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Management of MAS and Still's Disease: Challenges and opportunities

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Introducing the faculty

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Disclosures

- **Prof. Masaki Shimizu:**
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- **Prof. Fabrizio De Benedetti:**
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Agenda

Title	Speaker
Introduction	Masaki Shimizu
Challenges in diagnosis and early management	Masaki Shimizu
Future management strategies – a case study	Fabrizio De Benedetti
Q&A	All

Challenges in diagnosis and early management

Masaki Shimizu, MD, PhD

Department of Pediatrics, Perinatal and Maternal Medicine,
Graduate School of Medical and Dental Sciences,
Institute of Science Tokyo

Still’s disease

Still’s disease (comprising sJIA and AOSD) is a systemic inflammatory disorder of unknown aetiology, characterised by arthritis and systemic features:

Spiking fever

Arthralgia/arthritis

Serositis

Hyperferritinemia

Skin rash

Inflammation

Elevated liver enzymes

AOSD, adult-onset Still’s disease; sJIA, systemic juvenile idiopathic arthritis.

Fautrel B, et al. Ann Rheum Dis 2024;83:1614-27.

Still’s disease revisited

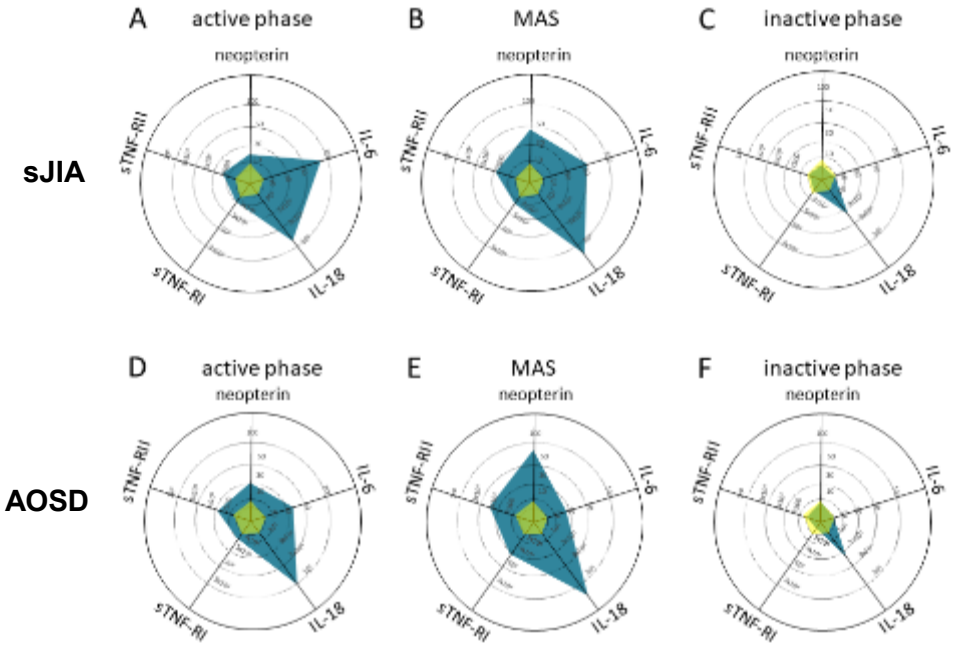
Diagnosis and management of Still’s disease[1]

EULAR/PReS recommendations for the diagnosis and management of Still's disease, comprising systemic juvenile idiopathic arthritis and adult-onset Still's disease

Fautrel B, Mitrovic S, De Matteis A, et al.
Ann Rheum Dis 2024

sJIA: <16 years
AOSD: >16 years

Similar pathogenesis[2]



Similar clinical manifestations[3]

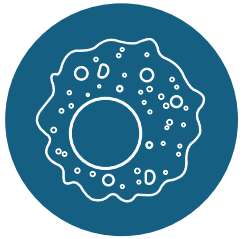
	sJIA	AOSD
Spiking fever	99%	94%
Salmon rash	90%	87%
Arthritis	95%	93%
Sore throat	15%	70%
Hypertrophy of the reticuloendothelial system	40-70%	50-70%
Serositis	20-50%	20-40%
Leukocytosis*	90%	86%
Association with MAS	7-10%	12-17%

*WBC count >10,000/mm^3.

AOSD, adult-onset Still’s disease; MAS, macrophage activation syndrome; sJIA, systemic juvenile idiopathic arthritis.

1. Fautrel B, et al. Ann Rheum Dis 2024;83:1614-27;
2. Inoue N, et al. Clin Immunol 2016;169:8-13;
3. Jamilloux Y, et al. Immunol Res 2015; 61:53-62.

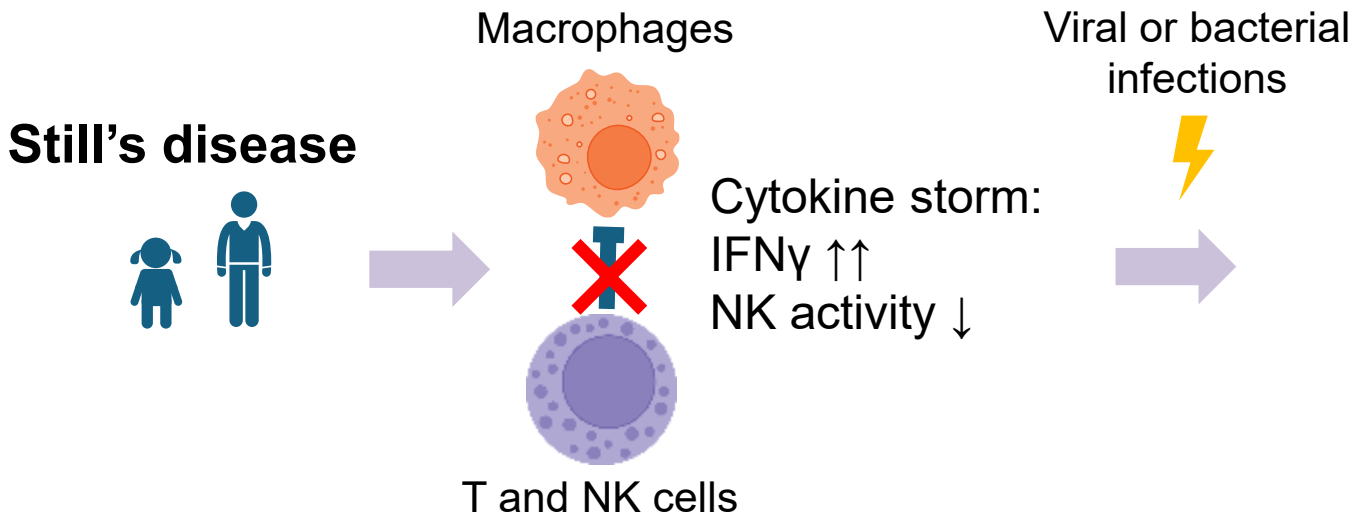
Macrophage activation syndrome (MAS)



MAS is a life-threatening complication of Still's disease[1], occurring in up to **17%** of patients[2]

Mortality associated with MAS has been reported to be **23%** (China) in children,[3] and **0%** (Japan[4]) to **10%** (Italy[5]) in adults

Development of MAS[6-8]



Clinical features of MAS[1]

- Persistent fever
- Elevated/rising ferritin[a]
- Cytopenia
- Coagulopathy
- Splenomegaly
- Hepatic dysfunction
- CNS dysfunction[b]

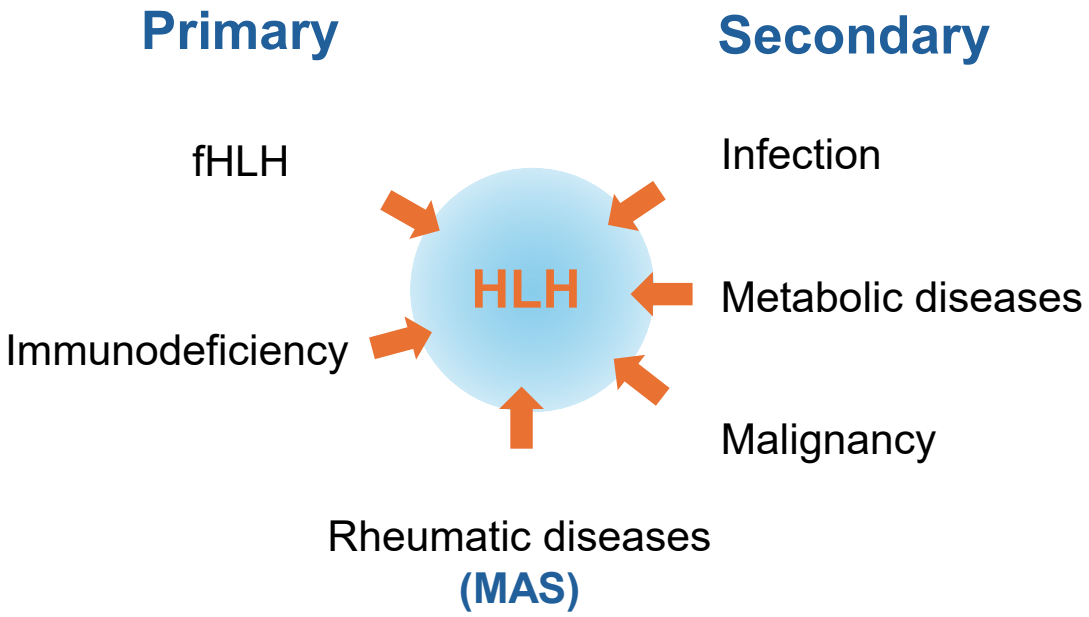
[a]Or other markers of inflammation, such as CRP and LDH.[1]
[b]Includes altered mental status, seizure, encephalopathy, CSF pleocytosis.[1]

AOSD, adult-onset Still's disease; CNS, central nervous system; IFNγ, interferon gamma; MAS, macrophage activation syndrome; NK, natural killer; sJIA, systemic juvenile idiopathic arthritis.

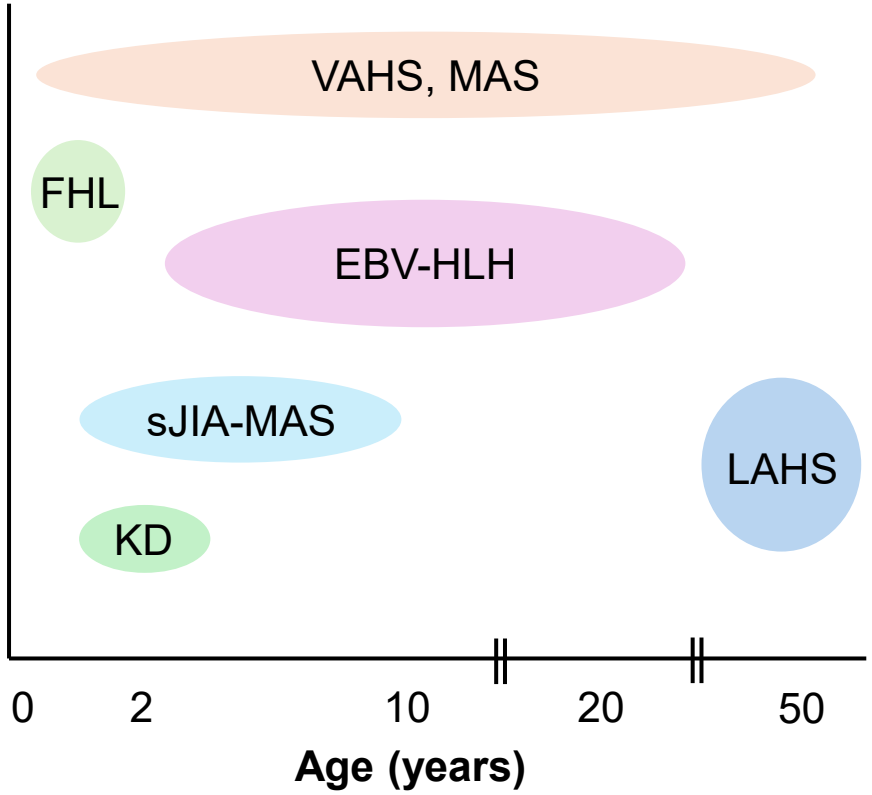
1. Shakoory B, et al. Arthritis Rheumatol 2023;75:1714-32; 2. Jamilloux Y, et al. Immunol Res 2015; 61:53-62; 3. Zeng HS,et al. World J Pediatri 2008;4:97-101; 4. Sugiyama T, et al. Arthritis Res Ther 2022;24; 5. Ruscitti P et al. J Rheumatol 2018;45:864-72; 6. Grom AA, et al. Nat Rev Rheumatol 2016;12:259-68; 7. Strippoli R, et al. J Rheumatol 2013;40:761-7; 8. Shakoory B, et al. Ann Rheum Dis 2023;82:1271-85.

MAS as a subtype of secondary HLH

Hemophagocytic Lymphohistiocytosis (HLH)[1]



Prevalence of secondary HLH/MAS at different ages[2]



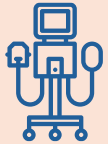
EBV, Epstein-Barr virus; fHLH, familial hemophagocytic lymphohistiocytosis, HLH, hemophagocytic lymphohistiocytosis; KD, Kawasaki disease; LAHS, lymphoma-associated hemophagocytic syndrome; MAS, macrophage activation syndrome; sJIA, systemic juvenile idiopathic arthritis; VAHS, viral associated hemophagocytic syndrome.

1. Iosim S, Henderson LA. Hematology/Oncology Clinics 2025;39:597-615;
2. Information based on speaker's own clinical and research experience.

The burden of MAS in Still's disease

ICU admissions

35%
admitted to ICU[a,1]



Up to **75%**
require mechanical ventilation[b,c,2,3]

Up to **75%**
require inotropic support[a,b,2,3]

Long hospital stay

Mean duration **45 days** (range 20–180 days) in patients who developed MAS[b,4]

Further relapses

25% of patients had **multiple relapses** during follow-up of up to 15 years[b,4]

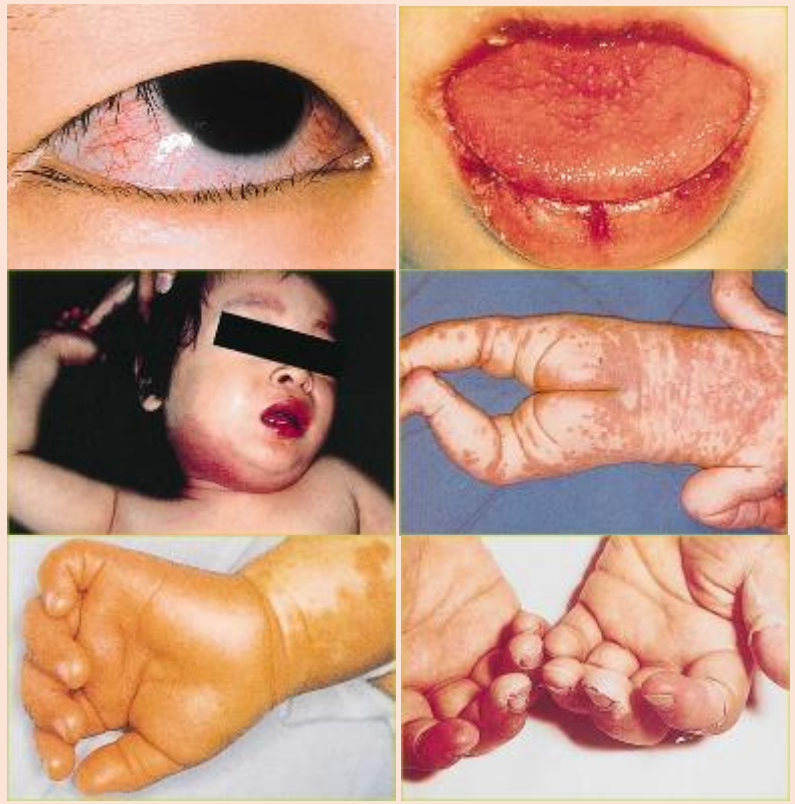
[a]Patients with sJIA. [b]Patients with AOSD. [c]Note this was in all-cause HLH/MAS.

AOSD, adult-onset Still's disease; HLH, hemophagocytic lymphohistiocytosis; ICU, intensive care unit; MAS, macrophage activation syndrome; sJIA, systemic juvenile idiopathic arthritis.

1. Minoia F, et al. Arthritis Rheumatol 2014;66:3160-9;
2. Buyse S, et al. Intensive Care Med 2010;36:1695-702;
3. Barba T, et al. Medicine (Baltimore) 2015;94:e2318;
4. Hot A, et al. Medicine (Baltimore) 2010;89:37-46.

Diagnostic dilemma: sJIA or Kawasaki disease

The incidence of Kawasaki disease is highest in Asian countries[1,2]



sJIA and Kawasaki disease have overlapping clinical manifestations:[3,4]

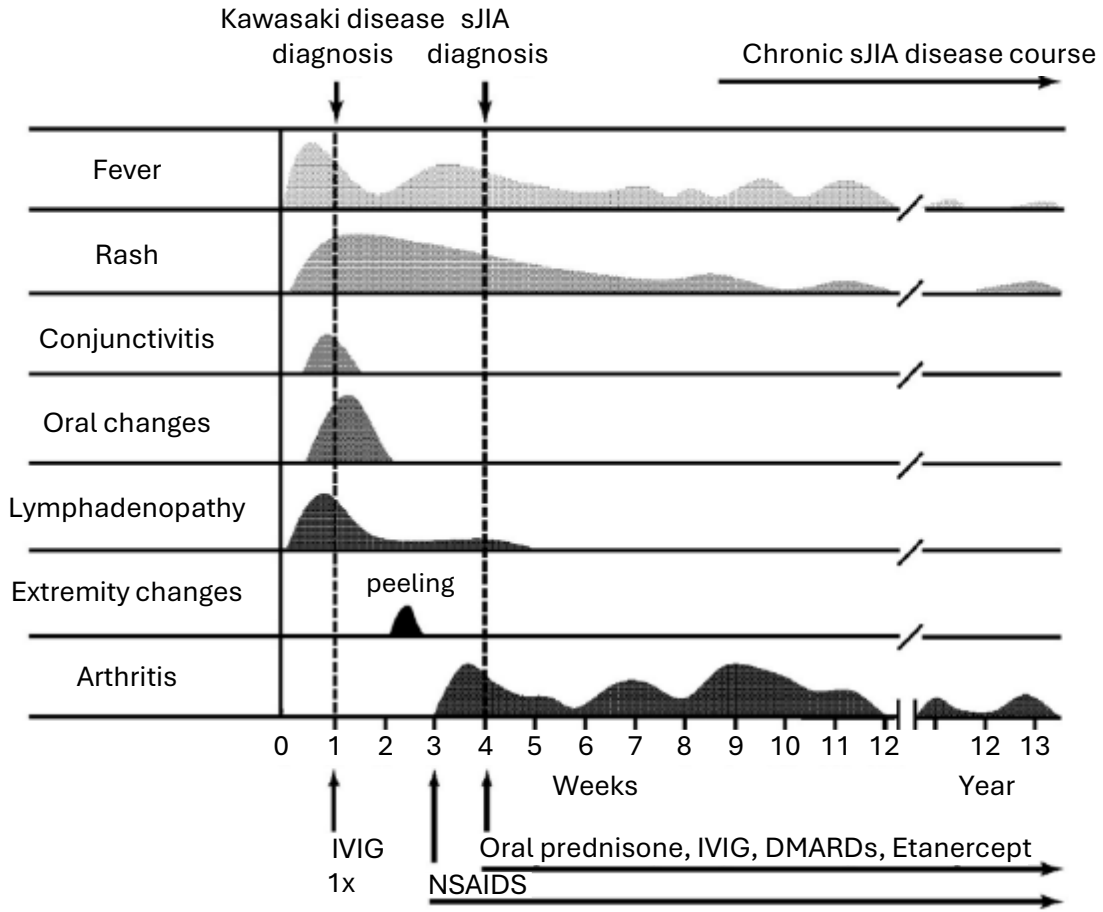
- Fever
- Rash
- Lymphadenopathy
- Arthritis
- ↑CRP, complication of MAS

There is no reliable biomarker for the diagnosis of sJIA; therefore, it can be challenging to differentiate sJIA from other inflammatory diseases[3]

CRP, c-reactive protein; MAS, macrophage activation syndrome; sJIA, systemic juvenile idiopathic arthritis.

1. Scuccimarri R. Pediatr Clin North Am 2012;59:425-45;
2. Japan Society of Kawasaki Disease. (n.d.). Case photos. Available at: https://www.jskd.jp/;
3. Dogra S, et al. Indian J Pediatr 2013;80:783-5;
4. Lee J, et al. Children (Basel) 2024;11:755.

A case of sJIA misdiagnosed as Kawasaki disease



Early diagnosis of sJIA is necessary to avoid developing MAS

DMARDs, disease modifying anti-rheumatic drugs; IVIG, intravenous immunoglobulin; MAS, macrophage activation syndrome; NSAIDs, non-steroidal anti-inflammatory drugs; sJIA, systemic juvenile idiopathic arthritis.

Go E, et al. Front Pediatr 2021;9:665815.

MAS in Still's disease is challenging to diagnose

Secondary forms of HLH are challenging to diagnose because of the clinical overlap with other conditions:[1,2]

- Infection[3-4]
- Sepsis[2,4]
- Rheumatoid disorders[2]
- Malignancy[2,4]
- Liver failure[1,4]
- Other immune disorders[1]

Diagnosis of MAS lies at the intersection of multiple specialties, including haematology, rheumatology, infectious diseases and critical care[2]

Other conditions with hyperinflammation that should be investigated to rule out MAS:[5]

Infection
Blood cultures, viral PCRs, etc.

Malignancy[a]
Bone marrow aspirate/biopsy, pan-imaging, etc.

Other
Genetic screening for inborn errors of immunity and heritable metabolic or rheumatic disorders

[a]Testing for malignancy should be performed prior to treatment with glucocorticoids, when possible, because glucocorticoids may obscure pathological diagnosis and/or staging of malignancy.[5]

HLH, hemophagocytic lymphohistiocytosis; MAS, macrophage activating syndrome; PCR, polymerase chain reaction.

1. Bseiso O, et al. Cureus 2022;14:e33175;
2. Carter SJ, et al. Rheumatology (Oxford) 2019;58:5-17;
3. Ishii E. Front Pediatr 2016;4:47;
4. Si SJ, et al. J Clin Immunol 2021;41:1213-8;
5. Shakoory B, et al. Arthritis Rheumatol 2023;75:1714-32.

