Immune responses that confer protection against severe disease and variants, short- and long-term protection

Florian Krammer

Mount Sinai Professor in Vaccinology

Icahn School of Medicine at Mount Sinai

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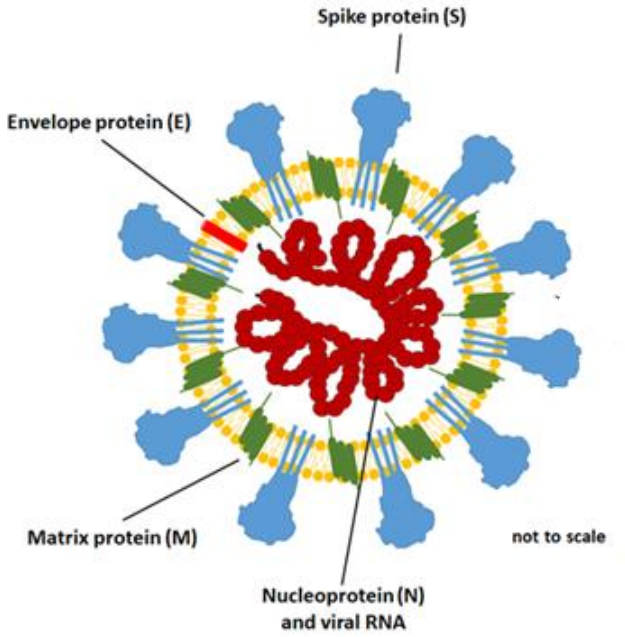
Mount Sinai

Adaptive immune responses to SARS-CoV-2

- **Neutralizing antibody responses in serum** (produced by plasmablasts and long lived plasma cells)
- **Binding antibody responses in serum** (produced by plasmablasts and long lived plasma cells)
- **Memory B cells**
- **T-cell mediated cellular immunity**
- **Mucosal immunity**

What do vaccines do?

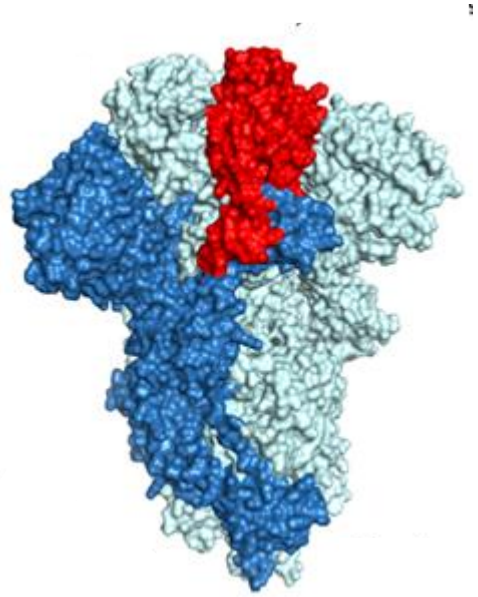
Infection-induced immunity



+ all other nonstructural proteins
likely some intra-host sequence diversity
potentially longer presence of antigen

