Immune Responses to COVID-19 Disease

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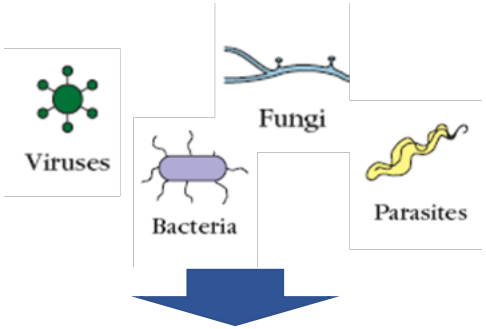
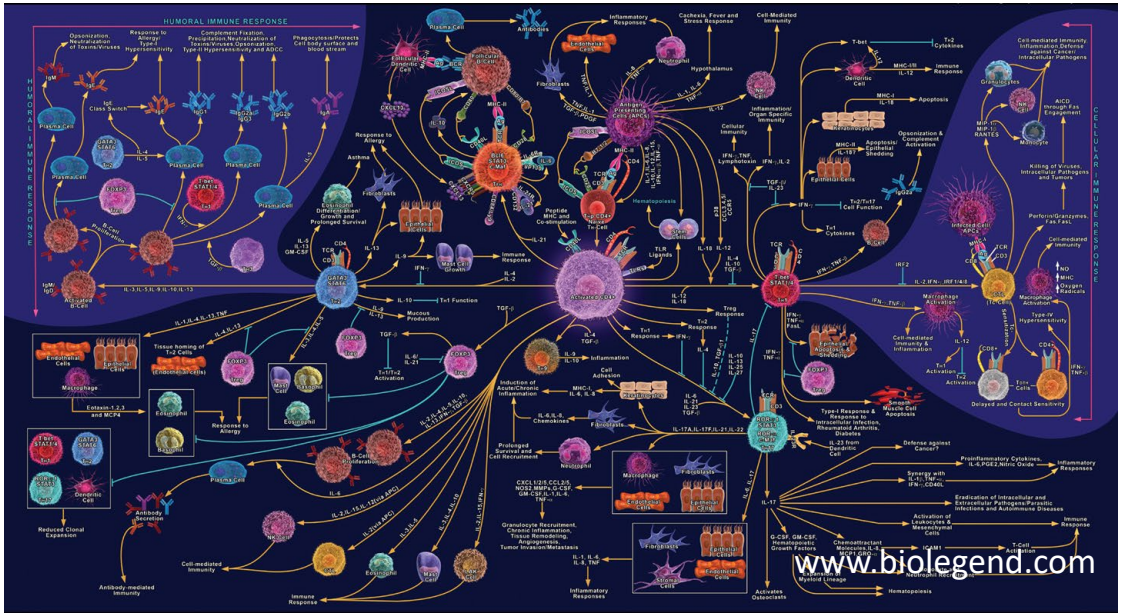
แขนงวิชาภูมิคุ้มกันวิทยาคลินิก
คณะเทคนิคการแพทย์
มหาวิทยาลัยเชียงใหม่

Immune response to microbial infection



Immune System

Immune Responses



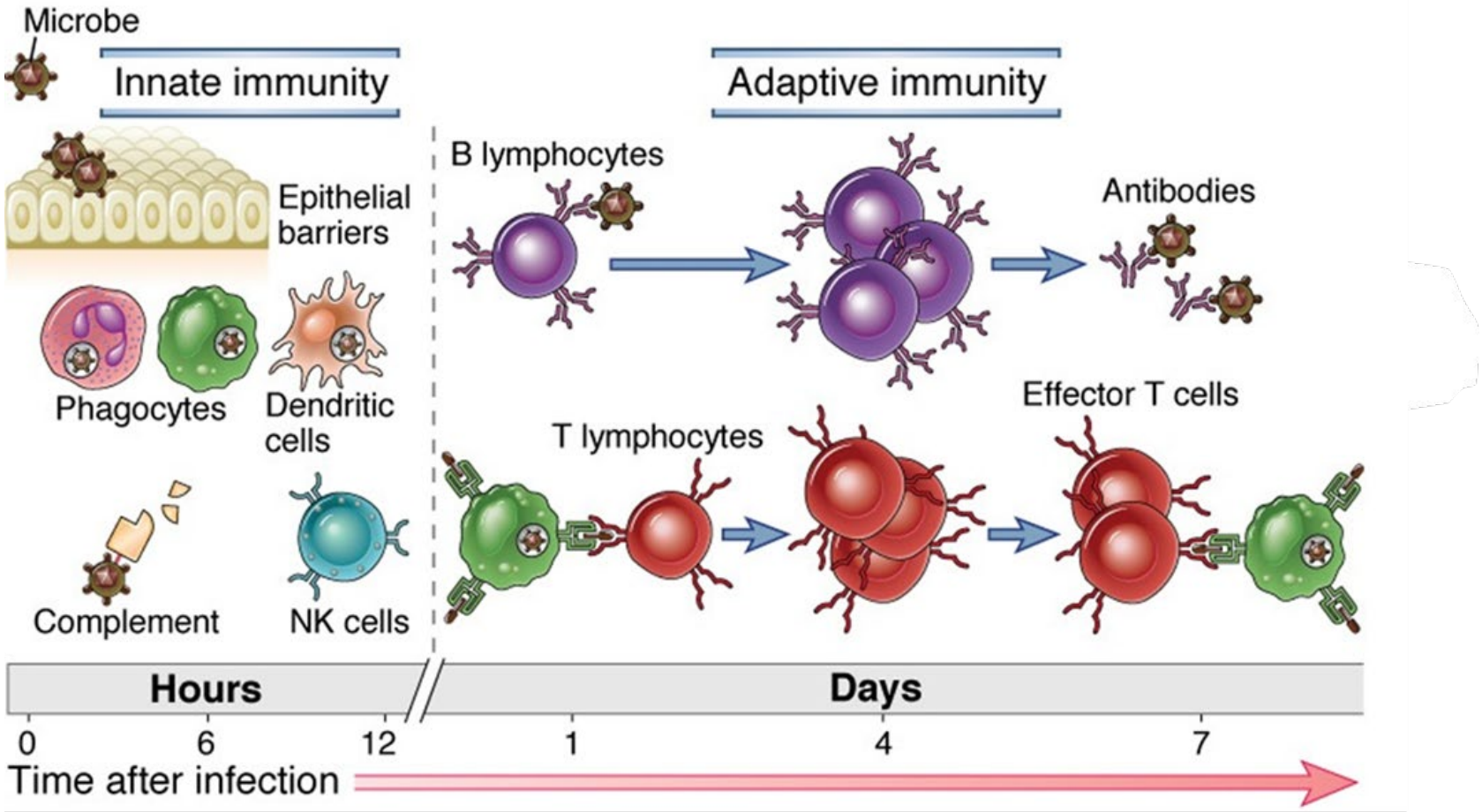
Elimination of microbes

Leukocytes: play major role in the immune system

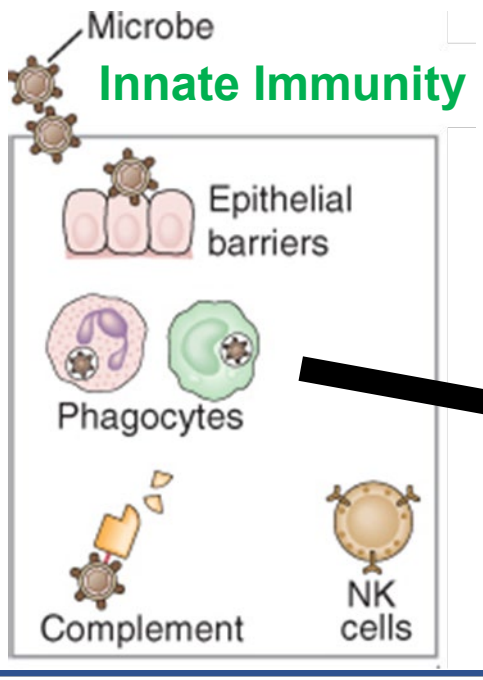
Immune system

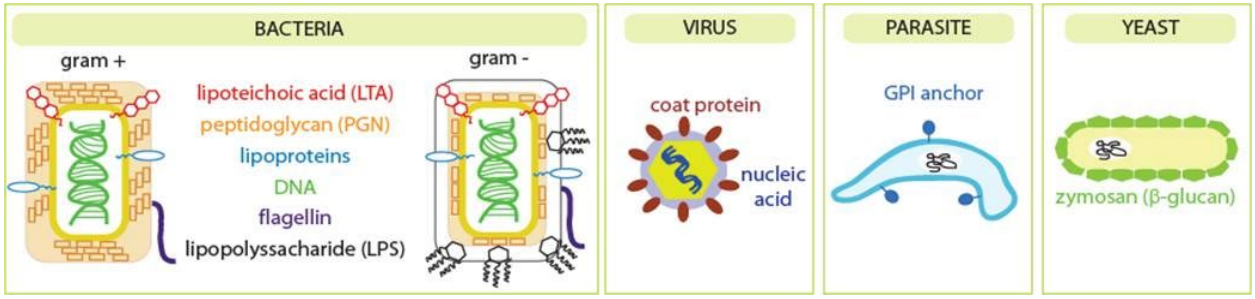
1. Innate immunity

2. Adaptive immunity



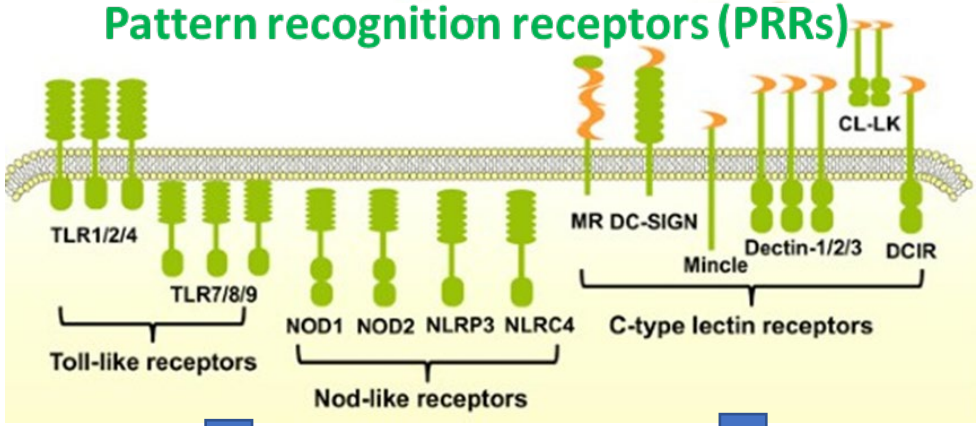
Abbas, Lichtman and Pillai. *Cellular and Molecular Immunology*,





Pathogen-Associated Molecular Patterns (PAMPs)

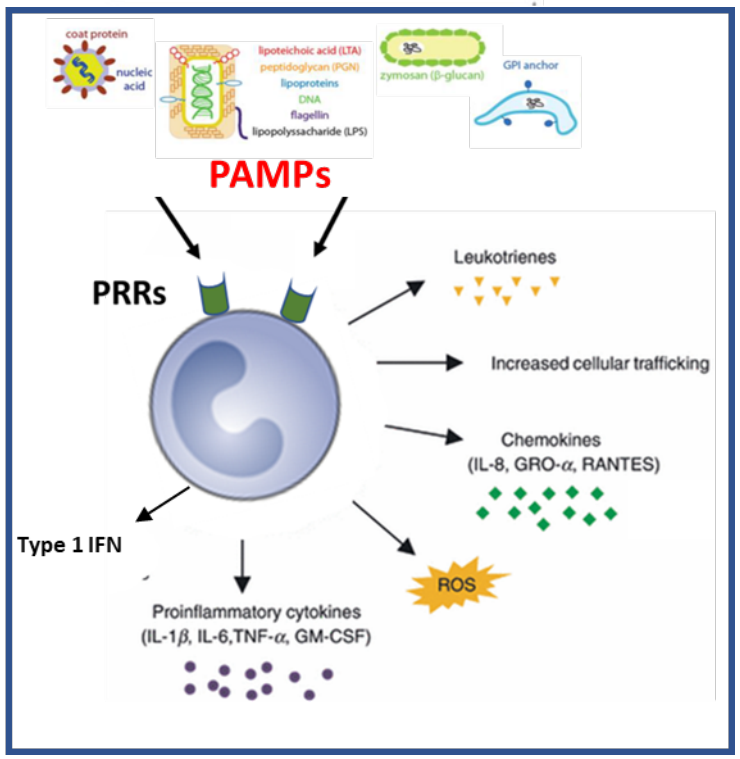
Pattern recognition receptors (PRRs)

