Session 3: Chronic Inflammation

Multisystem Inflammatory Syndrome in Children (MIS-C) Post-SARS-CoV-2 Infection

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Multisystem Inflammatory Syndrome in Children (MIS-C) Post-SARS-CoV-2 Infection

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September 9, 2022

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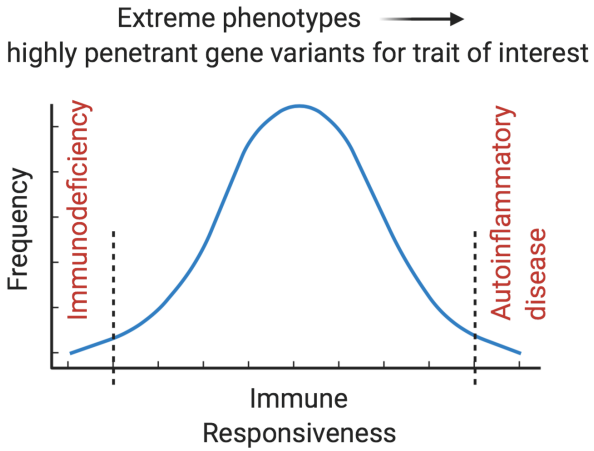
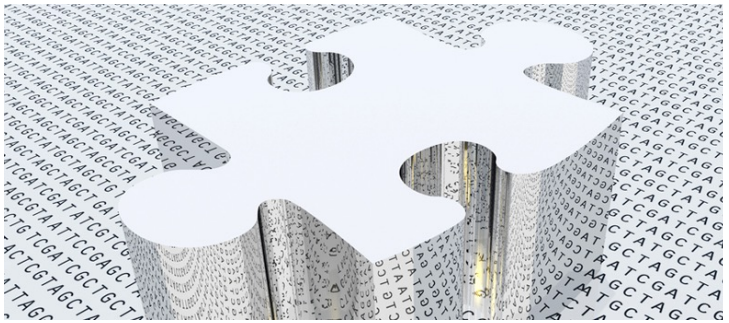
ve virology education
ame academic medical education
INTERNATIONAL WORKSHOP ON VIRAL INFECTIONS & INFLAMMATION 2022

Rare diseases, common insights





Graphic by Bruce Rolff, Shutterstock.

PI3K gene defects:
PIK3CD, PIK3R1 = **APDS**
PIK3CG = **IPGS**

Deficiency in ELF4, X-linked (**DEX**)

In Spring of 2020, we pivoted to apply our expertise on severe, rare, pediatric immune diseases to SARS-CoV-2-related disease.

Immunity

CellPress

Article

Immune dysregulation and autoreactivity correlate with disease severity in SARS-CoV-2-associated multisystem inflammatory syndrome in children

Anjali Ramaswamy,[1,14] Nina N. Brodsky,[1,2,14] Tomokazu S. Sumida,[1,3,14] Michela Comi,[1,3,14] Hiromitsu Asashima,[1,3] Kenneth B. Hoehn,[4] Ningshan Li,[5] Yunqing Liu,[5] Aagam Shah,[6,7] Neal G. Ravindra,[6,7] Jason Bishai,[6,7] Alamzeb Khan,[2] William Lau,[8,9] Brian Sellers,[8] Neha Bansal,[8,9] Pamela Guerrerio,[10] Avraham Unterman,[11] Victoria Habet,[2] Andrew J. Rice,[1] Jason Catanzaro,[2] Harsha Chandnani,[12] Merrick Lopez,[12] Naftali Kaminski,[11] Charles S. Dela Cruz,[11] John S. Tsang,[8,9] Zuoheng Wang,[5] Xiting Yan,[5,7] Steven H. Kleinstein,[4,13] David van Dijk,[6,7] Richard W. Pierce,[2] David A. Hafler,[1,3] and Carrie L. Lucas[1,15,*]

Multisystem inflammatory syndrome in children (MIS-C)

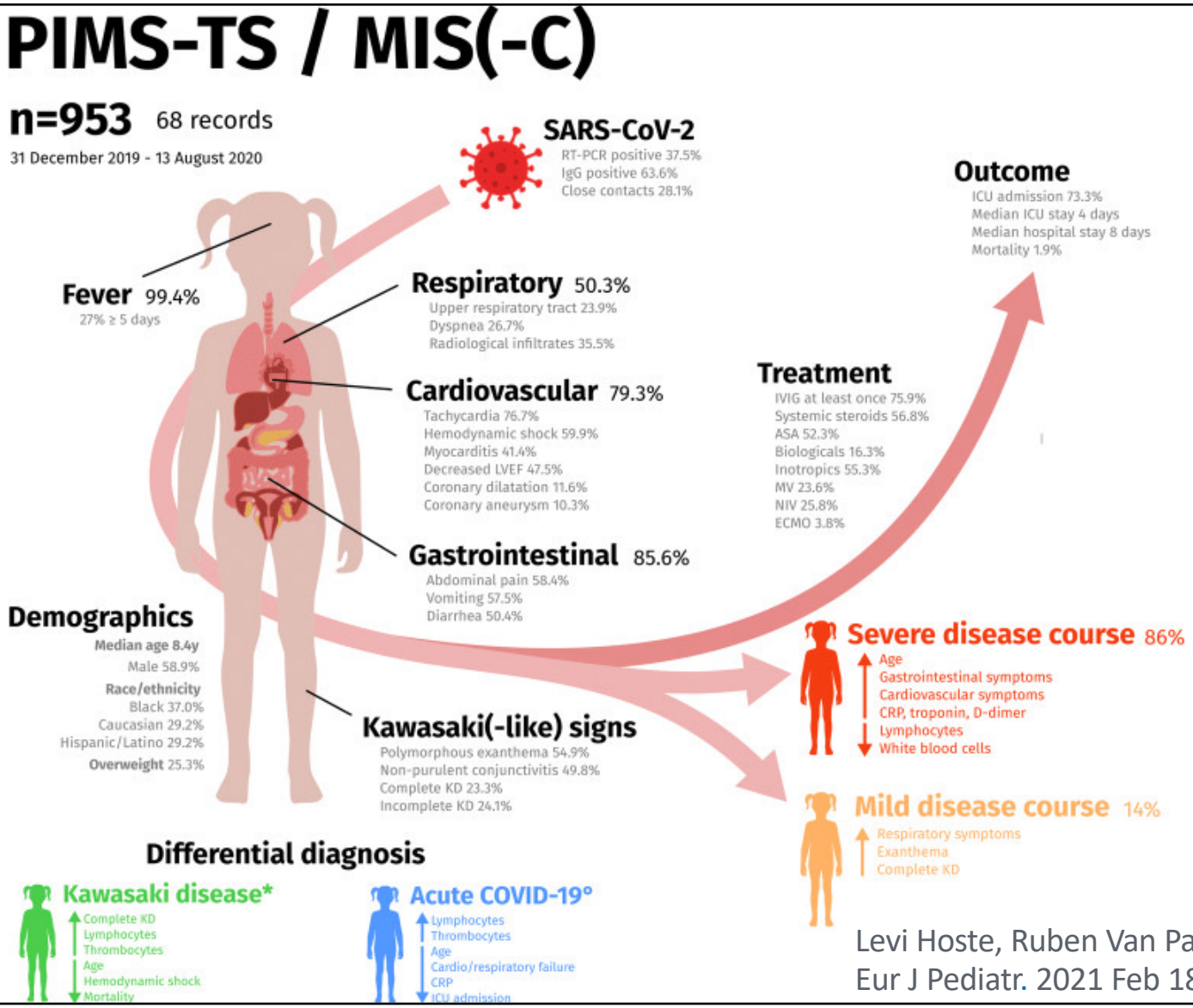
- April 2020: Rise in Kawasaki-like syndrome recognized in Italy
- April/May 2020: Royal College of Paediatrics, NYC, CDC, ECDC, WHO, PCIS issue health alerts

Some overlap with:

- Kawasaki disease/shock
- Myocarditis
- Septic shock
- TSS - Staph/Strep

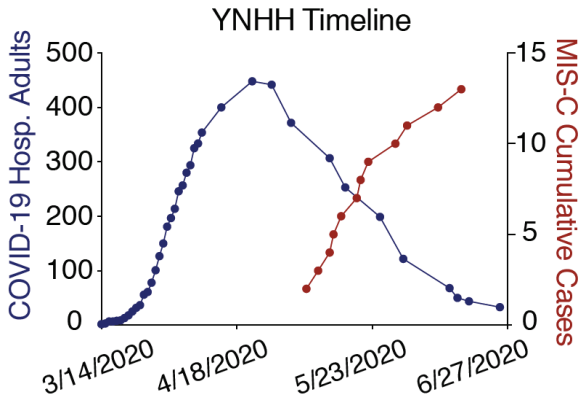
Case Definition

- An individual aged <21 years presenting with fever*, laboratory evidence of inflammation**, and evidence of clinically severe illness requiring hospitalization, with multisystem (>2) organ involvement (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic or neurological); AND
- No alternative plausible diagnoses; AND
- Positive for current or recent SARS-CoV-2 infection by RT-PCR, serology, or antigen test; or exposure to a suspected or confirmed COVID-19 case within the 4 weeks prior to the onset of symptoms



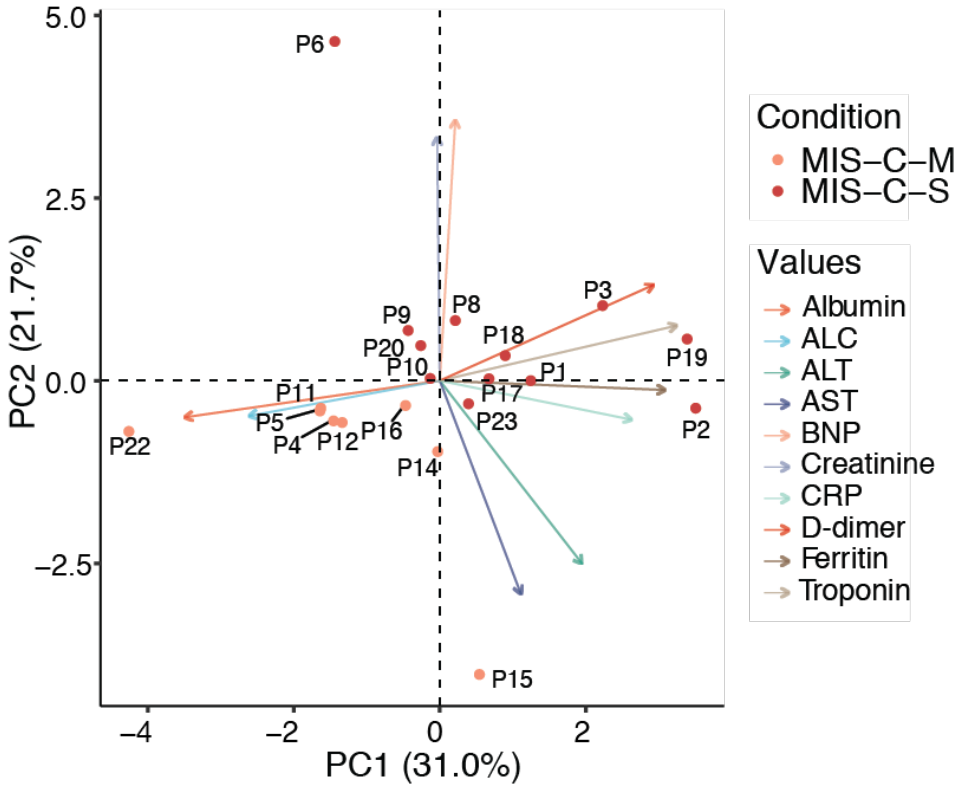
Levi Hoste, Ruben Van Paemel, Filomeen Haerynck
Eur J Pediatr. 2021 Feb 18;1-16.

23 MIS-C patients in our study were categorized clinically as severe or moderate



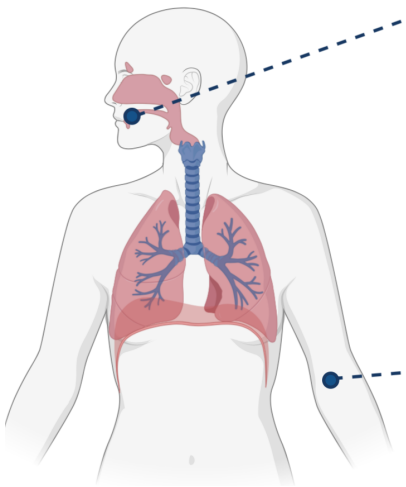
Severe: required vasoactive medications and/or positive pressure ventilatory (PPV) support.

Moderate: did not require this level of support, although some did require ICU admission.

