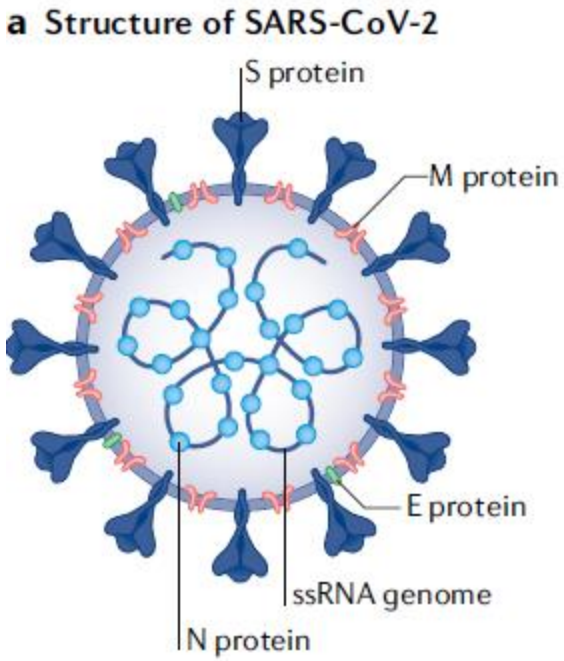
Immunopathology COVID-19 disease

Neda K. Dezfuli, PhD
Assistant professor of immunology

Dezful University of medical sciences

Interaction of virus with human



Systemic Disorders

Fever, Cough, Fatigue, Sputum Production, Headache

Haemoptysis,

Acute Cardiac Injury

Hypoxemia

Dyspnoea, Lymphopenia

Diarrhoea

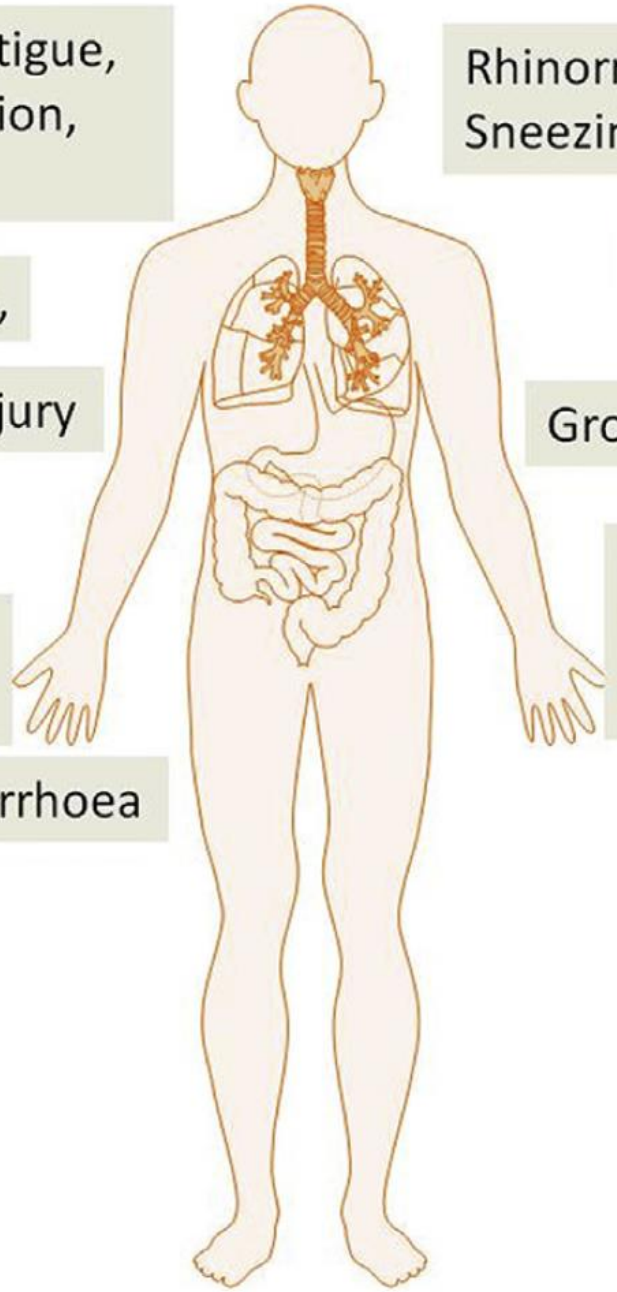
Respiratory Disorders

Rhinorrhoea, Sneezing, Sore Throat

Pneumonia

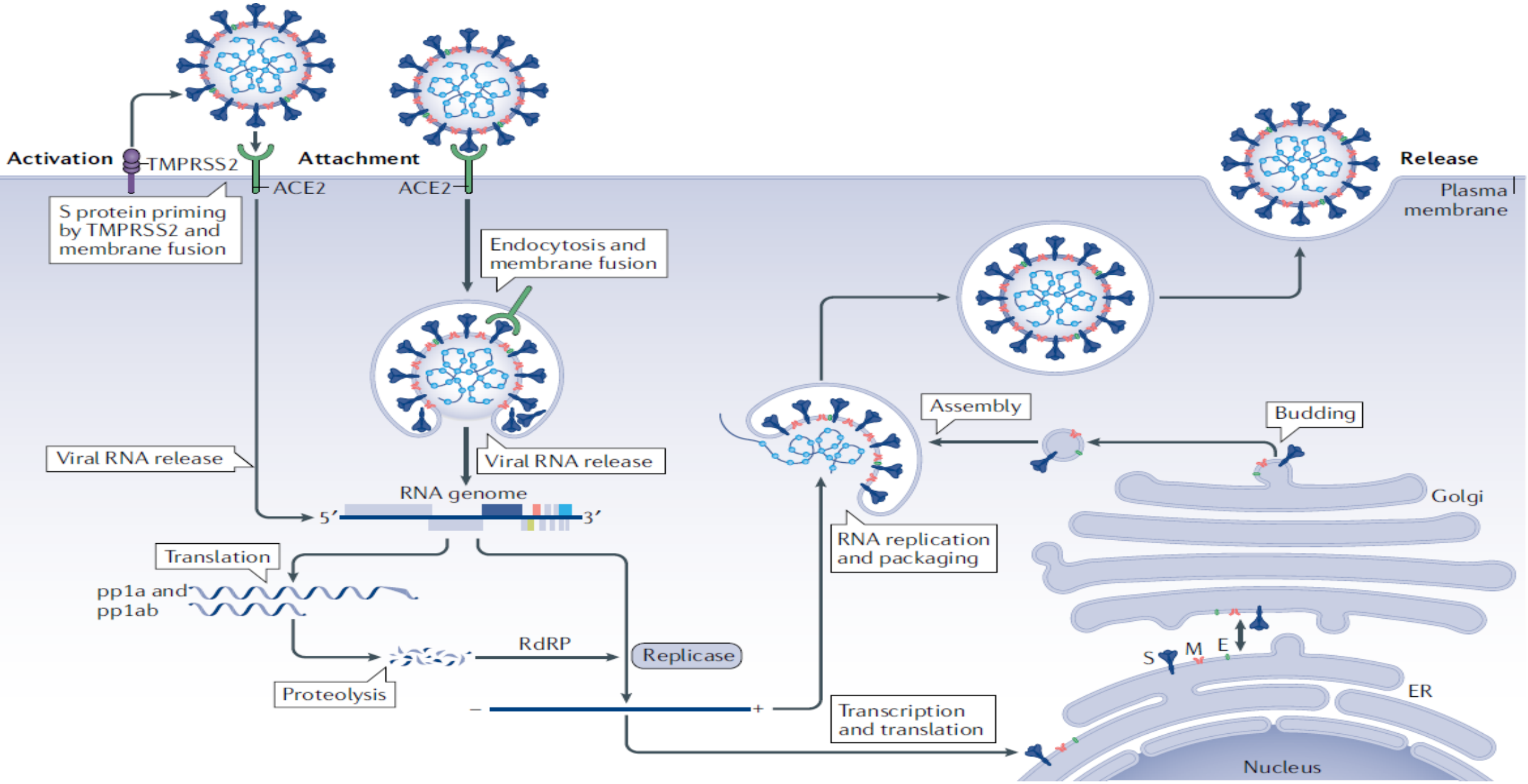
Ground-glass Opacities

RNAaemia, Acute Respiratory Distress Syndrome

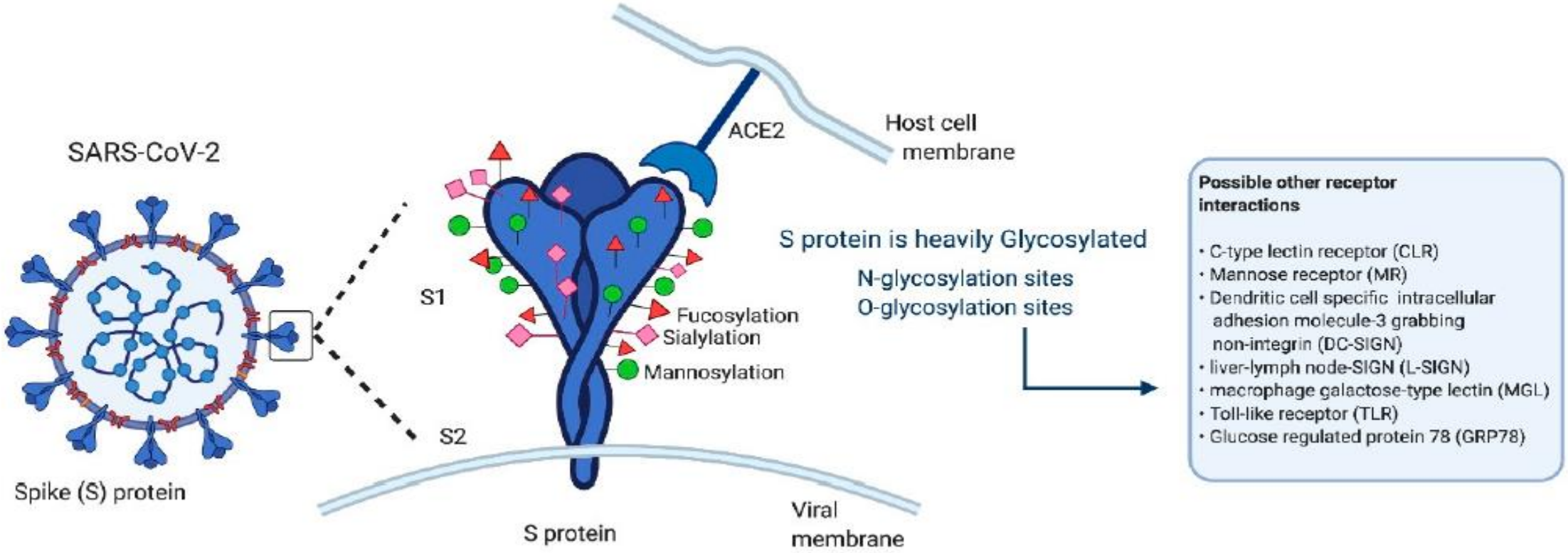


The scientific consensus is that COVID-19 has a natural origin

How virus invades the host cells



Spike protein and important candidates receptor



International Journal of *Molecular Sciences*

MDPI

Review

Can SARS-CoV-2 Virus Use Multiple Receptors to Enter Host Cells?

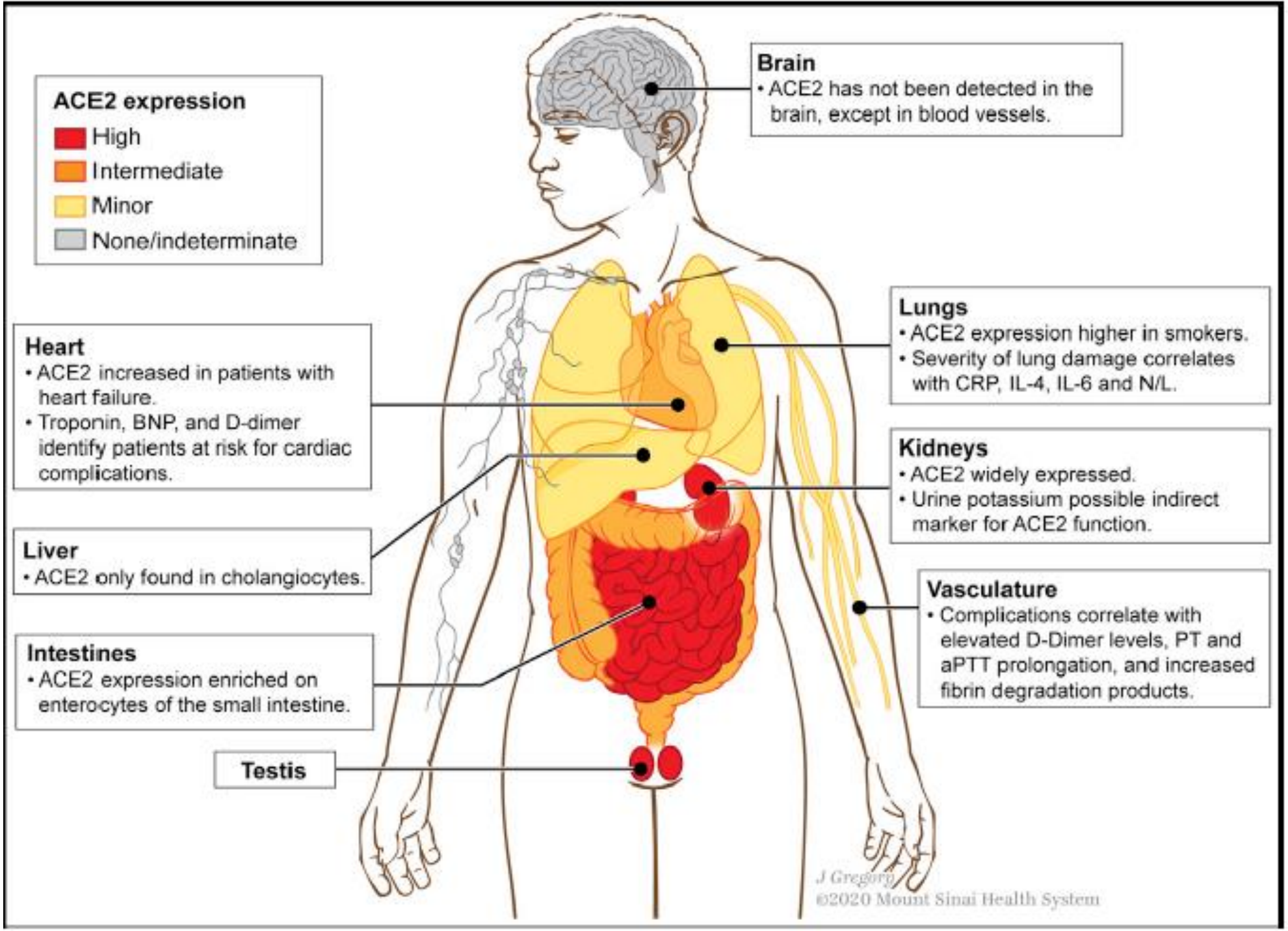
Laura Kate Gadanec, Kristen Renee McSweeney, Tawar Qaradakhi, Benazir Ali, Anthony Zulli *,† and Vasso Apostolopoulos *,†

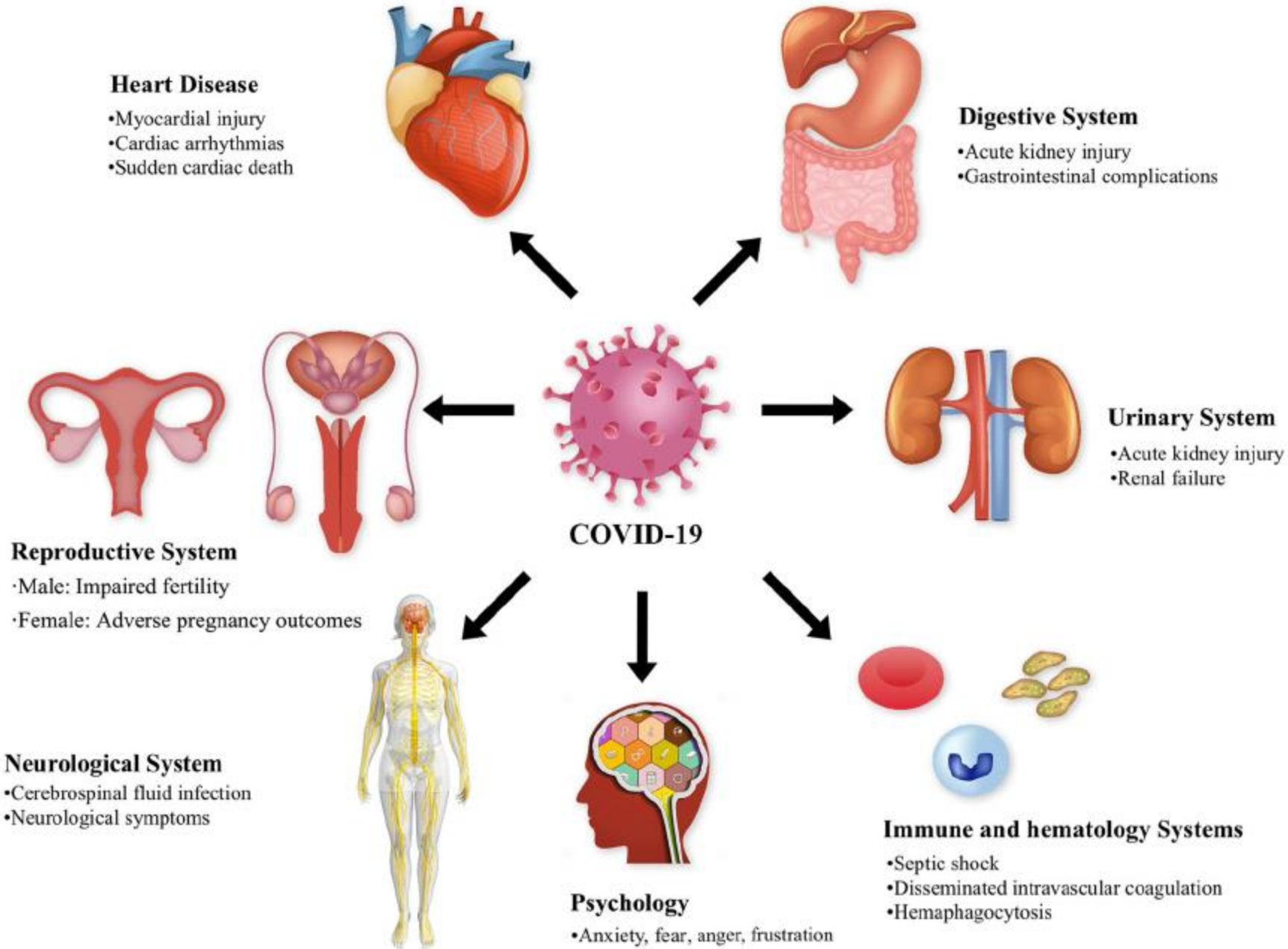
Transmission

- ✓Small droplets and aerosols, which can spread as an infected person.
- ✓Breathes, coughs, sneezes, speaks.
- ✓Contaminated surfaces and direct contact.
- ✓It can spread as early as two days before infected persons show symptoms (presymptomatic), and from asymptomatic individuals.
- ✓The incubation period is typically around five days but may range from one to 14 days
- ✓People remain infectious for up to ten days in moderate cases, and two weeks in severe cases.

Receptors for Virus

- ACE2

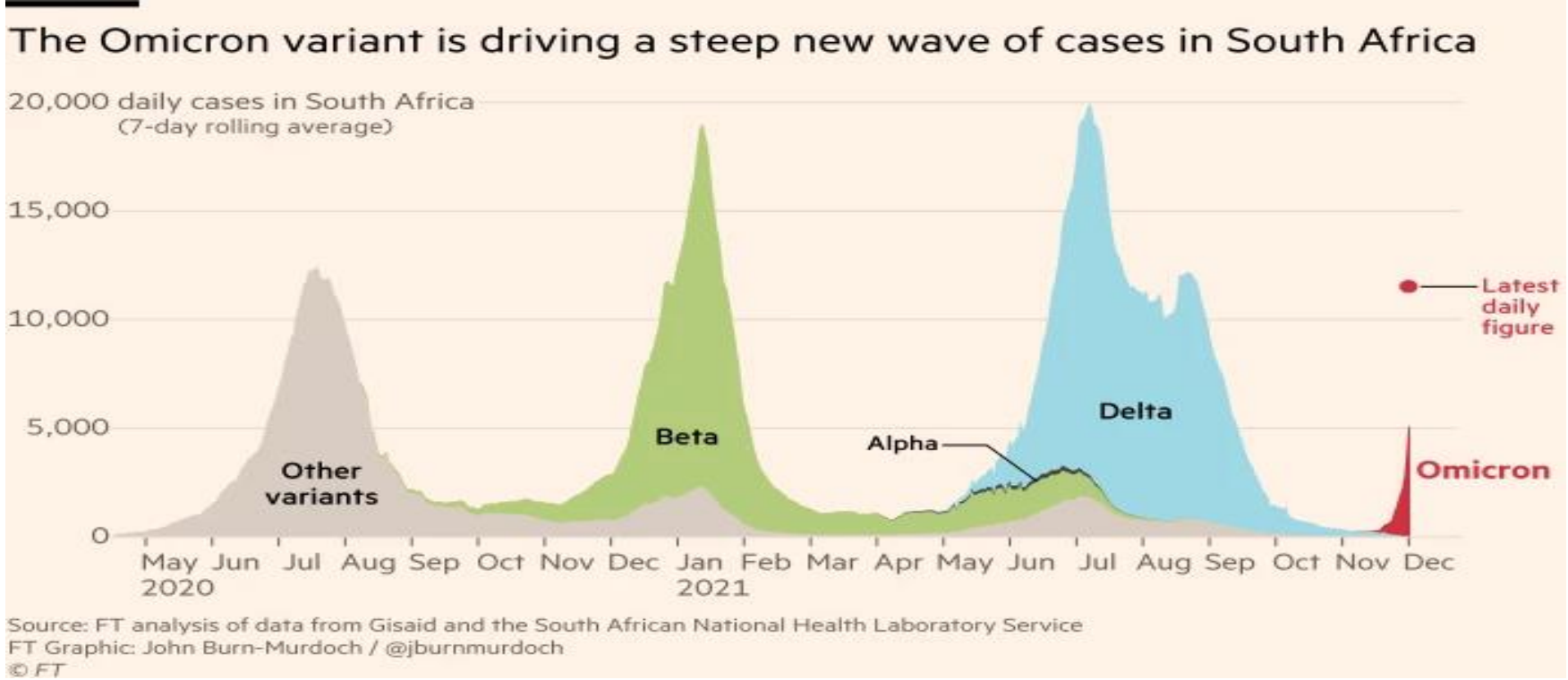



Heart Disease
•Myocardial injury
•Cardiac arrhythmias
•Sudden cardiac death
Digestive System
•Acute kidney injury
•Gastrointestinal complications
Urinary System
•Acute kidney injury
•Renal failure
COVID-19
Reproductive System
·Male: Impaired fertility
·Female: Adverse pregnancy outcomes
Neurological System
•Cerebrospinal fluid infection
•Neurological symptoms
Psychology
•Anxiety, fear, anger, frustration
Immune and hematology Systems
•Septic shock
•Disseminated intravascular coagulation
•Hemaphagocytosis

Variants of SARS-CoV-2

- "variant of concern" (VOC) for SARS-CoV-2 refers to viral variants with mutations in their RBD that dramatically improve binding affinity in the RBD-hACE2 complex while also causing fast dissemination in human populations.

