Probing disease mechanisms of long COVID

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Immunobiology

Molecular Cellular and Developmental Biology

Dermatology

Epidemiology

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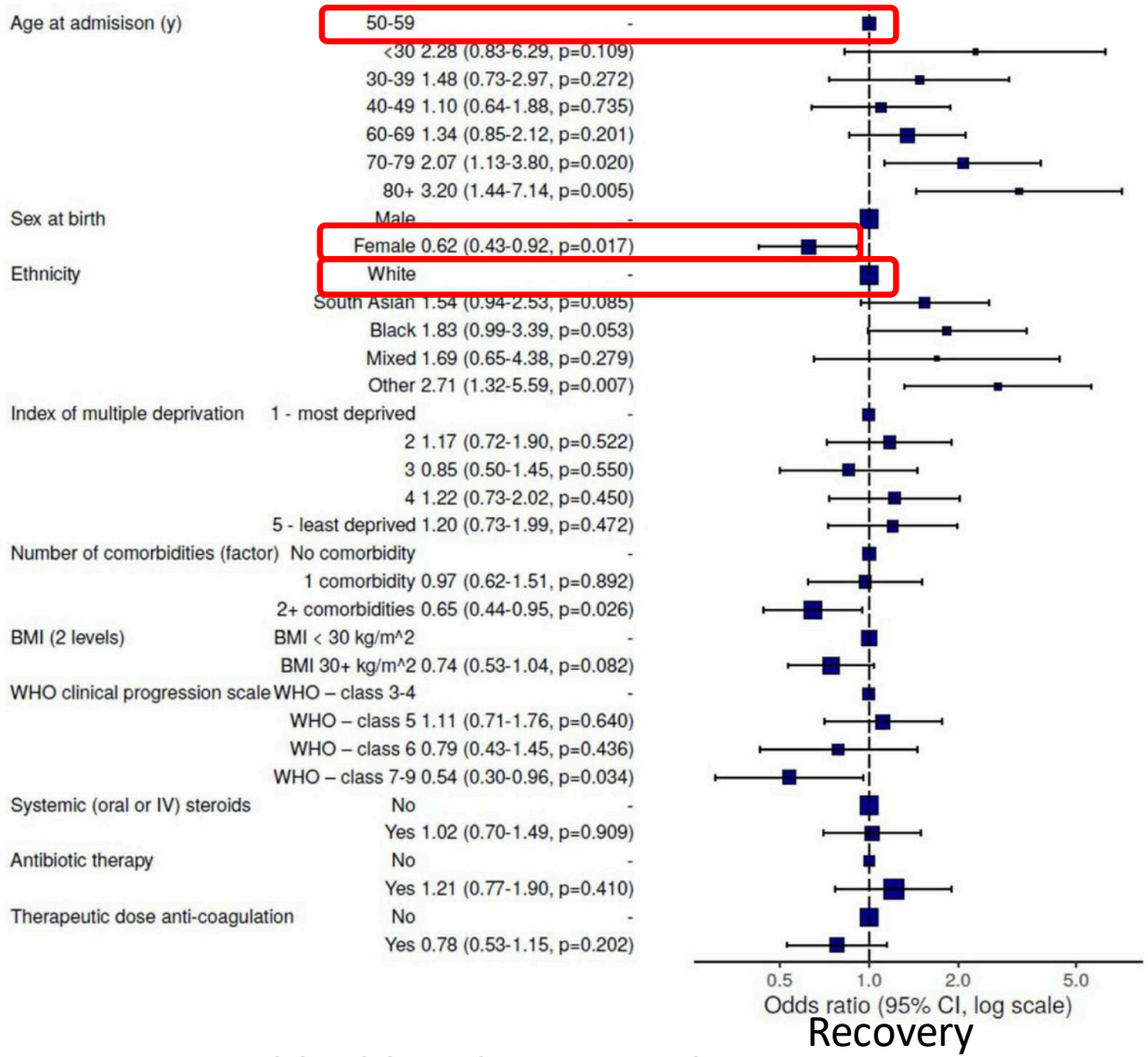
- Long COVID patients experience myriad symptoms weeks and months after infection
  - Most commonly fatigue (78%), post exertional malaise (72%), and cognitive dysfunction (55%)[1]
  - Majority have evidence of multiple organ disease[2]
- Significant % of COVID survivors develop long COVID
  - Over 5 million cases expected in the United States alone; approximate population of Colorado[3]
  - The UK's Office of National Statistics estimates that 13.7 % of people who have suffered a SARS-CoV-2 infection report long-term effects that lasted for at least 12 weeks after their diagnoses[4].
  - 63.2, 71.9 and 45.9% exhibited ≥1 post-COVID-19 symptom at 30, 60, or ≥90days after onset/hospitalization[5].
- Debilitating disease
  - 45% cases require a reduction in workload and 22% unable to return to work[1]

1) Davis, H.E., et al., *Characterizing Long COVID in an International Cohort: 7 Months of Symptoms and Their Impact EClinicalMedicine* 2021.
2) Dennis, A., et al., *Multi-organ impairment in low-risk individuals with long COVID*. BMJ Open 2021.
3) Office for National Statistics. *The prevalence of long COVID symptoms and COVID-19 complications*. Dec 16, 2020.
4) https://www.ons.gov.uk
5) Prevalence of post-COVID-19 symptoms in hospitalized and non-hospitalized COVID-19 survivors: A systematic review and meta-analysis, European Journal of Internal Medicine, 2021

Middle aged women face greater risk of debilitating long COVID



Recovery

Evans RA, et al; PHOSP-COVID Collaborative Group. *medRxiv* 2021

Women under 50 were;

