IMMUNOSEP

Personalized Immunotherapy in Sepsis: a precision medicine based approach

ΕΛΛΗΝΙΚΟ ΙΝΣΤΙΤΟΥΤΟ ΜΕΛΕΤΗΣ ΤΗΣ ΣΗΨΗΣ
HELLENIC INSTITUTE FOR THE STUDY OF SEPSIS

Immune dysregulation in COVID-19

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EUROPEAN SHOCK SOCIETY ESS 1983

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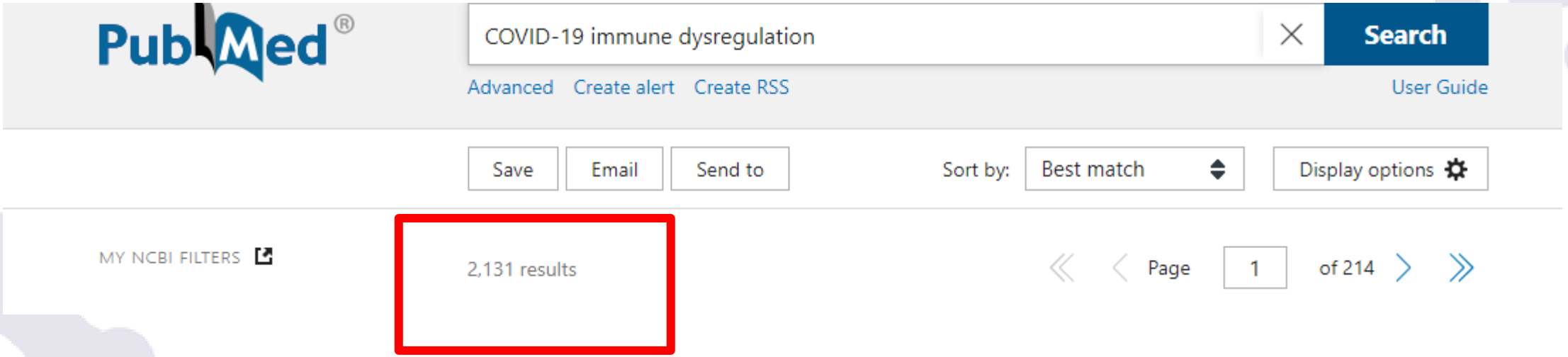
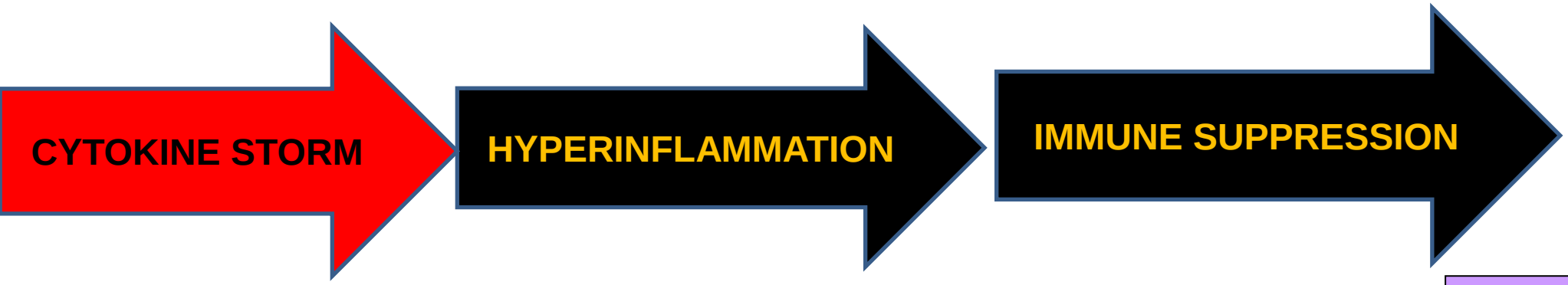
CONFLICT OF INTEREST DISCLOSURE

- No conflict of interest

Immune Dysregulation in COVID-19



WHAT WE THOUGHT ABOUT COVID-19 IMMUNE RESPONSE CONTINUUM……



IMMUNE RECONSTITUTION

DEATH

LONG-COVID

TRUE ?

- Cytokine levels elevated compared to normal people
- Patients exhibit hyperinflammation
- Immunosuppresion is common

Mudd PA,, et al. *Sci Adv* 2020; 6(50): eabe3024
Moore JB, June CH. *Science* 2020; 368(6490): 473.

Is it Innate Immunity?

Paludan SR, Mogensen TH. *Sci Immunol* 2022; 7(67)

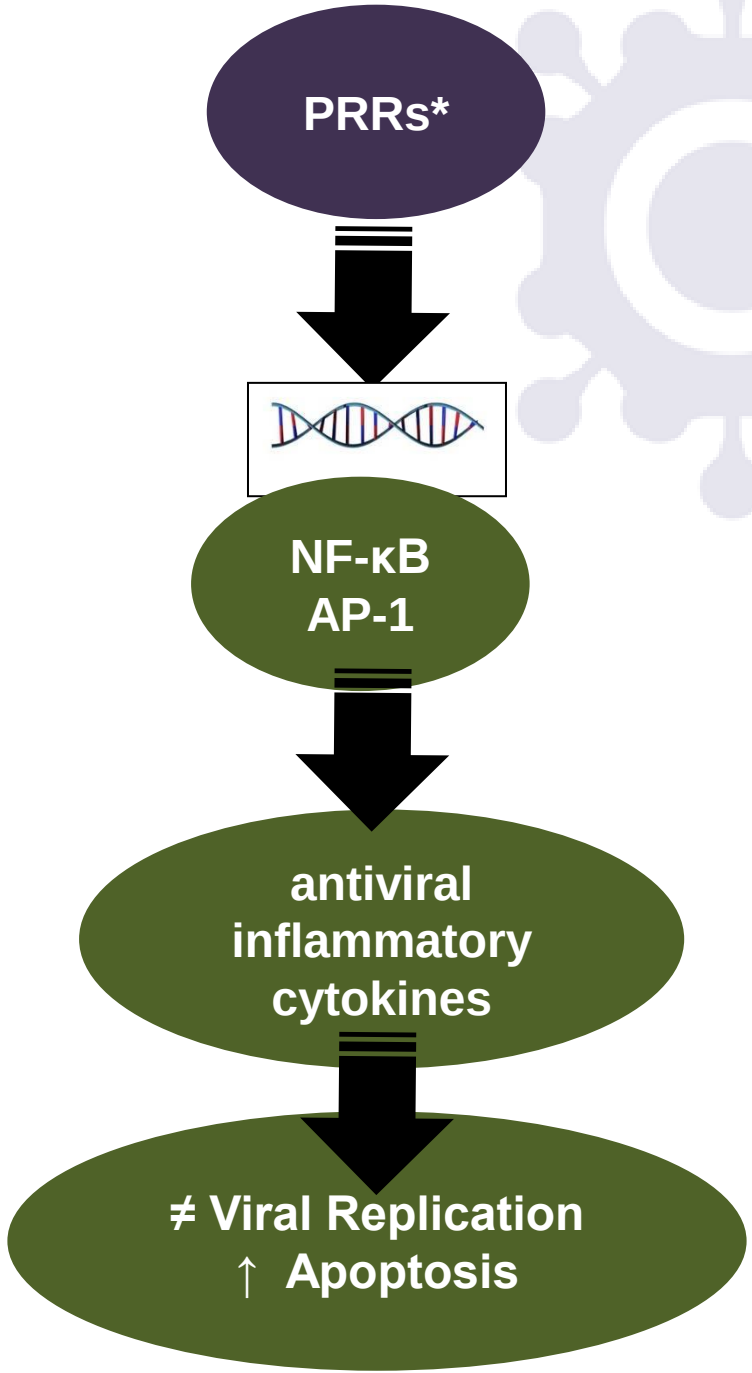
PAMPs*

- **Proteins from viral envelope, spikes, and nucleoproteins (N)**
- **single stranded RNA**

DAMPs*

- **S100A8/A9**
- **nucleic acids from dead cells**

*PRRs Pattern Recognition Receptor
*PAMPs Pathogen Associated Molecular Patterns
*DAMPs Danger Associated Molecular Patterns
* NF-κB Nuclear Factor κB
* Activator protein 1