Classification/diagnostic criteria for MAS/HLH

MAS has no single distinguishing characteristic and can be difficult to diagnose[1]

Diagnostic scores and classification criteria are available:

Classification criteria	HLH-type	Description
HLH-2004 criteria[2]	pHLH	Diagnostic guidelines primarily for pHLH
HScore[3]	sHLH	Weighted criteria to assess a patient's probability of having sHLH
MH score[4] and MS score[5]	MAS in sJIA/pHLH	A score to assist the identification of MAS in the setting of active sJIA and pHLH
EULAR/ACR/PRINTO[6]	MAS in sJIA	Classification criteria for MAS complicating sJIA

ACR, American College of Rheumatology; EULAR, European Alliance of Associations for Rheumatology; MAS, macrophage activation syndrome; pHLH, primary hemophagocytic lymphohistiocytosis; PRINTO, Paediatric Rheumatology International Trials Organisation; sHLH, secondary hemophagocytic lymphohistiocytosis; sJIA, systemic juvenile idiopathic arthritis.

1. Shakoory B, et al. Arthritis Rheumatol 2023;75:1714-32;
2. Henter JI, et al. Pediatr Blood Cancer 2007;48:124-31;
3. Fardet L, et al. Arthritis Rheumatol 2014;66:2613-20;
4. Minoia F, et al. J Pediatr 2017;189:72-8;
5. Minoia F, et al. Ann Rheum Dis 2019;78:1357-62;
6. Ravelli A, et al. Arthritis Rheumatol 2016;68:566-76.

EULAR/ACR/PRINTO classification criteria for MAS complicating sJIA

A febrile patient with known or suspected sJIA is classified as having MAS if the patient met:[1]

Feature	Criteria
Fever	Presence of fever
Hyperferritinemia	Ferritin >684 ng/mL
And any two of:	
Bone marrow involvement[a]	Platelets ≤181 × 10^9/L
AST	>48 U/L
Triglycerides	>156 mg/dL
Fibrinogen	≤360 mg/dL

[a]Leukopenia, anemia, and thrombocytopenia[2].

ACR, American College of Rheumatology; AST, aspartate aminotransferase;
EULAR, European Alliance of Associations for Rheumatology; MAS, macrophage activation syndrome;
PRINTO, Paediatric Rheumatology International Trials Organisation; sJIA, systemic juvenile idiopathic arthritis.

1. Ravelli A, et al. Ann Rheum Dis 2016;68:566-76;
2. Ravelli A. Curr Opin Rheumatol 2002;14:548-52.

Diagnosing MAS: MS score

The MS score had a strong capacity to discriminate MAS from active sJIA without evidence of MAS

Variables included:	β-coefficient
CNS involvement	2.44
Hemorrhagic manifestations	1.54
Active arthritis	−1.30
Platelet count ($\times 10^9$/L)	−0.003
Lactic dehydrogenase (U/L)	0.001
Fibrinogen (mg/dL)	−0.004
Ferritin (ng/mL)	0.0001

CNS, central nervous system; MAS, macrophage activating syndrome; MS, MAS/sJIA; sJIA, systemic juvenile idiopathic arthritis.

Minoia F, et al. Ann Rheum Dis 2019;78:1357-62.

Consider immunomodulatory therapy while diagnostic testing is ongoing

EULAR/ACR points to consider for treating HLH/MAS:

Consider initiating immunomodulatory treatment while diagnostic testing is ongoing in patients with probable HLH/MAS who have persistent, severe, or worsening inflammation or organ dysfunction

Choice of initial immunomodulatory treatment, such as glucocorticoids, requires balancing the risk of rapid HLH/MAS progression with the potential for obscuring worsening active infection or malignancy diagnosis and/or staging

Initial empiric immunomodulatory therapy could include:

- Glucocorticoids
- IL-1 receptor antagonist
- IVIg

Antimicrobial and antiviral therapies, and treatment of any underlying triggers or disorders should be administered in addition to immunomodulatory treatment and supportive care

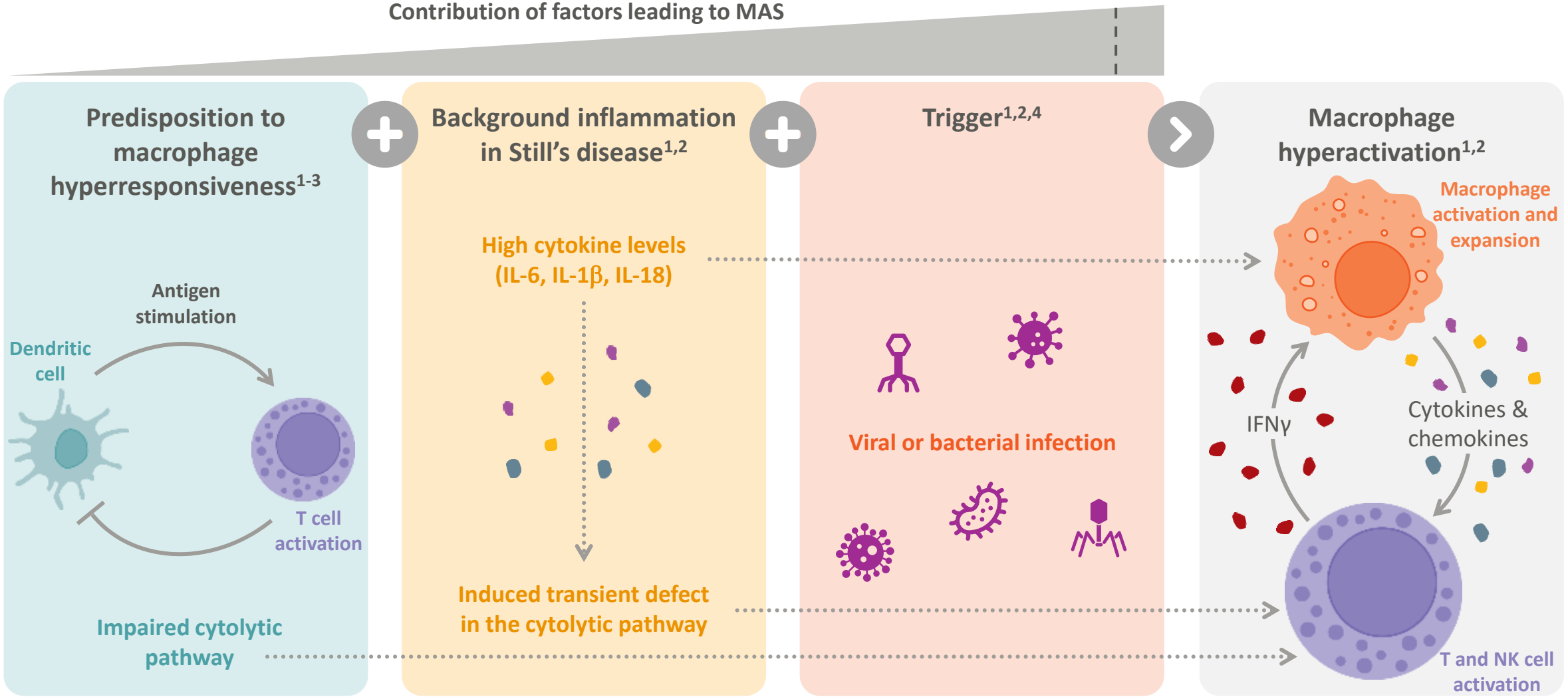
If prolonged immunomodulatory regimens are anticipated, antimicrobial and/or antiviral prophylaxis should be considered in consultation with an infectious disease expert

ACR, American College of Rheumatology; EULAR, European Alliance of Associations for Rheumatology; HLH, hemophagocytic lymphohistiocytosis; IL, interleukin; IVIg, intravenous immunoglobulin; MAS, macrophage activating syndrome.

Shakoory B, et al. Arthritis Rheumatol 2023;82:1271-85.

Threshold model in MAS

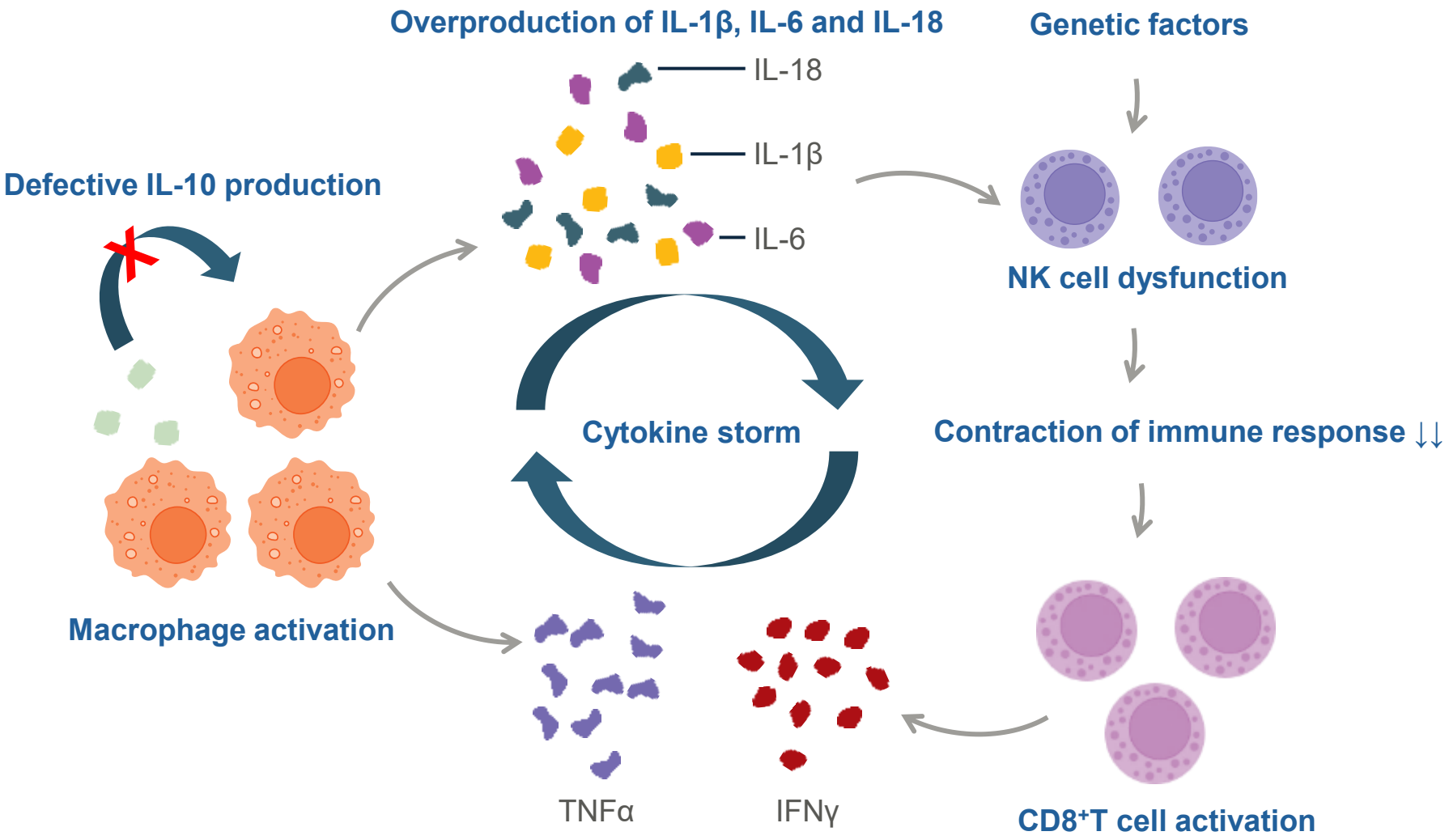
Contribution of factors leading to MAS



IFN, interferon; IL, interleukin; MAS, macrophage activation syndrome; NK, natural killer.

Figure adapted from Strippoli R, et al. J Rheumatol 2013;40:761-7 and Grom AA, et al. Nat Rev Rheumatol 2016;12:259-68.
1. Strippoli R, et al. J Rheumatol 2013;40:761-7; 2. Grom AA, et al. Nat Rev Rheumatol 2016;12:259-68;
3. Jordan MB. Immunol Rev 2024;322:339-50; 4. Shakoory B, et al. Ann Rheum Dis 2023;82:1271-85.

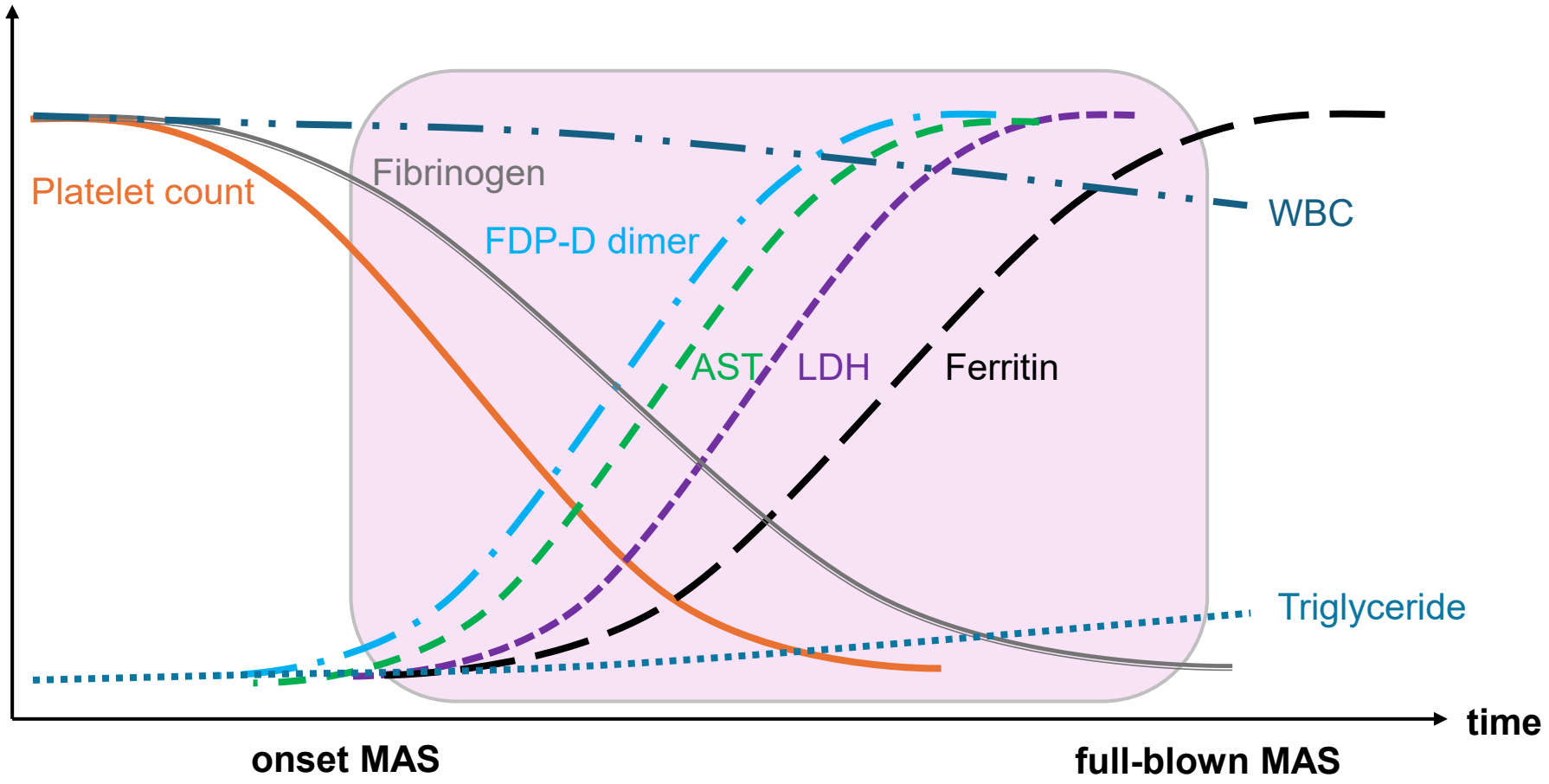
Cytokine storm in MAS



IFN, interferon; IL, interleukin; MAS, macrophage activation syndrome; NK, natural killer; TNF, tumour necrosis factor.

Figure adapted from Shimizu M. Immunol Med 2021;44:237-45.

Dynamics of laboratory parameters in MAS

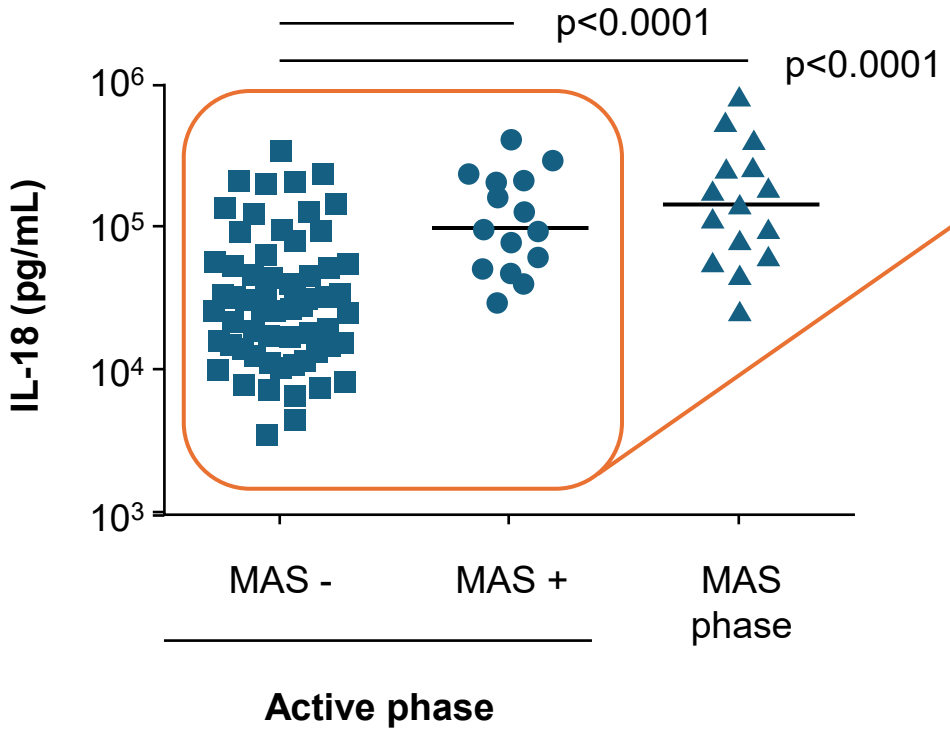


AST, aspartate aminotransferase; FDP, fibrin/fibrinogen degradation product; LDH, lactate dehydrogenase; MAS, macrophage activation syndrome; WBC, white blood cell.

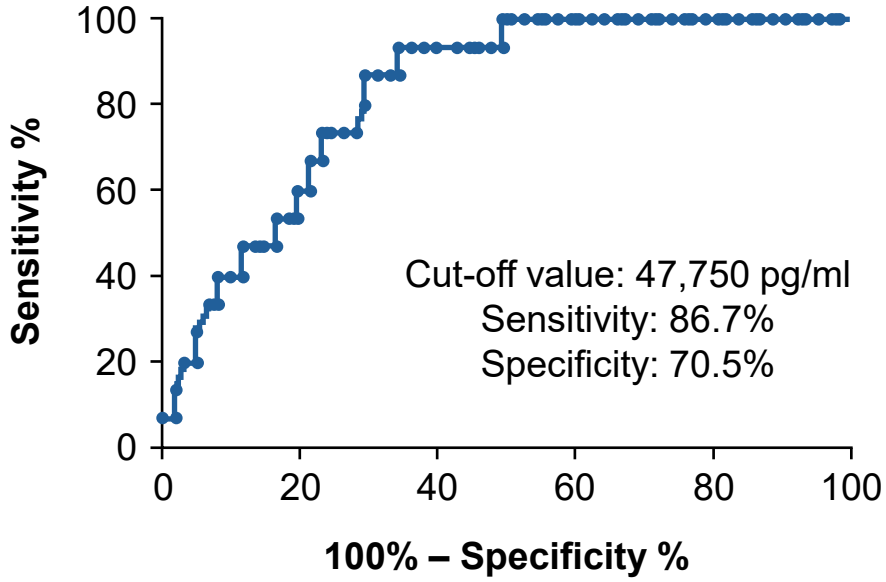
Kaneko S, et al. Clin Immunol 2023;248:109270.

Practical challenges in diagnosis: limited access to specialised laboratory tests

Serum IL-18 can predict the development of MAS*



IL-18 was higher in patients with active disease who later developed MAS (MAS+) than in those who did not (MAS-)



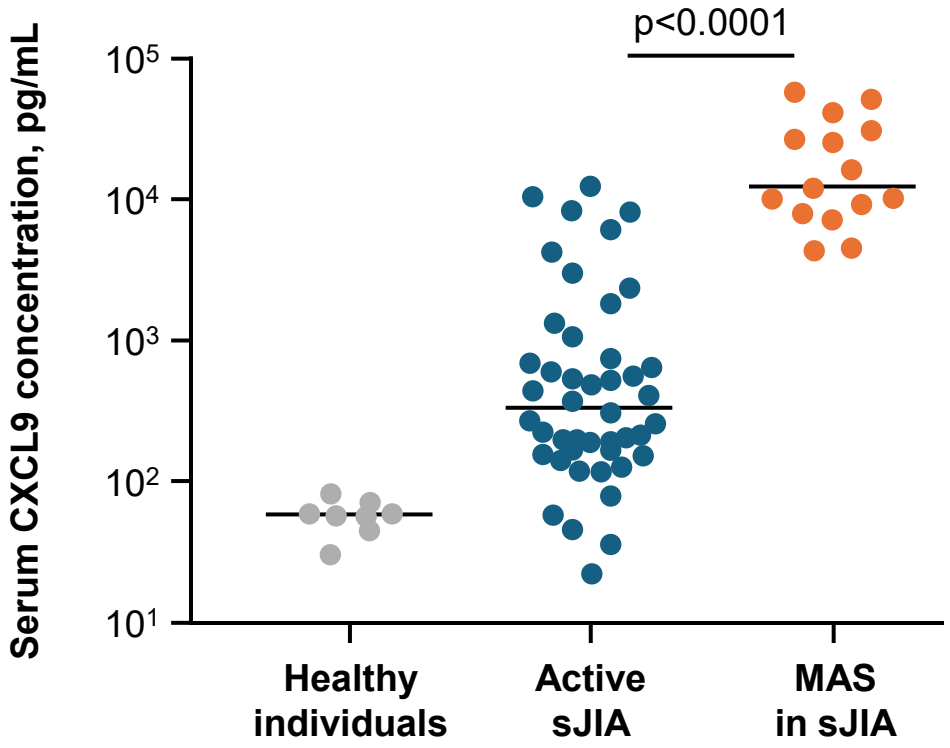
*In patients with sJIA with active disease who later developed MAS (MAS+) versus those who did not (MAS-).

IL, interleukin; MAS, macrophage activation syndrome; sJIA, systemic juvenile idiopathic arthritis.

Shimizu M et al. Clin Immunol 2015;160:277-81.

