

Immune Responses to SARS-CoV-2 cause severe COVID-19 in some and recovery in most

Clive Gray – Professor in Immunology

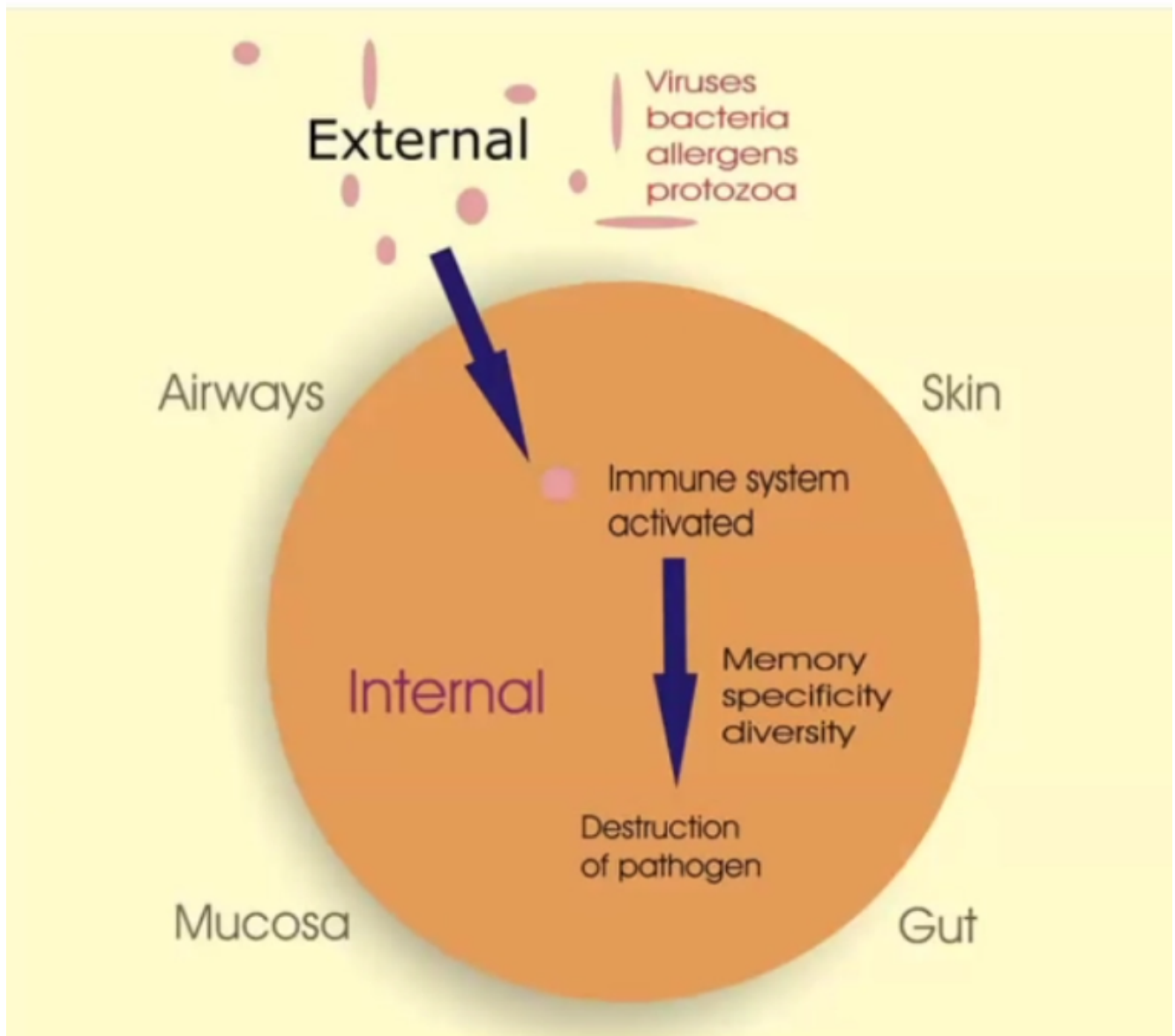
immunopaedia.org – useful web site for immunology resources.

Outline:

- Basics of Immunology
- A balance between inflammation and tolerance
- What happens to people who progress to severe COVID-19?
- What might be happening in SARS-CoV-2 infected people who remain asymptomatic, have few symptoms and recover?

