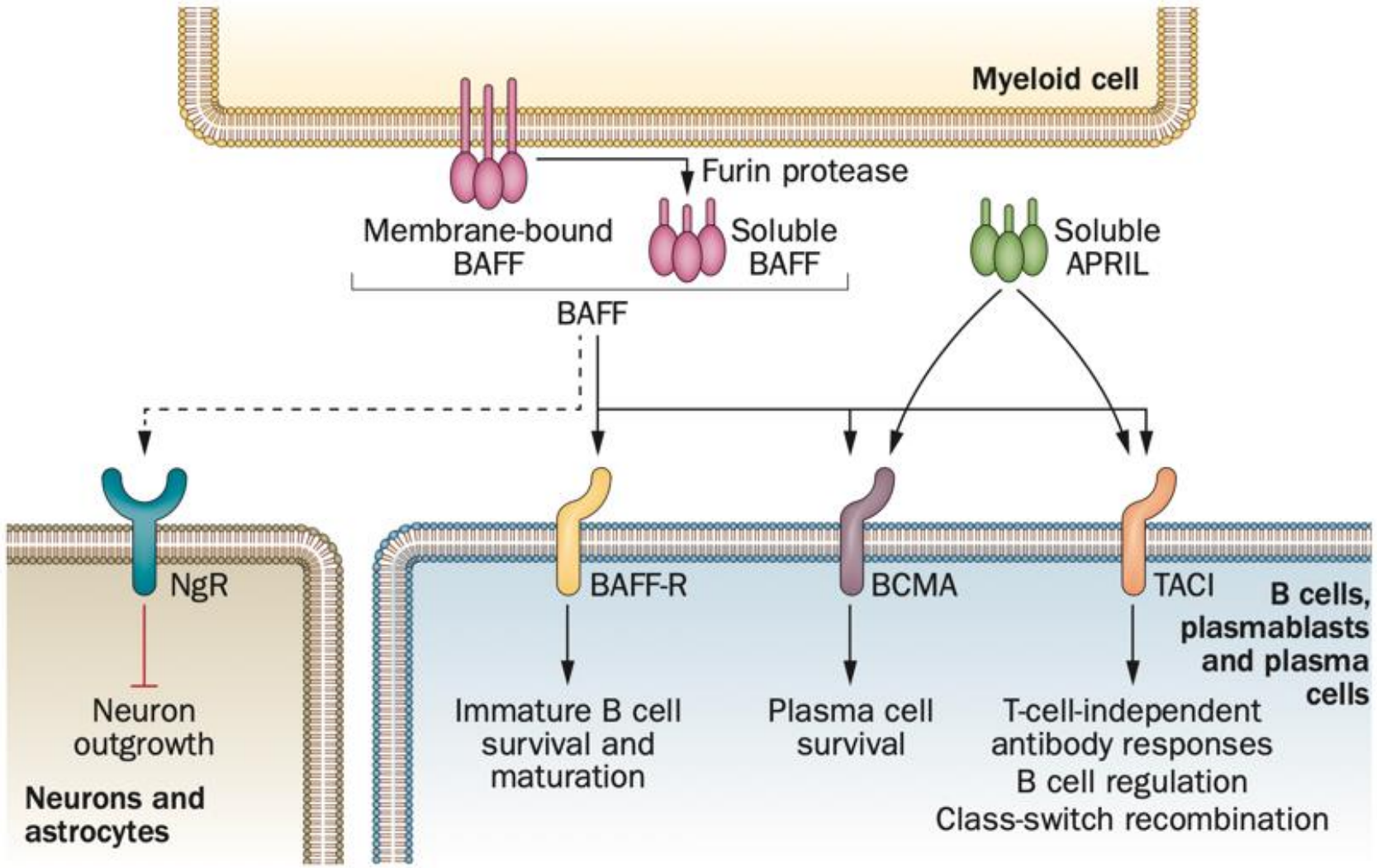
Croft M et al Nat Rev Rheumatol. 2017 April ; 13(4): 217–233

BAFF – a TNF superfamily member that exists in various forms…



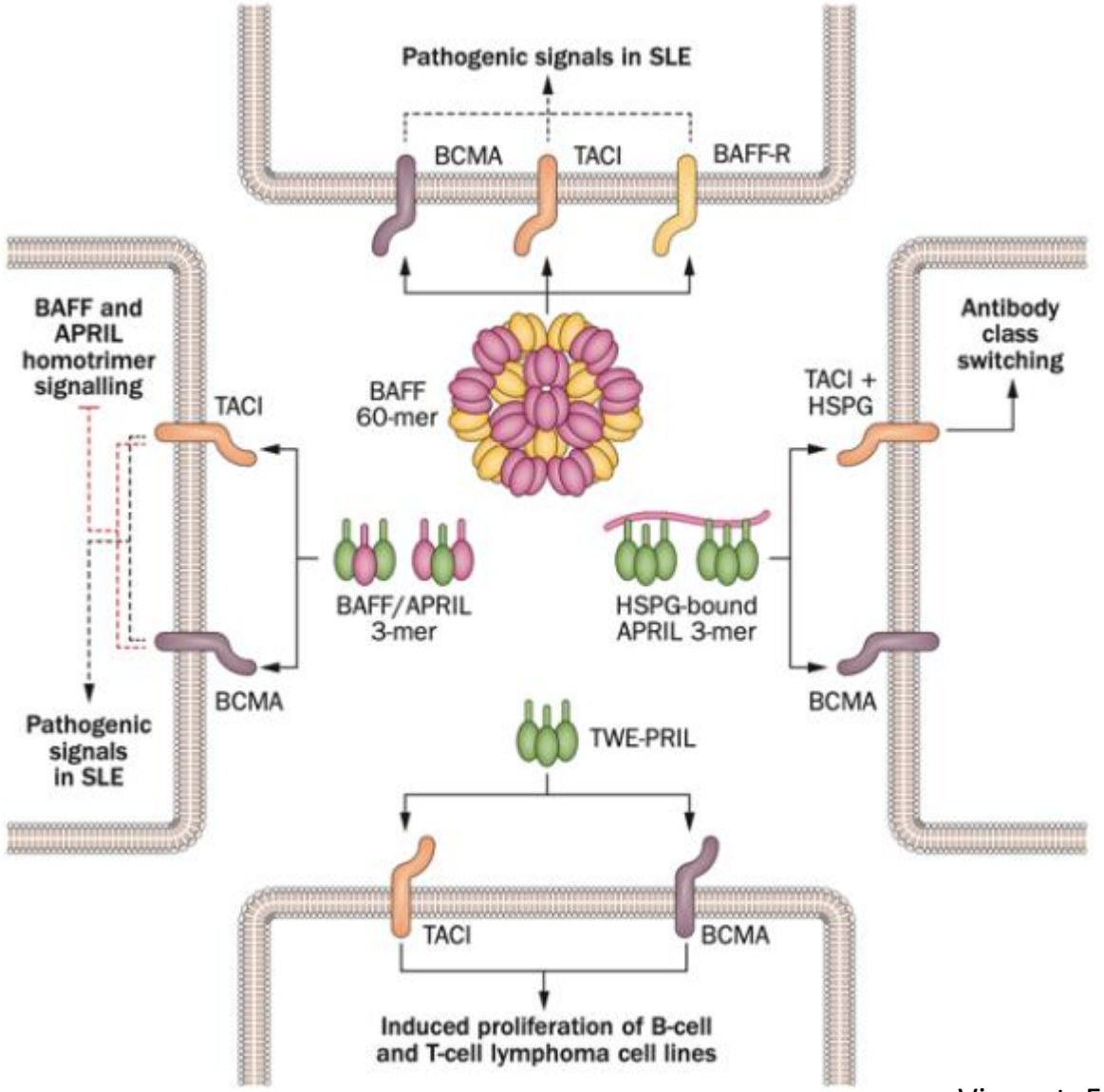
Eslami M et al Current Opinion in Immunology 2021, 71:75–80