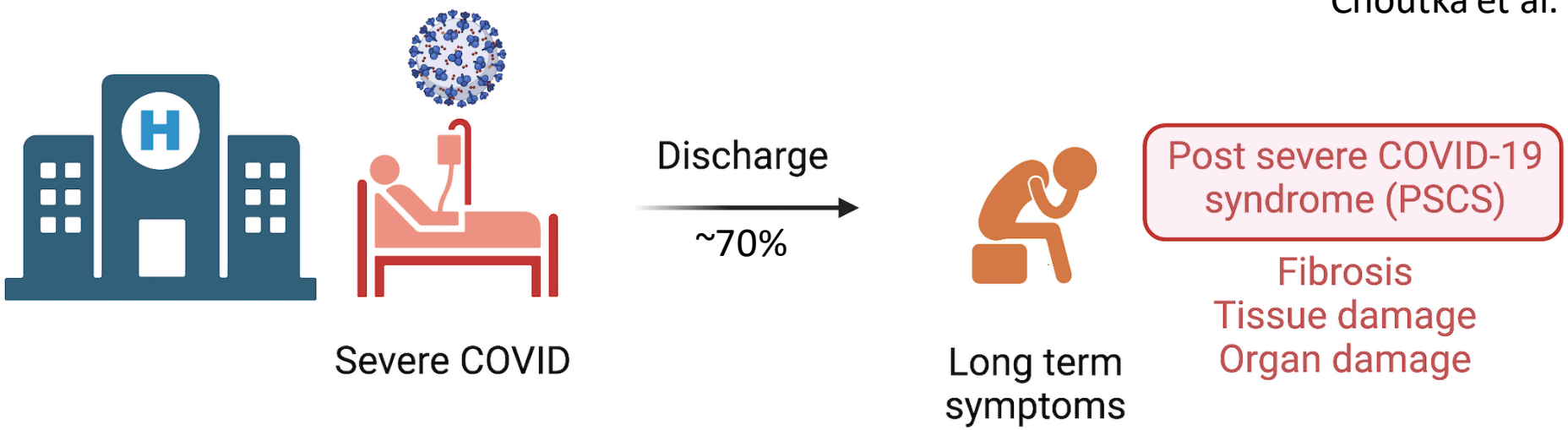
- 5x less likely to report feeling recovered
- 2x as likely to report worse fatigue
- 7x more likely to become more breathless, and more likely to have greater disability

than men of the same age who had been admitted to hospital with covid-19

Sigfrid L et al. *medRxiv* 2021

Two types of long COVID

Choutka et al. (in preparation)



via David Putrino

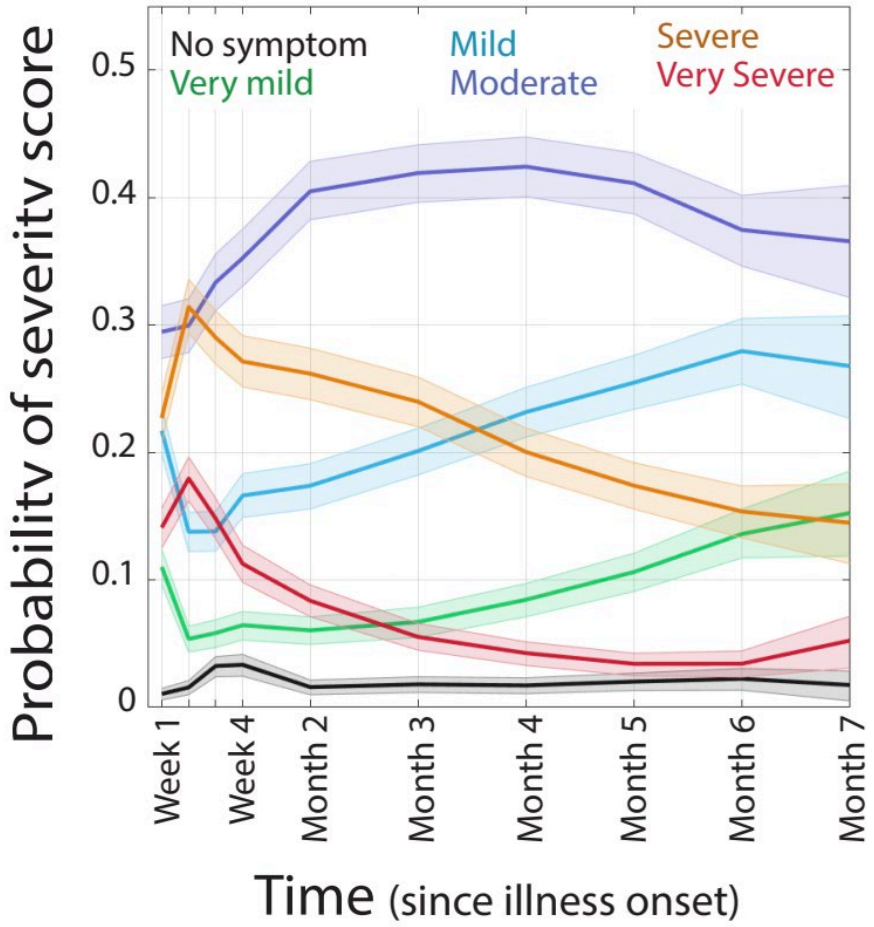
Nassarie et al. *JAMA Netw Open.* 2021;4(5):e2111417.

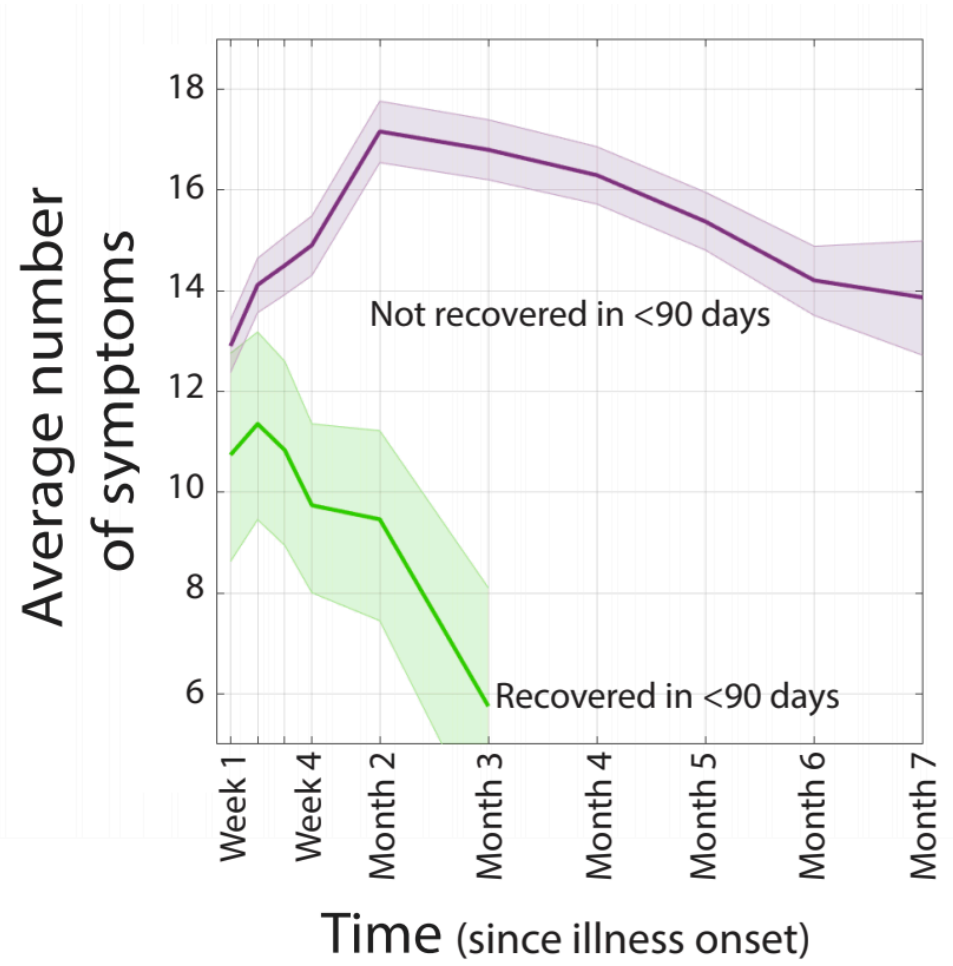
COVID-19 causes long lasting symptoms involving multiple organs