Internal : External world

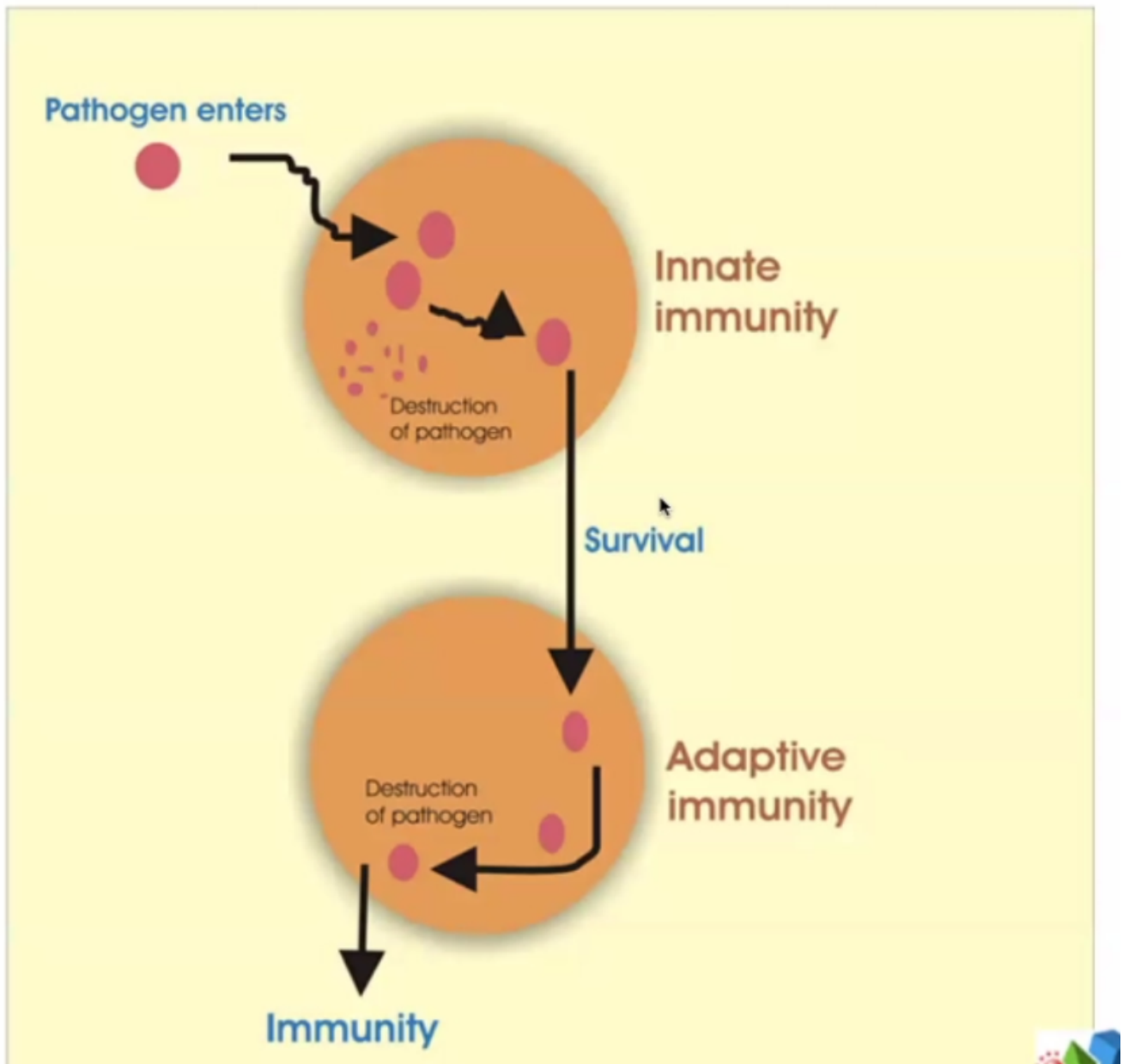
Internal:External World



~99% of time the pathogen gets destroyed, but the pathogen may survive in rare cases.

2 arms of immune responses:

Innate:Acquired Immunity

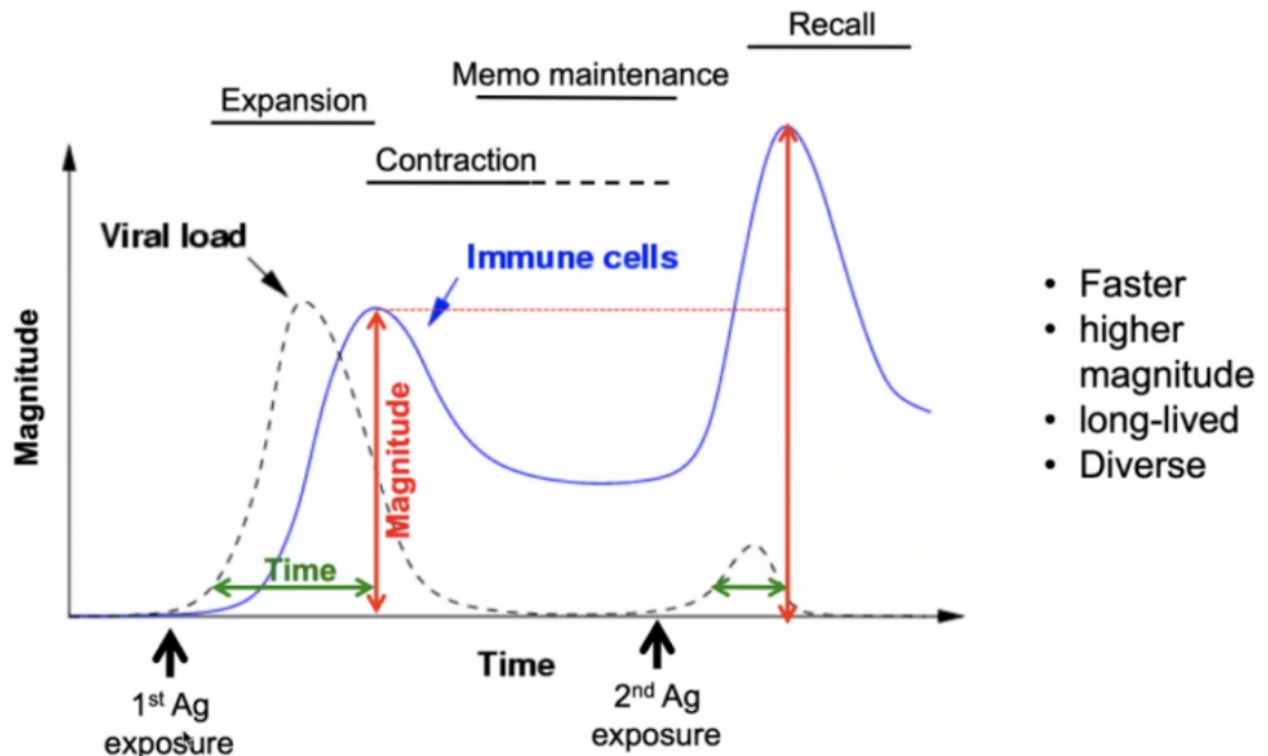


Innate – evolutionary response – very rapid – elements of innate immunity are found in bacteria, plants, lower vertebrates, squids, fish etc.

Some pathogens survive ->

Adaptive immunity – much more targeted / focussed. The immune system targets more specifically the pathogens which survive the innate immunity.

Immune Memory is essential preserving the self

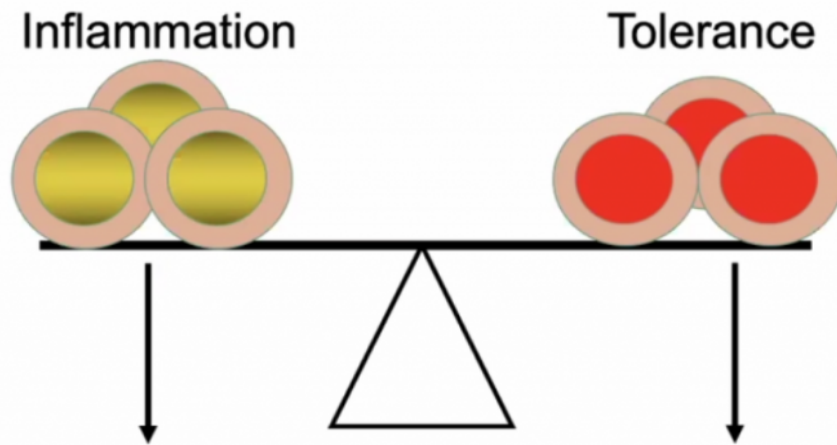


Infection initially -> expansion (peak after maximal viral load) -> contraction with some residual immunity (Memo Maintenance) -> with secondary response (Recall) there is a more rapid expansion (and higher peak) of the specific immunity.

