COVID-19 Immune Responses

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Immunisation Coalition
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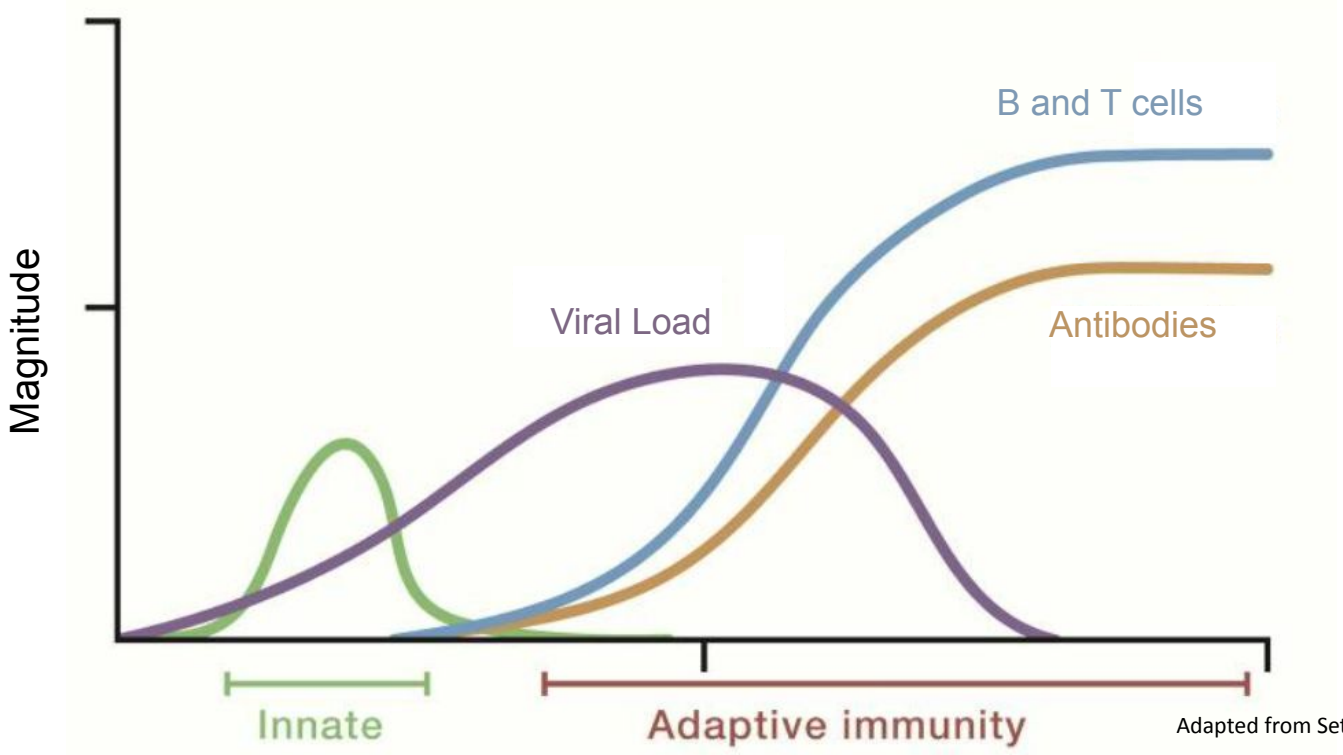
The adaptive immune response to SARS-CoV-2

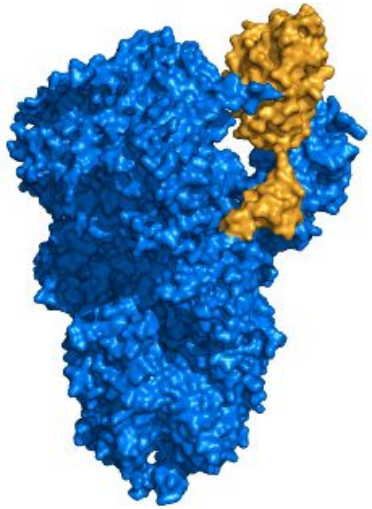


Adapted from Sette and Crotty, Cell 2021

- SARS-CoV-2 infection - Correlates of protection and disease severity
- COVID-19 vaccines: - Durability, boosting and variants
- Breakthrough infection

SARS-CoV-2 spike protein is the target of neutralising antibody responses

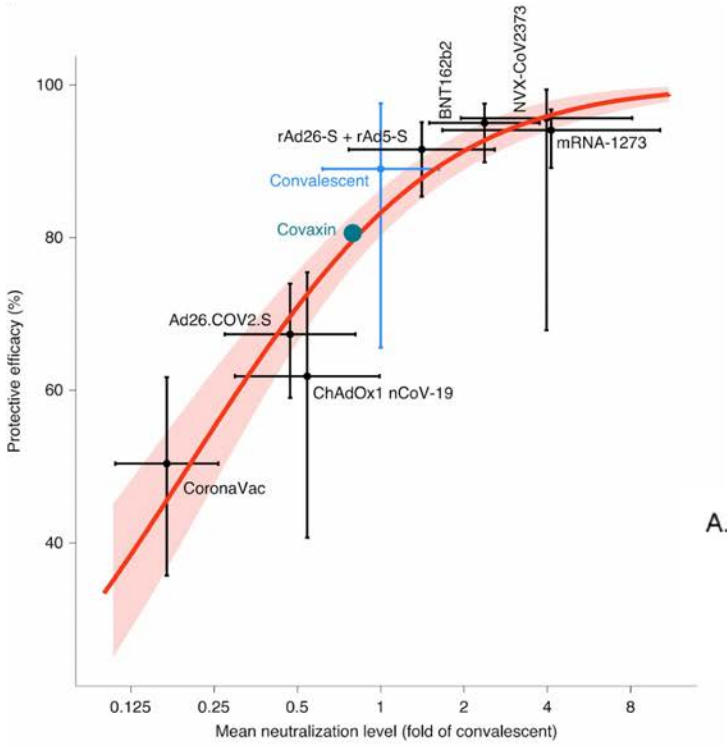
Receptor binding domain (RBD)



