Vaccine protection against SARS-CoV-2

Protection against Detectable Infection

Protection against Hospitalizations & Deaths

**Major**

**Minor**

Protection against Detectable Infection

- Antibodies
- T cells (CD4, CD8)

Protection against Hospitalizations & Deaths

- Antibodies
- T cells (CD4, CD8)
- Memory B cell
Evidence pointing to substantial protective contributions of T cells

- Early T cell responses correlate with better outcomes and lower viral loads
- CD8 T cells provide control in monkeys
- 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

Moderbacher et al. Cell Sept 2020
Tan et al, Cell Rep, 2021
Kalimuddin Cell Med, 2021
Conservation of T cell responses across SARS CoV2 variants

- CD4 and CD8 T cell responses largely preserved in fully vaccinated subjects for various variants (including Delta) irrespective of platform, by AIM and ICS
  - Effective recognition also after a single immunization
- Variant recognition of memory (5-6 months after vaccination) T cell responses, including Omicron
  - The majority of CD4 and CD8 epitopes is fully (100%) conserved in the various variants
  - The CD4 and CD8 epitope repertoire of memory T cells is broad
  - Consensus is emerging demonstrating that T cell responses are largely preserved in Omicron

Tarke et al Cell 2022
Reactivity is also detected in non-exposed individuals

- Pre-existing immunity could
  - influence the disease severity of subsequent SARS-CoV-2 infection
  - influence the outcome of SARS-CoV-2 vaccination

Grifoni et al., Cell  May 2020
Widespread evidence of cross-reactive T cell responses within coronaviruses

Mateus et al., Science, August 2020
Preexisting immune memory effect on low dose Moderna mRNA-1273 COVID-19 vaccine responses

Spike-specific CD4+ T cells (%)

Day 1

Spike-specific AM+ (OX40+CD137+)

Day 1

Spike-specific AM+ (OX40+CD137+)

Day 1

RBD IgG (ET)

Day 1

Samples

17 18 17 18 15 17 15 17

Median

0.075 0.020 0.26 0.080 0.32 0.16 0.23 0.12

Responder (%) 100 0 100 94 100 100 100 94

Samples

17 18 17 18 15 18 15 18

Median

3.4 3.1 107 44 1868 1312 182 147

Responder (%) 6 0 100 89 100 100 100 100

Mateus et al; Science, Sept 2021
Further evidence of cross-reactive T cells roles in prevention of symptomatic COVID-19

Pre-existing polymerase-specific T cells expand in abortive seronegative SARS-CoV-2 infection

Cross-reactive CD4+ T cells enhance SARS-CoV-2 immune responses upon infection and vaccination
Definition of cross-reactive coronavirus T cell epitopes

- Cross-reactive T cell responses can modulate antibody responses and likely also modulate disease severity.
- Several other coronaviruses are also of concern.
- Is a "pan-corona" or "pan-sarbeco" vaccine feasible?
- Map immunogenic and conserved regions in CCC.
- Experimentally determine epitopes/regions that are widely crossreactive.
- A T cell vaccine or vaccine component might be effective in broadly preventing severe disease and death.

To date we identified 87 NL63 epitopes and 79 OC43 epitopes.
Selection of representative coronaviruses for further conservation analysis

• Representative virus selection criteria:
  • Clustering based on genomic sequences
  • Sort clusters based on cluster size
  • Exclude clusters from uninteresting hosts: mouse, rat, cat, dog, cattle, horse, rabbit, swine, shrew
  • Exclude clusters with only 1 sequence

• For sarbeco, exactly 10 viruses were selected

• For alpha and beta (excluding sarbeco) groups, 15 to 16 representative viral sequences were included.
  • Since these viruses do not have consistent protein annotations more were included with the expectation that some viruses may have incomplete annotations.
Heat maps of epitope conservation in reference sarbeco, beta and alpha coronaviruses

NL63 epitopes

OC43 epitopes
Epitope specific T cell lines to establish cross-reactivity of human T cells

Original Epitope identified

14 days

T cell lines

Original Epitope identified
Definition of T cell epitopes broadly conserved across viral groups in other viral systems

• The human influenza T cell repertoire is broad and multispecific
  • Several studied defined HLA class I and class II epitopes consistently recognized in multiple subjects and conserved in the majority of the Flu strains
  • Immunization of HLA transgenic mice with a DNA plasmid encoding 20 different epitopes enhanced antibody responses and protected from lethal challenge

• Similar approaches defined epitopes immunogenic in humans and/or restricted by human HLA, and conserved in Old and New world Arenaviruses

• Infection with multiple DENV serotypes and vaccination with a tetravalent DENV vaccine biases responses towards conserved T cell epitopes

• DENV infection can influence T cell responses to ZIKV infection

• Crossreactivity amongst DENV, YF and ZIKV is low, but conserved epitopes mediate protection in animal models
Conclusions

• T cell inducing vaccine components as a broad concept to enhance preparedness against future possible pandemics

• T cell vaccine components might be effective in preventing severe disease for coronaviruses in general and sarbecoviruses in particular

• Several groups reported initial testing of SARS CoV2 vaccine components to broaden the spectrum of T cell reactivities (NantWorks /Immunitbio, Gritstone, Flowpharma, Walz group, Vaxxinity, and other academic groups)

• A similar strategy could be considered for several families of viruses of pandemic preparedness concern (Arenaviridae, Flaviviridae, Bunyavirales, Paramixoviridae, Togaviridae, Picornaviridae and Filoviridae)
  • Not to be seen as an alternative to antibody inducing strategies, but rather synergistic with those strategies

• A T cell inducing component could be produced, tested for safety and immunogenicity in small phase I trials, and even stockpiled, as a first line of defense from a new pandemic