Immune regulation:

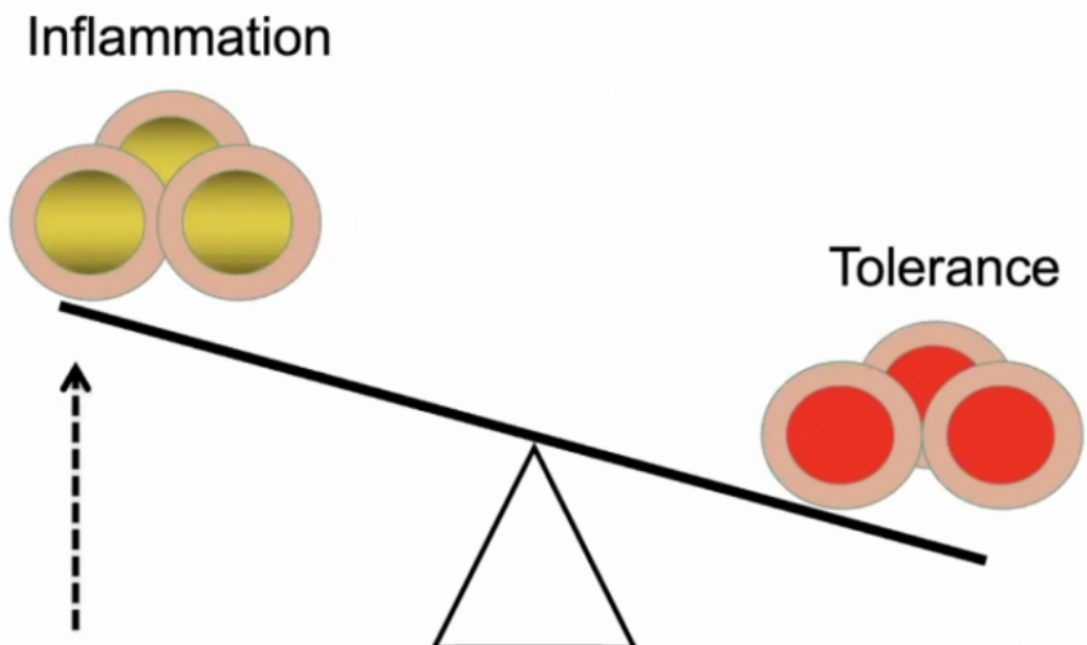
Predisposed conditions: DM, HPT, Obesity, would make an individual highly susceptible to inflammation due to in balance of Inflammation vs. Tolerance, see below.

The immunological equilibrium: balance between inflammation and tolerance



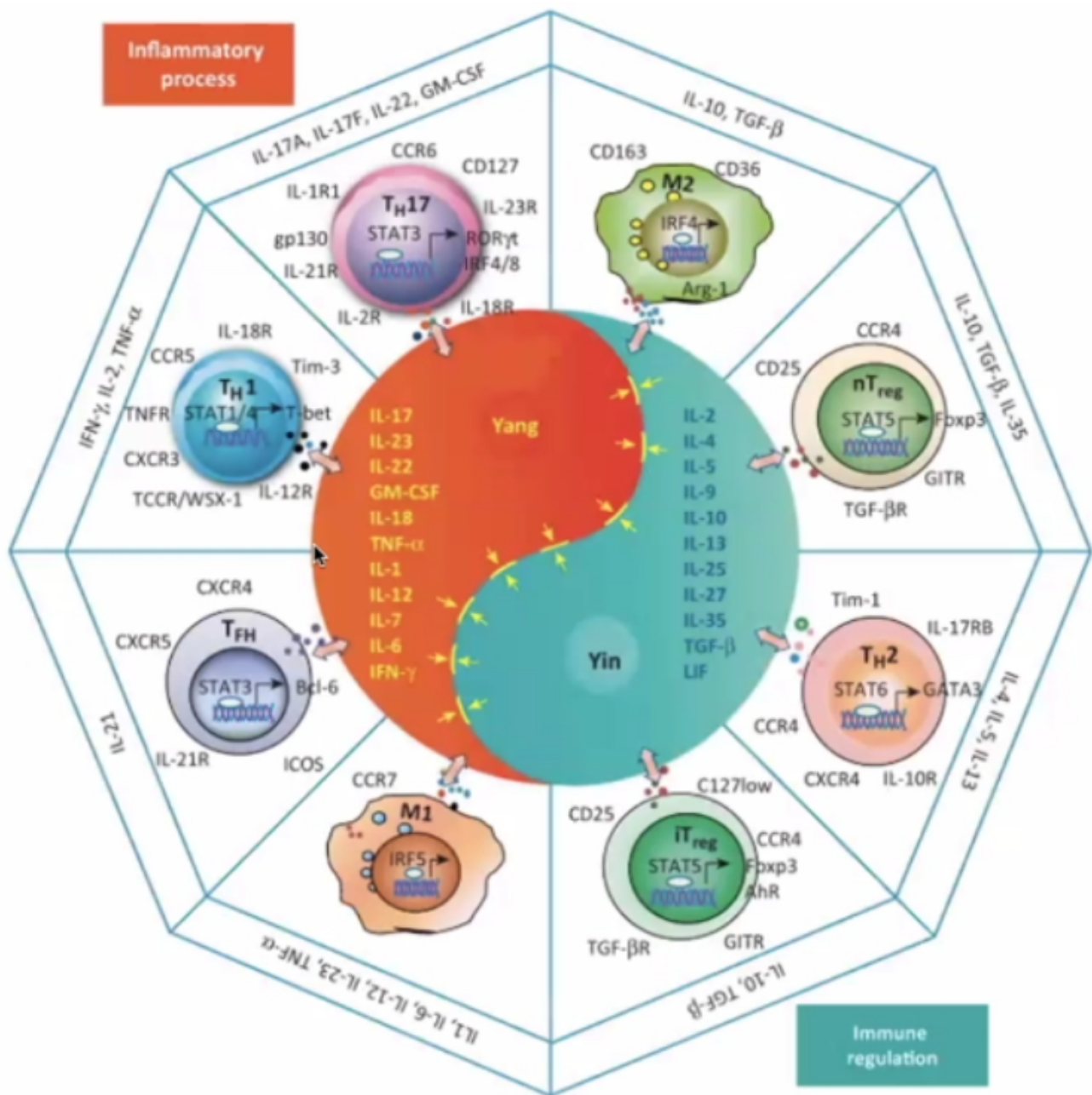
Normal: reactions against pathogens
Pathologic: inflammatory disease, e.g. caused by reactions against self

No response to self
Controlled response to pathogens



Pathogenic event

The Yin Yang of immunology:



TRENDS in Immunology

Yin – immune regulation; Yang – Inflammatory Process

Pro-inflammatory (Orange)

TH17 – inflammatory cells secreting the “calling signals” for leucocytes.

