Le interferonopatie

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AIEOP

ASSOCIAZIONE ITALIANA EMATOLOGIA ONCOLOGIA PEDIATRICA

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Roche	X						
Sanofi	X		X				
Regeneron	X						
Abbvie	X						
Apollo			X				

Interferons: functional definition

- Interfere with viral replication
- Inhibit cell growth
- Modulate immune response
  - Enhance antigen presentation by dendritic cells
  - Promote T lymphocyte responses
  - Promote B cell antibody production
  - Affect cytokine production

Interferons: classification

Based on the type of receptor through which they signal

- **Type I: IFN-α, IFN-β, IFN-ε, IFN-κ and IFN-ω**
  - **IFN-α/β receptor (IFNAR1 - IFNAR2 chains)**
  - **Produced in response to viral infections**
- **Type II: IFN-γ**
  - **IFNGR (IFNGR1 - IFNGR2 chains)**
  - **immune interferon**
- **Type III: IFNλ (1 to 4)**
  - **IL10R2 (also called CRF2-4) - IFNLR1 (also called CRF2-12**
  - **Mucosal protection from viruses**

Agenda

- **Type I IFNpathies → autoinflammation**
  - **Clinical presentations**
  - **Biomarkers**
  - **Targetted treatments**
- **Type II IFNpathies → hyperinflammation**
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Immune response and inflammatory response Own Goals

Autoinflammation

Activation of the **innate immunity** in the absence of triggers or in the presence of a trivial trigger (e.g. cold exposure) leading to chronic or recurrent systemic/tissue inflammation

Hyperinflammation

Activation of **innate and adaptive immunity** in response to a reasonable stimulus to do so (e.g. viral infection) that becomes **excessive** and leads to damage to the host

Autoimmunity

The recognition of epitope(s) of self-antigens by antigen receptors of **adaptive immune** cells (TCR, BCR) activates a pathogenic response with tissue damage

Adaptive immunity

BCR, B-cell receptor; TCR, T-cell receptor.

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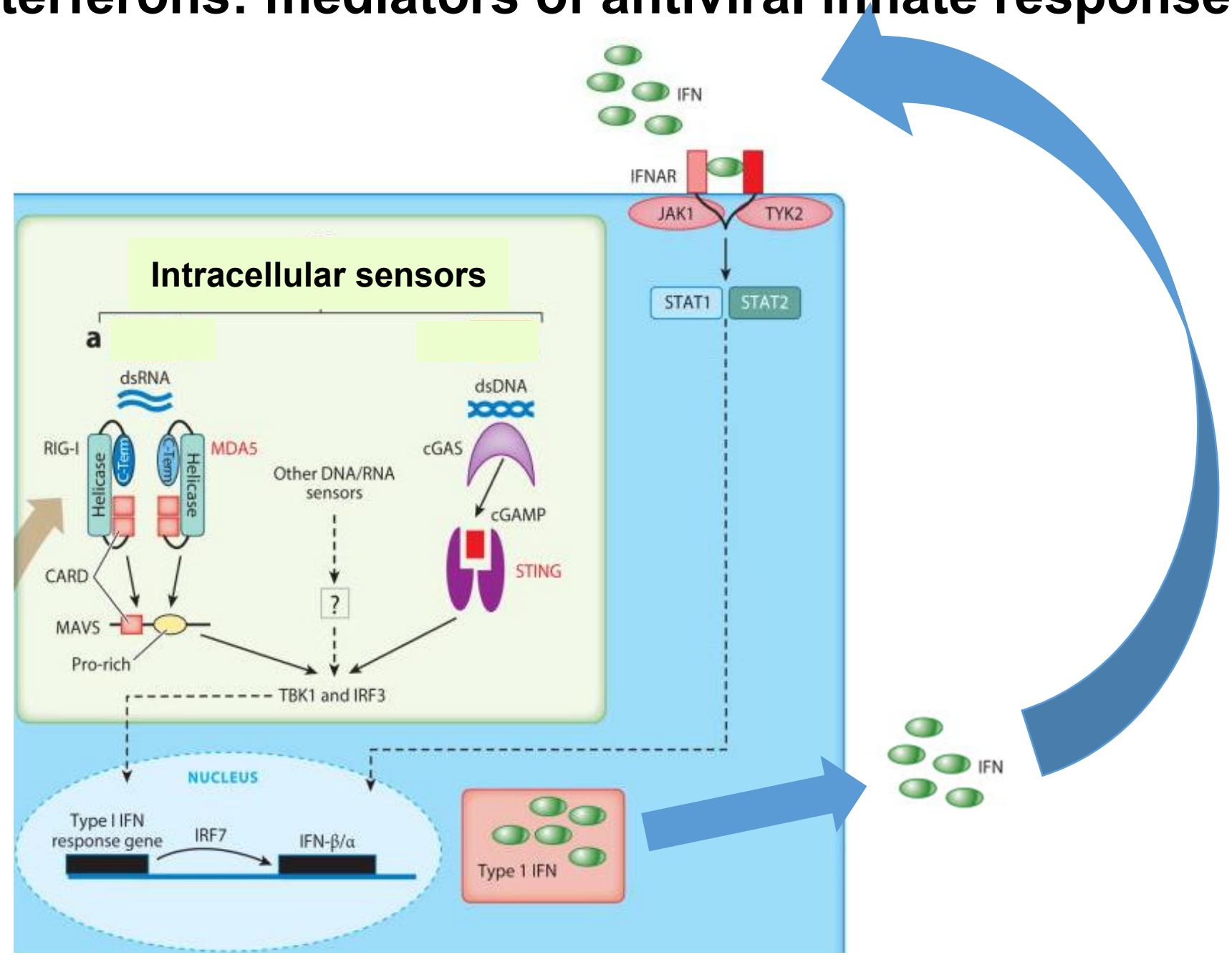
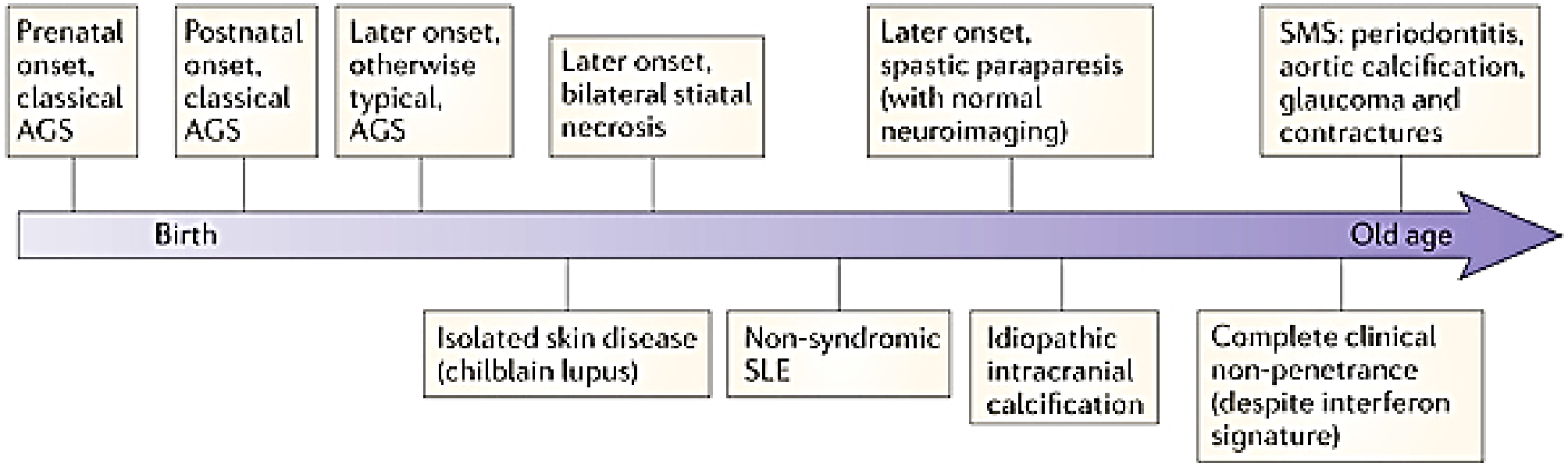
Type I Interferons: mediators of antiviral innate response



Aicardi-Goutieres Syndrome (AGS)
The first type I IFNpathy

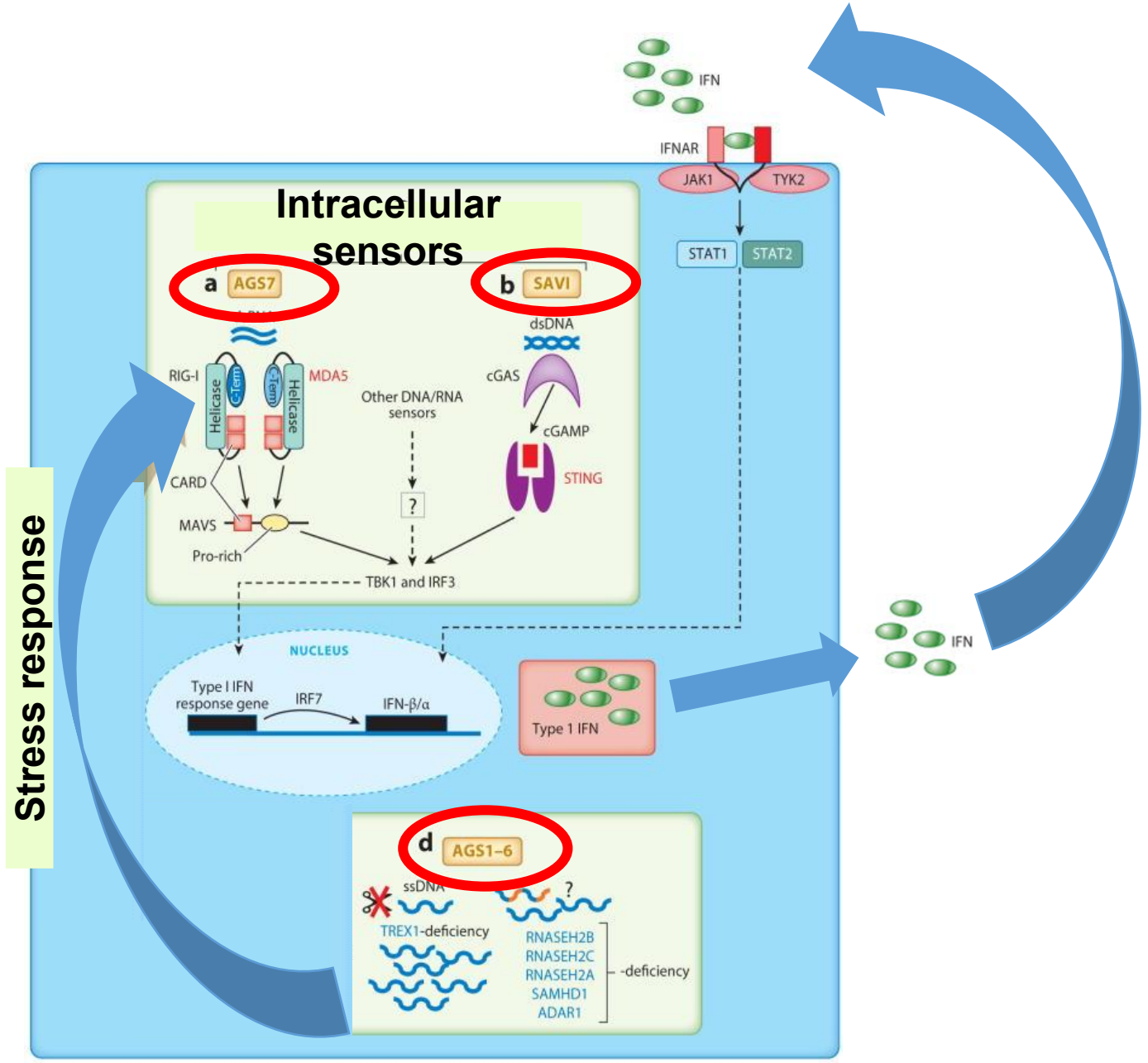
Classical early onset AGS

- Early onset of progressive CNS involvement with spasticity, dystonia
- High levels of type I IFN in CSF
- Basal ganglia calcifications
- Thrombocytopenia, hepatomegaly, chillblain lupus

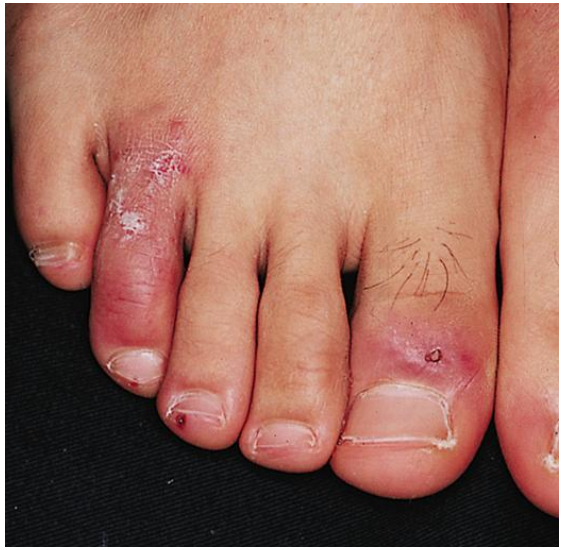


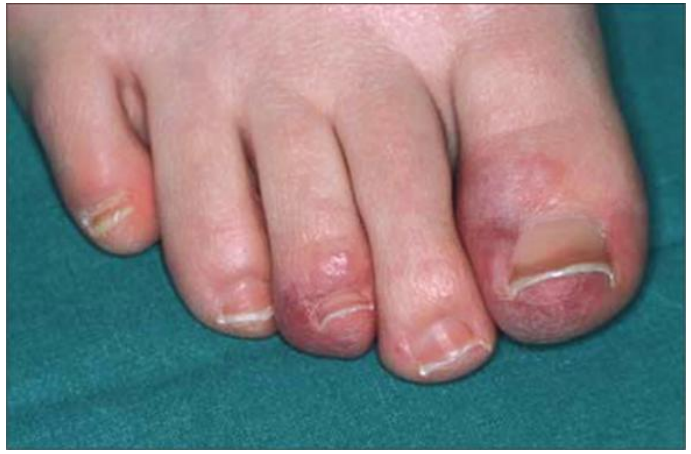
Crow Y, Nat Rev Immunol 2015

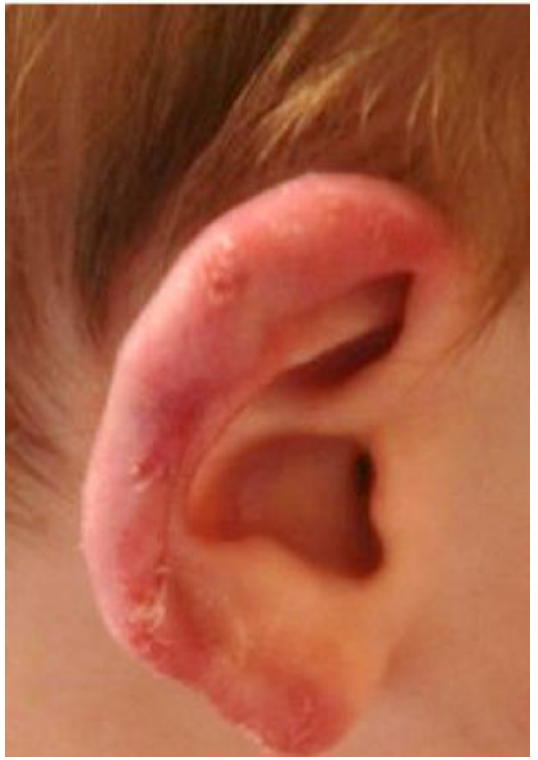
Autoinflammation: type I interferonopathies

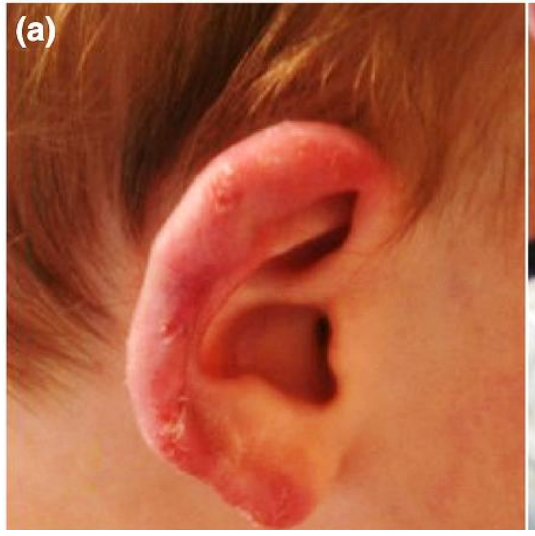


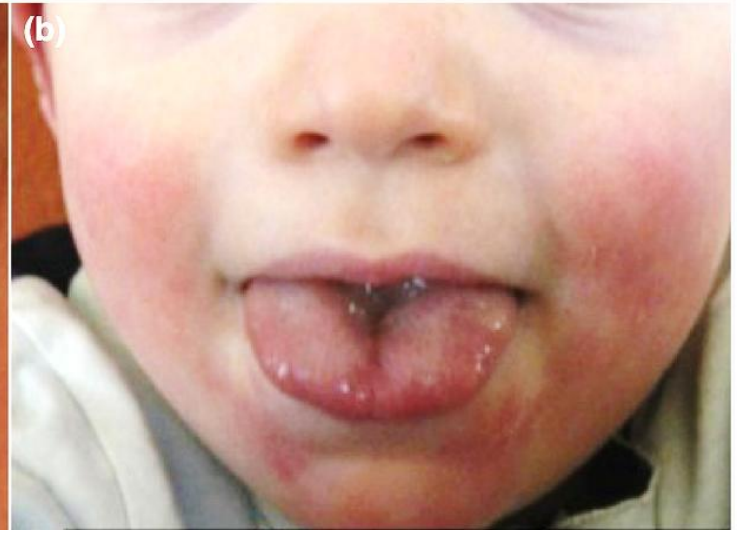
Skin features of Aicardi-Goutieres Syndrome