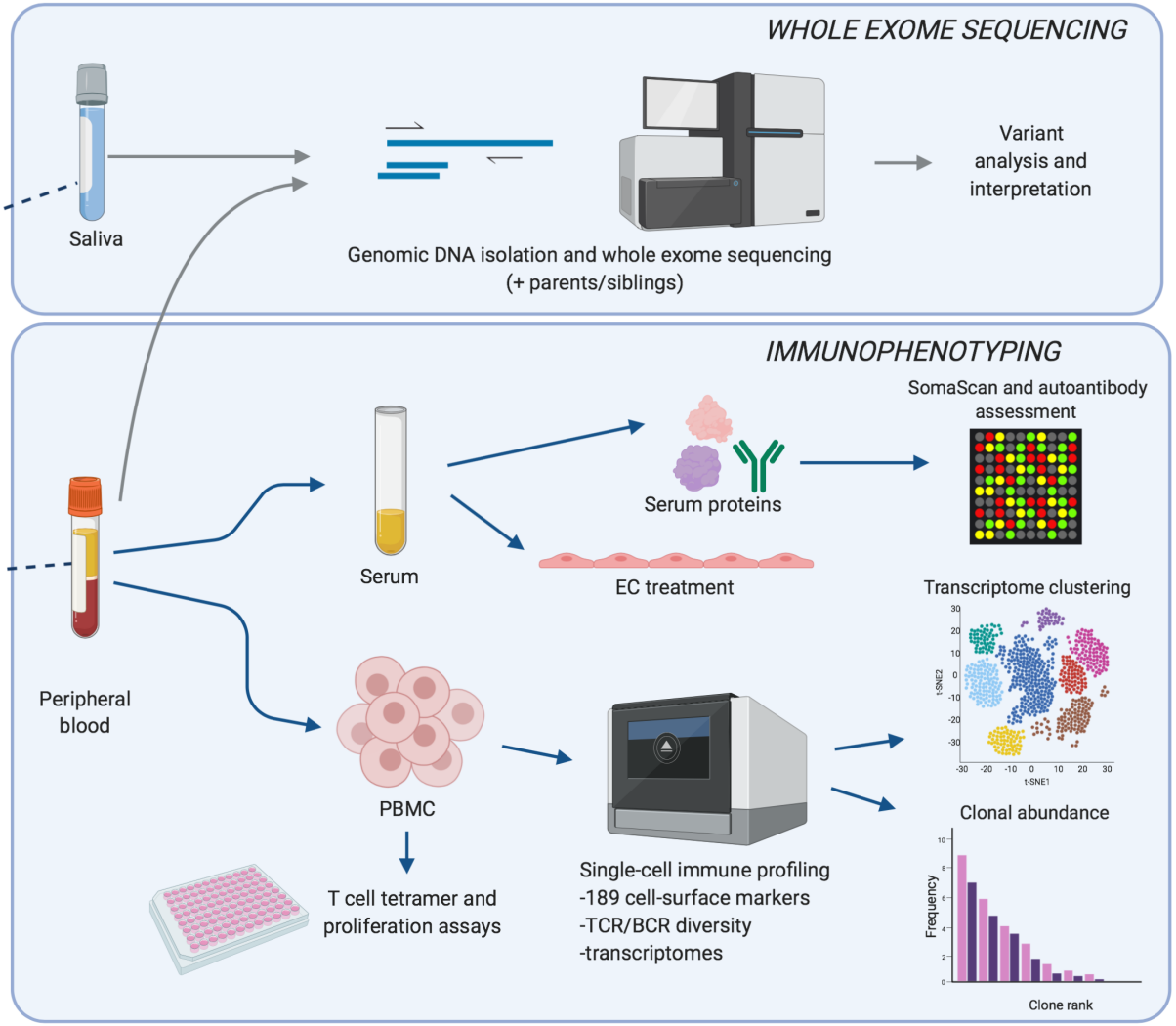


Our approach

COVID Human Genetic Effort
JL Casanova
H Su

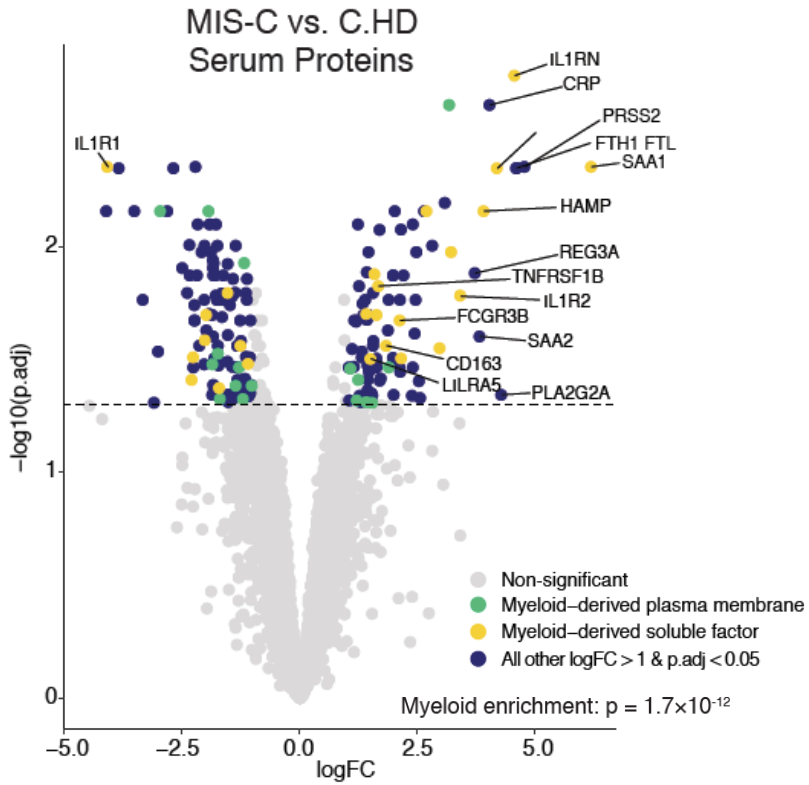


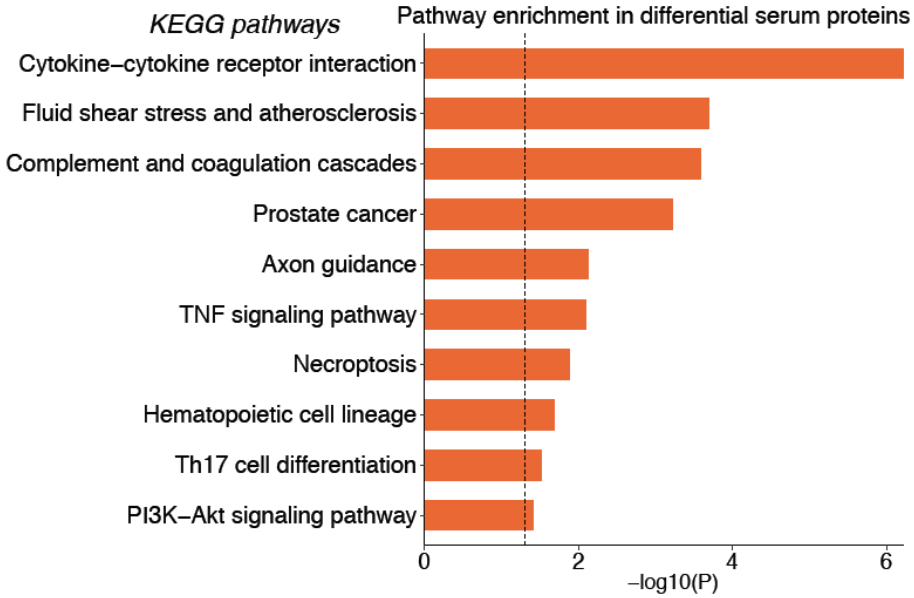
Nina Brodsky



Anjali Ramaswamy
Tomo Sumida
Michela Comi

Serum proteomics highlights cytokine storm pathways





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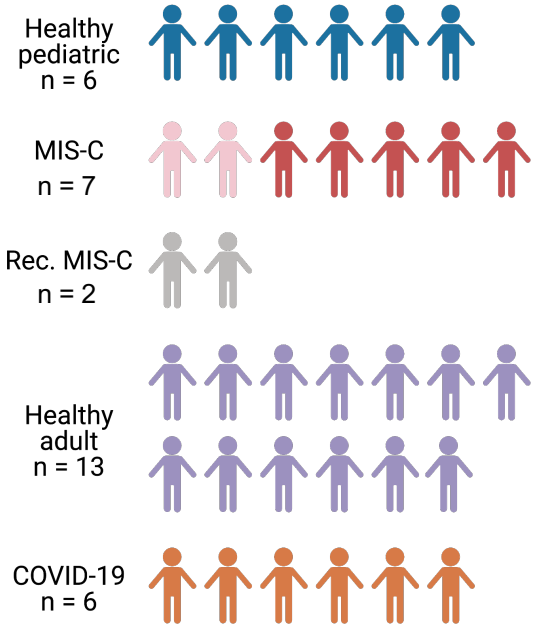
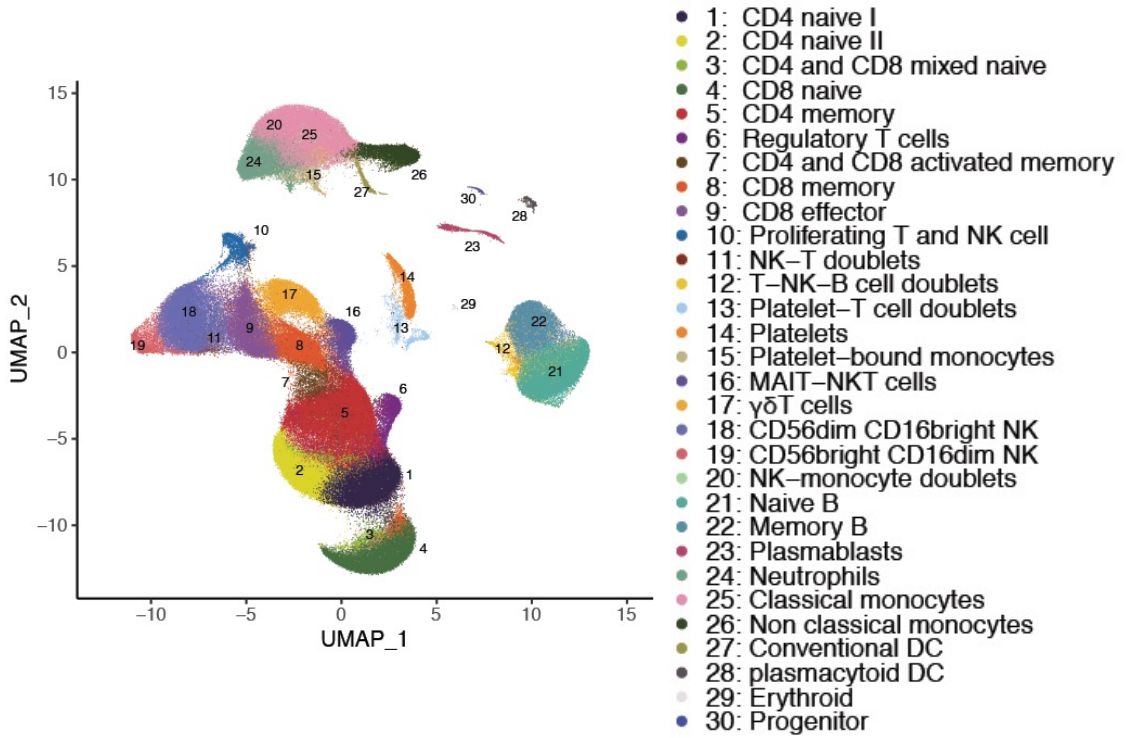
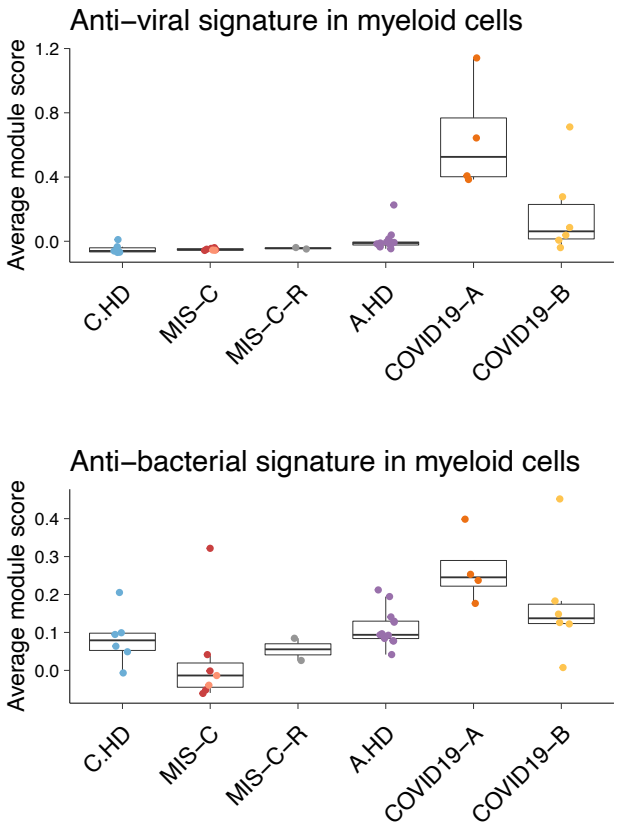
Collaboration with laboratory of Dr. John Tsang, NIAID

