Biomarkers and Underlying Mechanisms of Long COVID

Immune Mechanisms Underlying COVID-19 Pathology and PASC

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I have no relevant financial disclosures

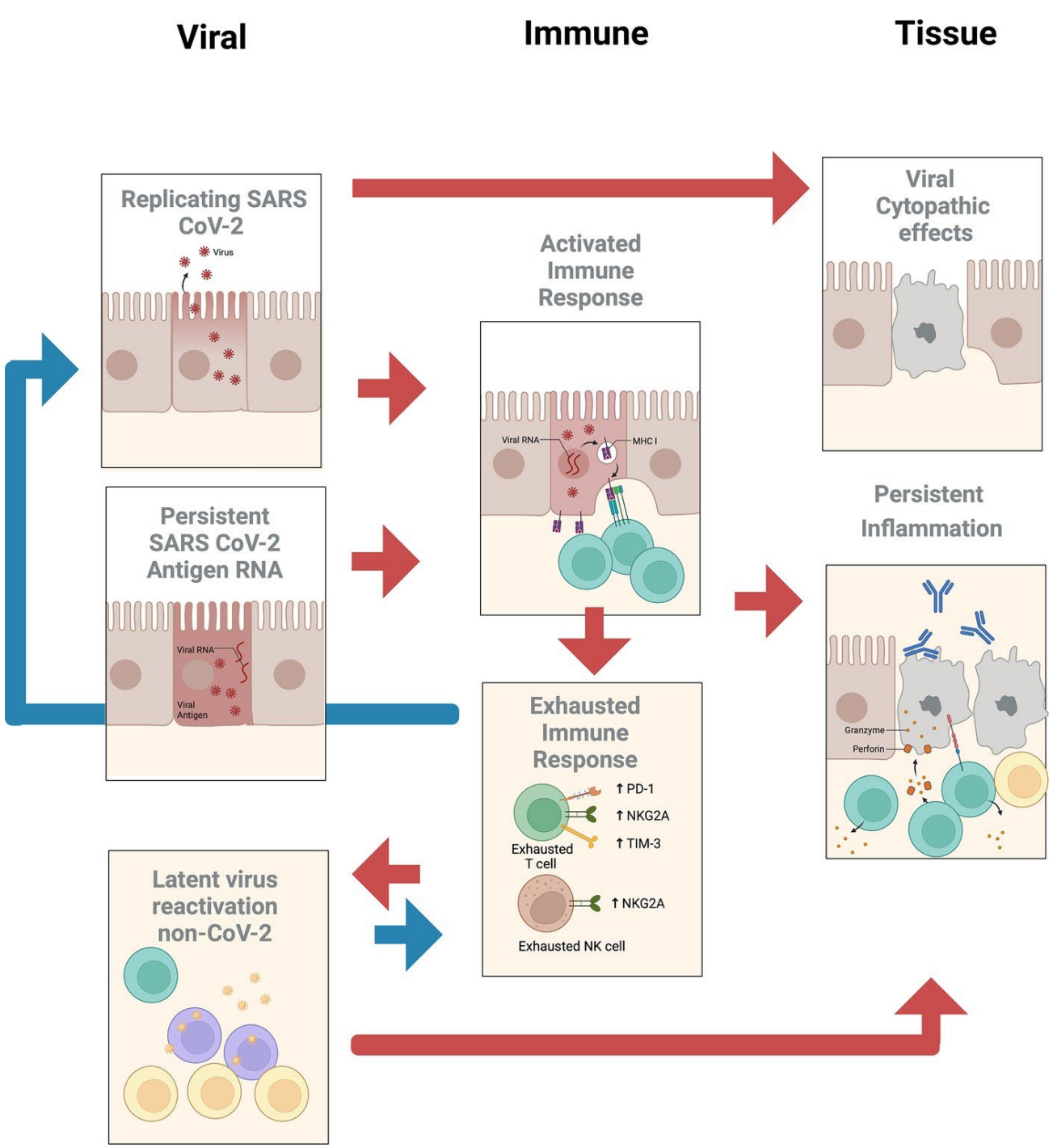
Likely key mechanisms involved

Duration and distribution of viral persistence

Immune dysregulation

Tissue injury related to viral persistence and immune response

Impact of viral persistence on immune responses and tissue damage in PASC



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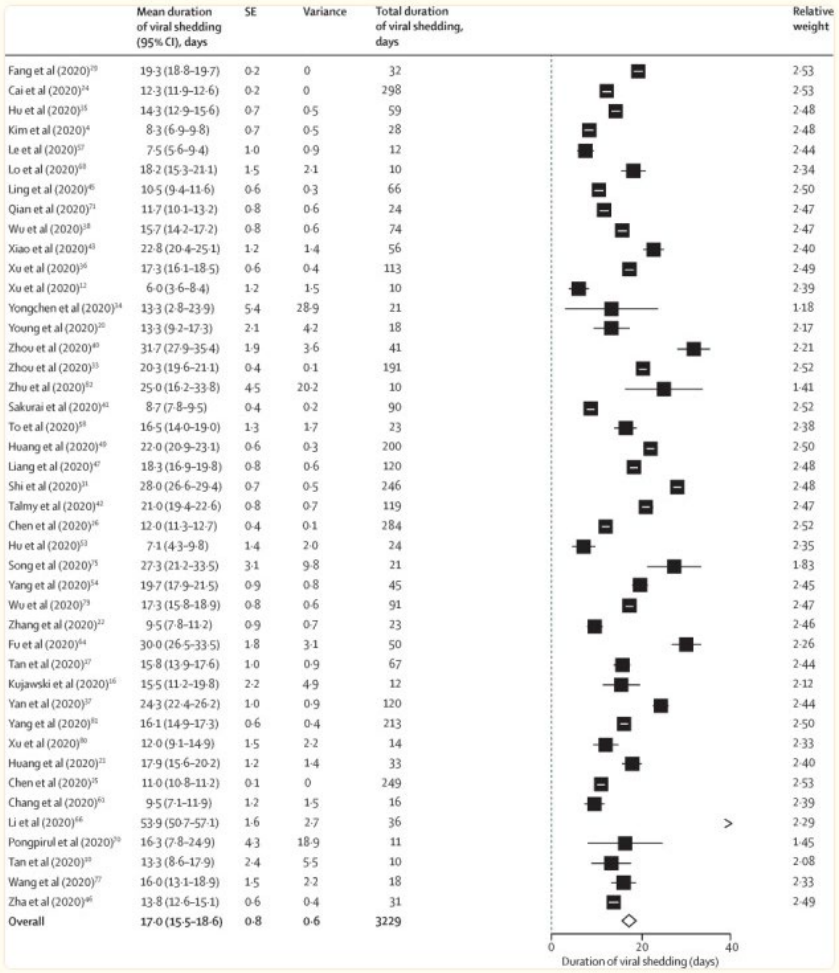
Duration of viral shedding

- Upper respiratory tract : mean 17 days (max 83 days)
- Lower respiratory tract: mean 14.6 days (max 59 days)
- GI tract, stool: mean 17.2 days (max 126 days)
- Serum-: mean 16.6 days (max 60 days)

