COVID-19 Vaccine

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COVID-19 Seminar: From Prevention to Control 2020

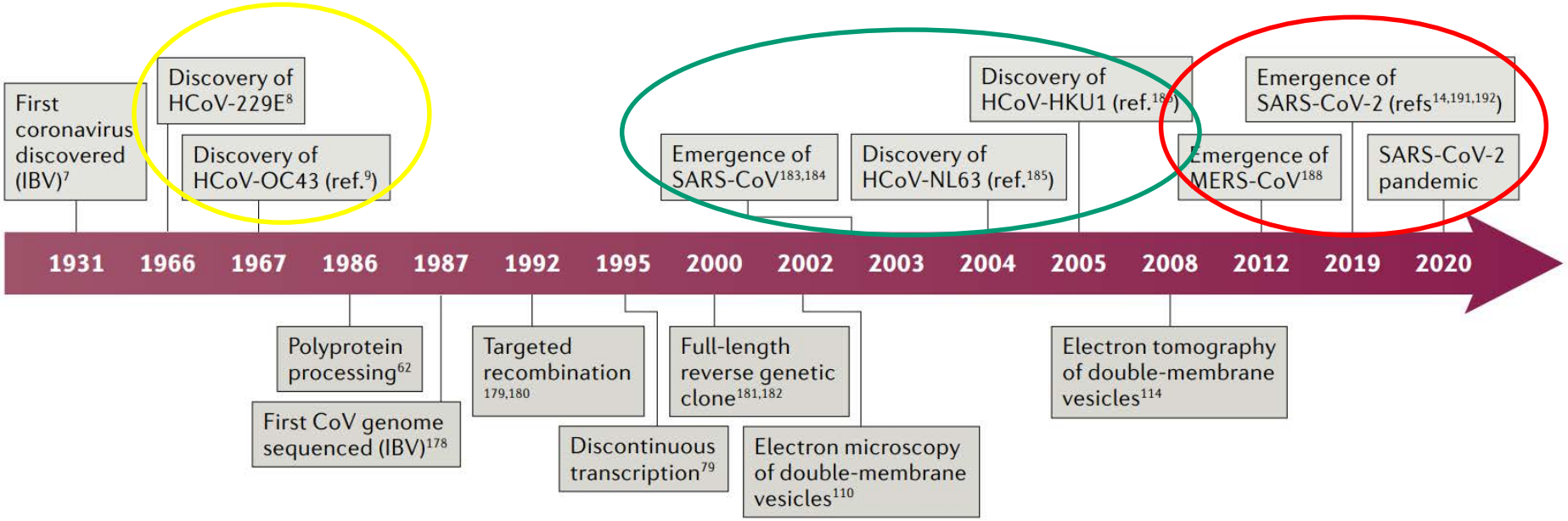
Outline

- **SARS-CoV2 & Host immune response**
- **Vaccine platform & design**
- **Leading candidates & Future**