Leveraging scRNAseq to elucidate MIS-C pathophysiology



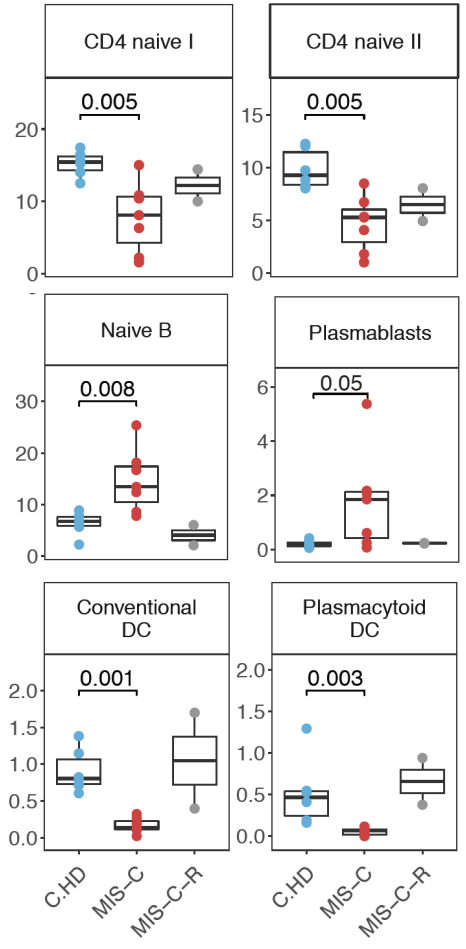


MIS-C is a post-infectious inflammatory episode



Signatures from Lydon et al. EBioMedicine. 2019.

NB:
-No EBV/CMV reads detected



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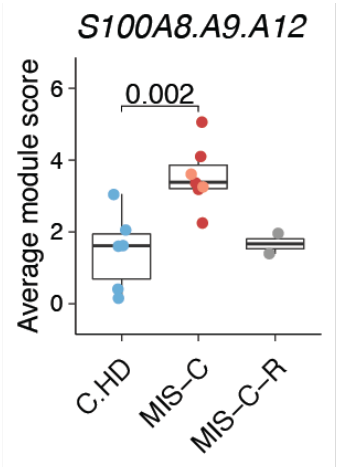
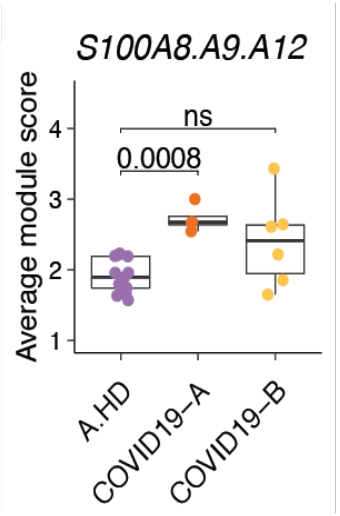
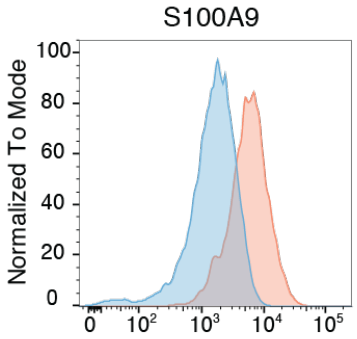
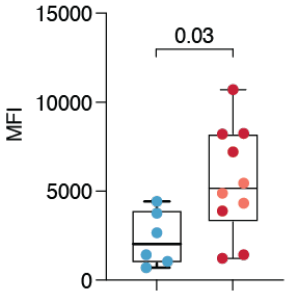
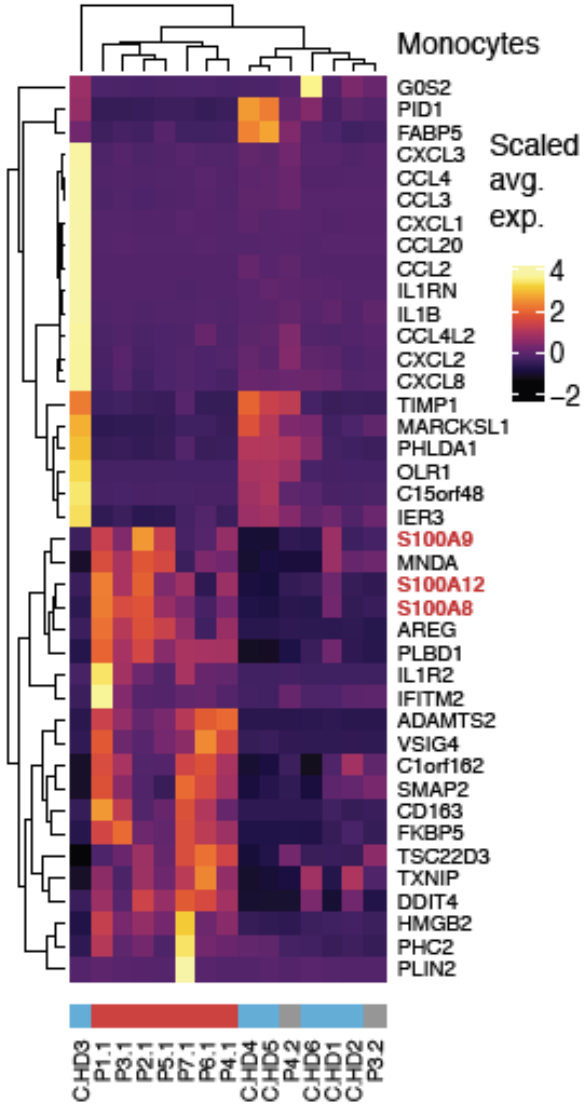
Elevated myeloid *S100A* alarmins