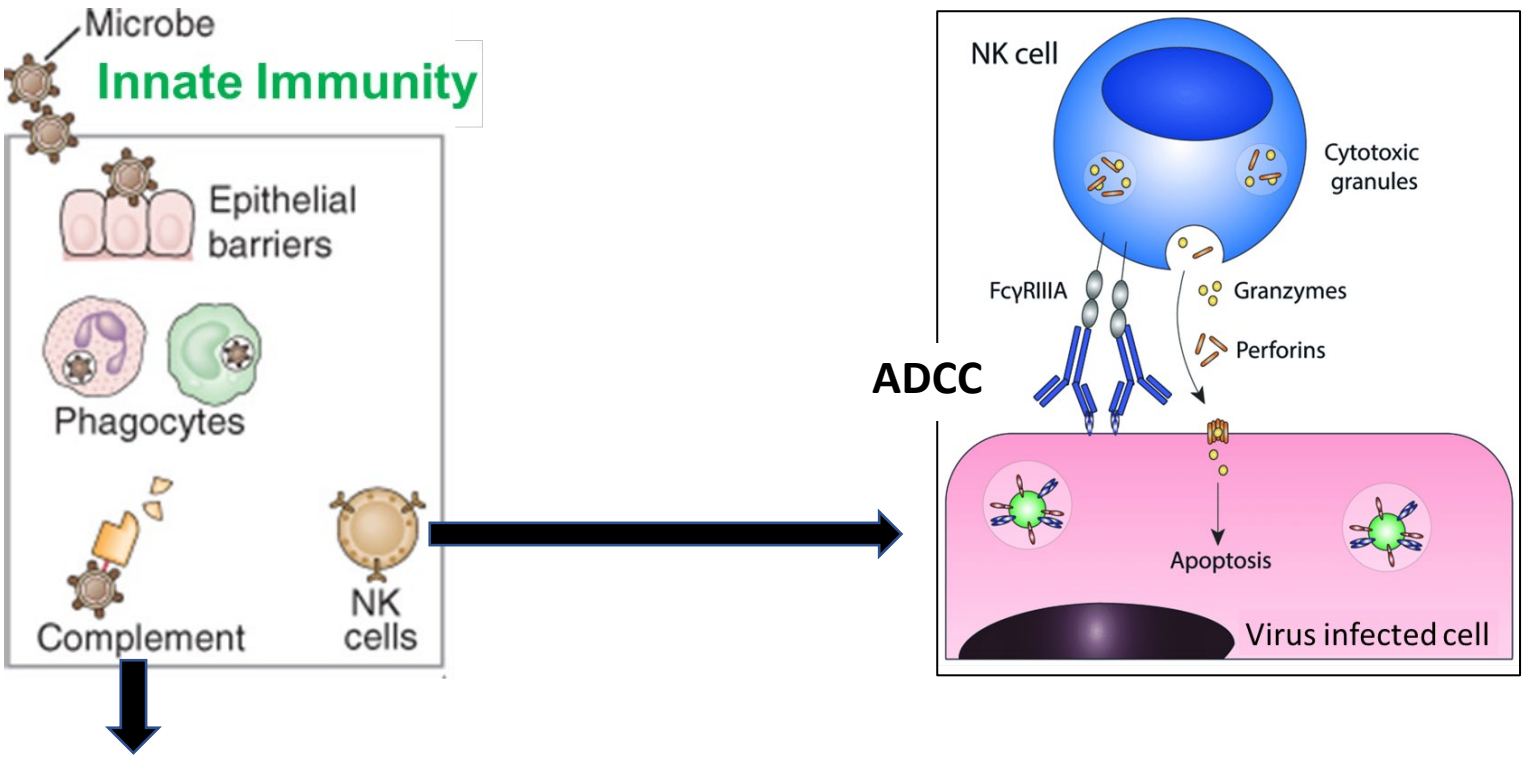


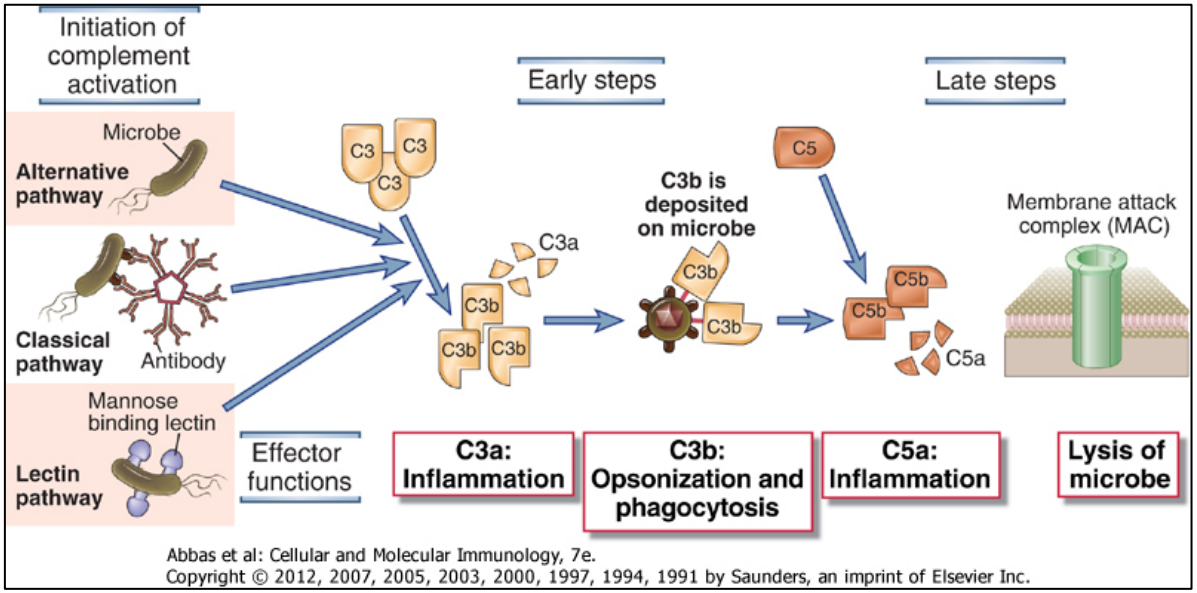
Signal transduction **Phagocytosis**

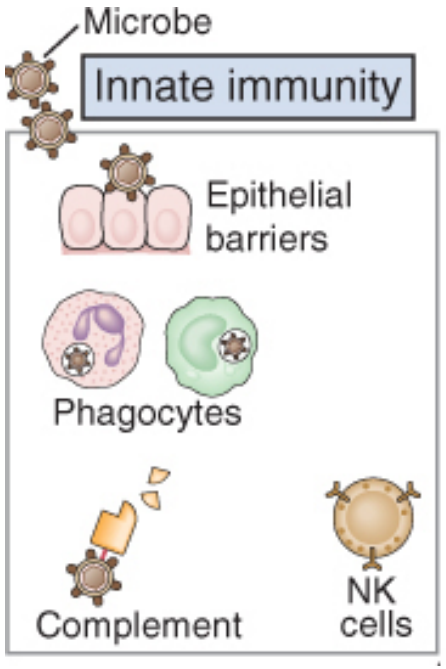
Antigen presentation

Adaptive immunity

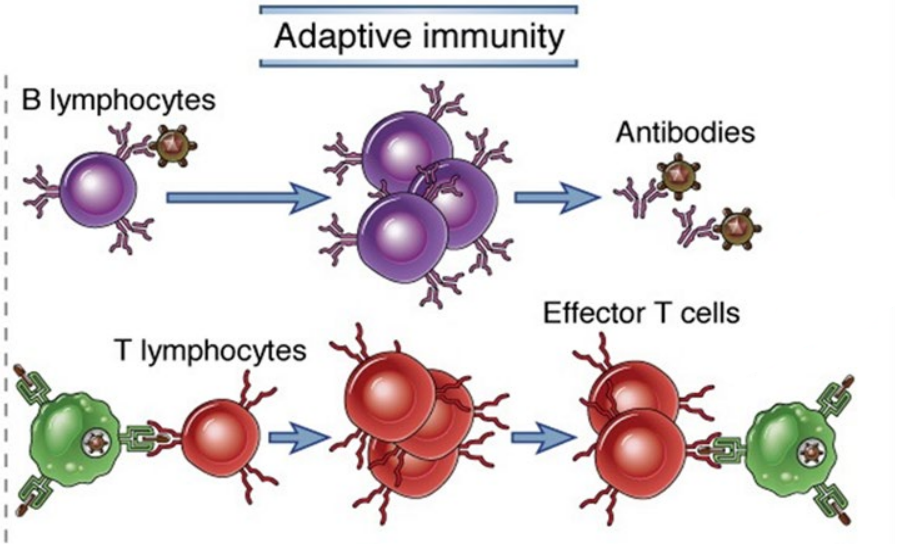








Activation

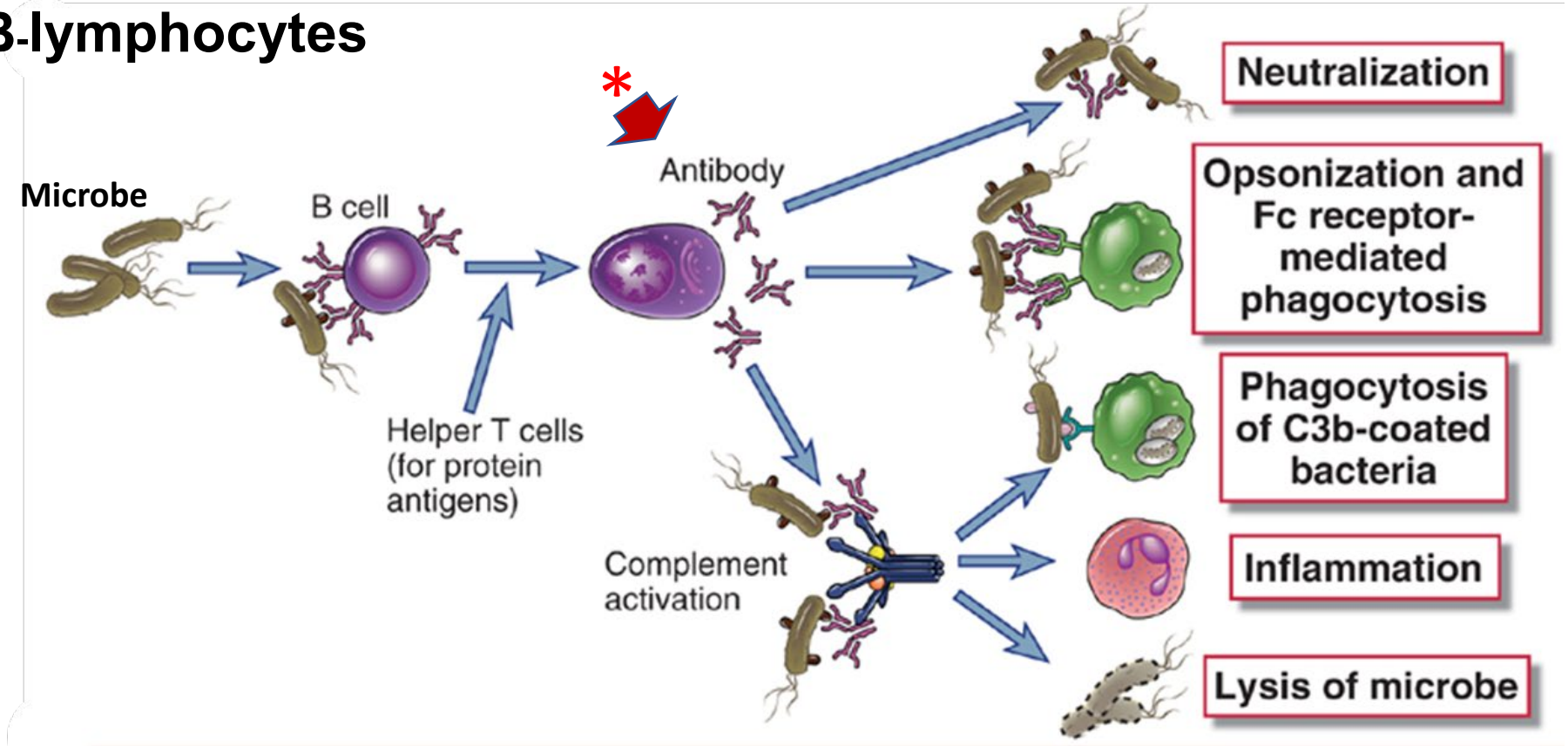


Adaptive Immunity

1. Humoral Mediated Immunity (HMI)
2. Cell-Mediated Immunity (CMI)

Humoral Mediated Immunity (HMI)

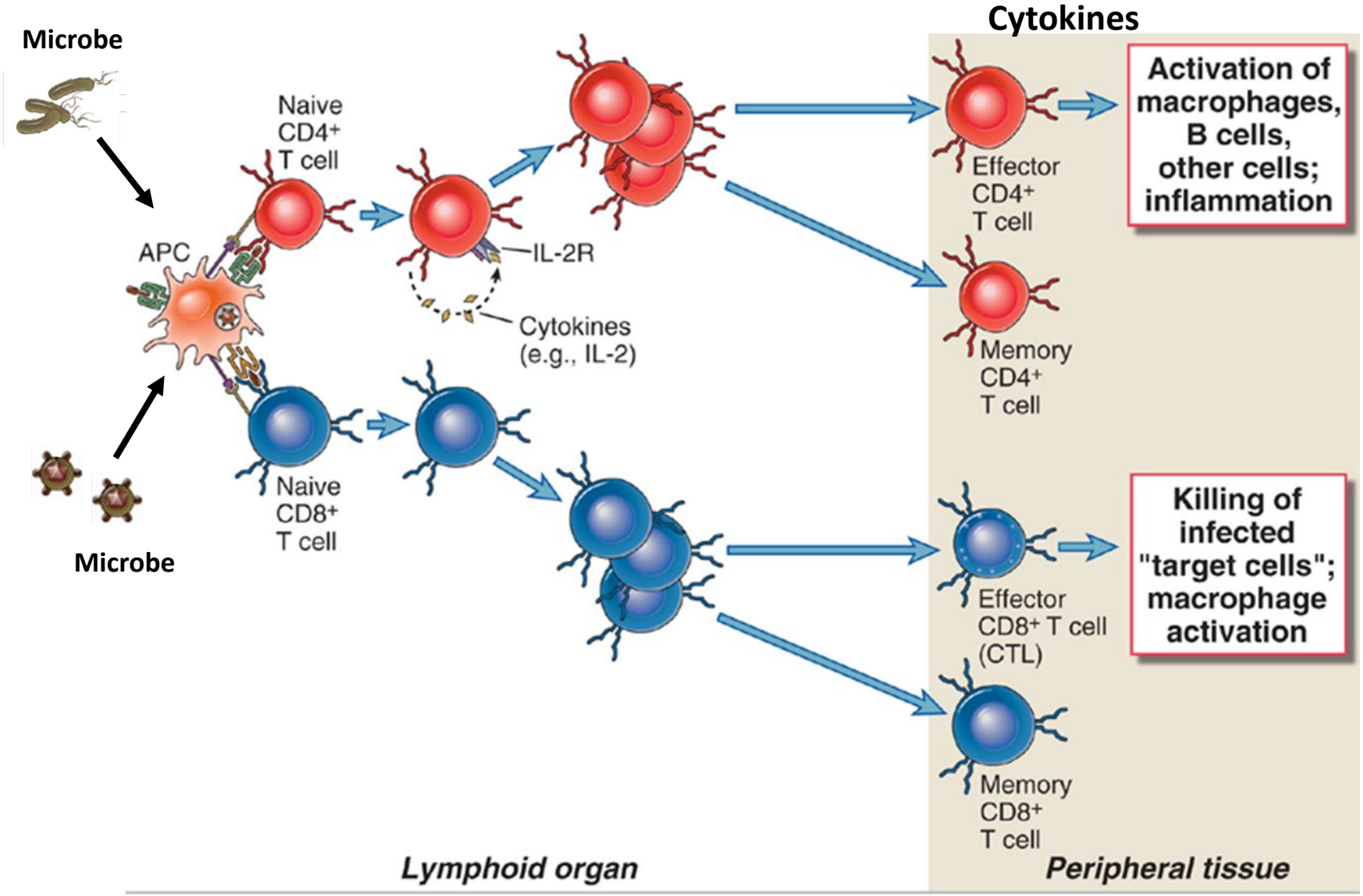
B-lymphocytes



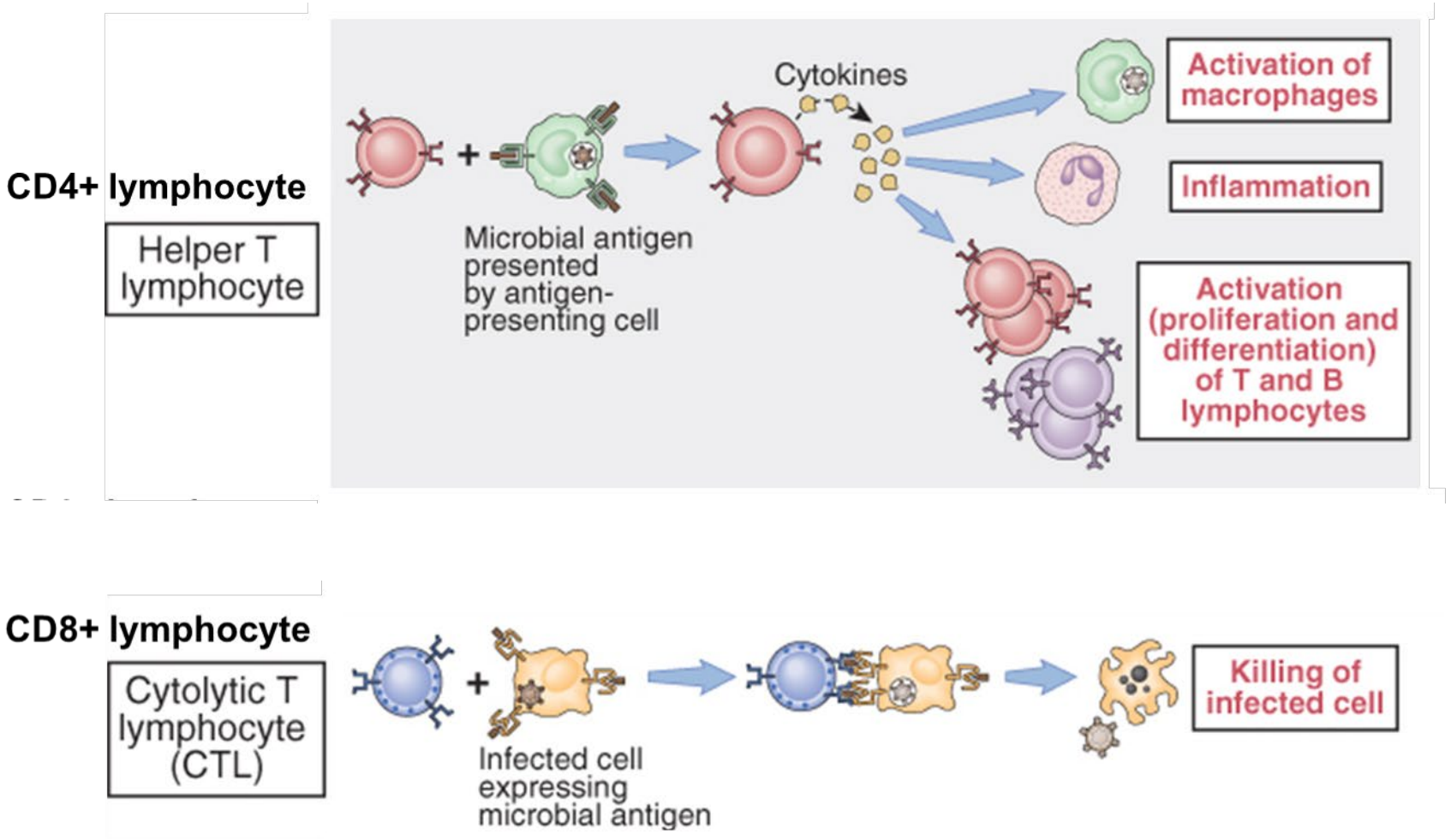
Memory B cells
Immunological Memory

Cell-Mediated Immunity (CMI)

T-lymphocytes: CD4 T cell; CD8 T cells

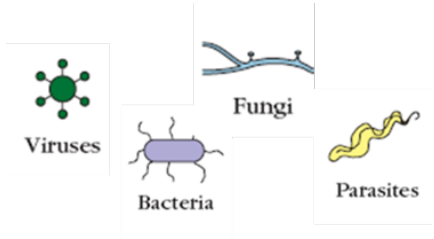


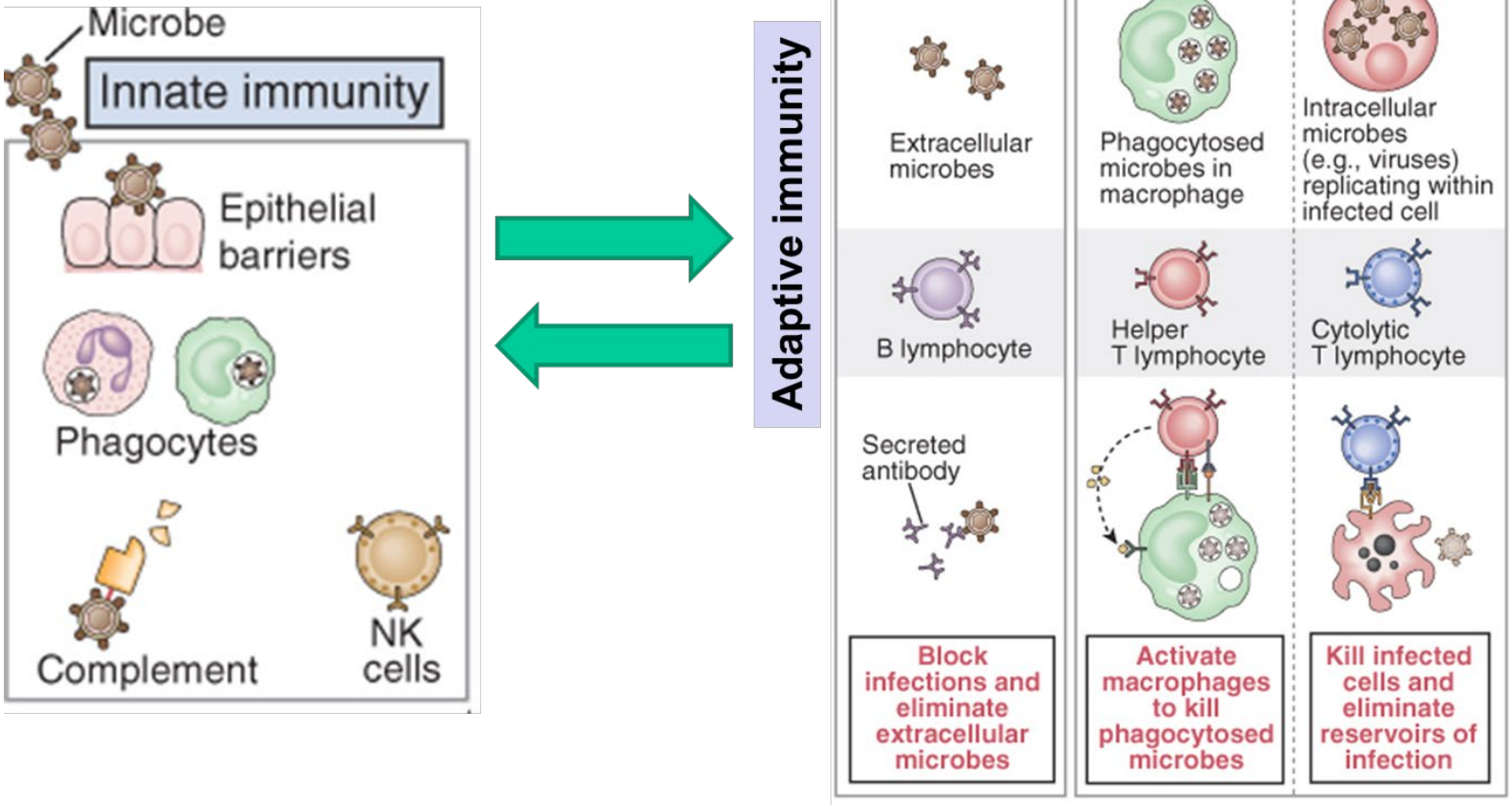
Cell-Mediated Immunity (CMI)



