

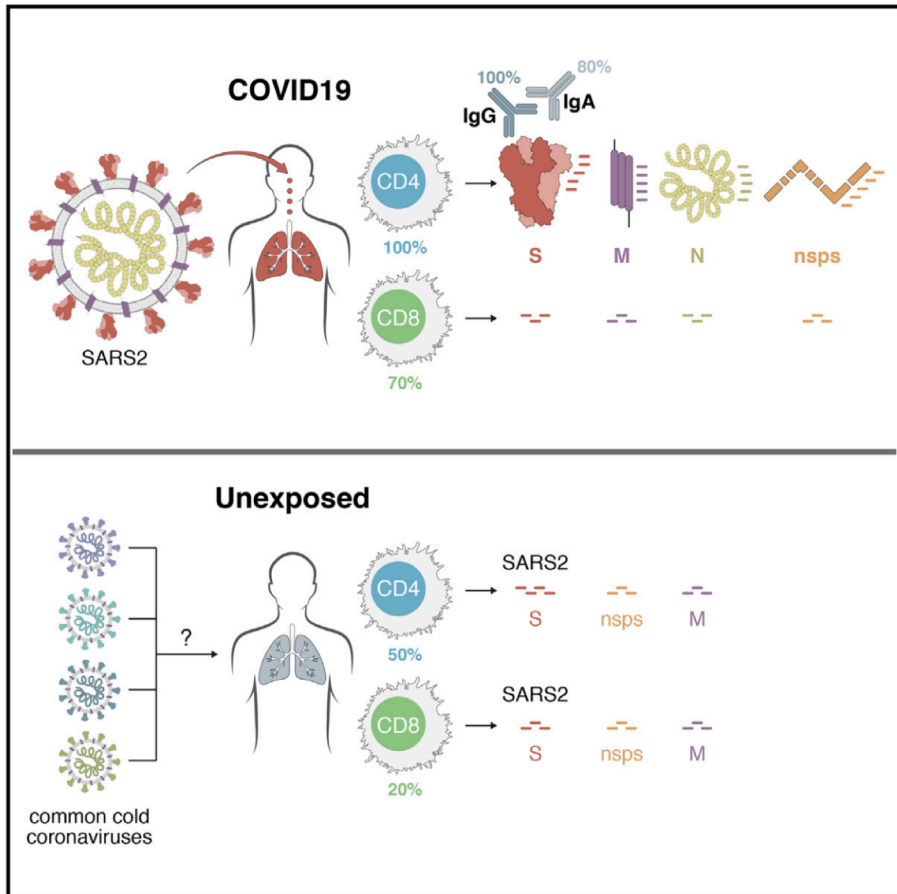
Antigen-specific adaptive immunity to SARS-CoV-2 in acute COVID-19 and associations with age and disease severity

ATS COVID-19 Seminar
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Targets of T Cell Responses to SARS-CoV-2 Coronavirus in Humans with COVID-19 Disease and Unexposed Individuals



- Previous study (Grifoni et al, *Cell* 2020) demonstrated that SARS-CoV-2-specific CD4 and CD8 T cells are detectable in recovered COVID-19 cases
- There is also a substantial fraction of the population with cross-reactive T cells