Practical challenges in diagnosis: limited access to specialised laboratory tests

CXCL9 levels may be useful in evaluating MAS disease activity[1,2]



- CXCL9 levels were elevated in MAS compared with active sJIA flares[1]
- Elevated CXCL9 reflects elevated IFNγ activity[2]

Bars represent median values.[1]

CXCL9, chemokine C-X-C motif ligand 9; IFNγ, interferon gamma; MAS, macrophage activation syndrome; sJIA, systemic juvenile idiopathic arthritis.

1. Mizuta M, et al. Cytokine 2019;119:182-7;
2. De Benedetti F, et al. Nat Rev Rheumatol 2021;17:678-91.

Practical challenges in diagnosis: limited access to specialised laboratory tests

The accuracy of serum biomarkers for the diagnosis of MAS*

Biomarkers	Cut-off values	Area under the ROC curve values
Neopterin	19.5	0.9465
CXCL9	3130	0.9333
sTNFR-II/I	3.796	0.9395
Ferritin	2560	0.8671
IL-18	69250	0.8895

*In patients with sJIA.

IL, interleukin; MAS, macrophage activation syndrome; ROC receiver operating characteristic; sJIA, systemic juvenile idiopathic arthritis; sTNFR, soluble tumour necrosis factor receptor.

Takakura M, et al. Clin Immunol 2019:208:108252.

Practical challenges in diagnosis: biologics modify clinical and laboratory findings

A systematic literature review identified patients with sJIA who developed MAS while being treated with biologics[1,*]

Some tocilizumab-treated patients who developed MAS were not classified as having MAS according to 2016 MAS classification criteria:

	Patients with **definite/probable MAS** (n=30)	Patients with **possible MAS** (n=5)
		
According to the 2016 MAS classification	MAS: 17 patients (56.7%)	MASS: 2 patients (40.0%)
Reasons for not meeting the 2016 MAS classification:	Afebrile: 7 patients Insufficient ferritin elevation: 6 patients	Afebrile: 1 patient Insufficient ferritin elevation: 2 patients

*Data for only Tocilizumab is shown. Tocilizumab is approved in Japan for the treatment of rheumatoid arthritis, polyarticular-course juvenile idiopathic arthritis, and sJIA.[2]

MAS, macrophage activation syndrome; sJIA, systemic juvenile idiopathic arthritis.

1. Schulert GS, et al. Arthritis Care Res 2018;70:409-19;
2. Fierce Biotech. ActemraÂ®, a Humanized Anti-Human IL-6 Receptor Monoclonal Antibody Obtained Approval for Indications of Rheumatoid Arthritis. 16 April 2008. Available at: https://www.fiercebiotech.com/biotech/actemra%C3%A2%C2%AE-a-humanized-anti-human-il-6-receptor-monoclonal-antibody-obtained-approval-for. Accessed June 2025.

Patients and physicians' perspectives on the diagnosis journey

Diagnosis is often delayed

" ⋯ If there was more awareness that if someone has a fever and there is no apparent cause and there are sepsis symptoms it could be HLH"
sHLH patient

"Difficulty is if the patient visits other specialists, who may treat it as refractory infection or severe infection, so the treatment will be delayed"
Haematologist

"There is no one test that is a marker for HLH, it is a combination of tests. That's the frustrating part, there is no one single test that you can do"
pHLH physician

HLH, hemophagocytic lymphohistiocytosis; sHLH, secondary hemophagocytic lymphohistiocytosis.

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

Conclusions

MAS is an under-recognised but life-threatening condition

Early diagnosis remains the biggest challenge due to symptom overlap with other conditions and lack of definitive tests

Leveraging classification criteria and potential biomarkers, such as IL-18 and CXCL9, is needed to improve management of MAS in Still's disease

IL, interleukin; CXCL9, chemokine C-X-C motif ligand 9; MAS, macrophage activation syndrome.

Future Management Strategies – A Case Study

Fabrizio De Benedetti

Ospedale Pediatrico Bambino Gesù,
Rome, Italy

August 2025 I NP-43721

Case study: Roberta, 13 years old

	DAY 1
	Persistent fever (2 weeks) Erythematous rash Arthralgia, arthritis (ankles, wrists)
WBC, x10^9/L	17.42
PLT, x10^9/L	349
Ferritin, ng/mL	890
CRP, mg/dL	25.8
Fibrinogen, mg/dL	680
d-dimers, ng/mL	>20
AST, U/L	37
LDH, U/L	529

Fever + rash + arthritis

(ILAR criteria for sJIA[1])

(Yamaguchi's criteria for AOSD[2])

Still's disease

AOSD, adult-onset Still's disease; AST, aspartate aminotransferase; CD, cluster of differentiation; CRP, C-reactive protein; CXCL9, chemokine (C-X-C motif) ligand 9; HLA-DR, human leukocyte antigen-DR isotype; IL-18, interleukin 18; ILAR, International League of Associations for Rheumatology; LDH, lactate dehydrogenase; MAS, macrophage activation syndrome; OPBG, Ospedale Pediatrico Bambino Gesù; PLT, platelet; sJIA, systemic juvenile idiopathic arthritis; WBC, white blood count.

1. Petty RE, et al. J Rheumatol 2004;31:390-2;
2. Yamaguchi M, et al. J Rheumatol 1992;19:424-30;
3. Ravelli A, et al. Arthritis Rheumatol 2016;68:566-76.

Case study: Roberta, 13 years old

	DAY 1
	Persistent fever (2 weeks) Erythematous rash Arthralgia, arthritis (ankles, wrists)
WBC, $x10^9$/L	17.42
PLT, $x10^9$/L	349
Ferritin, ng/mL	890
CRP, mg/dL	25.8
Fibrinogen, mg/dL	680
d-dimers, ng/mL	>20
AST, U/L	37
LDH, U/L	529
CXCL9, pg/mL*	**2,380**
IL-18, pg/mL*	**89,350**
$CD38^{pos}/HLADR^{pos}/CD8^{+}T$*	**6.8%**

Fever + rash + arthritis
(ILAR criteria for sJIA[1])
(Yamaguchi's criteria for AOSD[2])

+

Macrophage Activation Syndrome
(EULAR/ACR/PRINTO criteria for MAS[3])

Still's disease + MAS

*Normal values at OPBG
- CXCL9 <300 pg/ml
- IL-18 <800 pg/ml
- $CD38^{pos}/HLADR^{pos}/CD8^{+}T$ <10.6%

AOSD, adult-onset Still's disease; AST, aspartate aminotransferase; CD, cluster of differentiation; CRP, C-reactive protein; CXCL9, chemokine (C-X-C motif) ligand 9; HLA-DR, human leukocyte antigen-DR isotoype; IL-18, interleukin 18; ILAR, International League of Associations for Rheumatology; LDH, lactate dehydrogenase; MAS, macrophage activation syndrome; OPBG, Ospedale Pediatrico Bambino Gesù; PLT, platelet; sJIA, systemic juvenile idiopathic arthritis; WBC, white blood count.

1. Petty RE, et al. J Rheumatol 2004;31:390-2;
2. Yamaguchi M, et al. J Rheumatol 1992;19:424-30;
3. Ravelli A, et al. Arthritis Rheumatol 2016;68:566-76.

Case study: Roberta, 13 years old

	DAY 1	→ DAY 7
	Persistent fever (2 weeks) Erythematous rash Arthralgia, arthritis (ankles, wrists)	Symptoms unchanged + Splenomegaly
WBC, $x10^9$/L	17.42	**8.87**
PLT, $x10^9$/L	349	**180**
Ferritin, ng/mL	890	**3800**
CRP, mg/dL	25.8	26.2
Fibrinogen, mg/dL	680	500
d-dimers, ng/mL	>20	**>20**
AST, U/L	37	**88**
LDH, U/L	529	**1,623**
CXCL9, pg/mL*	**2,380**	**18,980**
IL-18, pg/mL*	**89,350**	**181,000**
$CD38^{pos}/HLADR^{pos}/CD8^{+}T$*	**6.8%**	**21.9%**

Fever + rash + arthritis
(ILAR criteria for sJIA[1])
(Yamaguchi's criteria for AOSD[2])

+

Macrophage Activation Syndrome
(EULAR/ACR/PRINTO criteria for MAS[3])

Still's disease + MAS

*Normal values at OPBG
- CXCL9 <300 pg/ml
- IL-18 <800 pg/ml
- $CD38^{pos}/HLADR^{pos}/CD8^{+}T$ <10.6%

AOSD, adult-onset Still's disease; AST, aspartate aminotransferase; CD, cluster of differentiation; CRP, C-reactive protein; CXCL9, chemokine (C-X-C motif) ligand 9; HLA-DR, human leukocyte antigen-DR isotype; IL-18, interleukin 18; ILAR, International League of Associations for Rheumatology; LDH, lactate dehydrogenase; MAS, macrophage activation syndrome; OPBG, Ospedale Pediatrico Bambino Gesù; PLT, platelet; sJIA, systemic juvenile idiopathic arthritis; WBC, white blood count.

1. Petty RE, et al. J Rheumatol 2004;31:390-2;
2. Yamaguchi M, et al. J Rheumatol 1992;19:424-30;
3. Ravelli A, et al. Arthritis Rheumatol 2016;68:566-76.

EULAR/ACR/PRINTO classification criteria for MAS complicating sJIA

MAS in sJIA (EULAR/ACR/PRINTO) classification criteria[1]

Both:

- Fever
- Ferritin >684 ng/mL (hyperferritinemia)

And any two of:

- Platelets ≤181 × 10^9/L (bone marrow involvement*)
- AST >48 U/L
- Triglycerides >156 mg/dL
- Fibrinogen ≤360 mg/dL

*Leukopenia, neutropenia, anaemia and thrombocytopenia.
ACR, American College of Rheumatology; AST, aspartate aminotransferase; CNS, central nervous system; EULAR, European Alliance of Associations for Rheumatology; HLH, haemophagocytic lymphohistiocytosis; MAS, macrophage activation syndrome; PRINTO, Paediatric Rheumatology International Trials Organisation; sJIA, systemic juvenile idiopathic arthritis.

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Additional points to consider for early diagnosis and management of HLH/MAS[2]

Recognisable clinical pattern:

- Cytopenias
- Activation of coagulation
- Hepatic dysfunction
- Splenomegaly
- CNS dysfunction

Laboratory diagnostics to screen for:

- Perform serial ferritin testing
- Perform routine laboratory evaluations
- Specialised biomarkers of hyper-inflammation

Inappropriately low or declining haemoglobin, platelet counts or white blood cells[2]

*Leukopenia, neutropenia, anaemia and thrombocytopenia.
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Case study: Roberta, 13 years old

	DAY 1	→ DAY 7
	Persistent fever (2 weeks) Erythematous rash Arthralgia, arthritis (ankles, wrists)	Symptoms unchanged + Splenomegaly
WBC, $x10^9$/L	17.42	**8.87**
PLT, $x10^9$/L	349	**180**
Ferritin, ng/mL	890	**3800**
CRP, mg/dL	25.8	26.2
Fibrinogen, mg/dL	680	500
d-dimers, ng/mL	>20	>20
AST, U/L	37	**88**
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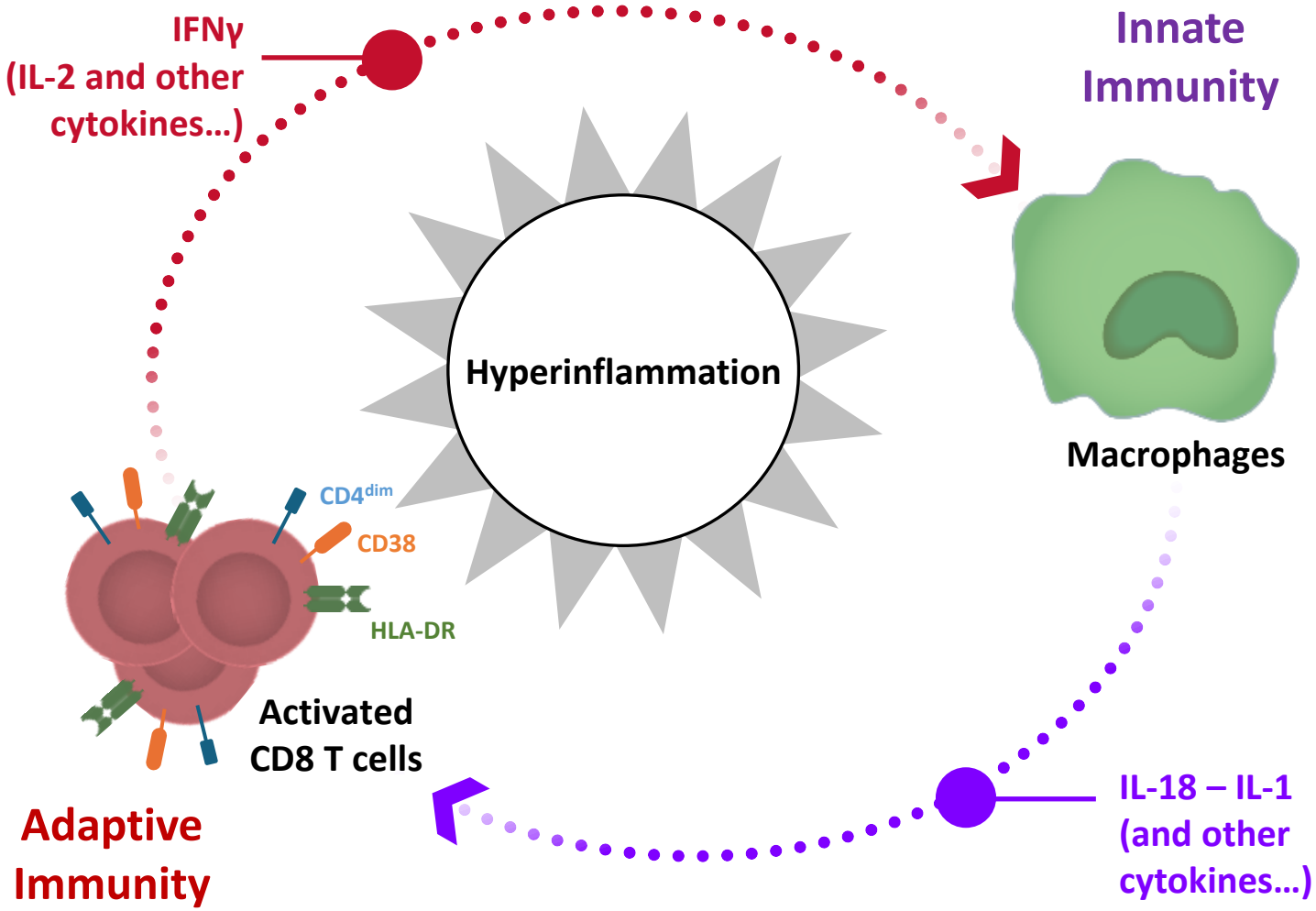
The vicious loop of hyperinflammation[1-3]

Specialised biomarkers in the diagnosis and monitoring of MAS

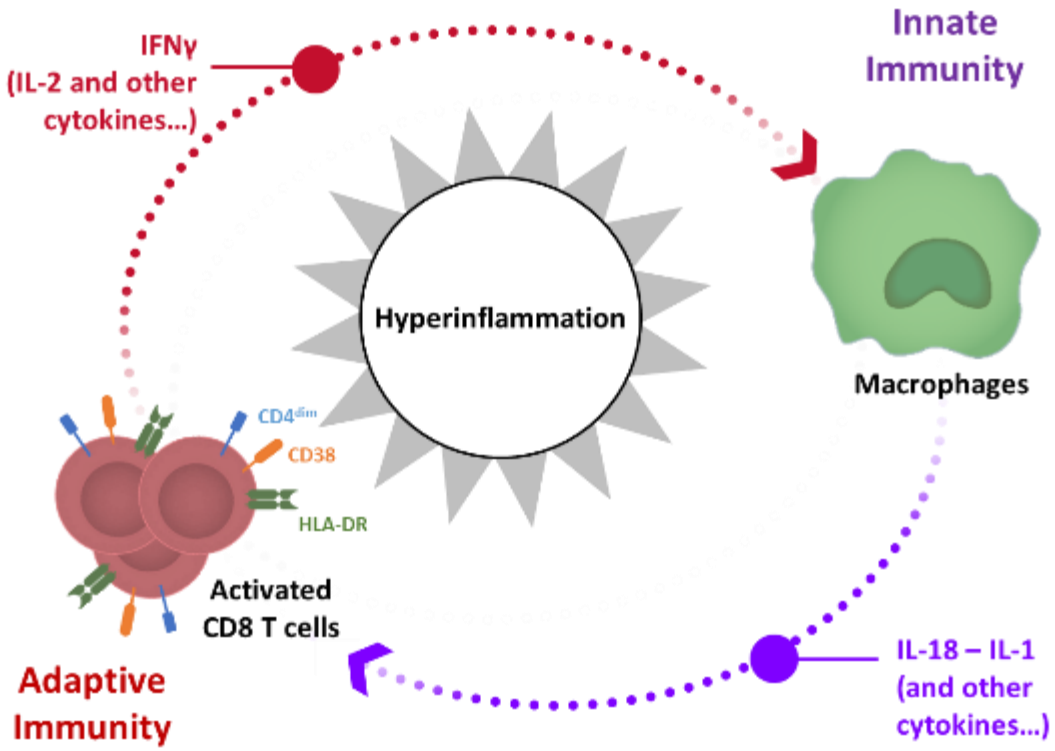


CD, cluster of differentiation; HLA-DR, human leukocyte antigen – DR isotope; IFN, interferon; IL, interleukin.

1. De Matteis A, et al. Blood 2022;140:262-73;
2. Jordan MB. Blood 2022;140:167-8;
3. De Benedetti F, et al. Nat Rev Rheumatol 2021;17:678-91.

The vicious loop of hyperinflammation[1-3]

Specialised biomarkers in the diagnosis and monitoring of MAS



Specialised biomarkers	HLH/MAS pathway
IL-18 levels[4]	Inflammasomes
CXCL9 levels[5]	IFNγ activity
Neopterin[6]	IFNγ activity
sCD25 levels[7]	T-cell activation
CD38+ HLADR+ CD8+ T lymphocytes[2] $CD4^{dim}$ CD8+ T lymphocytes[2]	T-cell activation

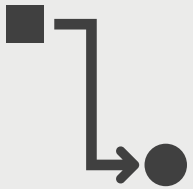
CD, cluster of differentiation; CXCL9, chemokine C-X-C motif ligand 9; HLH, hemophagocytic lymphohistiocytosis; HLA-DR, human leukocyte antigen-DR isotoype; IFNγ, interferon gamma; IL-18, interleukin 18; MAS, macrophage activation syndrome.

1. Shakoory B, et al. Arthritis Rheumatol 2023;75:1714-32; 2. Jordan MB. Blood 2022;140:167-8; 3. De Benedetti F, et al. Nat Rev Rheumatol 2021;17:678-91; 4. Weiss ES, et al. Blood 2018;131(13):1442-55; 5. Bracaglia C, et al. Ann Rheum Dis 2017;76(1):166-72; 6. Information is provided courtesy of Professor De Benedetti and is from his unpublished data; 7. Damoiseaux J. Clin Immunol 2020;218:108515.

Voicing patients' experiences

Patients need…

improved access to specialised laboratory tests
(e.g. IL-18, CXCL9, sCD25, adenosine deaminase 2)



cross-validation between different laboratories

standardised international cut-off values

training on MAS outside academic centres

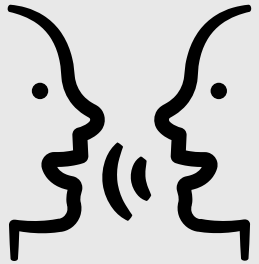
CD, cluster of differentiation; CXCL9, chemokine C-X-C motif ligand 9; IL-18, interleukin 18; MAS, macrophage activation syndrome.

Information based on speaker's own clinical and research experience.

Diagnostic biomarkers of hyperinflammation

Leveraging biomarkers is required to improve patient diagnosis and management: IL-18 and CXCL9 are useful biomarkers for the diagnosis and management of Still's disease and of MAS occurring in the context of Still's disease

Ongoing project supported through a PReS-CARRA Grant:



Speaking the Same Language: International cross-validation of emerging biomarkers for juvenile idiopathic arthritis

PIs: G Schulert & C Kessel, collaborating with C Bracaglia, S Canna, D Cabral, D Dissanayake, R Marsh, B Vastert, C Wouters

CXCL9, chemokine C-X-C motif ligand 9; IL-18, interleukin 18; PI, principal investigator.

Information based on speaker's own clinical and research experience.