TH1 – secreting IFN gamma; IL-2 ; TNF-alpha – cytokines causing inflammation

Macrophage – presents antigens – in lymph nodes and germinal

centres

T-Helper cells T-FH

Immune Regulation (Blue)

TH2 – hand in hand with TH1 (opposite)

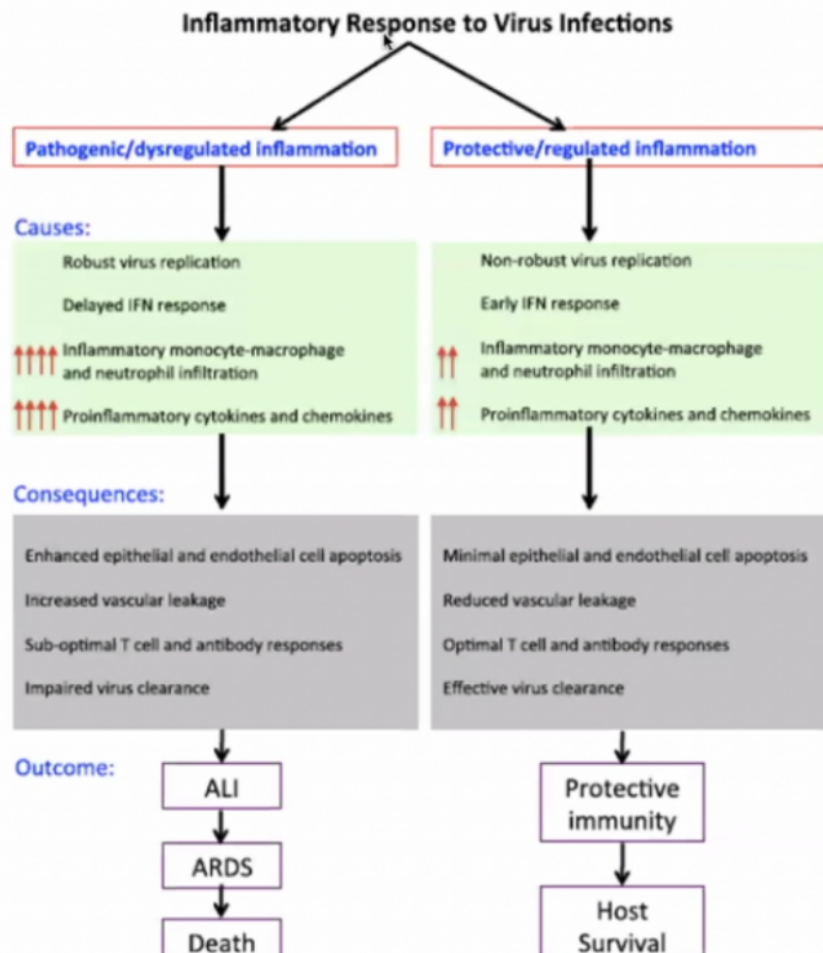
Regulatory cells (nT and iT regulatory cells)

Actual pathogen is not causing disease – but the immune response – thus this is what should be focussed on to treat the disease.