Respiratory viruses identified since 1997

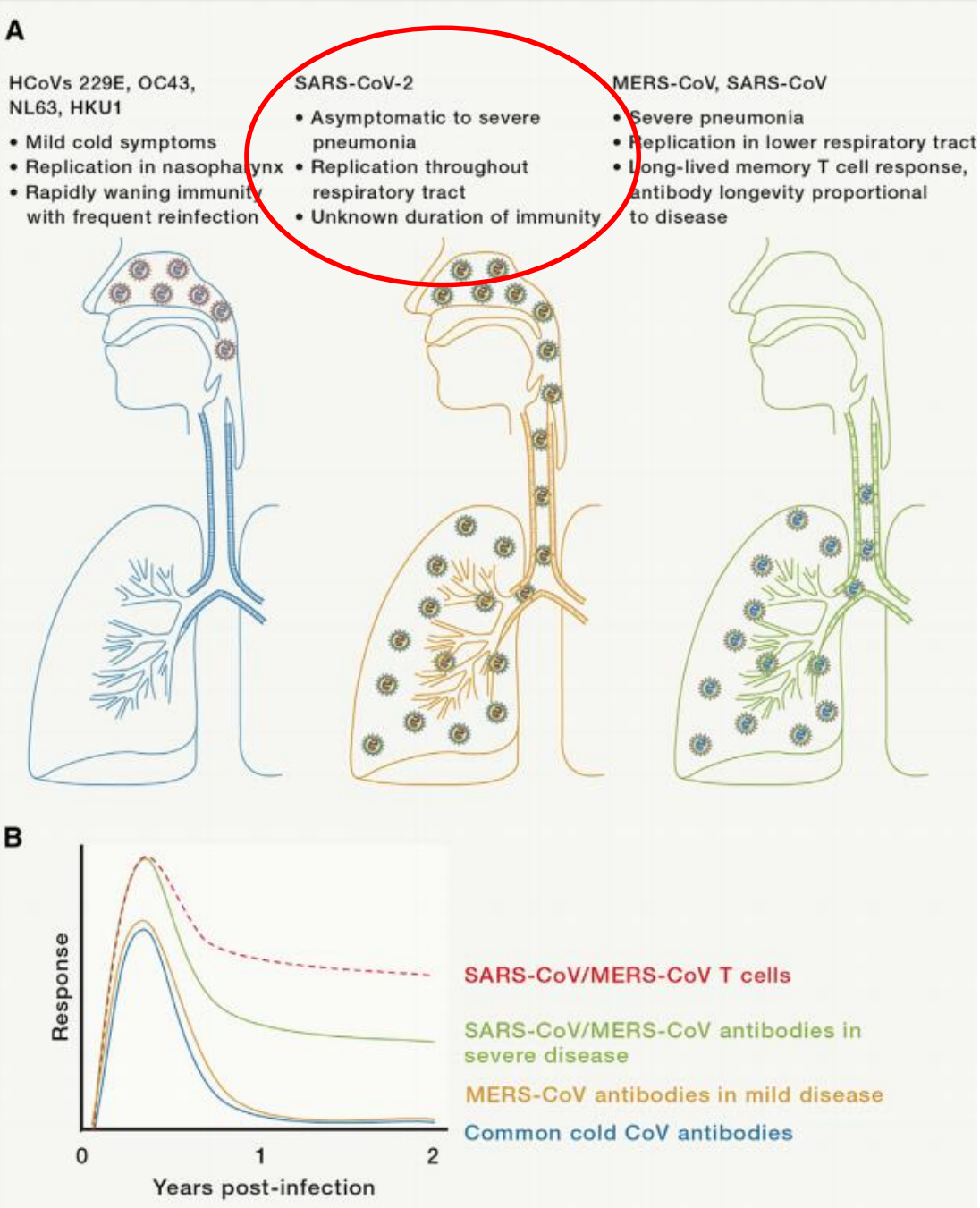
Year		Cases (deaths / CFR%)		
1997	H5N1	18	(6)	HK
1999	H9N2	2+ 5		HK & mChina
2001	hMPV			Netherlands
2002/3	SARS-CoV	8098	(774)	mChina, HK, World
2003/2015	H5N1	844	(449)	mChina, HK, World
2003	H7N7	89	(1)	Netherlands
2003/07/09	H9N2	1		HK
2004	H7N3	2		Canada
2004	H10N7	2		Egypt
2004	NL63 (CoV gp1)			Netherlands
2005	HKU1 (CoV gp2)			HK
2005	Bocavirus			Sweden
2007	HRV-C			HK
2009	pH1N1			N America/ HK/World
2012	MERS-CoV	>1500	(40%)	Middle East
2013/2018	H7N9	>1300	(30%)	mChina/ HK
2019/2020	SARS-CoV2	>66M	(>1.5M)	mChina/HK/World

Coronavirus



- **7 CoVs can infect human**
  - **4 cause common cold**
  - **2 cause severe pneumonia**
  - **SARS-CoV2 cause both**

Nat Rev Microbiol 2020 Oct 28;1-16. doi: 10.1038/s41579-020-00468-6



→ 17 years (T memory)

→ 2-3 years (B memory)

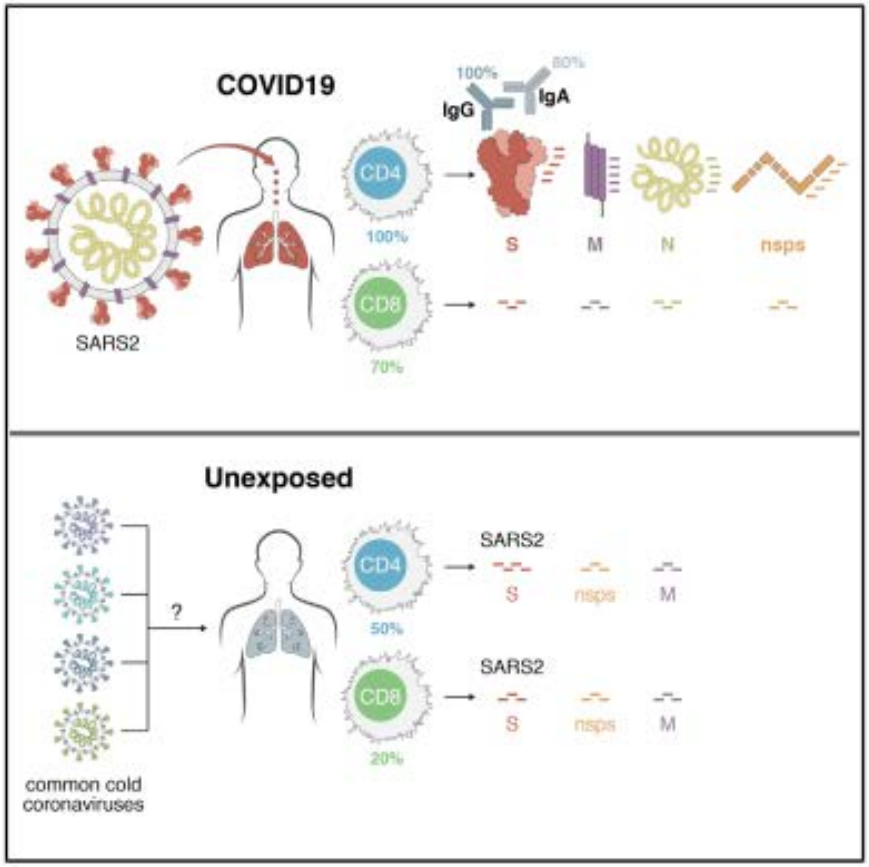
Memory T cells of SARS patient cross-react with SARS-CoV2 N protein

