The Gastrointestinal Tract and Long COVID

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Disclosures

1. Grant funding from:
    1. Takeda Pharma
    2. Genentech Pharma

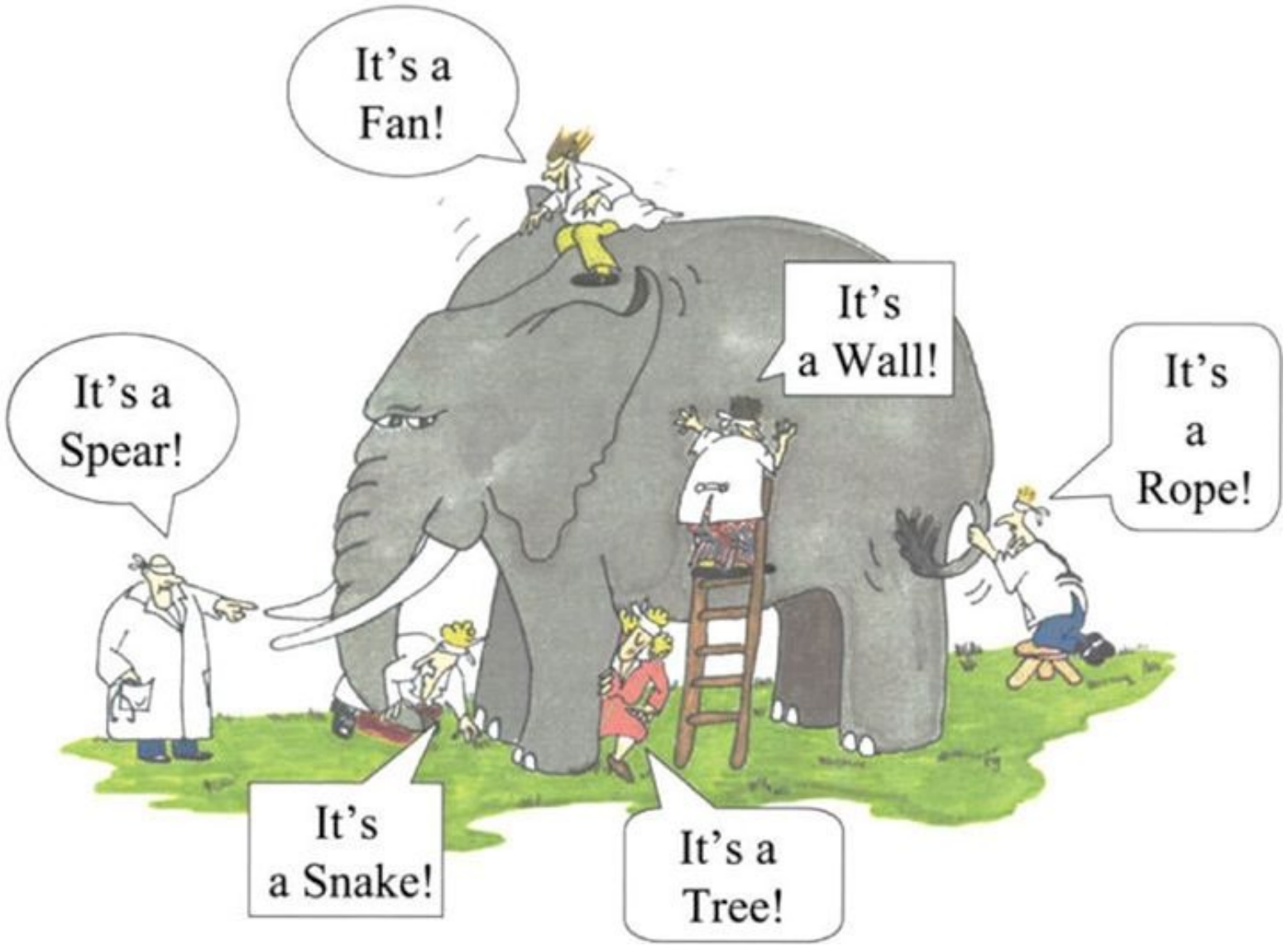
2. Speaking engagements for:
    1. Takeda Pharma
    2. Genentech Pharma
    3. Morphic
    4. Glaxo Smith Kline

NO RELATION TO THE PRESENT TOPIC

Outline of the presentation

- Rationale for studying the GI tract in COVID
- Acute infection studies
- Persistence of SARS-CoV-2 in the GI tract
- Ongoing and planned work

Prevailing hypothesis regarding the pathogenesis of Long COVID



Rationale for investigating the GI tract in COVID-19

- Patients demonstrate GI symptoms
- GI infection was demonstrated in SARS-CoV epidemic of 2003
- Multiple members of the Coronaviridae family can infect enterocytes
- Publications regarding infection of human enteroids by SARS-CoV-2 in vitro