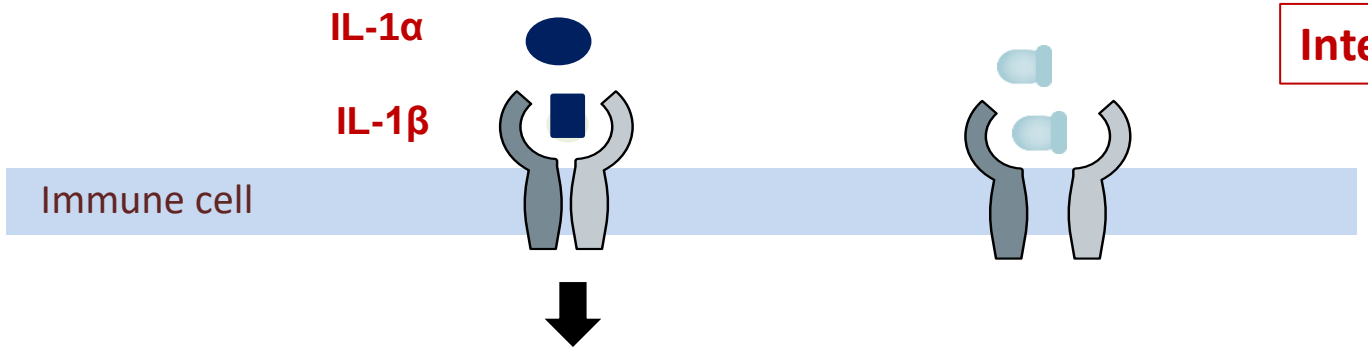


DANGER-ASSOCIATED MOLECULAR PATTERNS (DAMPs) IN COVID-19

Interleukin (IL)-1α
(directly released from the lung)

All other DAMPs

Interleukin (IL)-1β



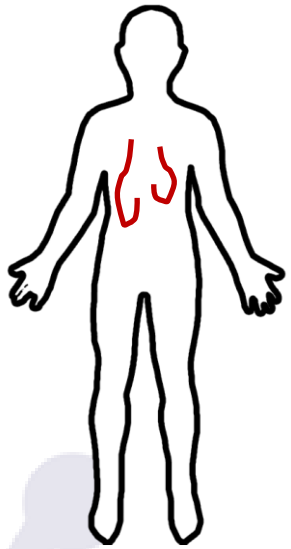
INFLAMMATION
ARDS

: Endogenous Antagonist

Renieris G, et al. J Innate Immun. 2022;14(6):643-656.

suPAR-GUIDED ANAKINRA TREATMENT FOR VALIDATION OF THE RISK AND EARLY MANAGEMENT OF SEVERE RESPIRATORY FAILURE BY COVID-19

THE SAVE STRATEGY



STOP
IL-1α
IL-1β

PREVENT
Unfavorable outcome

Pneumonia

- Hospitalization
- pO_2/FiO_2: 150-400
- Oxygen mask/nasal oxygen/high-flow oxygen
- suPAR ≥6 ng/ml

Anakinra

- Recombinant human receptor antagonist
- Blocks the action of IL-1α and IL-1β

suPAR: soluble urokinase Plasminogen Activator Receptor

The Paradox of COVID-19

Innate Immune System

Hyperinflammation

Immunosuppression

Fails to mount an adequate immune respone

Edema
Fibrosis
Thrombosis
ARDS
Death

Hyperstimulation of lymphocytes/monocytes cause a paradoxical imunosuppresive effect

Greek mythology: Chaos and Gaia

CHAOS

Transcription Factors

- Nuclear factor, erythroid 2-related factor (Nrf2) activation inhibits SARS-CoV-2 replication through type 1 IFN signaling and inhibits inflammatory cytokine release
- Nrf2 suppression in the lungs contributes to decreased antiviral action and increased cytokine levels
- Hypoxia-inducible factor 1a (HIF-1a) is increased in severe COVID-19, induces inflammatory organ damage, is correlated with mortality in elderly population.

Olagnier D, et al. *Nat Commun* 2020; 11(1): 1
Tian M, et al. *Signal Transduct Targeted Ther* 2021; 6(1): 1

What about the cytokines

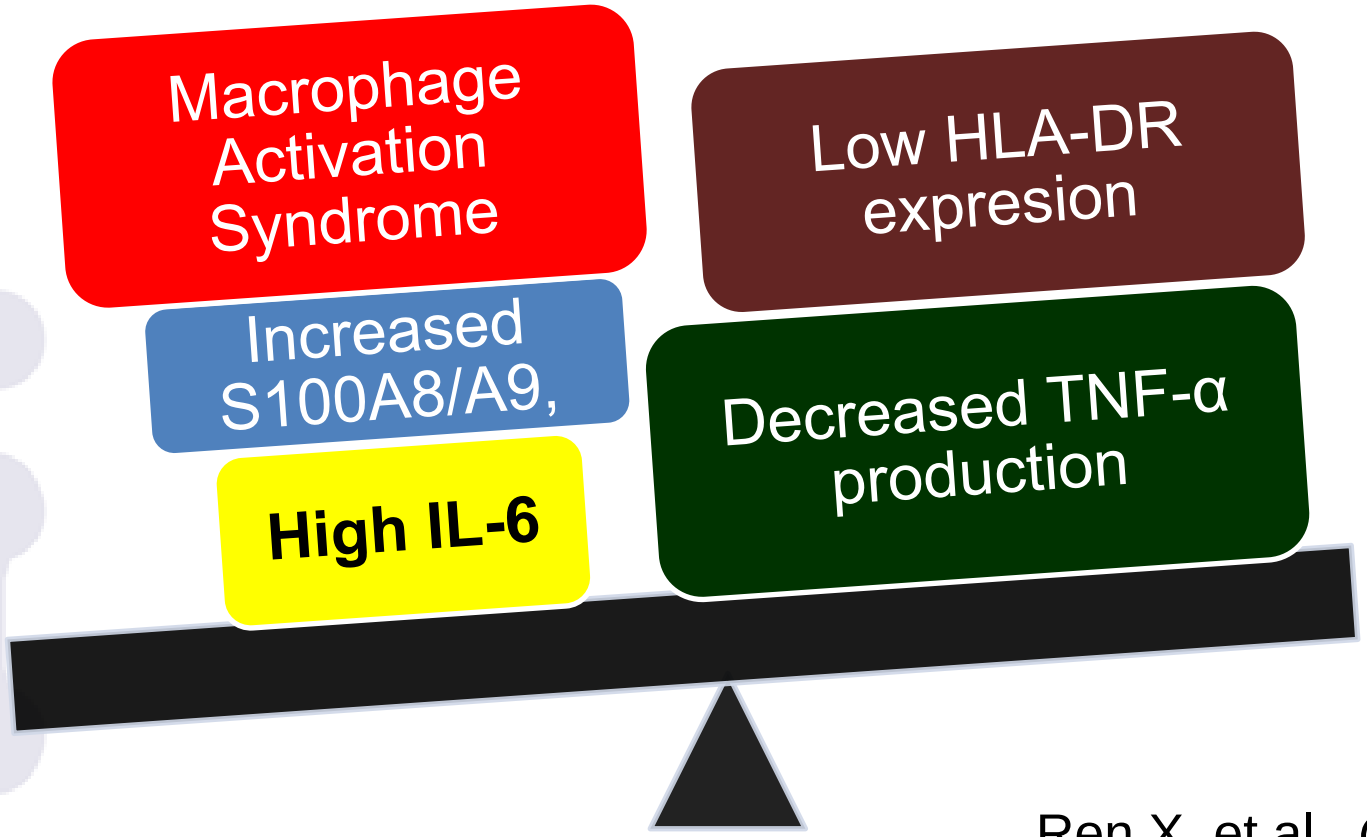
- Decreased early production of type I and type III interferons (IFN) allow for SARS-CoV-2 to replicate and cause severe cellular damage in the lungs
- Response of IFN delayed and reduced,
- Early and strong interleukin-6 (IL-6), interleukin-8 (IL-8), interleukin-10 (IL-10), and tumor necrosis factor-α (TNF-α), all of which predict disease severity and mortality
- Adaptive immune response cytokines interferon-gamma, IL-17 and IL-22 significantly decreased alongside with severity

Paludan SR, Mogensen TH. *Sci Immunol* 2022; 7(67)
Jansen NAF et al., *J Infect Dis.* 2021 23; 223(8): 1322

Monocyte function…two sides of the same coin?