(no live virus detected beyond D9 of illness)



	Mean duration of viral shedding (95% CI), days	SE	Variance	Total duration of viral shedding, days	Relative weight
Fang et al (2020)[39]	19·3 (18·8–19·7)	0·2	0	32	2·53
Cai et al (2020)[24]	12·3 (11·9–12·6)	0·2	0	298	2·53
Hu et al (2020)[35]	14·3 (12·9–15·6)	0·7	0·5	59	2·48
Kim et al (2020)[4]	8·3 (6·9–9·8)	0·7	0·5	28	2·48
Le et al (2020)[57]	7·5 (5·6–9·4)	1·0	0·9	12	2·44
Lo et al (2020)[48]	18·2 (15·3–21·1)	1·5	2·1	10	2·34
Ling et al (2020)[45]	10·5 (9·4–11·6)	0·6	0·3	66	2·50
Qian et al (2020)[71]	11·7 (10·1–13·2)	0·8	0·6	24	2·47
Wu et al (2020)[28]	15·7 (14·2–17·2)	0·8	0·6	74	2·47
Xiao et al (2020)[43]	22·8 (20·4–25·1)	1·2	1·4	56	2·40
Xu et al (2020)[26]	17·3 (16·1–18·5)	0·6	0·4	113	2·49
Xu et al (2020)[22]	6·0 (3·6–8·4)	1·2	1·5	10	2·39
Yongchen et al (2020)[34]	13·3 (2·8–23·9)	5·4	28·9	21	1·18
Young et al (2020)[20]	13·3 (9·2–17·3)	2·1	4·2	18	2·17
Zhou et al (2020)[40]	31·7 (27·9–35·4)	1·9	3·6	41	2·21
Zhou et al (2020)[33]	20·3 (19·6–21·1)	0·4	0·1	191	2·52
Zhu et al (2020)[52]	25·0 (16·2–33·8)	4·5	20·2	10	1·41
Sakurai et al (2020)[42]	8·7 (7·8–9·5)	0·4	0·2	90	2·52
To et al (2020)[58]	16·5 (14·0–19·0)	1·3	1·7	23	2·38
Huang et al (2020)[49]	22·0 (20·9–23·1)	0·6	0·3	200	2·50
Liang et al (2020)[47]	18·3 (16·9–19·8)	0·8	0·6	120	2·48
Shi et al (2020)[31]	28·0 (26·6–29·4)	0·7	0·5	246	2·48
Talmy et al (2020)[42]	21·0 (19·4–22·6)	0·8	0·7	119	2·47
Chen et al (2020)[46]	12·0 (11·3–12·7)	0·4	0·1	284	2·52
Hu et al (2020)[53]	7·1 (4·3–9·8)	1·4	2·0	24	2·35
Song et al (2020)[55]	27·3 (21·2–33·5)	3·1	9·8	21	1·83
Yang et al (2020)[54]	19·7 (17·9–21·5)	0·9	0·8	45	2·45
Wu et al (2020)[79]	17·3 (15·8–18·9)	0·8	0·6	91	2·47
Zhang et al (2020)[32]	9·5 (7·8–11·2)	0·9	0·7	23	2·46
Fu et al (2020)[44]	30·0 (26·5–33·5)	1·8	3·1	50	2·26
Tan et al (2020)[37]	15·8 (13·9–17·6)	1·0	0·9	67	2·44
Kujawski et al (2020)[36]	15·5 (11·2–19·8)	2·2	4·9	12	2·12
Yan et al (2020)[27]	24·3 (22·4–26·2)	1·0	0·9	120	2·44
Yang et al (2020)[81]	16·1 (14·9–17·3)	0·6	0·4	213	2·50
Xu et al (2020)[29]	12·0 (9·1–14·9)	1·5	2·2	14	2·33
Huang et al (2020)[21]	17·9 (15·6–20·2)	1·2	1·4	33	2·40
Chen et al (2020)[25]	11·0 (10·8–11·2)	0·1	0	249	2·53
Chang et al (2020)[60]	9·5 (7·1–11·9)	1·2	1·5	16	2·39
Li et al (2020)[56]	53·9 (50·7–57·1)	1·6	2·7	36	2·29
Pongpirul et al (2020)[70]	16·3 (7·8–24·9)	4·3	18·9	11	1·45
Tan et al (2020)[23]	13·3 (8·6–17·9)	2·4	5·5	10	2·08
Wang et al (2020)[77]	16·0 (13·1–18·9)	1·5	2·2	18	2·33
Zha et al (2020)[46]	13·8 (12·6–15·1)	0·6	0·4	31	2·49
Overall	**17·0 (15·5–18·6)**	**0·8**	**0·6**	**3229**	

Figure 2

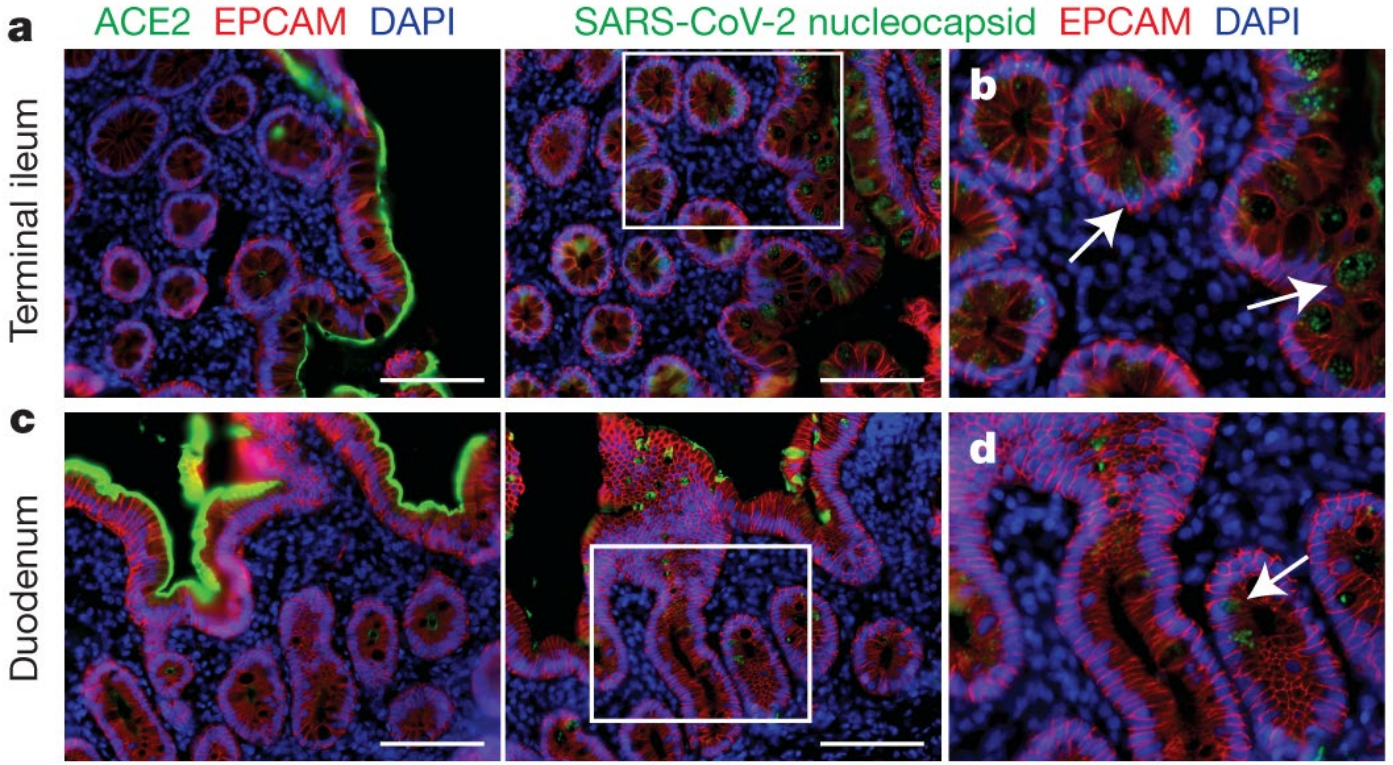
Pooled mean duration (days) of SARS-CoV-2 shedding from the upper respiratory tract (random-effects model)

