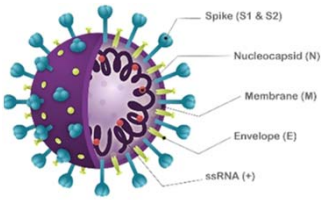
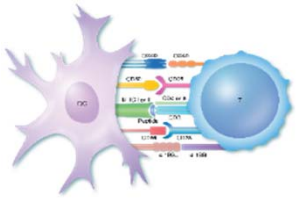
DukeNUS Medical School

SARS-CoV-2



T cells



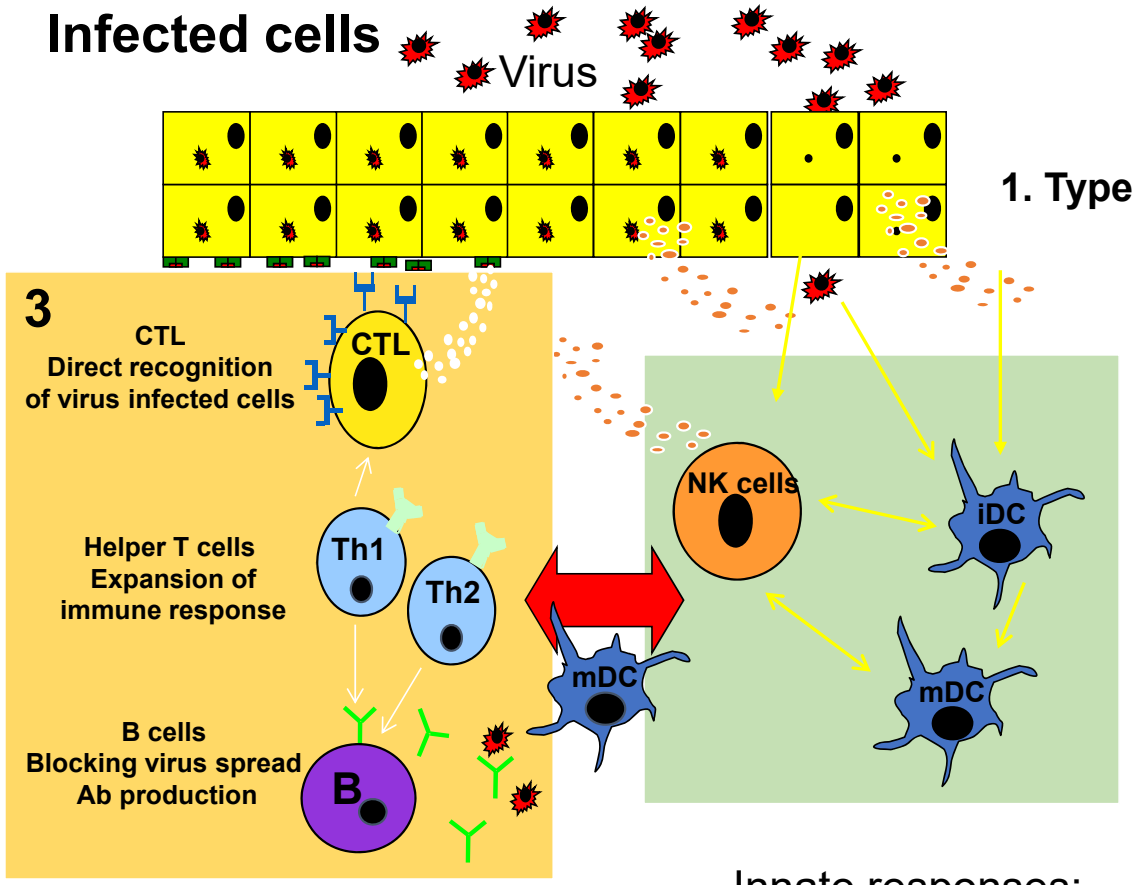
The protective role of SARS-CoV-2 T cells

(T cells specific for Non-Structural proteins..polymerase)

Antonio Bertoletti, MD

Program in Emerging Infectious Diseases

DUKE-NUS Medical School

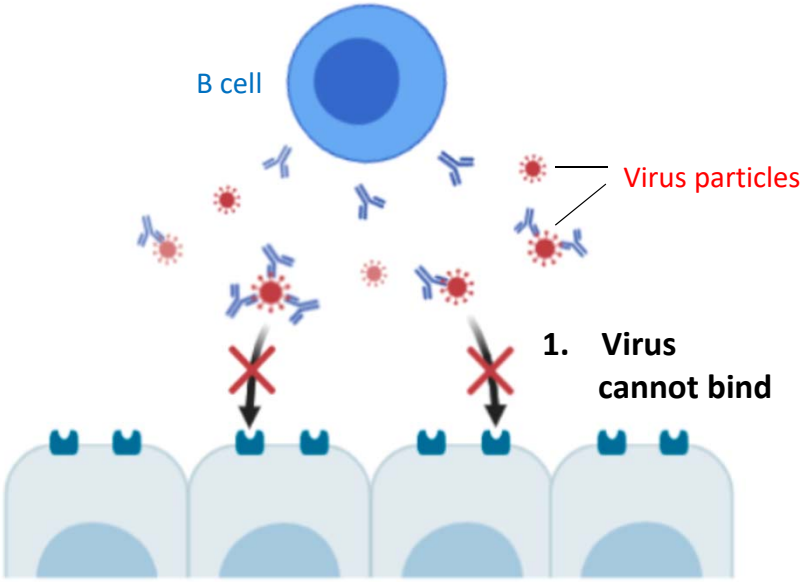


Adaptive responses:
final and persistent
control of infection

Innate responses:
•early viral containment
• maturation of adaptive
immunity

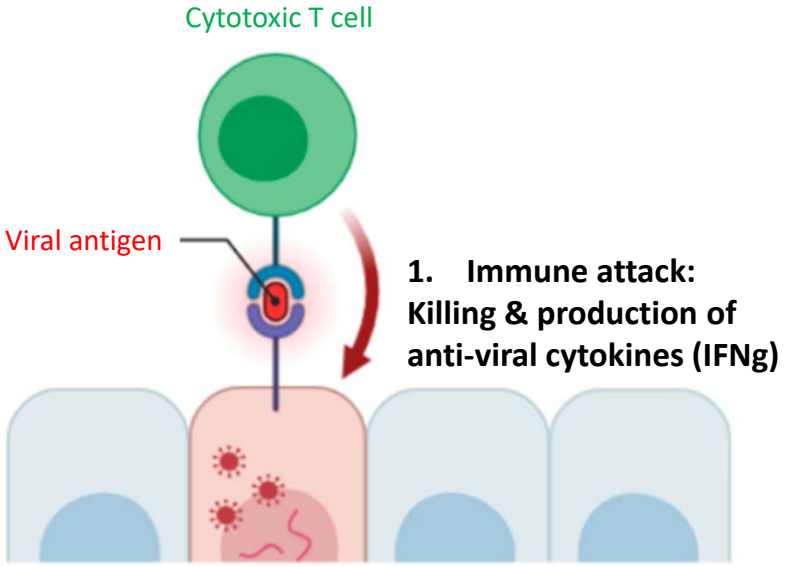
Two arms of adaptive immunity: B and T cells

B cells release neutralizing antibodies



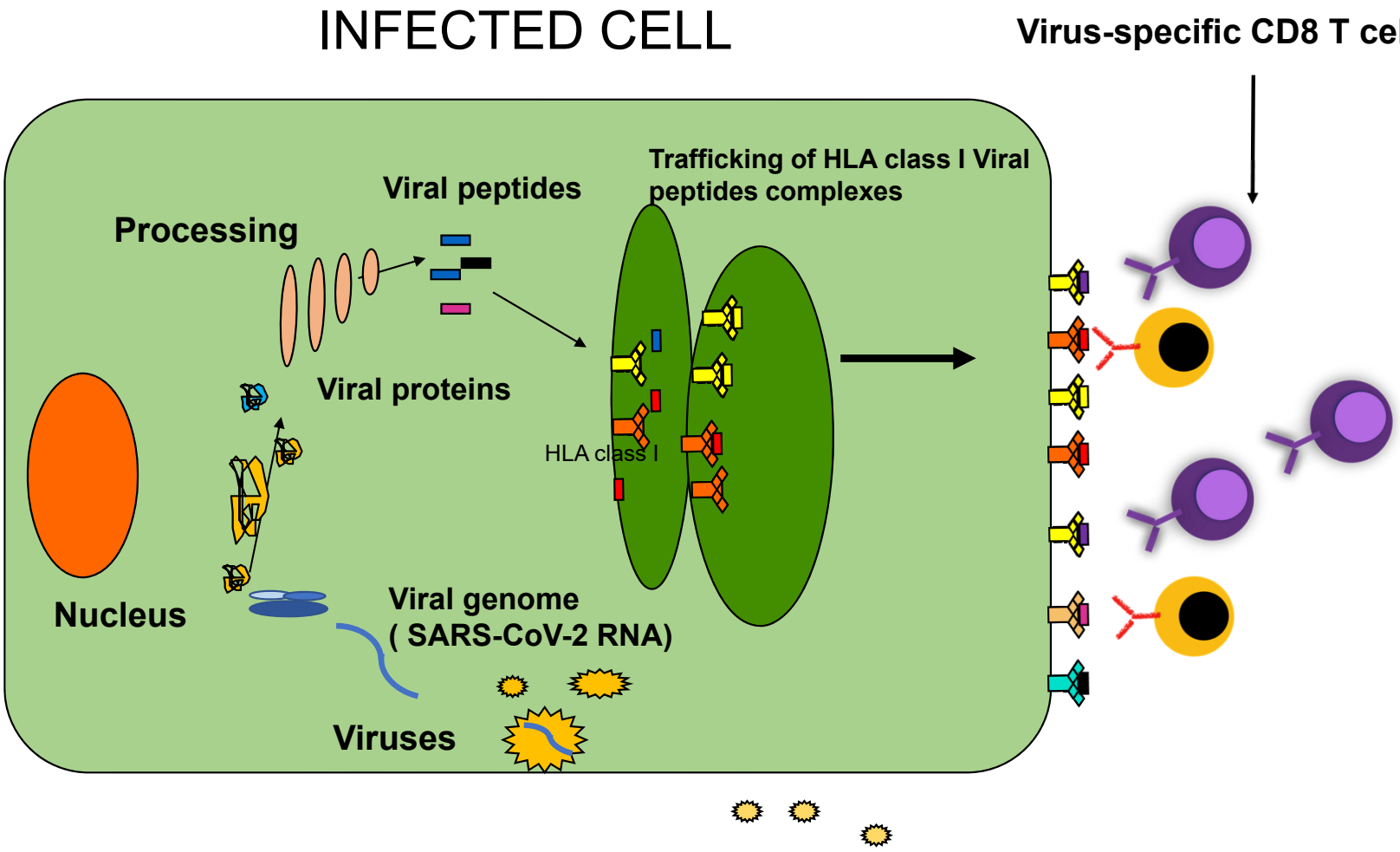
2. Cells not infected by virus ✔

Cytotoxic T cells recognize infected cell, leading to cell death



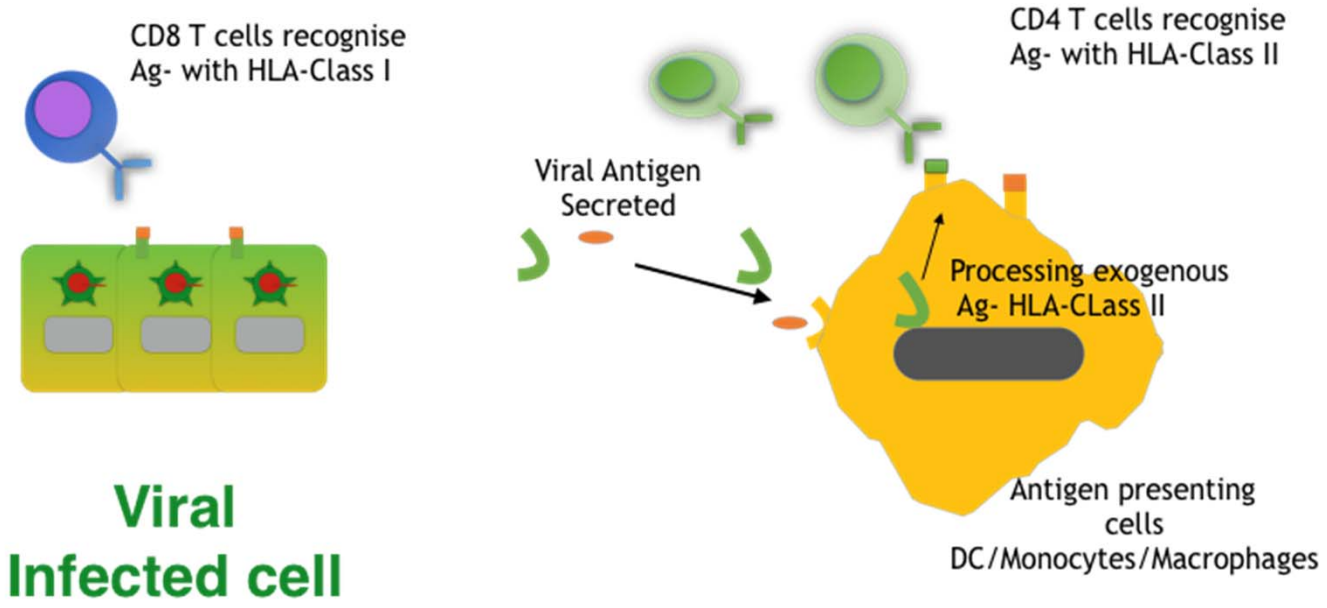
2. Infected cells killed ✔

CD8 T cell recognize short fragment of viral proteins presented by HLA-Class I molecules

