Overview of the immunology of protection from COVID-19 vaccines

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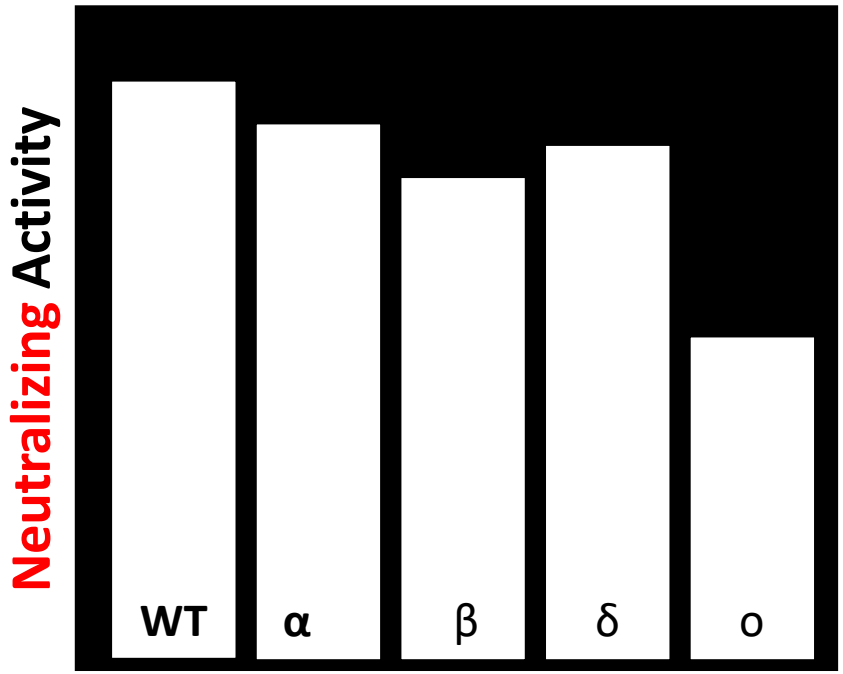
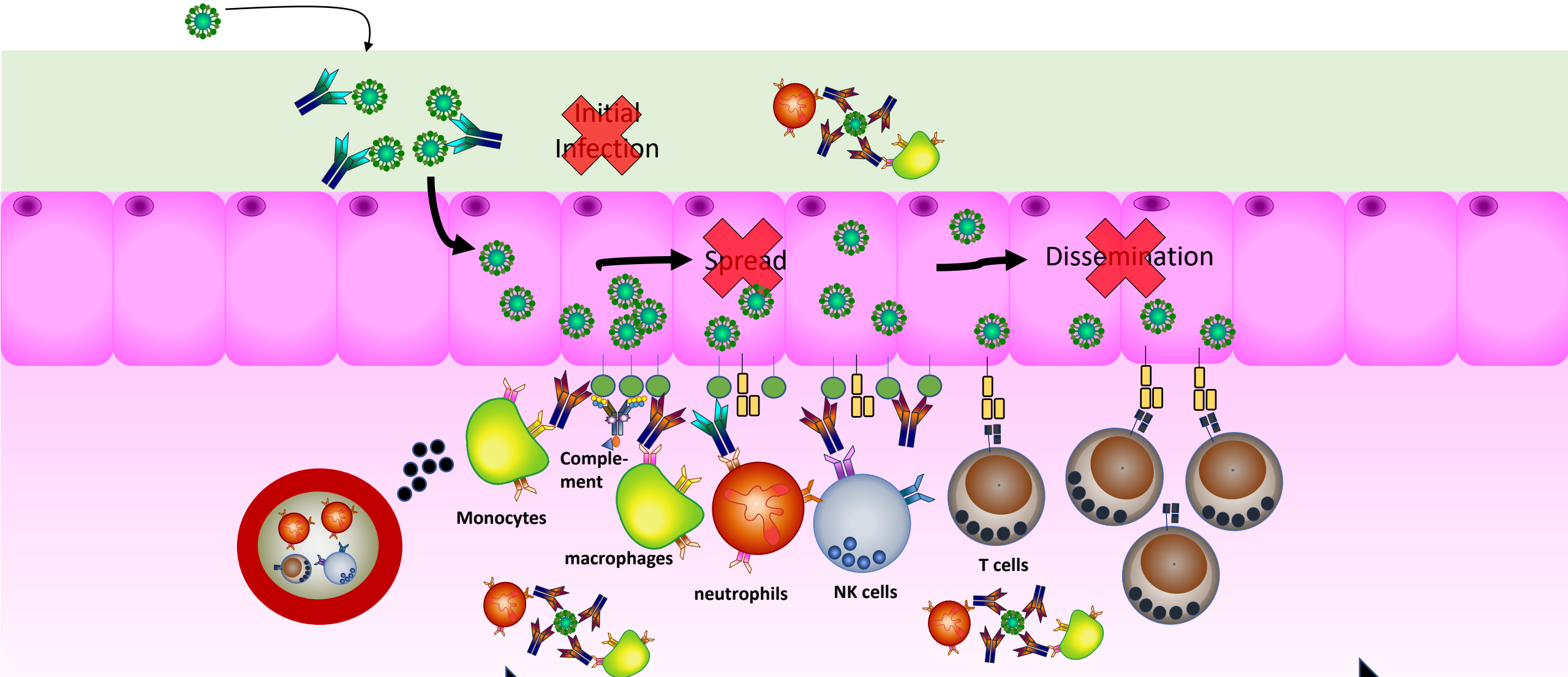
WHO Pathogen X Meeting