Organ System	Symptoms/manifestations
Systemic	Fever, Fatigue, post-exertional malaise
Neuropsychiatric	Memory deficit, loss of concentration, sleep difficulty, mood disorder, paresthesia, myelopathy, neuropathy
HEENT	Headache, dizziness, loss of taste and smell, blurry vision, tinnitus, sore throat
Endocrine	Hot/cold sensation, thyroid abnormalities, diabetes
Cardiovascular	Chest pain, palpitations, hypertension, angina, myocarditis, pericarditis, cardiac arrhythmias, postural orthostatic syndrome
Pulmonary	Shortness of breath, cough, interstitial lung disease
Musculoskeletal	Myalgia, arthralgia, weakness
Gastrointestinal	Diarrhea, vomiting, nausea, loss of appetite, hepatitis

HEENT = Head, Eyes, Ears, Nose, and Throat.

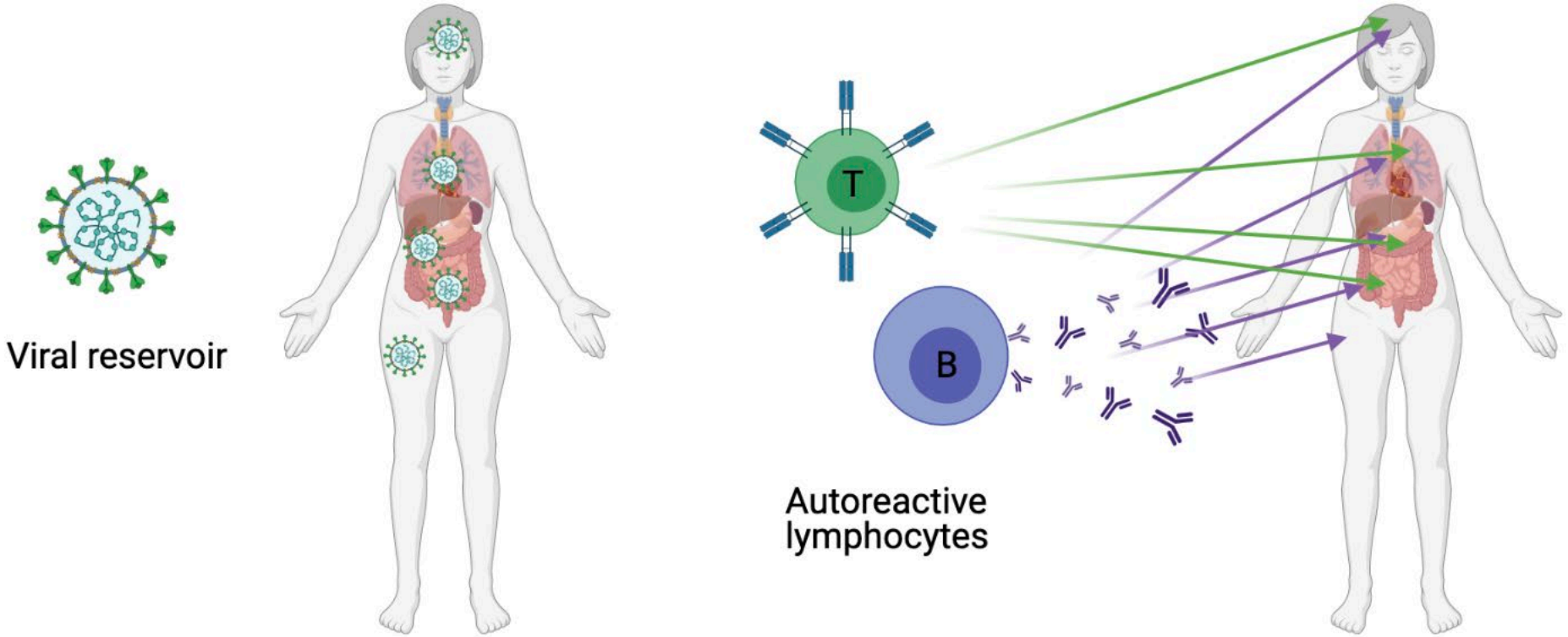
Long COVID symptom severity and duration