Major knowledge gaps in understanding immunity to SARS-CoV-2

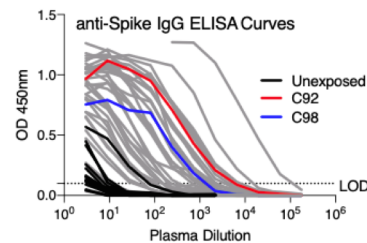
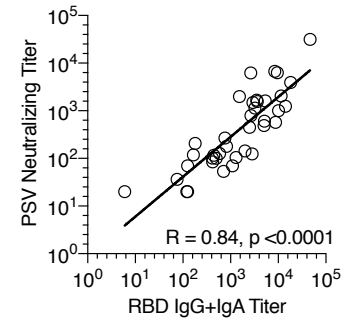
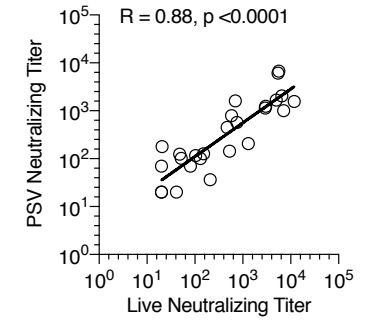
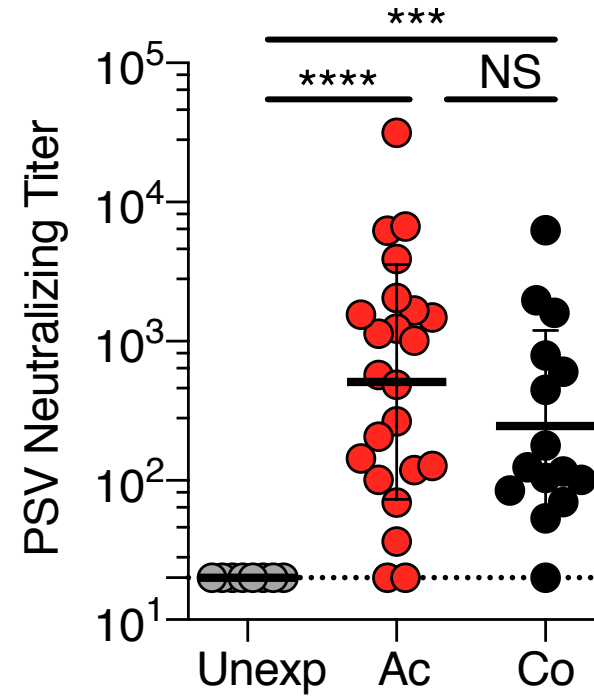
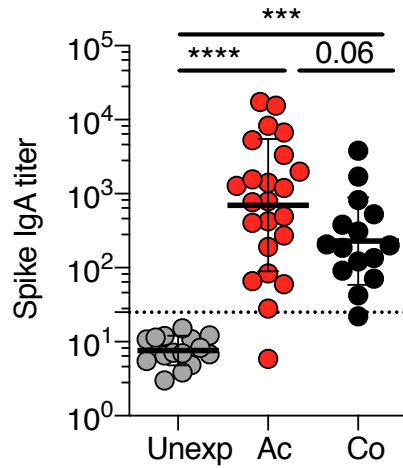
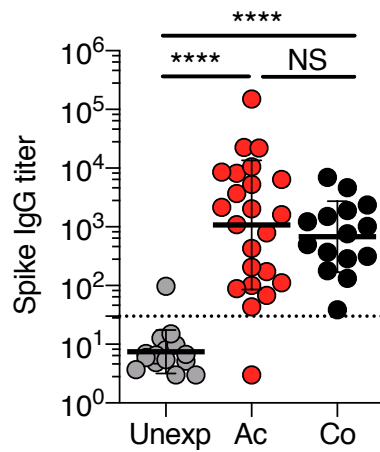
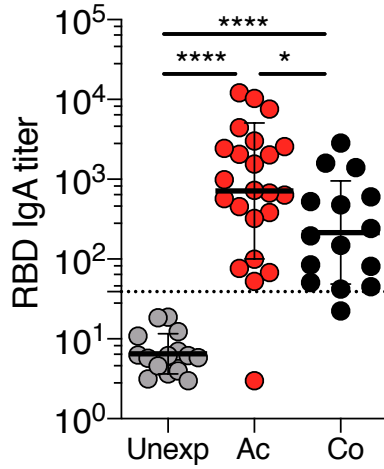
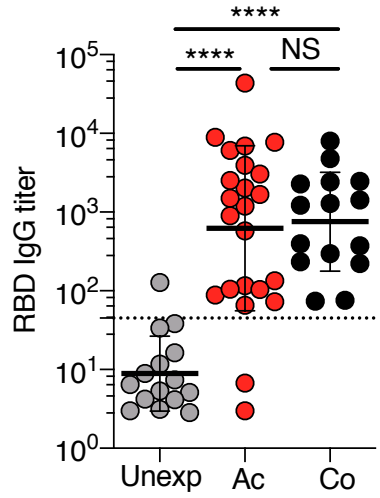
- ❑ How much of an adaptive immune response is there to COVID-19?
- ❑ What kind of immunity is important against COVID-19?
- ❑ Why do some people get severely ill and some people have mild disease?

Major knowledge gaps in understanding immunity to SARS-CoV-2

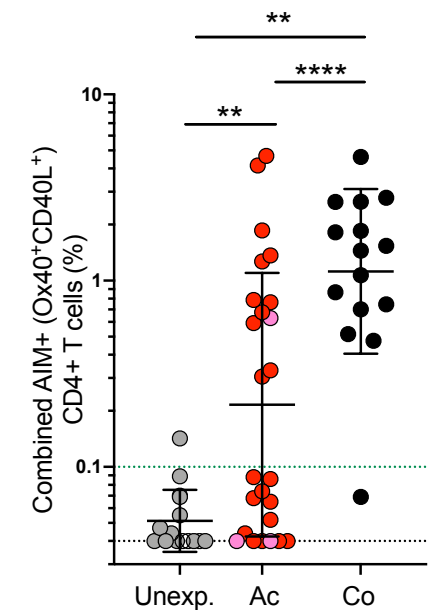
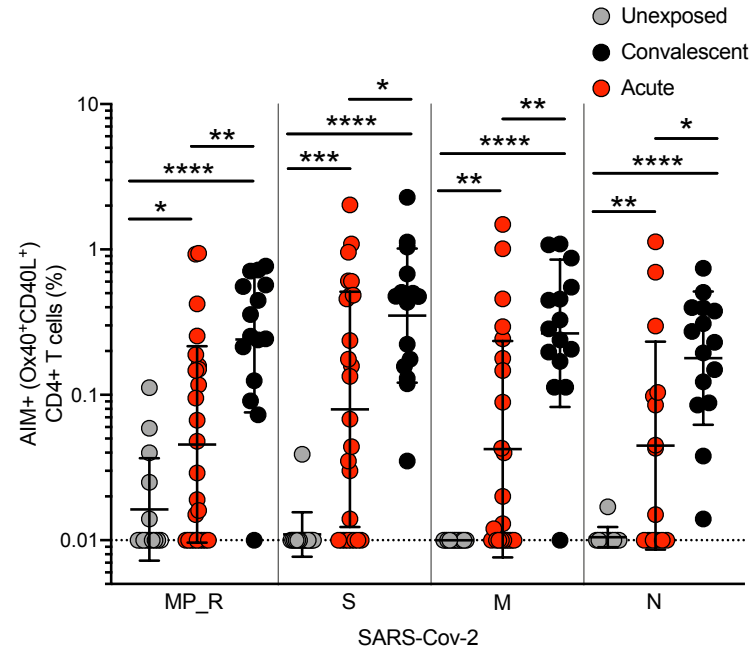
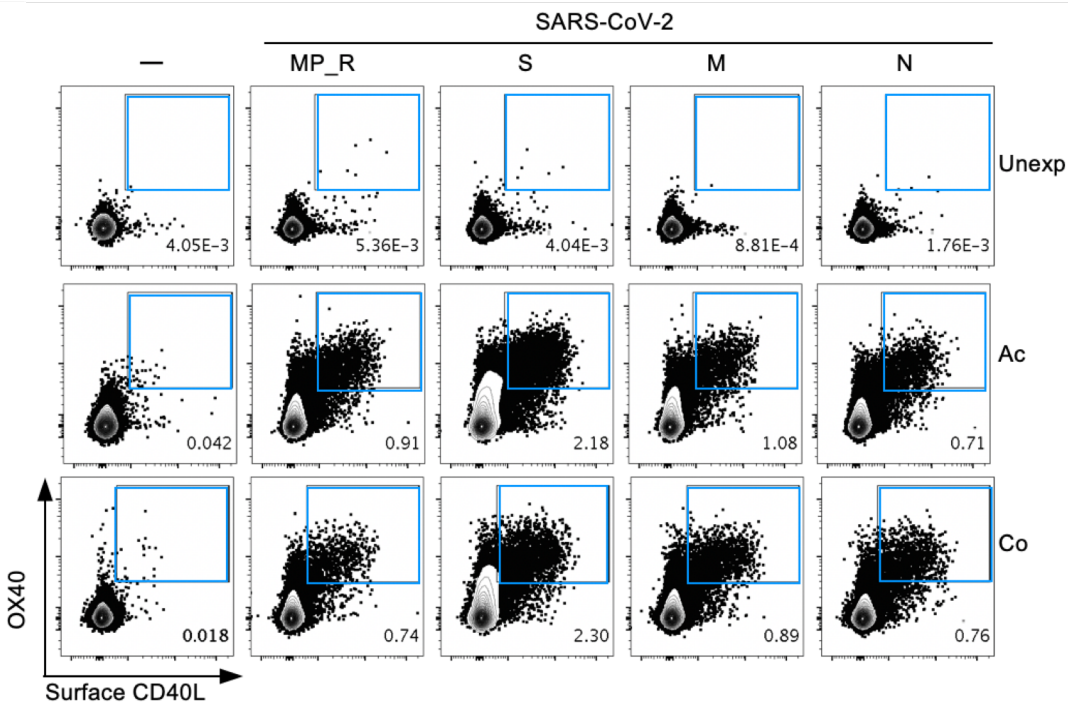
Assess all three arms of adaptive immunity across a wide-range of disease severity to better understand SARS-CoV-2 protective immunity

