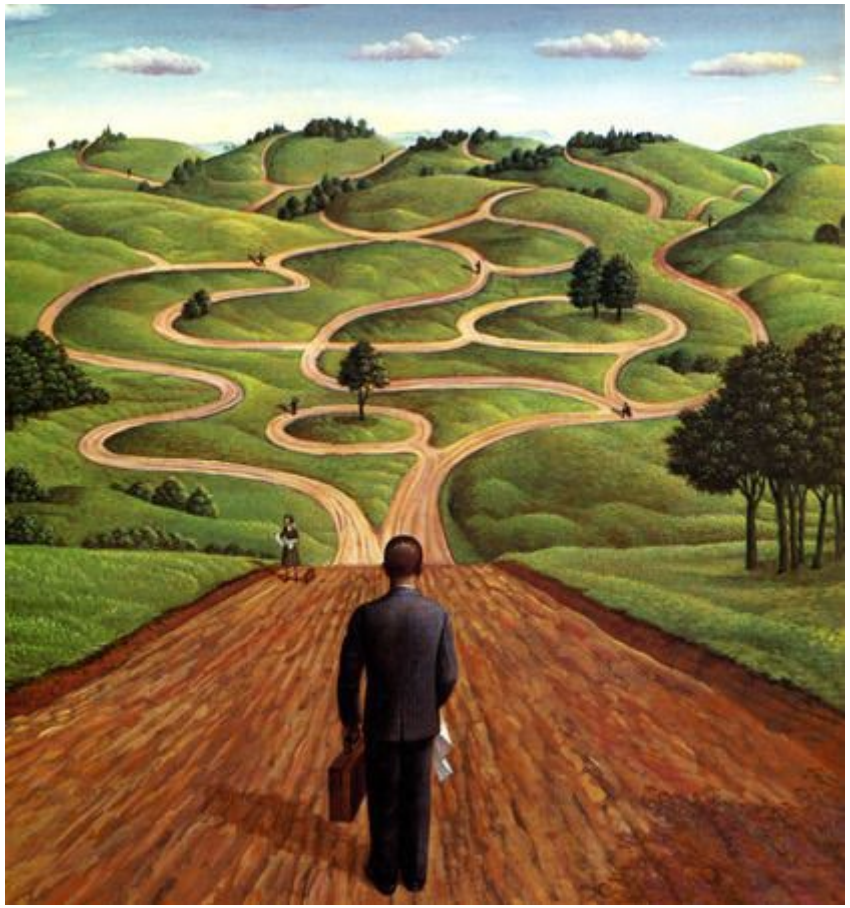
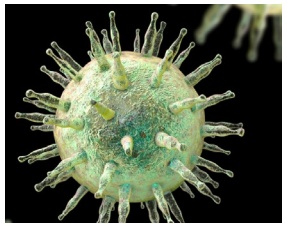
Patient Disease Journeys and Post-Acute Infection Sequelae

Jim Heath, ISB



PI, Pacific Northwest Consortium of RECOVER

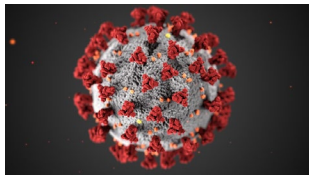
PASC Factors



EBV Viremia (blood)

~15% of patients

- Neurological PASC



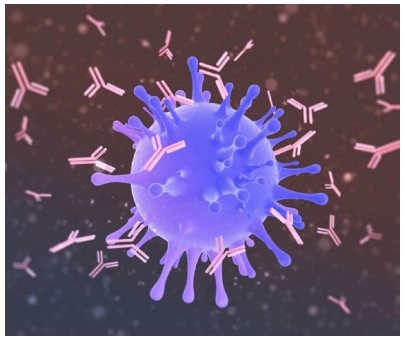
SARS-CoV-2 RNAemia (blood)

25% of patients

- Neurological PASC
- Fatigue PASC
- Covid-19 mortality
- sputum

20% of patients

- Respiratory viral (multiple symptoms)