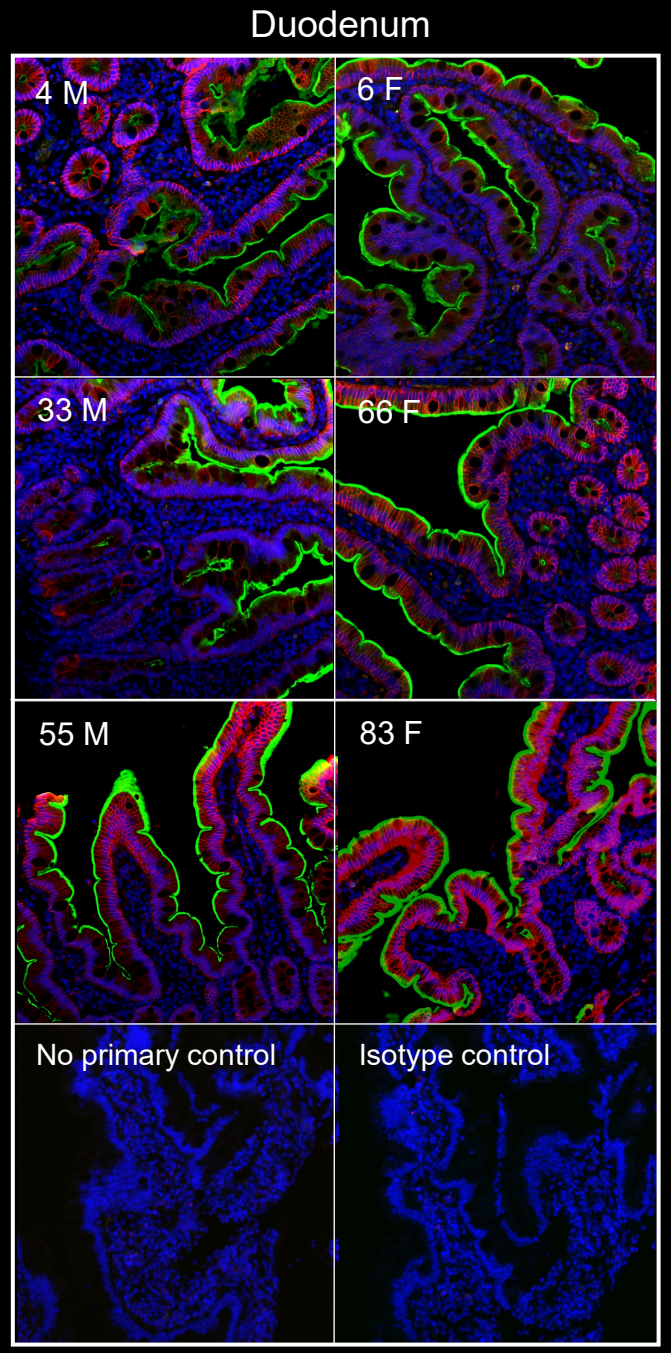

nature medicine
LETTERS
https://doi.org/10.1038/s41591-020-0912-6
Check for updates

Infection of bat and human intestinal organoids by SARS-CoV-2

Jie Zhou[1,2,6]✉, Cun Li[2,6], Xiaojuan Liu[2,6], Man Chun Chiu[2], Xiaoyu Zhao[2], Dong Wang[2], Yuxuan Wei[2], Andrew Lee[2], Anna Jinxia Zhang[1,2], Hin Chu[1,2], Jian-Piao Cai[2], Cyril Chik-Yan Yip[2], Ivy Hau-Yee Chan[3], Kenneth Kak-Yuen Wong[3], Owen Tak-Yin Tsang[4], Kwok-Hung Chan[2], Jasper Fuk-Woo Chan[1,2,5], Kelvin Kai-Wang To[1,2,5], Honglin Chen[1,2] and Kwok Yung Yuen[1,2,5]✉

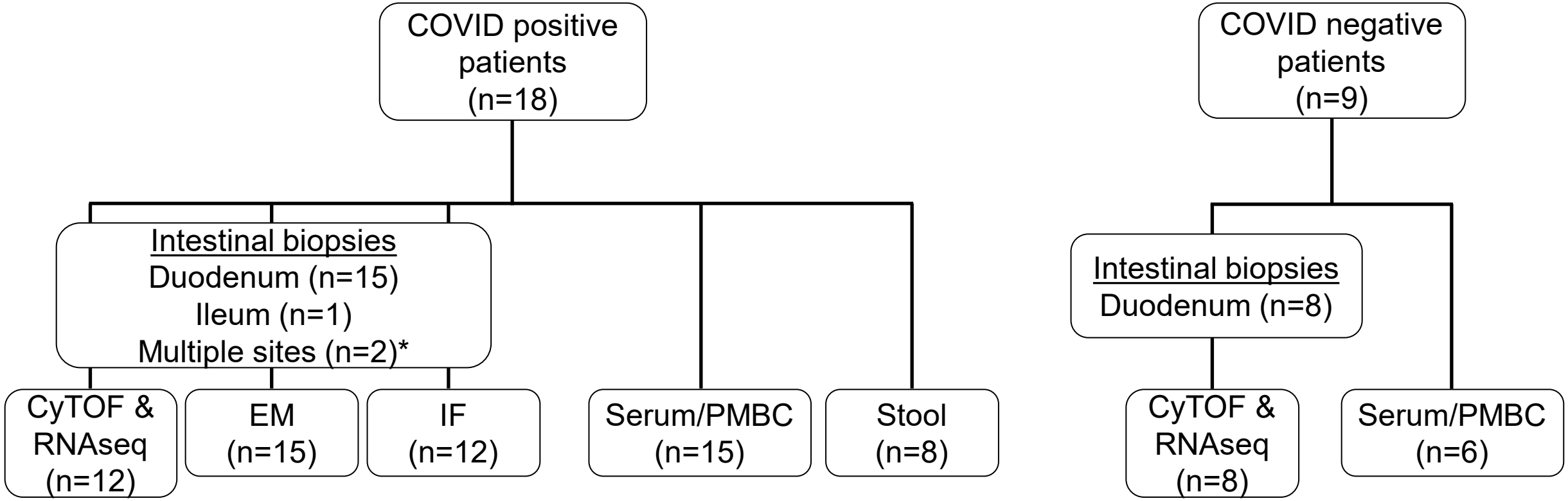
ACE-2 is physiologically expressed on the small intestinal brush border

