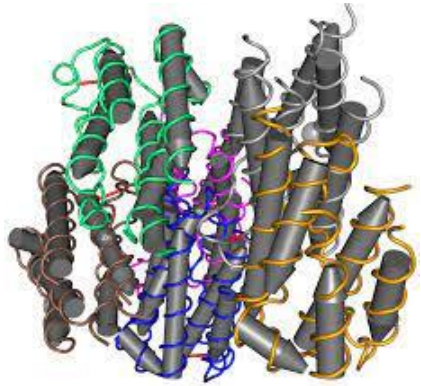
16-18 June 2023

4th IMMUNOLOGY WORKSHOP FOR CLINICIANS

AQUILA ATLANTIS HOTEL
HERAKLION - CRETE

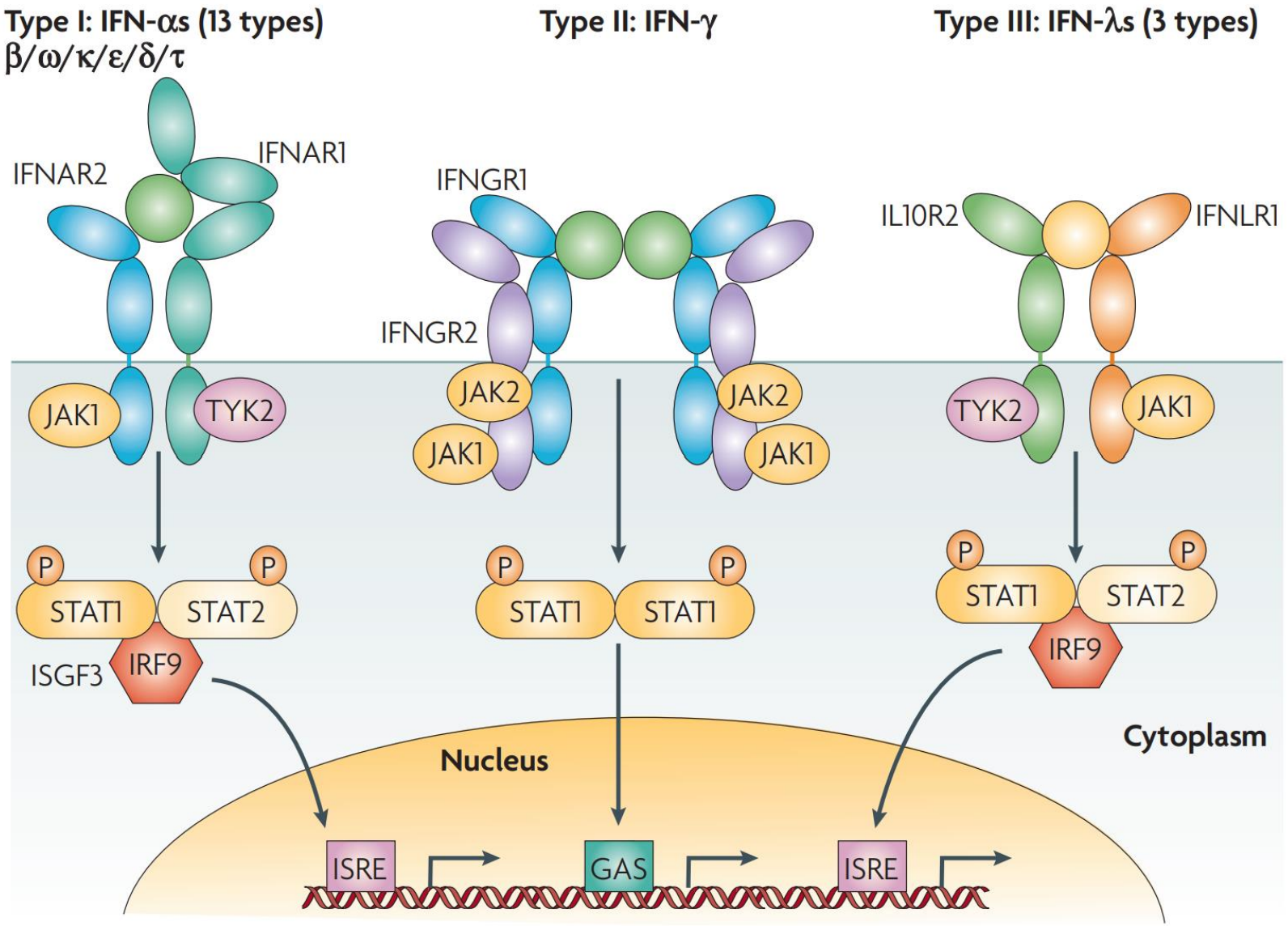
Current Immunological trends in clinical topics:

Cells and pathways producing interferon in health and disease



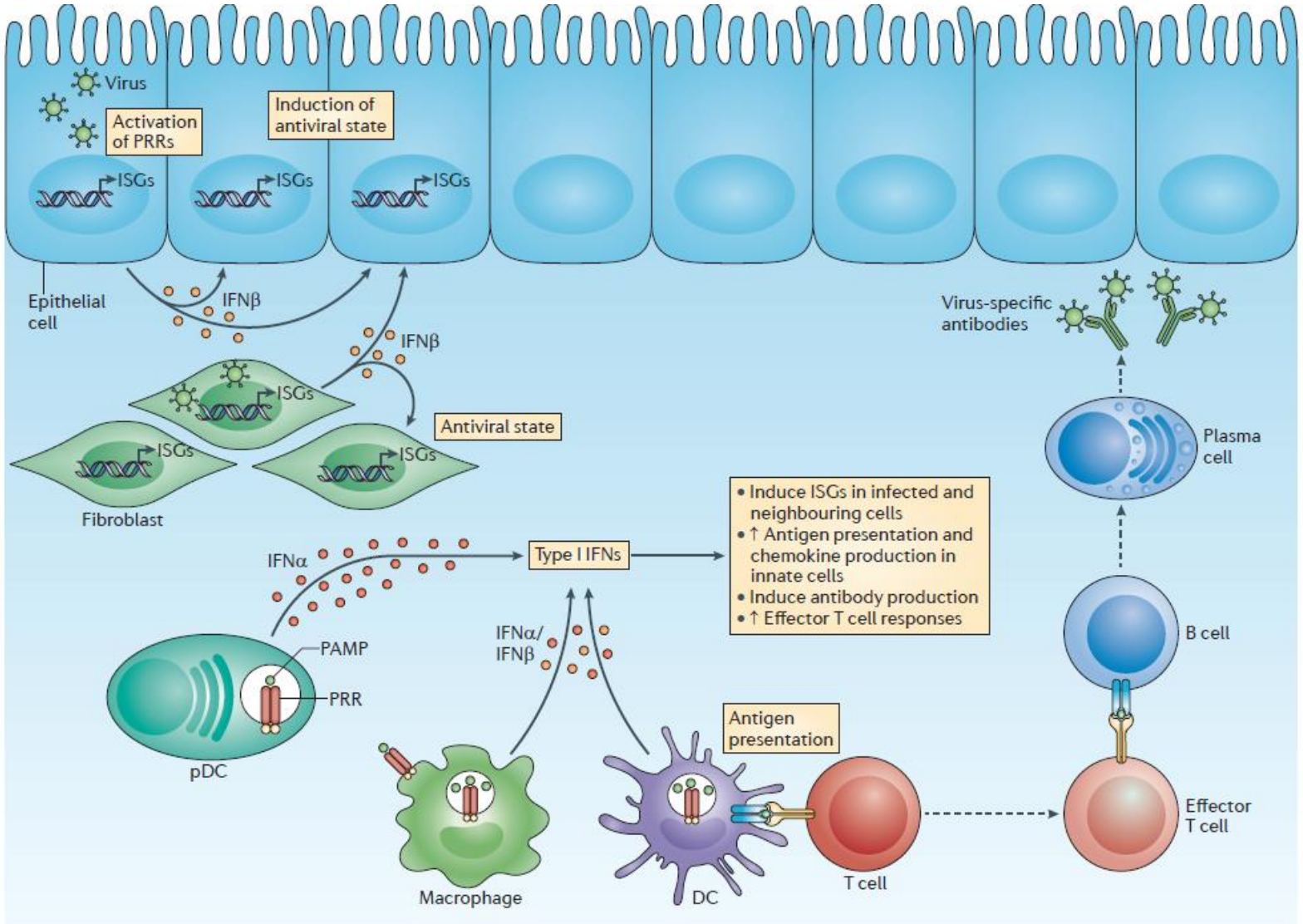
Aggelos Banos,
Rheumatology Resident, Asklepeion Voulas
PostDoctoral Fellow, BRFAA

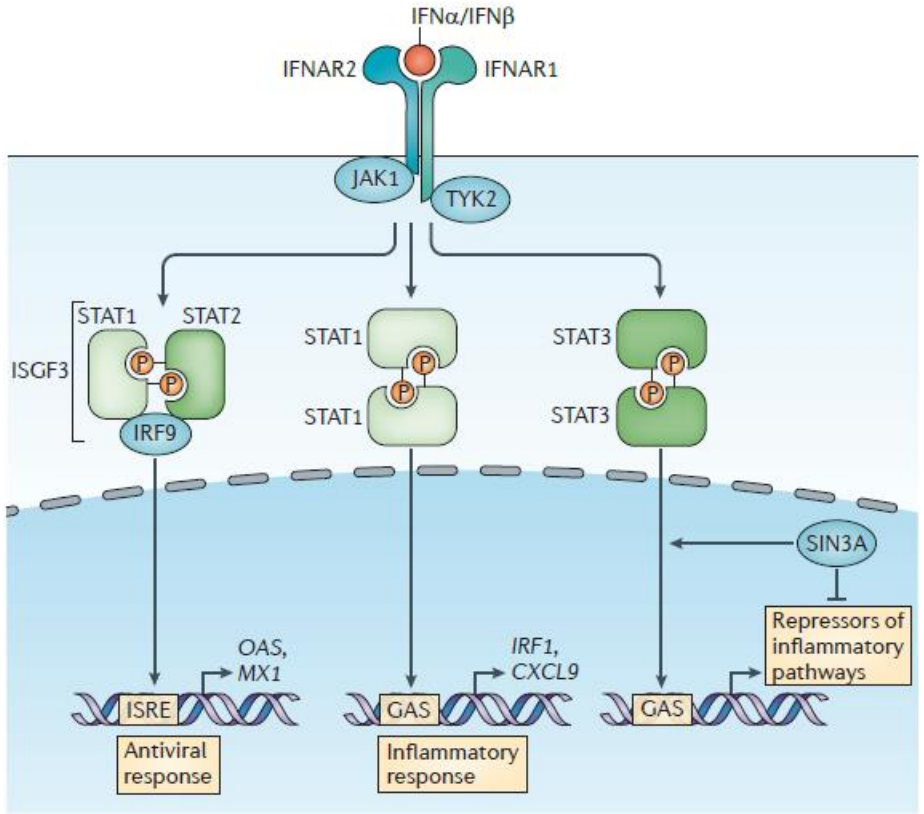
Type I, II and III interferons



Borden et al., Nat Rev Drug Discov., 2007

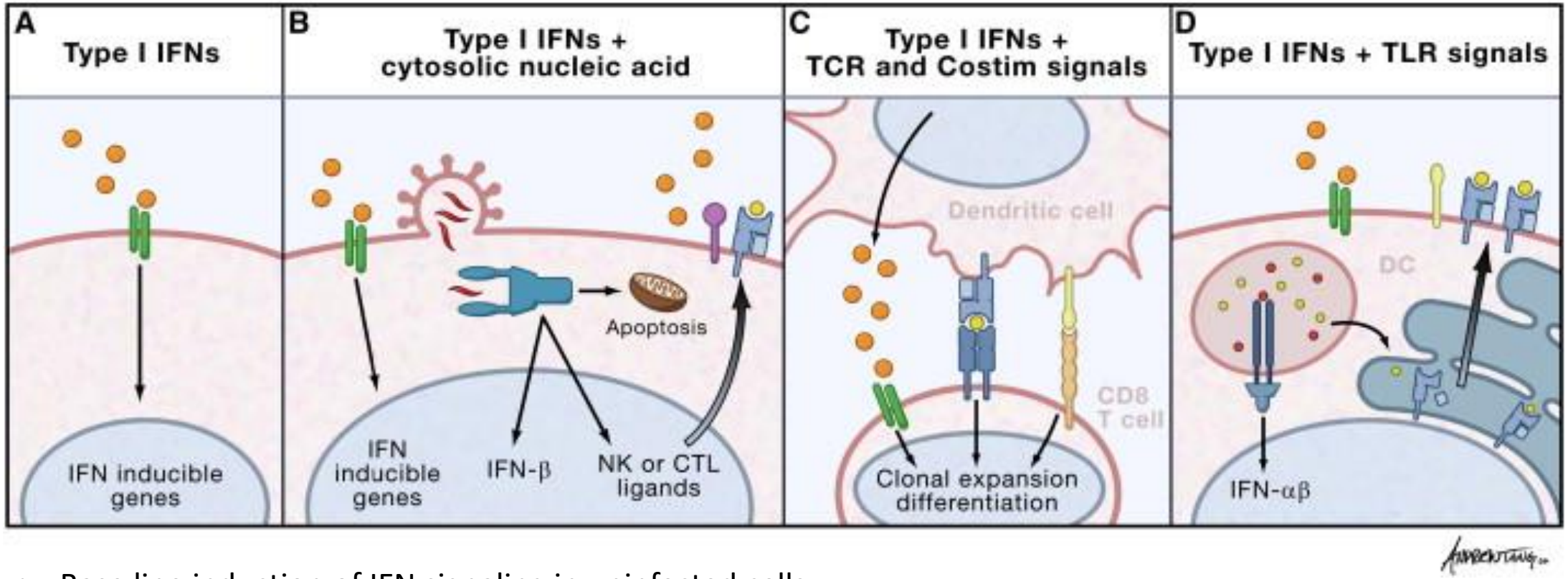
Regulation of type I interferon responses