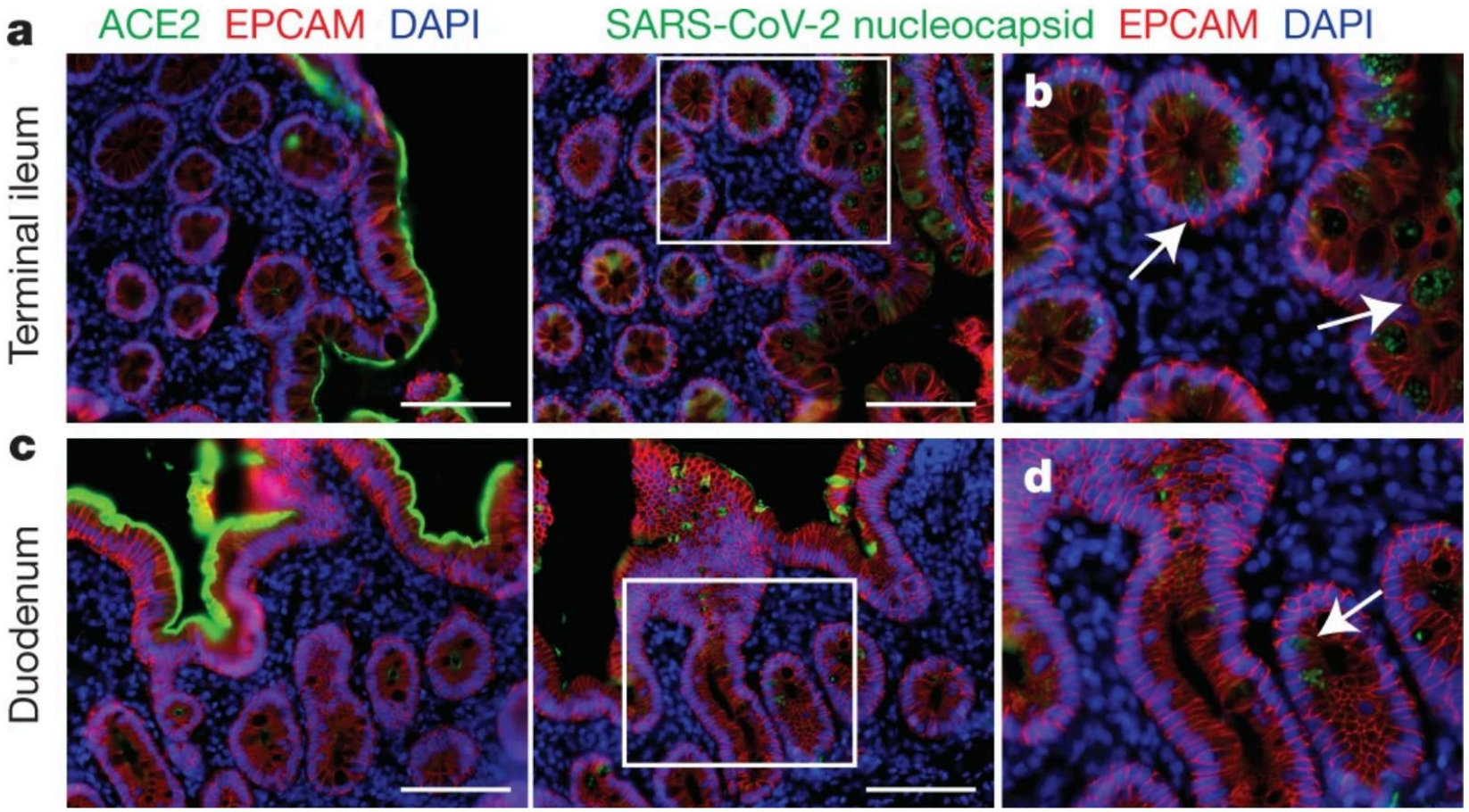
Davis, H.E., et al., *Characterizing Long COVID in an International Cohort: 7 Months of Symptoms and Their Impact EClinicalMedicine* 2021

Long COVID disease hypotheses



-Tissue Damage
-Dysbiosis
-Latent virus reactivation

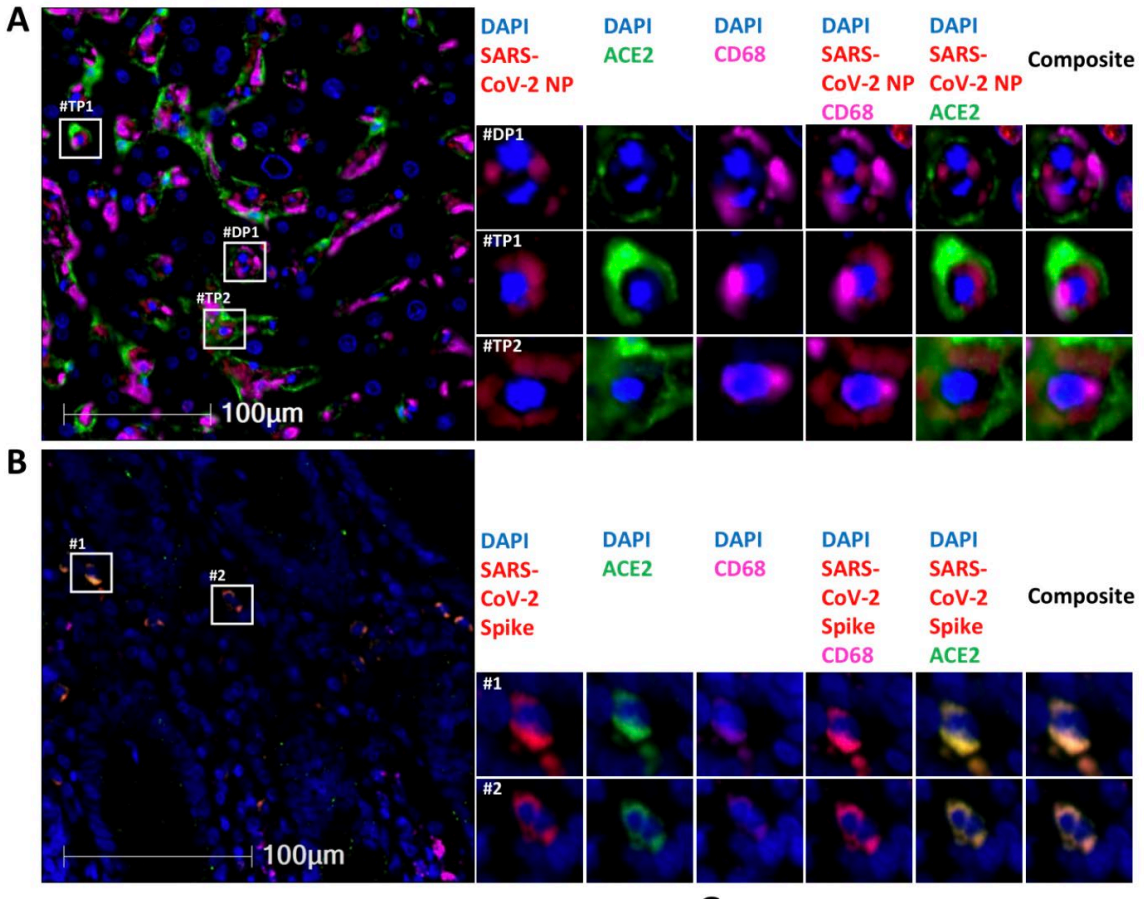
Viral reservoirs are seen in COVID patients



Intestinal biopsy 92 days from symptom onset
(5/14 patients had positive staining, 3/14 PCR+ for viral RNA after 3 months)

Gaebler, C., Wang, Z., Lorenzi, J.C.C. *et al.* Evolution of antibody immunity to SARS-CoV-2. *Nature* **591,** 639–644 (2021).