Suarez-farinas, Tokuyama, Gastroenterology 2020



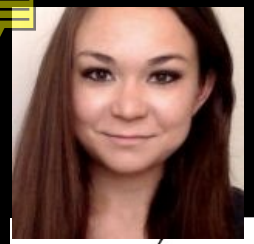
ACE2
EPCAM
DAPI

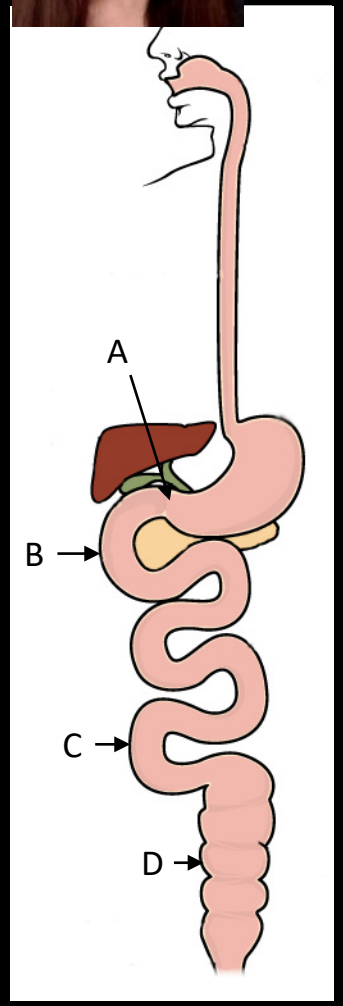
Acute COVID-19 cohort summary and sample description



*Case #19 was biopsied at the GEJ, duodenum and ileum sites
*Case #2 (pediatric) had the transplanted small intestine and native duodenum biopsied

#One Control only had blood available





Adapted from:
https://courses.lumenlearning.com/wm-biology2/chapter/invertebrates-and-vertebrate-digestive-systems/

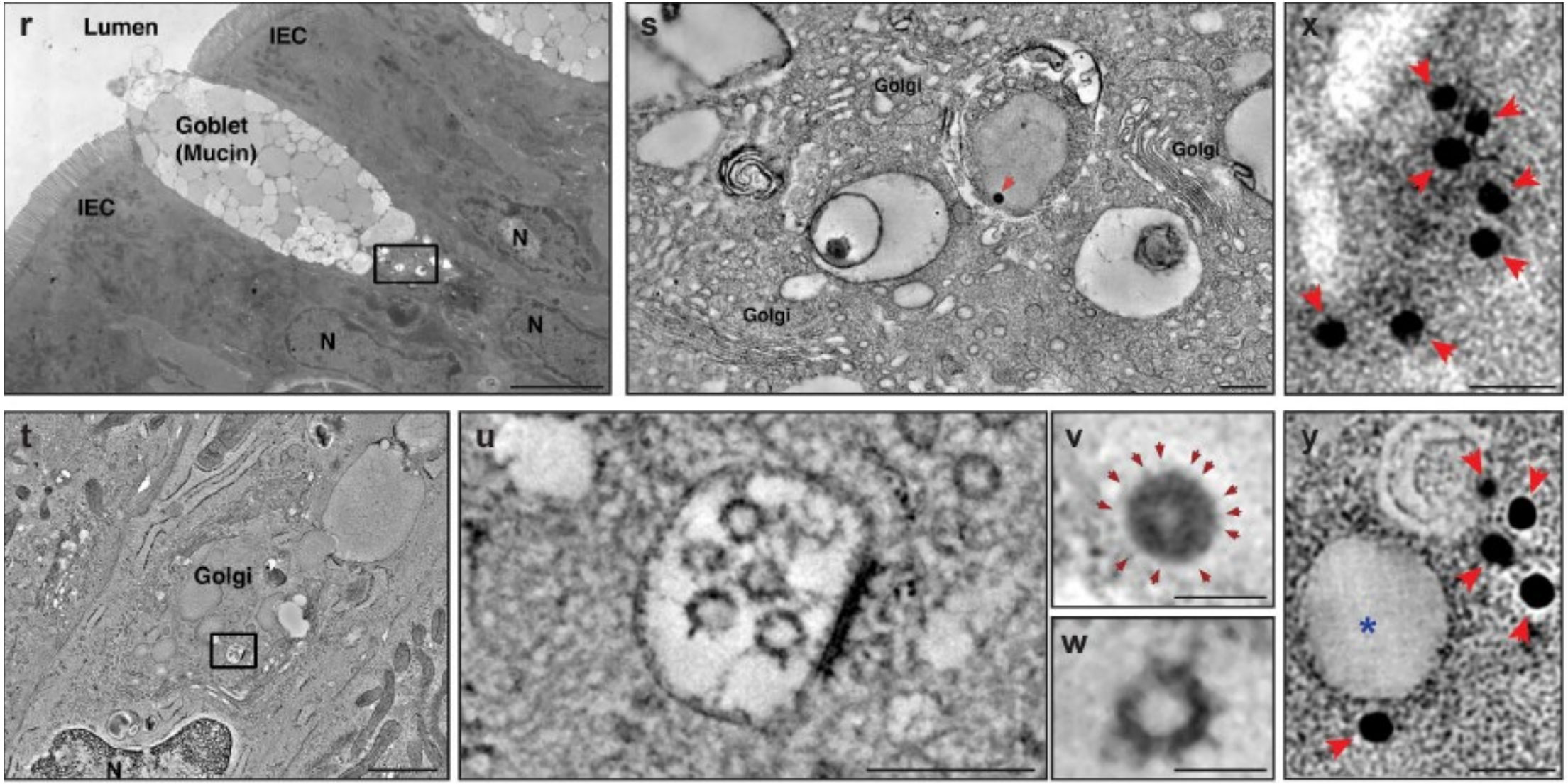
GE junction | Duodenum | Terminal Ileum | Left colon