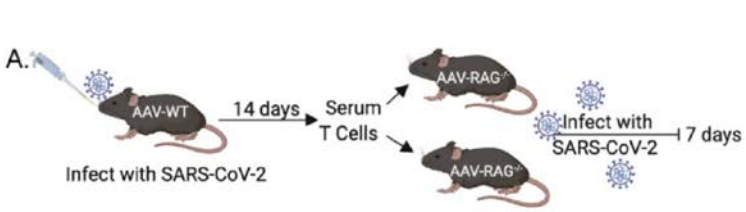
Spike protein (S)

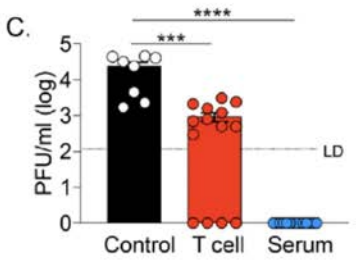
- Antibodies targeting epitopes within/near the RBD can neutralise SARS-CoV-2
  - Mutations within these key regions of the spike protein can lead to escape from neutralising responses
- Monoclonal antibodies with particularly potent neutralising activity are useful therapeutics
- Many currently approved vaccines target the spike protein
  - Aim to elicit high titres of neutralising antibodies, in addition to cellular responses

Neutralising antibodies as a correlate of protection for COVID-19



- Neutralising antibody titres can predict vaccine efficacy regardless of vaccine platform
- Animal studies support key role for antibodies in controlling viral replication



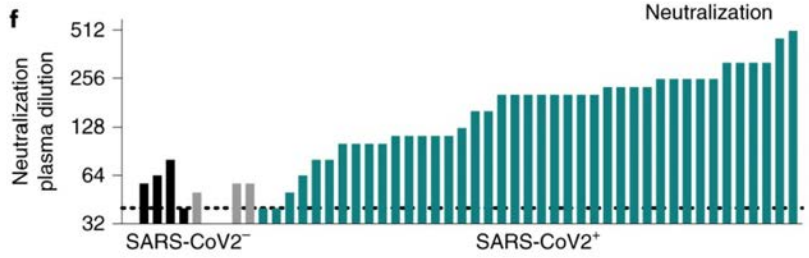


Khoury et al, Nat Med 2021

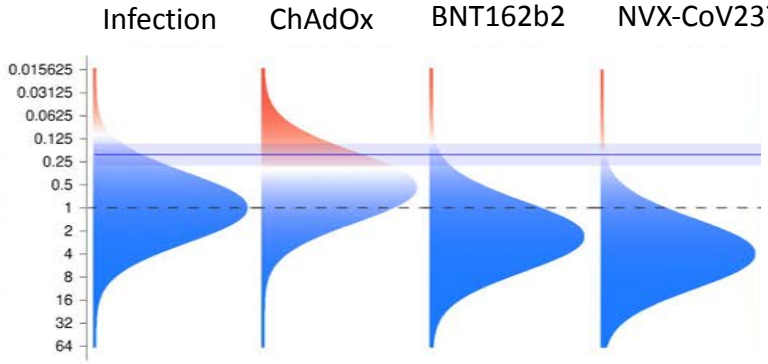
Israelow et al, Sci Immunol 2021

Natural infection and vaccination elicit variable neutralising antibody titres that wane over time

Mild/moderate COVID-19



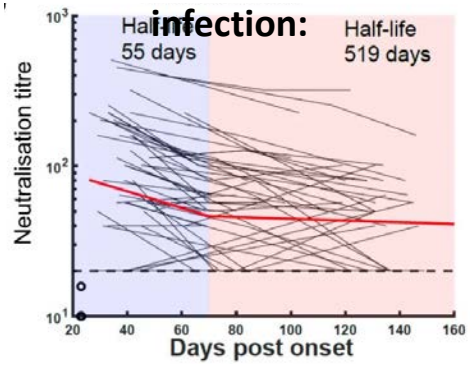
Juno et al, Nat Med 2020



Adapted from Khoury et al, Nat Med 2021

nAb titres wane over time, regardless of how immunity is established

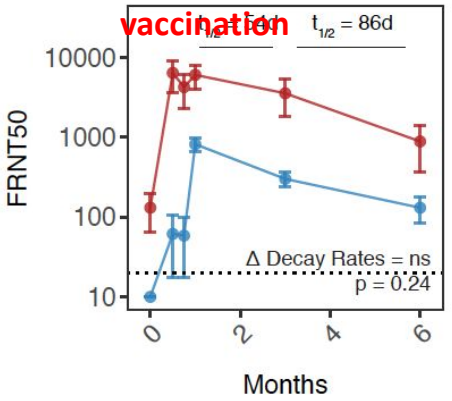
After infection:



Wheatley et al, Nat Comms 2021

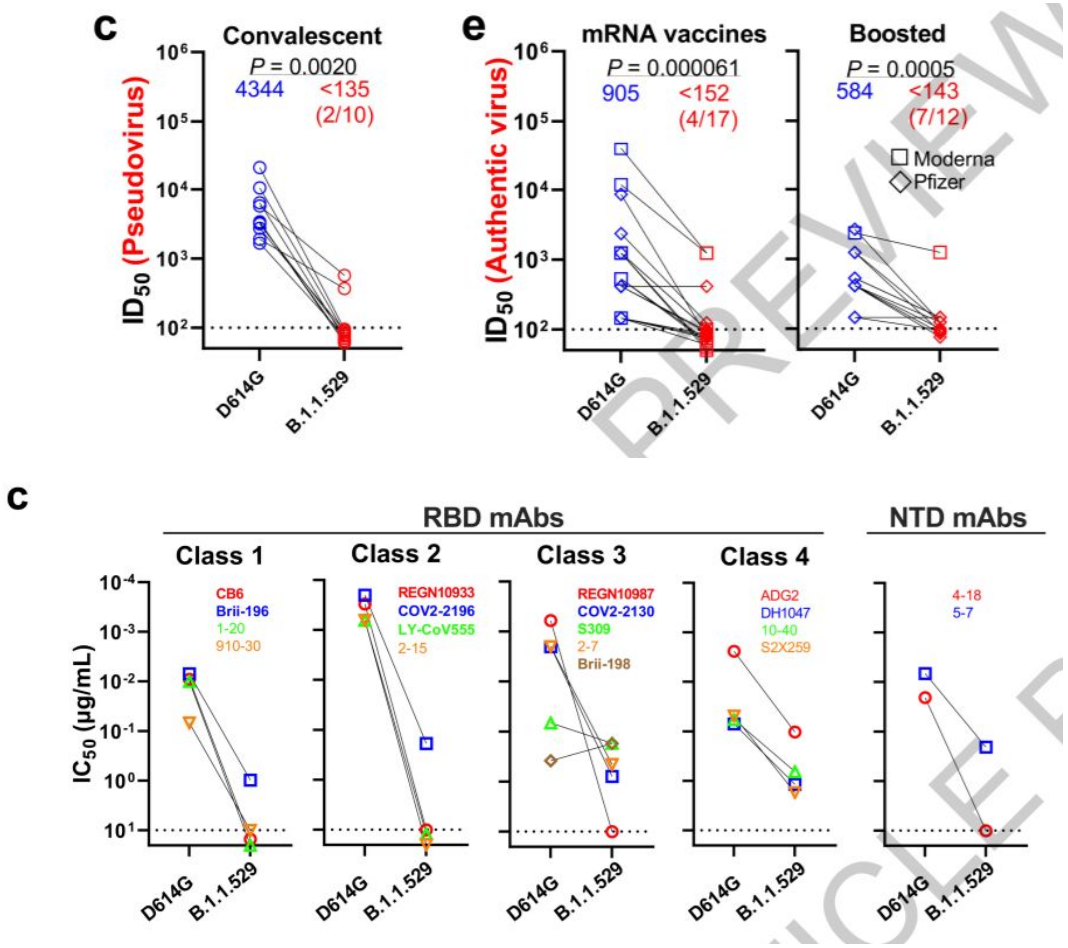
After vaccination

Infection + vaccination



Goel et al, Biorxiv 2021

Omicron evades the neutralising antibody response



- Combination of mutations throughout the RBD and spike result in poor recognition of Omicron by vaccines or infection from prior SARS-CoV-2 VOC
- Many monoclonal antibodies also lose recognition of the Omicron spike, reducing the therapeutic options for treating infections

Liu et al, Nat 2021

How do we establish long-term immunity against SARS-CoV-2?

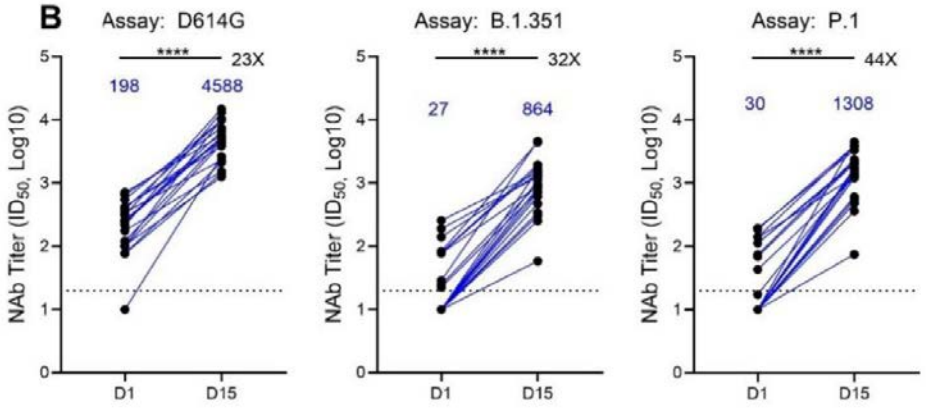
(1) Protection from (any) infection:

Repeated booster vaccines to maintain nAb titres

(2) Protection from severe disease:

Reliance on long-term SARS-CoV-2 specific memory B and T cells

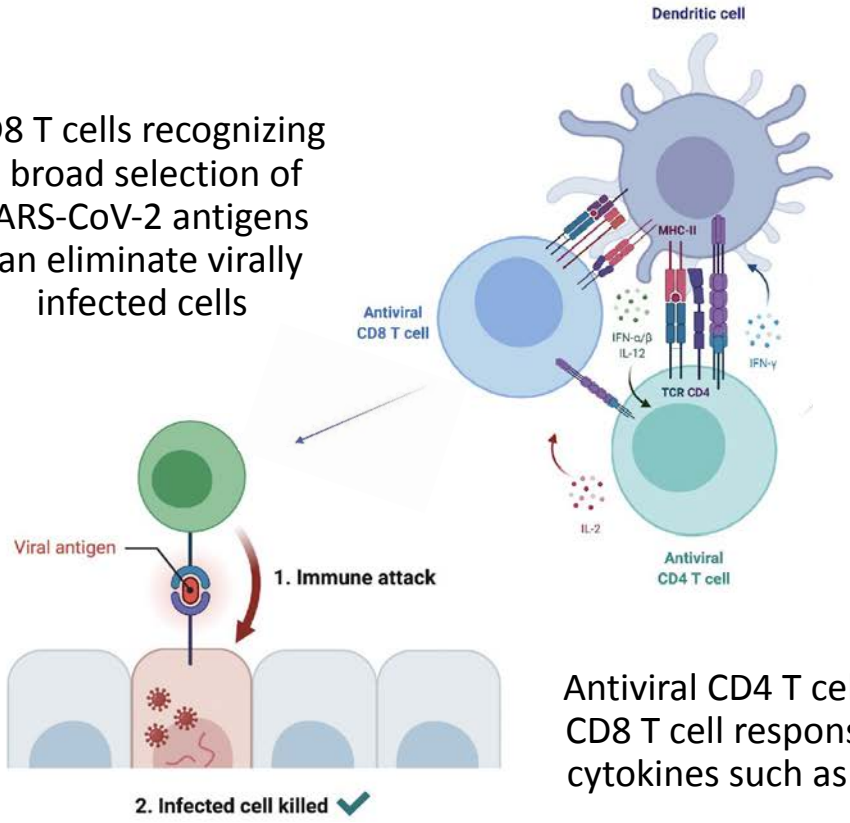
3rd dose of mRNA-1273 given ~7 months after initial 2-dose vaccination