SARS-CoV-2=severe acute respiratory syndrome coronavirus 2.

Cevik et al, Lancet Microbe, 2021

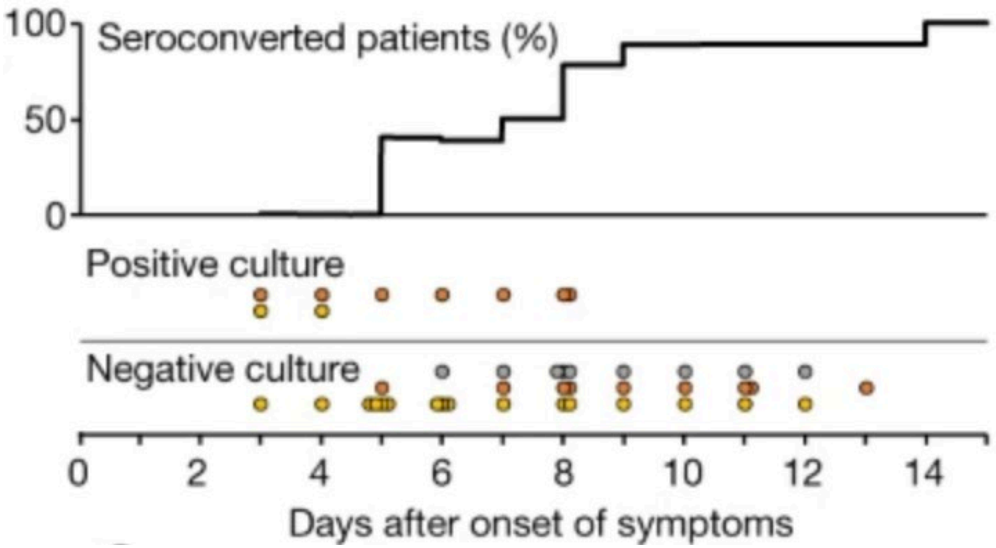
Duration of viral shedding

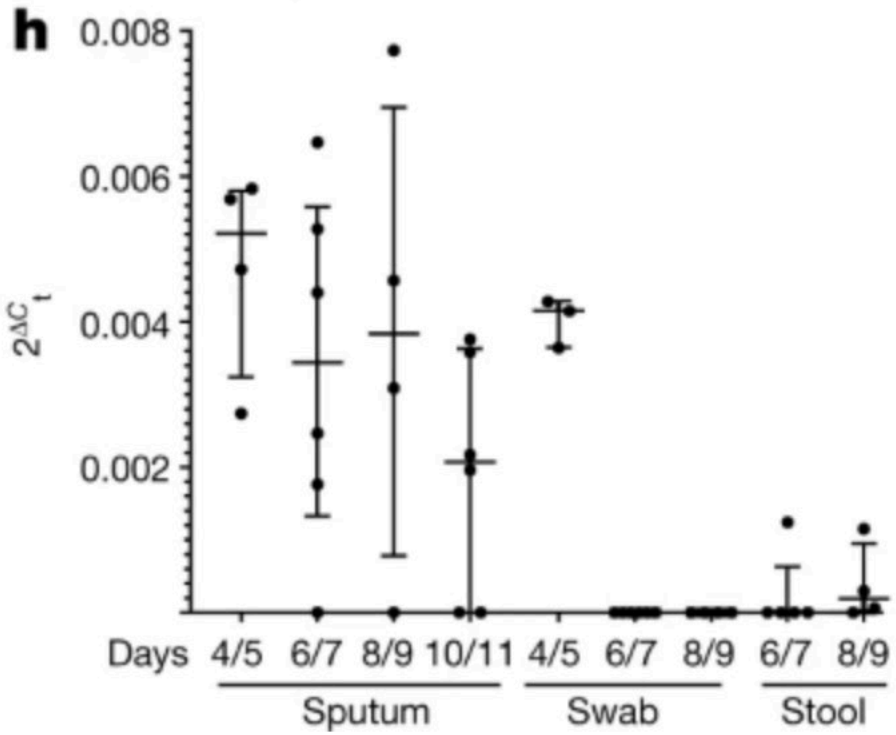
- Persistence of SARS-CoV-2 nucleic acids and immunoreactivity in small bowel by biopsy
- 7 out of 14 asymptomatic individuals
- Average 4 months after onset of COVID-19
- Not associated with tissue inflammation