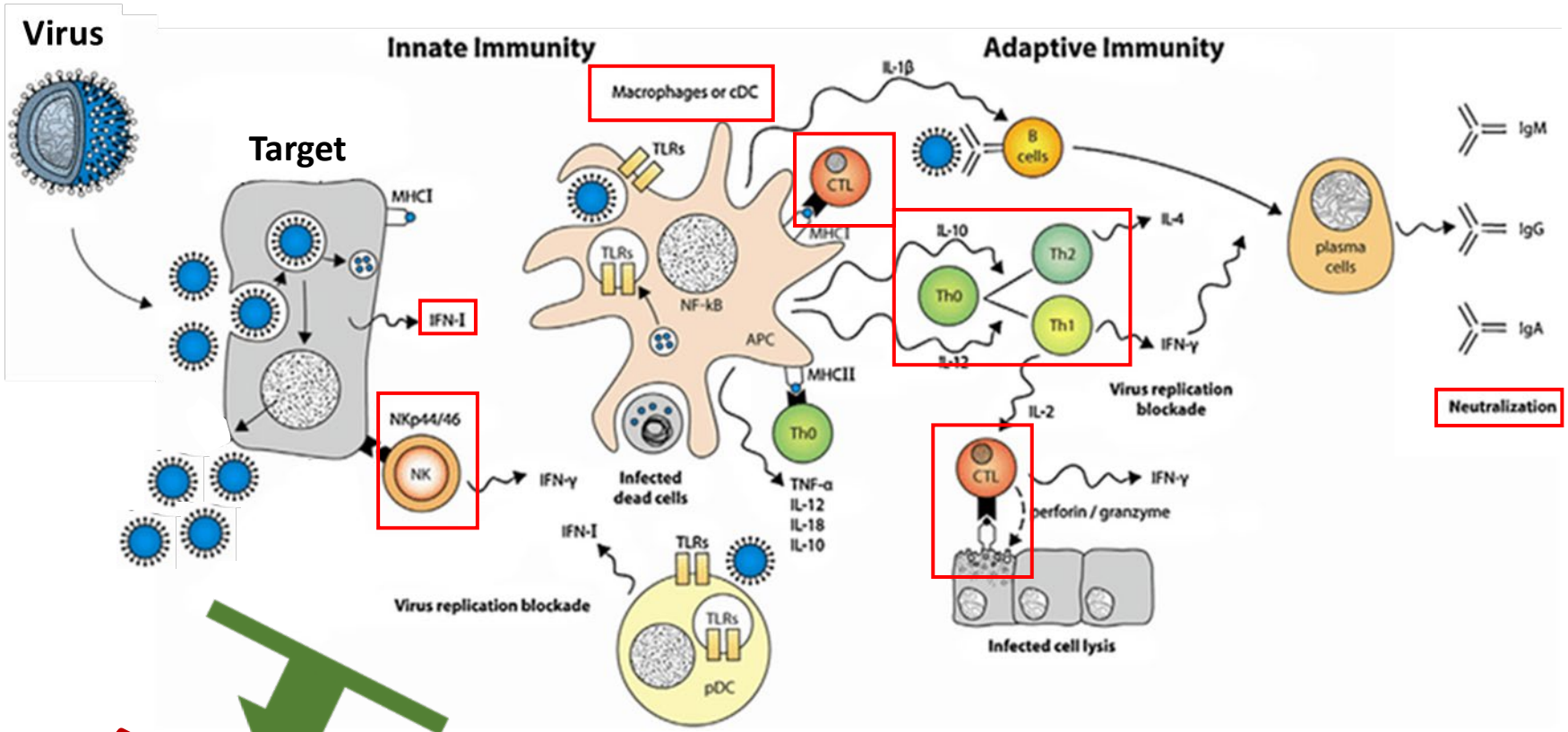
Abbas AK, Lichtman AH. Basic Immunology. 2nd edition, Saunder Elsevier, Philadelphia, PA, USA. 2006.

Immunity to microbial infection



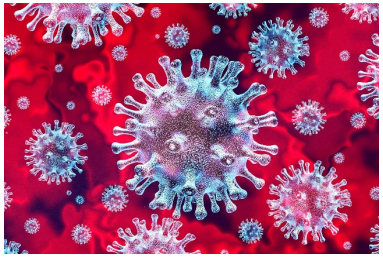


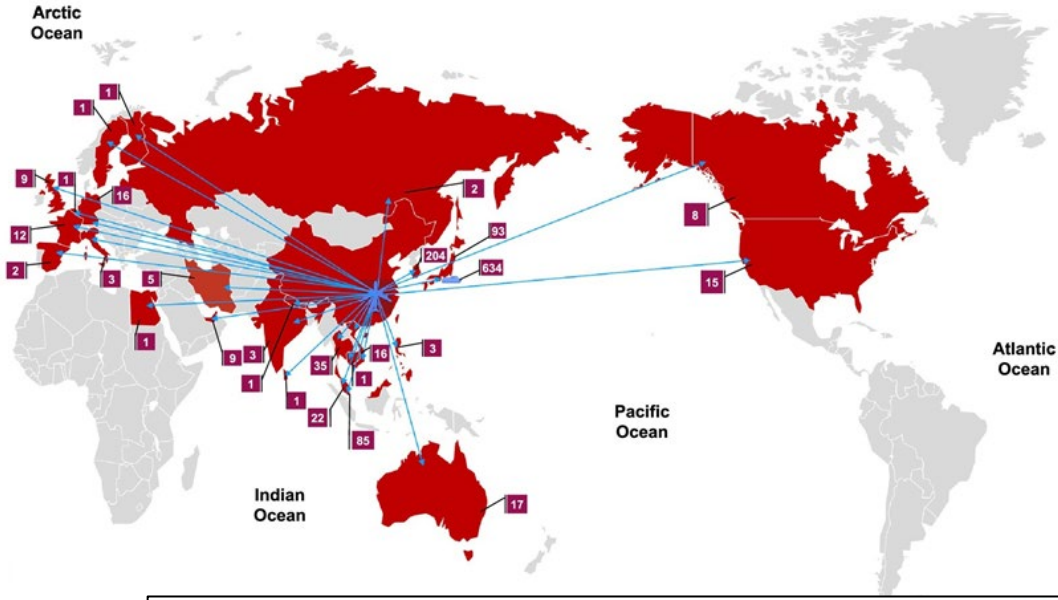
Immunity to Virus Infection



Protection

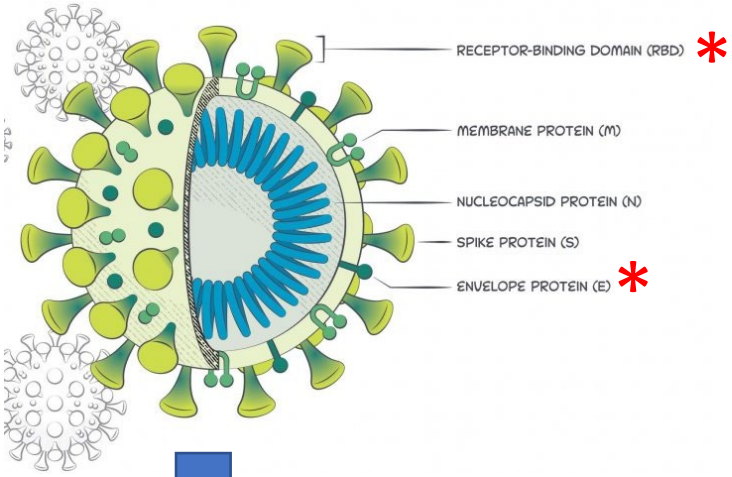
Wuhan
December 2019

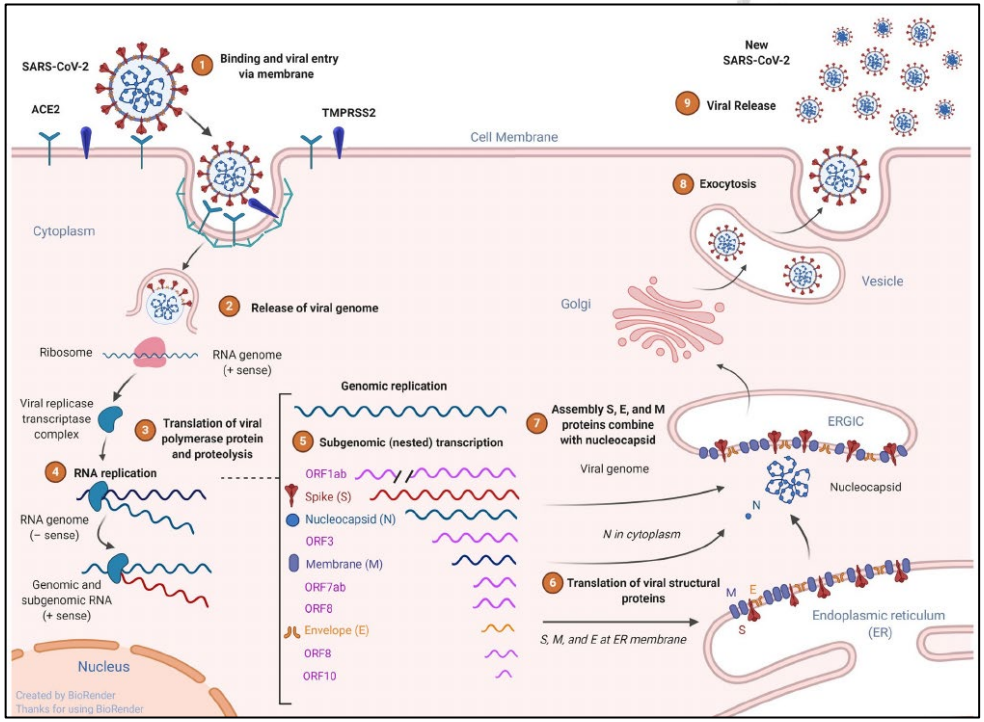




SARS-CoV 2

Family Coronaviridea



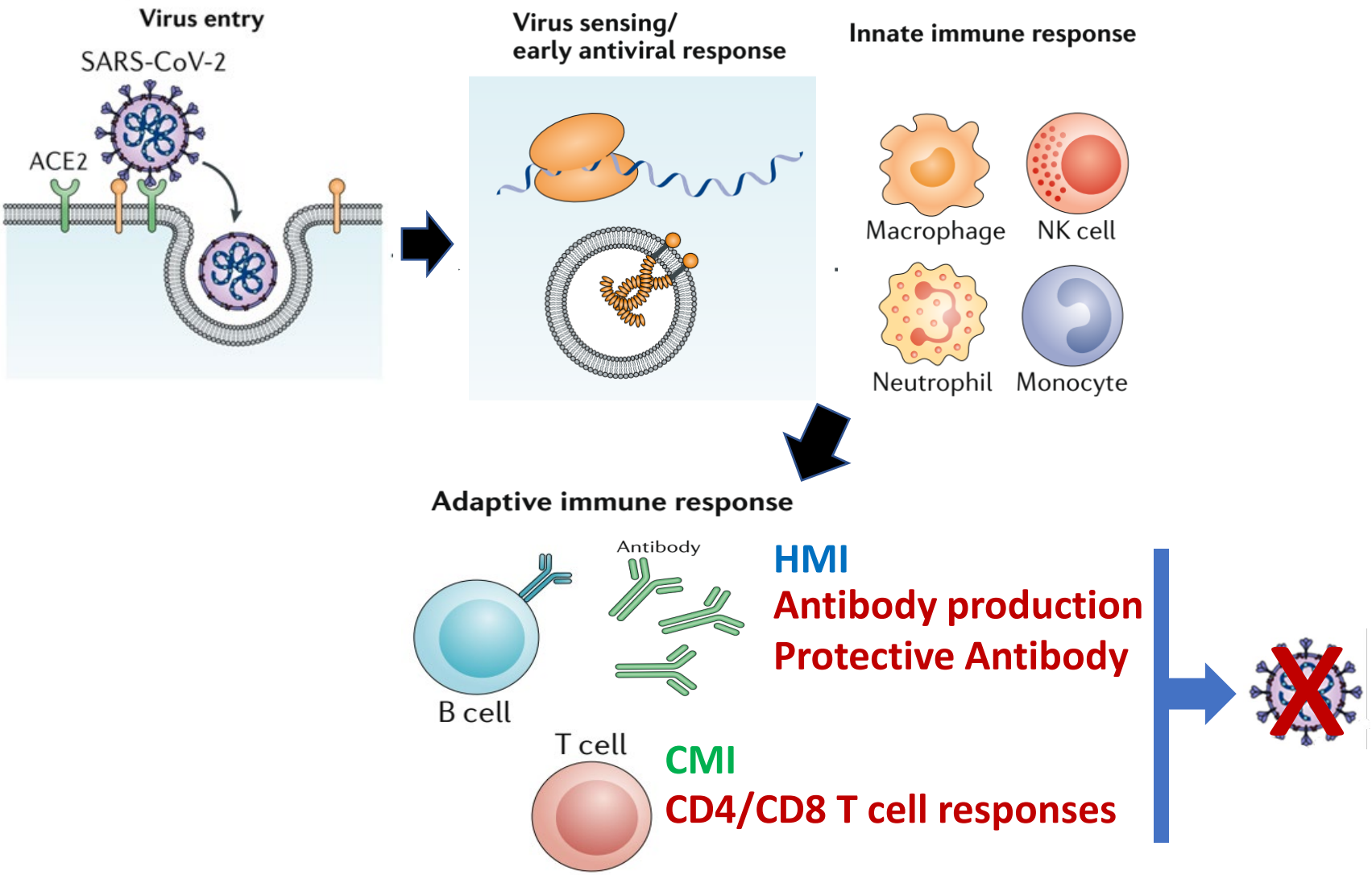


COVID 19 (CORONA VIRUS DISEASE 2019)

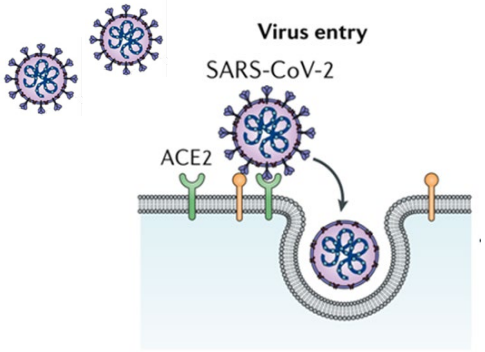
Allergy. 2020;75:1564–1581.

SARS-CoV-2

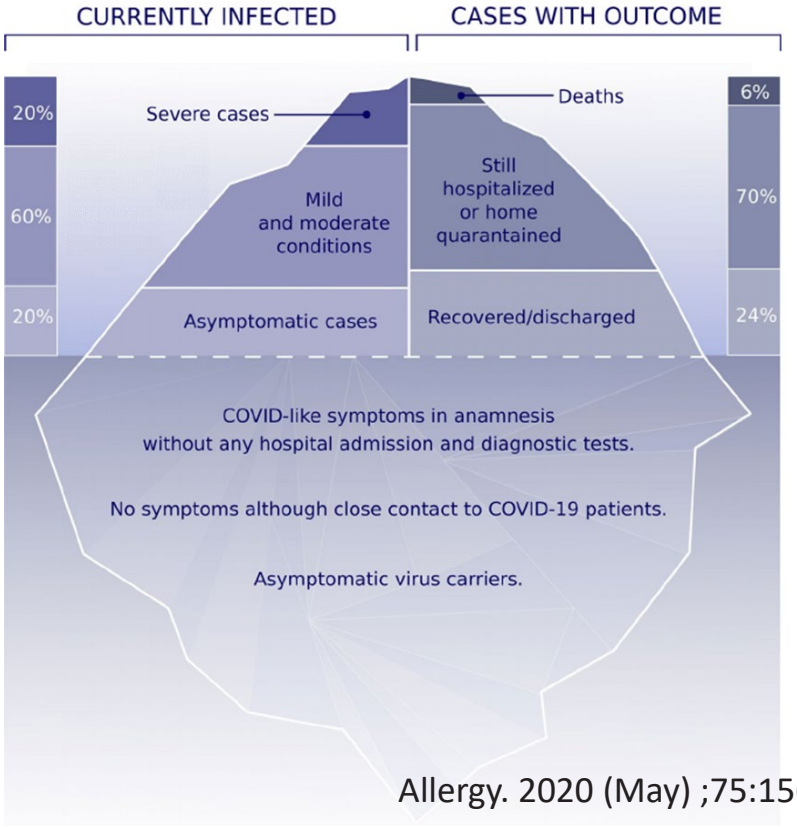
Immune responses



Nat Rev Immunol. 2020 Jun 11.