Case study: Roberta, 13 years old

	DAY 1 →	DAY 7
	Persistent fever (2 weeks) Erythematous rash Arthralgia, arthritis (ankles, wrists)	Symptoms unchanged + Splenomegaly
WBC, $x10^9$/L	17.42	8.87
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CXCL9, pg/mL*	2,380	18,980
IL-18, pg/mL*	89,350	181,000

Still's disease + MAS

↓

IV mPDN pulses: 30 mg/kg/day (max 1 g) for 3 days
IV mPDN: 3 mg/kg/day → oral PDN
Oral CyA: 5 mg/kg

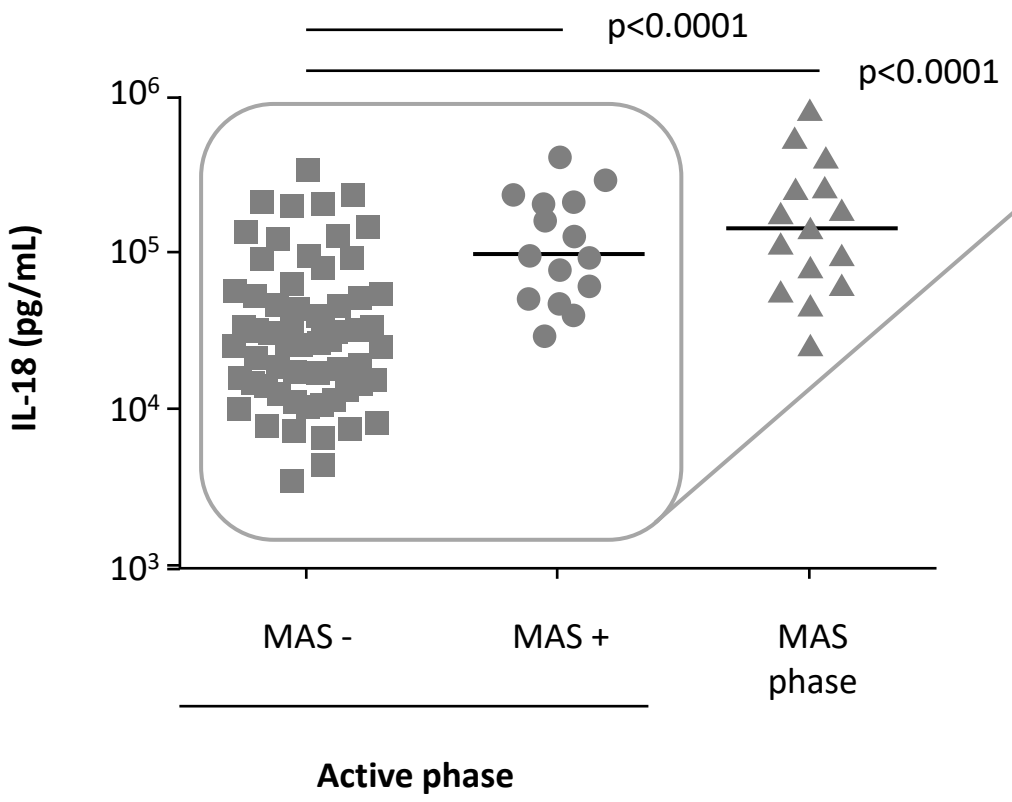
↓

Improvement → remission
Off GCs in 3 months
Off CyA in 6 months

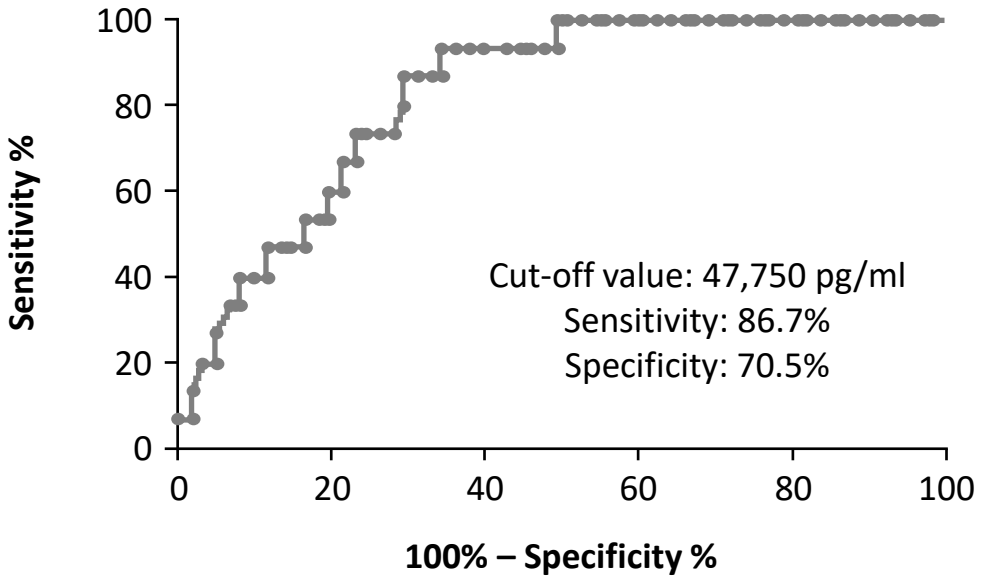
AST, aspartate aminotransferase; CRP, C-reactive protein; CXCL9, chemokine (C-X-C motif) ligand 9; CyA, cyclosporin A; GC, glucocorticoid; IL, interleukin; IV, intravenous; LDH, lactate dehydrogenase; MAS, macrophage activation syndrome; mPDN methylprednisolone; PDN, prednisolone; PLT, platelet; WBC, white blood count.

Predictors of MAS in Still's disease
Serum IL-18 levels predicts development of MAS

Serum IL-18 can predict the development of MAS*



IL-18 was higher in patients with active disease who later developed MAS (MAS+) than in those who did not (MAS-)

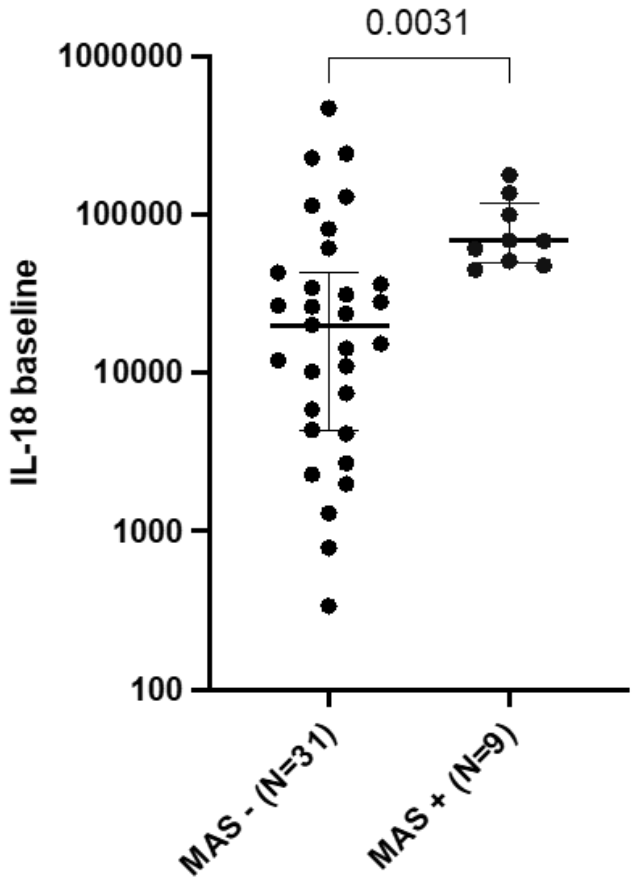


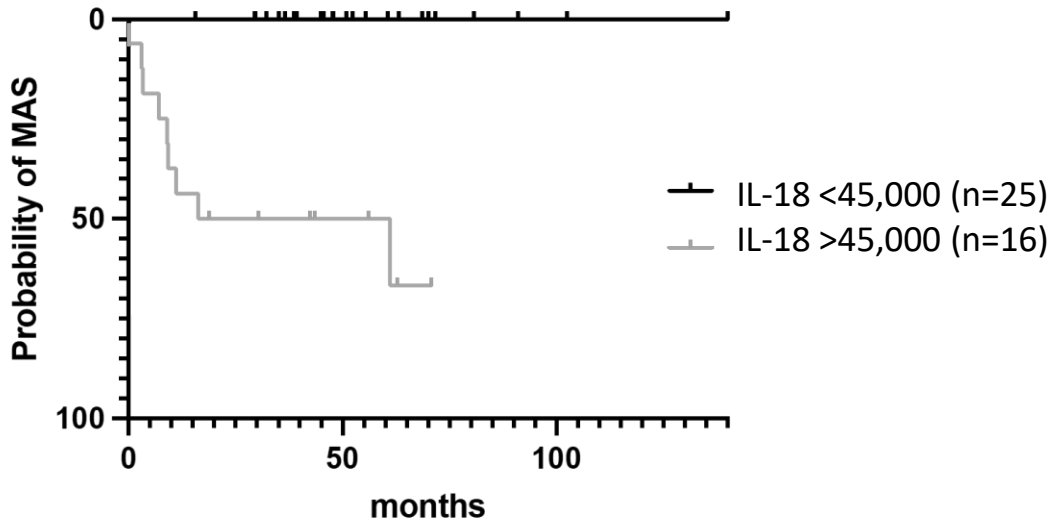
*In patients with sJIA with active disease who later developed MAS (MAS+) versus those who did not (MAS-).
IL, interleukin; MAS, macrophage activation syndrome; sJIA, systemic juvenile idiopathic arthritis.

Shimizu M et al. Clin Immunol 2015;160:277-81.

Predictors of MAS in Still's disease
Serum IL-18 levels predicts development of MAS

IL-18 levels are higher in patients **<u>at onset</u>** who later developed MAS (MAS+) than in those who did not (MAS-)





	Univariate analysis		Multivariate analysis	
Characteristics	OR (CI 95%)	p-value	OR (CI 95%)	p-value
IL-18 at onset (>45,000)	27 (4–556)	0.003	34 (3.3–1,536)	0.01
Splenomegaly	8.6 (1.7–51)	0.01	5 (0.67–90)	0.13
Neutrophils	1.1 (1.006–1.3)	0.05	1.2 (1.02–1.5)	0.05

IL, interleukin; CI, confidence interval; MAS, macrophage activation syndrome; OR odds ratio.

Trevisan M et al. Oral presentation presented at the Internationals Society of Systemic Auto Inflammatory Diseases (ISSAID), 8-10 April 2025, Paris, France.

Case study: Roberta, now 14 years old

	6 months later
	Fever (3 days) Rash Splenomegaly
WBC, x10^9/L	9.48
PLT, x10^9/L	256
Ferritin, ng/mL	2,500
CRP, mg/dL	17.8
Fibrinogen, mg/dL	410
d-dimers, ng/mL	>20
AST, U/L	45
LDH, U/L	602
CXCL9, pg/mL*	5,240
IL-18, pg/mL*	102,000

Flare with MAS

IV mPDN pulses: 30 mg/kg/day
Oral CyA: 5 mg/kg

AST, aspartate aminotransferase; CRP, C-reactive protein; CXCL9, chemokine (C-X-C motif) ligand 9; CyA, cyclosporin A; ICU, intensive care unit; IL, interleukin; IV, intravenous; LDH, lactate dehydrogenase; MAS, macrophage activation syndrome; mPDN methylprednisolone; PDN, prednisolone; PLT, platelet; WBC, white blood count.

Case study: Roberta, now 14 years old

	6 months later →	After 48 hours
	Fever (3 days) Rash Splenomegaly	Rapid worsening Oliguric Hypotensive shock ICU admission - ventilation, inotropes
WBC, $x10^9$/L	9.48	2.85
PLT, $x10^9$/L	256	98
Ferritin, ng/mL	2,500	28,250
CRP, mg/dL	17.8	26.2
Fibrinogen, mg/dL	410	201
d-dimers, ng/mL	>20	>20
AST, U/L	45	325
LDH, U/L	602	4,580
CXCL9, pg/mL*	5,240	29,380
IL-18, pg/mL*	102,000	245,000

Flare with MAS

IV mPDN pulses: 30 mg/kg/day
Oral CyA: 5 mg/kg

mPDN pulses: for a total of 12 pulses
IV CyA: targeting levels at 800 ng/ml
Ultrafiltration with Cytosorb

AST, aspartate aminotransferase; CRP, C-reactive protein; CXCL9, chemokine (C-X-C motif) ligand 9; CyA, cyclosporin A; ICU, intensive care unit; IL, interleukin; IV, intravenous; LDH, lactate dehydrogenase; MAS, macrophage activation syndrome; mPDN methylprednisolone; PDN, prednisolone; PLT, platelet; WBC, white blood count.

Voicing patients' experiences in the context of rapidly progressing sHLH (with or without Still's disease)

"Some patients **progress rapidly, requiring ICU-level care before diagnosis is confirmed**, emphasising the importance of collaboration with ICU unit/rheumatologists/infectious disease specialists"

"Hesitation in starting aggressive therapy due to **fear of over-immunosuppression**"

"Many patients undergo empiric **broad-spectrum antibiotics** before MAS is diagnosed"

"Concerns for the **side-effect of high-dose steroids**"

ICU, intensive care unit; MAS, macrophage activation syndrome; sHLH, secondary hemophagocytic lymphohistiocytosis.

Information based on speaker's own clinical and research experience.

Case study: Roberta, now 14 years old

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IV mPDN pulses: 30 mg/kg/day
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mPDN pulses: for a total of 12 pulses
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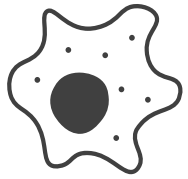
Ultrafiltration with Cytosorb

ICU admission: 21 days
Hospital admission: 69 days
mPDN (high dose < 1 mg/day): 58 days
Hypertension (triple therapy)
Striae rubrae
Vertebral fracture
Depression

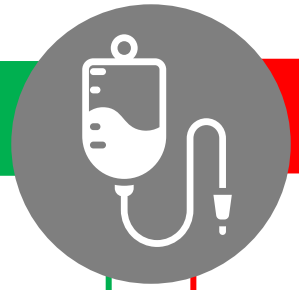
AST, aspartate aminotransferase; CRP, C-reactive protein; CXCL9, chemokine (C-X-C motif) ligand 9; CyA, cyclosporin A; ICU, intensive care unit; IL, interleukin; IV, intravenous; LDH, lactate dehydrogenase; MAS, macrophage activation syndrome; mPDN methylprednisolone; PDN, prednisolone; PLT, platelet; WBC, white blood count.

PROs and CONs of glucocorticoids in MAS/sHLH

PROs



- Highly effective in many patients because of broad anti-inflammatory and immunosuppressive effects[1]



CONs

- Glucocorticoids can be potentially damaging if Still's disease/MAS is misdiagnosed (e.g. malignancies)[2]
- High-dose glucocorticoids can lead to increased infection risk, glucose intolerance, hypertension, systemic osteoporosis with vertebral crash fracture, short stature with inadequate muscle control, muscle atrophy, striae rubra and neuropsychiatric effects[1,2]

MAS, macrophage activation syndrome; sHLH, secondary hemophagocytic lymphohistiocytosis.

1. Oray M, et al. Expert Opin Drug Saf 2016;15:457-65;
2. Information based on speaker's own clinical and research experience.

Need standardised treatment protocols

MAS treatment guidelines on the use of glucocorticoids are vague

Glucocorticoids:*

a) Oral prednisone/prednisolone or IV methylprednisolone	b) Dexamethasone (oral or IV)	c) High-dose IV methylprednisolone
1–2 mg/kg/day	10 mg/m²/day	10–30 mg/kg/day (max 1 g/day) for 1–3 days, followed by a) or b)

*Dosing schedules and substitution with other glucocorticoids and/or other (oral or intravenous) preparations can be based on preference, availability and patient need.
IV, intravenous; MAS, macrophage activation syndrome.

Shakoory B, et al. Arthritis Rheumatol 2023;75:1714-32.

The METAPHOR study: Real-life data on glucocorticoid use in MAS

Among patients with MAS (n=300):[1]

- **14%** received GCs as monotherapy
- **86%** received GCs as a co-medication
- MPN dose ranged from 2-30 mg/kg/day
- high-dose methylprednisolone pulses (10-30 mg/kg/day) was reported in **~60%** of studies

→ High-dose GCs are confirmed as the mainstay of treatment of MAS – although not based on any formal clinical trial

There is a risk of delayed or inadequate response in severe cases, and GC-refractory cases require additional interventions[2]

A systematic review was conducted to assess current treatment in MAS worldwide and to highlight any areas of major heterogeneity of practice.
GC, glucocorticoid; MAS, macrophage activation syndrome.

1. Baldo F, et al. Rheumatology 2025;64:32-44;
2. Information based on speaker's own clinical and research experience. .

Definition of severe MAS patients: The MAS clinical severity score (MCSS)

	MCSS score		
	0	1	2
High dose GCs (prednisone equivalent ≥2 mg/kg) for ≥10 days	NO	YES	
GCs pulses (≥30 mg/kg/day)	NO	<3	≥3
Other drugs (in addition to GCs and IL-1 inhibitor)	NO	YES	
Length of hospital admission (days)	<15	15–30	≥30
Intensive care unit admission	NO	YES	
Death	NO	YES	

Score range	
0-4	Mild MAS
5-8	Severe MAS

GC, glucocorticoid; MAS, macrophage activation syndrome; MCSS, MAS clinical severity score.

De Matteis A, et al. Semin Arthritis Rheum 2025;74:152812.

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Intensive care unit admission	NO	YES	
Death	NO	YES	

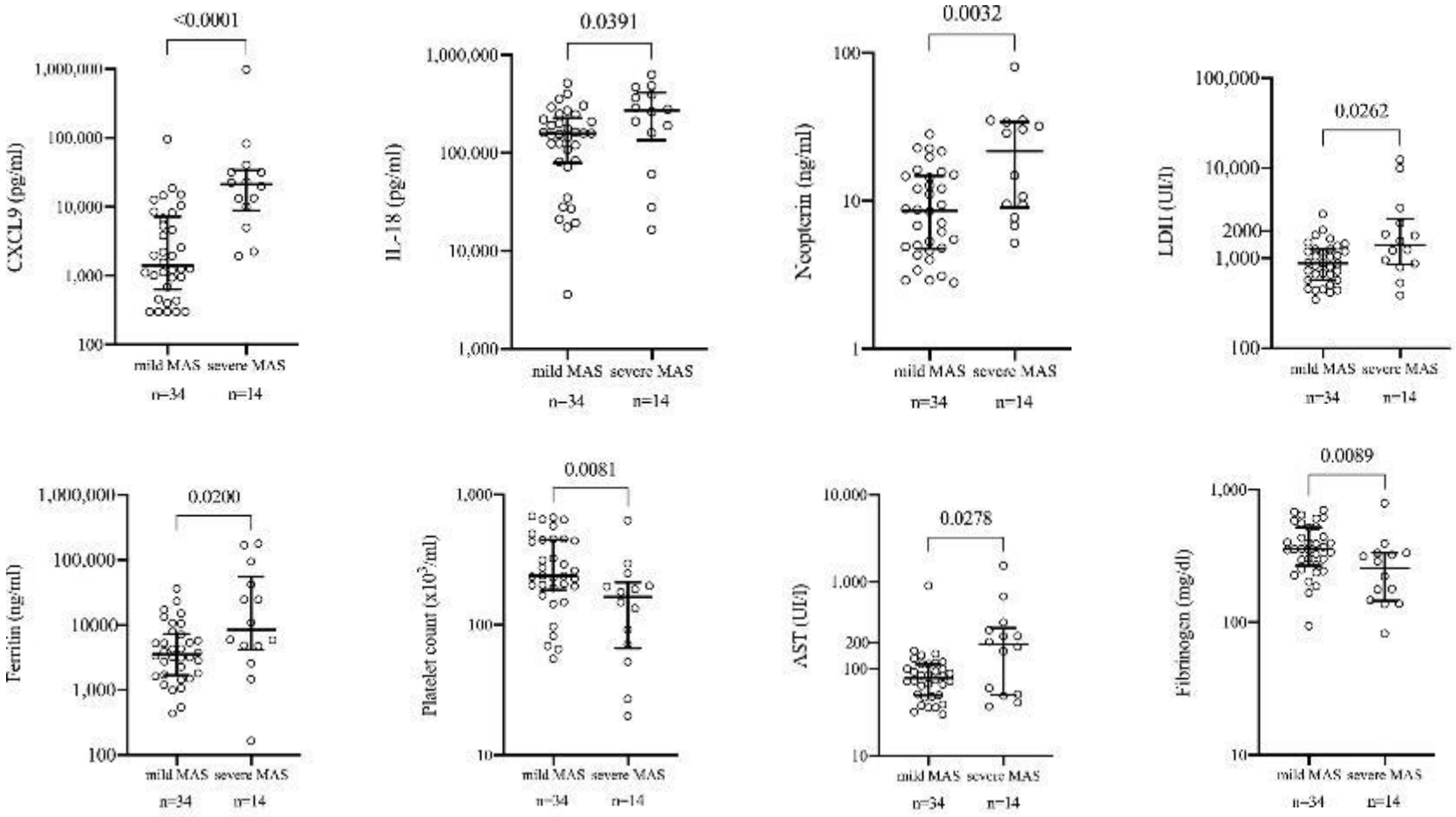
Score range	
0-4	Mild MAS
5-8	Severe MAS

Roberta's score: MCSS= 7

GC, glucocorticoid; MAS, macrophage activation syndrome; MCSS, MAS clinical severity score.

De Matteis A, et al. Semin Arthritis Rheum 2025;74:152812.

Risk stratification:
Identifying severe MAS patients at MAS onset



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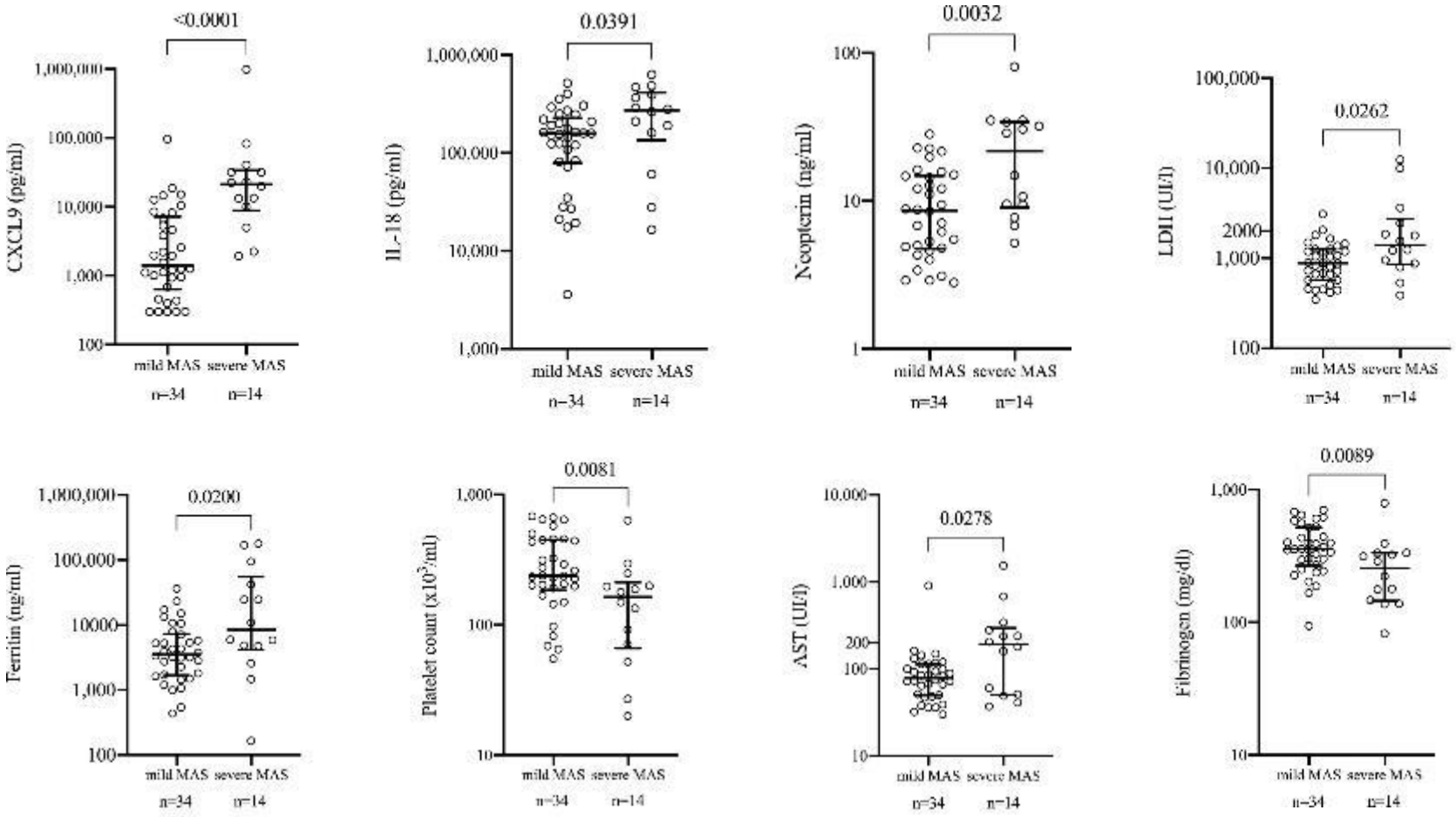


Each parameter alone does not predict MAS severity with clinically relevant reliability (sensitivity 64-86%, specificity 56-92%)

AST, aspartate aminotransferase; CXCL9, chemokine (C-X-C motif) ligand 9; IL, interleukin; LDH, lactate dehydrogenase; MAS, macrophage activation syndrome.