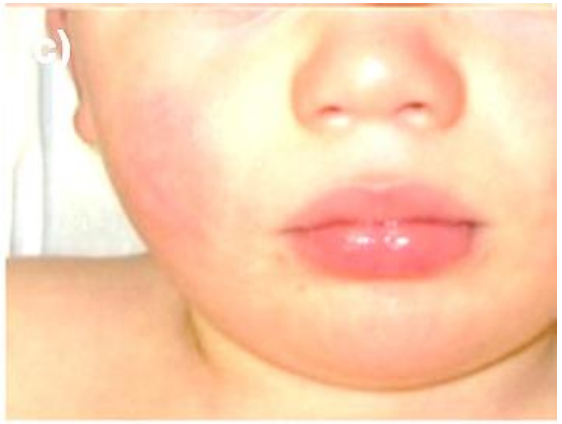


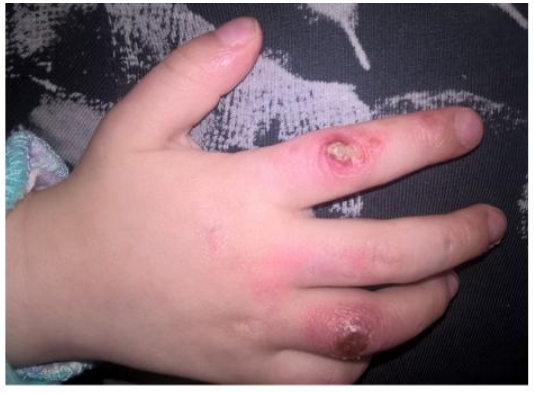


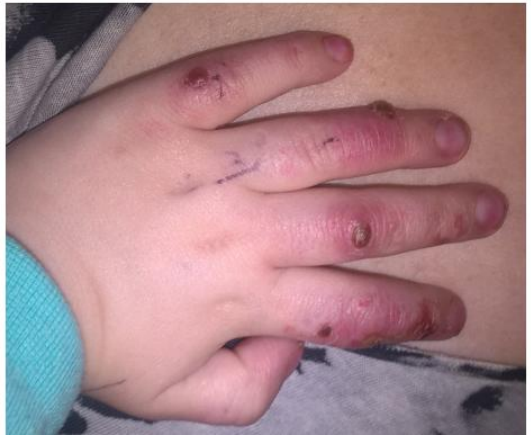


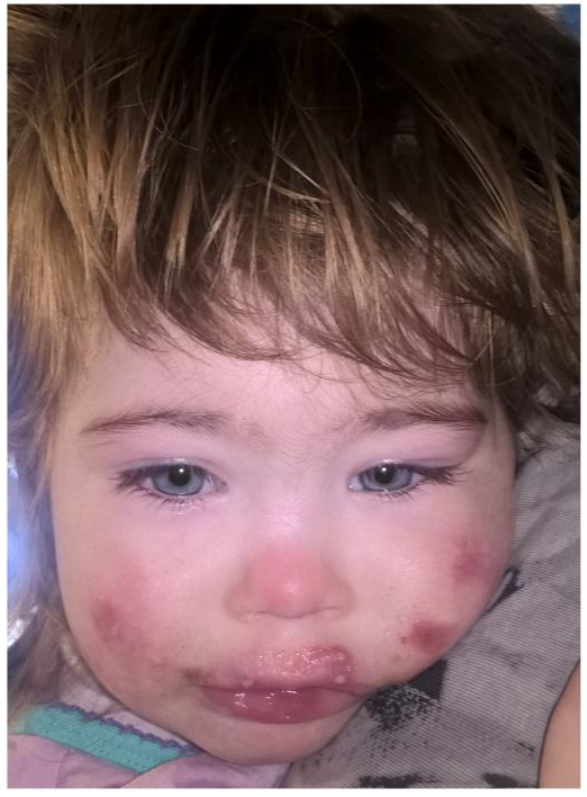






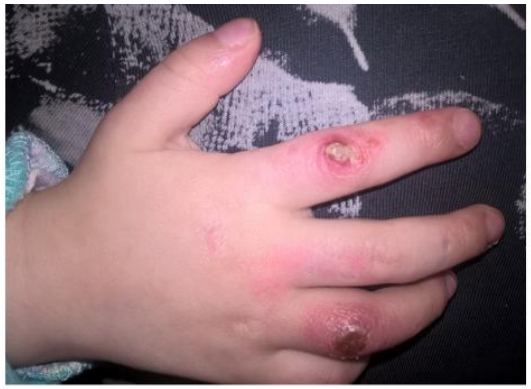


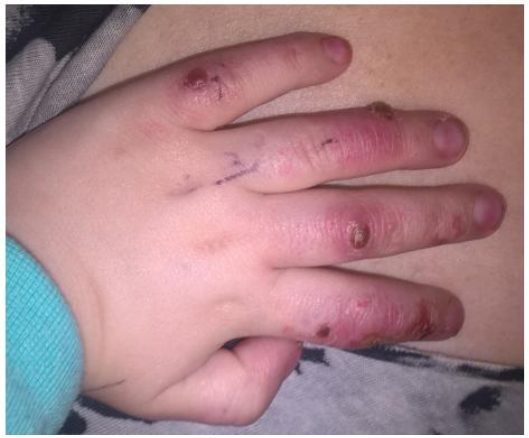


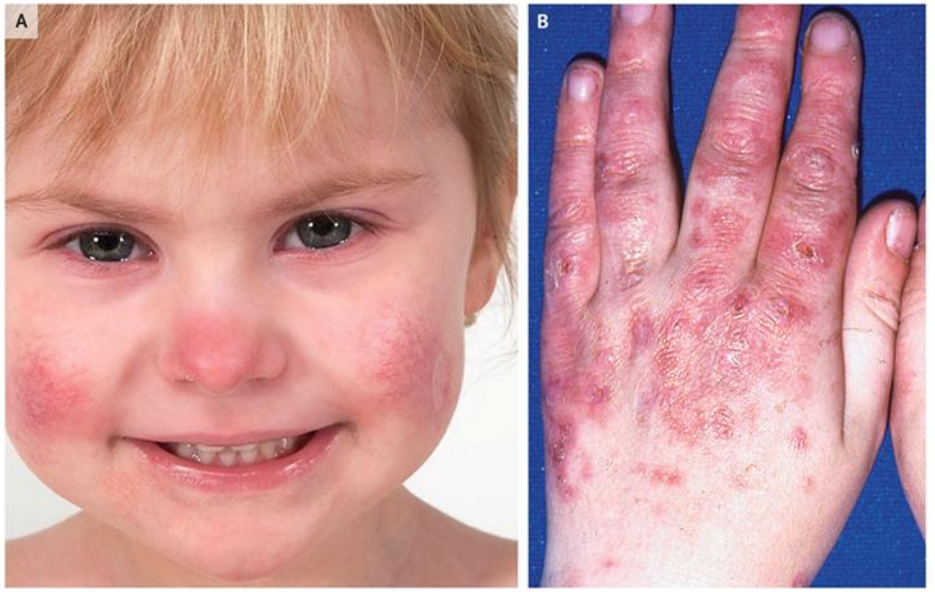


Sting Associated Vasculopathy with onset in Infancy (SAVI) syndrome

- Telangiectasic, pustular, or blistering rash (cheeks, nose, fingers, toes soles) worsened by cold exposure
- Eschar and secondary painful crusts covered ulcerated skin lesions
- Vascular inflammation limited to capillaries with microthrombotic vascular changes







Yin Liu et al, NEJM 2014

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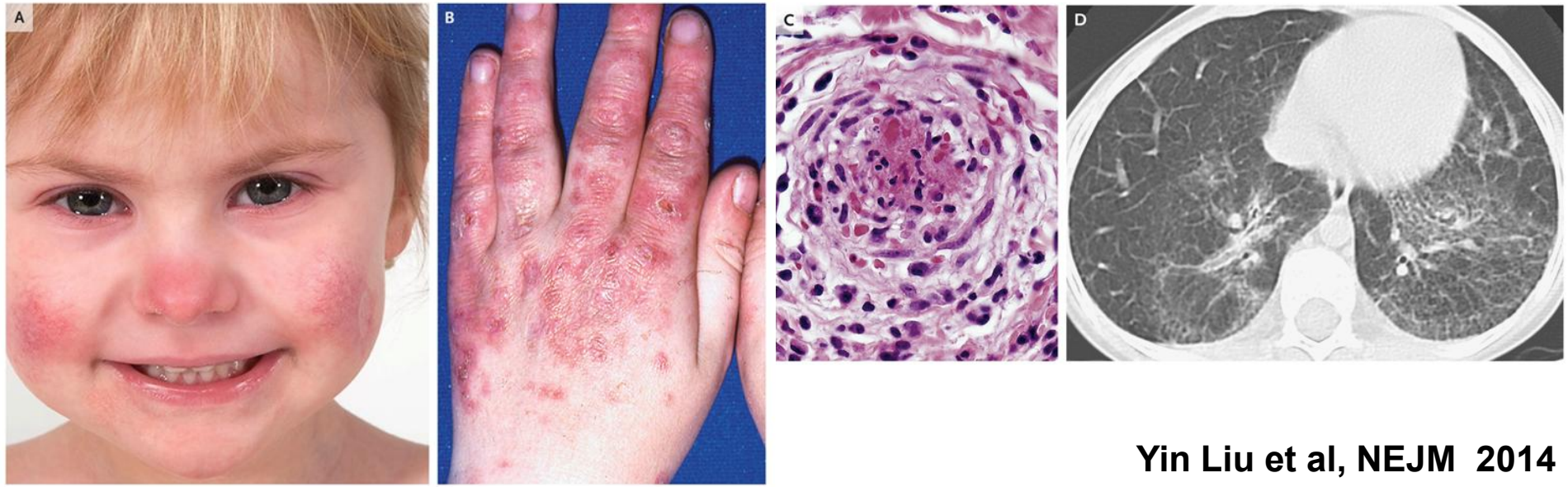
- Eschar and secondary painful crusts covered ulcerated skin lesions
- Vascular inflammation limited to capillaries with microthrombotic vascular changes
- Recurrent low-grade fever with elevations of ESR and CRP
- Interstitial lung disease with hilar or paratracheal lymphadenopathy



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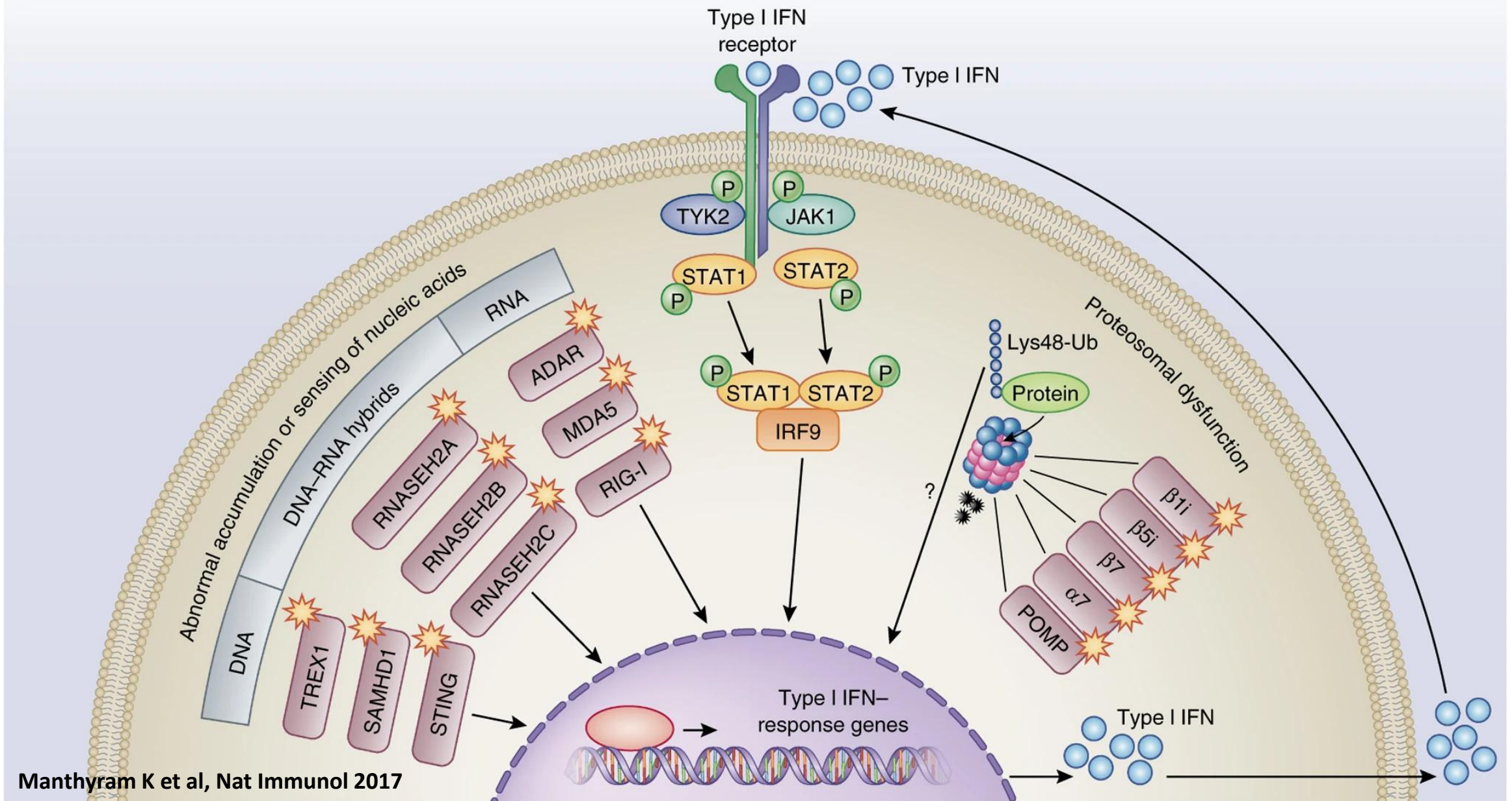
Autoinflammation: Type I interferonopathies



Manthyram K et al, Nat Immunol 2017

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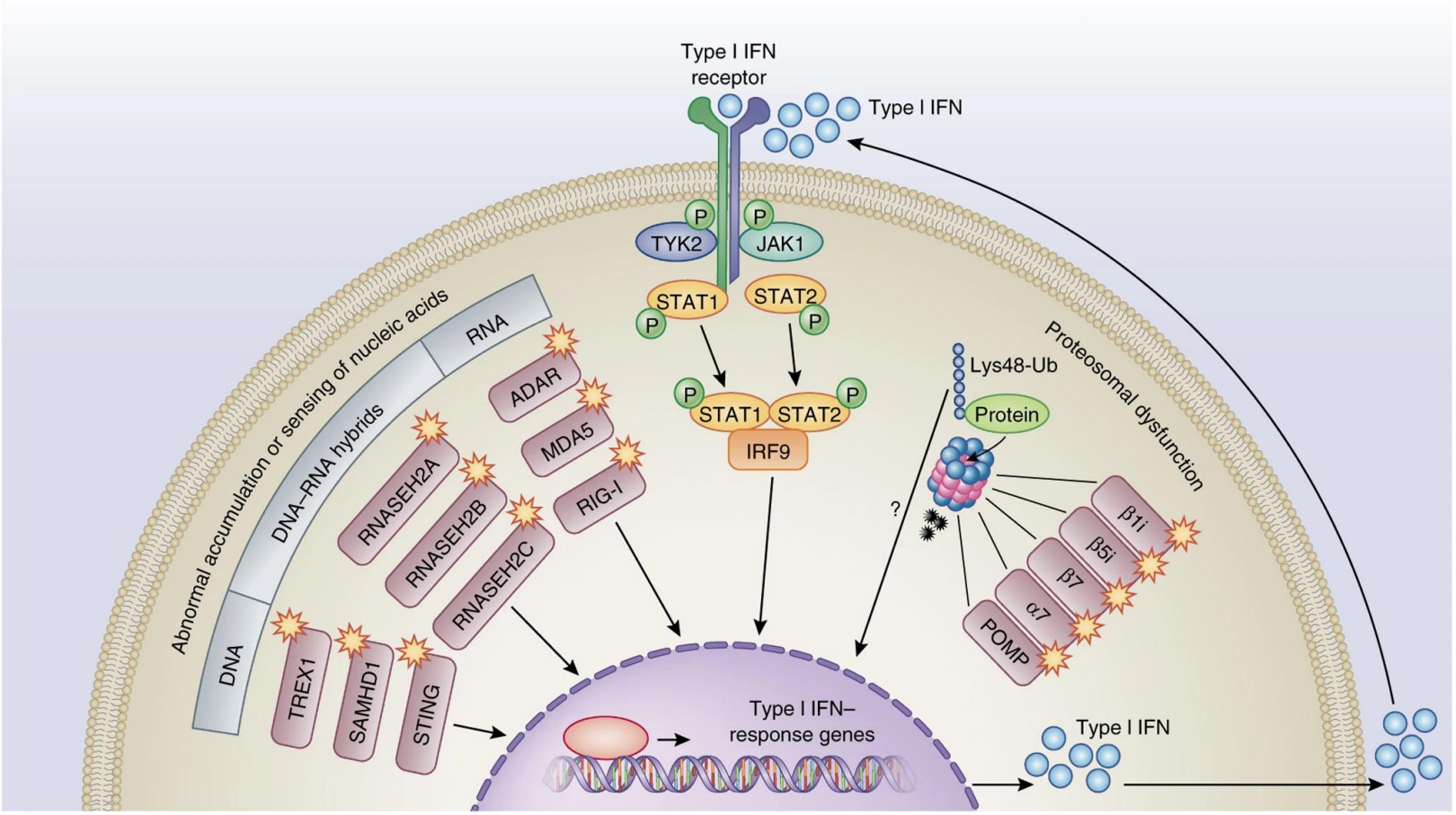

- **Skin inflammation/vasculopathy worsened by cold exposure**
- **CNS: basal ganglia calcification**
- **CNS: white matter disease**
- **Lung vasculitis**
- **+/- Low C3 levels**
- **Monogenic LUPUS**

Dysfunctional type I IFN regulation

Manthyram K et al, Nat Immunol 2017

Assessment of Type I Interferon Signaling in Inflammatory Disease
The type I IFN score (Type I IFNS)

Expression levels of 6 type I IFN-induced genes (RT-PCR)