Ivashkiv and Donlin, Nat Rev Immunol, 2014

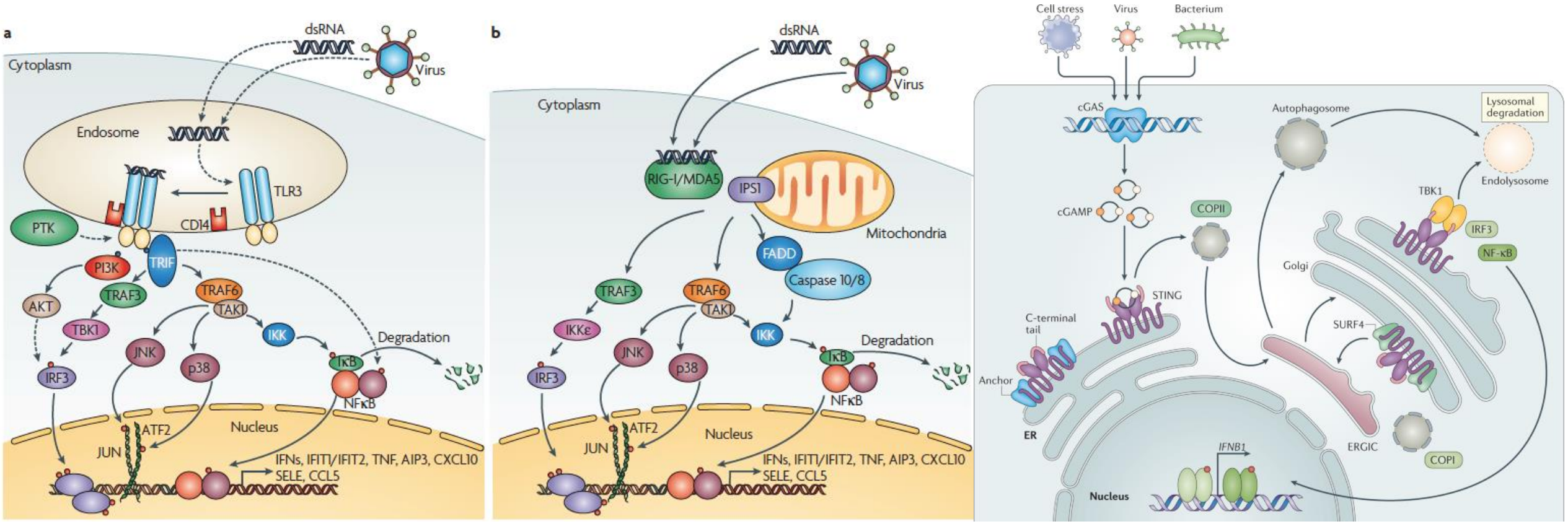
Type I IFN in host defense



- Base line induction of IFN signaling in uninfected cells
- Infection: sense of cytosolic nuclei acid→ IFN beta → paracrine activation
- Clonal expansion and differentitaion of CD8+ cells through IFN signaling
- DCs sense IFNs and cross-present antigens

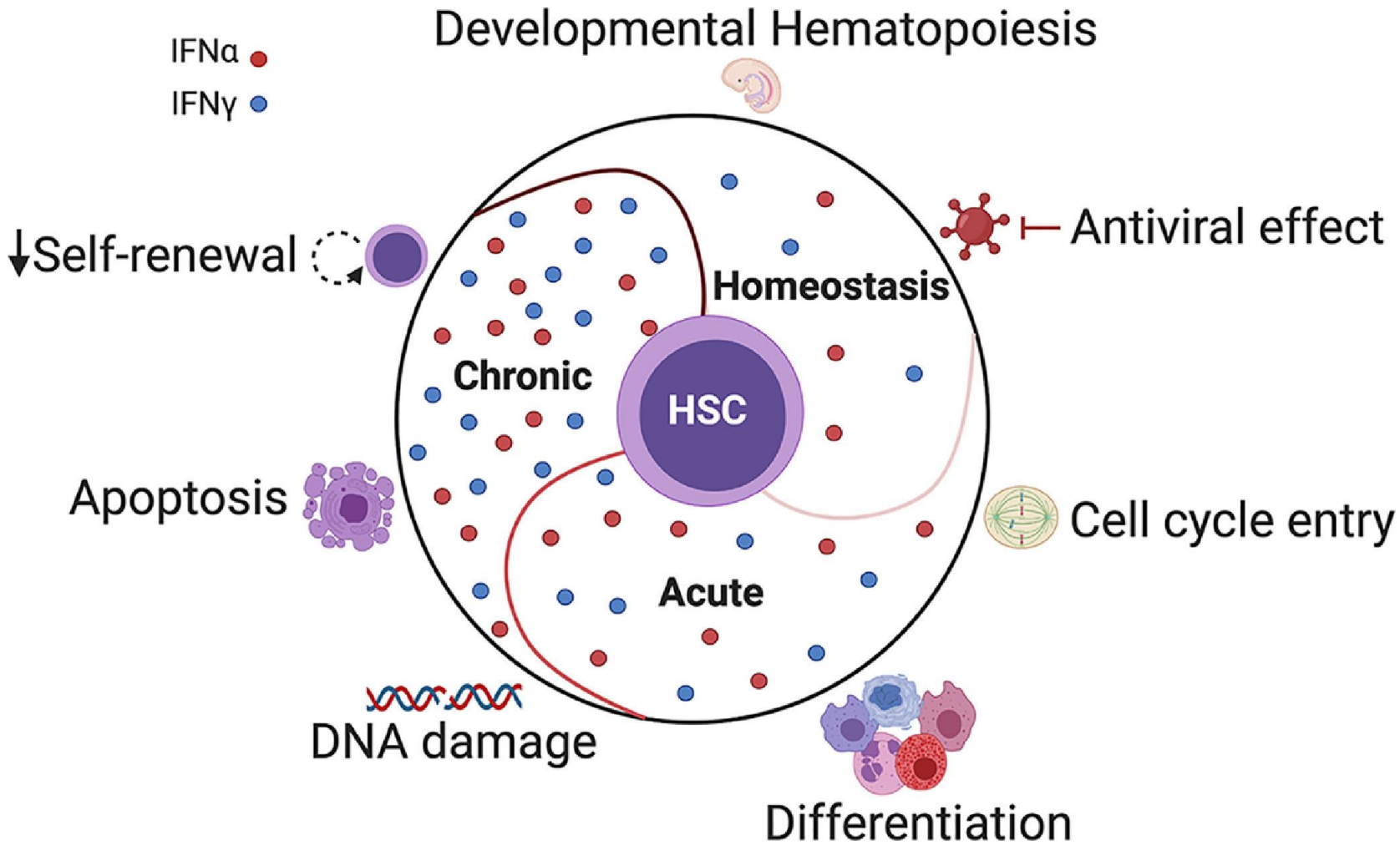
Stetson and Medzhitov, Immunity, 2006

Type I IFN signaling



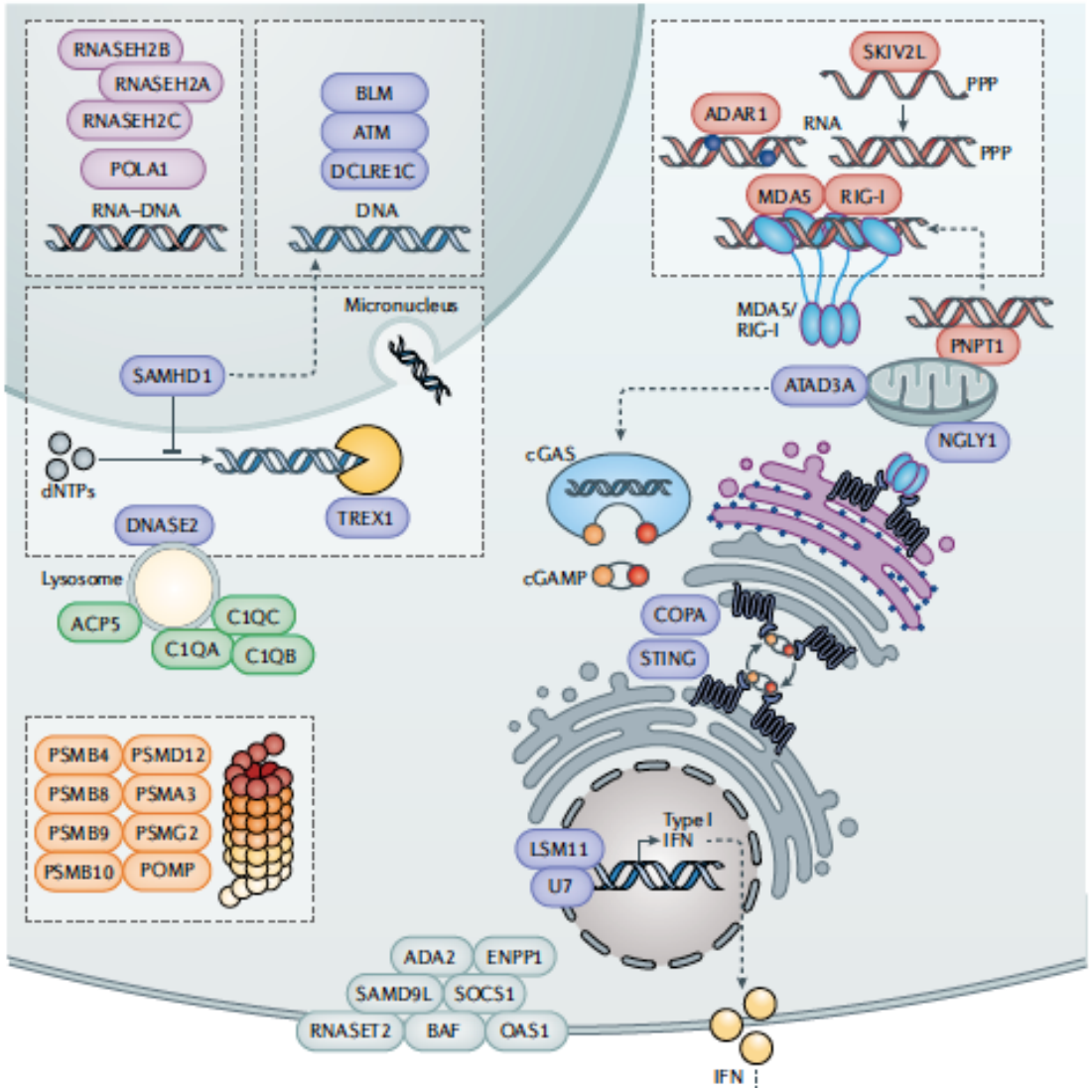
Ivashkiv and Donlin, Nat Rev Immunol, 2014

Effect of interferons in hematopoiesis



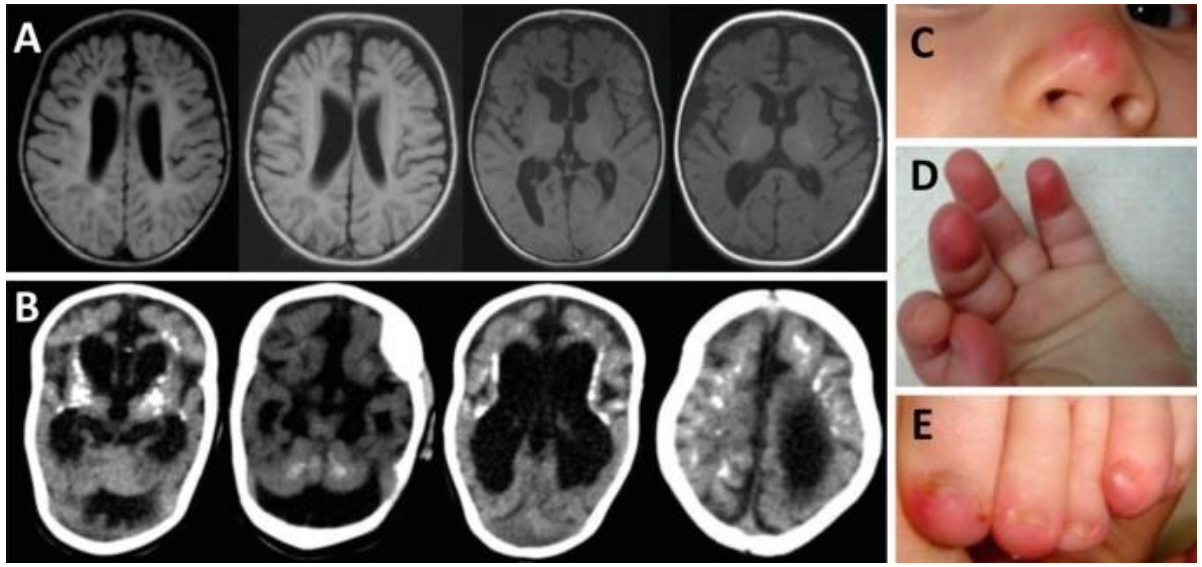
Demerdash Y et al, Exp Hem 2021

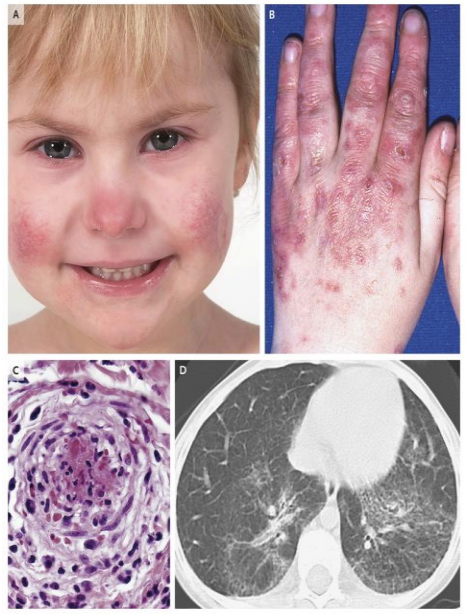
Genetic Interferonopathies



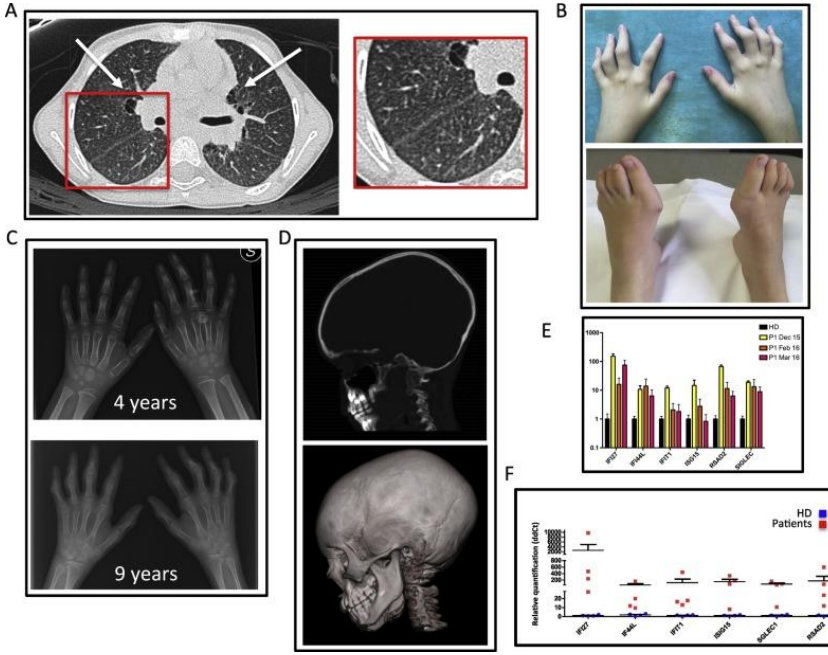
Crow and Stetson, Nat Rev Immun 2022
Tungler et al, Enc of Med Imm. 2019
Liu et al NEJM 2014
Volpi et al, Clinical Immunology 2018