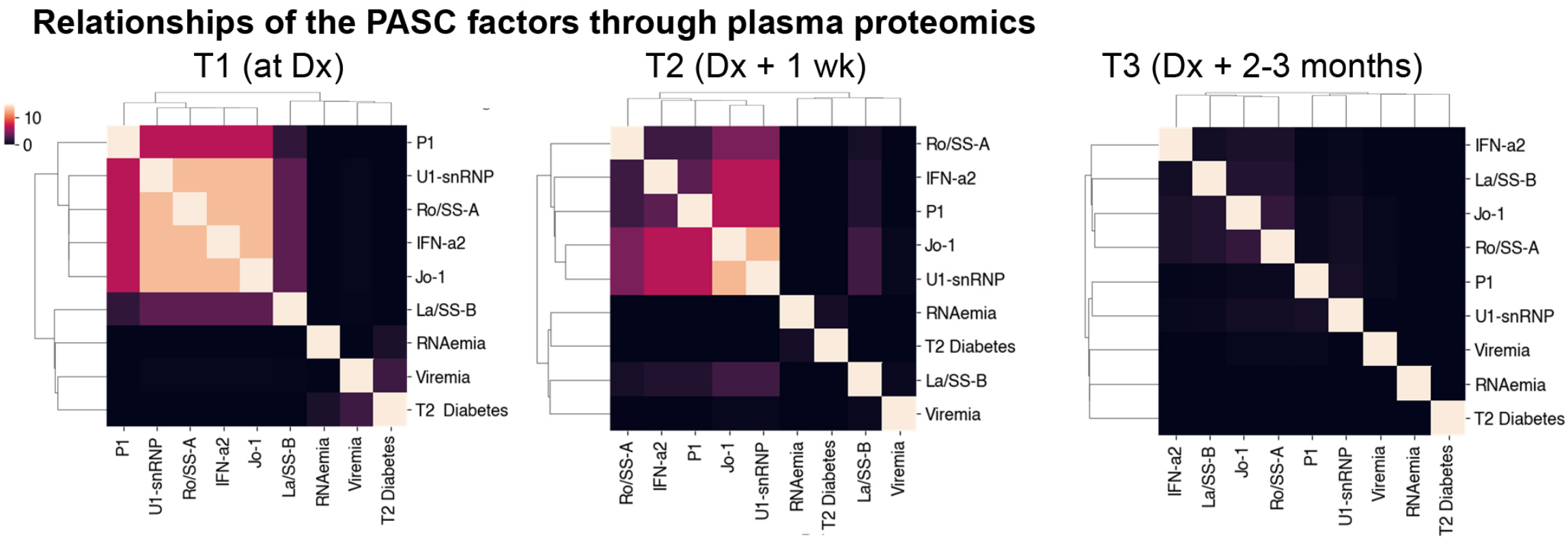
Sub-clinical levels of auto IgG Abs In around 25%

Clinical levels in only 1-2%

- sputum, GI,
- inability to exercise

Su, et al., Cell (2022)

Relationships between PASC factors are lost over time



The implication is that at COVID-19 diagnosis

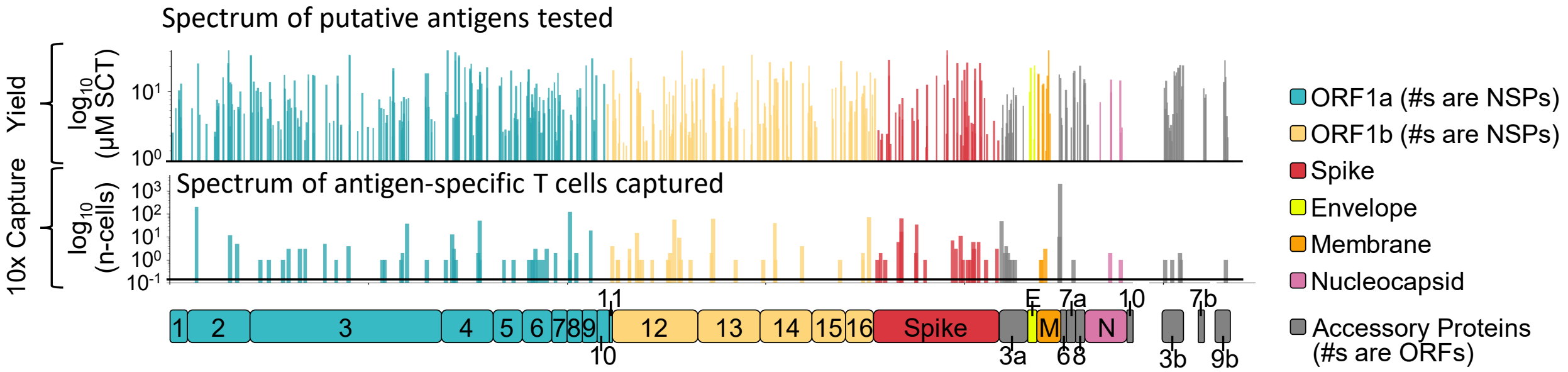
relationships between PASC factors are evident

suggests a limited number of therapies

At longer than 3 months post-acute disease, even the autoantibodies are no longer detected