Rice G et al, J Clin Immunol 2017

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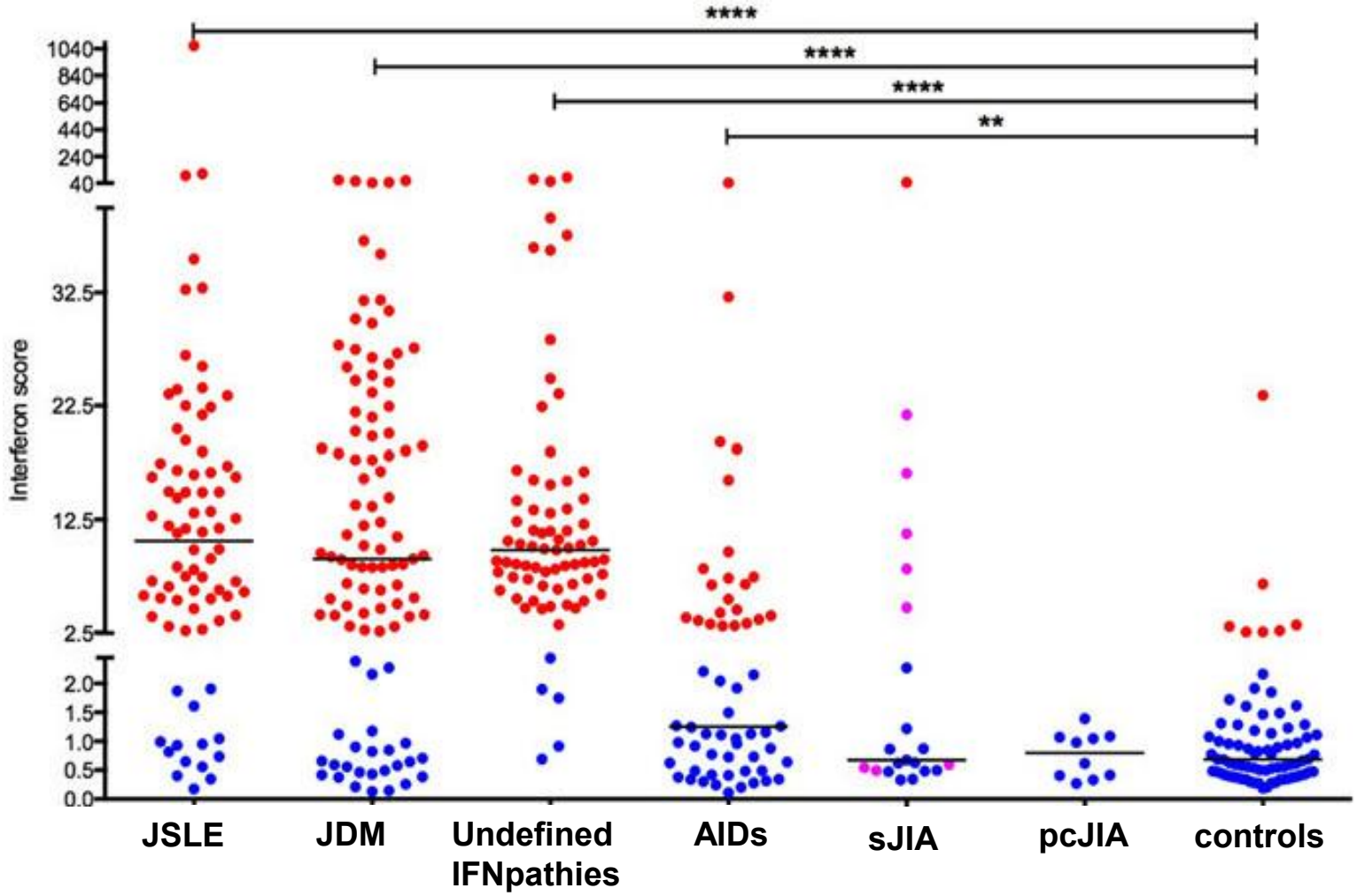

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Assessment of Type I Interferon Signaling in Inflammatory Disease
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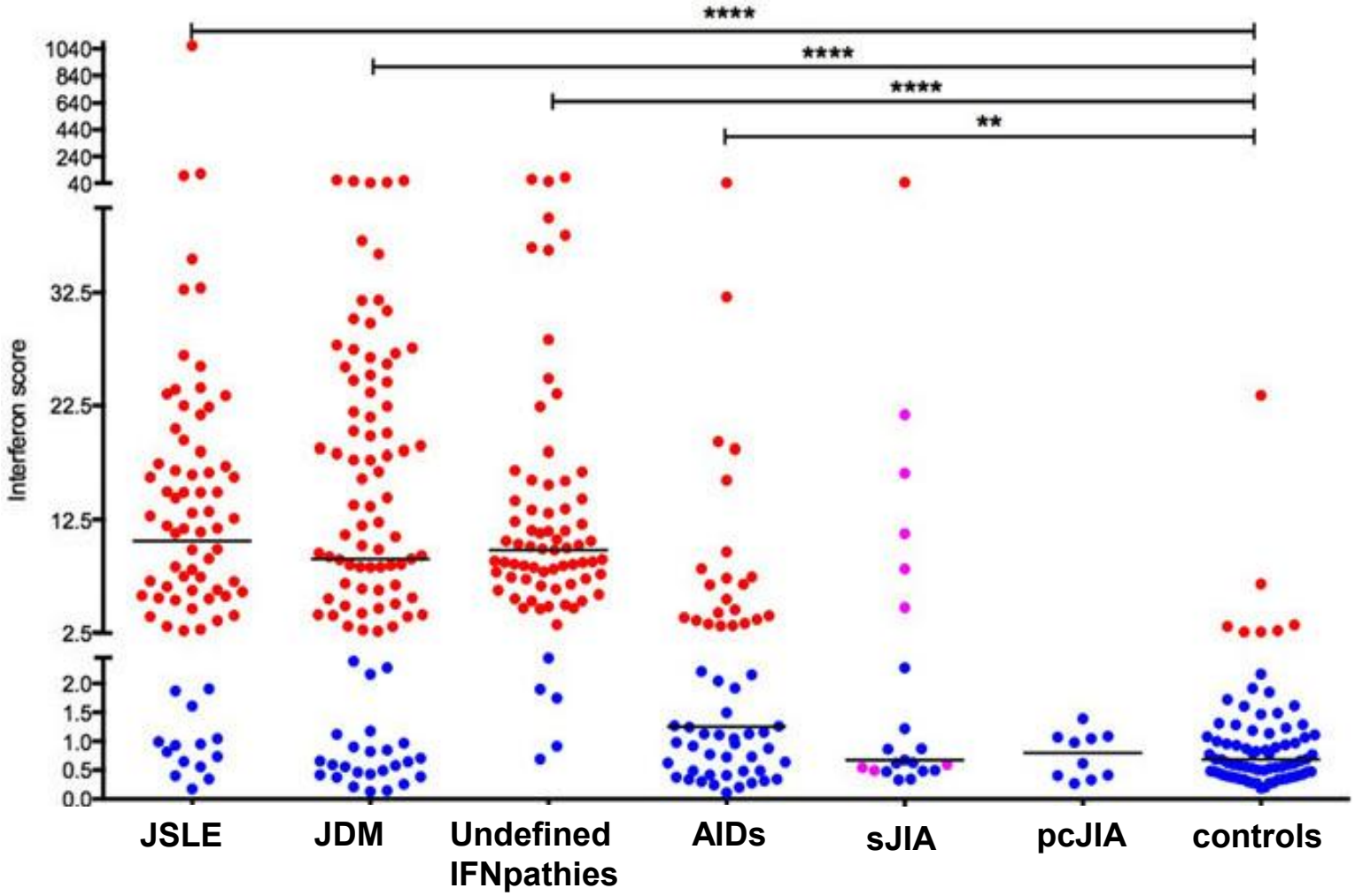
Implies

- **Use of tubes with stabilizer**
  Extraction of nucleic acids
- **RT- PCR**



Rice G et al, J Clin Immunol 2017

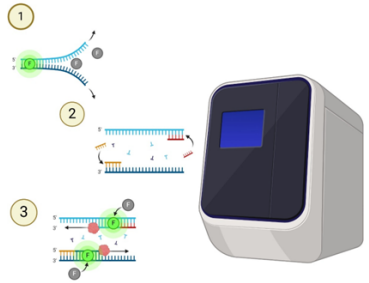
Diagnosing and monitoring patients with type I IFN-mediated diseases

Diagnostic Performance: SIGLEC-1 vs. Type I IFN Score

RETROSPECTIVE COHORT (n= 47)

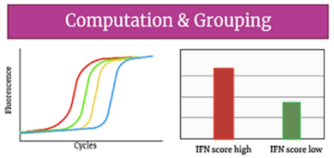
- 15 controls → (IFN SCORE < 2.05)*
- 7 AGS and SAVI patients
- 11 JDM patients
- 14 SLE

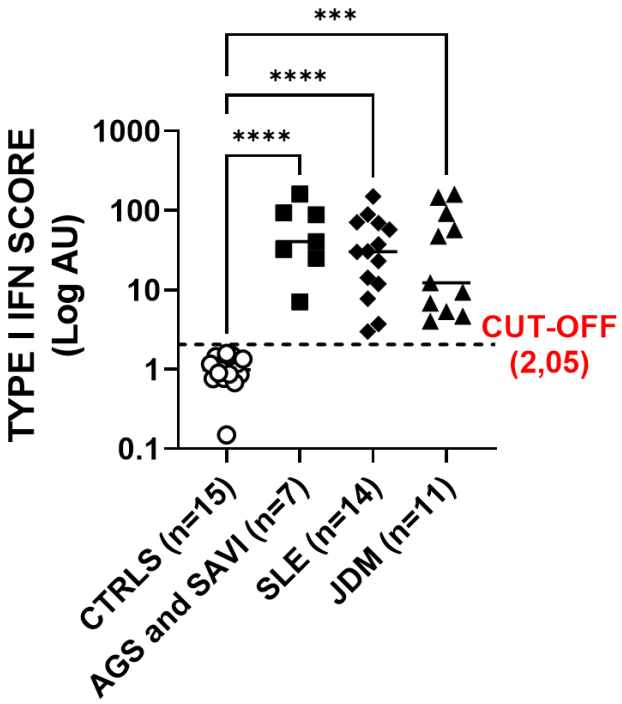
→ 32 Patients (IFN SCORE > =2.05)*

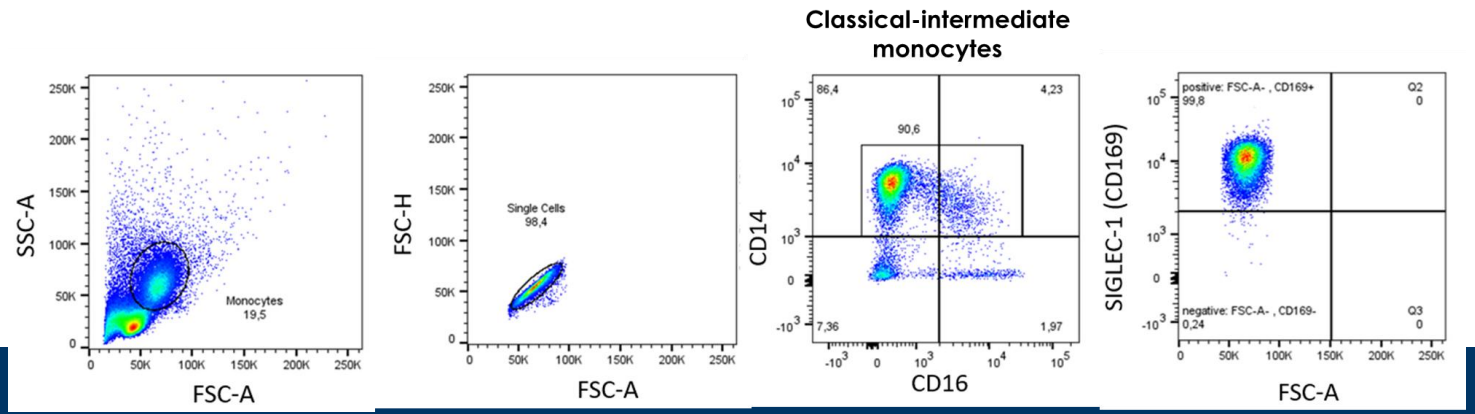


Expression of 6 Interferon-stimulated genes:

1) IFI44L
2) ISG15
3) IFI27
4) RSAD2
5) SIGLEC1
6) IFIT1







Antibody panel:

- CD14
- CD16
- SIGLEC-1 (CD169)

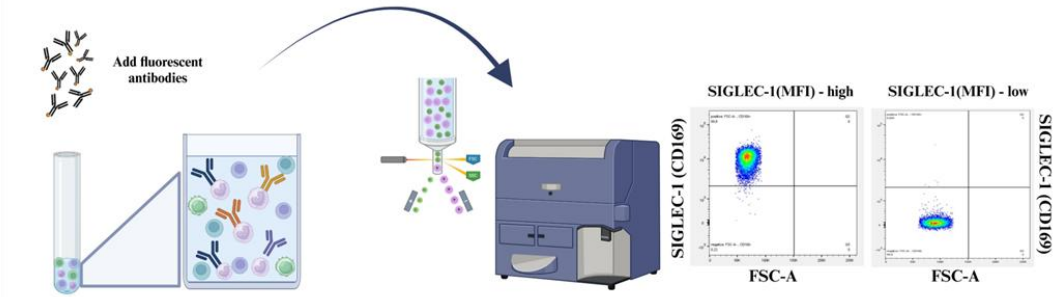
Matteo V. et al, Under revision

Diagnosing and monitoring patients with type I IFN-mediated diseases

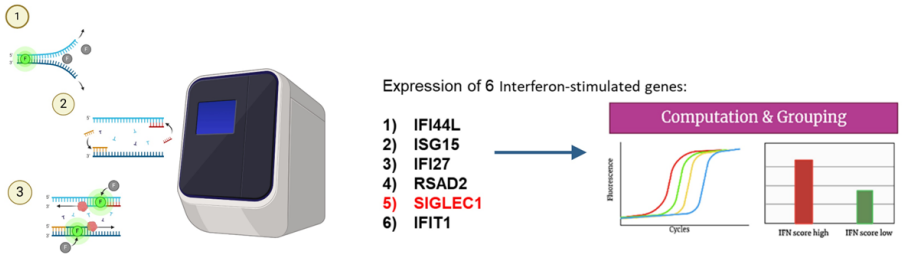
Prospective validation cohort (n=62)

- Suspected interferonopathy (n = 18)
- Suspected Sjogren syndrome (n = 1)
- Suspected JDM (n = 5)
- Suspected SLE (n = 14)
- Suspected AIDs (n =26)

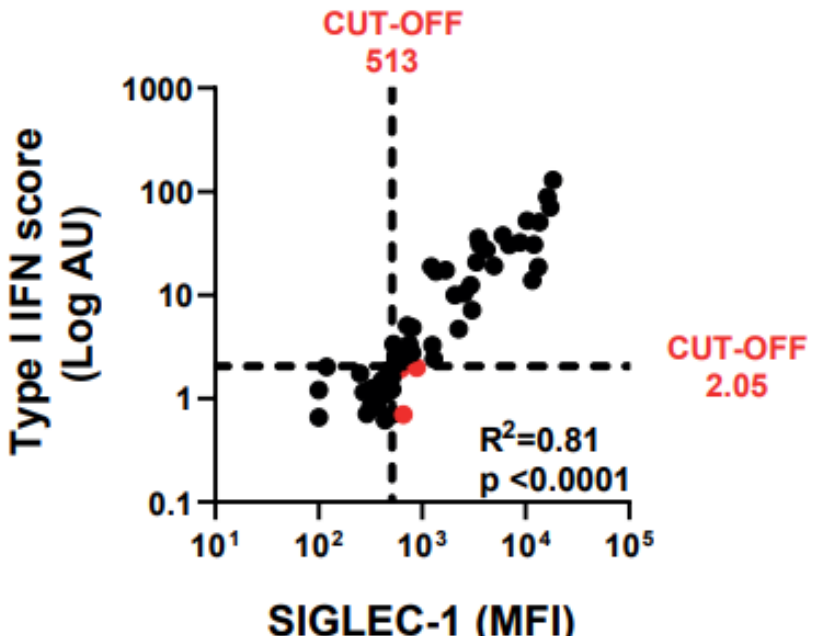
1. SIGLEC-1 evaluation at presentation



2. Validation through traditional Type I IFN score assessment in whole blood samples



✓ **SIGLEC-1 expression (MFI) is strongly correlated with Type I IFN Score**



Metric	Value (%)	Number of patients
PPV	92.10	35/38
NPV	100	24/24
Accuracy	95.16	59/62

Matteo V. et al, Under revision

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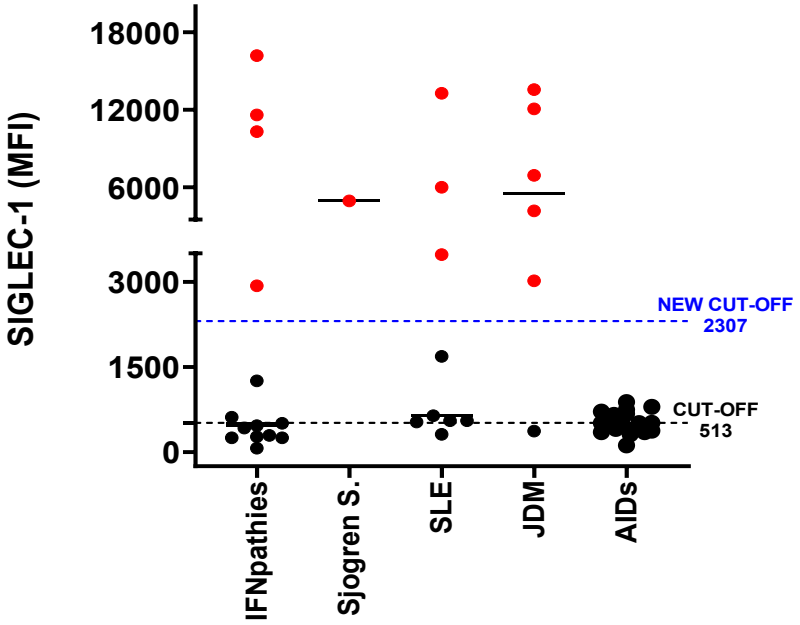
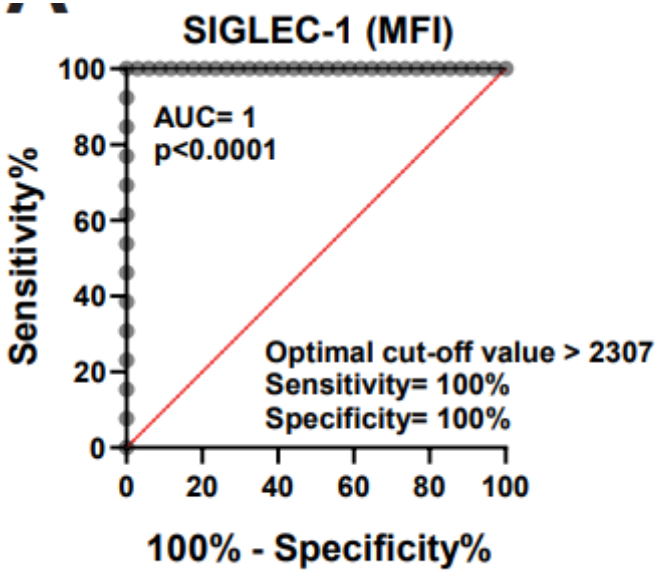