- ❑ Enrolled 54 subjects: 24 acute COVID-19, 15 convalescent COVID-19, 15 unexposed
- ❑ SARS-CoV-2-specific abs, including neutralizing abs
- ❑ antigen-specific CD4 and CD8 T cells
- ❑ 22-parameter immunophenotyping panel

Antibody responses in acute COVID-19



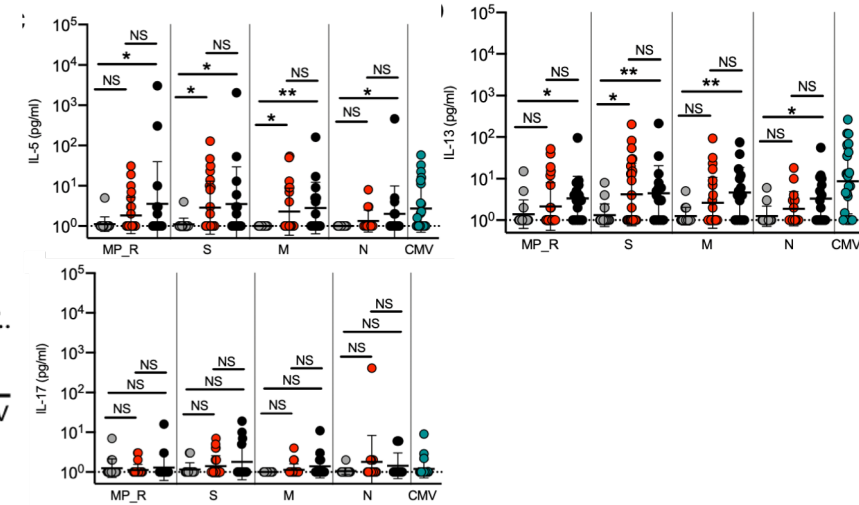
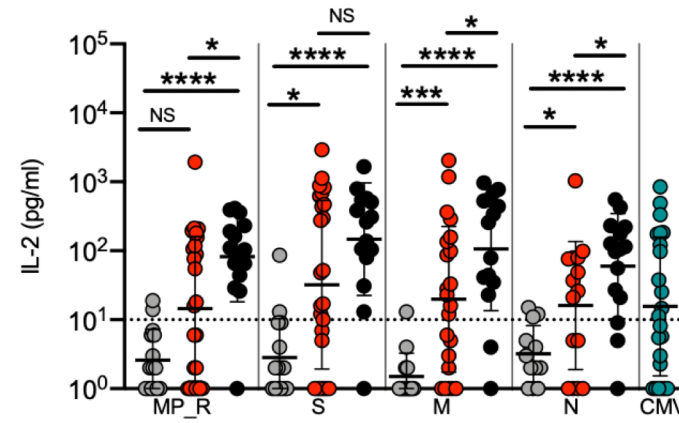
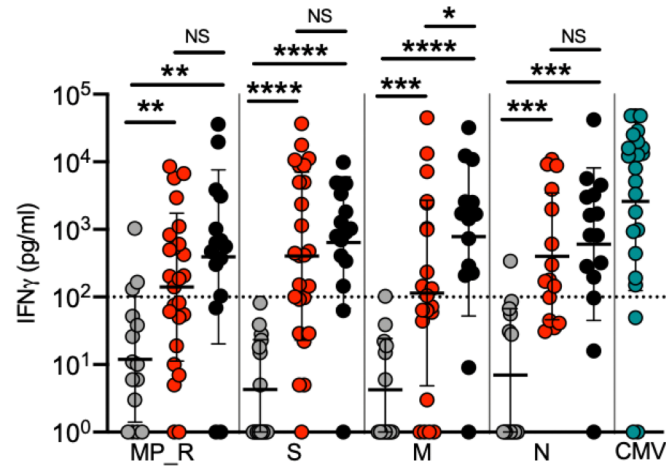
SARS2-specific CD4 T cell responses in acute COVID-19