Gaebler et al, Nature, 2021

How long is virus viable





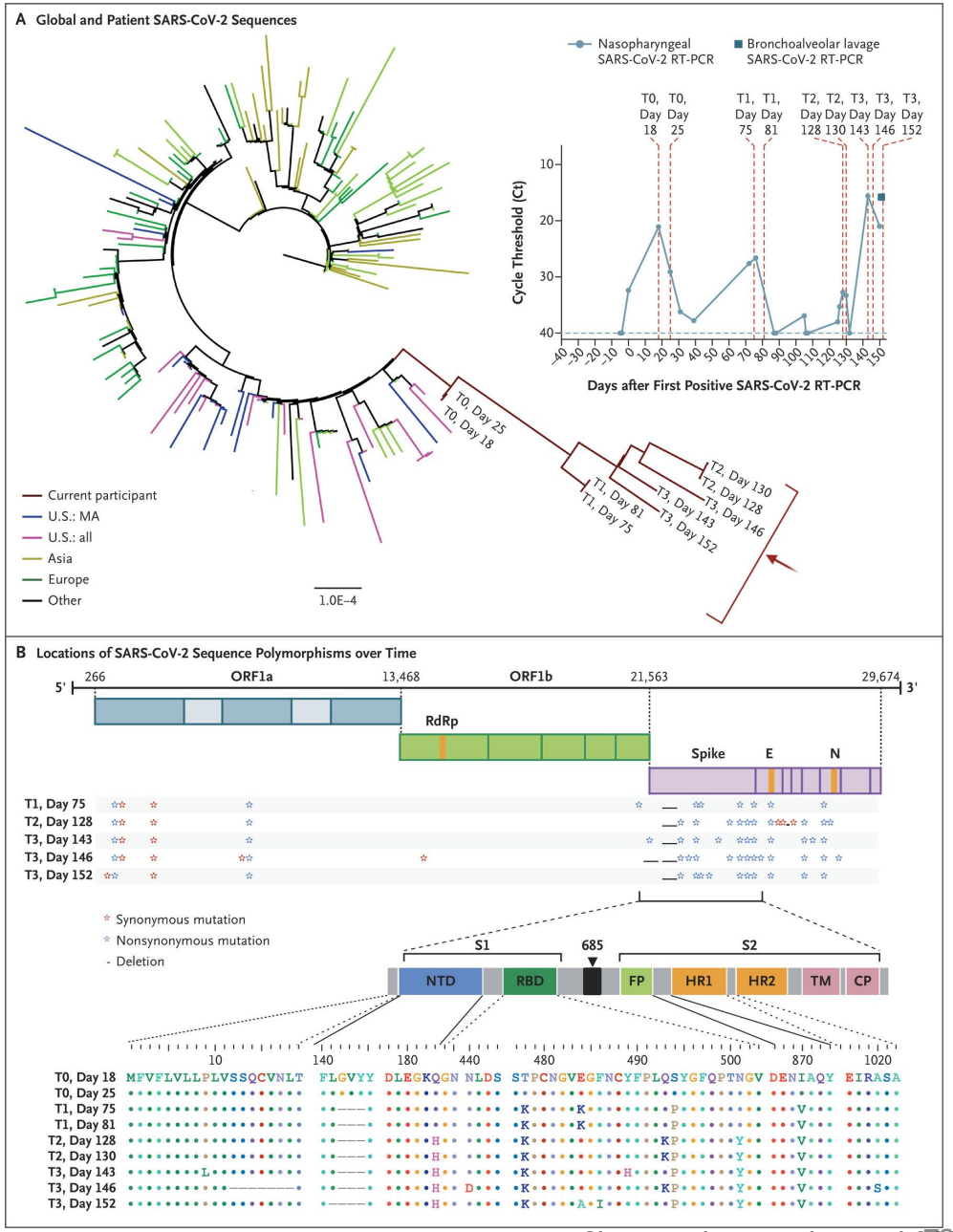
Wolfel et al, Nature 2020

8 days after symptom onset by culture

Bullard et al, CID, 2020

Viral Persistence in immunocompromised

- Virus persisted till D 152, (Infectious virus detected D 143)
- Virus can persist and evolve in IC populations
- Can accelerate the emergence of variants

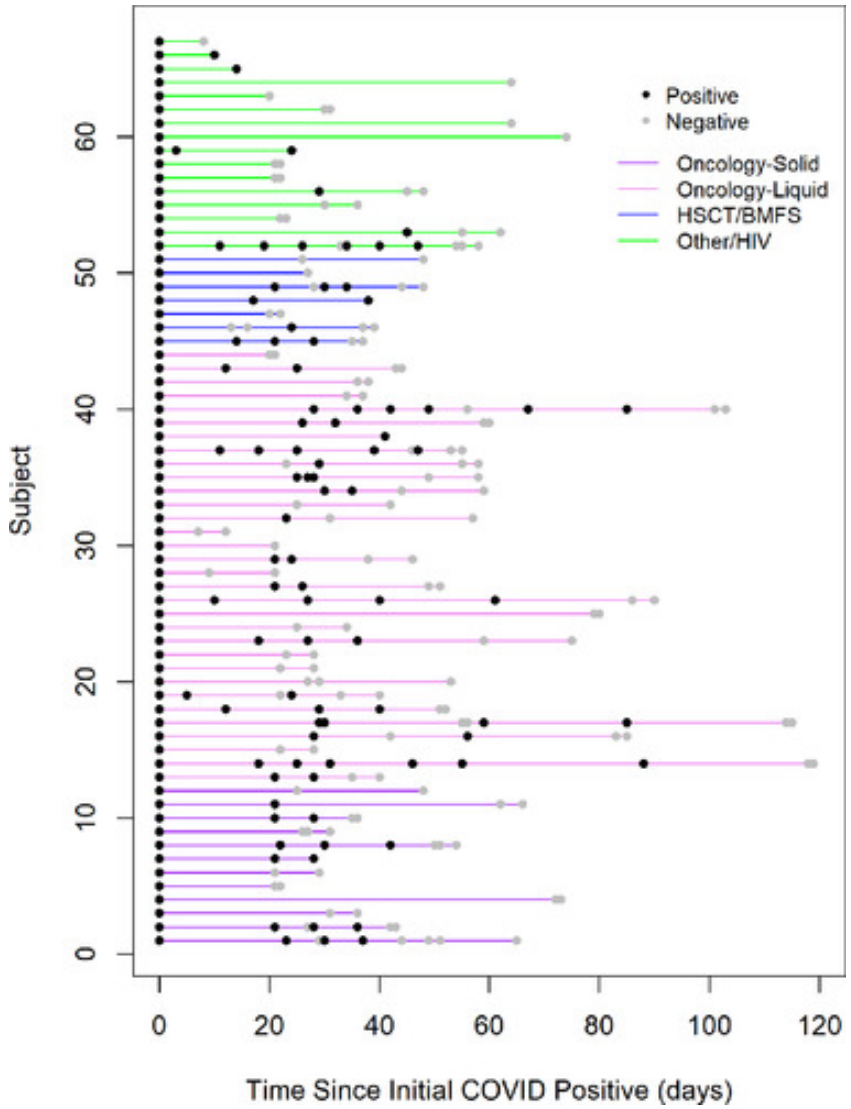


Choi et al. N Engl J Med 2020

Viral Persistence in children

- Persistently positive SARS-CoV-2 RNA in GI specimens
- SARS-CoV-2 RNA detected in GI specimens >70 days after illness onset >5 weeks after hospital admission.

