31st European Paediatric Rheumatology Congress

11-14 SEPTEMBER 2024
Gothenburg • Sweden

Exploring the Future of Macrophage Activation Syndrome in Still's Disease

PReS 2024, Gothenburg, Sweden

Sobi™-sponsored Symposium, Thursday 12 September 2024

Meeting sponsored by

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September 2024 I NP-36560

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Introducing the Faculty

Prof. Fabrizio De Benedetti (Chair)

Ospedale Pediatrico Bambino Gesù, Rome, Italy

Dr Fatma Dedeoglu

Harvard Medical School, Boston, MA, USA

Boston Children's Hospital, Boston, MA, USA

Prof. Petter Brodin

Imperial College, London, UK

Karolinska Institutet, Stockholm, Sweden

Disclosures

- **Prof. Fabrizio De Benedetti:**
  - Grants/research support: AbbVie; Novartis; Pfizer; Roche; Sanofi-Aventis; Sobi™
  - Consultancy and/or speaker fees: Novartis; Sobi™
- **Dr Fatma Dedeoglu:**
  - Advisory board member: Autoinflammatory Alliance
  - ISSAID Education Committee Chair
  - Royalties from UpToDate for chapter writing
- **Prof. Petter Brodin:**
  - Cofounder of Cytodelics AB
  - Executive board member of Kancera AB
  - Scientific advisor for Helaina Inc., Oxford Immune Algorithmics Ltd, Pixelgen Technologies AB, Scailyte AG, Sention Health AB and the Swedish Olympic Committee

Agenda

Time	Title	Speaker
16:00	Introduction	Fabrizio De Benedetti
16:02	Day-to-Day Challenges in Patient Management	Fatma Dedeoglu
16:17	Unravelling the Mechanisms	Petter Brodin
16:32	Emerging Management Strategies	Fabrizio De Benedetti
16:47	Q&A	All

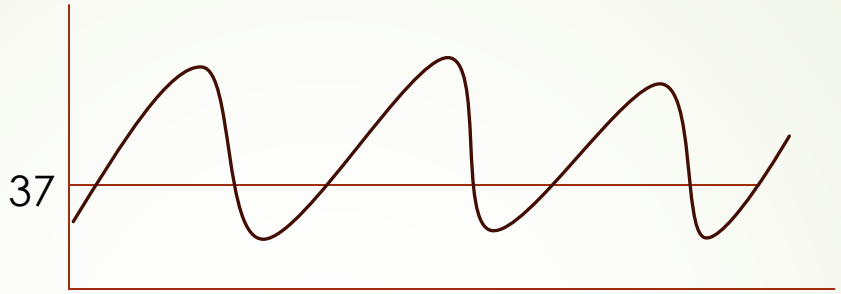
Day-to-Day Challenges in Patient Management

Fatma Dedeoglu, MD

Boston Children's Hospital,
Harvard Medical School,
Boston, MA, USA

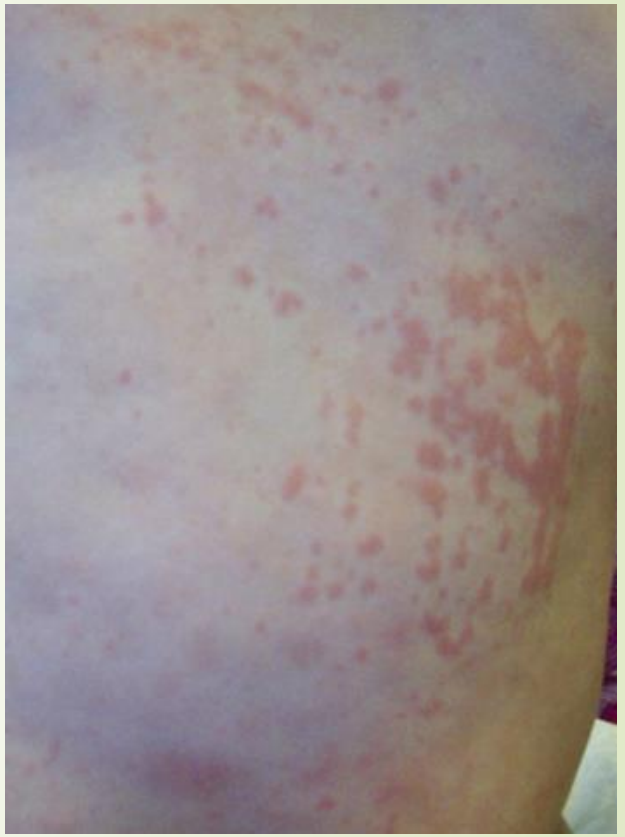
Systemic juvenile idiopathic arthritis (sJIA) & adult-onset Still's disease (AOSD)

Clinical Features*



- Idiopathic
- Quotidian fever
- Salmon colored rash
- Generalized lymphadenopathy
- Hepatosplenomegaly
- Serositis
- Arthralgia/arthritis
- Sore throat
- Labs: Anemia, leukocytosis (neutrophilia), thrombocytosis, elevated ferritin

- EXCLUDE
  - Infections
  - Malignancies
  - Other systemic inflammatory rheumatic diseases



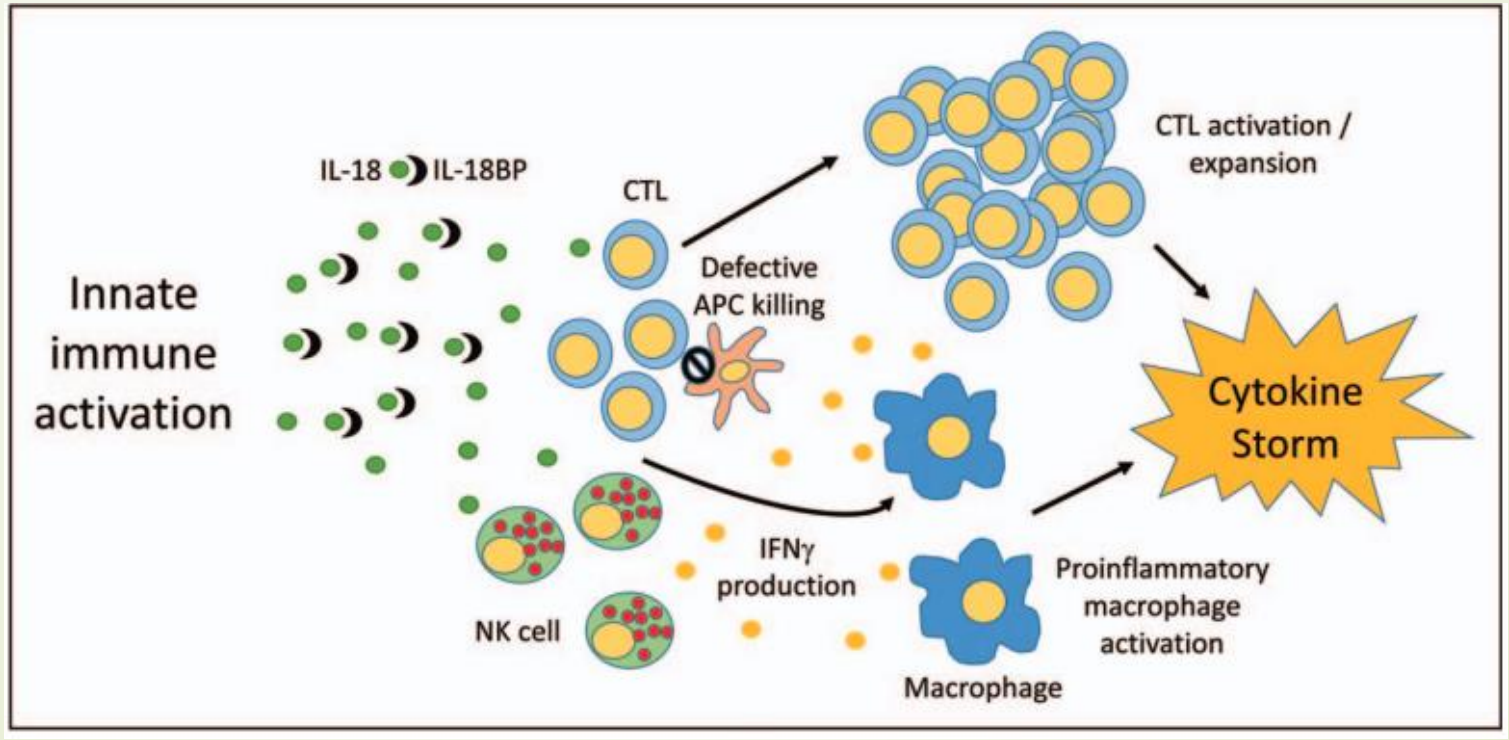
Lee JJY, Schneider R. Pediatr Clin North Am 2018;65:691–709.

- MACROPHAGE ACTIVATION SYNDROME (MAS)

*Based on current literature and personal experience.

MAS is

- *an hyperinflammatory response stemming from massive activation of T cells and macrophages triggered by infections, malignancies, or rheumatic diseases leading to uncontrolled hypersecretion of proinflammatory cytokines*



Yasin S, Schulert G. Curr Opin Rheumatol 2018;30:514–520.

Clinical Features of MAS*

- Persistent fever
- Diffuse persistent rash
- CNS disfunction
- Rising ferritin
- Hepatic dysfunction
- Cytopenia
- Coagulopathy
- Rising IL-18 and CXCL9

- MAS may progress quickly
- Mimics sepsis
- Common Triggers of MAS
  - Still's disease flare
  - medication change
  - infections

These features individually may be non-specific, but when exist together should prompt consideration of MAS

*Based on current literature and personal experience.

Other Features of MAS

- Subclinical MAS may be present in 31–53% of patients with known or suspected sJIA

- One-third of sJIA patients with MAS carry rare heterozygous variants of familial HLH genes

- Biologics may mask MAS symptoms

Behrens EM et al. J Rheumatol 2007;34:1133–1138;
Bleesing J et al. Arthritis Rheum 2007;56:965–971;
Yasin S, Schulert G. Curr Opin Rheumatol 2018;30:514–520.

Criteria and Scores

Table 1. Diagnostic and classification scores for MAS, secondary HLH, and familial HLH.

2016 MAS Classification Criteria [7]	HScore for secondary HLH [12]	MH Score to differentiate MAS from familial HLH [10▪]
A febrile patient with known or suspected SJIA is classified as having MAS if:	Known immunosuppression: 0 (no) or 18 (yes)	Age of onset: 0 (>1.6 years), 37 (≤1.6)
(1) Ferritin >684 ng/ml	Fever: 0 (<38.4), 33 (38.4–39.4), 49 (>39.4)	PMN count: 0 (>1.4×10^9/l), 37 (≤1.4)
AND	Organomegaly: 0 (no), 23 (liver or spleen), 38 (both)	Fibrinogen: 0 (>131 mg/dl), 15 (≤131)
(2) Any 2 of the following:	Cytopenias: 0 (0–1 line), 24 (2 lines), 34 (3 lines)	Splenomegaly: 0 (no), 12 (yes)
Platelets ≤181×10^9/l	Ferritin: 0 (<2000 ng/ml), 35 (2–6000), 50 (>6000)	Platelets: 0 (>78×10^9/l), 11 (≤78)
AST >48 U/l	Triglycerides[a]: 0 (<133 mg/dl), 44 (133–354), 64 (>354)	Hemoglobin: 0 (>8.3 g/dl), 11 (≤8.3)
Triglycerides >156 mg/dl	Fibrinogen: 0 (>250 mg/dl), 30 (≤250)	Best cutoff: 60 (≥60 indicative of familial HLH)
Fibrinogen ≤360 mg/dl	AST: 0 (<30 U/l), 19 (≥30)	
	Hemophagocytosis: 0 (no) 35 (yes)	
	Best cutoff: 169 (≥169 indicative of reactive HLH)	

Yasin S., Schulert G. Curr Opin Rheumatol 2018;30:514–520.

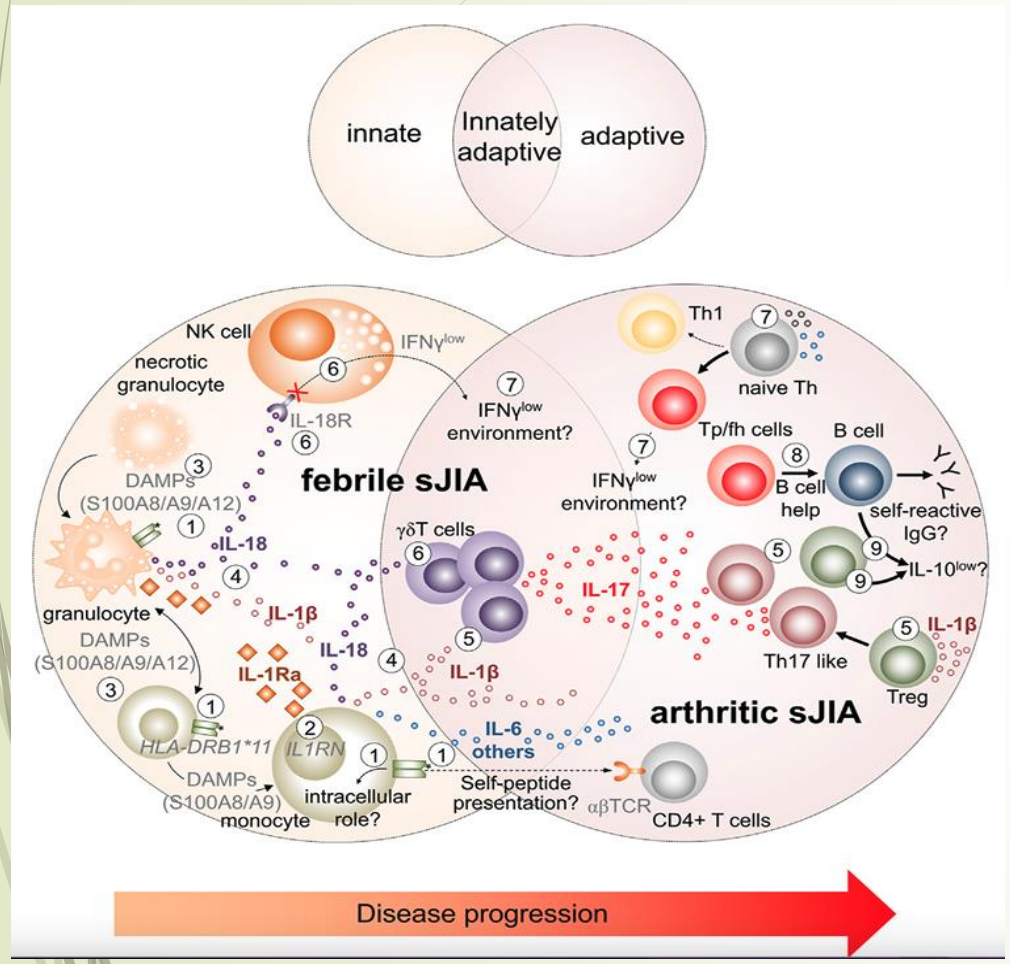
- 23/76 patients (30%) diagnosed with MAS at a total of 32 episodes
- 18/32 MAS episodes 18 (56%) fulfilled 2016 MAS classification criteria

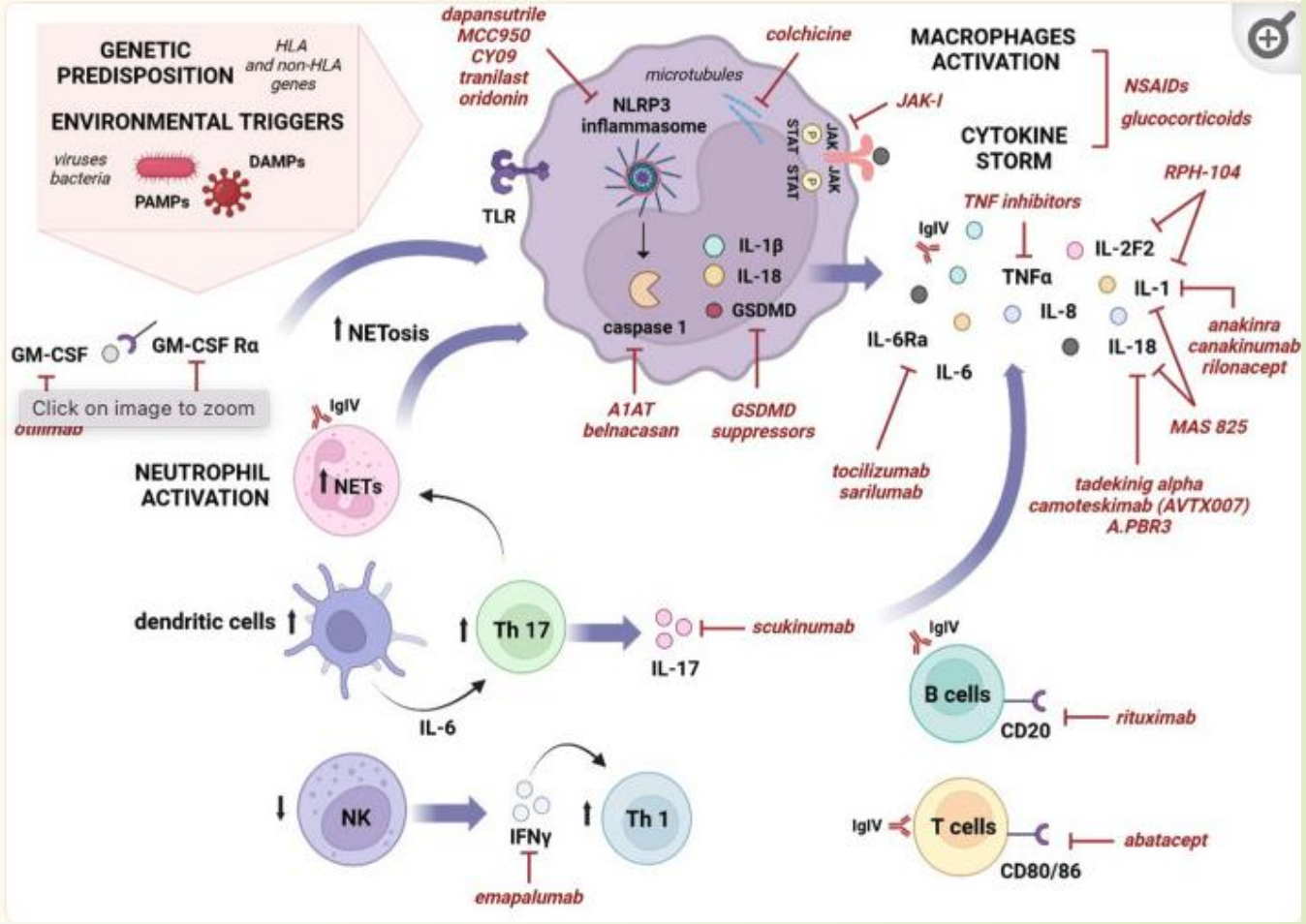
Baris HE et al.
Clin Rheumatol 2018;37:3263–3273.

- 2016 MAS classification criteria may not be as sensitive at the onset for sJIA and AOSD

Shimizu M et al. Arthritis Care Res (Hoboken) 2017; DOI: 10.1002/acr.23482;
Ahn SS et al. J Rheumatol 2017;44:996–1003.

Pathophysiology is Complex





Schulert GS, Kessel C. Rheum Dis Clin North Am 2023;49:895–911
Bindoli S et al. Drugs 2024;84:257–274.

CHALLENGES – through SF's JOURNEY

Permission to present video provided by family of the patient.

Day-to-Day Life by sJIA/MAS/ILD Parents

- "It can feel daunting to manage all of the moving pieces of multiple medications, being followed by various specialists, while still closely monitoring clinical presentation and being present as a parent, but as time passes, the juggling begins to feel more natural and less scary"

"We are definitely project managers"

"PA process is maddening, another thing to follow and worry about; with some other doctor that does not know your child, making decisions that have a huge impact on your child"

Quotes are from parents of the patient; permission to present quotes and photo were provided.

Challenges and Unmet Needs

Diagnostic and Therapeutic Odyssey

- Rarity – lack of natural history
- Often affecting many organs
- Mimicking other conditions
- Scarce treatment options
- Heterogeneity
  - Disease course
  - Treatment response
- Delay in critical tests being available to clinical arena
- Gaps in linking genetics to functional testing
- Finding correct biomarker *(accessible, detectable, stable, specific)*
- Medications (not available or available but not accessible – *insurance denial or partially accessible – inadequate dosing)*
- Vaccinations

Efthimiou P et al. Semin Arthritis Rheum 2021;51:858–874;
Ambler WG et al. Ann Med 2022;54:1839–1850;
Mittal S et al. Diseases 2024;12:166;
Hinze CH et al. Nat Rev Rheumatol 2023;19:778–789.

Challenges and Unmet Needs*

Obstacles to day-to-day care

- Unpredictability
- Access to care
  - Finding a specialist
  - Tests
  - Treatments
- Lack of awareness (both medical community and public)

Getting approvals for testing and treatment

Difficulties in getting supportive care (PT/OT, psychosocial)

Tolerating medications

School- and work-related issues

Experts

Internet superusers

Case Managers

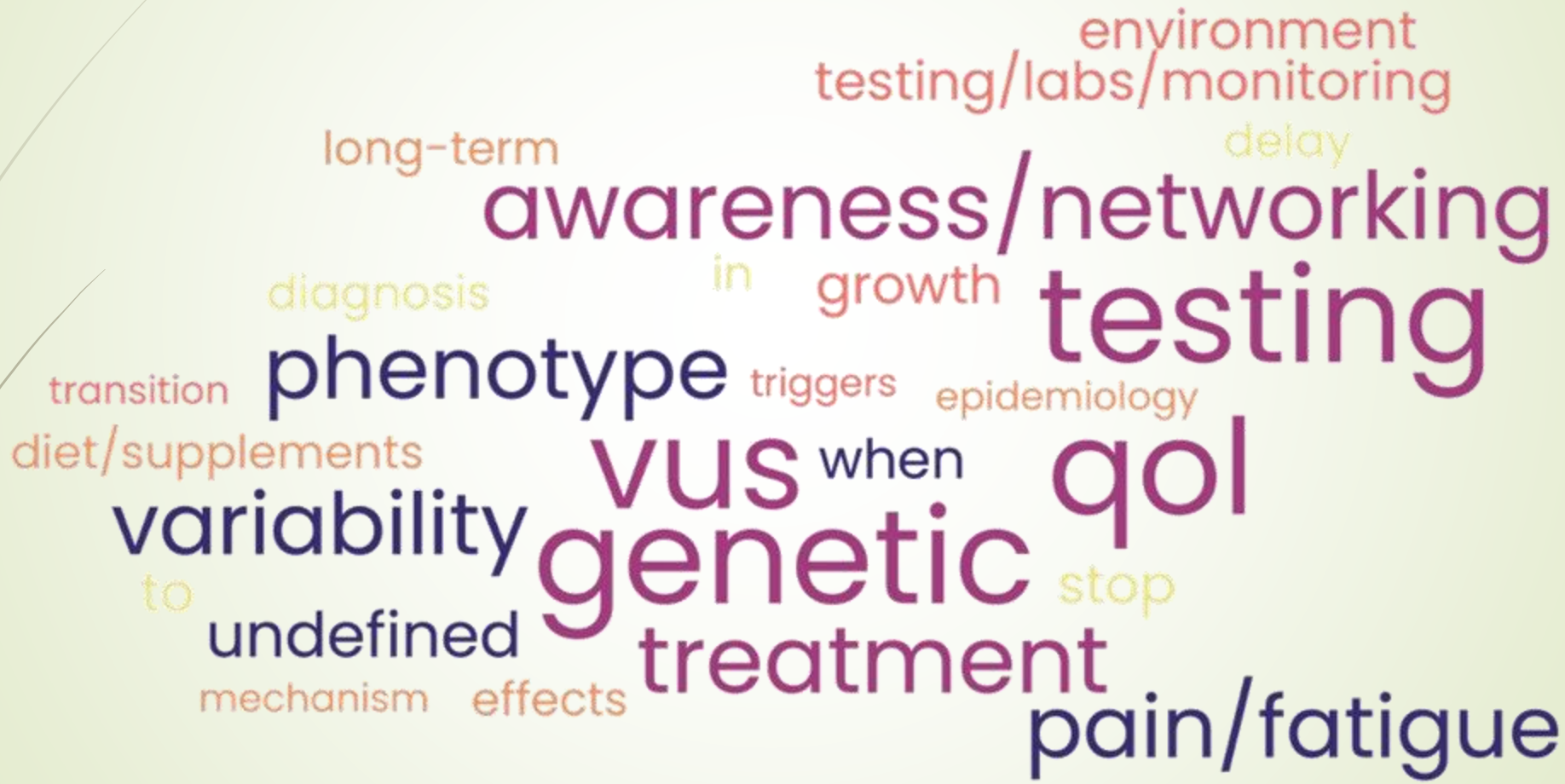
*Based on personal experience.