Aicardi-Gutierez Syndrome



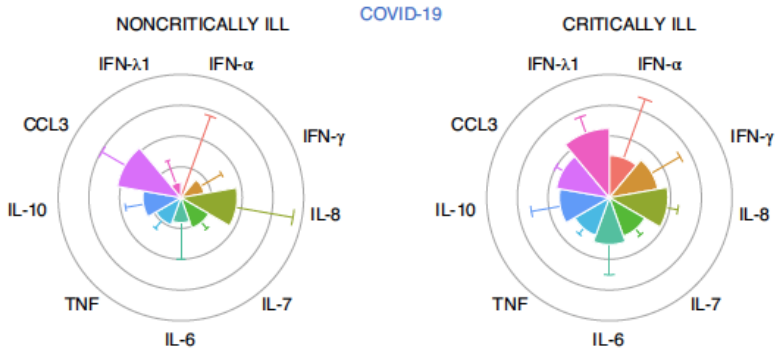


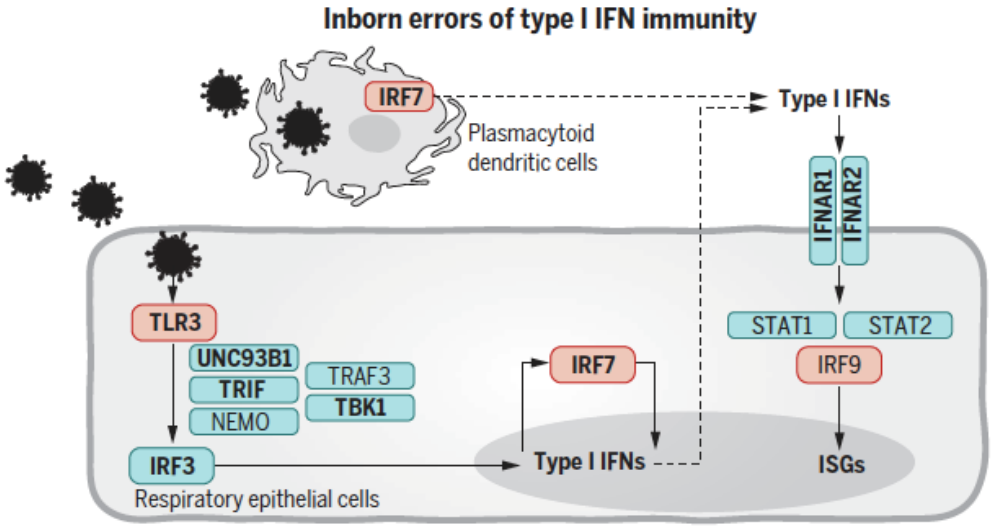
SAVI Syndrome

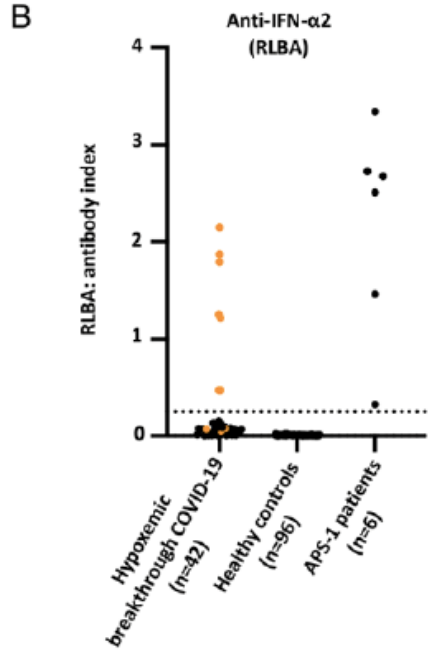


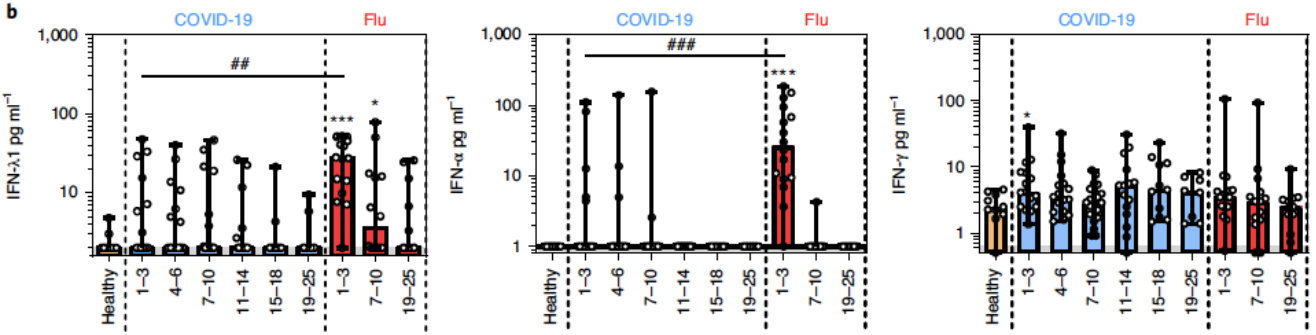
COPA syndrome

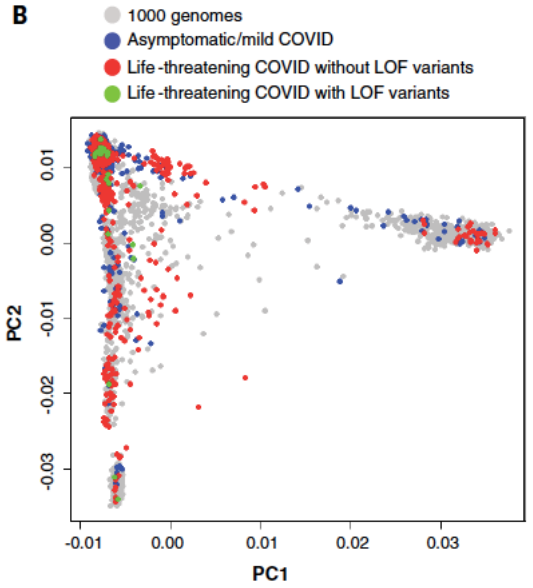
IFNs in COVID19

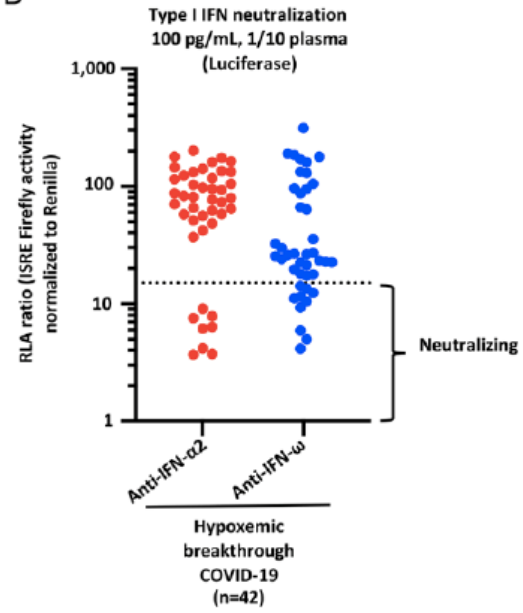






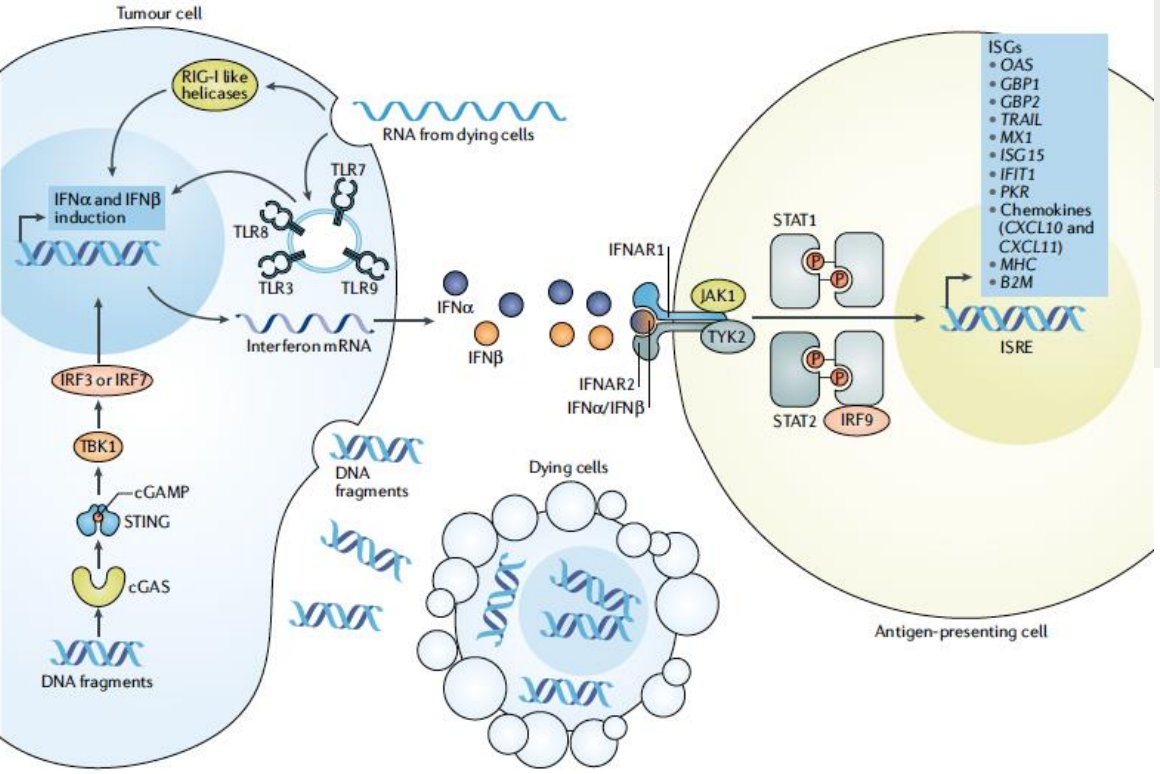


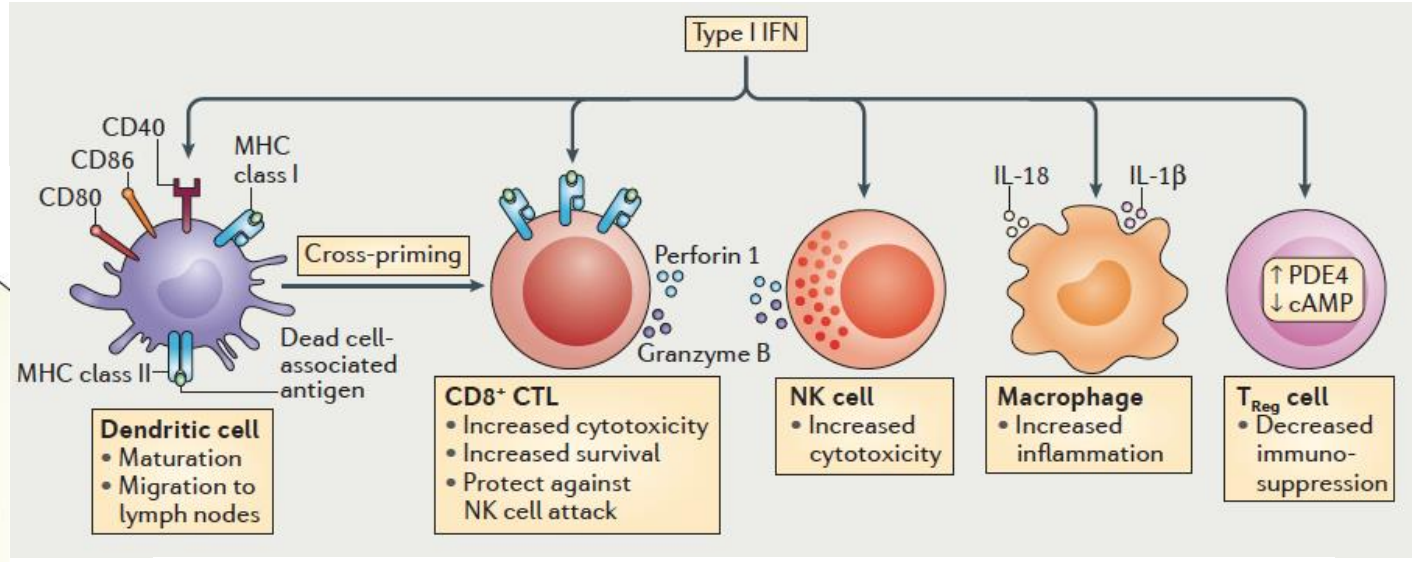


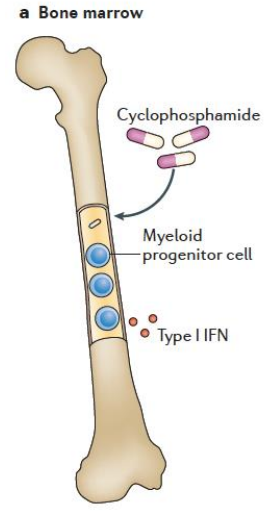


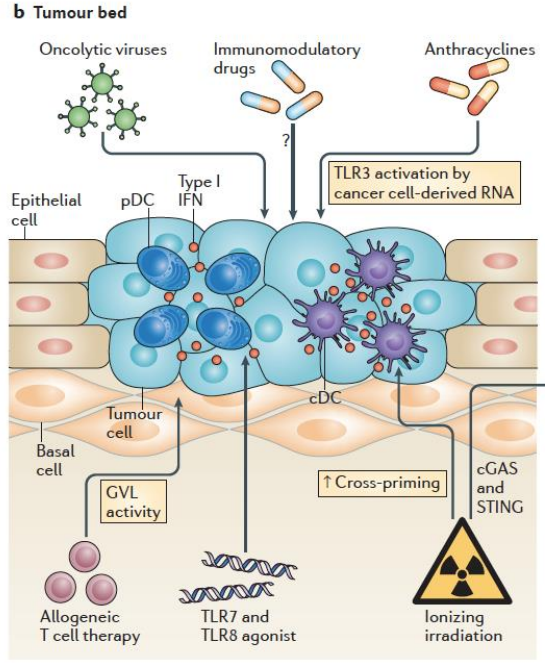
Galani I. et al, Nat Immun 2021
Bastard P. et al, Science Immunology 2022
Zhang Q, et al Science 2020