Real-World Diagnostic Performance of SIGLEC-1

62 patients followed longitudinally (6-months)

- 13 IFN-mediated disease
- 33 alternative diagnoses
- (16 undiagnosed)

Diagnostic Accuracy:

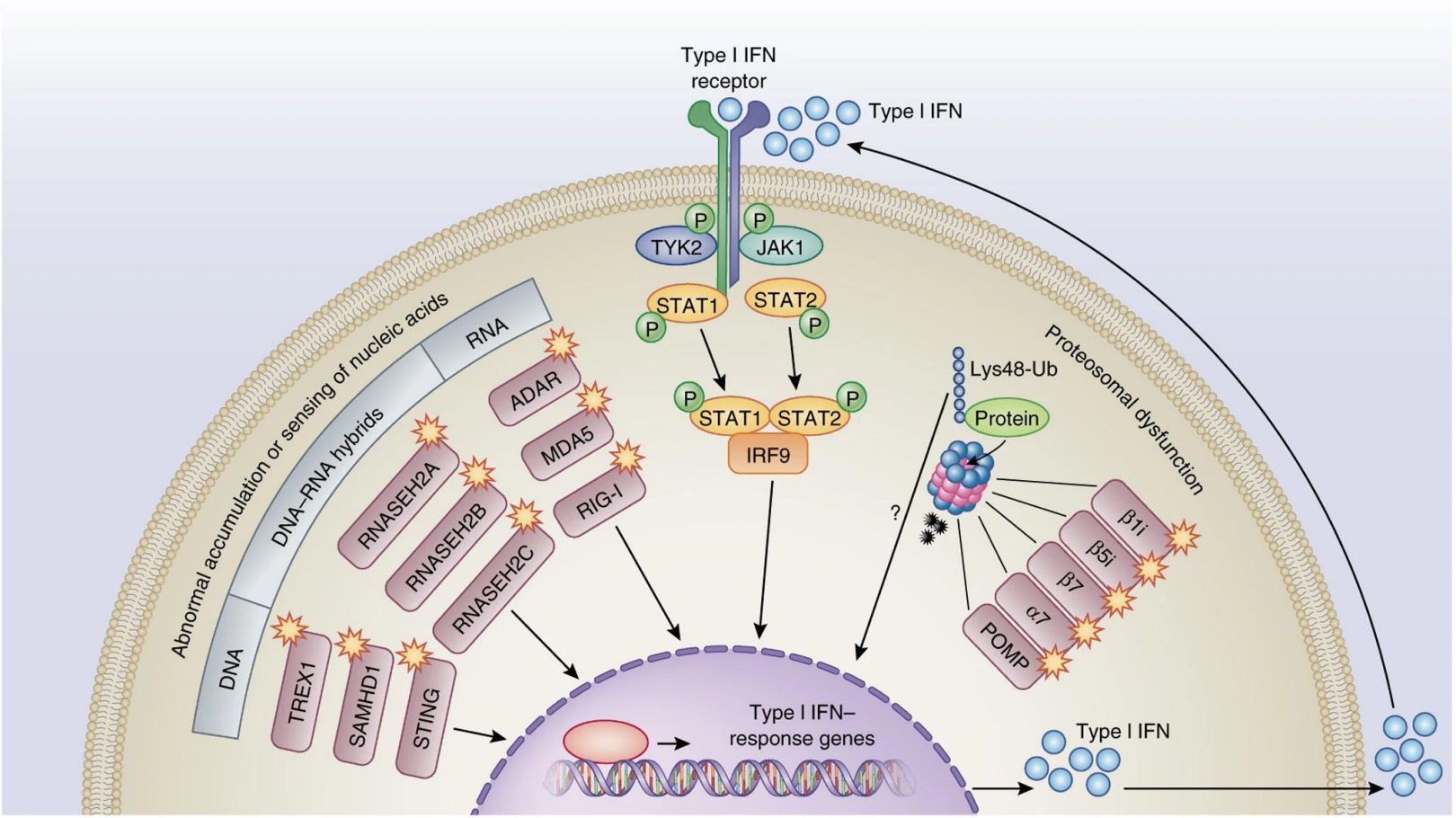
- All 13 IFN-mediated cases above SIGLEC-1 threshold
- Complete concordance with Type I IFN score

ROC Analysis:

- Optimal cut-off: **2307 MFI**
- **100% sensitivity & specificity**
- **AUC = 1.0**

Matteo V. et al, Under revision

Type I interferonopathies: targeted treatments



- **Type I IFN**
- **Type I IFN receptor**
- **Jak**

Manthyram K et al, Nat Immunol 2017

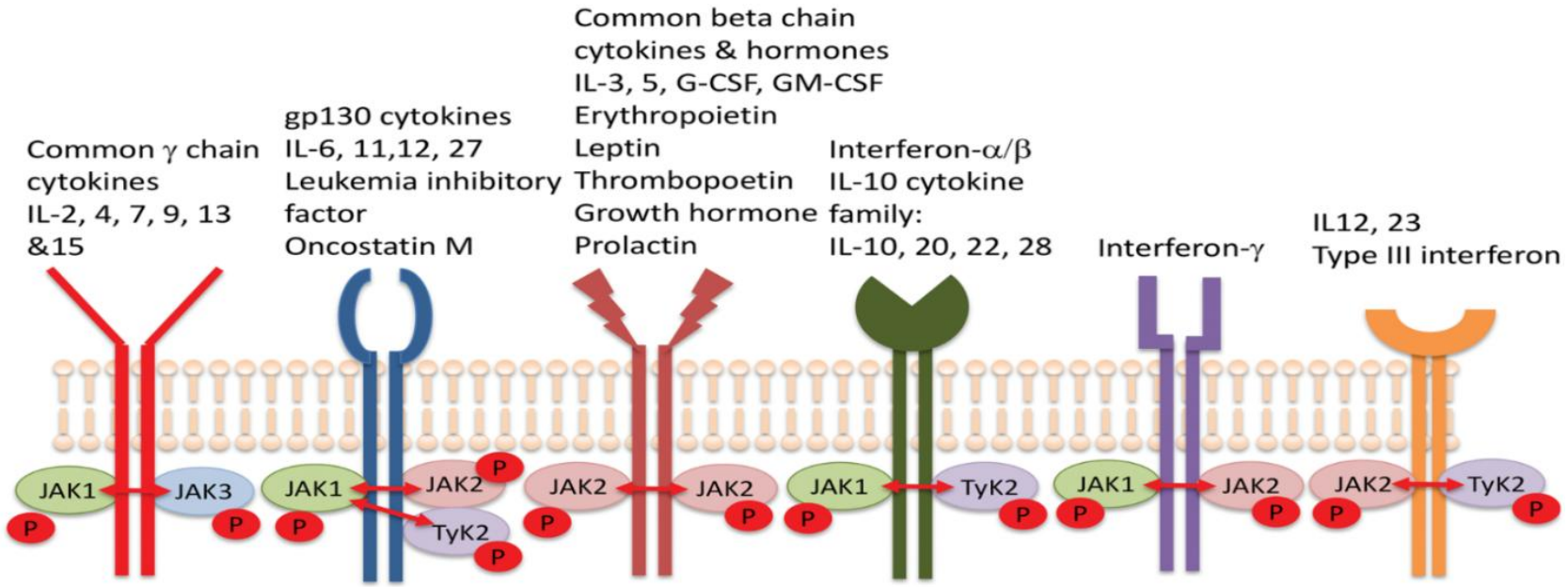
Janus Kinases (JAK)

JAKs are required for critical functions

JAKs are highly conserved and non-redundant

JAK isoform deficiency leads to severe clinical phenotypes:

- **JAK1 KO: perinatal death**
- **JAK2 KO: embryonic lethal (defective erythropoiesis)**
- **JAK3 KO: severe immunodeficiency (mice and humans)**
- **TYK2 KO: susceptible to virus (defective IFN response)**

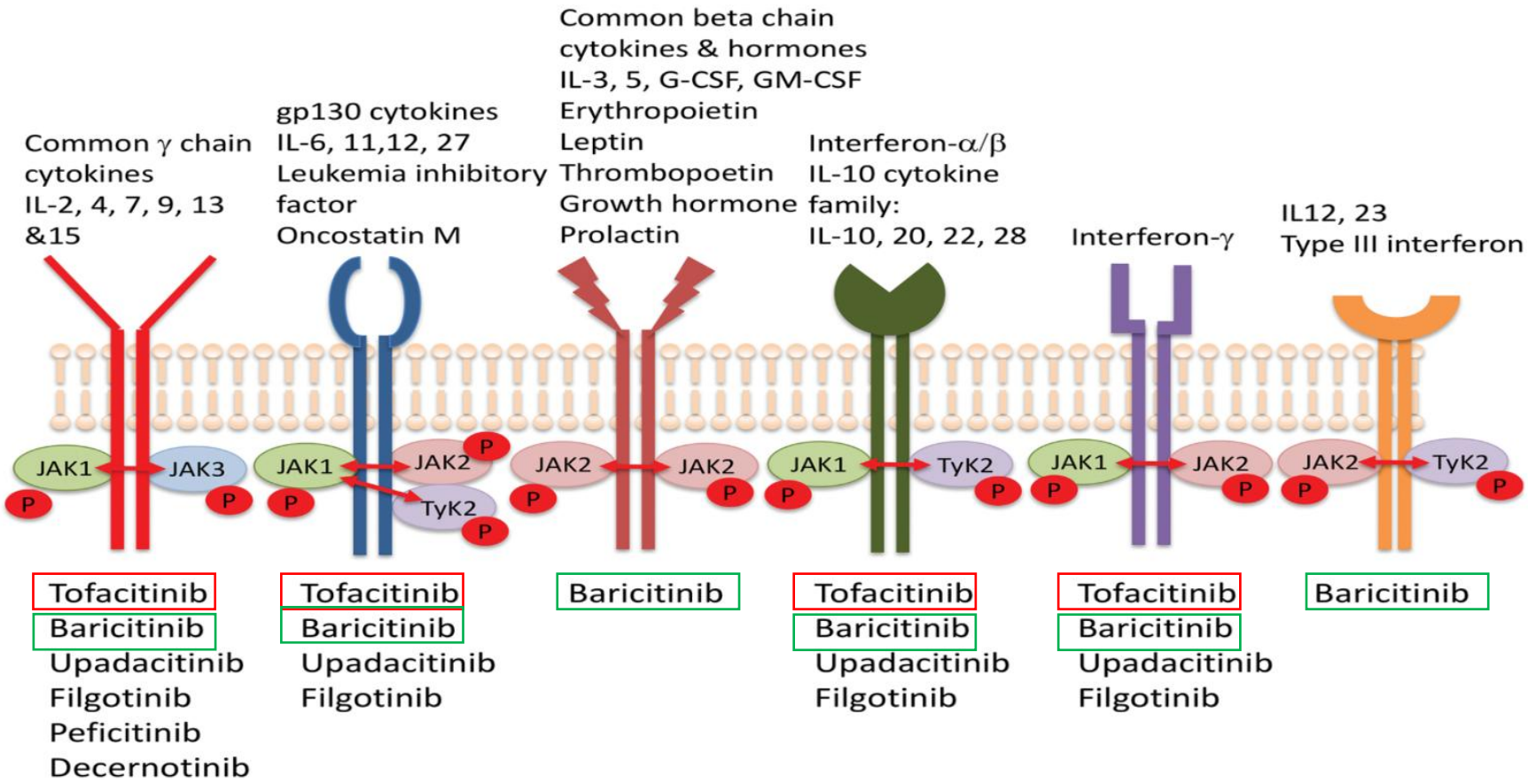


JAK inhibitors

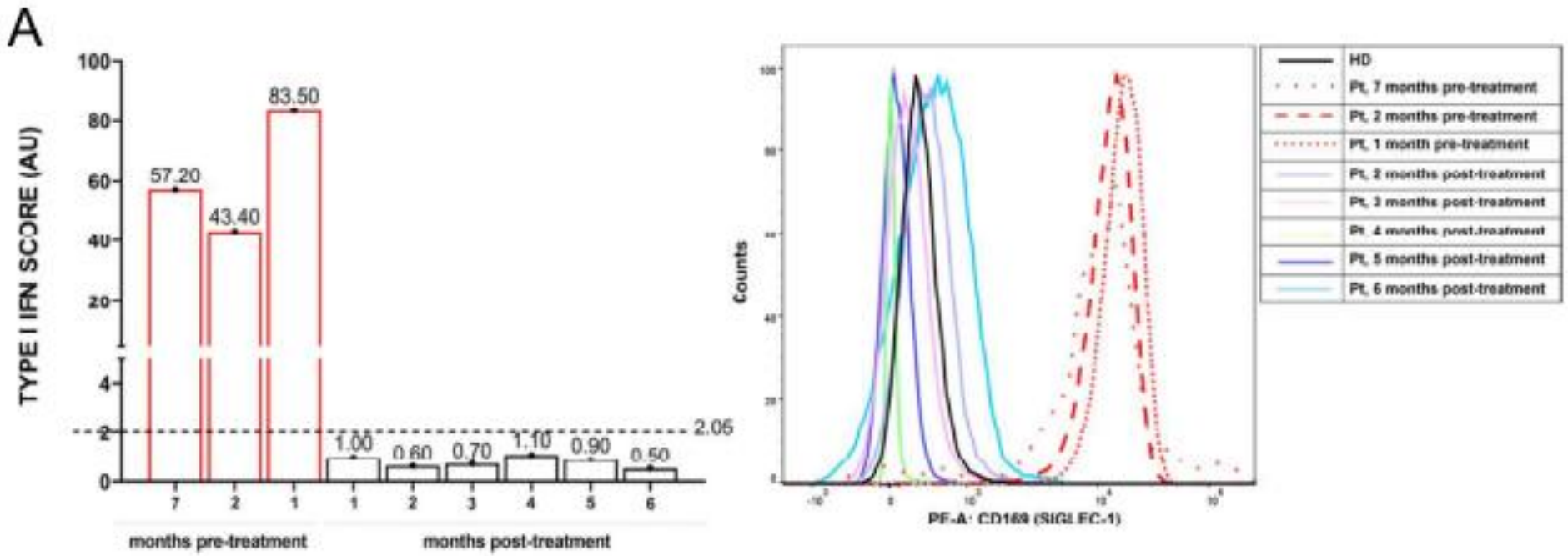
IL-1 and IL-18 receptors do not signal through JAK/STAT

The objective is not to block the JAK pathway completely

The objective is to reversibly reduce the activity of one or more JAK isoform



ANIFROLUMAB IN MONOGENIC LUPUS CAUSED BY TREX1 MUTATION



Moran-Aövarez P, Journal of Clinical Immunology 2025

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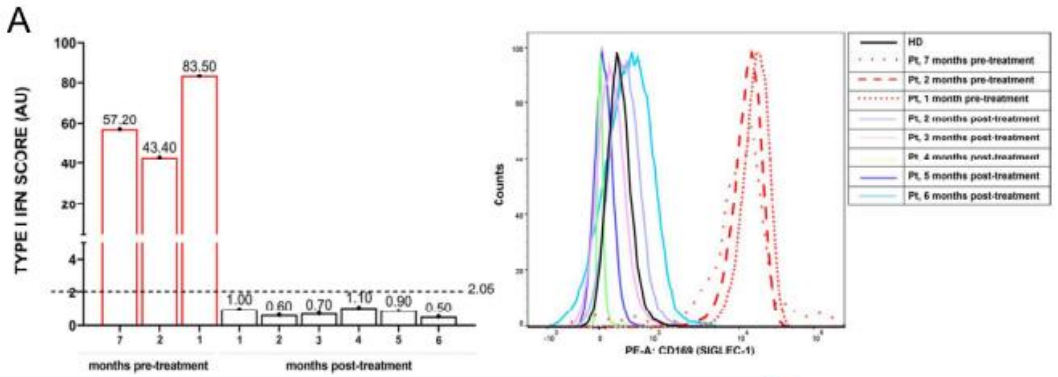

