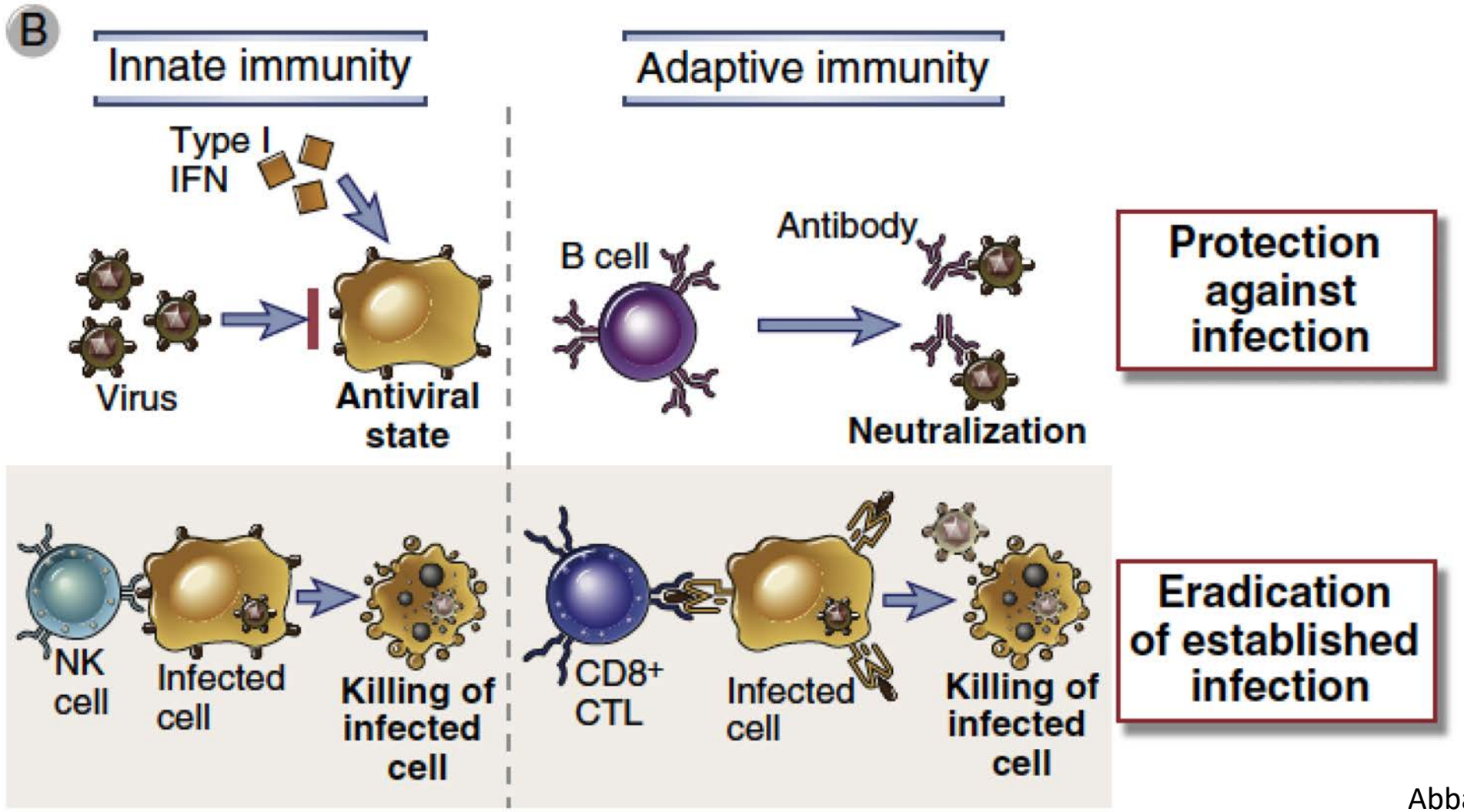
IMMUNOLOGY OF COVID-19

Drs. Duygu Sag & Gerhard Wingender

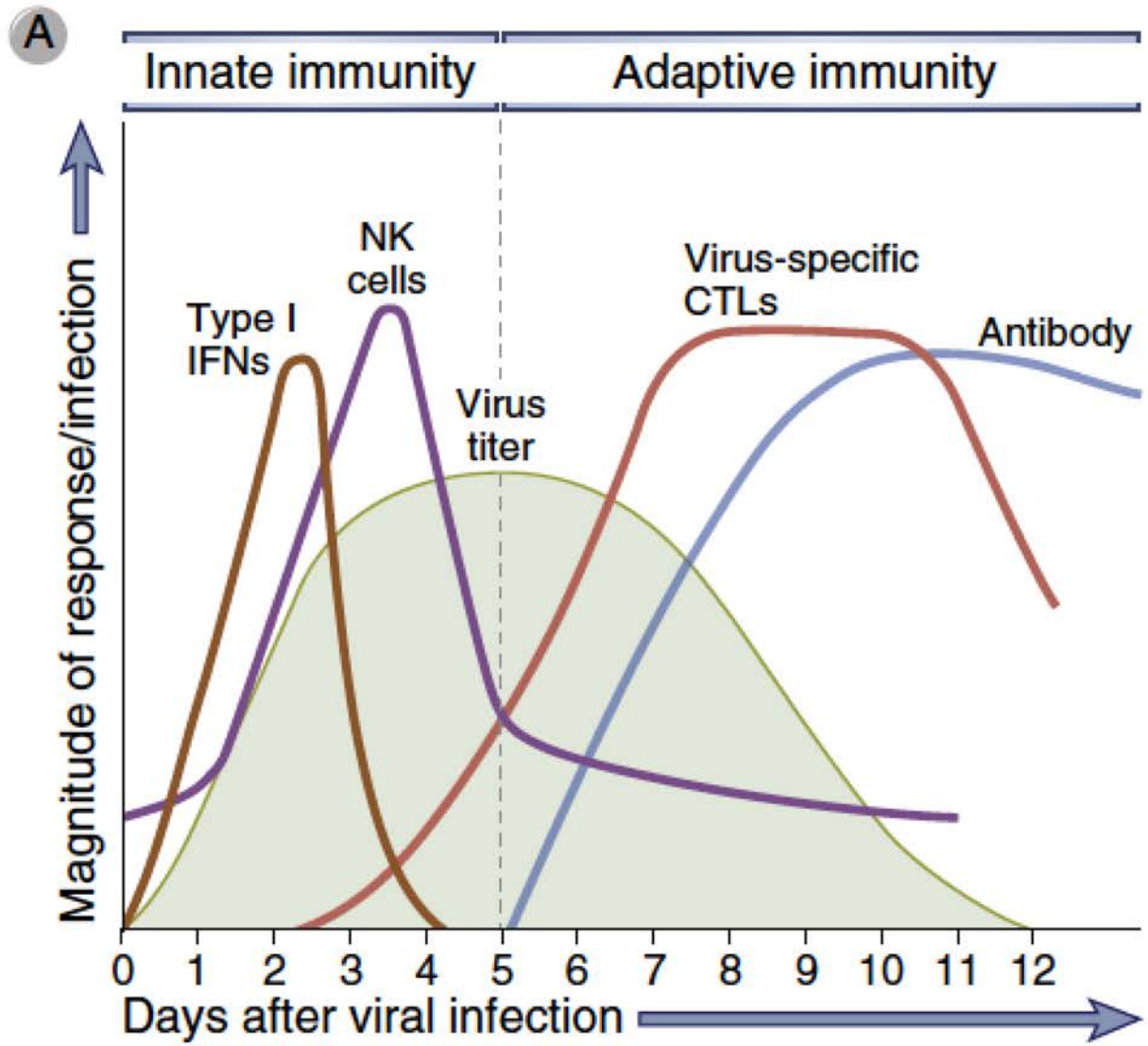
24.04.2020

Immune Responses Against Viruses



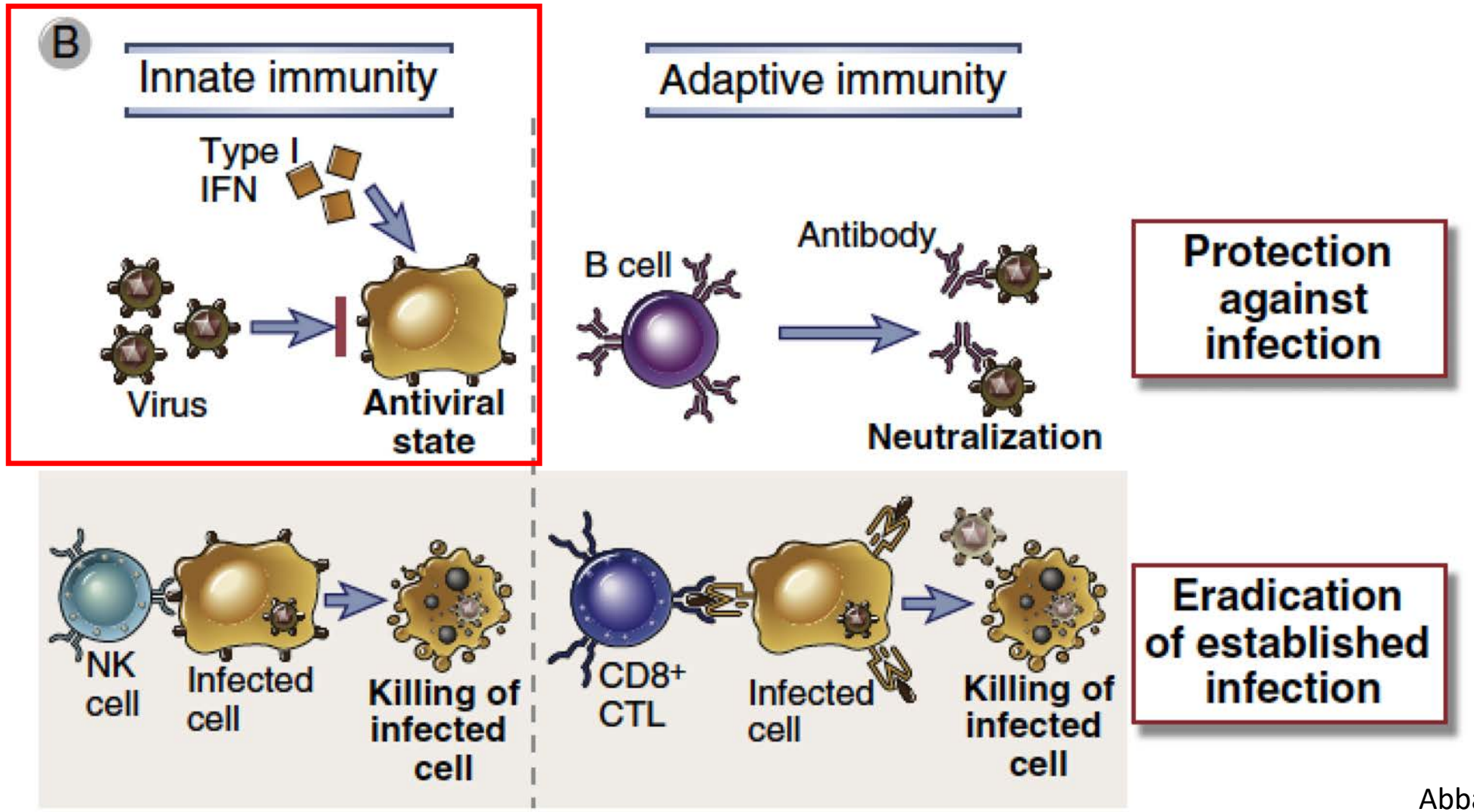