MAS has a High Disease Burden

- One-third to one-half require ICU admission
- Prolonged hospital stay
- Increased economic burden

Minoia F et al. Arthritis Rheumatol 2014;66:3160–3169;
Hot A et al. Medicine 2010;89:37–46;
Mittal S et al. Diseases 2024;12:166.

What Do Patients Want to Know?



Word cloud generated from patient responses when asked what topics should be addressed at workshops for general autoinflammatory diseases, including sJIA/MAS.

Diagnostic Journey of Patients With HLH

Patient and healthcare professional perspectives

- Patient associations can provide valuable support
- Quantitative and qualitative interviews
- 9-11 specialist help is sought
- Persistent fever, persistent tiredness/fatigue and an enlarged abdomen (patient)
- Fever and hepatosplenomegaly (physicians)
- Lack of knowledge and awareness (target the right audience)
- 57–63% misdiagnosis, delay in diagnosis
- Need for guidelines and algorithms
- Need for communication and support

Machado T et al. Hematology 2024;29:2358261.

Patient Organization Survey

Nikki Tennermann

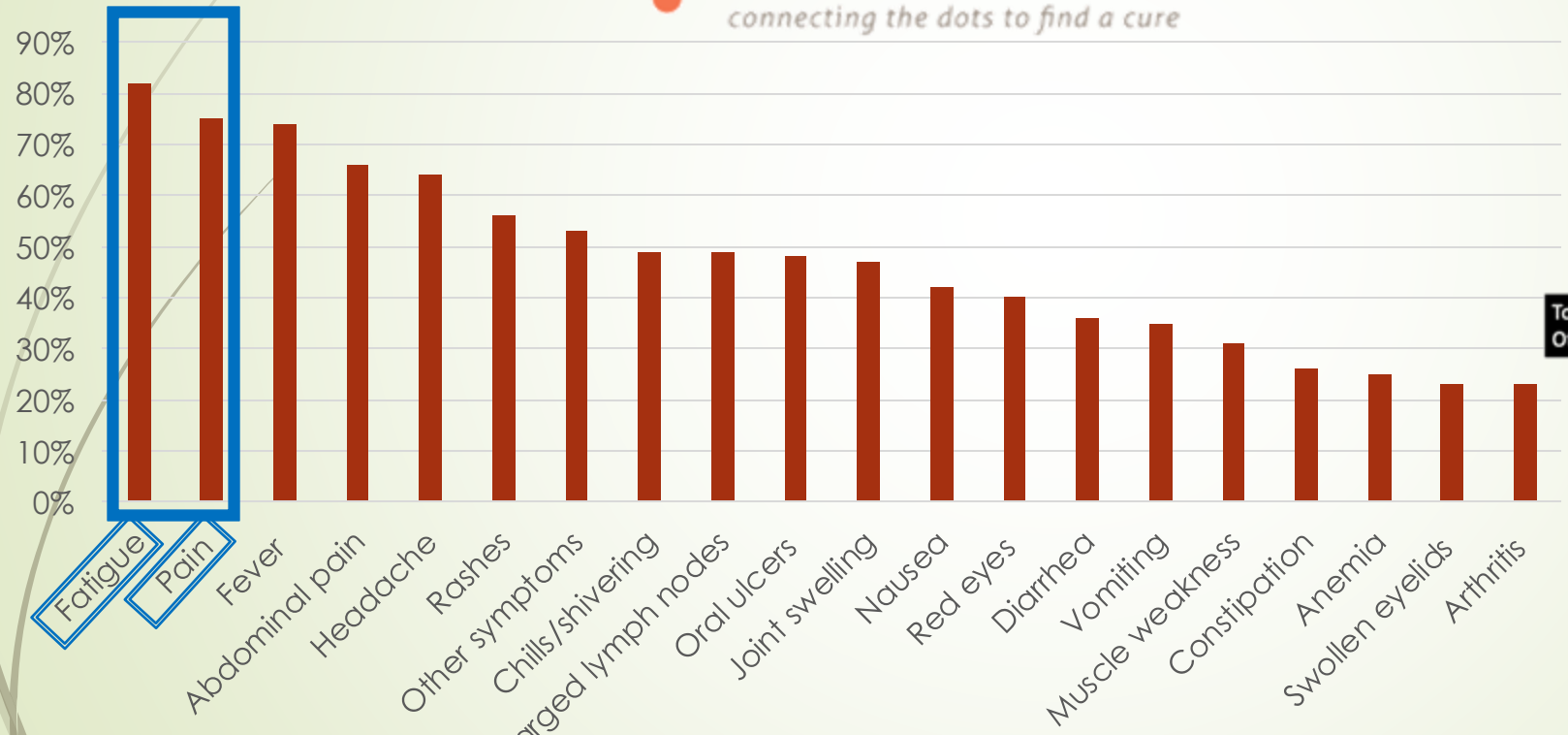
Mariana C. Marques

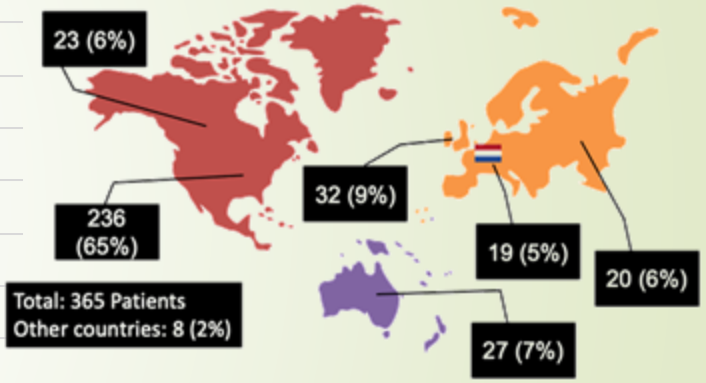
& Amanda Marsden

AUTOINFLAMMATORY ALLIANCE formerly known as The NOMID Alliance

SYSTEMIC JIA FOUNDATION
connecting the dots to find a cure

KAISZ





ENCA

Vaisz

Marsden A, Marques MC, Tennermann N, … Durrant K, Dedeoglu F. Patients perspectives on living with a systemic autoinflammatory disease: impact on quality of life. Manuscript in preparation.

Survey Underscores

Treat the patients, not just their disease

- Burden of disease is way beyond chemical or clinical disease control, and includes whole family needs
- Engaging patients in designing studies is essential
- Collaboration is the cornerstone of progress

Marsden A, Marques MC, Tennermann N, … Durrant K, Dedeoglu F. Patients perspectives on living with a systemic autoinflammatory disease: impact on quality of life. Manuscript in preparation.

Some Guidance is Better Than None

The 2022 EULAR/ACR Points to Consider on HLH/MAS

CHALLENGES

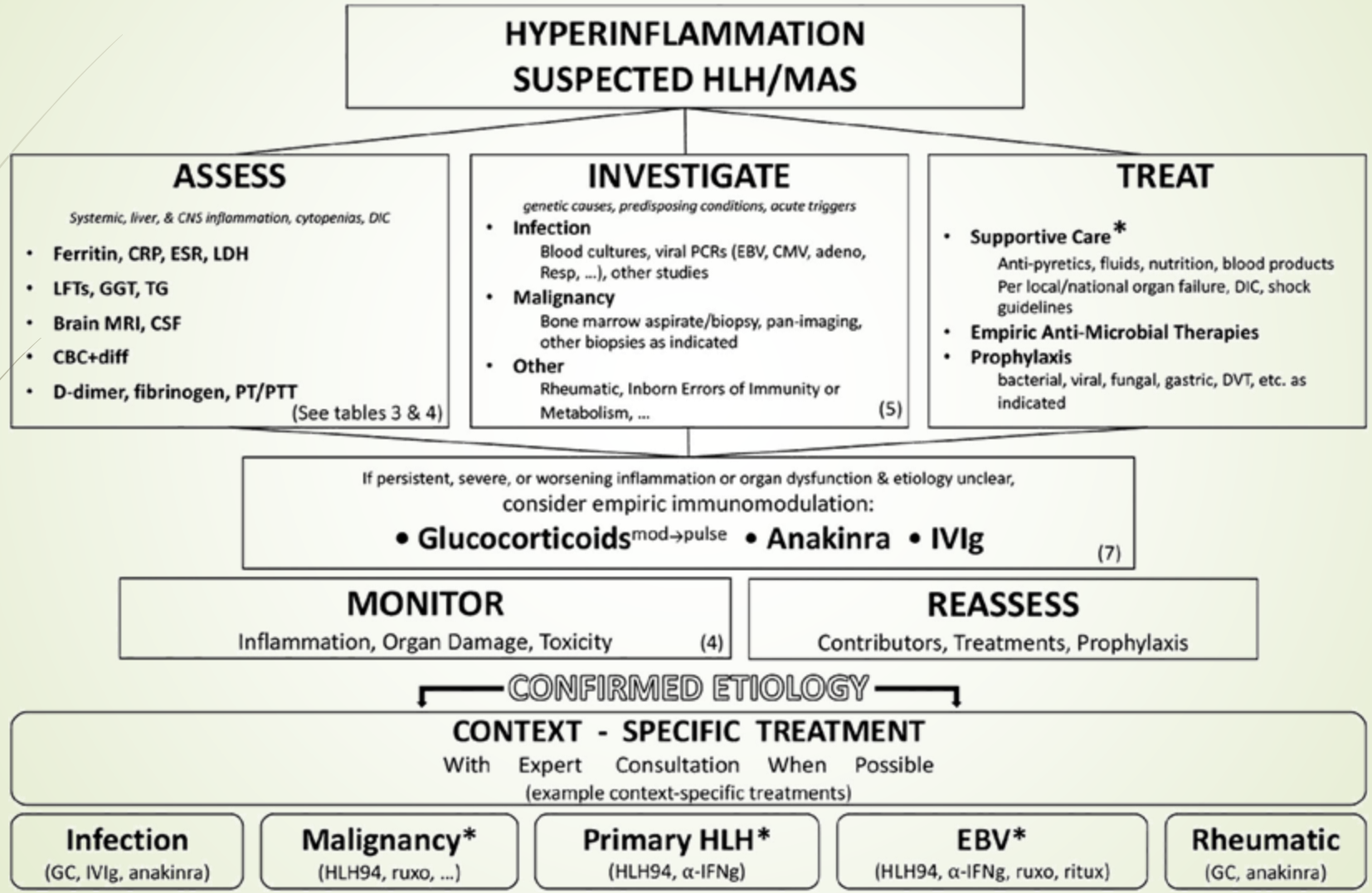
- Broad differential of systemic hyperinflammation
- Multifactorial: genetic predisposition, triggers (infections, immunotherapies, rheumatic disease – sJIA, malignancy)
- Lack of guidance during the early stages

AIM

- Recognizing HLH/MAS
- Identifying its contributors
- Intervening despite diagnostic ambiguity
- Monitoring for progression and organ damage

Shakoory B et al. Arthritis Rheumatol 2023;75:1714–1732.

The 2022 EULAR/ACR Points to Consider on HLH/MAS



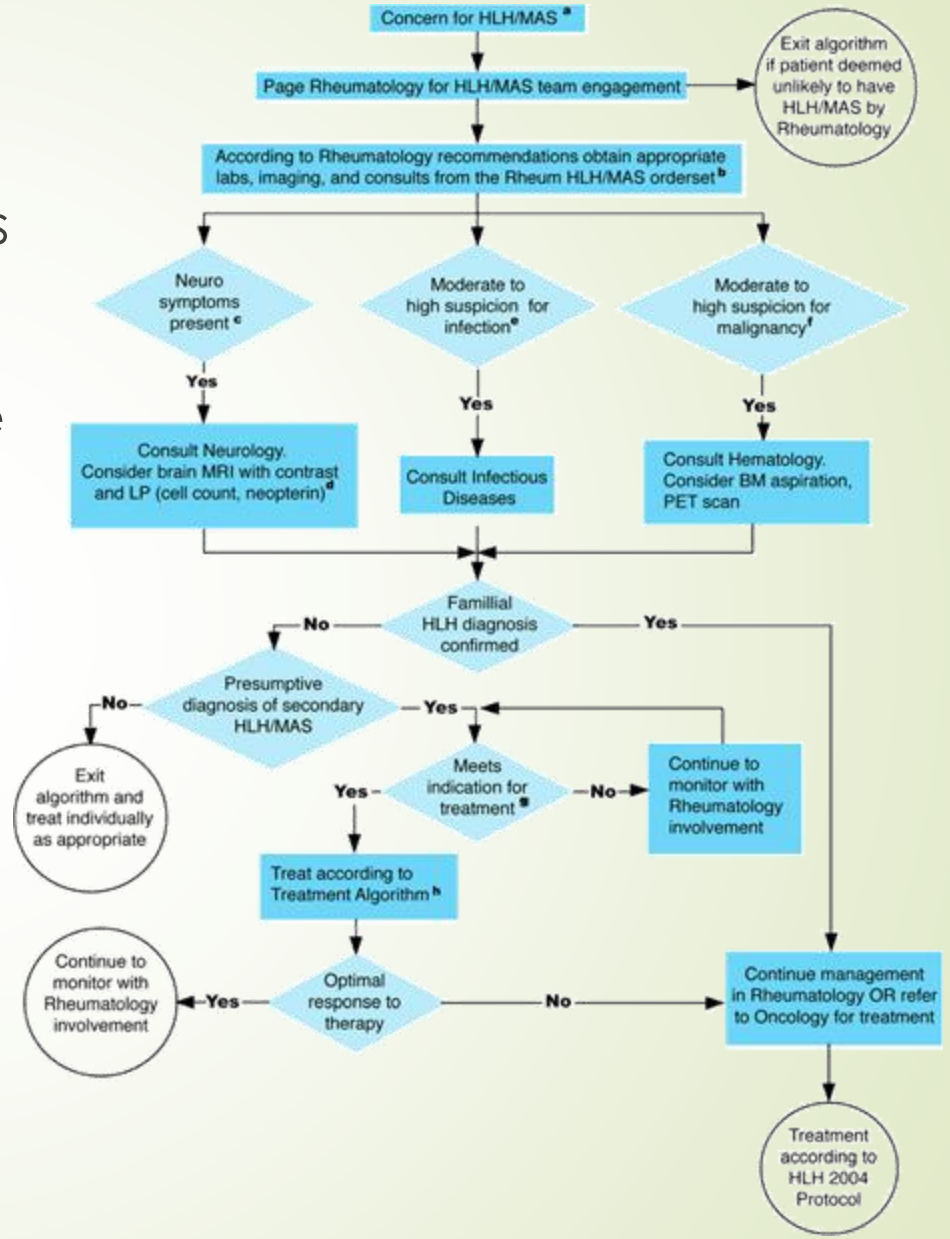
*For further guidance, see www.histiocytesociety.org/HLH-consensus.

Shakoory B et al. Arthritis Rheumatol 2023;75:1714–1732.

Guidelines Can Help

- An evidence-based guideline improves outcomes for patients with hemophagocytic lymphohistiocytosis and macrophage activation syndrome

- Mortality reduced from 50% to 6%



Taylor ML et al. J Rheumatol 2022;49:1042–1051.

Collaborations

- Patient organizations
- Research organizations
- Legislative bodies
- Industry

- *Forming network and consortia (to gather patients/to ease research)*

De Santis M et al. Ann Ist Super Sanità 2019;55:283–291;
Dwyer A et al. Orphanet J Rare Dis 2022;17:354;
Damy T et al. Amyloid 2022;29:165–174.

Collaborations

Patient organizations can be connectors with multidimensional role in:

- addressing patient-family needs
- involving in research
- promoting altruism in academia
- mandating data sharing

  - *Novel research types (such as pragmatic trials) and collaborations should consider Availability, Accessibility, Affordability, Acceptability and strive to be culturally responsive*

Nguyen CQ et al. Health Expect 2022;25:3175–3191;
Douglas CMW et al. Orphanet J Rare Dis 2022;17:344.

SUMMARY-1

- Need to improve delivery of care
- Need to understand & monitor disease activity and damage better
- Need more precise outcome measures
- Need to provide more comprehensive support

SUMMARY-2

- Need to improve interpretation of test results (biomarkers, genetics)
- Need to understand influence of epigenetics better
- Need to improve preventive care, vaccinations
- Need to gauge treatment response and withdrawal better

SUMMARY-3

Understanding challenges help in:

- improving patient care
- enhancing communications
- informed decision making
- better policy and support systems
- research and development

Conclusion 1

- MAS in the setting of Still's disease presents complex challenges
- We are at a critical juncture in addressing the unmet needs of patients
- Focus should be on:
  - early diagnosis
  - increasing disease awareness
  - personalizing treatment plans
  - improving medication access
  - supporting patients through their journey to improve QoL

Conclusion 2

- Addressing these unmet needs requires **COLLABORATION** among health care providers, researchers, patient advocacy groups, regulatory agencies, and industry
- Surveys, short form, points to consider guidelines, efforts of harmonization of data among registries all demonstrate the potential of working together to make meaningful progress
- Ongoing research and innovation such as identifying new therapeutic targets are critical

References

- Shakoory B, Geerlinks A, Wilejto M, Kernan K, Hines M, Romano M, Piskin D, Ravelli A, Sinha R, Aletaha D, Allen C, Bassiri H, Behrens EM, Carcillo J, Carl L, Chatham W, Cohen JI, Cron RQ, Drewniak E, Grom AA, Henderson LA, Horne A, Jordan MB, Nichols KE, Schulert G, Vastert S, Demirkaya E, Goldbach-Mansky R, de Benedetti F, Marsh RA, Canna SW. The 2022 EULAR/ACR points to consider at the early stages of diagnosis and management of suspected haemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS). Arthritis Rheumatol. 2023 Oct;75(10):1714–1732
- Ruscitti P, Cantarini L, Nigrovic PA, McGonagle D, Giacomelli R. Recent advances and evolving concepts in Still's disease. Nat Rev Rheumatol. 2024 Feb;20(2):116–132
- Correia Marques M, Ombrello MJ, Schulert GS. New discoveries in the genetics and genomics of systemic juvenile idiopathic arthritis. Expert Rev Clin Immunol. 2024 Sep;20(9):1053–1064
- Lee J, Bae KS, Rhim JW, Lee S-Y, Jeong DC, Kang JH. Macrophage activation syndrome in children: update on diagnosis and treatment. Children. 2024 Jun;11(7):755
- Shenoi S, Horneff G, Cidon M, Ramanan AV, Kimura Y, Quartier P, Foeldvari I, Zeft A, Lomax KG, Gregson J, Abma T, Campbell-Hill S, Weiss J, Patel D, Marinsek N, Wulffraat N. The burden of systemic juvenile idiopathic arthritis for patients and caregivers: an international survey and retrospective chart review. Clin Exp Rheumatol. 2018 Sep–Oct;36(5):920–928
- Ruscitti P, Feist E, Canon-Garcia V, Rabijns H, Toennessen K, Bartlett C, Gregg E, Miller P, McGonagle D. Burden of adult-onset Still's disease: a systematic review of health-related quality of life, utilities, costs and resource use. Semin Arthritis Rheum. 2023 Dec;63:152264
- Minoia F, Davì S, Horne A, Demirkaya E, Bovis F, Li C, Lehmberg K, Weitzman S, Insalaco A, Wouters C, Shenoi S, Espada G, Ozen S, Anton J, Khubchandani R, Russo R, Pal P, Kasapcopur O, Miettunen P, Maritsi D, Merino R, Shakoory B, Alessio M, Chasnyk V, Sanner H, Gao YJ, Huasong Z, Kitoh T, Avcin T, Fischbach M, Frosch M, Grom A, Huber A, Jelusic M, Sawhney S, Uziel Y, Ruperto N, Martini A, Cron RQ, Ravelli A. Pediatric Rheumatology International Trials Organization; Childhood Arthritis and Rheumatology Research Alliance; Pediatric Rheumatology Collaborative Study Group; Histiocyte Society. Clinical features, treatment, and outcome of macrophage activation syndrome complicating systemic juvenile idiopathic arthritis: a multinational, multicenter study of 362 patients. Arthritis Rheumatol. 2014 Nov;66(11):3160–3169

THANK YOU

Our Patients and Families

CARRA
Childhood Arthritis and Rheumatology Research Alliance

CRMO FOUNDATION
research | awareness | education

Cure Blau Syndrome

Canadian Autoinflammatory Network
Réseau Auto-inflammatoire Canadien

dada2 FOUNDATION

Arthritis Foundation

SYSTEMIC JIA FOUNDATION
connecting the dots to find a cure

KAISZ
AUTO-INFLAMMATIE NEDERLAND

CARRA Autoinflammatory Patient Advocacy Group

ENCA

Boston Children's Hospital (BCH) Rheumatology Program and Autoinflammatory Clinic staff

Unravelling the Mechanisms

Petter Brodin M.D., Ph.D.
Garfield Weston chair, Professor of Pediatric Immunology &
Honorary consultant, Pediatric Immunology