systemic immunity
mucosal immunity

Vaccine-induced immunity



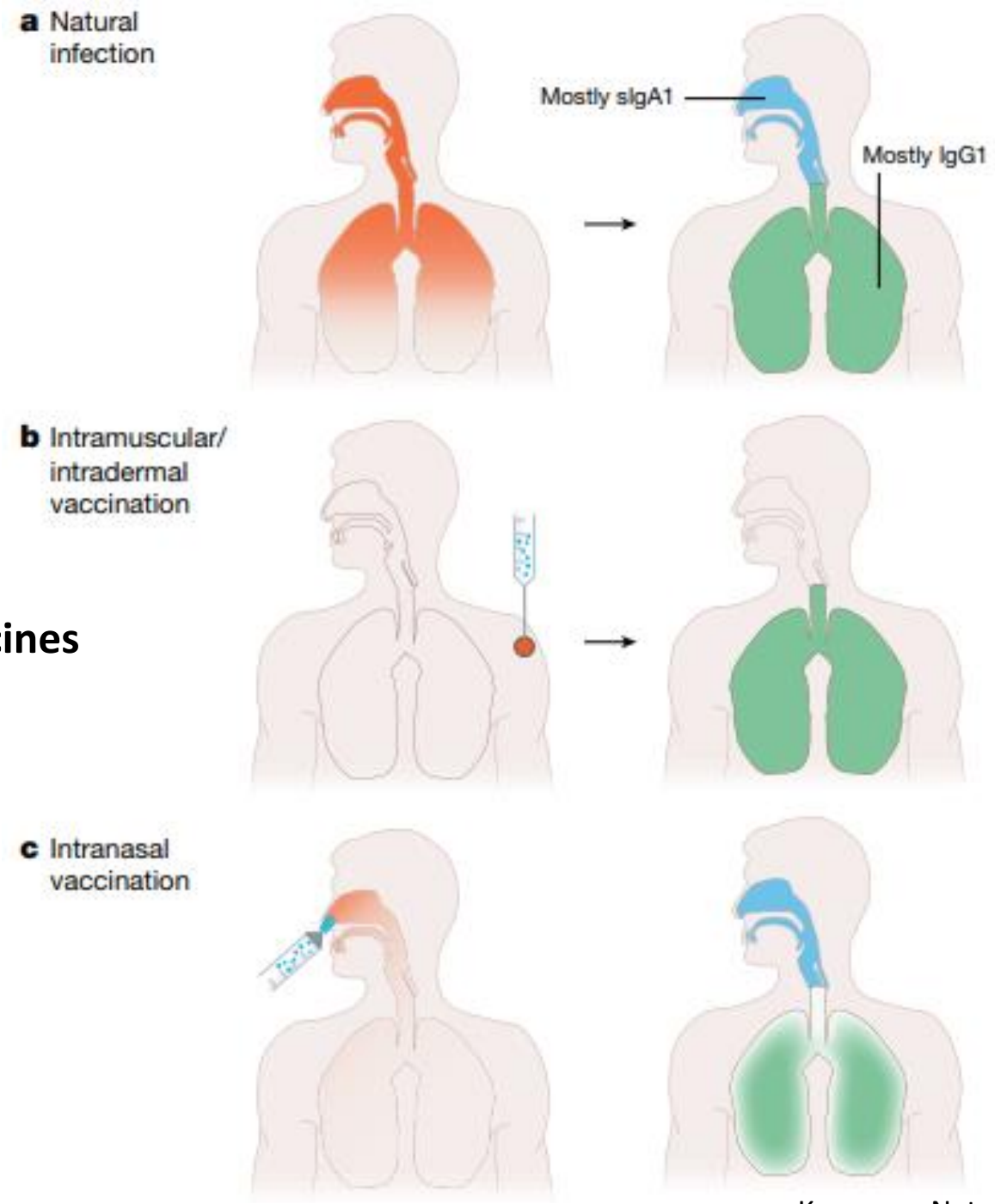
***except inactivated vaccines**

one consensus spike

systemic immunity

What do vaccines do?

All currently licensed COVID-19 vaccines



Krammer, Nature, 2020

Protection from infection

- Mechanistically, this can really only be achieved by neutralizing antibodies
- Antibodies need to be present on mucosal surfaces of the upper and lower respiratory tract
- For SARS-CoV-2 vaccination this is IgG which ends up on mucosal surfaces
  - Good protection of the lower respiratory tract
  - Little in the URT, and levels may decline rapidly
- After natural infection locally produced sIgA may be the main mechanism of protection in the upper respiratory tract
- Virus dose and viral fusogenicity may be factors here as well

Protection from disease

- The virus infects cells but replication is significantly reduced
- Potential contributing factors
  - Neutralizing antibodies at suboptimal levels
  - Non-neutralizing antibodies via effector functions
  - T-cells
  - Memory B cells which differentiate into plasmablasts and quickly increase (neutralizing) antibody levels
- The effect of T-cells and memory B cells likely depends strongly on incubation time – which is already very short for the recent Delta and Omicron variants