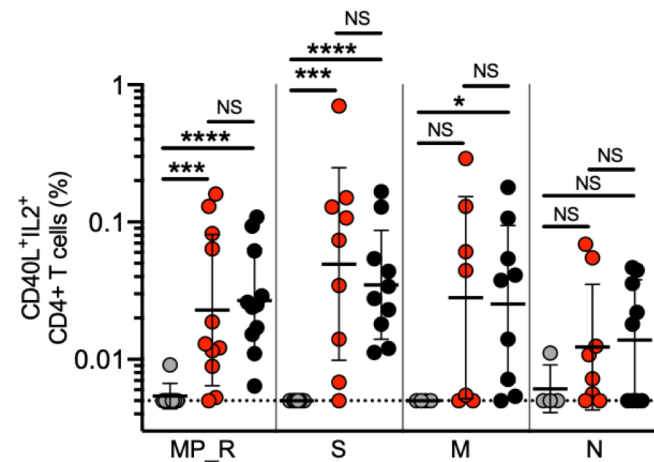
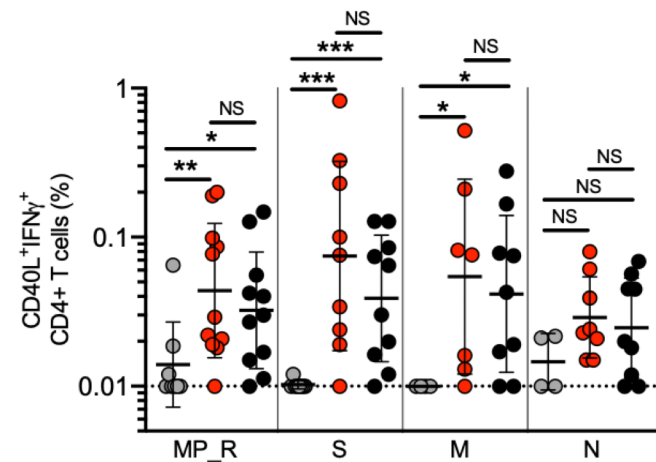
Activation-induced marker (AIM) assays provide a cytokine-independent and highly sensitive measure of antigen-specific T cell responses.

