Understanding T cell immunity to COVID-19 and relationships to vaccine correlates and mechanisms of protection

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The simplest option for any vaccine development is high level, long lasting, neutralizing antibodies.

Various lines of evidence point to substantial protective contributions of T cells against COVID-19.

It is quite reasonable to consider that hospitalization-level COVID-19 is prevented by any decent combination of antibody, CD4, and CD8 T cells.

T cells can be measured as potential correlates of immunity, but it has not been done so to date for COVID-19 vaccines.
What are mechanisms of protective immunity against COVID-19?

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➢ This virus is clearly susceptible to neutralizing antibodies.

➢ 26 of 28 previous licensed human vaccines have antibodies as the mechanism or correlate of immunity.

➢ Antibodies are the only mechanism that can provide truly sterilizing immunity.

➢ Antibodies are a correlate of CD4s: Neutralizing antibody responses almost always depend on CD4 T cell responses. Thus, antibodies are usually a surrogate marker of vaccine-specific CD4 T cells, at least T_{FH} cells.

Adaptive immunity to SARS-CoV-2 and COVID-19 Cell 2021
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- T cell responses correlate with better outcomes and lower viral loads in SARS-CoV-2 infection
- CD8 T cells provide control in monkeys
- Regeneron and Lilly outpatient and inpatient monoclonal antibody clinical trials. Modest impact on viral loads
- Agammaglobulinemic and B cell depleted individuals
  - moderately increased risk of hospitalization with COVID-19
  - COVID-19 in ocrelizumab-treated people with MS is predominantly mild
- 1-dose of Moderna or Pfizer vaccine provided substantial protection in the absence of detectable neutralizing antibodies in most individuals
- Kinetics and tissue distribution of COVID-19
It is all a race
A race between the virus and your immune system.
Vaccines get rid of the race. You then have the headstart instead of the virus.
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Evidence of T cell roles in prevention of symptomatic COVID-19

Three recent studies on pre-existing crossreactive memory T cells provide additional evidence of the value of T cell memory against COVID-19

- Weiskopf, Crotty, Sette and colleagues
- Thiel and colleagues
- Maini and colleagues
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Vaccine protection against SARS-CoV-2

Protection against Detectable Infection

Protection against Hospitalizations & Deaths

Major

Minor
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Conditions where this may be important:

**Natural immunity**
- when antibody titers are low

**Vaccine-generated immunity (currently used COVID vaccines)**
- When antibody titers decline
- Immunocompromised or immunosuppressed individuals
- Different time windows post-vaccination
  - T cell and binding antibodies to RNA vaccines detected faster than neutralizing antibodies
  - Immune memory compartments can have substantially different kinetics
- Neutralizing antibody escape variants (B.1.351 and J&J vaccine example?)

**Novel vaccines with T cell dominant mechanisms of action**
- T cell only vaccines or CD8 T cell dominant vaccines
- Mucosal vaccines that may have more complex mechanisms of action
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It is possible to do T cell correlates of protection studies in humans. This is a solved problem. The HIV Vaccine Trials Network (HVTN) has done this for over a decade.

Even when T cells are mechanistically important for protection, evidence lags compared to antibodies because:

- T cell studies are more resource intensive (~30 times)
- T cell assays are more challenging to standardize across labs (live cells)
- The simple passive transfer burden-of-proof available for antibodies is not available
- Complexities of T cell contributions: CD4 T cells, CD8 T cells, subsets, functionalities, tissue location.
Q&A