BAFF – the intricacies of a complex system



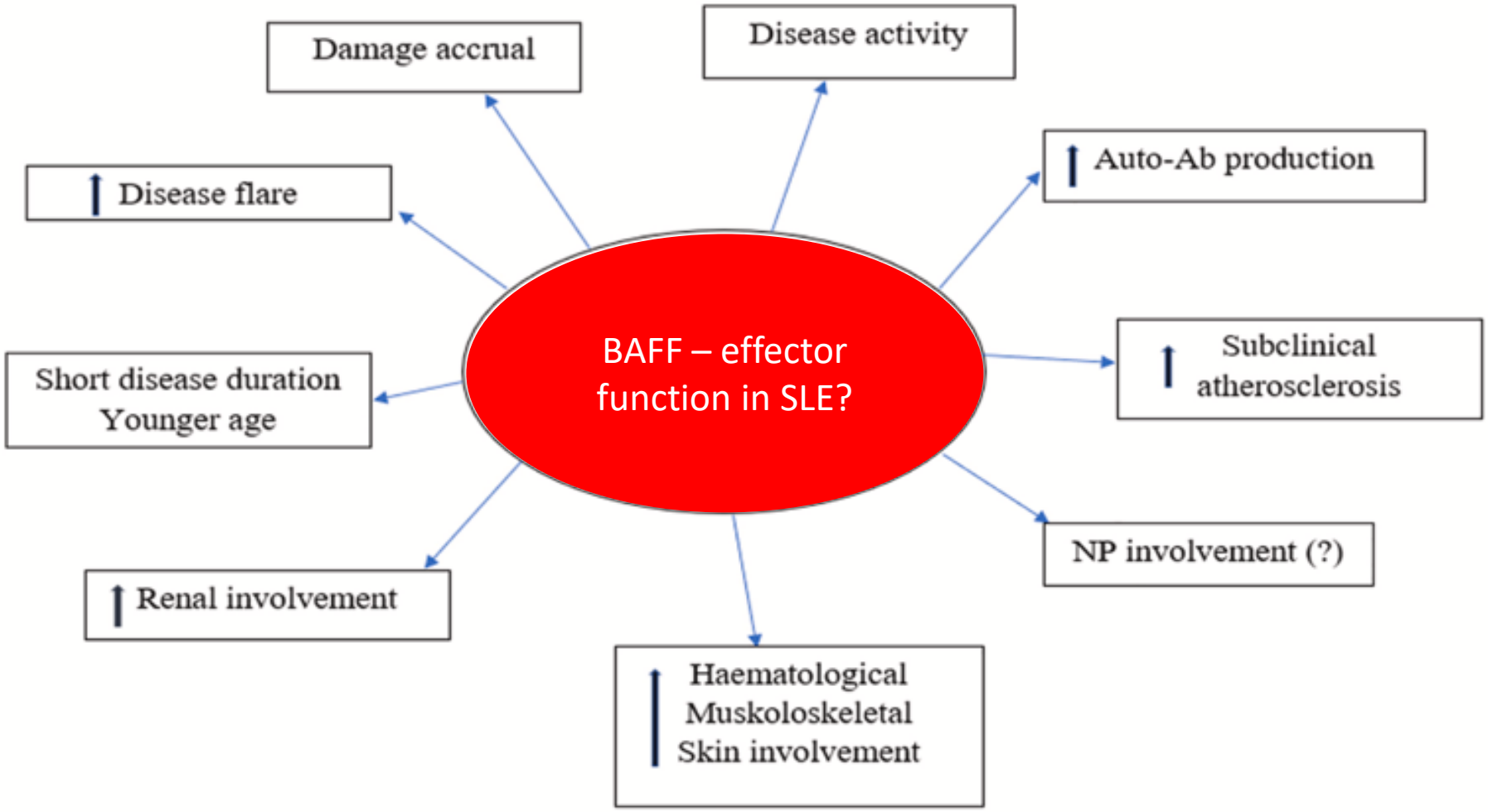
Vincent, F. B. *et al. Nat. Rev. Rheumatol.* 10, 365–373 (2014);

BAFF – and in several forms what does it do…?



Vincent, F. B. *et al. Nat. Rev. Rheumatol.* 10, 365–373 (2014);

BAFF – potential effector function in SLE?



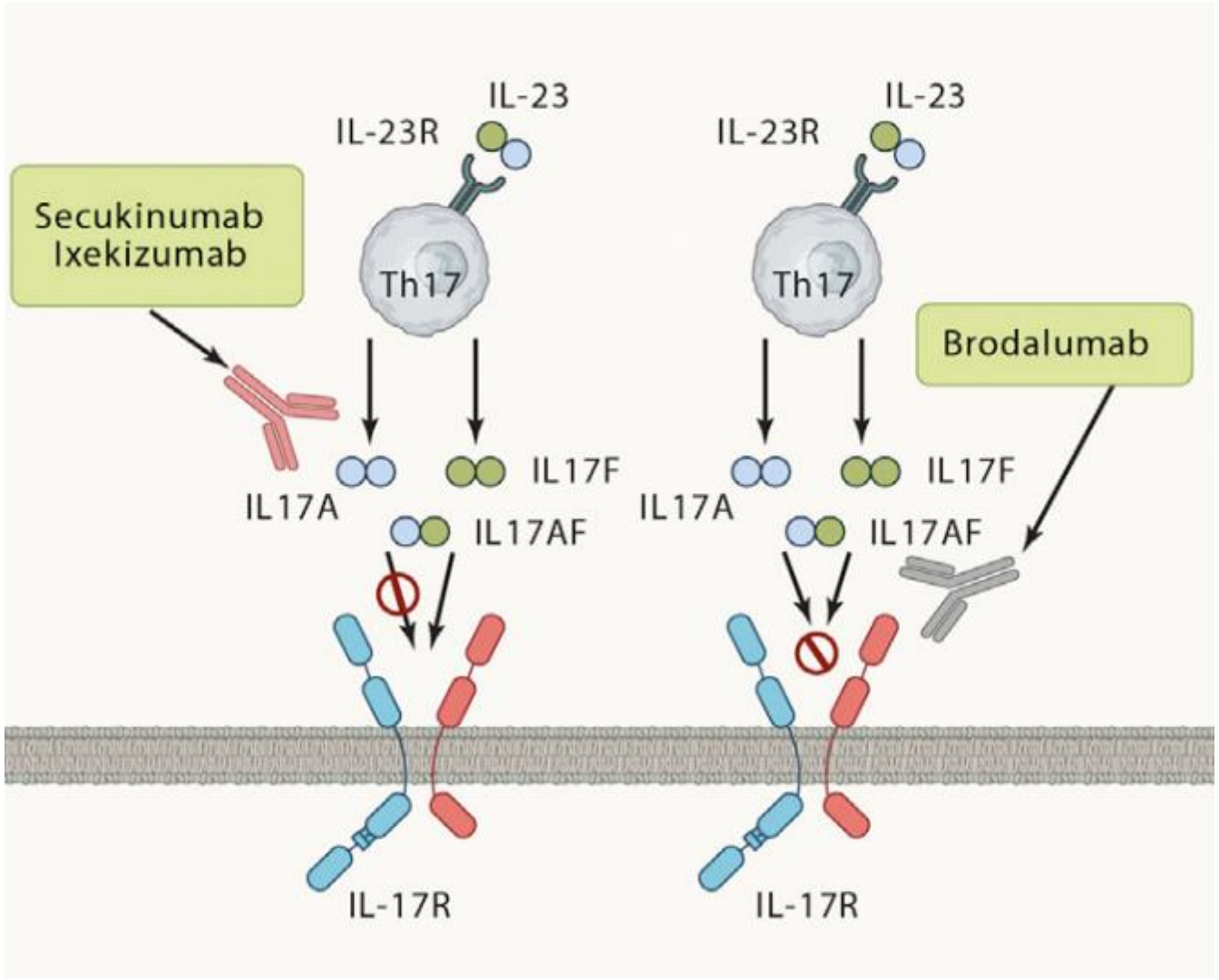
Mockel T et al Autoimmunity Reviews 20 (2021) 102736