- Increased viral replication increases the likelihood of SARS-CoV-2 mutations forming.



New names proposed for Covid variants

Country/region	Scientific name	WHO name
Kent, UK	B.1.1.7	Alpha
South Africa	B.1.351	Beta
Brazil	P.1	Gamma
India	B.1.617.2	Delta

Source: WHO

BBC

WHO renames SARS-CoV-2 variants

From alpha to lambda

Variants of concern

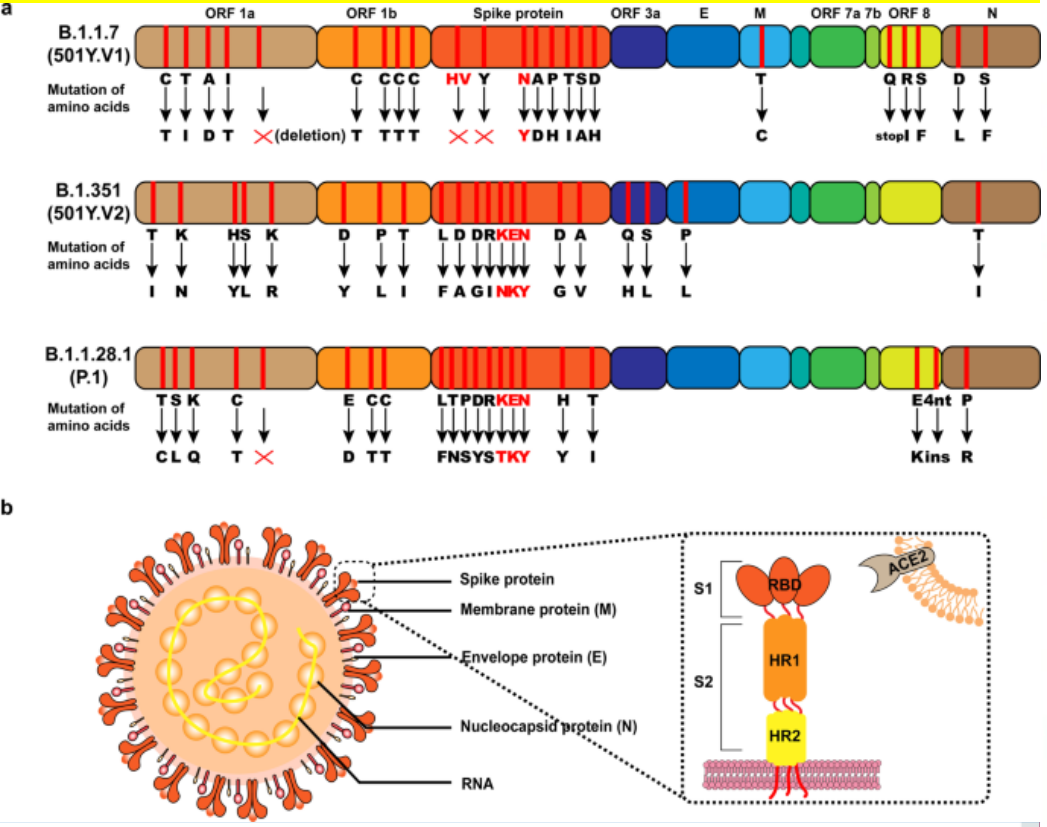
WHO label		Lineage	First documented samples
α	Alpha	B.1.1.7	UK Sep. 2020
β	Beta	B.1.351	South Africa May 2020
γ	Gamma	P.1	Brazil Nov. 2020
δ	Delta	B.1.617.2	India Oct. 2020

Variants of interest

ε	Epsilon	B.1.427/ B.1.429	USA Mar. 2020
ζ	Zeta	P.2	Brazil Apr. 2020
η	Eta	B.1.525	*Multiple* Dec. 2020
θ	Theta	P.3	Philippines Jan. 2021
ι	Iota	B.1.526	USA Nov. 2020
κ	Kappa	B.1.617.1	India Oct. 2020
λ	Lambda	C.37	Peru Aug. 2020

DW Source: WHO

Variants and mutations

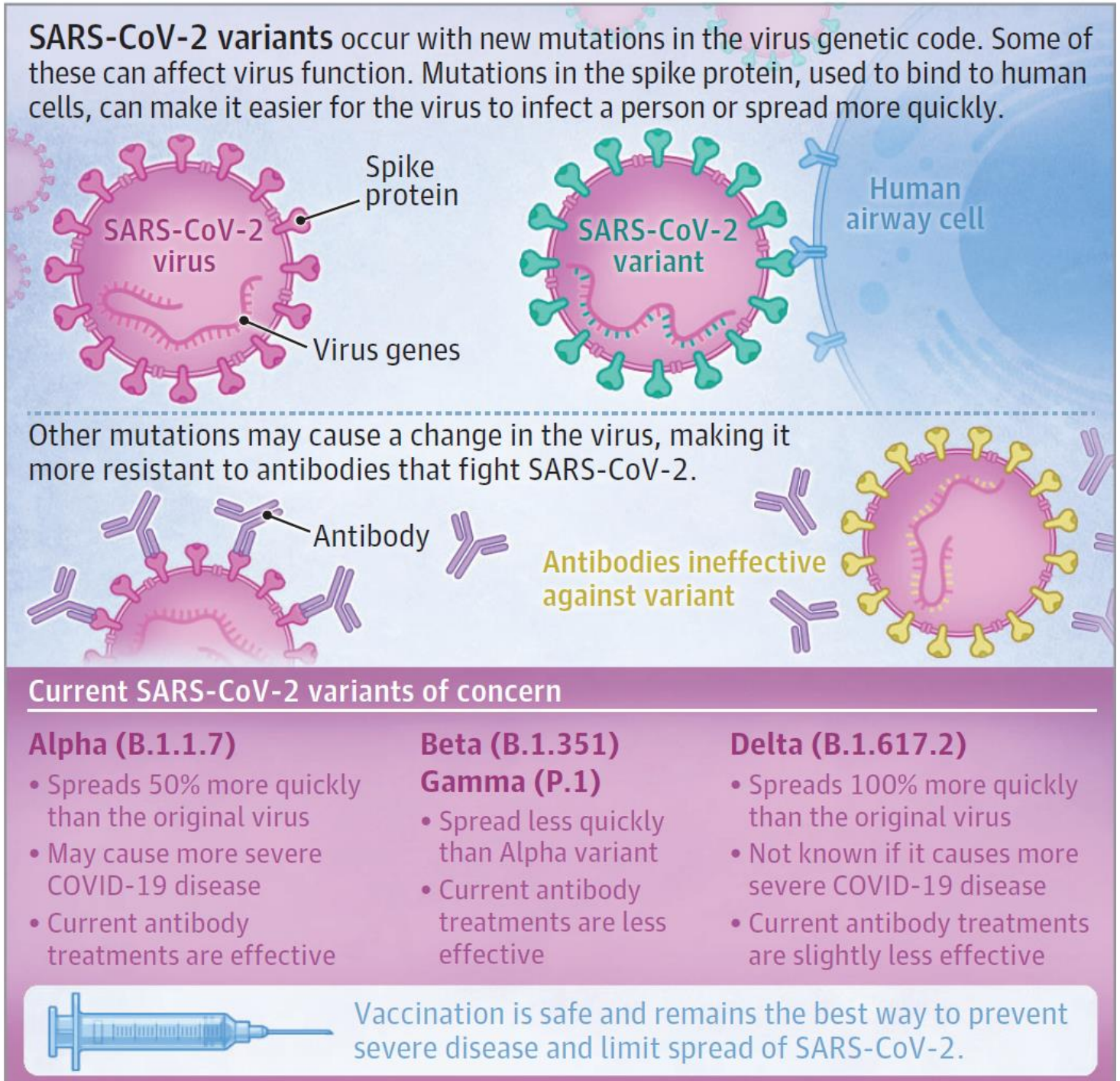


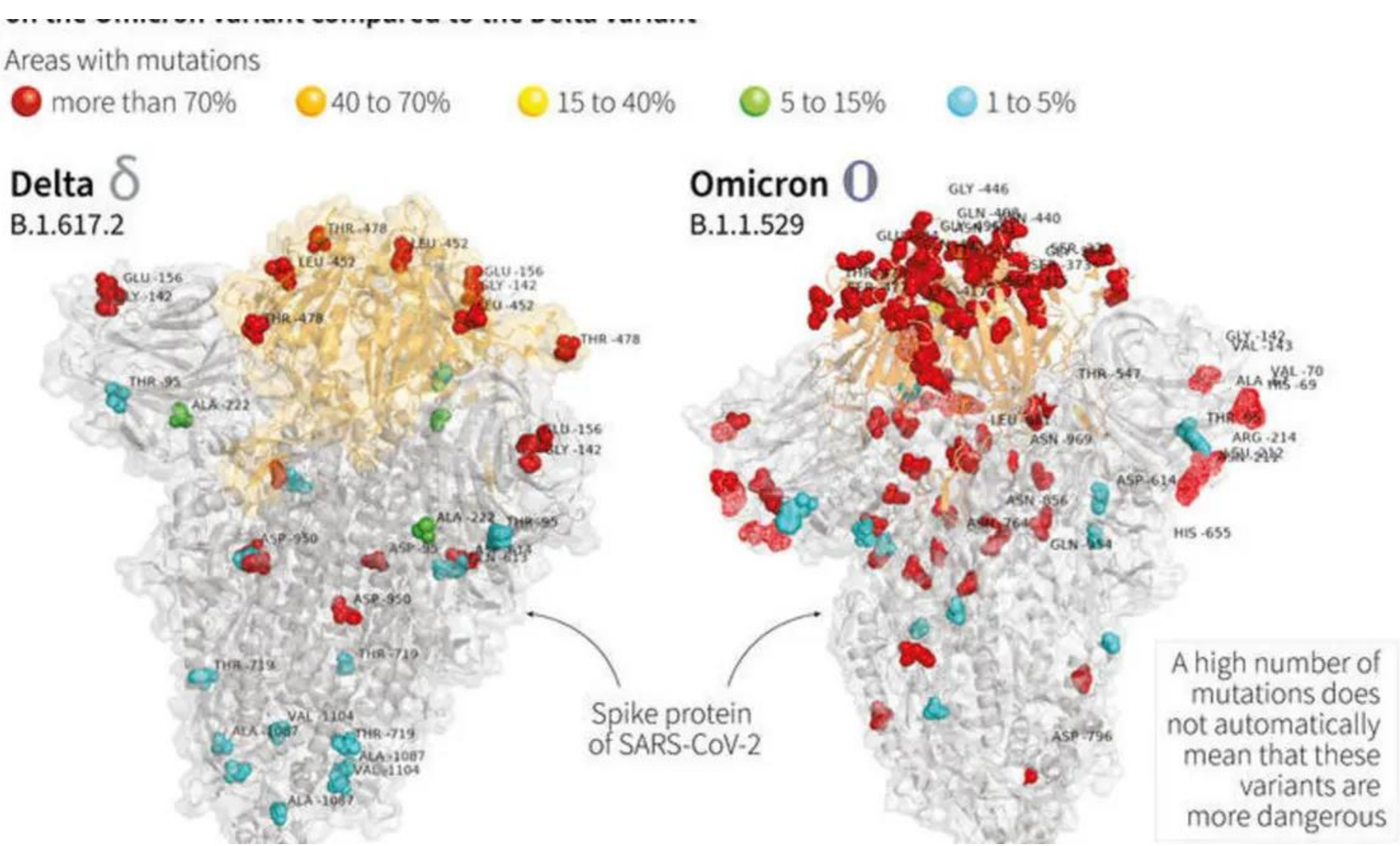
REVIEWS

Check for updates

SARS-CoV-2 variants, spike mutations and immune escape

William T. Harvey[1,2,8], Alessandro M. Carabelli[3,8], Ben Jackson[4], Ravindra K. Gupta[5], Emma C. Thomson[6,7], Ewan M. Harrison[3,7], Catherine Ludden[3], Richard Reeve[1], Andrew Rambaut[4], COVID-19 Genomics UK (COG-UK) Consortium, Sharon J. Peacock[3] and David L. Robertson[2]✉*




Areas with mutations
more than 70%
40 to 70%
15 to 40%
5 to 15%
1 to 5%
Delta δ
B.1.617.2
Omicron O
B.1.1.529
Spike protein of SARS-CoV-2
A high number of mutations does not automatically mean that these variants are more dangerous

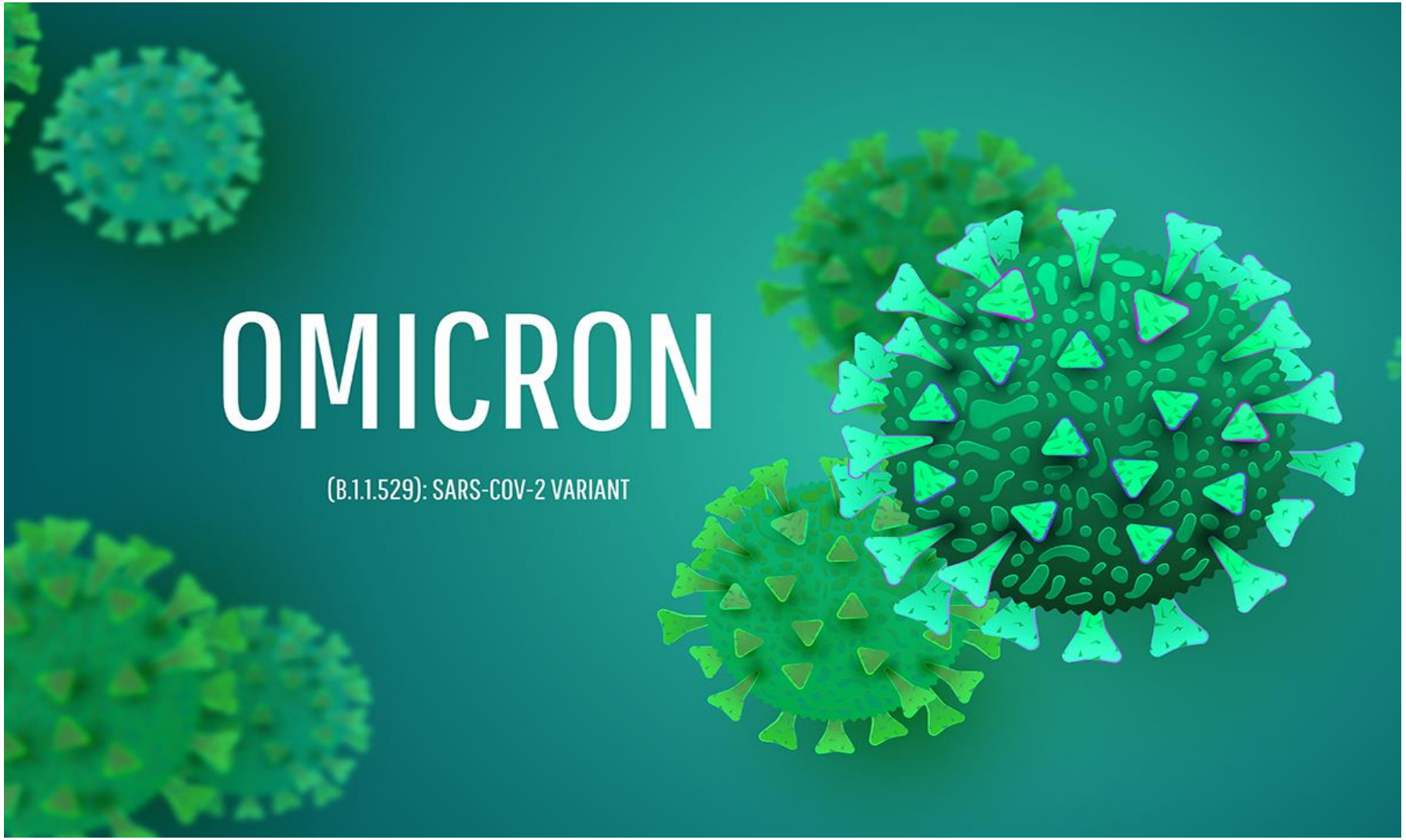
Delta Variant

- The Delta variant (B.1.617.2) was discovered for the first time in India in late 2020. The Delta version may have invaded over 163 nations by August 24, 2021.

- The World Health Organization stated in June 2021 that the Delta strain is on its way to becoming the most prevalent strain in the world.

- Therefore, the Delta variant was changed from Variant of Interest (VOI) to VOC. According to present evidence, the SARS-CoV-2 Delta VOC is 40%–60% more transmissible than the Alpha (B.1.1.7) VOC and may be associated with an increased risk of hospitalization. The Delta VOC mostly endangers those who are unvaccinated or just partially vaccinated.

SARS-CoV-2 Variants and immune response



Omicron

- On November 26, 2021, the WHO Technical Advisory Group on Virus Evolution (TAG-VE) proposed that variant B.1.1.529, commonly known as Omicron, be identified as a VOC.

- The TAG-VE made this decision after discovering that Omicron has several mutations that might impact how quickly it spreads or the severity of the disease it causes.

Omicron

- Computational studies to examine the Delta and Omicron variants shows Omicron variant had a higher affinity for ACE2 than the Delta variant due to a significant number of mutations in the SARS-CoV-2 RBD, indicating a higher potential for transmission.

- In comparison to the Delta variant, both the entire spike protein and the RBD in Omicron include a high proportion of hydrophobic amino acids such as leucine and phenylalanine.

Omicron

- The Omicron variation includes 30 mutations in the Spike protein, half of which are in the RBD, according to the multiple alignments .

- T478 loop in RBD is a common mutation seen in Delta and Omicron variants .

- RBD has the potential to be developed into an efficient and safe subunit vaccine against SARS-CoV-2 due to its ability to produce very robust neutralizing Ab responses.

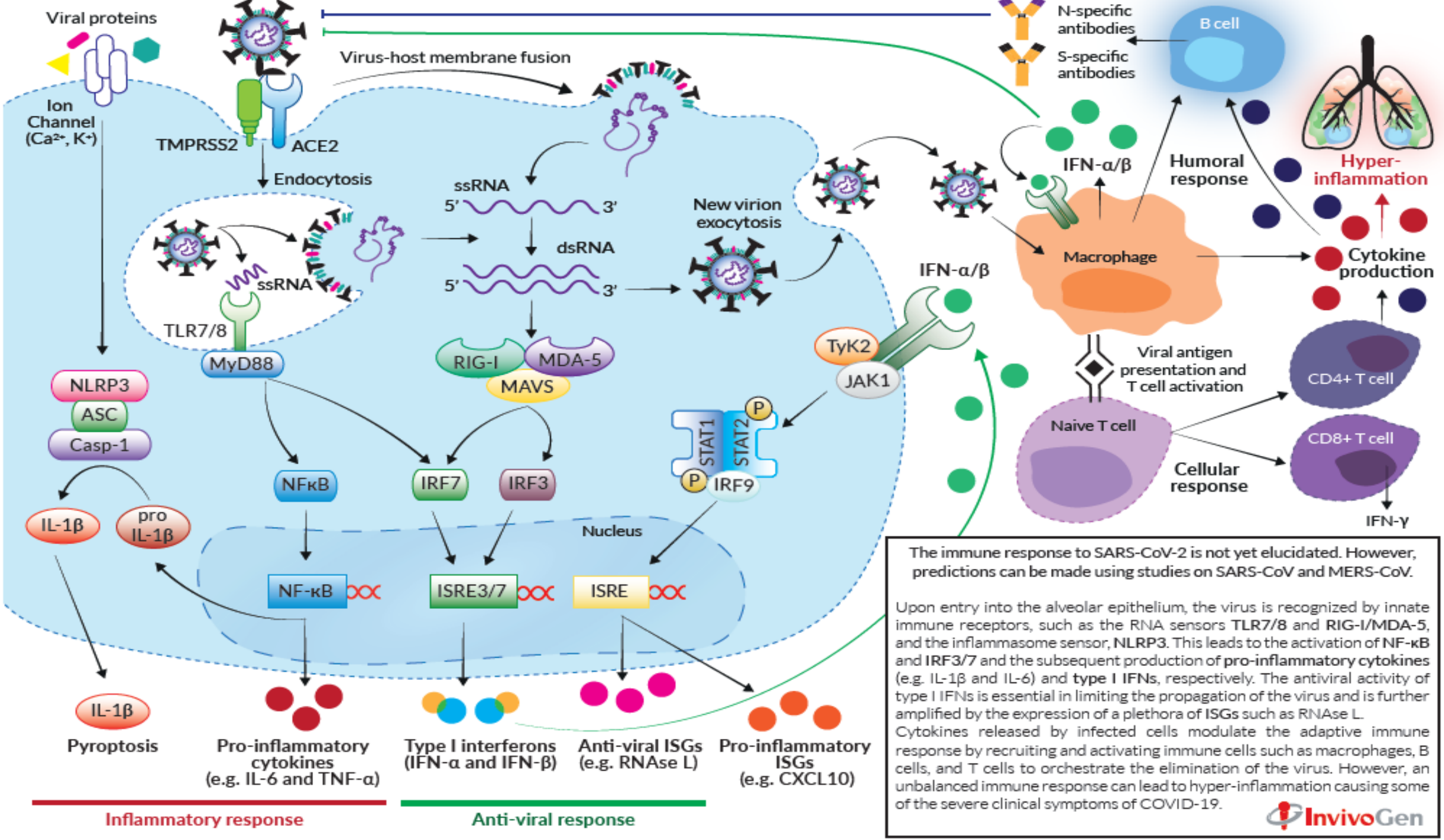
Why Omicron Is Putting More Kids in the Hospital

- Experts believe the jump in pediatric hospitalizations is likely the result of a confluence of factors.

- One of them is Omicron's more contagious nature, and another may be the variant's newfound preference for airway passages above the lungs, which can be more easily blocked in small children.