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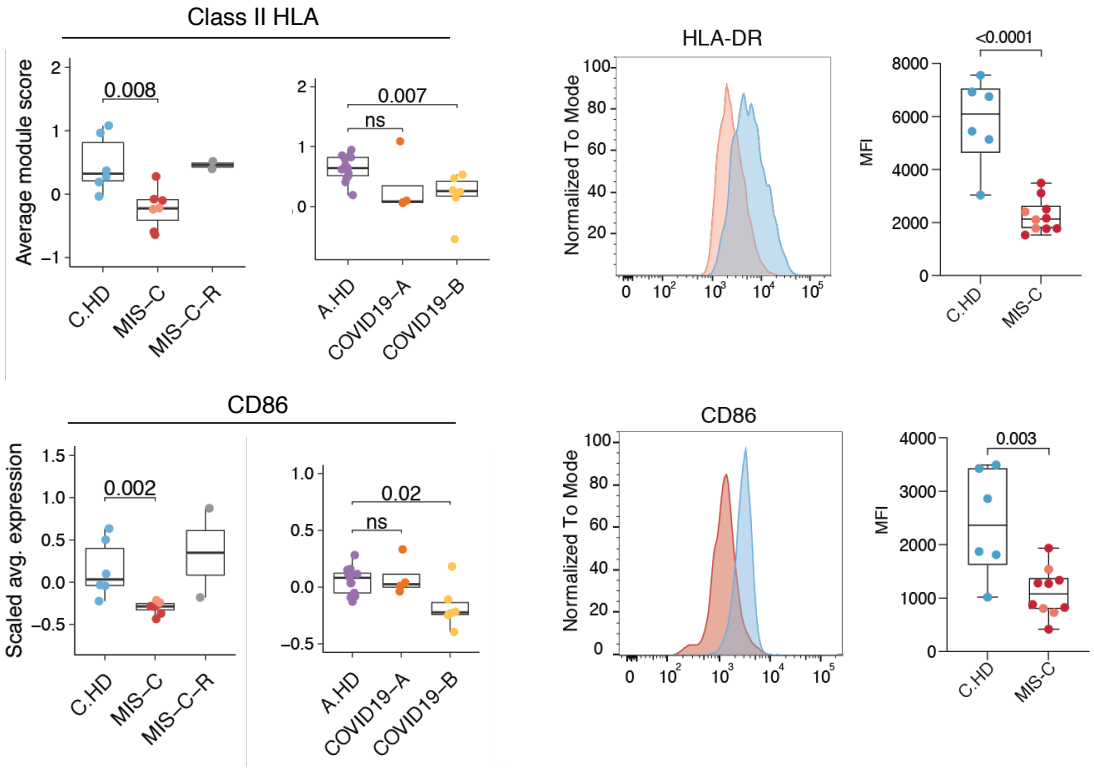
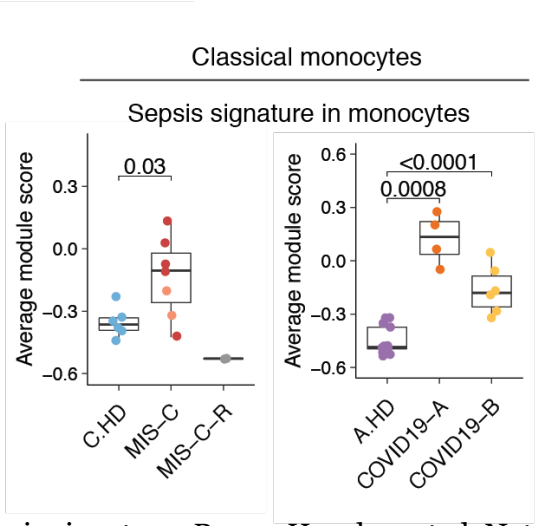
C.HD MIS-C-S MIS-C-M MIS-C-R

Reduced HLA-II and CD86 with sepsis-like signature

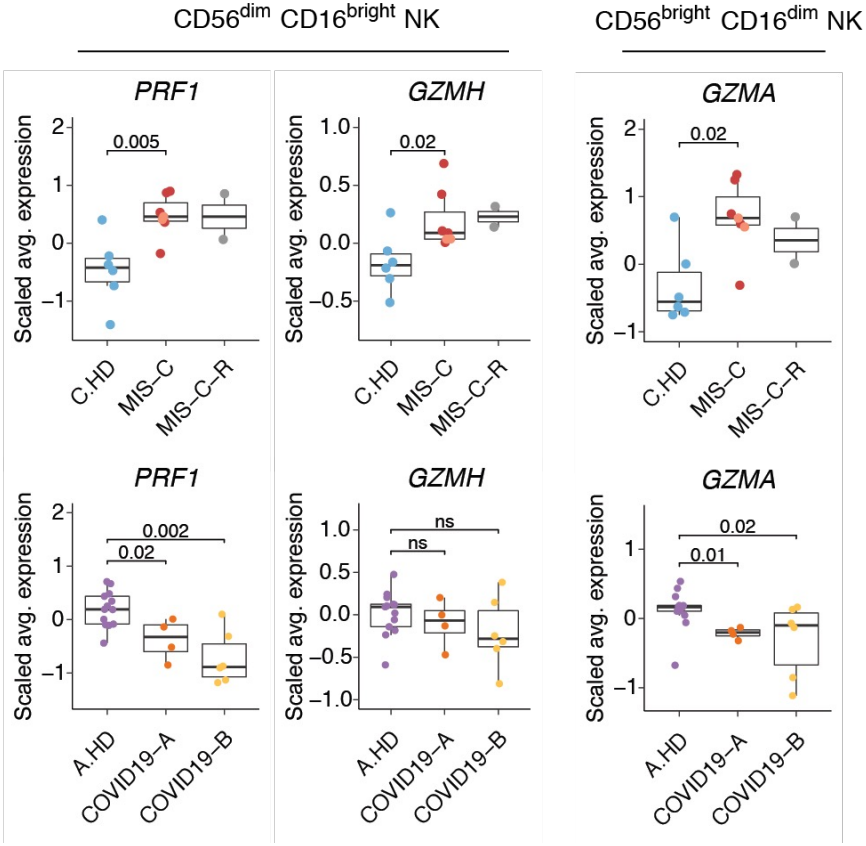


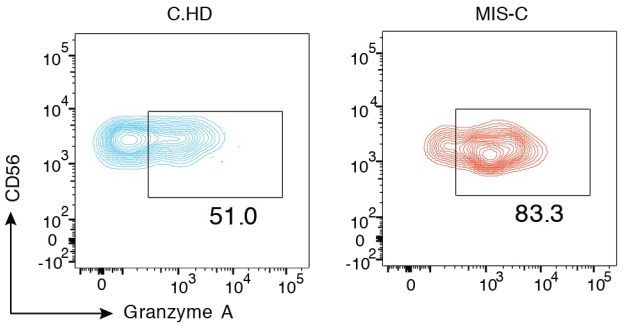


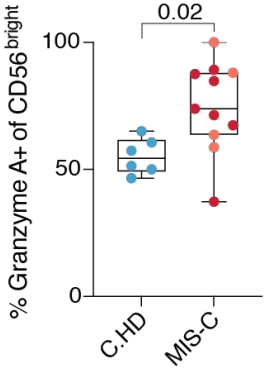
Sepsis signature: Reyes, Hacohen et al. Nat Med. 2020.

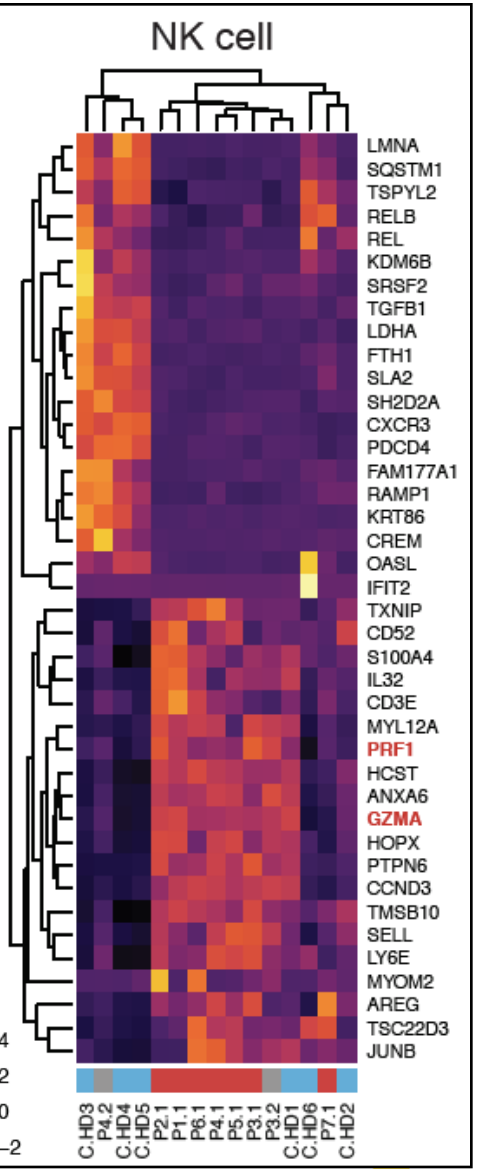
C.HD MIS-C-S MIS-C-M MIS-C-R

Elevated NK (CD8) cytotoxicity genes









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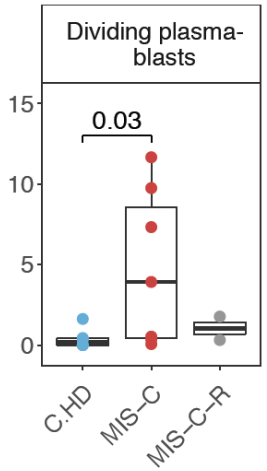
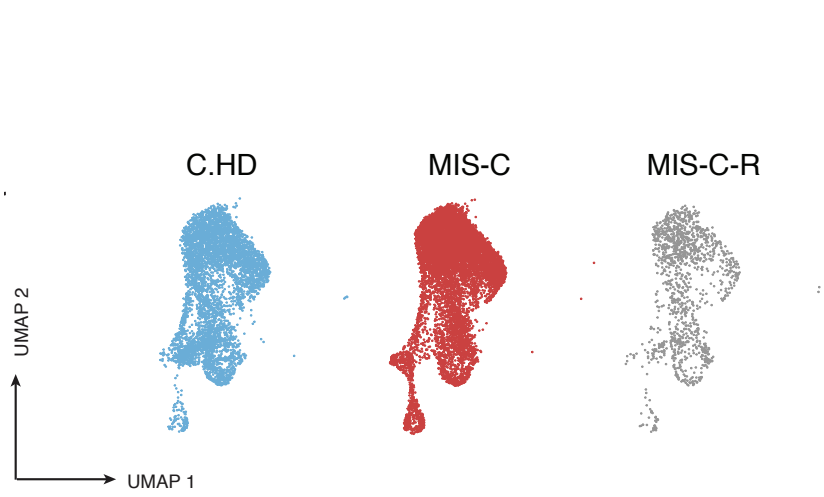
C.HD MIS-C-S MIS-C-M MIS-C-R