Viral protein and RNA are found in the colon, appendix, ileum, haemorrhoid, liver, gallbladder and lymph nodes of convalescent individuals

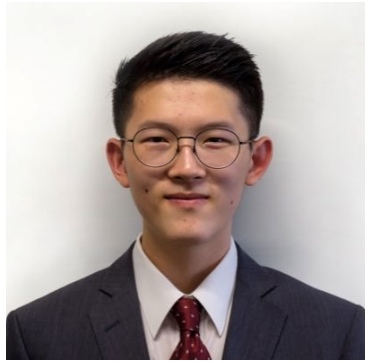


Five patients who recovered from COVID-19, ranging from 9 to 180 days after testing negative for SARS-CoV-2, were examined for presence of viral protein and RNA

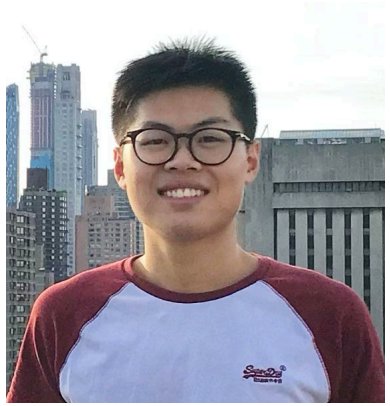
Cheung CCL, Goh D, Lim X, et al. Gut. doi:10.1136/gutjnl-2021-324280