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IMPERIAL

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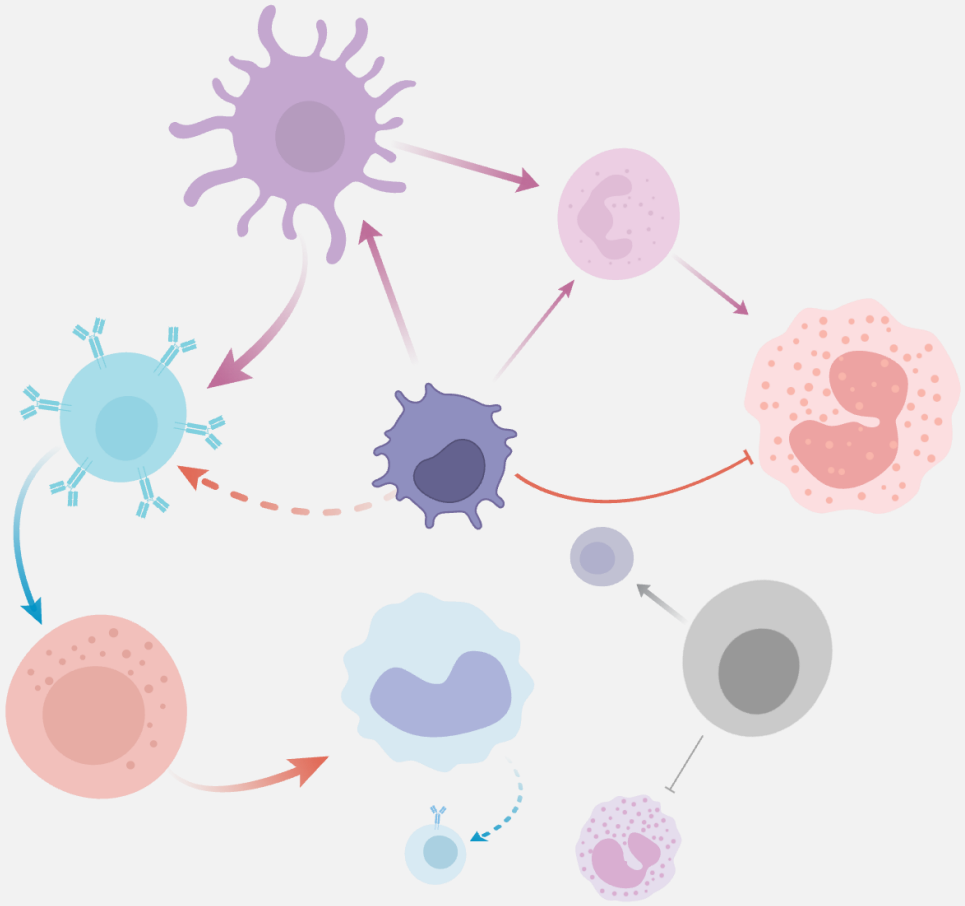
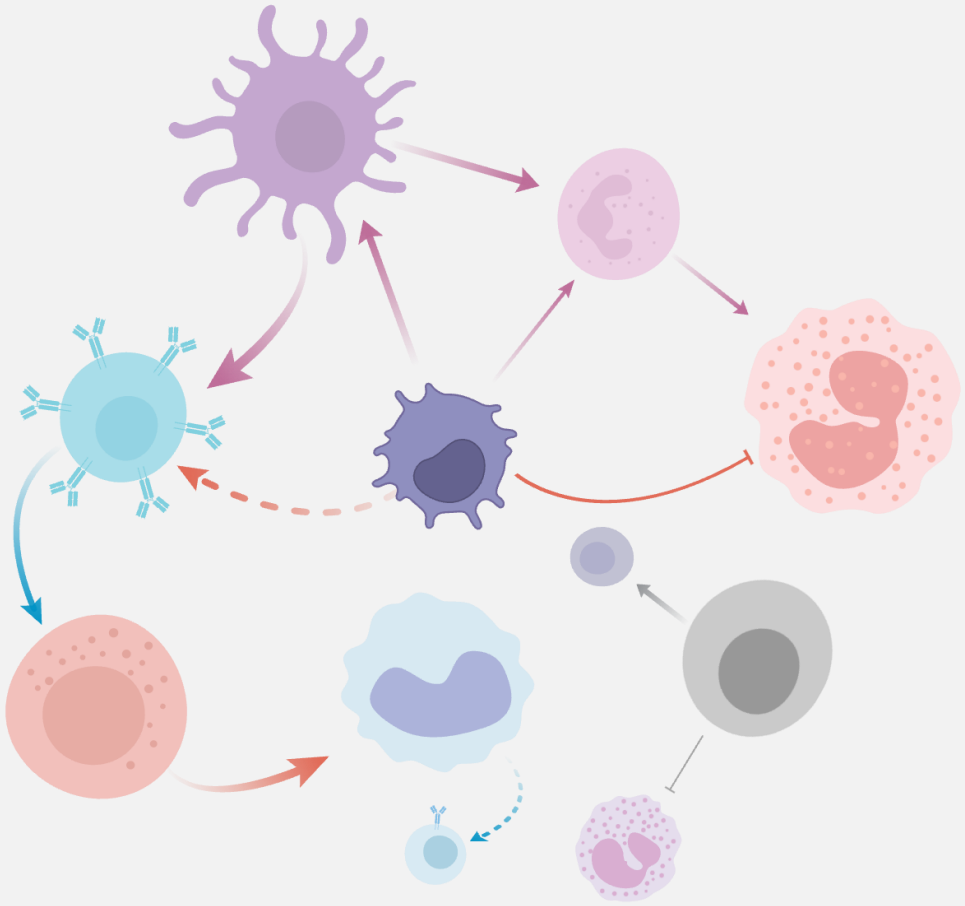
MAKING SENSE OF HUMAN IMMUNE SYSTEMS



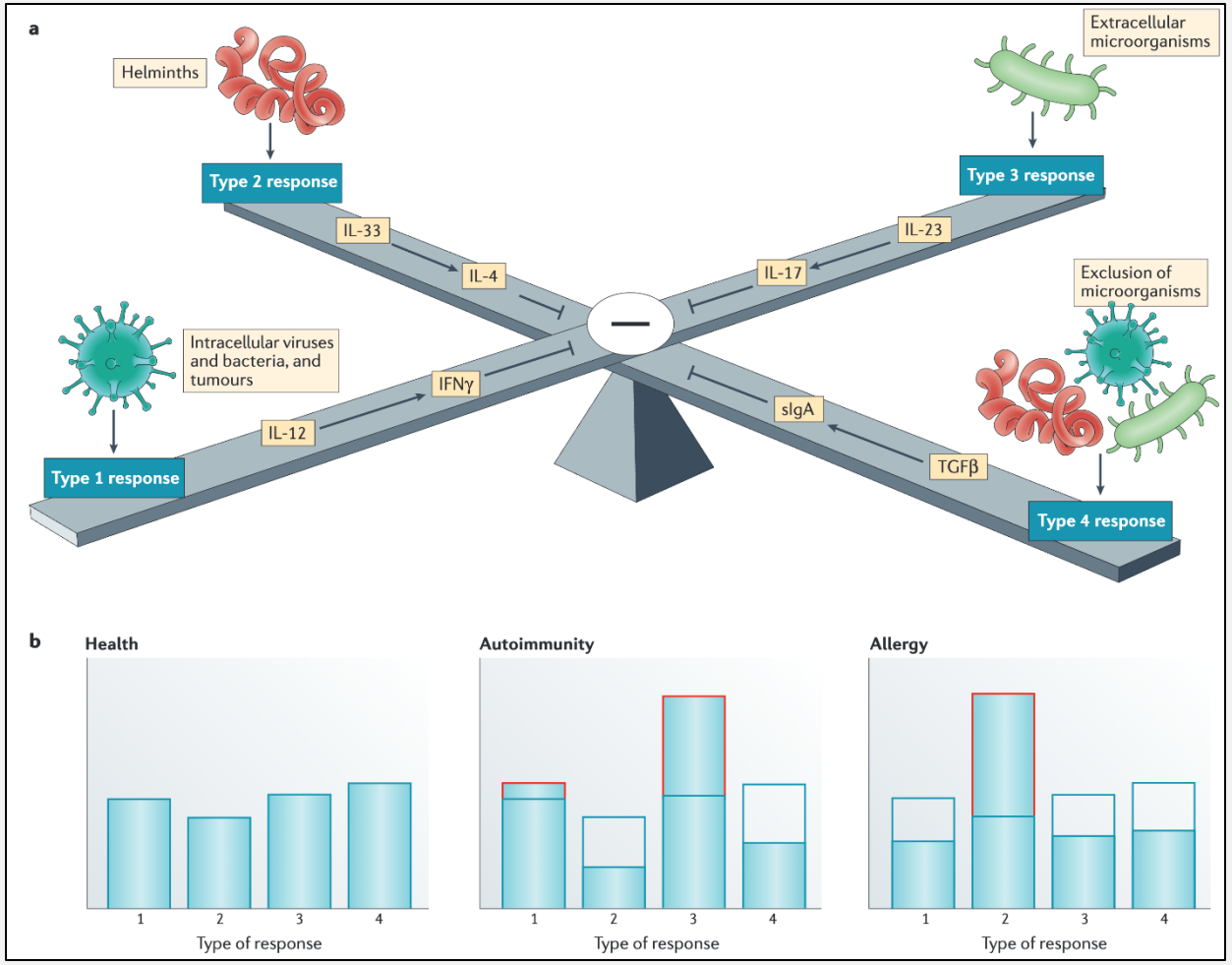
SYSTEMS IMMUNOLOGY

Forlin et al. Trends in Immunology 2023;44:577–584.

MAKING SENSE OF HUMAN IMMUNE SYSTEMS – AN EQUILIBRIUM MODEL



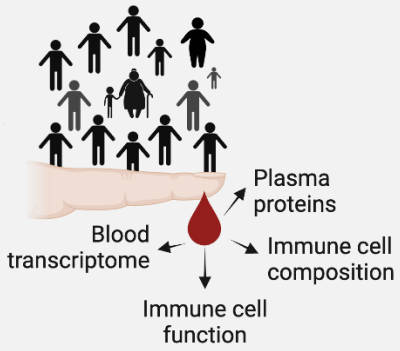
SYSTEMS IMMUNOLOGY



Forlin et al. Trends in Immunology 2023;44:577–584.

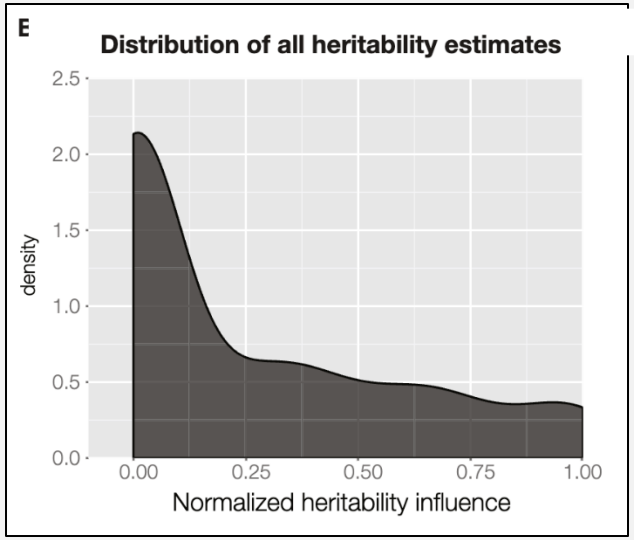
Eberl G. Nat Rev Imm 2016;16:524–532.

HUMAN IMMUNE VARIATION



HERITABLE

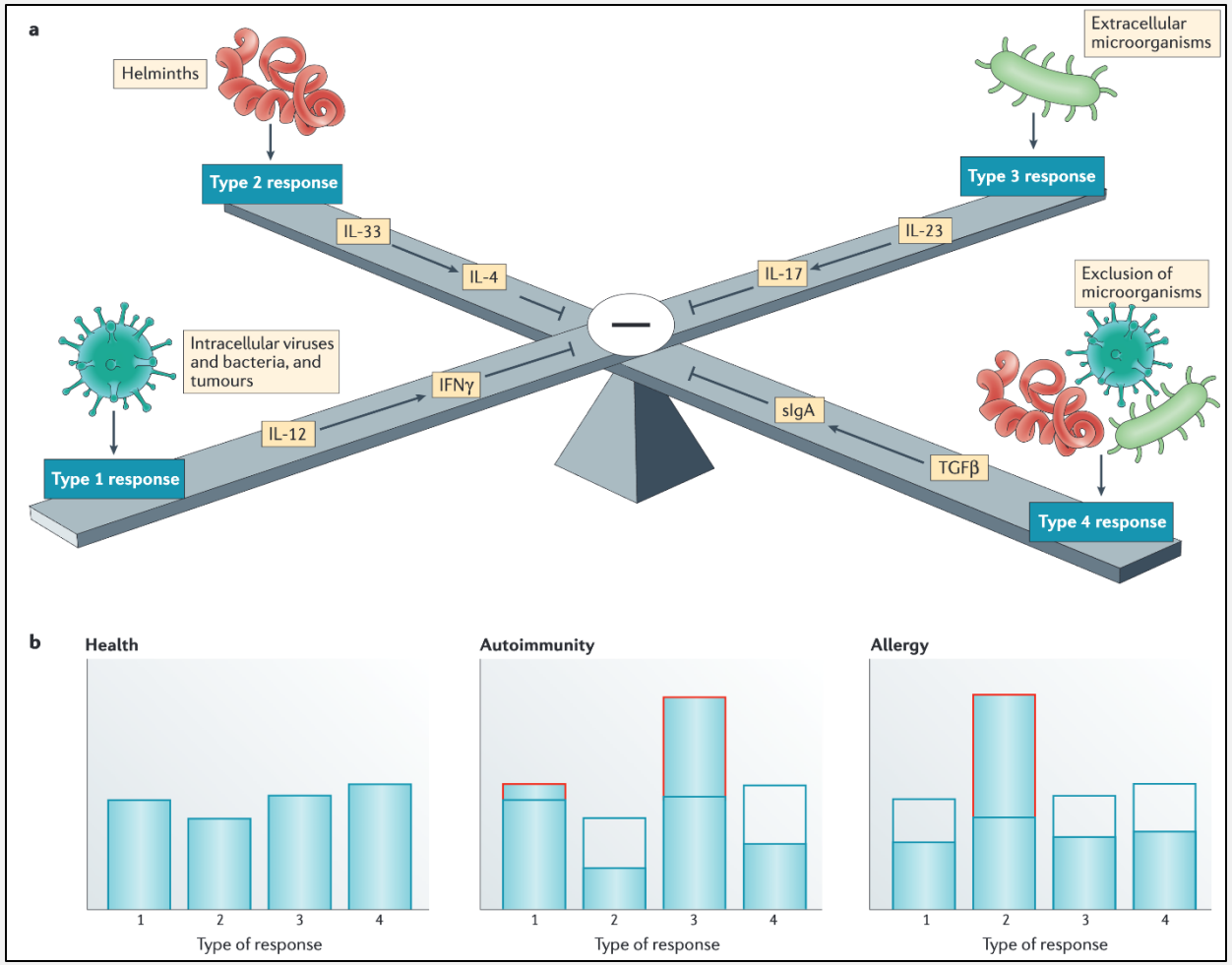
NON-HERITABLE

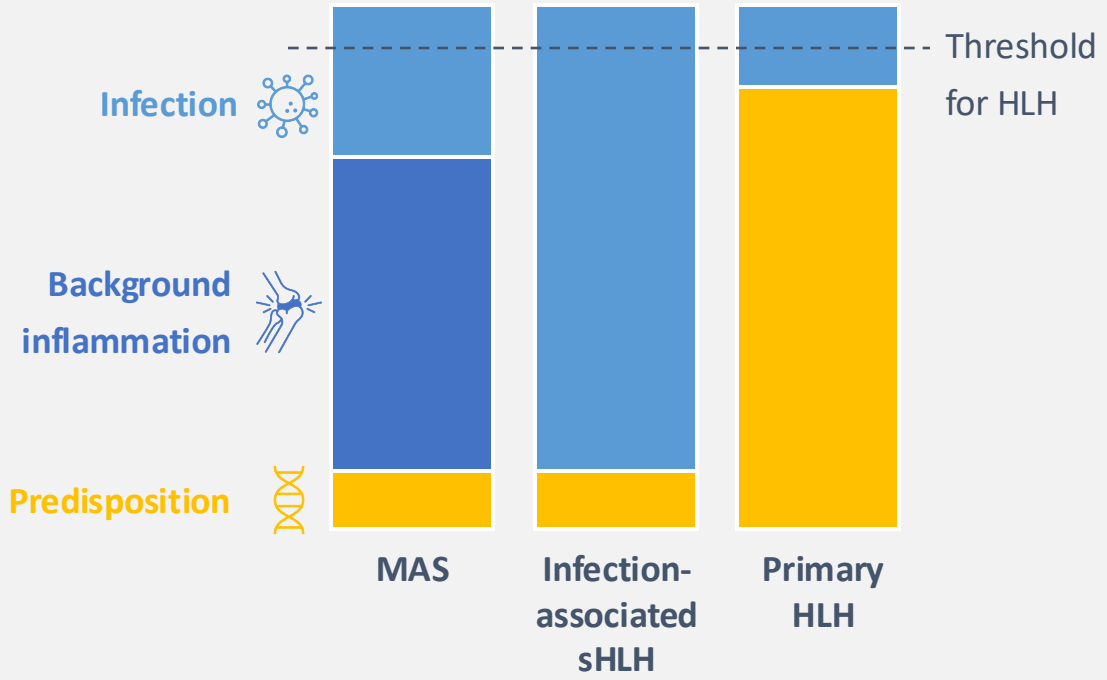


Brodin_Lab

Brodin et al. Cell 2015;160:37–47.

MACROPHAGE ACTIVATION SYNDROME – UNCONTROLLED TYPE 1 RESPONSES

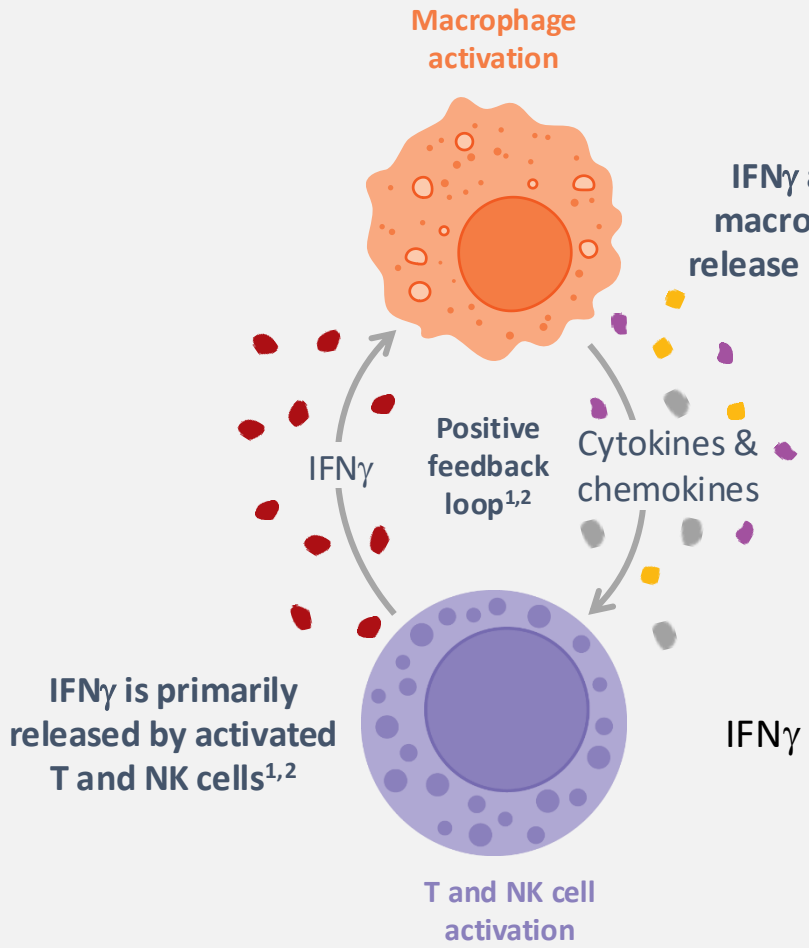




Eberl G. Nat Rev Imm 2016;16:524–532.

Adapted from Strippoli R, Caiello I, De Benedetti F. J Rheumatol 2013;40:761–767.

MACROPHAGE ACTIVATION SYNDROME – UNCONTROLLED TYPE 1 RESPONSES



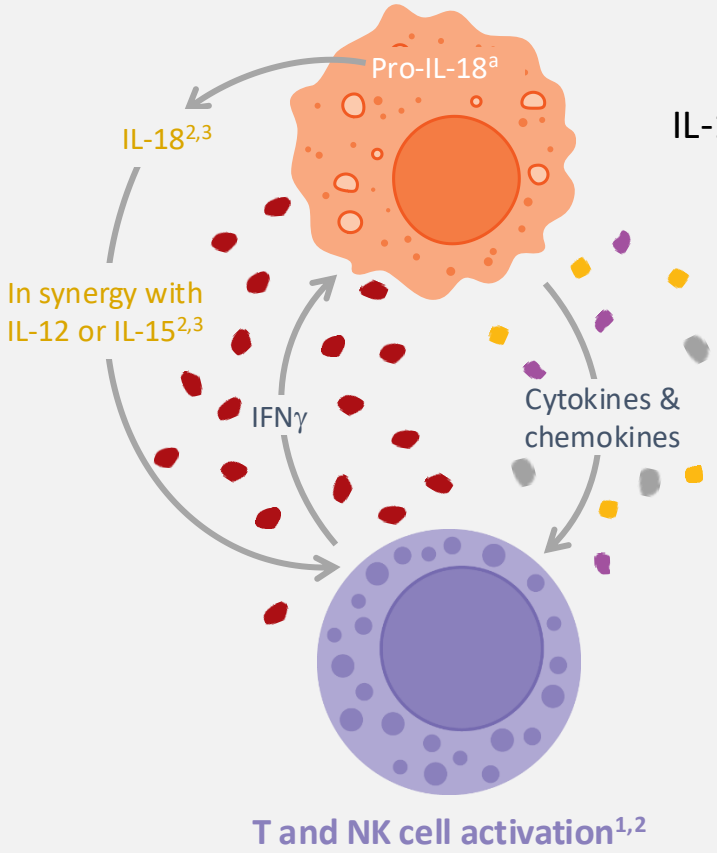
IFNγ drives the pathophysiology of MAS[1]

[a]IL-18 requires inflammasome activation to be secreted.[2,6]

IFNγ, interferon gamma; IL, interleukin; NF- κB, nuclear factor kappa B; NK, natural killer; TNFα, tumor necrosis factor alpha.

1. Bseiso O et al. Cureus 2022;14:e33175; 2. Fajgenbaum DC, June CH. N Engl J Med 2020;383:2255–2273; 3. Krei JM et al. Clin Exp Immunol 2021;203:174–182;
4. Carter SJ et al. Rheumatology (Oxford) 2019;58:5–17; 5. Torti FM, Torti SV. Blood 2002;99:3505–3516; 6. Canna SW, De Benedetti F. Pediatr Rheumatol Online J 2024;21(Suppl 1):79.