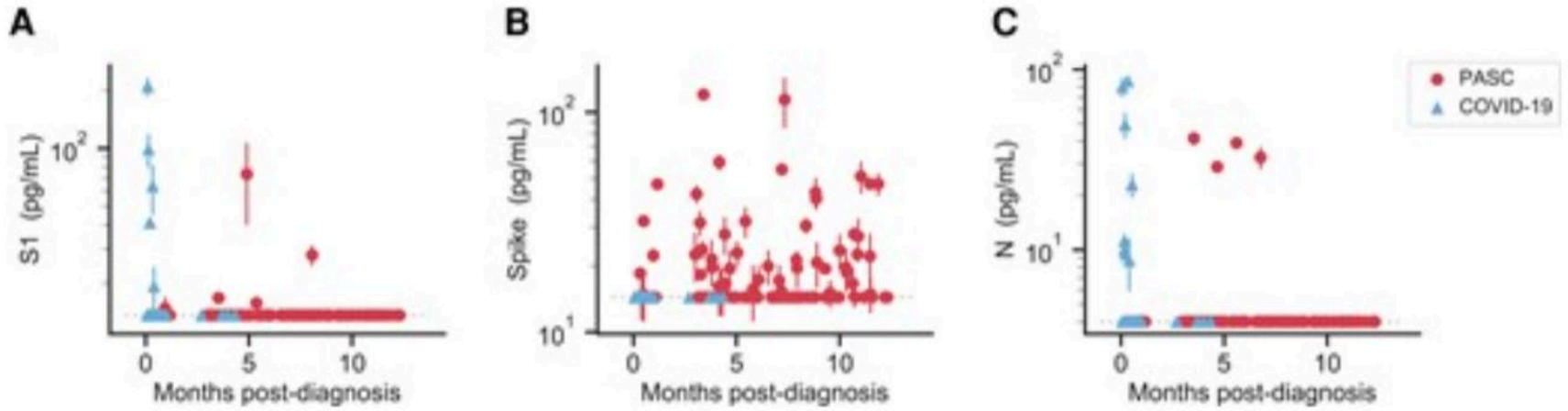
Benvari et al, World J Pediatr, 2022



Median time to 2 -ve tests in IC children: 42 days

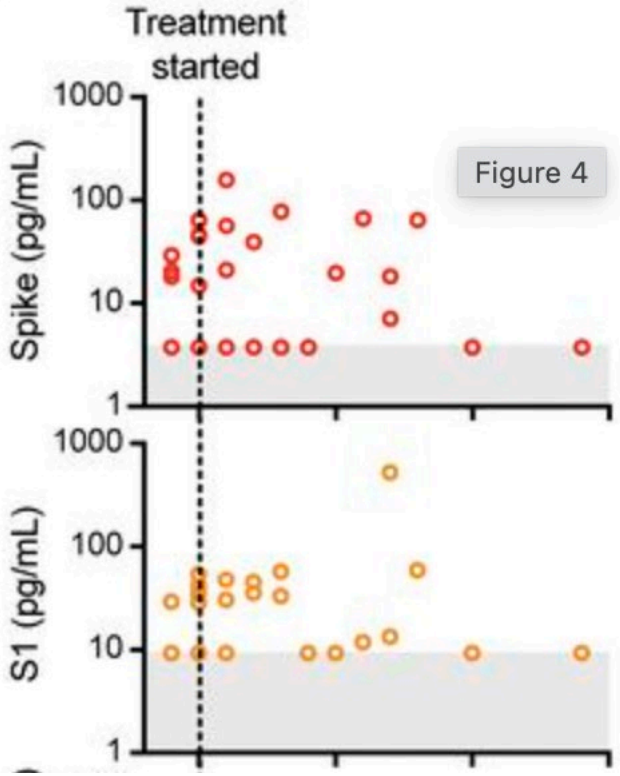
Dolan et al. Pediatr Blood Cancer

SARS-CoV-2 spike detected predominantly in PASC patients up to 12 months after diagnosis.



Swank et al, CID 2022

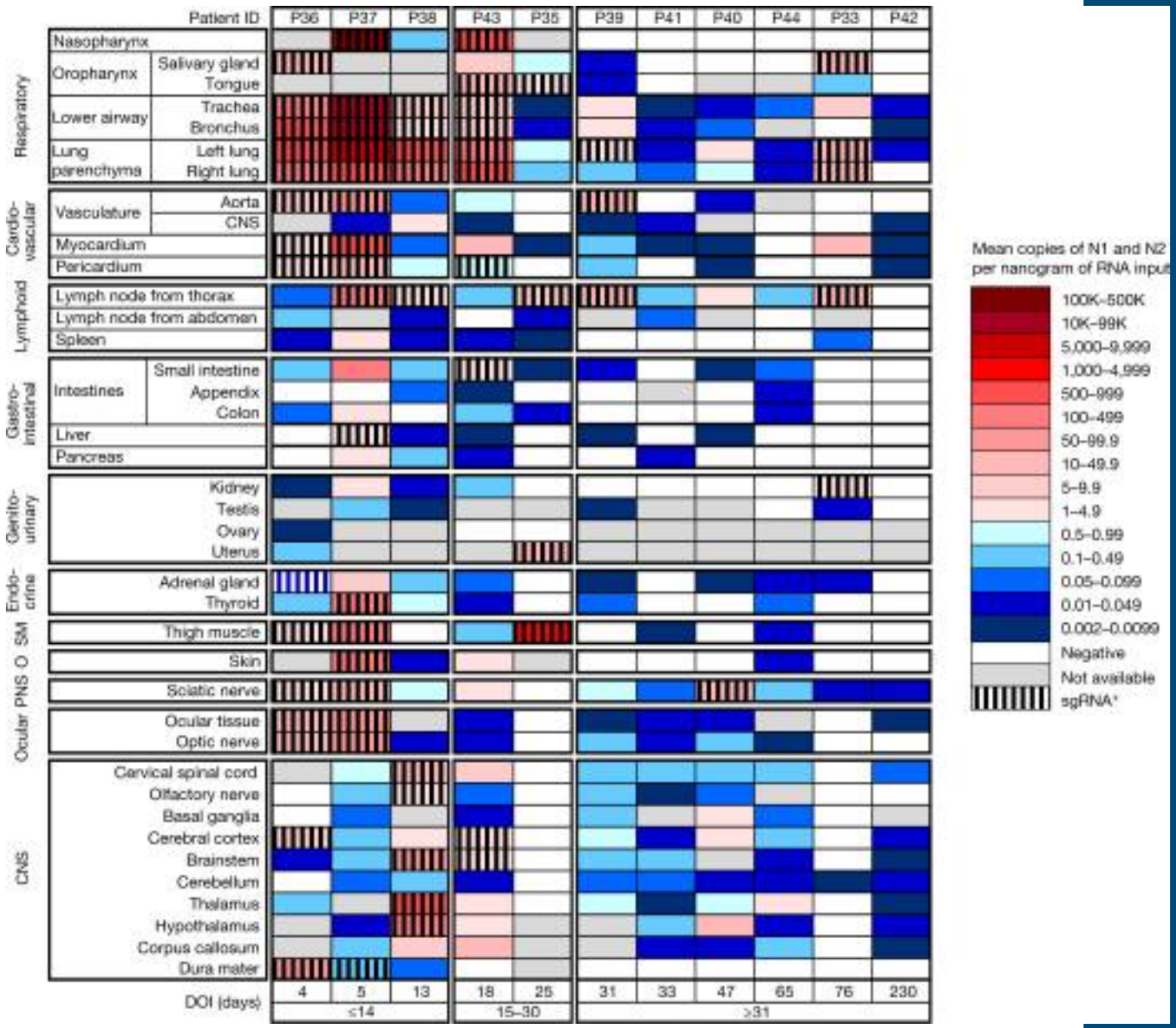
Elevated SARS-CoV-2 antigen found in patients with MIS-C



Yonker et al. JCI 2021

Viral Persistence at Autopsy

- SARS-CoV-2 RNA detected in 84 distinct anatomical locations and body fluids
- Significantly ($P < 0.0001$) higher burden detected in respiratory compared with non-respiratory tissues