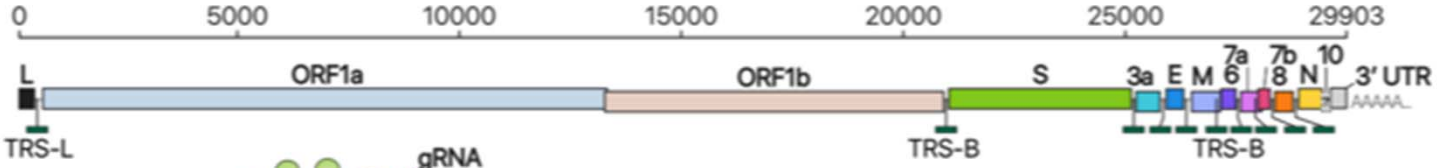


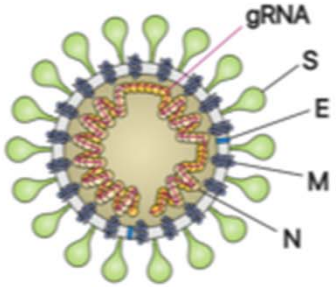
THE ROLE of VIRUS SPECIFIC T CELLS

Virus-specific CD8 and CD4 T cells

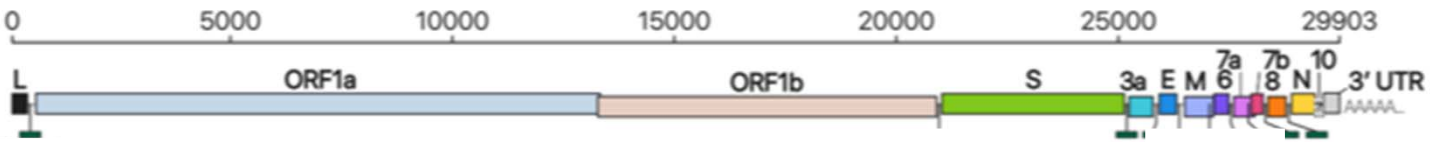


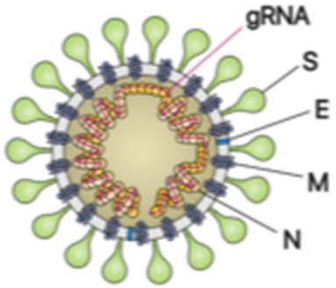
SARS-CoV-2





RNA organization





SARS-CoV-2
NON Structural and structural proteins

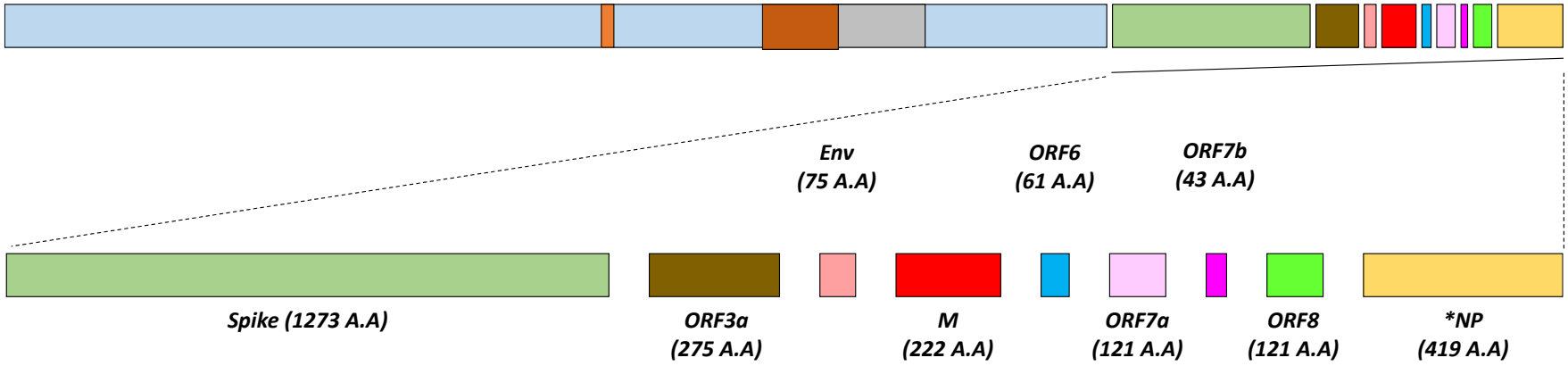
NON-Structural

Structural

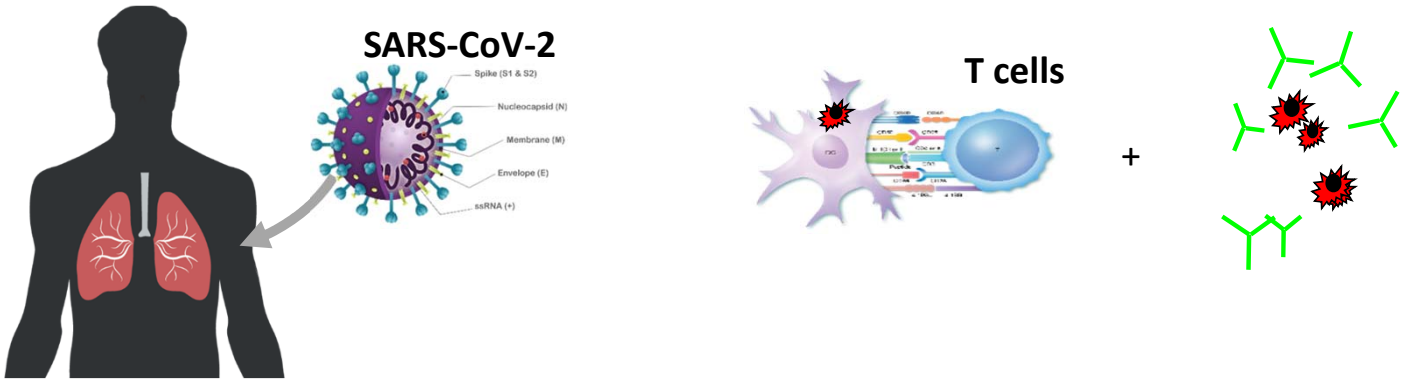
ORF1 (7096 A.A)

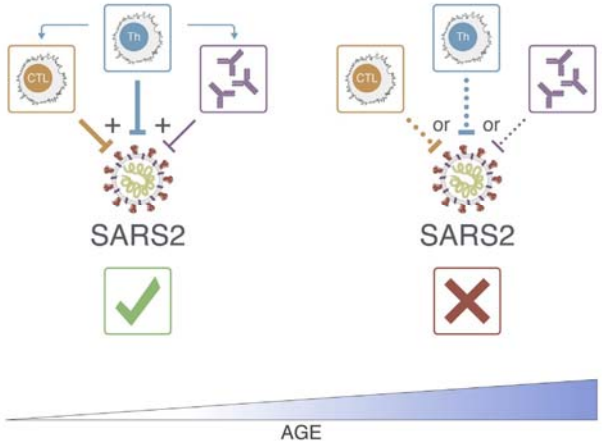
**NSP7 (83 A.A)*

**NSP-12 and NSP13 (601 A.A)*



Background



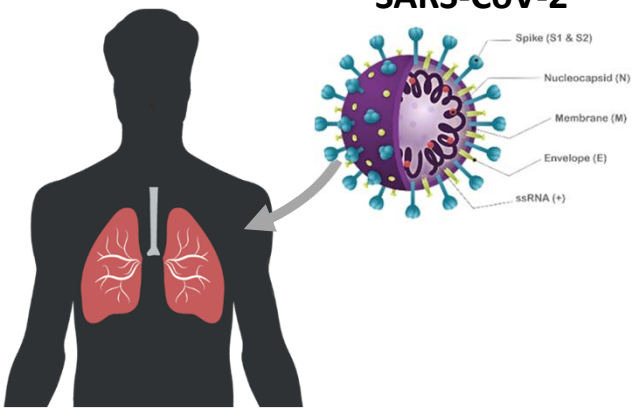


Coordinated induction of humoral and cellular immunity

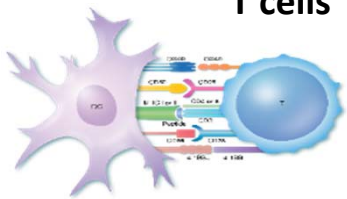
1 Rydyznski Moderbacher C, *et al.* Antigen-Specific Adaptive Immunity to SARS-CoV-2 in Acute COVID-19 and Associations with Age and Disease Severity. *Cell* 2020; **183**: 996–1012.e19.

Background

SARS-CoV-2



T cells



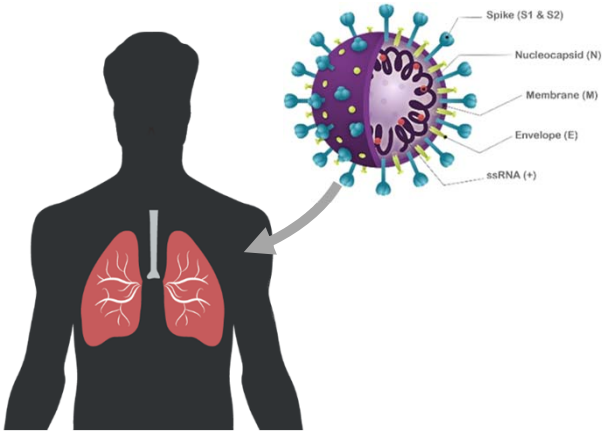
Animal Model of Coronavirus infection:

Zhao J, *et al.* Airway Memory CD4 + T Cells Mediate Protective Immunity against Emerging Respiratory Coronaviruses. *Immunity* 2016; **44**: 1379–1391.

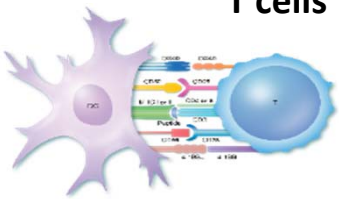
Zhao J, et al.. T cell responses are required for protection from clinical disease and for virus clearance in severe acute respiratory syndrome coronavirus-infected mice. *Journal of Virology* 2010; **84**: 9318–9325.

Background

SARS-CoV-2

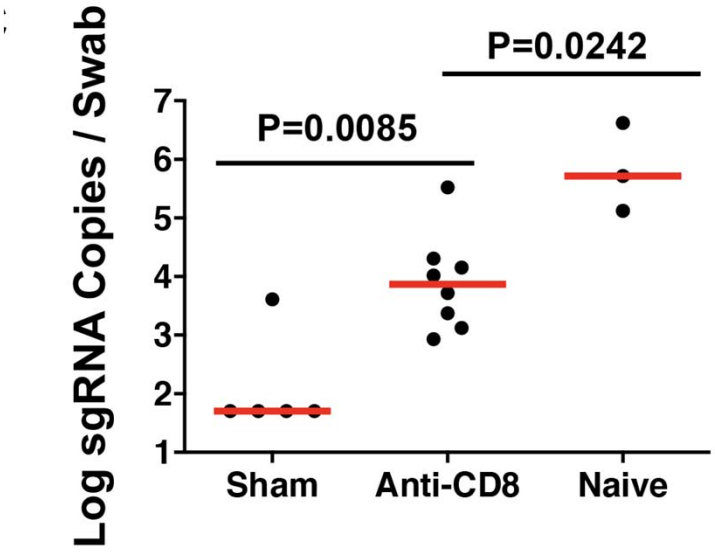


T cells



Convalescent Animals

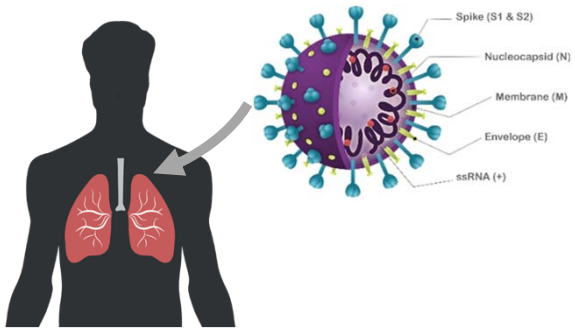
Rhesus macaques are better protected from re-infection if they have CD8+ T cells



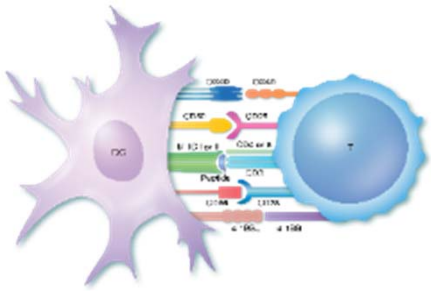
McMahan, K. et al. Correlates of protection against SARS-CoV-2 in rhesus macaques. *Nature* (2020).