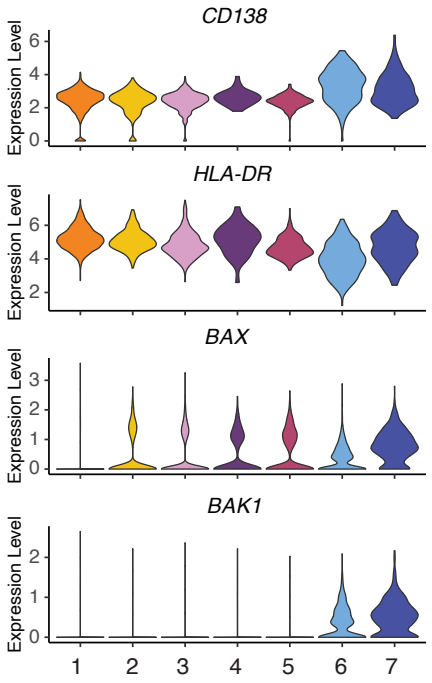
Recap

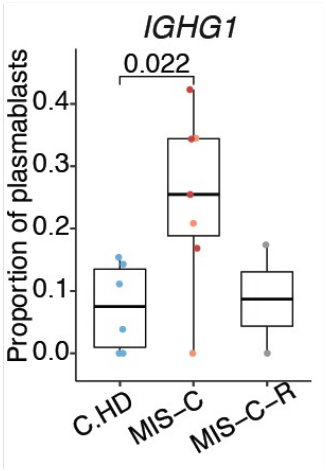
- No evidence of:
  - gene signature for respiratory viral/bacterial infection
  - EBV/CMV reactivation or correlation with initial EBV/CMV exposure
- Cannot rule out persistence of virus/particles in tissues (gut?)
- Innate response includes: elevated cytokines, S100A genes, and cytotoxicity signature of NK cells
- What about the adaptive immune response by T/B cells?

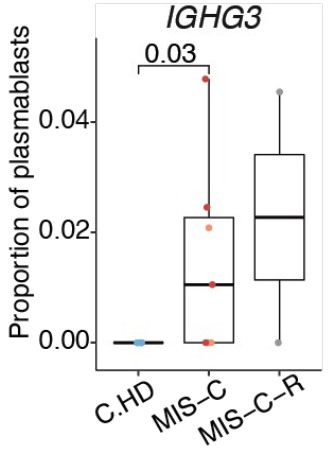


Expansion of short-lived plasmablasts enriched for IgG1/IgG3



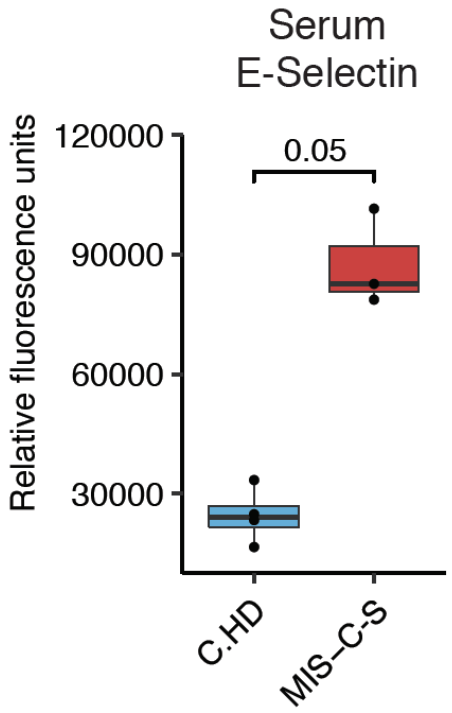


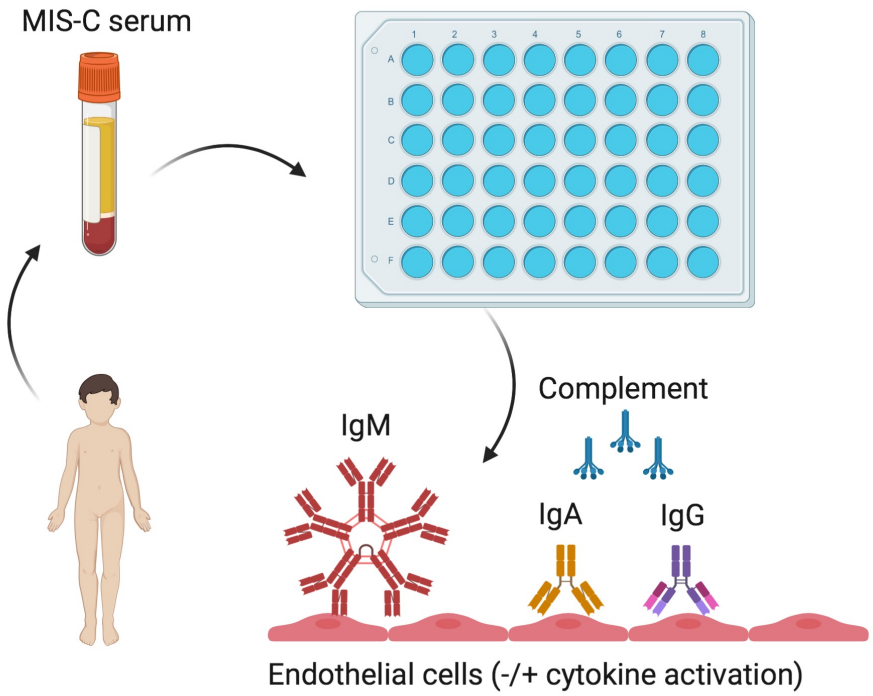




C.HD MIS-C-S MIS-C-M MIS-C-R

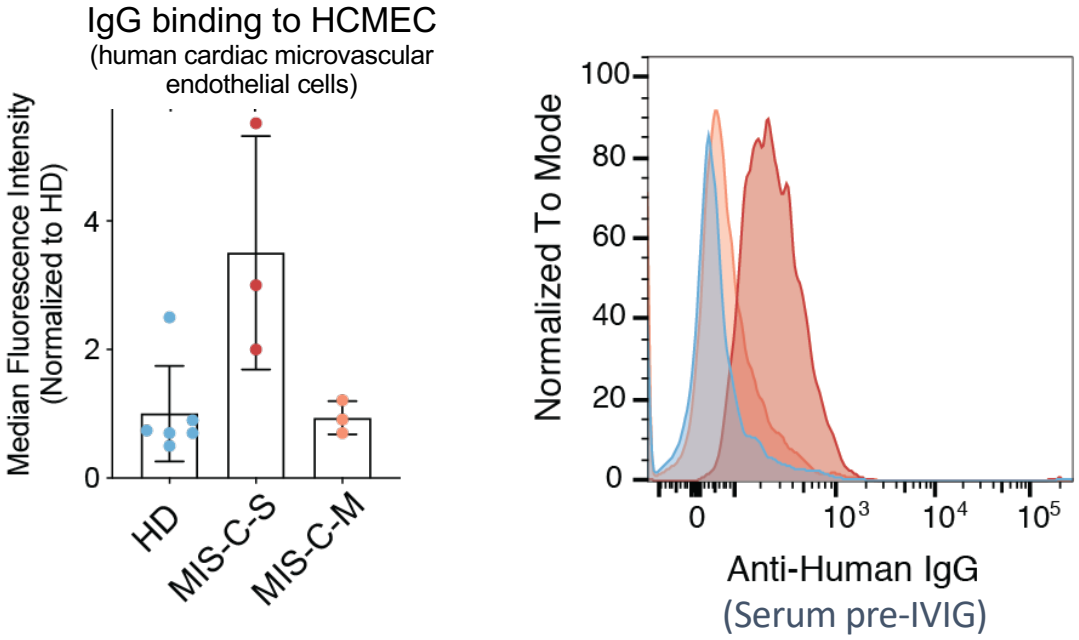
Severe MIS-C patients exhibit: elevated serum E-selectin