Nature 2020; 584:457
Immunity 2020; 53: 248

Cell

Targets of T Cell Responses to SARS-CoV-2 Coronavirus in Humans with COVID-19 Disease and Unexposed Individuals

Graphical Abstract



In Brief

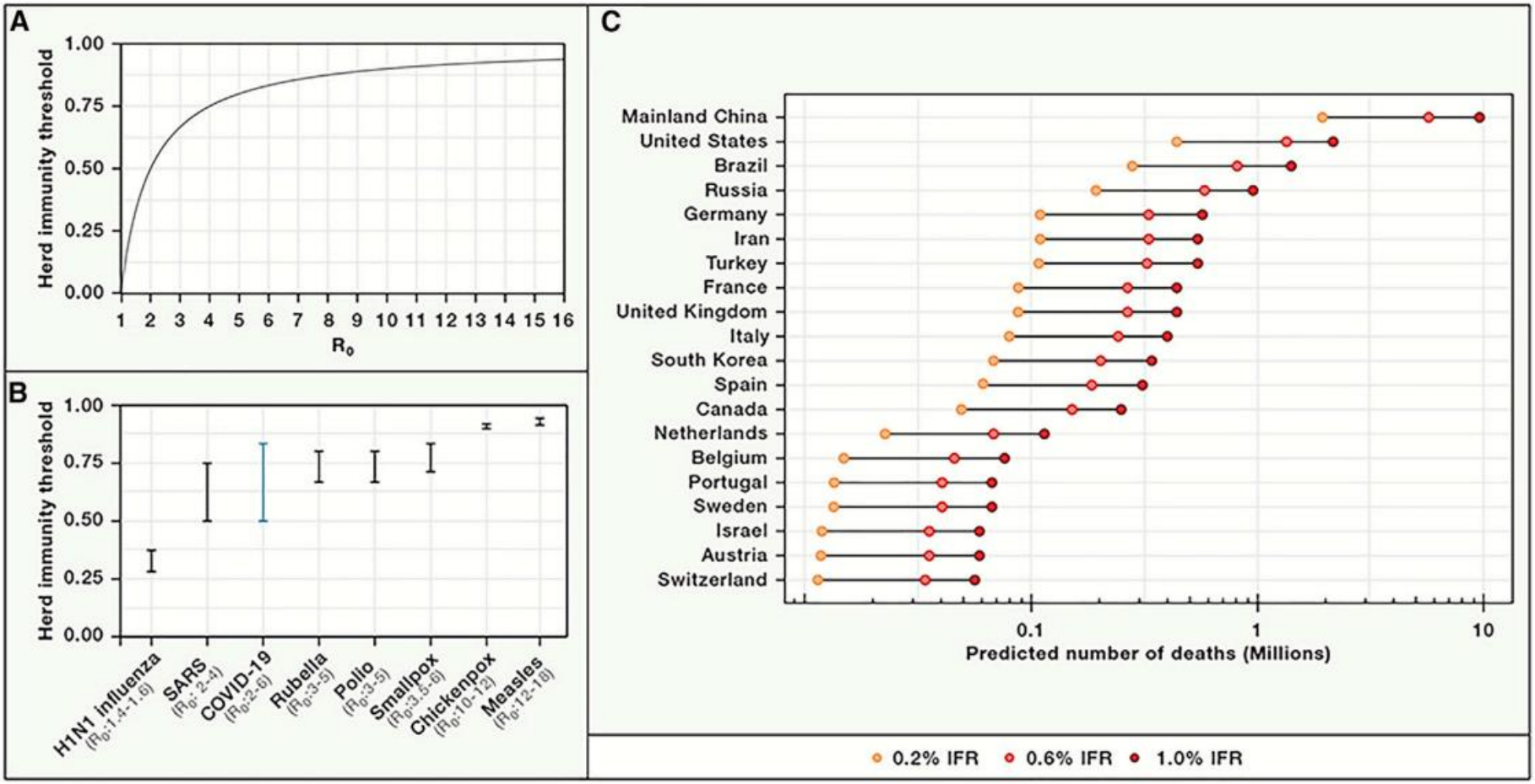
An analysis of immune cell responses to SARS-CoV-2 from recovered patients identifies the regions of the virus that is targeted and also reveals cross-reactivity with other common circulating coronaviruses