Protection from severe disease

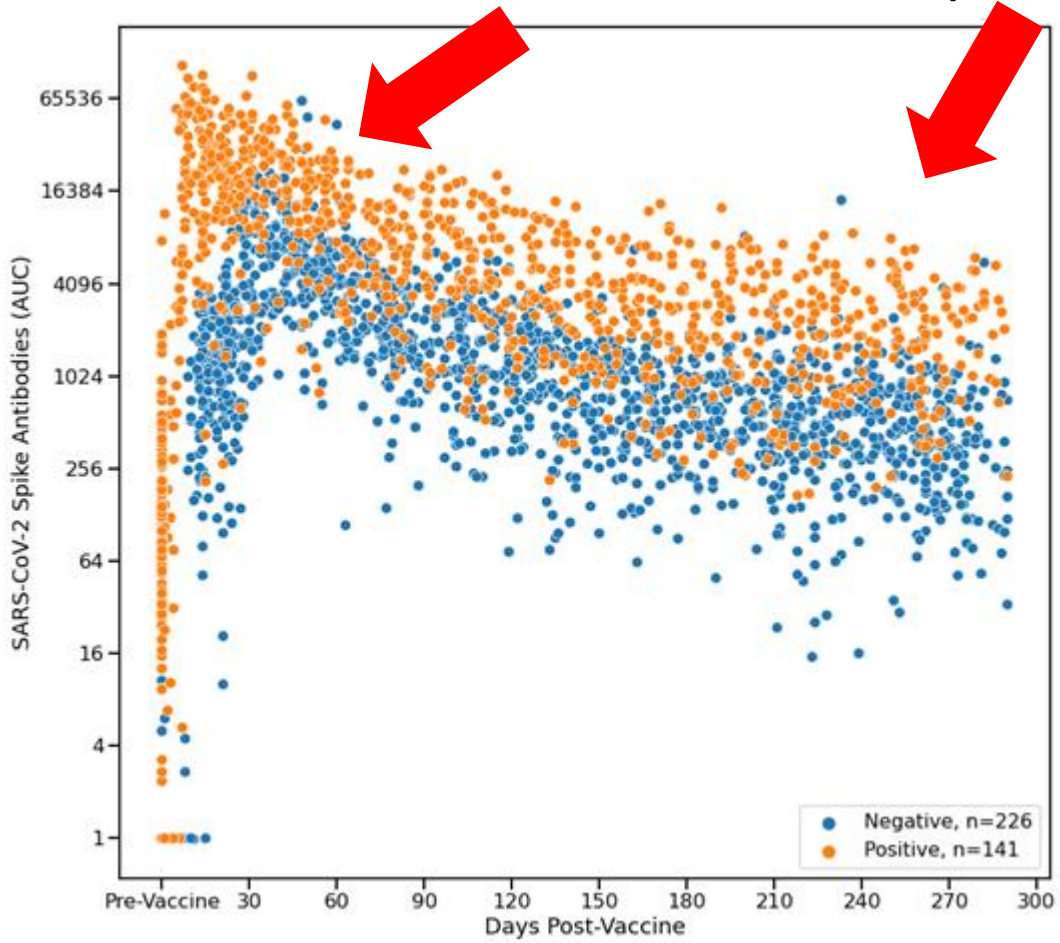
- The virus infects cells, spreads, causes symptoms but replication is significantly slowed/attenuated, especially in the lower respiratory tract
- Potential contributing factors:
  - Neutralizing antibodies at suboptimal levels, but high enough IgG titers to protect the lower respiratory tract
  - Non-neutralizing antibodies via effector functions
  - T-cells
  - Memory B cells which differentiate into plasmablasts and quickly increase (neutralizing) antibody levels
- T-cells and memory B cells have significantly more time to respond since disease progression takes time

Longevity of immune responses

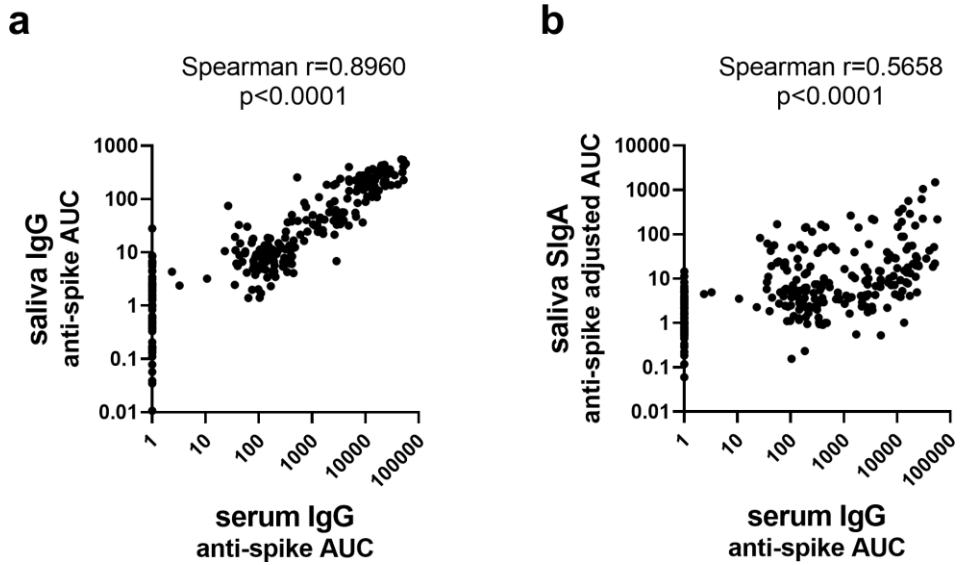
- **Serum antibody levels peak, wane and stabilize**