Drs. Ric Pierce and Jordan Pober

Severe MIS-C patients exhibit: increased serum IgG binding to endothelial cells



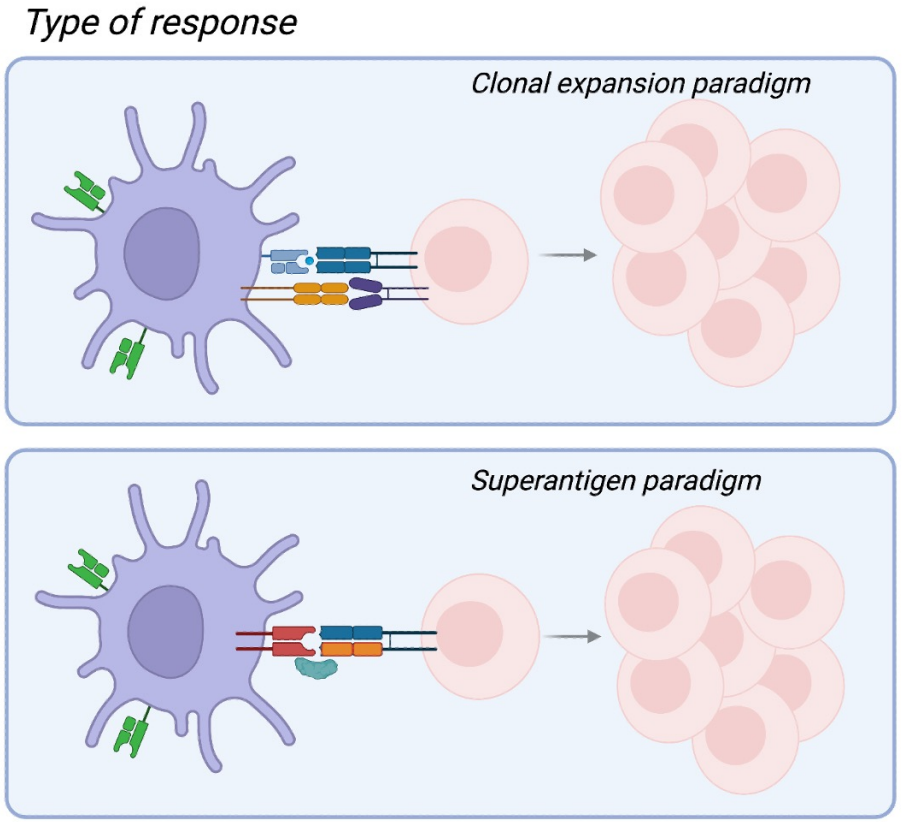
- It is unknown if autoantibodies are a cause or consequence of tissue damage.
- How to account for the delay between SARS-CoV-2 infection and MIS-C?

Superantigen drives broad activation of T cells expressing specific β chains

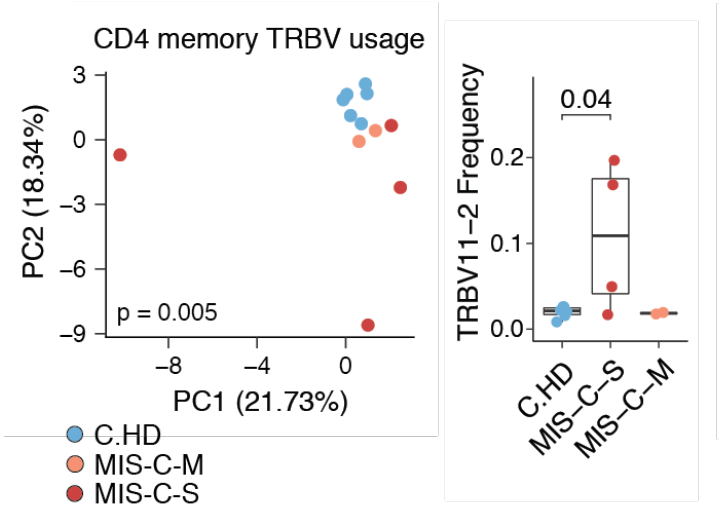
Examples:

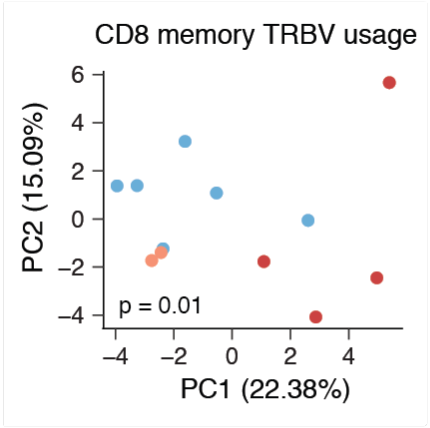
- Staphylococcal toxic shock toxin – TSS
- Staphylococcal enterotoxins – food poisoning
- Staphylococcal exfoliating toxins – scalded skin syndrome
- Streptococcal pyrogenic exotoxins – shock

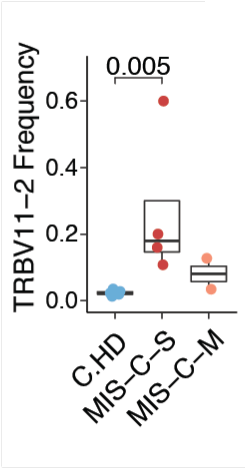
- Is there evidence for this in MIS-C?



Severe MIS-C patients exhibit: TCR skewing with expanded TRBV11-2 (TCR Vβ 21.3)

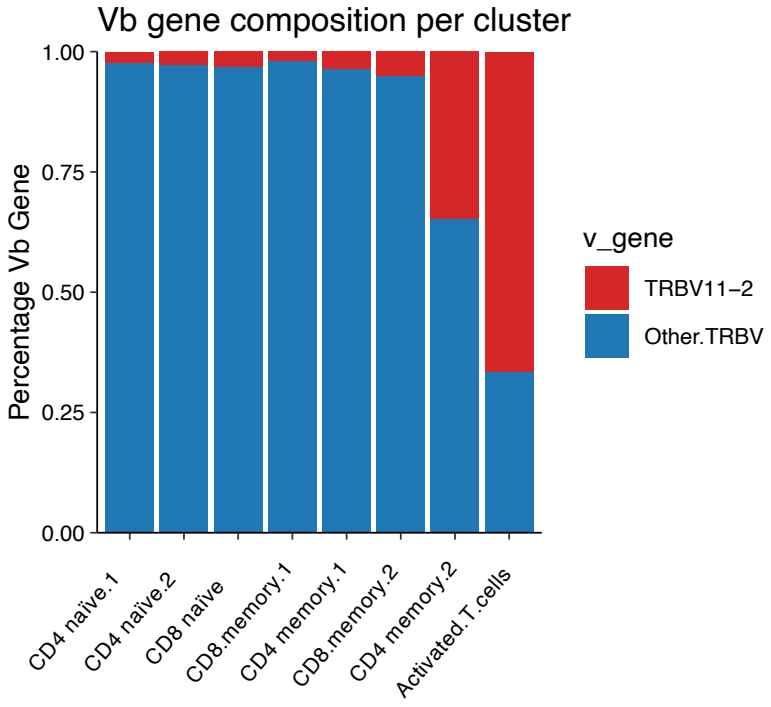






Also reported by Moshe Arditi's team in Porritt et al. JCI 2021 and seen by others (Alex Belot, Nichola Cooper, Filomeen Haerynck/Simon Tavernier, Gigi Notarangelo, etc.)