De Matteis A, et al. Semin Arthritis Rheum 2025;74:152812.

Risk stratification:
Identifying severe MAS patients at MAS onset

Multiple combinations were tested to identify a suitable approach to biomarker-driven risk stratification

Prognostic score for severe MAS based on values at disease diagnosis

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

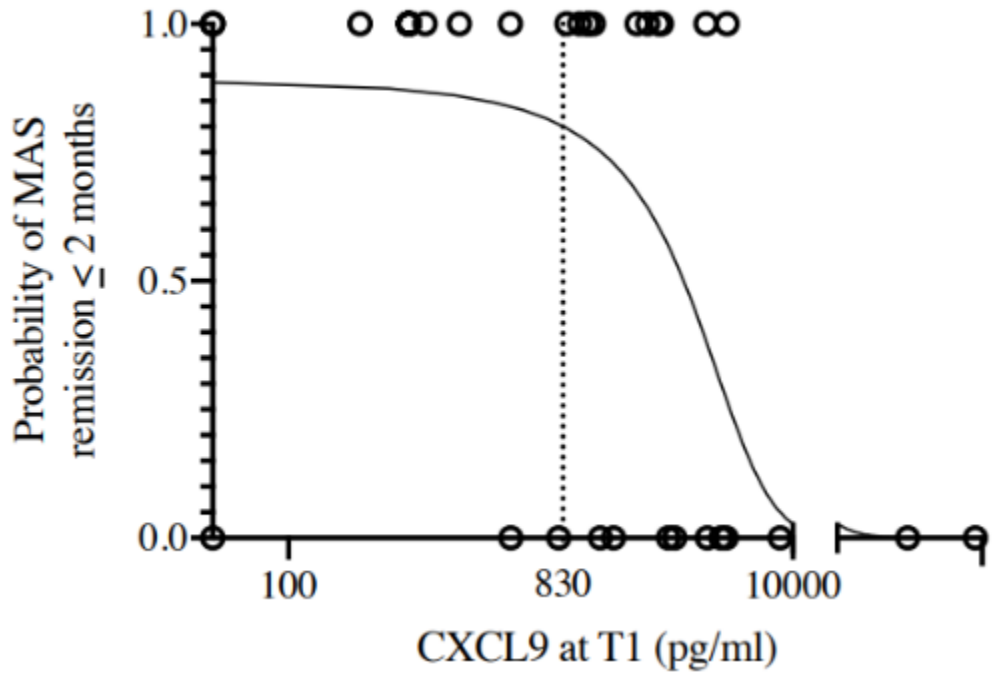
CXCL9, chemokine (C-X-C motif) ligand 9; LDH, lactate dehydrogenase; MAS, macrophage activation syndrome; NPV, negative predictive value; PLT, platelet; PPV, positive predictive value.

De Matteis A, et al. Semin Arthritis Rheum 2025;74:152812.

Risk stratification:
Identifying patients who require treatment intensification

CXCL9 levels at 5-15 days (T1) from treatment initiation predict MAS remission within 2 months

The likelihood of achieving MAS remission within 2 months decreases with increasing levels of CXCL9



CXCL9, chemokine (C-X-C motif) ligand 9; MAS, macrophage activation syndrome; T1, 5-15 days.

De Matteis A, et al. Semin Arthritis Rheum 2025;74:152812.

Risk stratification:
Identifying patients who require treatment intensification

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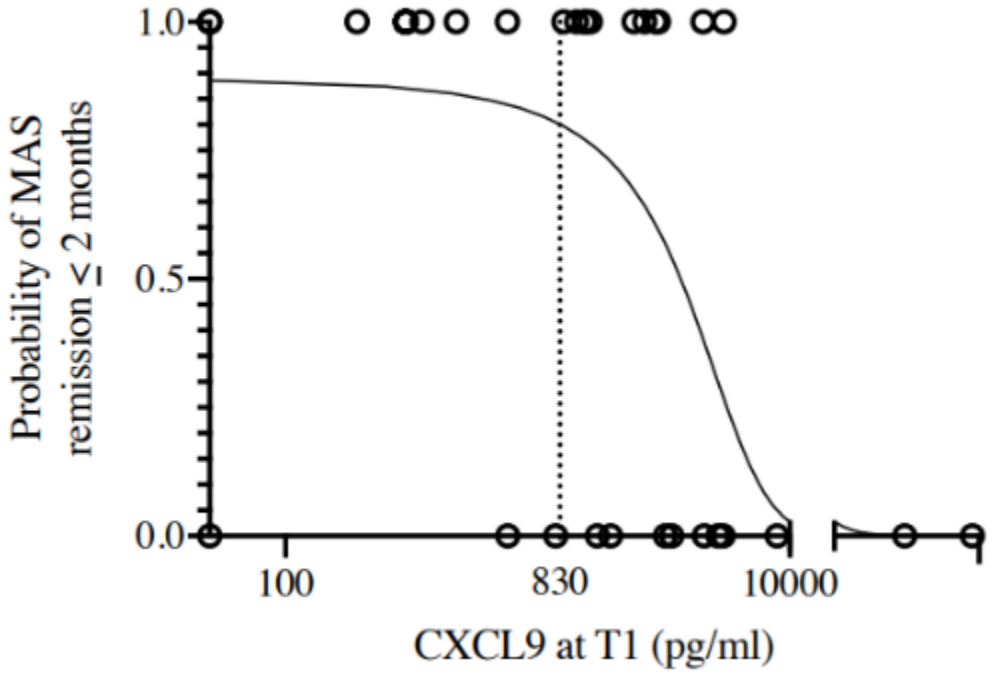
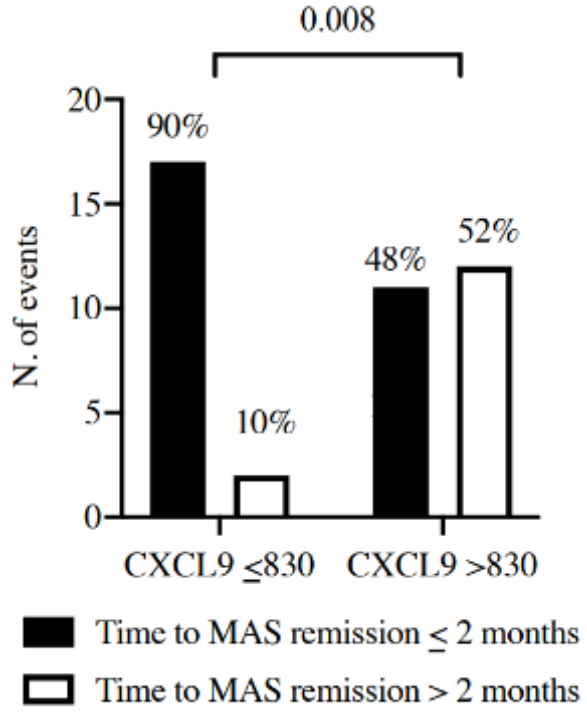


CXCL9 ≤830 pg/ml associated with 9.3-fold greater probability of achieving MAS remission within 2 months



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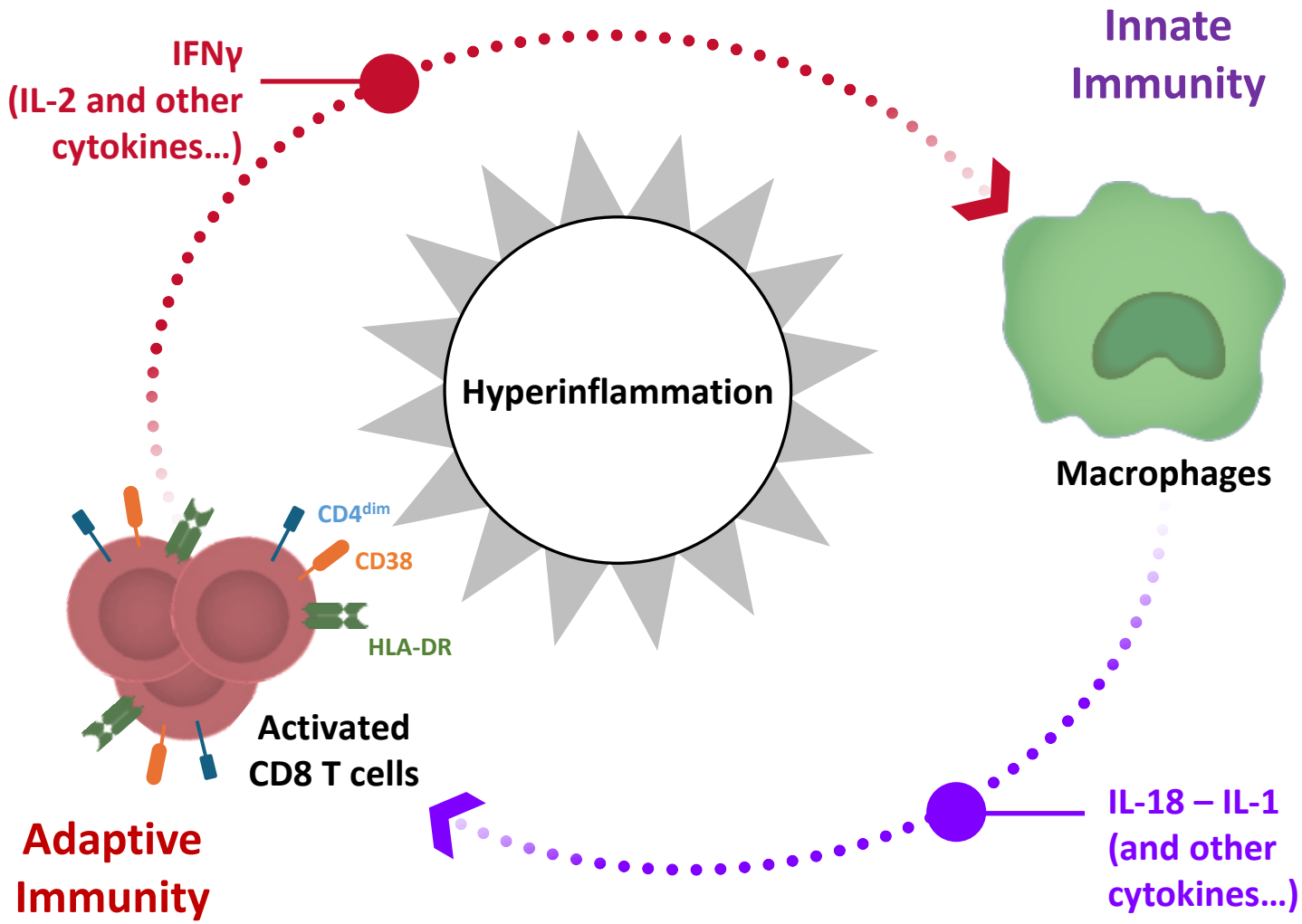
The vicious loop of hyperinflammation[1-3]

Novel therapeutic approaches



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2. Jordan MB. Blood 2022;140:167-8;
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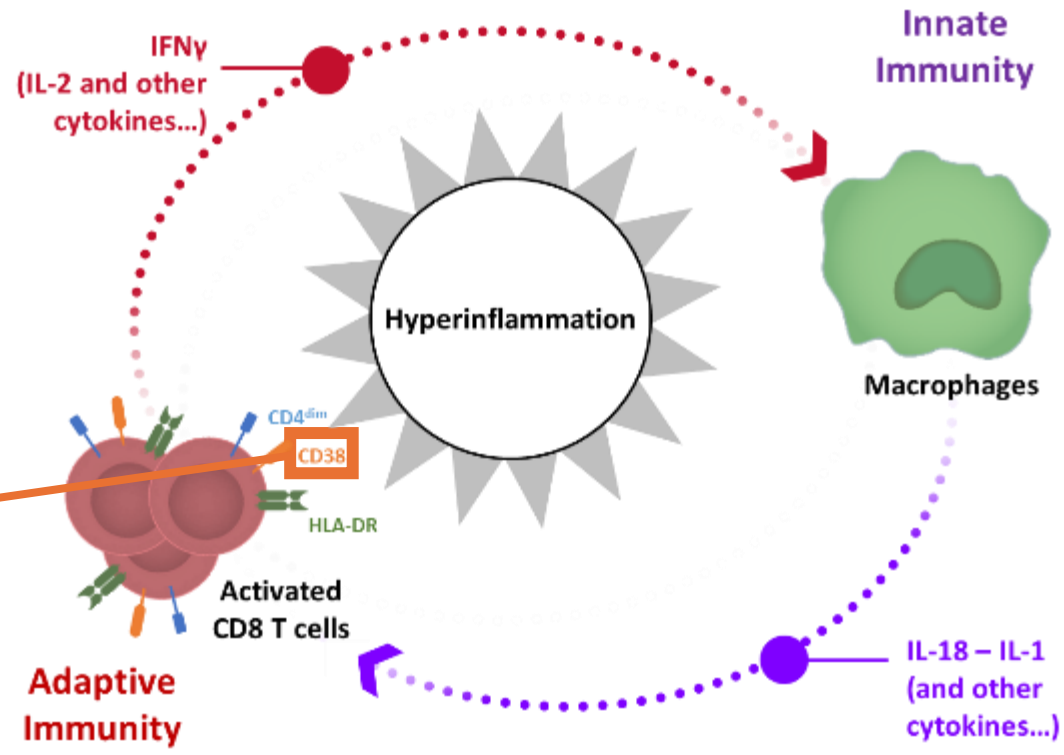
The vicious loop of hyperinflammation[1-3]

1. Broad targeting of activated T cells or cytokines



Targeting CD38^{pos} CD8 cells

- Depleting all activated CD8 (and CD4) T cells
- Depleting all plasma cells

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The vicious loop of hyperinflammation[1-3]

1. Broad targeting of activated T cells or cytokines

Targeting the JAK/Stat pathway

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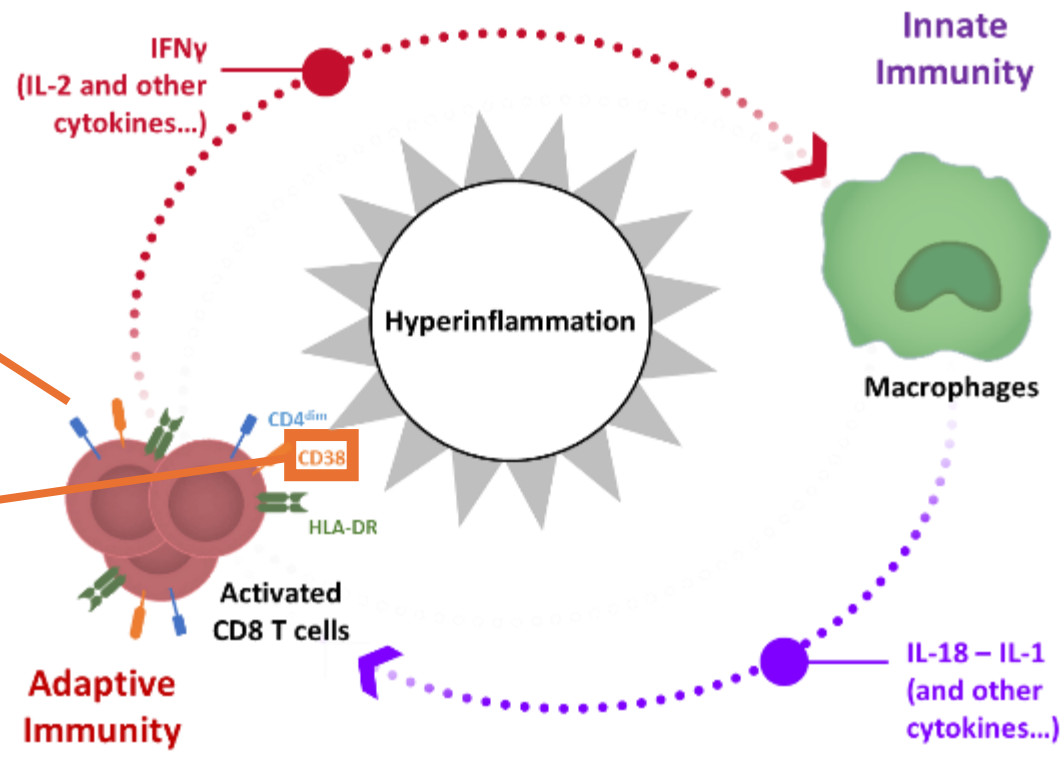

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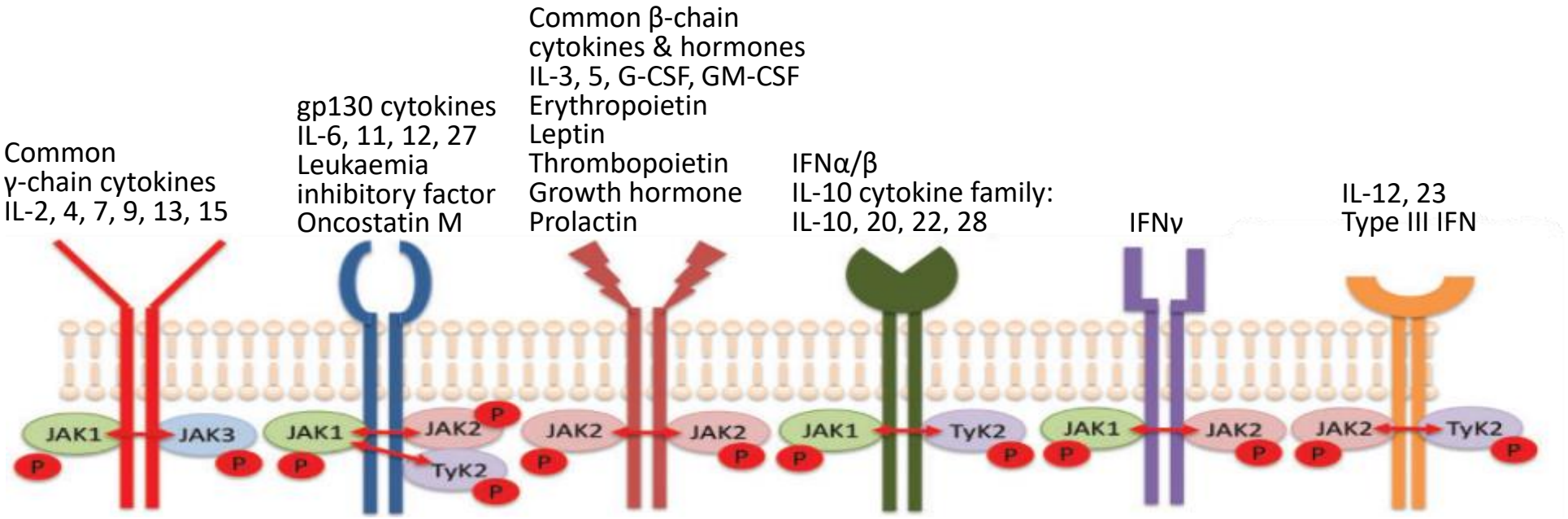
Janus kinases (JAK)



JAKs are highly conserved and non-redundant and required for critical functions

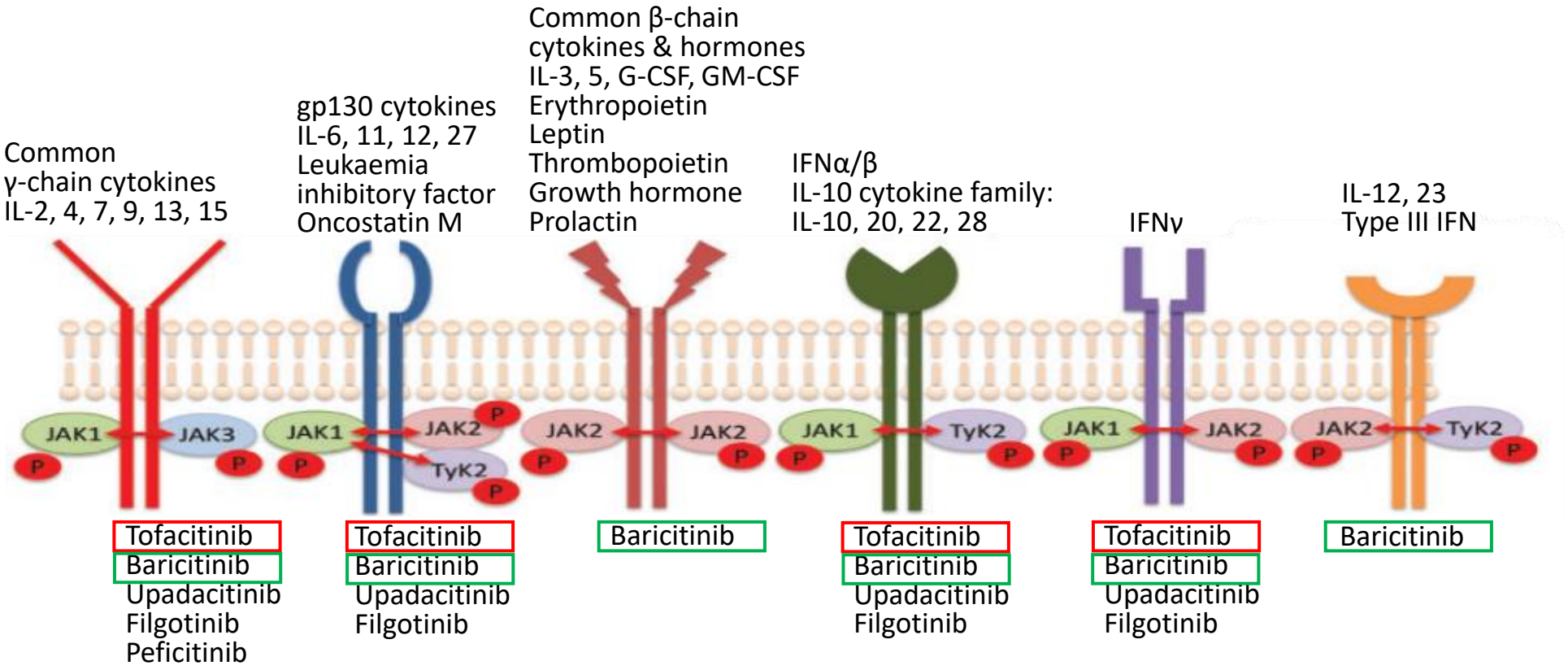
JAK isoform deficiency leads to severe clinical phenotypes:

- 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)

G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; gp, glycoprotein; IFN, interferon; IL, interleukin; JAK, janus kinase; KO, knockout; TYK, tyrosine kinase.