Antiviral CD4 T cell responses in acute COVID-19

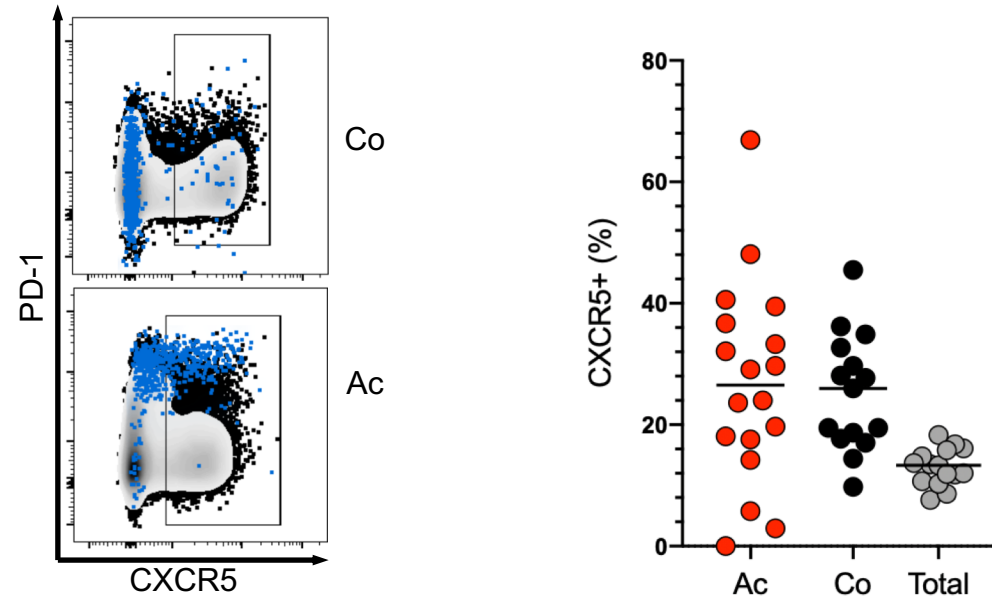
Secreted cytokines



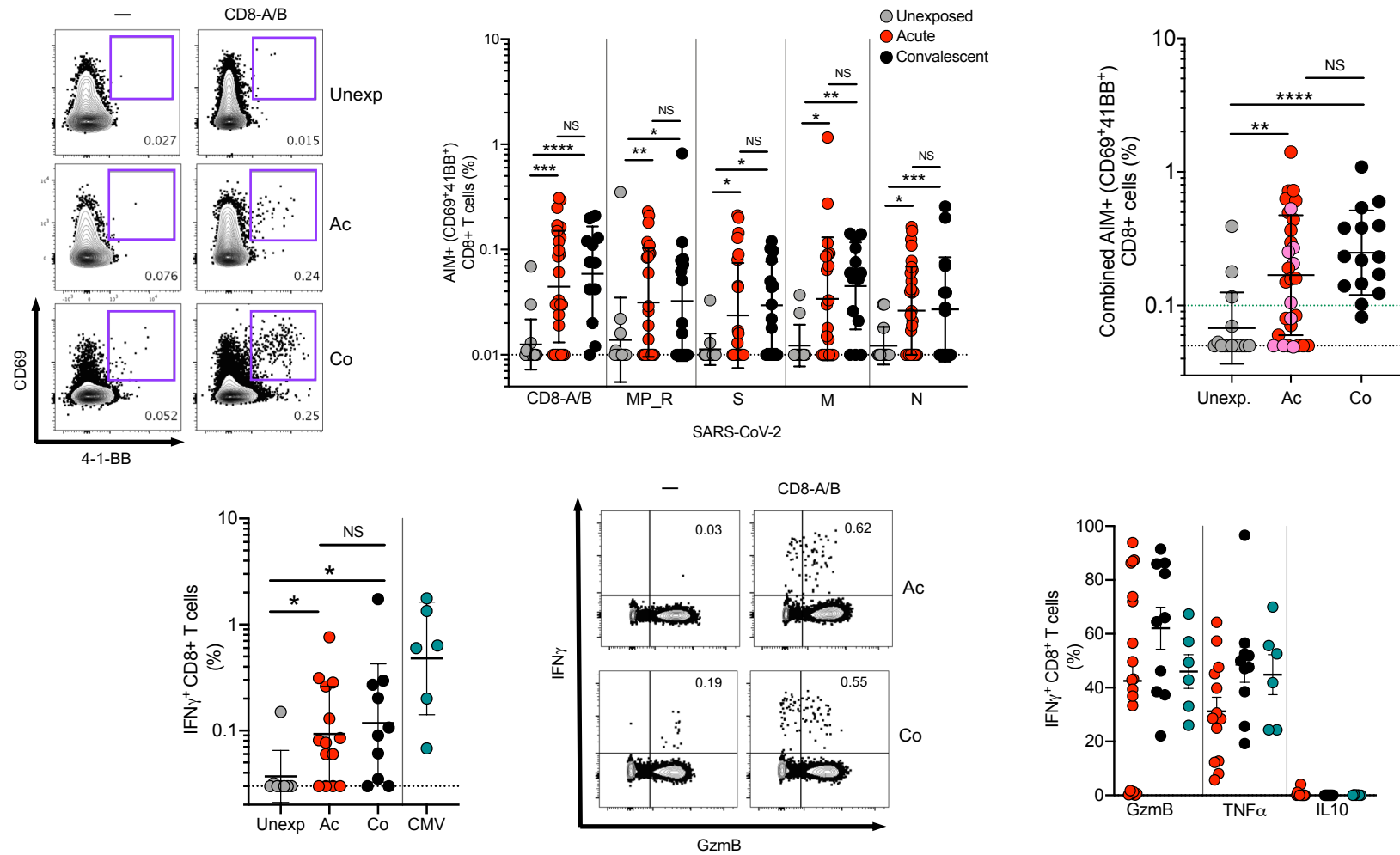
intracellular cytokines



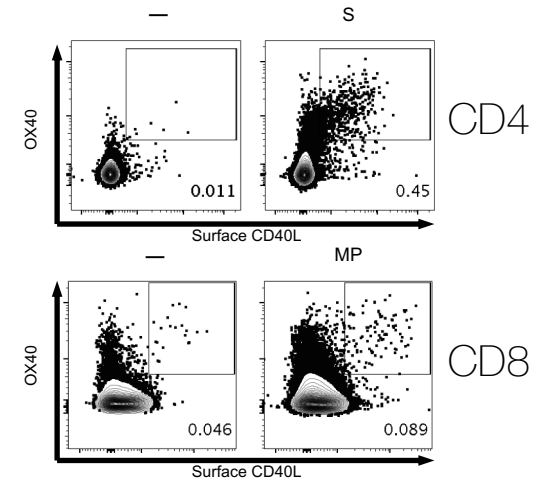
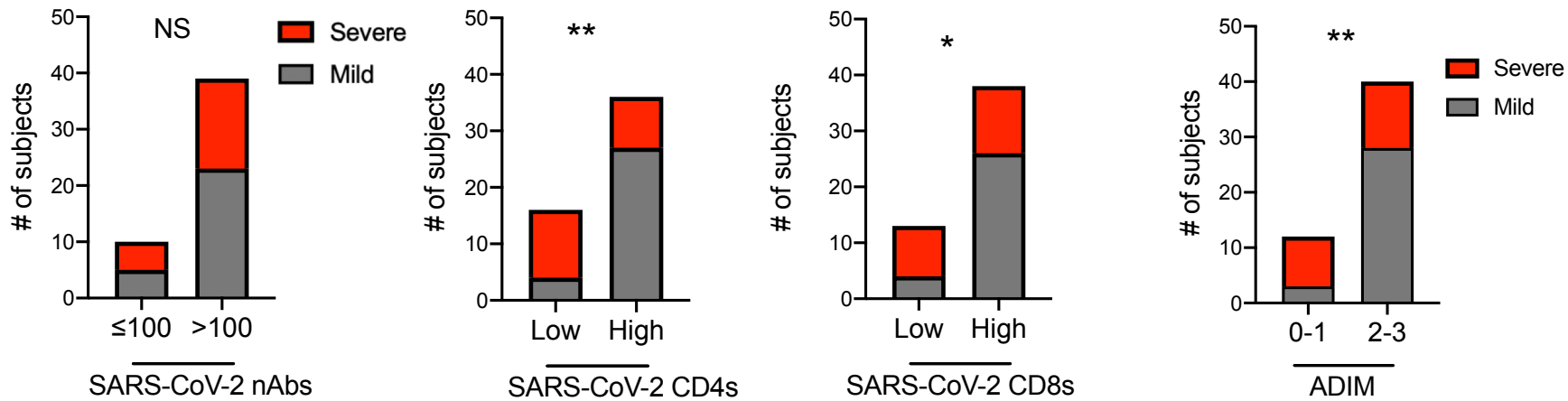
SARS2-specific cT_{FH} responses in acute COVID-19