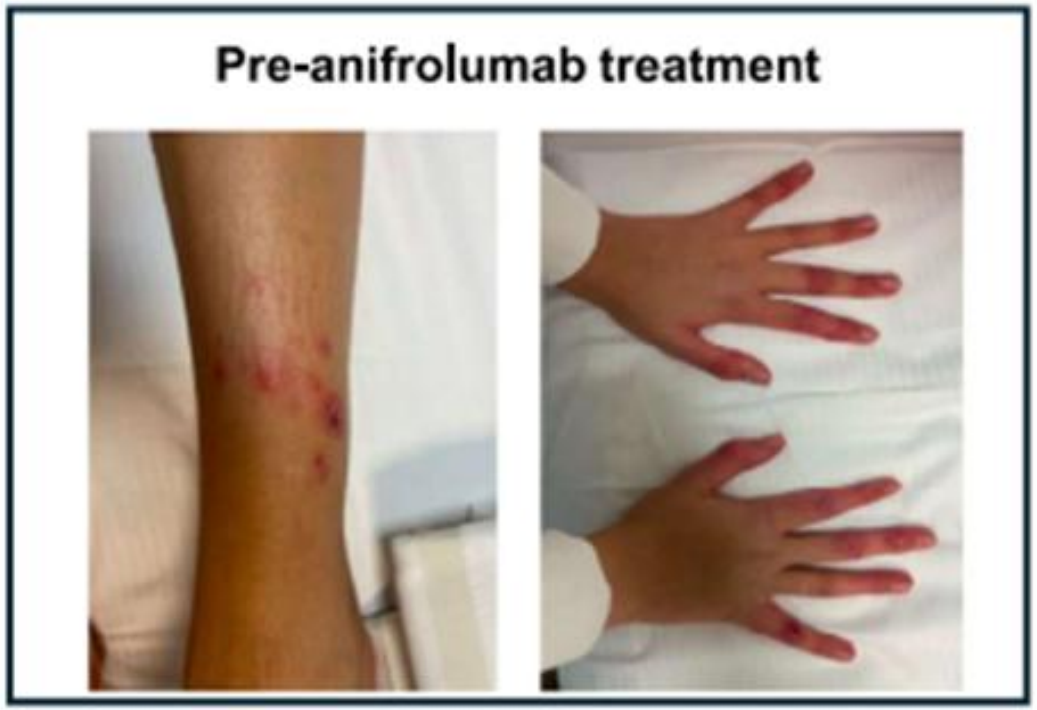

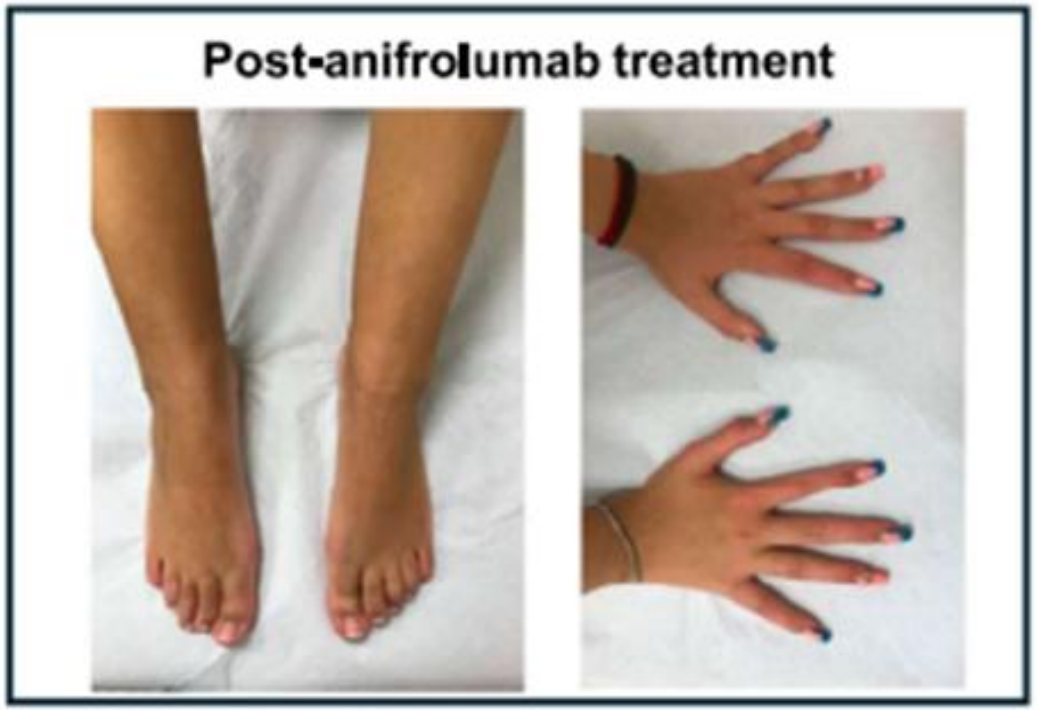

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Innate immunity

Adaptive immunity

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Recommendation

The 2022 EULAR/ACR points to consider at the early stages of diagnosis and management of suspected haemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS)

- **Convenors: Scott Canna, Fabrizio de Benedetti**
- **Fellows: Bita Shakoory, Ashley Geerlinks, Marta Wilejto**
- **Steering Committee: Kate Kernan, Melissa Hines, Erkan Demirkaya, Angelo Ravelli, Rashmi Sinha, Rebecca Marsh, Raphaela Goldbach-Mansky**

(Washington DC, August 2019)

Ann Rheum Dis 2023

What's in a name? Hyperinflammation – cytokine storm – HLH/MAS syndrome

The recognisable pattern

- Persistent fever
- Splenomegaly
- Inappropriately low Hb, PLT counts, and/or WBCs (NEUs, LYMPHs)
- Hepatic dysfunction (increased ALT, AST, bilirubin)
- Coagulopathy (low fibrinogen, increased PT/INR, increased d-dimers)
- CNS dysfunction
- Elevated and/or rising ferritin
- Elevated and/or rising levels of other markers of inflammation/damage (CRP, LDH)

Clinical and laboratory findings are individually nonspecific
They must be evaluated collectively and longitudinally

ALT, alanine transaminase; AST, aspartate aminotransferase; CAR-T, chimeric antigen receptor-T; CNS, central nervous system; CRP, c-reactive protein; EBV, Epstein–Barr virus; Hb, haemoglobin; HLH, haemophagocytic lymphohistiocytosis; LDH, lactate dehydrogenase; MAS, macrophage activation syndrome; MIS-C, multisystem inflammatory syndrome in children; NEU, neutrophil; LYMPH, lymphocyte; PLT, platelet; PT/INR, prothrombin time/international normalized ratio; WBC, white blood cell.

What's in a name? Hyperinflammation – cytokine storm – HLH/MAS syndrome

Familial/monogenic HLH

Secondary HLH

Infection-associated HLH

EBV-HLH

The recognisable pattern

- Persistent fever
- Splenomegaly
- Inappropriately low Hb, PLT counts, and/or WBCs (NEUs, LYMPHs)
- Hepatic dysfunction (increased ALT, AST, bilirubin)
- Coagulopathy (low fibrinogen, increased PT/INR, increased d-dimers)
- CNS dysfunction
- Elevated and/or rising ferritin
- Elevated and/or rising levels of other markers of inflammation/damage (CRP, LDH)

Macrophage activation syndrome

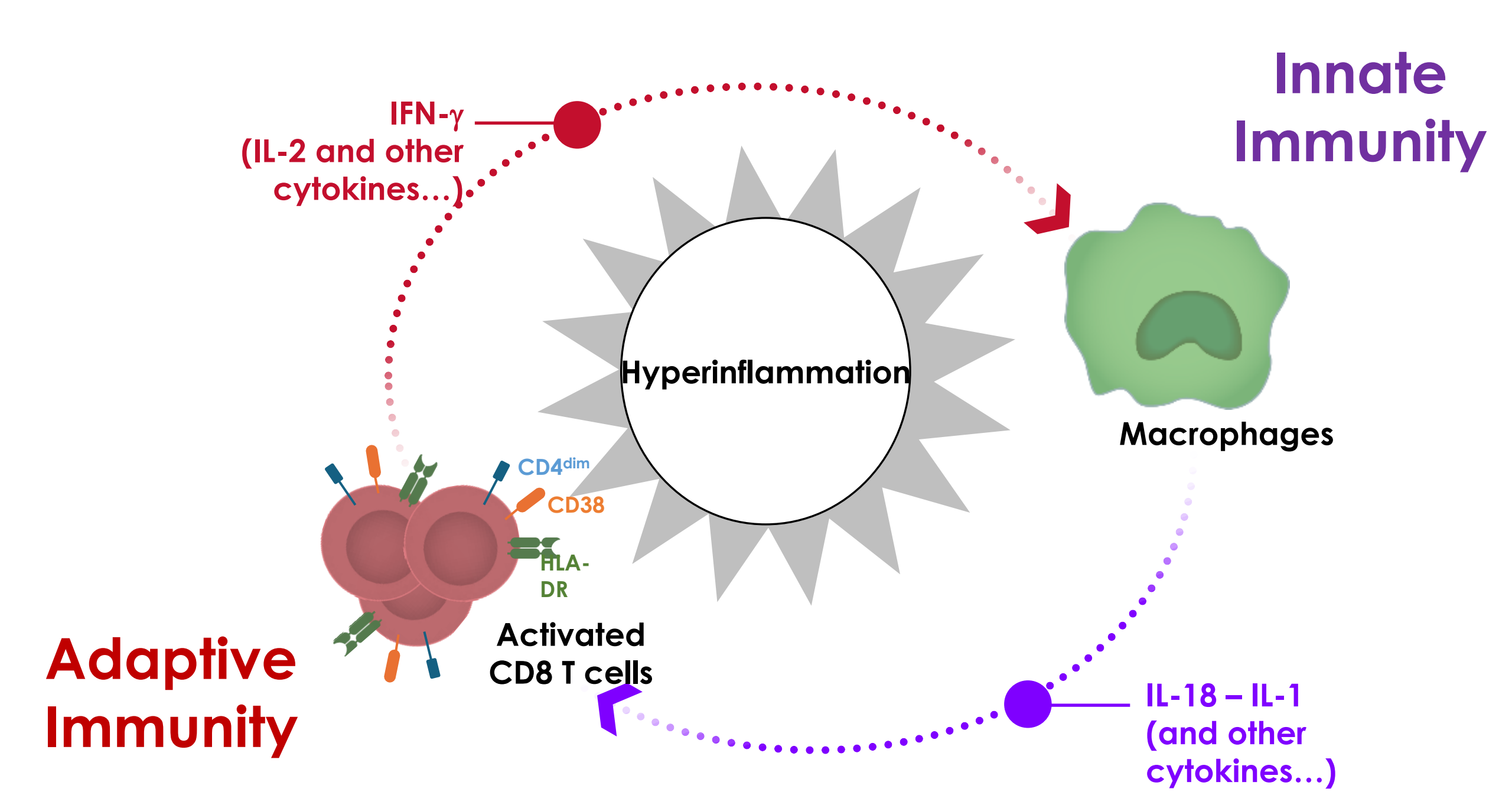
Hyperferritinemic sepsis

MIS-C

Cytokine release syndrome (CAR-T cells)

Clinical and laboratory findings are individually nonspecific
They must be evaluated collectively and longitudinally

ALT, alanine transaminase; AST, aspartate aminotransferase; CAR-T, chimeric antigen receptor-T; CNS, central nervous system; CRP, c-reactive protein; EBV, Epstein–Barr virus; Hb, haemoglobin; HLH, haemophagocytic lymphohistiocytosis; LDH, lactate dehydrogenase; MAS, macrophage activation syndrome; MIS-C, multisystem inflammatory syndrome in children; NEU, neutrophil; LYMPH, lymphocyte; PLT, platelet; PT/INR, prothrombin time/international normalized ratio; WBC, white blood cell.



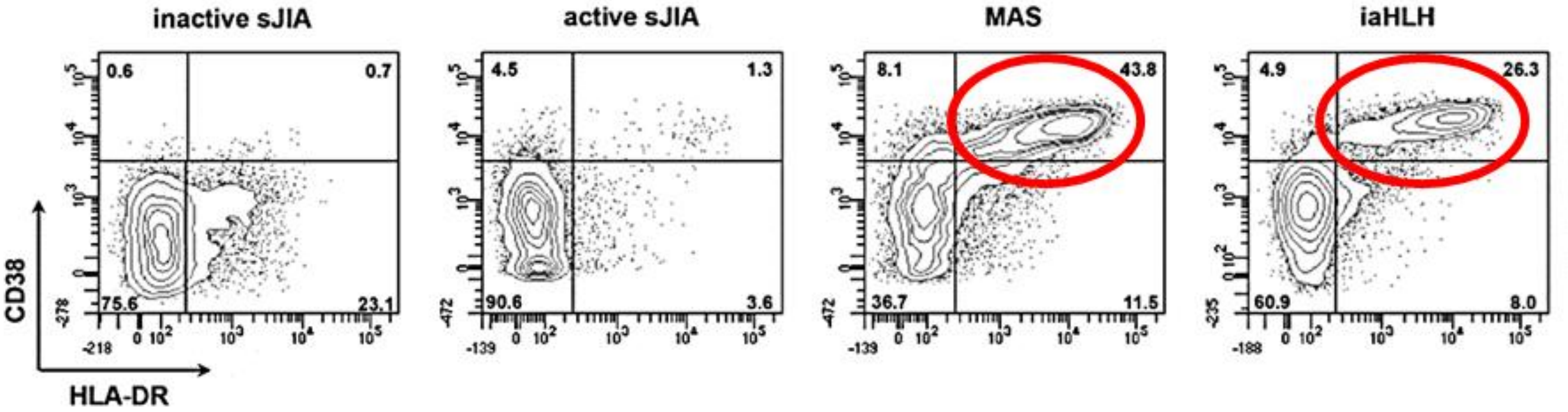
CD, cluster of differentiation; HLA-DR, human leukocyte antigen – DR isotope; IFN, interferon; IL, interleukin.

Adaptive immunity in hyperinflammation: CD8$^+$ T cells

Activated CD8$^+$ T cells (CD38^{high}HLA-DR$^+$ or CD4^{dim}) are expanded in patients with familial HLH and sHLH (including infection-associated HLH, MAS and others)[1,2]

CD8$^+$CD38^{high}HLA-DR$^+$ T cells

- Show features of recently and persistently activated T cells (PD-1, CD95…)[1]
- Predominantly effector memory T cells with cytotoxic differentiation[1]



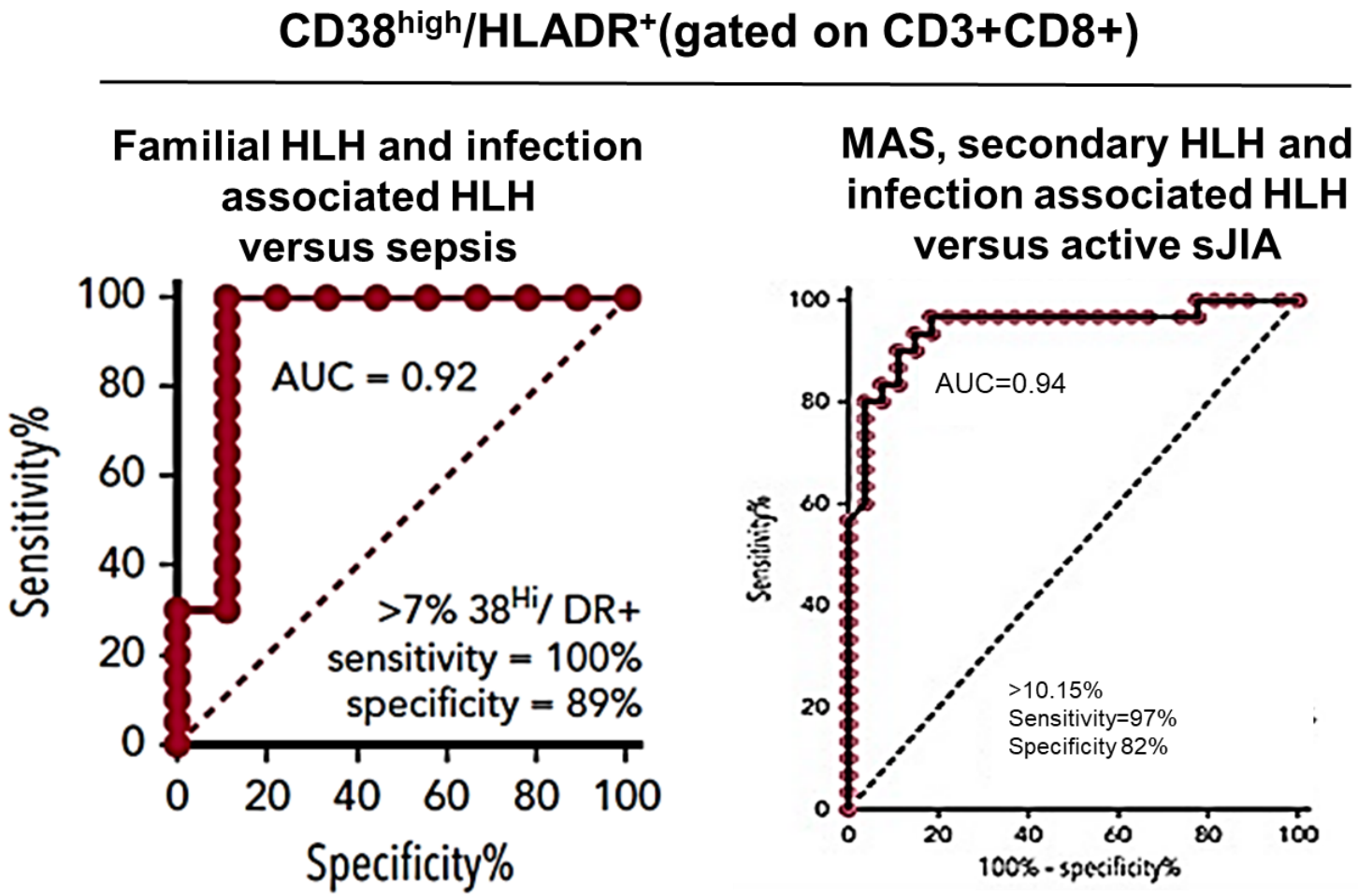
Gated on CD3$^+$CD8$^+$

Chaturvedi V et al. Blood 2021; De Matteis A et al. Blood 2022

Adaptive immunity in hyperinflammation: CD8^{+} T cells

Activated CD8^{+} T cells (CD38^{high}HLA-DR^{+} or CD4^{dim}) are expanded in patients with familial HLH and sHLH (including infection-associated HLH, MAS and others)[1,2]

- Effectively discriminate HLH and MAS from sepsis or active Still's disease



Chaturvedi V et al. Blood 2021
De Matteis A et al. Blood 2022

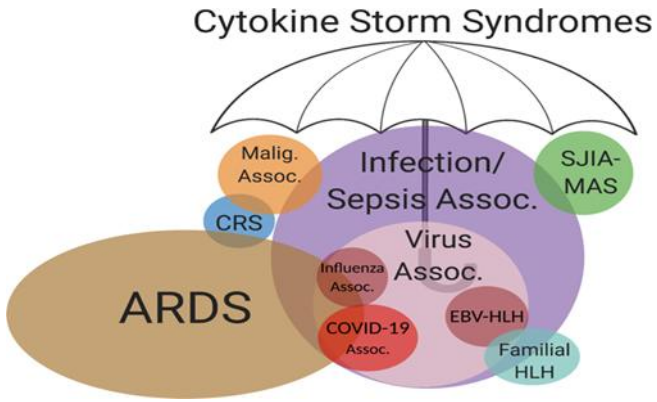
CD8⁺ T Cell Phenotyping in Hyperinflammation

Editorial

Here be dragons: A universal profile of recent T-cell (hyper)activation?