Abbas, 7th ed.

Immune Responses Against Viruses



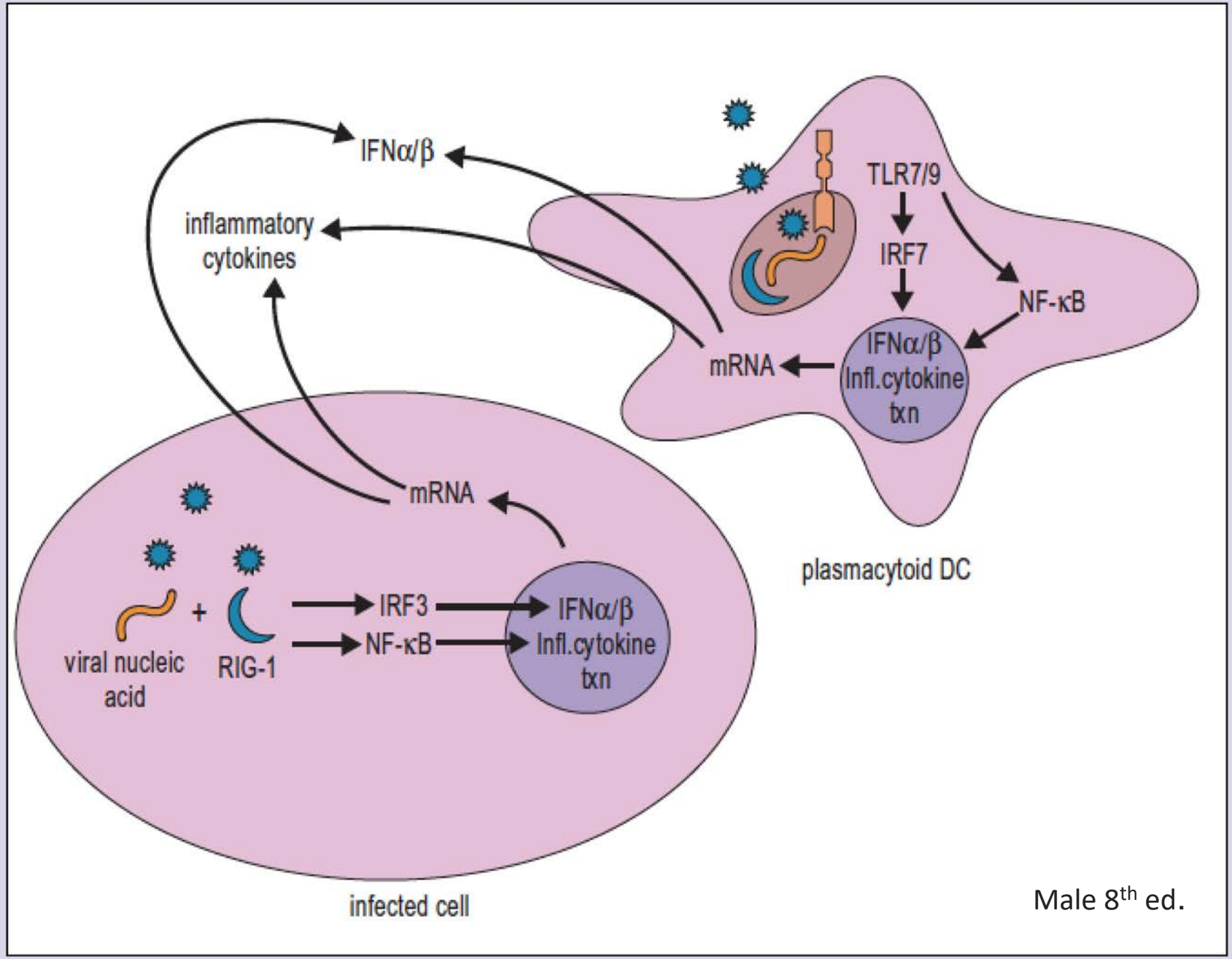
Abbas, 7th ed.

Immune Responses Against Viruses



Abbas, 7th ed.

Pathways by which type I IFN production can be triggered following virus infection