MACROPHAGE ACTIVATION SYNDROME – UNCONTROLLED TYPE 1 RESPONSES



IL-18 promotes IFNγ secretion in patients with MAS in Still's disease[1,2]

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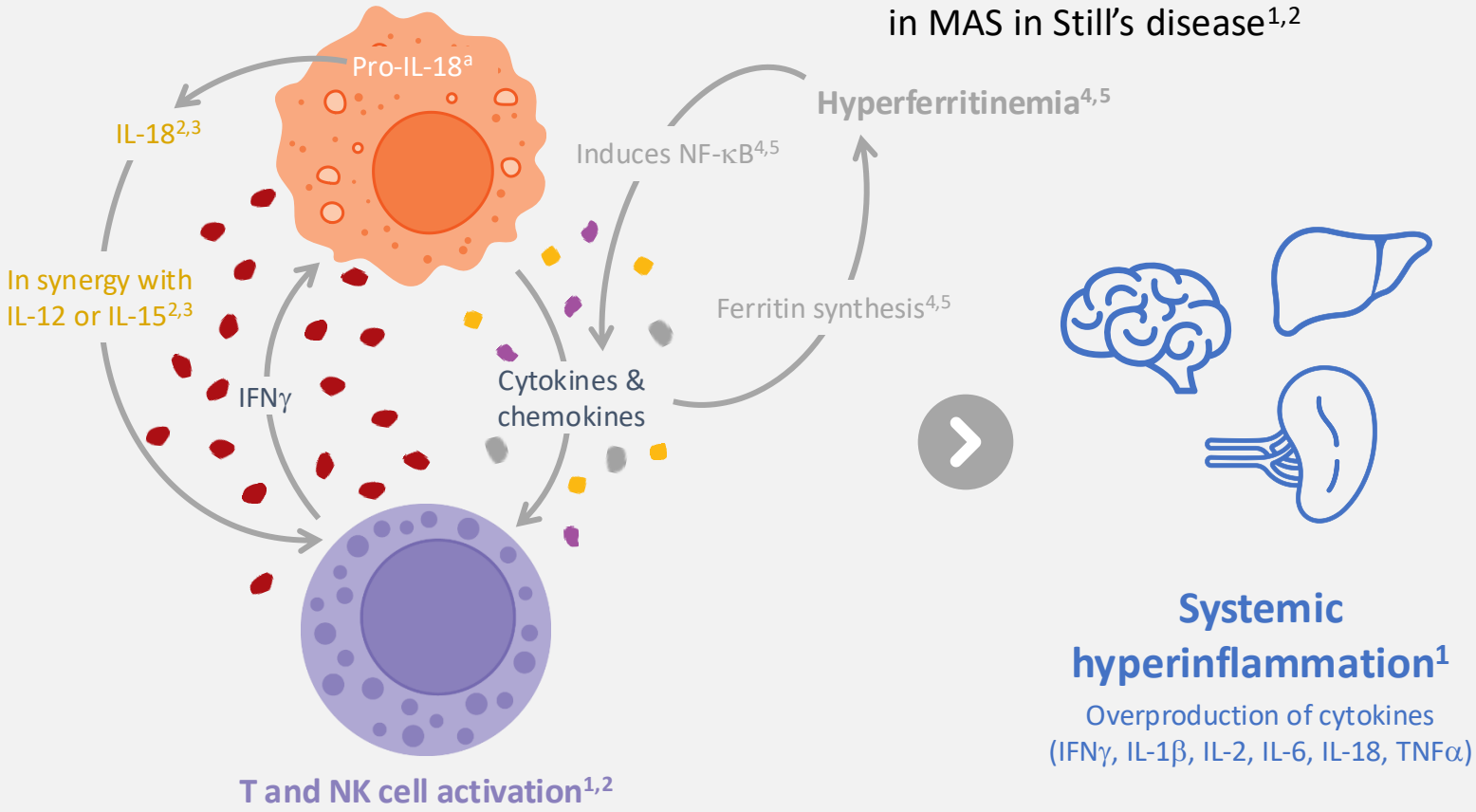
MACROPHAGE ACTIVATION SYNDROME – UNCONTROLLED TYPE 1 RESPONSES

Hyperferritinemia contributes to hyperinflammation in MAS in Still's disease[1,2]



Systemic hyperinflammation[1]

Overproduction of cytokines (IFNγ, IL-1β, IL-2, IL-6, IL-18, TNFα)

[a]IL-18 requires inflammasome activation to be secreted.[2,6]

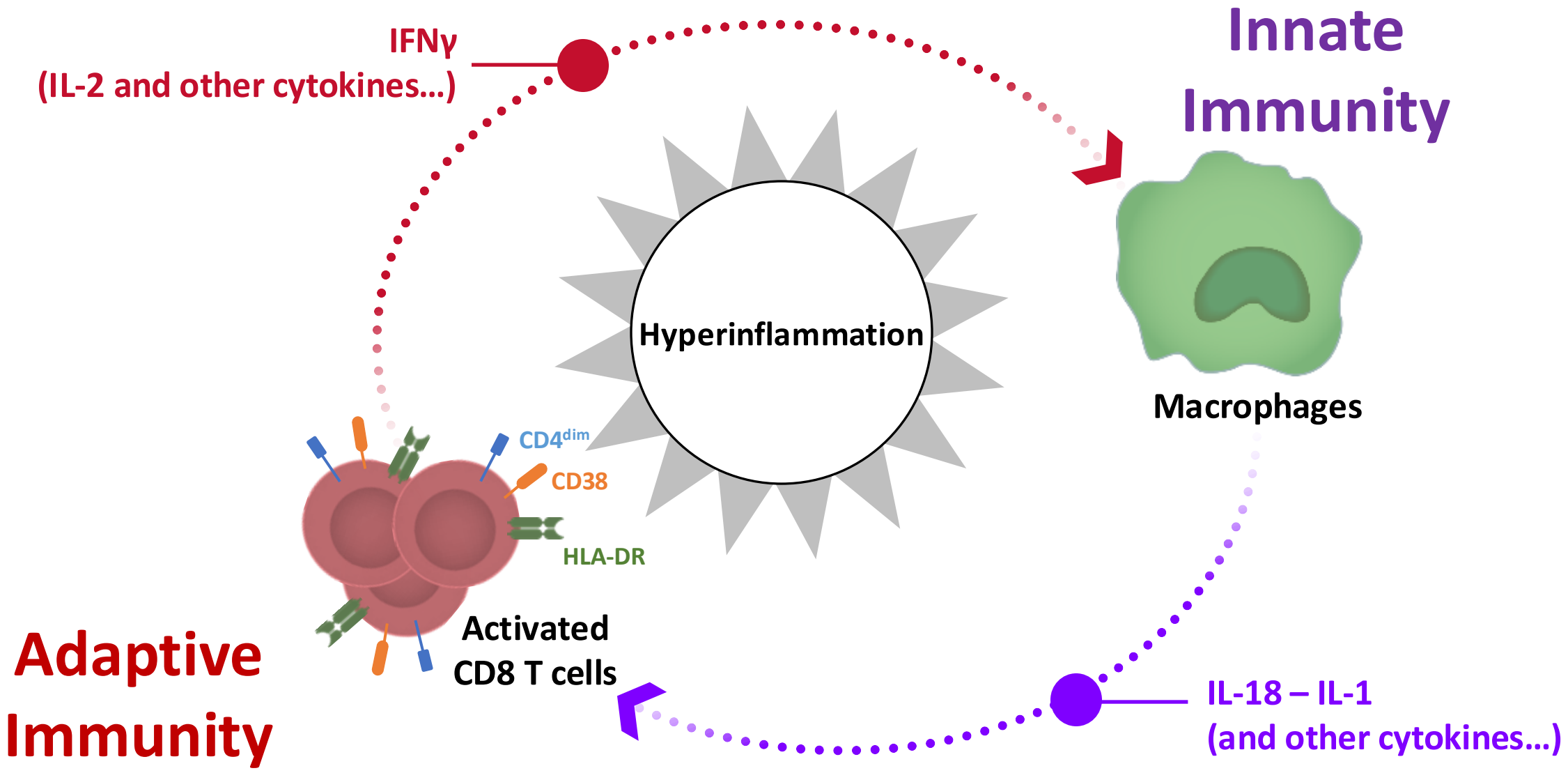
IFNγ, interferon gamma; IL, interleukin; NF- κB, nuclear factor kappa B; NK, natural killer; TNFα, tumor necrosis factor alpha.

1. Bseiso O et al. Cureus 2022;14:e33175; 2. Fajgenbaum DC, June CH. N Engl J Med 2020;383:2255–2273; 3. Krei JM et al. Clin Exp Immunol 2021;203:174–182;
4. Carter SJ et al. Rheumatology (Oxford) 2019;58:5–17; 5. Torti FM, Torti SV. Blood 2002;99:3505–3516; 6. Canna SW, De Benedetti F. Pediatr Rheumatol Online J 2024;21(Suppl 1):79.

Emerging Management Strategies

Fabrizio De Benedetti

The *Simplified* Vicious Loop of Hyperinflammation[1–3]



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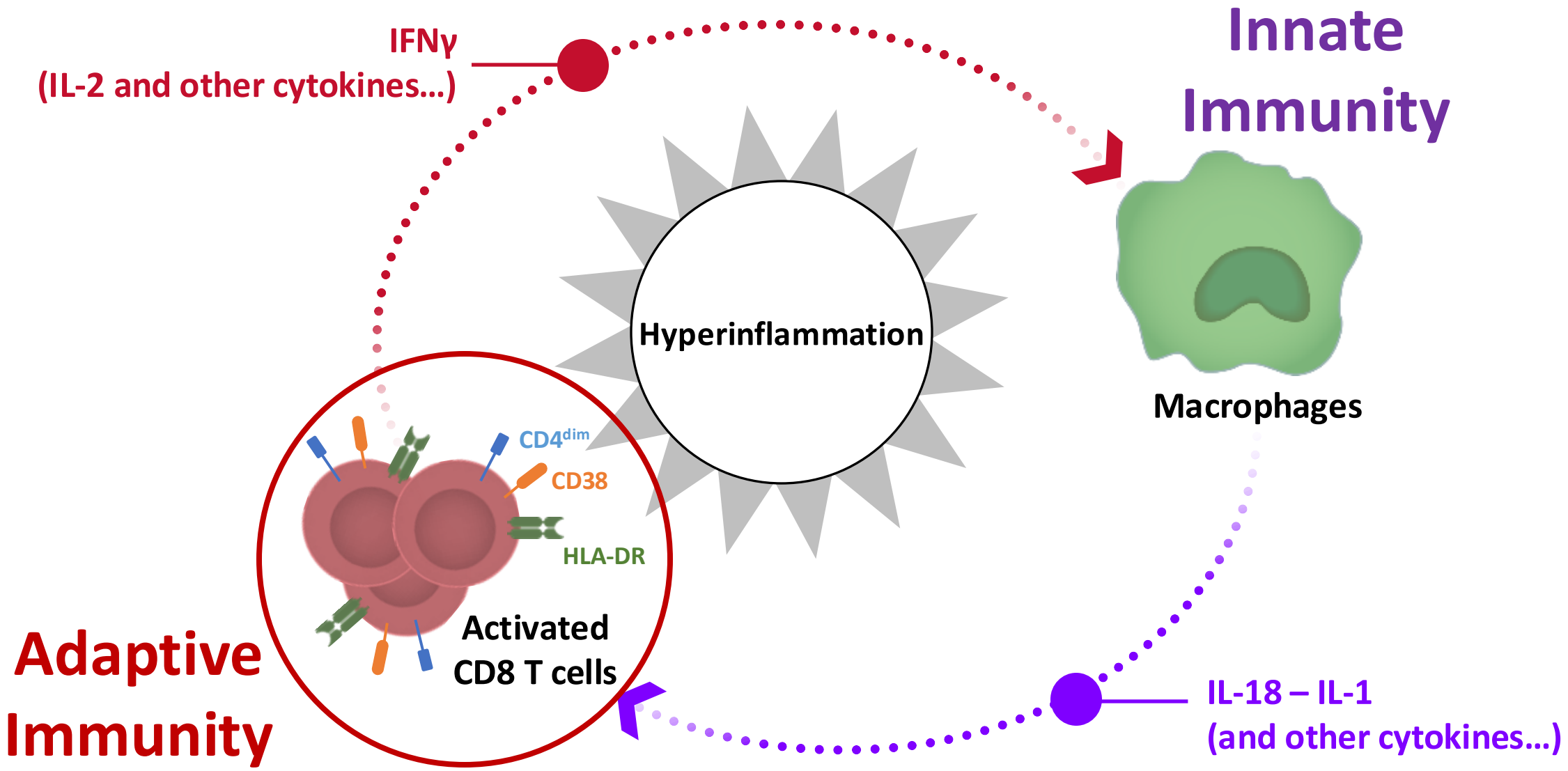
1.De Matteis A et al. Blood 2022;140:262–273; 2. Jordan MB. Blood 2022;140:167–168; 3. De Benedetti F et al. Nat Rev Rheumatol 2021;17:678–691.

The *Simplified* Vicious Loop of Hyperinflammation[1–3]



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Adaptive Immunity in Hyperinflammation: CD8+ T cells

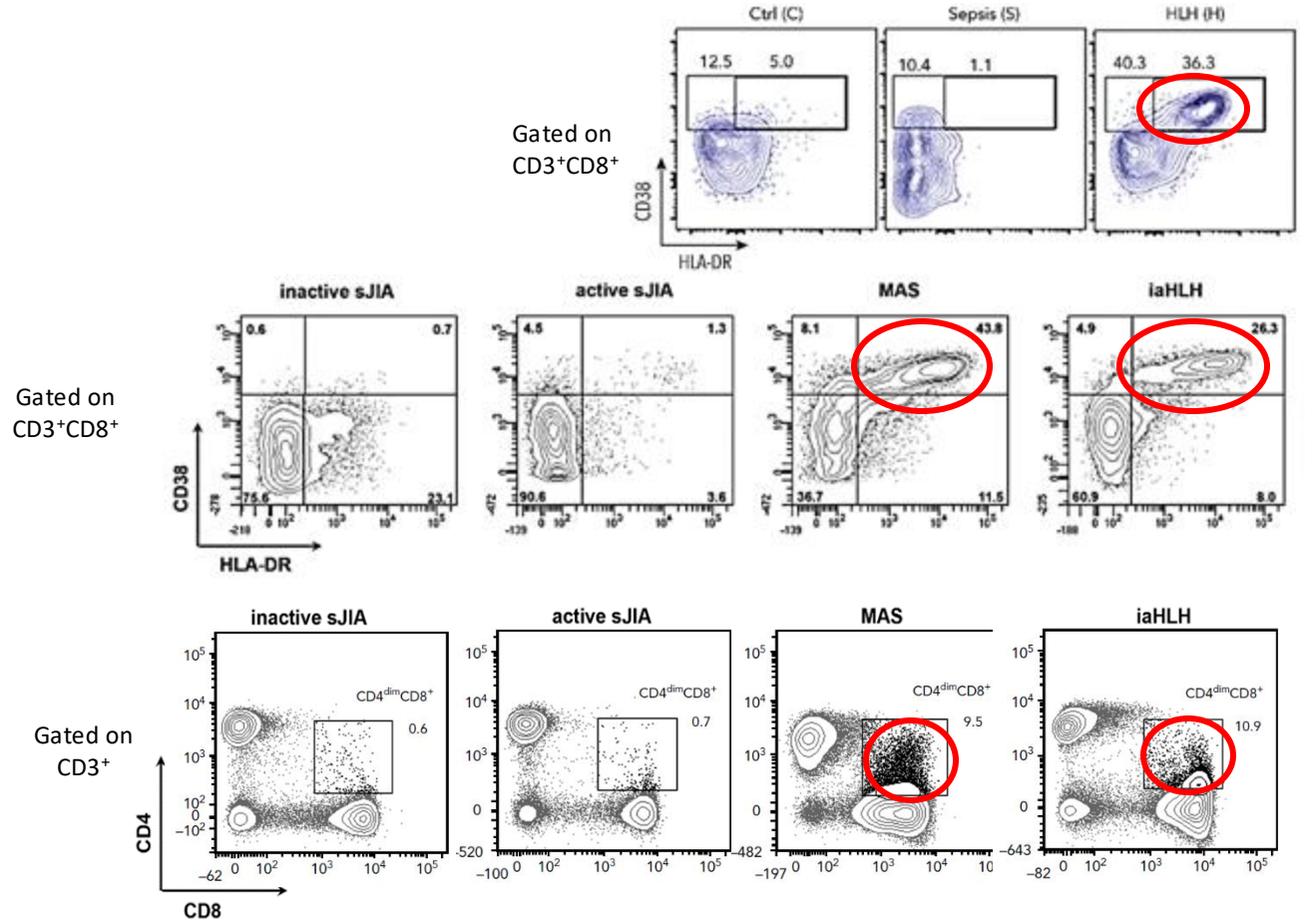
Activated CD8⁺ T cells are expanded in patients with familial HLH and sHLH (including infection-associated HLH, MAS and others)[1,2]

CD8⁺CD38^{high}HLA-DR⁺ T cells[1,2]

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

CD4^{dim} CD8⁺ T cells[2]

- Show features of recently and persistently activated T cells (CD25, PD-1, CD95…)
- Large overlap with CD38⁺/HLA-DR⁺



Top panel: figure from Chaturvedi V et al. Blood 2021;137:2337–2346. T-cell activation profiles distinguish hemophagocytic lymphohistiocytosis and early sepsis. Copyright © 2021 The American Society of Hematology. Reprinted with permission. Middle and bottom panels: figures from De Matteis A et al. Blood 2022;140:262–273. Expansion of CD4dimCD8+ T cells characterizes macrophage activation syndrome and other secondary HLH. Copyright © 2022 The American Society of Hematology. Reprinted with permission. CD, cluster of differentiation; HLA-DR, human leukocyte antigen – DR isotope; HLH, haemophagocytic lymphohistiocytosis; iaHLH, infection-associated haemophagocytic lymphohistiocytosis; MAS, macrophage activation syndrome; PD-1, programmed cell death protein 1; sHLH, secondary hemophagocytic lymphohistiocytosis; sJIA, systemic juvenile idiopathic arthritis.

1. Chaturvedi V et al. Blood 2021;137:2337–2346; 2. De Matteis A et al. Blood 2022;140:262–273.

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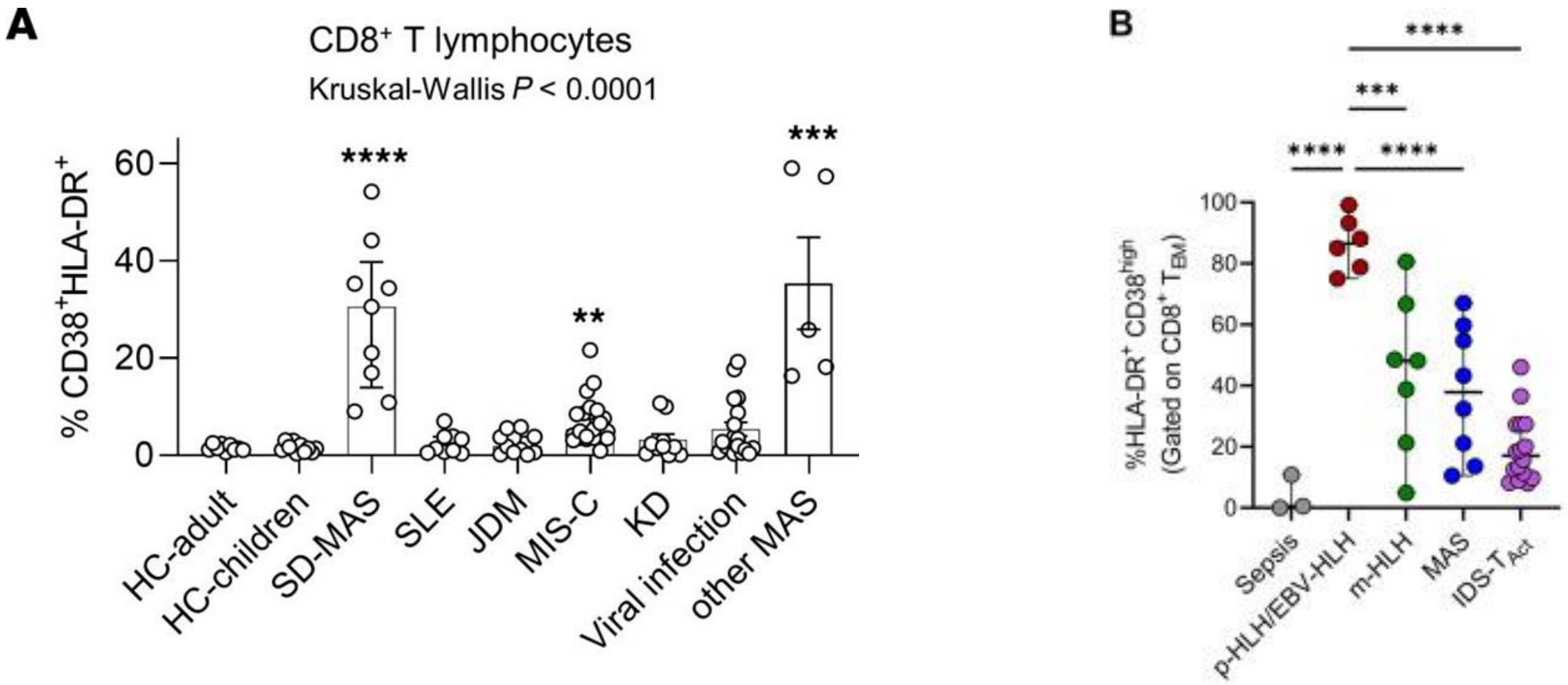

Left panel: Huang Z, et al. J Clin Invest. 2023;133:e165616. ; Right panel: Nguyen TH, et al. J Allergy Clin Immunol. 2024;153:309–319.