Autoantibodies in COVID-19

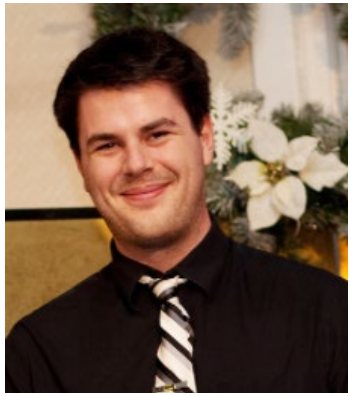
Aaron Ring



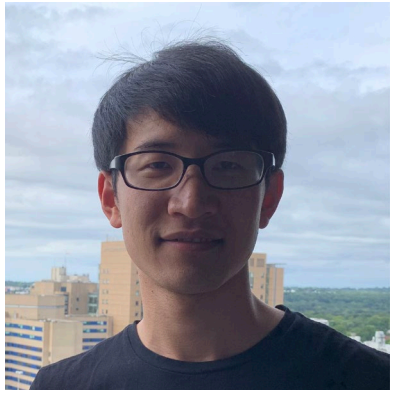
Eric Wang



Tianyang Mao



Jon Klein

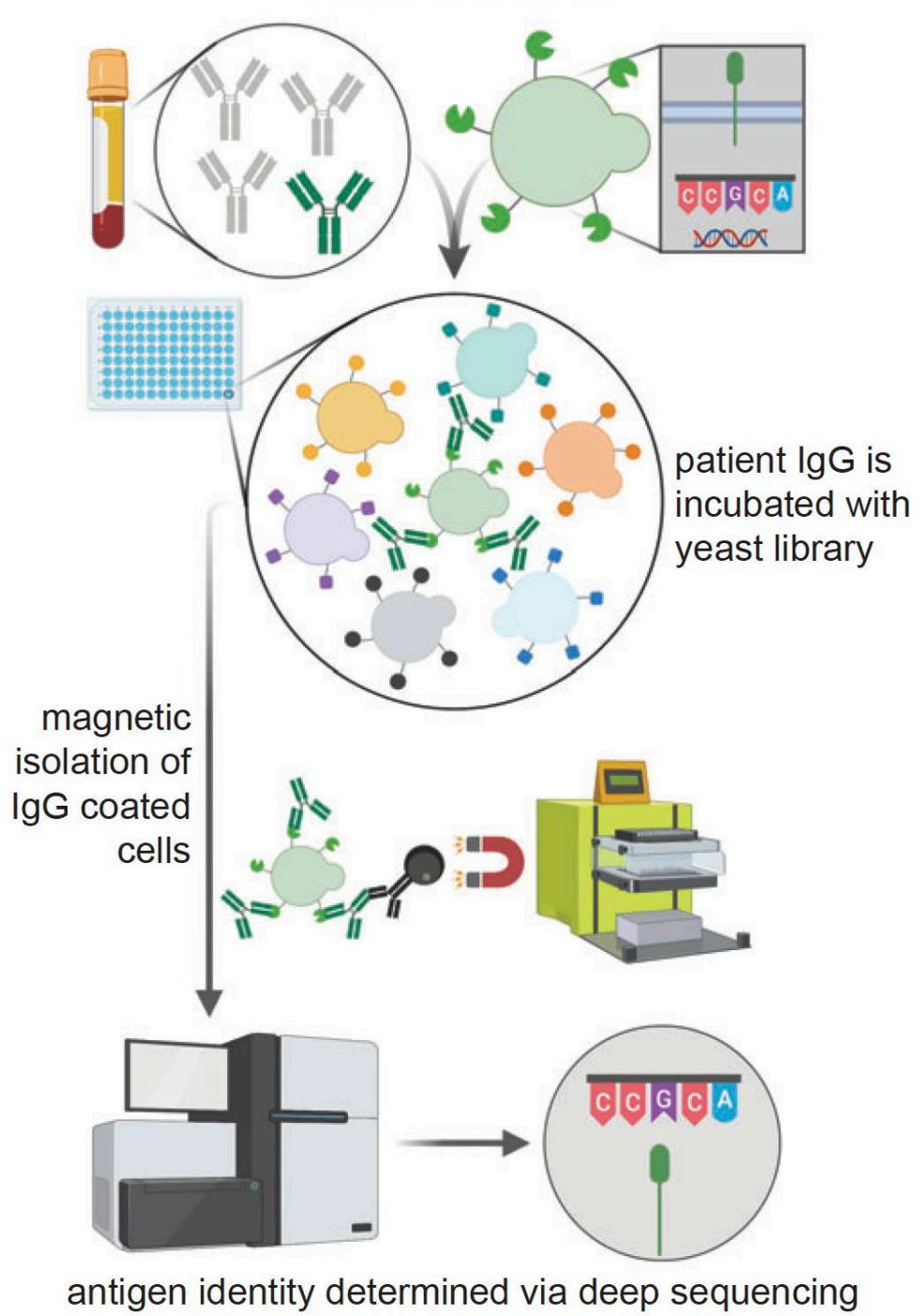


Yile Dai

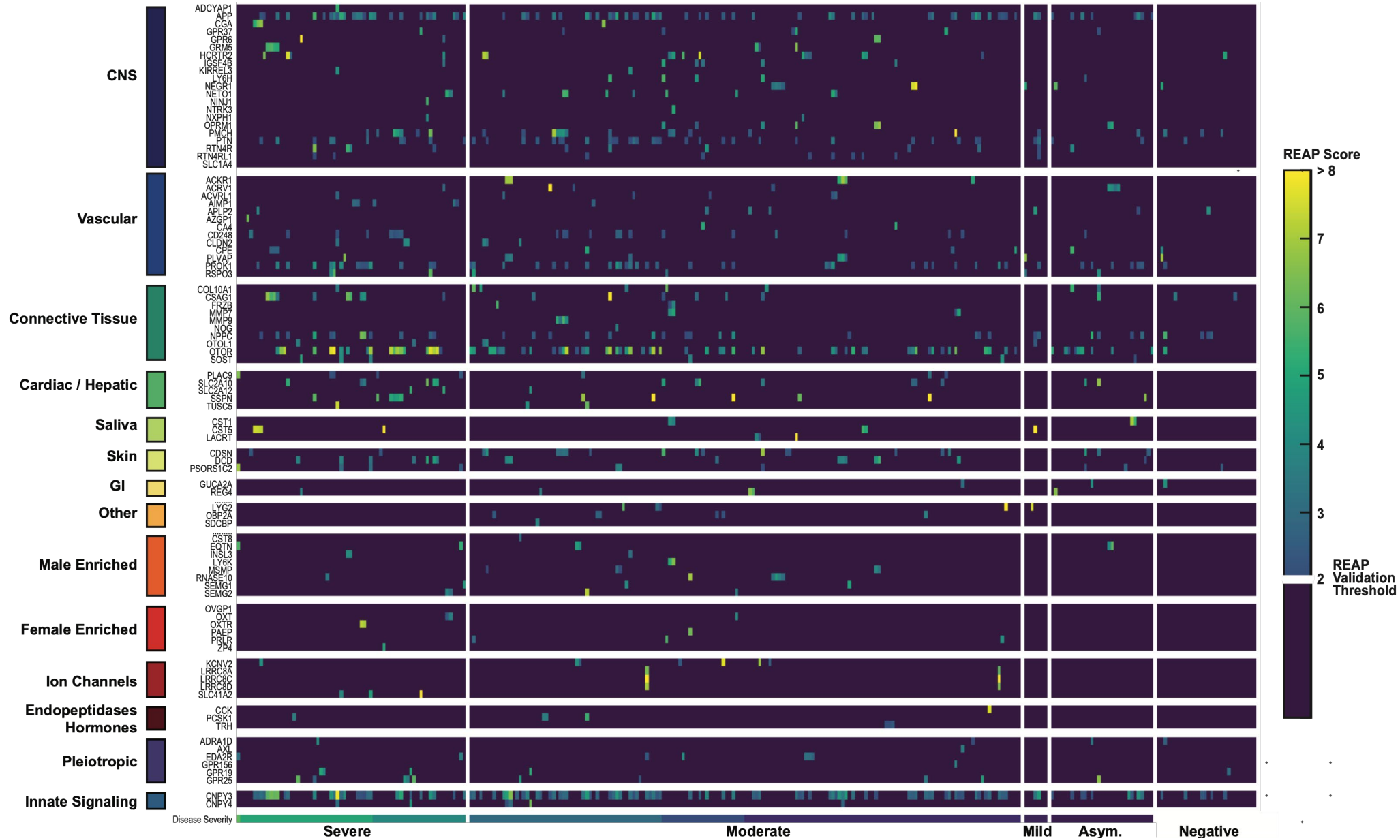
Wang et al. *Nature* (2021)

Rapid Extracellular Antigen Profiling (REAP)

- Comprehensive, genetically barcoded library of ~3,000 extracellular /secreted proteins (exoproteome) displayed on yeast.
- Efficient display of human extracellular proteins (disulfide bonds, glycosylation, chaperones)



Autoantibodies in COVID-19 patients target a wide range of tissue-associated proteins



Other reports demonstrating autoantibodies in acute and long COVID

- Bastard, P. et al. Autoantibodies against type I IFNs in patients with life-threatening COVID-19. *Science* **370**, eabd4585 (2020).
- Combes, A. J. et al. Global absence and targeting of protective immune states in severe COVID-19. *Nature* **591**, 124–130 (2021).
- Zuo, Y. et al. Prothrombotic autoantibodies in serum from patients hospitalized with COVID-19. *Sci. Transl. Med*. **12**, eabd3876 (2020).
- Woodruff, M. C., Ramonell, R. P., Lee, F. E.-H. & Sanz, I. Relaxed peripheral tolerance drives broad de novo autoreactivity in severe COVID-19. Preprint at https://doi.org/10.1101/2020.10.21.20216192 (2020).
- Zhou, Y. et al. Clinical and autoimmune characteristics of severe and critical cases of COVID-19. *Clin. Transl. Sci*. **13**, 1077–1086 (2020).
- Song E et al. Divergent and self-reactive immune responses in the CNS of COVID-19 patients with neurological symptoms. *Cell Rep Med* 2(5):100288 (2021).
- Zuniga M et al. Autoimmunity to Annexin A2 predicts mortality among hospitalised COVID-19 patients. *European Respiratory Journal* (2021).
- Chang, S. E. et al. New-onset IgG autoantibodies in hospitalized patients with COVID-19. *Nat Commun* **12,** 5417 (2021).
- Gerd Wallukat et al., Functional autoantibodies against G-protein coupled receptors in patients with persistent Long-COVID-19 symptoms, *Journal of Translational Autoimmunity* (2021)

Are there any treatments that impact long COVID symptoms?