Highlights

- Measuring immunity to SARS-CoV-2 is key for understanding COVID-19 and vaccine development
- Epitope pools detect $CD4^+$ and $CD8^+$ T cells in 100% and 70% of convalescent COVID patients
- T cell responses are focused not only on spike but also on M, N, and other ORFs
- T cell reactivity to SARS-CoV-2 epitopes is also detected in non-exposed individuals

Cell 2020; 181: 1689-1501

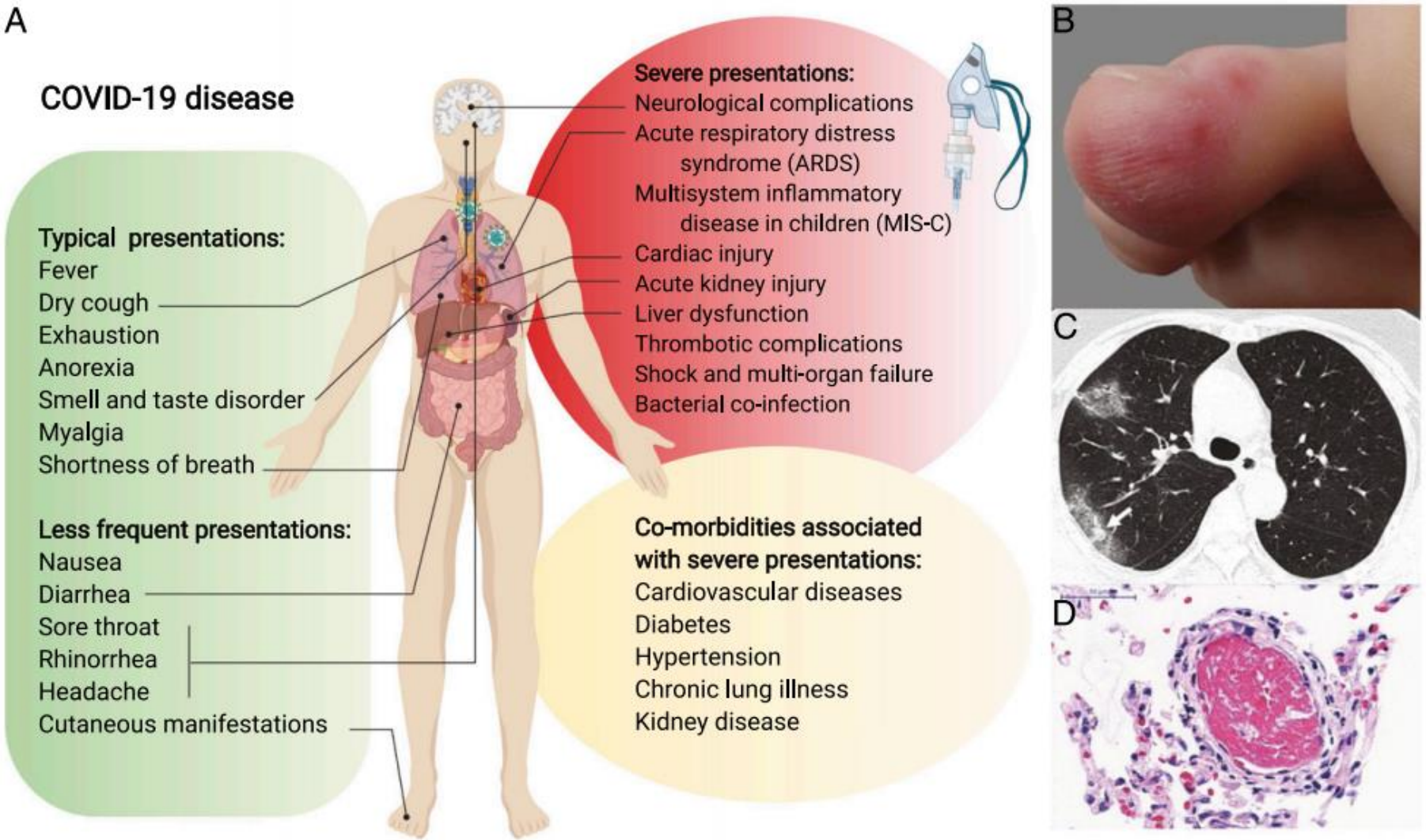
Herd Immunity, R_o and Deaths



Virus	Ro
H1N1 Influenza	1.4 to 1.6
SARS	2 to 4
COVID-19	2 to 6

Immunity 2020; 52: 737-741

Clinical disease presentations of COVID-19



J Immunol 2020
doi/10.4049/jimmunol.2000526

ACE2 Expressions

(transmembrane protease serine 2, TMPRSS2)