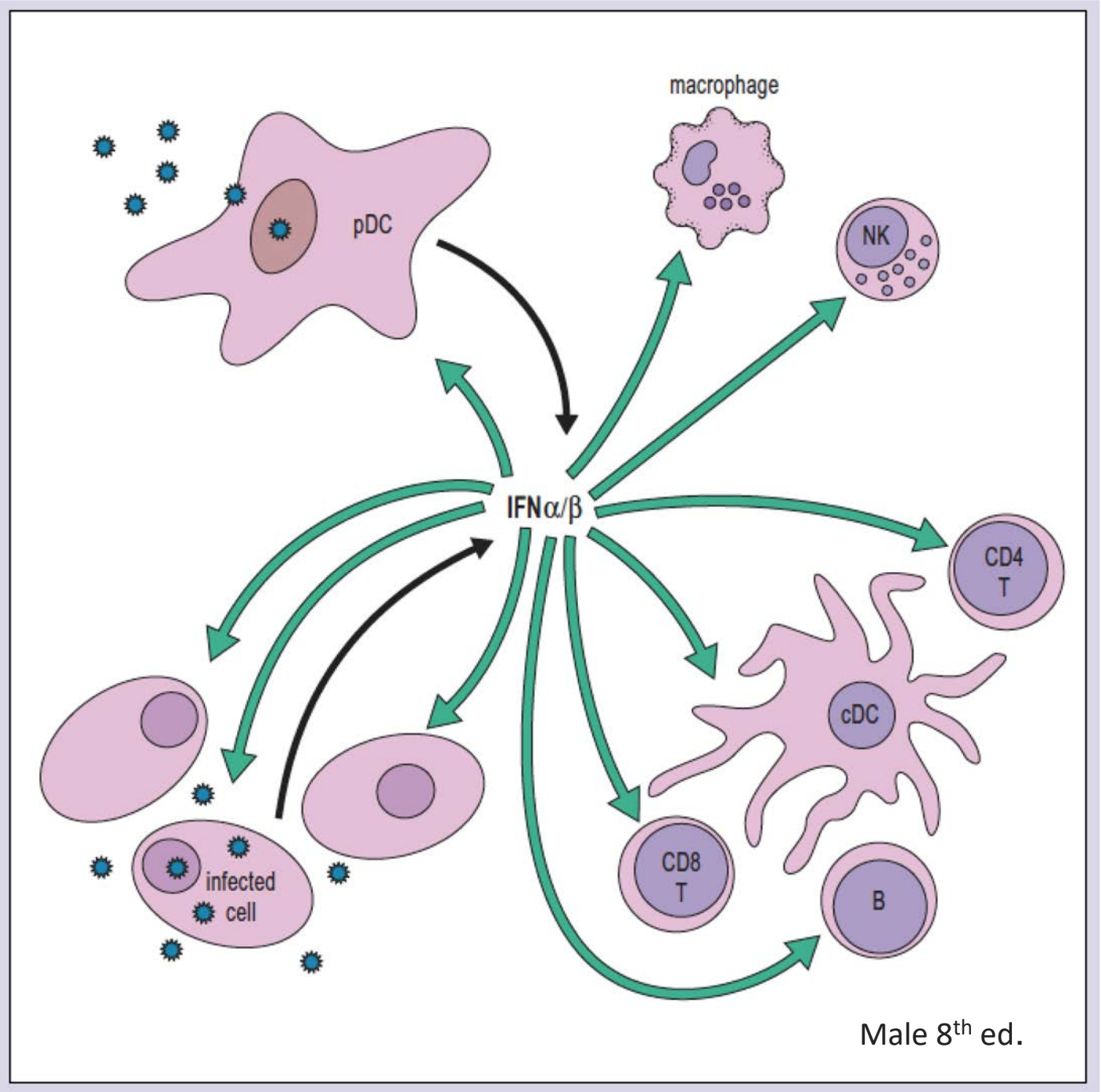


Male 8th ed.

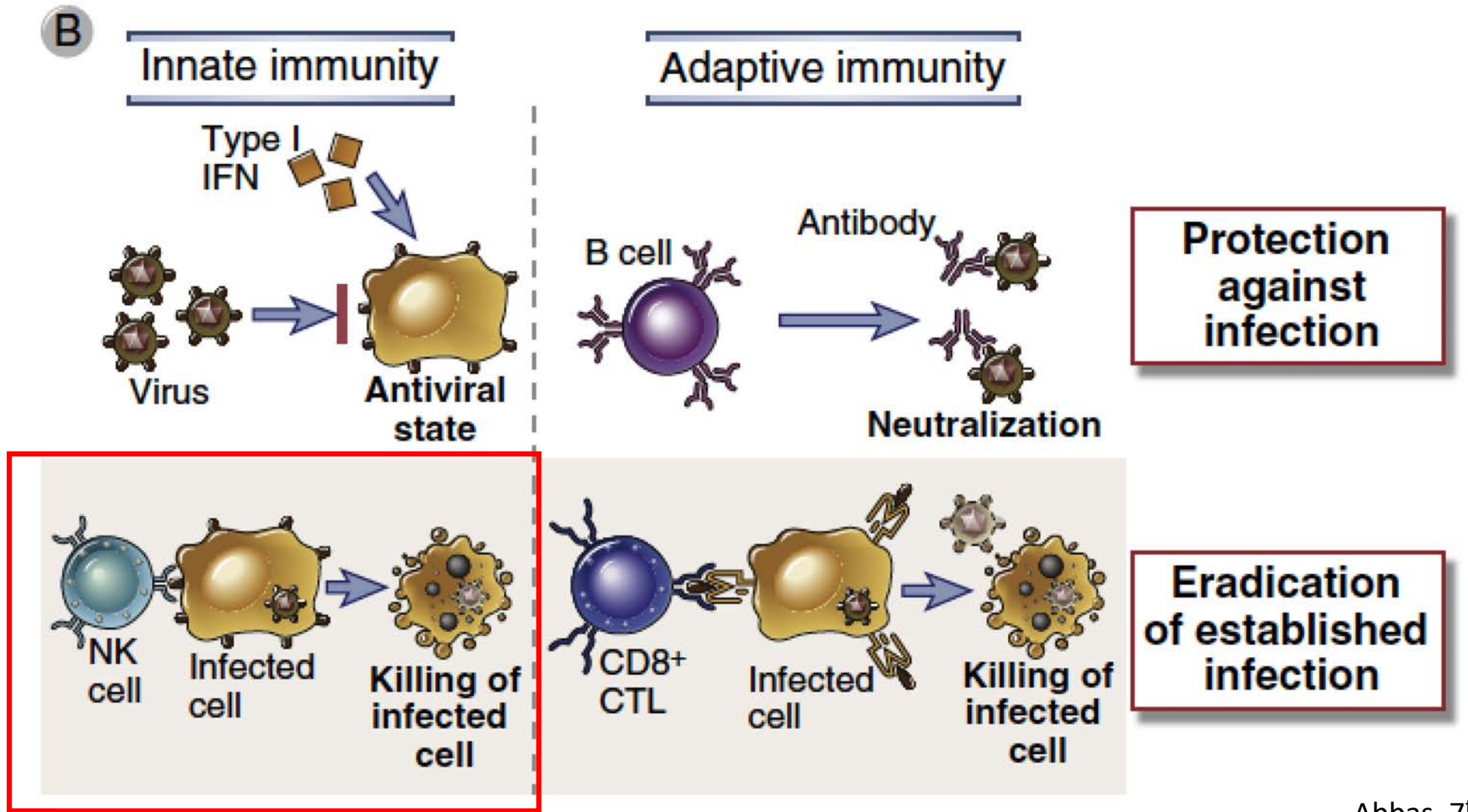
Type I IFNs activate anti-viral response genes.

- inhibit eukaryotic initiation factor (eIF)-2a, hence blocking the translation of viral mRNA.

- initiate apoptosis via Bcl-2 and caspase-dependent mechanisms, killing the cell before virus can be released.