Respiratory Infections

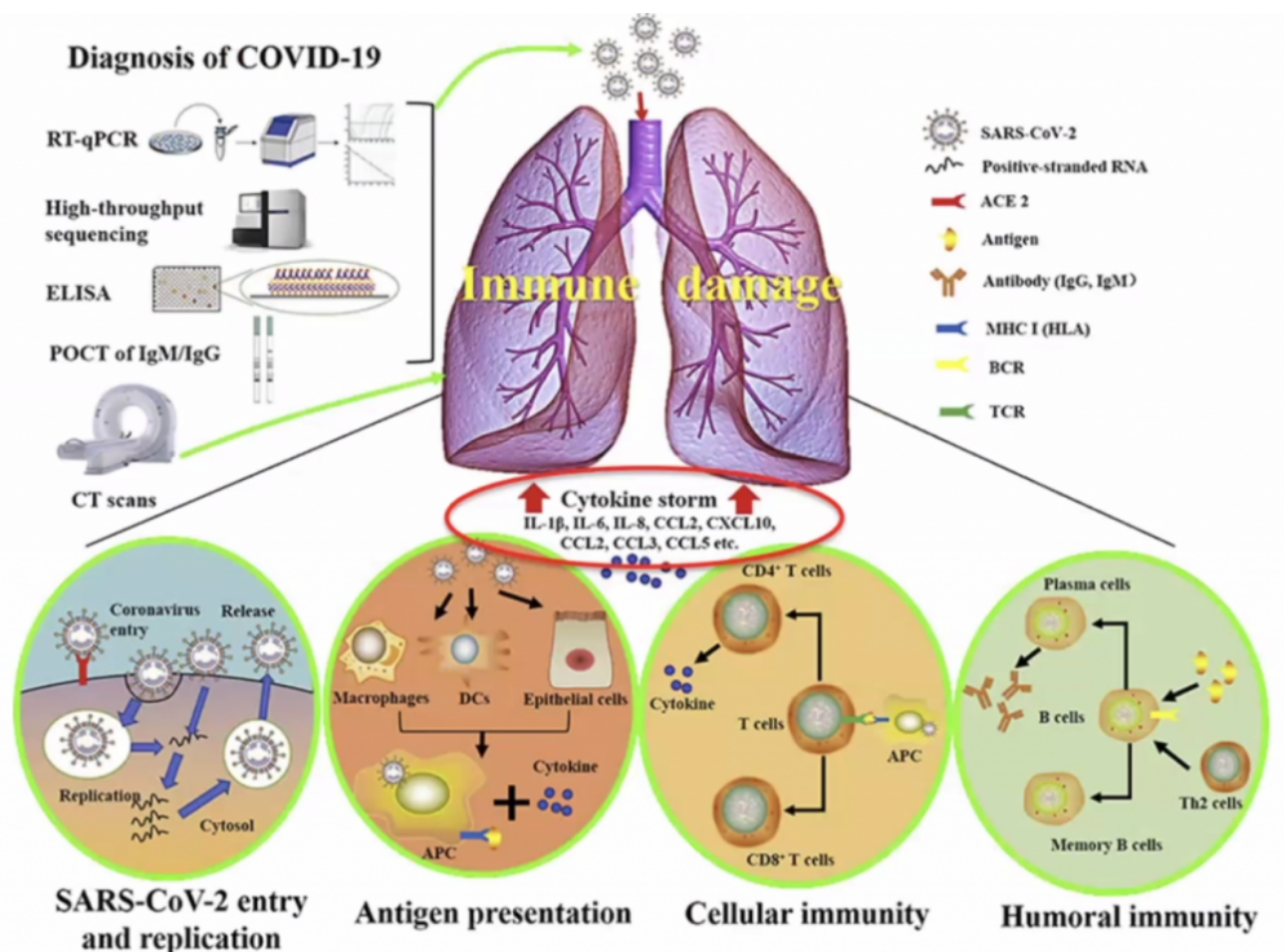
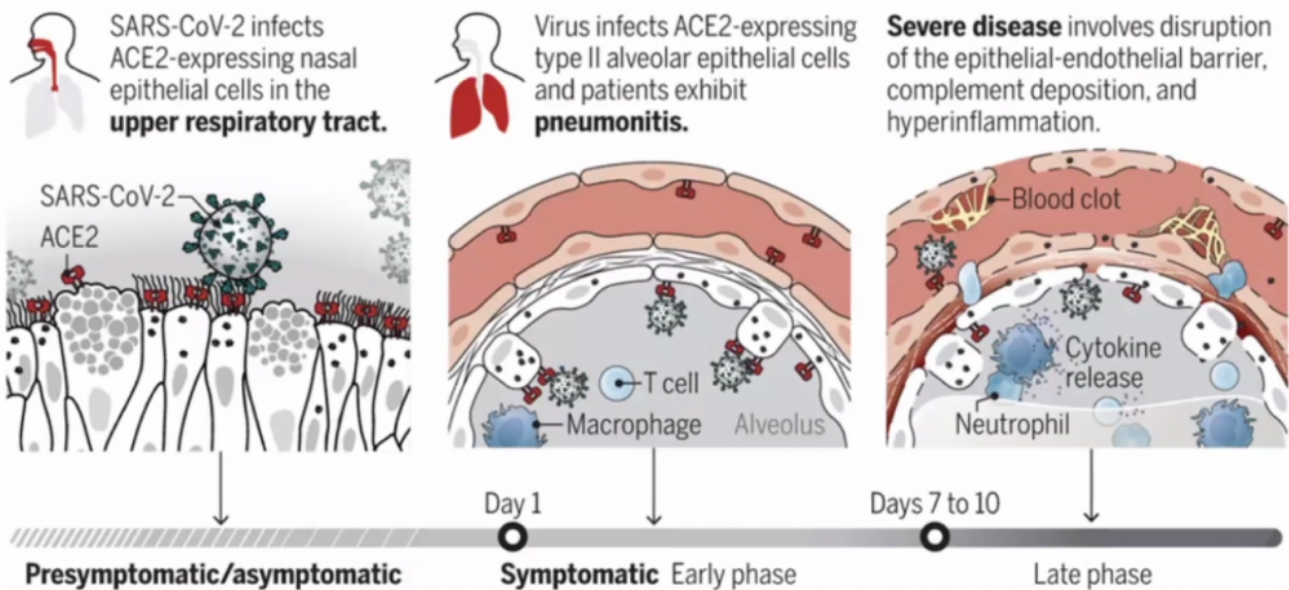
Virus	Entry receptor	Common symptoms	Clinical complications
Rhinovirus	ICAM-1 or LDL	Rhinorrhea, coryza, sneezing, sore throat, cough	Asymptomatic, mild to moderate upper-respiratory tract illness, bronchitis
Common coronavirus	Strain specific	Fever, rhinorrhea, coryza, sneezing, sore throat, cough	Mild to moderate upper-respiratory tract illness
Adenovirus	Strain specific penton	Fever, rhinorrhea, coryza, sneezing, sore throat, cough, pink eye, diarrhea, bladder infections	Mild to moderate upper-respiratory tract illness, croup, tonsilitis
Seasonal influenza	Sialic acids	Fever, rhinorrhea or stuffy nose, coryza, sore throat, cough, headache, myalgia	Mild to moderate upper-respiratory tract illness, bronchitis, croup
RSV	Nucleolin	Fever, rhinorrhea, coryza, sore throat, cough, wheezing, shortness of breath	Mild to moderate upper-respiratory tract illness, bronchitis, bronchiolitis, croup
Enterovirus D68	Sialic acids alpha2-6	Rhinorrhea, sneezing, cough, mouth blisters, myalgia; wheezing and dyspnea in more severe cases	Mild to moderate upper-respiratory tract illness, bronchitis, bronchiolitis, pneumonia
Pandemic influenza	Sialic acids	Fever, coryza, rhinorrhea or stuffy nose, sore throat, cough, headache, shortness of breath, dyspnea, myalgia	Bronchitis, croup, pneumonia, diffuse alveolar damage, acute respiratory distress syndrome, respiratory failure
SARS-CoV	ACE2	Fever, chills, cough, shortness of breath, dyspnea, myalgia	Rapidly progressive pneumonia, diffuse alveolar damage, severe acute respiratory distress syndrome, respiratory failure, fibrosis
MERS-CoV	CD26	Fever, chills or rigors, coryza, sore throat, non-productive cough, sputum production, shortness of breath, dyspnea, headache, vomiting, diarrhea, myalgia	Rapidly progressive pneumonia, diffuse alveolar damage, severe acute respiratory distress syndrome, respiratory failure, septic shock and multi-organ failure

Protective versus pathogenic inflammatory responses to pathogenic hCoV infections



Dose of the virus (viral load) is key to how you respond to the virus – Initial High dose in viral load likely will lead to high inflammatory response; Low dose (non-robust virus replication) may cause a less severe inflammatory response.