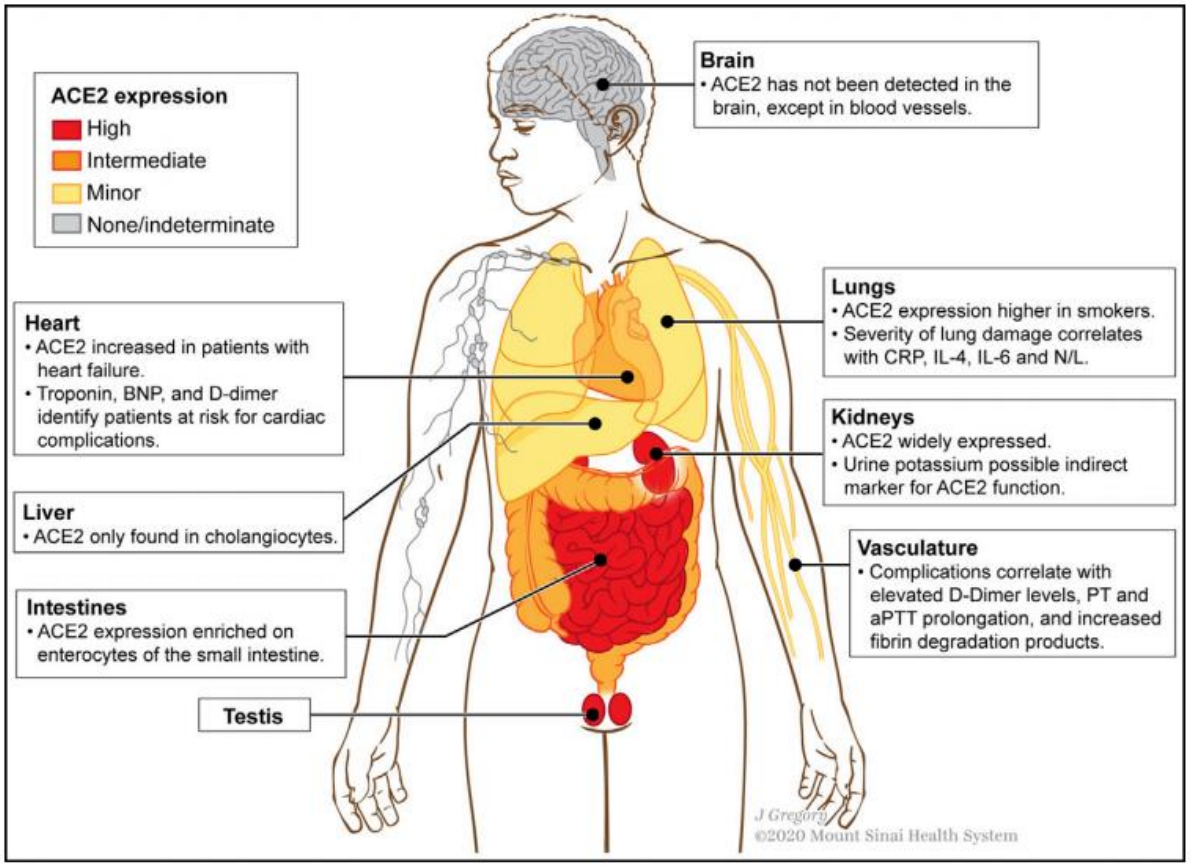


Figure 5. ACE2 Expression in Organs and Systems Most Frequently Implicated in COVID-19 Complications

The gastrointestinal tract, kidneys, and testis have the highest ACE2 expressions. In some organs, different cell types have remarkably distinct expressions; e.g., in the lungs, alveolar epithelial cells have higher ACE2 expression levels than bronchial epithelial cells; in the liver, ACE2 is not expressed in hepatocytes, Kupffer cells, or endothelial cells but is detected in cholangiocytes, which can explain liver injury to some extent. Furthermore, ACE2 expression is enriched on enterocytes of the small intestine compared to the colon.