Summary of our studies on SARS-CoV-2 T cells

SARS-CoV-2



T cells



SARS-CoV-2 T cells detected:

COVID-19 patients
Healthy unexposed
SARS-convalescent

Le Bert *et al.* **Nature 2020**

Early SARS-CoV-2 T cells in acute patients:

Mild disease
Rapid clearance

Tan *et al*. **Cell Reports 2021**

SARS-CoV-2 T cells in asymptomatic:

Magnitude similar to symptomatic
Higher cytokine production

Le Bert *et al.* **JEM 2021**

Early SARS-CoV-2 T cells in vaccinated:

T cells are induced early after vaccination

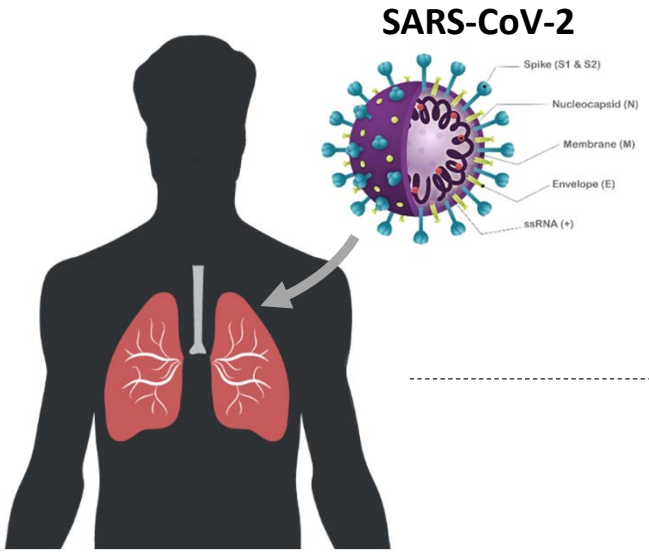
Kalimuddin *et al.* **MED 2021**

Aim: Kinetic of adaptive immunity

National Centre for Infectious Diseases
David Lye
Mark I-Cheng Chen

Singapore General Hospital
SingHealth
Jenny Low
Shirin Kalimuddin
Wei Yee Wan

Analyse the dynamic changes of virological and immunological parameters from disease onset to convalescence or death



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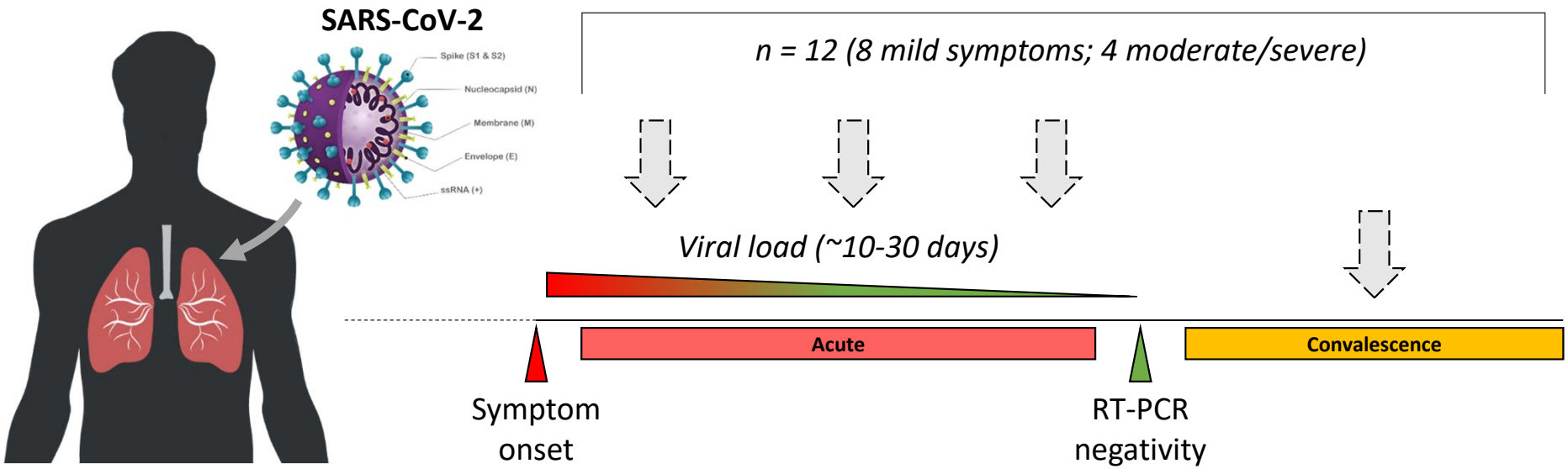
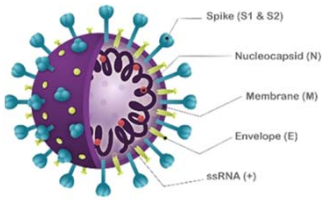
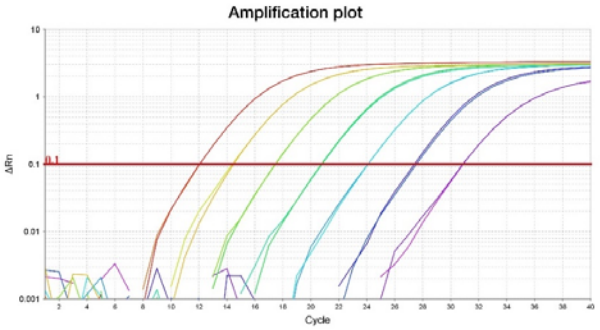


Mild: presence of fever or respiratory symptoms but not requiring supplemental oxygen
Moderate: requiring oxygen supplementation FiO2<0.5
Severe: requiring oxygen supplementation FiO2>0.5, high flow oxygen and/or mechanical ventilation

Methods

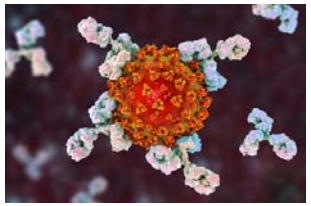
Viral load

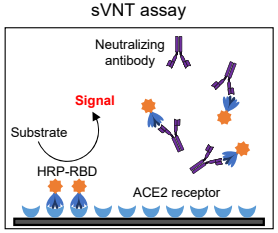


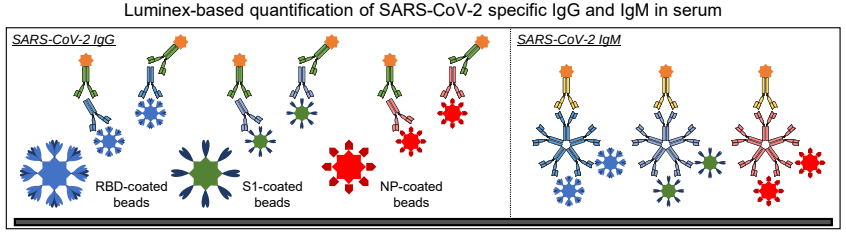


Relative quantification of SARS-CoV-2 viral load from respiratory tract

Antibodies

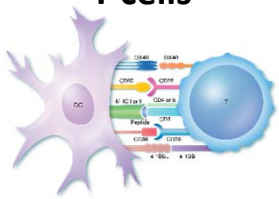


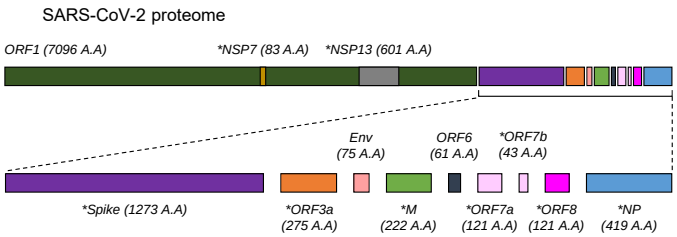


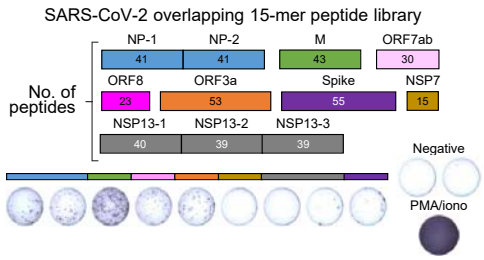


Quantification of SARS-CoV-2 RBD-, S1-, NP- and neutralising antibodies

T cells

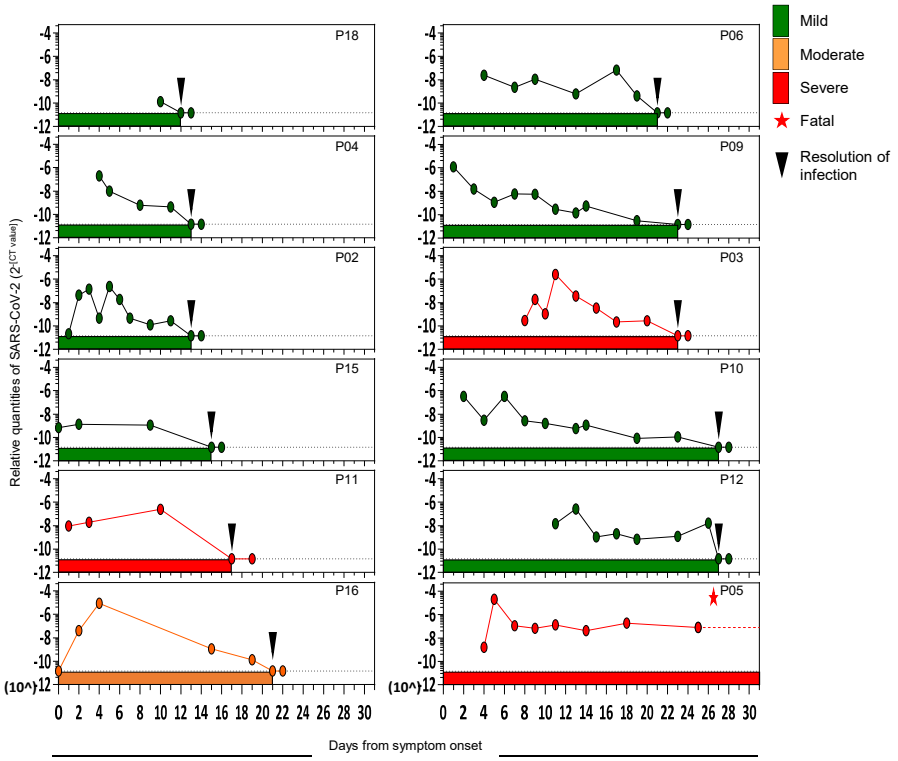


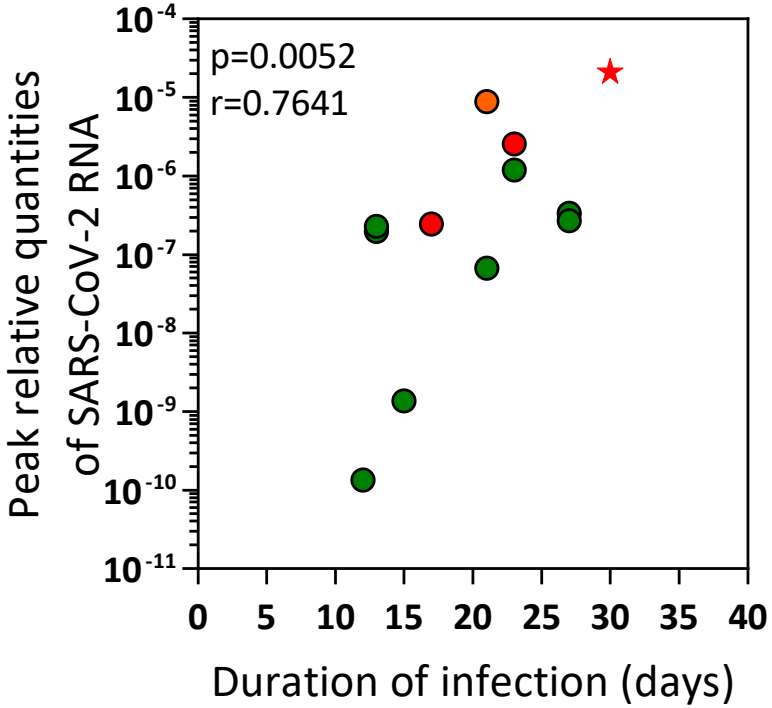




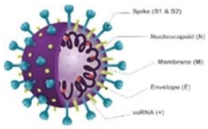
Quantification of SARS-CoV-2 specific T cells