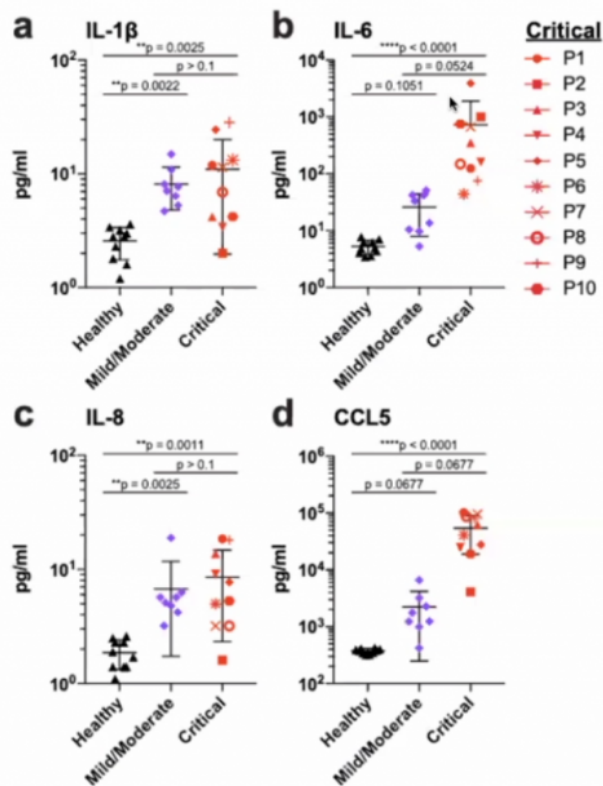
Key phases of disease progression



CCL's allow leucocytes to migrate, hence in a **cytokine storm**, with high level of **migration**, the leucocytes causes severe local inflammation due to migration of leucocytes to local

sites.

CCR5 inhibitors?



When patients were treated with a [CCR5](#) blocking antibody ([leronlimab](#)), there was rapid reduction in plasma IL-6 and a significant decrease in SARS-CoV-2 plasma viremia.

Blocking CCR5 inhibits the migration of Inflammatory-inducing cells, such as monocytes and macrophages

CCL5 blocking antibodies leads to rapid reduction of IL-6. Dexamethasone is not so much an inhibitor of CCR5, but it prevents the hyperinflammation by inhibiting the majority of the inflammatory pathway.

Recovery: what might be going on?

South Africa

Current percentage distribution of all cases



88.6% recovery
2.36% mortality (254/10⁶ popn)

Global

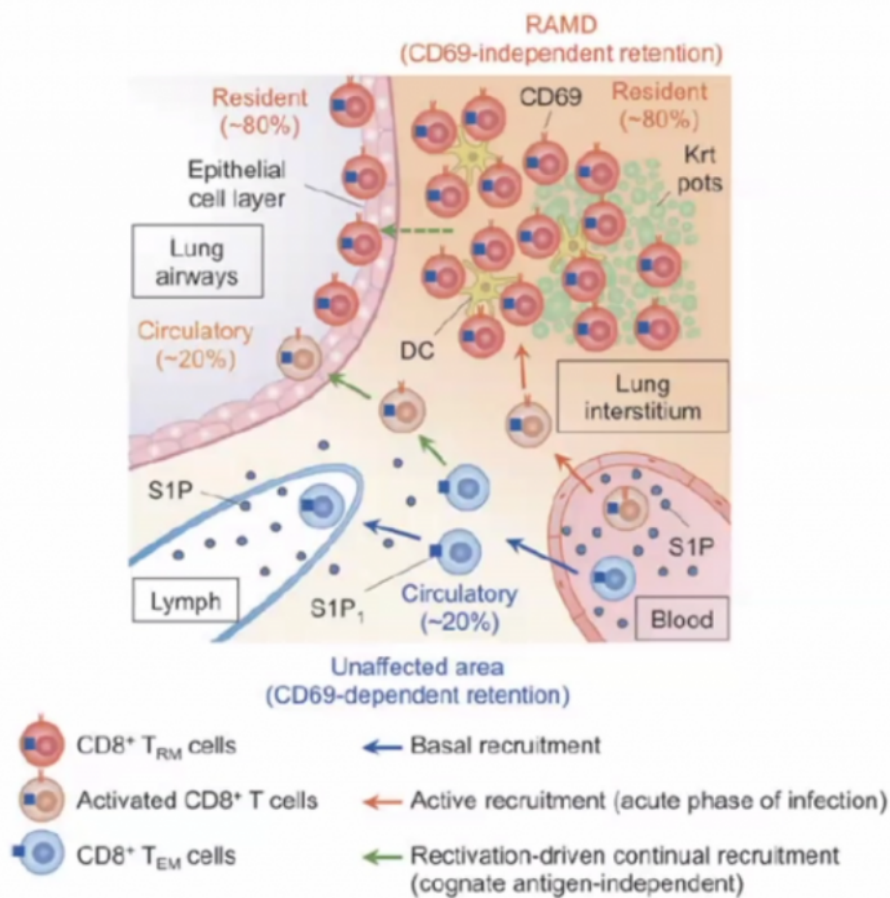
Current percentage distribution of all cases



72% recovery
3.24% mortality (116/10⁶ popn)

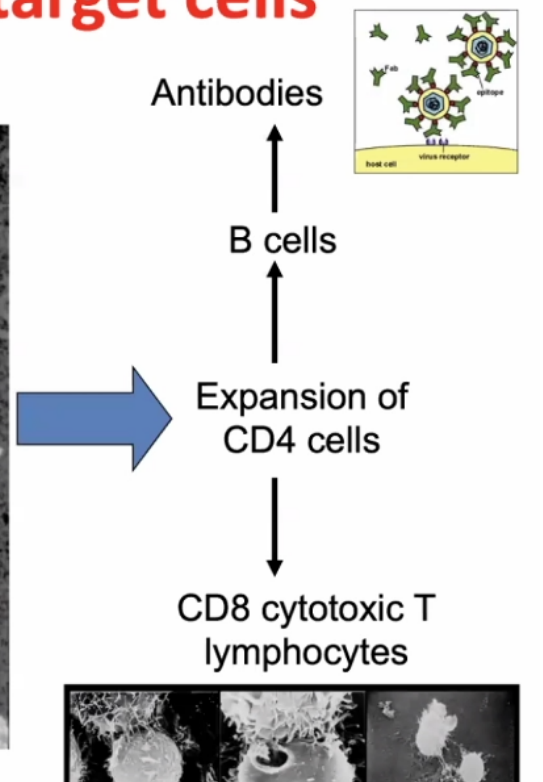
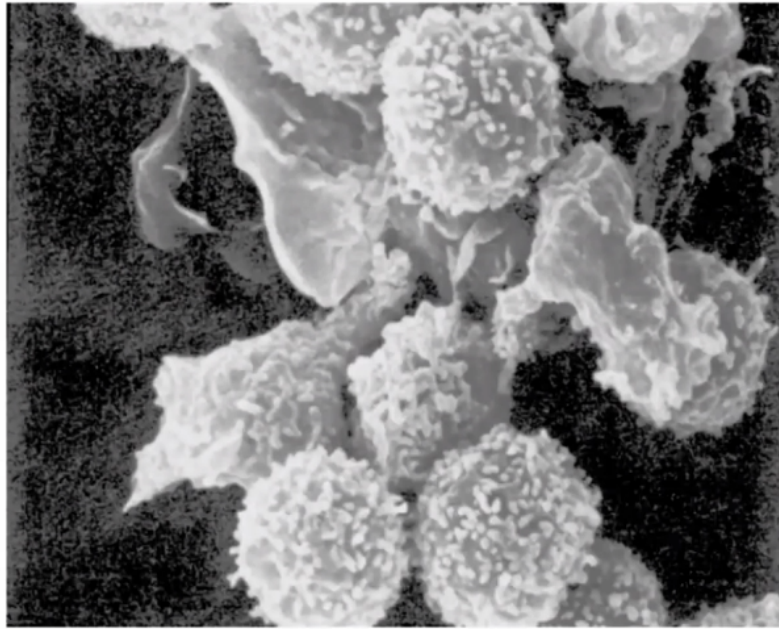
CD8 cells