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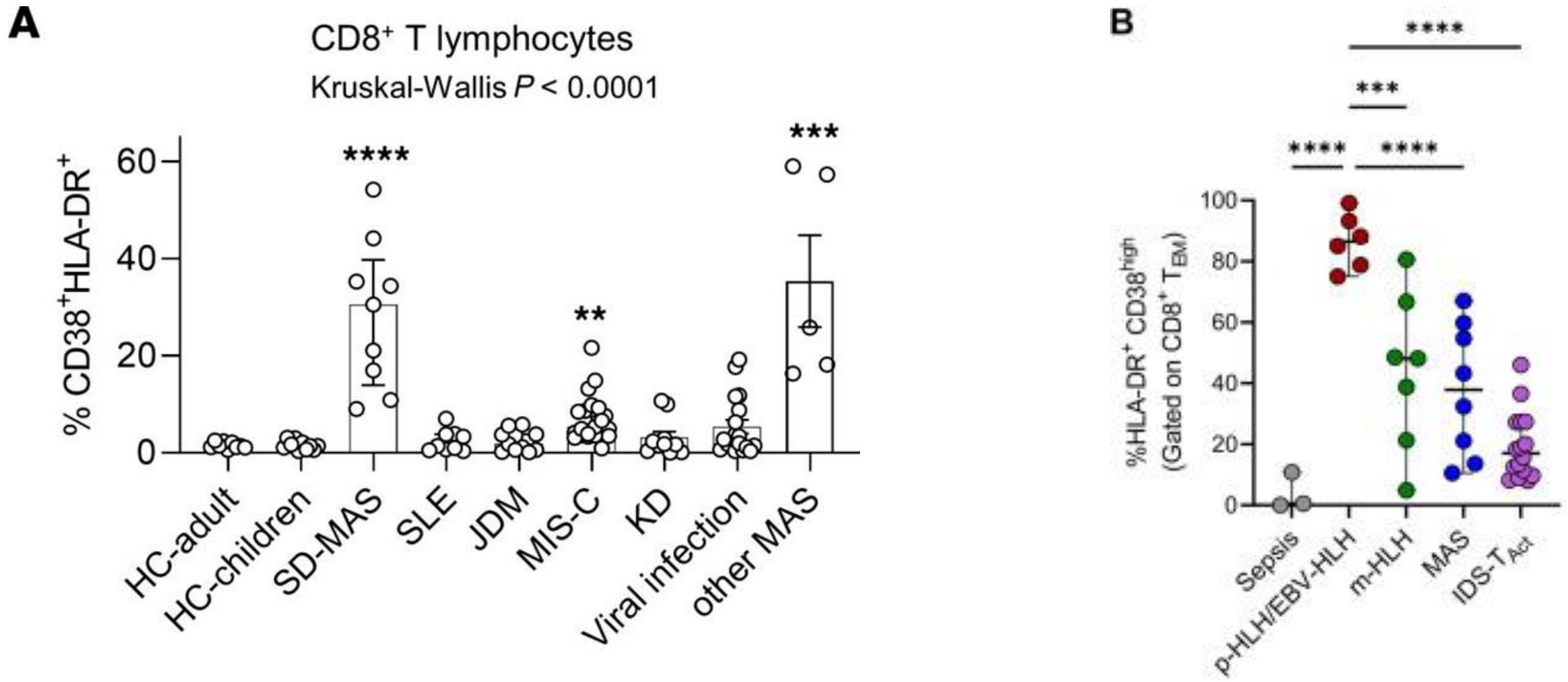
Adaptive Immunity in Hyperinflammation: CD8+ T cells

Activated CD8⁺ T cells are expanded in patients with familial HLH and sHLH (including infection-associated HLH, MAS and others)[1,2]

Frequency of activated CD8⁺ T cells distinguishes reliably HLH/MAS from sJIA and infections



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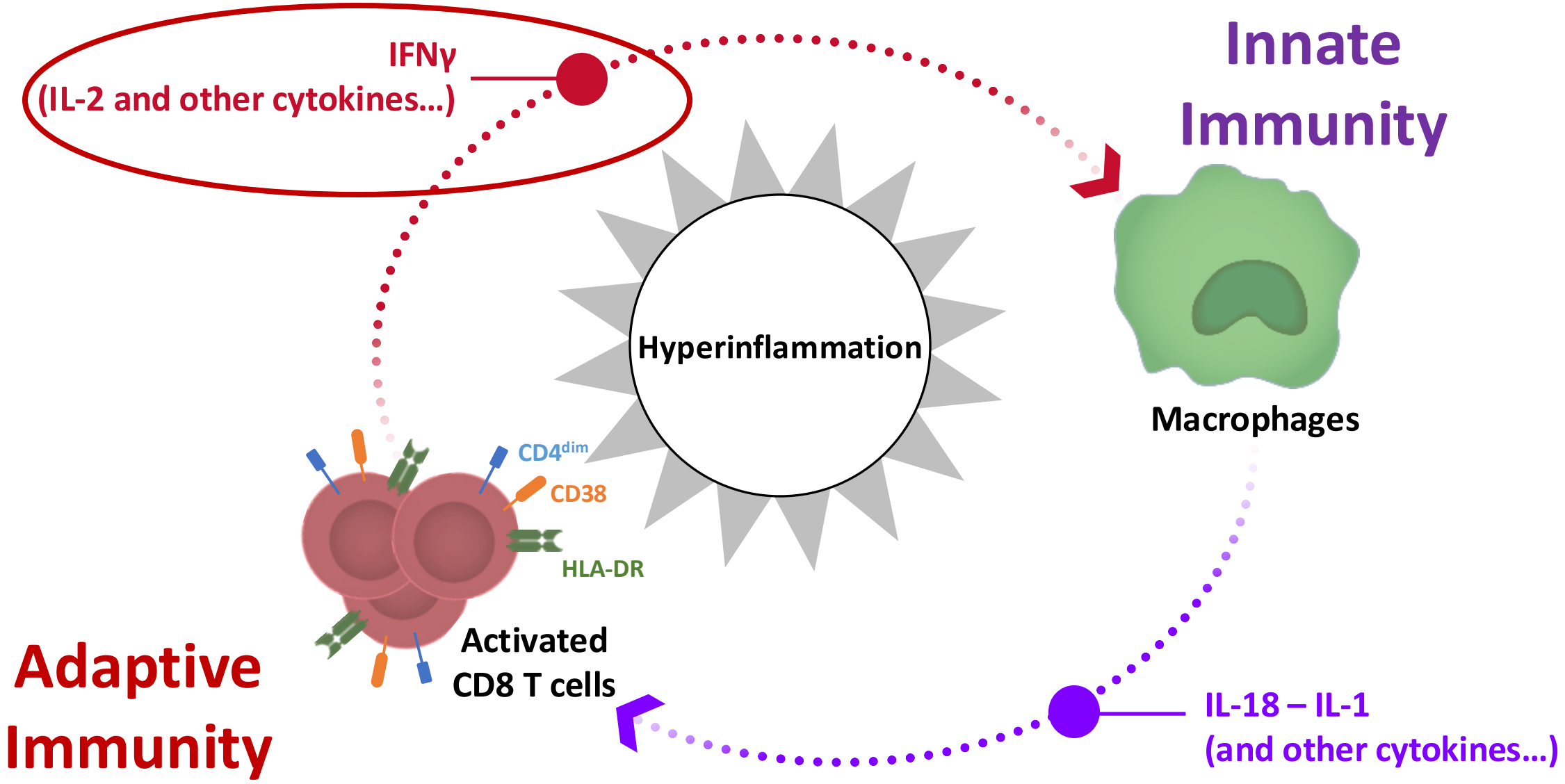
The *Simplified* Vicious Loop of Hyperinflammation[1–3]



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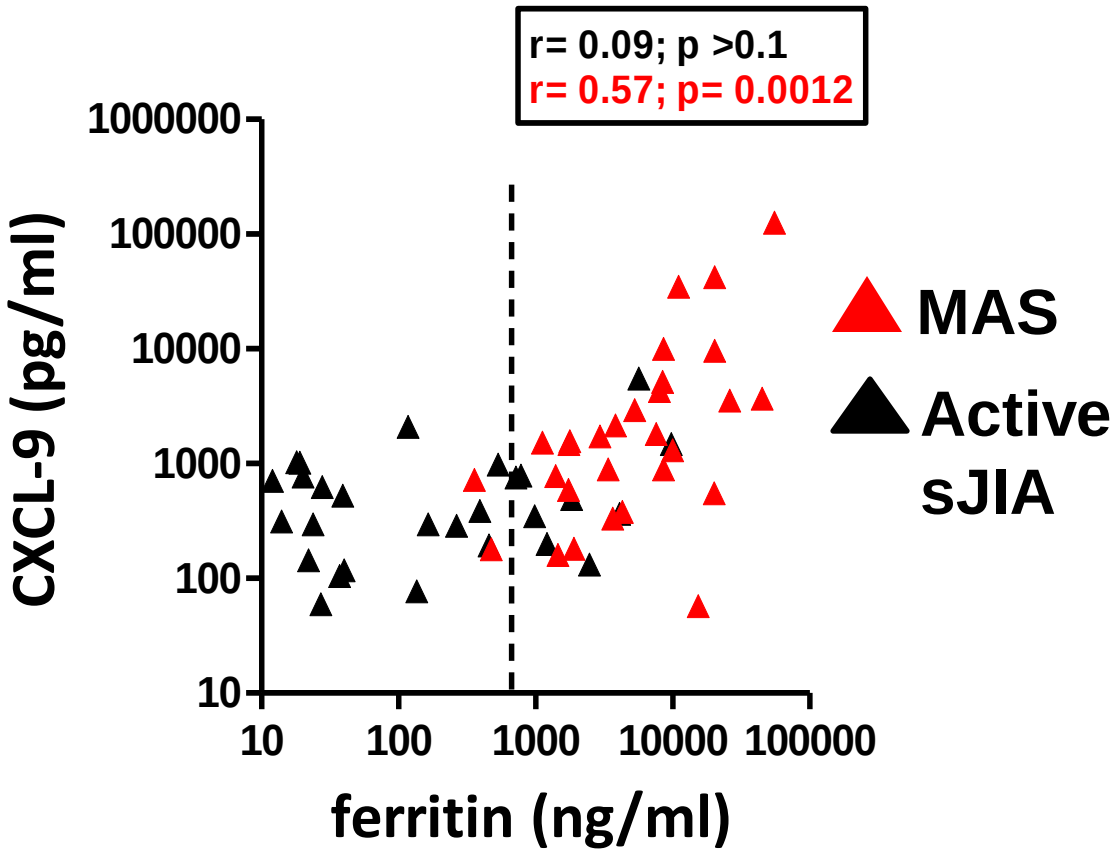
Elevated Levels of IFNγ and IFNγ-Induced Chemokines Characterise Patients With MAS Complicating sJIA

Annals of the Rheumatic Diseases

Bracaglia C et al. Ann Rheum Dis 2017;76:166–172.*

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

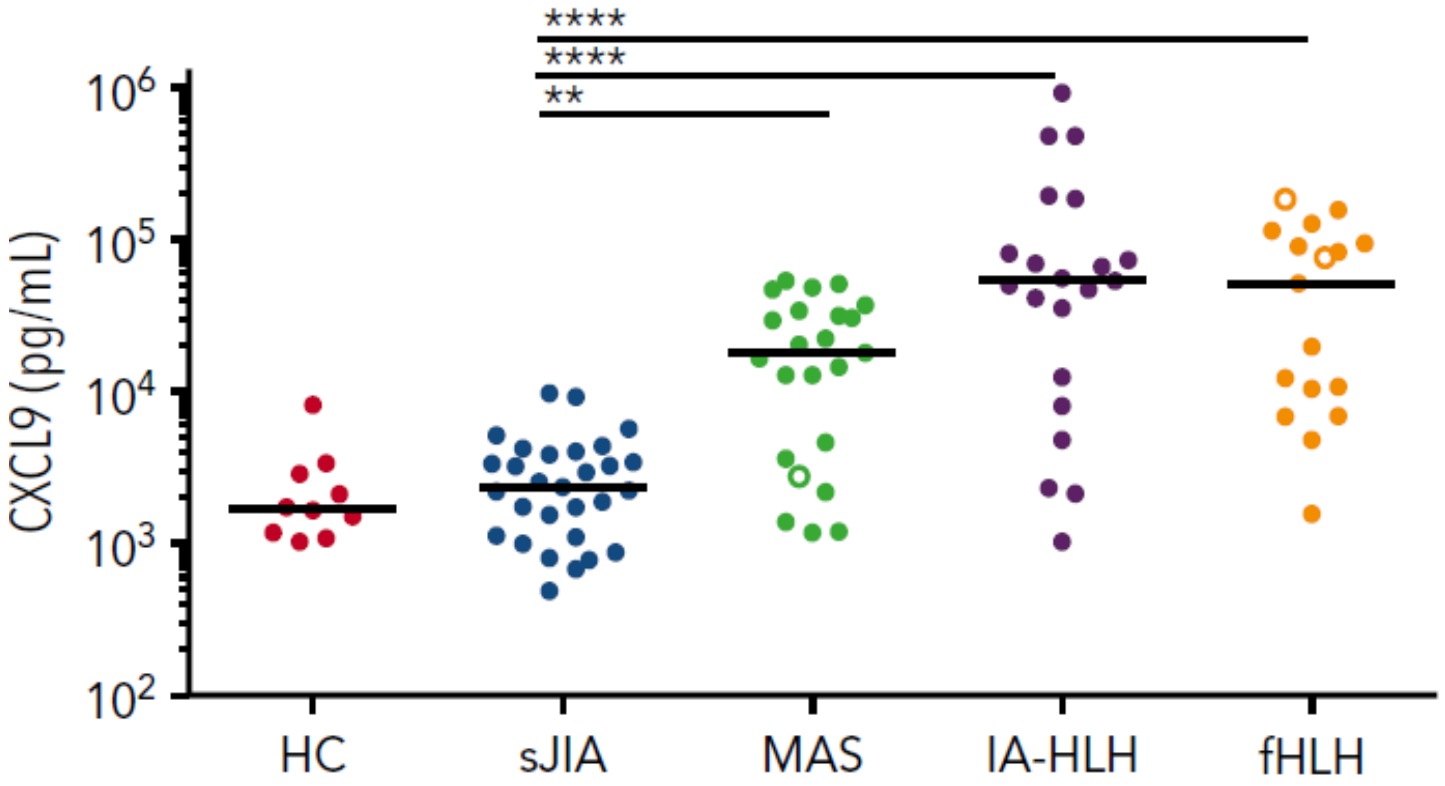


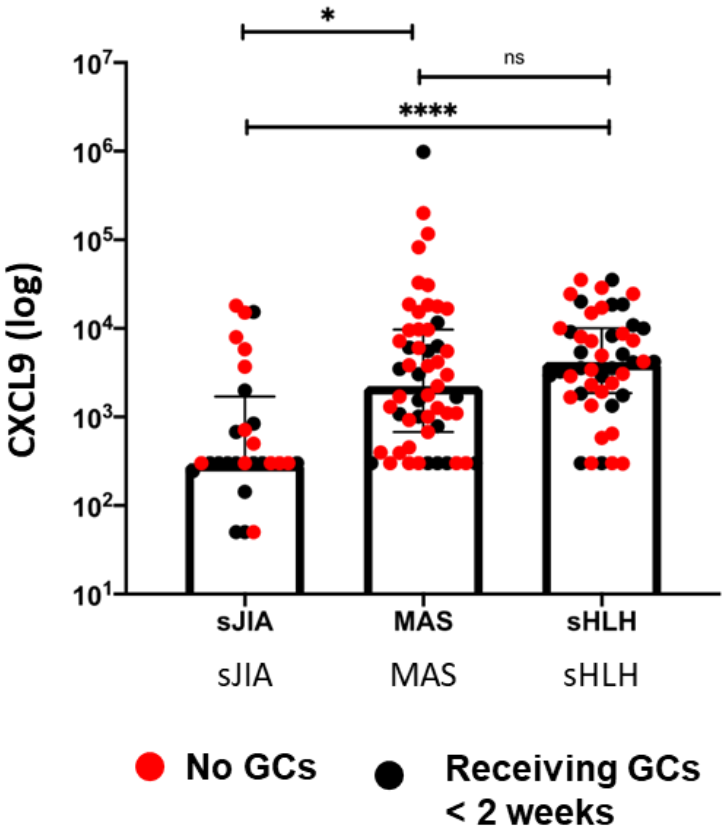
MAS	CXCL9	
	Spearman R	*p*
Ferritin	0.57	0.0012
NEU	−0.54	0.017
PLT	−0.65	0.0002
ALT	0.66	0.0012
LDH	0.84	0.0001
Act sJIA		
Ferritin	0.09	>0.1
NEU	0.002	>0.1
PLT	0.14	>0.1
ALT	0.23	>0.1
LDH	0.28	>0.1

*data shown in table and figure are not reported in published manuscript.

CXCL9 (other IFNγ-related biomarkers) in Different Forms of HLH/MAS

- Normal CXCL9 in active sJIA
- Increased CXCL9 in MAS, infection-associated HLH, secondary HLH and primary HLH



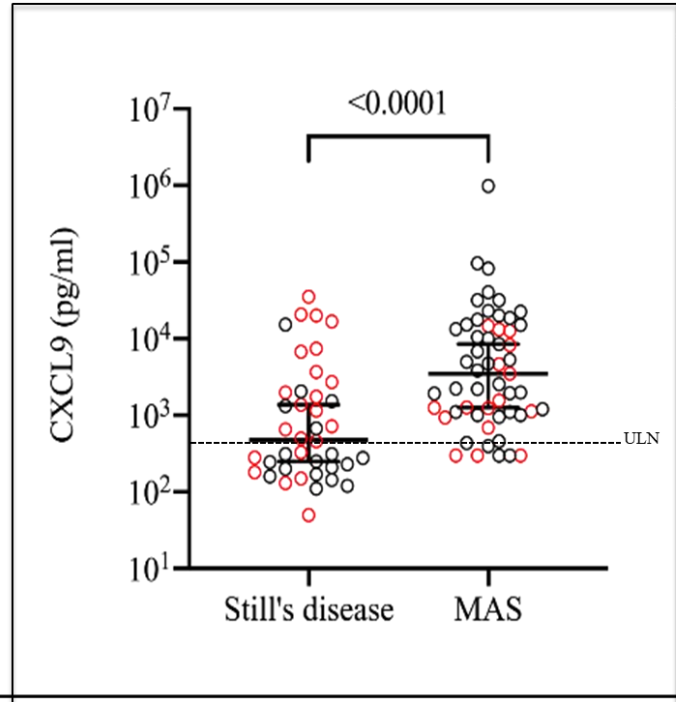


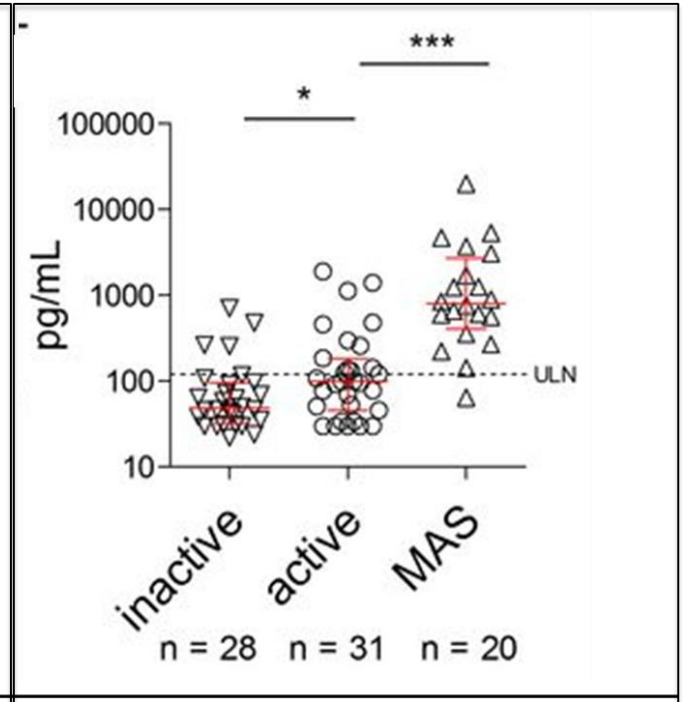
Weiss EC et al. Blood 2018;131:1442–1455.

De Matteis A et al. submitted PRES 2024, oral presentation scheduled 12 Sept (14:54)

CXCL9 (other IFNγ-related biomarkers) in Different Forms of HLH/MAS

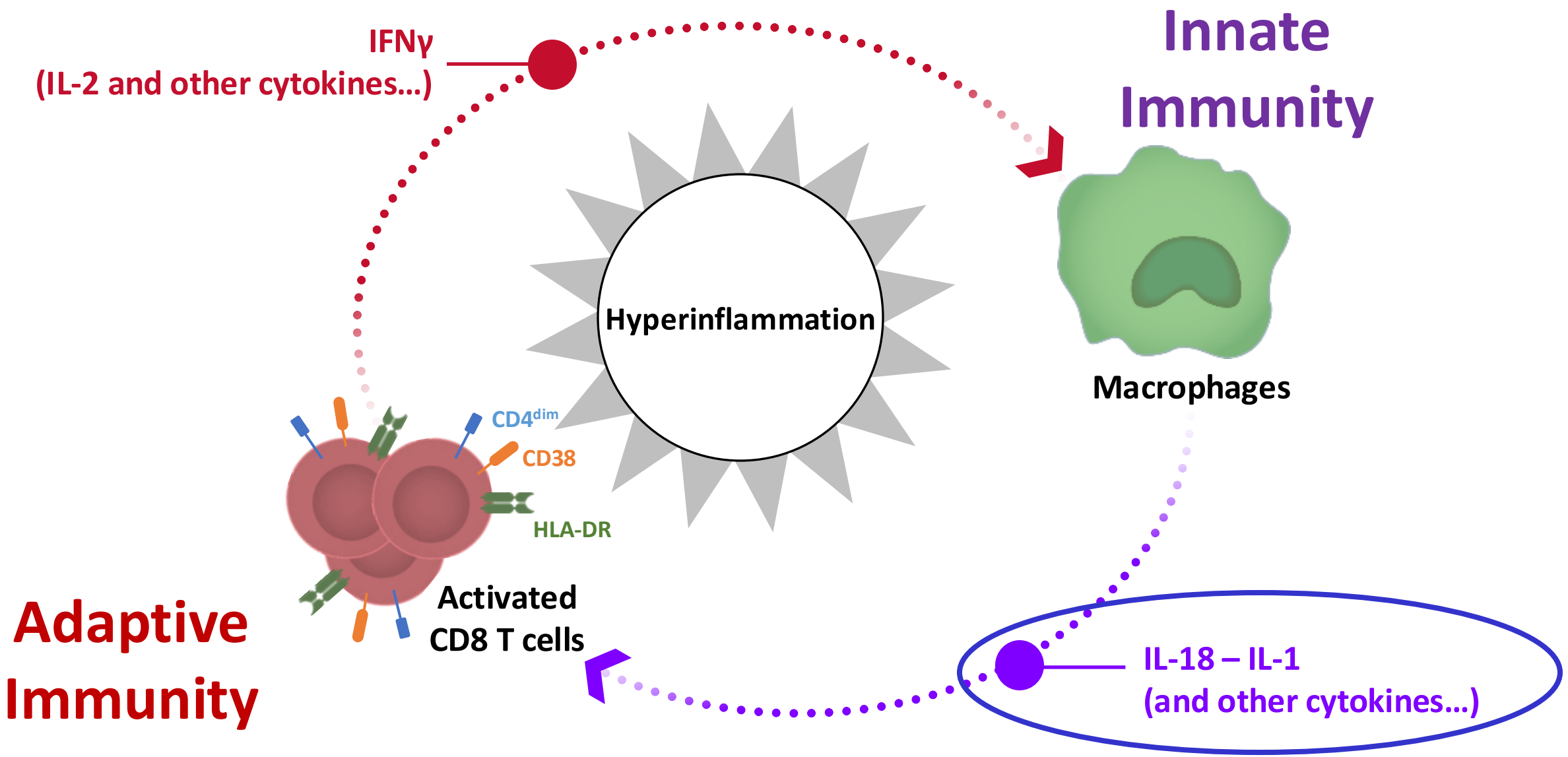
- Normal CXCL9 in active sJIA
- Increased CXCL9 in MAS, infection-associated HLH, secondary HLH and primary HLH
- CXCL9 levels discriminates MAS form active sJIA
- Neopterin and ADA2 levels discriminates MAS from active sJIA





Best cut-off	**>830 pg/ml**	**>203 ng/ml**
Se (%)	**84**	**90**
Sp (%)	**60**	**77**
	De Matteis A et al, submitted	Lee PY et al, ARD 2020

The *Simplified* Vicious Loop of Hyperinflammation[1–3]