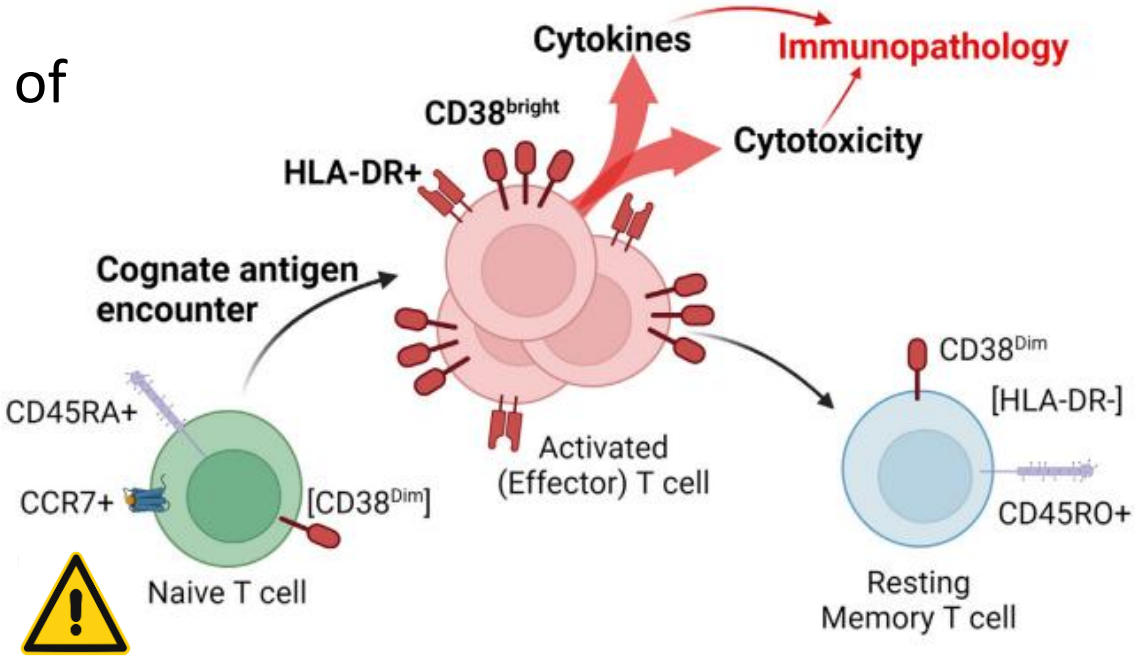
Check for updates

Michael B. Jordan, MD[a,b] *Cincinnati, Ohio*

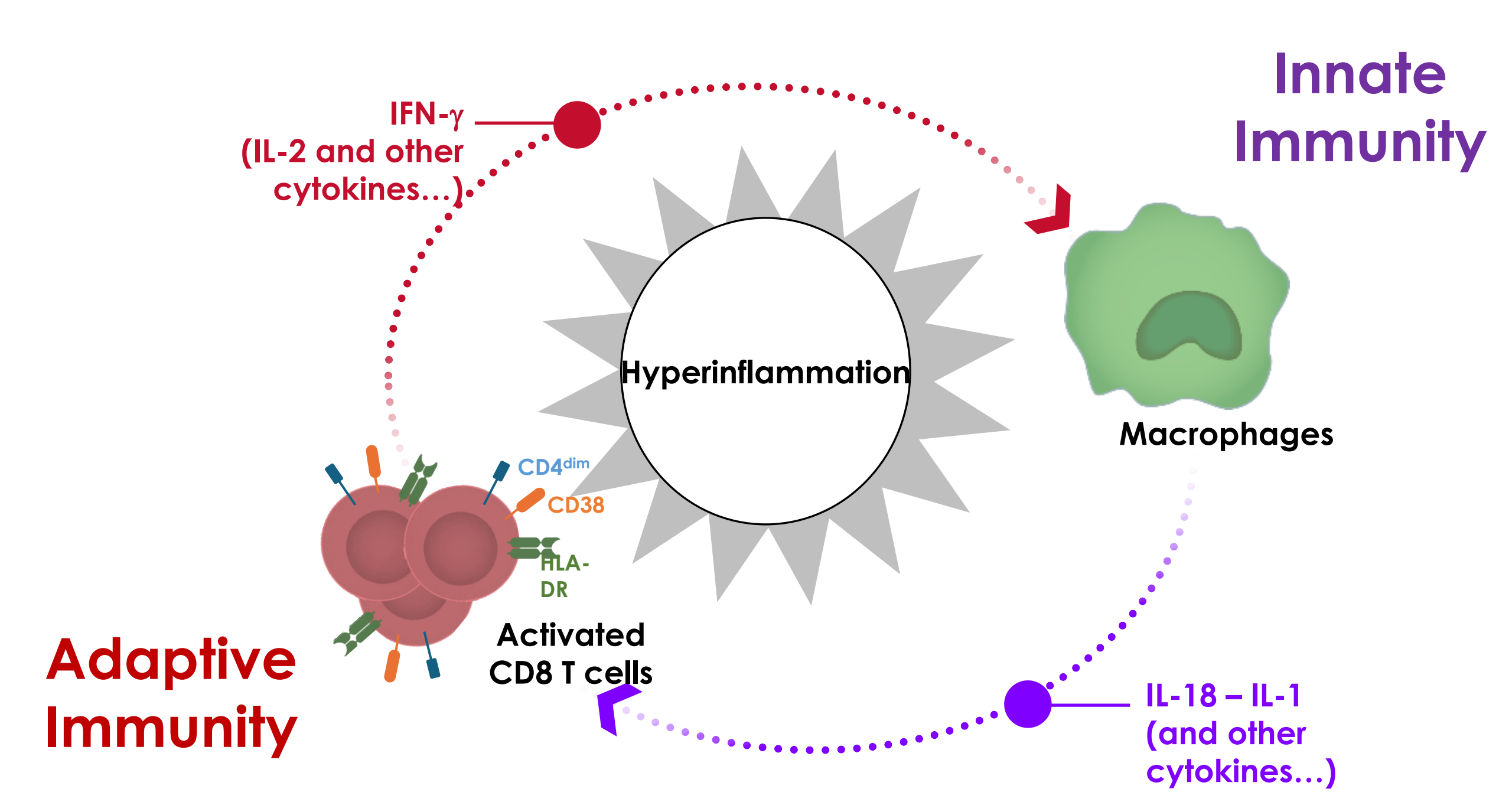


CD38^{high}/ HLA-DR^{+} CD8^{+} T cells

- ✓ PRACTICAL and FAST flow cytometric **BIOMARKER** of **immune hyperactivation**
- ✓ Can **refine diagnosis, monitor disease, and guide urgent therapy**
- ✓ Inform **targeted therapies** (e.g., emapalumab, daratumumab)
- ✓ Provide insights into **disease pathogenesis**
- ✓ **Validated thresholds needed** for standardized use



Michael B Jordan, JACI 2024 Jan



CD, cluster of differentiation; HLA-DR, human leukocyte antigen – DR isotope; IFN, interferon; IL, interleukin.

Elevated levels of IFNγ and IFNγ-induced chemokines characterise patients with MAS complicating sJIA

Bracaglia C et al, Ann Rheum Dis 2017

Annals of the Rheumatic Diseases

Bracaglia C et al, Ann Rheum Dis 2017

Elevated levels of IFNγ and IFNγ-induced chemokines characterise patients with MAS complicating sJIA

Bracaglia C et al, Ann Rheum Dis 2017

Annals of the Rheumatic Diseases

In MAS, but not in active sJIA, levels of CXCL9 were increased and were significantly correlated with ferritin, AST, and LDH levels and with neutrophils and PLT counts

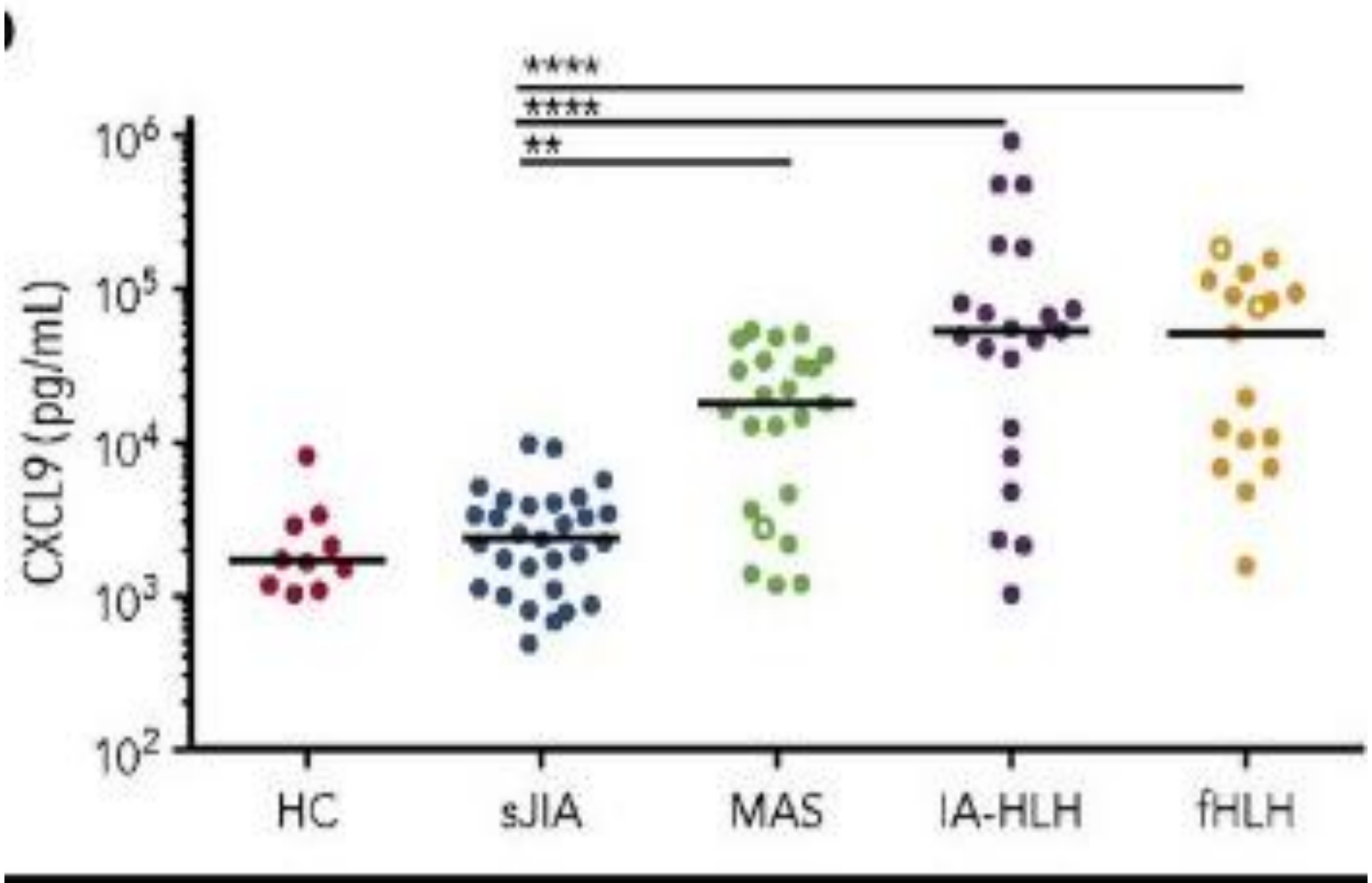
Act sJIA	CXCL9	
	Spearman R	*p*
Ferritin	0,09	>0,1
NEU	0,002	>0,1
PLT	0,14	>0,1
ALT	0,23	>0,1
LDH	0,28	>0,1

MAS	CXCL9	
	Spearman R	*p*
Ferritin	0,57	0,0012
NEU	-0,54	0,017
PLT	-0,65	0,0002
ALT	0,66	0,0012
LDH	0,84	0,0001

Bracaglia C et al, Ann Rheum Dis 2017

CXCL9 in different forms of HLH/MAS

- CXCL9 normal in active sJIA
- CXCL9 increased in MAS, in infection-associated HLH, indifferent forms of secondary HLH and in primary HLH



Weiss EC et al, Blood 2018

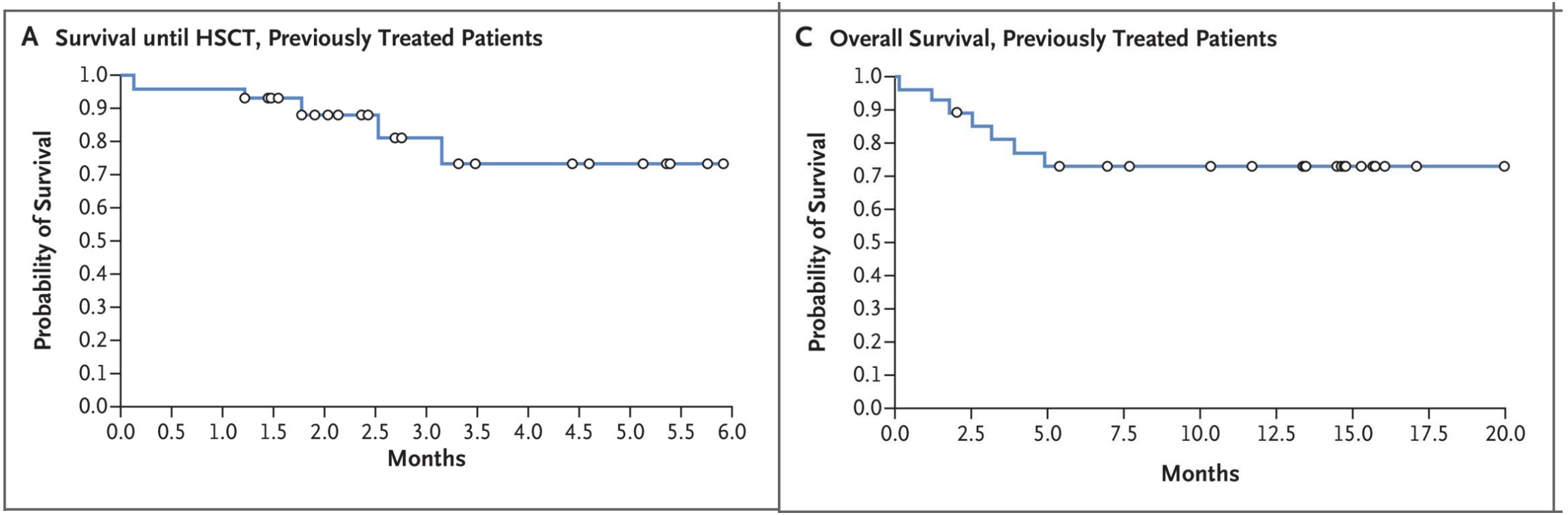
Over-production of IFNγ is present and pathogenic in several different animal models of HLH and MAS (de Benedetti Nat Rev Rheumatol 2021)

Human Disease	Mutation	Trigger	High IFN-γ	IFN-γ blockade	Ref
Familial HLH (cytotox)	PRF1	LCMV-infection	YES	Benefit	1,2
Familial HLH (cytotox)	UNC13D	LCMV infection	YES	Not tested	3
Familial HLH (cytotox)	STX11	LCMV-infection	YES	Not tested	4
Familial HLH (cytotox)	RAB27A	LCMV-infection	YES	Benefit	2
Familial HLH (Inflammasome)	SH2D1A	LCMV-infection	YES	Not tested	5
Infection-associated sHLH	None	TLR9 stimulation	YES	Benefit	6
MAS	IL-18 transgenic	TLR9 stimulation	YES	Benefit	7
MAS	IL18BP -/-	TLR9 stimulation	YES	Benefit	8
MAS	IL-6 transgenic	TLR4 stimulation	YES	Benefit	9

1) Jordan MB, Blood 2004; 2) Pachlopnik Schmid J, Embo Mol Med 2009; 3) Crozat K, JEM 2007; 4) Kogl T, Blood 2013; 5) Czar MJ, PNASS 2001; 6) Behrens E, JCI 2011; 7) Weiss SE, Blood 2018; 8) Girard-Guyonvarc'h C, Blood 2018 9) Prencipe G, JACI 2018

Emapalumab in Children with Primary Hemophagocytic Lymphohistiocytosis

F. Locatelli, M.B. Jordan, C. Allen, S. Cesaro, C. Rizzari, A. Rao, B. Degar, T.P. Garrington, J. Sevilla, M.-C. Putti, F. Fagioli, M. Ahlmann, J.-L. Dapena Diaz, M. Henry, F. De Benedetti, A. Grom, G. Lapeyre, P. Jacqmin, M. Ballabio, and C. de Min



Multidiscipline review, FDA (https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/761107Orig1s000MultidisciplineR.pdf); Locatelli F et al, NEJM 2020

OPEN ACCESS

CLINICAL SCIENCE

Efficacy and safety of emapalumab in macrophage activation syndrome

Fabrizio De Benedetti ,[1] Alexei A Grom ,[2,3] Paul A Brogan ,[4] Claudia Bracaglia ,[1] Manuela Pardeo,[1] Giulia Marucci,[1] Despina Eleftheriou,[4] Charalampia Papadopoulou ,[4] Grant S Schulert ,[2,3] Pierre Quartier,[5,6] Jordi Antón ,[7,8] Christian Laveille,[9] Rikke Frederiksen,[10] Veronica Asnaghi,[10] Maria Ballabio,[10] Philippe Jacqmin,[11] Cristina de Min[10]

- **MAS occurring in the context of AOSD and sJIA**
- **Open-label single arm trial in patients who have failed high dose glucocorticoids (plus anakinra and/or cyclosporin)**
- **Prompt decrease in CXCL9 levels demonstrating neutralization of IFNγ**