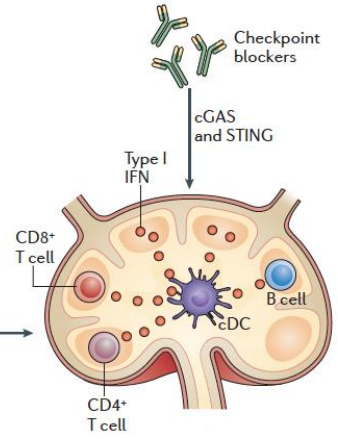
Interferon impact on cancer biology



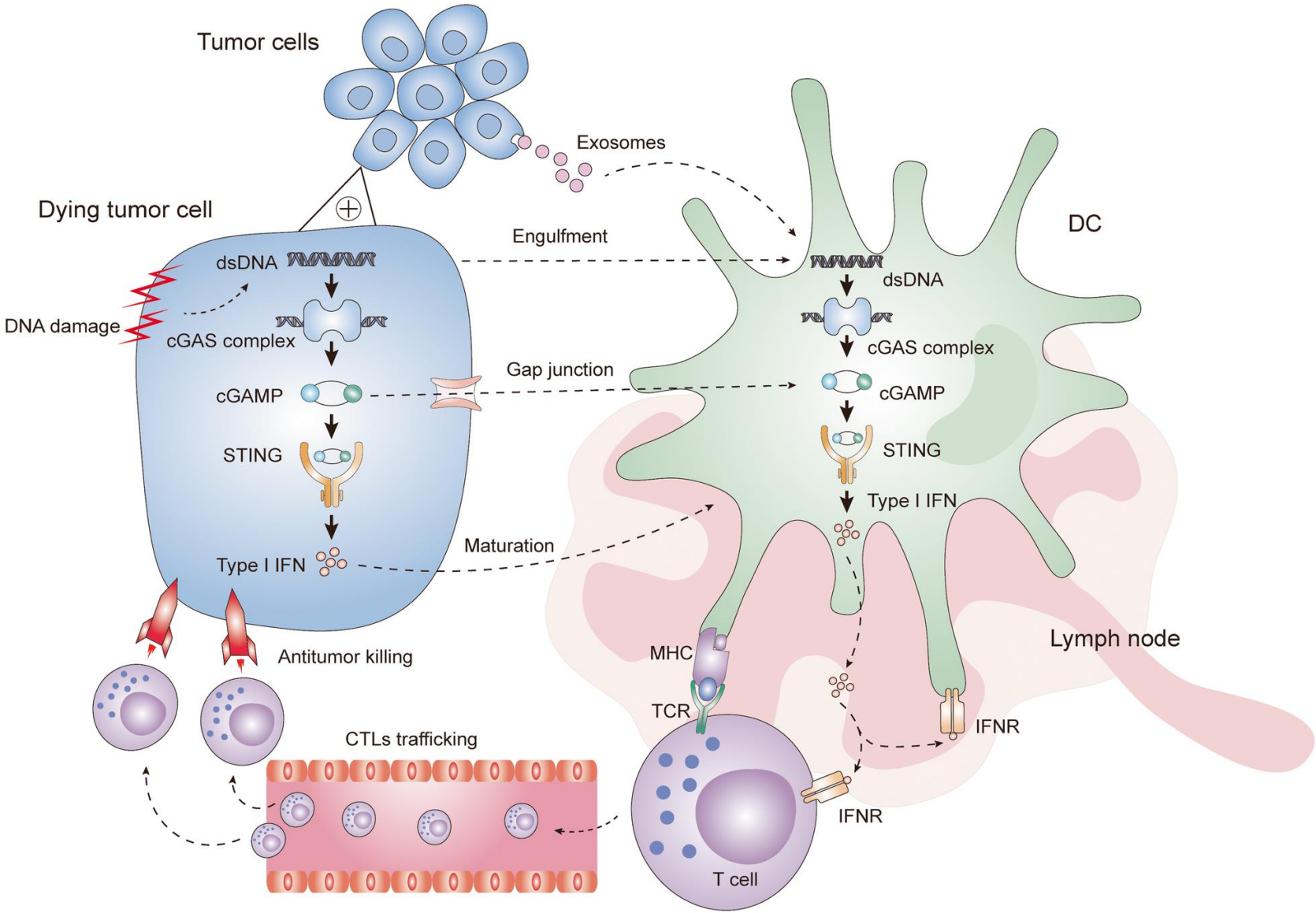






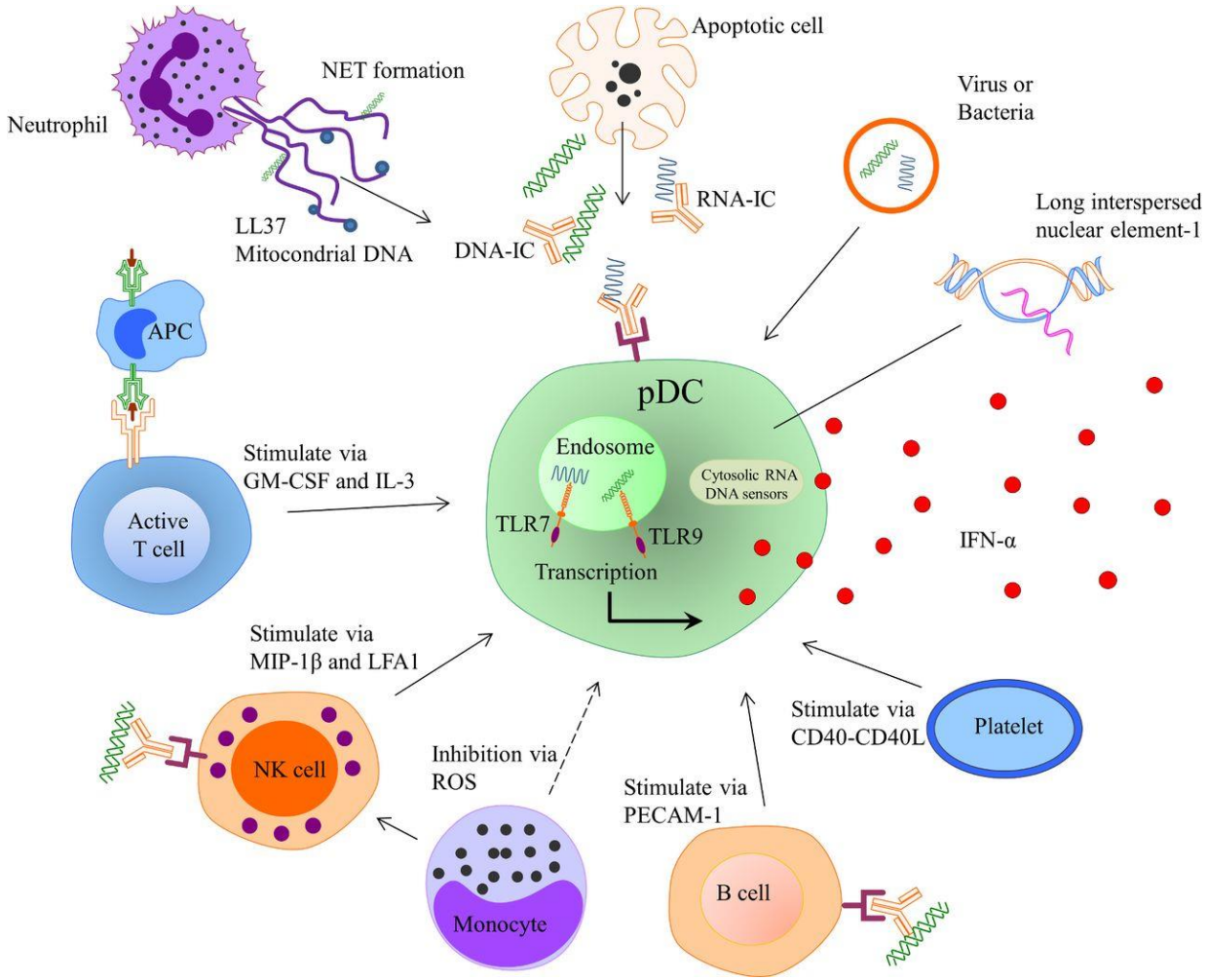


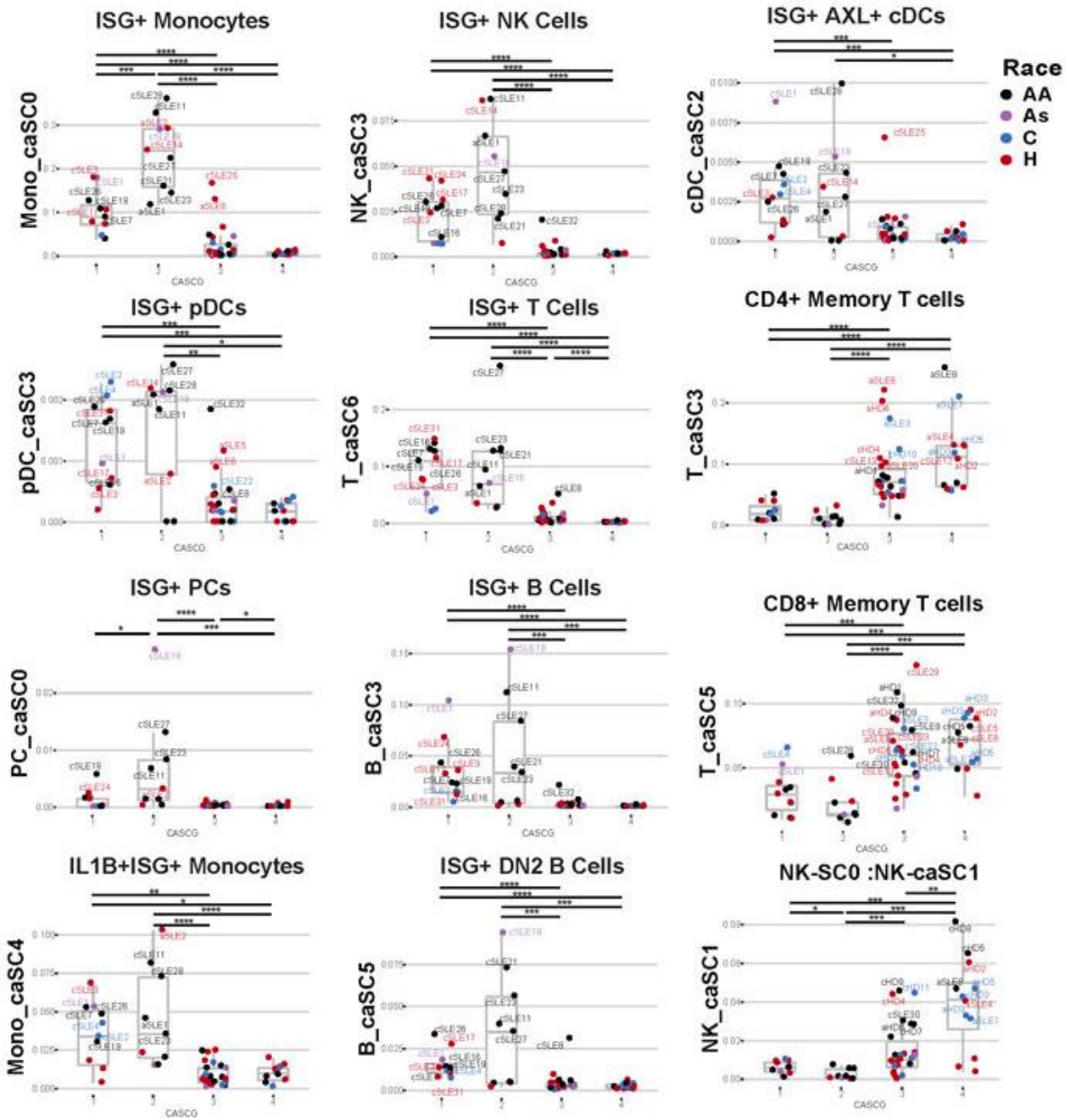
cGAS/STING pathway and Type I IFN in tumor immunity



Zheng J, Molecular Cancer 2020

IFN pathway in SLE
Cell type-specific profile

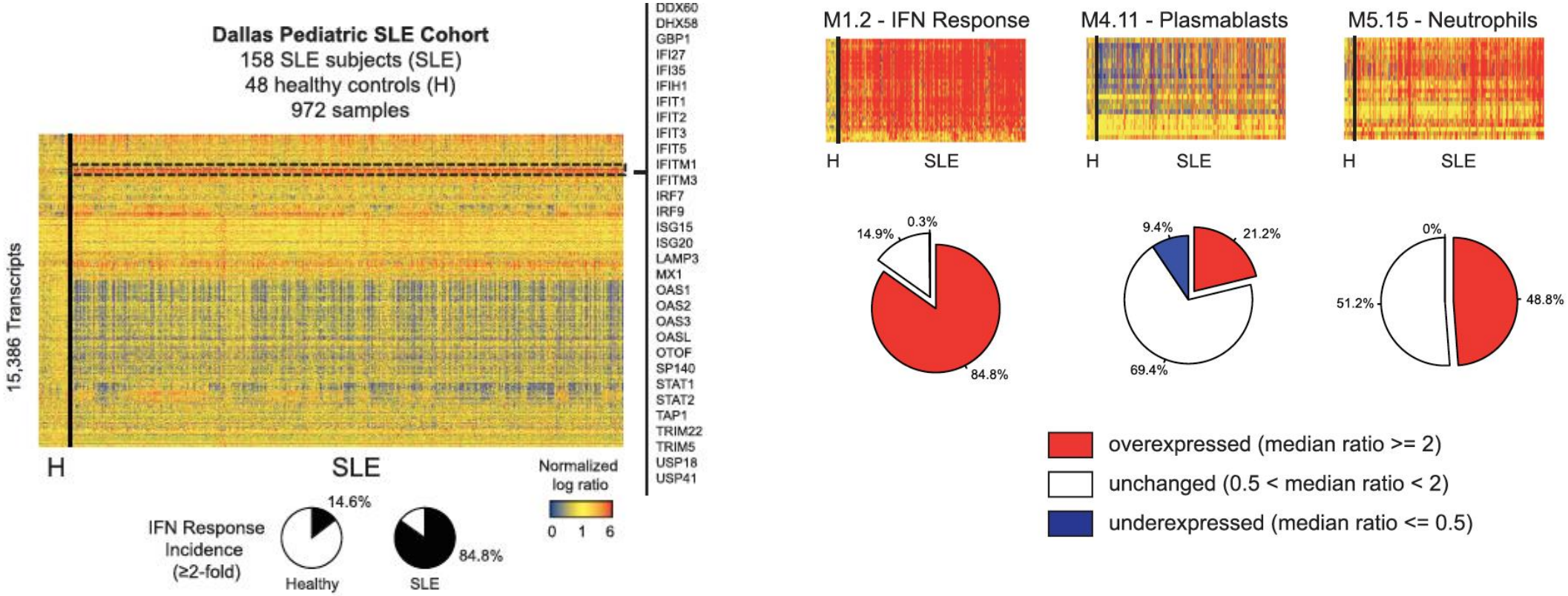


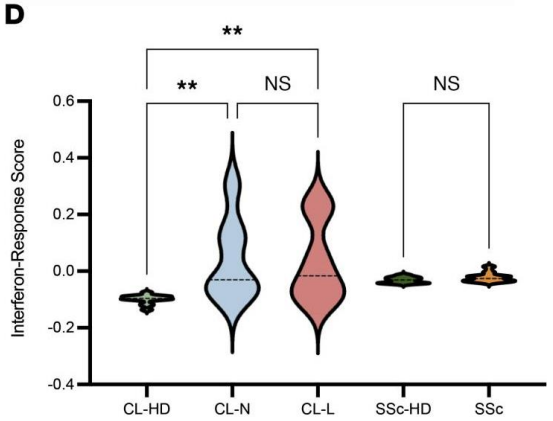


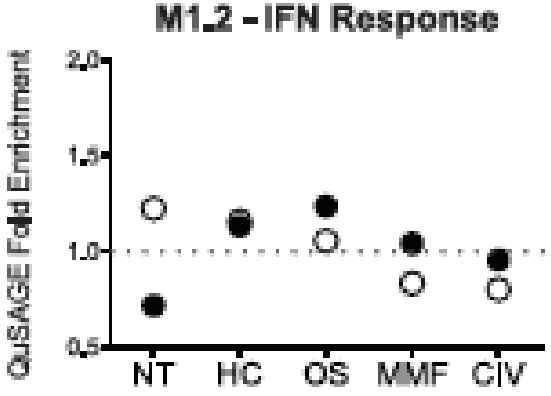
Ronnblom L. et al, Lupus Science and Medicine. 2018