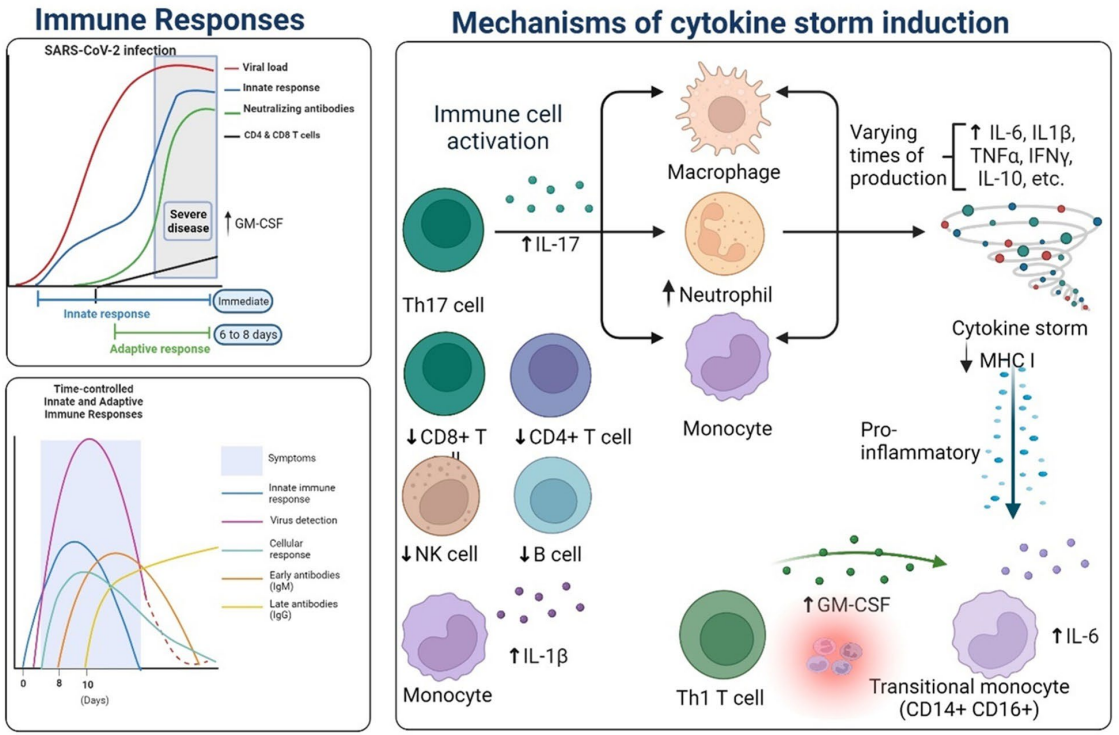
Stein et al, Nature 2022

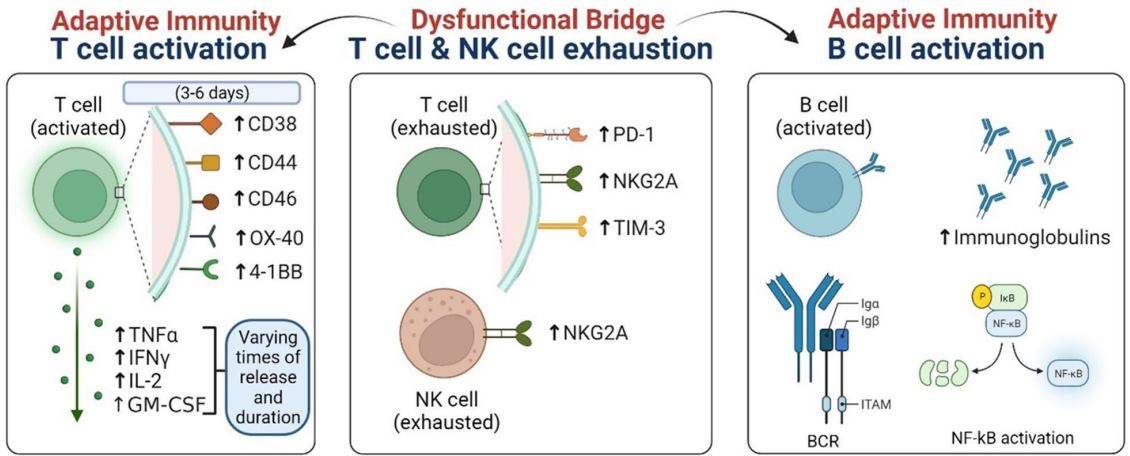
Key questions regarding two major divisions of persistent virus related to PASC

- What are the mechanisms of SARS CoV-2 persistence when detected in PASC
  - Does it involve replication or is it non-replicating?
  - Persistence of RNA or of antigen/immune complexes?
  - Are mechanisms different with regards to the tissue site?
- Are reactivated latent pathogens the cause or effect of PASC symptoms?
  - To what extent are reactivated latent viruses such as EBV involved in different subpopulations with PASC?
- Viral persistence mechanisms may provide a rationale for selecting populations for distinct treatment approaches

Bradfute et al, Elife, 2023

Immune Mechanisms in COVID-19 & Potentially in Long COVID (PASC)