SARS2-specific CD8 T cell responses in acute COVID-19



Adaptive immunity associations with disease severity



Subject negative for neutralizing antibodies

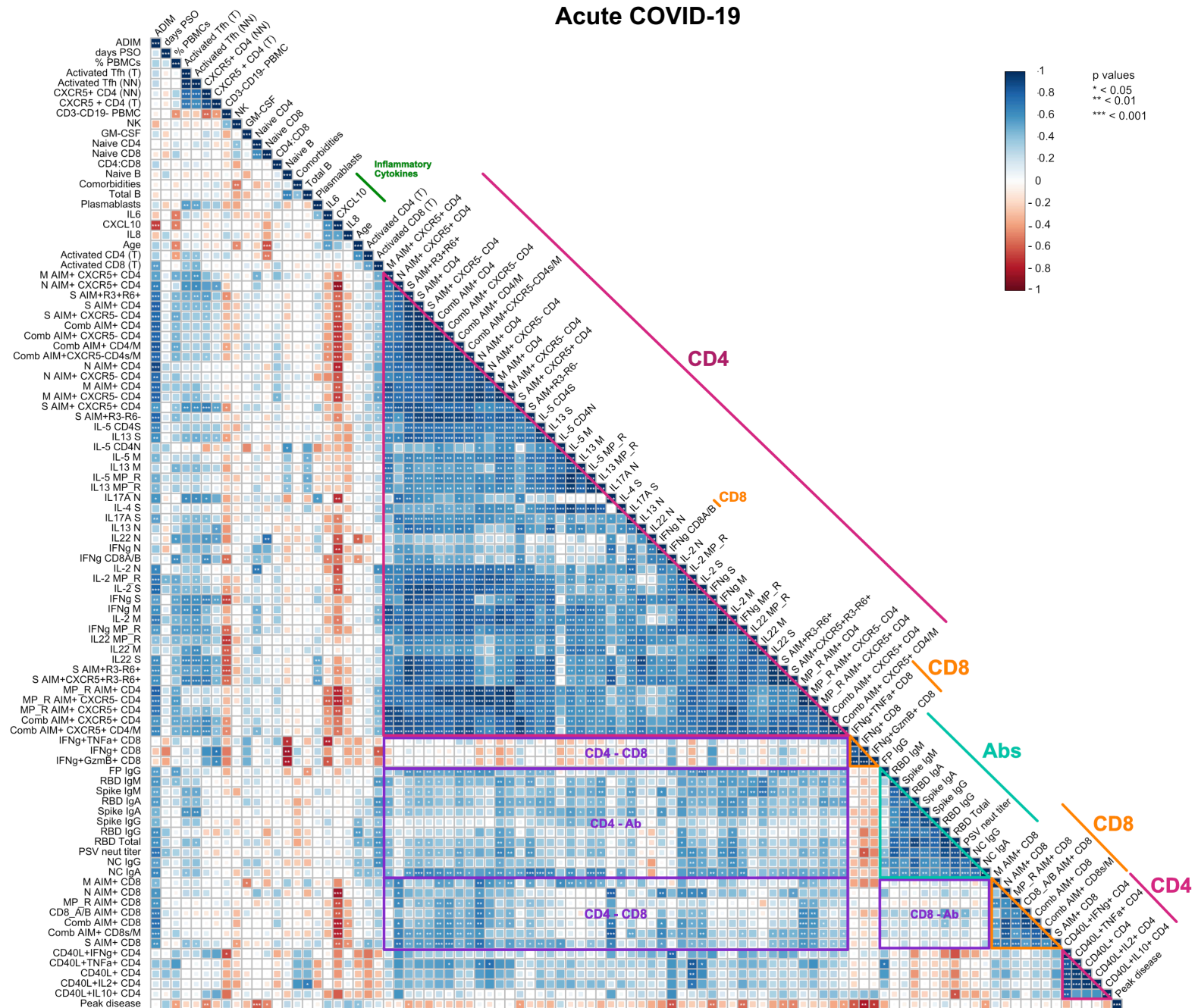
Adaptive Immunity (ADIM) score

SARS2-specific:

- Neutralizing antibodies
- CD4 T cells
- CD8 T cells

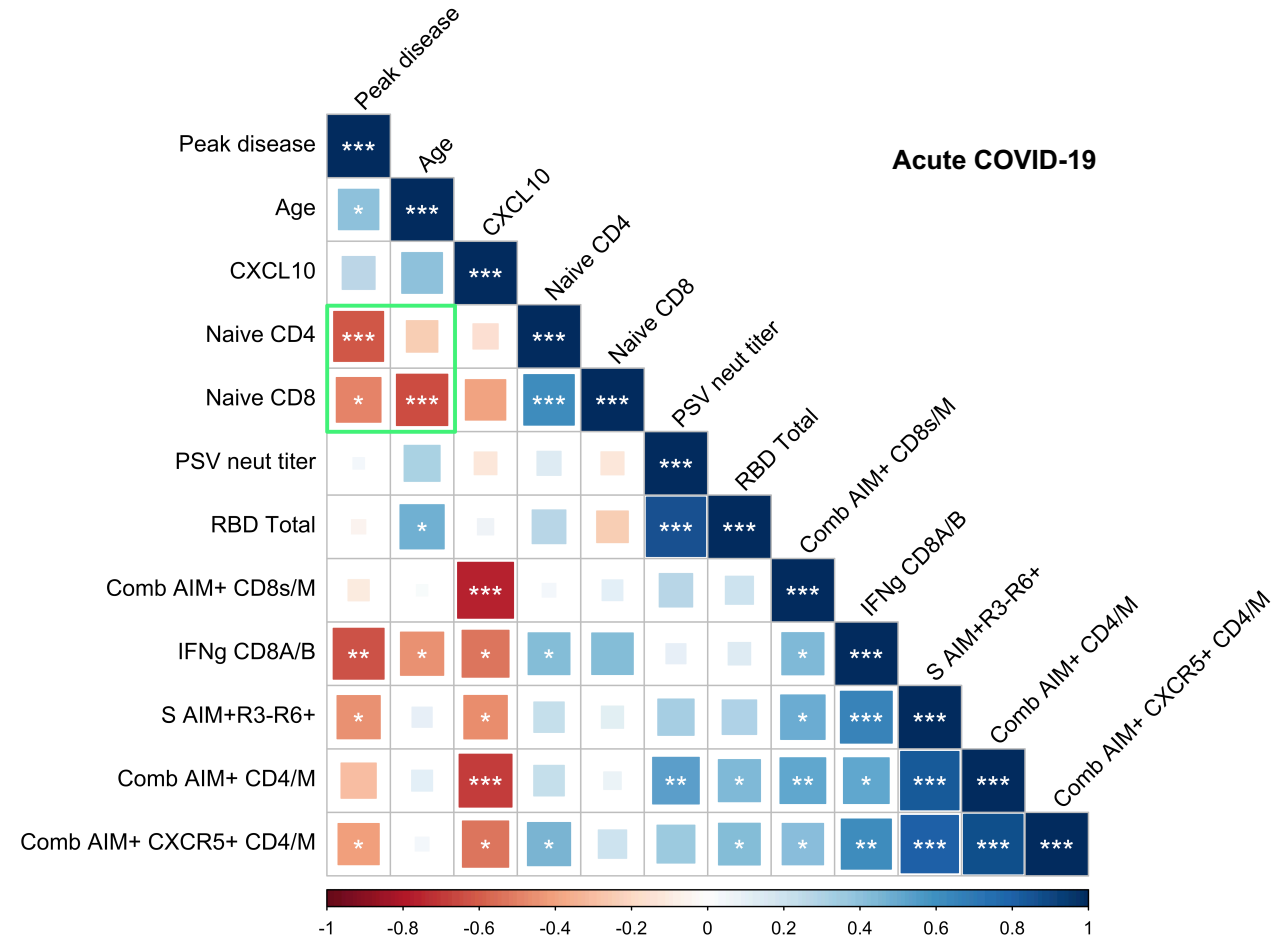
Coordinated adaptive immunity is protective immunity

Acute COVID-19



Spearman correlogram

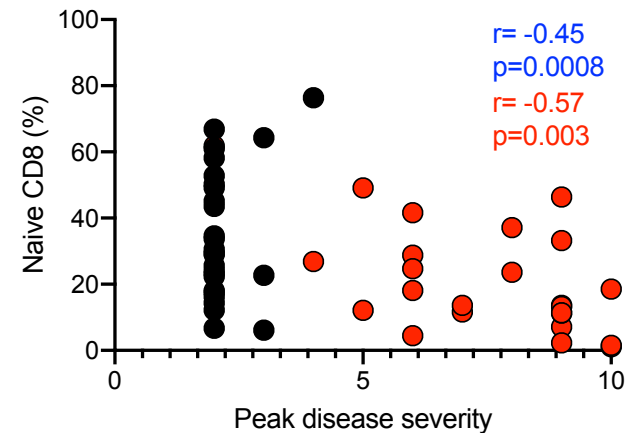
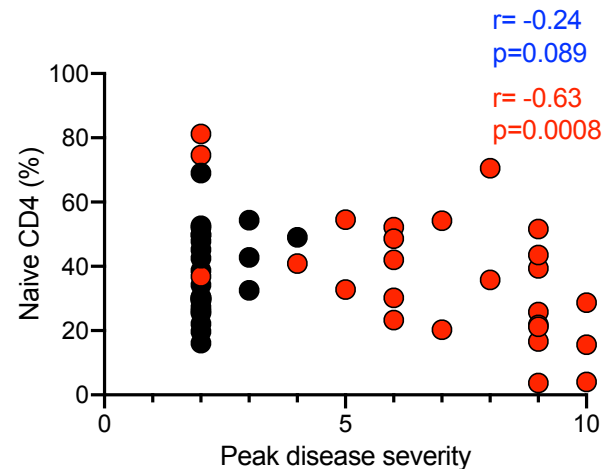
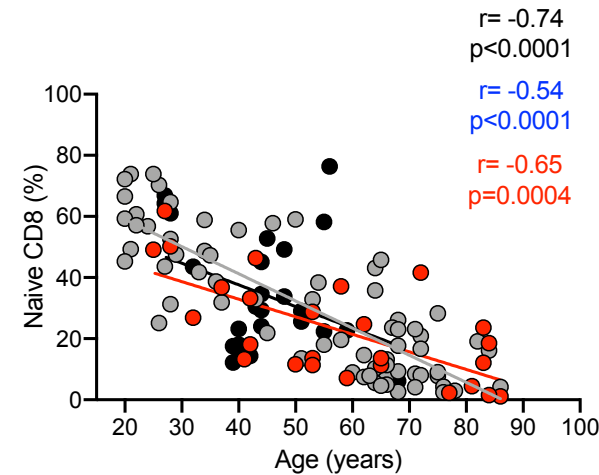
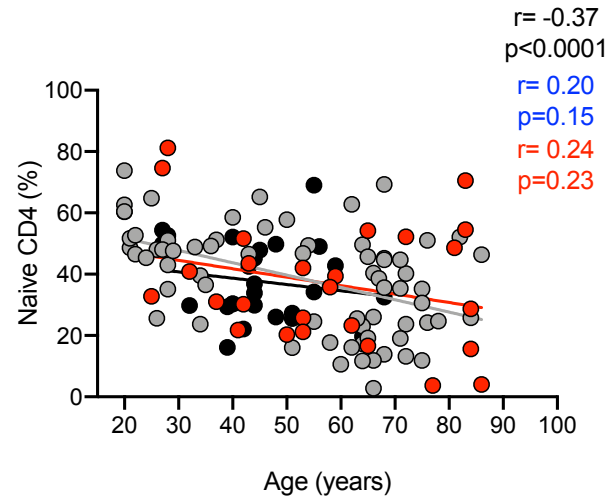
What about age may be causal in the poor adaptive immune response to COVID-19?