Immune response against the virus

- Innate immune response
- Cell mediated response
- Humoral response

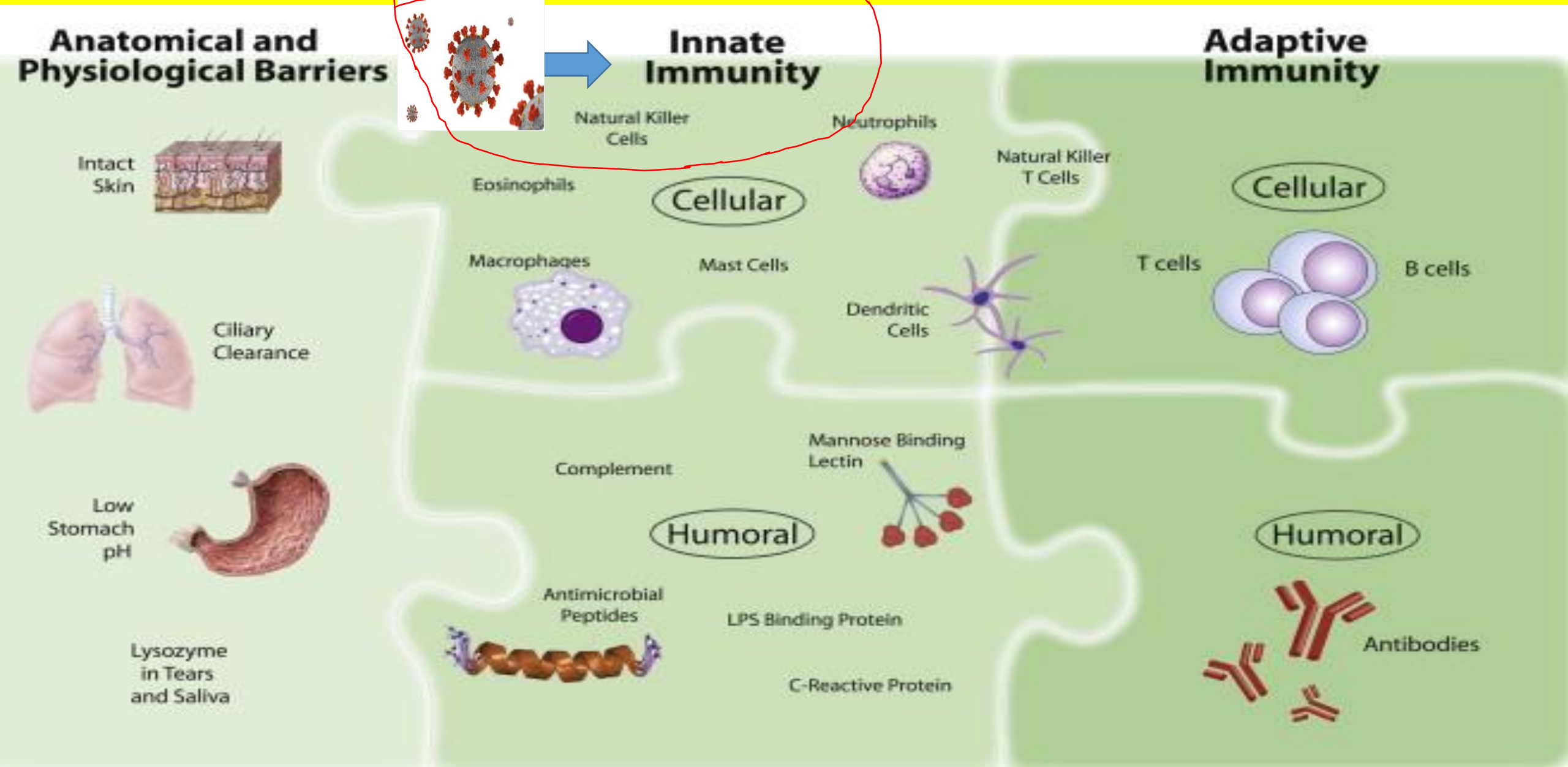


The immune response to SARS-CoV-2 is not yet elucidated. However, predictions can be made using studies on SARS-CoV and MERS-CoV.

Upon entry into the alveolar epithelium, the virus is recognized by innate immune receptors, such as the RNA sensors **TLR7/8** and **RIG-I/MDA-5**, and the inflammasome sensor, **NLRP3**. This leads to the activation of **NF-κB** and **IRF3/7** and the subsequent production of **pro-inflammatory cytokines** (e.g. IL-1β and IL-6) and **type I IFNs**, respectively. The antiviral activity of type I IFNs is essential in limiting the propagation of the virus and is further amplified by the expression of a plethora of **ISGs** such as RNAse L.
Cytokines released by infected cells modulate the adaptive immune response by recruiting and activating immune cells such as macrophages, B cells, and T cells to orchestrate the elimination of the virus. However, an unbalanced immune response can lead to hyper-inflammation causing some of the severe clinical symptoms of COVID-19.

InvivoGen

Innate Immunity



Role of Neutrophils in pathogenesis of COVID-19

Neutrophils

- Neutrophils play a crucial role in the first line of cell-mediated defense against microbes.
- They phagocytose bacteria and clear them by fusion with their cytoplasmic granules containing proteases, defensins, antimicrobial peptides or reactive oxygen species (ROS). Additionally, they can form neutrophil extracellular traps (NETs), in which parts of the nucleus together with granules are actively released.
- Neutrophils and activated platelets can elicit a process termed immunothrombosis in blood vessels where they contribute to the formation of a fibrin mesh that can trap pathogens.
- HIF-1α is expressed at low levels in circulating neutrophils, but upregulated in hypoxic conditions of inflamed tissue.
- HIF pathway:

✓ Increase the expression of antimicrobial peptides and promote degranulation

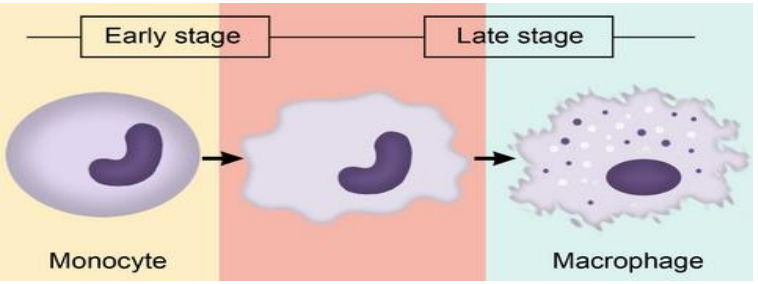
✓ Inhibits apoptosis of neutrophils prolonging their life time in inflamed tissue

- Upon SARS-CoV-2 infection, elevated numbers of neutrophils have been observed in the nasopharyngeal epithelium and later in the more distal parts of the lung .

- Plasma levels of some mediators such as RETN, HGF, and LCN2, typically produced by neutrophils, were recently proposed as predictive for critical illness and mortality.

Role of MQ in pathogenesis of COVID-19

Role of macrophages in pathogenesis of COVID-19



Alveolar macrophages, which reside in proximity to type I and type II epithelial alveolar cells

Interstitial macrophages, which are preferentially abundant between the microvascularendothelium and alveolar epithelium zone

Both macrophages divided into two functional phenotypes.

M1: Which are activated by PAMPs that are also expressed by viruses. Their activity is then promoted by Th1 cells, and induce recruitment of immune cells into the lung parenchyma.

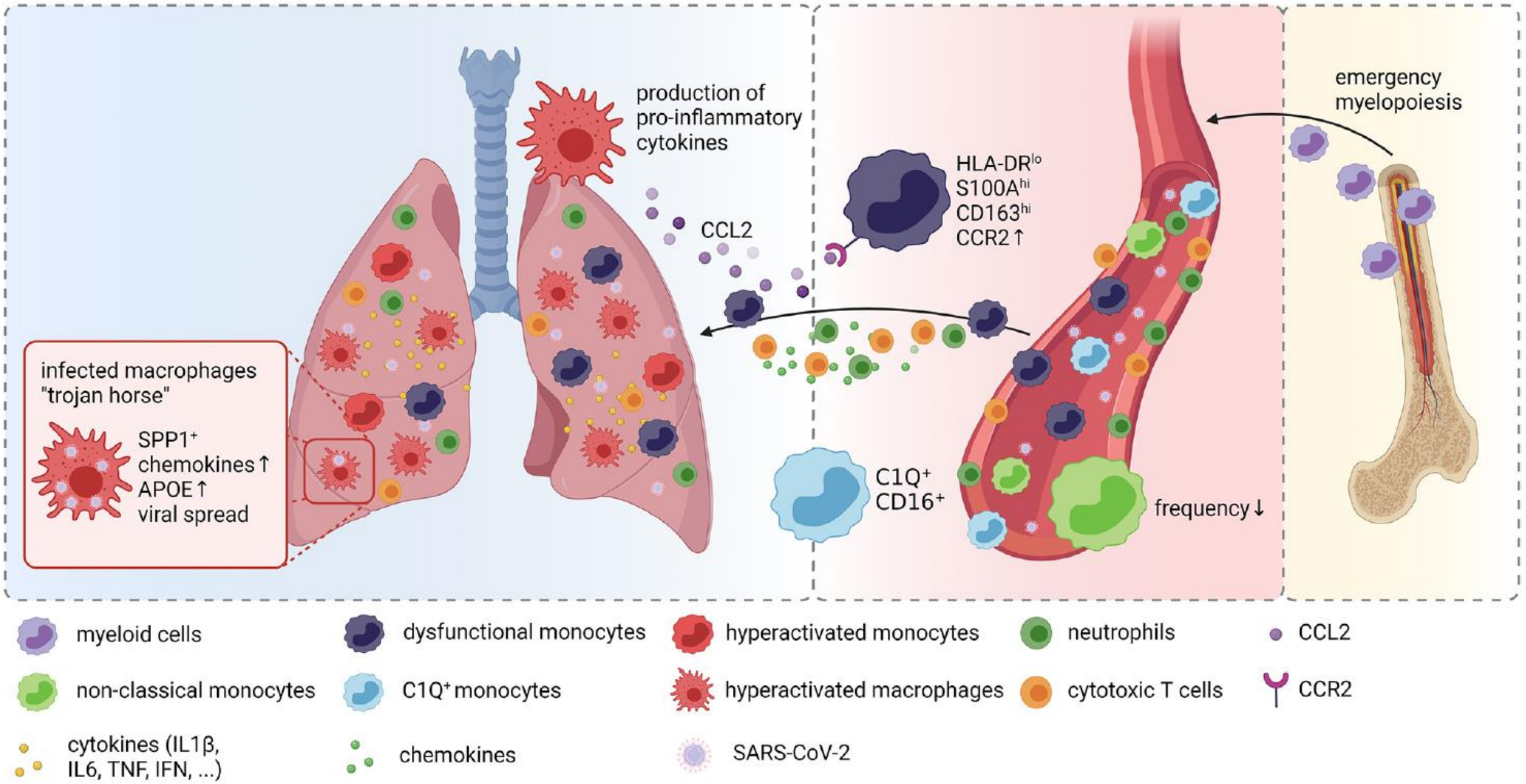
M2: The second population includes the alternatively activated macrophages which are activated by Th2 cells by means of IL-4 and IL-13 and activation of M2 macrophages triggers the release of anti-inflammatory cytokines, which restrict inflammation and promote tissue repair

- Human monocyte-derived DC and macrophages shows both cell are permissive to SARS-CoV-2 but did not support productive viral replication.

- Peripheral blood reported reduced percentages of total monocytes in the blood of severe COVID-19 cases.

- Reduced HLA-DR and CD86 expression together with elevated levels of IL-1β, IL-6, IL-8, IL-10, IL-17 and IFN-γ were observed in children with multisystem inflammatory syndrome associated with SARS-CoV-2 infection

Monocytes and macrophages in COVID-19

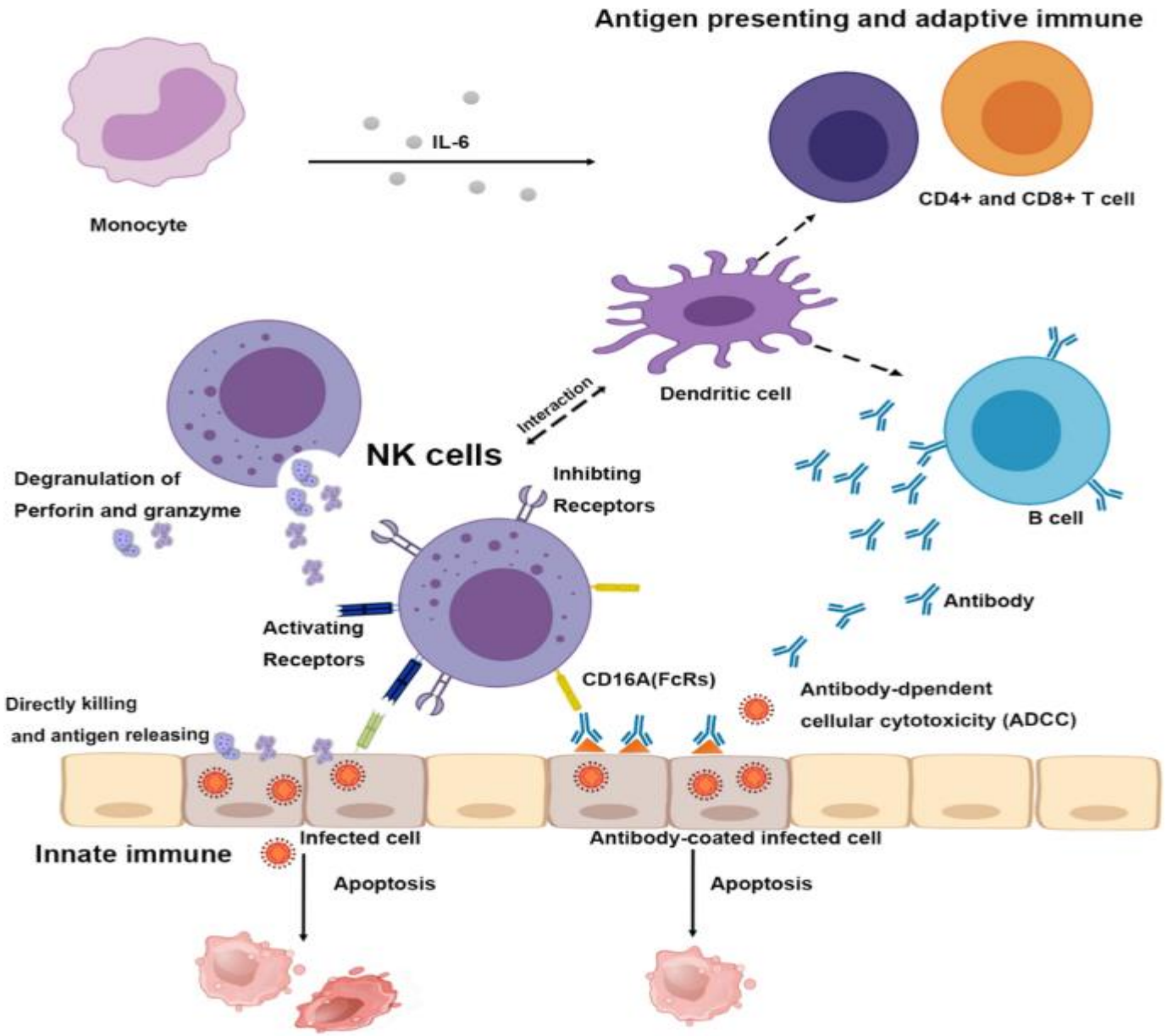


Natural Killer cells and SARS-COV-2

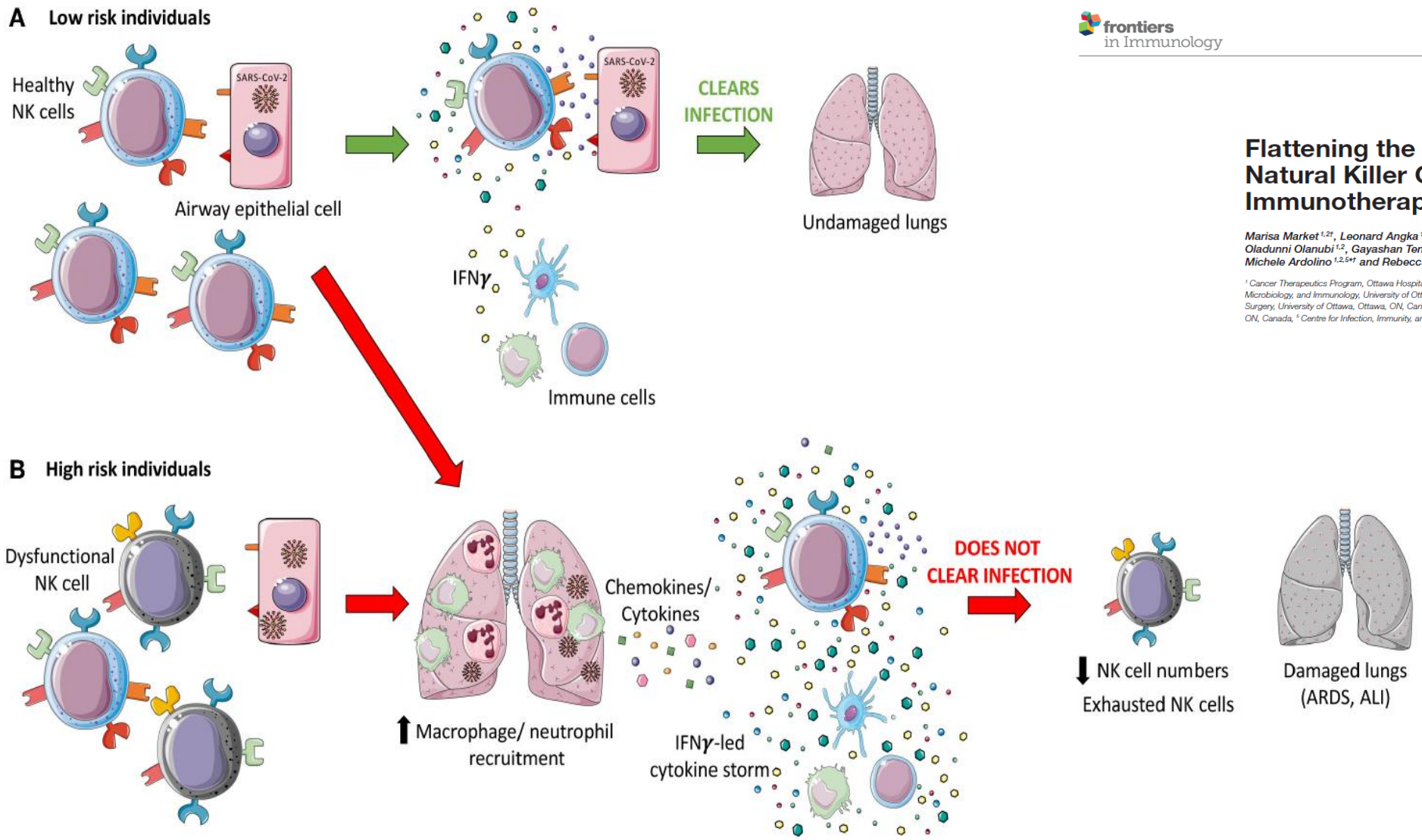
NK cells and Viral infection

- NK cells can eliminate virus-infected cells via CD16-mediated antibody-dependent cell-mediated cytotoxicity (ADCC).
- NK cells are not thought to have permanent tissue residency but instead move dynamically between the blood and tissues, such as the lungs.
- With age, patients with deficiency of NK cells, obesity and cancer linked to increased COVID-19 severity due to the decreased number or un-functionality of NK cells.