Vaccine protection is observed across variants of concern - despite loss of neutralization



How does the immune system collaborate to drive protection against viral infection?



Correlates of immunity against COVID-19

Natural Immunity

-antibodies are sufficient, but not required for protection

-antibody quality (neutralization + Fc-functions) modulate disease

-cross-reactive T cells modulate disease severity

-neutropenia, diabetes, BMI, age, sex, associated with severe disease

-Interferons are critical for protection

Vaccine Induced Immunity

-binding and neutralizing antibodies are correlates of immunity at peak immunogenicity

-high titers are required to block transmission

-immunity against severe disease persists after neutralizing antibodies wane

-memory B and T cells persist

-the first vaccine exposure imprints immunity, affecting future antibody evolution

Hybrid Immunity

-infection associated priming induces tissue resident immunity and more effective antibody isotypes

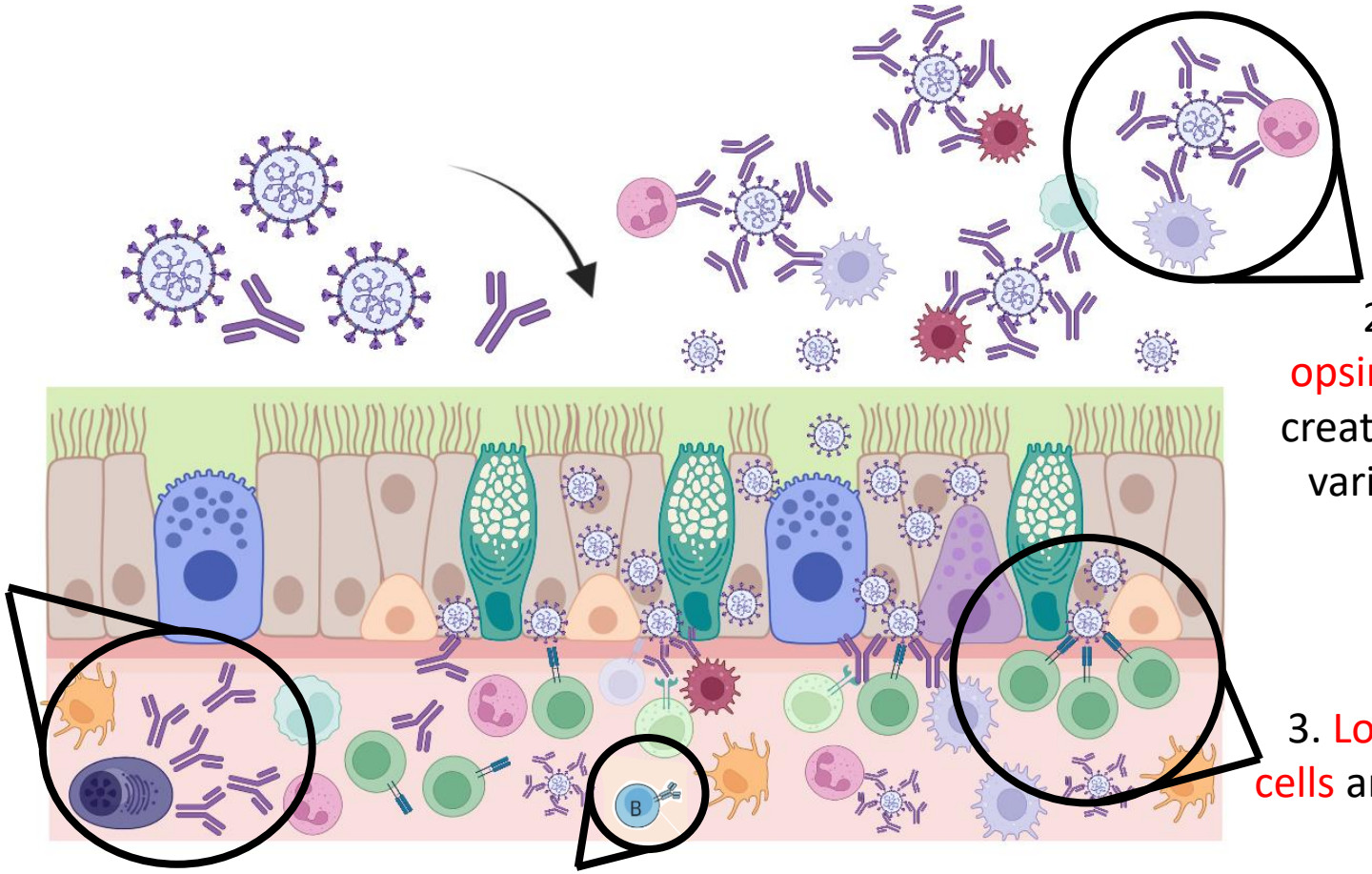
-infection associated immunity may have superior, albeit still imperfect, cross-reactivity

-infection associated priming or boosting may reshape the landscape of innate immune cells at the respiratory barrier

-infection associated priming may broaden the immune response to additional viral antigens (nucleocapsid, etc.) or across Spike

Multiple tissue-resident immune mechanisms are likely key to protection against this rapidly evolving virus

1. Tissue resident plasma cells are needed to persistently produce high titer antibody isotype responses



2. Long-lived binding opsinophagocytic antibodies create a bottleneck to control variant viruses that escape neutralization

3. Long-lived tissue resident T cells are key to rapid clearance of infected cells

4. Tissue resident memory B cells respond to variants, generating variant specific neutralizing responses

Conclusions

- SARS-CoV-2:
  - While the design of a transmission blocking vaccine against SARS-CoV-2 remains an aspirational dream, due to its high R_o, current vaccines attenuate disease through a multi-cellular mechanism.
  - Because we understand this mechanism of disease control, we can now design next-generation vaccines able to relieve symptomatology as well as prevent death.
- Pathogen X:
  - Understanding immunity at the portal of entry and site of viral replication is key to the design of vaccines against prototypical pathogens.
  - The explosion of immunological tools must be weaved in strategically to inform vaccine development, rather than explain vaccine deficiencies, to accelerate global deployment of highly effective vaccines.