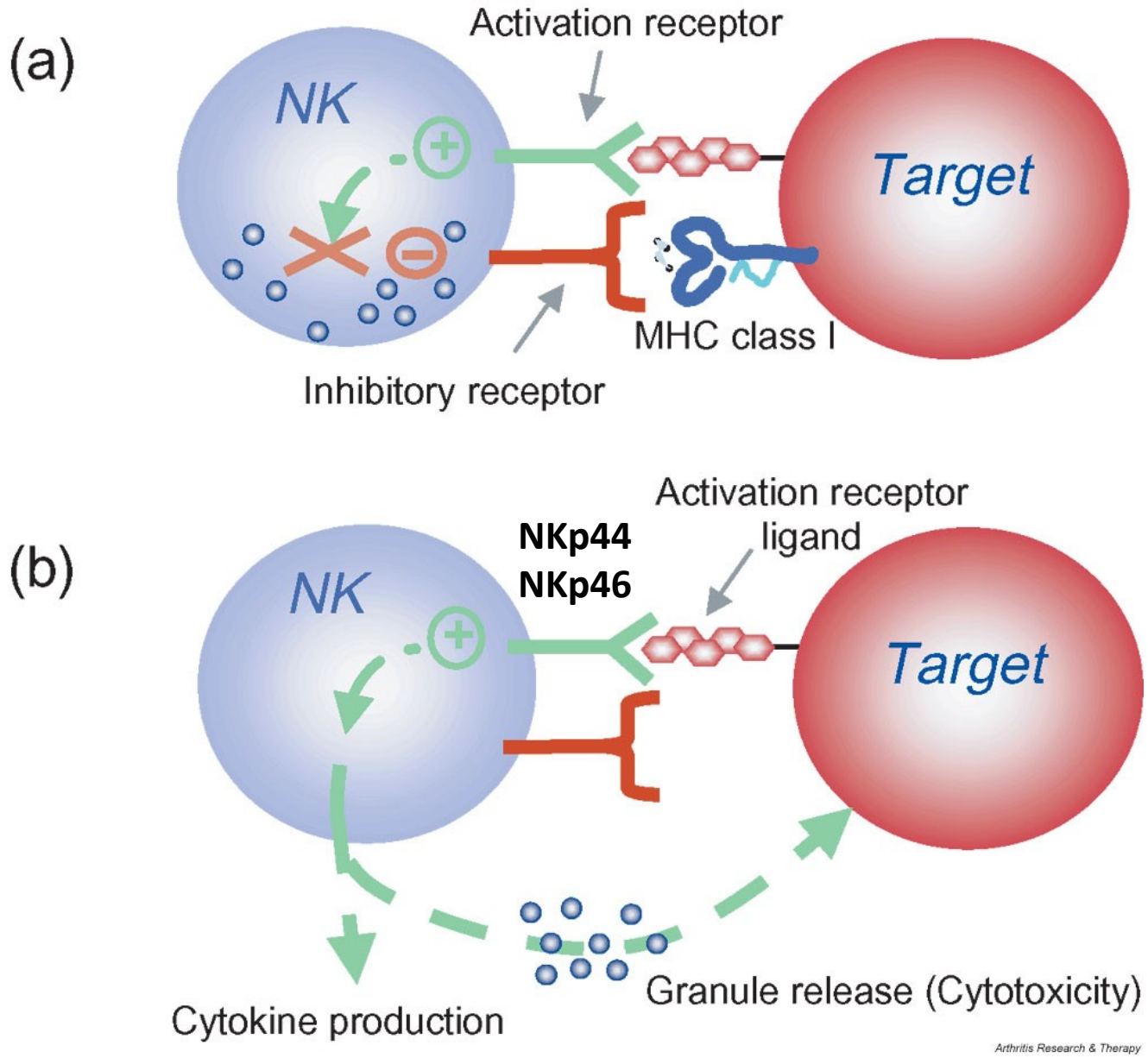


Immune Responses Against Viruses

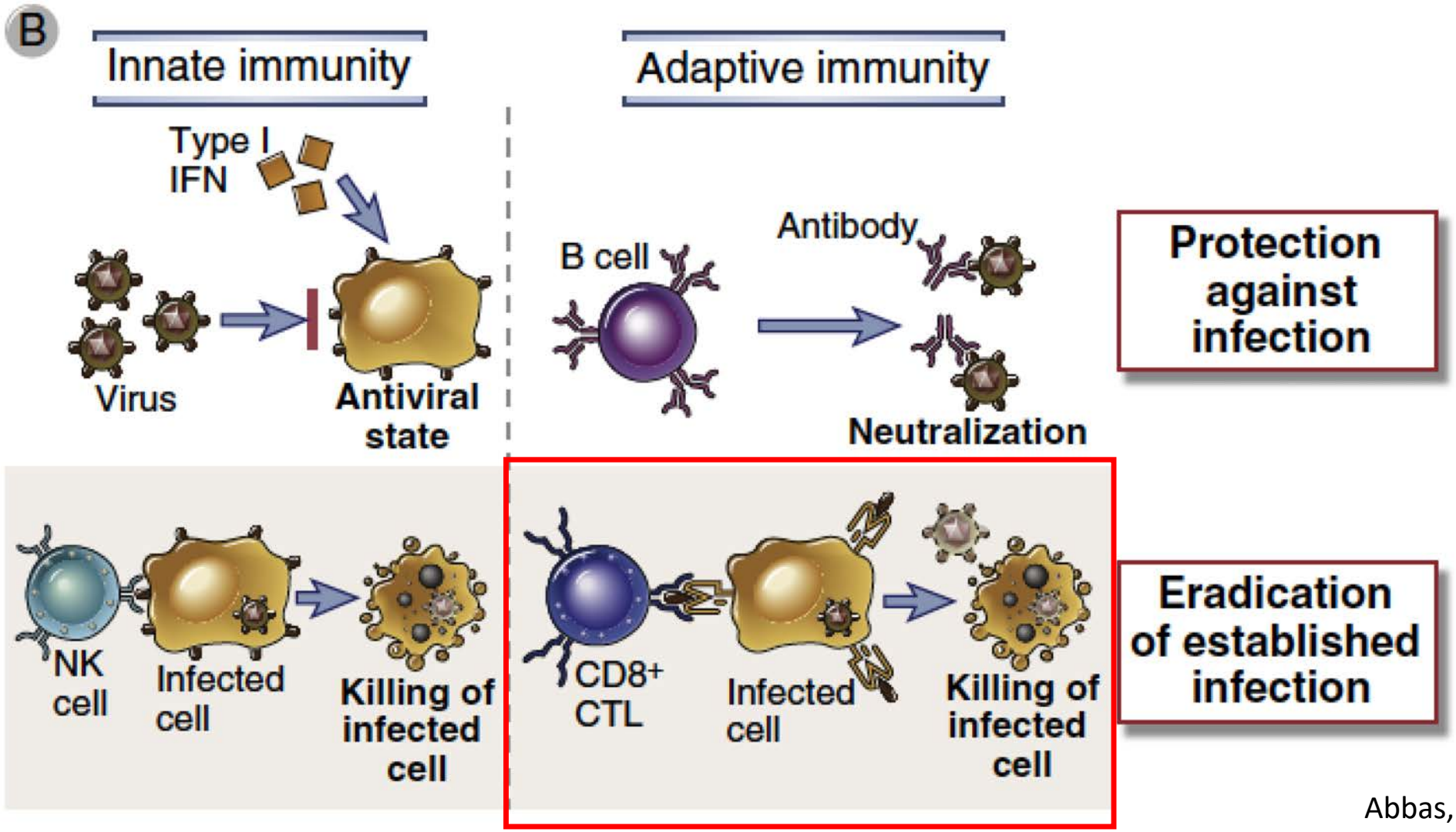


Abbas, 7th ed.