The Importance of Mapping the Patient Disease Journey

A SARS-CoV-2 viral proteome-wide library of pMHC-like multimers



Plus libraries of

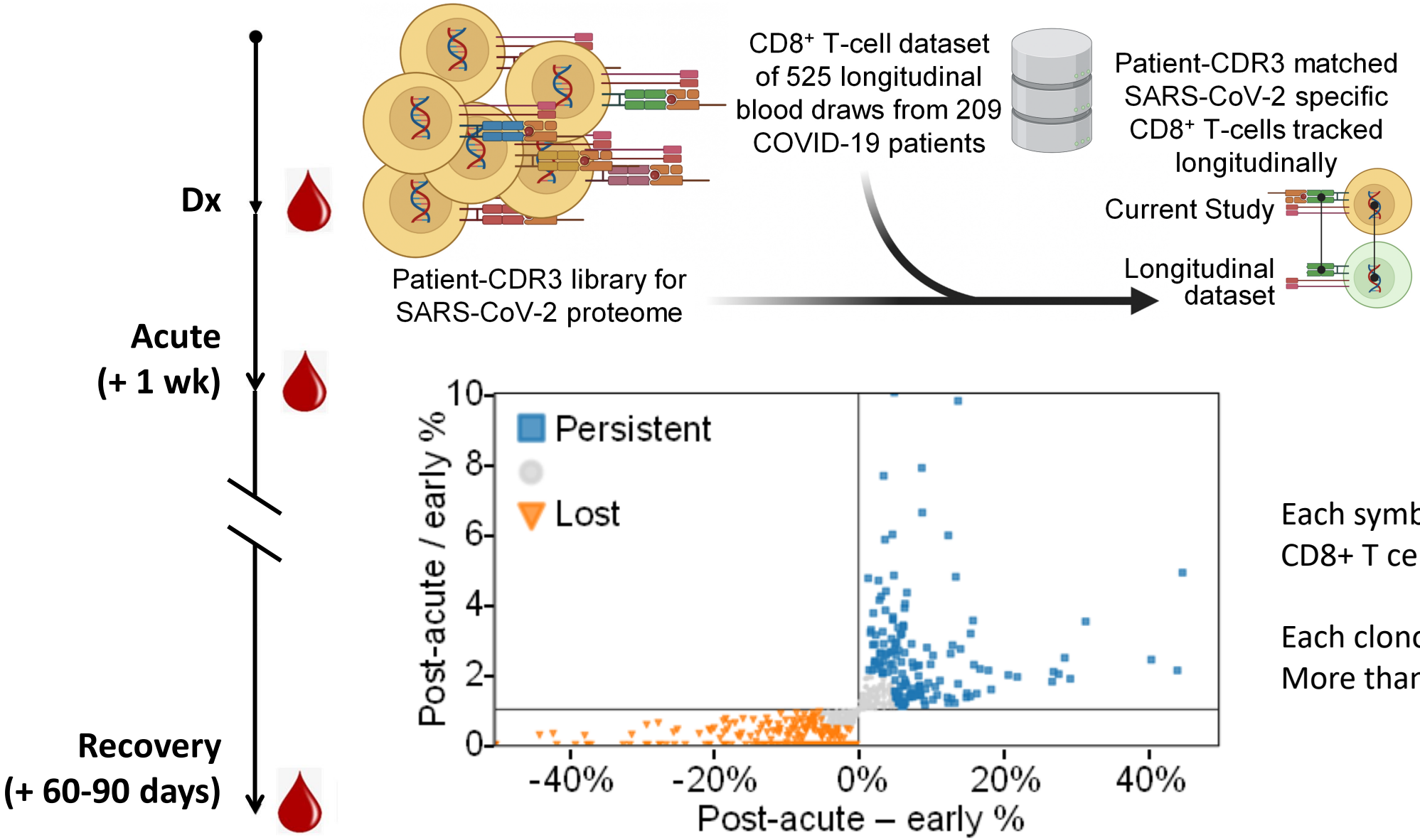
- A*02.01 CMV

Around 650 single-chain trimers used

See also four recent papers where we used this tech

Foy, Nature 2022
Puig-Suis, Nature 2023
Chour, NatCommBio 2023
Finton, Front. Immun. 2023