Special CD8⁺ cells in the lung: possible protection



Within interstisium, the CD8 cells are present and

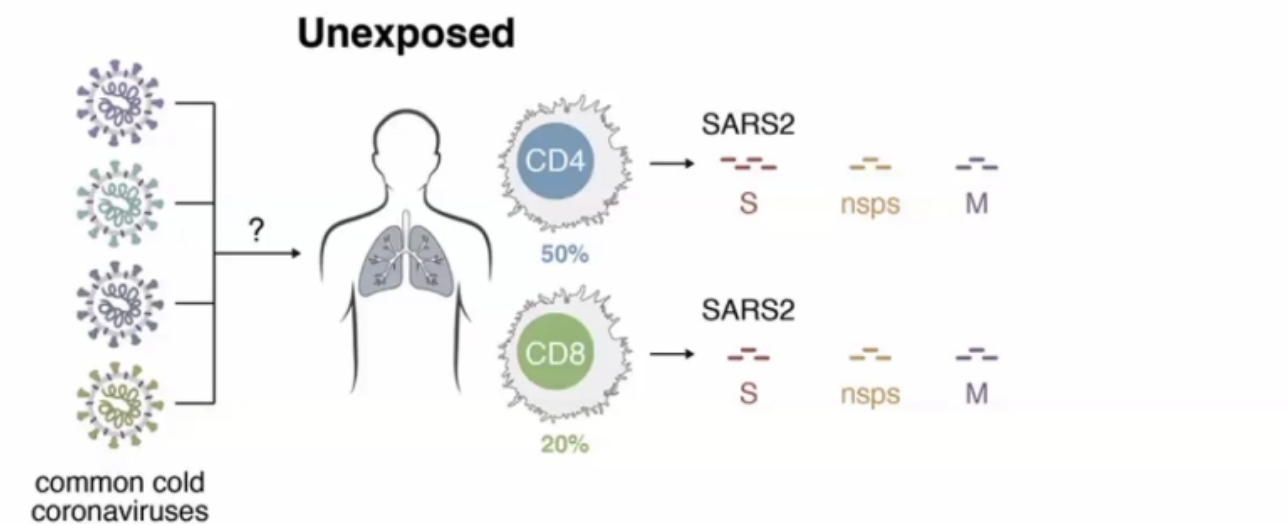
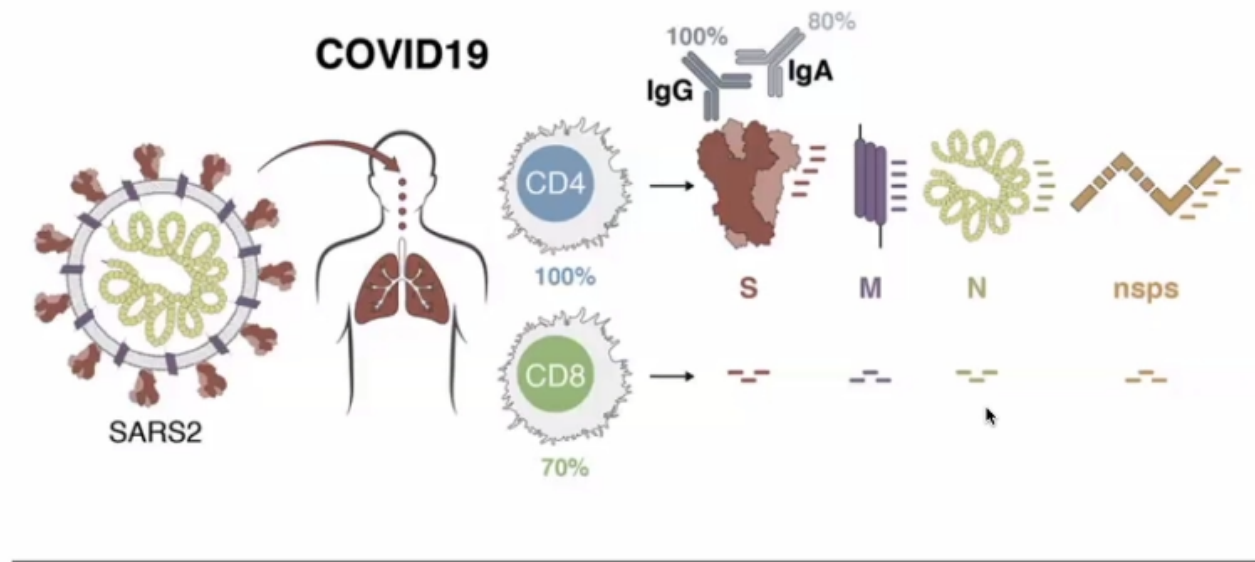
CD4⁺ cells help B cells makes antibody and CD8 cells kill target cells



CD4 cells activates CD8 cells, hence called T-helper cells.