Killing of virus infected cells by NK cells

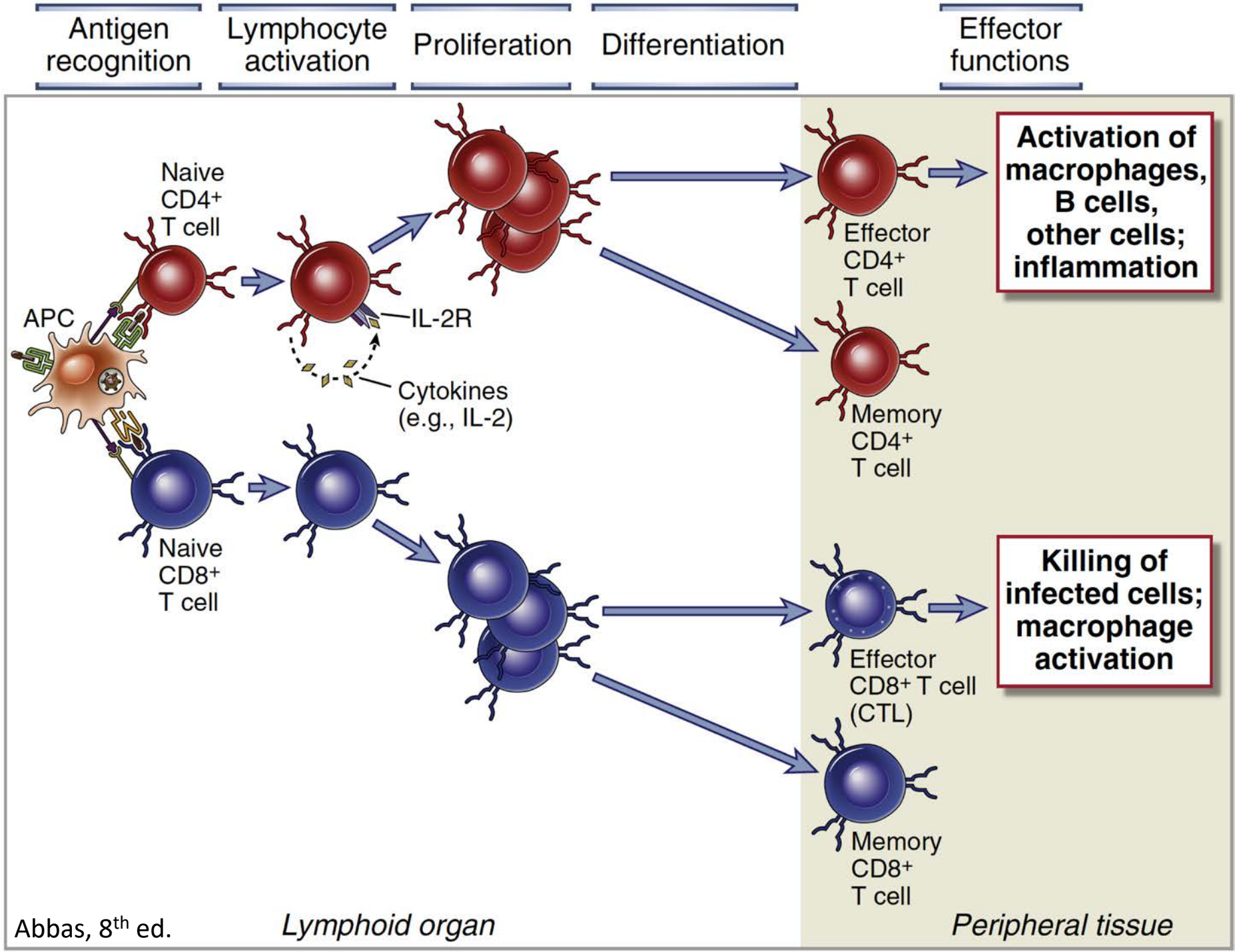


Immune Responses Against Viruses



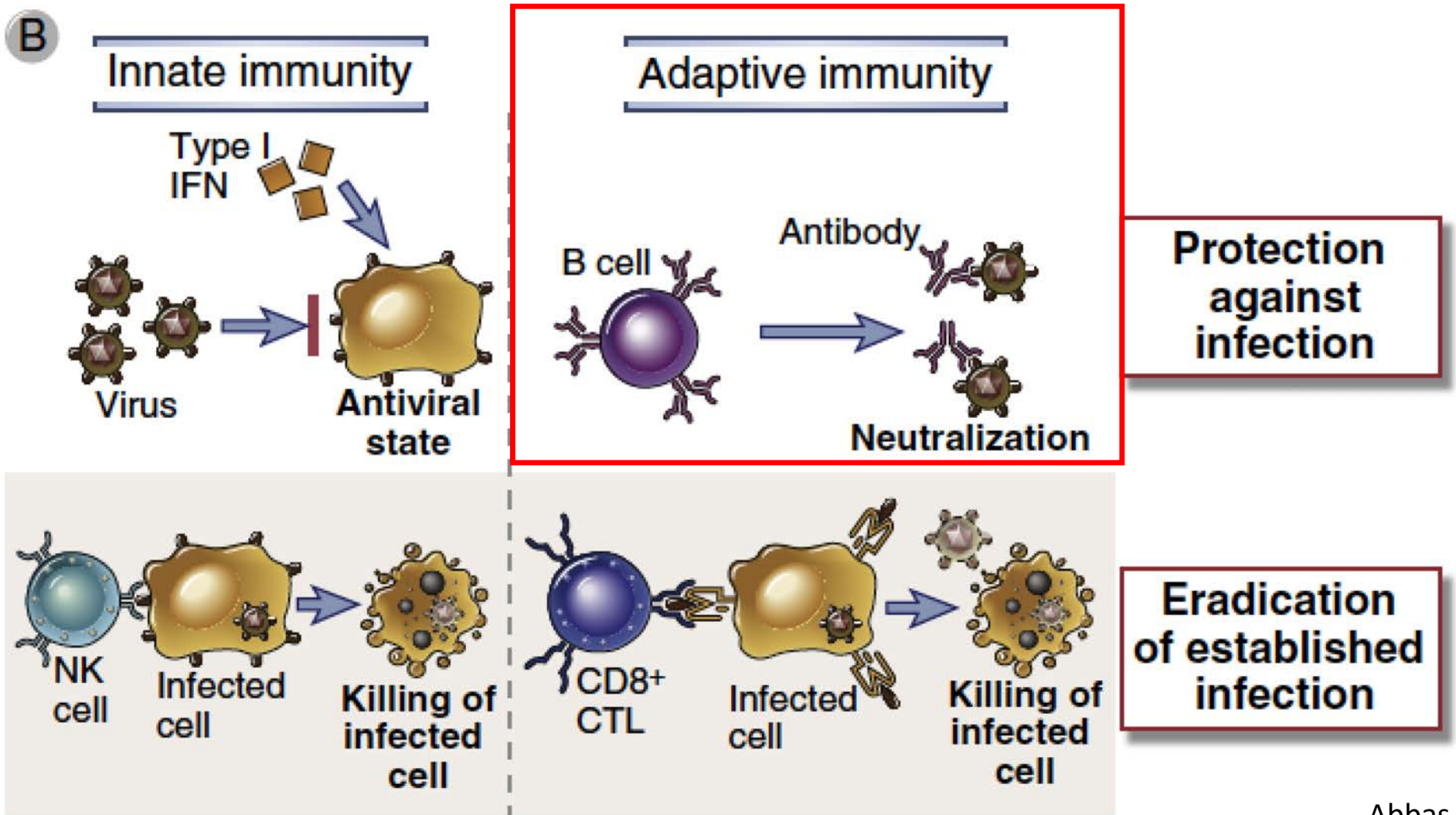
Abbas, 7th ed.

T cell activation and killing of virus infected cells



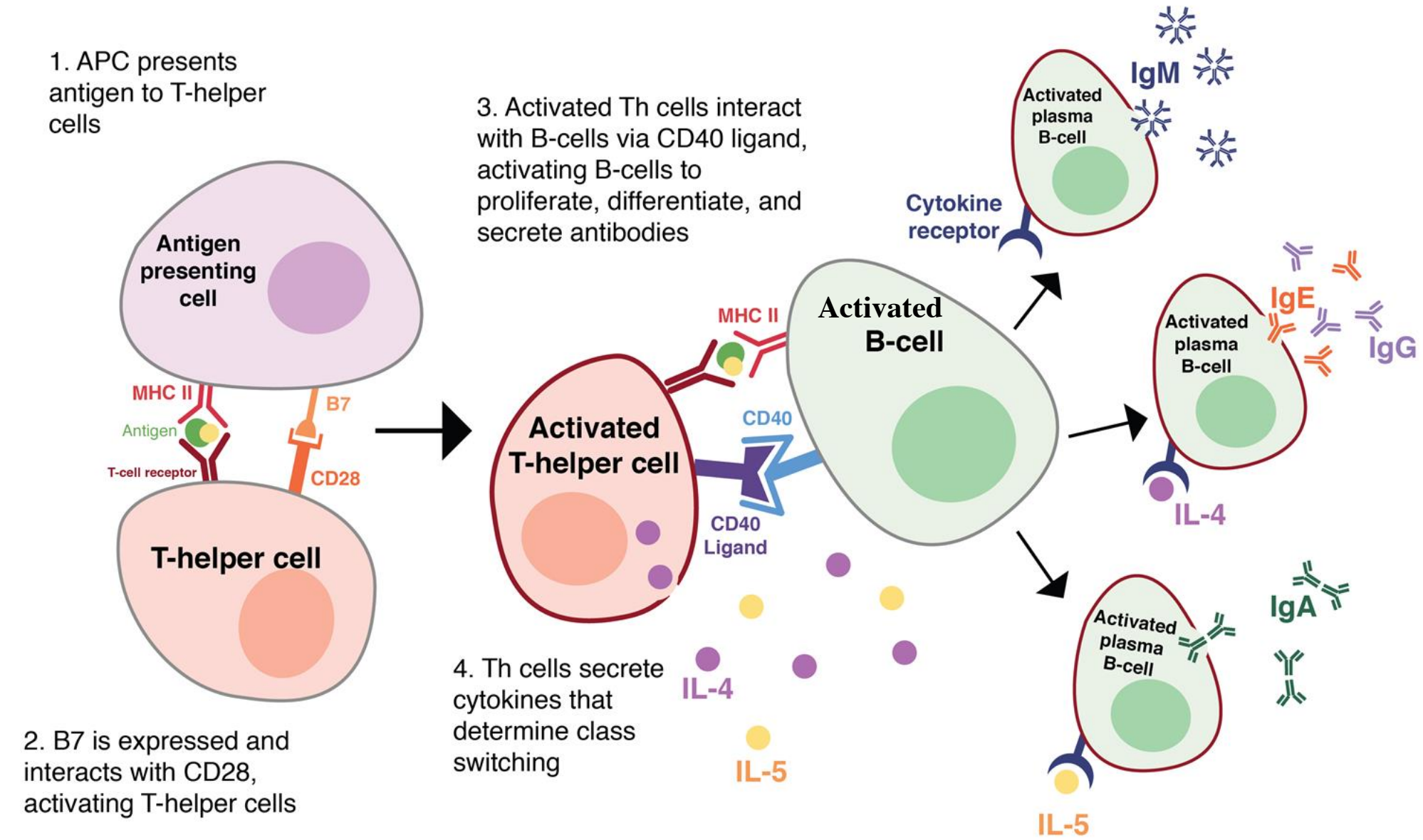
Abbas, 8th ed.