The IL-17 cytokine superfamily

	IL-17A	IL-17F	IL-17RA	IL-23R	IL-6R	IL-12B	IL-1R2
PsA	rs2275913	rs763780					
AS	rs2275913	rs763780	rs4819554	rs1004819[a] rs12141575 rs10889677[b] rs1495965[a] rs6677188[d] rs220181 rs2201841[a] rs11805303 rs11578380[d] rs924080[d] rs11209032[a] rs1735018 rs76418789 rs1884444 rs11209026[a] rs924080[d] rs11465804[a] rs1343151[a] rs11578380[d] rs10489629[a] rs11465817 rs6677188[d] rs6693831 rs7517847[a]	rs4129267	rs6871626 rs6556416	rs2310173[c]

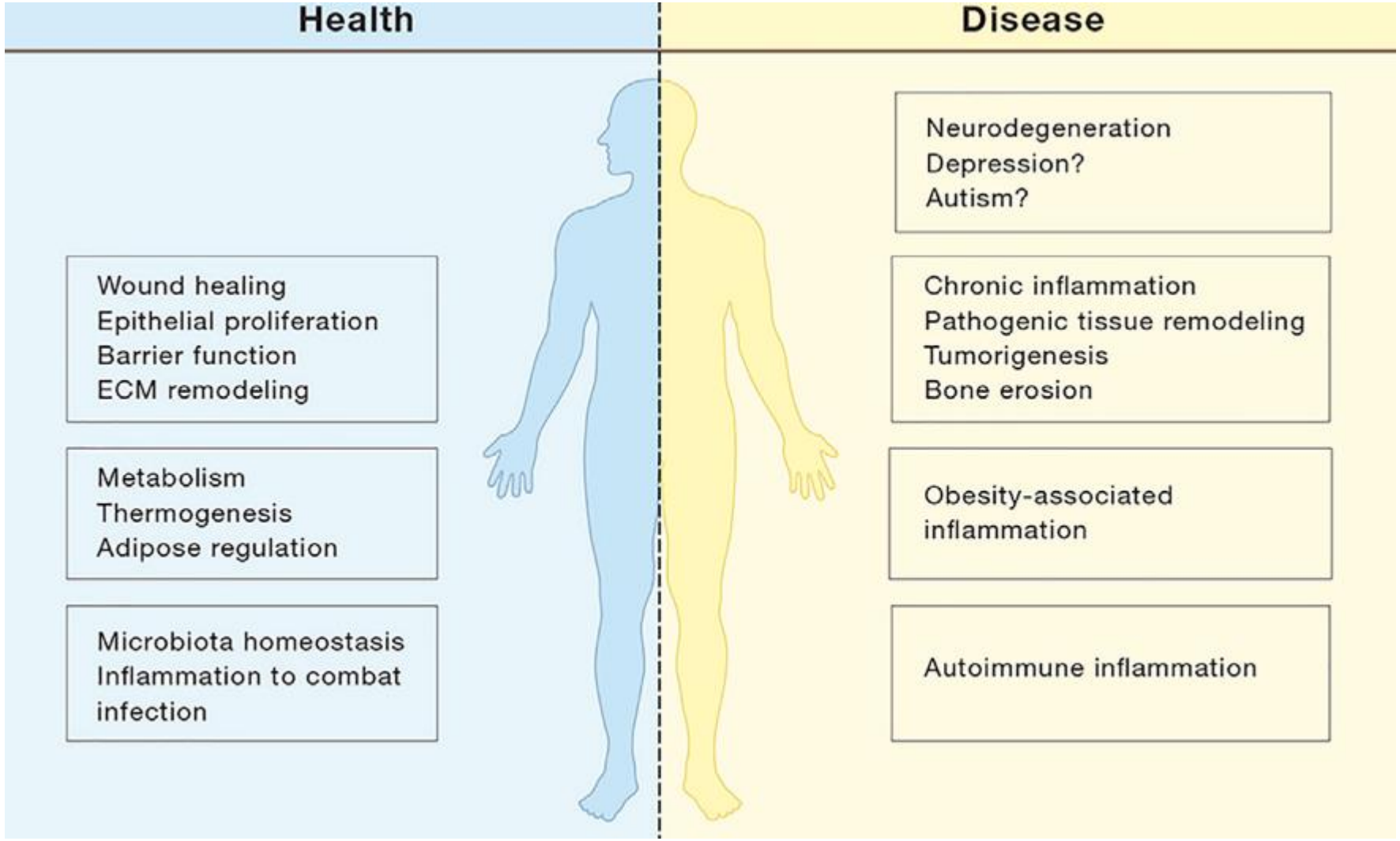
McGonagle DG, et al. Ann Rheum Dis 2019;78:1167–1178