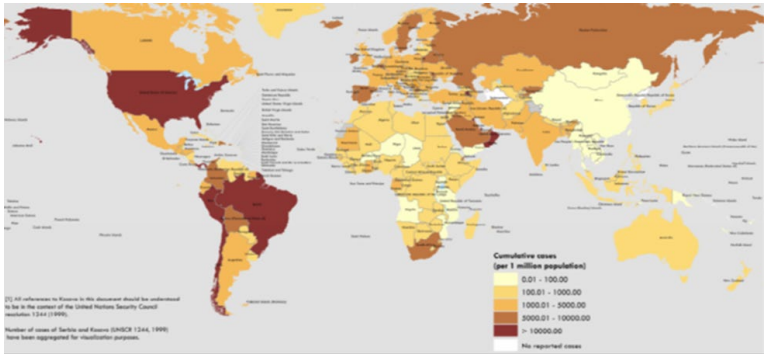


SARS-CoV 2 infection

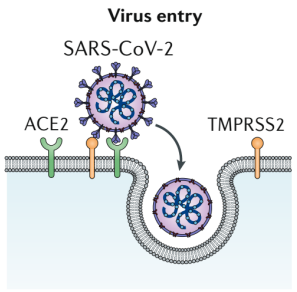


Allergy. 2020 (May) ;75:1564–1581.

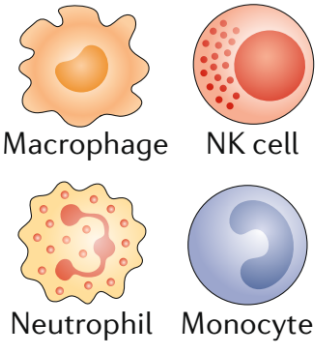
Pandemics



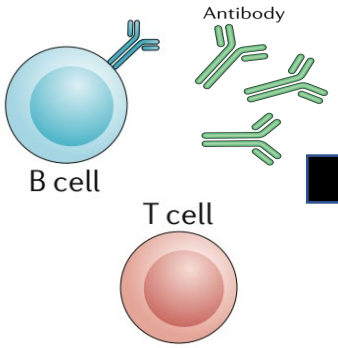
SARS-CoV-2



Innate immune response



Adaptive immune response



????

HMI

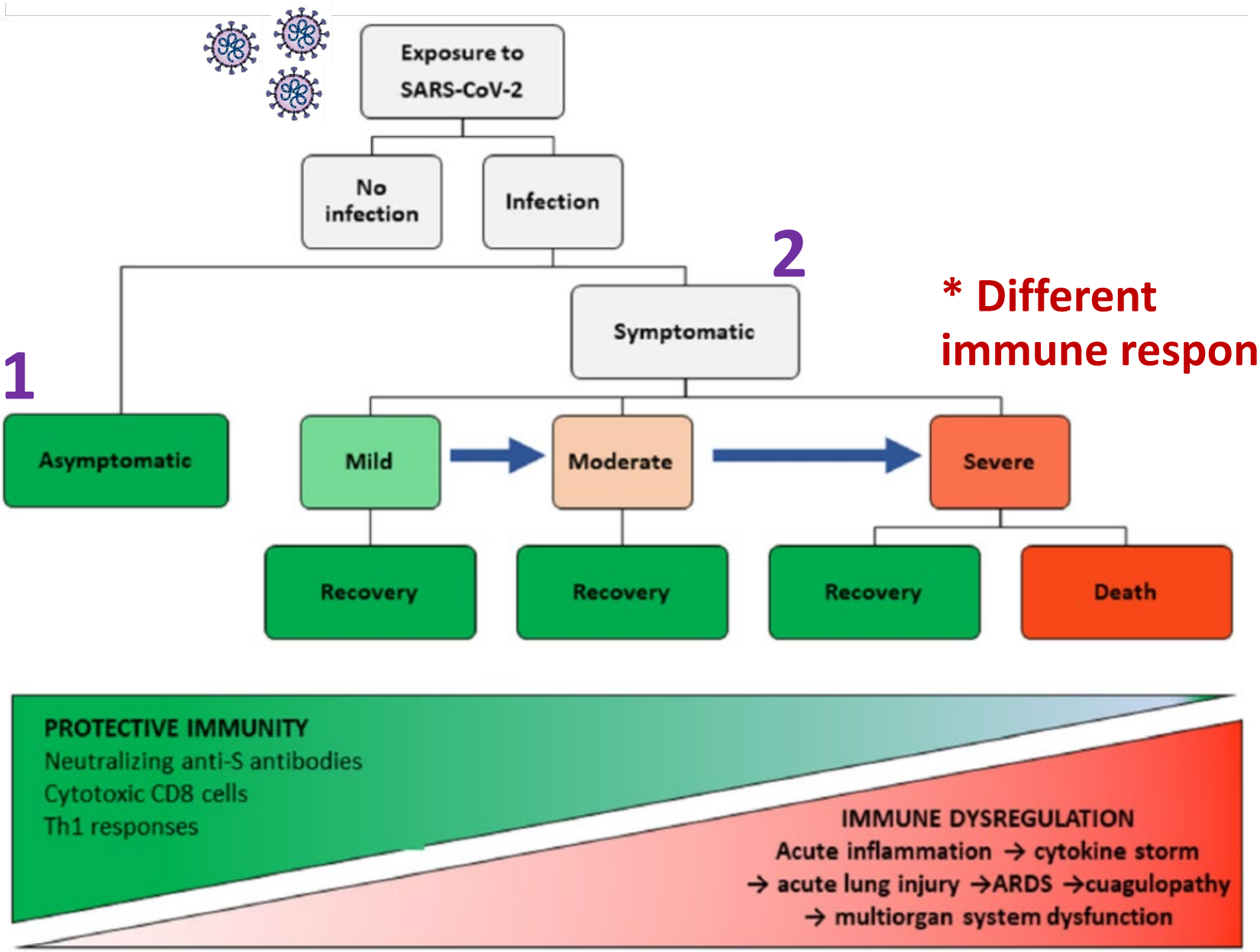
Antibody production ?

Protective Antibody ?

CMI

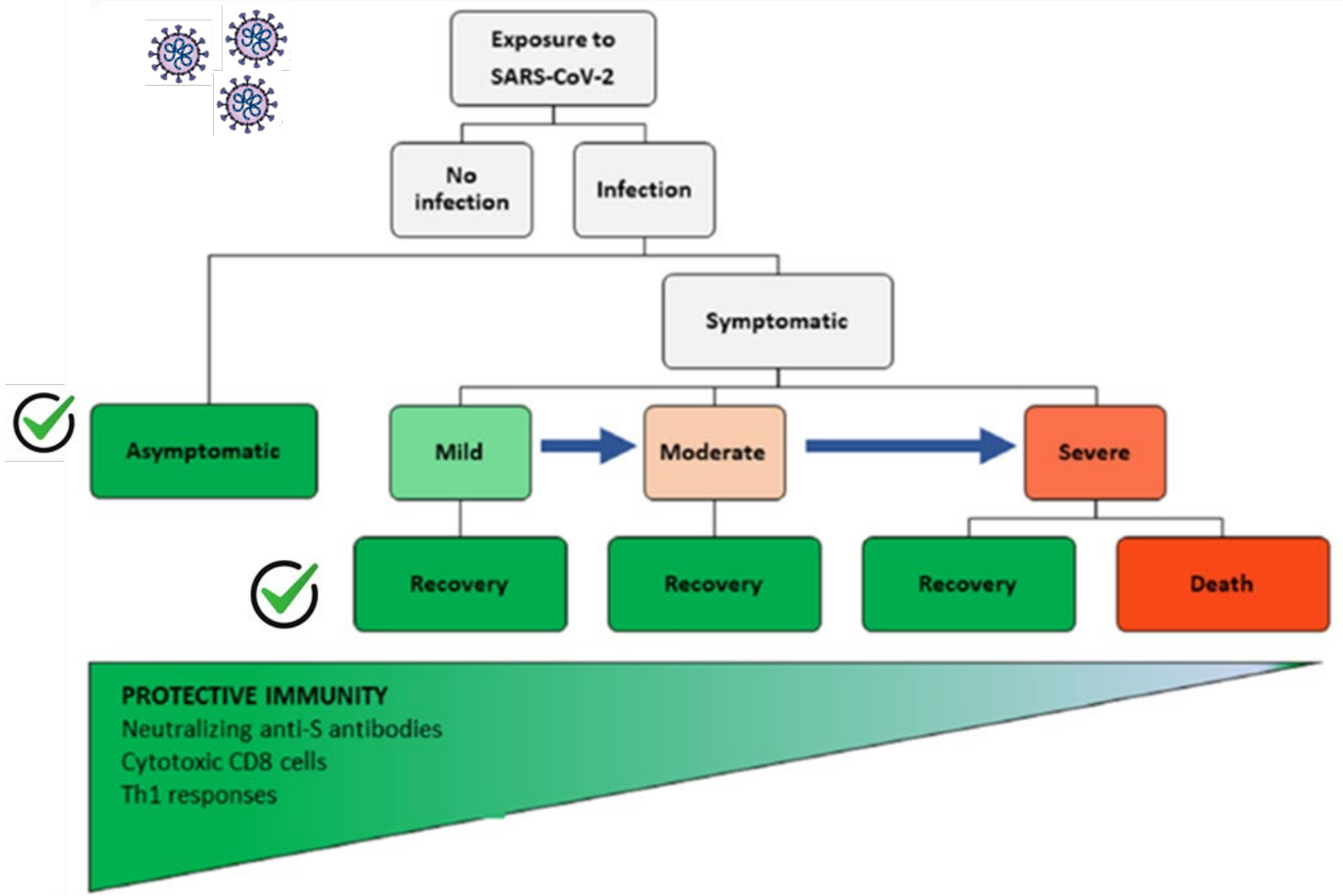
T cell responses ?