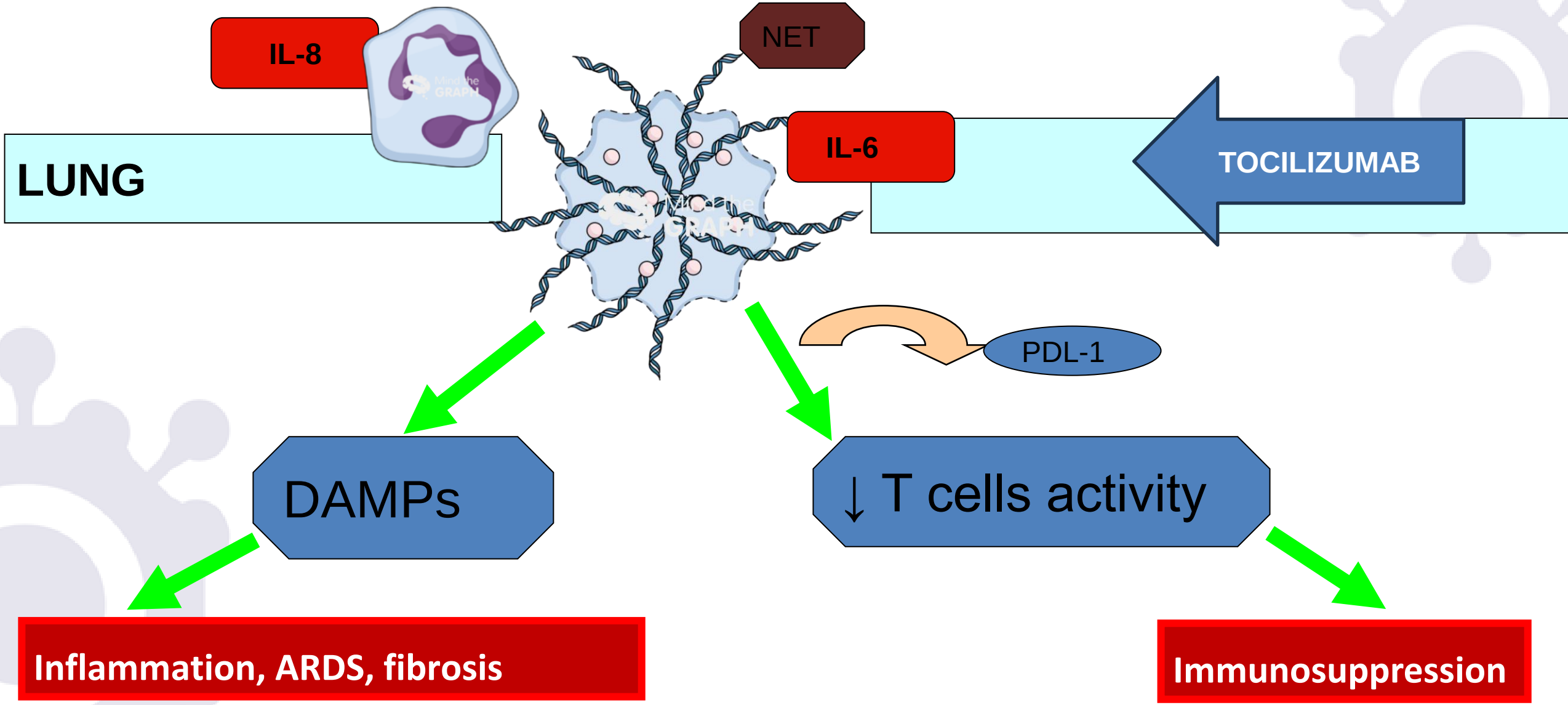
Cytokine Storm

Immunosuppression



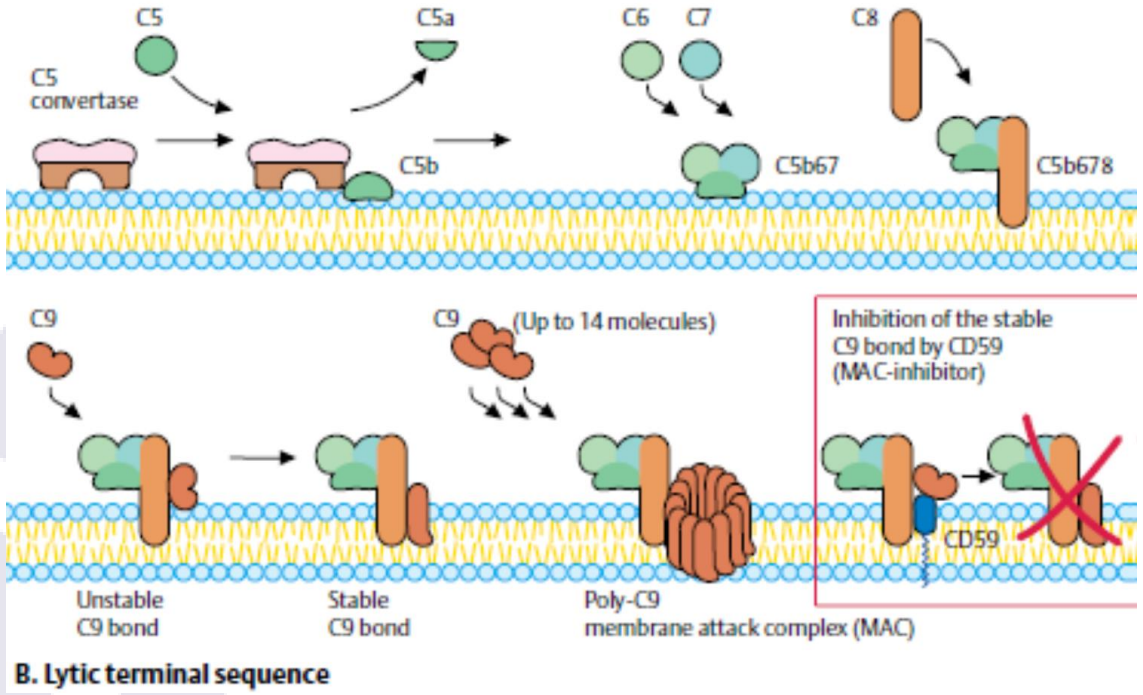
Ren X, et al., *Cell* 2021; 184(7): 1895
Paces J, et al . *Physiol Res* 2020;69(3): 379.

Neutrophils…part of the COVID-19 Paradox?



Davitt E, et al. *Best Pract Res Clin Haematol.* 2022; 35(3): 101401

How about complement activation?



B. Lytic terminal sequence

- C3, C4d, and C5a are significant elevated in severe COVID-19
- viral N antigen interaction with mannan-binding lectin serine protease 2 (MASP-2) activates the lectin pathway leading to cellular deposition of the membrane attack complex (MAC)
- This MAC deposition occurs in vascular walls, bronchial epithelial cells, macrophages, and lymphocytes, leading to cellular damage and intravascular coagulation leading to ARDS

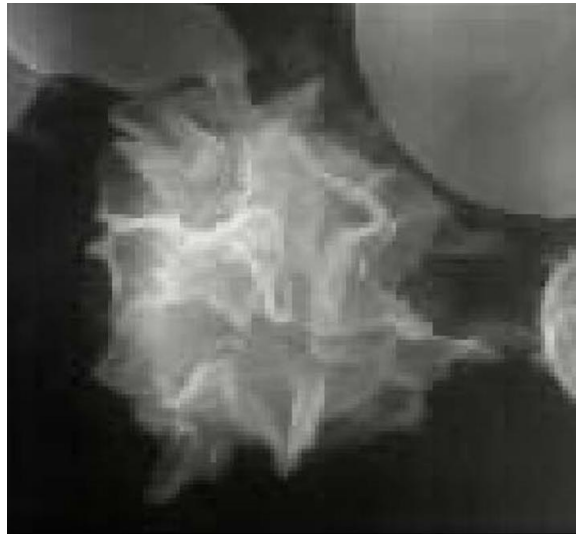
The role of dendritic cells

- Viral RNA activates endosomal TLR7 located in pDCs and produce type I and type III IFNs
- Early decrease in circulating pDCs?
- Apoptotic signaling of pDCs is increased and antigen-presenting cDCs is inhibited in severe disease
- STAT3 activation pathway inhibit DC function in and antigen presentation despite high levels of IL-6 associated with severe COVID-19