NK cells and SARS-CoV-2



Hypothesized dual role of NK cells during COVs infections



frontiers in Immunology
REVIEW
published: 23 June 2020
doi: 10.3389/fimmu.2020.01512

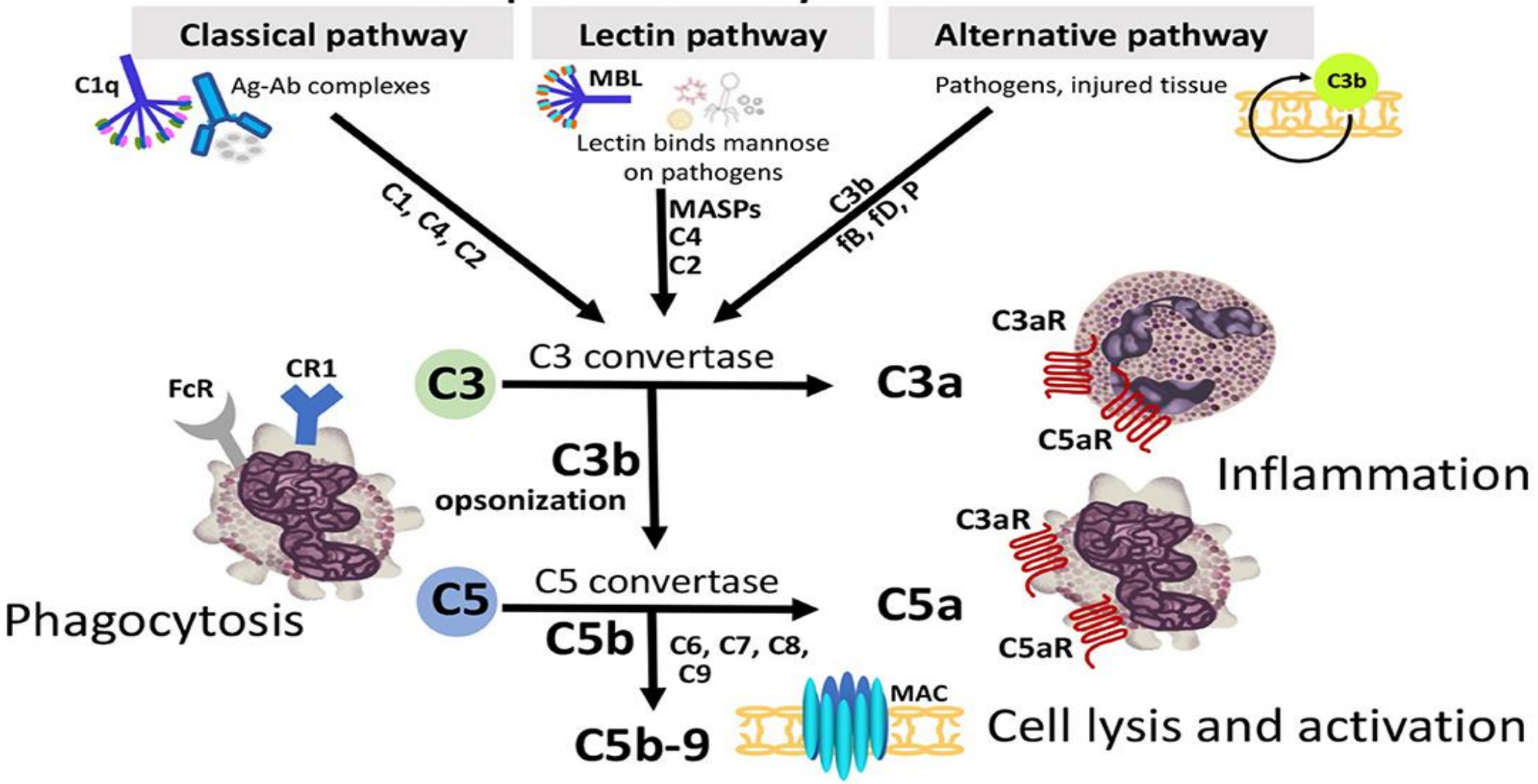
Flattening the COVID-19 Curve With Natural Killer Cell Based Immunotherapies

Marisa Market[1,2†], Leonard Angka[1,2†], Andre B. Martel[1,2,3], Donald Bastin[4], Oladunni Olanubi[1,2], Gayashan Tennakoon[1], Dominique M. Boucher[2], Juliana Ng[1], Michele Ardolino[1,2,5†] and Rebecca C. Auer[1,2,3*†]*

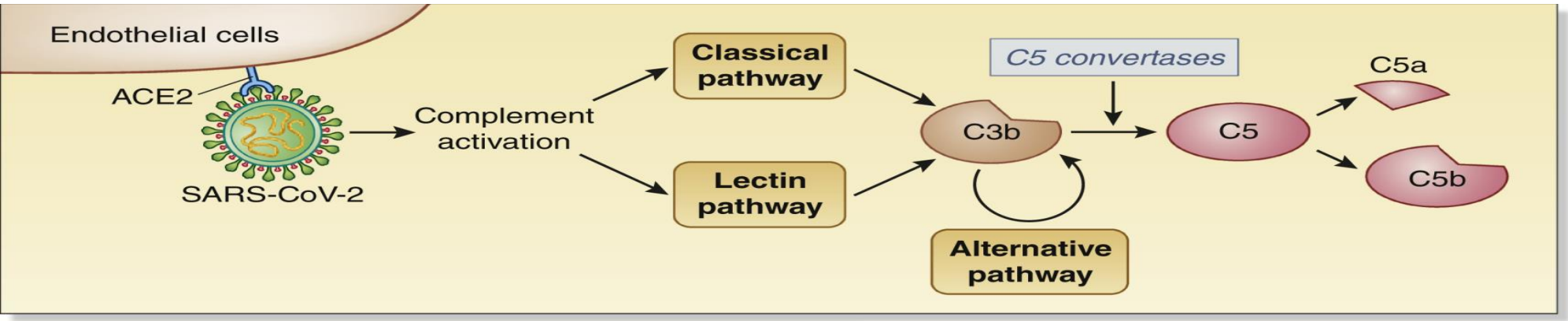
[1] Cancer Therapeutics Program, Ottawa Hospital Research Institute, Ottawa, ON, Canada, [2] Department of Biochemistry, Microbiology, and Immunology, University of Ottawa, Ottawa, ON, Canada, [3] Division of General Surgery, Department of Surgery, University of Ottawa, Ottawa, ON, Canada, [4] Schulich School of Medicine, University of Western Ontario, London, ON, Canada, [5] Centre for Infection, Immunity, and Inflammation, University of Ottawa, Ottawa, ON, Canada

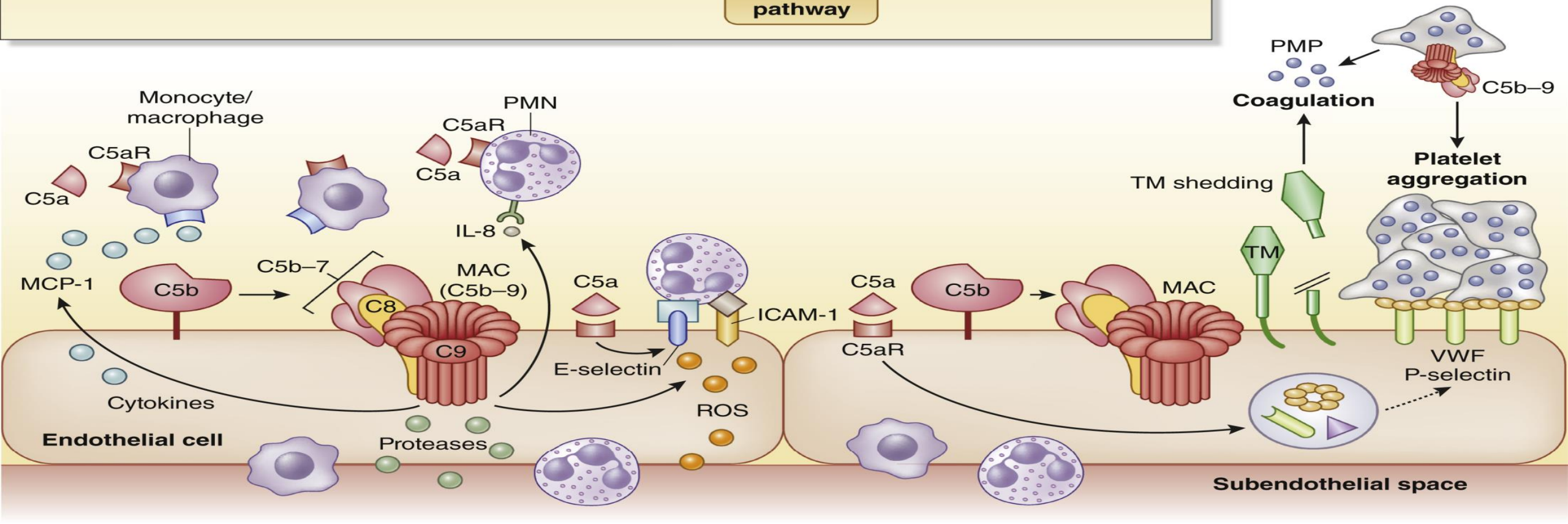
Complement and COVID-19

Complement System

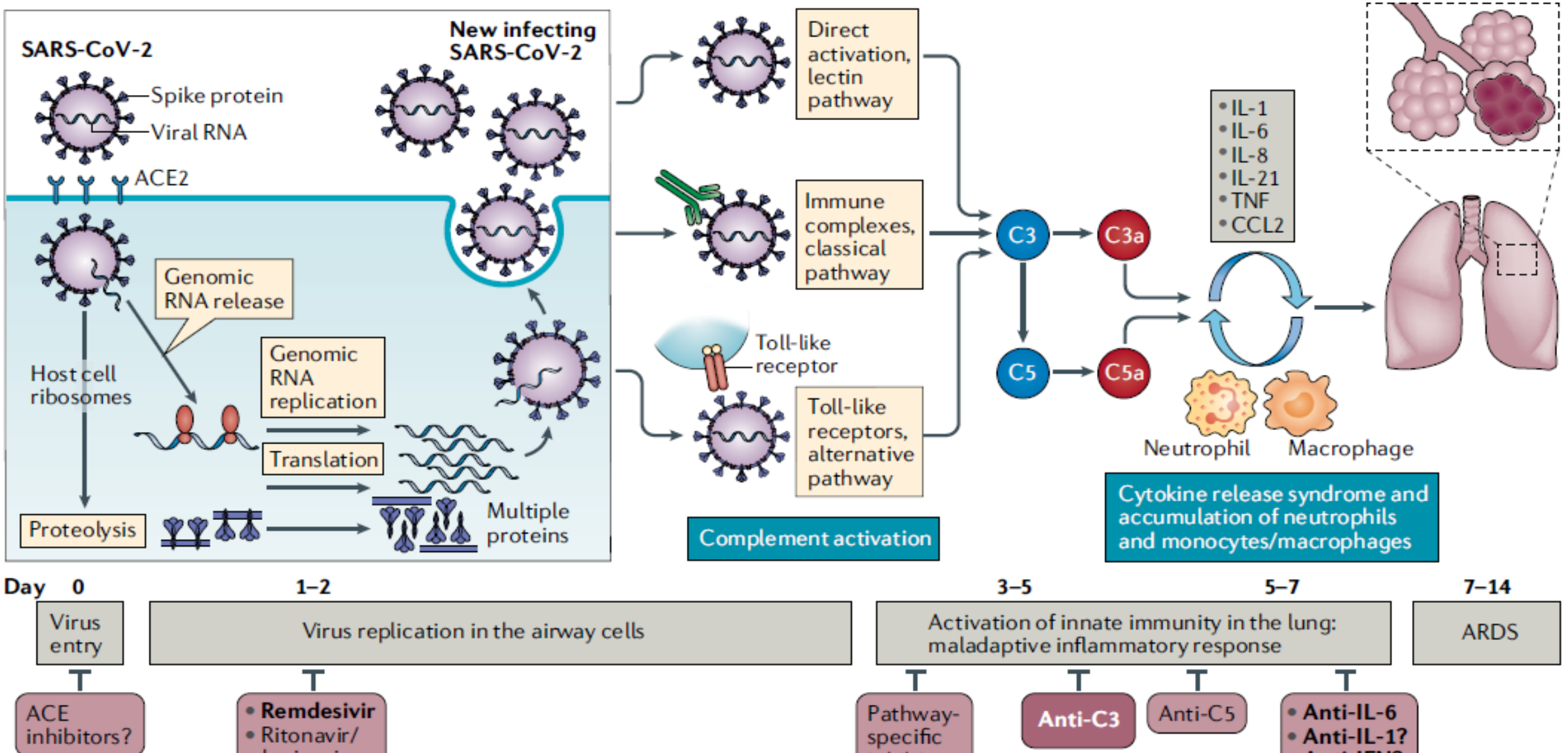


Complement system and SARS-CoV-2



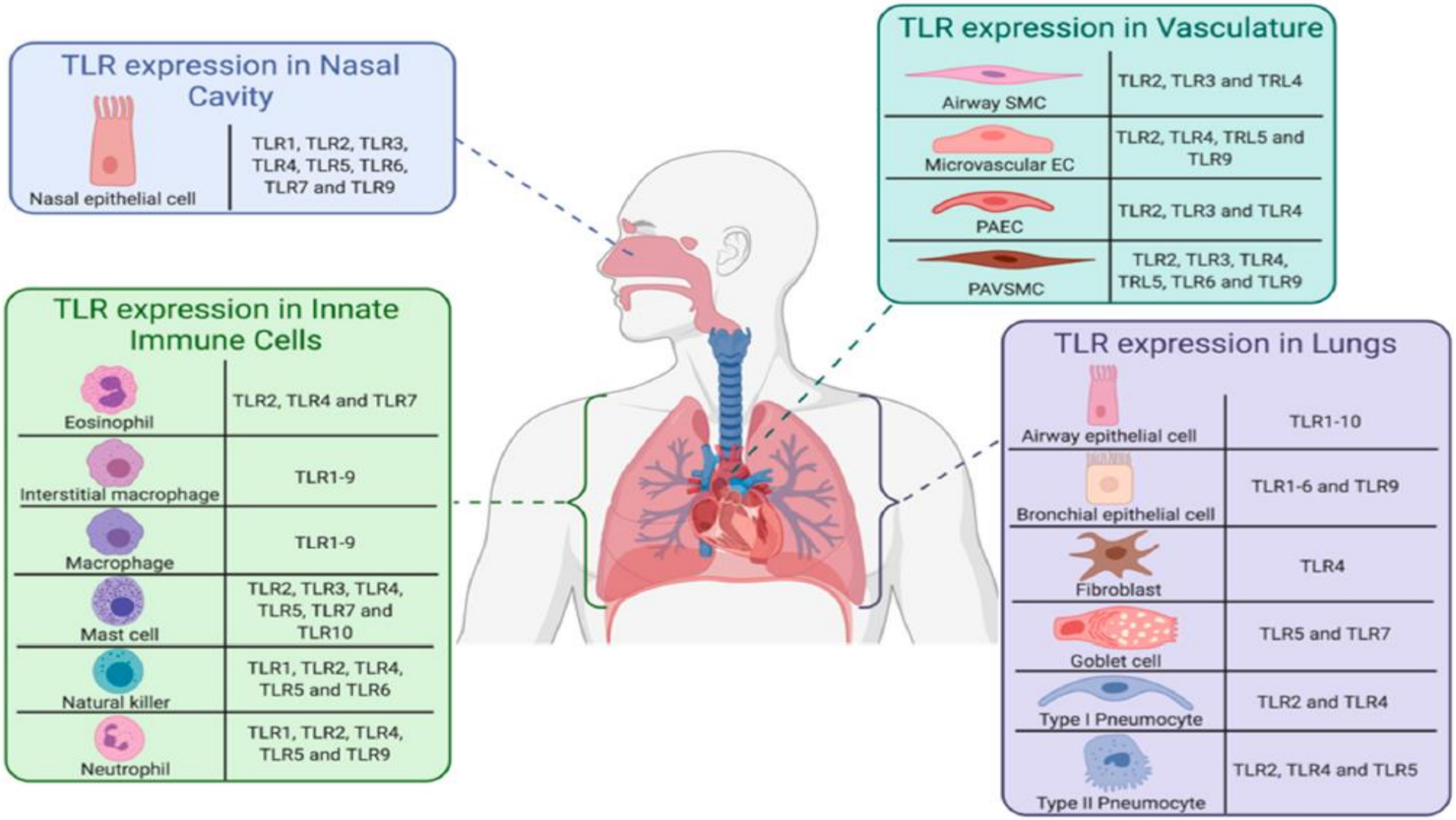


Complement and SARS-CoV-2



Role of TLRs in the pathogenesis of COVID-19

TLRs on different innate immune cells



Involvement of TLRs with SARS-CoV-2 (1)

- TLR1/2/6 activation and subsequent signal transduction may be in part responsible for clinical immunopathological manifestations experienced by patients infected with COVID-19.
- TLR-binding efficacy of S protein by direct binding of S protein of SARS-CoV2 to TLR1 and 6 has been shown.
- Direct engagement between TLR3 and the S protein of SARS-CoV-2 has yet to be established.

Involvement of TLRs with SARS-CoV-2 (2)

- Uncontrolled TLR4-mediated inflammation has been suggested to contribute to immunopathological consequences in COVID-19 patients.

- PBMC of patients have increased expression of TLR4 and its downstream signaling adapter molecules

- Elevated levels of circulating TLR4 DAMPs in patients may be responsible for the feed-forward loop of the persistent inflammation, resulting in cytokine storm,

Involvement of TLRs with SARS-CoV-2 (3)

- The ability of TLR7/8 to reduce replication of viruses has been demonstrated in HIV-1, influenza, and MERS-CoV, as upon entry into the cell viral ssRNA binds to TLR7/8 promoting activation and antiviral immunity.

- Activation of TLR7 and TLR8 induces the recruitment of the adaptor molecule MyD88, resulting in the release of pro-inflammatory cytokines and chemokines , and type I (IFN alpha and IFN-beta) and III IFNs (IFN-lambda) , which have been shown to aid in viral clearance and reduced replication.

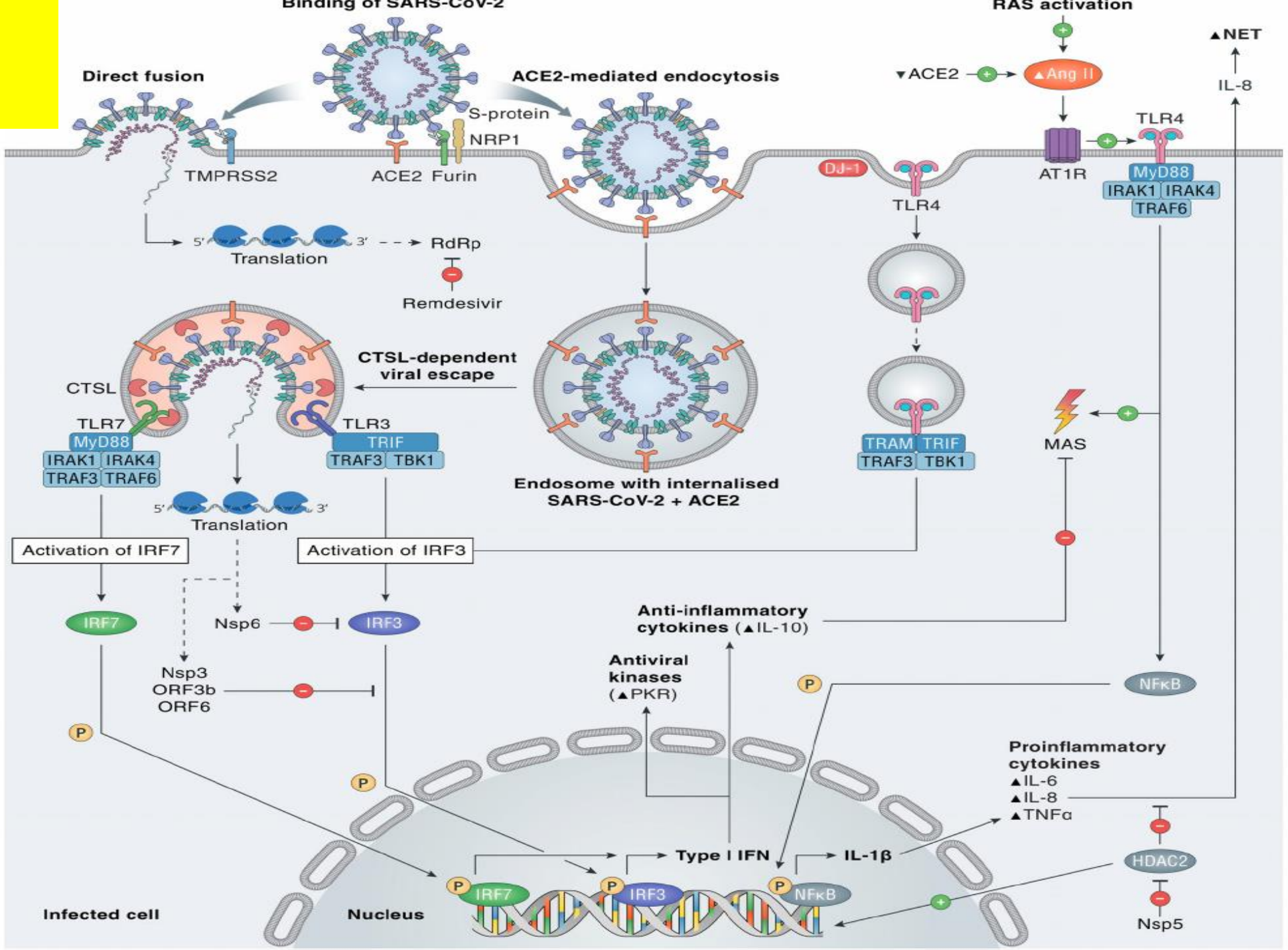
Role of TLRs receptors in recognitions of SARS-CoV-2 compartments

INVITED REVIEW

COVID-19: immunopathology, pathophysiological mechanisms, and treatment options

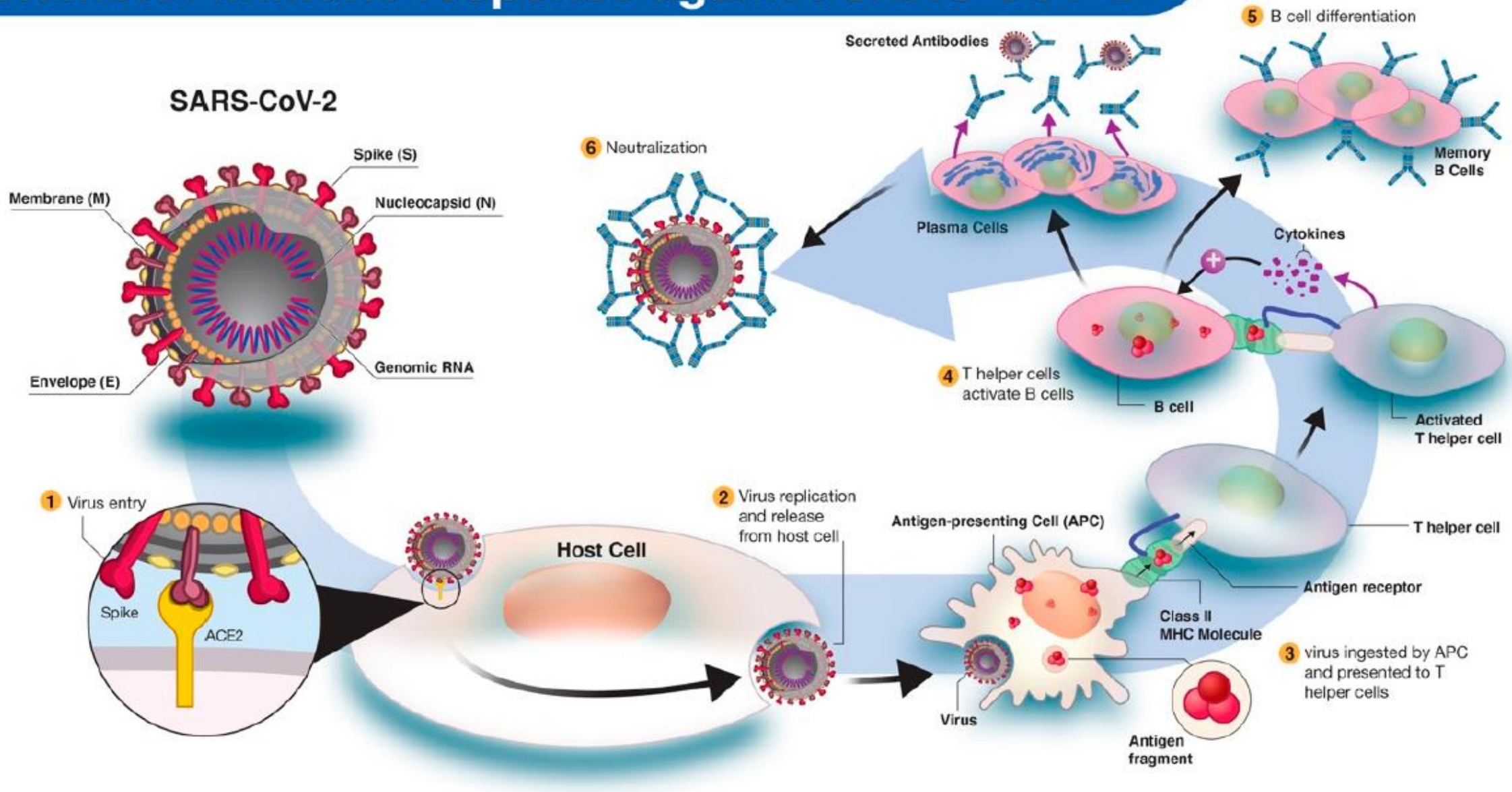
Larissa E van Eijk[1†], Mathijs Binkhorst[2†], Arno R Bourgonje[3‡], Annette K Offringa[4‡], Douwe J Mulder[5], Eelke M Bos[6], Nikola Kolundzic[7,8], Amaal E Abdulle[5], Peter HJ van der Voort[9], Marcel GM Olde Rikkert[10], Johannes G van der Hoeven[11], Wilfred FA den Dunnen[1], Jan-Luuk Hillebrands[1§] and Harry van Goor[1§*]