Nehar-Belaid D. et al, Nat Immun. 2020

Molecular Stratification of Lupus Patients





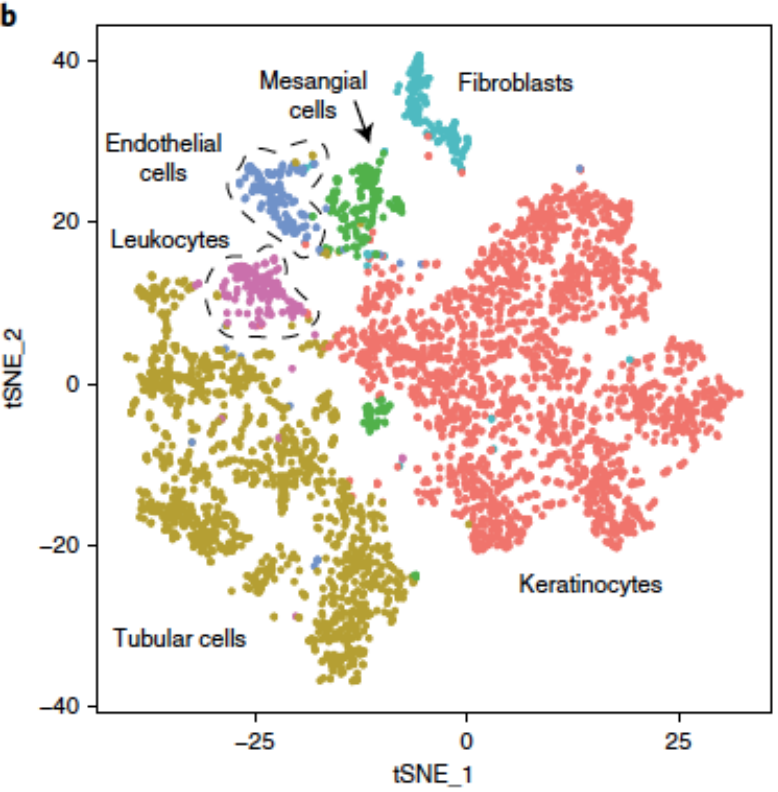


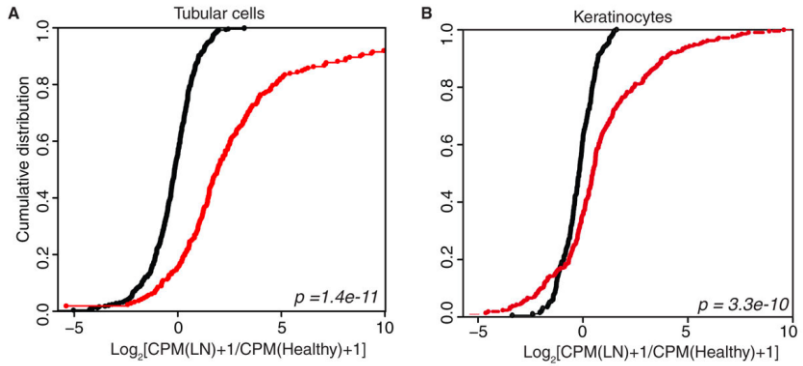
- IFN signature correlates with active disease
- SLE specific signature
- Differential therapy response to IFN signature

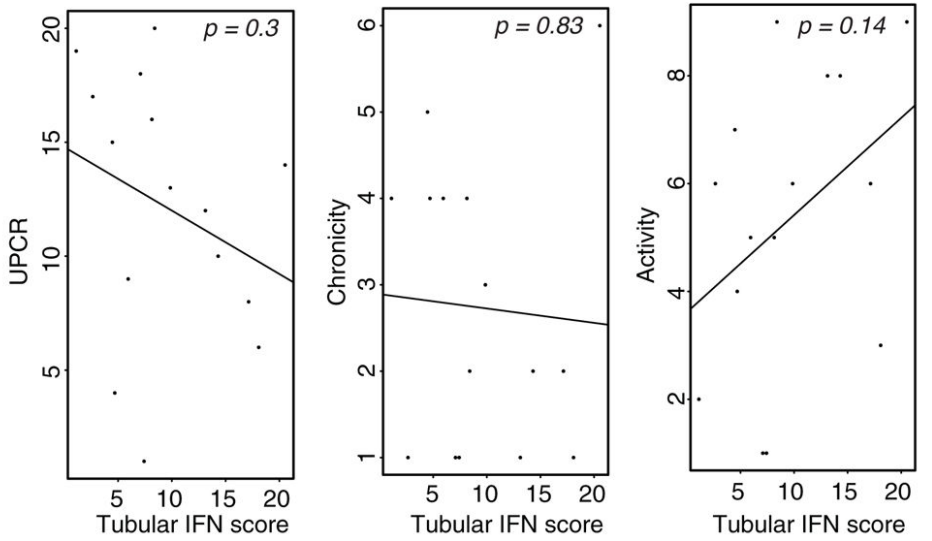
Banchereau et al. Cell 2016

nature immunology
RESOURCE
https://doi.org/10.1038/s41590-019-0386-1

Tubular cell and keratinocyte single-cell transcriptomics applied to lupus nephritis reveal type I IFN and fibrosis relevant pathways

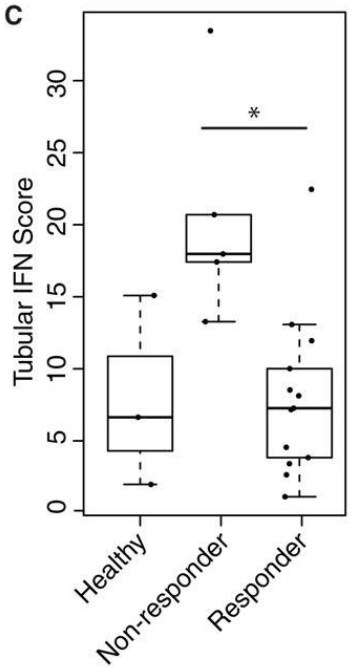


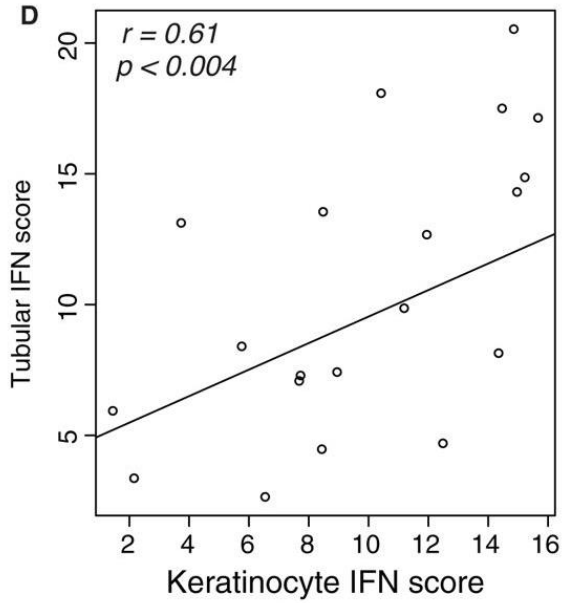




- Higher tubular IFN score in non-responders
- High correlation of keratinocyte vs tubular IFN score
- High correlation of LN damage indices to IFN score

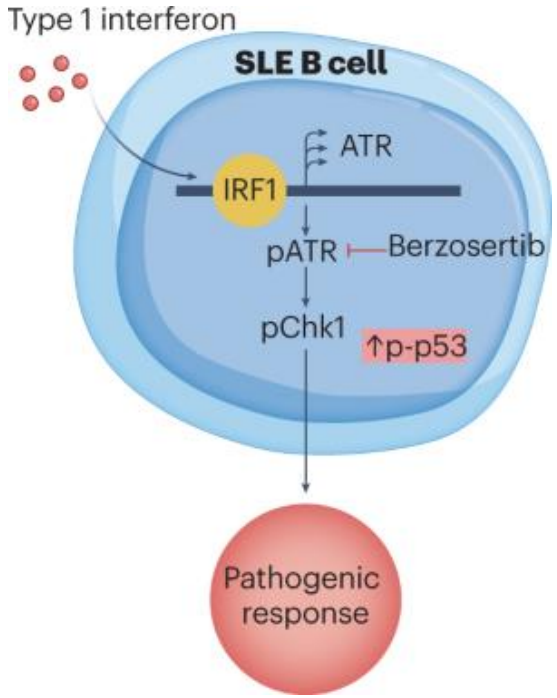
Single-cell analysis of the same individual: Skin vs Kidney