Wu et al, Biorxiv 2021

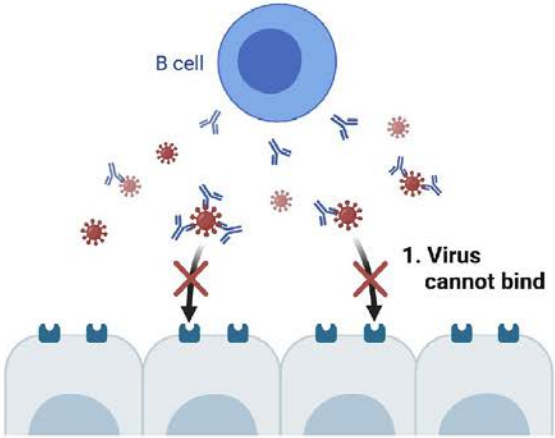
T cells and the antiviral immune response

CD8 T cells recognizing a broad selection of SARS-CoV-2 antigens can eliminate virally infected cells

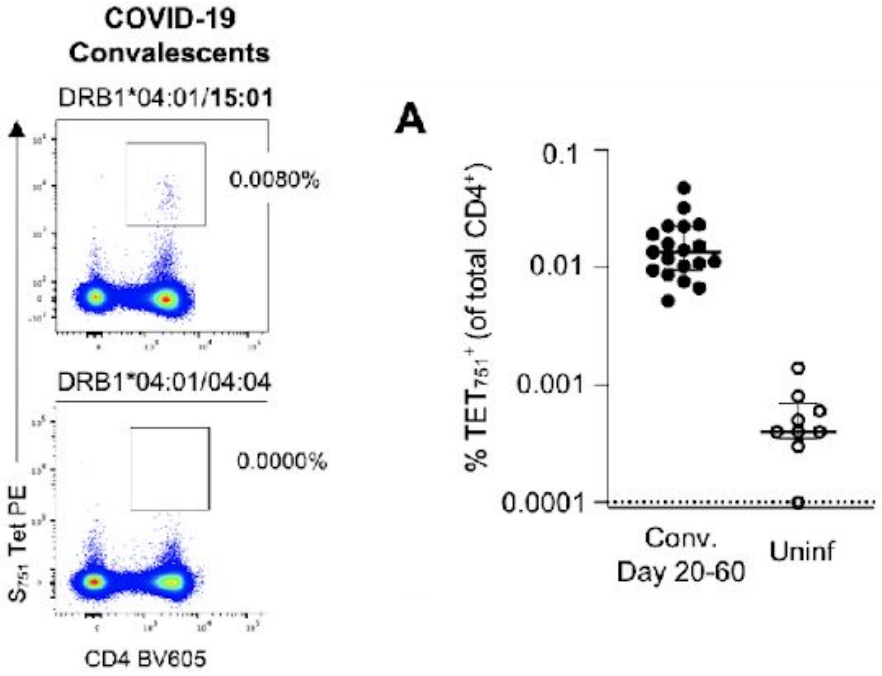


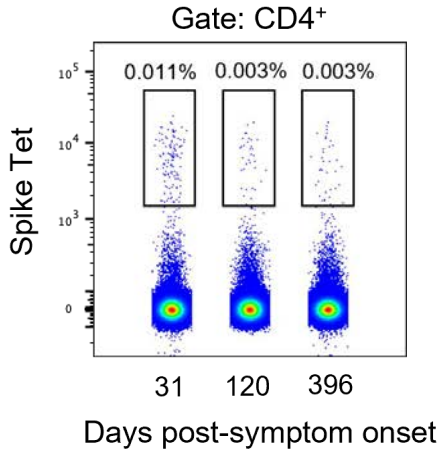
Antiviral CD4 T cells support the CD8 T cell response and secrete cytokines such as IFNg, TNF, etc

CD4 Tfh cells can support the B cell response and promote antibody production – particularly relevant f spike protein, which is the of neutralizing antibodies



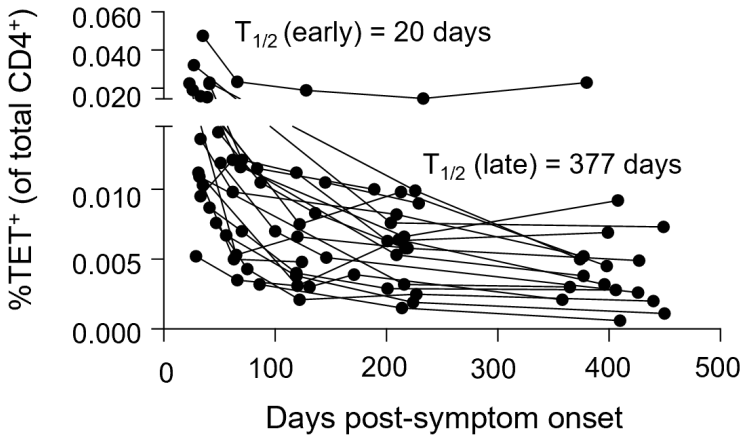
Mild COVID-19 establishes long-lasting CD4+ T cell memory





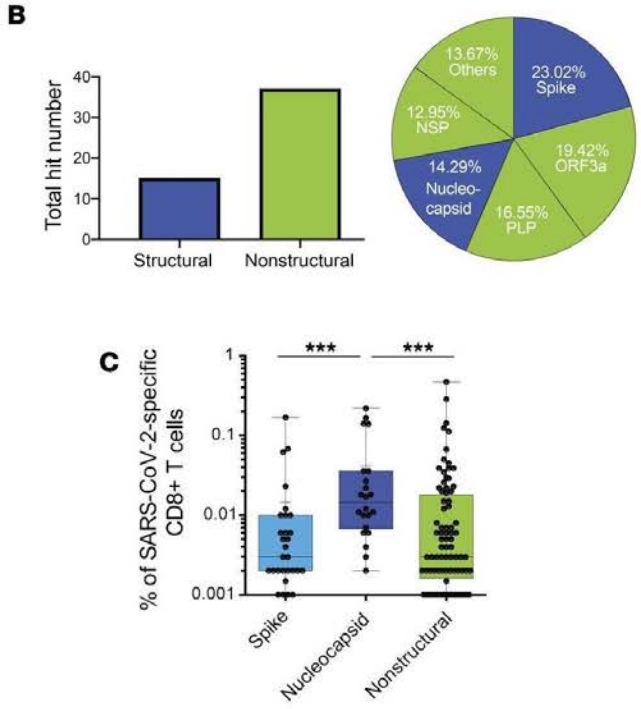
- Developed an HLA-DRB1*15 spike tetramer to precisely track the kinetics CD4 T cell memory formation after mild/moderate COVID-19