Immune Responses Against Viruses



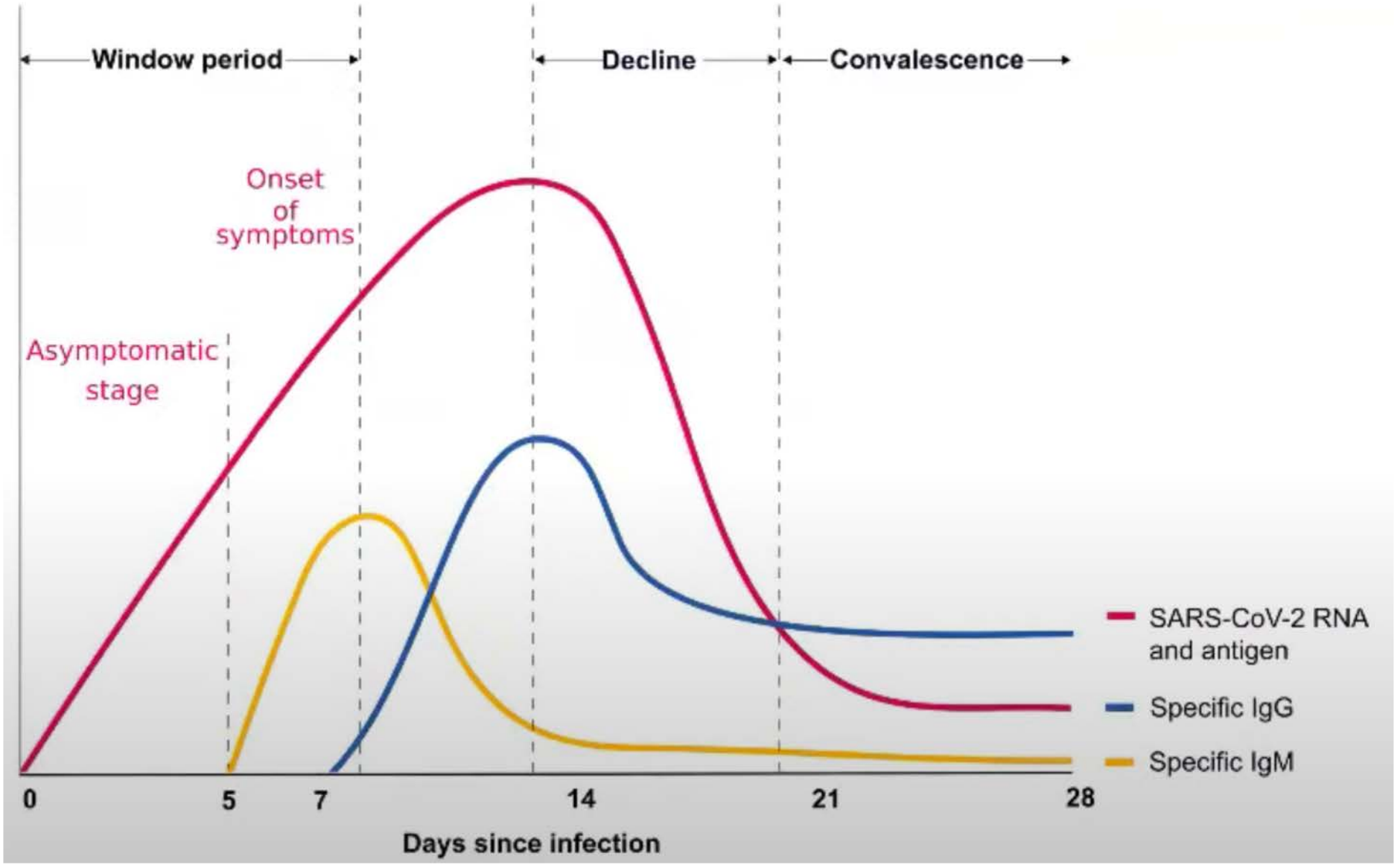
Abbas, 7th ed.

Activation and Class-switching of B-cells



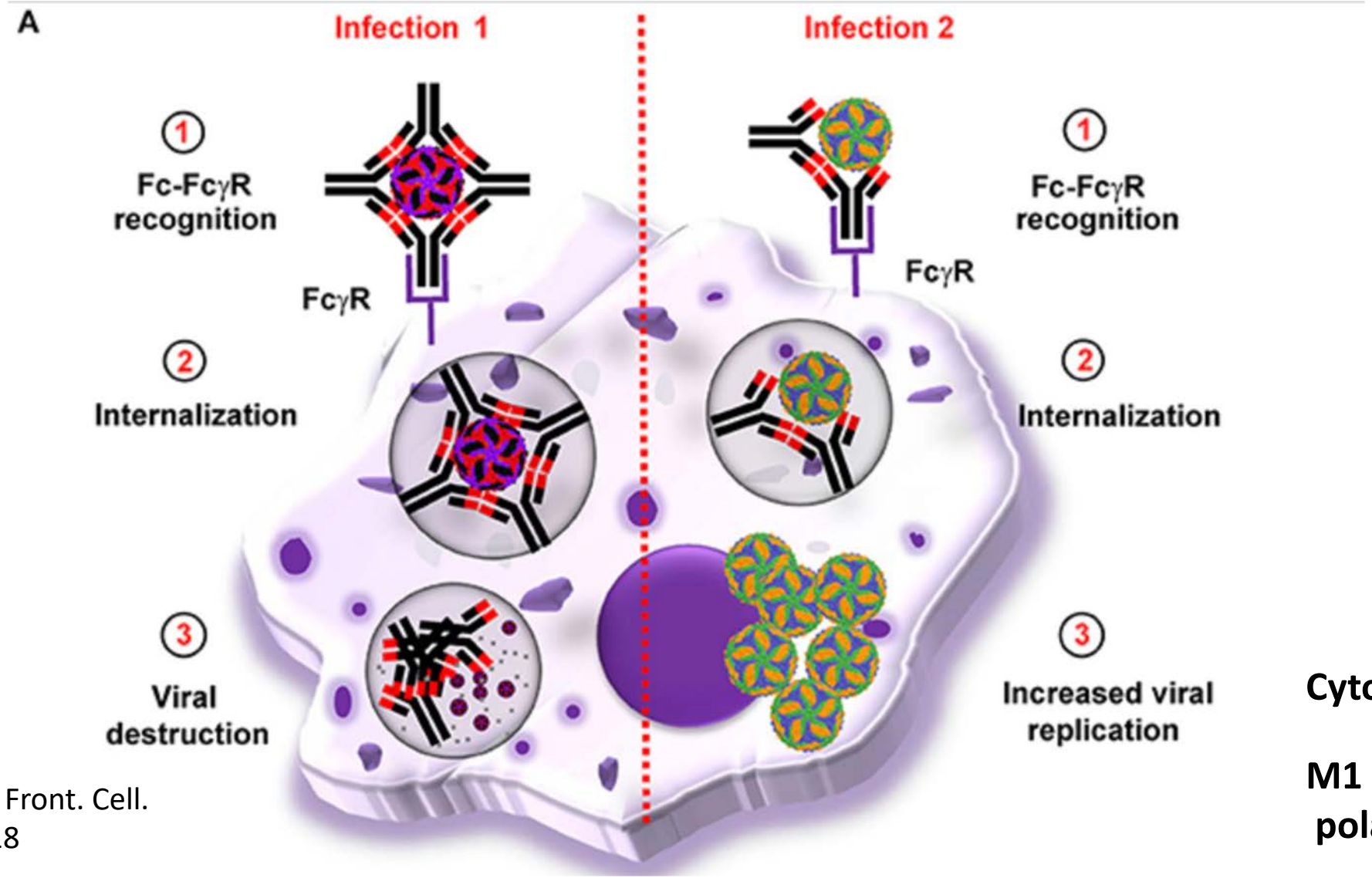
Lucy Liu

Antibody Response Against SARS-Cov2



Cezmi Akdiş, submitted

Antibody-dependent Enhancement (ADE)



Martin-Acebes et al, Front. Cell. Infect. Microbiol 2018

Cytokine storm

M1 macrophage polarization

Antibody-dependent Enhancement (ADE)

- ADE ensues when antibodies binding to the virus particle **fail to efficiently neutralize the virus**.
- This may occur if:

1) the Abs is not specific enough to neutralize
2) the Ab concentration is below the threshold for neutralization.