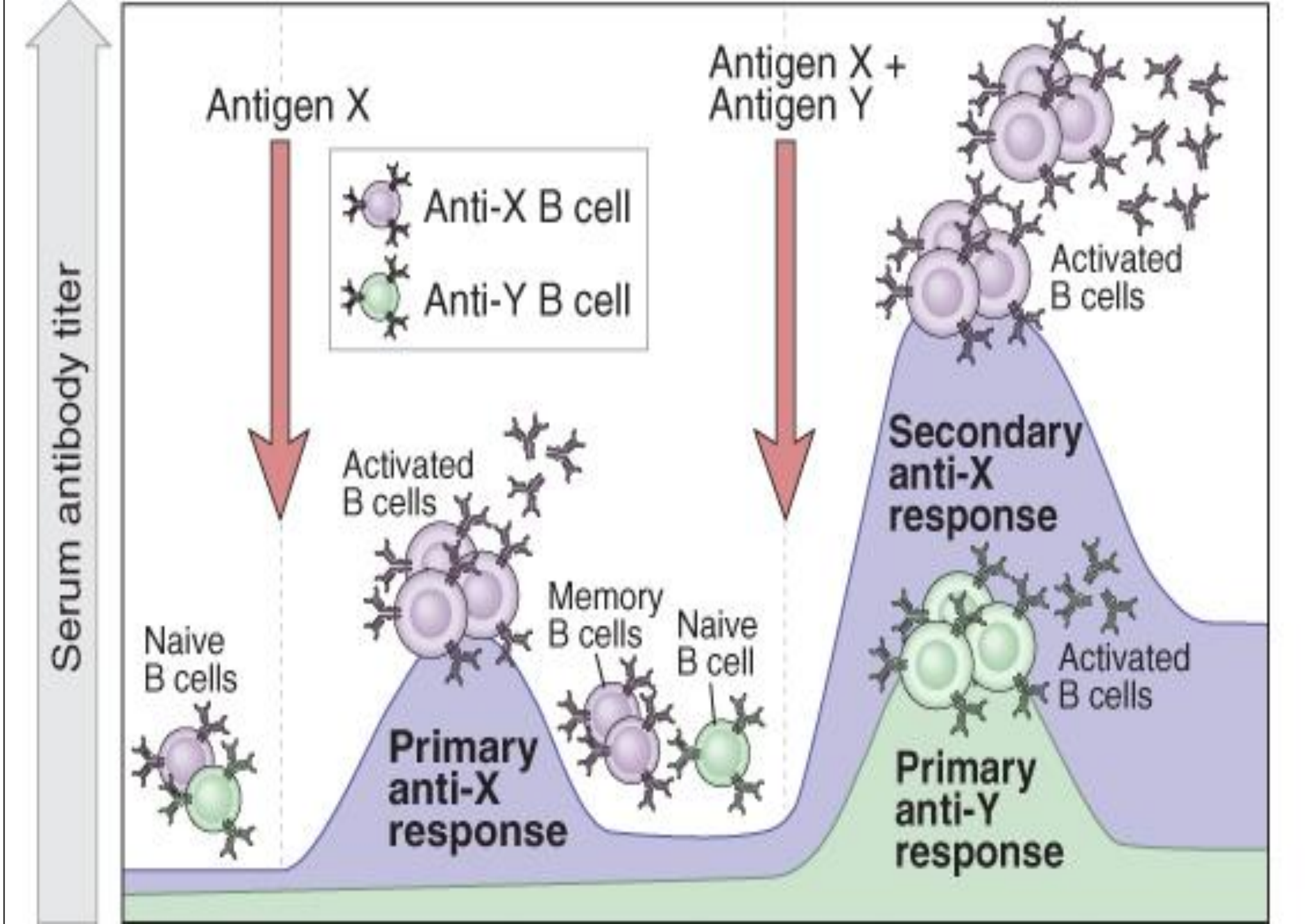
Journal of Pathology
J Pathol July 2021; **254**: 307–331
Published online 25 March 2021 in Wiley Online Library (wileyonlinelibrary.com) DOI: 10.1002/path.5642

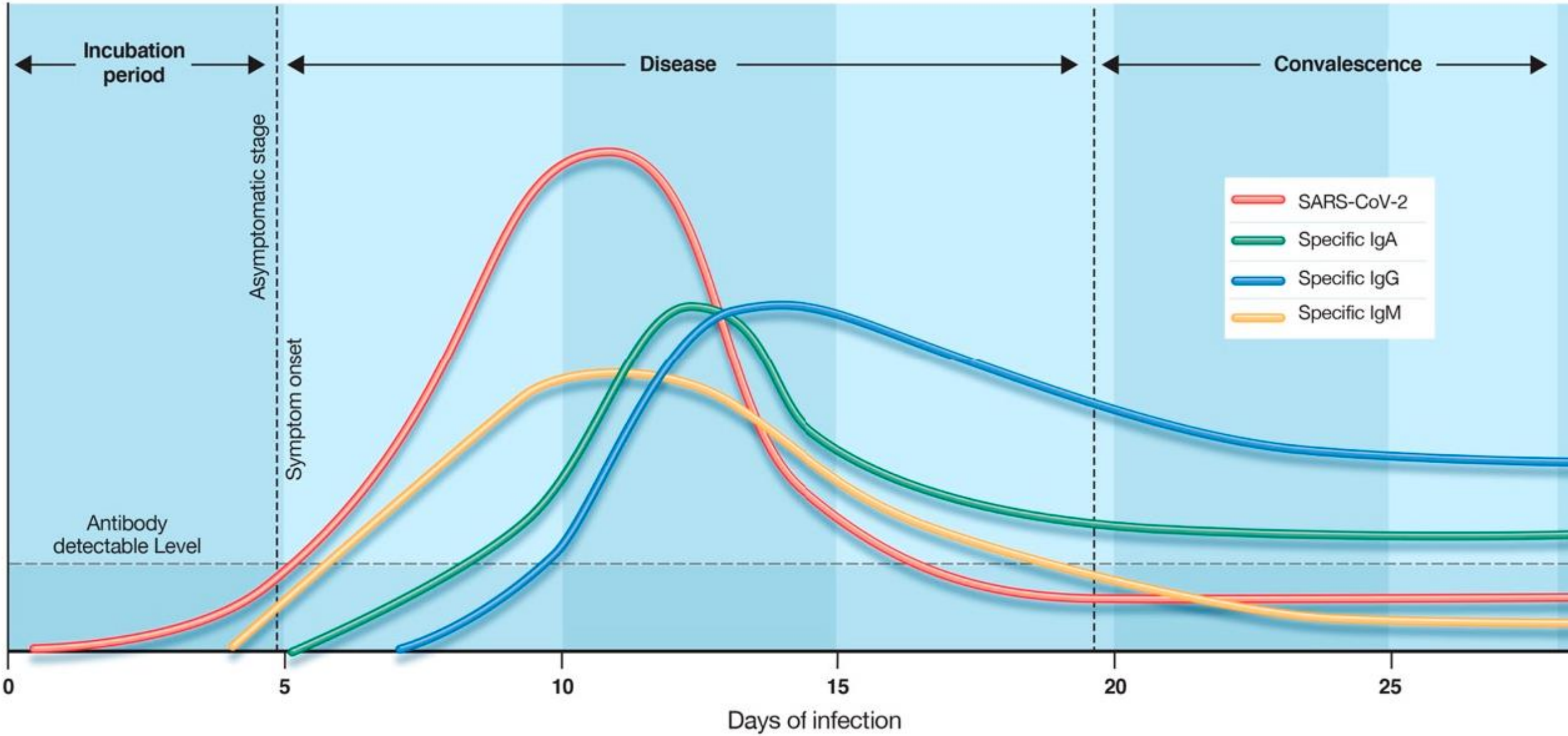


Humoral response to SARS-CoV-2

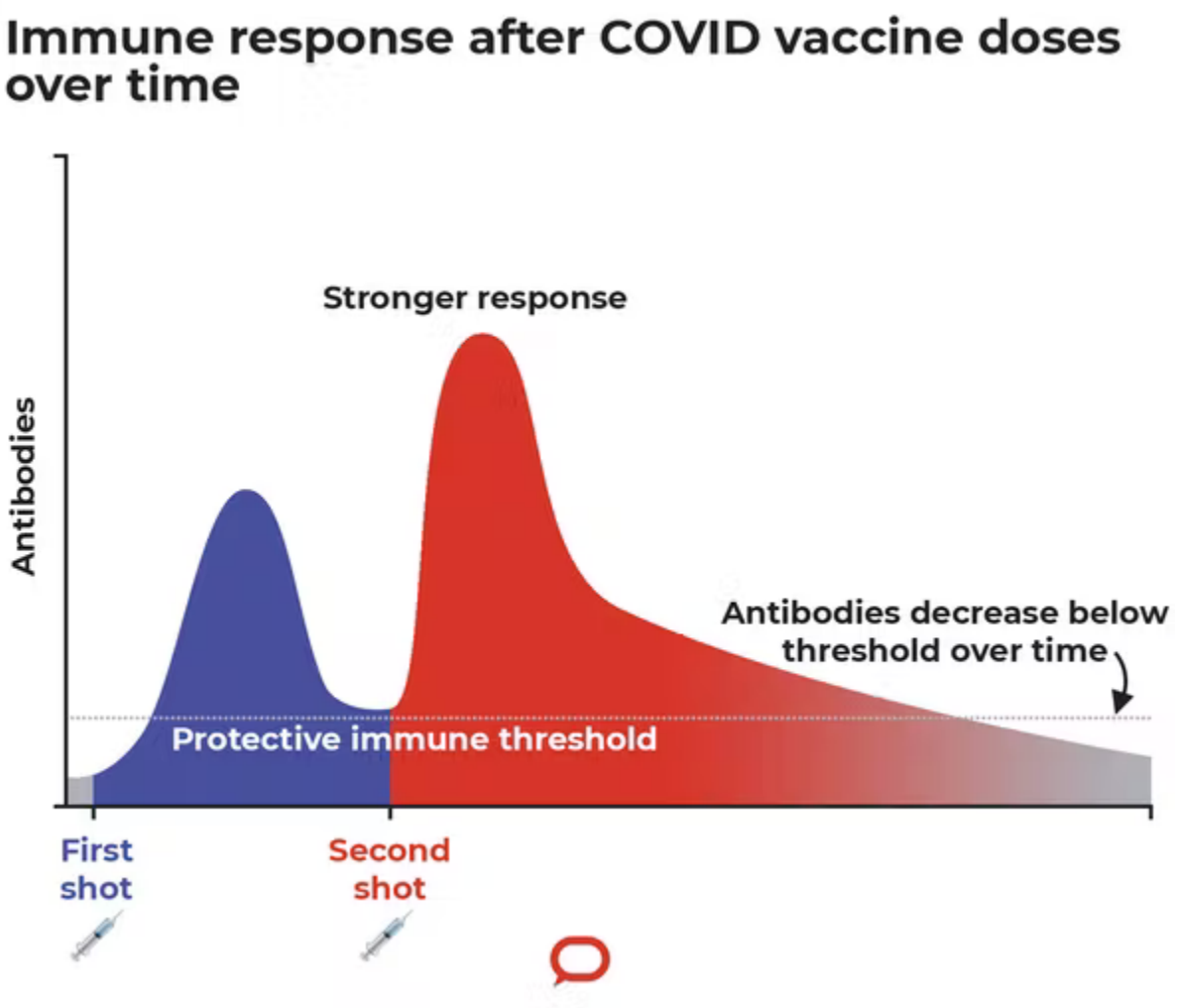
Humoral immune response against SARS-CoV-2

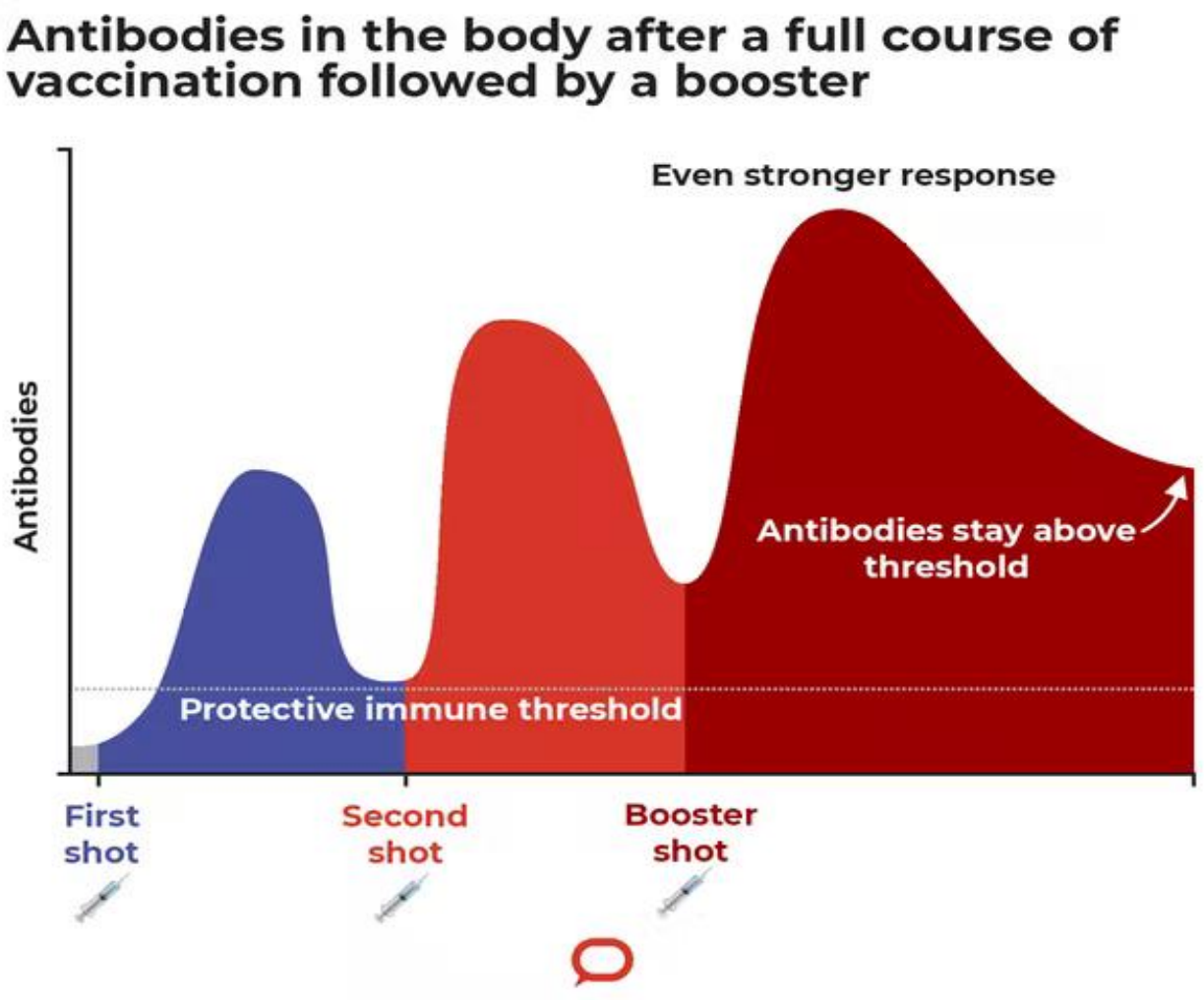



Serum antibody titer
Antigen X
Antigen X +
Antigen Y
Anti-X B cell
Anti-Y B cell
Activated
B cells
Secondary
anti-X
response
Activated
B cells
Memory
B cells
Naive
B cell
Naive
B cells
Primary
anti-X
response
Activated
B cells
Primary
anti-Y
response

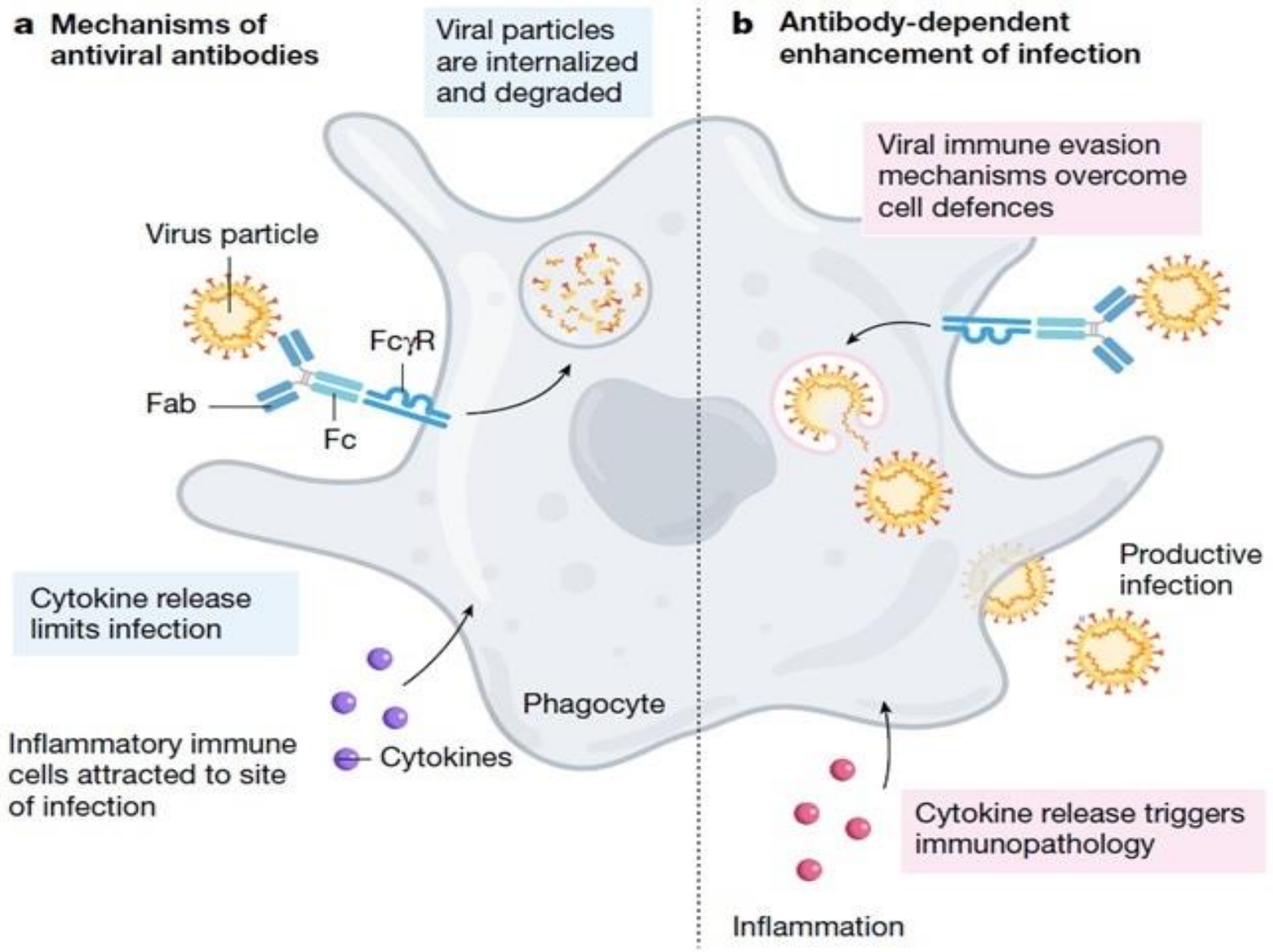

Incubation period
Disease
Convalescence
Asymptomatic stage
Symptom onset
SARS-CoV-2
Specific IgA
Specific IgG
Specific IgM
Antibody detectable Level
0
5
10
15
20
25
Days of infection

Should I get my COVID vaccine booster?
Yes, it increases protection against COVID, including Omicron





Antibody-dependent enhancement (ADE)



What we currently know about COVID-19 immunity

- People who recover from even mild cases of COVID-19 produce antibodies that are believed to protect against infection for at least 5 to 7 months, and could last much longer.'
- The presence of antibodies only means that you've been exposed in the past.

- Herd immunity is the concept that if enough people are protected from infection, either by gaining immunity from having the infection or receiving a vaccine, then the chance of a nonimmune person contracting the disease is exceedingly low.

- A vaccine will help us control the virus by creating herd immunity.

T cells response in COVID-19

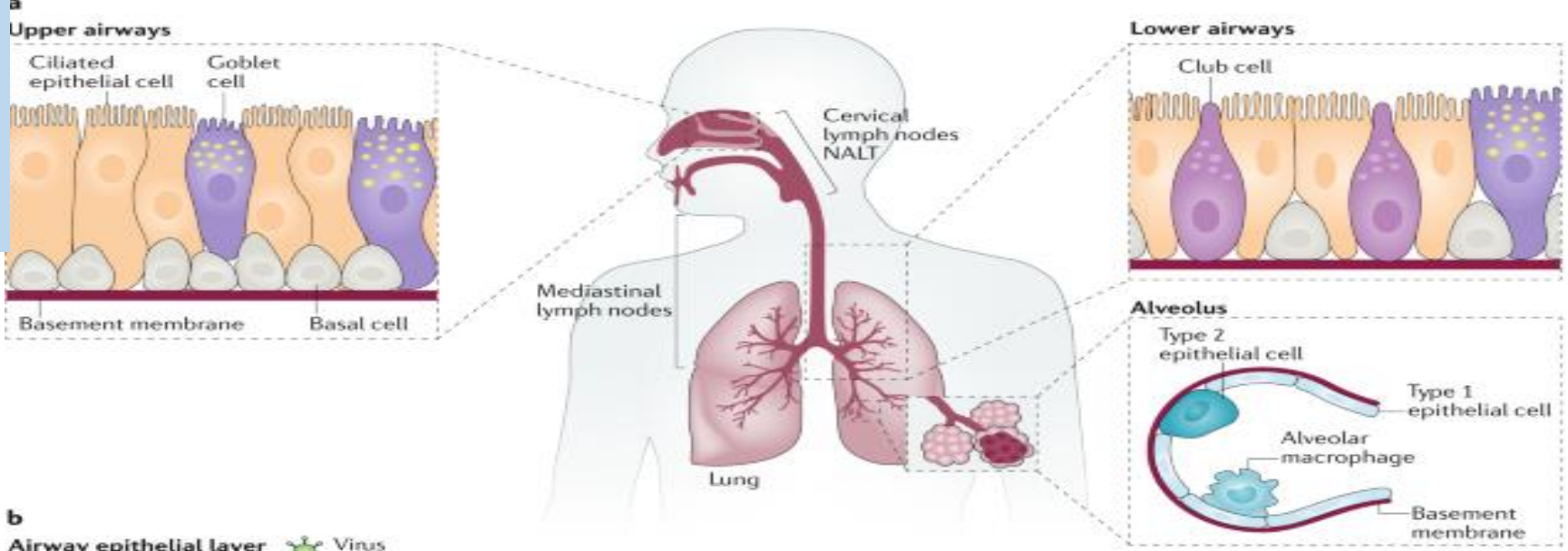
- Similar to other respiratory viral infections T cells, have a prominent role in SARS-CoV-2 infection.