Choy, EH. Rheumatology (Oxford) 2019;58:953-62.

JAK inhibitors



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

The objective is <u>not</u> to block the JAK pathway completely

The objective is to reversibly <u>reduce</u> the activity of one or more JAK isoform

G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; gp, glycoprotein; IFN, interferon; IL, interleukin; JAK, janus kinase; KO, knockout; TYK, tyrosine kinase.

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The vicious loop of hyperinflammation[1-3]

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- Dimming multiple cytokine receptors
- Dimming signalling of >30 cytokines

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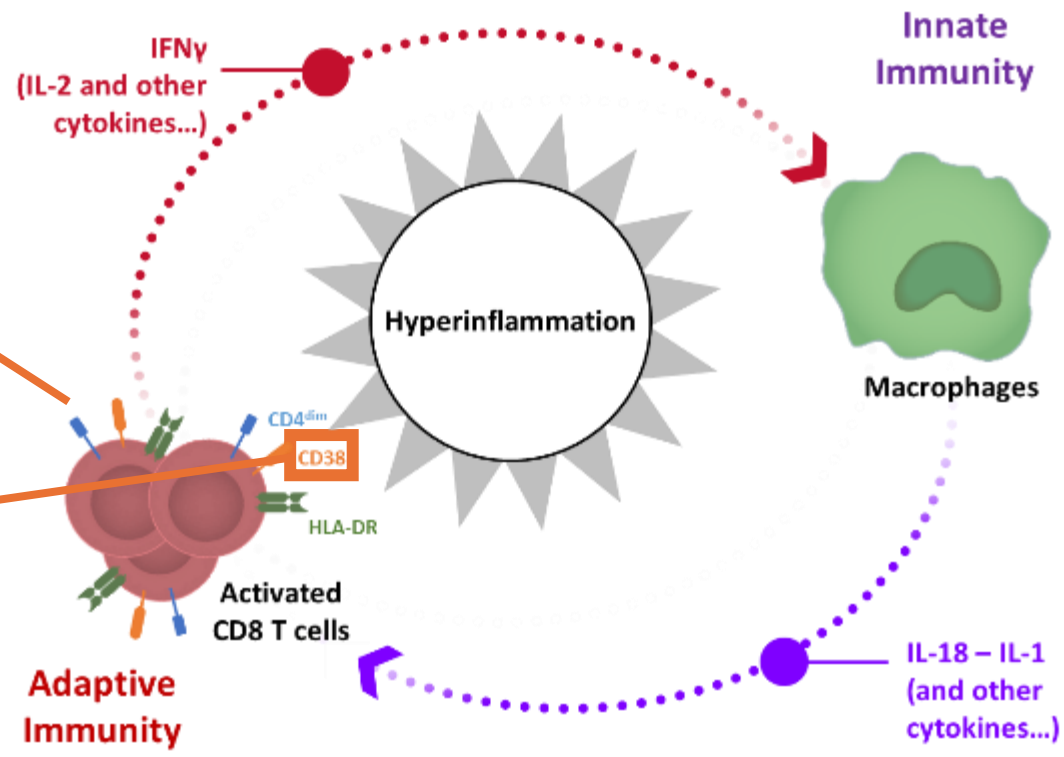

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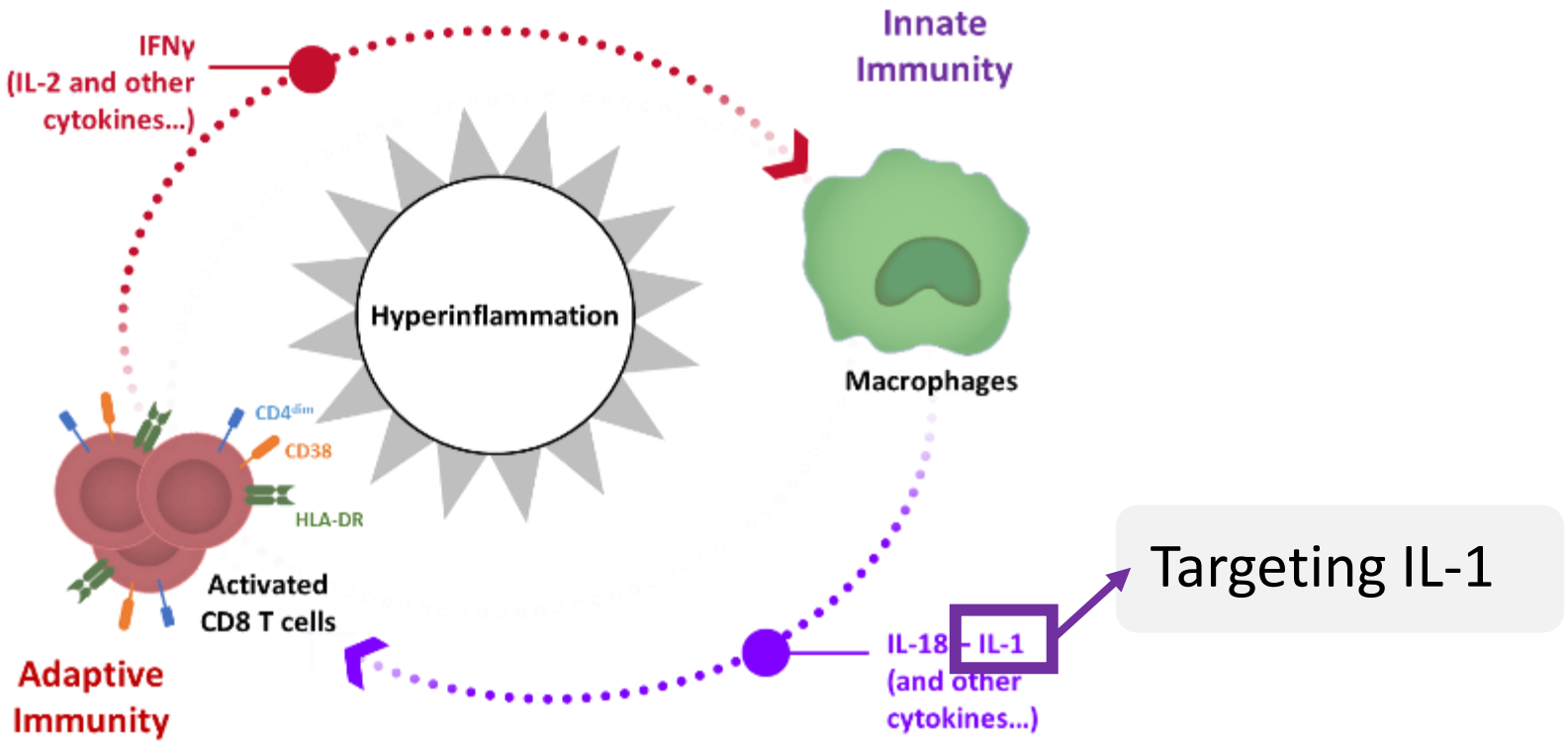
The vicious loop of hyperinflammation[1-3]

2. Precise targeting of pathogenic cytokines



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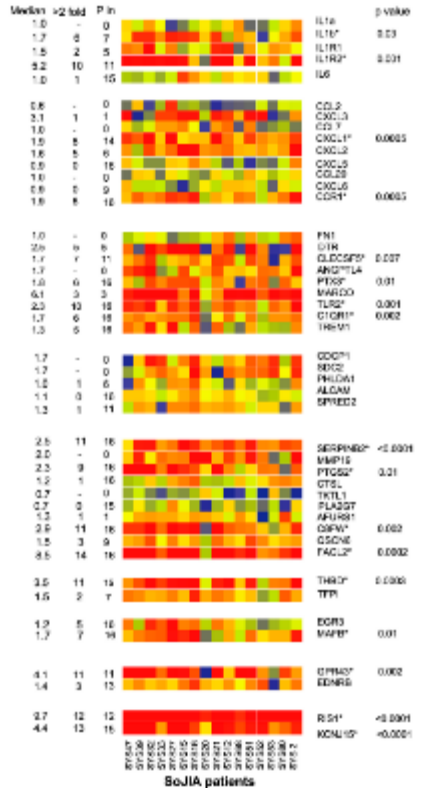
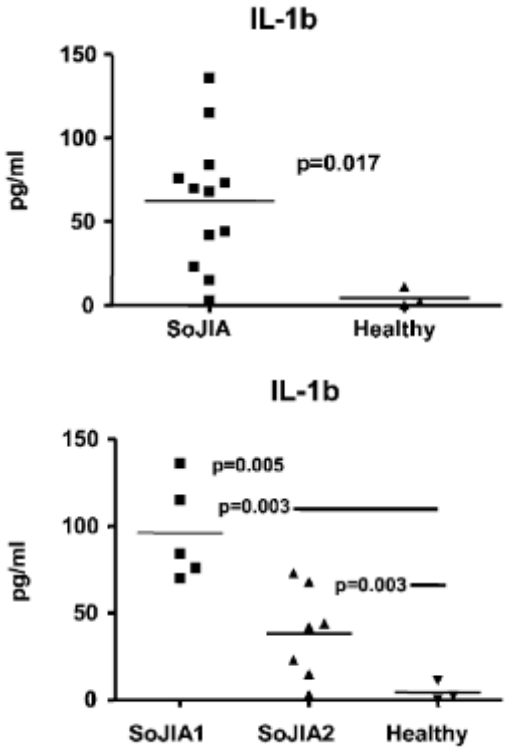
IL-1 in Still's disease

- Sera from sJIA patients induce IL-1β production from normal PBMC[1]
- Increased expression of IL-1β related genes





AOSD, adult-onset Still's disease; IL, interleukin; PBMCs, peripheral blood mononuclear cells; sJIA, systemic juvenile idiopathic arthritis.

1. Pascual V, et al. J Exp Med 2005;201:1479-86;
2. Nirmala N, et al. Pediatric Rheumatol 2015;13:50.

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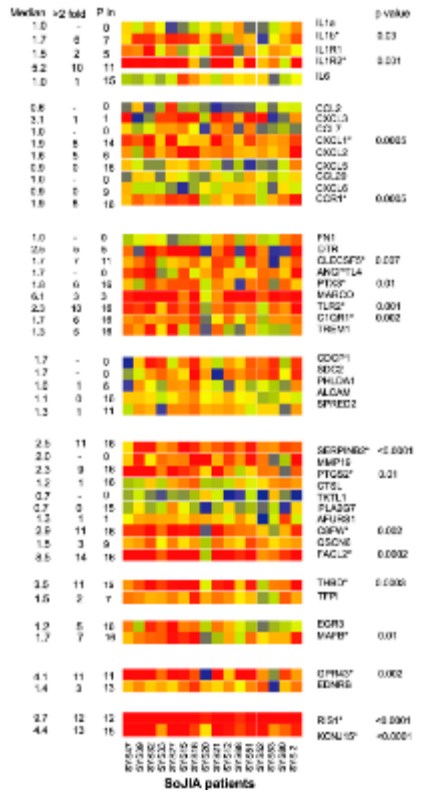
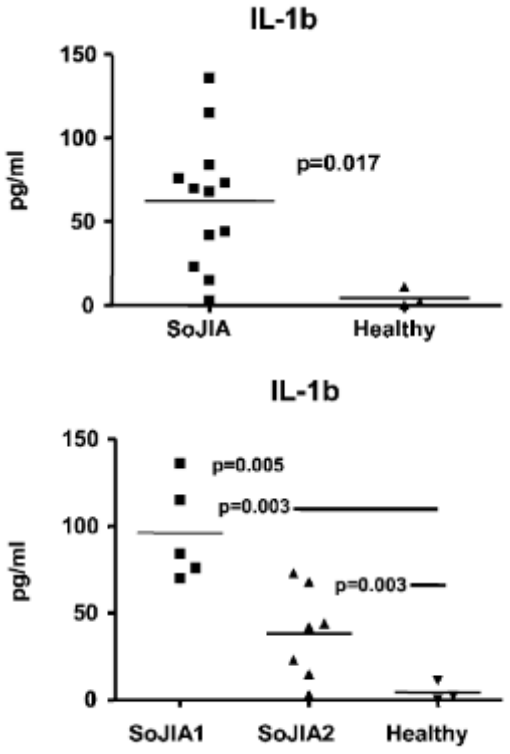
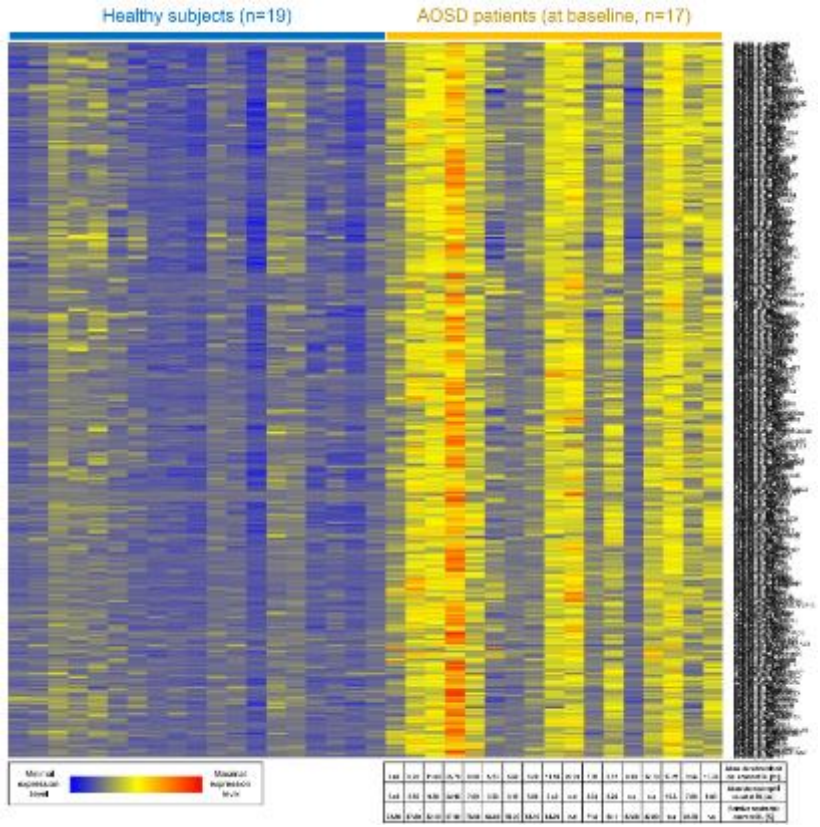




- Genes down regulated following canakinumab treatment in sJIA are markedly upregulated in AOSD[2]



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The vicious loop of hyperinflammation[1-3]

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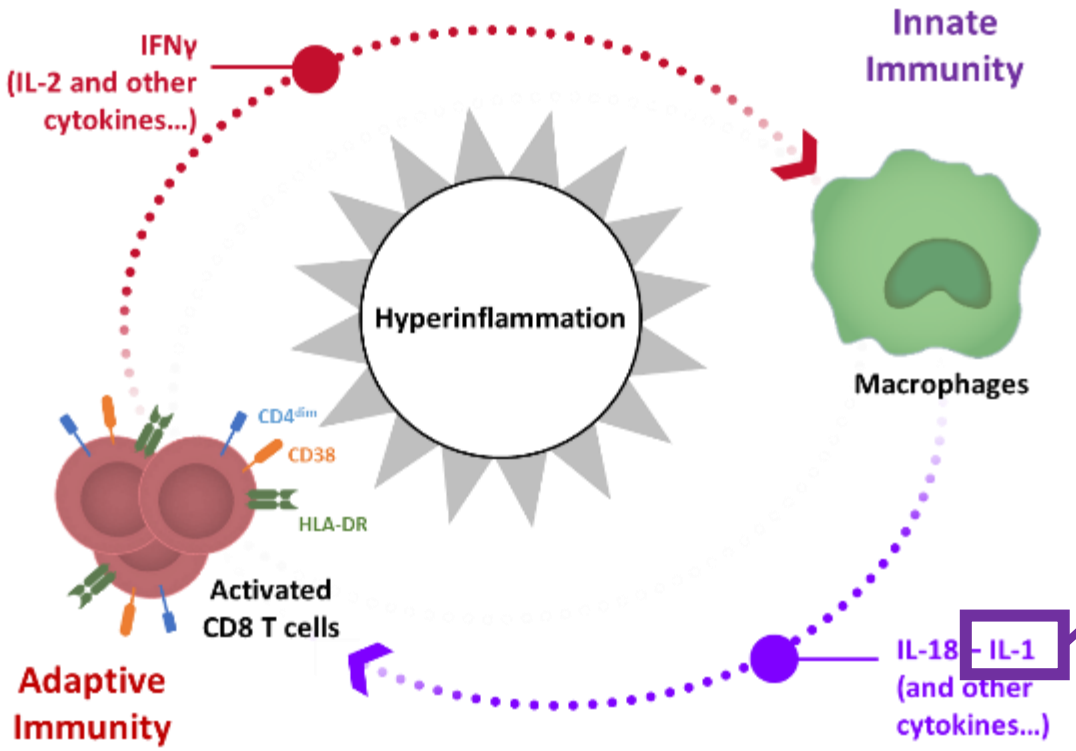

Targeting IL-1

- Patients with Still's disease show elevated IL-1β levels
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The vicious loop of hyperinflammation[1-3]

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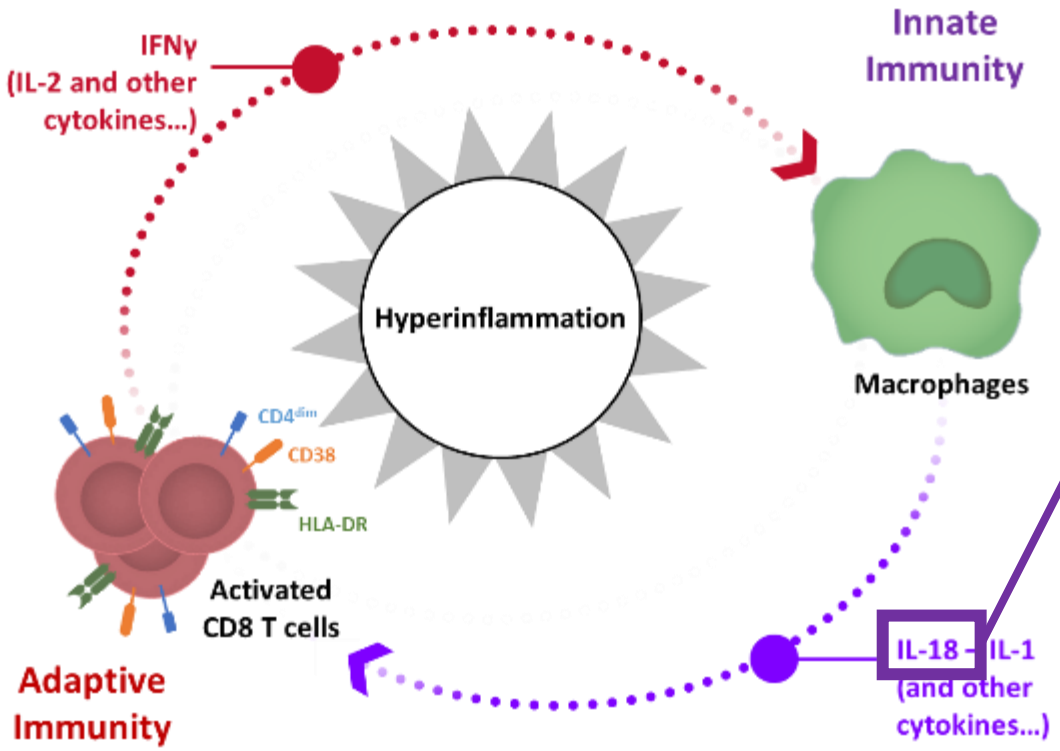

Targeting IL-18

Targeting IL-1

- Patients with Still's disease show elevated IL-1β levels
- Levels correlate with disease activity, response to treatment and severity

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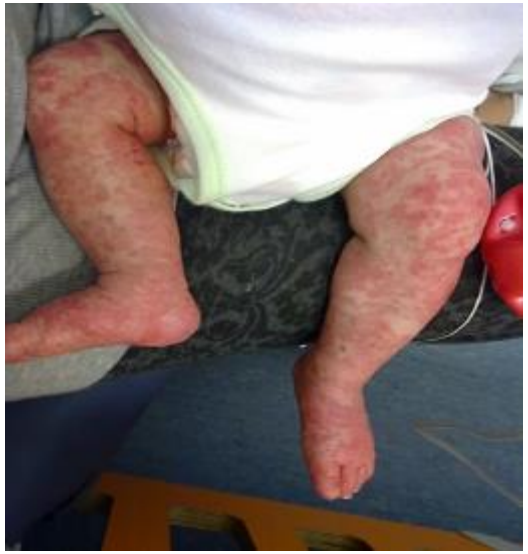
IL-18–driven monogenic disorders (NLRC-4 and CDC42): autoinflammation, intestinal inflammation and MAS[1,2]

- Early-onset fever
- Rash
- Vomiting/diarrhoea
- Splenomegaly
- Cytopenia
- Recurrent MAS/HLH



ATP, adenosine triphosphate; CDC42, cell division cycle 42; CXCL9, chemokine (C-X-C motif) ligand 9; HD, healthy donor; HLH, hemophagocytic lymphohistiocytosis; IL, interleukin; LPS, lipopolysaccharide; ND, not detectable; NLRC4, NOD-Like receptor family CARD domain containing 4; US, unstimulated.