Laing AG, et al. *Nat Med* 2020; 26(10) :1623
Davitt E, et al. *Best Pract Res Clin Haematol*. 2022; 35(3): 101401

The role of Natural Killer Cells

- Severe COVID-19 is marked by NK cell cytopenia
- Less capable of producing IFN and TNF-α
- Overproduction of IL-6, IL-8 inhibits NKs function, again, through STAT3 pathway



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Adaptive Immunity Dysregulation

- Lymphopenia is predictive of poor outcomes and is a risk factor for secondary hospital-acquired infections, accounting for 50% of estimated mortality secondary to COVID-19
- T cell exhaustion (PD-1* upregulation $CD4^+$ lymphocytes)
- FOXP3-mediated negative regulatory mechanisms of T-cell activation are impaired
- Atypical T-cell differentiation seems to occur in COVID-19, producing T-cells that partially resemble Th1, Th2, Th17 and Tfh but lack their cardinal features

Kalfaoglu B, et al.,*Biochem Biophys Res Commun*. 2021; 538: 204

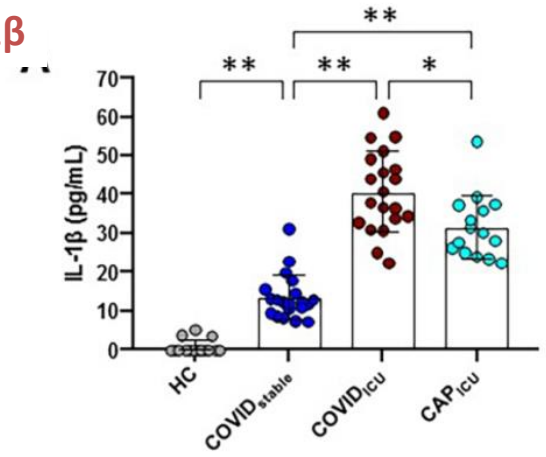
* PD-1 Programmed cell death 1

IMMUNE RESPONSES IN COVID-19: TH1 TO TH2 IMBALANCE

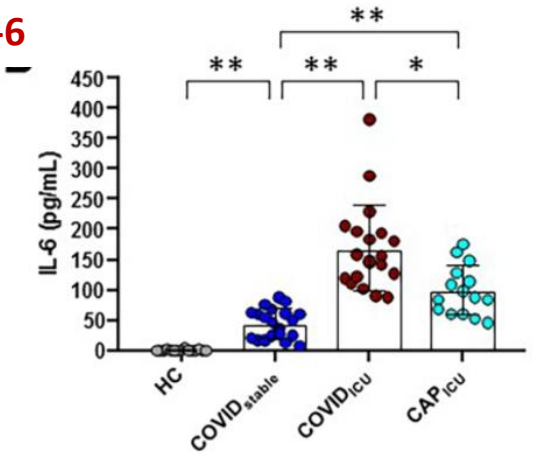
(McElvaney OJ, et al. *Am J Resp Crit Care Med* 2020; 202: 812-81)

- Healthy (HC, n=20)
- $COVID_{stable}$ (n=20)
- $COVID_{ICU}$ (n=20)
- CAP: community-acquired pneumonia (n=20)