ACE2 EPCAM DAPI

Nucleocapsid EPCAM DAPI

A B C D

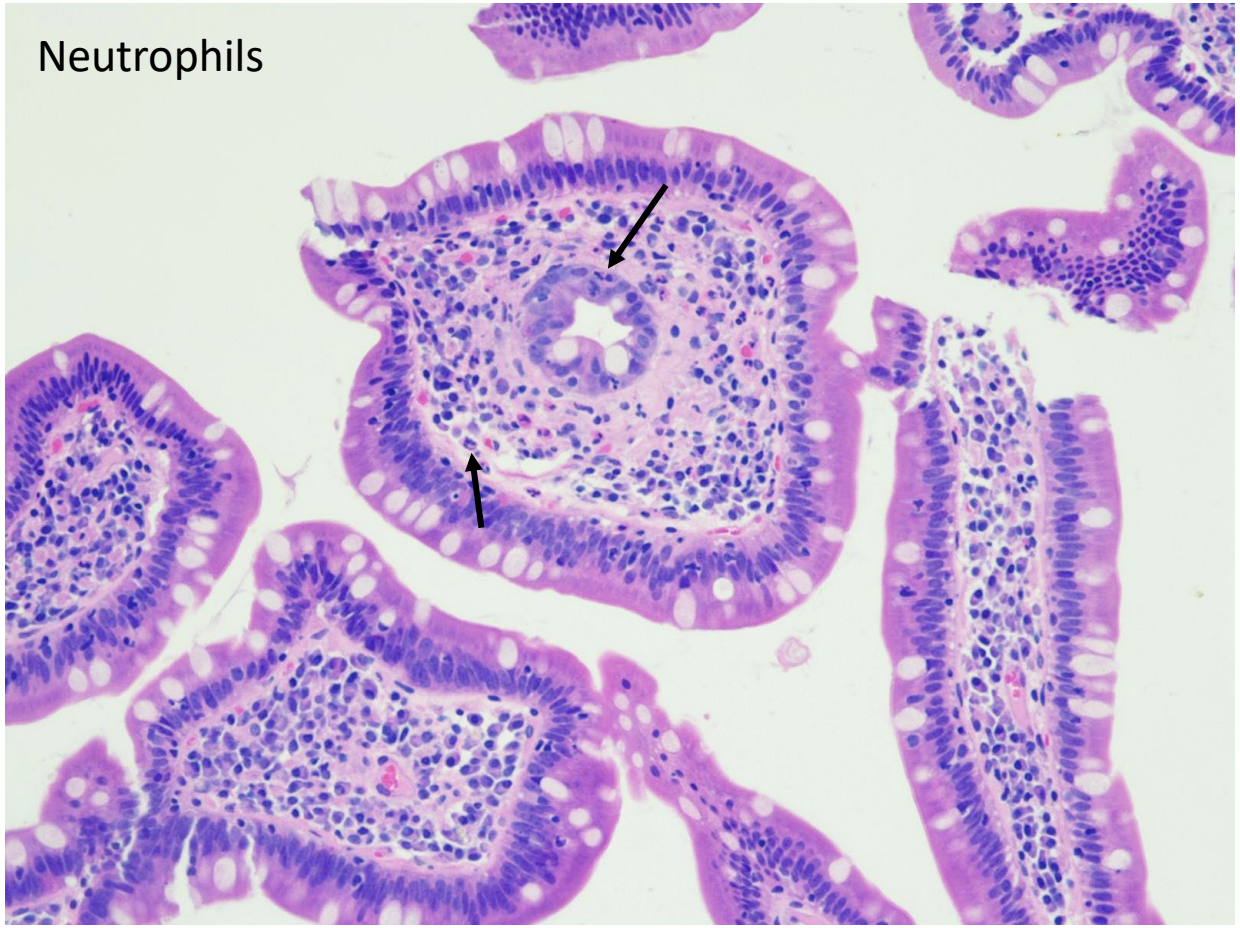
200µm



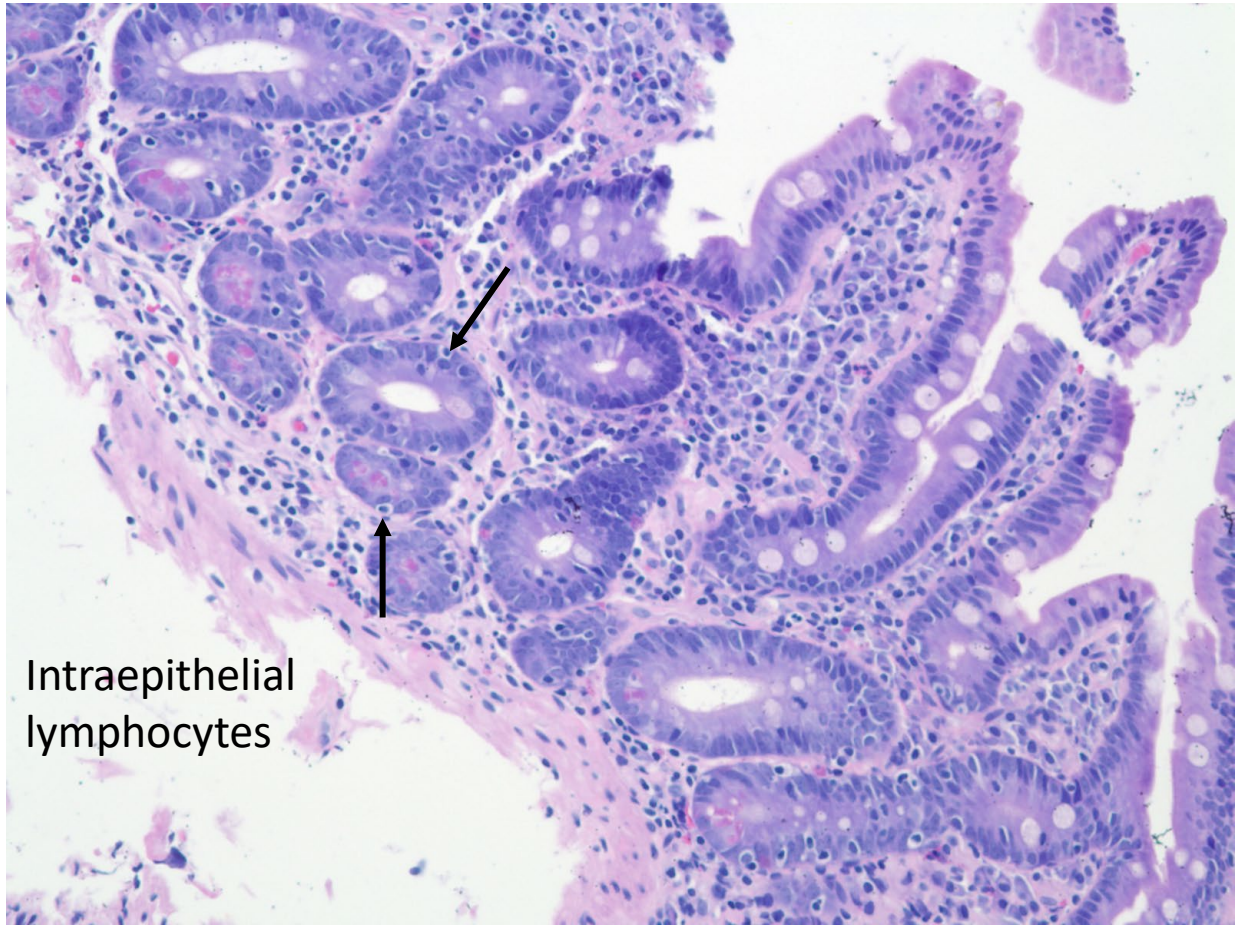
Livanos et al, Gastroenterology 2021

M. Ladinsky, P. Bjorkman

Mild evidence of intestinal inflammation based on cellular infiltrates



Patient 8 (duodenum)