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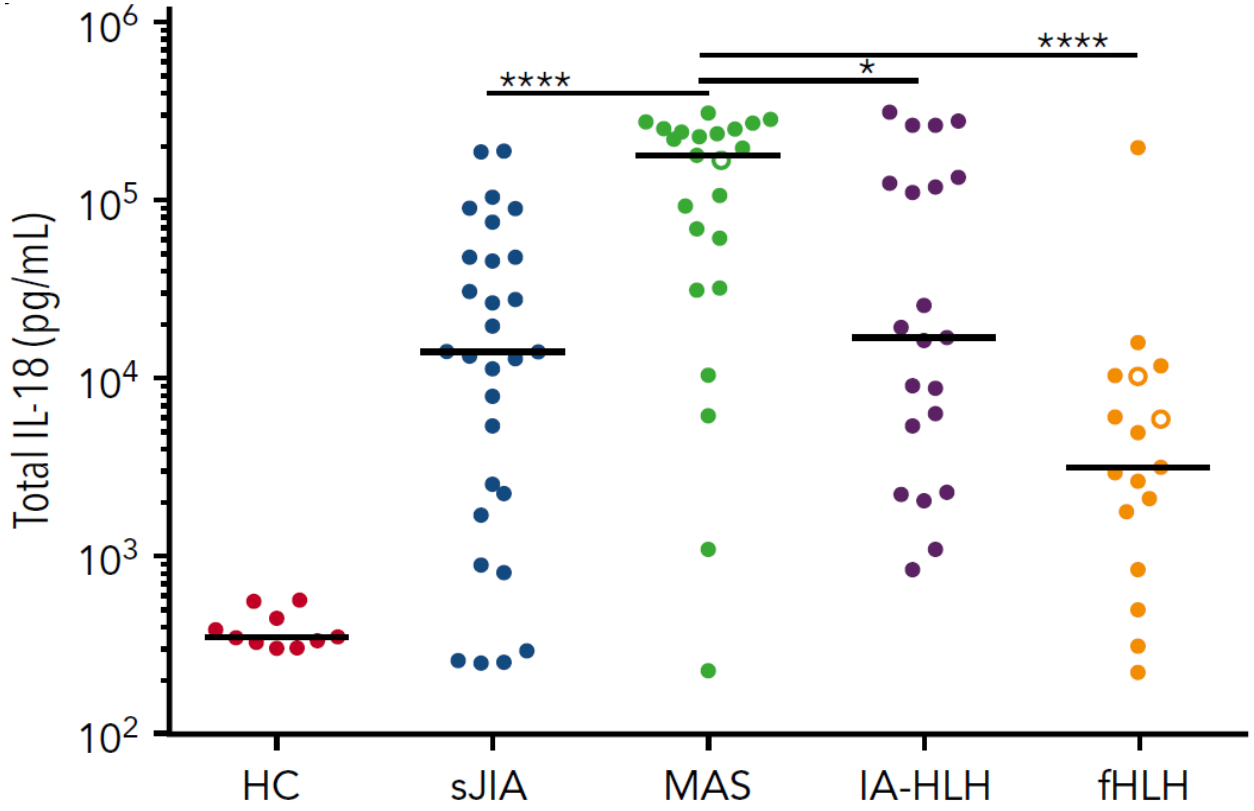
IL-18 in Different Forms of HLH/MAS

- Increased in active sJIA and markedly increased in MAS
- Variably increased in infection-associated HLH, but moderately increased in familial HLH



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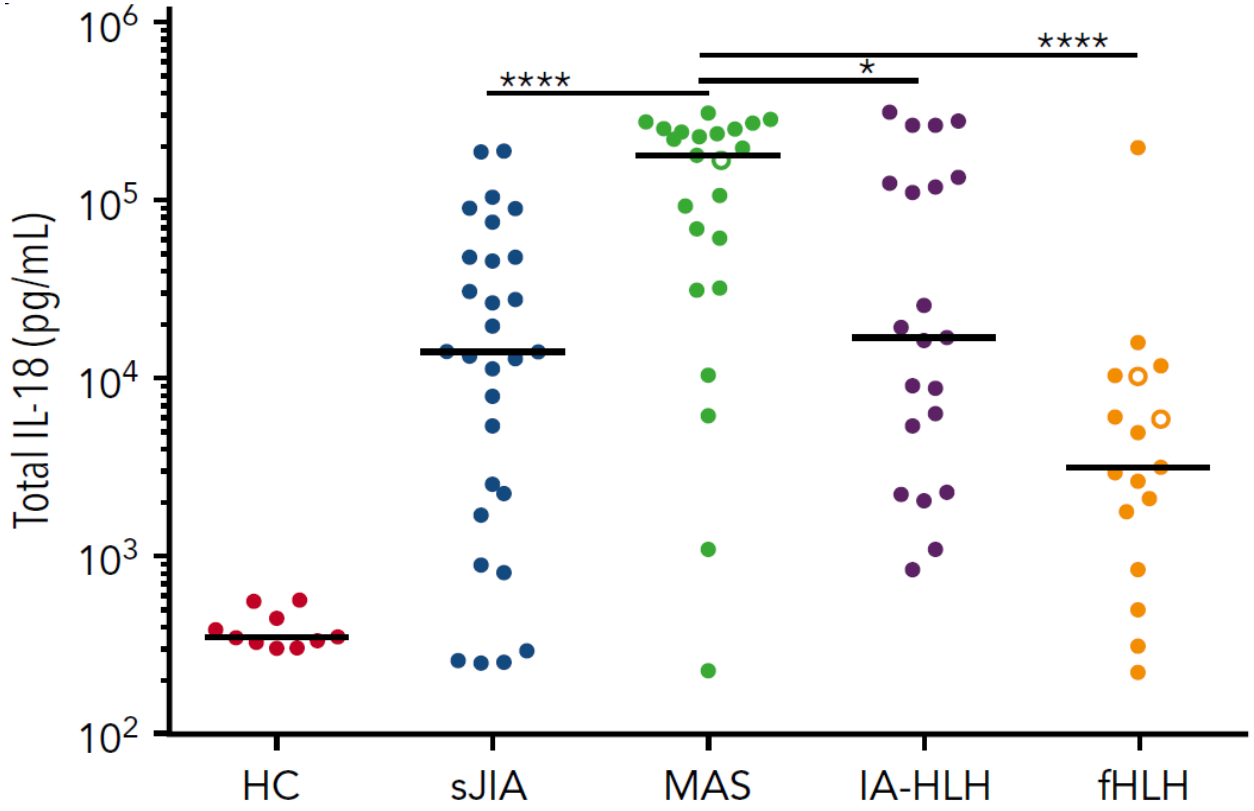
IL-18 in Different Forms of HLH/MAS

- Increased in active sJIA and markedly increased in MAS
- Variably increased in infection-associated HLH, but moderately increased in familial HLH
- Discriminates MAS vs active sJIA



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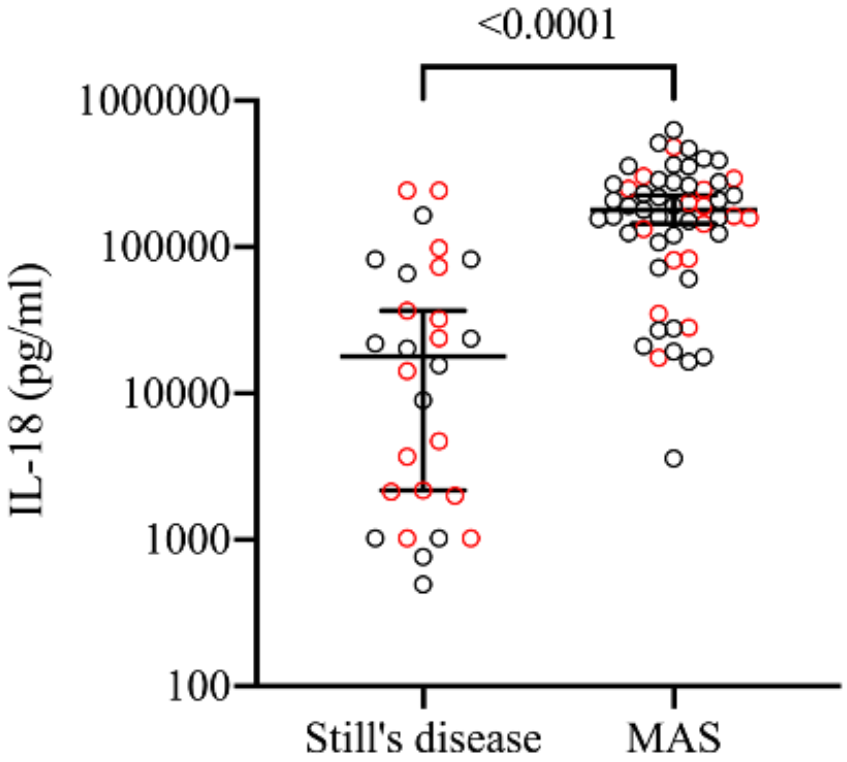


	Best cut-off	Se (%)	Sp (%)
IL-18	>83000 pg/ml	76	75

De Matteis A et al. submitted PRES 2024, oral presentation scheduled 12 Sept (14:54)

Do Laboratory Parameters/Novel Biomarkers at Onset Predict MAS Course Severity?

De Matteis A et al. submitted PRES 2024, oral presentation scheduled 12 Sept (14:54)

Do Laboratory Parameters/Novel Biomarkers at Onset Predict MAS Course Severity?

MAS clinical severity score (MCSS)

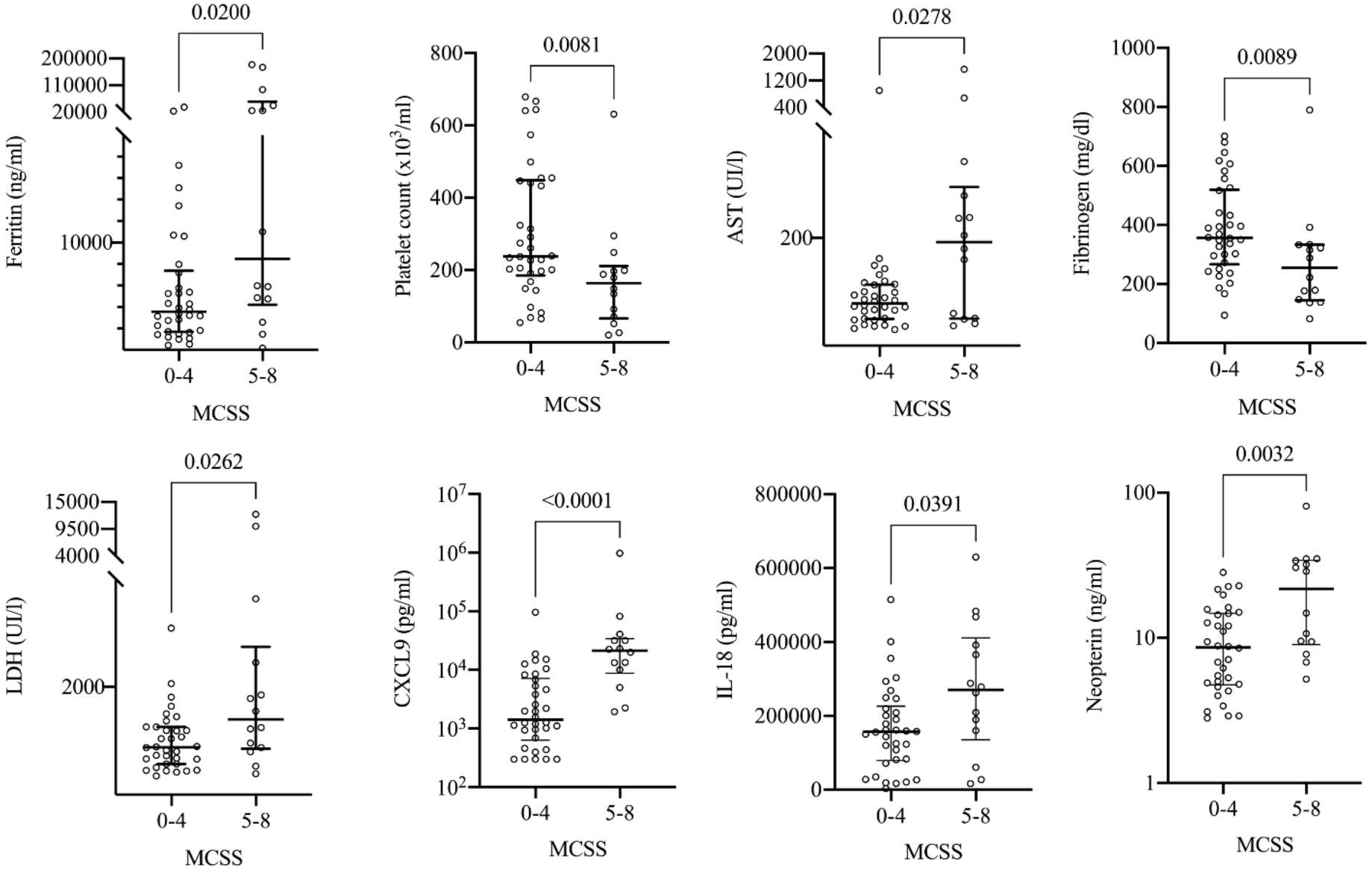
	Score		
	0	1	2
High dose of GCs (prednisone ≥2 mg/kg/die) for at least 10 days	NO	YES	
GC pulses (30 mg/kg/die)	NO	<3	≥3
Other drugs (in addition to GCs and anakinra)	NO	YES	
Length of hospitalization (days)	<15	15–30	≥30
Intensive care unit	NO	YES	
Death	NO	YES	

Score: range 0–8
Mild MAS ≤4; severe MAS >4

34/48 (71%): mild MAS
14/48 (29%): severe MAS

De Matteis A et al. submitted PRES 2024, oral presentation scheduled 12 Sept (14:54)

Do Laboratory Parameters at MAS Onset Predict MAS Course Severity?



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Do Laboratory Parameters at MAS Onset Predict MAS Course Severity?

Each laboratory parameter alone does not predict MAS severity with clinically relevant reliability (sensitivity 64–86%, specificity 60–92%). But…

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Do Laboratory Parameters at MAS Onset Predict MAS Course Severity?

Each laboratory parameter alone does not predict MAS severity with clinically relevant reliability (sensitivity 64–86%, specificity 60–92%). But…

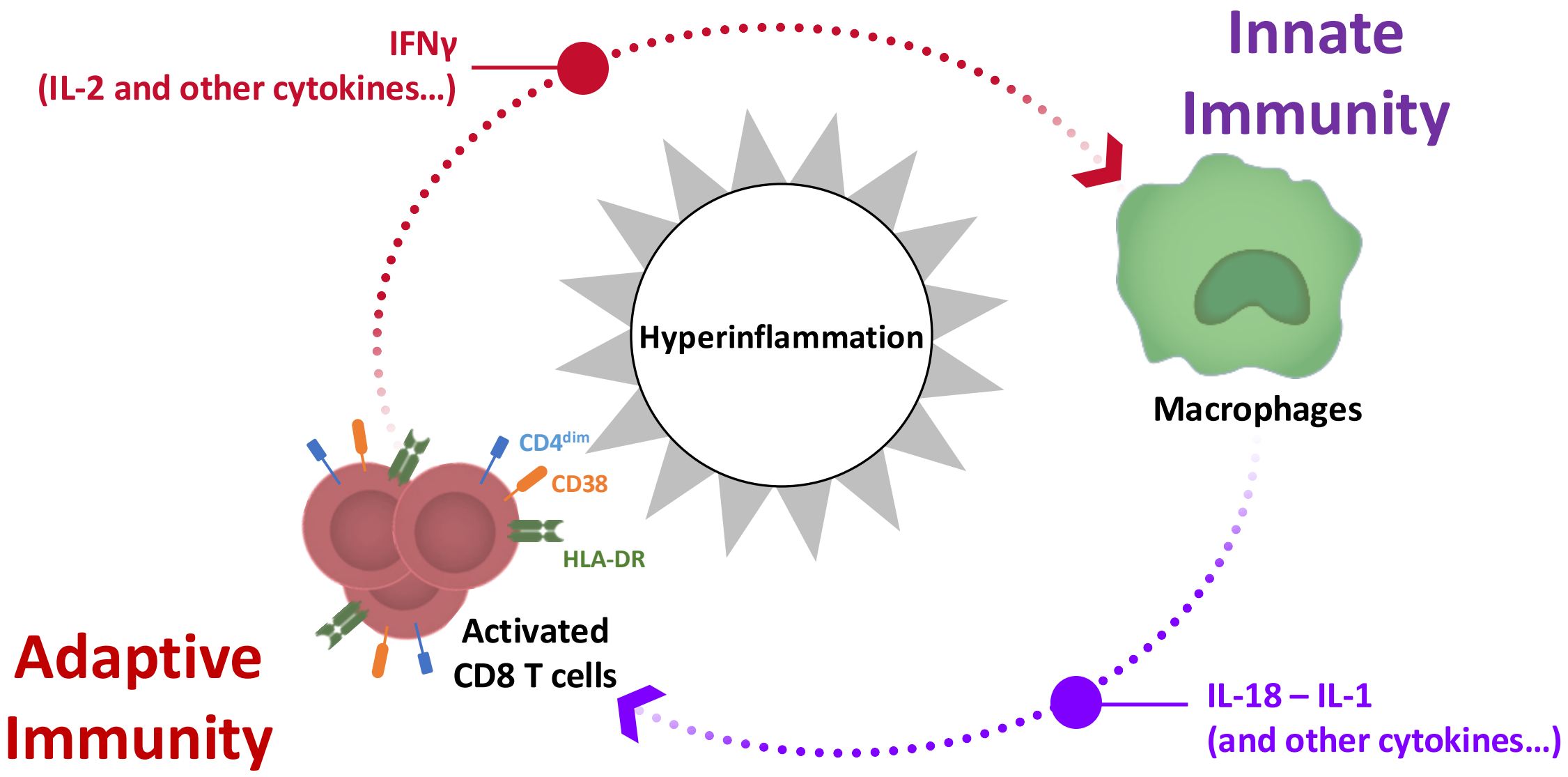
Combination of multiple parameters including CXCL9

Prognostic score for severe MAS

CXCL9 >1750 pg/ml and any two of the following: **PLT <250 x10^9/liter** **Ferritin >4500 ng/ml** **Fibrinogen ≤340 mg/dl** **LDH >1200 U/L**	**Sensitivity: 100%** **Specificity: 74%** **PPV: 61%** **NPP: 100%**

De Matteis A et al. submitted PRES 2024, oral presentation scheduled 12 Sept (14:54)

The *Simplified* Vicious Loop of Hyperinflammation[1–3]



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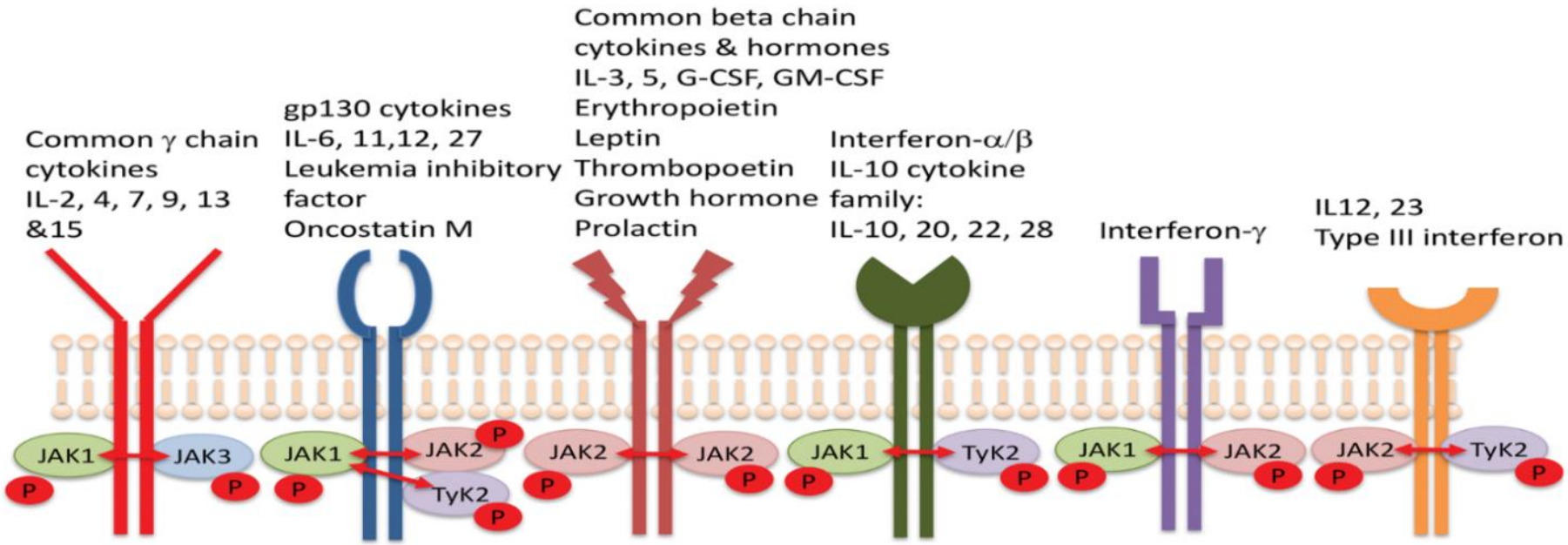
Janus Kinases (JAK)

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)



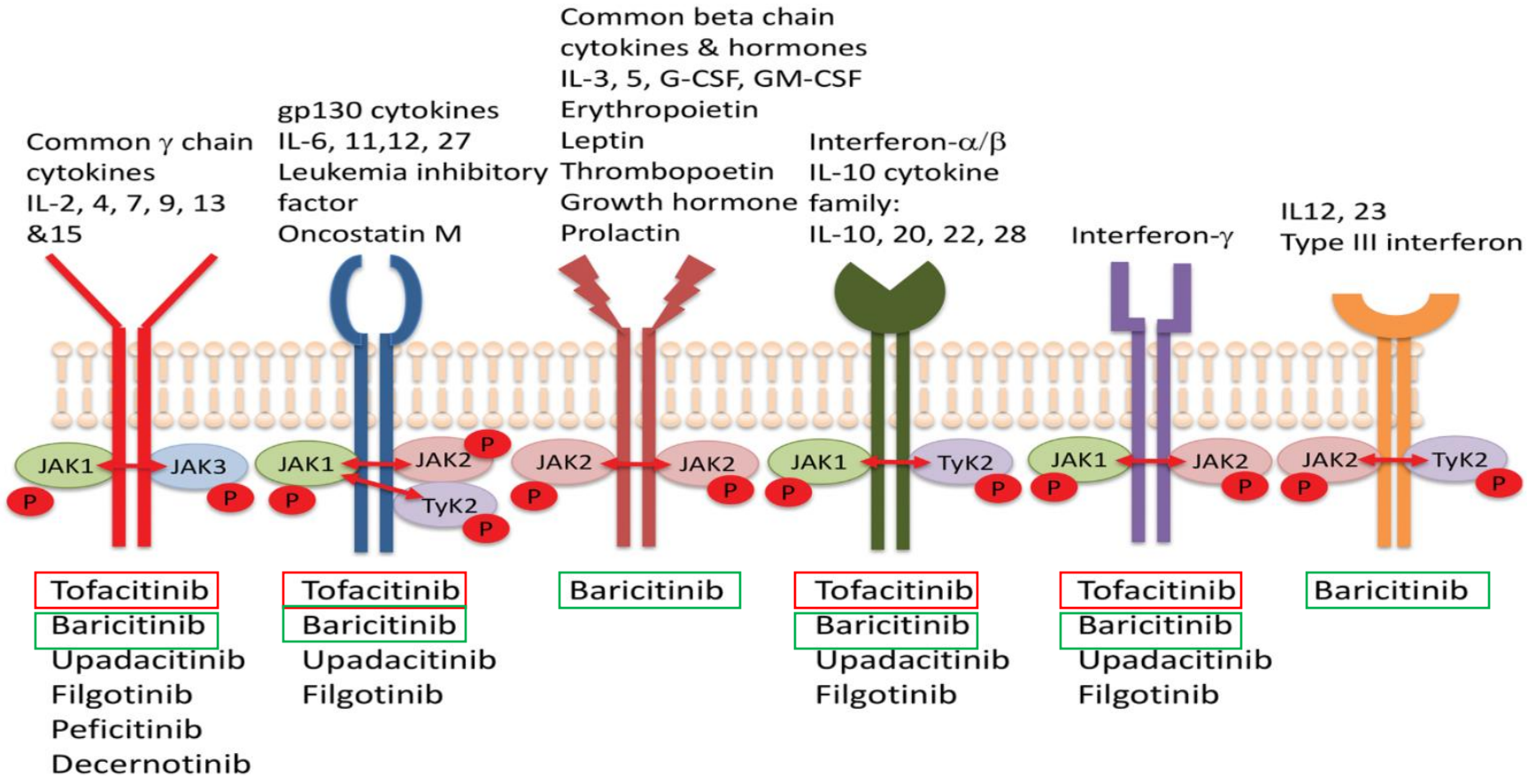
Choy EH. Rheumatology (Oxford) 2019;58:953–962.