Viral load "+" correlates with disease severity

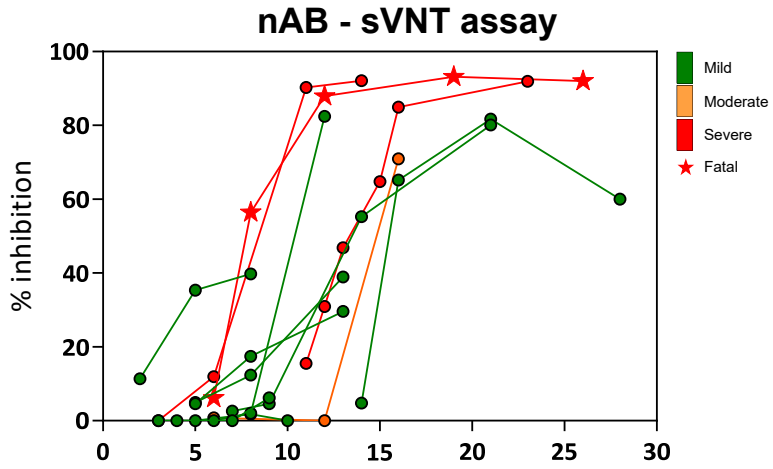




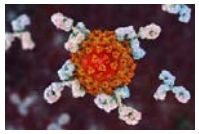
Viral load



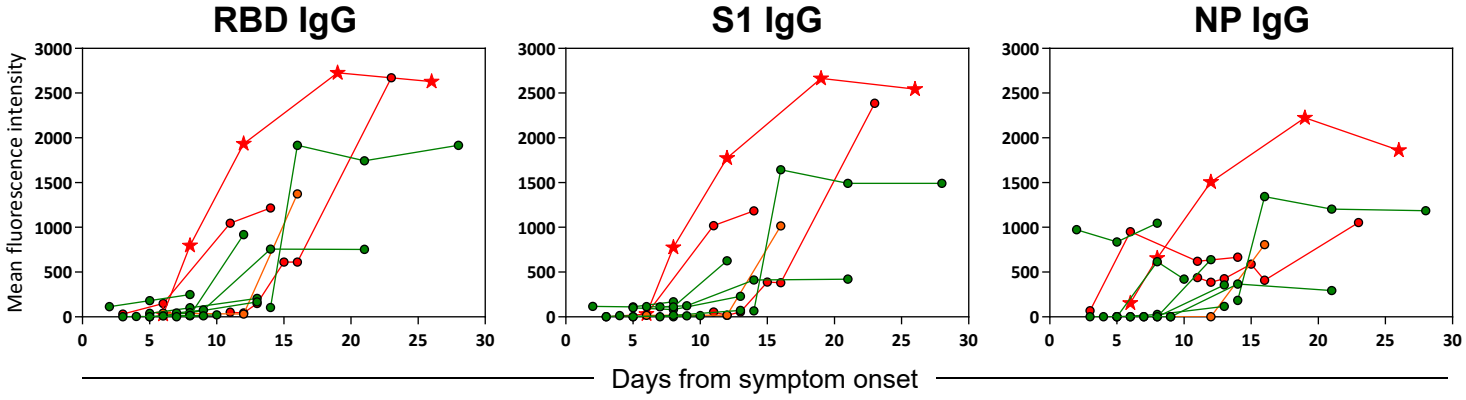
Dynamics of SARS-CoV-2 specific antibody response



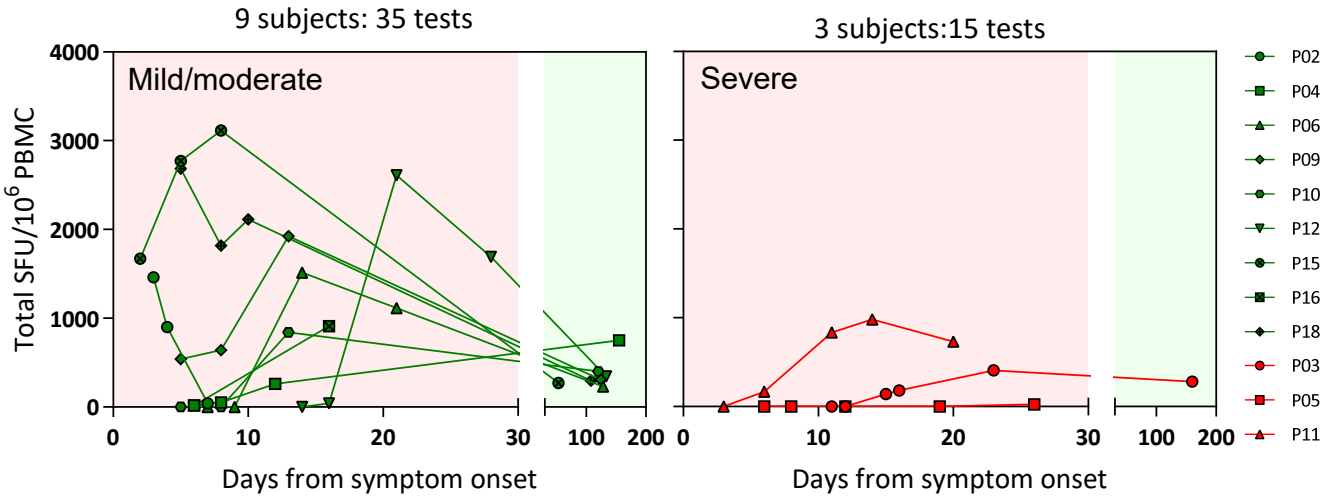
Antibodies



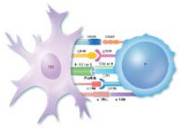
11/12 COVID-19 patients have detectable SARS-CoV-2 antibody responses

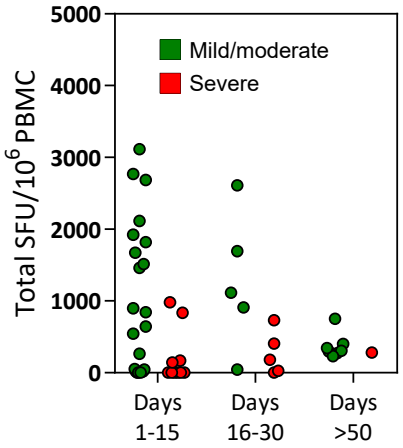


Dynamics of SARS-CoV-2 specific T cell response



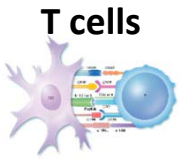
T cells

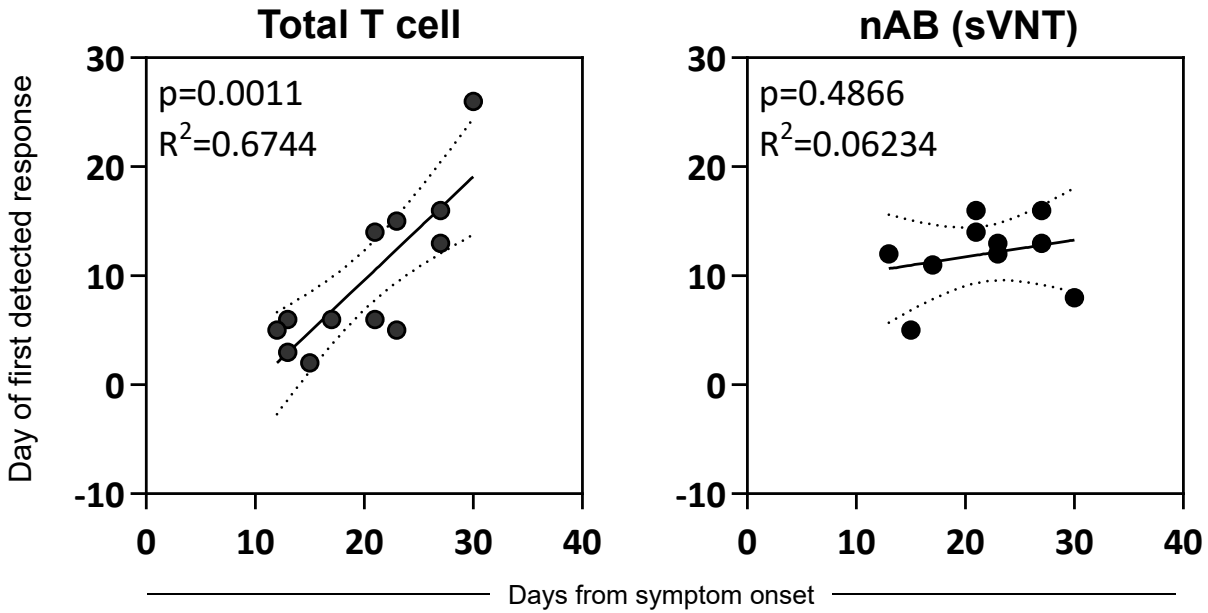




- High frequency SARS-CoV-2 specific T cells is associated with mild disease.

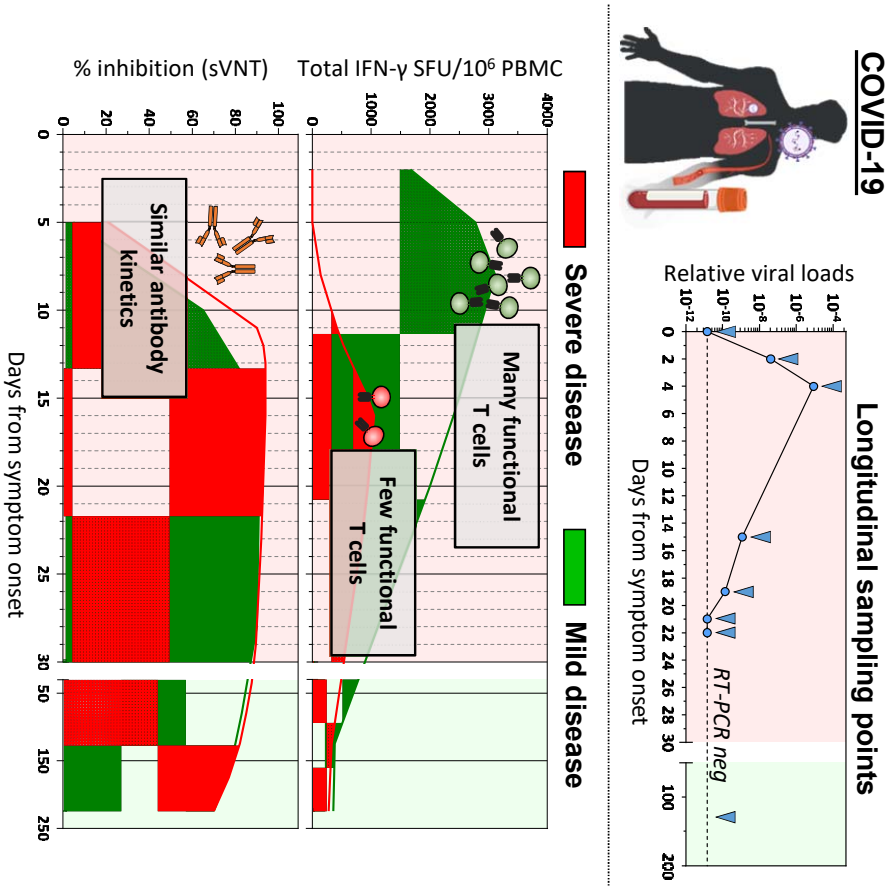
Time of T cell appearance and duration of infection





- Early appearance of virus-specific T cells correlates with a shorter duration of infection.

Conclusions I



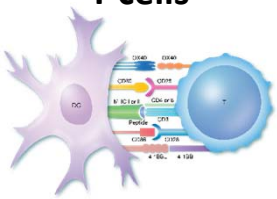
- Quantity of virus-specific antibodies positively correlated with COVID-19 severity.
- Quantity of virus-specific T cells is directly associated with mild disease.
  - Early induction of SARS-CoV-2 specific T cells is associated with accelerated viral clearance
  - Delayed induction of low numbers of SARS-CoV-2 specific T cells was seen in severe COVID-19

Early induction of T cells important for control of SARS-CoV-2 infection

T cell response against Non-Structural Proteins

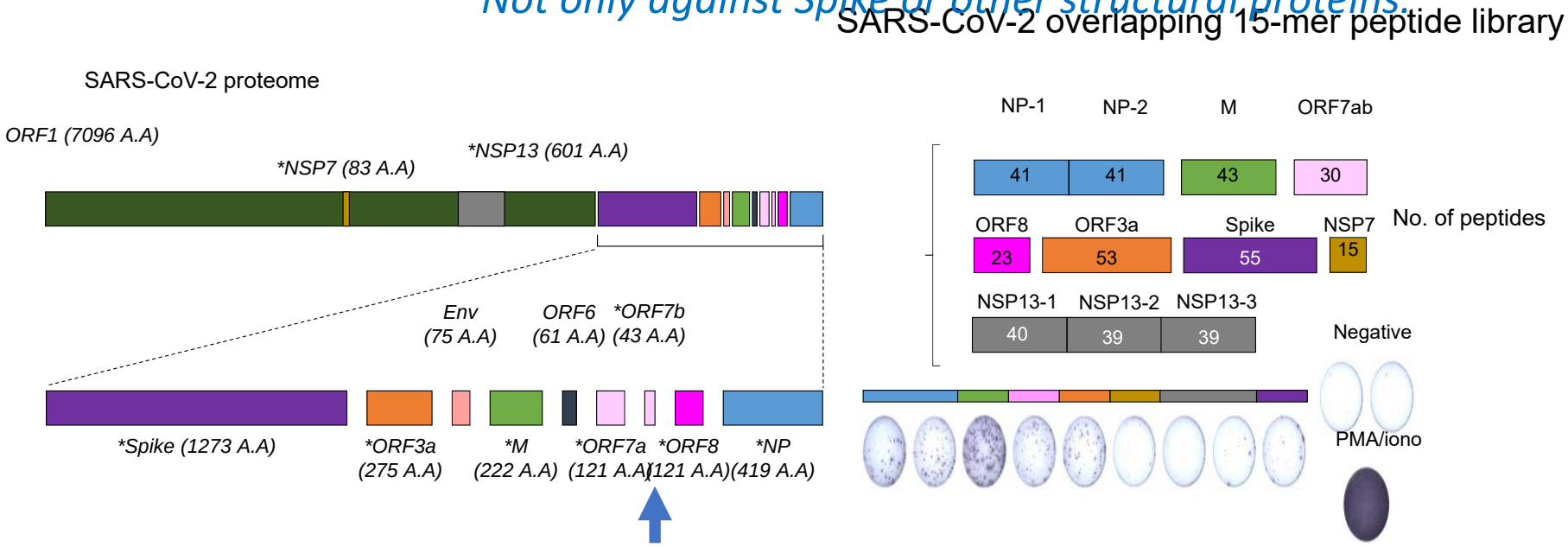
Kinetic of SARS-CoV-2 T cell

T cells



Quantification of SARS-CoV-2 specific T cells

Not only against Spike or other structural proteins.