Vaccines' impact on long COVID symptoms

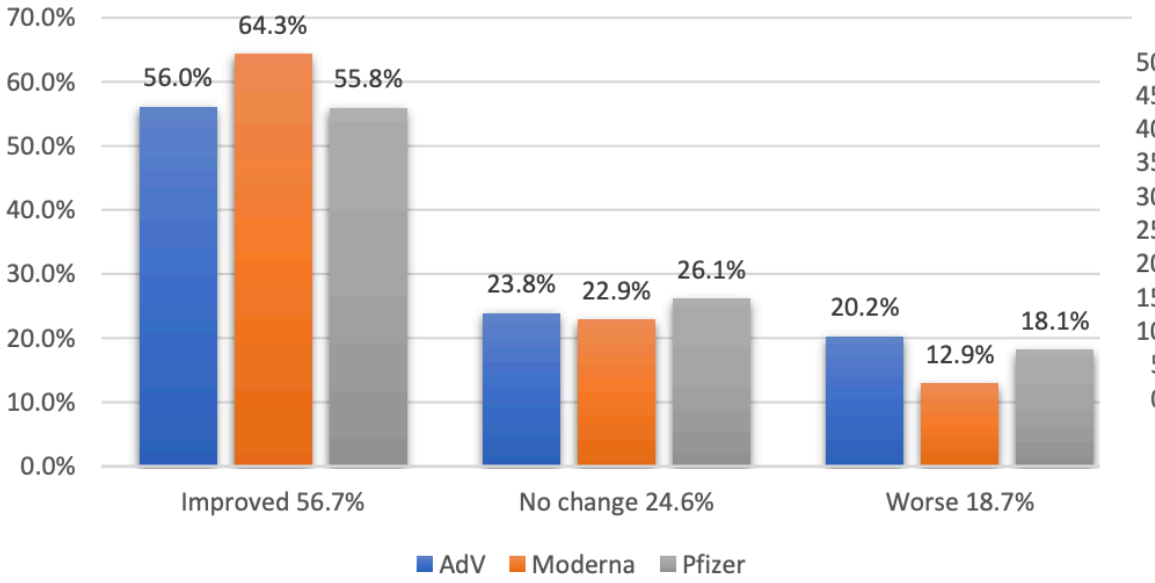


Figure 7: Change in symptom scores before and after vaccination

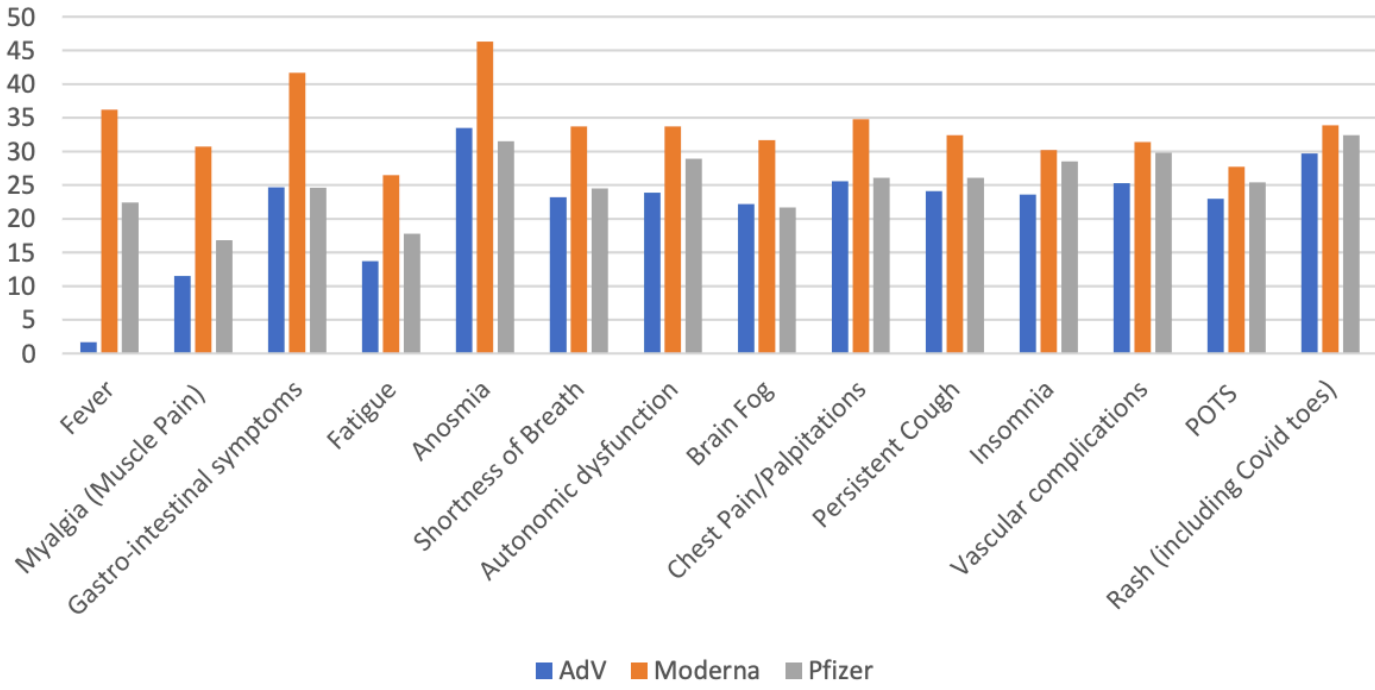


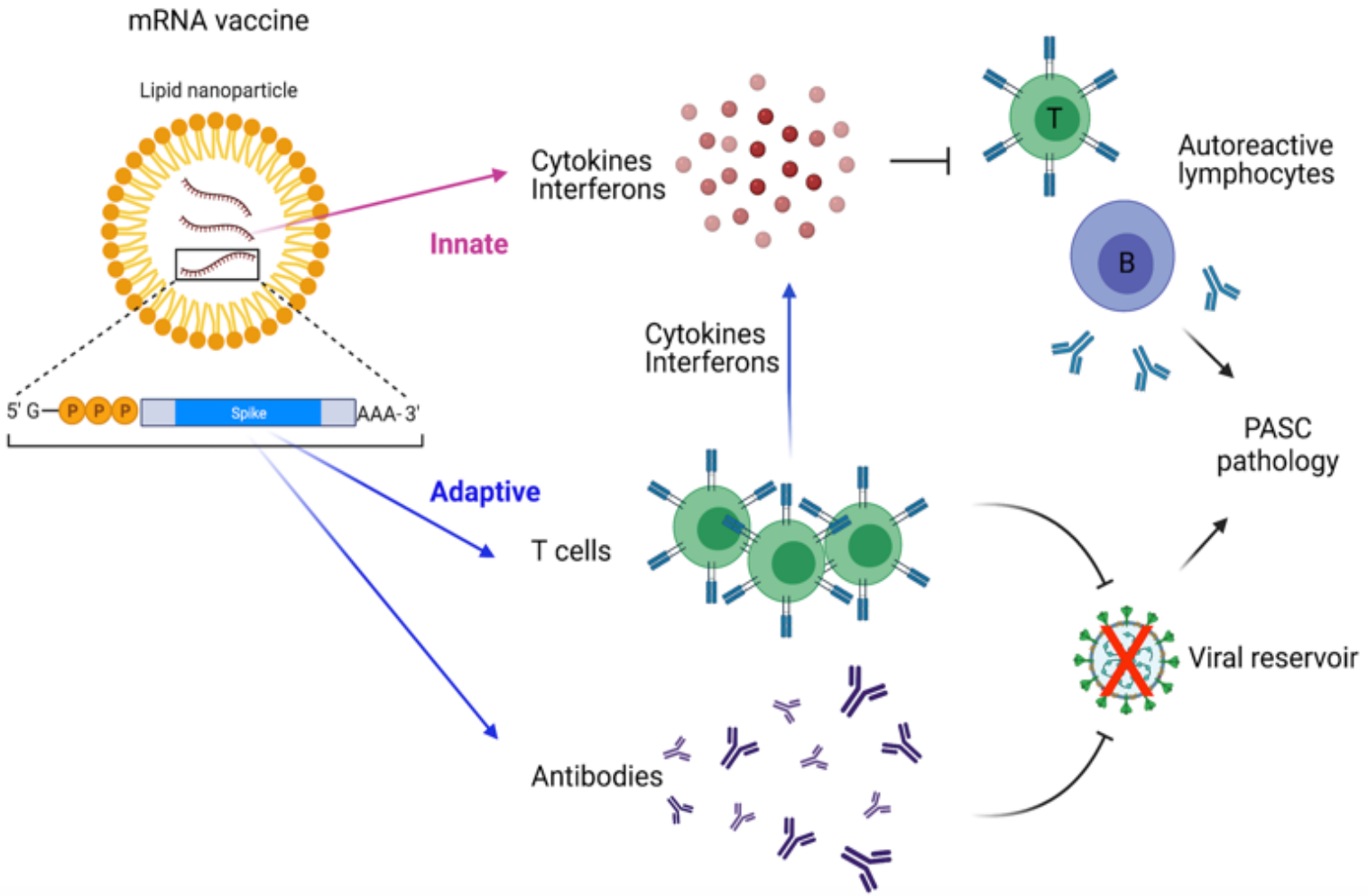
Figure 9: Percentage change in symptom scores before and after first vaccination dose