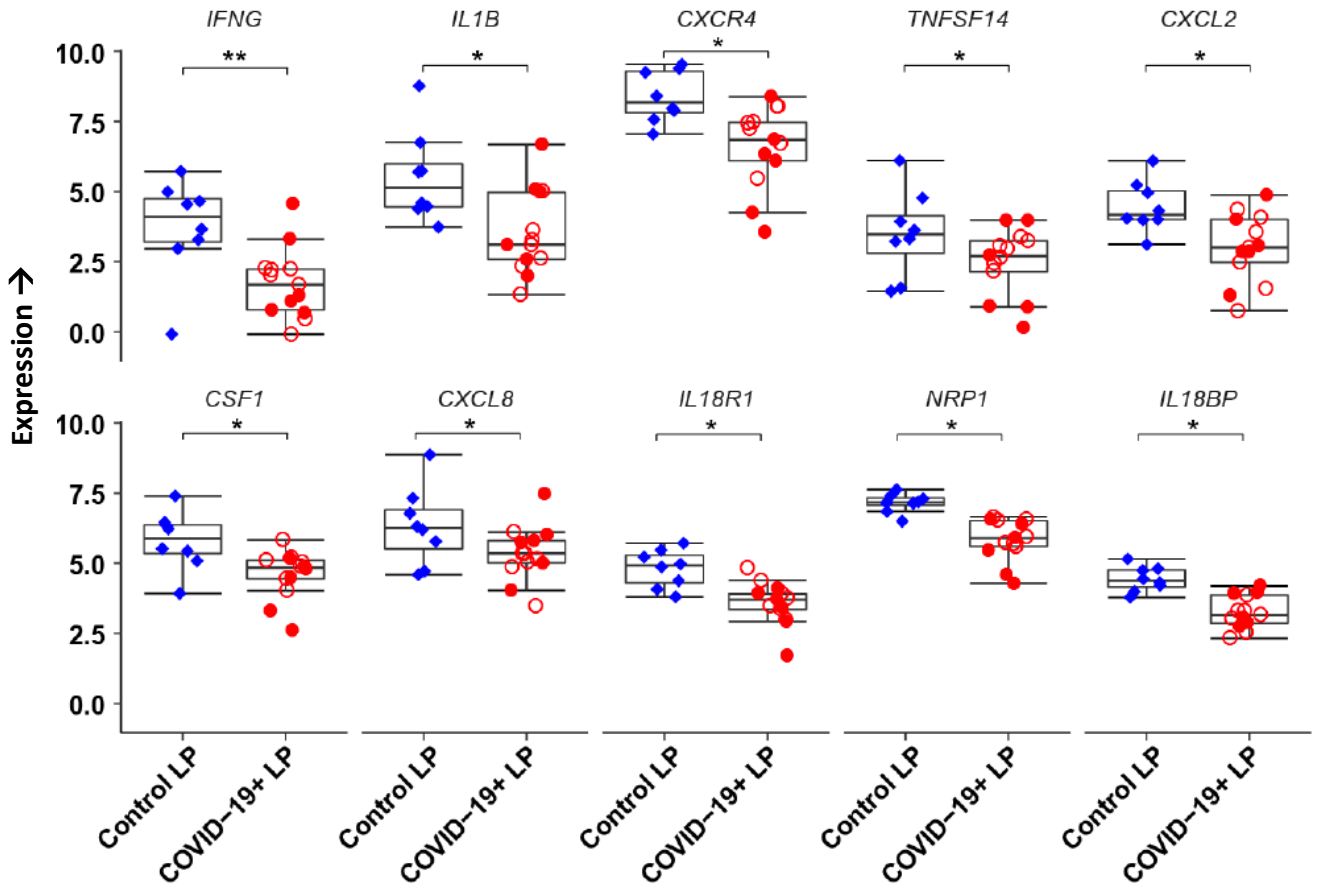


Patient 9 (duodenum)

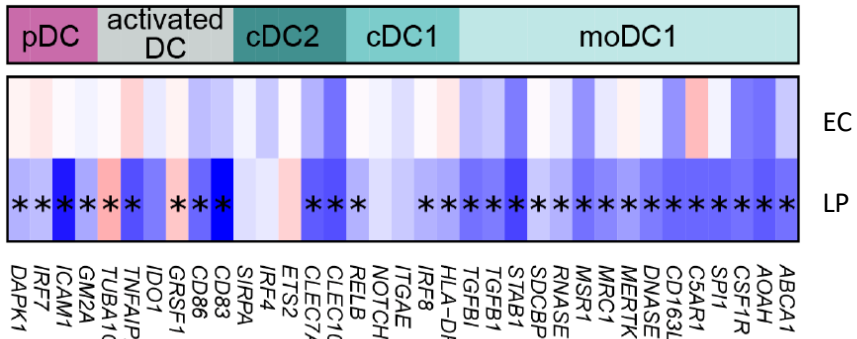
H&E, 20x mag

Intestinal biopsies during and immediate post acute phase show unexpected attenuation of inflammatory pathways

Reduced expression of key chemokines and cytokines



Reduced expression of DC-related genes



CONTROLS

COVID-19

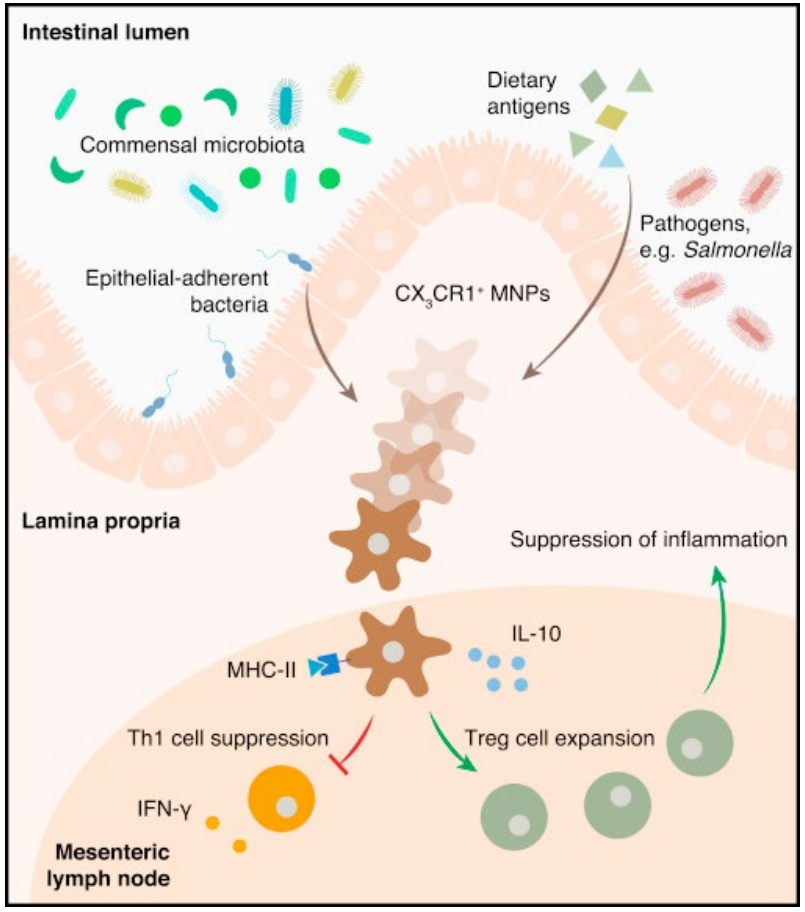
Livanos, Jha, Tokuyama, Gastroenterology, 2021

Summary

- SARS-CoV-2 viral particles can be detected by IF and EM in intestinal tissue of patients with concurrent (or recent) COVID-19
- The majority of COVID-19 patients examined in the acute to post acute stage show patchy and mild signs of intestinal inflammation (neutrophils, architectural distortion and/ or intraepithelial lymphocytes)
- Intestinal biopsies during and immediately post acute COVID-19 showed an unexpected decrease myeloid cells and inflammatory pathways when compared to normal volunteer-derived biopsies