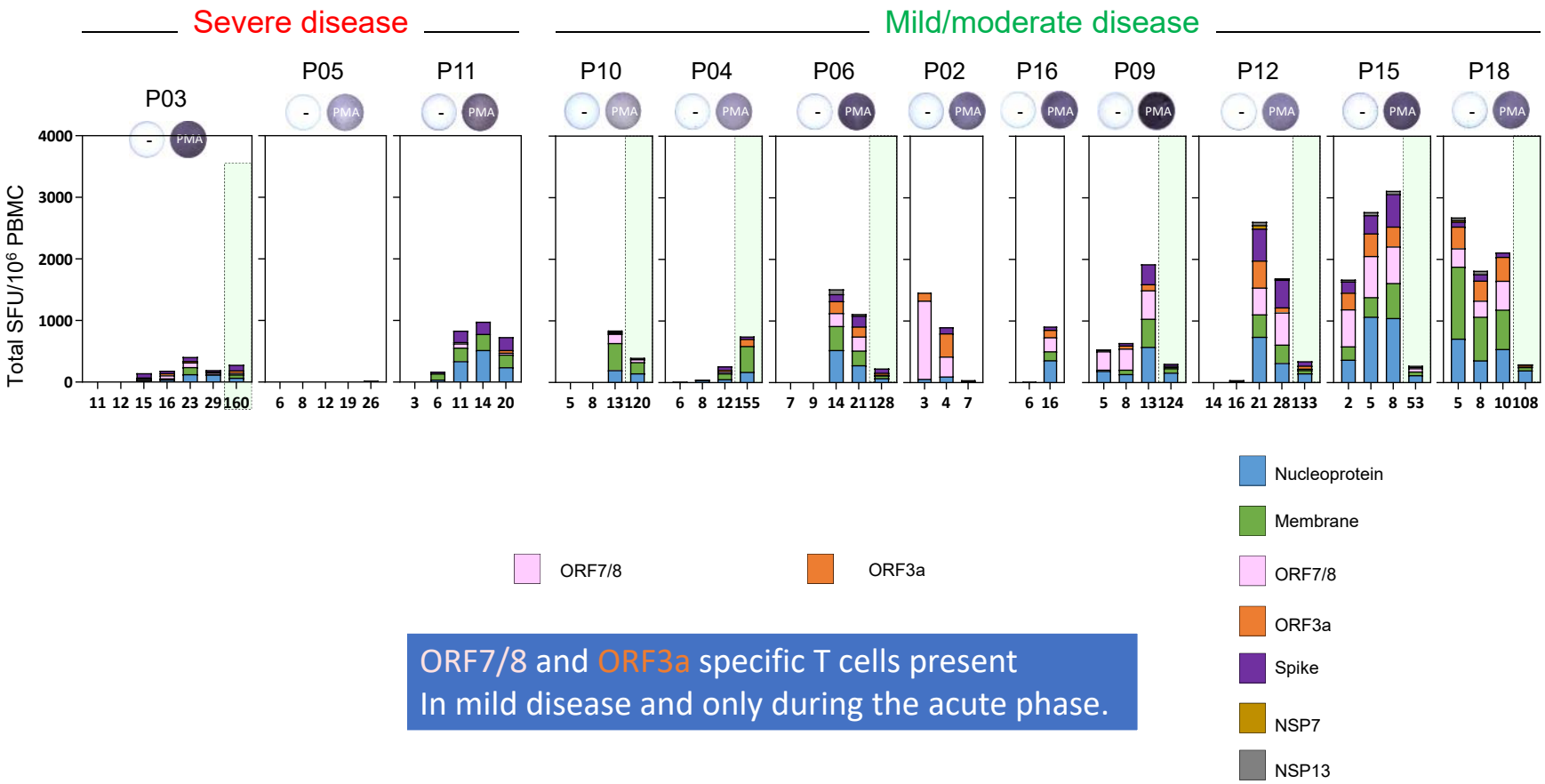


ORF-7/8: They are not required for Viral replication (But can increase viral replication)
Deletions found in SARS-CoV-2 (associated with mild infections)

Young et al Lancet 2020: 396, 603-11/

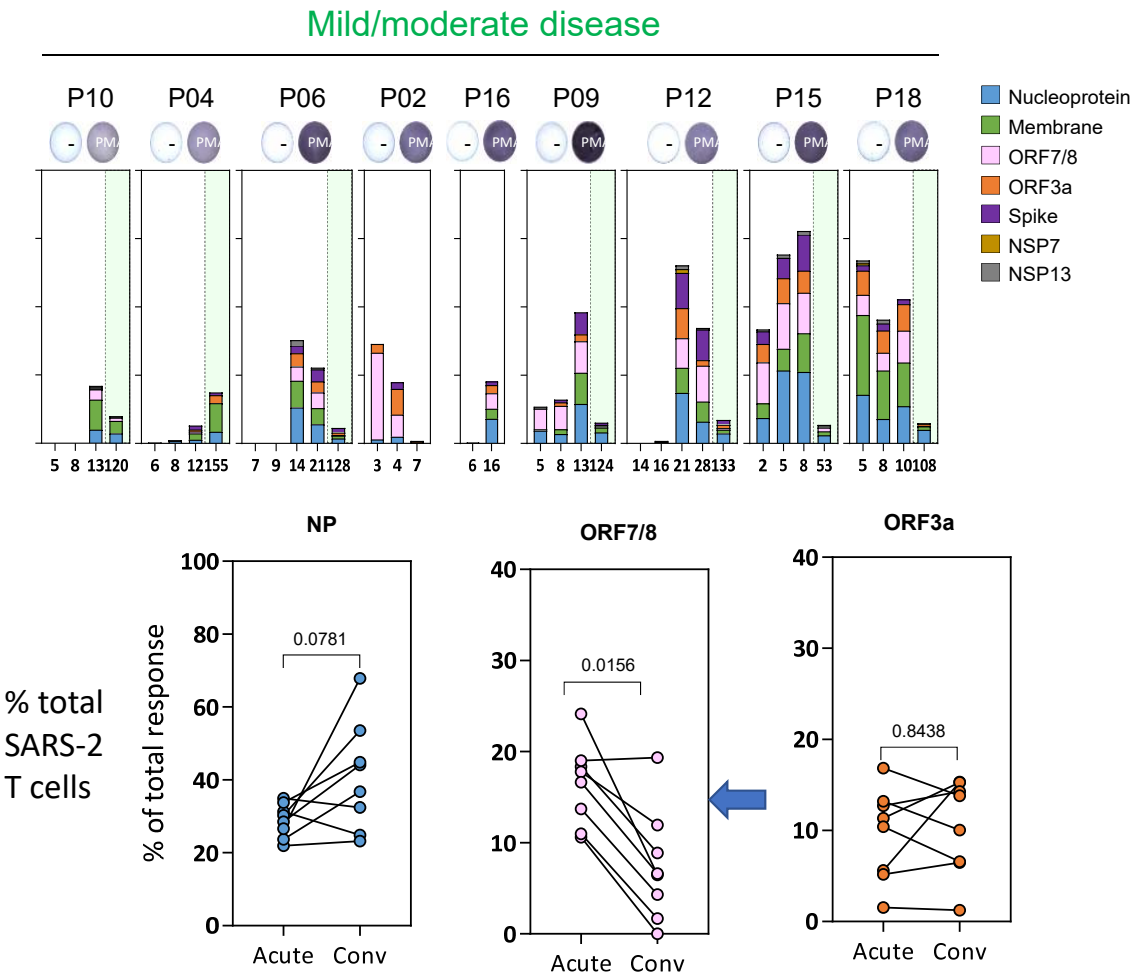
Kee J et al bioRXiv https://doi.org/10.1101/2021.11.10.468057;

T cell response to individuals SARS-CoV-2 proteins



ORF7/8 and ORF3a specific T cells present
In mild disease and only during the acute phase.

ORF7/8 –specific T cells are enriched during the initial phase of infection

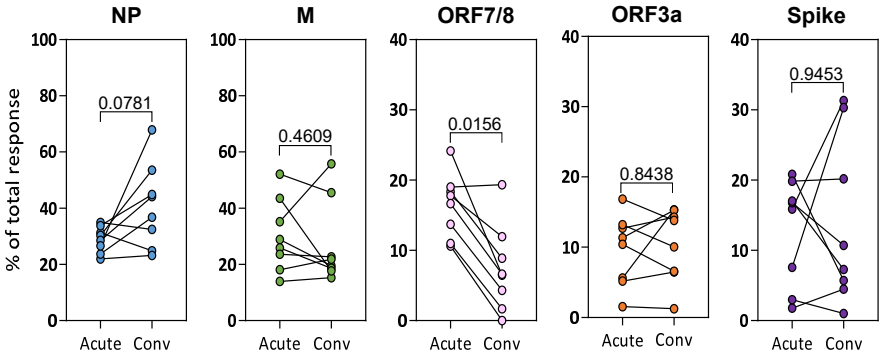


ORF8 antibodies response are accurate serological markers of early SARS-CoV-2 infection.

Hachim et al. Nat Immunol 2020, 21:1293-1301

Question

- What are the reasons of this different kinetic?



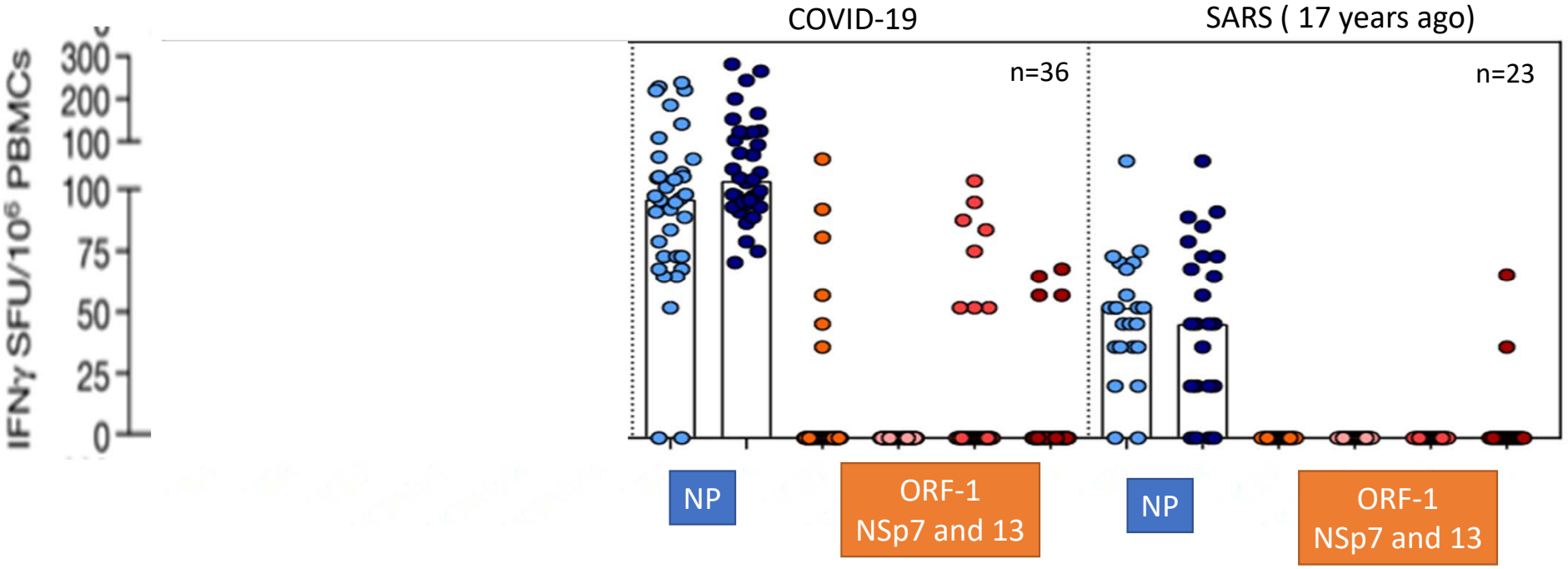
a) ORF-1 proteins produced first during the viral replication. (??)

b) Presence of memory CoV specific T cells cross-recognizing SARS-CoV-2 proteins (*Others Coronaviruses? Commensal bacteria?)*

Bartolo et al SARS-CoV-2-specific T cells in unexposed adults display broad trafficking potential and cross-react with commensal antigens BioRxiv https://doi.org/10.1101/2021.11.29.470421

SARS-CoV-2 T cells primed by other Coronaviruses ?