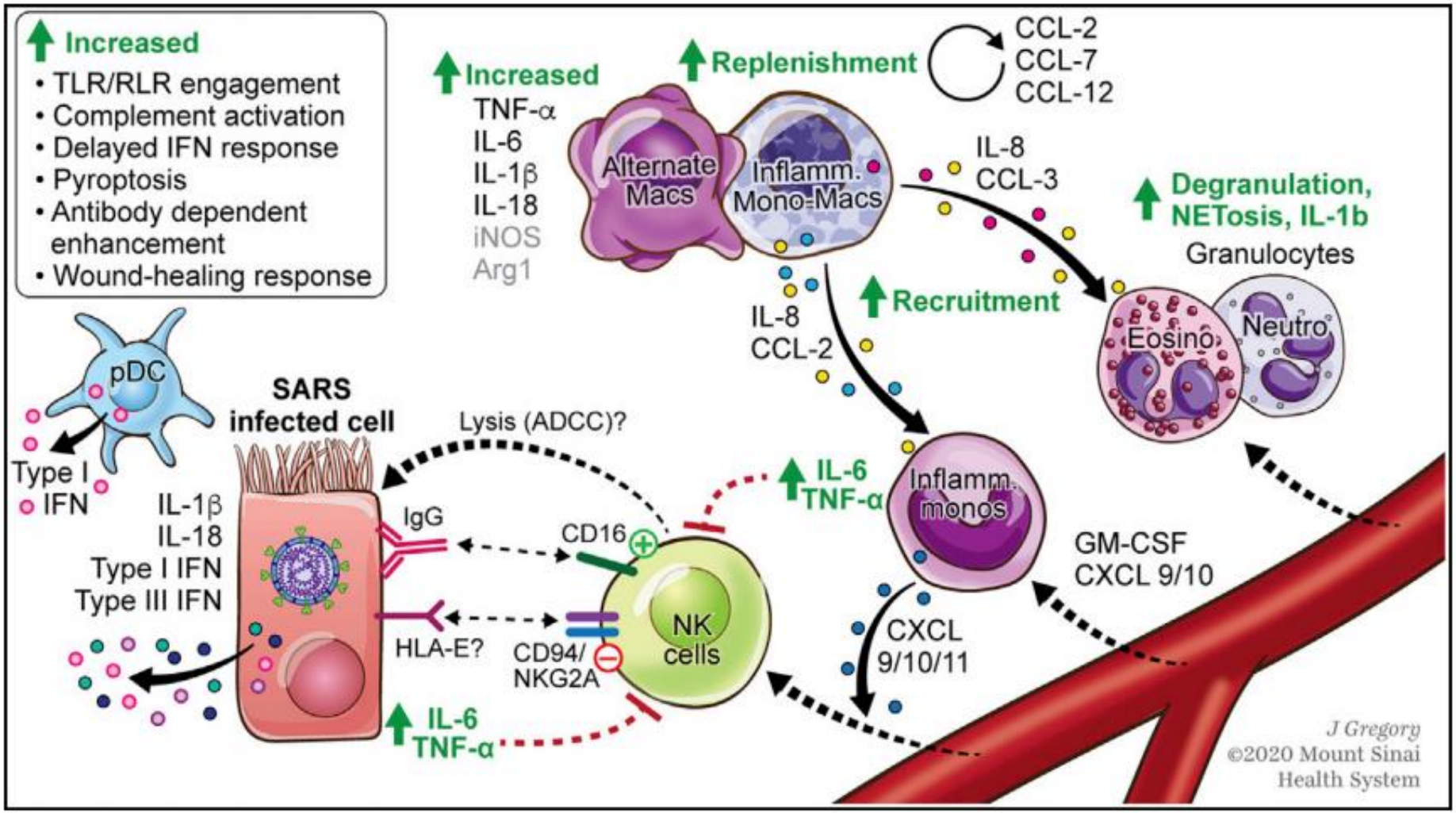
ACE2, angiotensin-converting enzyme 2; BNP, B-type natriuretic peptide; CRP, C-reactive protein; IL, interleukin; N/L, neutrophil-to-lymphocyte ratio; PT, prothrombin time; aPTT, activated partial thromboplastin time.