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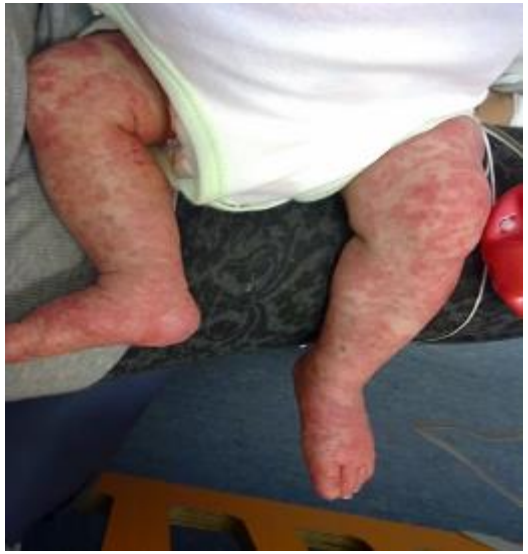
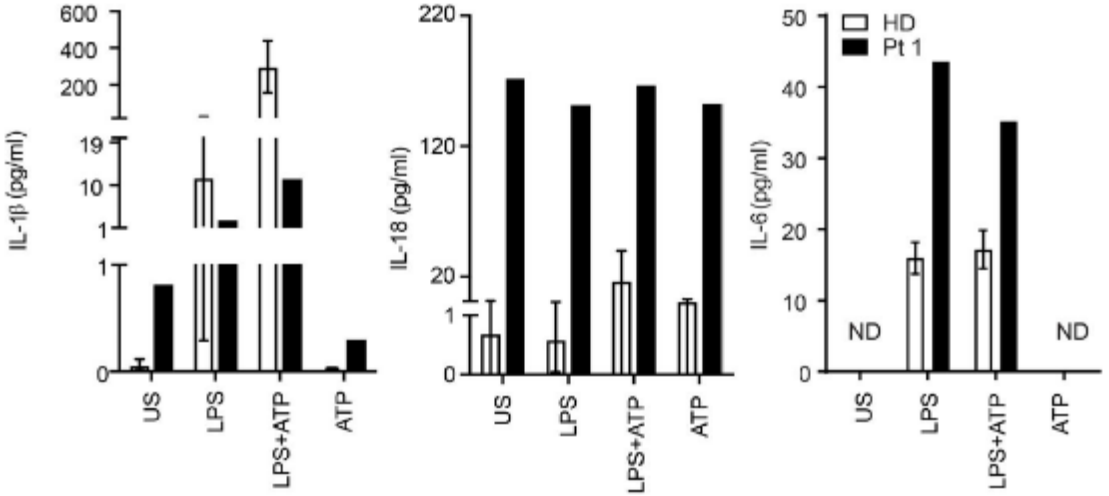
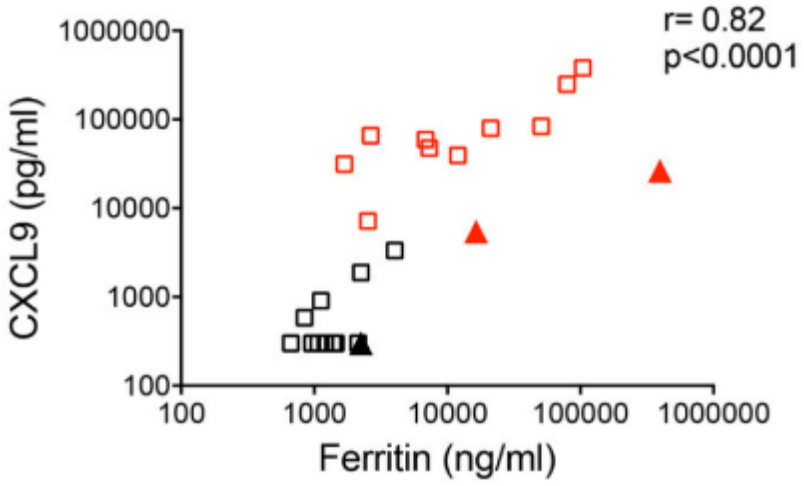


- Overproduction of IL-18 by monocytes/macrophages
- High levels of IL-18
- High levels of CXCL9 during MAS/HLH[2]





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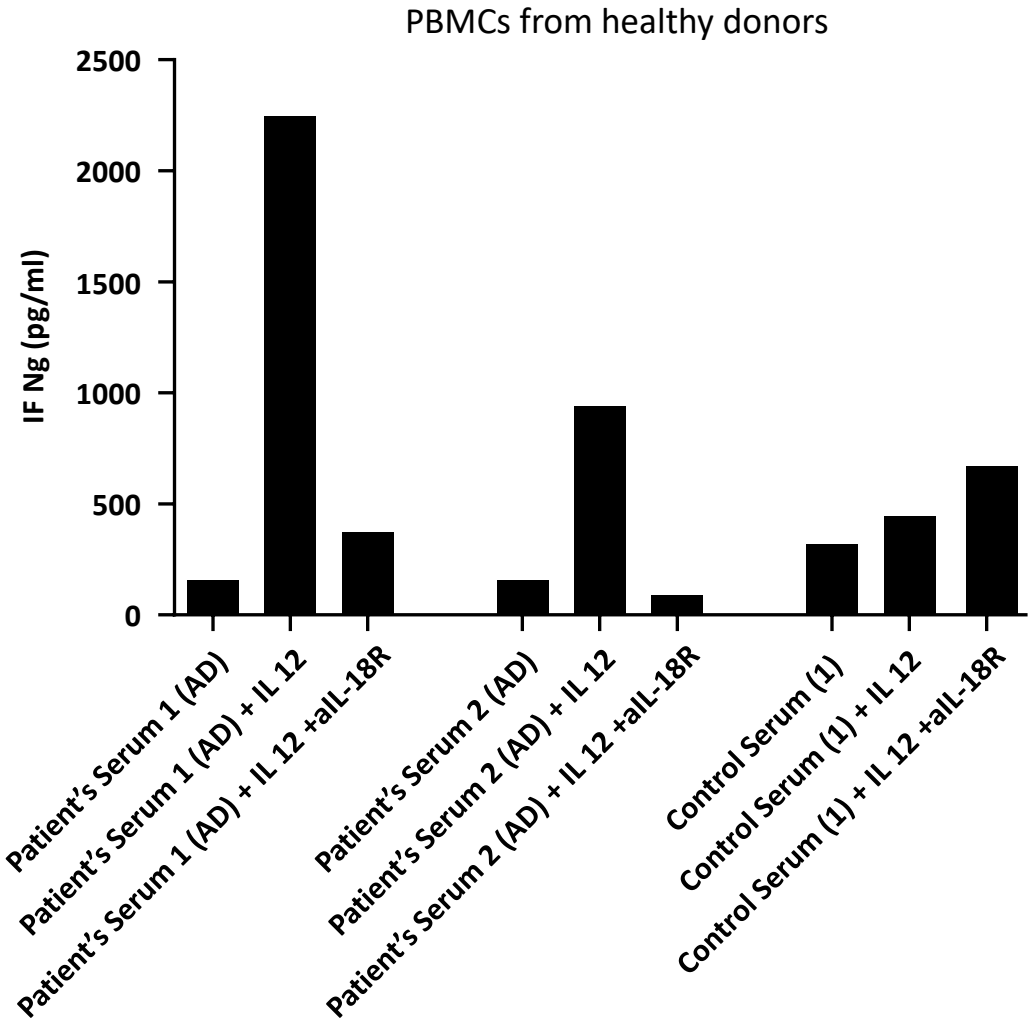
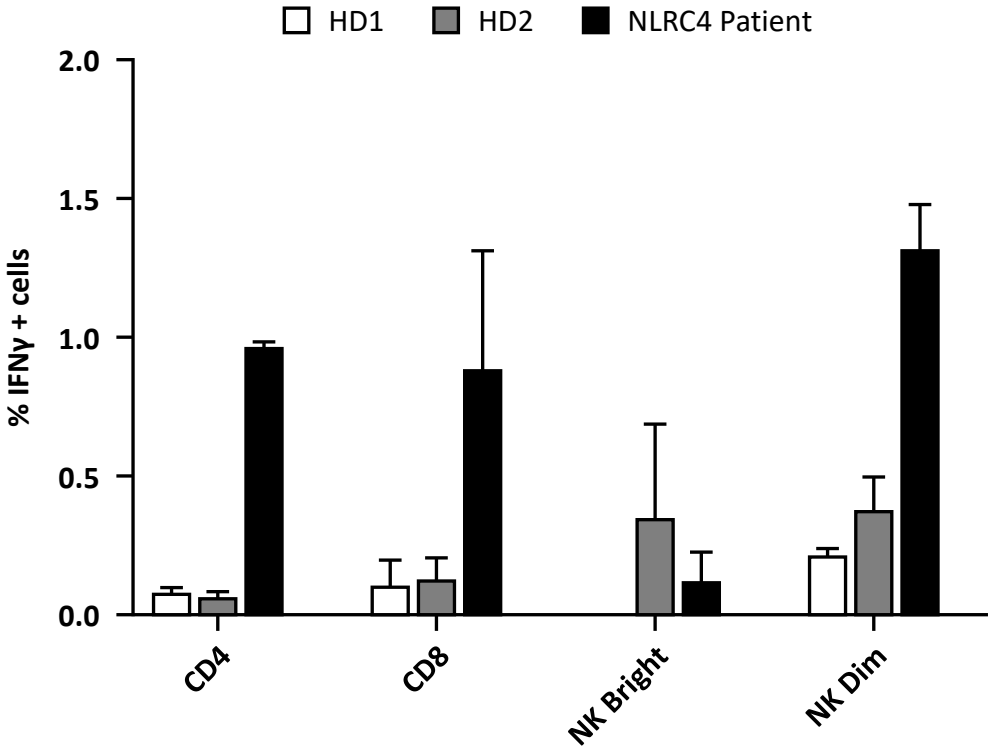
IL-18 present in sera of NLRC4 patients induce IFNγ production by PBMCs from healthy donors



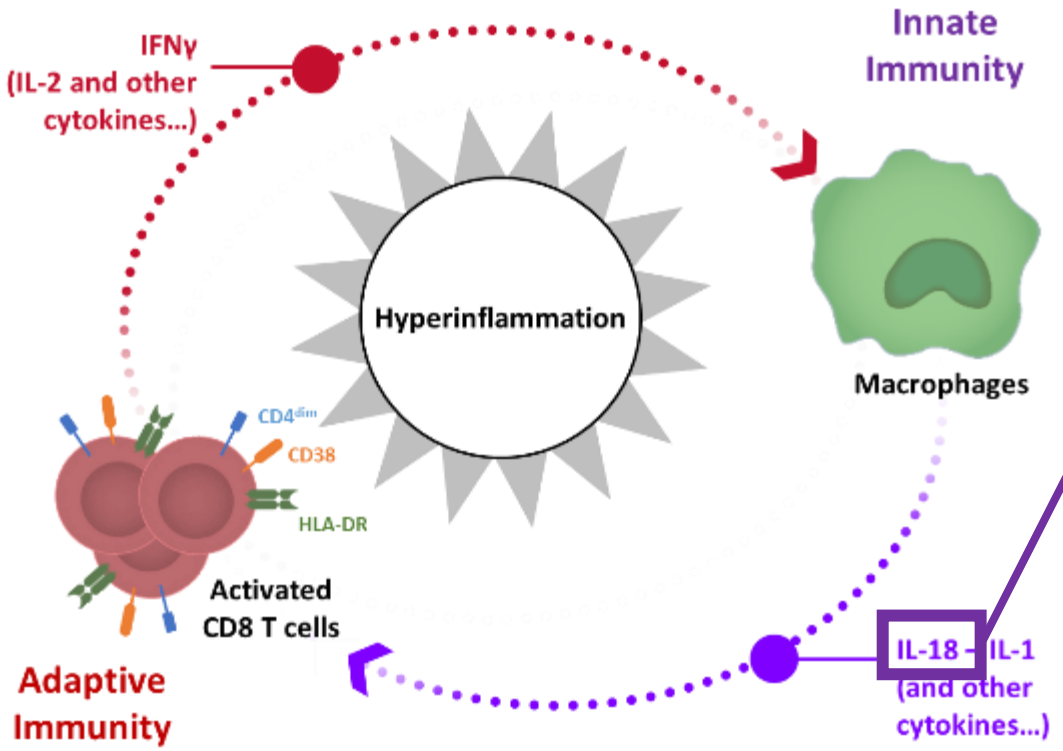


AD, AID patients; IFNγ, interferon gamma; IL, interleukin; PBMCs, peripheral blood mononuclear cells.

De Benedetti F et al. Oral presentation presented at the Internationals Society of Systemic Auto Inflammatory Diseases (ISSAID), 31-3 April 2019, Genoa, Italy.

The vicious loop of hyperinflammation[1-3]

2. Precise targeting of pathogenic cytokines



Targeting IL-18

- Involved in sHLH/MAS pathogenesis
- Inducer of IFNγ production

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- Patients with Still's disease show elevated IL-1β levels
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CD, cluster of differentiation; HLA-DR, human leukocyte antigen – DR isotope; IFN, interferon; IL, interleukin; MAS, macrophage activation syndrome; sHLH, secondary hemophagocytic lymphohistiocytosis.

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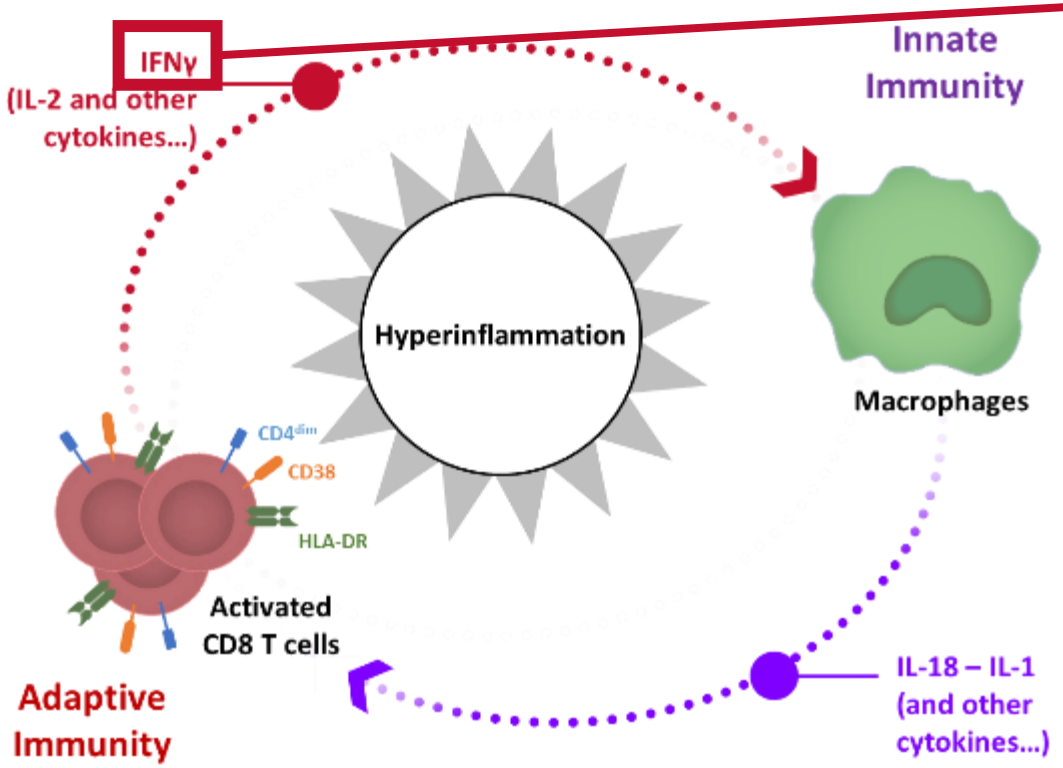

Targeting IFNγ

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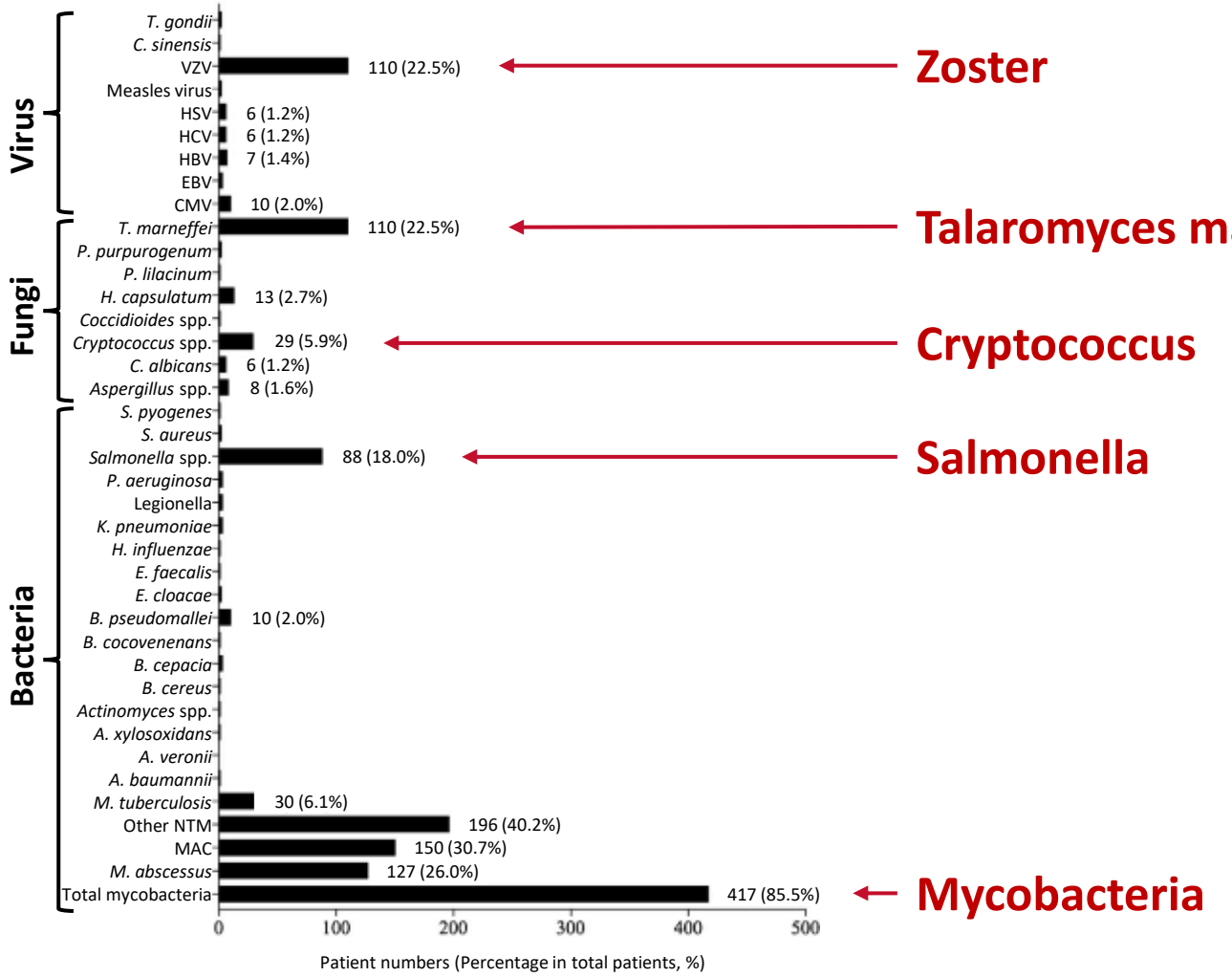
Over-production of IFNγ is present and pathogenic in several different animal models of HLH and MAS

Human disease	Mutation	Trigger	High IFNγ	IFNγ blockade
Monogenic HLH (cytotox)[1,2]	PRF1	LCMV-infection	YES	Benefit
Monogenic HLH (cytotox)[3]	UNC13D	LCMV infection	YES	Not tested
Monogenic HLH (cytotox)[4]	STX11	LCMV-infection	YES	Not tested
Monogenic HLH (cytotox)[2]	RAB27A	LCMV-infection	YES	Benefit
Monogenic HLH (Inflammasome)[5]	SH2D1A	LCMV-infection	YES	Not tested
Infection-associated sHLH[5]	None	TLR9 stimulation	YES	Benefit
MAS[7]	IL-18 transgenic	TLR9 stimulation	YES	Benefit
MAS[8]	IL-18 BP -/-	TLR9 stimulation	YES	Benefit
MAS[9]	IL-6 transgenic	TLR4 stimulation	YES	Benefit

HLH, hemophagocytic lymphohistiocytosis; IFN, interferon; IL, interleukin; LCMV, lymphocyte choriomeningitis virus; MAS, macrophage activation syndrome; TLR, toll-like receptor.

1. Jordan MB, et al. Blood 2004;104:735-43; 2. Schmid JP, et al. EMBO Mol Med 2009;1:112-24; 3. Crozat K, et al. J Exp Med 2007;204:853-63;
4. Kögl T, et al. Blood 2013;121:604-13; 5. Czar MJ, et al. Proc Natl Acad Sci USA 2001;98:7449-54; 6. Behrens EM, et al. J Clin Invest 2011;121:2264-77;
7. Weiss SE, et al. Blood 2018;131:1442-55; 8. Girard-Guyonvarc'h C, et al. Blood 2018;131:1430-41;
9. Prencipe G, et al. J Allergy Clin Immunol 2018;141:1439-49.

Anti-IFNγ autoantibody-associated immunodeficiency



A. baumannii, Acinetobacter baumannii; A. veronii, Aeromonas veronii; A. xylosoxidans, Achromobacter xylosoxidans; B. cereus, Bacillus cereus; B. cepacia, Burkholderia cepacia; B. cocovenenans, Burkholderia cocovenenans; B. pseudomallei, Burkholderia pseudomallei; C. albicans, Candida albicans; C. sinensis, Clonorchis sinensis; CMV, Cytomegalovirus; E. cloacae, Enterobacter cloacae; E. faecalis, Enterococcus faecalis; EBV, Epstein-Barr virus; H. capsulatum, Histoplasma capsulatum; H. influenzae, Haemophilus influenzae; HBV, Hepatitis B virus; HCV, Hepatitis C virus; HSV, Herpes simplex virus; K. pneumoniae, Klebsiella pneumoniae; MAC, Mycobacterium avium complex; M. abscessus, Mycobacterium abscessus; M. tuberculosis, Mycobacterium tuberculosis; NTM, non-tuberculous mycobacterium; P. aeruginosa, Pseudomonas aeruginosa; P. lilacinum, Purpureocillium lilacinum; P. purpurogenum, Penicillium purpurogenum; S. aureus, Staphylococcus aureus; S. pyogenes, Streptococcus pyogenes; T. gondii, Toxoplasma gondii; T. marneffei, Talaromyces marneffei; VZV, Varicella-Zoster virus.

Shih HP, et al. Curr Opin Immunol 2021;72:206-14.