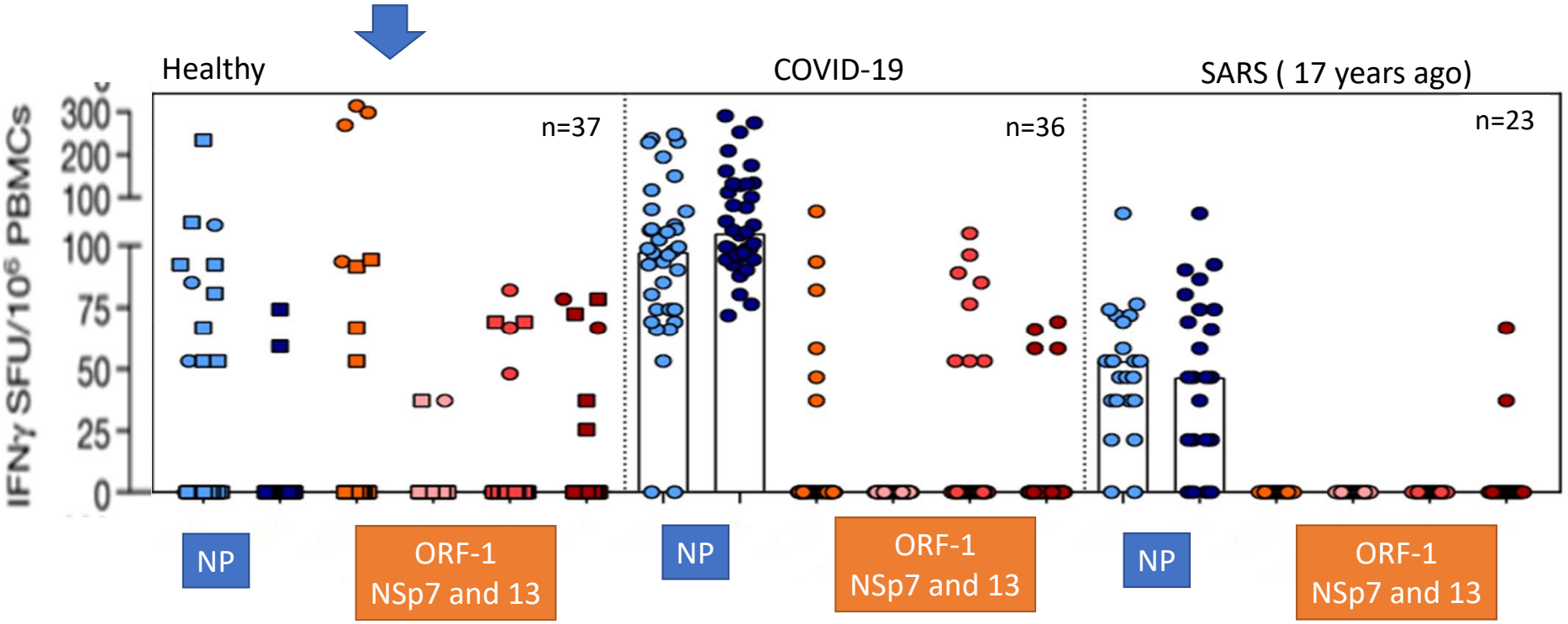
SARS-CoV-1 infected individuals have SARS-coV-2 T cells…same sequence /memory T cells



Le Bert N, Tan A et al. Nature 2020

SARS-CoV-2 T cells primed by other Coronaviruses ?

SARS-CoV-2 T cells also in healthy individuals (tested before 2020)

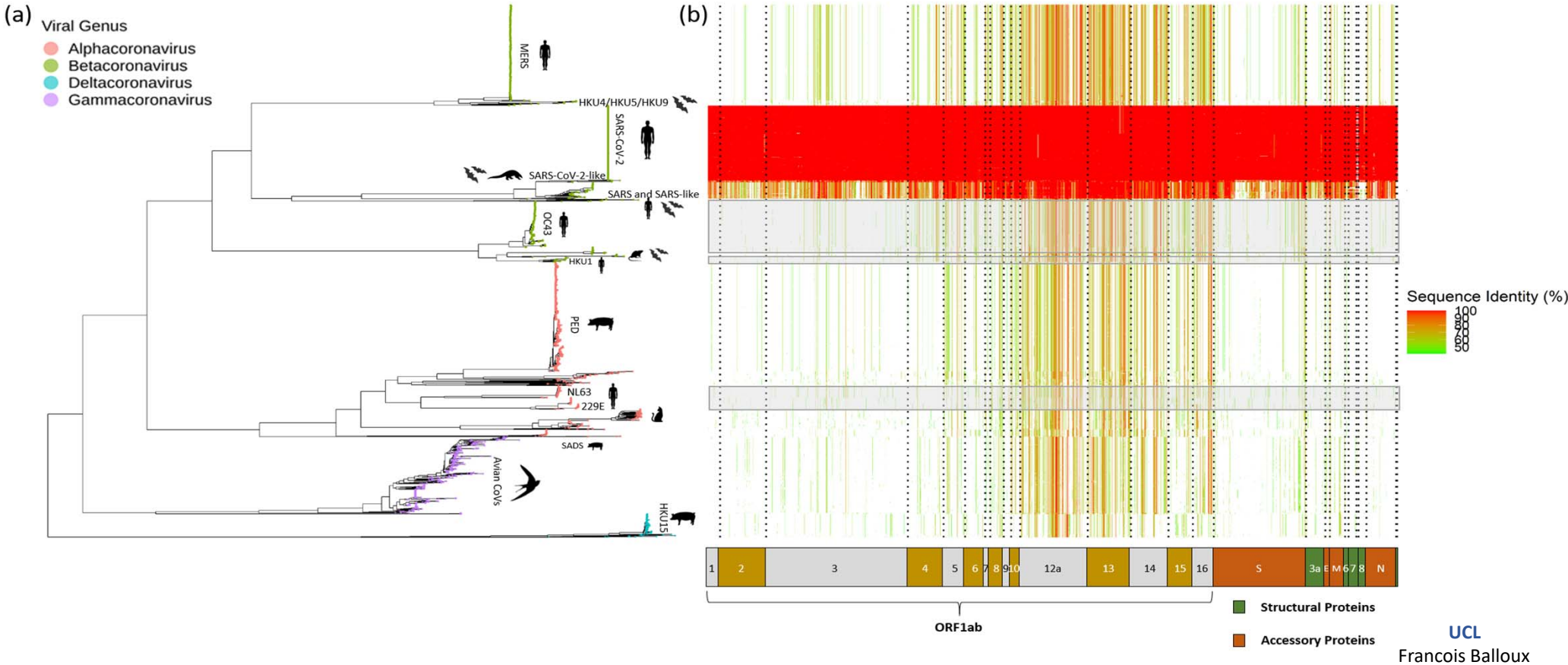


Le Bert N, Tan A et al. Nature 2020

SARS-CoV-2 T cells primed by other Coronaviruses ?

Characterize the T cell response to SARS-CoV-2 proteins with high homology between different Coronaviruses

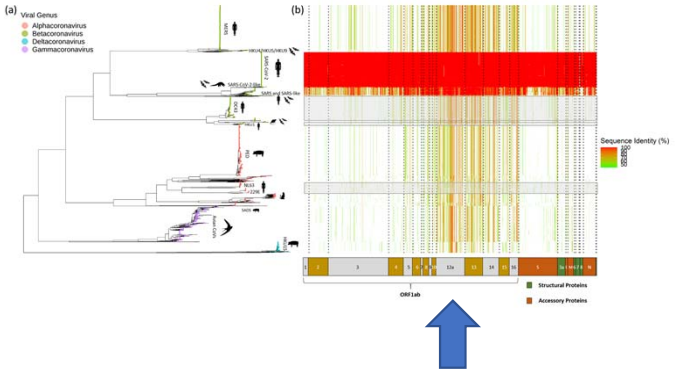
Conservation analysis of SARS-CoV-2-derived 15-mer peptides across the *Coronaviridae*.



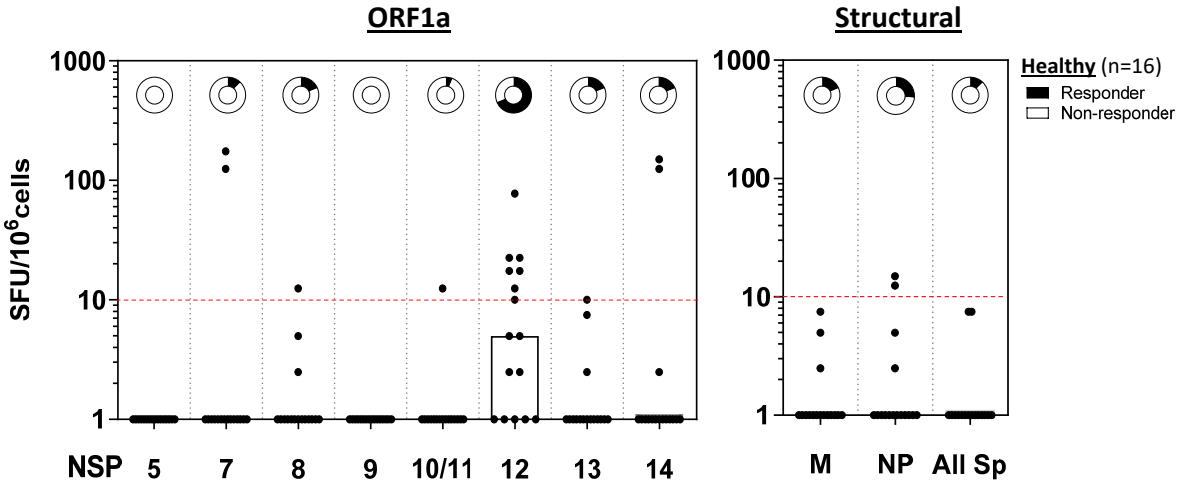
Heatmap visualising the homology of SARS-CoV-2-derived 15-mer peptide sequences across the family.

UCL
Francois Balloux
Cedric Tan
Lucy van Dorp

T cell response to SARS-CoV-2 structural and non-structural proteins healthy individuals (before 2018)



NSP 12 homology



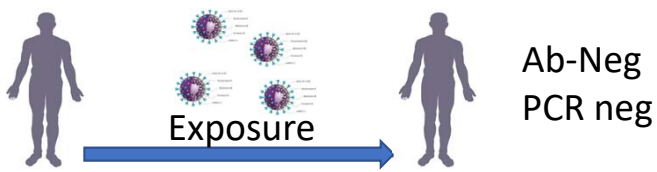
NSP-12= polymerase
necessary for the viral mRNA production

PBMC of healthy individuals test in direct ex vivo Elispot
Against different conserved region of SARS-CoV-2 proteins

Questions

Do T cells specific for NSP-12 (Polymerase)-play a role in SARS-CoV-2 control?

Are cross-reactive NSP-12 (Polymerase)-specific T cells protective?



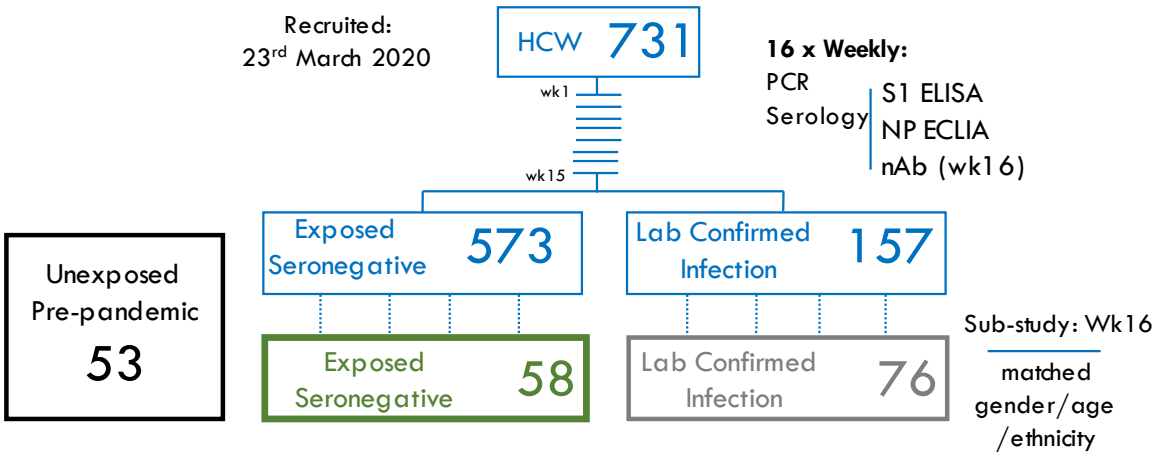
We need exposed individuals (not vaccinated)
And samples before and after exposure !

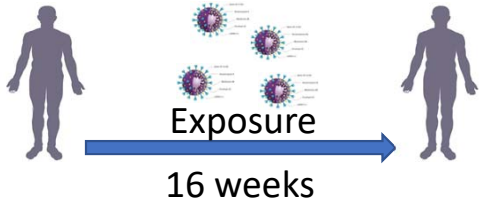
Experiments in Exposed Seronegatives

Maini Lab, UCL
Leo Swadling
Mariana Diniz
Oliver Amin
Nathalie Schmidt
Gloryanne Aidoo-Micah
Anna Jeffery-Smith
Stephanie Kucykowicz
Sabela Lens
Laura Pallett
Nekisa Zakeri
Alice Burton
Jessica Davies

UCL
Mahdad Noursadeghi
Aneesh Chandran
Emily Shaw-Wise
Laura McCoy
Benny Chain

Experiments in Exposed Seronegatives

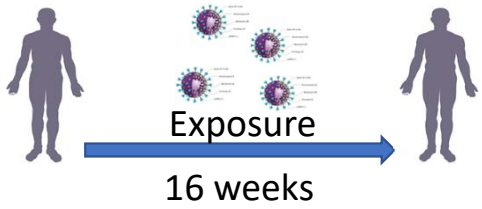




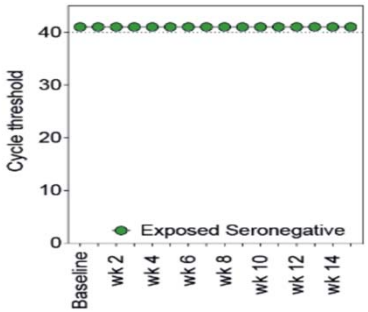
Truly not-infected?

Or show signs of abortive infection?