Immunity 2020; 52: 910

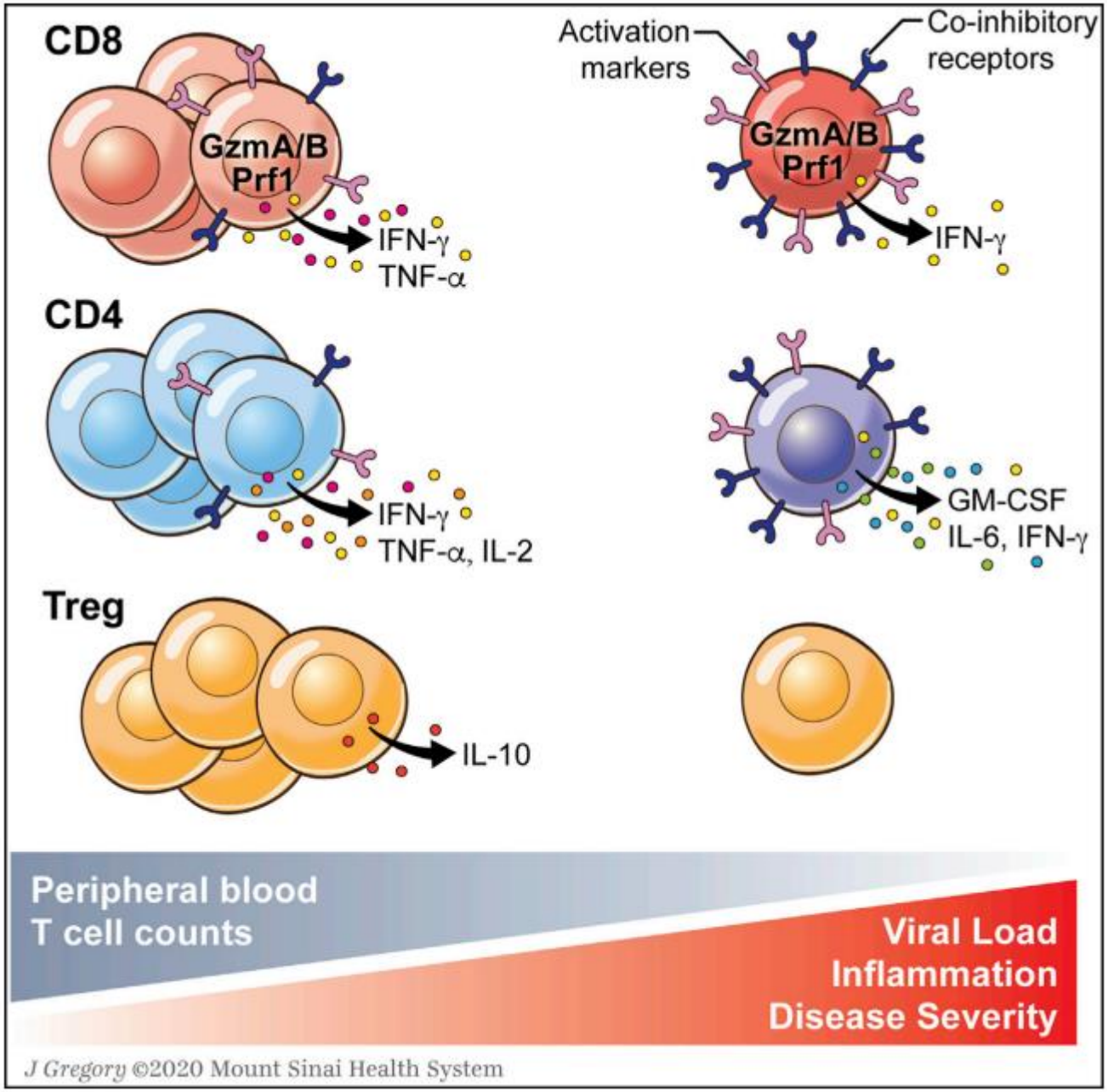
↓ Type 1 IFN
↑ TNF-α, IL-6/1/18

Figure 2. SARS-CoV-2 Infection Results in Myeloid Cell Activation and Changes NK Cell Function

Based on data from preliminary COVID-19 studies and earlier studies in related coronaviruses.