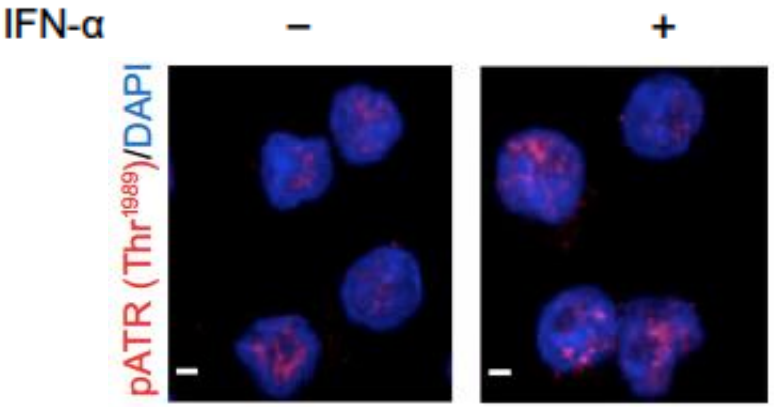




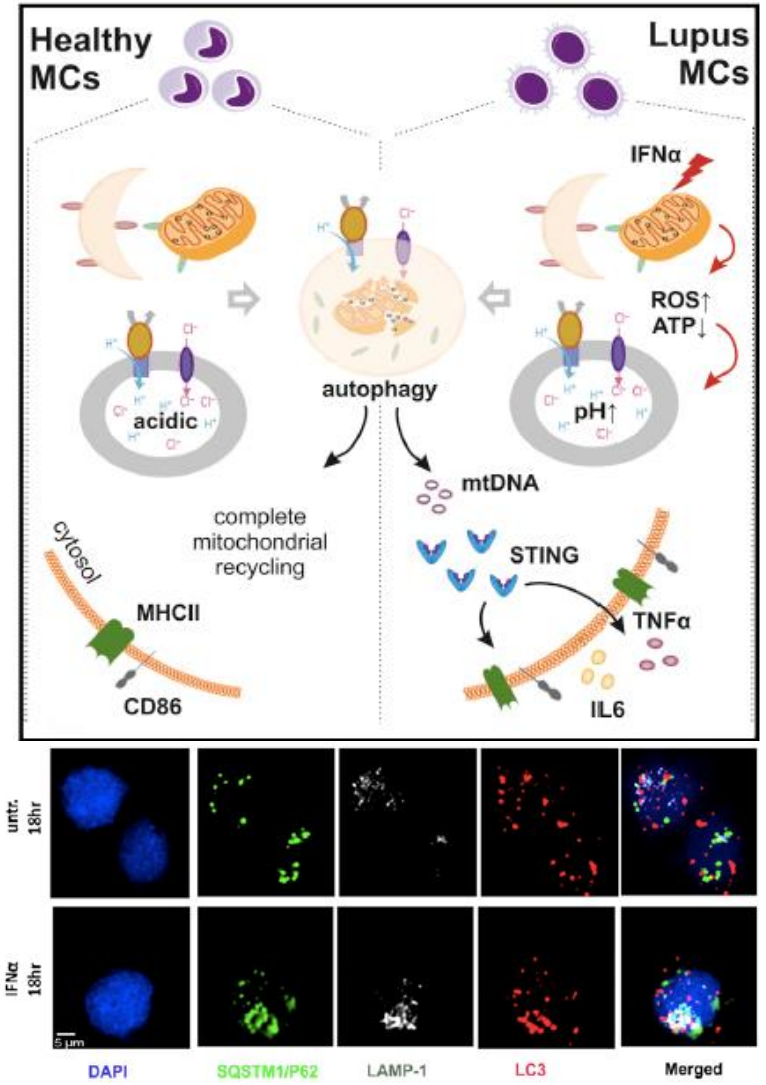
Der E., et al. *Nat Immun*. 2019

Different mechanisms promote autoimmunity through IFN signaling

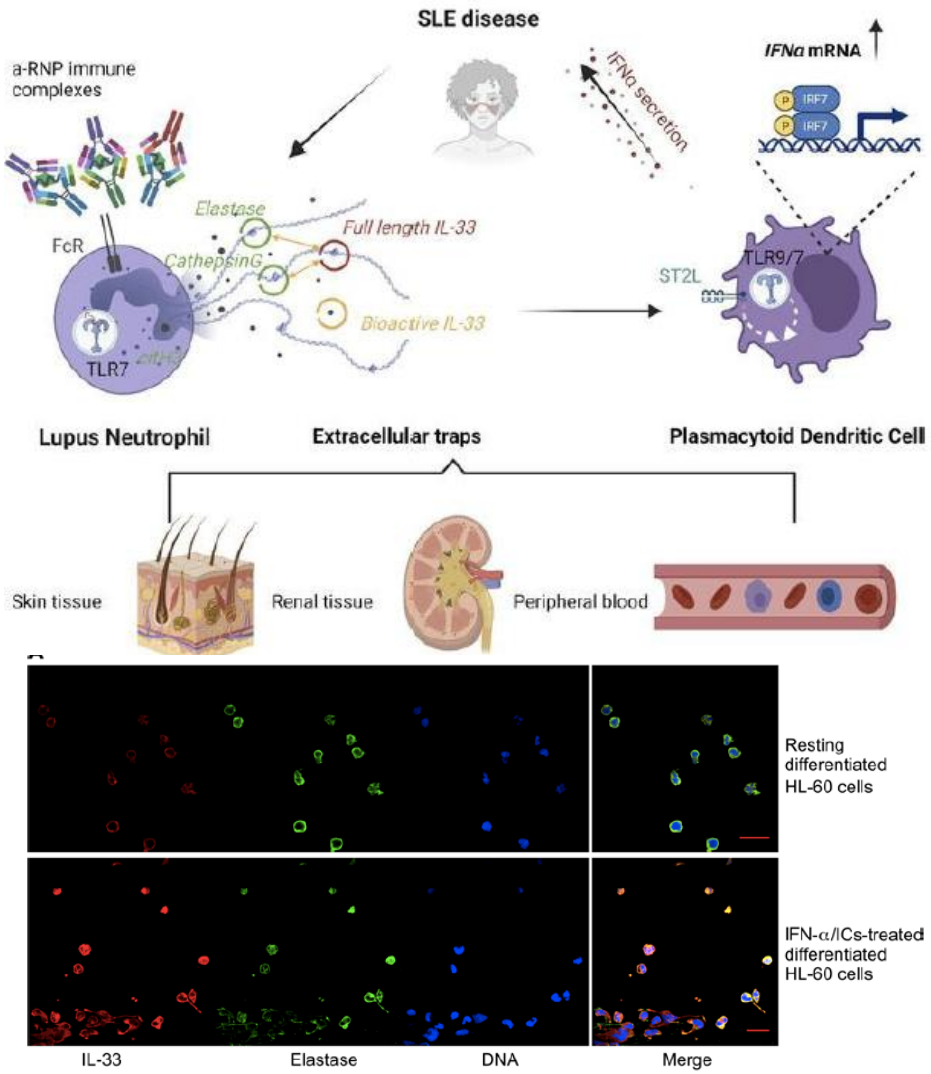




Manolakou T et al, Science Advances 2022



Gkirtzimanaki K et al, Cell Rep 2018

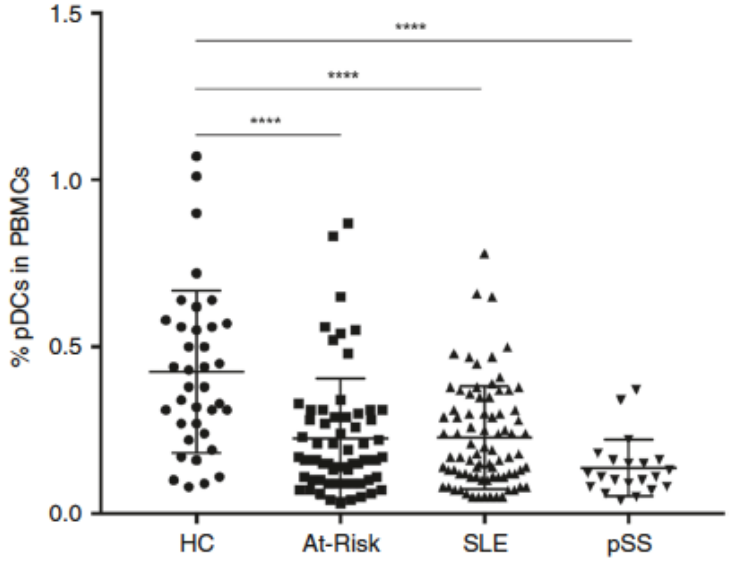


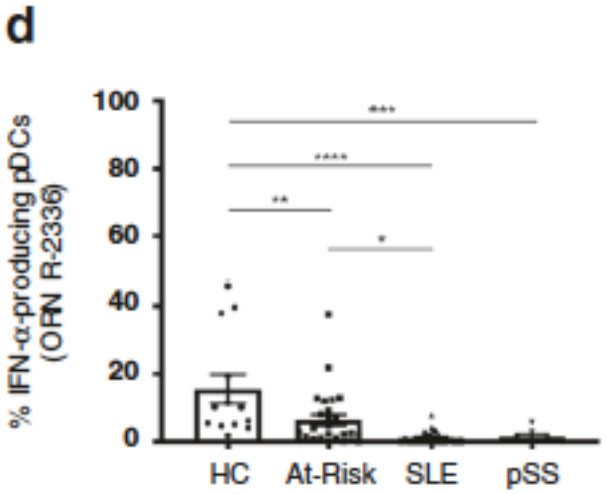
Georgakis S et al, JCI insight 2021

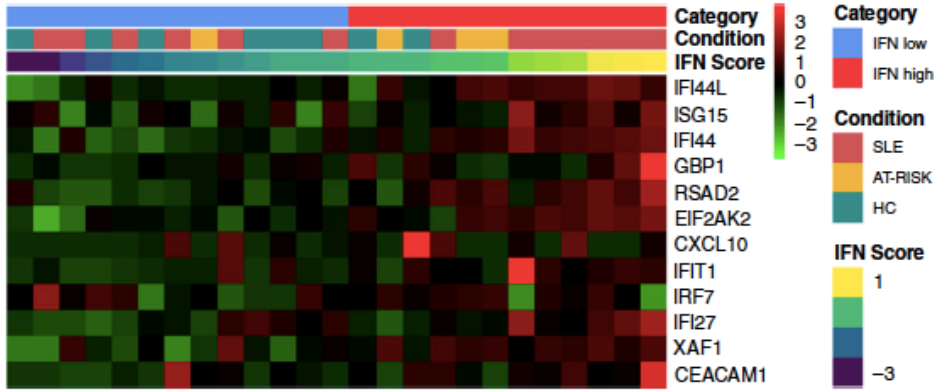
Functionally impaired plasmacytoid dendritic cells and non-haematopoietic sources of type I interferon characterize human autoimmunity

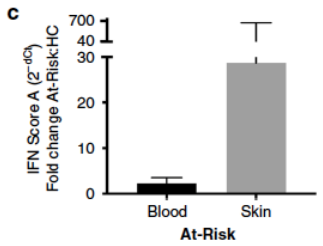
Antonios Psarras[1,2,3], Adewonuola Alase[1], Agne Antanaviciute[4], Ian M. Carr[4], Md Yuzaiful Md Yusof[1,2], Miriam Wittmann[1,2], Paul Emery[1,2], George C. Tsokos[3] & Edward M. Vital[1,2]✉

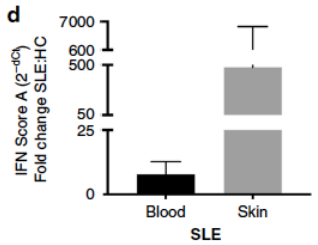
Current theories of the cell source of IFNs

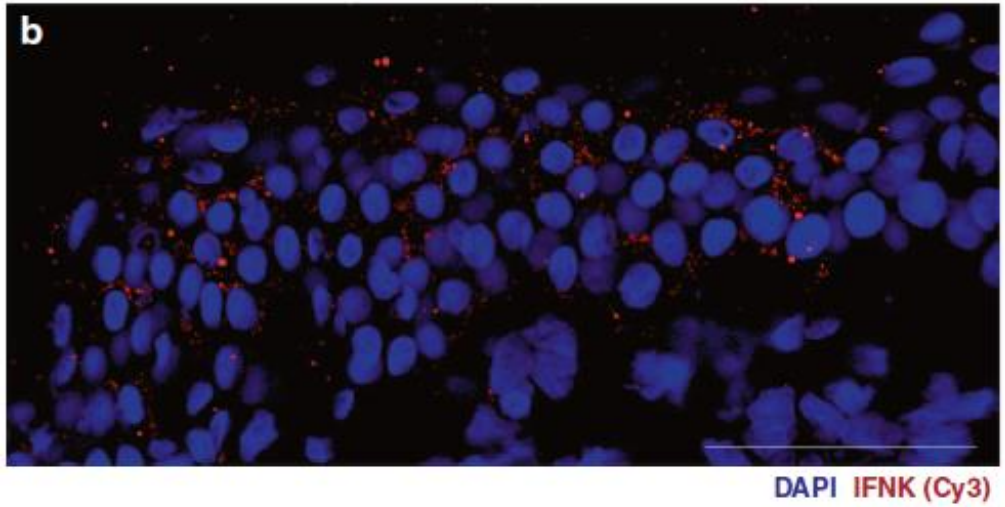


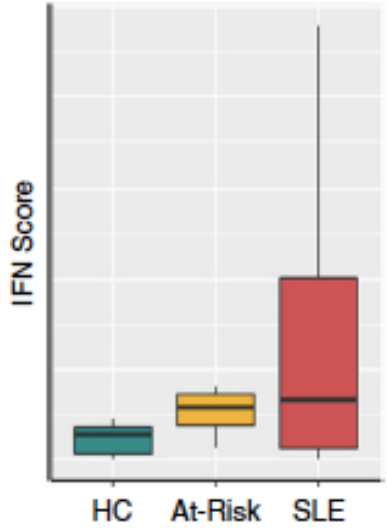






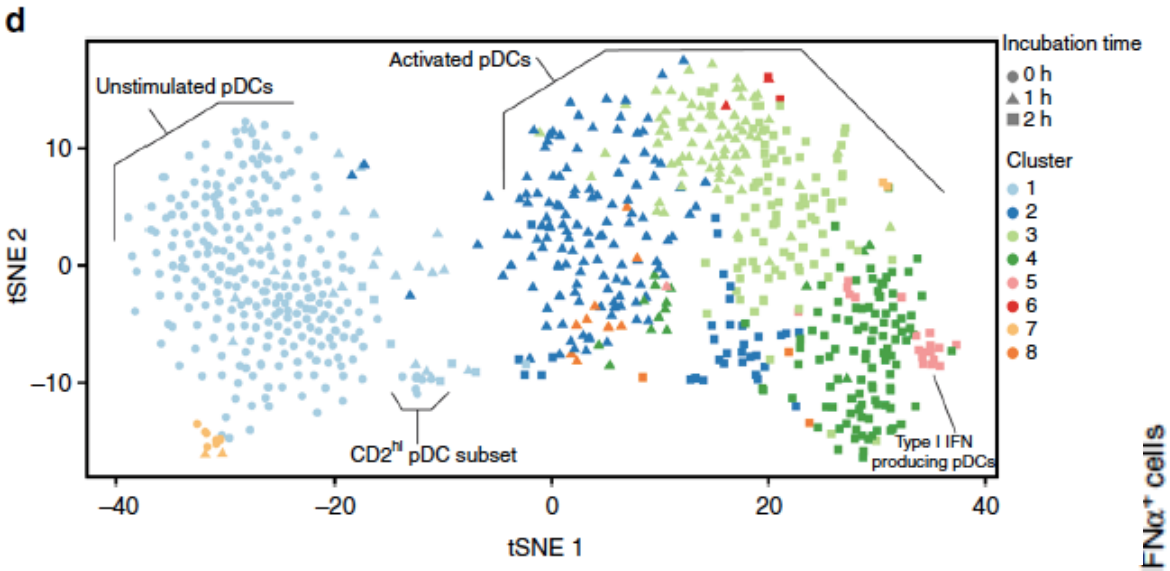


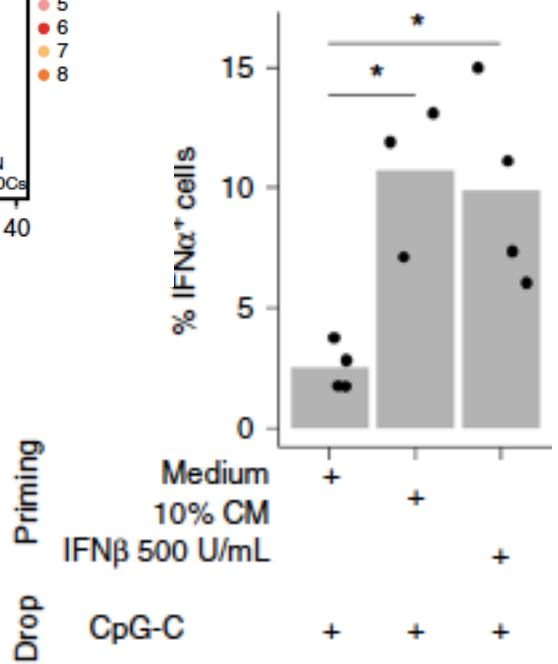


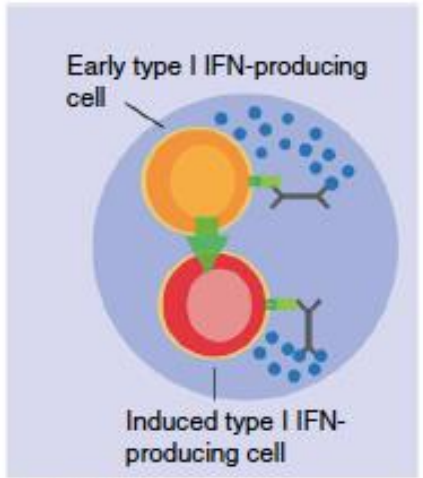


Single-cell analysis reveals that stochasticity and paracrine signaling control interferon-alpha production by plasmacytoid dendritic cells

Florian Wimmers[1,2], Nikita Subedi[3,4], Nicole van Buuringen[1], Daan Heister[1], Judith Vivié[5], Inge Beeren-Reinieren[1], Rob Woestenenk[6], Harry Dolstra[6], Aigars Piruska[7], Joannes F.M. Jacobs[8], Alexander van Oudenaarden[5], Carl G. Figdor[1], Wilhelm T.S. Huck[7], I. Jolanda M. de Vries[1] & Jurjen Tel[1,3,4]

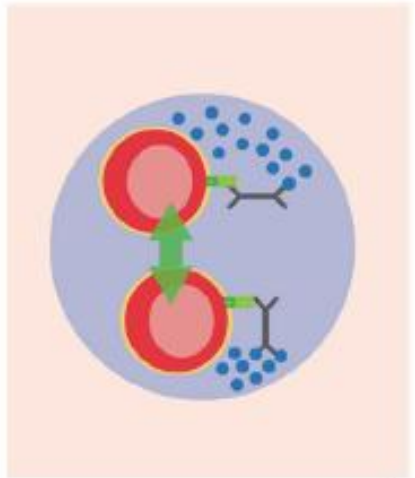






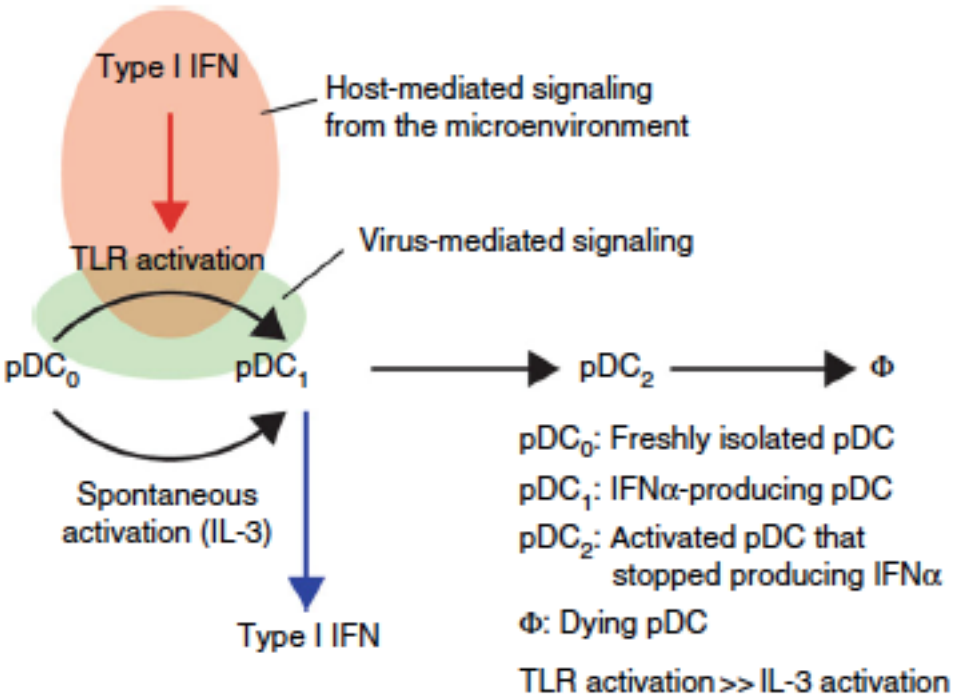
Model blue: $y \sim a \times x + a$

Rare early type I IFN-producing cell induces type I IFN production in co-encapsulated cell