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



Choy EH. Rheumatology (Oxford) 2019;58:953–962.

Current treatment in macrophage activation syndrome worldwide: a systematic literature review to inform the METAPHOR project

Baldo F…… Vastert S and Minoia F (on behalf of the MAS/sJIA PReS WP)

Rheumatology 2024

RHEUMATOLOGY

Ruxolitinib-based regimen in children with primary hemophagocytic lymphohistiocytosis

Jian Ge, Qing Zhang, Honghao Ma, Dong Wang, Yunze Zhao, Ting Zhu, Wenqian Wang, Chenxin Zhou, Ang Wei, Hongyun Lian, Maoquan Qin, Jun Yang, Zhigang Li, Tianyou Wang, Rui Zhang

Hematologica 2024

haematologica

JAK Inhibition in Murine HLH

JAK inhibition for murine HLH requires complete blockade of IFN-γ signaling and is limited by toxicity of JAK2 inhibition[1]

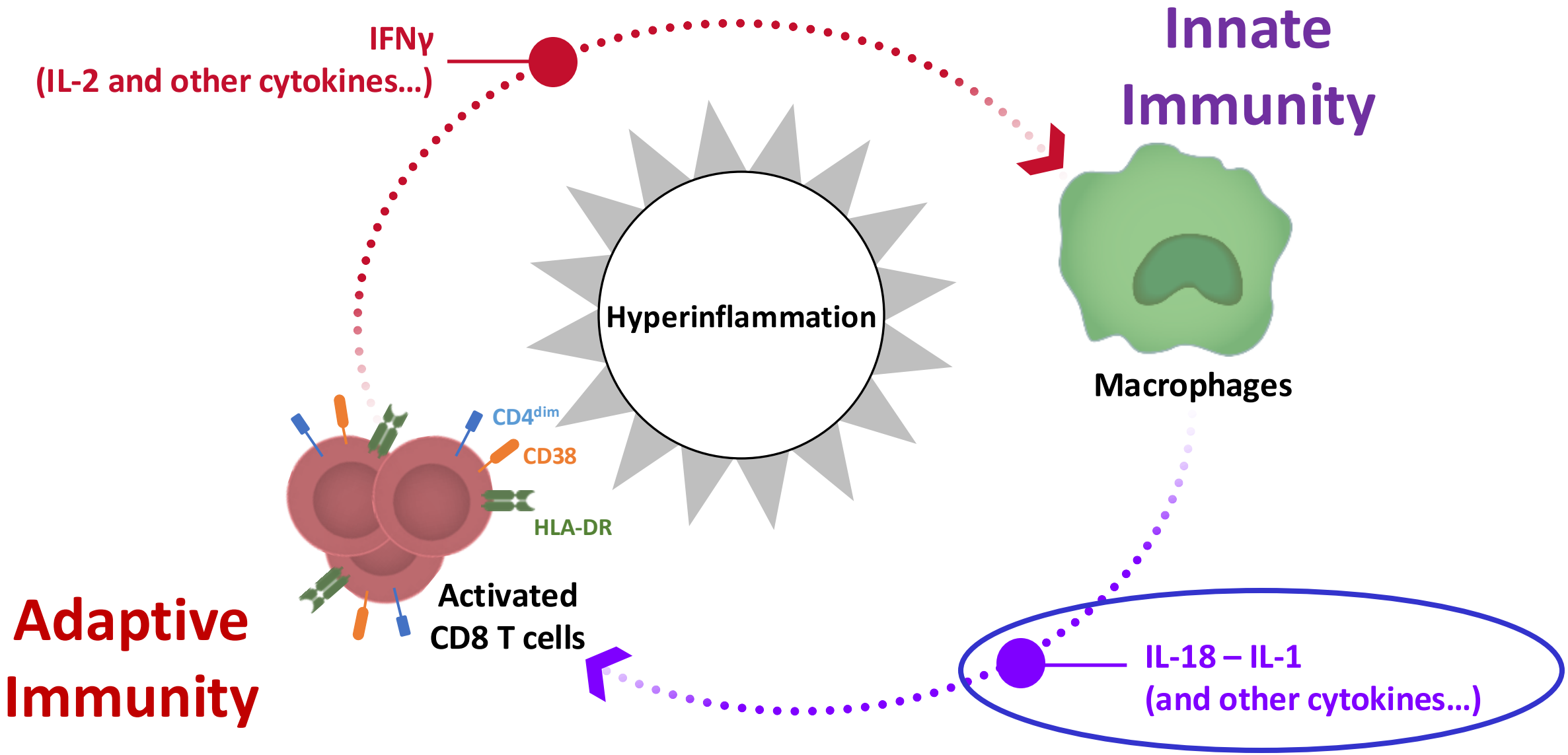
- Intermittently administered ruxolitinib failed to prevent HLH development or treat established HLH
- High doses of ruxolitinib blocked IFN-γ signaling only transiently
- Only continuously administered drug could prevent HLH development or treat established HLH
- Continuously administered ruxolitinib was therapeutic in a narrow dose range because of toxicity due to Jak inhibition

Differential effects of itacitinib (jak1 sel), fedratinib (jak2 sel) and ruxolitinib (jak1/2) in mouse models of hemophagocytic lymphohistiocytosis[2]

- Itacitinib (jak1 sel), but not fedratinib (jak2 sel), significantly improved survival and clinical scores in CpG-induced secondary HLH
- In primary HLH (*Prf1*$^{-/-}$) mice. Itacitinib and fedratinib performed suboptimally. Ruxolitinib demonstrated excellent clinical efficacy in both HLH models

1. Chaturvedi V et al. Blood 2021;138:1034–1039; 2. Keenan C et al. Blood 2024;143:2386–2400.

The *Simplified* Vicious Loop of Hyperinflammation



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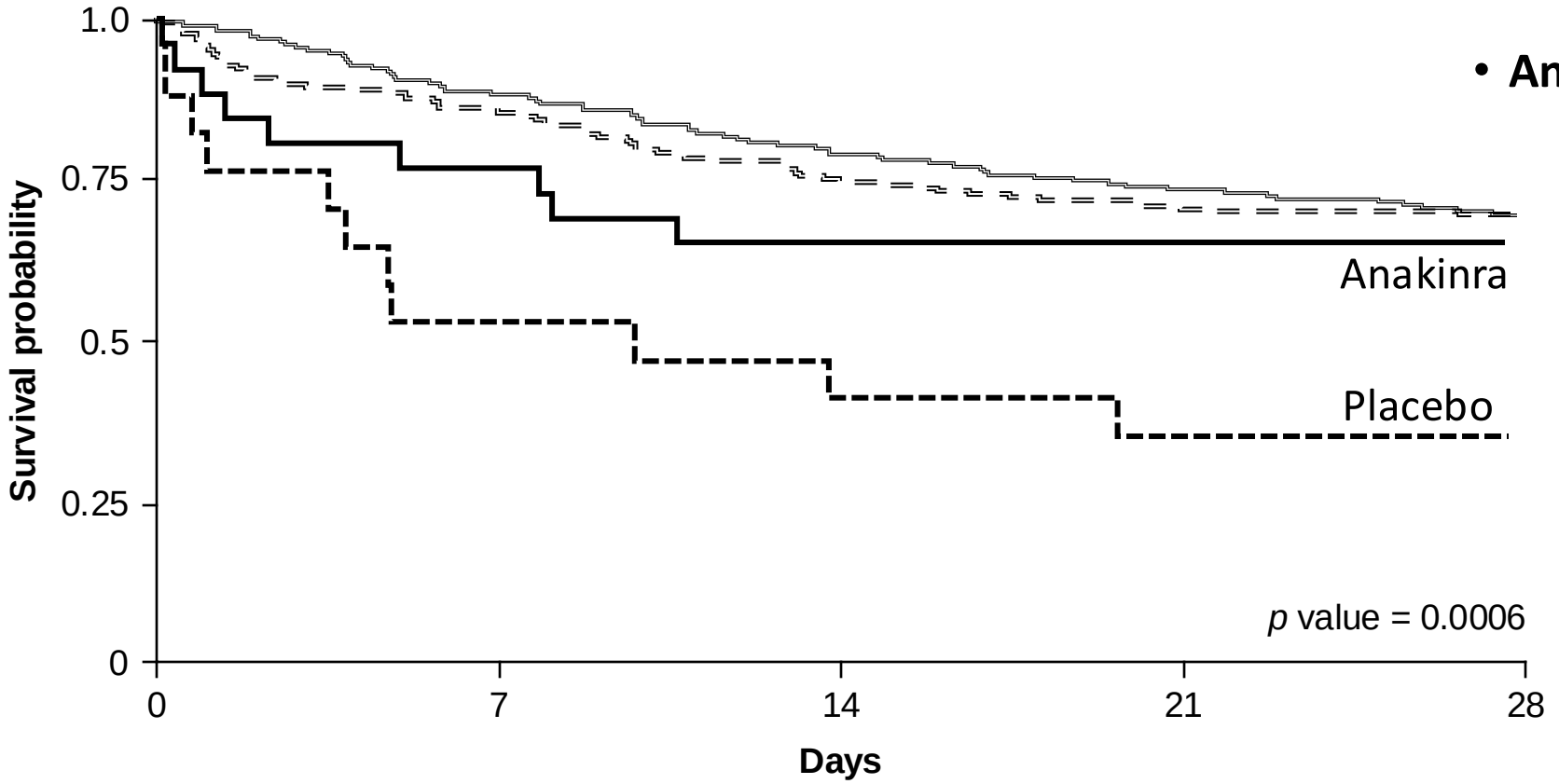
Interleukin-1 Receptor Blockade is Associated With Reduced Mortality in Sepsis Patients With Features of the Macrophage Activation Syndrome

Re-analysis of a Prior Phase III Trial



- **Anakinra 48 mg/Kg/h i.v.**

Increase in LFT
+
Increase in d-dimer

Shakoory B et al. Crit Care Med 2016;44:275–281.

IL-1 Inhibition in Hyperinflammation: Anakinra[1–3]

- Recombinant human IL-1 receptor antagonist
- Case series (various forms of secondary HLH including MAS in Still´s disease) with variable dosing regimens
- Effective at least in some/many patients
- Used (off-label) often intravenously at «*high*» dose (5–15 mg/Kg/day)
- Does not interfere with differential diagnosis (malignancies)
- Safety is very reassuring

1. Miettunen PM et al. Rheumatology 2011;50:417–419; 2. Eloseily EM et al. Arthritis Rheumatol 2020;7:326–34; 3. Mehta P, et al. Lancet Rheumatol. 2020;2:e589–e590.

Monogenic HLH/MAS		
Defective cytotoxicity		
FHL-2	PRF1	Pore-forming protein
FHL-3	UNC13D	Vesicle priming (granule exocytosis)
FHL-4	STX11	Vesicle transport and fusion
FHL-5	STXBP2 (UNC18B)	Vesicle transport and fusion
CHS	LYST	Vesicle transport
GS-2	RAB27A	Vesicle docking
Inflammasome activation (IL-18opathies)		
NLRC4 GOF	NLRC4	NLRC4 nflammasome activation
NOCAHR	CDC42	Pyrin and NLRC4-Inflammasome activation
XLP-1/XLP-2	SH2DIA/BIRC4	Activation of monocytes and lymphocytes
Secondary HLH or Acquired HLH or Reactive HLH		
Infections (EBV, Leishmania, H1N1…)		
Rheumatic diseases (s-JIA…) → MAS or rheuma-HLH		
Malignancies (lymphoma…)		
Unknown trigger		

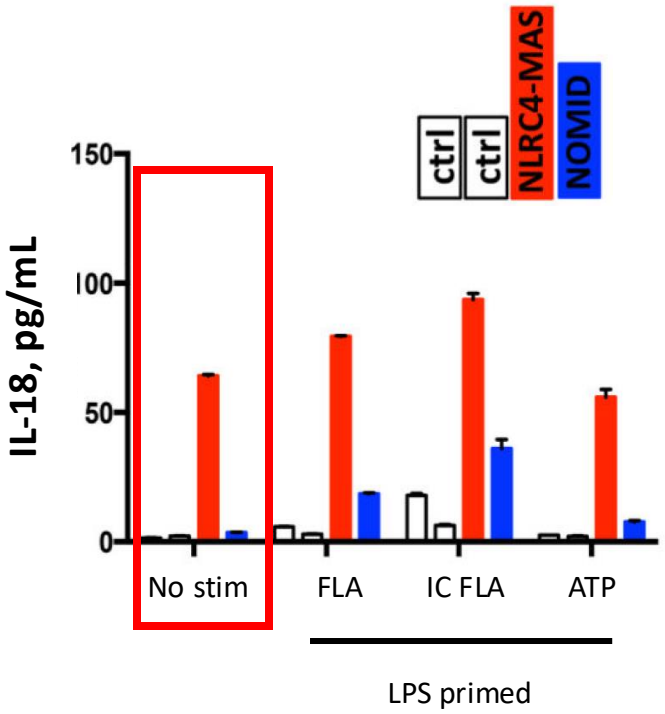
<1 %

Unpublished data.

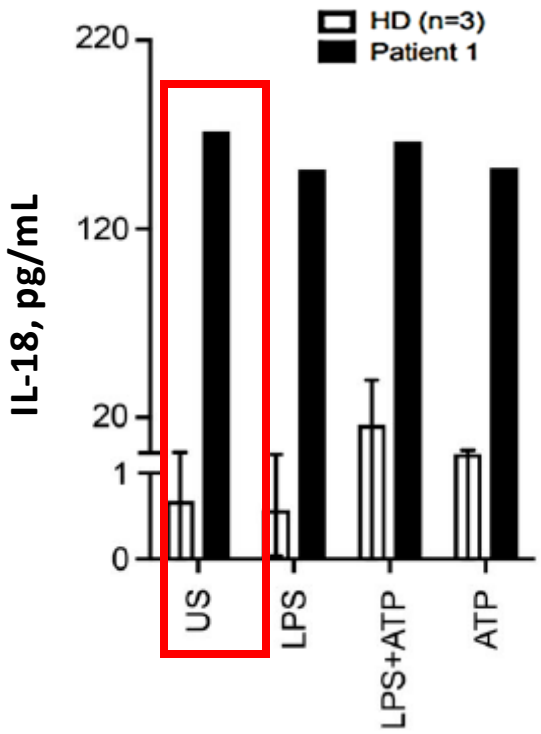
Monogenic IL-18opathies1−3

Predisposition to HLH/MAS through IFNγ production

Gain of Function mutations in *NLRC4*[1]



p.R186C mutation in *CDC42*[3]



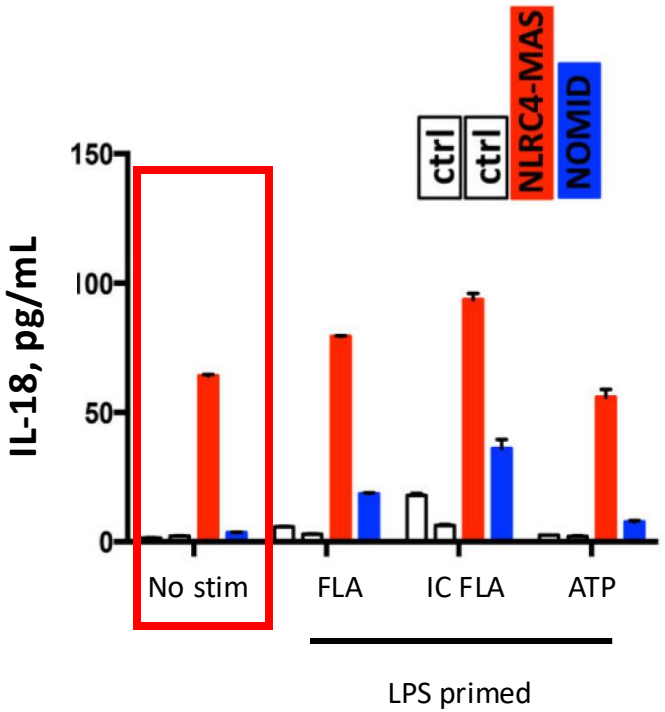
- **Moderate increase in IL-1β production**
- **Massive increase in IL-18 production**

Left panel: Canna SW et al. Nat Genet 2014;46:1140−1146. Figures reproduced with permission © 2014 Nature America Inc, part of Springer Nature. Centre and right panels: figures reproduced with permission from Lam MT et al. J Exp Med 2019;216:2778−2799. ATP, adenosine triphosphate; ctrl, control; FLA, flagellin; HD, healthy donor; HLH, haemophagocytic lymphohistiocytosis; IC-FLA, liposomal flagellin; IFN, interferon; IL, interleukin; LPS, lipopolysaccharide; MAS, macrophage activation syndrome; no stim, no stimulation; NOMID, neonatal-onset multisystem inflammatory disease; US, unstimulated. 1. Canna SW et al. Nat Genet 2014;46:1140−1146; 2. Romberg N et al. Nat Genet 2014;46:1135–1139; 3. Lam MT et al. J Exp Med 2019;216:2778−2799.

Monogenic IL-18opathies1–3

Predisposition to HLH/MAS through IFNγ production

Gain of Function mutations in *NLRC4*[1]



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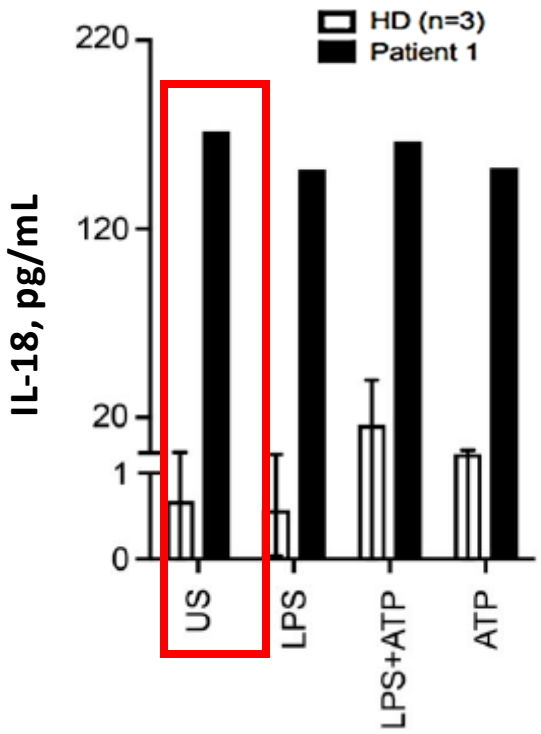
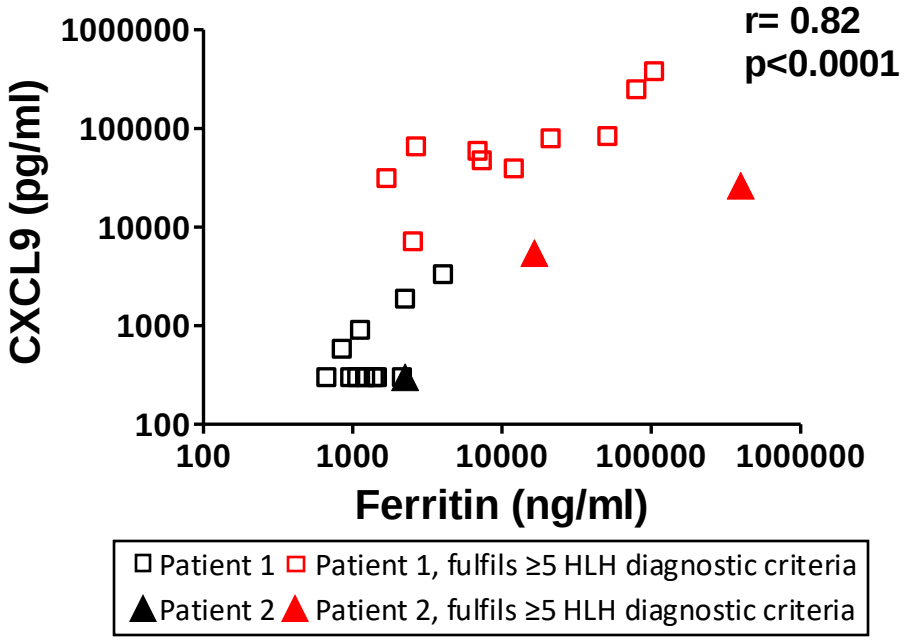


- **Moderate increase in IL-1β production**
- **Massive increase in IL-18 production**
- **Activation of the IFNγ pathway during HLH/MAS**



Left panel: Canna SW et al. Nat Genet 2014;46:1140–1146. Figures reproduced with permission © 2014 Nature America Inc, part of Springer Nature. Centre and right panels: figures reproduced with permission from Lam MT et al. J Exp Med 2019;216:2778–2799. ATP, adenosine triphosphate; ctrl, control; FLA, flagellin; HD, healthy donor; HLH, haemophagocytic lymphohistiocytosis; IC-FLA, liposomal flagellin; IFN, interferon; IL, interleukin; LPS, lipopolysaccharide; MAS, macrophage activation syndrome; no stim, no stimulation; NOMID, neonatal-onset multisystem inflammatory disease; US, unstimulated. 1. Canna SW et al. Nat Genet 2014;46:1140–1146; 2. Romberg N et al. Nat Genet 2014;46:1135–1139; 3. Lam MT et al. J Exp Med 2019;216:2778–2799.