The vicious loop of hyperinflammation[1-3]

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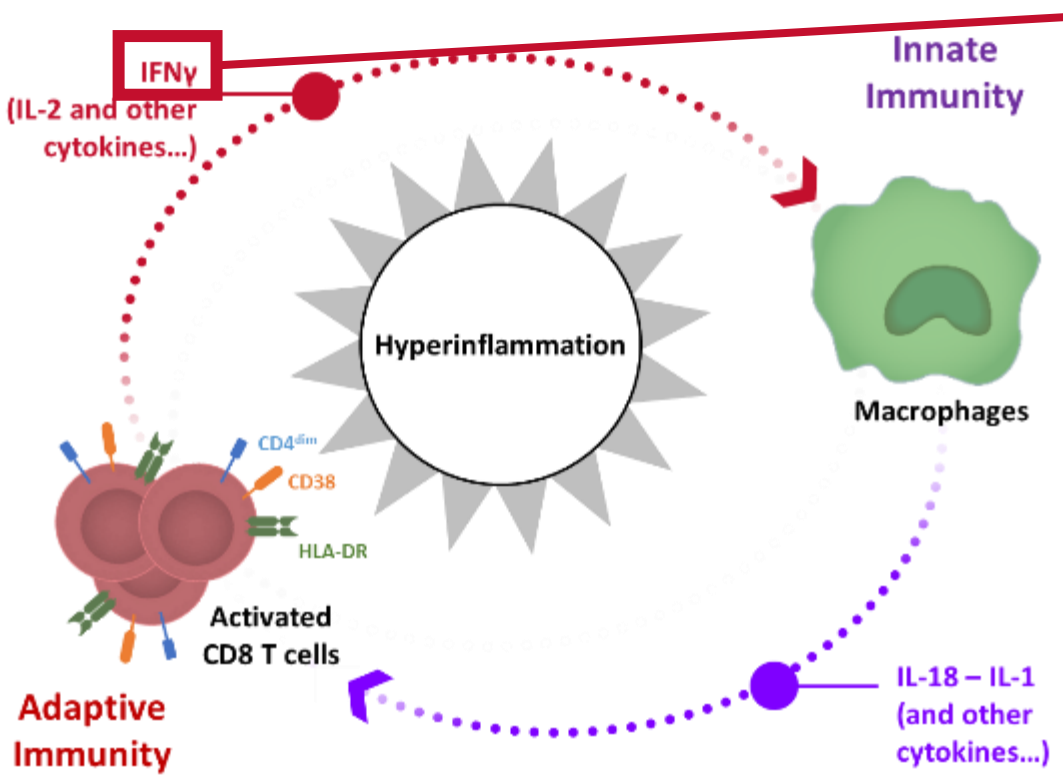

Targeting IFNγ

Involved in sHLH/MAS pathogenesis

- CXCL9 related to MAS severity
- Effect of IFNγ deficiency are known

Targeting IL-18

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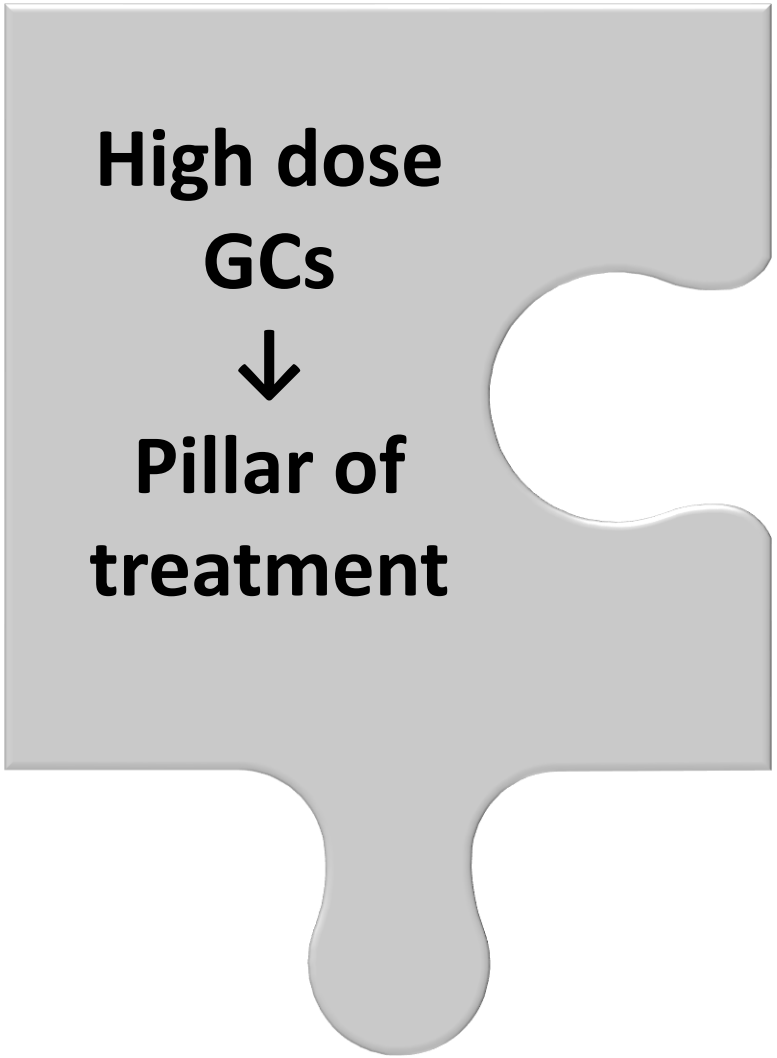
Conclusions: Future management



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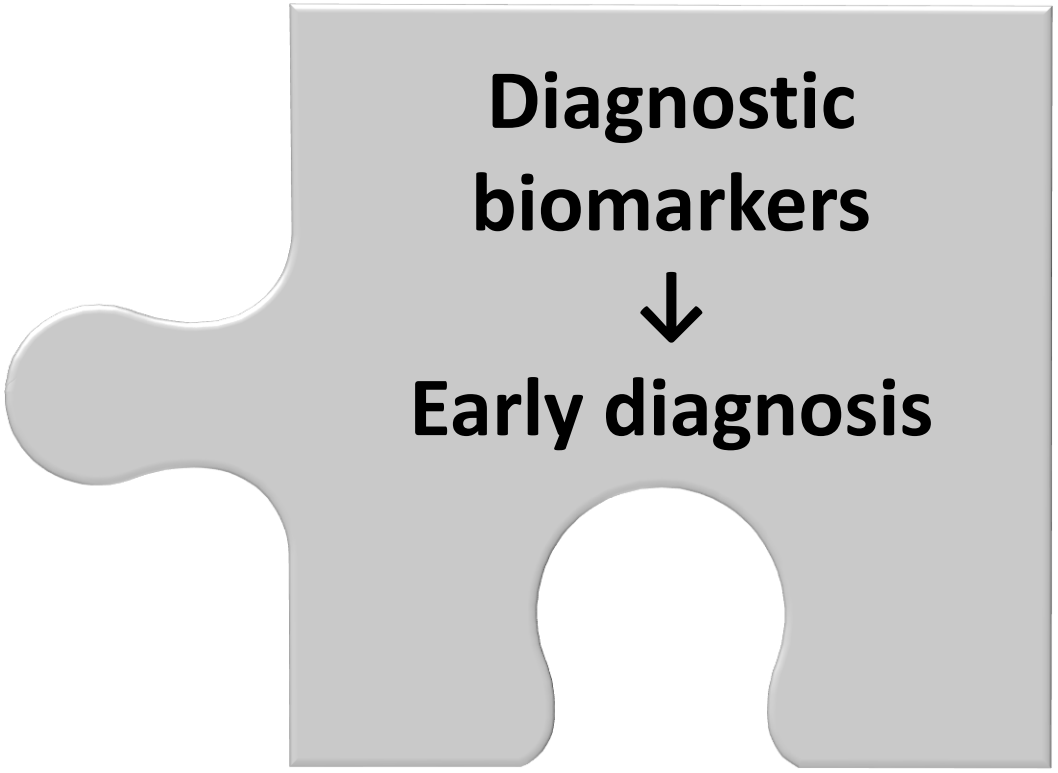

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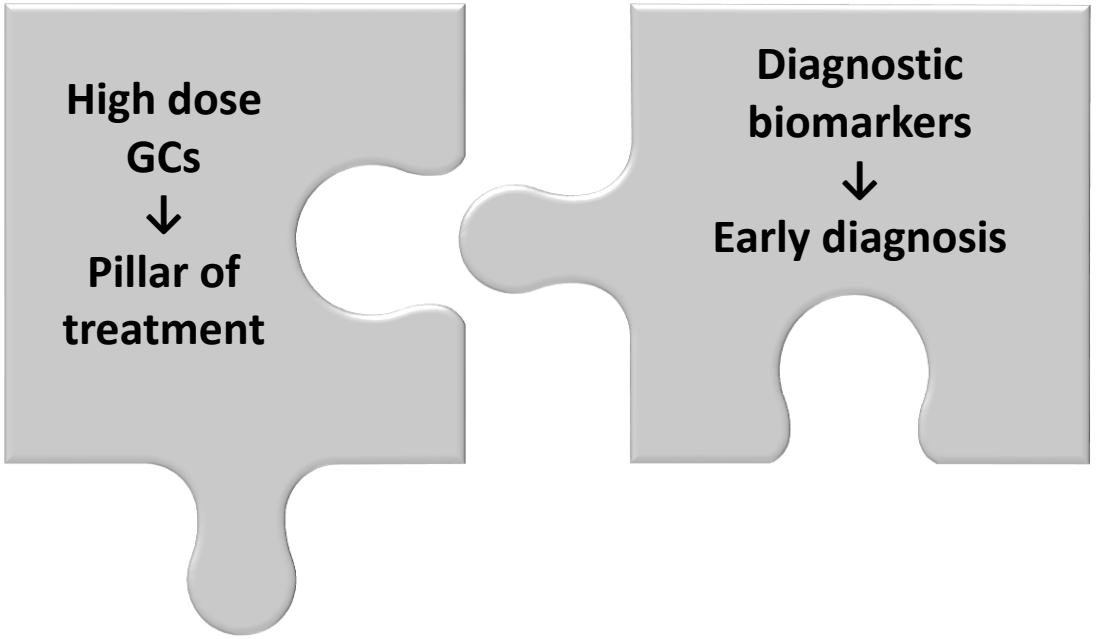
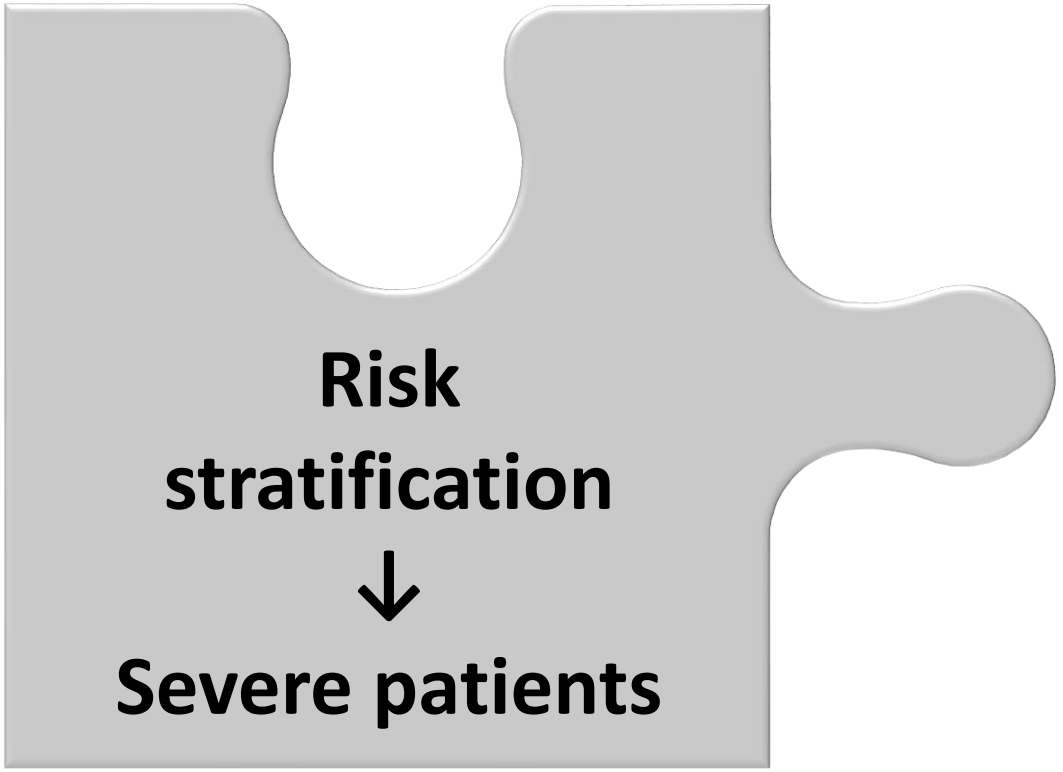
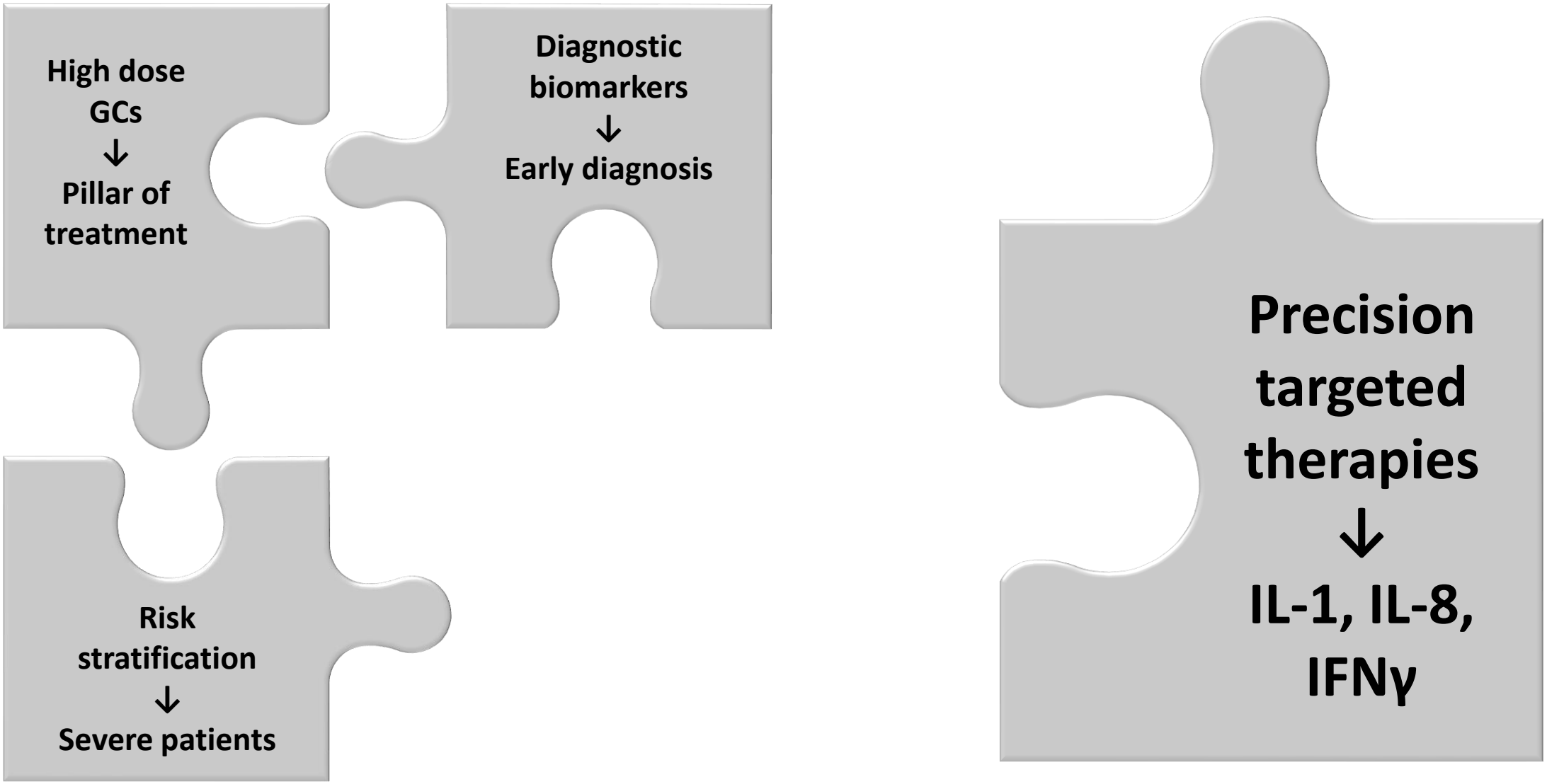
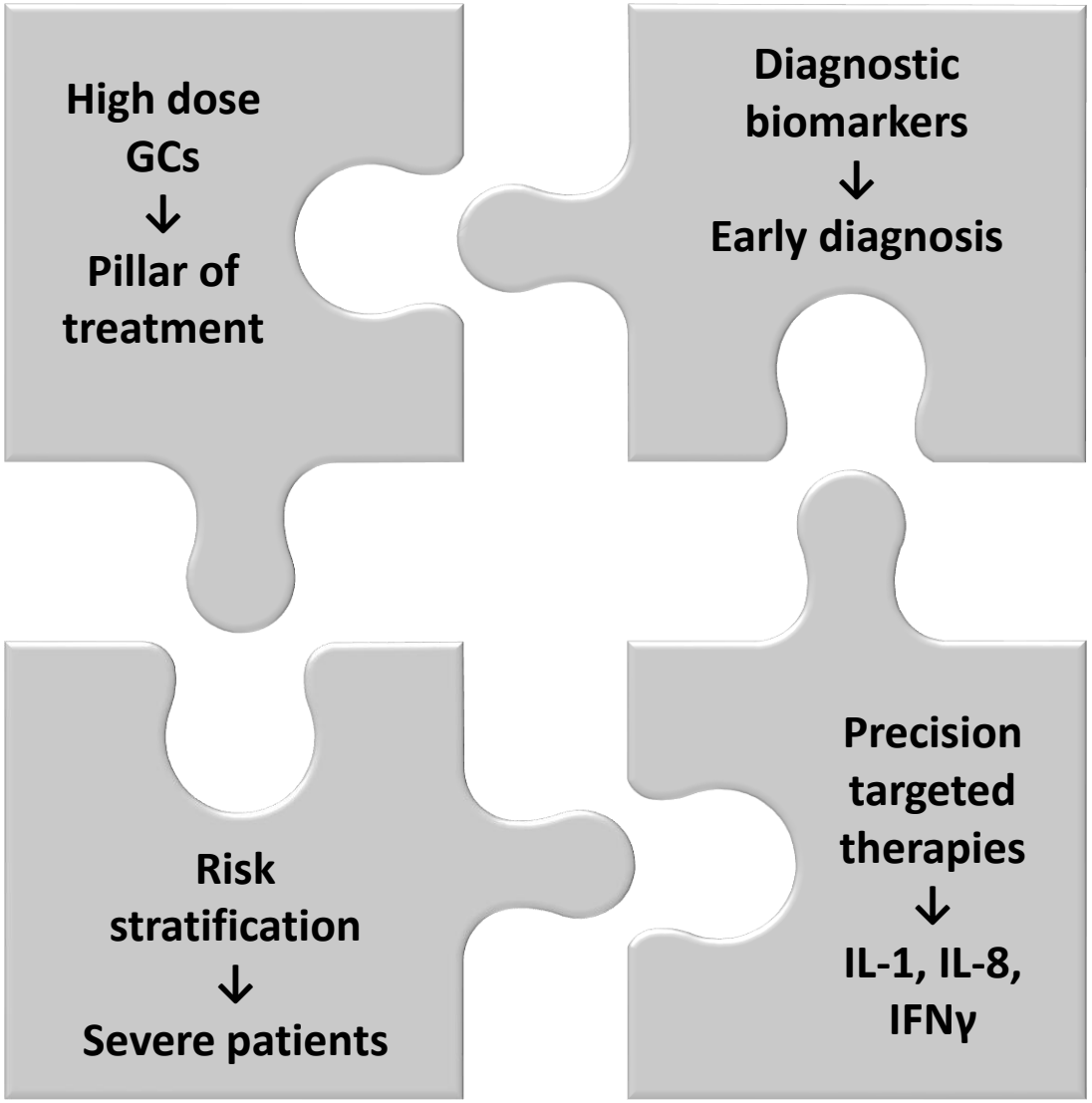




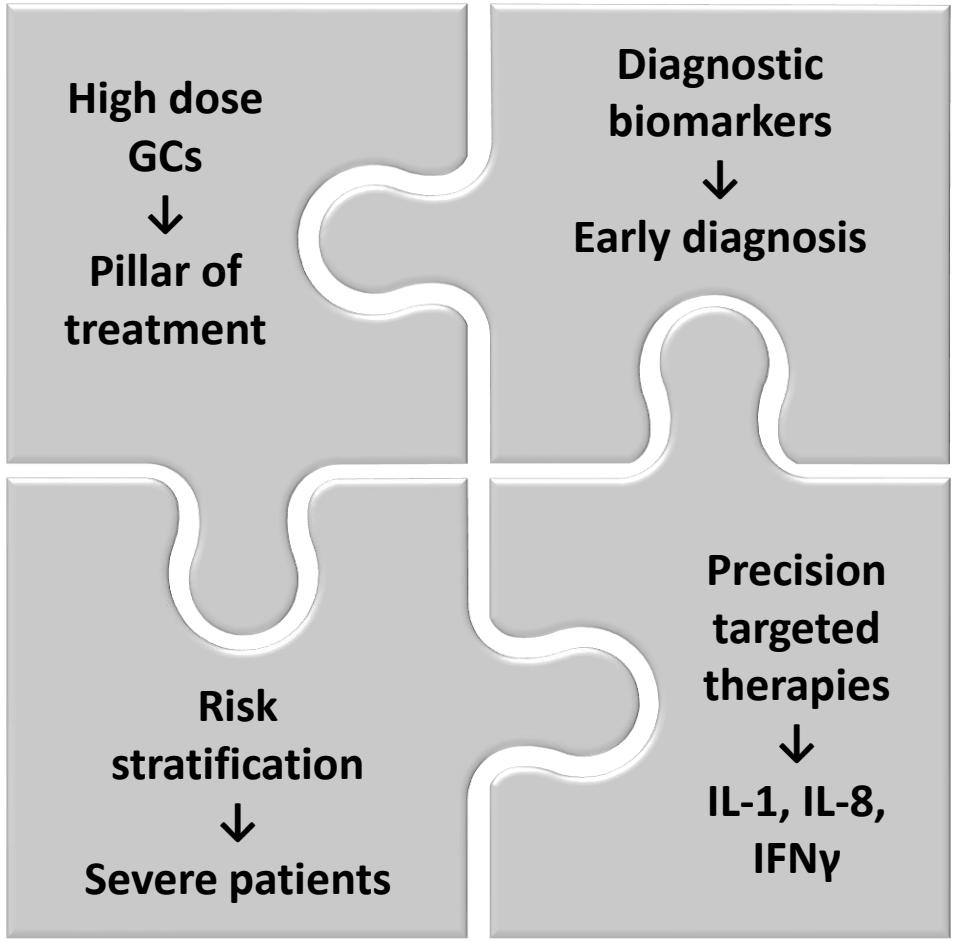
Conclusions: Future management



Conclusions: Future management



Conclusions: Future management



Glucocorticoids

- Essential
- Insufficient for optimal MAS control

Early detection

- Clinical and laboratory pattern
- Specialised biomarkers

Risk stratification tools

Targeted modulation

- Inflammatory cytokines
- Immune response

Q&A

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