Immune Responses to SARS-CoV-2 infection



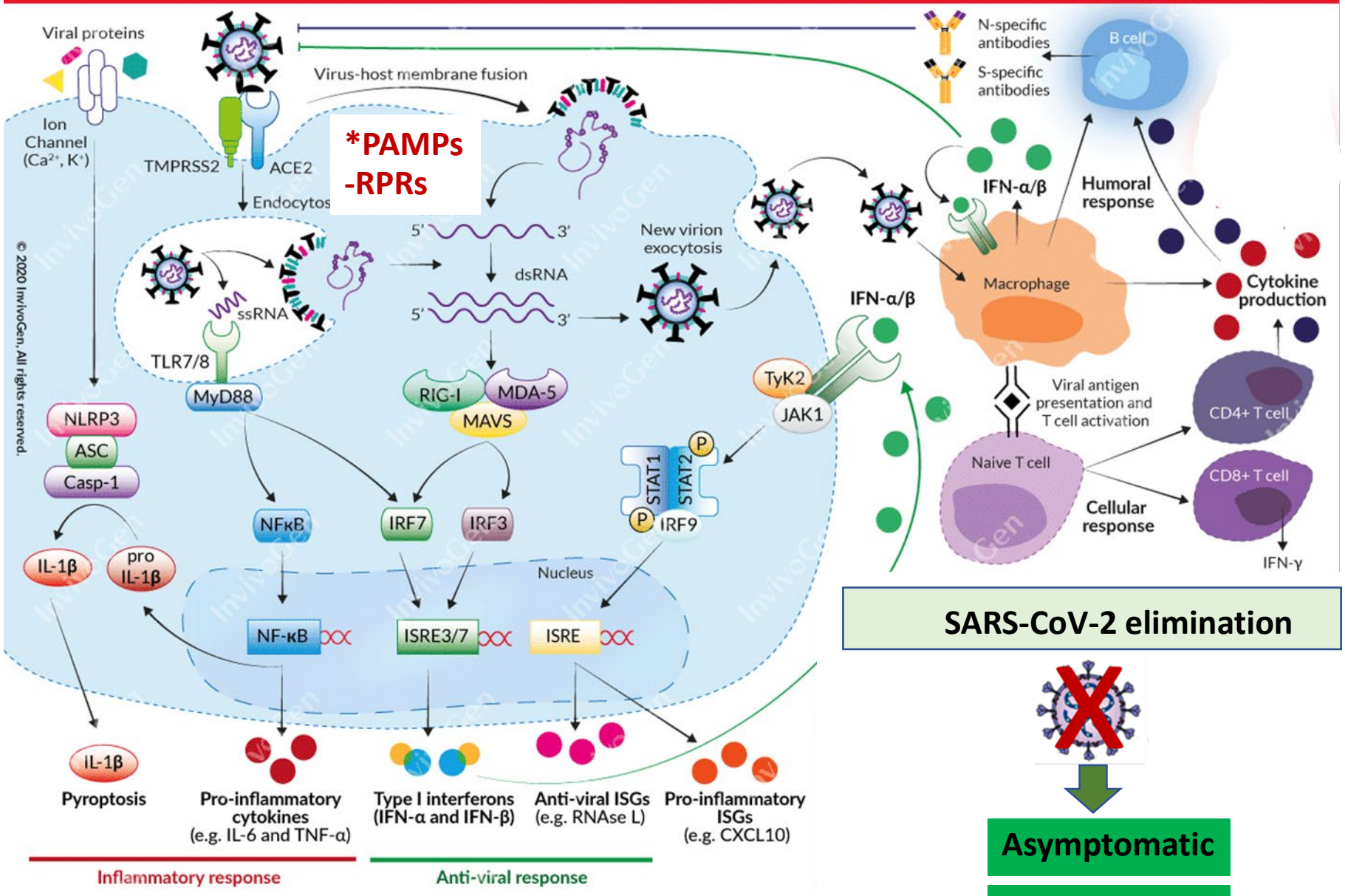
*** Different immune responses**

Frontiers in Immunology. June 2000



SAR-CoV-2 induce protective immune responses

Predicted host immune responses to SARS-CoV-2

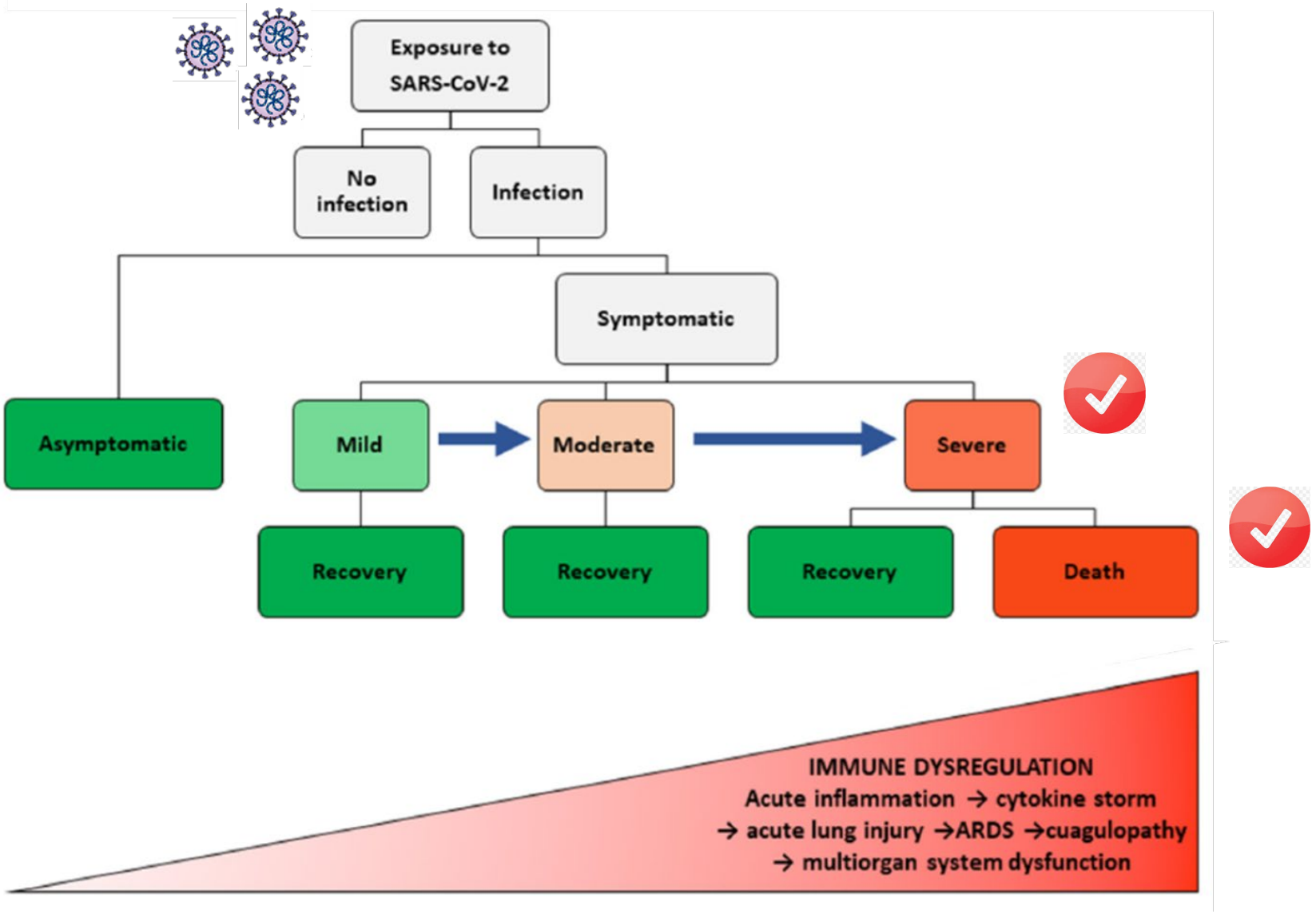


SARS-CoV-2 elimination

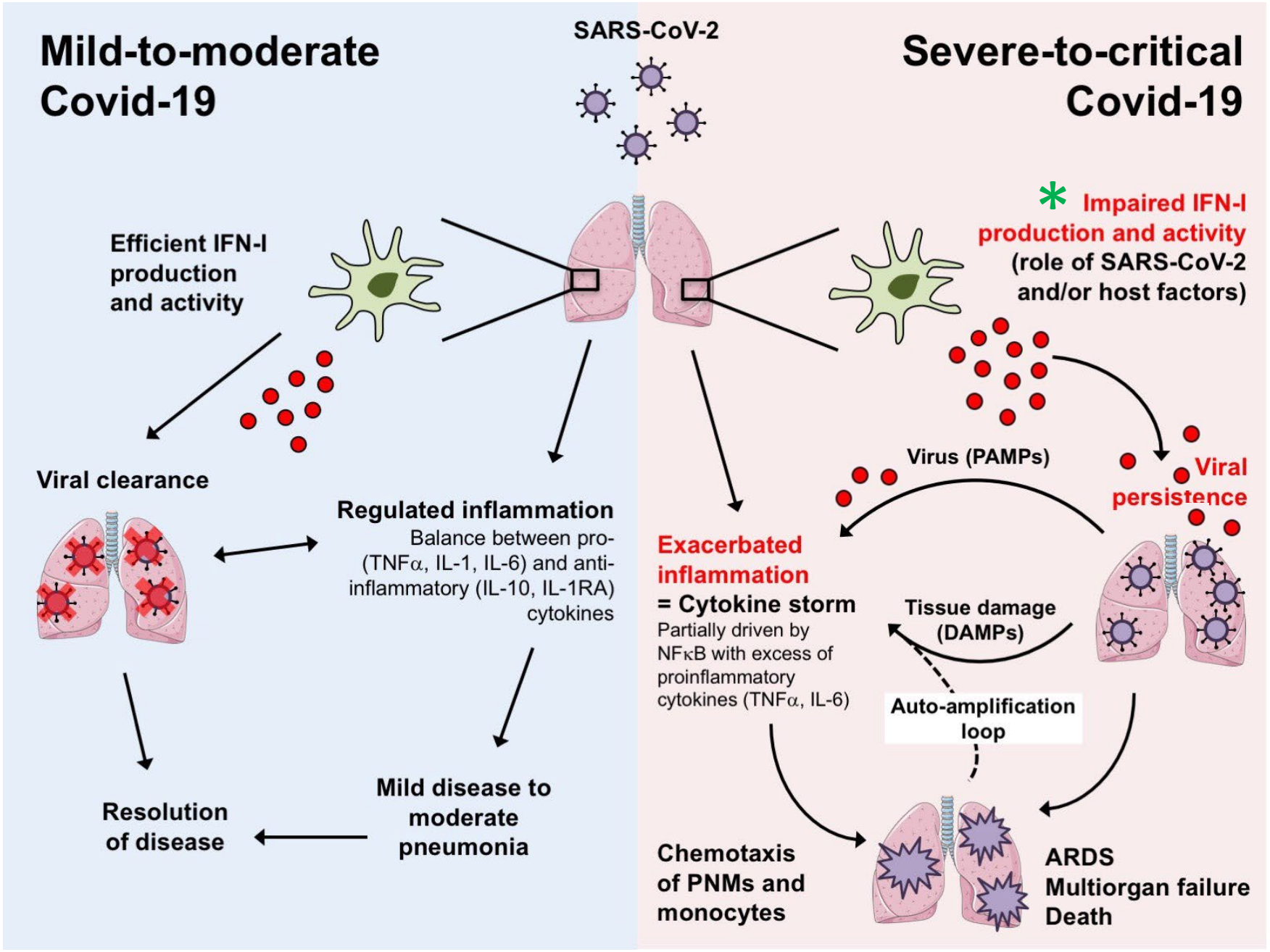
Asymptomatic

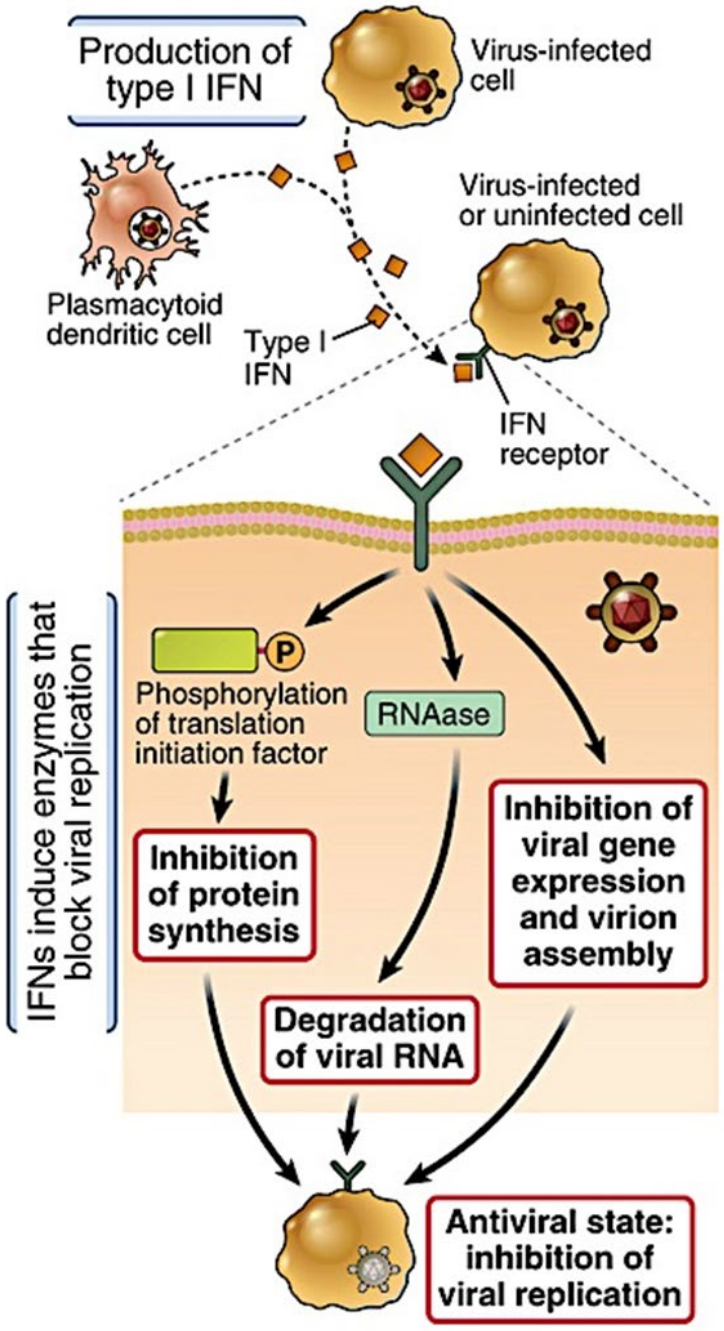
Recovery

SAR-CoV-2 induce protective immune responses



SAR-CoV-2 induce Hyper-immune responses

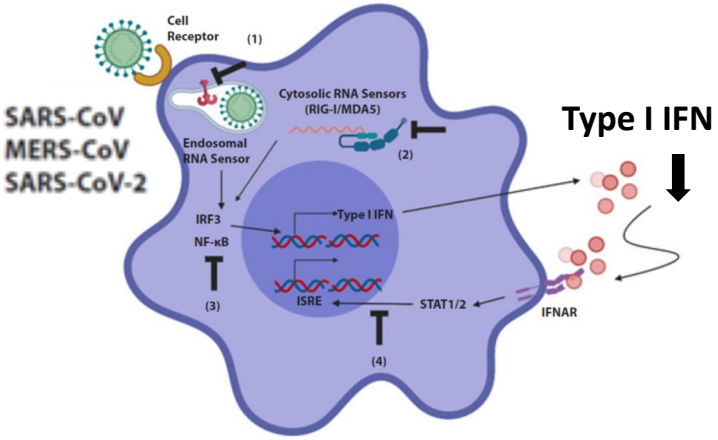

Mild-to-moderate Covid-19
SARS-CoV-2
Severe-to-critical Covid-19
Efficient IFN-I production and activity
* Impaired IFN-I production and activity (role of SARS-CoV-2 and/or host factors)
Viral clearance
Regulated inflammation
Balance between pro- (TNFα, IL-1, IL-6) and anti-inflammatory (IL-10, IL-1RA) cytokines
Virus (PAMPs)
Viral persistence
Exacerbated inflammation
= Cytokine storm
Partially driven by NFκB with excess of proinflammatory cytokines (TNFα, IL-6)
Tissue damage (DAMPs)
Auto-amplification loop
Resolution of disease
Mild disease to moderate pneumonia
Chemotaxis of PNMs and monocytes
ARDS
Multiorgan failure
Death



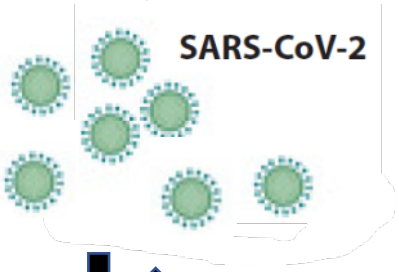
Severe-to-critical Covid-19

Impaired IFN-I production and activity (role of SARS-CoV-2 and/or host factors)

Viral persistence



*Inhibit Type I IFN



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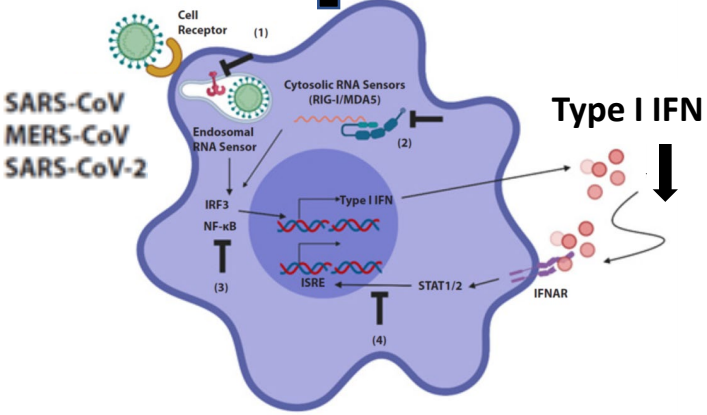
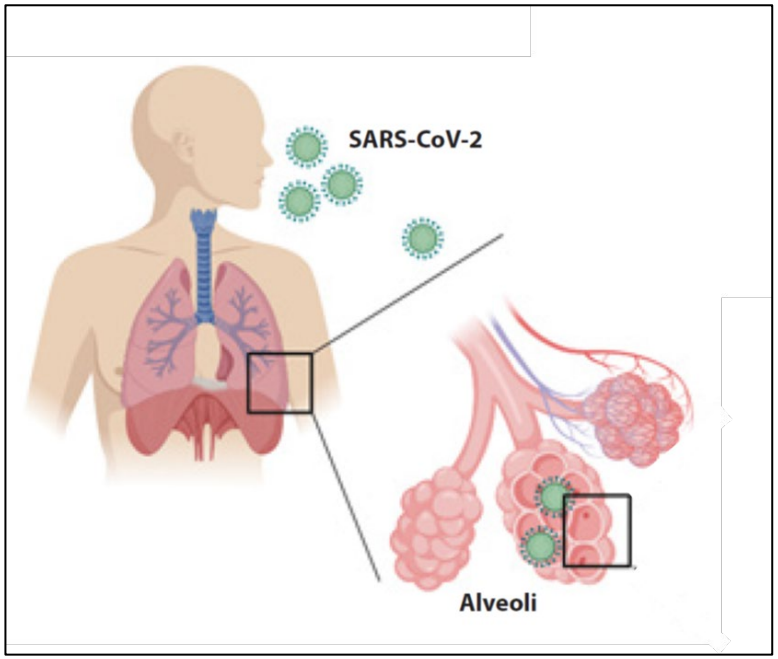
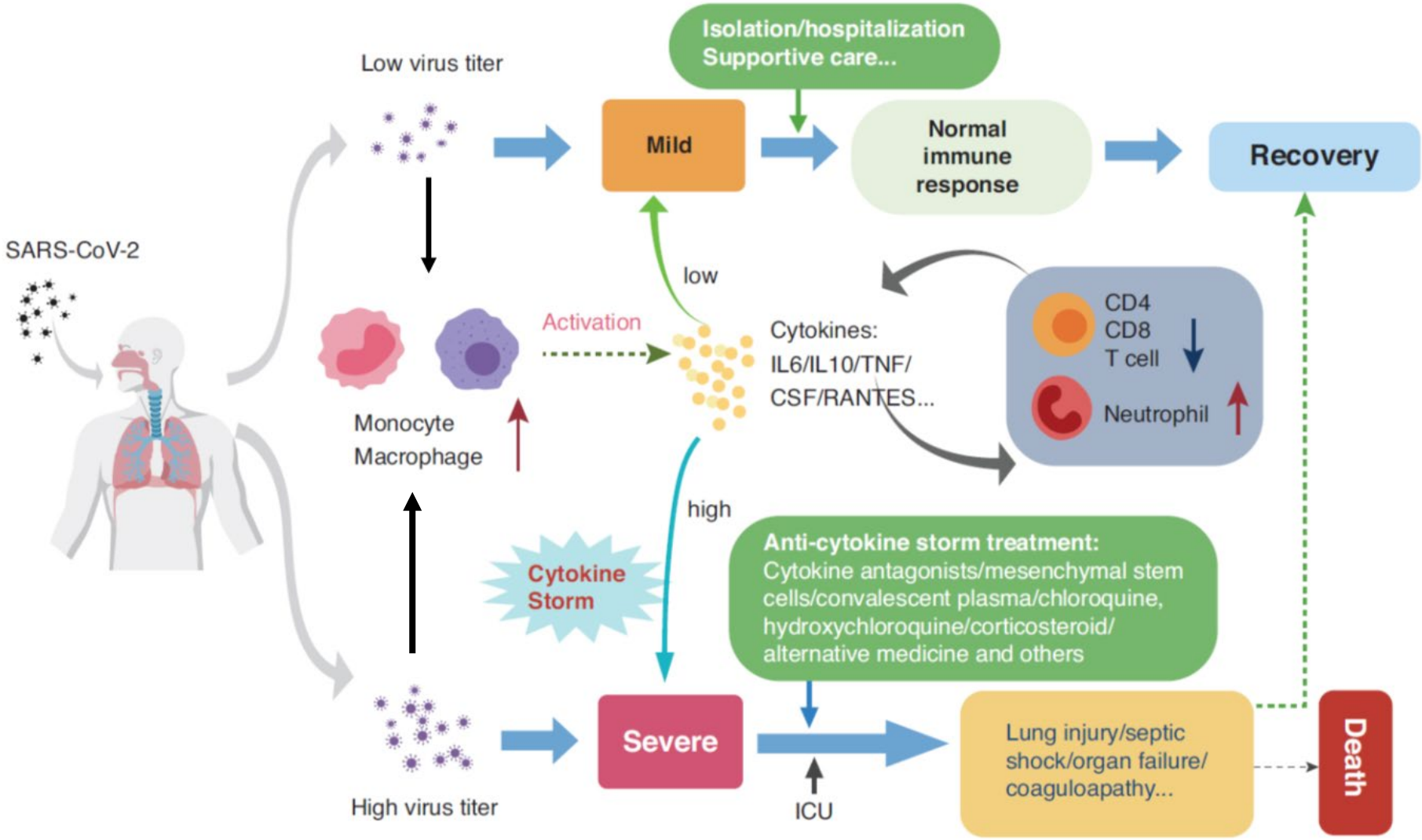




IMMUNE DYSREGULATION
Acute inflammation → cytokine storm
→ acute lung injury →ARDS →cuagulopathy
→ multiorgan system dysfunction