- Tracks well with total spike-specific T cell responses measured by activation assays



Wragg et al, Res Sq, 2021

CD8 T cells recognise an array of SARS-CoV-2 antigens, and may contribute to survival in immunocompromised patients

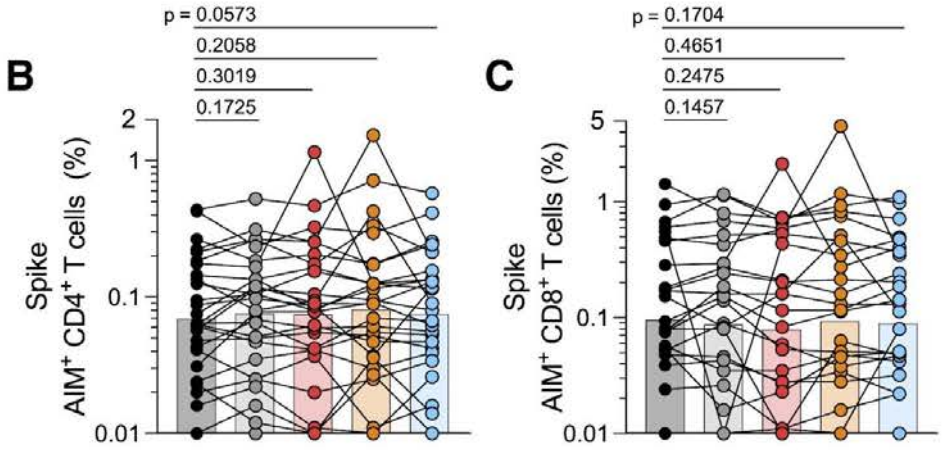


- Broad CD8 T cell recognition of viral antigens can facilitate elimination of infected cells
- SARS-CoV-2-specific CD8 T cells express an array of cytolytic molecules (perforin, granzymes, CD107a)
- Tetramer-based tracking of CD8 T cell responses suggests their frequencies are stable over many months

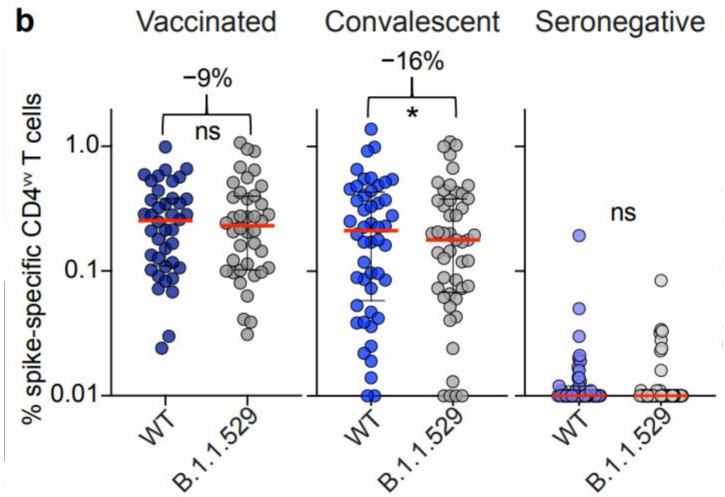
Kared et al, JCI, 2021

T cell recognition of the viral spike protein is not compromised by variants of concern

- CD4 and CD8 T cell responses are largely unaffected by mutations in VOC due to high number of immunogenic epitopes outside the RBD
- T cell responses to non-spike antigens also maintained

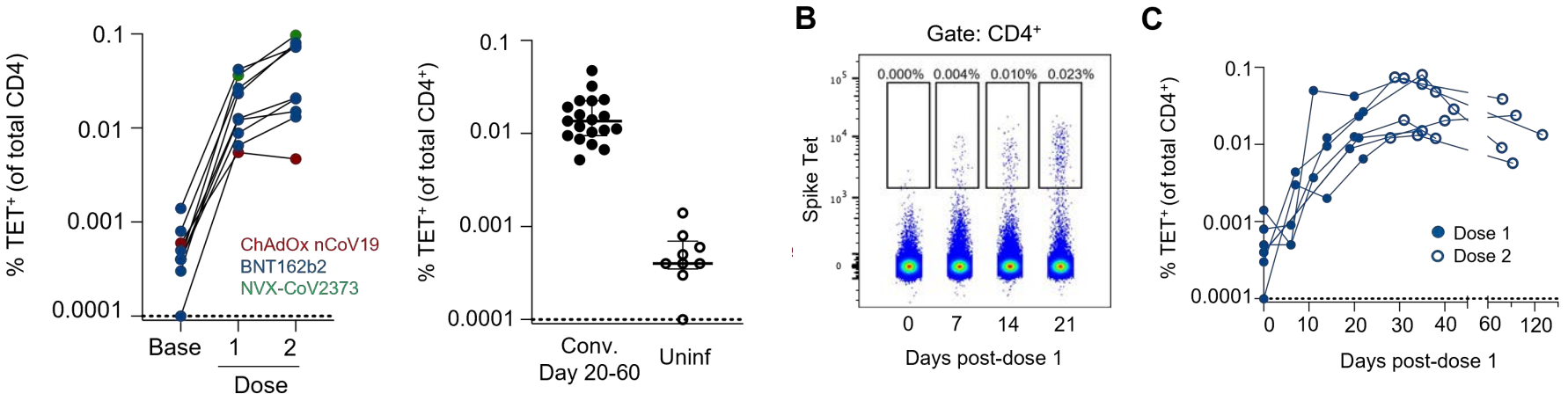


Tarke et al, Cell Rep Med, 2021



Gao et al, Nat Med, 2022

SARS-CoV-2 spike-based vaccines elicit similar frequencies of CD4+ T cells to infection