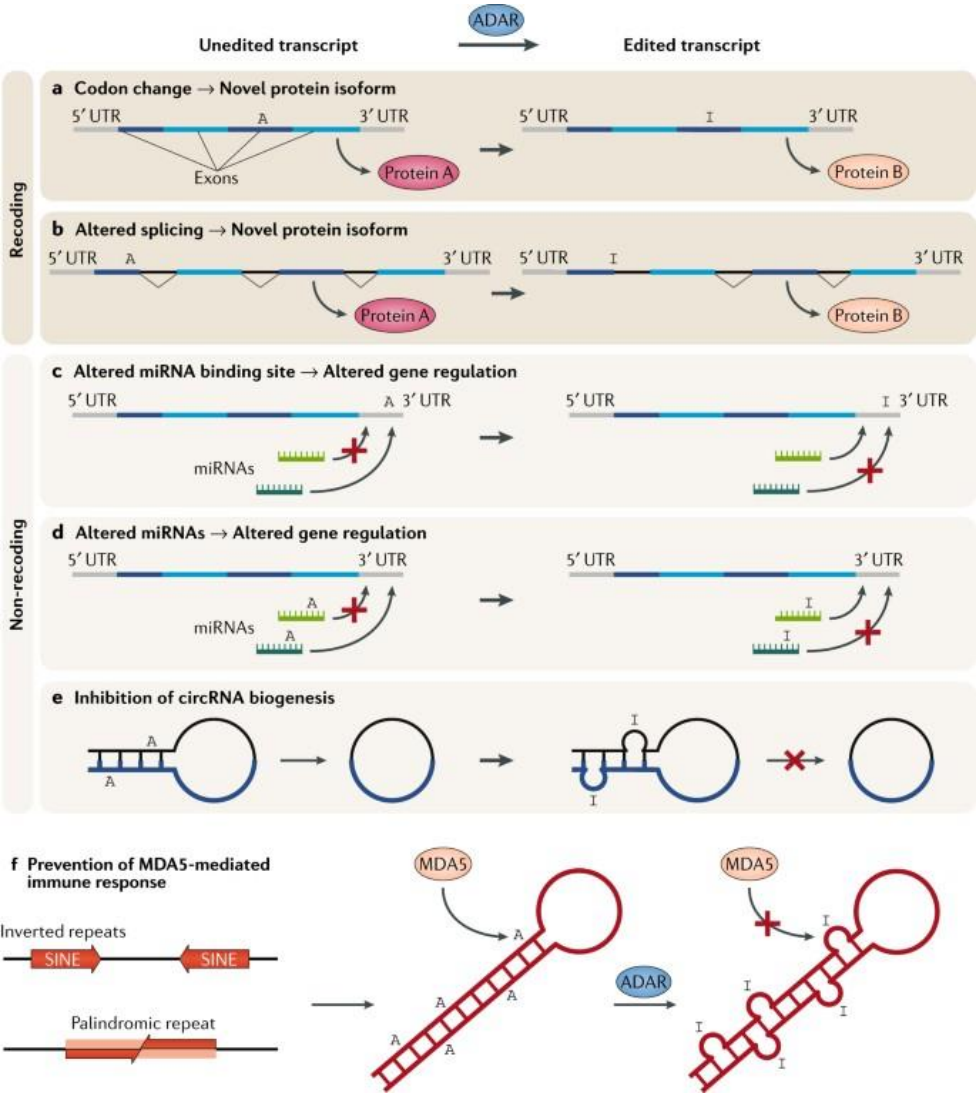


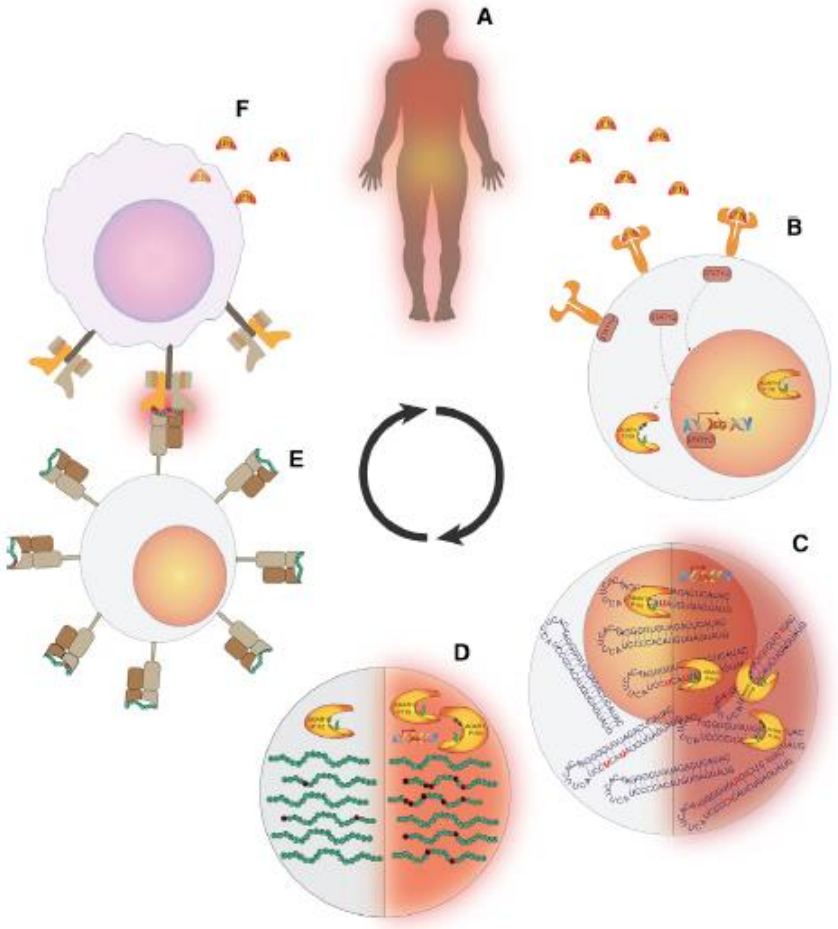
Model Red: $y \sim 2 \times x \times (100 + x)^{-1} \times$

Interaction between two random cel induces type I IFN production in bot



RNA editing (A-to-I) as mechanism of inflammatory response



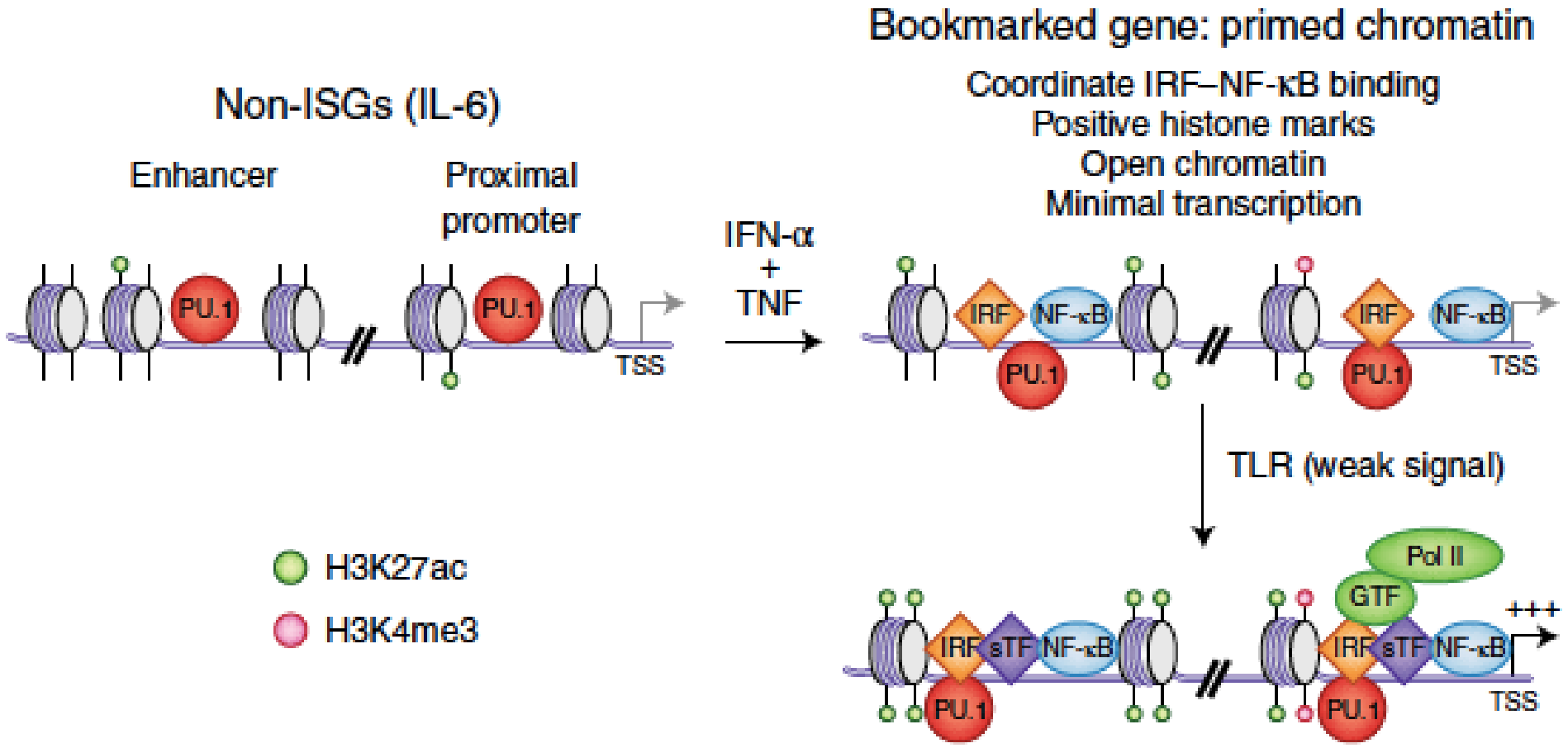


RNA editing in SLE

- Interferon uptake in cells
- JAK-STAT pathway
- ADAR1 upregulation
- Higher editing rates
- More recoded proteins
- Degradation-epitope formation
- Antigen presentation
- Trigger of immune response
- Loop

Eisenberg et al., *Nature Rev Genetics*, 2018
Roth SH et al., *Cell Reports*, 2018

Epigenetic regulation through type I IFN



Barrat F et al, Nat Immun 2019

2022 EULAR points to consider for the measurement, reporting and application of IFN-I pathway activation assays in clinical research and practice

Javier Rodríguez-Carrio ,[1] Agata Burska,[2] Philip G Conaghan ,[2] Willem A Dik,[3] Robert Biesen ,[4] Maija-Leena Eloranta,[5] Giulio Cavalli,[6] Marianne Visser,[7] Dimitrios T Boumpas ,[8] George Bertsias,[9] Marie Wahren-Herlenius ,[10,11] Jan Rehwinkel,[12] Marie-Louise Frémond ,[13] Mary K Crow ,[14] Lars Rönnblom ,[5] Marjan A Versnel ,[15] Edward M Vital [2]

Fundamental/basic unmet needs

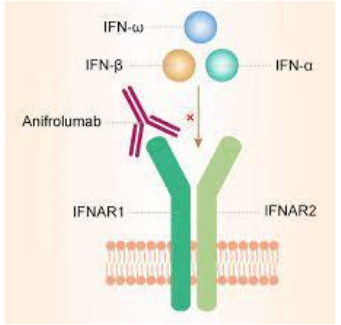
- ⇒ A better understanding of whether different type I interferons (IFN-Is), in particular IFNαs, have unique and/or redundant functions may help in the development of more precise tools for clinical use.
- ⇒ For IFN-stimulated genes:
  - ⇒ Identify the sets of ISGs induced by different IFNs in relevant primary cell types.
  - ⇒ Characterise differences in cell sensitivity to IFN-Is and tissue and cell-specific ISGs profiles.
  - ⇒ Characterise molecular, cellular and biochemical functions of ISGs.
  - ⇒ Identify which of the hundreds of ISGs typically induced actually mediate pathology in rheumatic and musculoskeletal diseases (RMDs).
  - ⇒ Investigate IFN-repressed factors.
- ⇒ Development of assays that directly, sensitively and specifically measure subtypes of IFN-I.