Ann Rheum Dis 2023

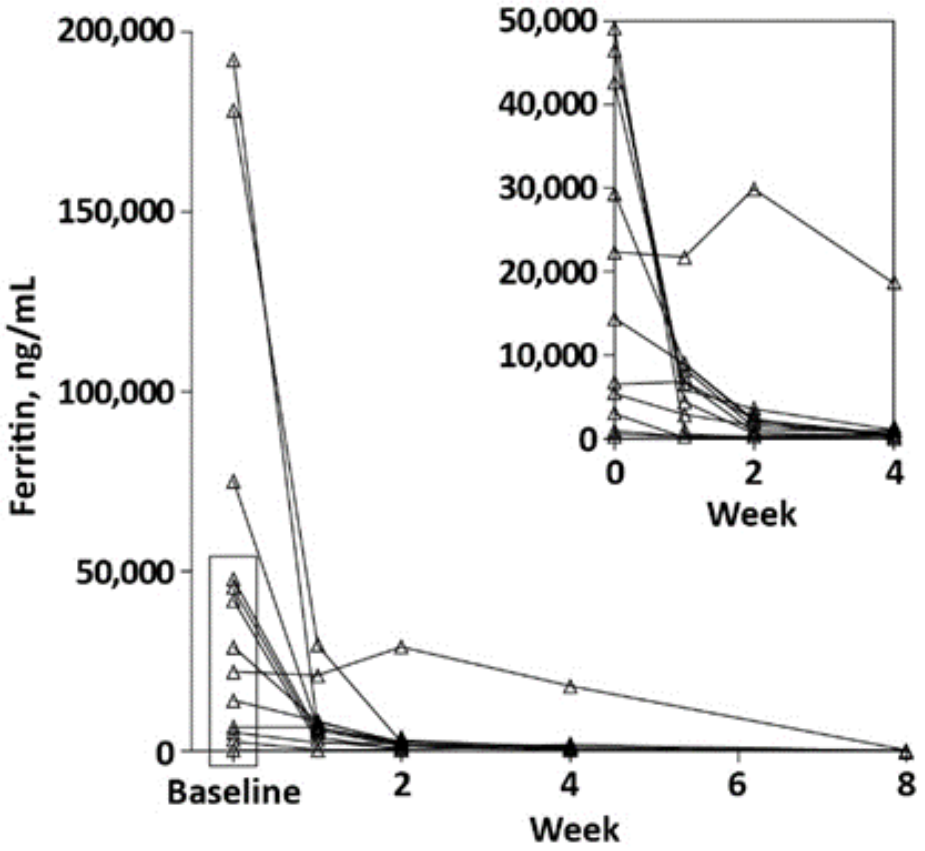
OPEN ACCESS

CLINICAL SCIENCE

Efficacy and safety of emapalumab in macrophage activation syndrome

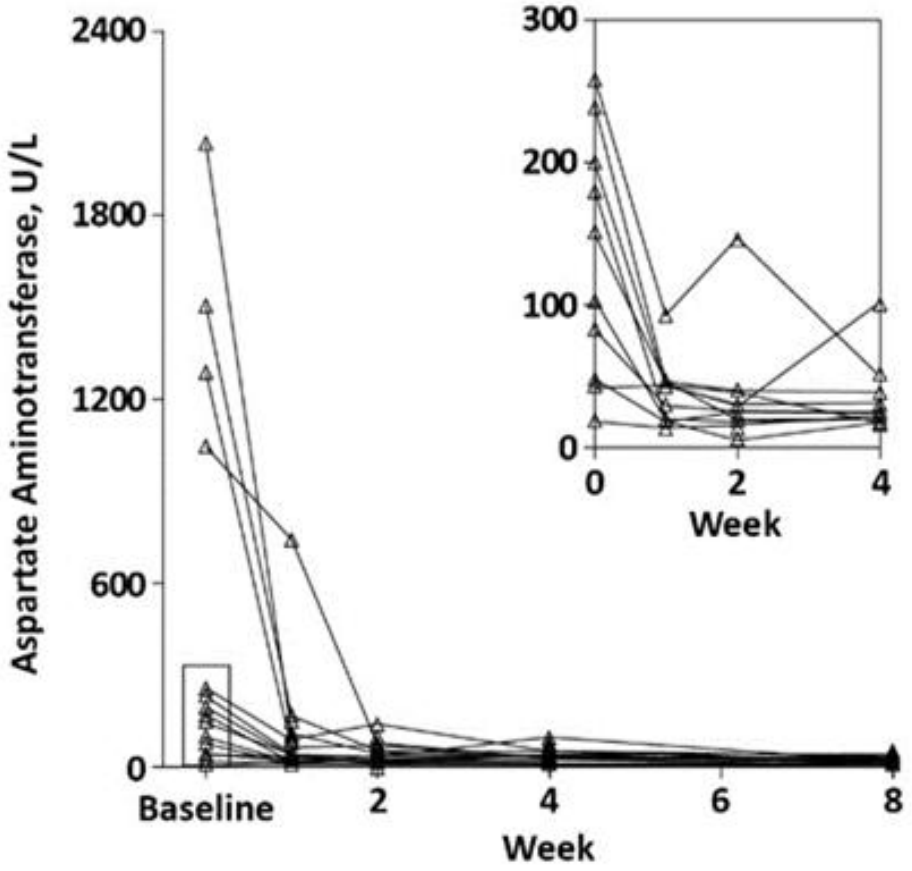
Annals of the Rheumatic Diseases

Ferritin



The insert shows in detail changes from baseline to week 4 for patients with baseline levels of ferritin below 50.000 ng/mL.

Aspartate Aminotransferase



The insert shows in detail changes from baseline to week 4 for patients with baseline levels of AST below 300 U/L.

De Benedetti et al, Ann Rheum Dis 2023

Emapalumab for MAS on top of anakinra for sJIA

sJIA/AOSD flares while receiving emapalumab

- **6 out of 9 (66.7%) patients who did not receive anakinra (for the underlying sJIA) had a flare**
- **No sJIA flares were observed in the 5 patients (0%) who continued anakinra**

- No increase in the rate of overall or infectious AEs was observed during concomitant treatment with anakinra and emapalumab compared with emapalumab alone

De Benedetti et al, Ann Rheum Dis 2023

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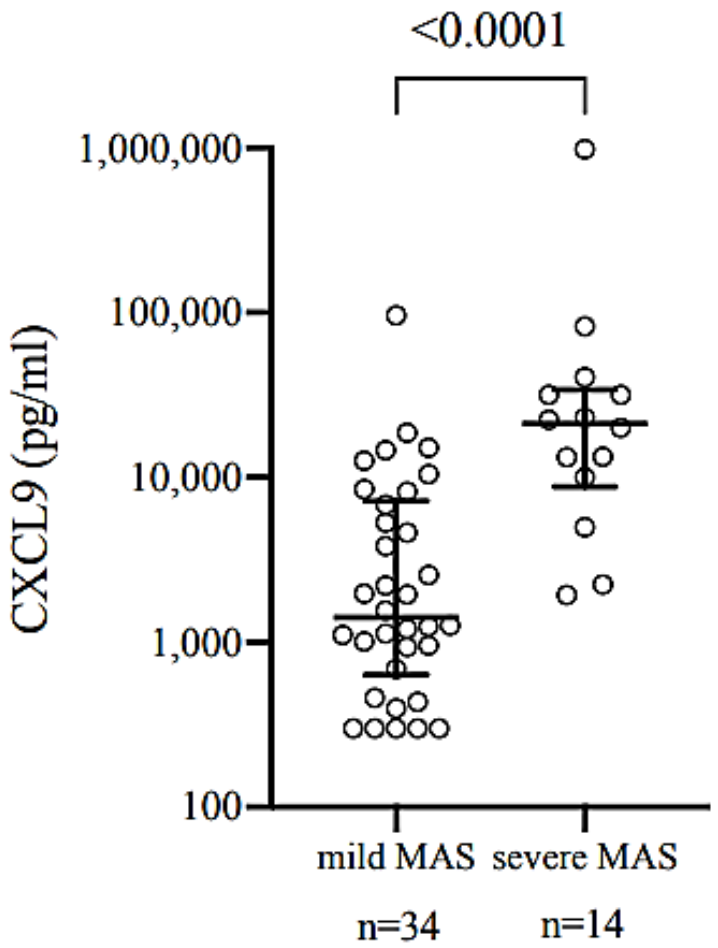
	Emapalumab	Emapalumab and anakinra
Exposure (days at risk)	303	506
AEs Number of events	45	43
AEs Rate per 100 patient-days	14.9	8.5
Infectious AEs Number of events	5	5
Infectious AEs Rate of per 100 patient-days	1.7	1.0

De Benedetti et al, Ann Rheum Dis 2023

CXCL9 levels in the management of patients with MAS

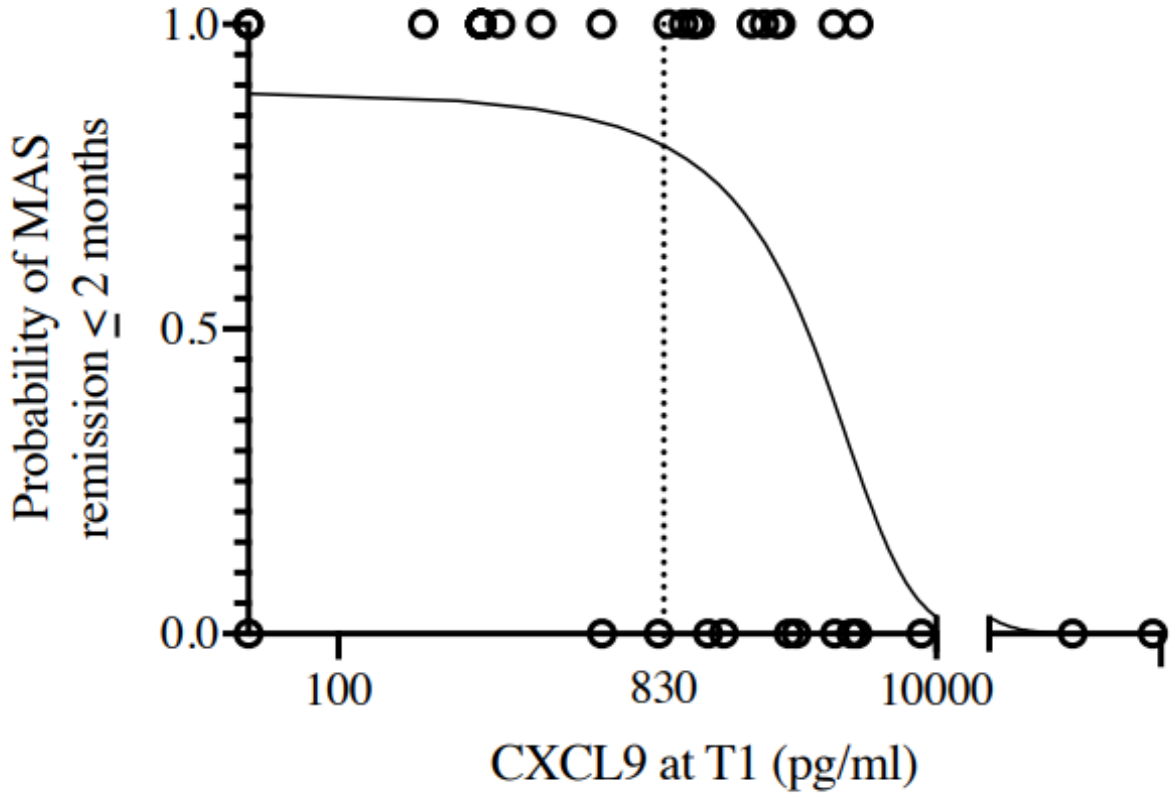
Higher CXCL9 levels at baseline are present in patients with severe MAS

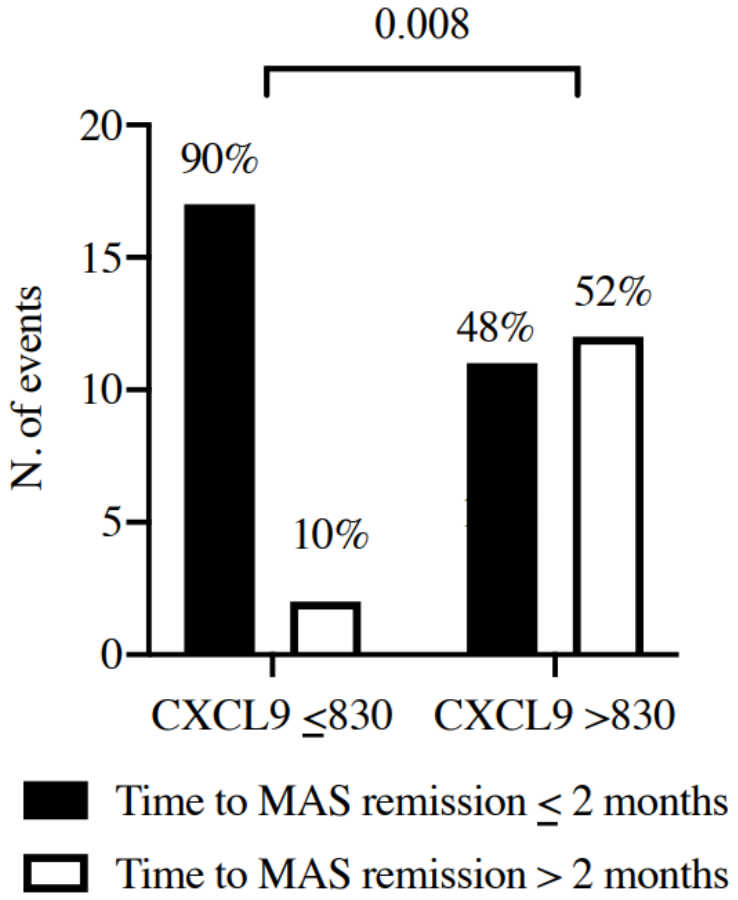


De Matteis A, submitted

CXCL9 levels in the management of patients with MAS

CXCL9 levels > 830 pg/ml at 5-15 days after initiation of therapy are associated with longer time to MAS remission and to higher risk of not achieving remission at 2 months (OR 9.3)

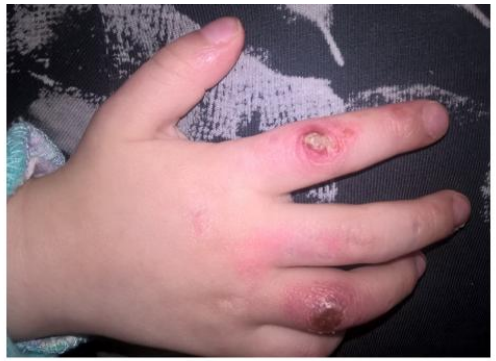


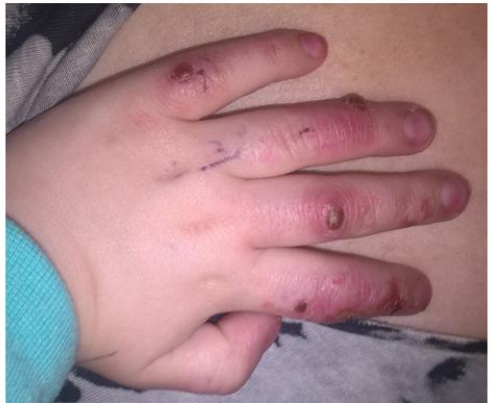


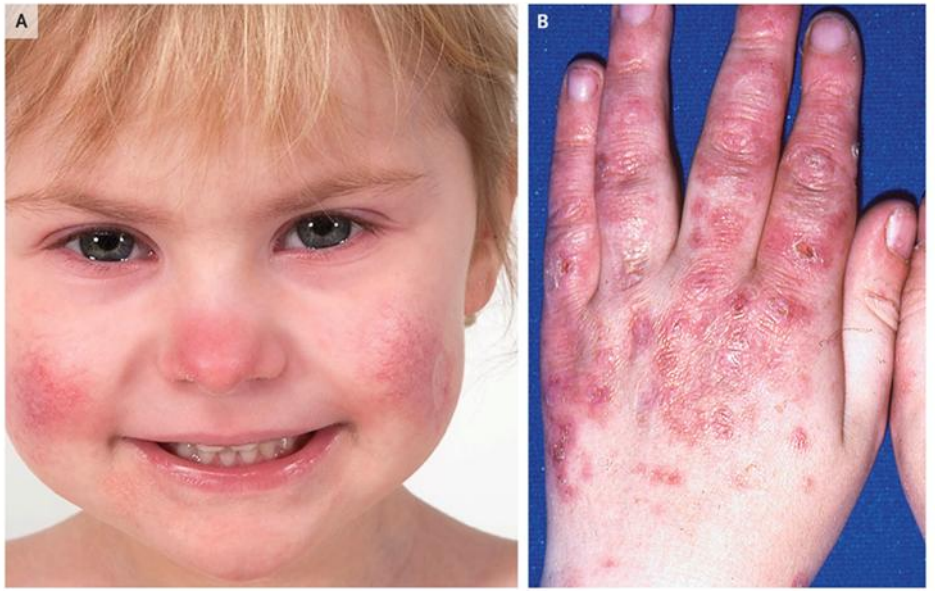
De Matteis A, submitted

Sting Associated Vasculopathy with onset in Infancy (SAVI) syndrome

- **Telangiectasic, pustular, or blistering rash (cheeks, nose, fingers, toes soles) worsened by cold exposure**
- **Eschar and secondary painful crusts covered ulcerated skin lesions**
- **Vascular inflammation limited to capillaries with microthrombotic vascular changes**







Yin Liu et al, NEJM 2014

PNAS

RESEARCH ARTICLE | IMMUNOLOGY AND INFLAMMATION

Gaoa KM et al. PNAS 2022

Radioresistant cells initiate lymphocyte-dependent lung inflammation and IFNγ-dependent mortality in STING gain-of-function mice