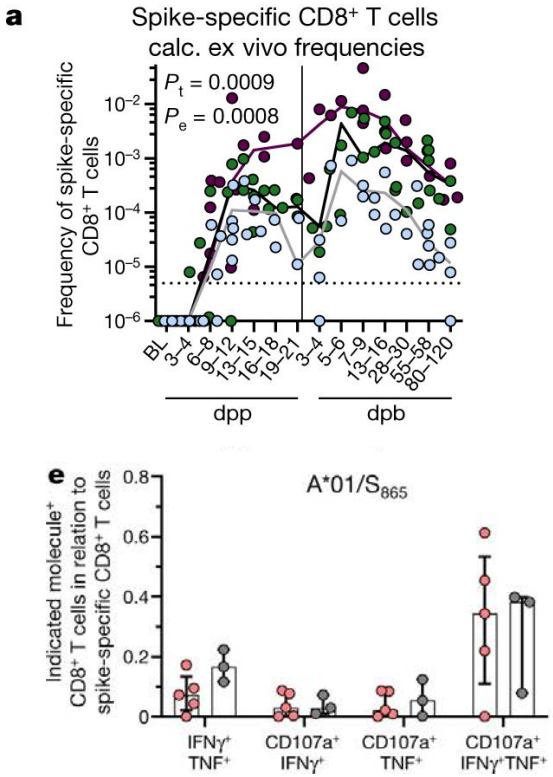


Spike epitope-specific T cells are similarly expanded by mRNA, adenoviral and protein-based vaccines, with frequencies after dose 1 similar to the frequency established by mild infection

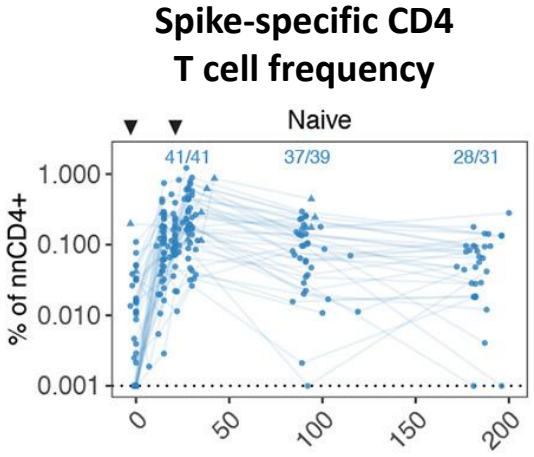
CD4 T cell responses are evident by day 7 after dose 1, preceding the IgG response by ~4 days

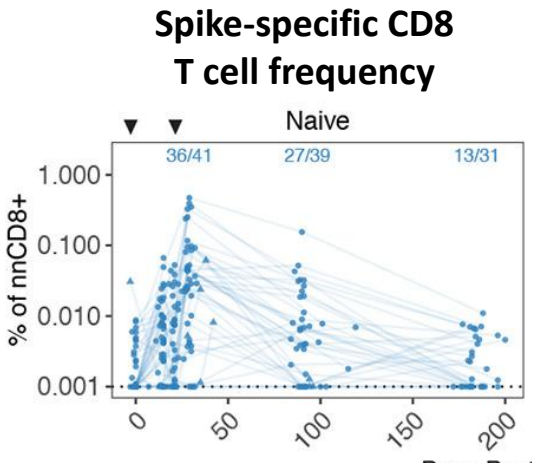
Wragg et al, Res Sq, 2021

COVID-19 vaccines elicit cytotoxic spike-specific CD8 T cells that wane over 6 months



Oberhardt et al, Nature 2021

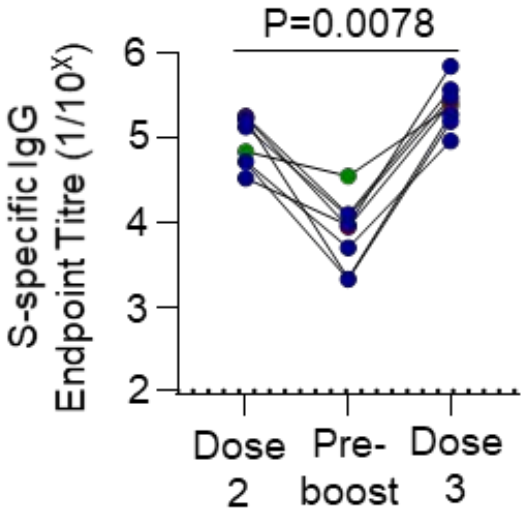


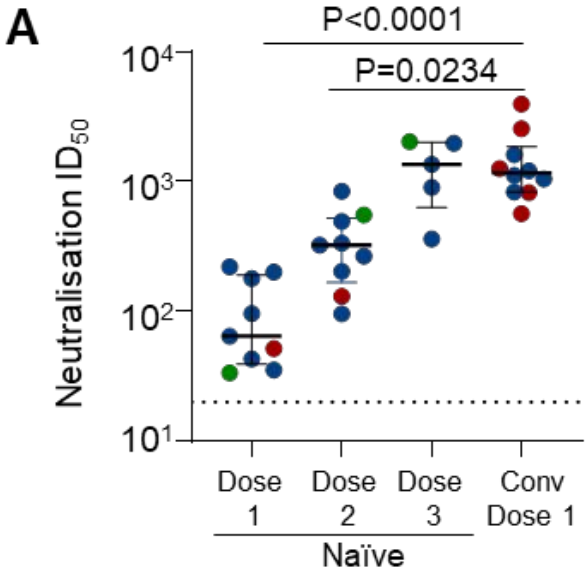


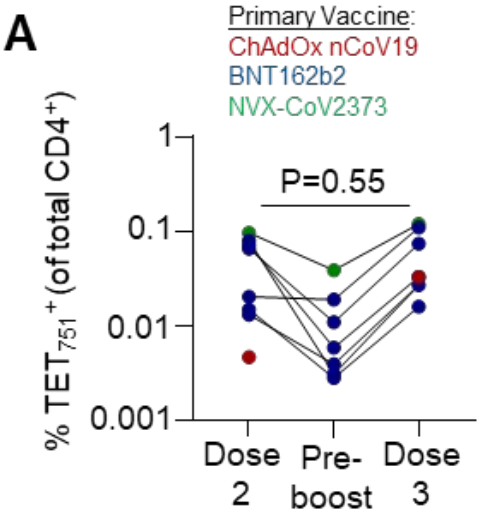
At both the total and epitope-specific level, CD8 T cell responses appear to wane between 1 and 6 months post-vaccination, while CD4 T cell responses appear to be more stable

Goel et al, Science 2021

How does the immune response to a 3rd vaccine dose compare to the 2-dose schedule?