Overview of PASC timeline and immune cell involvement

Generated with BioRender.com by Dr.Sherif

Mohandas et al, Elife, 2023

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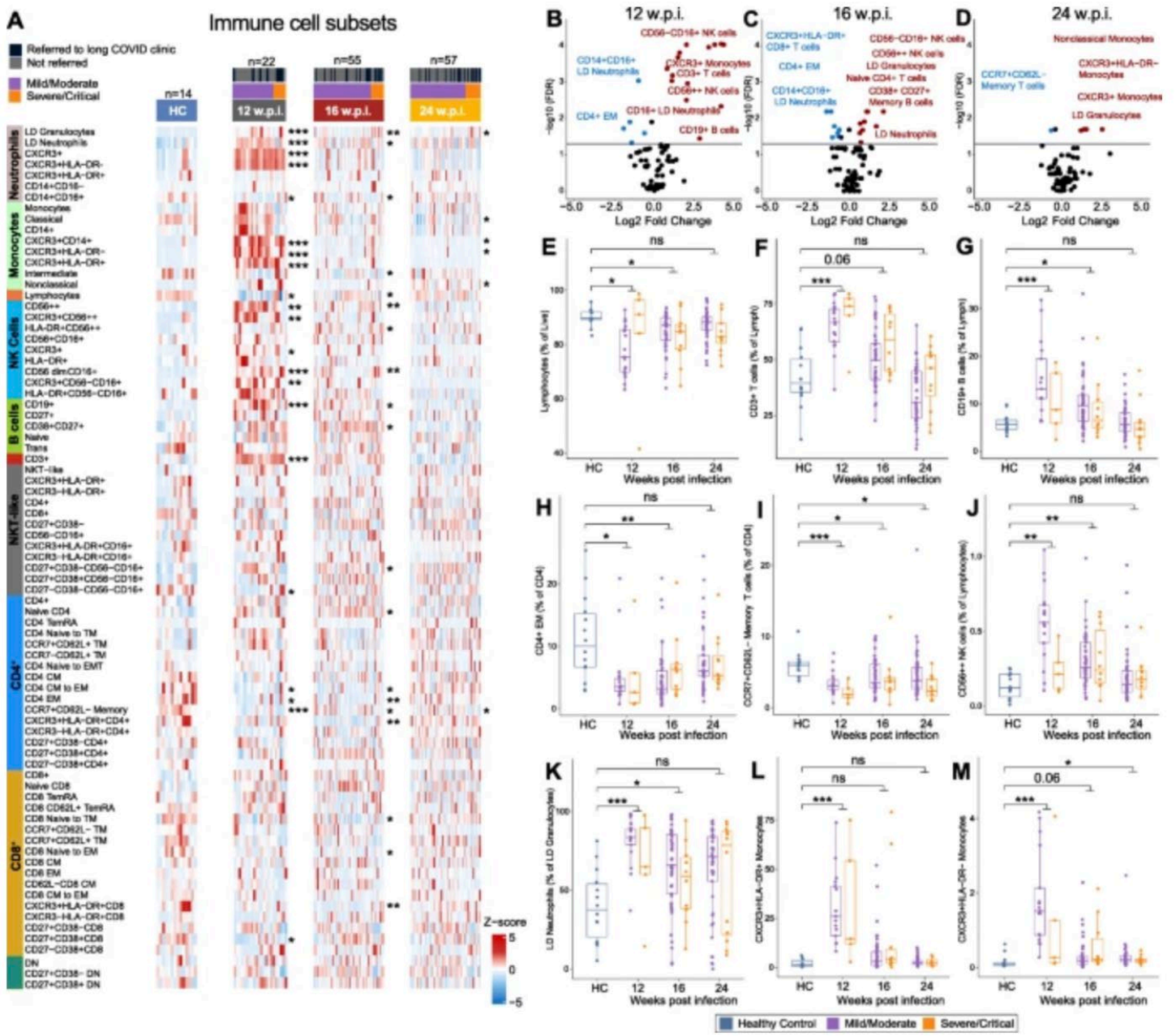
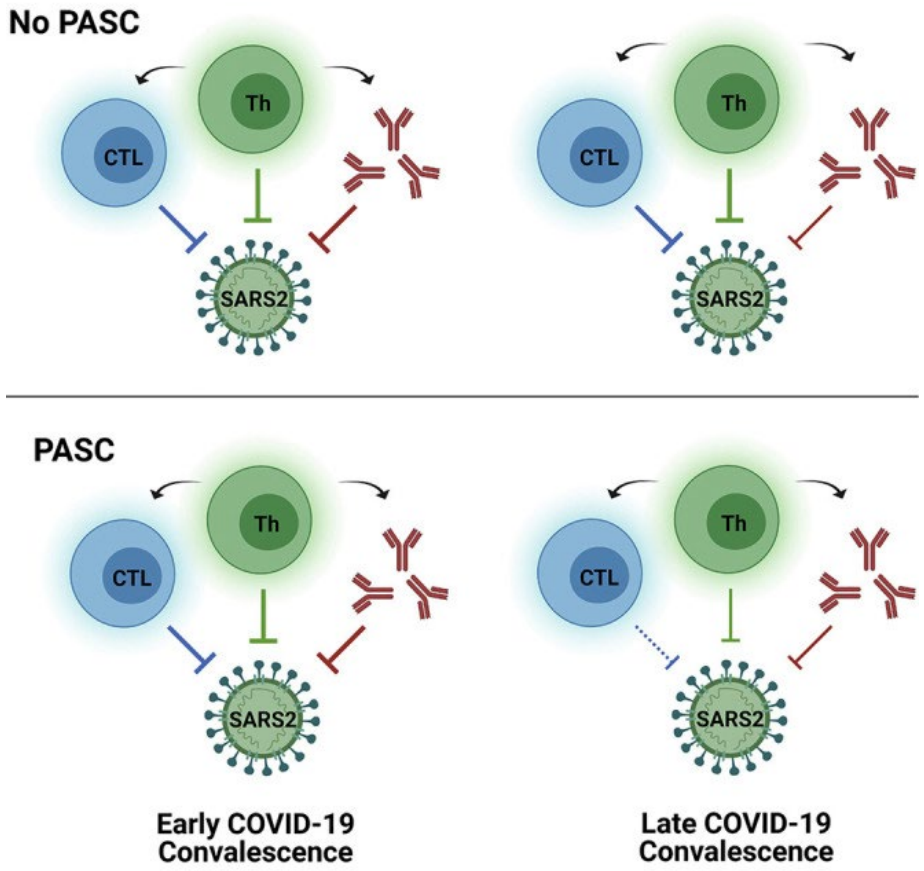
Long-term perturbation of the peripheral immune system months after SARS-CoV-2 infection



Ryan et al, BMC Medicine, 2022

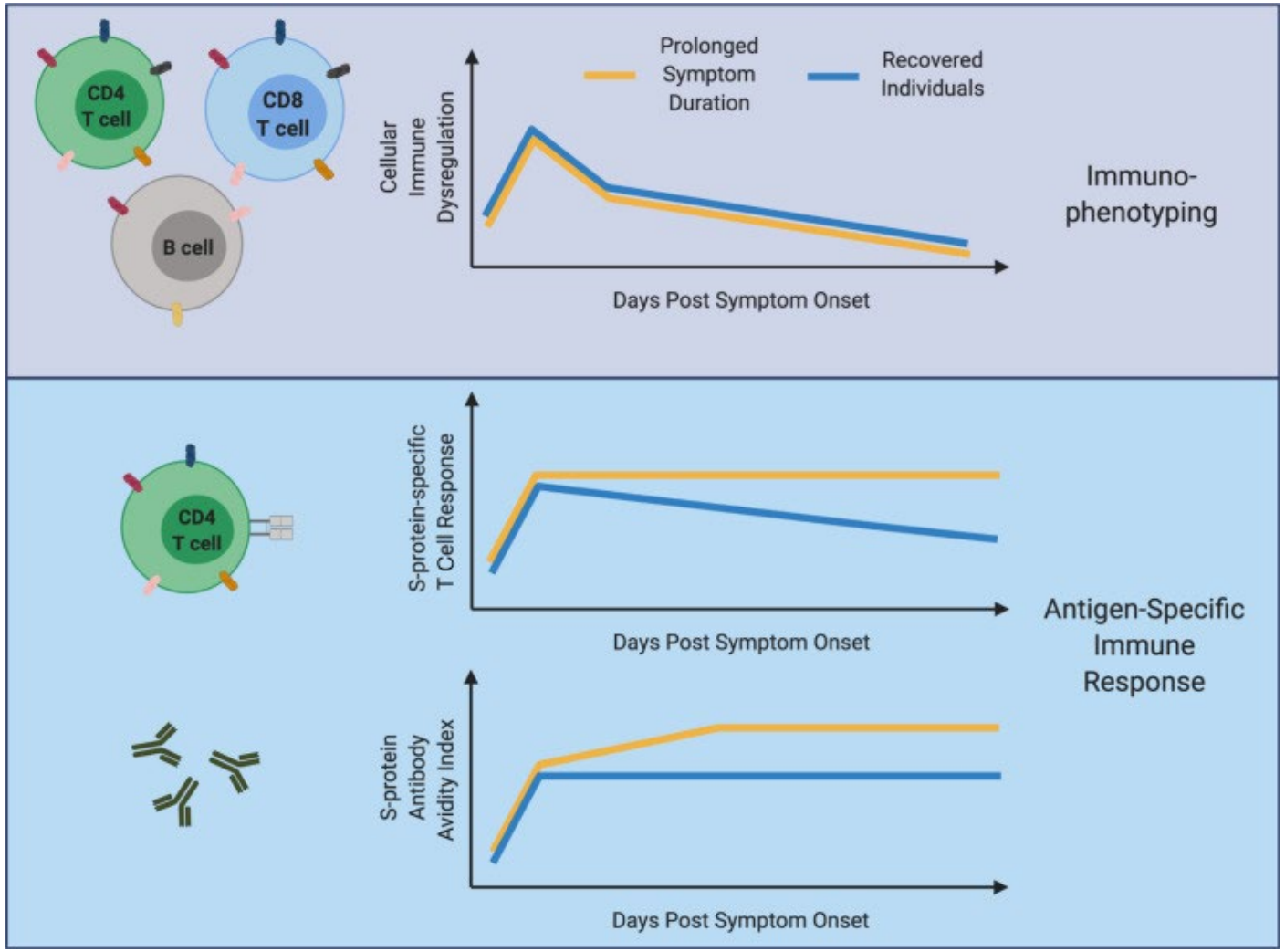
Long-term SARS-CoV-2-specific immune and inflammatory responses in individuals recovering from COVID-19 with and without post-acute symptoms