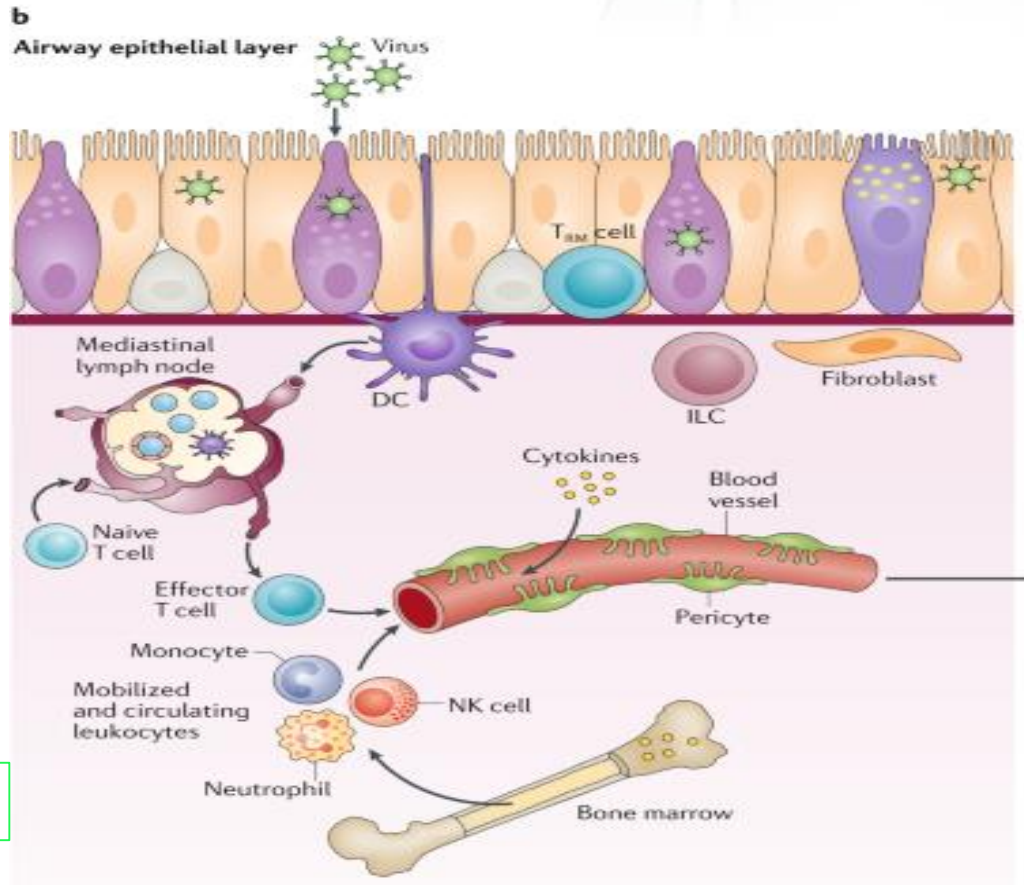
- T cell immunity at early time points after COVID-19 generally appears to be relatively resilient across a spectrum of disease severity.

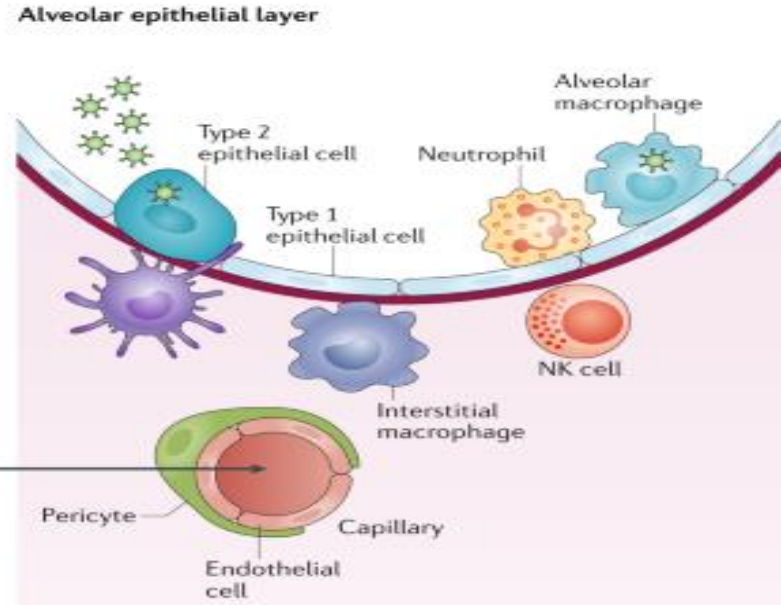
- Disease might occur in different patients at either end of this immune response spectrum (virus-mediated pathology & T cell-driven immunopathology)

Activation of cell mediate immunity following innate immunity

The main molecular and cellular changes elicited by influenza virus infection of the respiratory system.

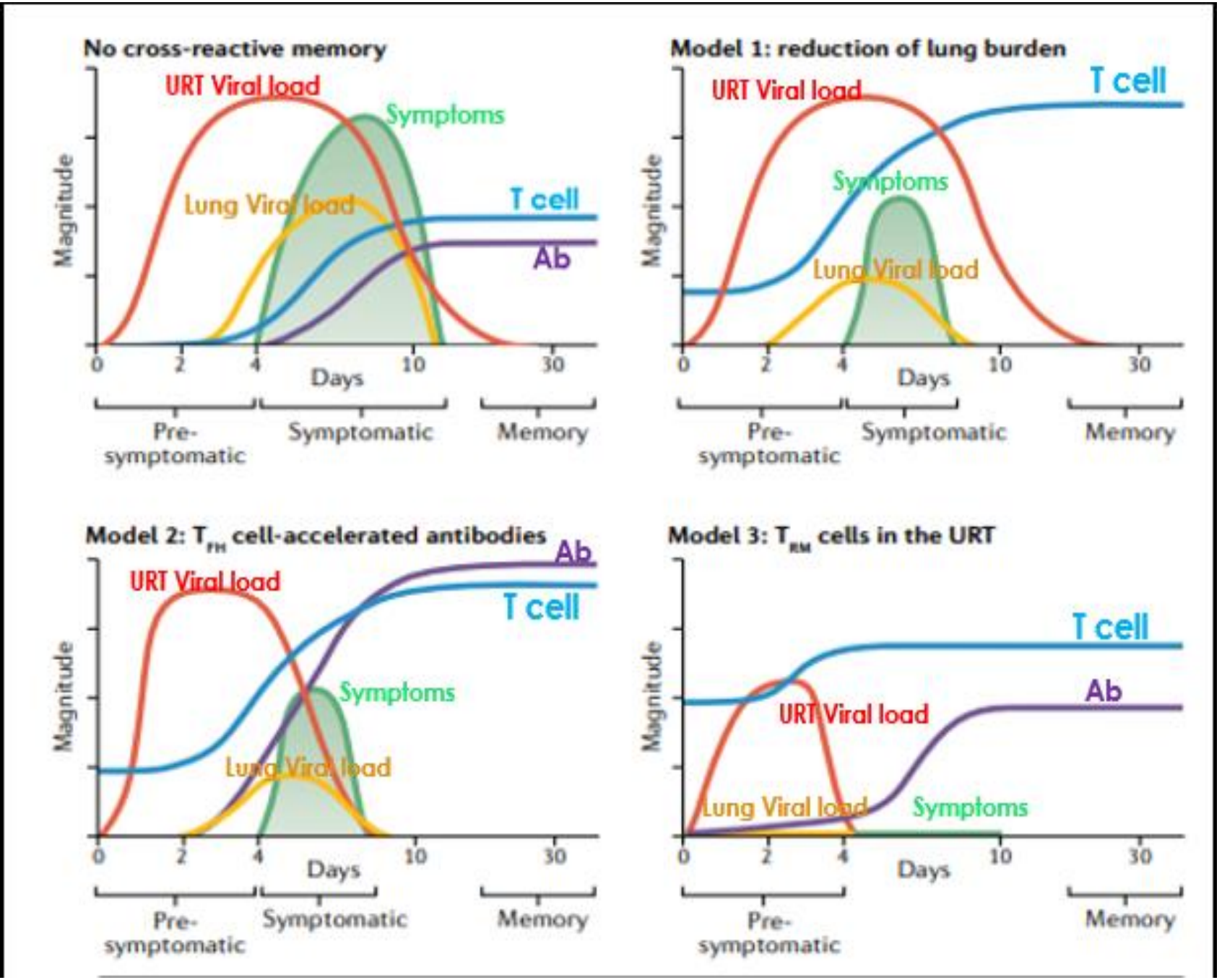






Nature review immunology,2020

Timelines of cell mediate response after exposure to SARS-CoV-2



Timelines of viral (SARS-CoV-2) burden in the lungs and upper respiratory tract (URT) and immune responses

1. Cross-reactive CD4+ memory T cells reduce COVID-19 symptoms and lung viral load but have minimal impact on URT viral load.

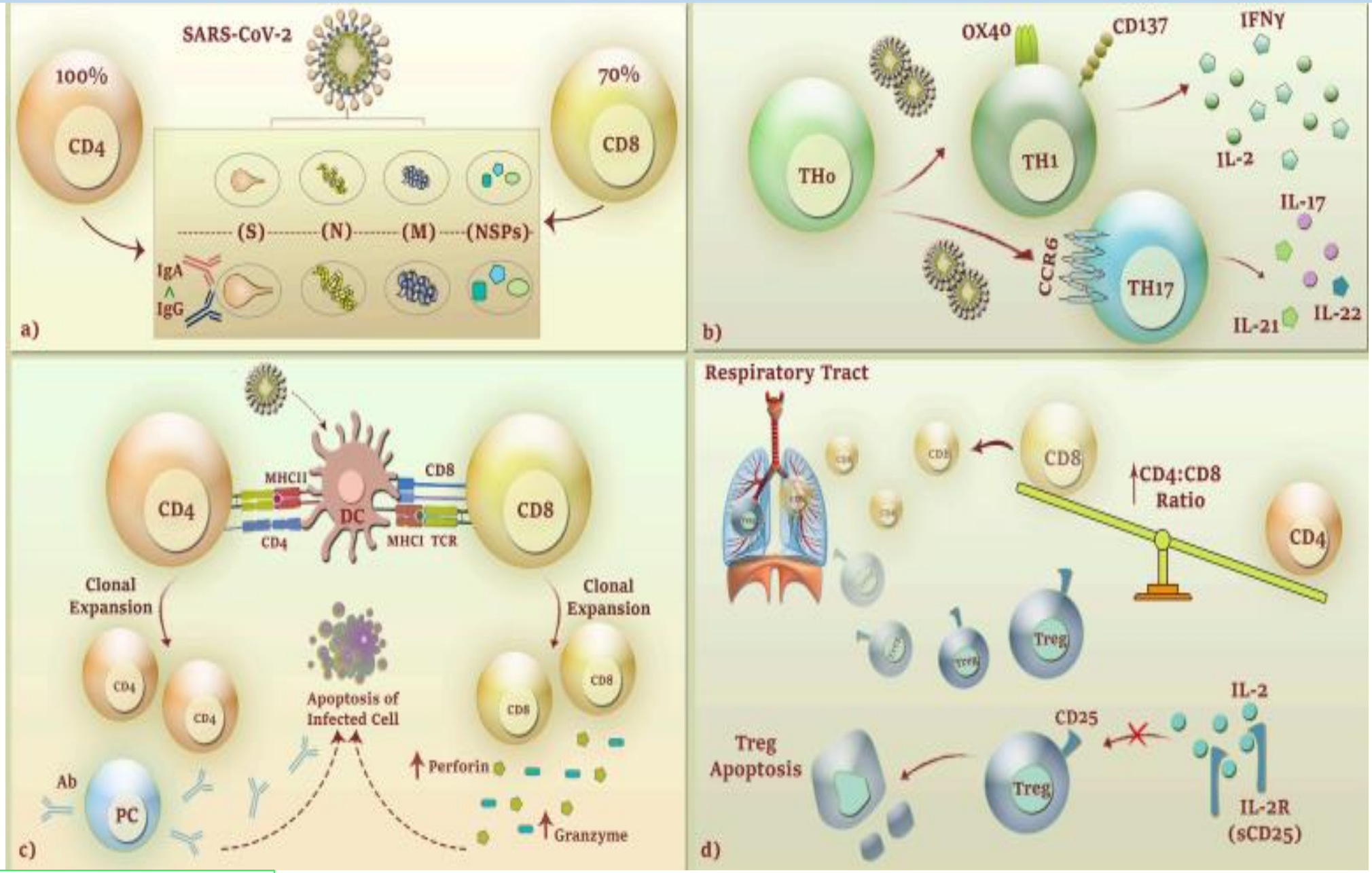
2. Cross-reactive memory TFH cells trigger a faster and better antibody response, resulting in accelerated control of virus in the URT and lungs.

3. Cross-reactive CD4+ TRM cells at the site of infection enable rapid control of virus in the URT and lungs.

Nature Reviews Immunology 2020

Activation Subsets of T cells in COVID-19

Interaction of T cells with SARS-CoV-2

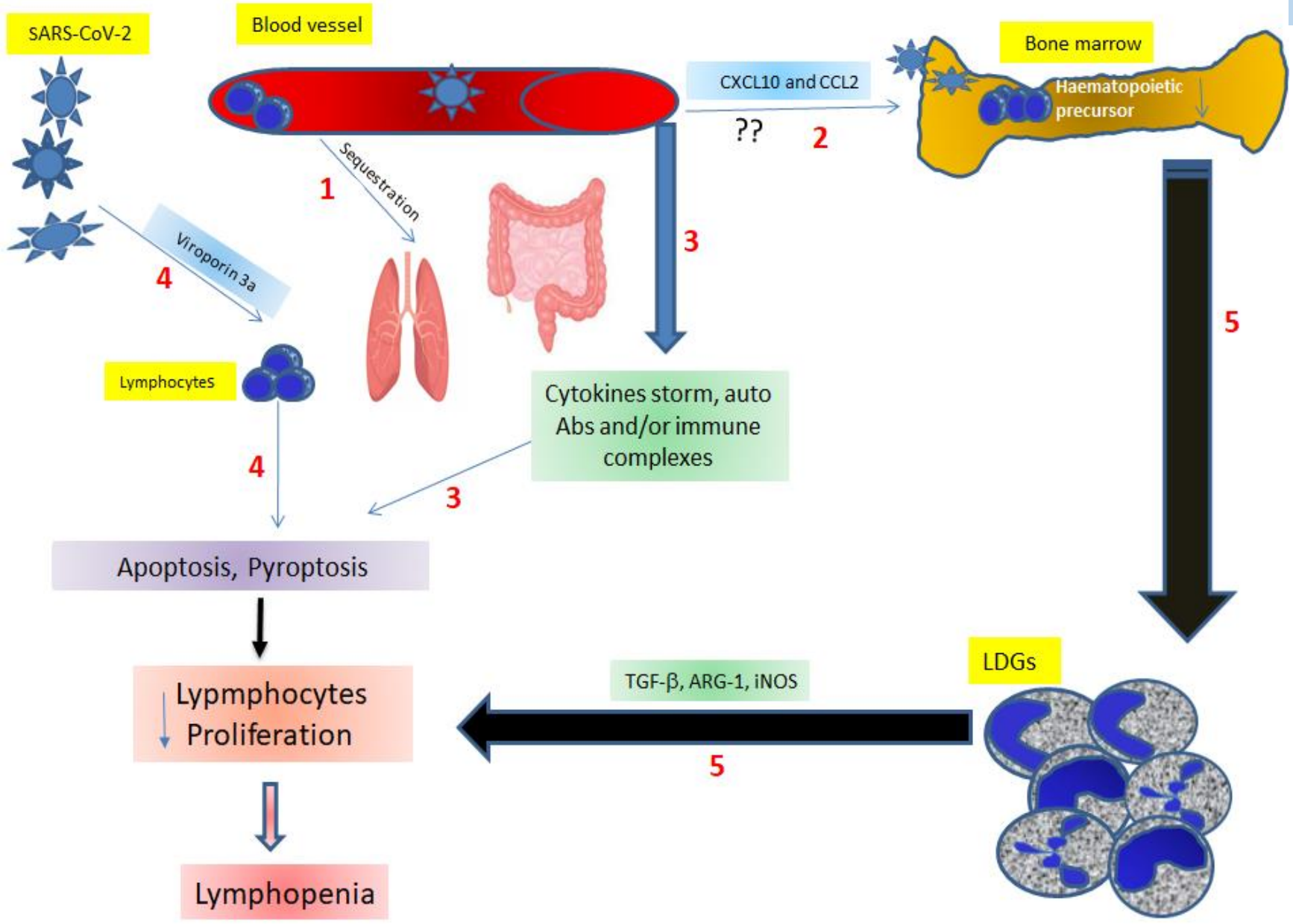


International Immunopharmacology 2021

Lymphopenia in COVID-19 (1)

- Lymphopenia is associated with severe disease but is reversed when patients recover.
- Transient lymphopenia in other infections (influenza A H3N2 virus, human rhinovirus) occurs for only 2–4 days around symptom onset and rapidly recovers.
- COVID-19 lymphopenia may be more severe or persistent than in other infections and seems to be more selective for T cell lineages.
- lymphopenia has reported to affect CD4+ T cells, CD8+ T cells, B cells and NK cells whereas other data suggest that SARS-CoV-2 infection has a preferential impact on CD8+ T cells.

Fig. 1



Mortaz et al , submitted paper JOCI 2021

Mechanisms which lead to lymphopenia in COVID-19 patients.

1) Redistribution of lymphocytes in vital organs such as lungs and intestinal.

2) Suppressive effects of increased serum levels of chemokine's such as CXCL-10 and CCL-2 on the haematopoiesis of stem cells in bone marrow.

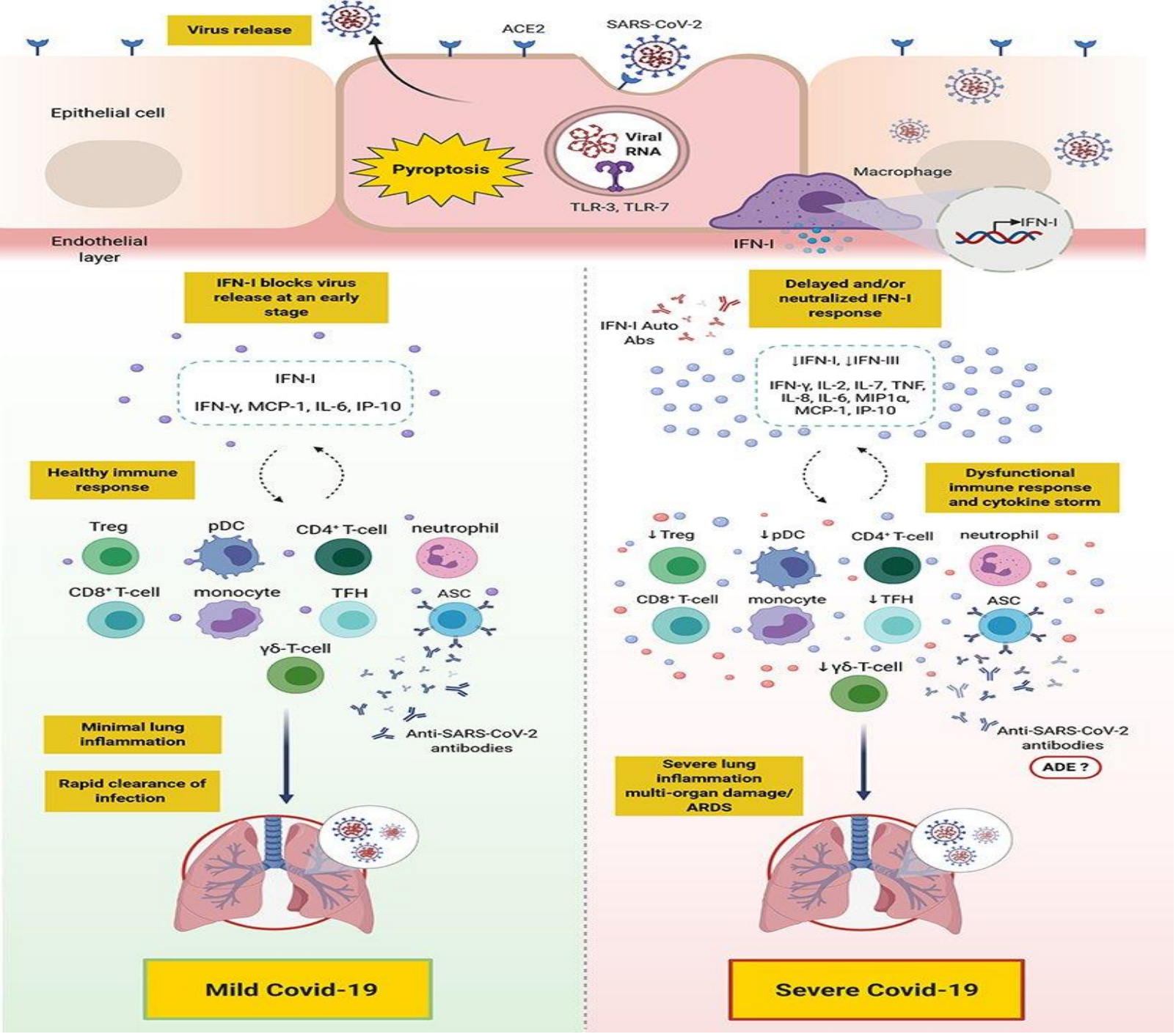
3) Induction of cytokine storm and autoantibodies and other immune complexes on the apoptosis of lymphocytes.