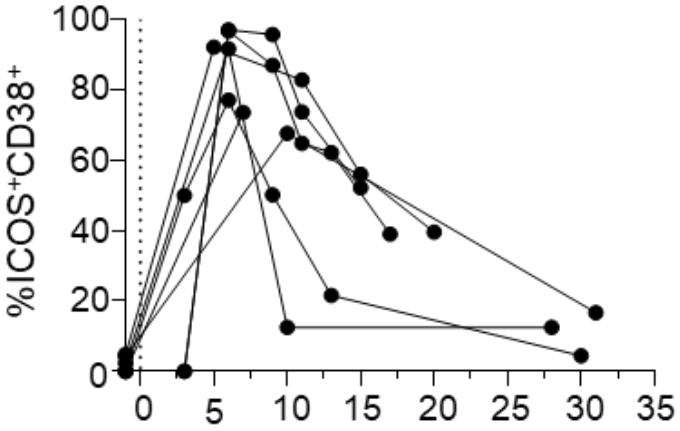


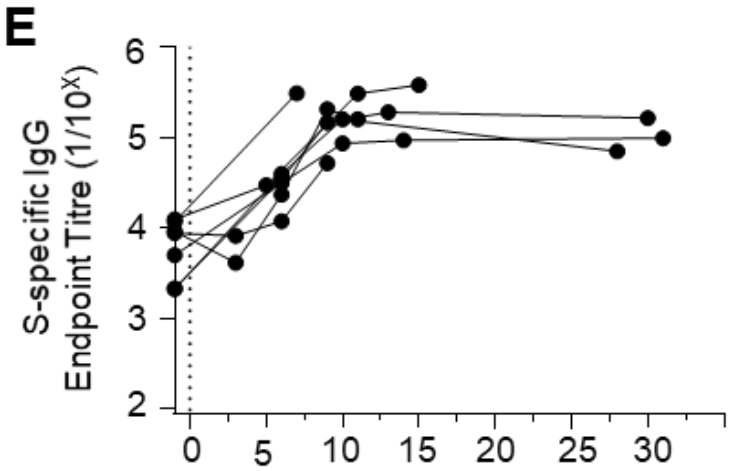




- Antibody responses following dose 3 exceed those elicited by dose 2
- Neutralising titres after the 3rd dose are comparable to titres found in "hybrid immunity" cohorts (infection + vaccination)
- T cell responses are restored by the 3rd dose, but do not exceed those of dose 2

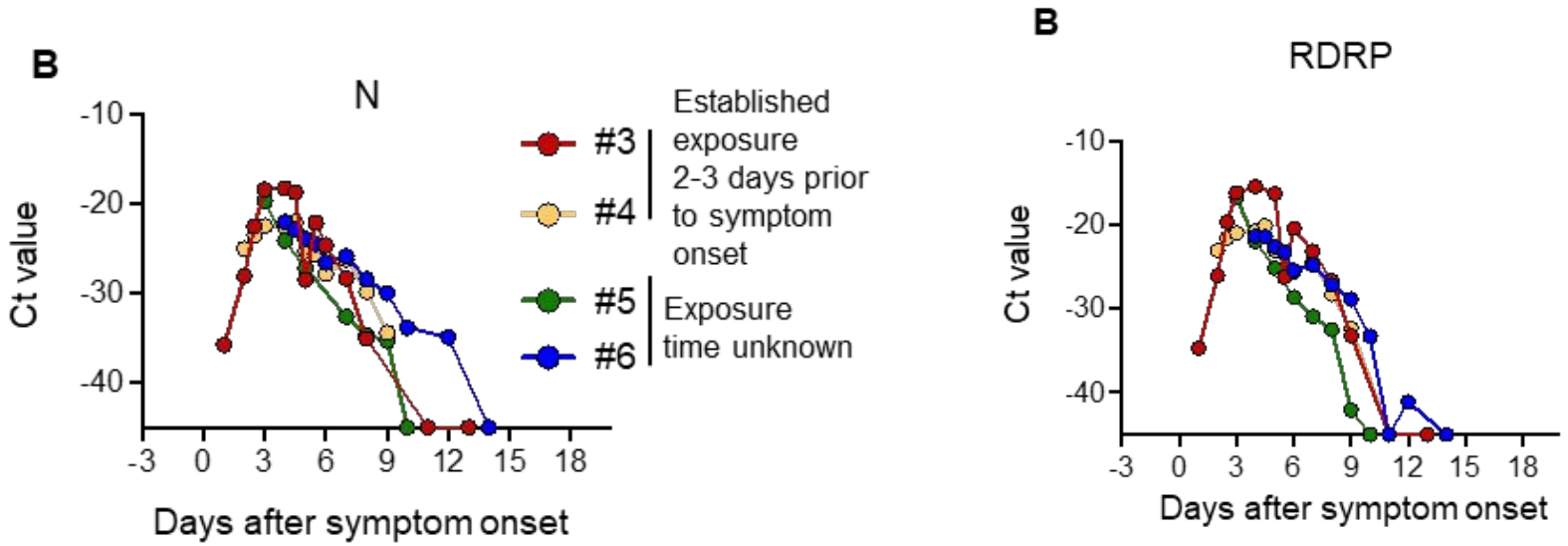
Recall of immune memory by a 3rd vaccine dose occurs within 5 days





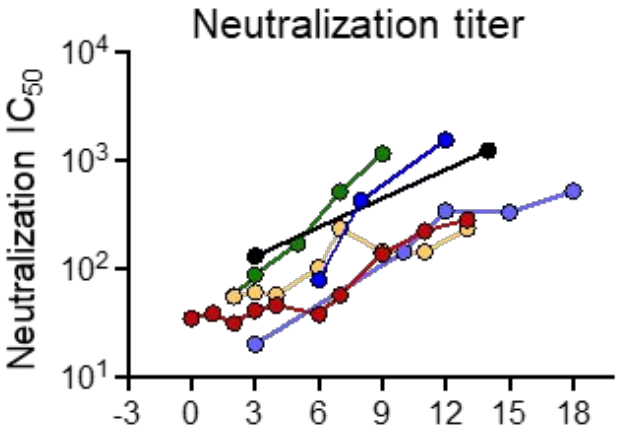
- Activation and expansion of spike-specific T cells occurs between days 3 and 5 post-vaccination, then declines after day 12
- In contrast, the antibody response peaks around day 10 and remains stable for at least 4 weeks