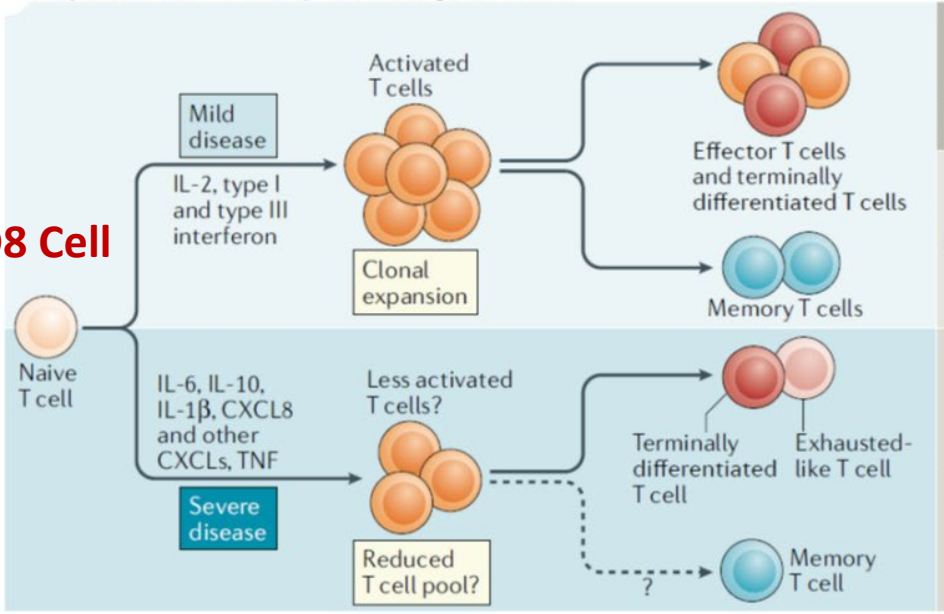
APJAI; 2020



J Leucocyte Biology; 2020

Proposed CD8⁺ T cell response during COVID-19

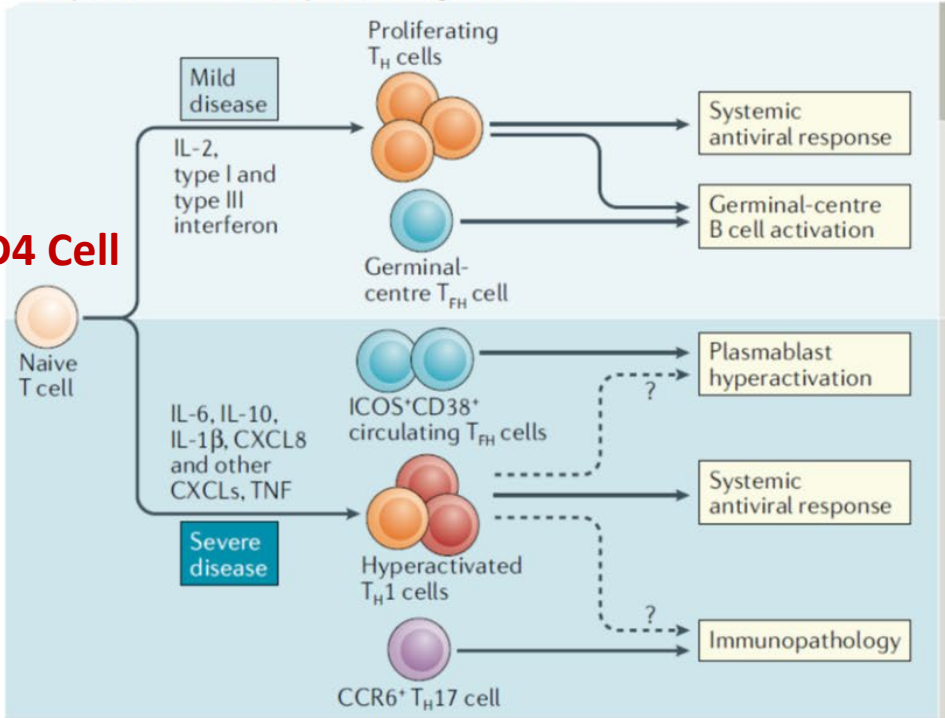
CD8 Cell



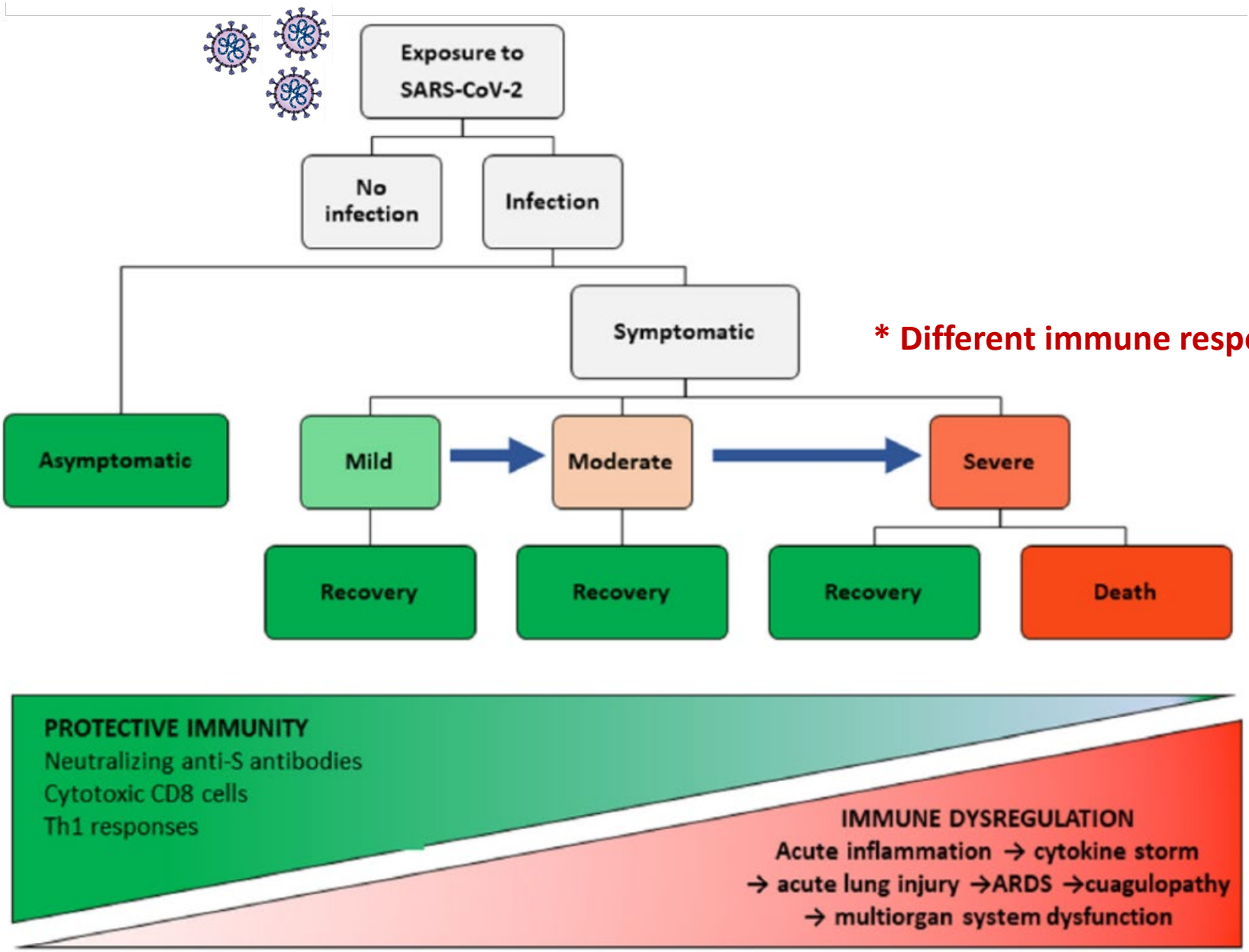
Cell number	TCR clonality	Cell cycle state	Cytokines, chemokines and cytotoxicity	Co-inhibitory signals
Normal or increased	**Dominant clones detected**	**Ki67$^{+/-}$**	**IFNγ^{+}** IL-2^{+} CD107a^{++} **TNF^{+}** **GZMB^{+}**	**PD1$^{+/-}$** **TIM3$^{+/-}$** **CD38^{+}** CD39$^{+/-}$
Strongly decreased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

Proposed CD4⁺ T cell response during COVID-19

CD4 Cell



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^{+}

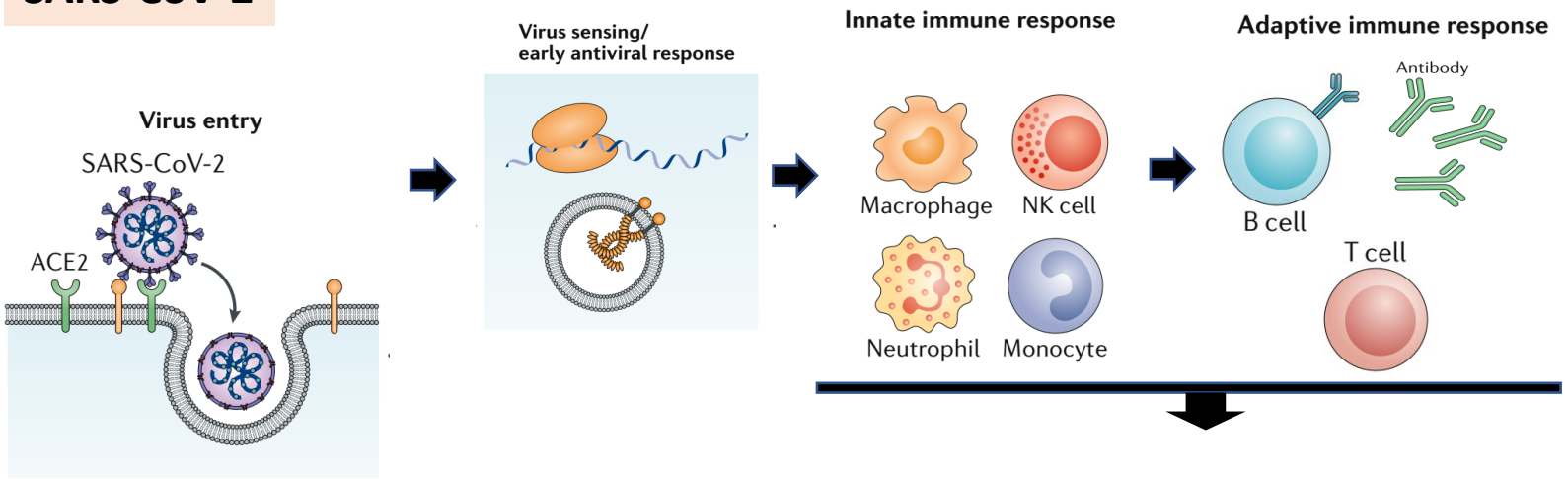


*** Different immune responses**

Frontiers in Immunology. June 2000

Immune responses to viral infection

SARS-CoV-2



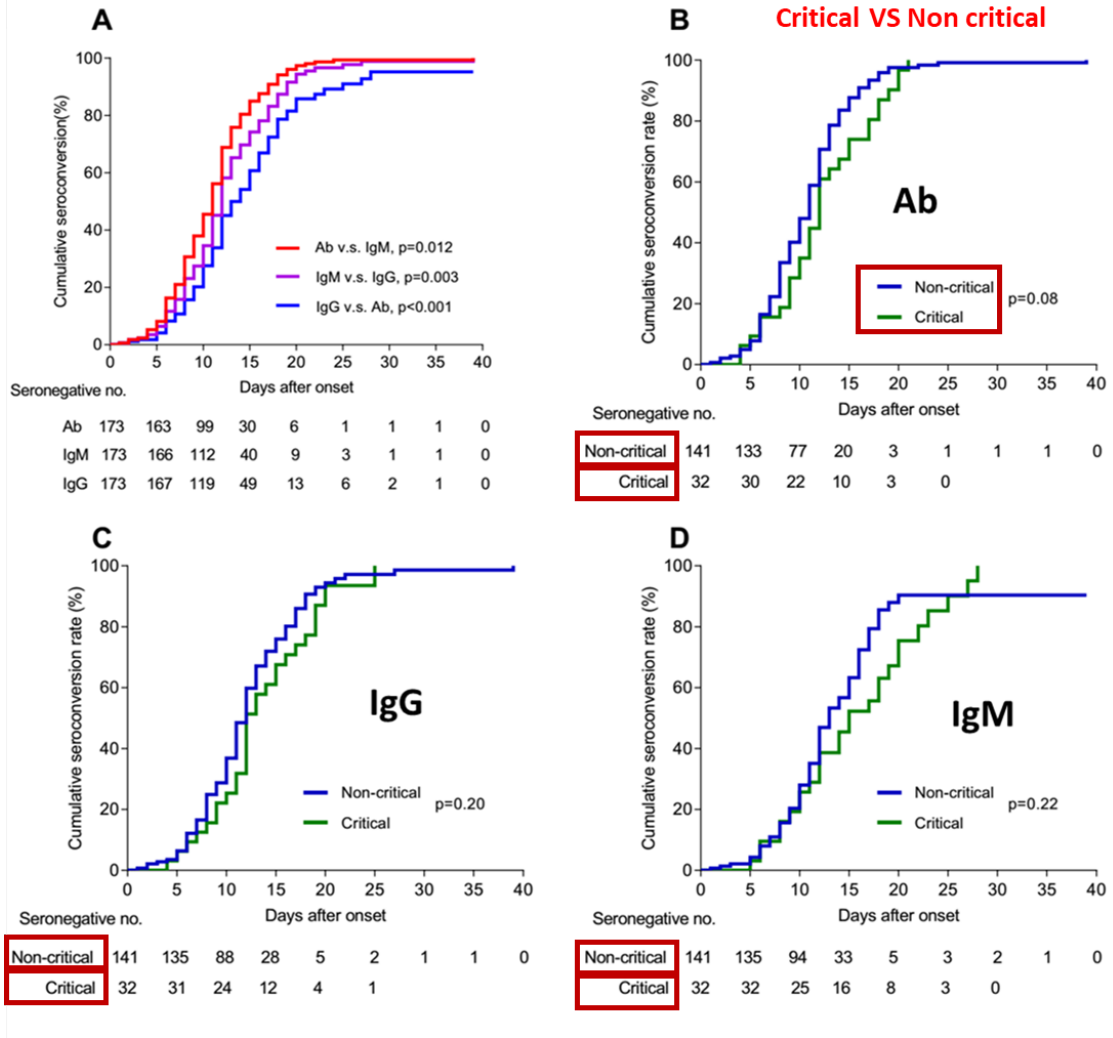
HMI

Antibody production ?

Protective Antibody ?

Nat Rev Immunol. 2020 Jun 11.

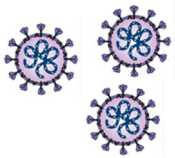
Antibody production ?



N=173 COVID-19 patients confirmed SARS-CoV-2

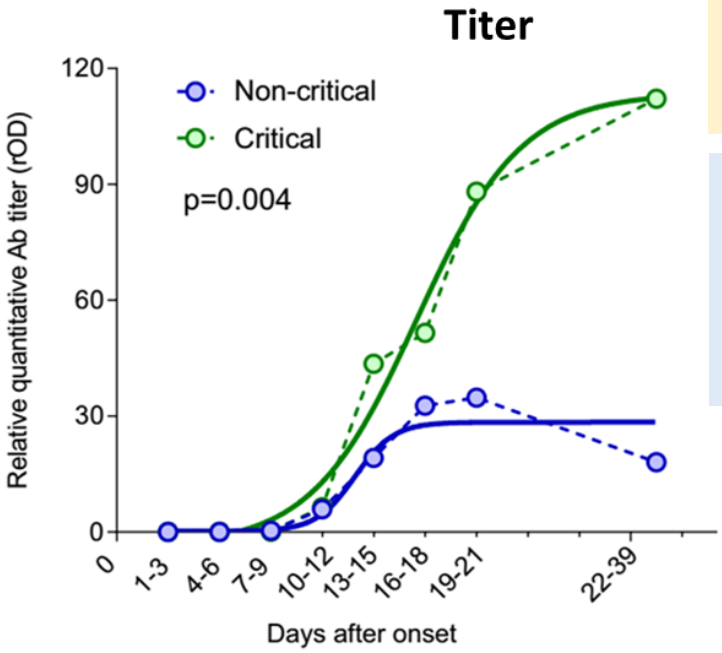
ELISA
Antigen:
SARS-CoV-2 S protein with RBD

CARS-CoV-2



✓ **Antibody production**
IgG, IgM
Non-critical
Critical

Clin Infect Dis; 2020 Mar 28; Zhao J, et. al. (CHINA)

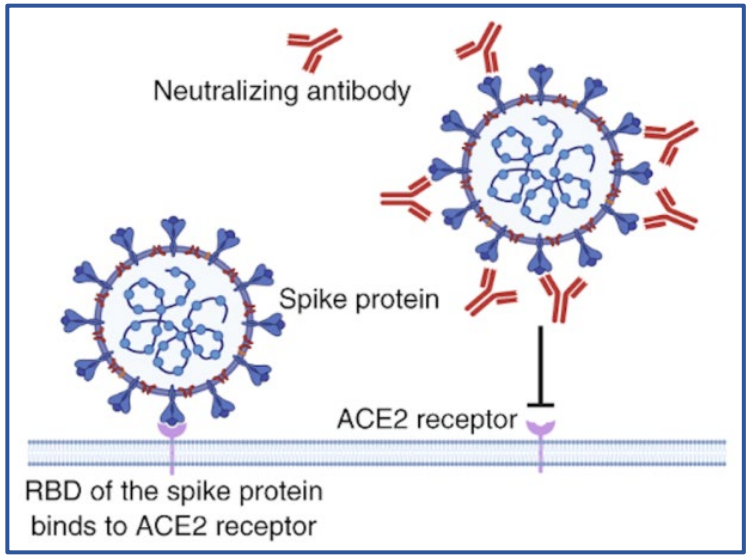


Antibody titer in critical patients > non-critical patients

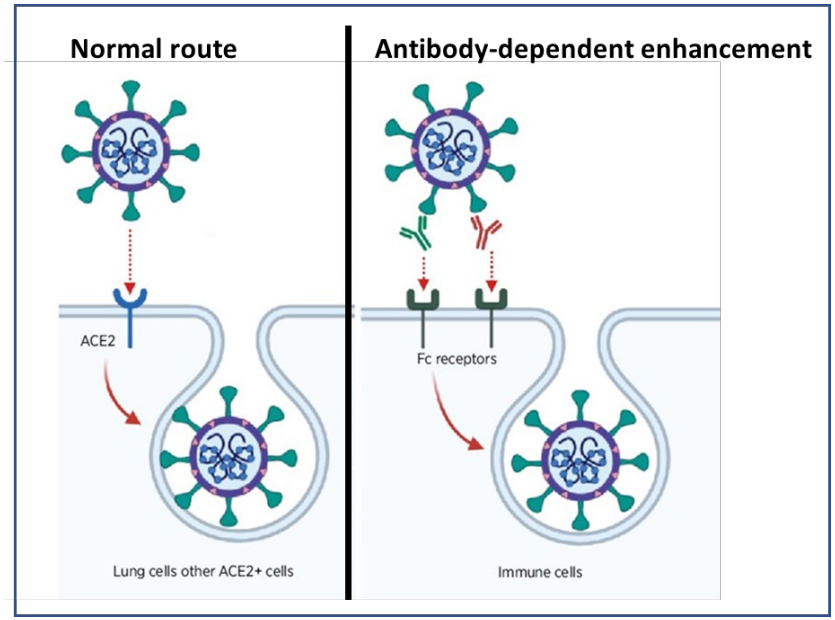
1. Antibody is a risk factor of critical illness.
2. Antibody-dependent enhancement which was commonly found in SAR-CoV / DV patients.
3. Antibodies is not sufficient for virus clearance.

High virus titer induced more antibody responses ?