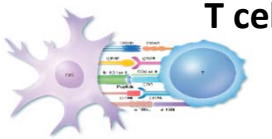
Experiments in Exposed Seronegatives



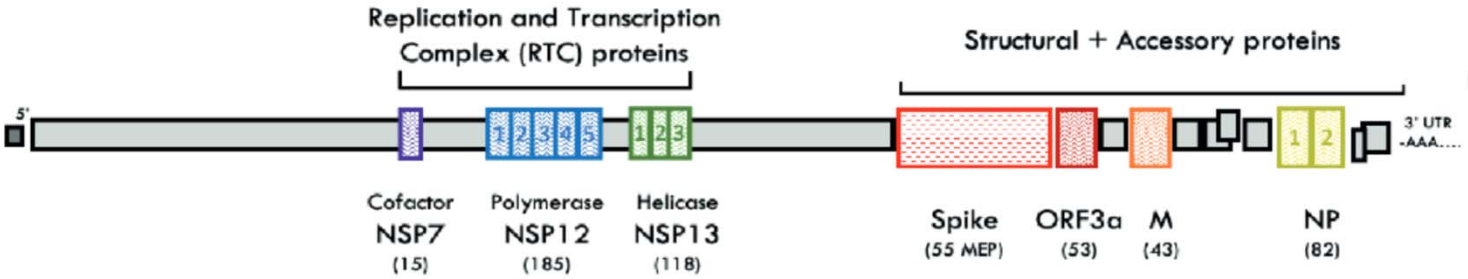
Ab-Neg
PCR neg



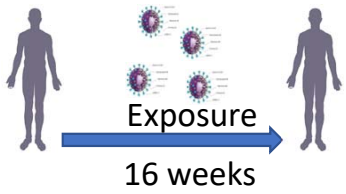
T cell analysis with peptides (Elispot and ICS)



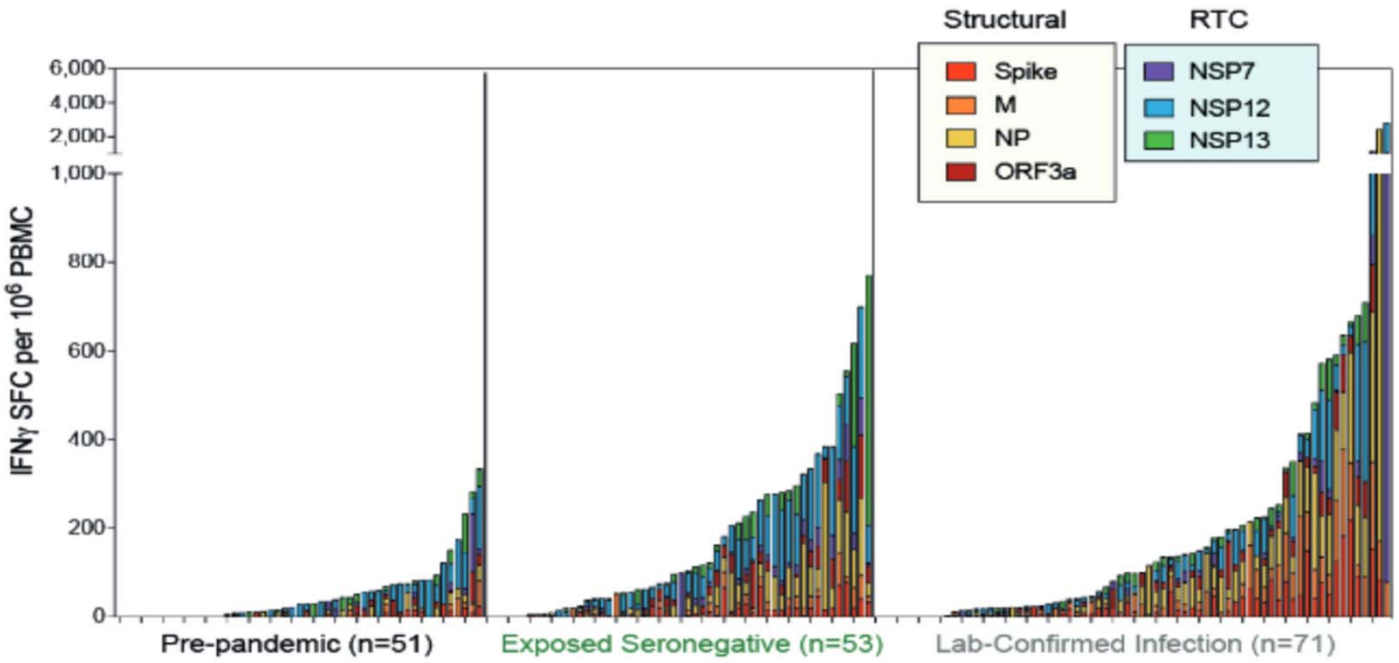
T cells



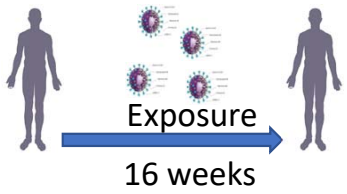
Exposed individuals have stronger SARS-CoV-2 T cell response than pre-pandemic



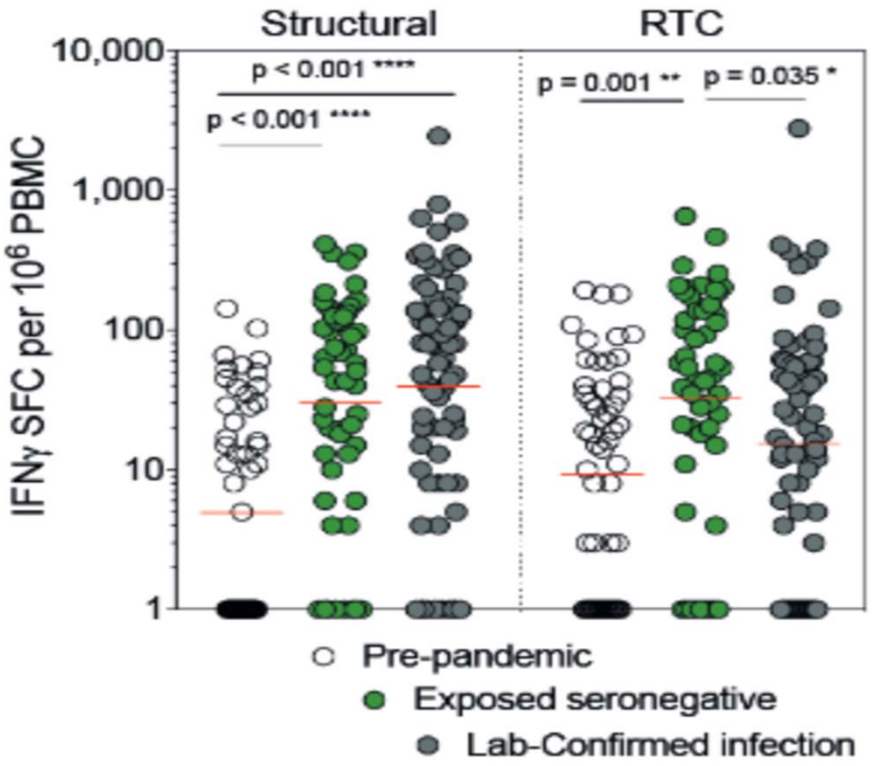
Ab-Neg
PCR neg



Exposed individuals recognize preferentially Polymerase/NSP proteins

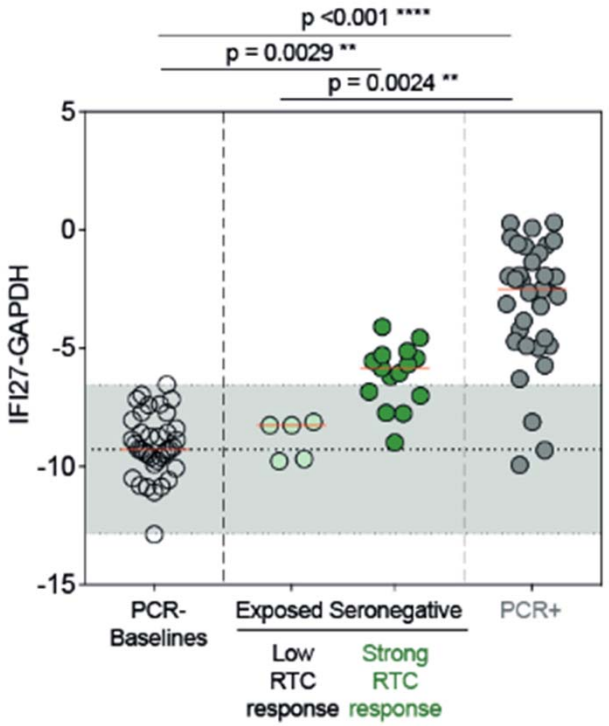


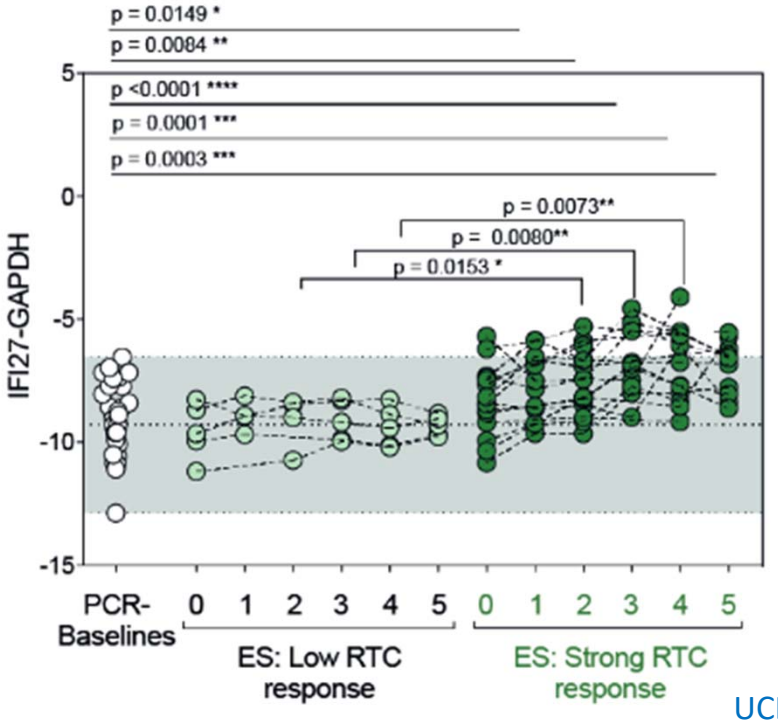
Ab-Neg
PCR neg



Exposed seronegatives with strong NSP-12-T cell response show blood transcriptomic signature of infection

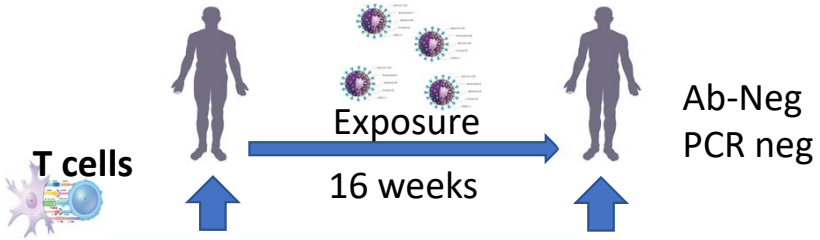
IFI27 –early transcriptomic signature of COVID-19 infection Gupta et al Lancet Microbe 2020

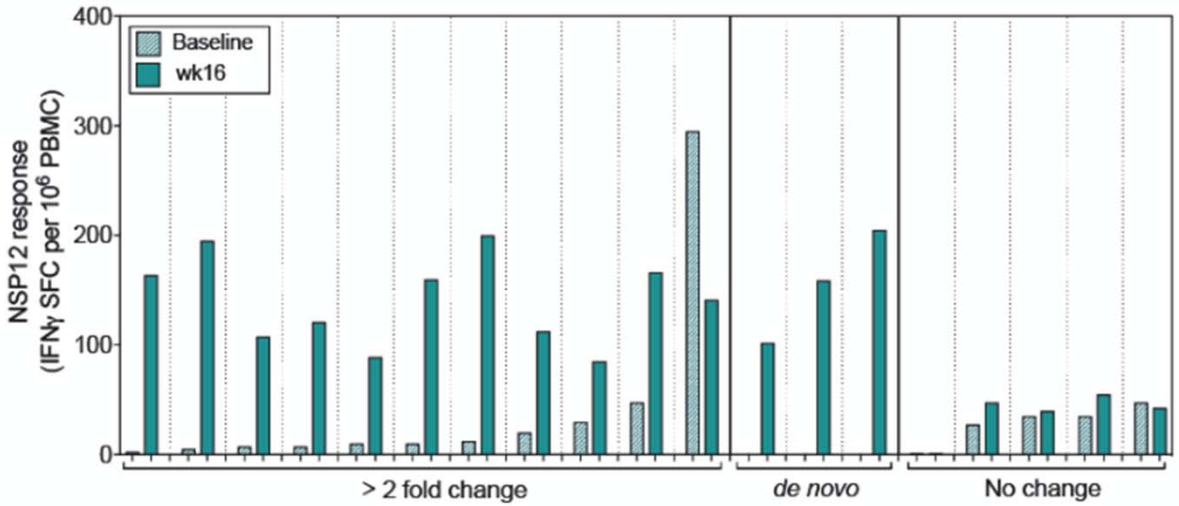


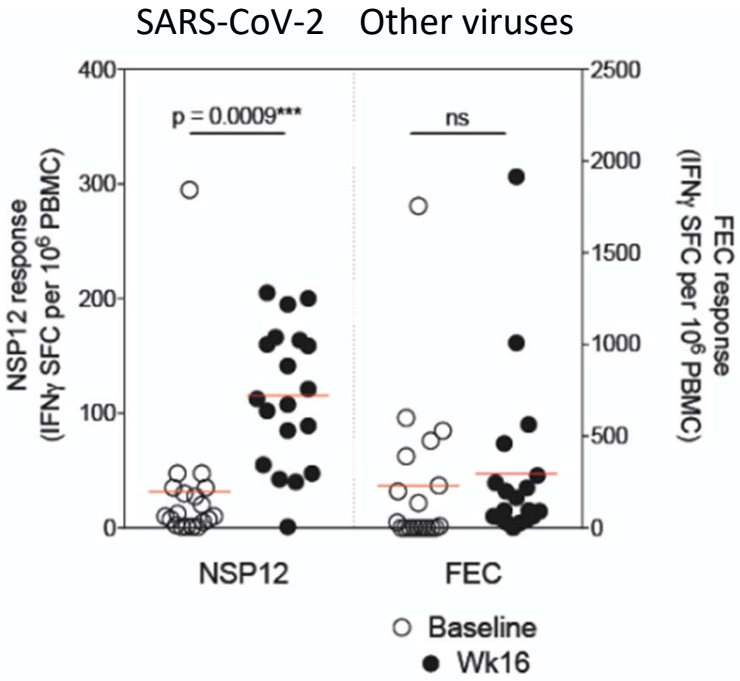


UCL
Maddy Noursadeghi
Aneesh Chandran

In vivo expansion of polymerase-specific T cells in abortive infection







Leo Swalding et al, Nature 2021

Conclusions II

1.Pre-existing cross-reactive T cells possibly (?) induced by closely related coronaviruses can expand upon exposure to SARS-CoV-2.