4) Effect of viroporin 3a of virus on apoptosis and pyroptosis of lymphocytes

5) Role of LDGs cells as cells with production some mediators suppress the lymphocyte proliferation

Activation of T cells in critical ill patients

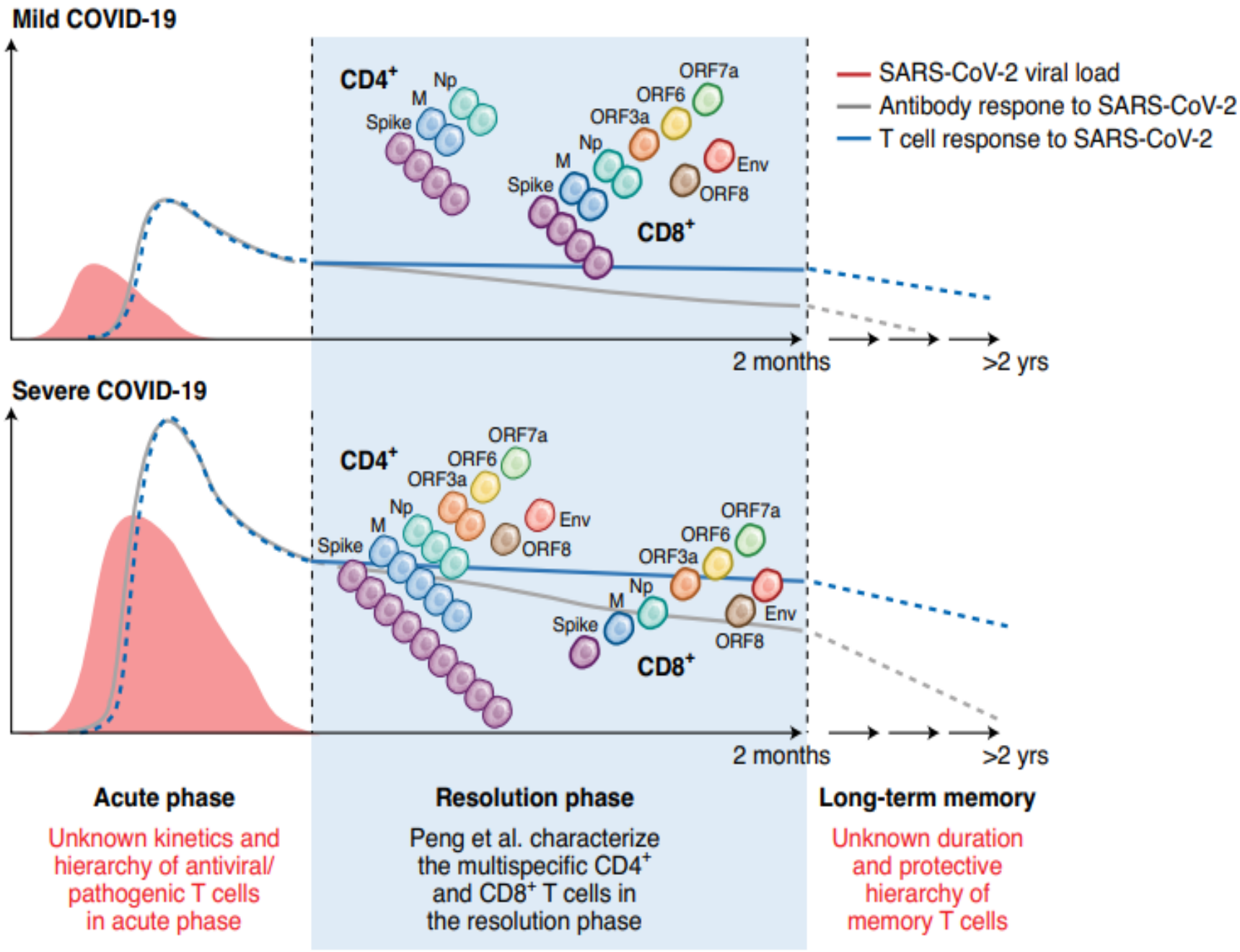
Overall depiction of the immune response in mild versus severe Covid-19



- Viral load and co-morbidities could have a major impact on quality of the T cell response
- In severe COVID-19 including high levels of systemic cytokines or chemokines, most or delayed or defective type I interferon responses could potentially skew T cell responses (hyperactivation / hypoactivation/ an ineffective differentiation state (TH17 cells, exhausted T cells)

ImmunoTargets and Therapy 2021

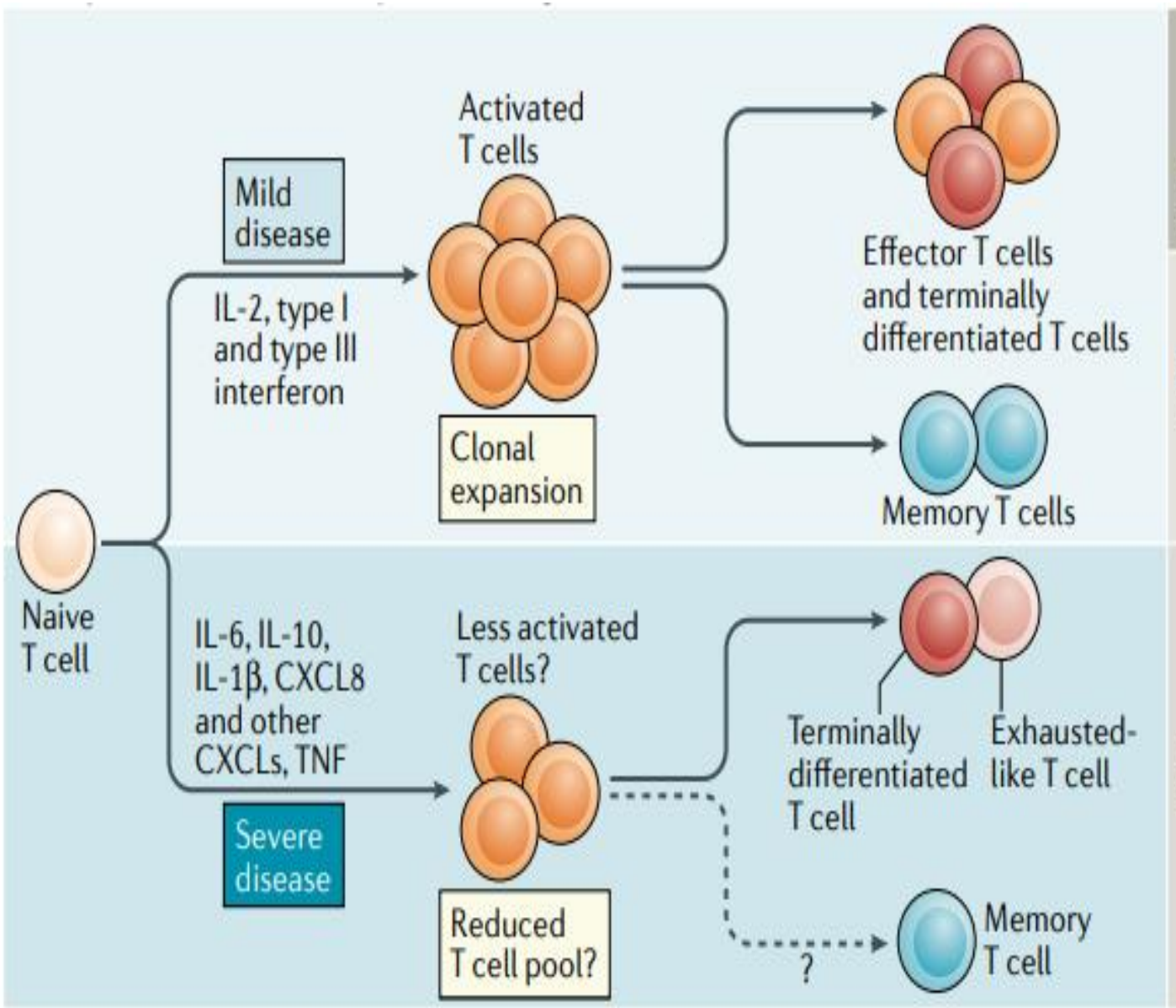
Frequency and specificity of T cells in the resolution phase of mild or severe COVID-19



- The <u>total T cell</u> response is <u>stronger</u> and broader in <u>severe</u> cases (assumed to have had higher viral burden), correlating with <u>stronger antibody</u> responses
- However, there are, proportionally, more CD8+ T cells in mild disease.

Nature Immunology | VOL 21 | November 2020

Proposed CD8+ T cell response during COVID-19

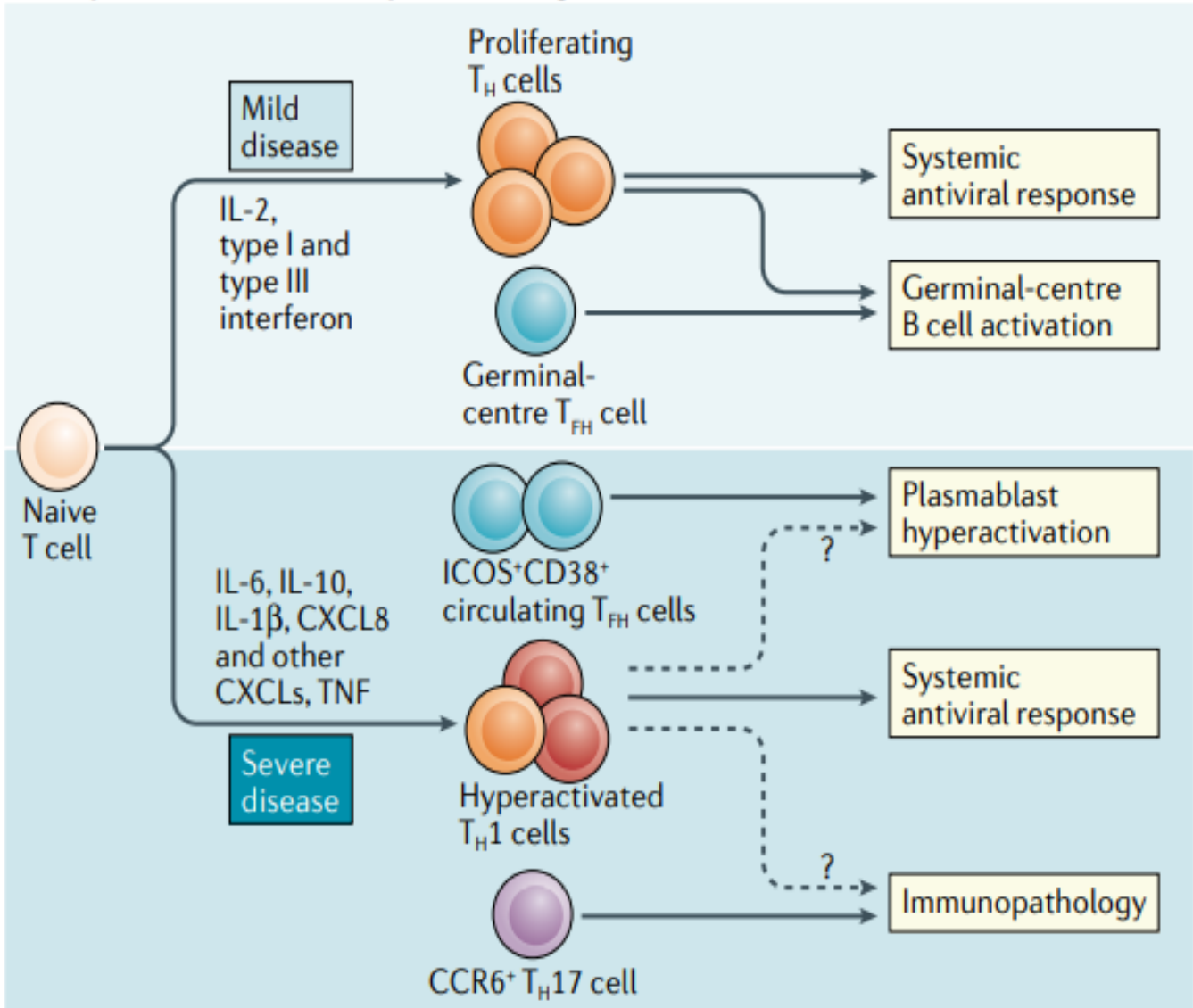


Cell number	TCR clonality	Cell cycle state	Cytokines, chemokines and cytotoxicity	Co-inhibitory signals
Normal or increased	**Dominant clones detected**	**Ki67**$^{+/-}$	**IFNγ**$^{++}$ IL-2^{+} CD107a^{++} **TNF**$^{+}$ **GZMB**$^{+}$	**PD1**$^{+/-}$ **TIM3**$^{+/-}$ **CD38**$^{+}$ CD39$^{+/-}$
Strongly decreased	**Lack of dominant clones**	**Ki67**$^{+/+}$	**IFNγ**$^{+}$ IL-2$^{+/-}$ CD107a^{+} **GZMB**$^{++}$ Perforin^{++} CCL3^{+} CCL4^{++} IL-1β^{+}	**PD1**$^{++}$ **TIM3**$^{++}$ **CD38**$^{++}$ CD39^{+} NKG2A^{+} KLRs^{+} **LAG3**$^{+}$ **CTLA4**$^{+}$ TIGIT^{+}

Nature Reviews | Immunology, 2020

Proposed CD4+ T cell response during COVID-19

b Proposed CD4⁺ T cell response during COVID-19



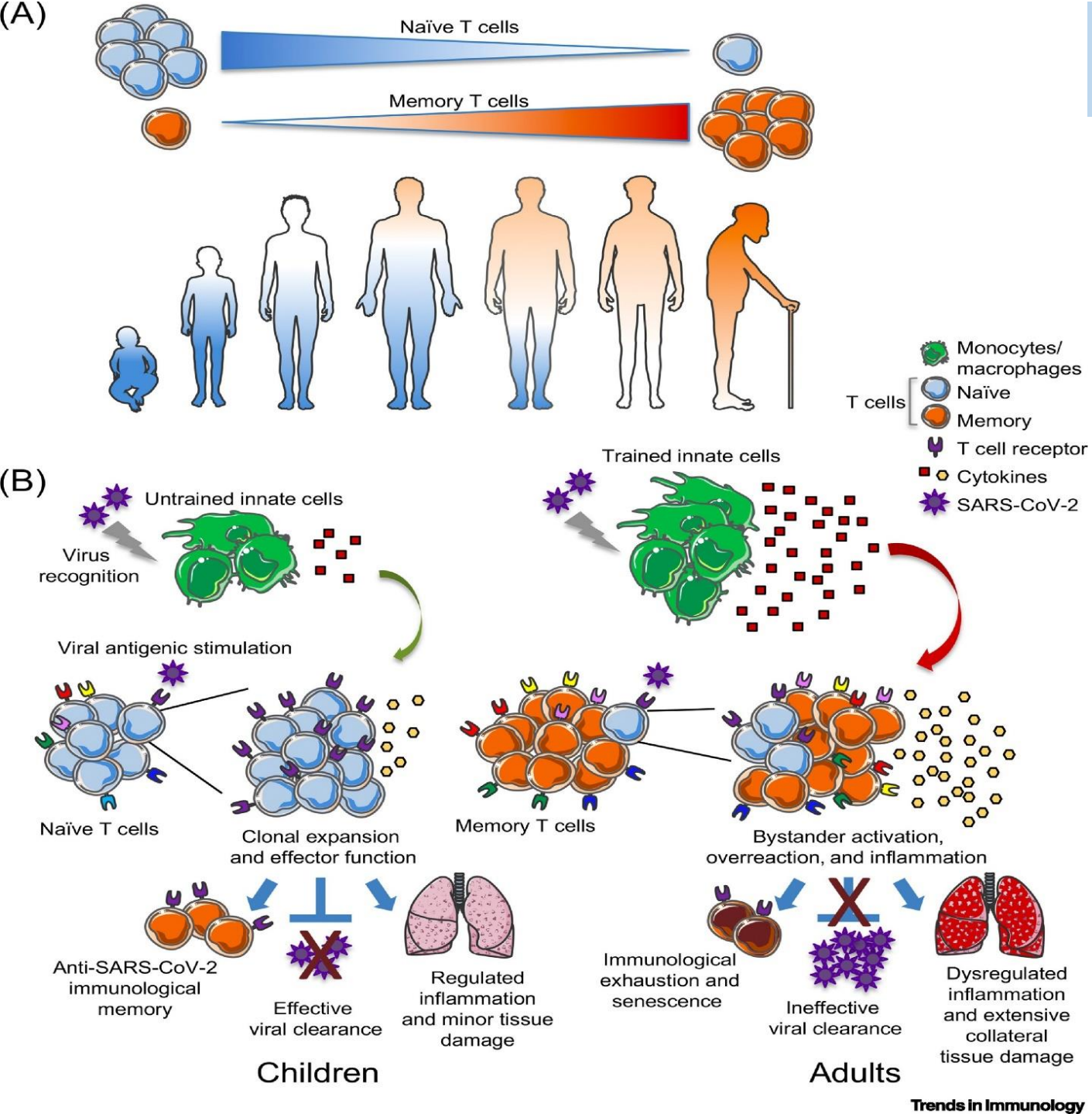
Cell number	Lineage specificity	Cell cycle state	Humoral immune memory	Co-stimulatory and co-inhibitory signals
Normal or increased	**T_H1 cell**, T_H2 cell, germinal-centre T_{FH} cell	**$Ki67^{+/-}$**	**Efficient**	**$CD38^{+/-}$** **$ICOS^{+/-}$** $CD95^-$ $CX3CR1^{+/-}$ **$PD1^{+/-}$** **$TIM3^{+/-}$** $CD39^{+/-}$
Immune cell subtype dependent	**Circulating T_{FH} cell**, **T_H17 cell**, **hyper-T_H1 cell** (T_{reg} cell?)	**$Ki67^{+/+}$**	Unknown	**$CD38^{++}$** **$ICOS^{++}$** $CD95^+$ $CX3CR1^+$ **$PD1^+$** **$TIM3^+$** $CD39^+$ TIGIT⁺

Nature Reviews | Immunology, 2020

Co-morbidities related with CD4, CD8 in COVID-19 (1)

- Cardiovascular disease, diabetes, and obesity, aging , male sex and the ABO blood type, could affect the clinical outcomes for patients with COVID-19
- Age-related reduction in T cell clonal diversity (CD4+ T cells and CD8+ T cells) is associated with impaired responses to viral infections
- Advanced age associated with T cell senescence, contributes to ineffective responses to infections However, senescent T cells may also paradoxically be pro-inflammatory and therefore perhaps contribute to immunopathology
- Older patients experience more severe lymphopenia during COVID-19

Expansion of memory versus naive T Cells with age and reaction with SARS-CoV-2



Trends in Immunology 2021

Co-morbidities related with CD4, CD8 and COVID-19 (2)

- Men with COVID-19 have higher rates of hospitalization and mortality than women, and among severe cases of disease, men have more severe lymphopenia.

- There may also be a bias to stronger CD4+ and CD8+ T cell activation in women with COVID-19 .

- It is unclear whether these sex biases relate to X chromosome-encoded immune genes and/or the role of sex hormones in regulating immune responses

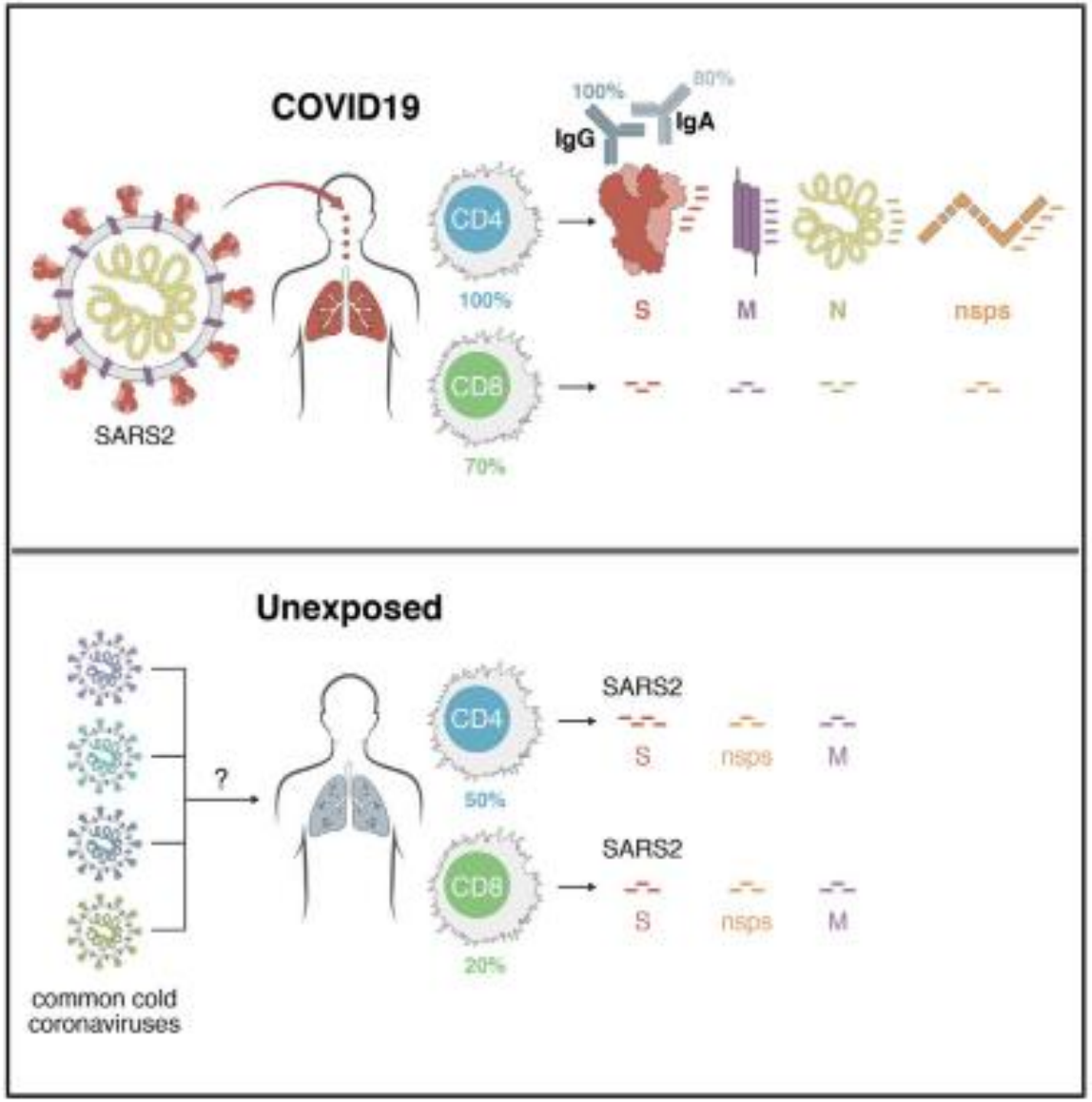
- Obesity can also directly affect T cell responses to influenza vaccination or infection, asthma and chronic inflammation.