- Such ADE is principally mediated by **IgG** antibodies, however, **IgM along with complement**, and **IgA** antibodies have also been shown to be capable of ADE.

Antibody-dependent Enhancement (ADE)

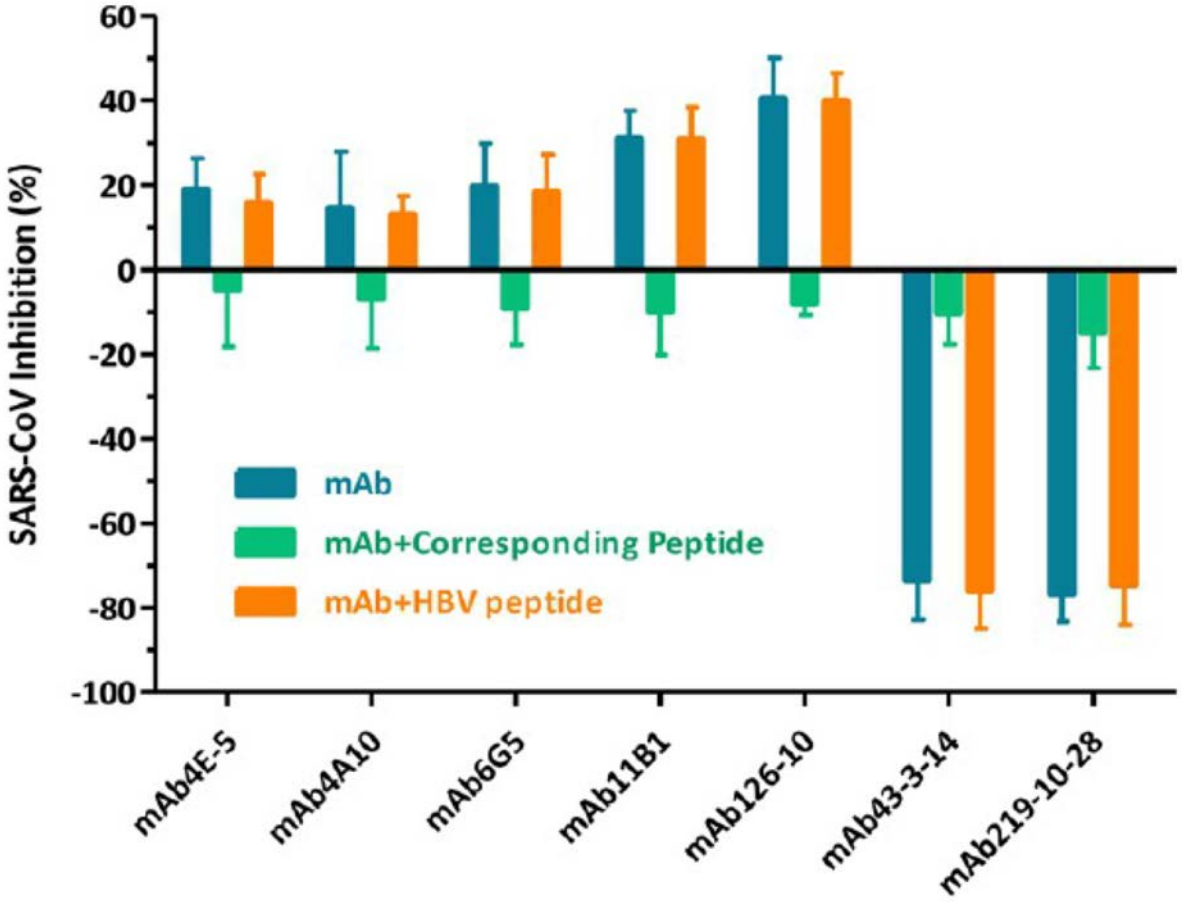
- This phenomenon is observed during secondary infection with a heterotypic virus of the same genus, wherein preexisting antibodies against the primary (sensitizing) infection bind to the (secondary) virus, but fail to neutralize it. e.g. Denge virus, influenza

ADE of SARS-CoV

- Antibodies specific to the viral surface **spike glycoprotein (S)** are capable of enhancing viral infection of immune cells, particularly monocytes and macrophages.
- Internalization of the immune complexes by cellular **Fcγ** Receptors, mainly **Fcγ RIIA**, is the suggested mechanism.
- Although demonstrated recently in rhesus monkeys the occurrence of SARS-ADE and its association with disease severity in humans are still debated, with different clinical studies reporting both protective and disease-enhancing effects of anti-SARS-CoV antibodies.

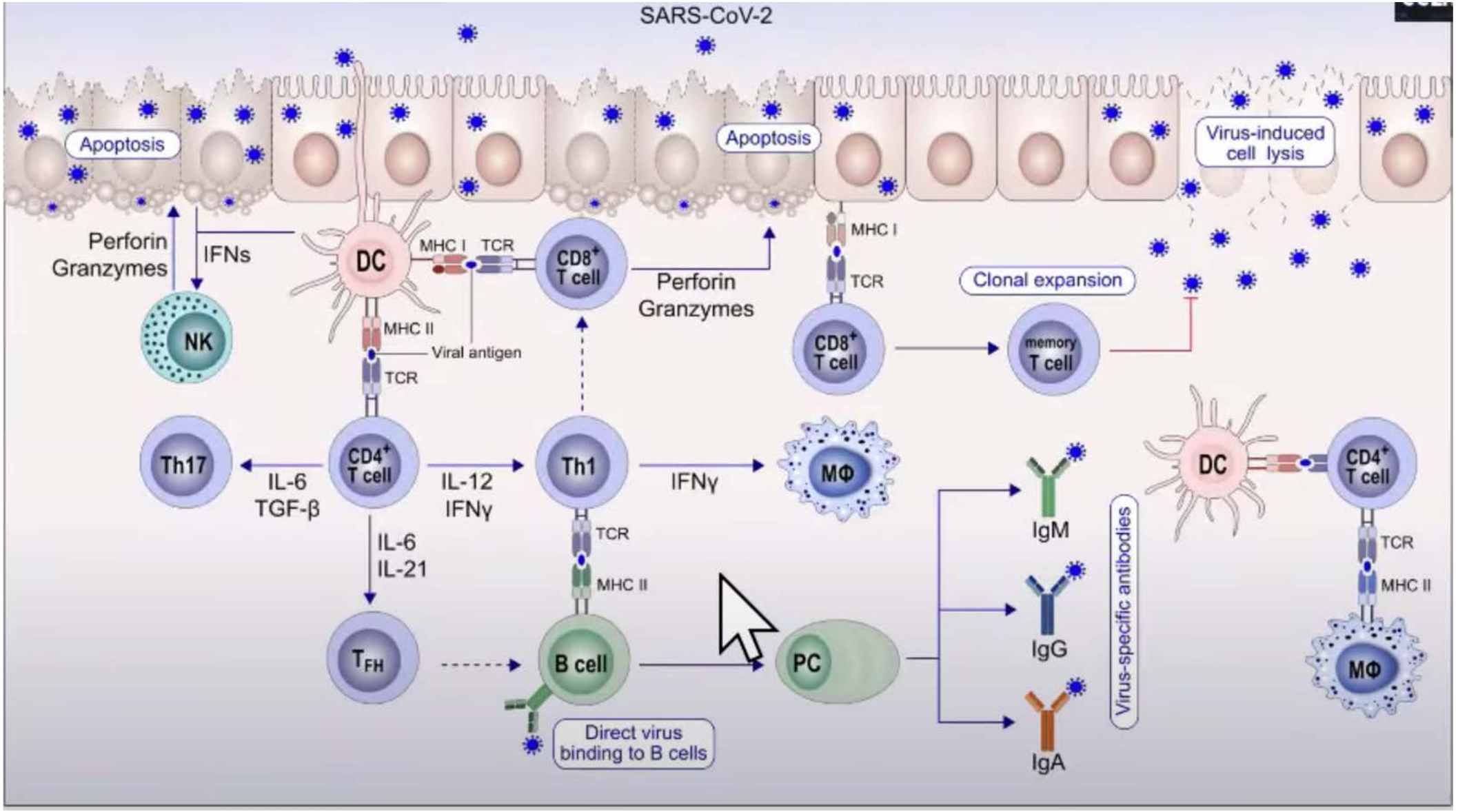
ADE of SARS-CoV

- In rhesus macaques, the spike glycoprotein peptides **S471–503 , S604–625 , and S1164–1191** elicited antibodies that efficiently prevented infection in non-human primates.
- Peptide-based vaccines against SARS-CoV could be engineered to avoid ADE via elimination of the **S597–603 epitope.**