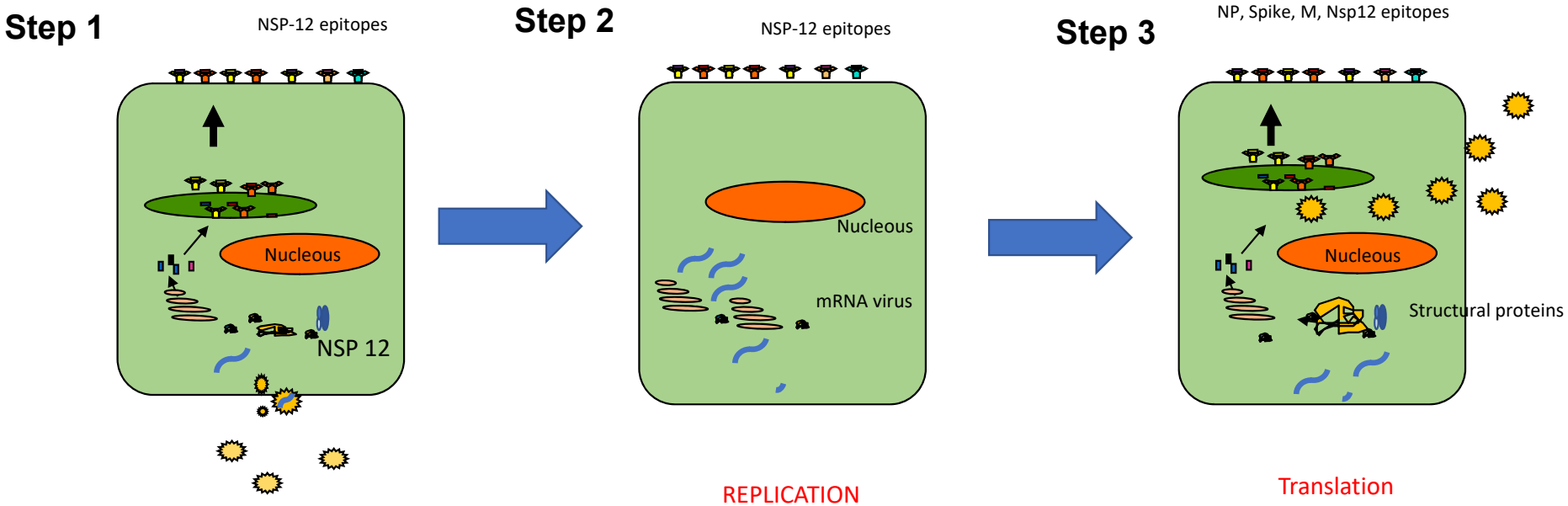
2. Expansion of Polymerase (NSP-12) T cells is detected in individuals exposed to the virus and with possible abortive infection (initial replication with low production of new virions).

3. T cells recognising the RTC may be particularly effective at **early control** of infection and may offer **pan-coronaviridae reactivity**, arguing for their inclusion and assessment in **next-generation vaccines**

HYPOTHETICAL MODEL

Abortive infection?

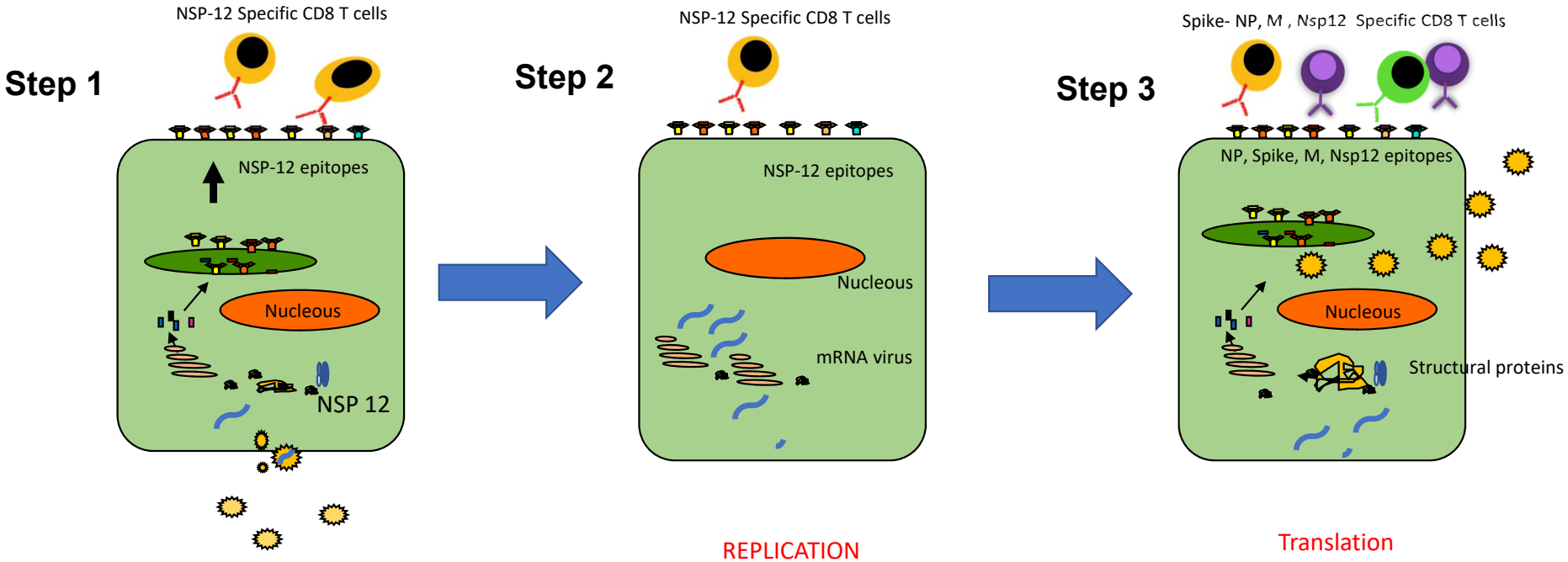
Hypothesis about early recognition of infected cells before formation of whole virions



Translation and Replication Dynamics of Single RNA Viruses. Cell 2020, Boersma et al

Abortive infection?

Hypothesis about early recognition of infected cells before formation of whole virions



Virus infection
Translation
NON-structural Protein
NSP12

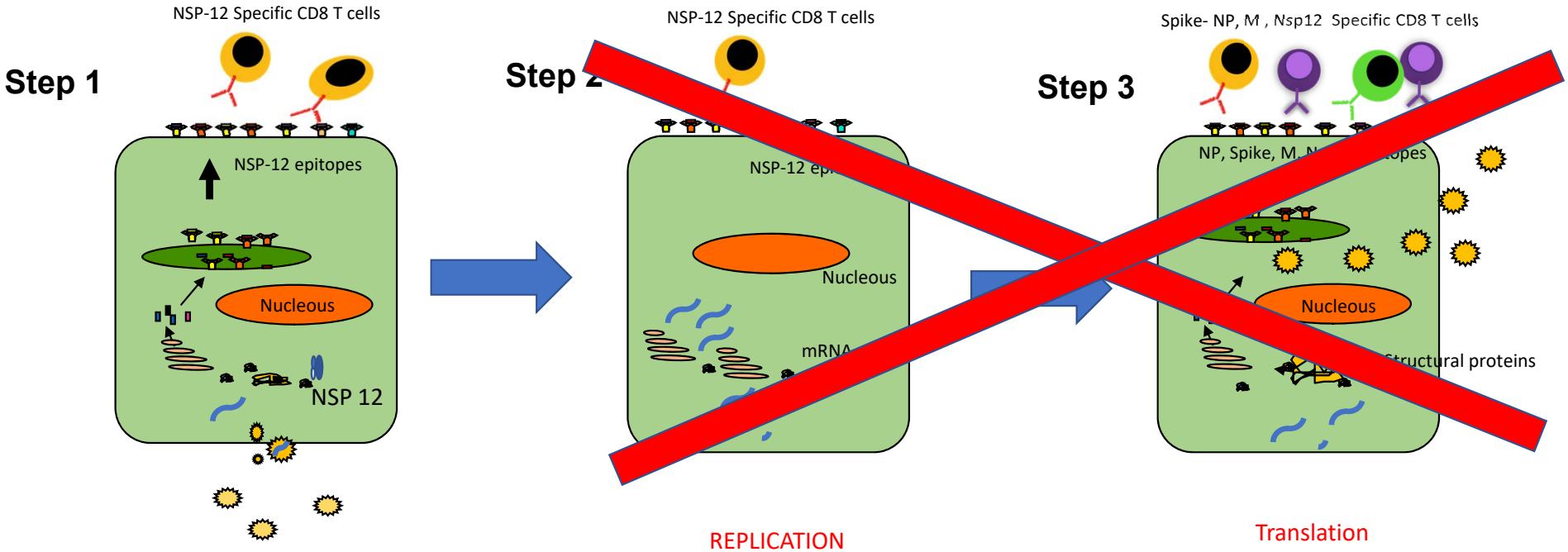
REPLICATION
mRNA of whole virus+
structural proteins

Translation
Production of whole viruses
mRNA of whole virus+
structural proteins

Translation and Replication Dynamics of Single RNA Viruses. Cell 2020, Boersma et al

Abortive infection?

Hypothesis about early recognition of infected cells before formation of whole virions



Translation and Replication Dynamics of Single RNA Viruses. Cell 2020, Boersma et al

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NUS National University of Singapore
Yong Loo Lin School of Medicine

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David Lye
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Nina Le Bert


COVIDsortium
COVID-19 consortium
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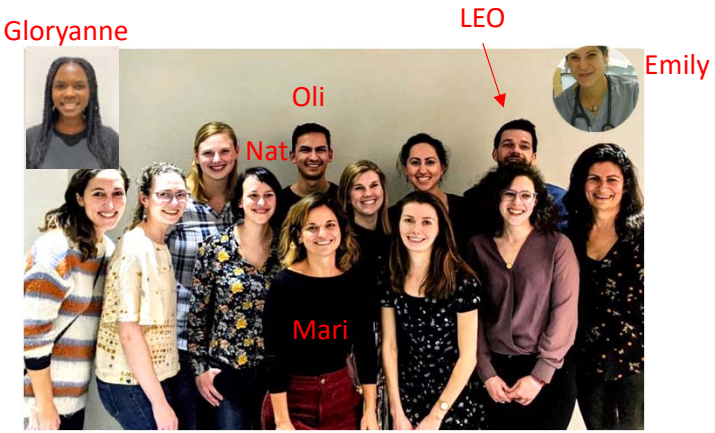
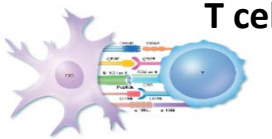
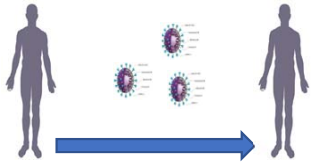
Sachs
CITADEL
GW
pharmaceuticals
kusuma
trust
BARTS
CHARITY


Gloryanne
LEO
Emily
Oli
Nat
Mari

Pattern of SARS-CoV-2- T cell response

T cells

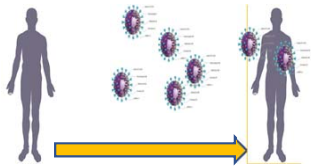




Ab-Neg
PCR neg

Abortive infection

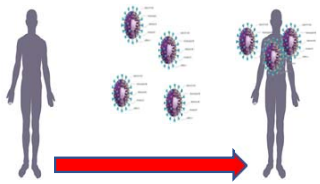
Polymerase-specific T cells
Non-structural-specific T cells



Ab-Pos
PCR +

Asymptomatic/mild infection

Membrane/spike/NP-T cells
Structural -specific T cells



Ab-Pos
PCR ++

Severe infection

Low quantity SARS-CoV-2 specific T cells