IL-18 Inhibition in Hyperinflammation

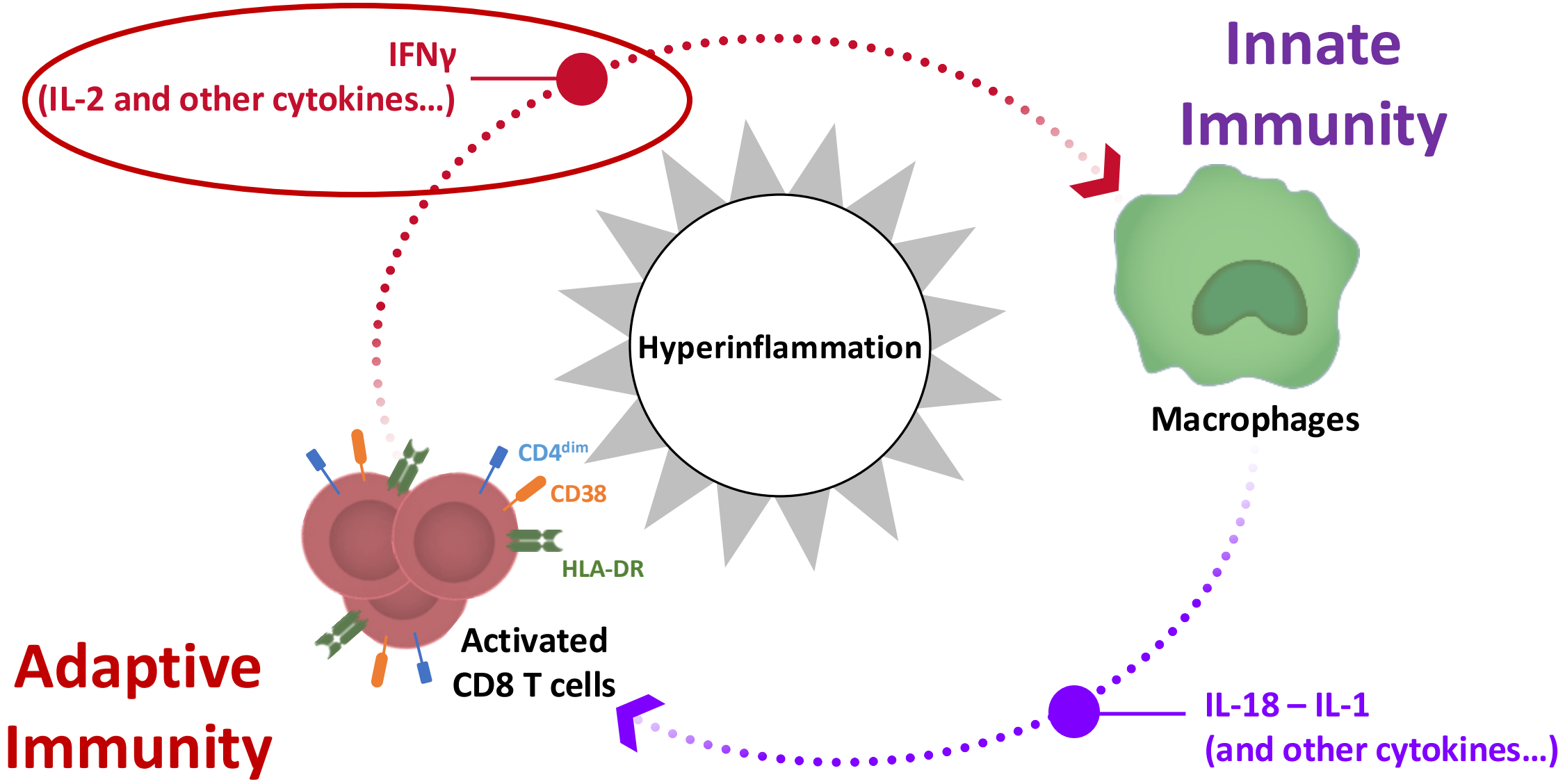
MAS825 (bispecific IL-1β and IL-18 antibody)

- Bispecific antibody that neutralizes IL-1 with one arm and IL-18 with the other arm (MAS825)
- Inhibition of both IL-1β and IL-18 may result in a more effective down-modulation of inflammasome effects and may prevent development of MAS/HLH

NLRC4 patients, with a second basket in $CDC42_{cterm}$ and XIAP deficiency. A three-period study, with an open-label, single-arm active treatment in Period 1 followed by a randomized-withdrawal, double-blinded, placebo-controlled design in Period 2, and an open label, long-term safety follow-up in Period 3 (ClinicalTrials.gov NCT04641442)

- Lead PI Fabrizio de Benedetti

The *Simplified* Vicious Loop of Hyperinflammation



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

1.De Matteis A et al. Blood 2022;140:262–273; 2. Jordan MB. Blood 2022;140:167–168; 3. De Benedetti F et al. Nat Rev Rheumatol 2021;17:678–691.

Over-Production of IFNγ is Present and Pathogenic in Several Different Animal Models of HLH and MAS

Human disease	Mutation	Trigger	High IFNγ	IFNγ 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. 2022;140:167–168; 2. Schmid PJ et al. EMBO Mol Med. 2009;1:112–124; 3. Crozat K et al. J Exp Med. 2007;204:853–863; 4. Kögl T et al. Blood. 2013;121:604–613;
5. Czar MJ et al. Proc Natl Acad Sci. 2001;98:7449–7454; 6. Behrens EM et al. J Clin Invest. 2011;121:2264–2277; 7. Weiss ES et al. Blood 2018;131:1442–1455;
8. Girard-Guyonvarc'h C et al. Blood. 2018;131:1430–1441; 9. Prencipe G et al. J Allergy Clin Immunol. 2018;141:1439–1449.

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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**

De Benedetti et al. Ann Rheum Dis 2023;82:857–865.

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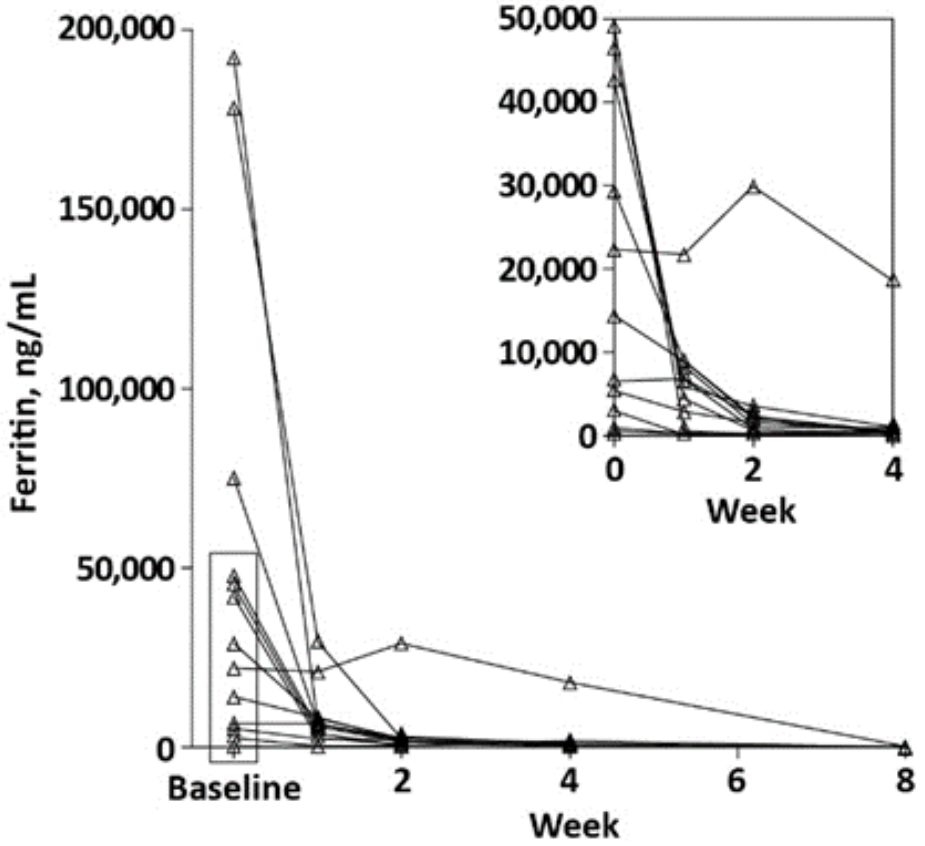
CLINICAL SCIENCE

Efficacy and safety of emapalumab in macrophage activation syndrome

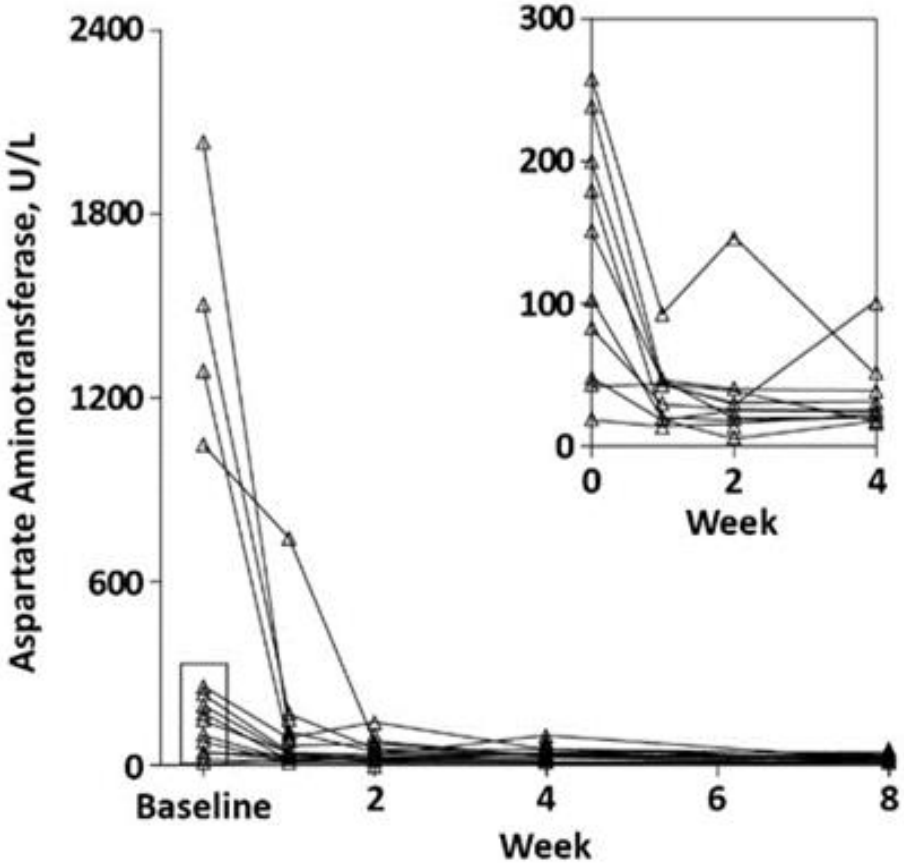
Annals of the Rheumatic Diseases

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

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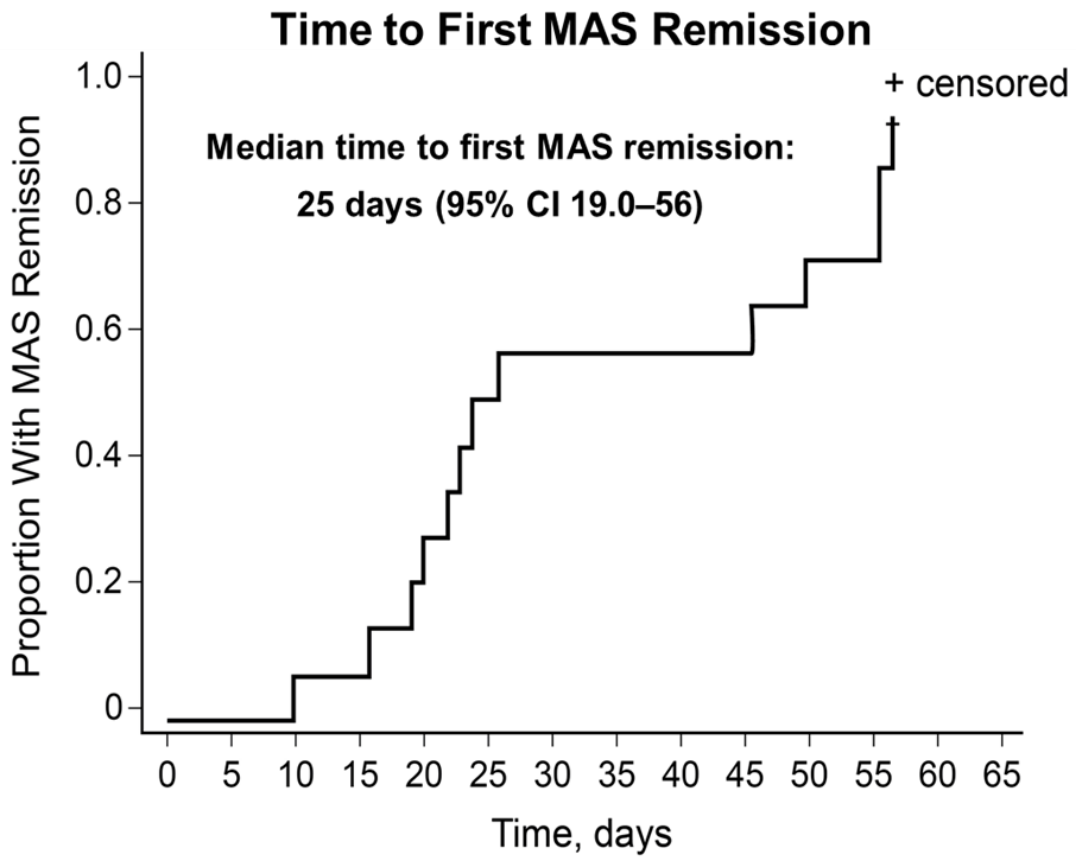

MAS REMISSION: Resolution of MAS signs and symptoms (VAS ≤1/10) and normalization of MAS laboratory parameters
(WBC >Lower Limit of Normal; PLT >Lower Limit of Normal; LDH <1.5× Upper Limit of Normal; ALT <1.5× Upper Limit of Normal; AST <1.5× Upper Limit of Normal; Fibrinogen >100 mg/dL; Ferritin ≤80% from values at baseline or <2000 ng/mL, whichever is lower

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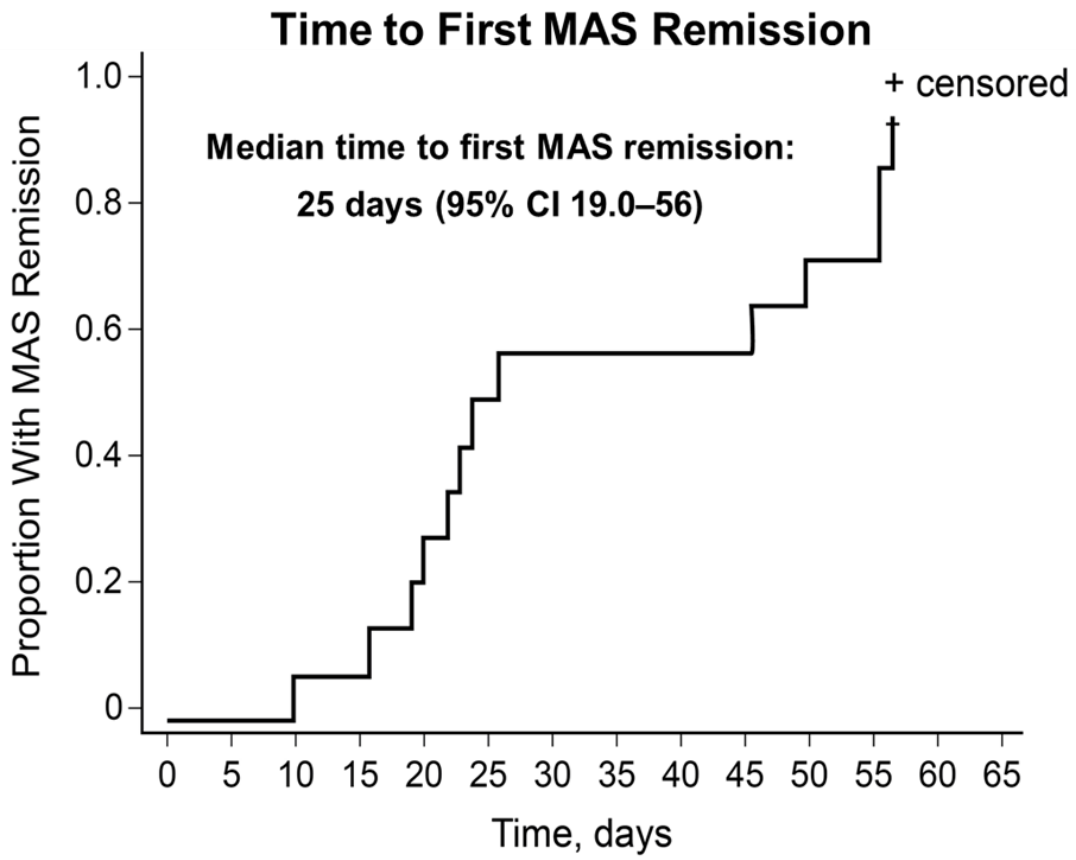
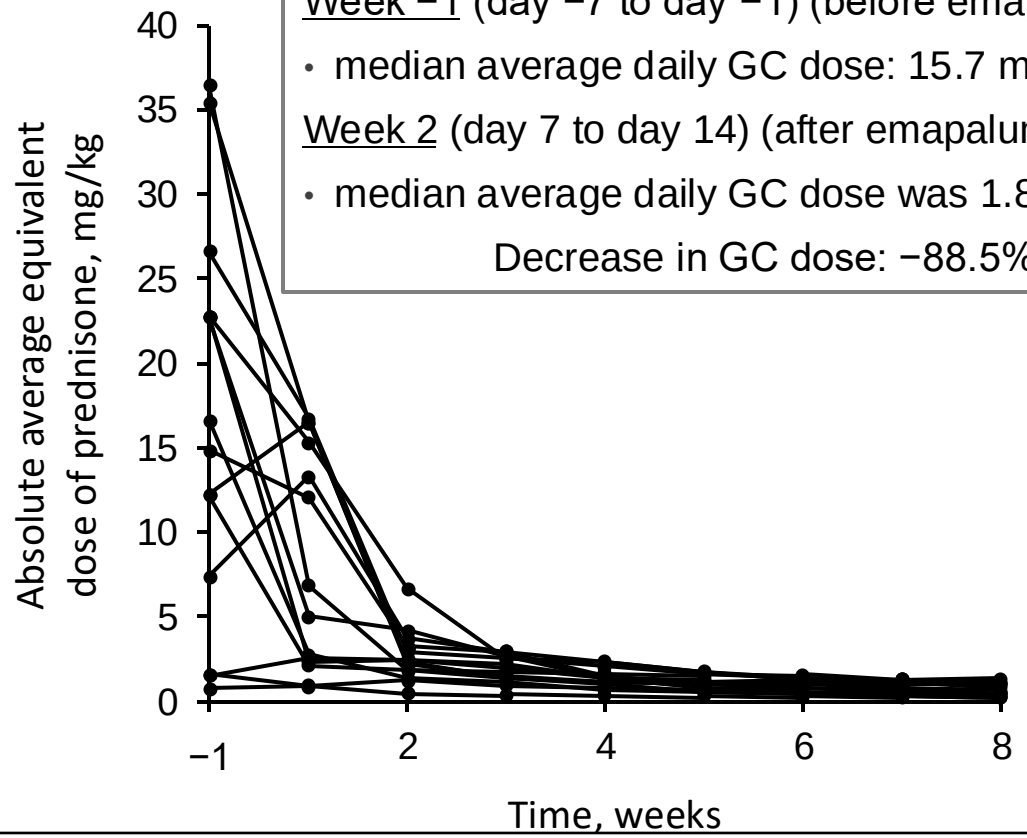
Efficacy and safety of emapalumab in macrophage activation syndrome





Week −1 (day −7 to day −1) (before emapalumab)
- median average daily GC dose: 15.7 mg/kg

Week 2 (day 7 to day 14) (after emapalumab)
- median average daily GC dose was 1.8 mg/kg

Decrease in GC dose: −88.5%

MAS REMISSION: Resolution of MAS signs and symptoms (VAS ≤1/10) and normalization of MAS laboratory parameters
(WBC >Lower Limit of Normal; PLT >Lower Limit of Normal; LDH <1.5× Upper Limit of Normal; ALT <1.5× Upper Limit of Normal; AST <1.5× Upper Limit of Normal; Fibrinogen >100 mg/dL; Ferritin ≤80% from values at baseline or <2000 ng/mL, whichever is lower

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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;82:857–865.

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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 per 100 patient-days	1.7	1.0

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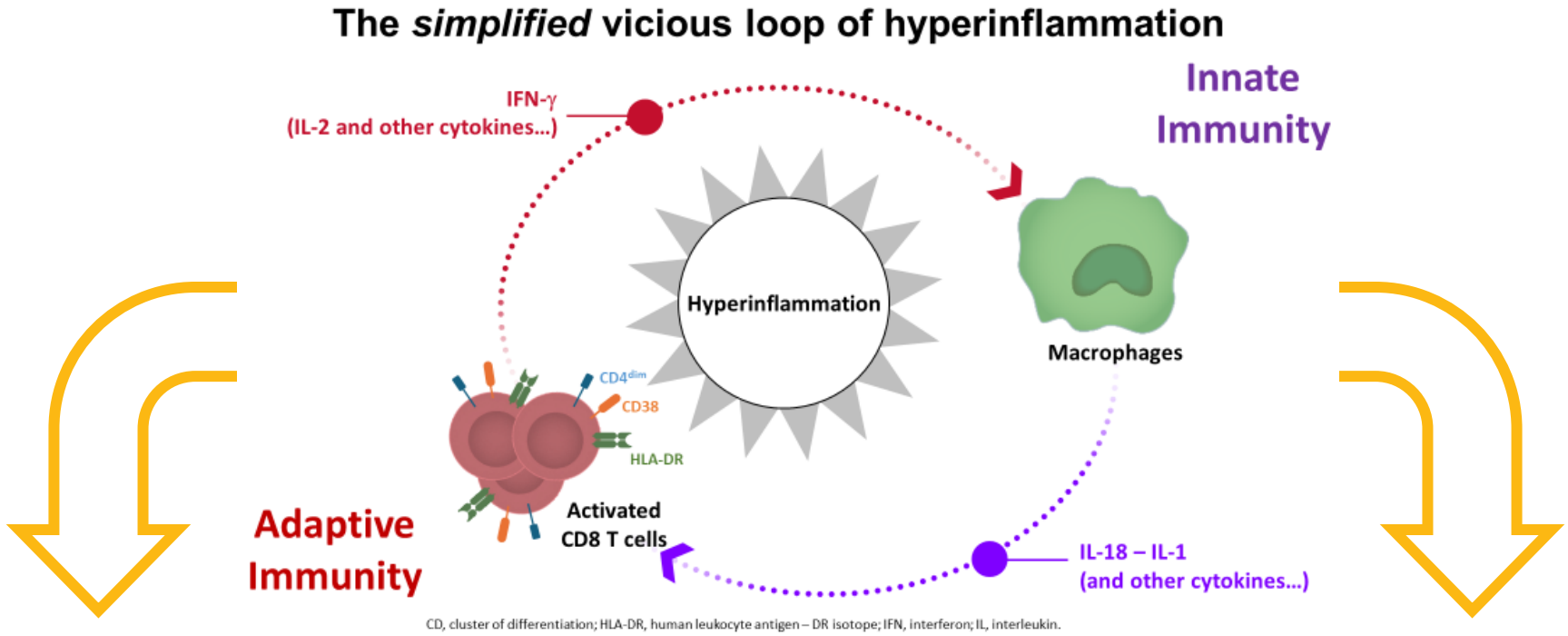
Management Strategies



<u>Novel biomarkers for</u>

- Diagnosis
- Prognosis and monitoring

<u>Investigational treatments targeting</u>

- JAK
- IL-1
- IL-18
- IFNγ

Q&A

31st European Paediatric Rheumatology Congress
PRES 2024
25th Anniversary of PReS
11-14 SEPTEMBER 2024
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