Age is a major COVID-19 risk factor

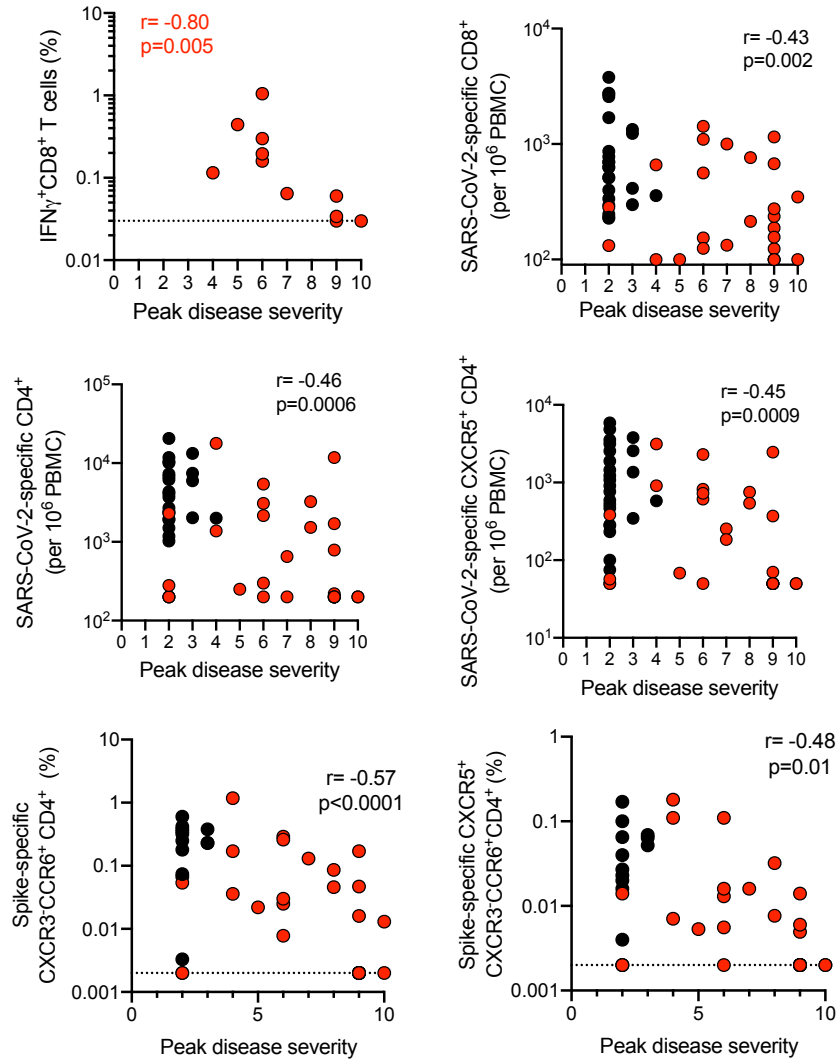
Naive T cell abundance is one immunological component of that risk

- Unexposed
- Convalescent
- Acute



Statistics
Full data set (Ac, Co, Unexp)
COVID-19 disease (Ac, Co)
Acute COVID-19

Strong SARS-CoV-2-specific T cell responses associated with lower COVID-19 disease severity



Summary

- ❑ T cell and antibody responses in 'average' cases of COVID-19 look like protective immune responses and largely match antiviral immune response expectations.
- ❑ Coordinated adaptive immunity is protective immunity :
 - Responses involving multiple arms of adaptive immunity were better than partial responses
 - We observed no convincing evidence of causal negative associations of adaptive immunity with disease severity
- ❑ Age is a major COVID-19 risk factor, and adaptive immunity shortcomings are part of that problem
 - Poorly coordinated antibody and T cell response
 - Limited naive T cell repertoire

Potential implications for vaccine design

- ❑ Ideal vaccine: nAbs alone or nAbs + T cells?
- ❑ Role of pre-existing cross-reactive T cells in this coordinated adaptive response?
- ❑ Interplay of innate and adaptive immune responses?
 - Balancing immunosenescence with inflammaging

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