*3. Neutralizing antibody?



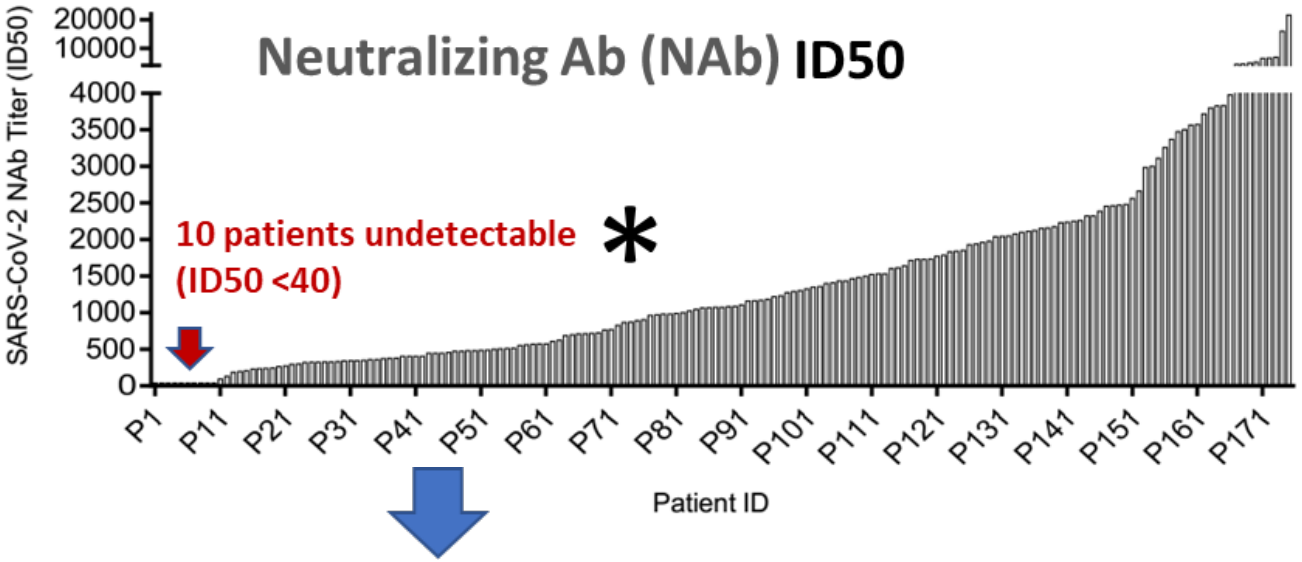
*2. Antibody-dependent enhancement



COVID-19 Recovered patients (mild symptoms)

N=175

Neutralization test: Pseudotyped-lentiviral-vector-based neutralization



- **SARS-CoV-2**

→ **neutralizing antibodies occurred 10-15 days after onset.**

- **10 patients did not develop neutralizing antibody ?**

MedRxiv; preprint 2020 April 20; Wo F, at. Al. (CHINA)

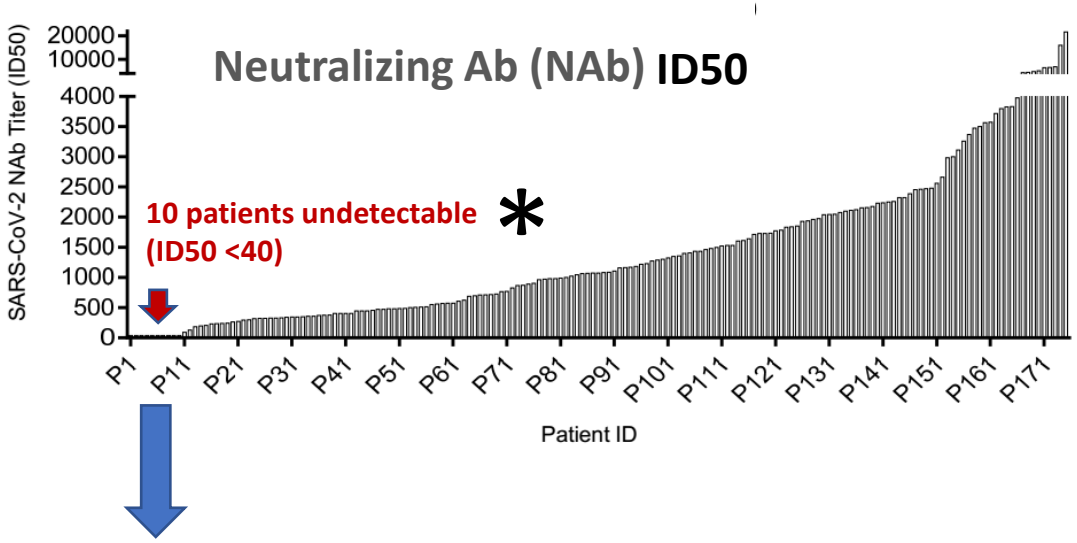
Table 2. Clinical characteristics of ten COVID-19 recovered patients with undetectable level of SARS-CoV-2 specific NAbs.

ID	Age (Years)	Gender	ID50[a]	ID80[a]	Length of Hospital (Days)	Disease Duration (Days)	Temp (°C)	Viral RNA tests	Symptoms
P1	30	F	<40	<40	22	31	37.8	+	fever and stuffy nose
P2	35	F	<40	<40	17	22	37.6	+	Cough, sore muscles, and stuffy nose
P3	16	M	<40	<40	9	12	37.7	+	Stuffy nose, runny nose, and cough
P4	39	F	<40	<40	8	12	38.1	+	Cough
P5	40	M	<40	<40	13	14	37.9	+	Cough and chest pain
P6	33	F	<40	<40	13	15	37.4	+	Fatigue
P7	61	F	<40	<40	18	22	37.2	+	Chill
P8	39	F	<40	<40	21	23	38.1	+	Sore throat, cough, and fatigue
P9	26	F	<40	<40	8	9	38	+	Cough
P10	31	F	<40	<40	12	23	38.4	+	Cough and dizziness

[a] ID50, ID80: < 40 represents the NAb titers were under the detectable level in neutralization assay.

COVID-19 Recovered patients (mild symptoms)

N=175

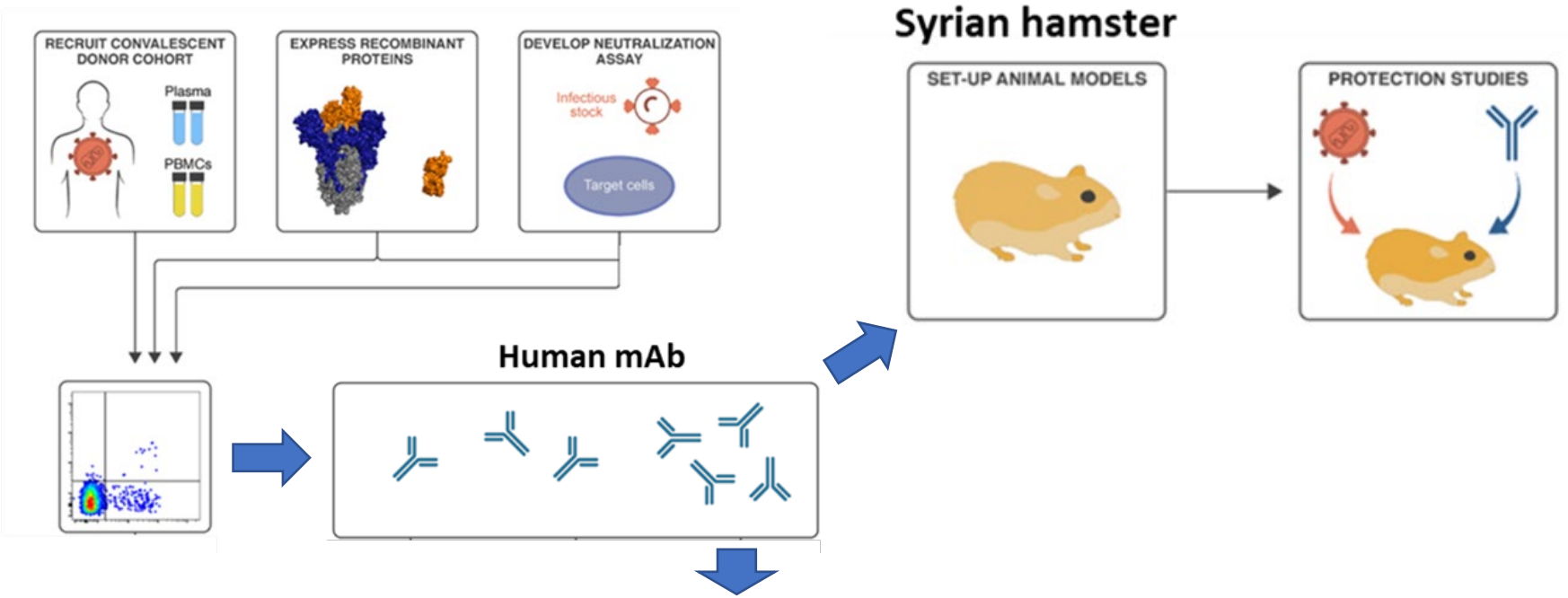


10 patients undetectable (ID50 <40) = Mild symptom

- **No neutralizing antibody ???**
- **Other protective immune responses ???**

Protective Antibody ?

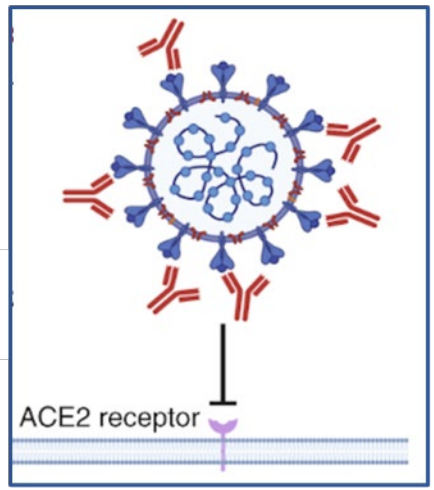
Human monoclonal antibody (mAb)



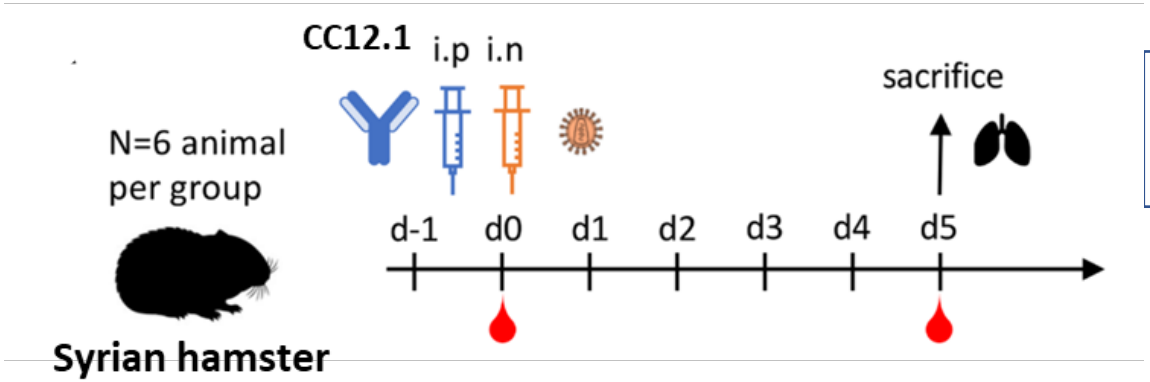
mAb CC12.1

→react RBD epitope of SARS-CoV-2

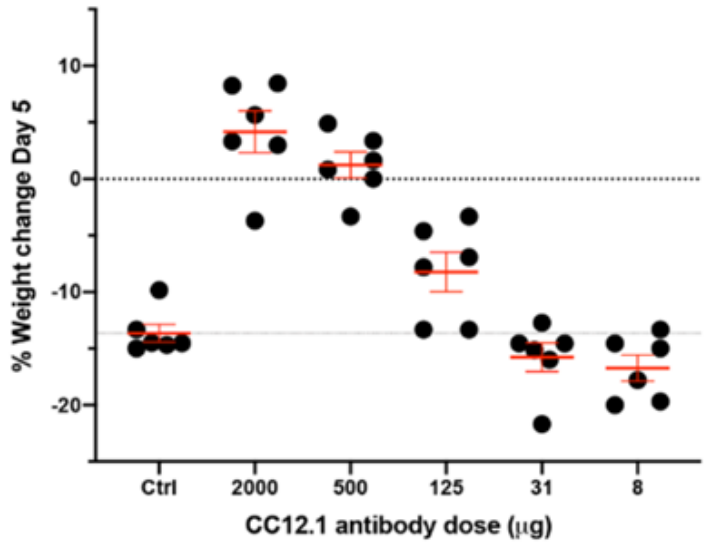
RBD= Region binding domain

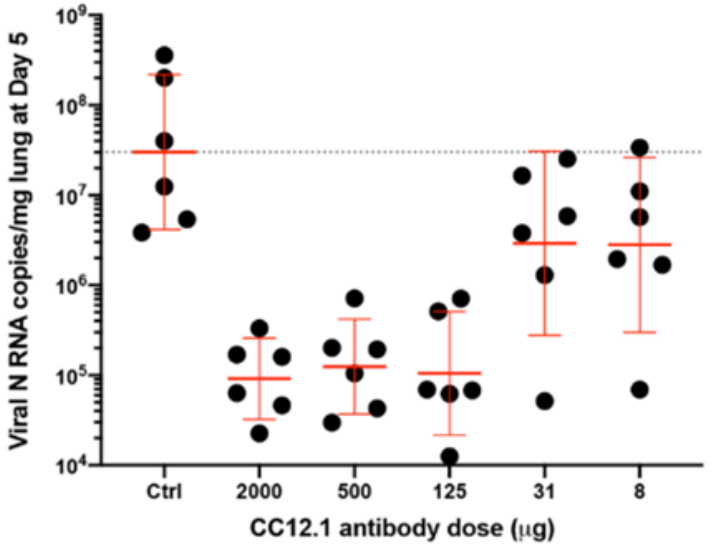


Science; 2020 June 15; Rogers FT, et. al; USA



mAB CC12.1
→ react RBD epitope



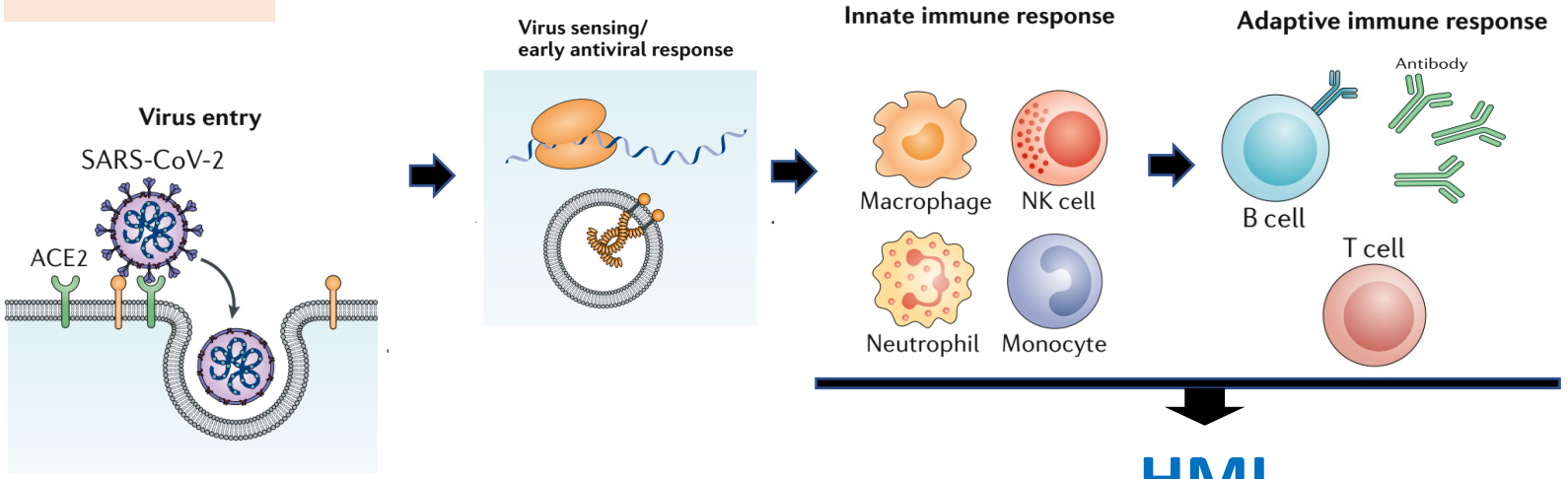


→ Passive transfer of an antibody provides protection against disease in high-dose SARS-CoV-2 challenge in Syrian hamsters