Kinetics of SARS-CoV-2 specific CD8+ clonotypes

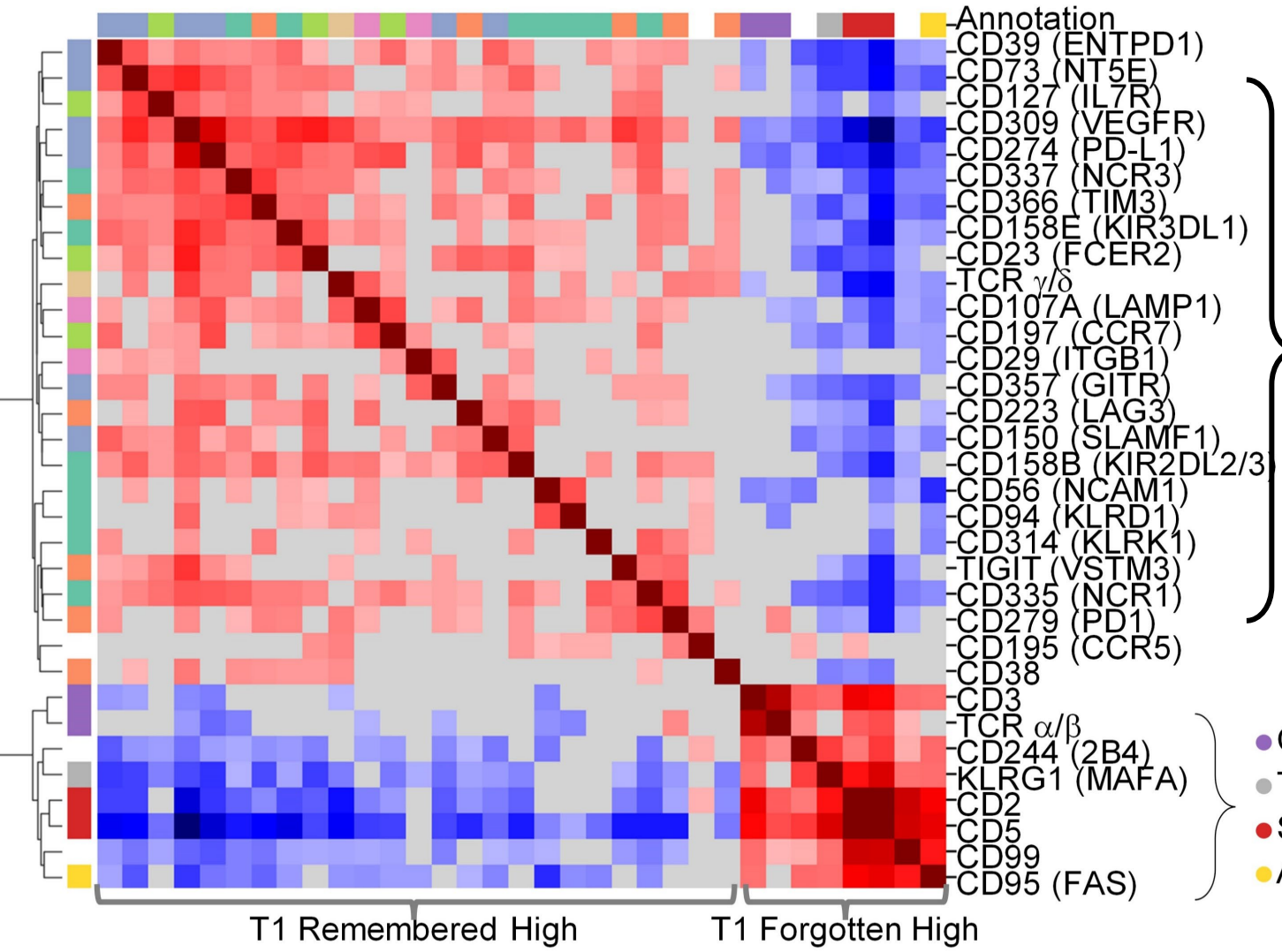


Each symbol represents a CD8+ T cell clonotype

Each clonotype is represented by More than 3 cells

Persistent SARS-CoV-2 specific CD8+ T cells identified at Dx

All these cells classify as cytotoxic; proteomics resolve sub-phenotypes