The IL-17 cytokine superfamily



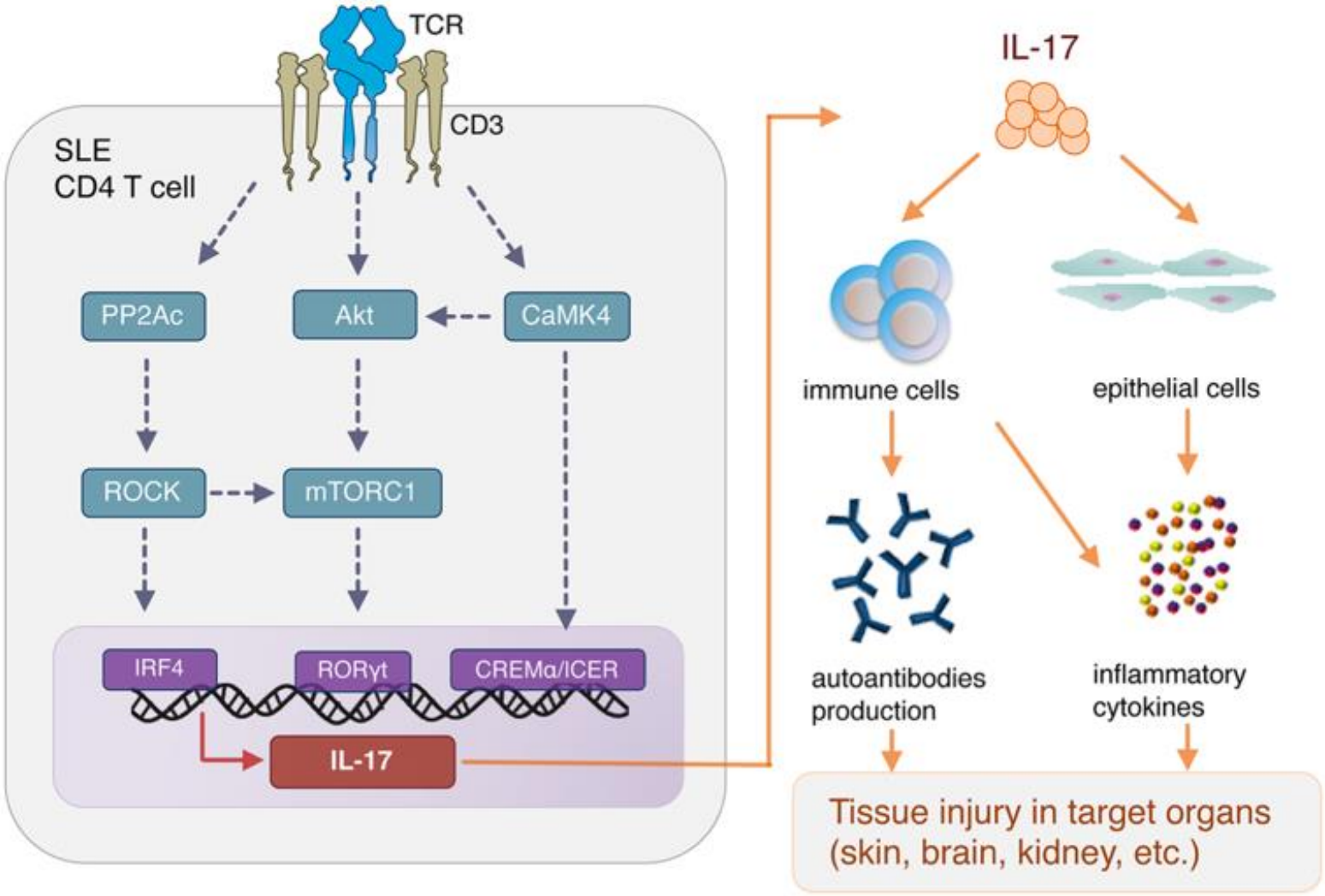
McGeachy M et al DG, et al. Immunity 50, April 16, 2019

The IL-17 cytokine superfamily - two edged sword…



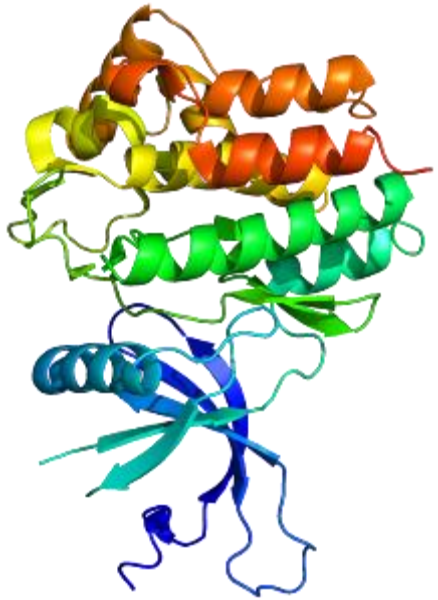
McGeachy M et al DG, et al. Immunity 50, April 16, 2019

The IL-17 cytokine superfamily – role in SLE…?



Koga T, Ichinose K, Kawakami A and Tsokos GC (2021) Front. Immunol. 11:624971. doi: 10.3389/fimmu.2020.624971

JAK family: beautiful molecules in a fabulous system



JAK1

JAK2

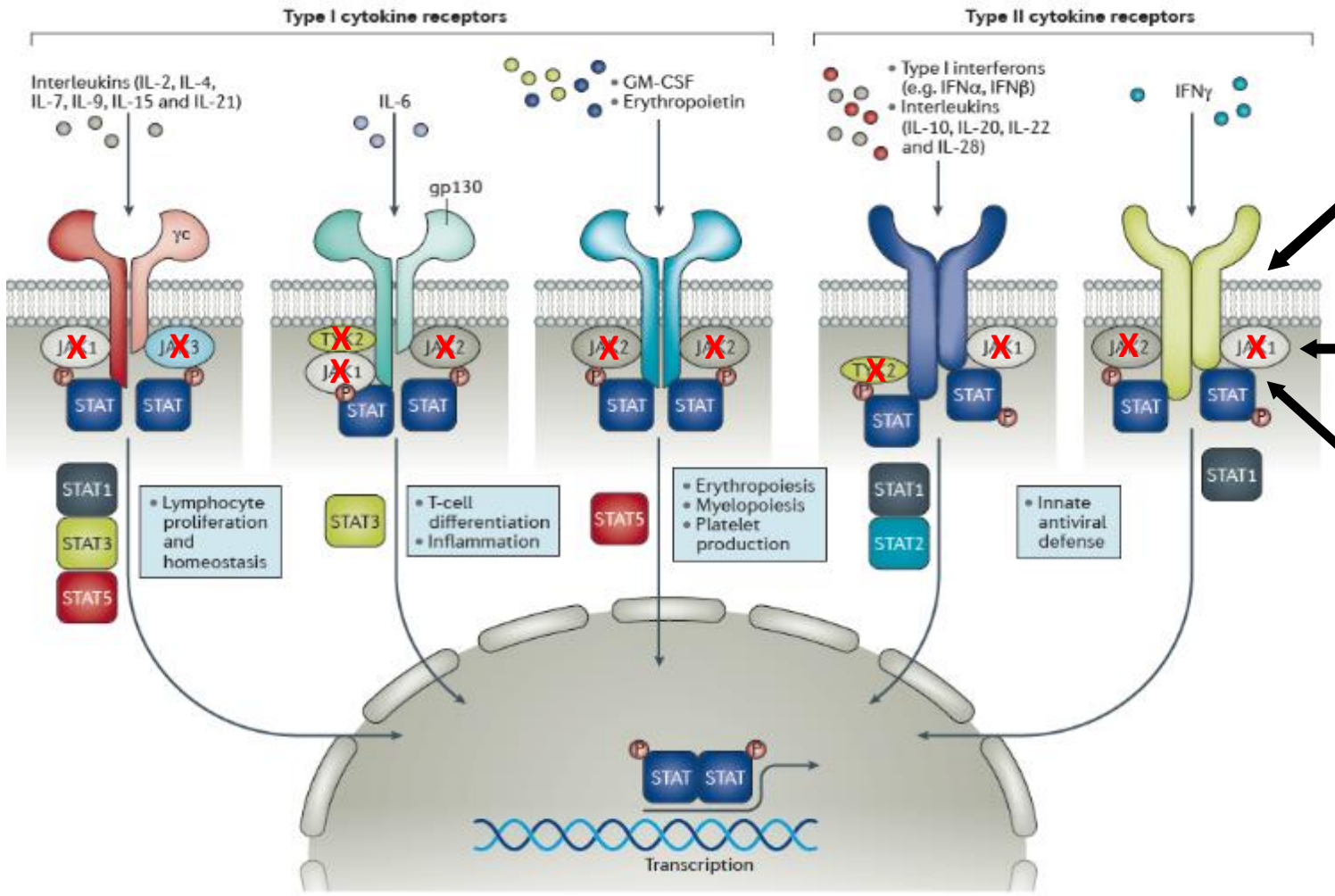
JAK3

TYK2

1. O'Shea JJ et al. Ann Rev Med 2015;66:311–28; 2. Velasquez NLA & Boggon TJ. Curr Drug Targets 2011;12;546–55

JAK, janus kinase; TYK, tyrosine kinase

JAK modulation – diverse functions across a range of SLE related cytokines…



Tofacitinib[3,4]
- Small-molecule pan-JAK inhibitor
- Oral dosing with or without MTX