Protective Antibody

Immune responses to SARS-CoV-2 infection

SARS-CoV-2

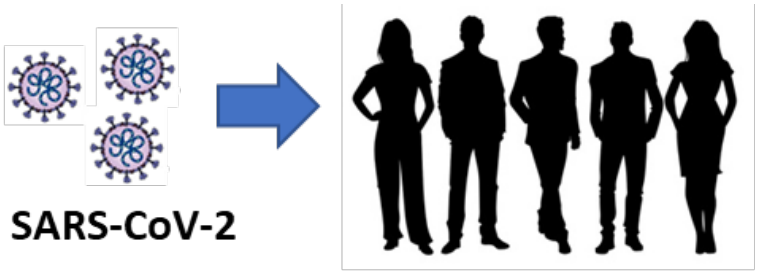


HMI

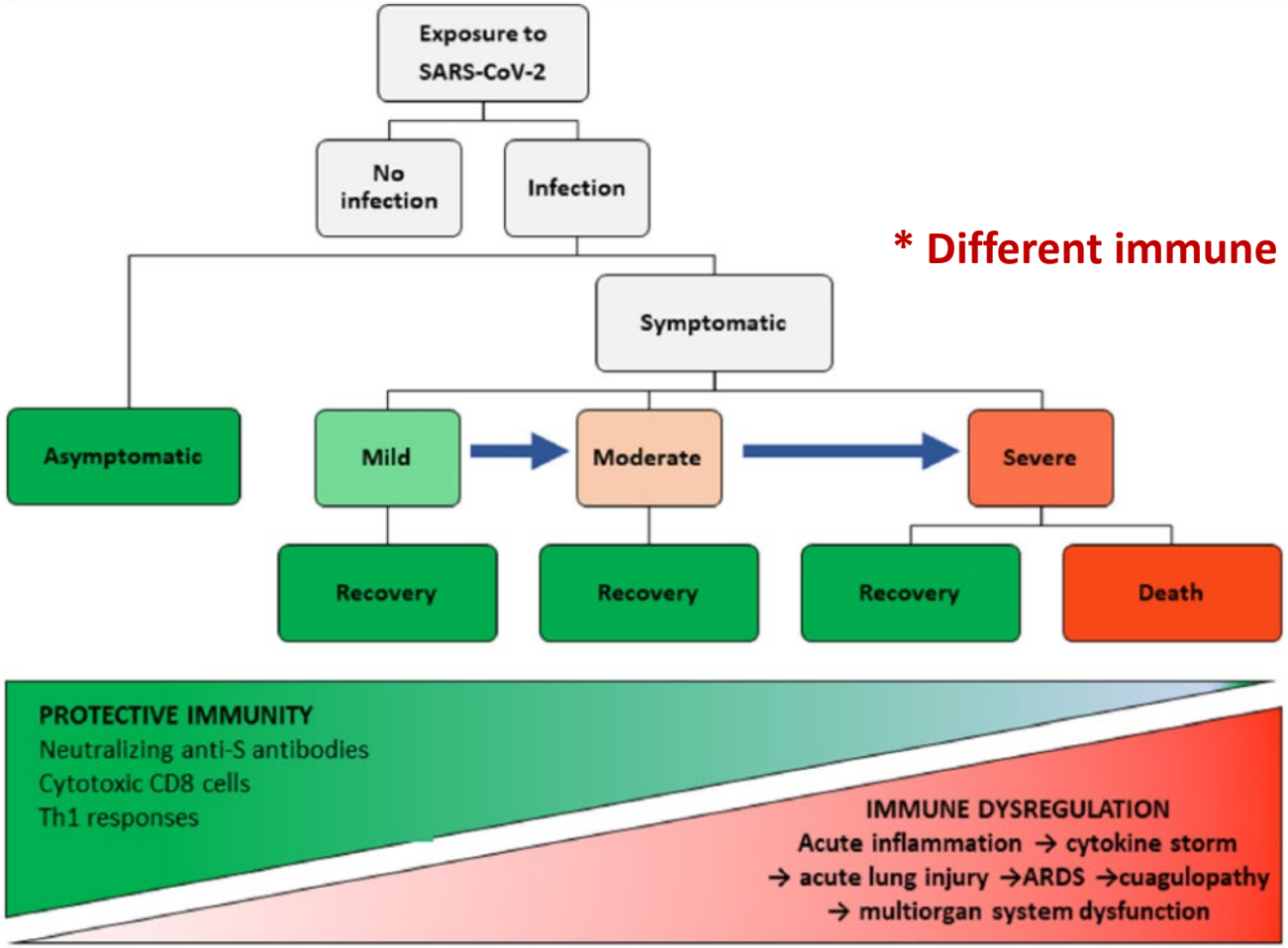
✓ **Antibody production**

→ **Neutralizing antibody**

✓ **Protective Antibody !!!**



Immune responses ?



*** Different immune responses**

Frontiers in Immunology. June 2000

LAST UPDATE: 02 August 2020

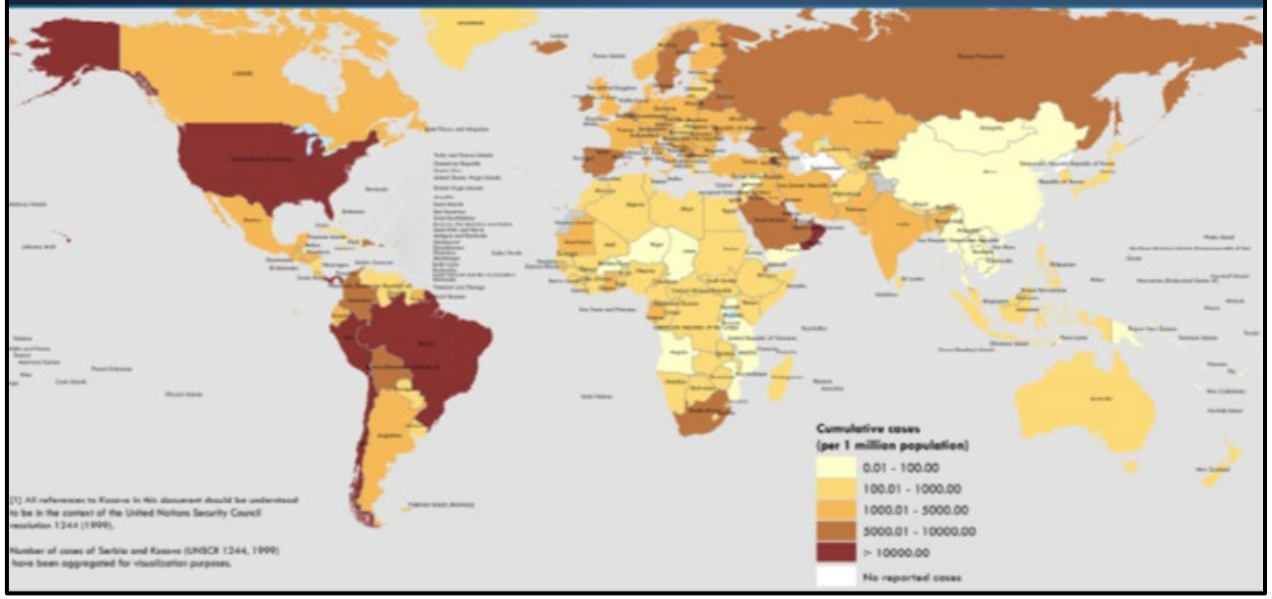
CORONAVIRUS
UPDATE
34

What we know about the COVID-19 immune response

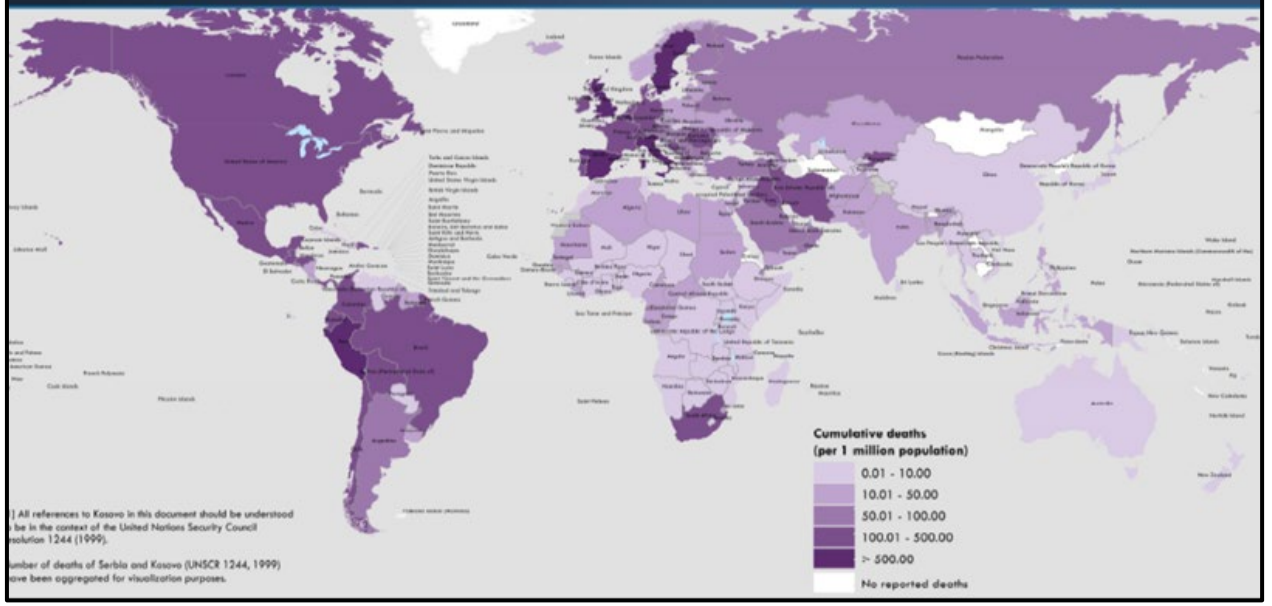
THE LATEST ON COVID-19 IMMUNITY & THE CURRENT GLOBAL SITUATION

World Health Organization | EPI·WiN | infodemic MANAGEMENT

COVID-19 cases per 1 million population



COVID-19 deaths per 1 million population



The immune response to viral infections

INFECTION CAN BE STOPPED AT THIS STAGE

PHASE ONE → → → PHASE TWO

Innate immune response

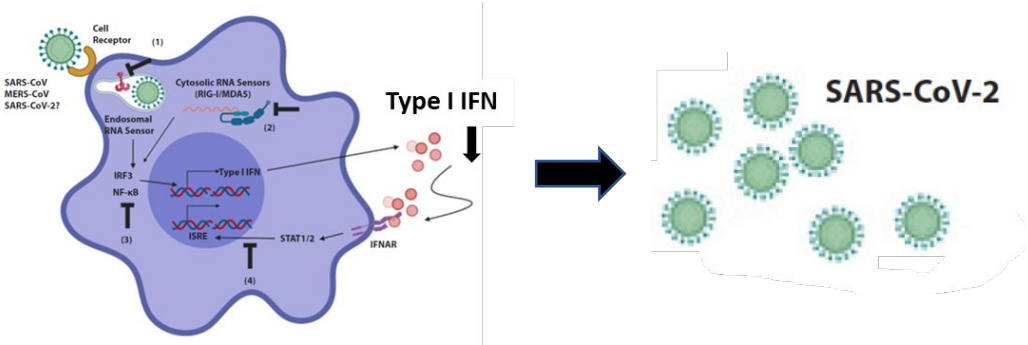
- General response to ANY infection
- Innate immune response cells secrete interferons[1] and other chemicals (cytokines)
- Interferons interfere with virus replication
- Phase 2 is triggered[2]

Adaptive immune response

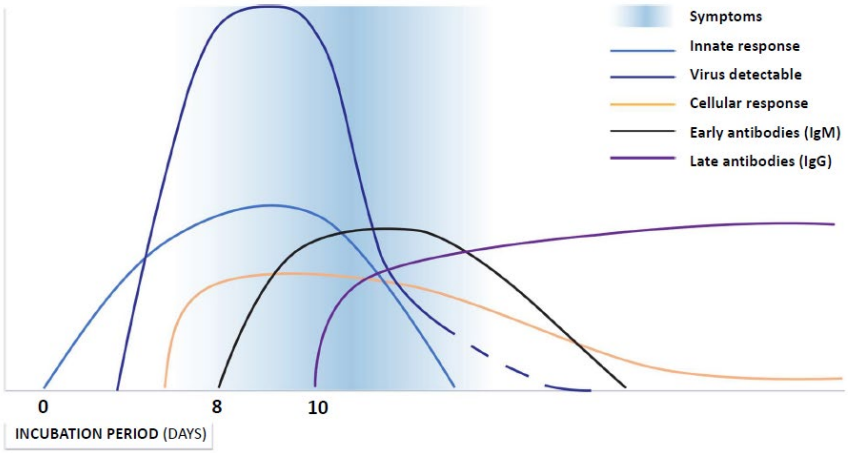
- Specific response to the infection
- Starts after 6 - 8 days
- Involves two types of white blood cells
  - T cells (cellular response)
  - B cells (antibody response)

[1] Interferons and cytokines cause fever, muscle aches, etc - the early symptoms of infection

[2] A 'weaker' innate response (e.g. in elderly people or those with underlying health problems) may result in delayed stimulation of the adaptive response.



The immune response to viral infections in general

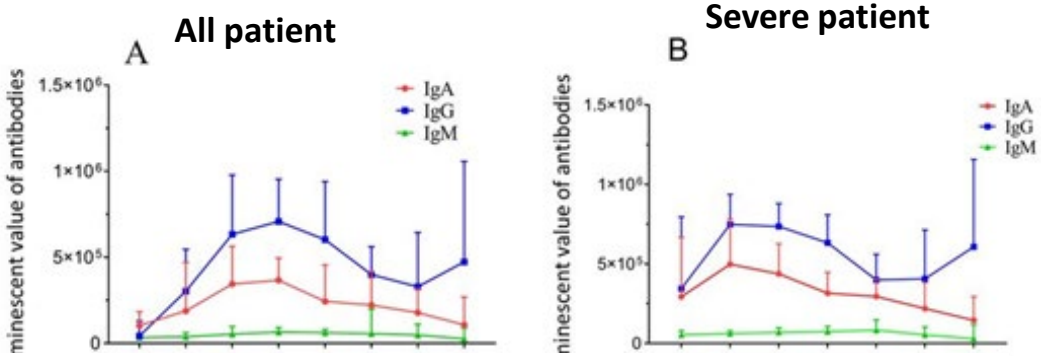


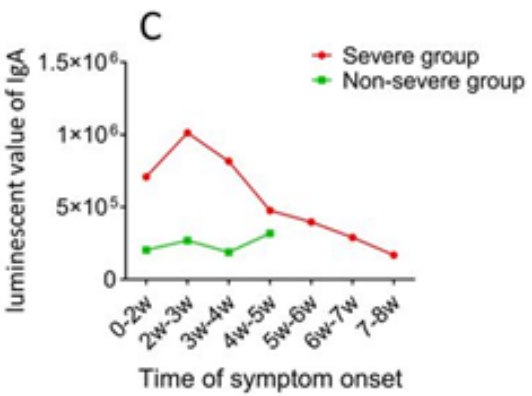
SARS-CoV-2

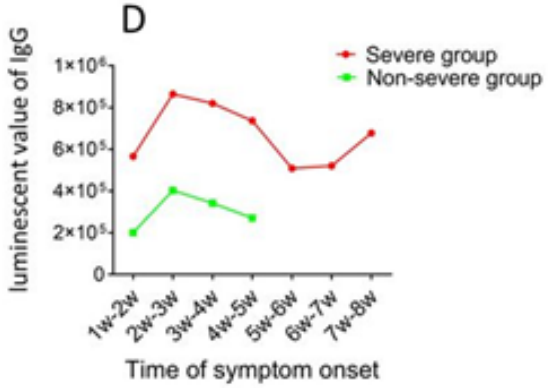
IgG antibodies are produced at the same time as IgM or 2-3 days later.

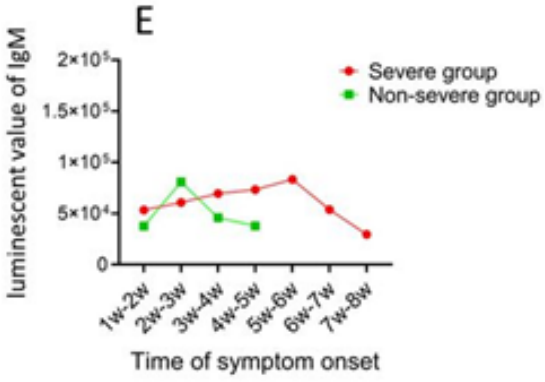
Secondary infection
Cross react with common CoV

European Respiratory Journal 2020; May
China









What do we know about the immune response to COVID-19?

- Most COVID-19 patients who recovered have antibodies to the SARS-CoV-2 virus detectable in their blood.
- Most COVID-19 patients develop antibodies about 1-3 weeks after symptoms start. This is around the time when many patients start to recover.
- Patients who have had more severe disease appear to have **higher levels of important neutralizing antibodies**.
- Patients who had mild or asymptomatic COVID-19 have **low levels of neutralizing antibodies** (or even undetectable levels).
- In these persons it is possible the innate immune response and the T cell response cleared the virus
- Recent studies have shown that **neutralizing antibodies may disappear after 3 months**[1,2,3]

[1] https://www.nejm.org/doi/full/10.1056/NEJMc2025179 published 21 July 2020

[2] https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/2768834 published 21 July 2020

[3] https://www.medrxiv.org/content/10.1101/2020.07.09.20148429v1.full.pdf published 11 July 2020

Does the presence of antibodies against COVID-19 mean a person is immune and protected from being infected again?

No one knows yet!

- Generally, a person who recovers from a viral infection is protected against new infection, if the antibodies are of adequate quality (neutralizing antibodies) and quantity (high levels)
- Changes in the virus sequence can make prior immunity less effective (eg. as happens with the influenza virus)
- Protection from re-infection with the common cold caused by other milder coronaviruses is short-term (sometimes less than a year)
- For other coronaviruses, such as Severe Acute Respiratory Syndrome (SARS), antibodies have been detected a few years later.

For COVID-19, we do not yet have enough data to confirm if antibodies protect, what antibody levels are required, or how long protection will last.

At the present time, there is no role for a COVID-19 'immunity certificate'

- Some have asked if the presence of antibodies to the virus that causes COVID-19 could serve as the basis for an **'immunity certificate''** to enable individuals to travel or return to work.
- This rests on the as-yet unproven assumption that infection provides long-term protection against re-infection. Antibody-mediated immunity **is not yet sufficiently** understood to offer any guarantees of protection against re-infection.
- So **a positive antibody test cannot be used to exempt anyone from public health measures** in their community or at work or to group people in settings such as schools, dormitories, or correctional facilities.

There is currently insufficient information to conclude whether people who have recovered from COVID-19 and have antibodies are protected from a second infection.

Immune Responses to COVID-19 Disease

?


THANK YOU