Plasmablast derived (periphery)

Long lived plasma cell derived (bone marrow)

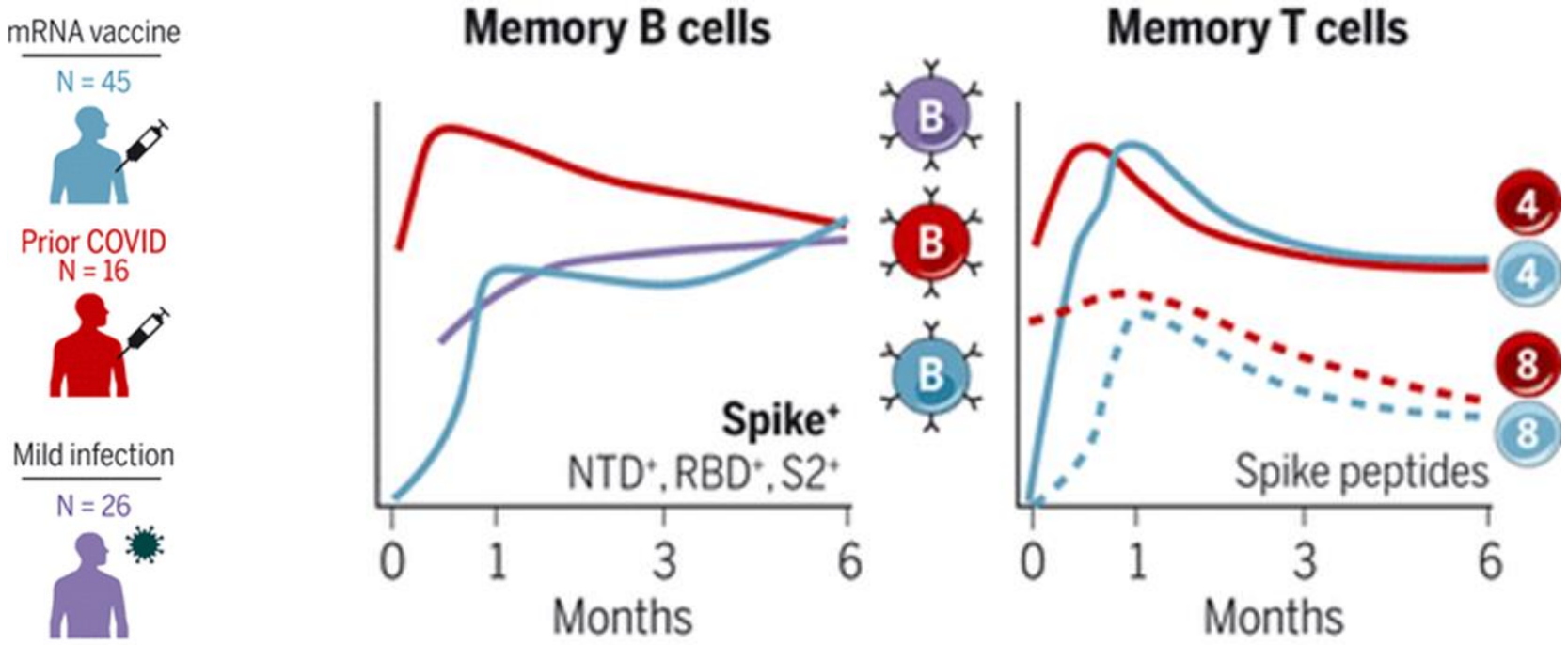


Mucosal IgG correlates with serum IgG, sIgA does not



Longevity of immune responses

- **T-cell and memory B-cell responses are long lived**



Goel *et al.*, Science, 2021

Variants make everything more complicated

- Antigenic changes mediate escape from (neutralizing) antibody response
- To a lesser degree, antigenic changes also impact on binding antibody and T-cell responses
- Variants may also indirectly ‘escape’
  - High viral loads/more robust virus replication may increase how much virus is shed and that may increase infectious dose for exposed individuals
  - Higher fusogenicity may facilitate escape from antibodies due to faster cell entry
  - Shorter incubation time means less time for an anamnestic response to prevent (severe) disease