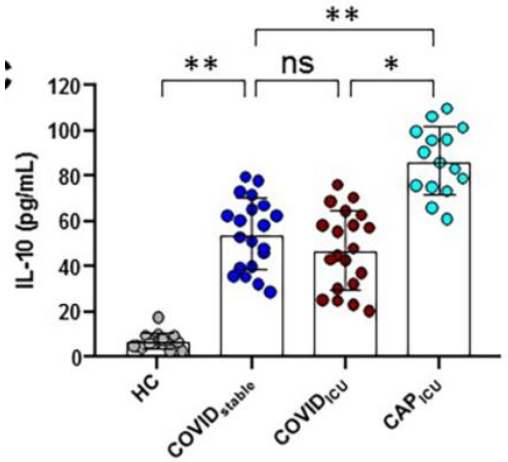
IL-1β



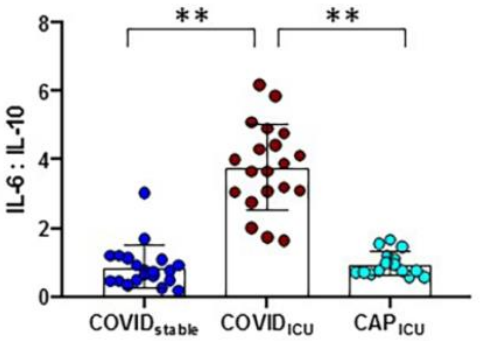
IL-6



IL-10

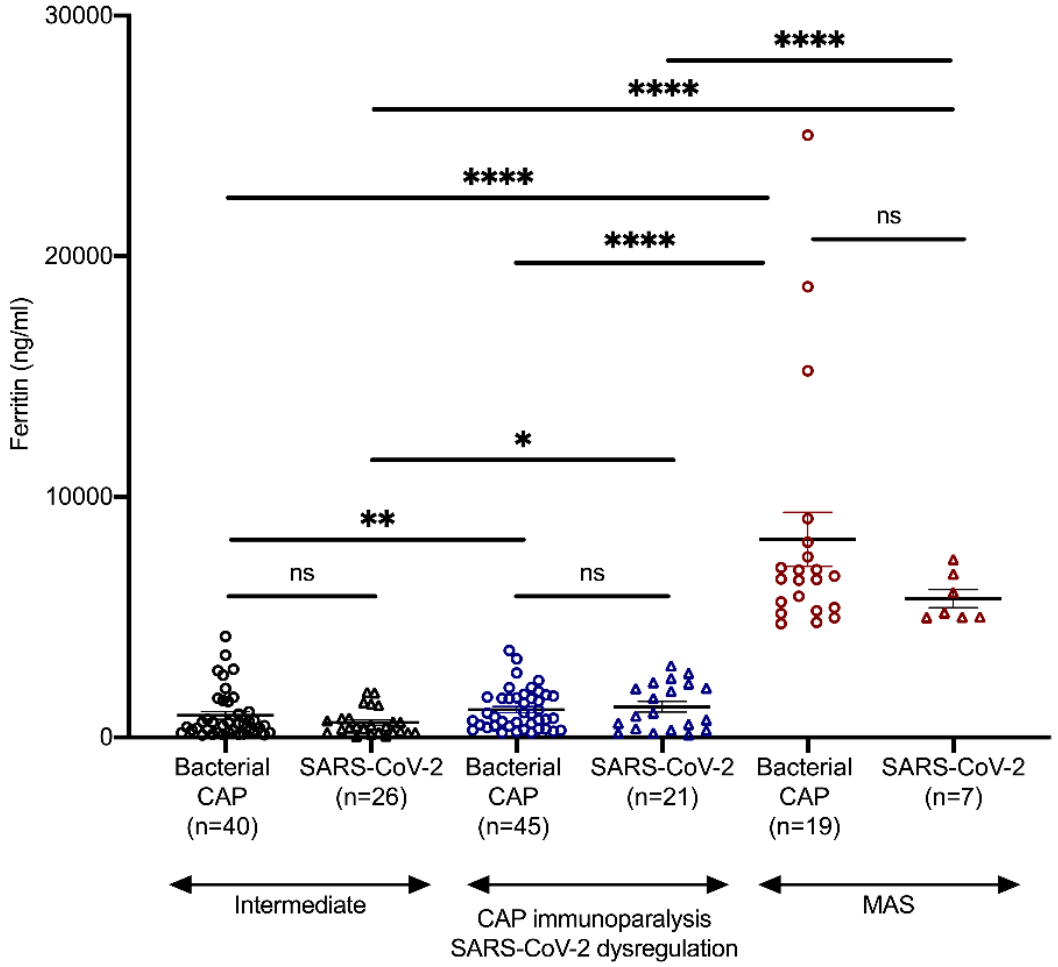


IL-6/ IL-10



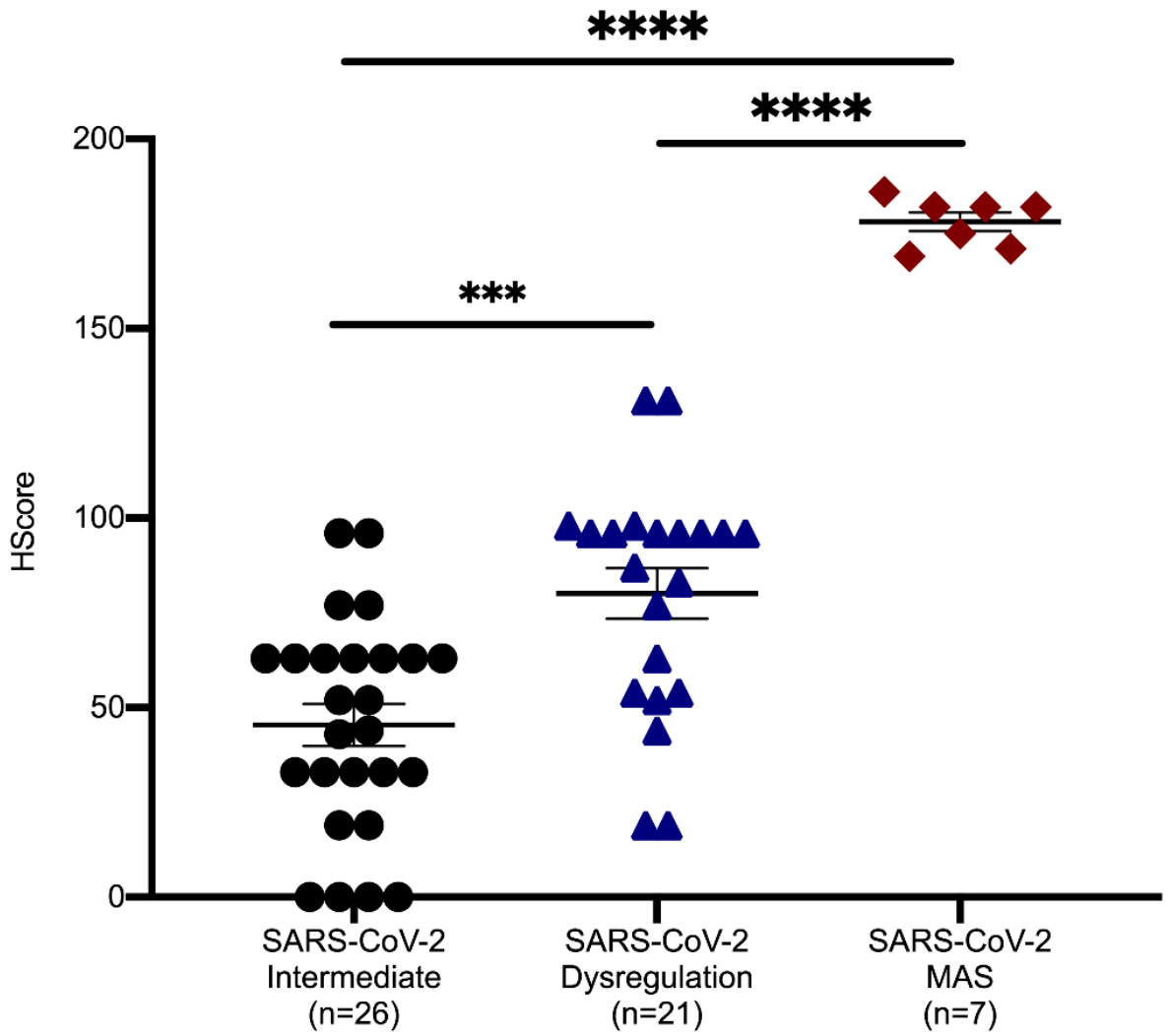
*p<0.05
**p<0.01

FERRITIN

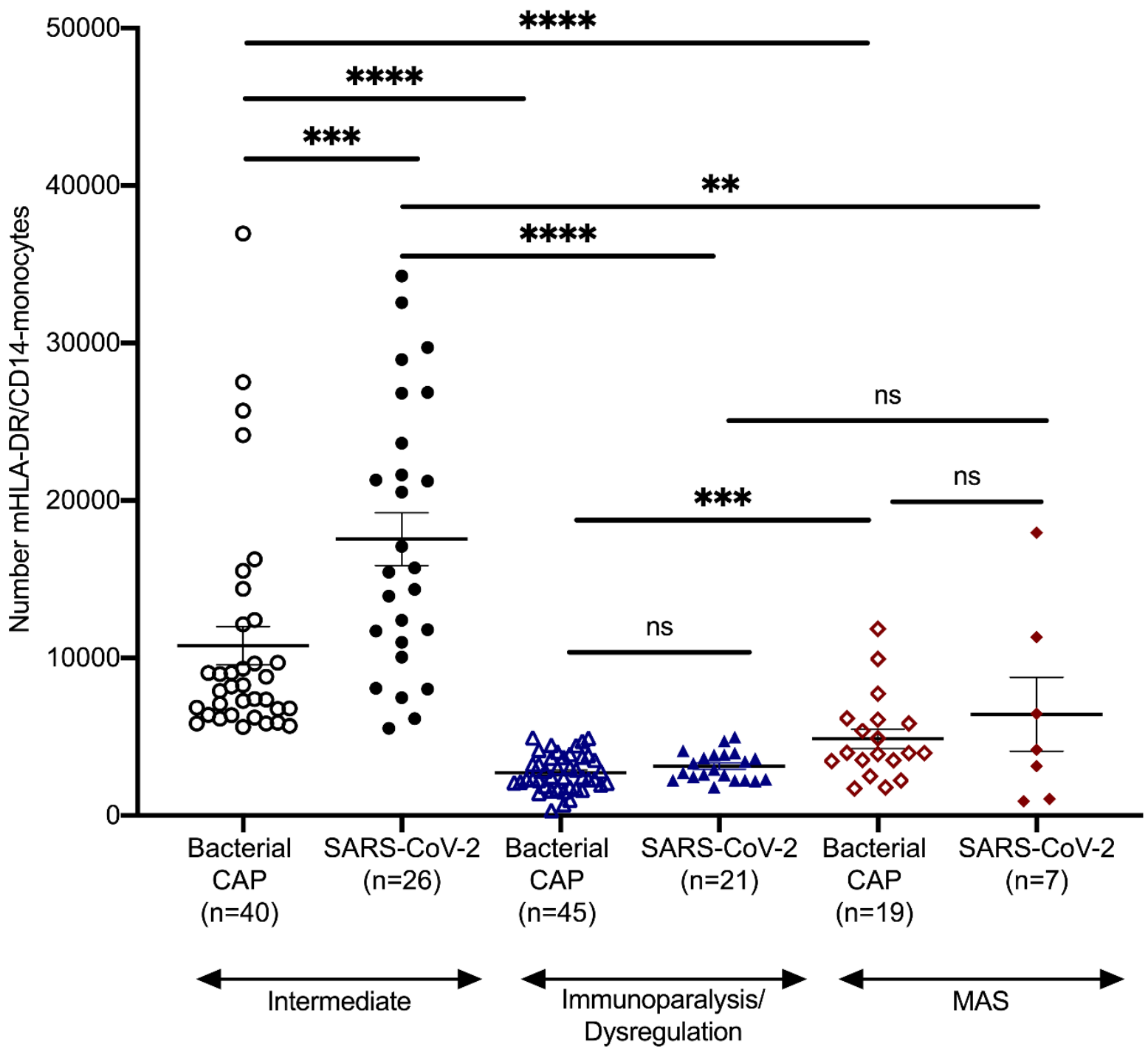


CAP: community-acquired pneumonia
MAS: macrophage activation syndrome
ns: non-significant
*p<0.05
**p<0.01
***p<0.001
****p<0.0001