Recognition - Research - Rehab

LongCovidSOS

Vaccines and long COVID

Vaccines may improve long COVID symptoms by eliciting robust antiviral antibodies to clear the viral reservoir, or divert autoimmune lymphocytes through innate and adaptive cytokines.



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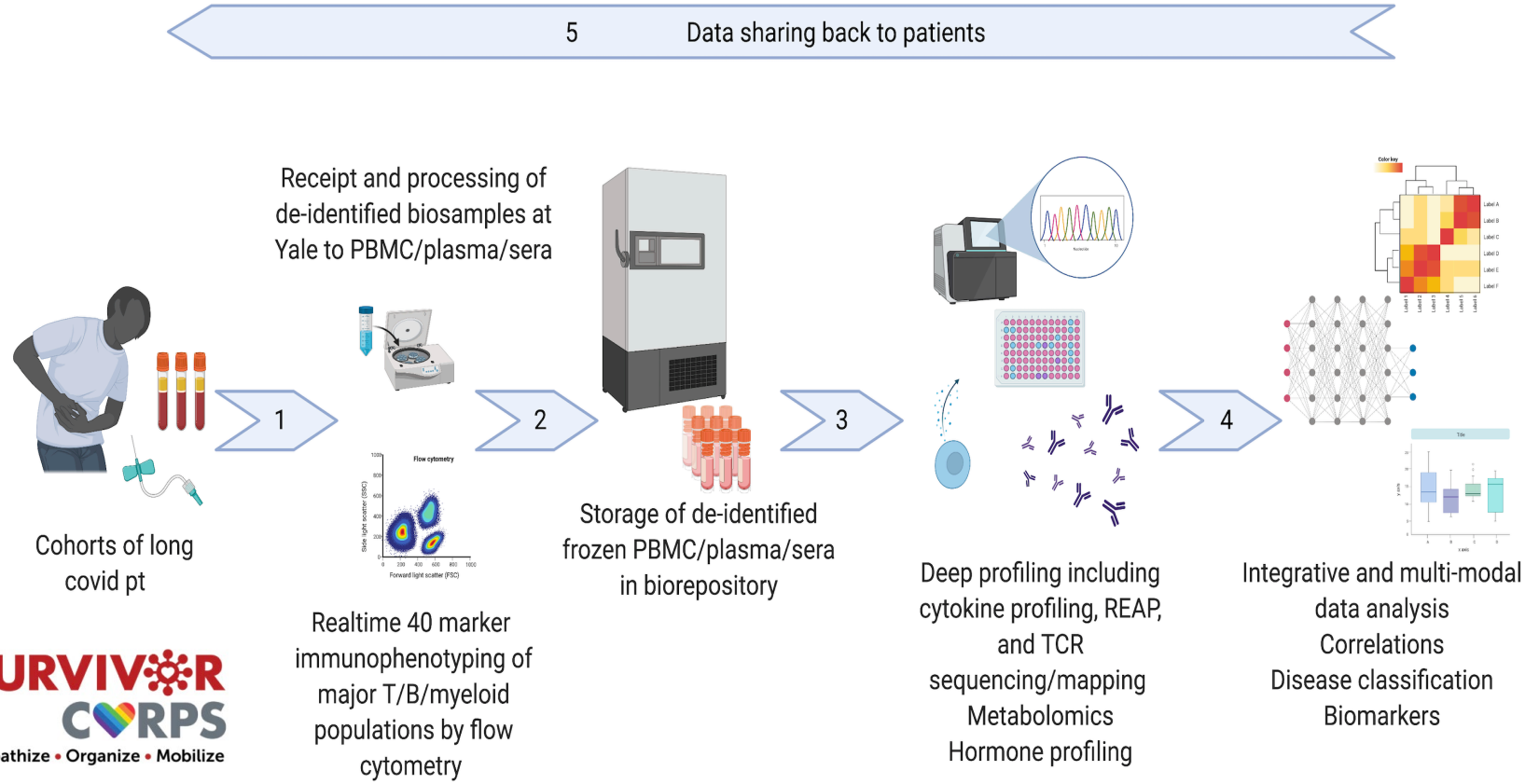
Our Mission

To understand immunological and physiological determinants of disease pathogenesis of long COVID to inform rational diagnosis and therapy

Workflow



Harlan Krumholz (longitudinal)
David Putrino (cross sectional)

Aaron Ring
Ruslan Medzhitov
Adaptive Biotech
Serimmune

David van Dijk
Wade Schulz

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  - Tianyang Mao
  - Annsea Park
  - Jon Klein
  - Julio Silva
  - Yong Kong
  - Melissa Linehan
  - Huiping Dong
  - Maria Tokuyama
  - Takehiro Takahashi
  - Miyu Moriyama
  - Peiwen Lu
  - Carolina Lucas
  - Benjamin Israelow
  - Eric Song
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  - Mario Pena Hernandez
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  - John Frank
  - Valter Silva Monteiro
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  - Saad Omer
  - Charles Dela Cruz
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  - Nathan Grubaugh
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- Mount Sinai LC team
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  - Laura Tabacof
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  - Hannah Davis
  - Lisa McCorkell
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  - Hannah Wei
- Immune profiling and data analysis team
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  - Ruslan Medzhitov
  - David Van Dijk
  - Wade Schulz
  - Adaptive Biotechnologies
  - Serimmune