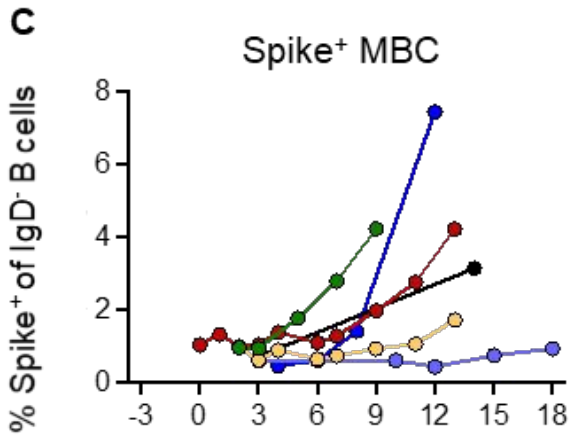
What is the impact of a breakthrough infection on immunity?

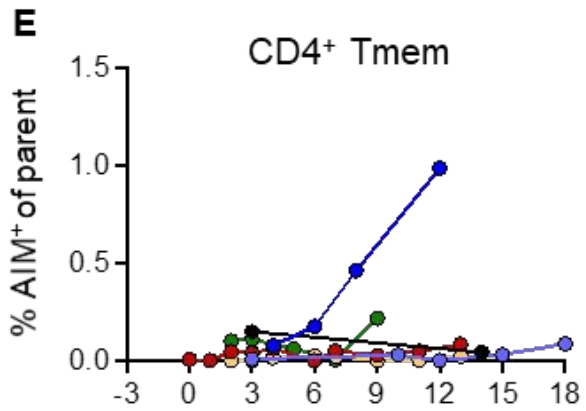


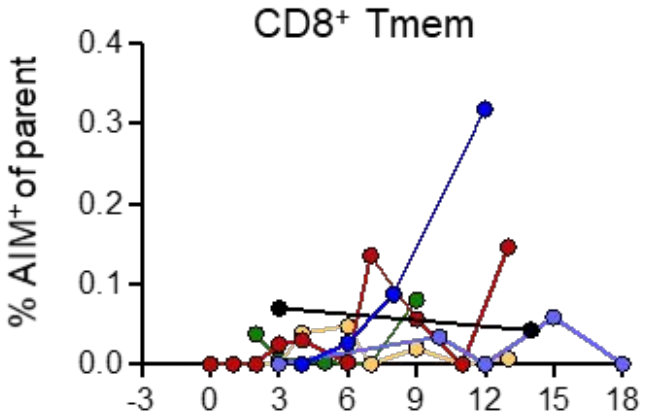
- Cohort of breakthrough infections recruited at the end of 2021, during the delta wave in Melbourne
- Longitudinal sampling (daily in some cases) from the day of symptom onset for both nasal swabs and blood samples
- Precise exposure date known for 2 of the cases

Recall of immune memory occurs after an initial delay



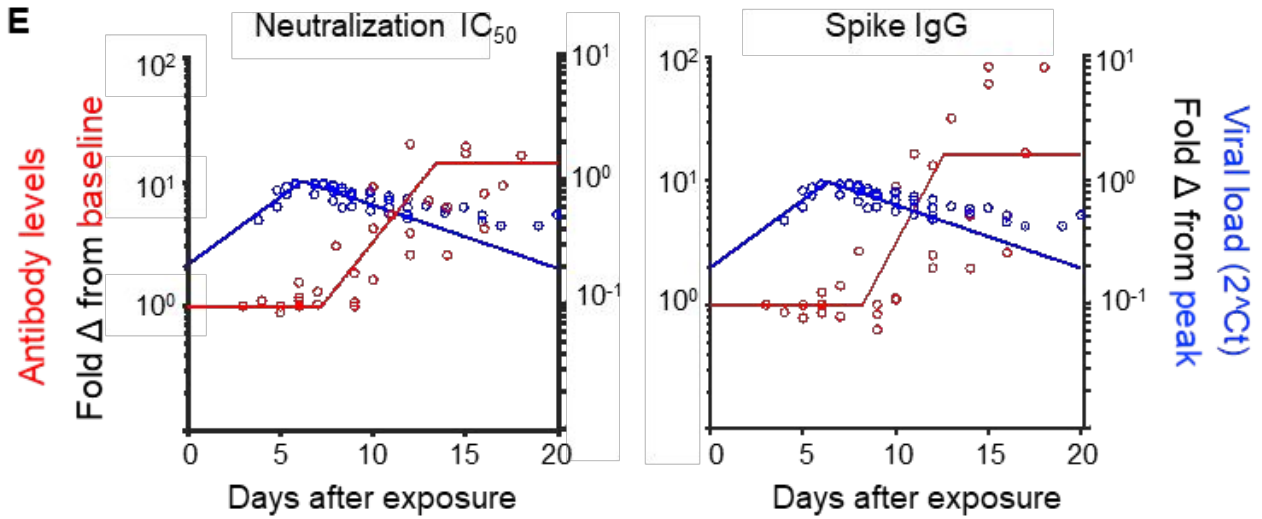






- Early neutralising titres were low, and increased mainly after day 7 post-symptom onset
- Memory B cell proliferation occurred late as well
- Little evidence for T cell recall in most people

Decline in viral replication coincides with the increase in neutralising antibody titres after day 6-7 post-symptom onset



- How will this differ with omicron breakthrough infections?
- Does T cell recall increase with greater disease severity?
- Can we predict the severity of breakthrough infection based on pre-existing immune responses?

Immune memory established by SARS-CoV-2 infection or vaccination

Antibodies and Memory B cells

- Rapidly produce antibodies after antigen exposure
- Frequencies in blood increase for ~6 months after vaccination or infection
- Good recognition of variants of concern, until omicron

CD4+ T cells

- Support of B cell and CD8 T cell responses
- Specific subsets correlate with neutralising antibody titres
- Robust recognition of SARS-CoV-2 spike following both infection and vaccination

CD8+ T cells

- Cytotoxic functions, killing of infected cells
- Induced at modest levels by both infection and vaccination
- Spike-specific CD8 T cell populations are relatively stable following infection

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