HEMOPHAGOCYTOSIS SCORE



HLA-DR on CD14-cells



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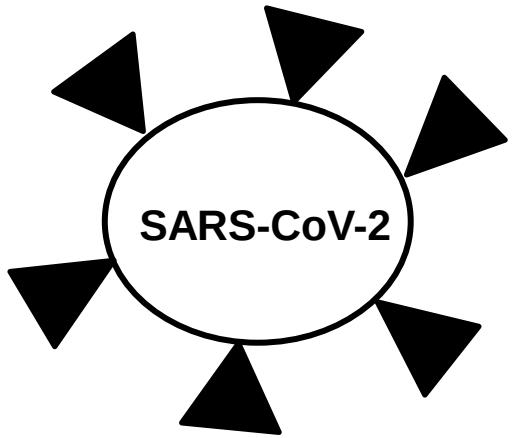
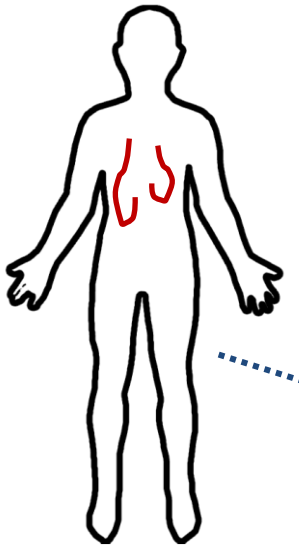
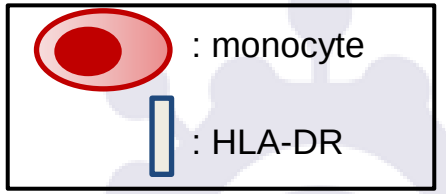
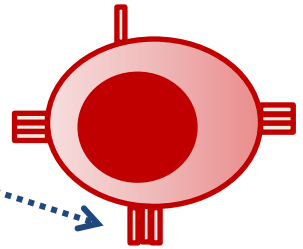




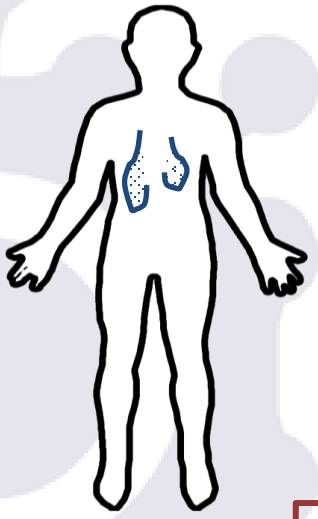
Infiltrates
↑CRP
↑D-dimers
↑AST/ALT

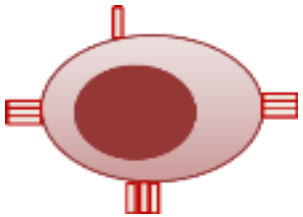




Vivid antigen-presentation

Macrophage activation: IL-1β (25%)



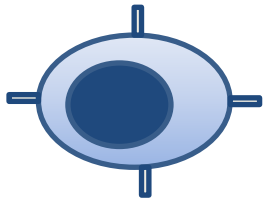


↑↑↑CRP/ferritin/TGs
↑↑D-dimers
↑↑AST/ALT

↑↑TNFα
↑↑IL-1β
↑↑IL-6

Moderate antigen-presentation

Immune dysregulation: IL-6 (75%)