JCI insight

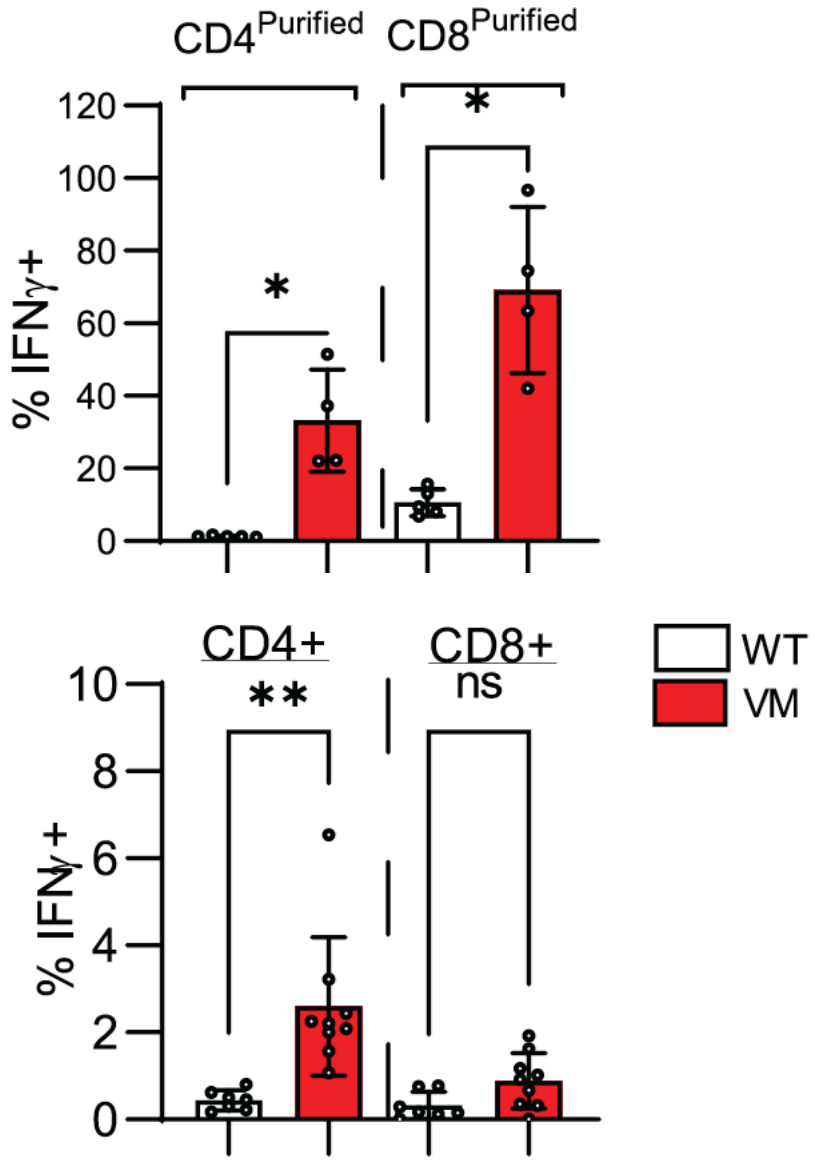
Stinson WA et al. JCI insight 2022

The IFN-γ receptor promotes immune dysregulation and disease in STING gain-of-function mice

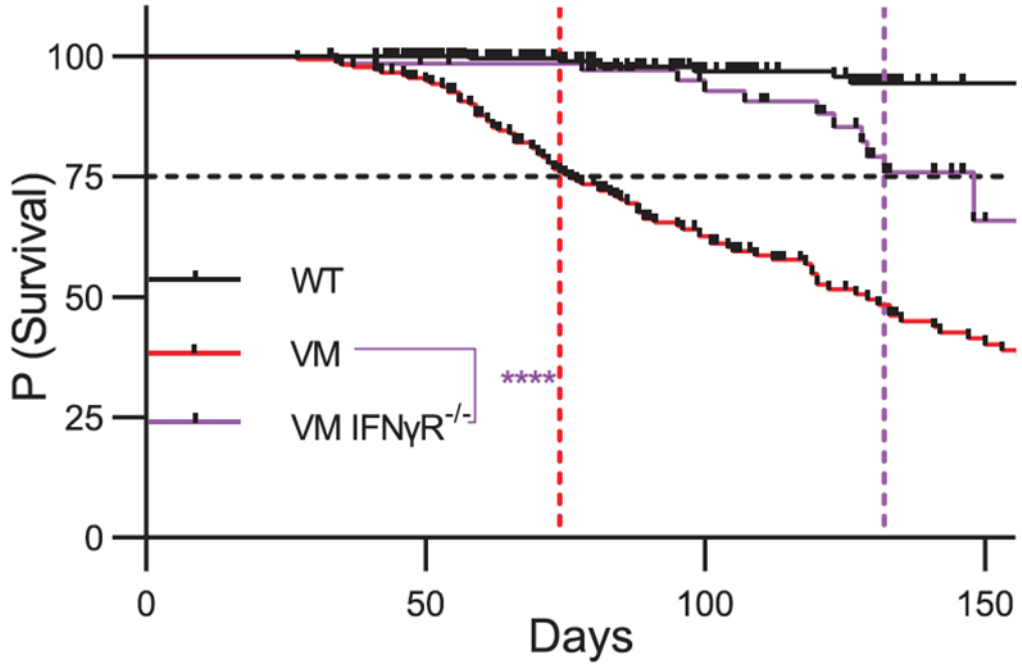
V154M (VM) SAVI T Cells Produce IFNγ

Spleen T cells
Anti-CD3-CD28
stimulated

Lung T cells
unstimulated

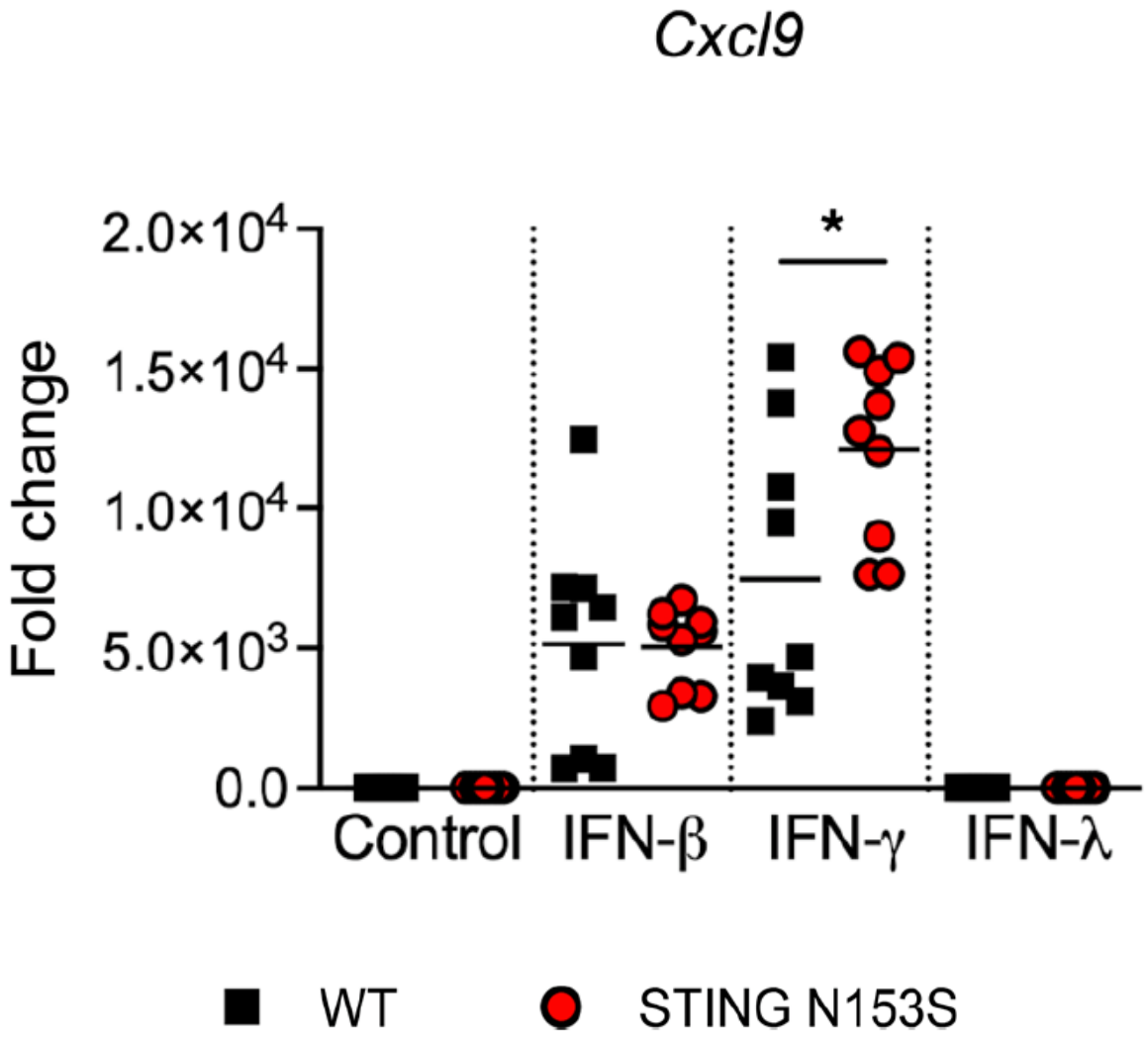


IFNγR contributes to VM SAVI mortality



Gaoa KM et al. PNAS 2022 Jun 21;119(25)

Bone marrow–derived macrophages have increased response to IFN-γ (*Cxcl9* expression)



Stinson WA et al. JCI insight 2022

PNAS RESEARCH ARTICLE | IMMUNOLOGY AND INFLAMMATION

Radioresistant cells initiate lymphocyte-dependent lung inflammation and IFNγ-dependent mortality in STING gain-of-function mice

JCI insight

The IFN-γ receptor promotes immune dysregulation and disease in STING gain-of-function mice

In two mice models (different mutations) of SAVI IFNγ appeared to play a major role compared to type I IFN

- High levels of IFNγ and of IFNγ-induced genes
- IFNγR deletion leads to improvement in lung disease and survival (the latter only in one of the models)
- High levels of IFNγ induced chemokines (e.g. CXCL9)
- Hyper-response of macrophages to IFNγ

Gaoa KM et al. PNAS 2022

Stinson WA et al. JCI insight 2022

nature

https://doi.org/10.1038/s41586-025-09536-4

Accelerated Article Preview

STING induces ZBP1-mediated necroptosis independently of TNFR1 and FADD

Received: 9 December 2024

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Accelerated Article Preview
Published online: 20 August 2025

Konstantinos Kelepouras, Julia Saggau, Debora Bonasera, Christine Kiefer, Federica Locci, Hassan Rakhsh-Khorshid, Louisa Grauvogel, Ana Beatriz Varanda, Martin Peifer, Elena Loricchio, Antonella Montinaro, Marijana Croon, Aleksandra Trifunovic, Giusi Prencipe, Antonella Insalaco, Fabrizio De Benedetti, Henning Walczak & Gianmaria Liccardi

nature

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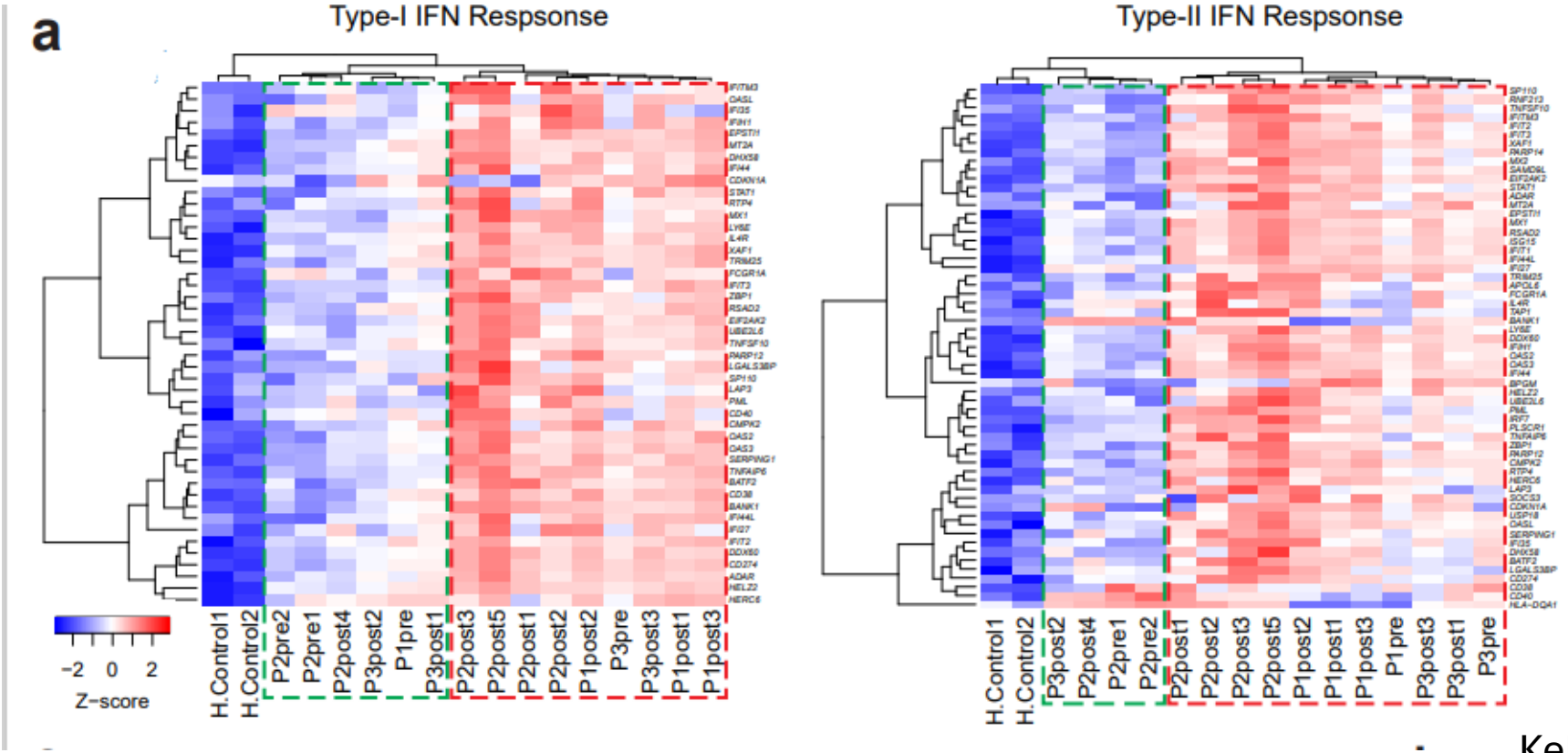
STING induces ZBP1-mediated necroptosis independently of TNFR1 and FADD



Kelepouras K, Nature 2025

nature

https://doi.org/10.1038/s41586-025-09536-4

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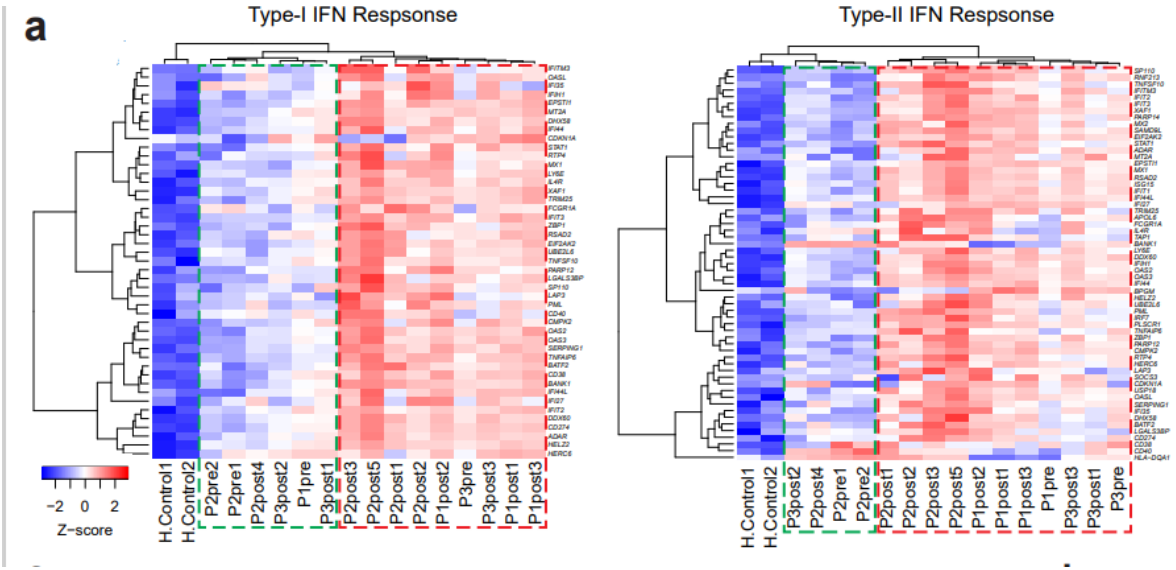
STING induces ZBP1-mediated necroptosis independently of TNFR1 and FADD



IFITM3	*Ifitm3*
ISG15	*Isg15*
IRF7	*Irf7*
STAT1	*Stat1*
STAT2	*Stat2*
IFI35	*Ifi35*
IFI27	*Ifi27*
IFI44	*Ifi44*
GBP3	*Gbp3*
GBP5	*Gbp5*
SIGLEC1	*siglec1*
MX1	*Mx1*
MX2	*Mx2*
USP18	*Usp18*
RSAD2	*Rsad2*
RTP4	*Rtp4*
BST2	*Bst2*
XAF1	*Xaf1*
PARP9	*Parp9*
PARP12	*Parp12*
PARP14	*Parp14*
HERC5	*Herc6*
TAP1	*Tap1*
TRIM5	*Trim5*
EPSTI1	*Epsti1*
SAMD9L	*Samd9l*
TRIM25	*trim25*

Kelepouras K, Nature 2025

- Type I IFNpathies → autoinflammation
  - Clinical presentations (skin vasculitis)
  - Biomarkers (type I score, monocytes Siglec-1 expression)
  - Targeted treatments (anifrolumab, Jaki)
- Type II IFNpathies → hyperinflammation
  - Clinical presentations (clinical and laboratoy pattern)
  - Biomarkers (Activated CD8, CXCL9)
  - Targetted treatments (emapalumab)

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