-Identified lower and more rapidly waning month 4, N-specific $CD8^+$ T cell responses ($IFN\gamma^-/CD107a^+$ and $IFN\gamma^+$) in those with PASC
-Trend toward higher IL6 in PASC
-No association between viral shedding, PASC symptoms, or immune responses

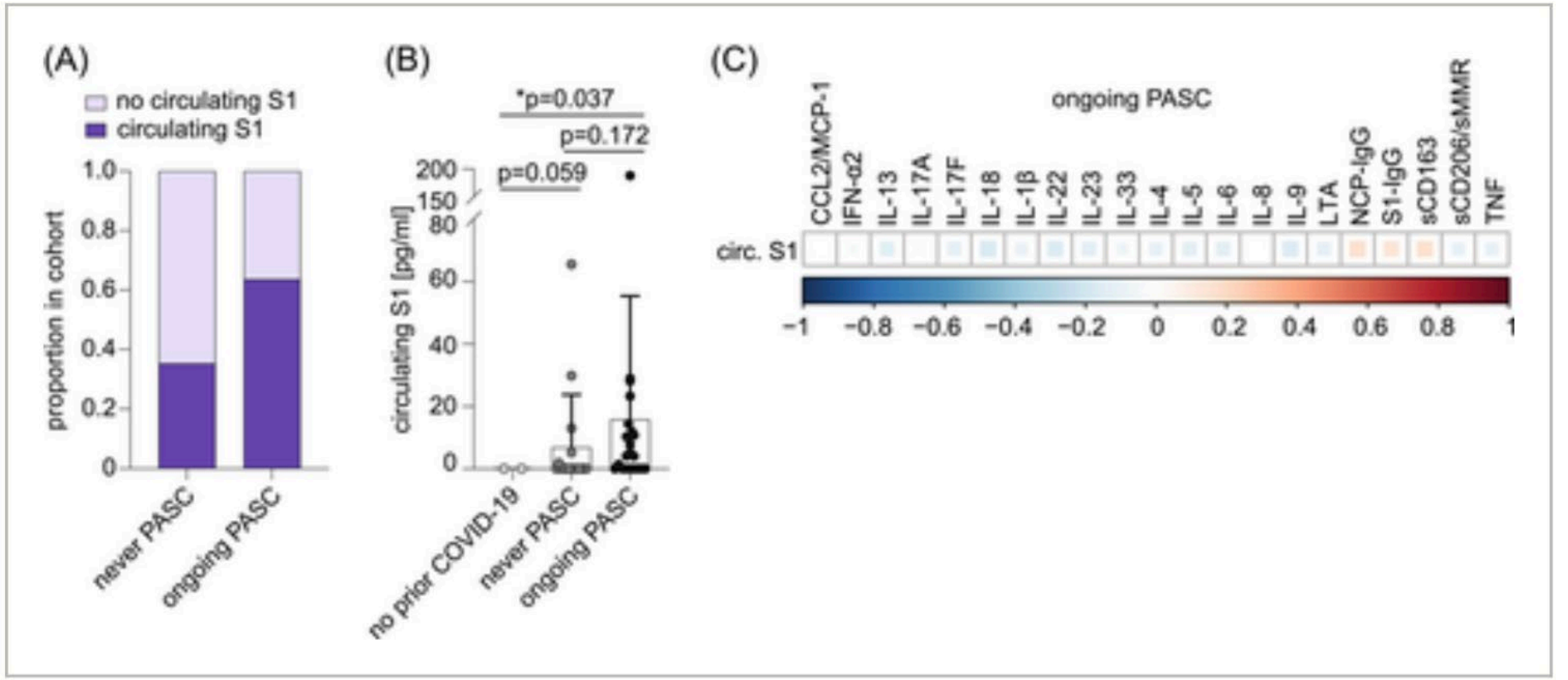
Peluso et al. Cell Rep, 2021

Duration of post-COVID-19 symptoms is associated with sustained SARS-CoV-2-specific immune responses



Files et al. JCI insight, 2021

Liquid biomarkers of macrophage dysregulation and circulating spike protein illustrate the biological heterogeneity in patients with post-acute sequelae of COVID-19



Schultheiß et al. *J Med Virol*. 2022

Mechanistic role of immune response in PASC

- Both innate and adaptive immune responses play an essential role in protection from SARS-CoV-2 infection
- They also have the potential to be detrimental when dysregulated.
- Overactive and persistent immune responses due to viral or host factors will likely impact the severity of the long-term sequelae like MIS-C, MISA, or PASC.
- Does neutrophil activation and increased spontaneous NET formation have a role in immune dysregulation and exacerbation of autoimmunity in PASC?
- Are autoantibodies mechanistically tied to specific forms of tissue injury in PASC?

Mohandas et al, Elife, 2023

Possible underlying causes of tissue damage

- SARS-CoV-2 injury to one or more organs may be due to:
  - Persistent reservoirs of the replicating virus or its remnants in several tissues
  - Re-activation of latent pathogens in COVID-19 immune-dysregulated tissue
  - SARS-CoV-2 interactions with host microbiome/virome communities
  - Clotting/coagulation dysregulation or dysfunction
  - Dysautonomia or autonomic dysfunction
  - Autoimmunity due to molecular mimicry between pathogen & host proteins

- The individualized nature of PASC symptoms suggests that different therapeutic approaches may be required to best manage specific patients

Sherif et al, Elife, 2023

Conclusions/Challenges

- SARS-CoV-2 viral proteins can persist in various tissues for a long time
- Immune dysregulation is seen in patients with PASC
- Specific tissue injury may play a role in the diversity of symptomology
- Biological heterogeneity in PASC adds a layer of complexity
- Understanding the nature and location of long-term SARS-CoV-2 persistence, associated immune response and tissue injury and their correlation with PASC subtypes could provide more insights into PASC pathogenesis

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THANK YOU