↑↑CRP
↑↑D-dimers
↑↑AST/ALT

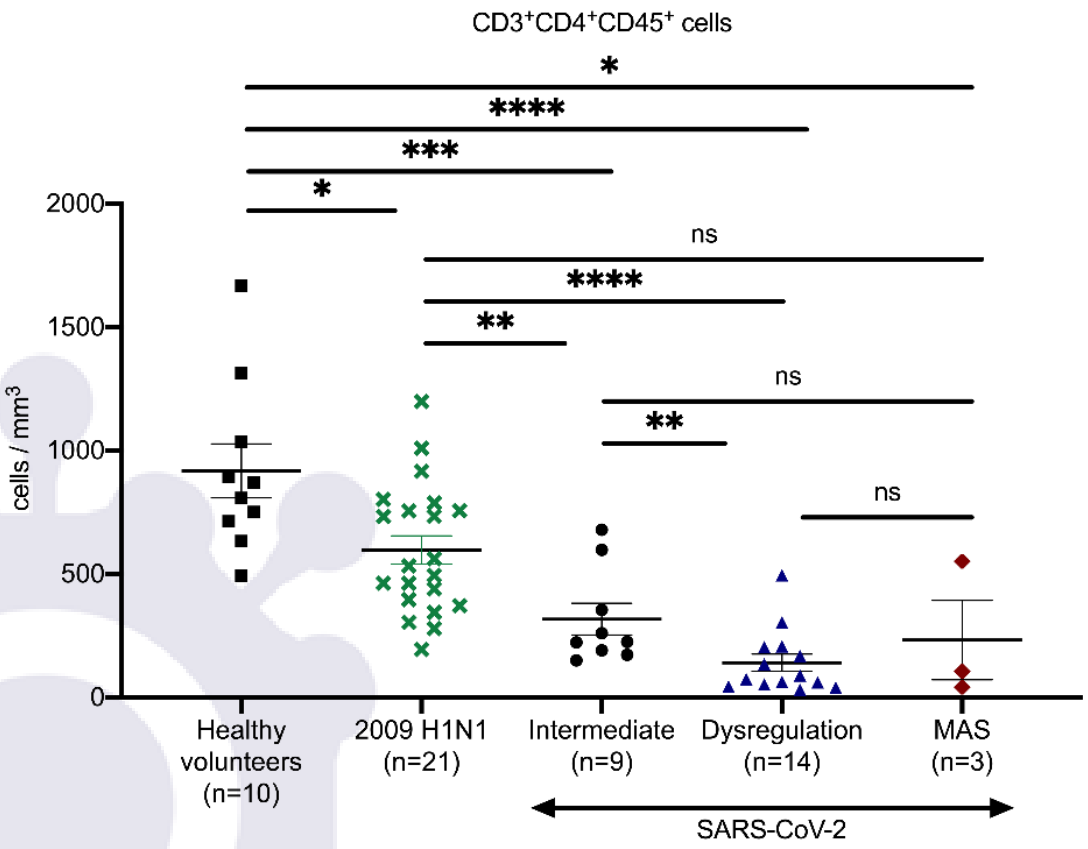
Weak antigen-presentation

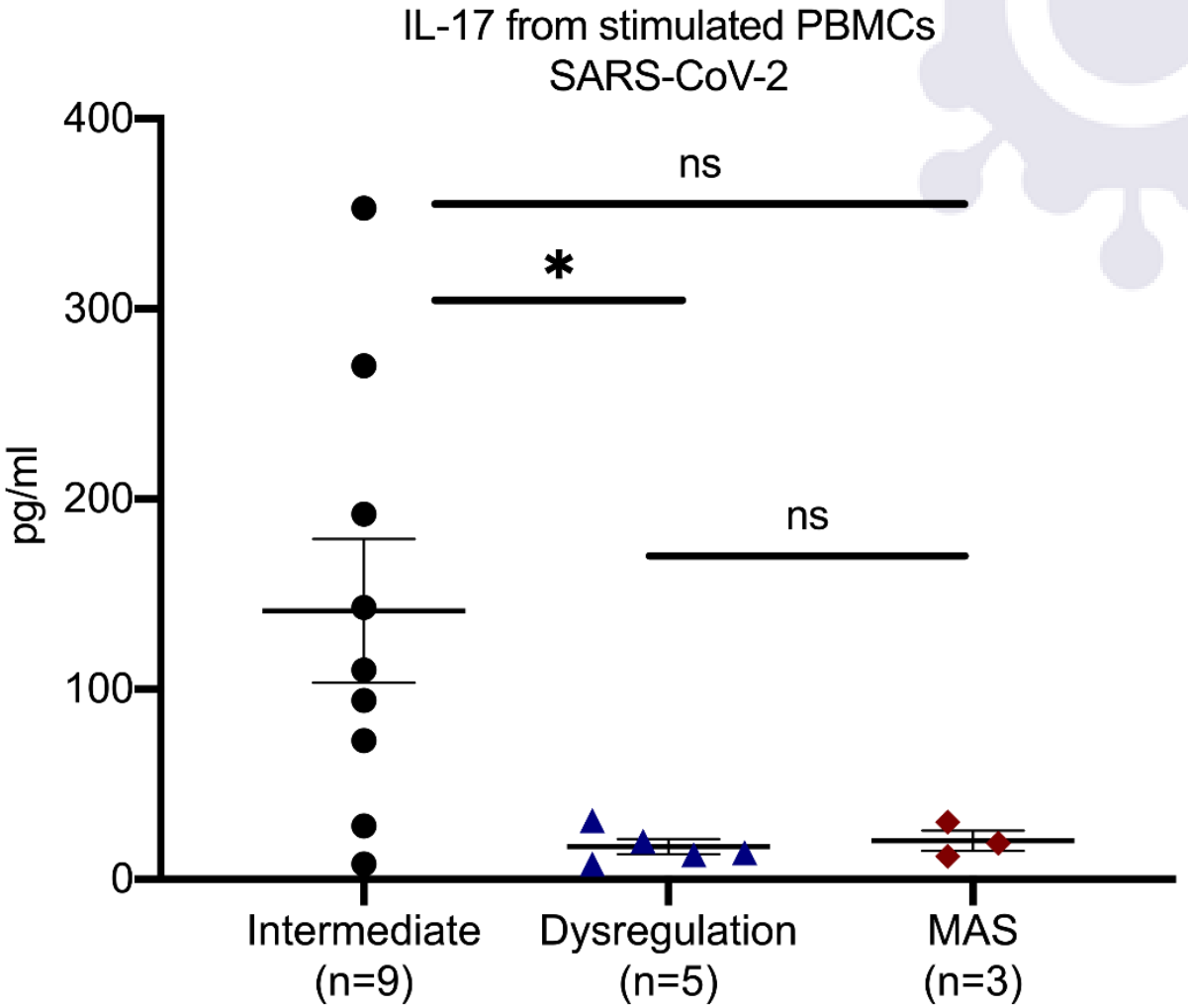
↑↑TNFα
↑↑IL-6

↓↓ CD4-/CD8-/T17-lymphocytes
↓ B-lymphocytes,↓IgGs
↓↓ NKT-/NK-cells

Giamarellos-Bourboulis EJ, et al. *Cell Host Microbe* 2020; 27: 992

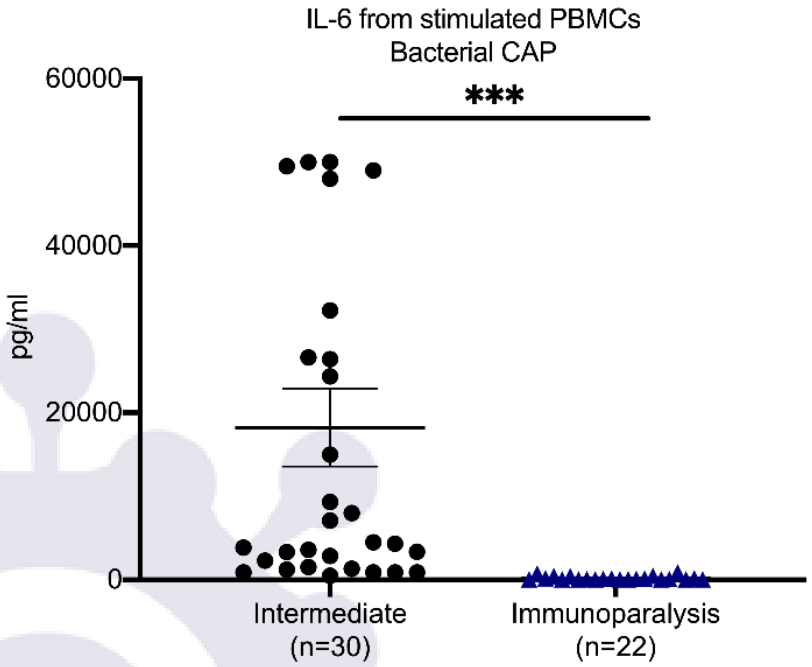
HYPO-FUNCTIONING T-CELLS

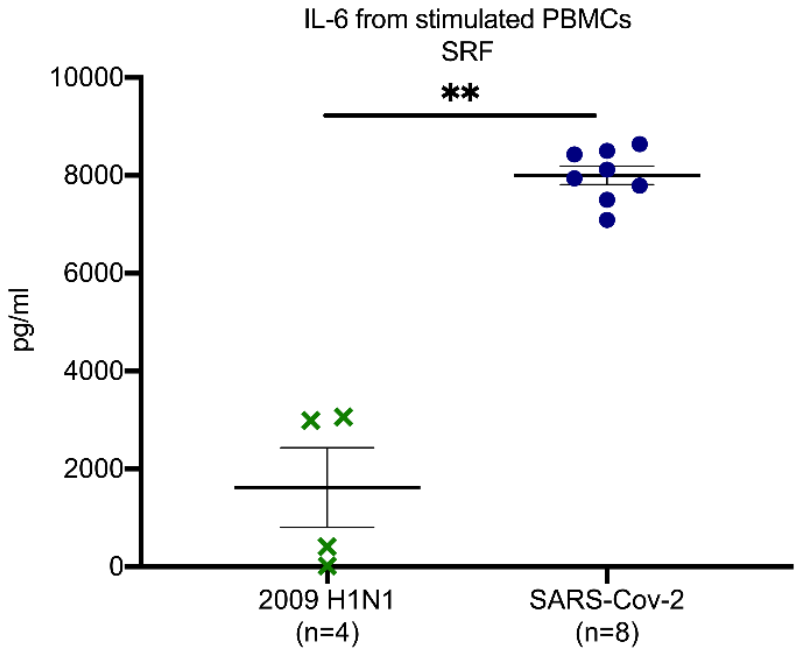


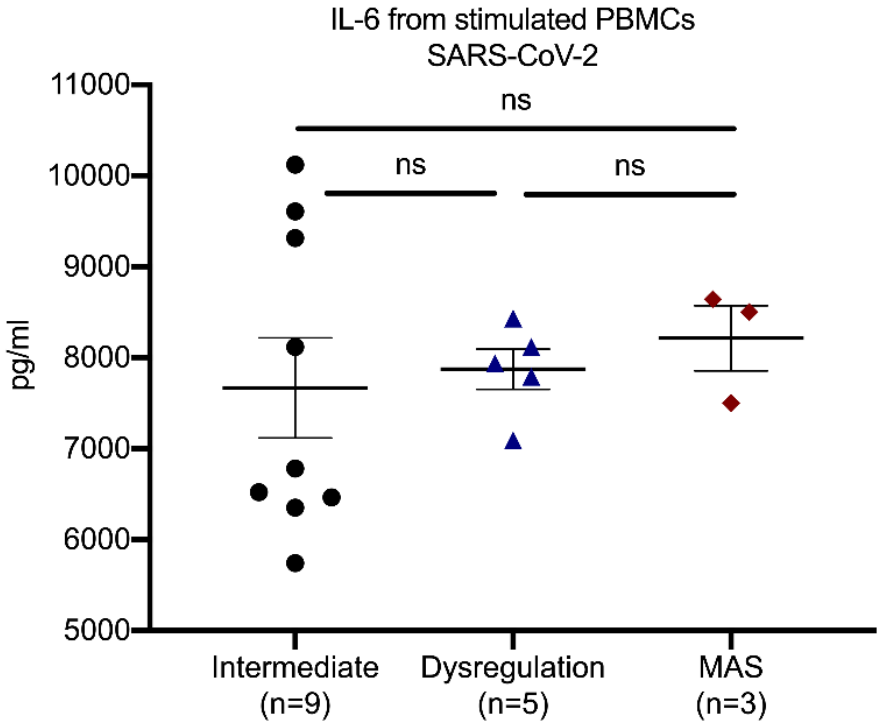


IL: interleukin
MAS: macrophage activation syndrome
ns: non-significant
PBMCs: peripheral blood mononuclear cells
*p<0.05; **p<0.01; ***p<0.001; ****p<0.0001