Baricitinib[5]
- Small-molecule JAK 1/2 inhibitor
- Oral dosing with or without MTX

Filgotinib[6*] **and upadacitinib**[7*]
- Small-molecule selective JAK1 inhibitors
- Oral dosing with or without MTX

JAK, janus kinase; MTX, methotrexate; STAT, signal transducers and activators of transcription

1. Westhovens R et al. *Ann Rheum Dis* 2017;76:998–1008; 2. Winthrop KL et al. *Nat Rev Rheumatol* 2017;13:234–43; 3. Fleischmann R et al. *Lancet* 2017;390:457–66; 4. Fleischmann R et al. *New Engl J Med* 2012;367:495–507; 5. Fleischmann R et al. *Arthritis Rheumatol* 2017;69:506–17; 6. Kavanaugh A et al. *Ann Rheum Dis* 2017;76:1009–19; 7. Voss J. *Arthritis Rheumatol* 2013;65(Suppl10):2374.

To understand the contribution(s) of distinct mediators…

- Major mediators in the patho-immune responses (the actors)
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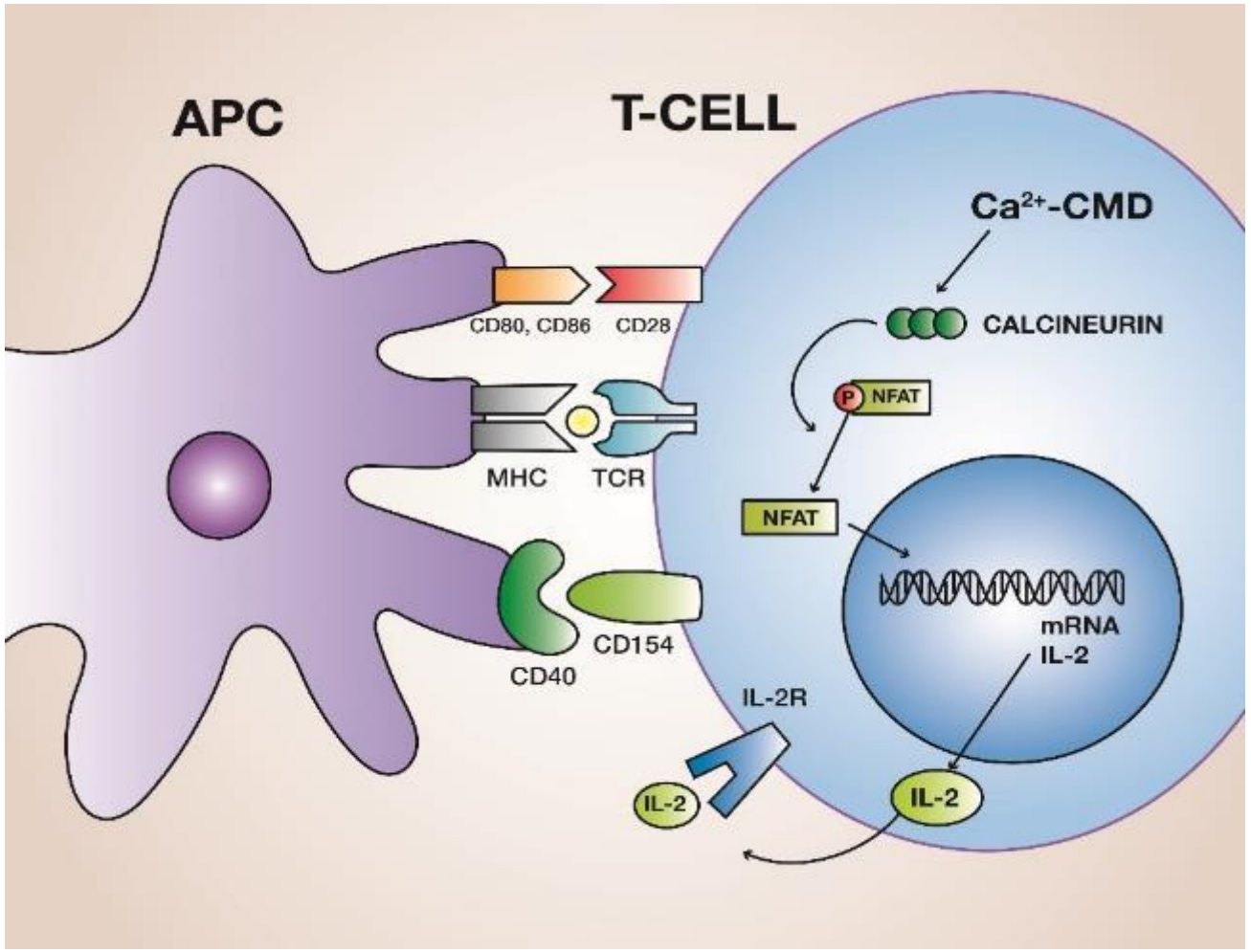
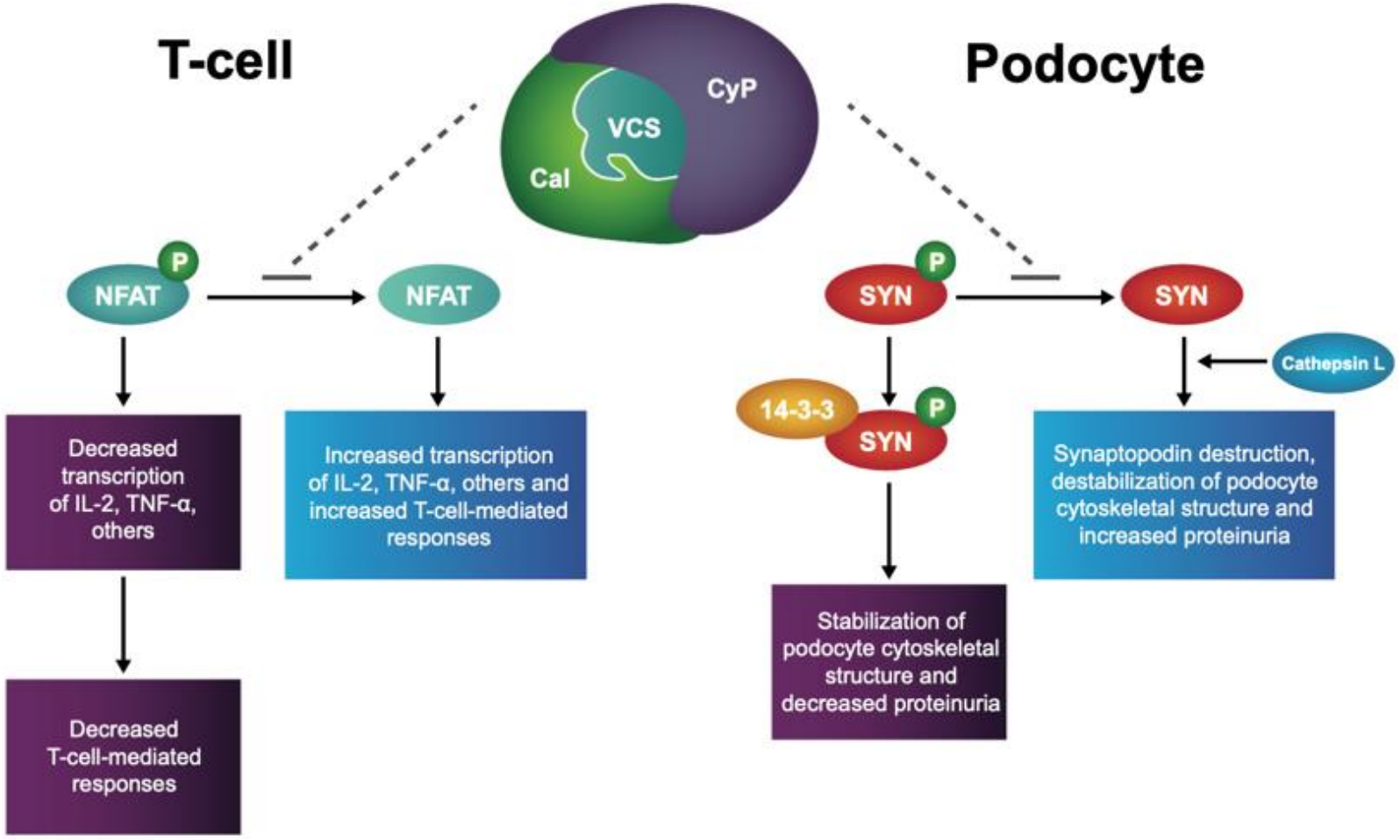
Molecular basis for CNI in SLE?