Livanos, Jha, Tokuyama, Gastroenterology, 2021

Intestines default to inducing tolerance against luminal antigens

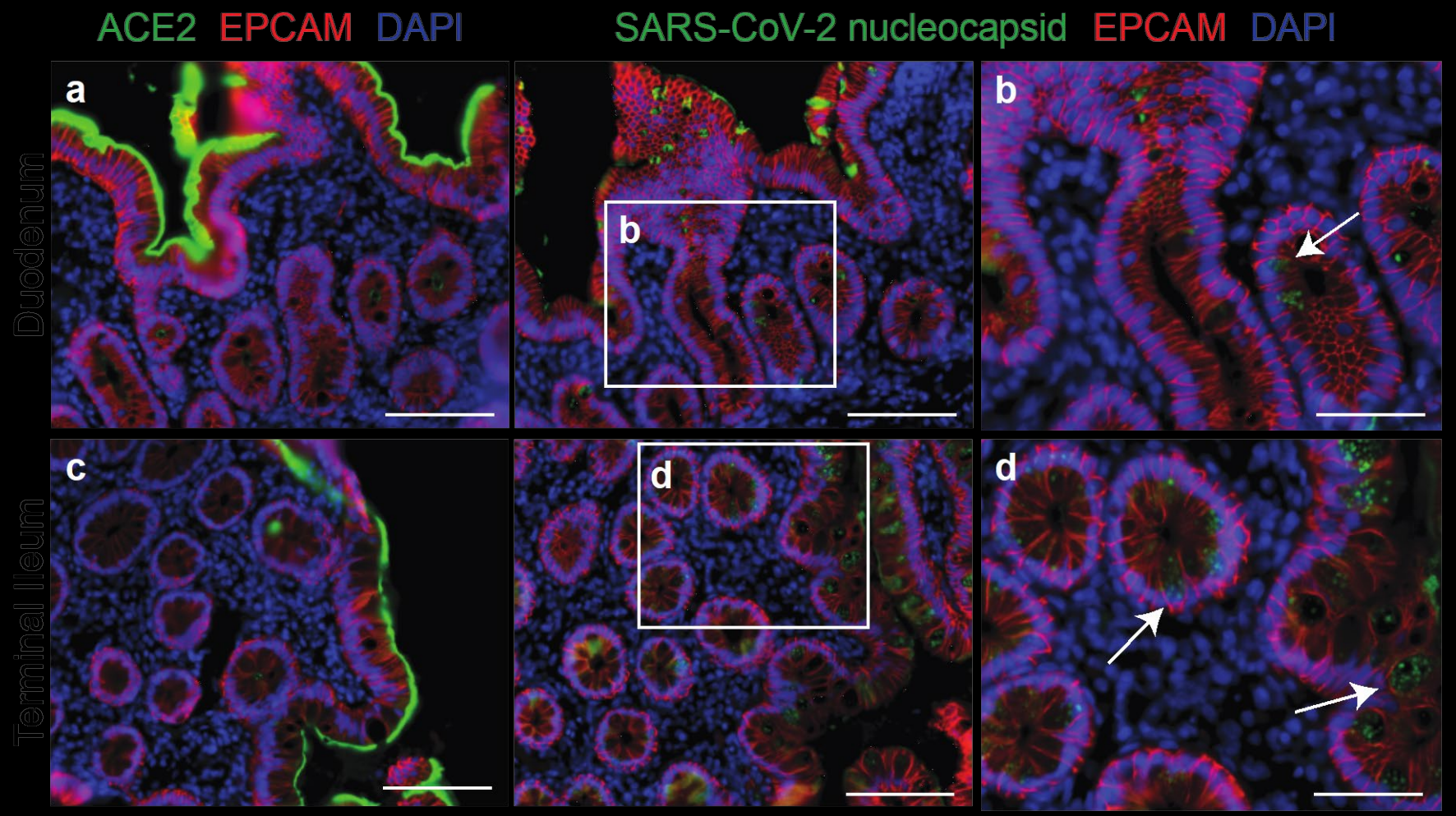


Speculation: Lack of sterilizing immunity in the gut during initial infection may allow for viral persistence

Persistence of SARS-CoV-2 in the GI tract

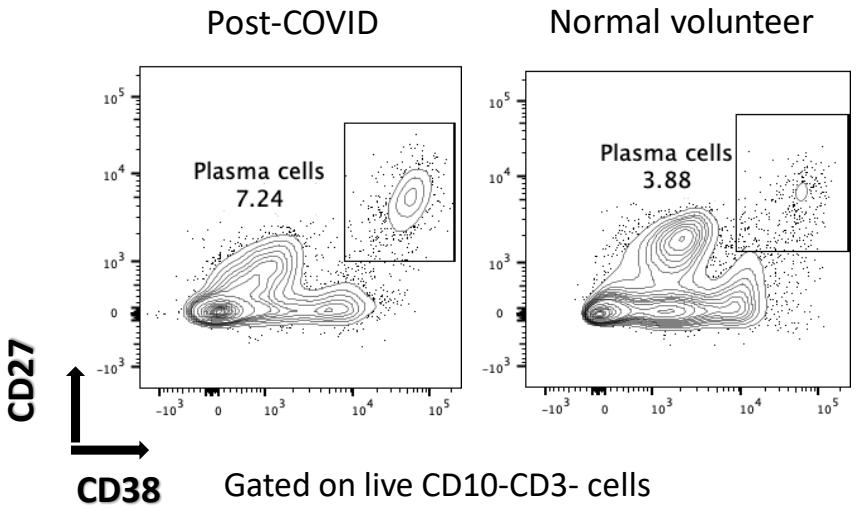
- Initially 14 subjects (now > 50) with prior diagnosis of COVID-19
- Studied at 4 months post infection (range, 2.8-5.7 months) (now upto 2 year)
- Immunostaining for NP antigens
- PCR and sequence verification of SARS-CoV-2
- Insitu hybridization
- Cellular subset examination