Markers on persistent cells

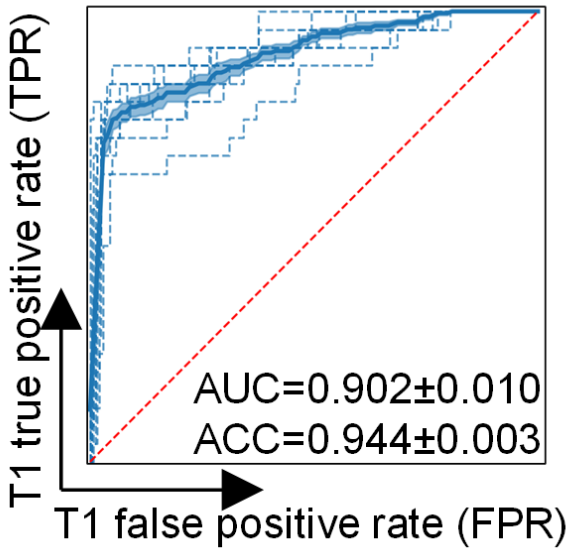
- Regulatory like
- Undifferentiated
- NK-related
- Exhaustion
- TCR γ/δ
- Effector function

○ Not annotated

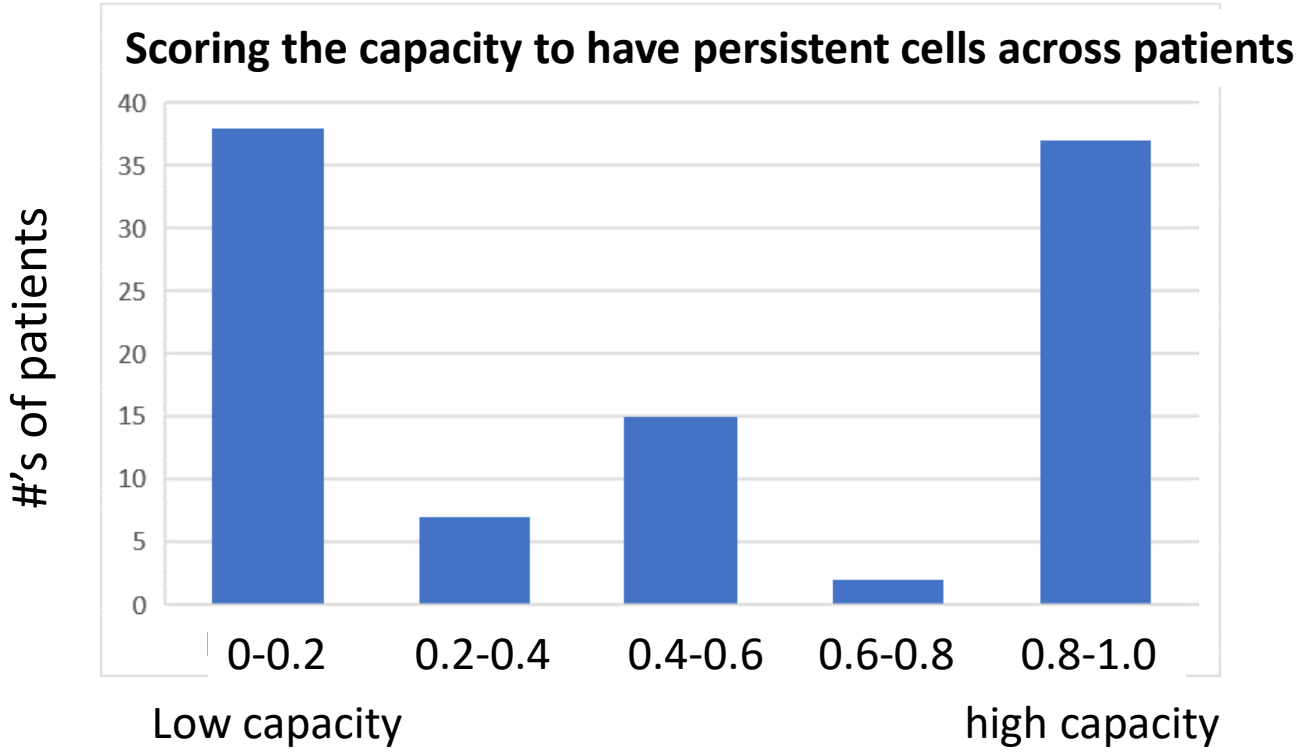
- CD3/TCR α/β
- Terminal
- Stimulation
- Apoptosis