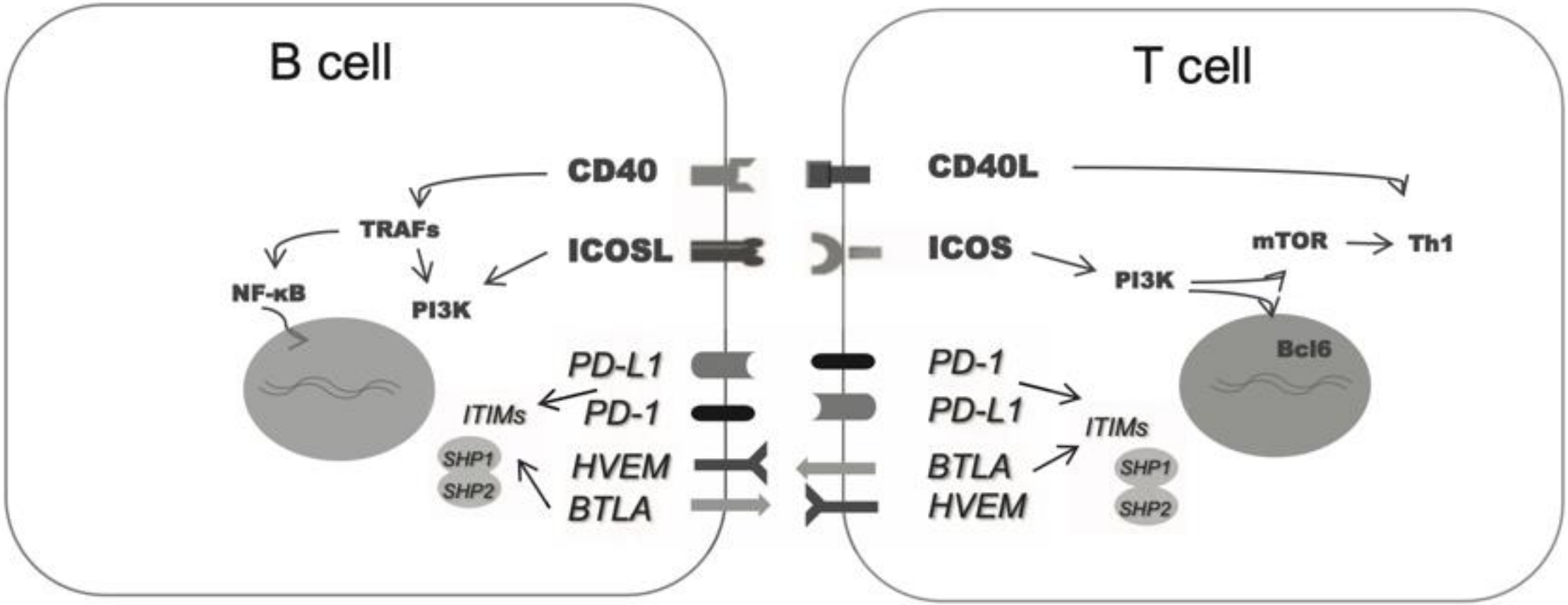
Ponticelli C et al al *J. Clin. Med.* **2021**, *10*, 4832

Effector role for CNI in SLE?



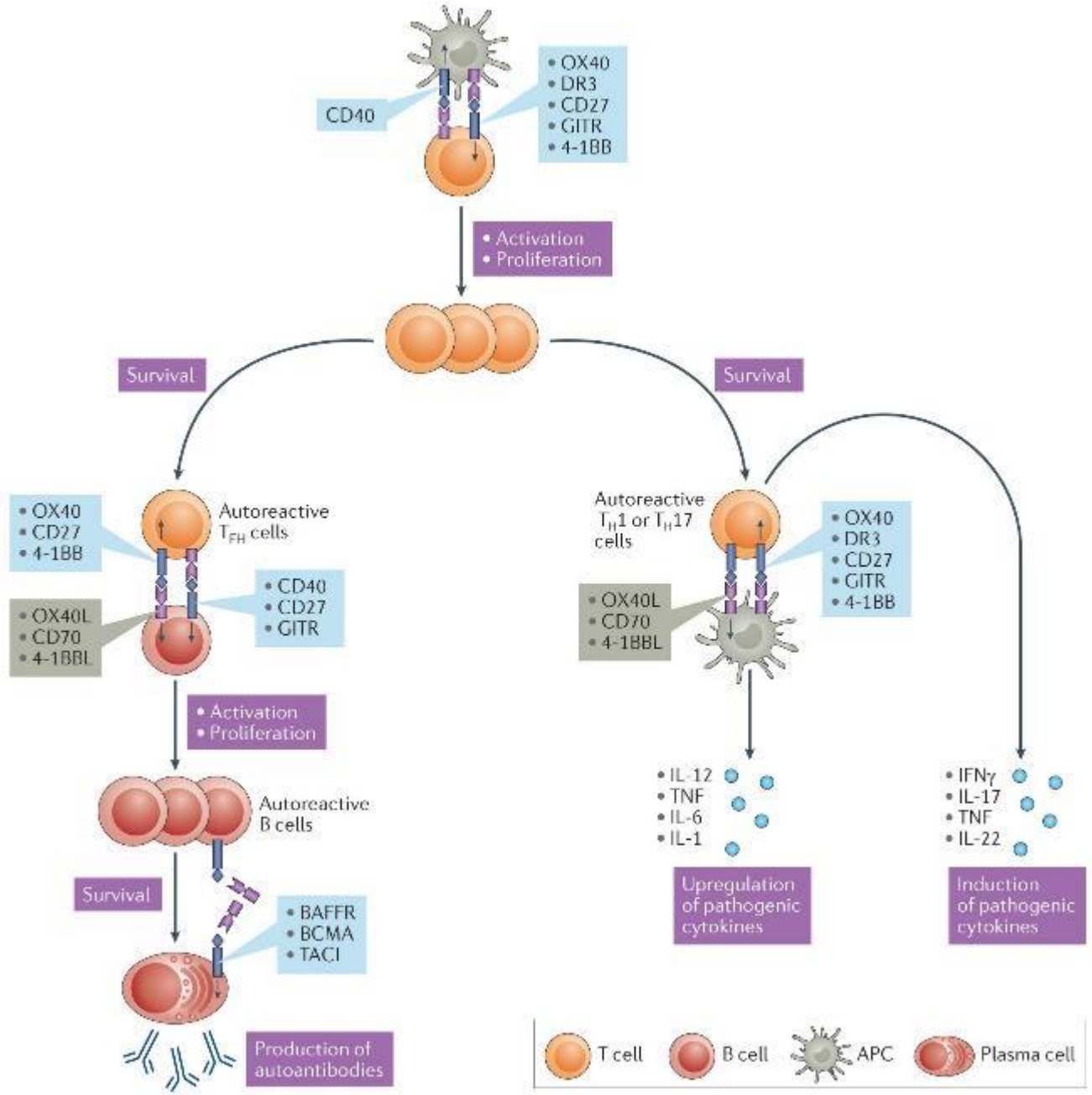
Teun van Gelder, et al (2022): Expert Review of Clinical Pharmacology, DOI: 10.1080/17512433.2022.2092470