SARS-CoV-2 persists in the GI tract well beyond the resolution of clinical disease

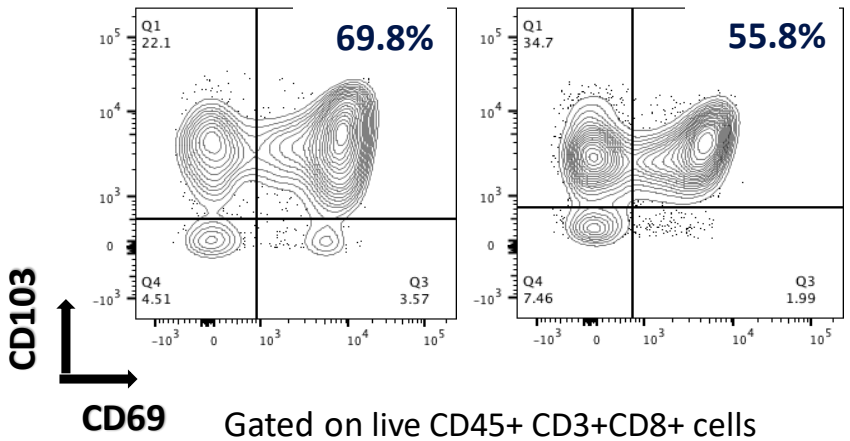


Gabler et al, Nature 2021

Significant increase in plasma cells and tissue resident memory T cells

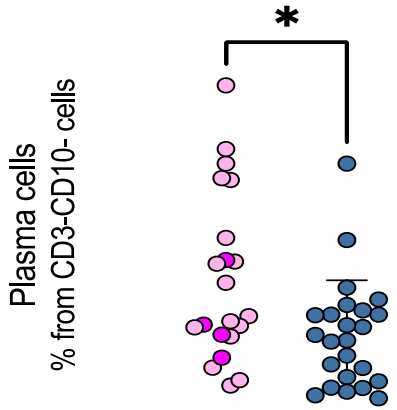


Gated on live CD10-CD3- cells



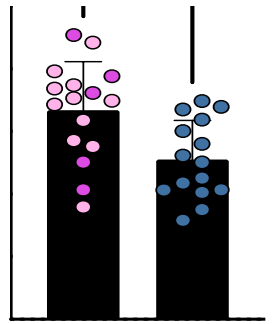
Gated on live CD45+ CD3+CD8+ cells

Plasma cells (CD19-CD38+CD27+)



Terminal Ileum

Tissue Resident memory cells (CD103+CD69+)



Normal Volunteer
Post-COVID IF positive
Post-COVID IF negative

Unpublished

Summary of persistent immune cell abnormalities in the GI tract

- Persistence of viral proteins can be seen in our cohort for more than one year
- Innate and adaptive immune cell abnormalities persist in the intestinal mucosa of COVID-recovered individuals
- Abnormalities may reflect viral persistence or prolonged immune dysregulation in the intestines
- We have not been able to culture live virus out of the intestines

Key Take Away Points

- Long COVID is a heterogeneous disorder with multiple organ system manifestations, dominated by neuropsychiatric and systemic symptoms
- Prevailing hypotheses include immune dysregulation, autoimmunity and persistence of viral reservoirs
- Intestinal viral reservoirs could potentially be associated with attenuated inflammation and less than ‘sterilizing protection’ during the acute phase of illness

Where are we going with this?

Investigating the role of the GI tract in the pathogenesis of Long COVID

Patient cohort

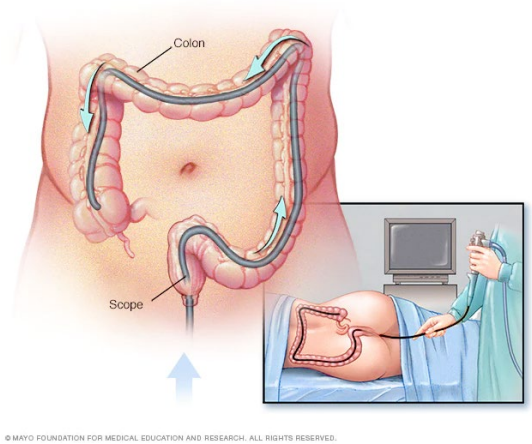
Spatial transcriptomics

Project coordination

Balvi Foundation Funded

Proposed studies

Group 1: Long COVID patients with GI symptoms (n=20)
Group 2: Long COVID patients without GI symptoms (n=10)
Group 3: Post-COVID but no long COVID (n=10)



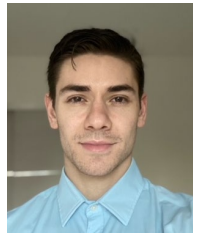
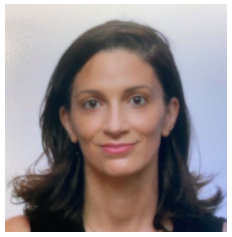
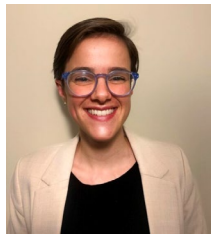
Transcriptomic profiling with scRNA seq
Advanced microscopy
Flow cytometry
Serological studies
Viral culture
Spatial transcriptomics
Spatial metatranscriptomics
Biobanking of tissue

Acknowledgements

@MehandruLab





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