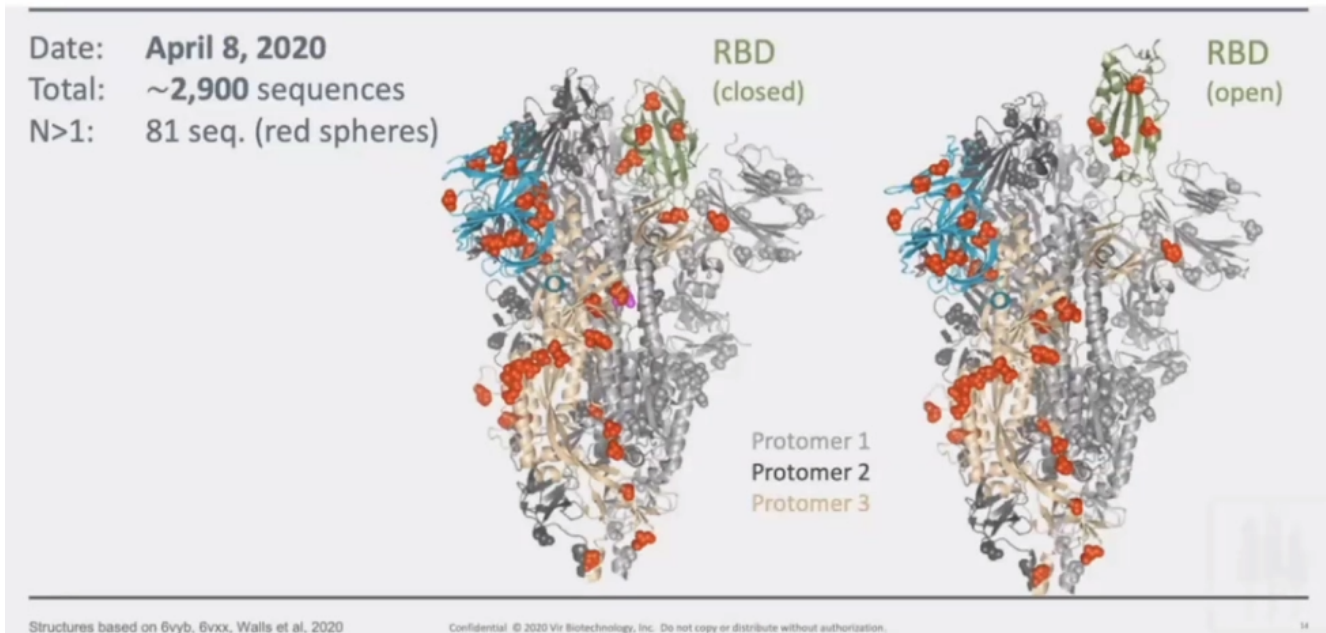
Is there Evidence for pre-existing immunity?

- Preexisting T cell immunity existed to H1N1 in the adult population ([Greenbaum et al 2009](#))
- The presence of cross-reactive T cells was found to correlate with less severe disease ([Sridhar et al 2013](#); [Wilkinson et al 2012](#))
- Substantial cross-reactive coronavirus T cell memory has been observed ([Grifoni et al 2020](#))

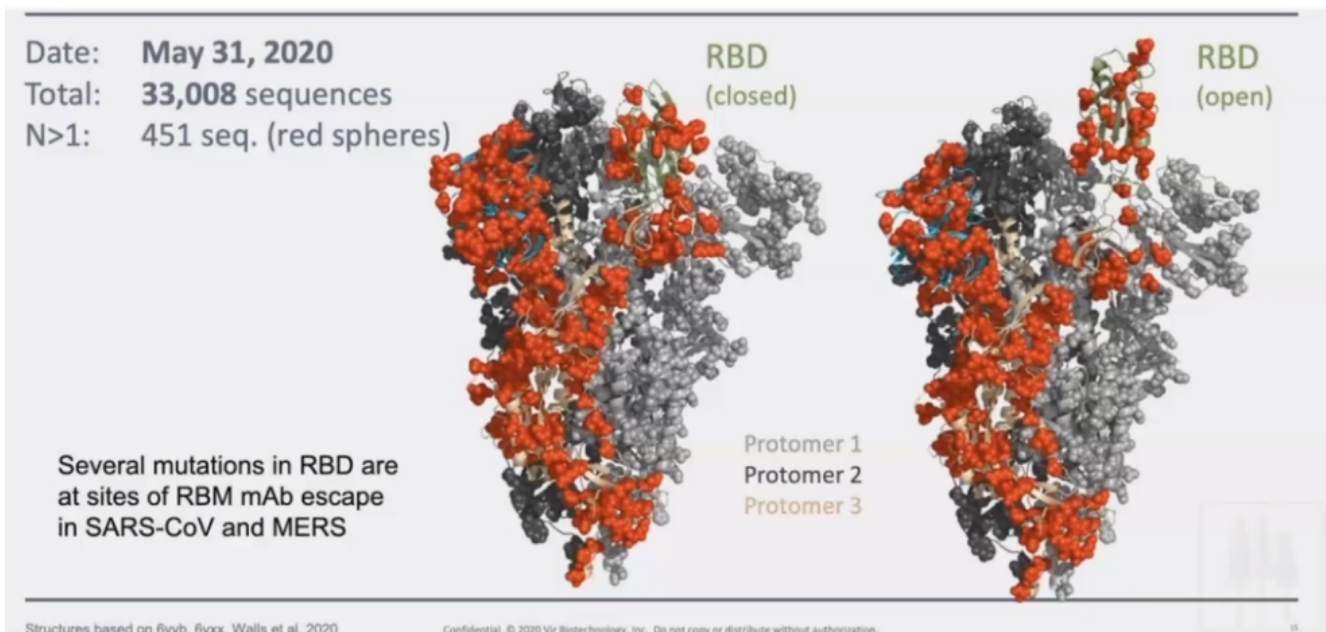


T-cell responses are very prevalent to COVID-19 exposed individuals. BUT CD4 cells and CD8 cells can also react to the SARS2 viral proteins in unexposed individuals.

Rapid Evolution of SARS-CoV-2



RBD – receptor binding domain (Spike-protein); Orange is the amount of amino acids which are changeable.



Orange amino acids are those which are changeable – illustrating how the virus has mutated in a month.

Conclusions

- Hyperinflammation involving chemokines and inflammatory innate and adaptive immune cells migrate to “hot” areas of damage (lung, heart, GIT etc)
- Key to treatment is to either dampen inflammation or to block the migration of inflammatory cells to the lungs
- The majority of infected people recover. Is this due to some form of pre-existing immunity?
- Evidence suggest this may be the case.