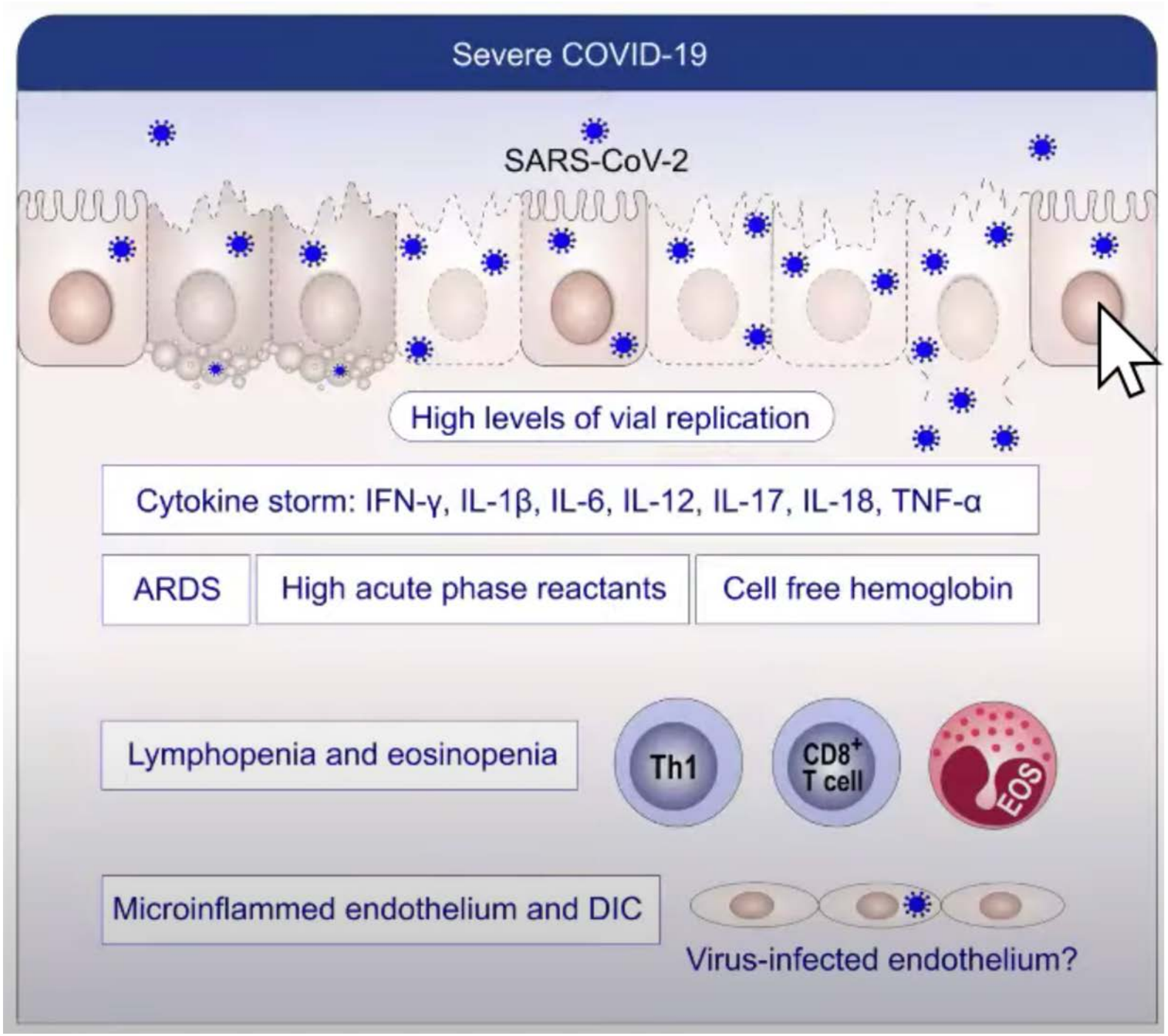


Wang et al, ACS Infect. Dis. 2016

IDEAL IMMUNE RESPONSE AGAINST SARS-Cov2 VIRUS AND THE VACCINE



Cezmi Akdiş, submitted



Cezmi Akdiş, submitted

Innate immune response

Information on:
SARS-CoV; SARS-CoV-2

Lung:

- Immune cells (macrophages, lymphocytes) can be infected, but the infection is non-productive. However, macrophages (and DCs) become more inflammatory (and M⌀ less tissue protective).
- Type I (IFNa/b) response appears impaired (preliminary data).
- IL-6, IL-8, and MCP1 were elevated in the lungs of fatal cases.

PBMCs:

- High frequency of neutrophils and low frequency of lymphocytes (mostly T and NK cells) in PBMCs of patients correlated with severe disease (similar for SARS-CoV-2).
- Elevated levels of pro-inflammatory cytokines (IL-6, IL-8, MCP1) correlated with severe disease (preliminary data). Mouse data suggest that most of the cytokines derived from innate cells. Pro-inflammatory cytokine levels were higher in ICU patients than non-ICU patients (IL-6 levels correlated with disease severity)
- SARS-CoV activates the complement pathway.

Adaptive immune response: B cells

Information on:
SARS-CoV; SARS-CoV-2

Lung:

- Presence of some anti-S-protein antibodies together with high titers of SARS-CoV can aggravate disease (via boosting pro-inflammatory macrophage responses = antibody-dependent enhancement). SARS-CoV non-survivors had early and stronger Ab-titers than survivors. However, such a situation would not occur following vaccination (high Ab-titers, but low viral-titers).

PBMCs:

- Most patients produce antibodies in 5-14 days, their amount and quality directly correlated with the severity of disease (preliminary data).
- From all structural proteins (M, E, N, S) only the S protein elicited neutralizing Abs.
- For SARS-CoV, basically all patients produced neutralizing Abs. For SARS-CoV-2, some patients the anti-S-protein antibody titers were low or even absent (?!? N=1 and disputed in the commentaries).
- After recovery from SARS-CoV, the Ab-titers (peak after approx. 2 months) decreased over time and were largely undetectable 2-3 years later.

Adaptive immune response: T cells

Information on:
SARS-CoV; SARS-CoV-2

Lung:

- Strong influx of T cells, in particular $CD8^+$ T cells (i.e. cytotoxic T cells, CTLs). Such CTLs are essential for effective clearance of virus-infected cells.

PBMCs:

- High frequency of neutrophils and low frequency of lymphocytes (mostly T and NK cells) in PBMCs of patients correlated with severe disease (similar for SARS-CoV-2). The PBMC-lymphopenia preceded lung injury (preliminary data). The T cell numbers recovered within 2-3 months ($CD8^+$ T cell) or one year ($CD4^+$ T cell).
- However, these T cells appear functionally impaired.
- After recovery from SARS-CoV, antigen-specific T cells could be measured six or even 17 years after recovery (in contrast to Abs).

Type of the immune response:

- A Th1-response (aimed usually against intracellular pathogens) is beneficial, whereas a Th2-response (aimed usually against extracellular pathogens) is often harmful. Increased Th2 responses were seen in SARS-CoV patients with fatal infection (preliminary data). A Th2-bias was seen in aged mice and monkeys, and in mice vaccinated with the whole S-protein (the latter could be avoided when using only the ACE2-binding part of the S-protein was used for the vaccination).

Treatment

Information on:
SARS-CoV; SARS-CoV-2

Passive immunization:

- Transfer of antibodies from SARS-CoV recovered patients (convalescent plasma therapy) effective for SARS-CoV and SARS-CoV-2 patients, in particular when given early. *[this also indicates that Ab-dependent enhancement is not a real issue in a natural setting]*

Corticosteroids:

- High doses of steroids delivered little benefit and might even harm; however, low doses might be beneficial (preliminary data).

IL-6 inhibitors:

- Tocilizumab (αIL-6R-Ab) appears beneficial in severe cases.

hydroxycholoroquine not effective