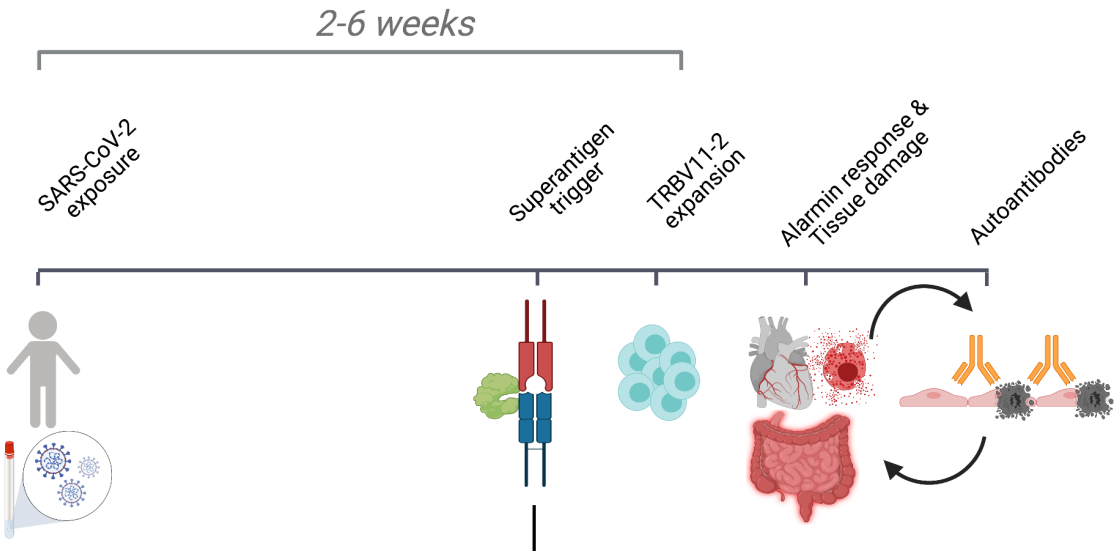
TRBV11-2+ T cells are activated/memory subtypes



Investigations ongoing to further characterize these T cells.

- High for activation markers
- No specific TCR alpha chain pairing
- No evidence conclusively showing this is driven directly by SARS-CoV-2 (adult data)

Hypothetical drivers of MIS-C



Genetic susceptibility alleles

SARS-CoV-2:
-Rare, delayed, direct effect of SARS-CoV-2 in youth? Spike in plasma of MIS-C patients (Yonker…Fasano, et al. JCI. 2021)

Other SAg source:
-Secondary infection with another pathogen?
-Heightened sensitivity to usually benign levels of SAg?
-Increased SAg toxin production by microbiome?
-Relevance of carrier status?

Reduced incidence of MIS-C over time

Table 2. Nationwide Data on the Incidence of MIS-C During the Alpha, Delta, and Omicron Waves in Israel

Pandemic wave data[a]	Alpha	Delta	Omicron	Total
MIS-C cases, No. (%)[b]	103 (40.5)	115 (45.3)	36 (14.2)	254
SARS-CoV-2 infections in persons younger than 18 y, No.[c]	188 800	233 585	946 779	1 369 164
MIS-C incidence rate[d]	54.5	49.2	3.8	
MIS-C incidence rate ratio (95% CI)[e]	14.34 (9.81-20.96)	12.94 (8.90-18.81)	1 [Reference]	

[a] Each wave was a 16-week period: Alpha, December 20, 2020, to April 10, 2021; Delta, July 18, 2021, to November 13, 2021; and Omicron, November 21, 2021, to March 12, 2022.

[b] Cases of multisystem inflammatory syndrome in children (MIS-C) were limited to patients aged 0 to 18 years.

[c] According to the Israel Ministry of Health SARS-CoV-2 data set.

[d] Incidence rates were calculated using number of cases as numerator, with number of SARS-CoV-2 pediatric infections as denominator, per 100 000.

[e] Incidence rate ratios use the rate of MIS-C cases in the Omicron wave as a referent group, with 95% CIs.

Potentially relevant variables: prior CoV2 infection, vaccination, CoV2 variant, release from quarantining

Acknowledgements

Patients and families

Lucas Lab:

- Nina Brodsky
- Anjali Ramaswamy
- Andrew Rice

David Hafler Lab:

- Tomo Sumida
- Hiro Asashima
- Michela Comi

Jordan Pober

Ric Pierce Lab:

- Alamzeb Khan

John Tsang (NIH)

- Steve Kleinstein Lab:
  - Kenneth Hoehn
- Xiting Yan Lab:
  - Ningshan Li
- David Van Dijk Lab:
  - Aagam Shah
  - Jason Bishai
- Naftali Kaminski Lab:
  - Rami Unterman

- Pediatric Critical Care
  - Nurses
  - Victoria Habet
- Pediatric Infectious Disease
  - Carlos Oliveira
- Jason Catanzaro
- Yale Biorepository team
  - Albert Ko
  - Akiko Iwasaki
- Harsha Chandnani, Merrick Lopez (Loma Linda University)

- Biorender: schematics

- Funding:

NIH National Institute of Allergy and Infectious Diseases

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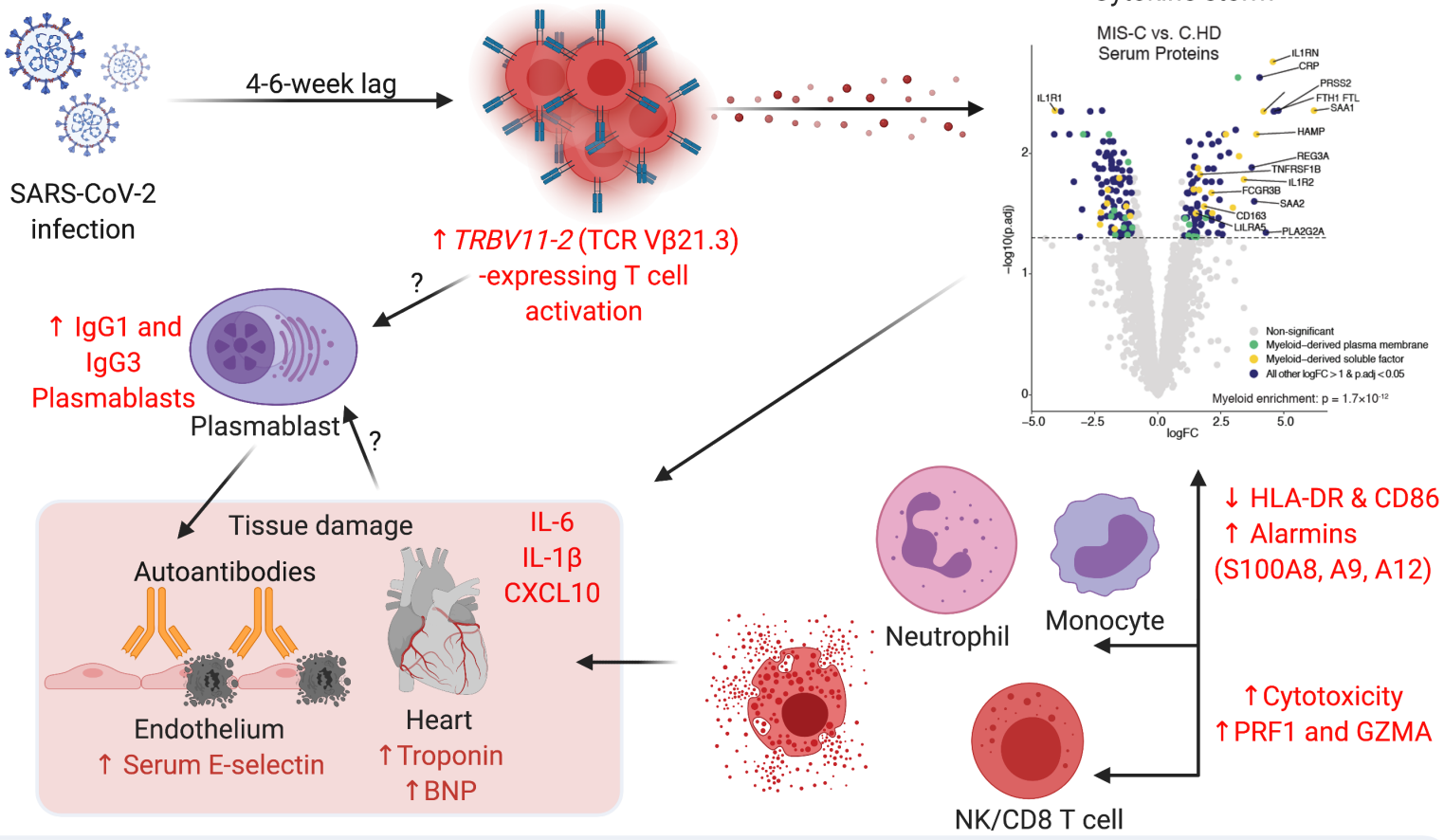
MIS-C Working Model



Key open questions:

1. What drives superantigen-like expansion of T cells expressing *TRBV11-2*/TCR Vβ21.3?
2. Why are children (average age 8-9) most susceptible?
3. Genetic susceptibility?