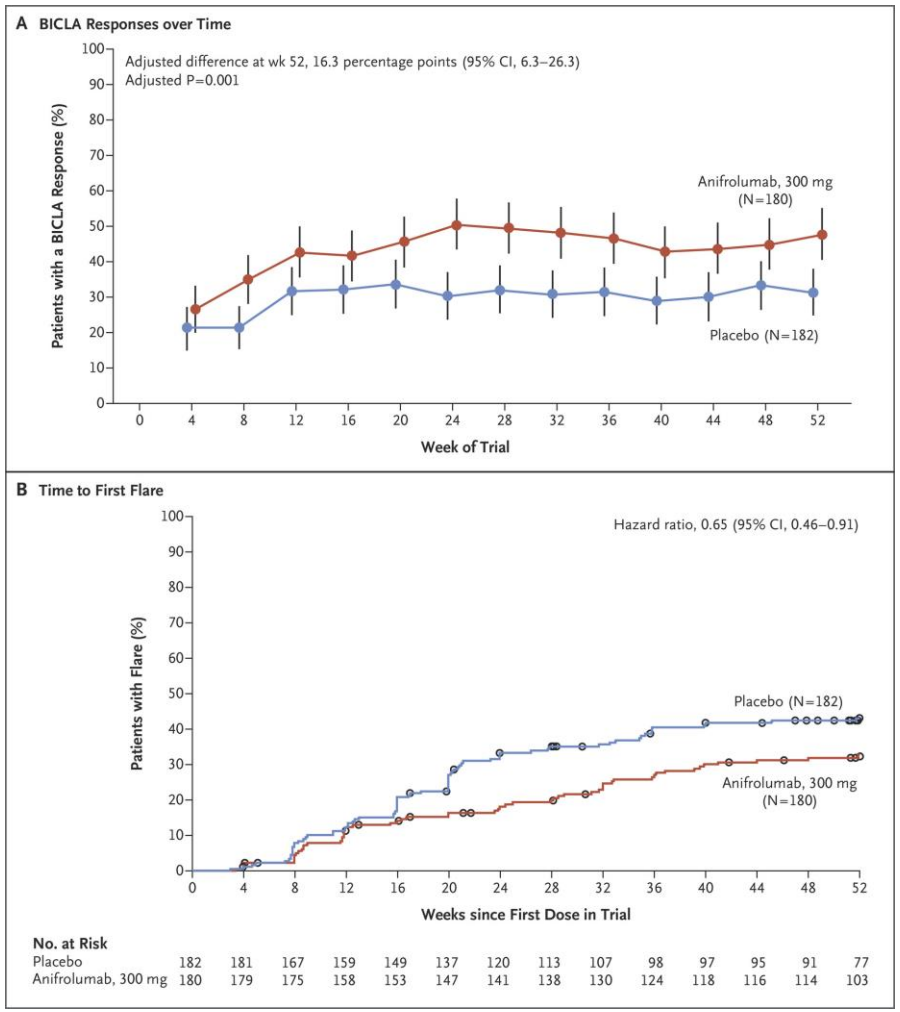
Table 1 Overarching principles and points to consider for the measurement and reporting of IFN-I pathway assays in clinical research and practice

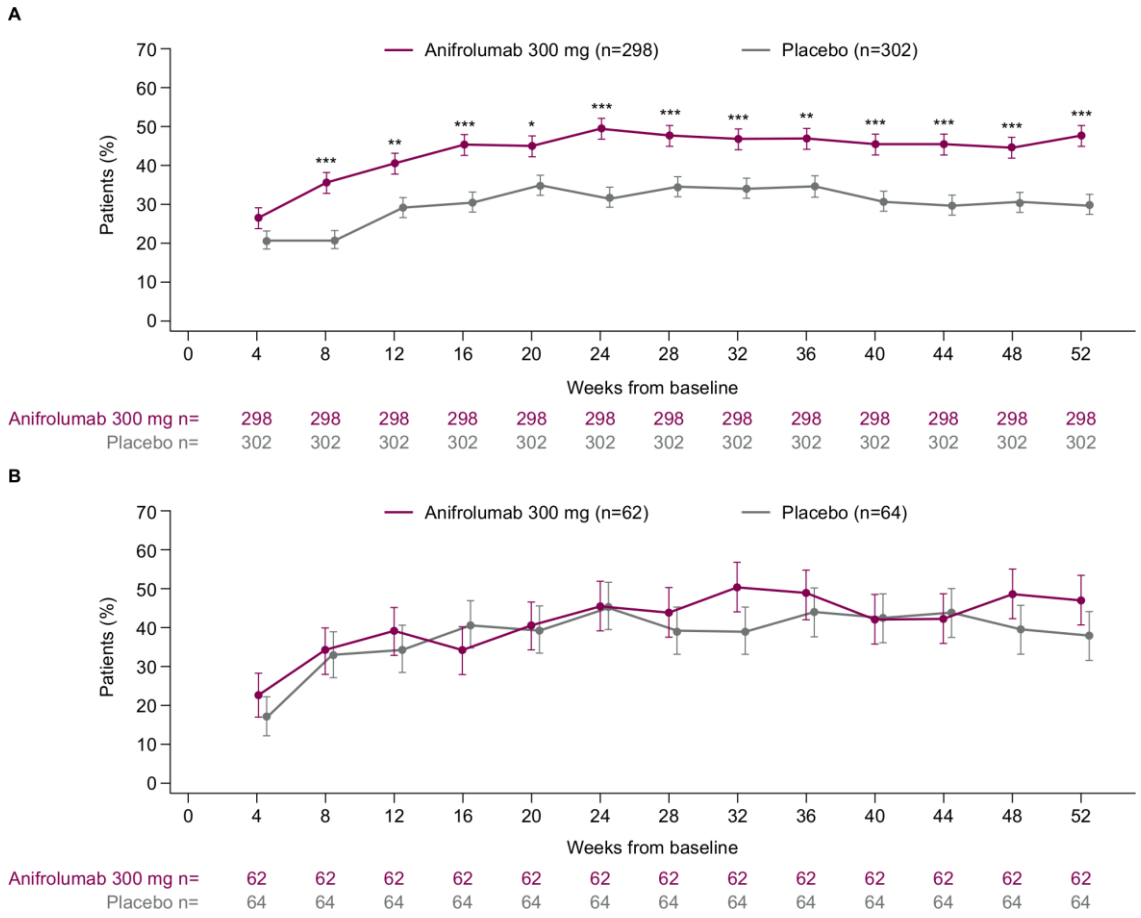
	Level of evidence	Level of agreement (mean±SD), n (%) scorings ≥8/10
Overarching principles		
A.The IFN pathway is a complex system with multiple subtypes of IFNs and diverse downstream effects on gene and protein expression.	N/A	9.76±0.66 17 (100)
B. IFN-I pathway activation is a common hallmark in many RMDs. Although IFN-I pathway activation is associated with some clinical manifestations, the utility of IFN-I pathway assays in clinical practice requires further validation for most contexts.	N/A	9.29±0.98 16 (94.1)
Points to consider		
1. Task force consensus terminology should be considered for reporting IFN assays measurement.	5	9.58±0.79 17 (100)
2. Existing assays measure different aspects of the IFN-I pathway; they do not reflect the entirety of the pathway and some are not specific for IFN-I. The most appropriate assay will depend on the research or clinical question and should be justified.	4	9.76±0.56 17 (100)
3. Publications on novel IFN-I pathway assays should report whether they specifically reflect IFN-I, and to the extent possible, which IFN-I is measured.	5	9.58±0.61 17 (100)
4. For assays that evaluate pathways downstream of the IFN-I receptor (eg, IFN-stimulated gene expression or protein scores) the choice of components needs to be justified. For gene expression scores, the known subsets of IFN-stimulated genes should be described separately.	5	9.41±0.87 16 (94.1)
5. IFN-I pathway is consistently activated in several RMDs, but assays measuring IFN-I pathway activation cannot be currently recommended for diagnostic purposes.	2b/3b	8.58±1.83 12 (70.5)
6. IFN-I pathway assays define more severe subgroups within many RMDs, so they should be considered in stratification studies.	2b/3b	8.70±1.31 12 (70.5)
7. IFN-I pathway activation is associated with disease activity in some RMDs, especially SLE and myositis, but its added value in clinical decision making is uncertain.	2b/3b	8.82±1.18 14 (82.3)
8. IFN-I pathway assays can predict disease exacerbations, in particular flare occurrence in patients with SLE, but further work should be performed to determine to what extent they outperform current instruments.	2b	9.00±1.00 16 (94.1)
9. IFN-I pathway assays might predict progression from preclinical autoimmunity to clinical disease.	2b	8.00±1.69 11 (64.7)
10. In SLE, IFN-I pathway assays may be useful in predicting response to IFN-I targeting therapies.	2b	8.76±1.20 14 (82.3)
11. IFN-I pathway assay results may be affected by some treatments (eg, IFN-targeted therapies and high-dose glucocorticoids), and timing of sample collection should be taken into account and reported.	2b/3b	9.70±0.46 17 (100)

IFN-I, type I interferon; RMD, rheumatic and musculoskeletal disease; SLE, systematic literature review.

Anifrolumab: IFN targeted therapy in SLE



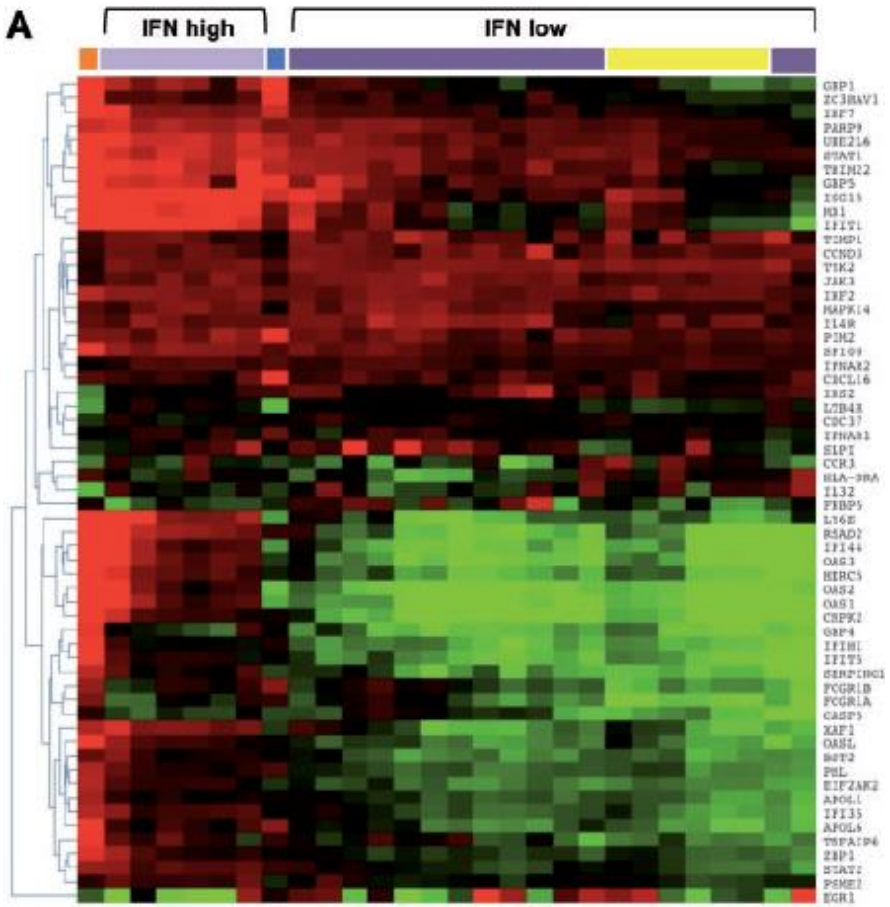


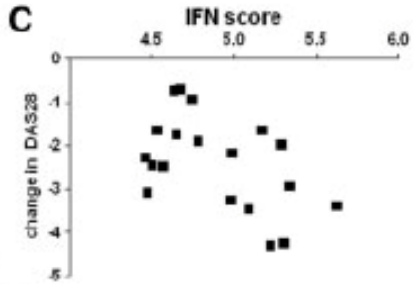


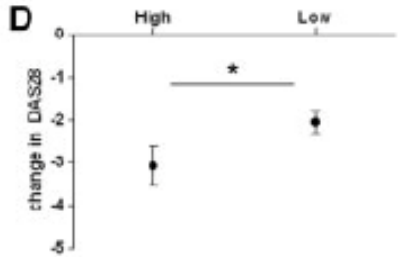
Vital et al. ARD 2021
Morand et al NEJM 2020

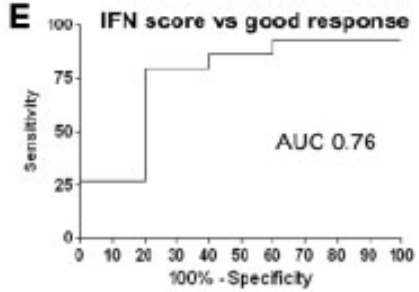
Interferon gene expression signature in rheumatoid arthritis neutrophils correlates with a good response to TNFi therapy

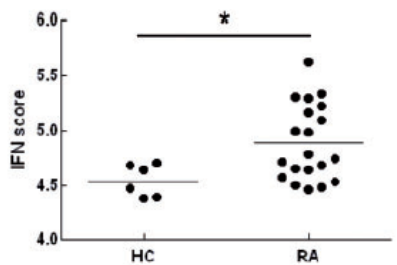
Helen L. Wright[1], Huw B. Thomas[1], Robert J. Moots[2] and Steven W. Edwards[1]





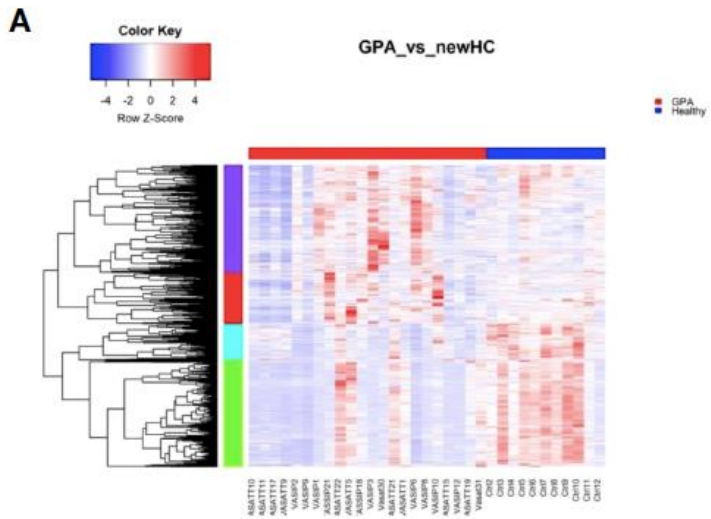


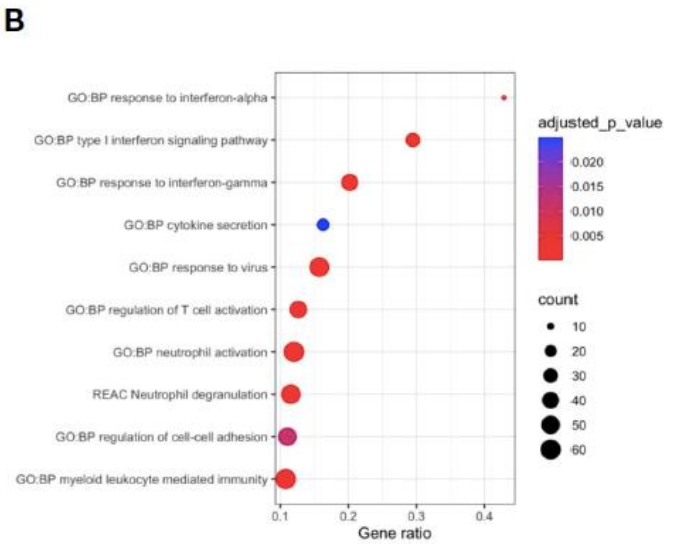




The genomic landscape
ANCA-associated vasculi
Distinct transcriptional signatures, molecular endotypes and comparison with systemic lupus erythematosus

Aggelos Banos[1†], Konstantinos Thomas[2†], Panagiotis Garantziotis[1,3†], Anastasia Filia[1], Nikolaos Malissovas[1], Antigone Pieta[1,4], Dimitrios Nikolakis[1,5,6,7], Alexandros G. Panagiotopoulos[2], Aglaia Chalkia[8], Dim George Bertsias[9,10], Dimitrios T. Boumpas[1,4,11†] and Dimitrios Vassilopoulos[2,11*†]



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YOU