Checkpoints in SLE?



Stefanski & Dorner T Curr Opin Rheumatol 2021, 33:592 – 597

A pivotal role for the CD40 pathway in SLE



Croft M et al Nat Rev Rheumatol. 2017 April ; 13(4): 217–233

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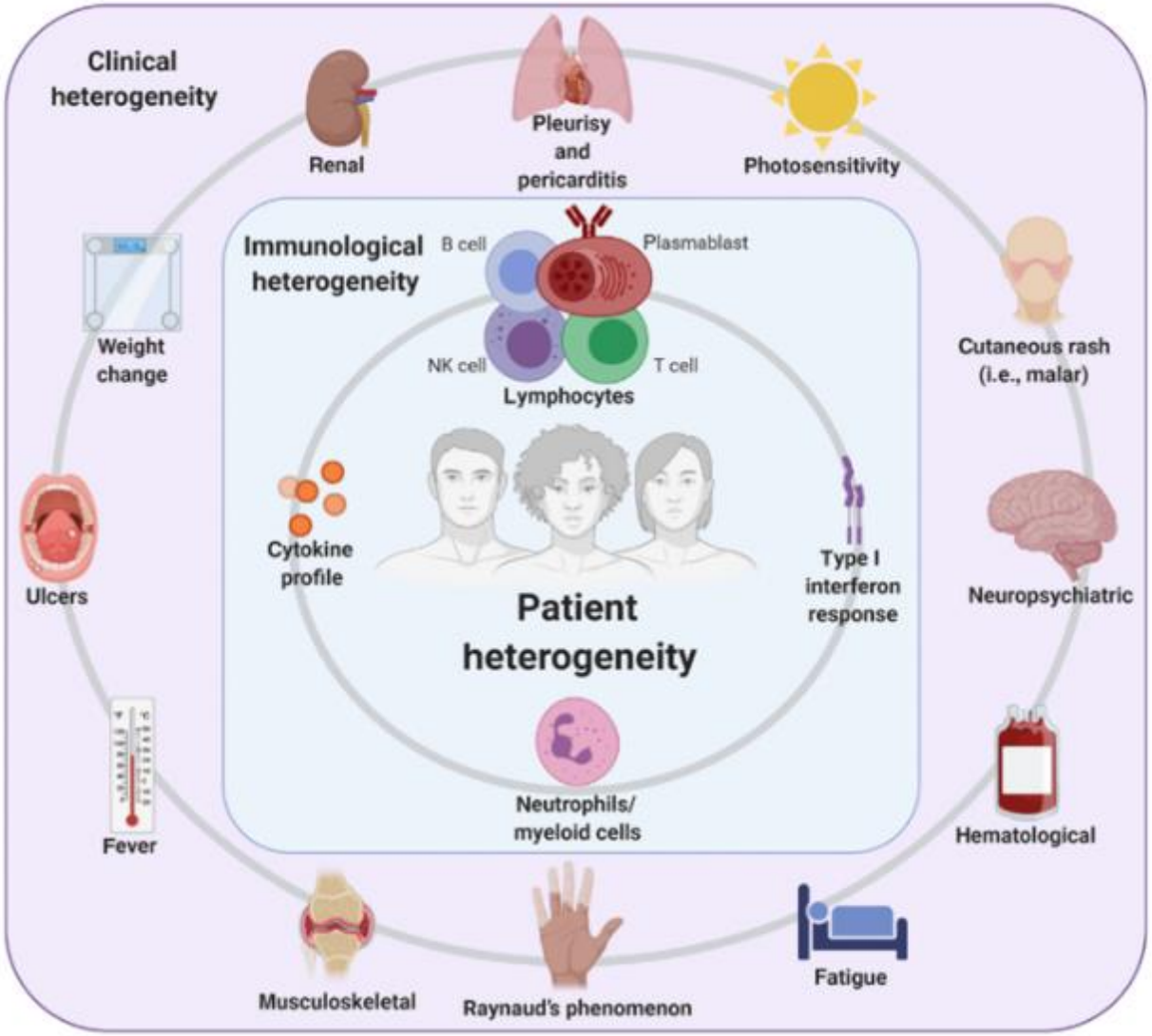
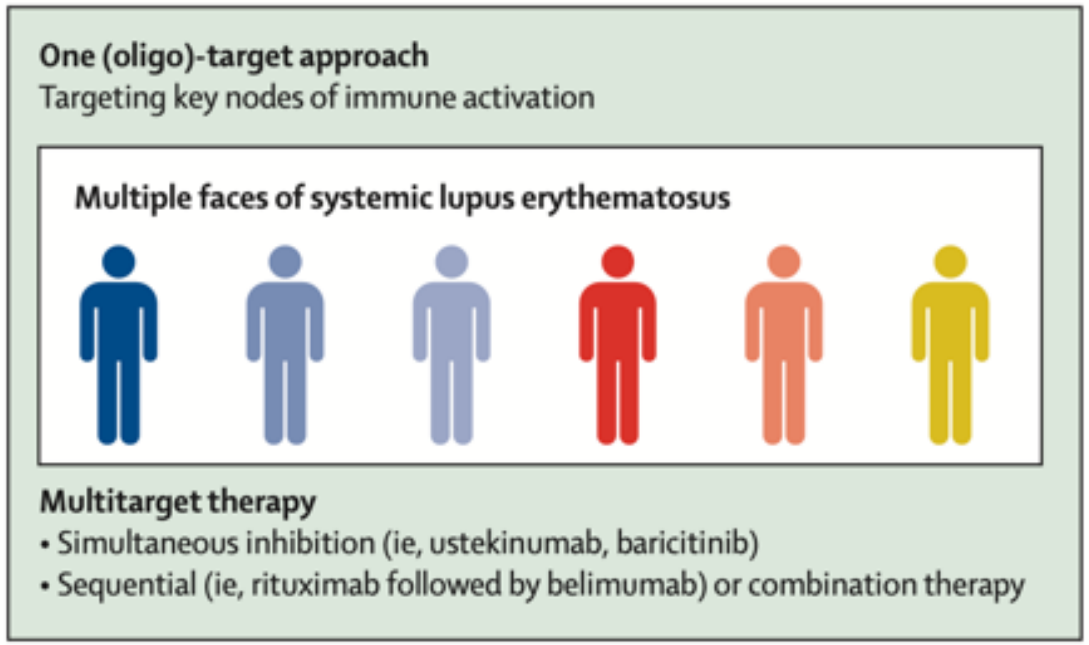
- Pathogenesis in tissues (the venues & screen sets)
  - All tissues are not created identical