Markers on lost cells recall short-lived effectors.
Herndler-Brandstetter, D. *et al. Immunity* **48**, 716 (2018).

Predicting, at diagnosis, which cells will persist



Which patients have cells that persist?



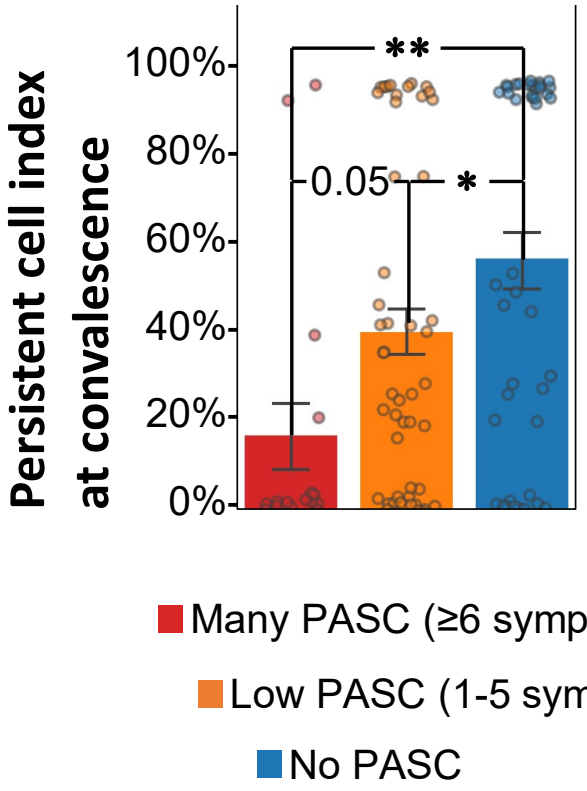
These patients are more likely to have genetic signatures associated with auto-immune disease, and much more likely to have long covid

These patients are protected from long-covid

Animal models will not reflect this diversity!

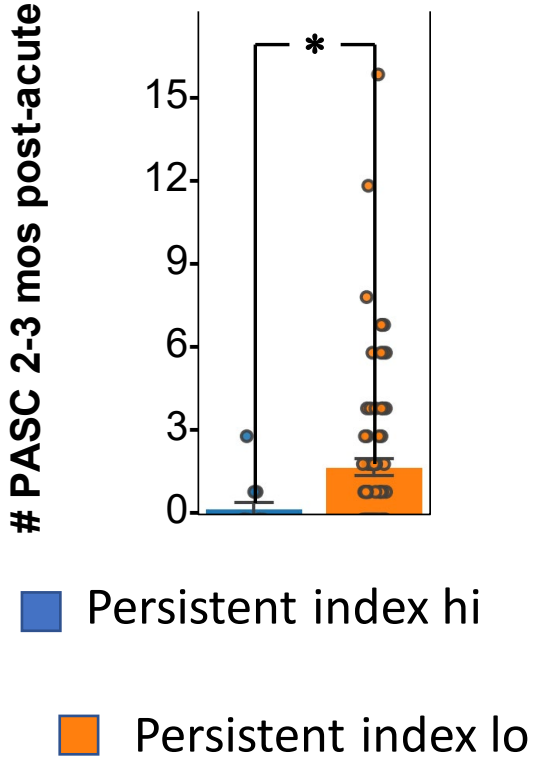
The presence of these early memory phenotypes are protective of PASC

INCOV cohort of COVID-19 patients
(full range of acute disease severities)



Jason Goldman
Swedish Medical Ctr
Seattle

HAARVI cohort
(almost all mild infections)



Helen Chu
UW Medical

conclusions

All of our data points to biological and immunological heterogeneity that is not captured in animal models

It indicates that the root causes of PASC may be decipherable, but will be much harder to decipher if you are only able to study the patients after chronic disease has set in