Memory T cells in COVID-19

- Memory CD4+ T cells and CD8+ T cells were detected in 100% and 70% of COVID-19 patients who recovered, respectively

- Memory T cell responses were detected for multiple SARS-CoV-2 proteins, including not only spike protein but also nucleoprotein and membrane protein

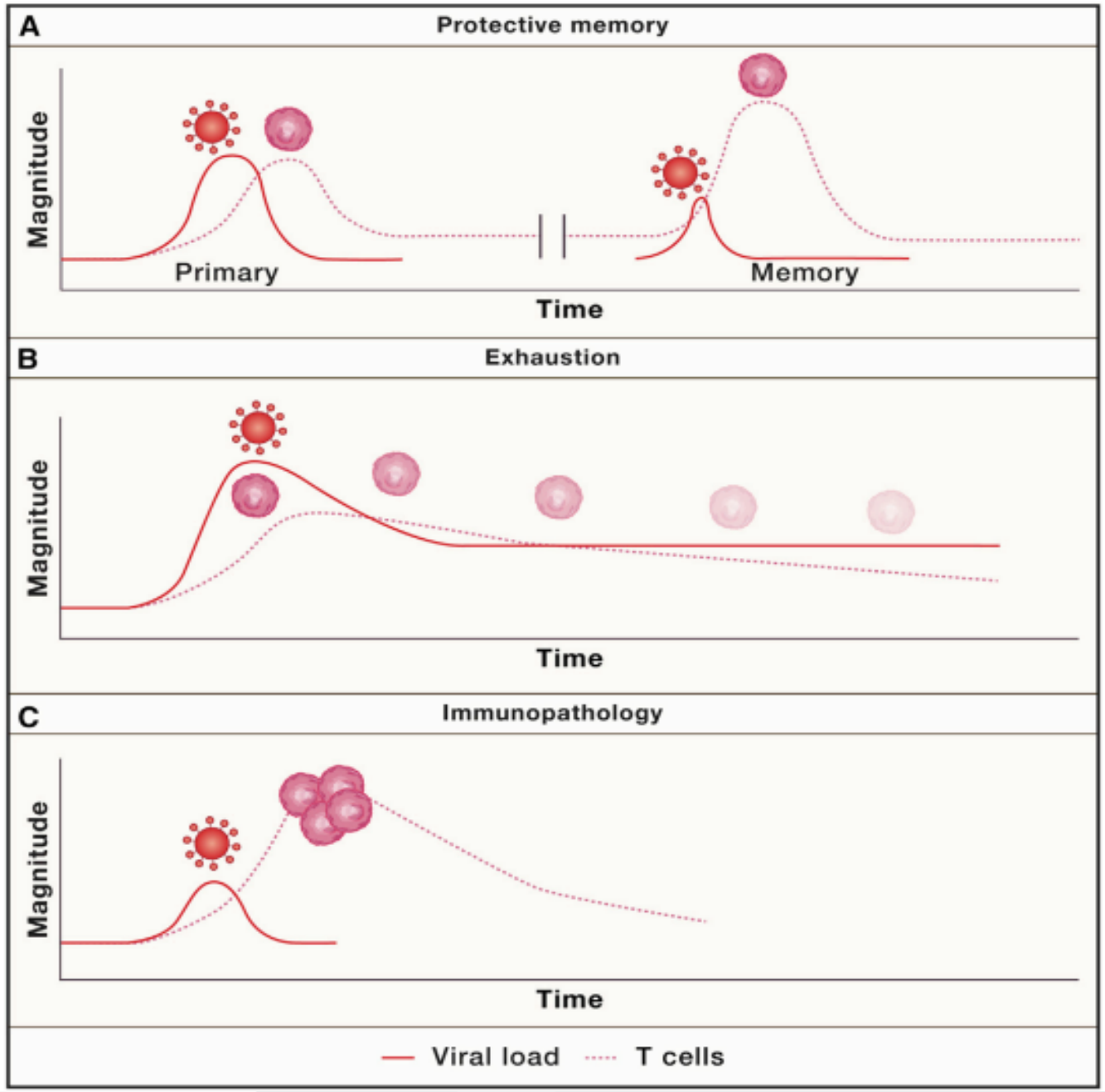
SARS-CoV-2 reactive T cell responses in unexposed individuals



- SARS-CoV-2-reactive CD4+ and CD8+ T-cell responses were detected in up to 50% and 20% of unexposed individuals, respectively, may result from previous infection by cross-reactive common-cold coronaviruses (CCCoVs)
- pre-existing SARS-CoV-2-reactive T cells interfere with the development of a competent SARS-CoV-2-specific T-cell response by an 'original antigenic sin' phenomena
- A recent study reported that COVID-19 patients with a recent history of CCCoV infection have significantly milder disease

Cell , 2020

Outcomes of primary immune responses and effects on memory cells development



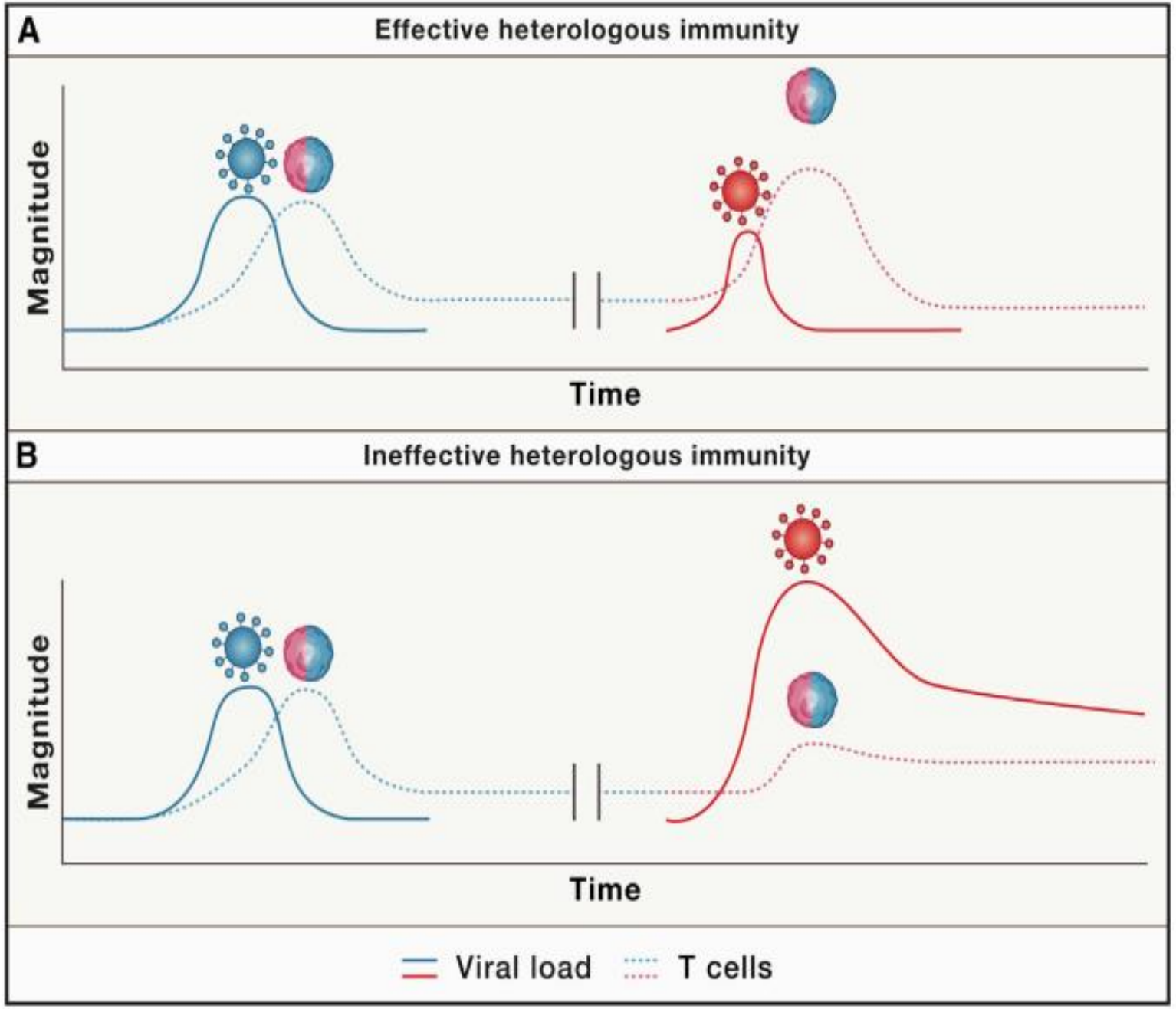
(A) Appropriate T cell response specific to that pathogen develops and contributes to control and of the infectious agent. The T cell population is then maintained at a low frequency as a mixture of memory subsets.

(B) If the immune response cannot clear the infectious agent, a chronic infection will develop. This can cause T cells to enter a so-called exhausted state rather than developing classical memory.

(C) If the initial response is too strong , the immune response can cause damaging immunopathology, potentially including a cytokine storm. This can be fatal, and survivors may have lasting changes in subsequent immunity .

Immunity 54, January 12, 2021

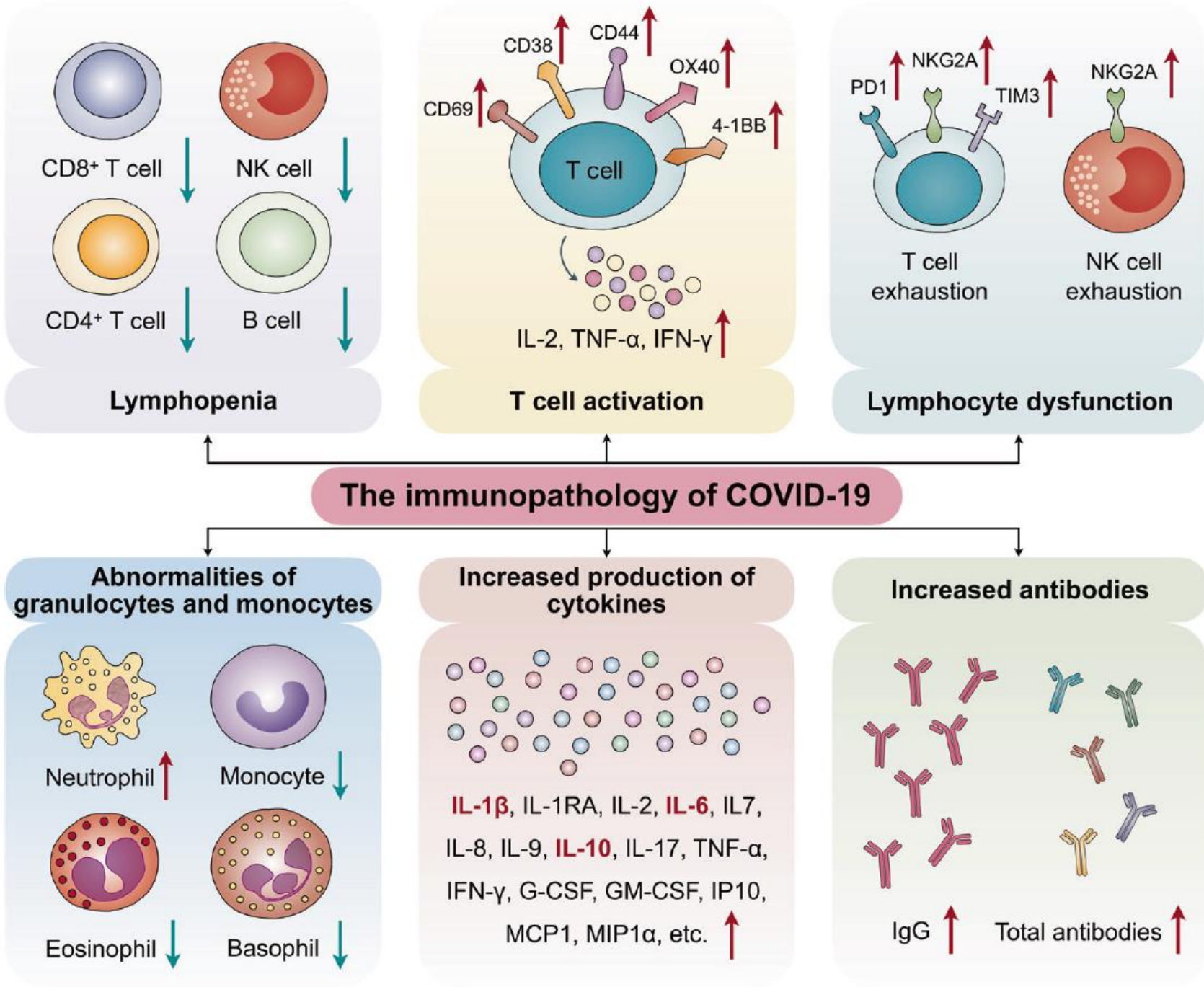
Heterologous Immunity to Viruses

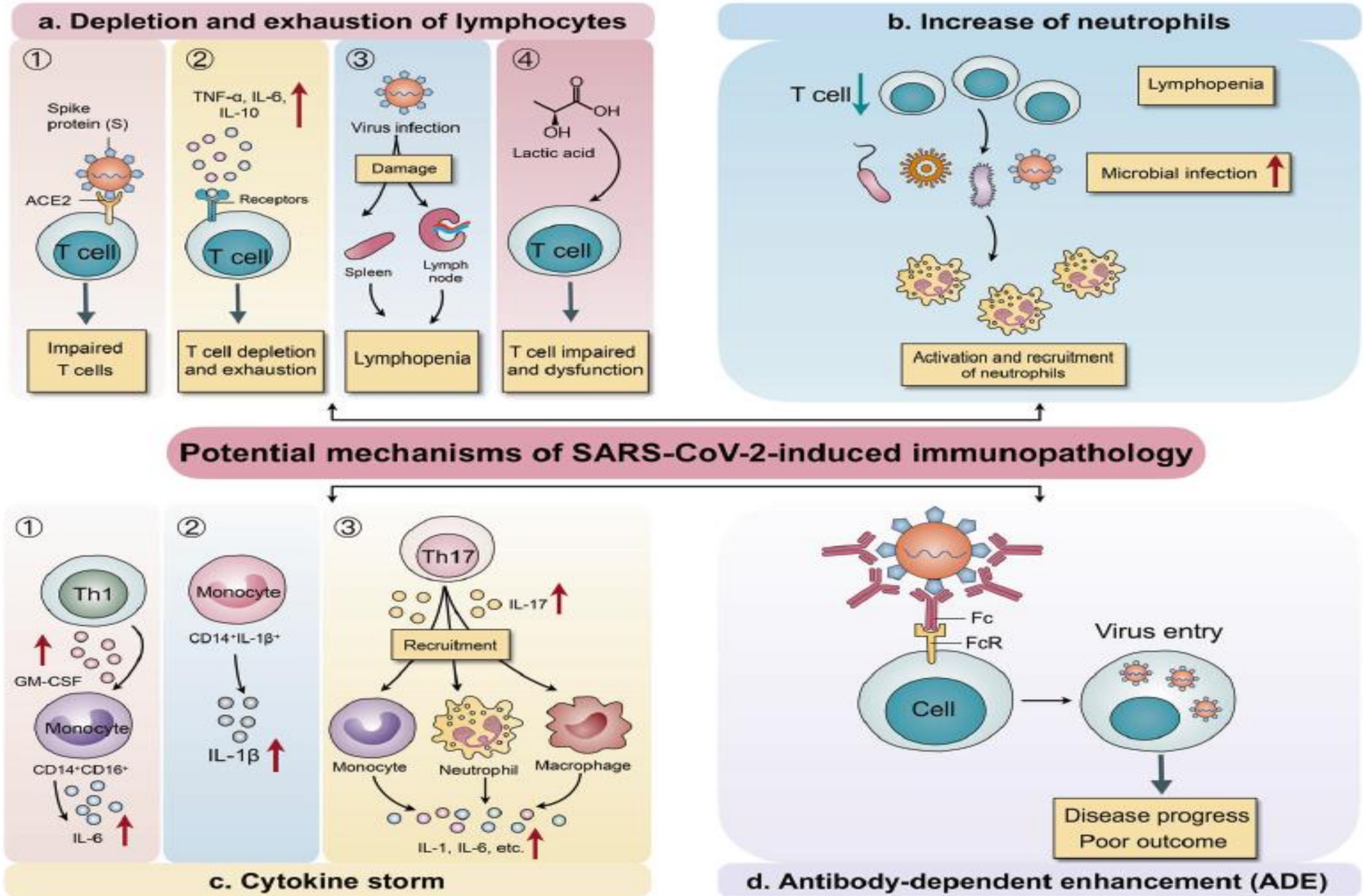


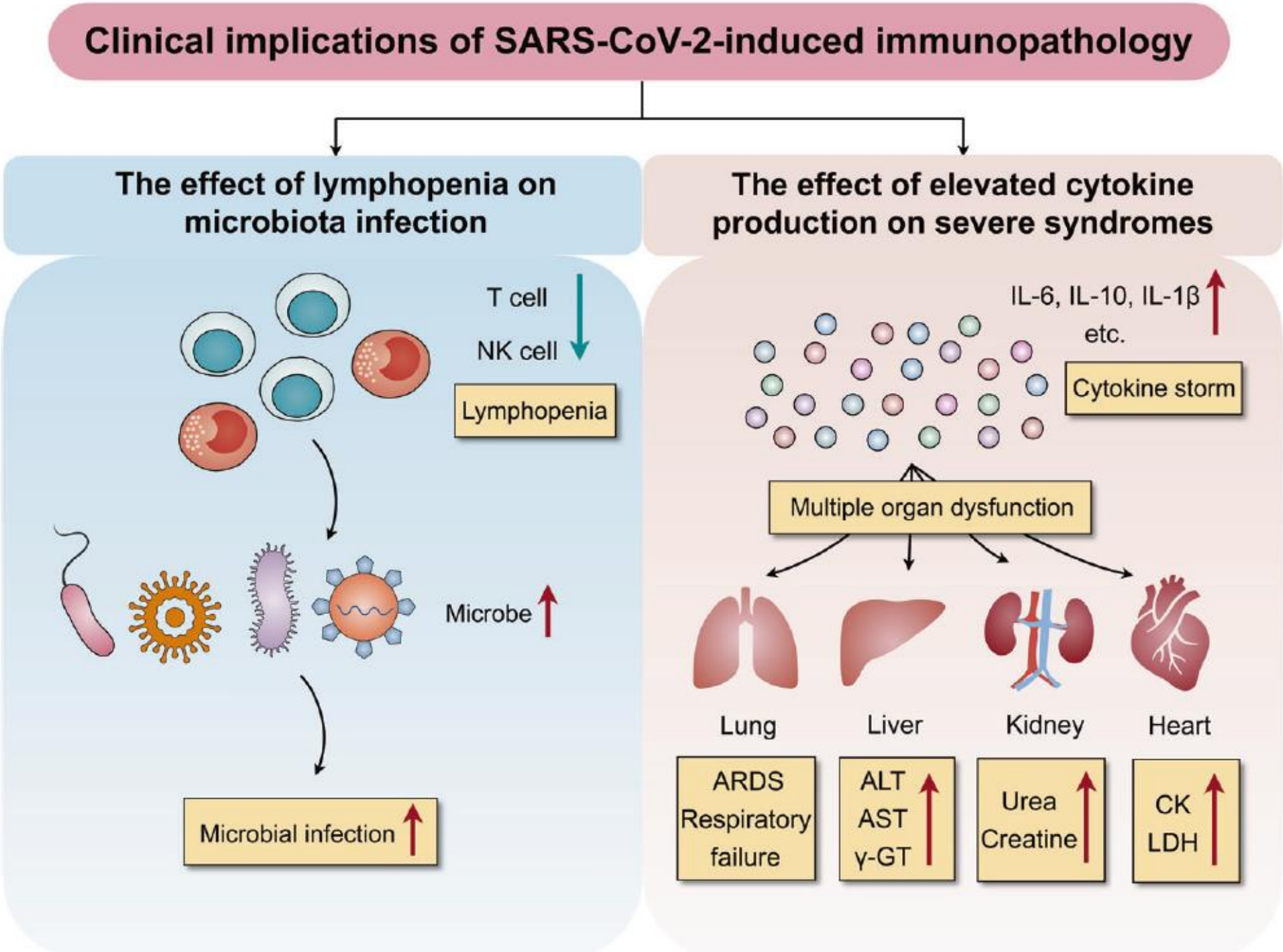
(A) Cross-reactive T cells mediate a rapid and effective immune response, this results in a memory-like heterologous immune response to the red virus, mediating enhanced control compared to a de novo primary response.

(B) Cross-reactive T cells may be incapable of mediating an effective immune response to the red virus, instead causing immunopathology and/or suppressing the de novo primary response to that pathogen by outcompeting antigen-specific naive T cells.

Immunity 54, January 12, 2021


CD8⁺ T cell
NK cell
CD4⁺ T cell
B cell
Lymphopenia
CD38
CD44
OX40
CD69
4-1BB
T cell
IL-2, TNF-α, IFN-γ
T cell activation
PD1
NKG2A
TIM3
NKG2A
T cell exhaustion
NK cell exhaustion
Lymphocyte dysfunction
The immunopathology of COVID-19
Abnormalities of granulocytes and monocytes
Neutrophil
Monocyte
Eosinophil
Basophil
Increased production of cytokines
IL-1β, IL-1RA, IL-2, IL-6, IL7, IL-8, IL-9, IL-10, IL-17, TNF-α, IFN-γ, G-CSF, GM-CSF, IP10, MCP1, MIP1α, etc.
Increased antibodies
IgG
Total antibodies


a. Depletion and exhaustion of lymphocytes
①
Spike protein (S)
ACE2
T cell
Impaired T cells
②
TNF-α, IL-6, IL-10
Receptors
T cell
T cell depletion and exhaustion
③
Virus infection
Damage
Spleen
Lymph node
Lymphopenia
④
OH
OH
Lactic acid
T cell
T cell impaired and dysfunction
b. Increase of neutrophils
T cell
Lymphopenia
Microbial infection
Activation and recruitment of neutrophils
Potential mechanisms of SARS-CoV-2-induced immunopathology
①
Th1
GM-CSF
Monocyte
CD14+CD16+
IL-6
②
Monocyte
CD14+IL-1β+
IL-1β
③
Th17
IL-17
Recruitment
Monocyte
Neutrophil
Macrophage
IL-1, IL-6, etc.
c. Cytokine storm
Fc
FcR
Cell
Virus entry
Disease progress
Poor outcome
d. Antibody-dependent enhancement (ADE)


Clinical implications of SARS-CoV-2-induced immunopathology
The effect of lymphopenia on microbiota infection
The effect of elevated cytokine production on severe syndromes
T cell
NK cell
Lymphopenia
Microbe
Microbial infection
IL-6, IL-10, IL-1β etc.
Cytokine storm
Multiple organ dysfunction
Lung
Liver
Kidney
Heart
ARDS Respiratory failure
ALT AST γ-GT
Urea Creatine
CK LDH

THANKS FOR YOUR ATTENTION