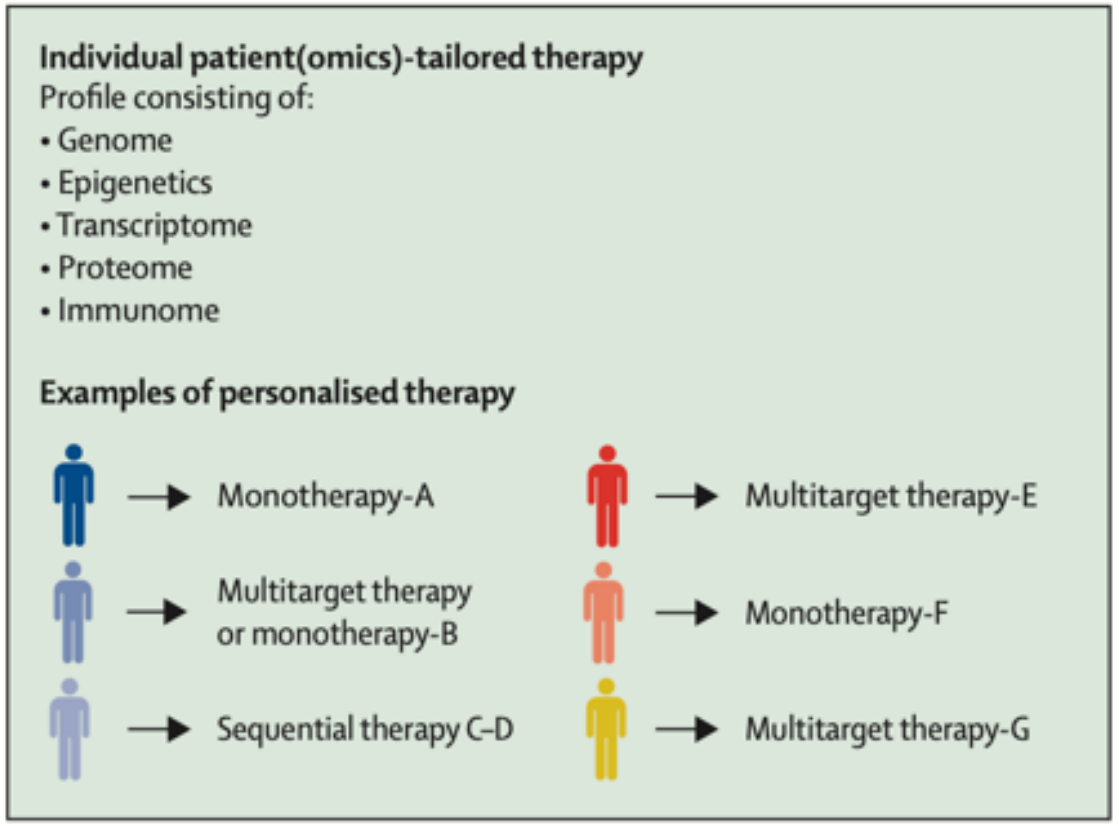
SLE is clinically heterogeneous – so too its immunology?



Allen M et al Trends in Molecular Medicine, February 2021, https://doi.org/10.1016/j.molmed.2020.09.009

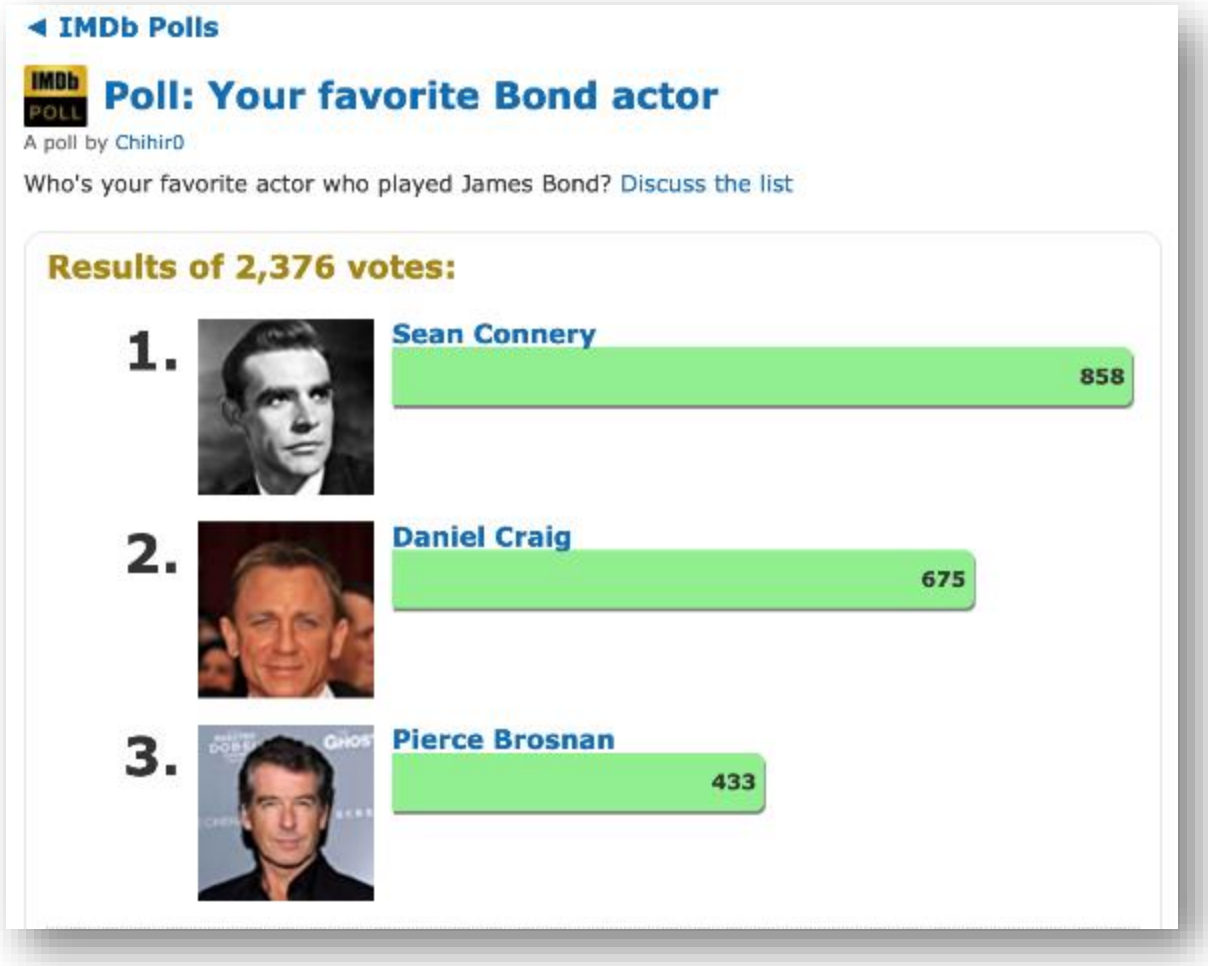
SLE is clinically heterogeneous – towards immunologic precision?





Dorner T & Furie R. Lancet Vol 393 June 8, 2019

No consensus on James Bond either…



https://www.imdb.com/poll/TUbLpUvRmyo/results?ref_=po_sr