NO EXHAUSTION FOR CYTOKINE PRODUCTTION # SEPSIS







CAP: community-acquired pneumonia
IL: interleukin
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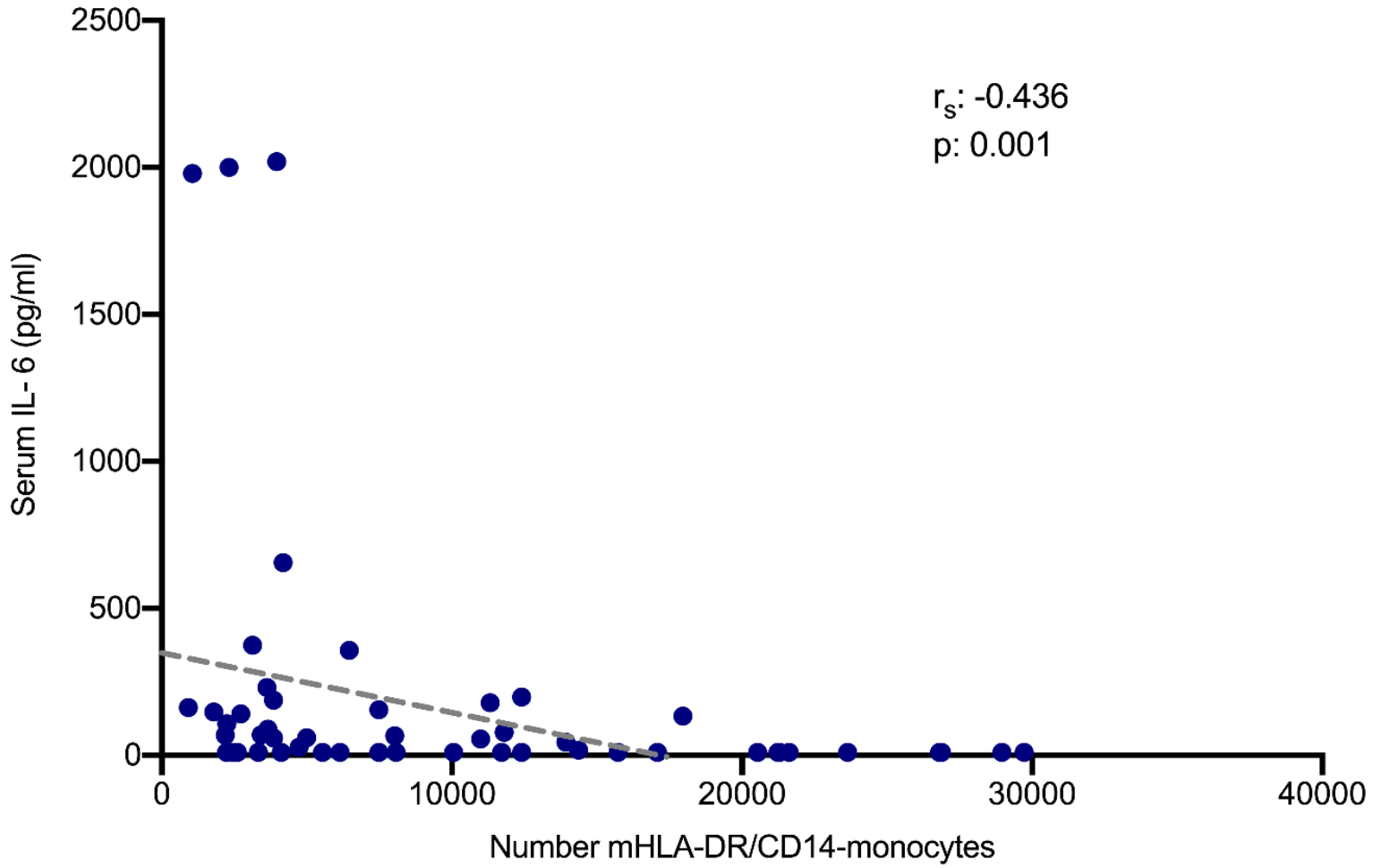
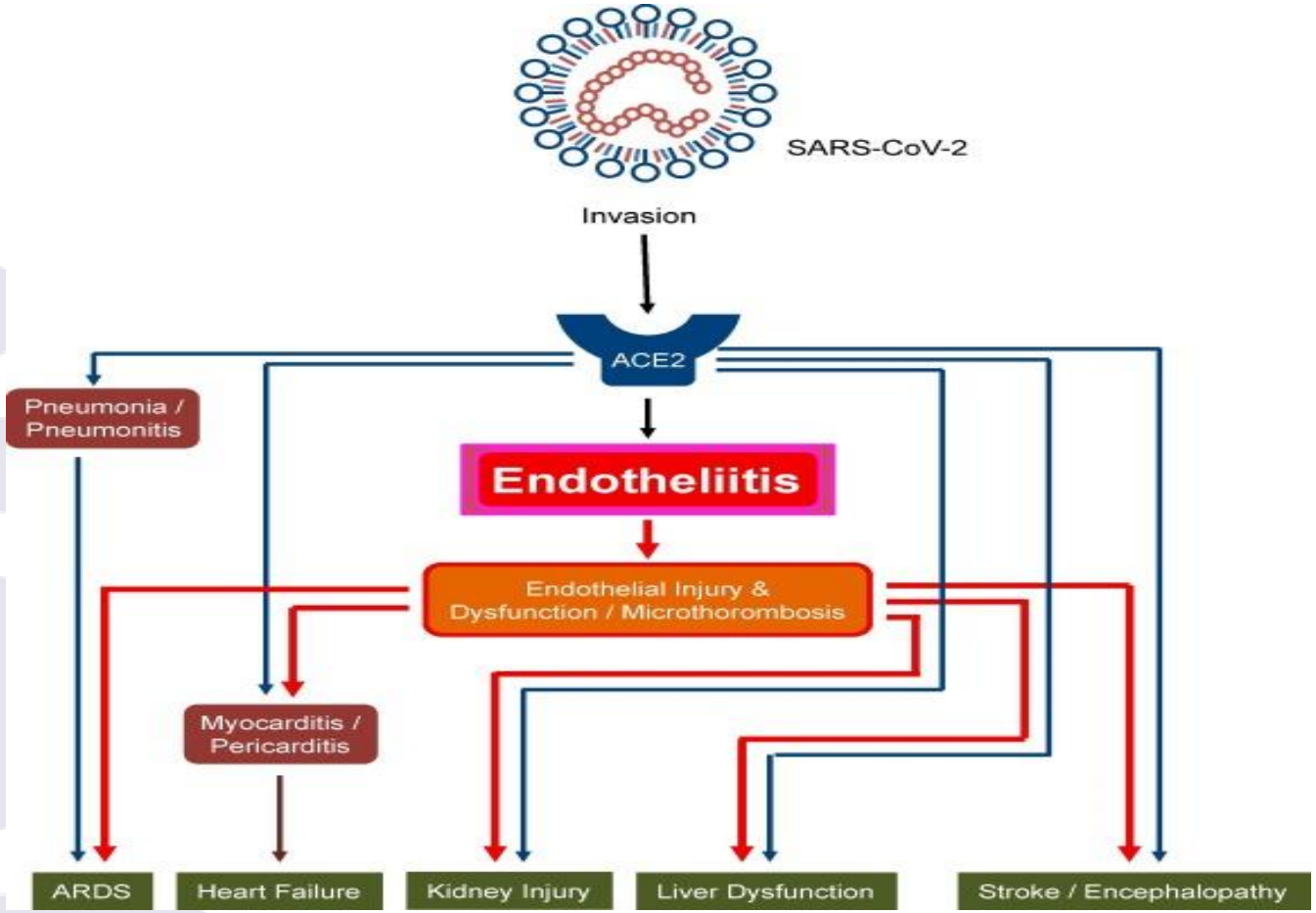
IL-6 DRIVES ↓↓↓ HLA-DR EXPRESSION

(Giamarellos-Bourboulis EJ, et al. *Cell Host Microbe* 2020; 27: 992-1000)



COVID-19 endothelitis



Hypercoagulation is a characteristic feature in the pathophysiology of COVID19 pneumonia

Traditionally attributed to vascular endothelitis

Endothelial injury triggers immunothrombosis; platelet dysfunction and microthrombi formation

Overexpression of CD42b/CD62p on platelets perpetuates the ominous cycle of immunothrombosis-immune dysregulation in severe COVID-19

Hattori Y. et. al. *Biochem Pharmacol* 2022 197: 11490
Solomonidi

Take home message

- Innate immune system overstimulation leads to hyperinflammation , cytokine storm, tissue damage and impaired antigen presentation
- Adaptive Immune demonstrates significant dysregulation with prominent T cell exhaustion, CD4 cell and NK cell cytopenia
- Patient can exhibit MAS or Immune dysregulation/suppression with very low HLA-DR but these immune states are not mutually excluded.

stop sepsis save lives

Spot It
Treat It
BEAT IT