Immunity 2020; 52: 910



Lymphopenia

↓

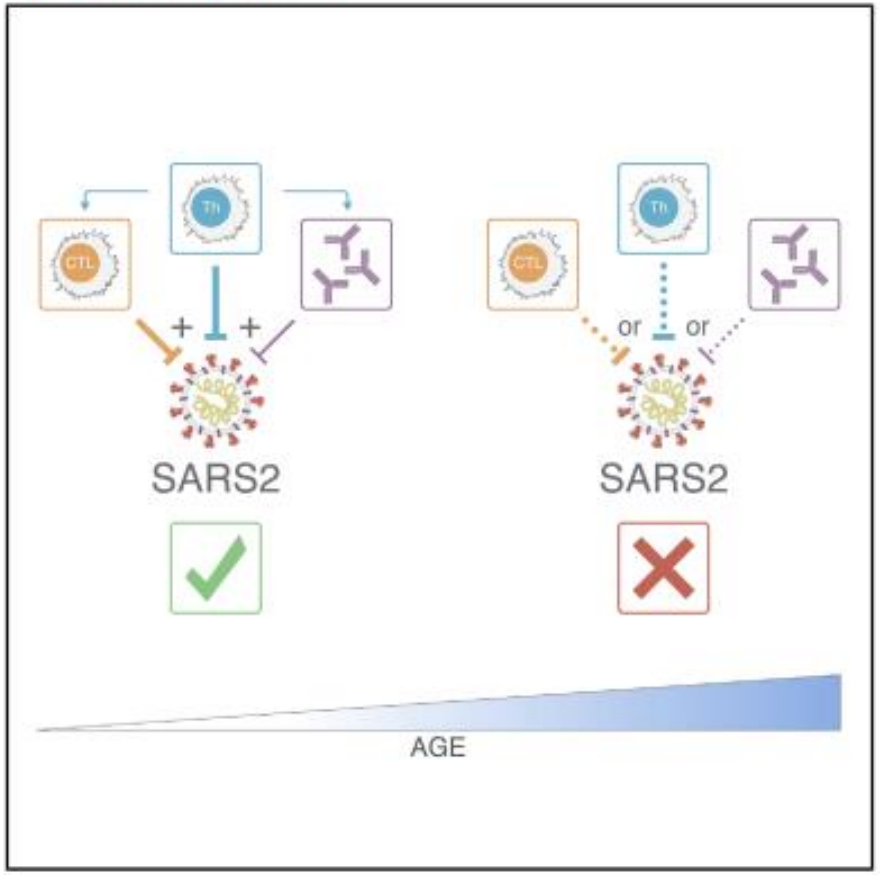
Severity

Immunity 2020; 52: 910

Cell

Antigen-Specific Adaptive Immunity to SARS-CoV-2 in Acute COVID-19 and Associations with Age and Disease Severity

Graphical Abstract



In Brief

Analysis of SARS-CoV-2-specific adaptive immune responses during acute COVID-19 identifies coordination between SARS-CoV-2-specific CD4 T cells and CD8 T cells to limit disease severity. Aged individuals often exhibit uncoordinated adaptive responses, potentially tied to scarcity of naive T cells, highlighting immunologic risk factors linked to disease severity.

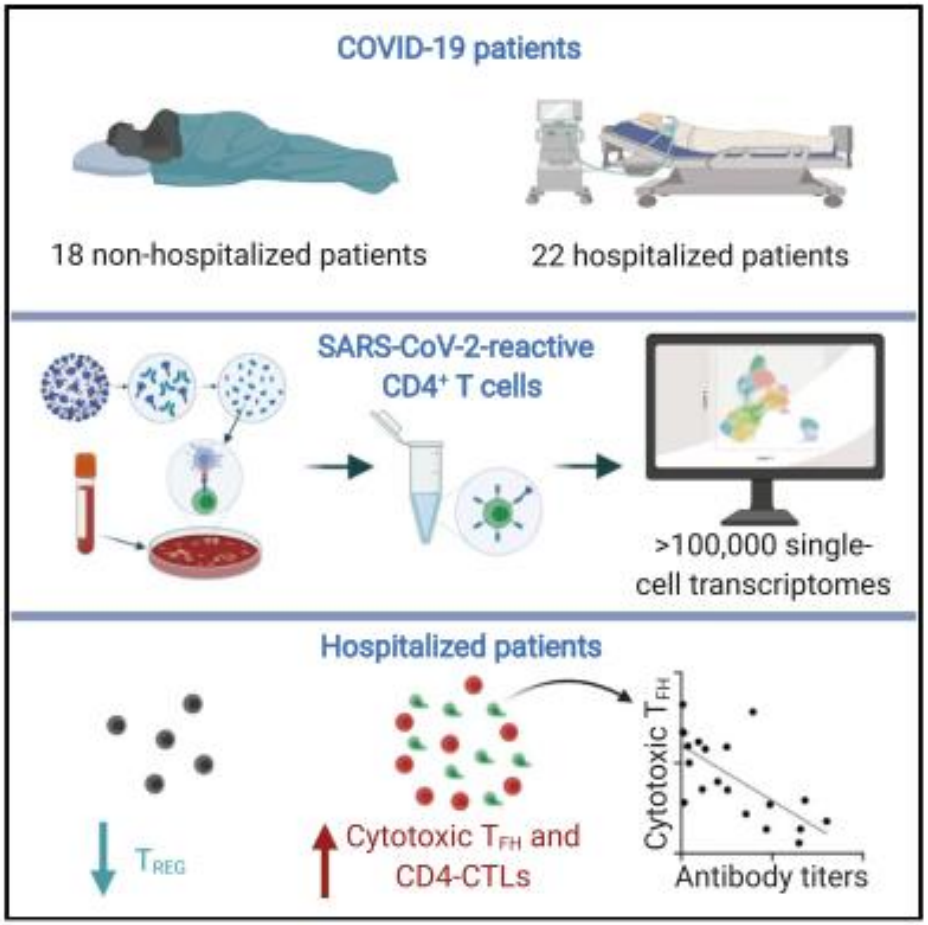
Highlights

- Adaptive immune responses limit COVID-19 disease severity
- Multiple coordinated arms of adaptive immunity control better than partial responses
- CXCL10 may be a biomarker of impaired T cell responses in acute COVID-19
- Aging and scarcity of naive T cells may be linked risk factors for severe COVID-19

Cell

Imbalance of Regulatory and Cytotoxic SARS-CoV-2-Reactive CD4⁺ T Cells in COVID-19

Graphical Abstract



In Brief

Analyses of CD4⁺ T cells from 40 COVID-19 patients show that hospitalization is associated with increased cytotoxic follicular helper cells and cytotoxic T helper cells and a reduction in regulatory T cells.

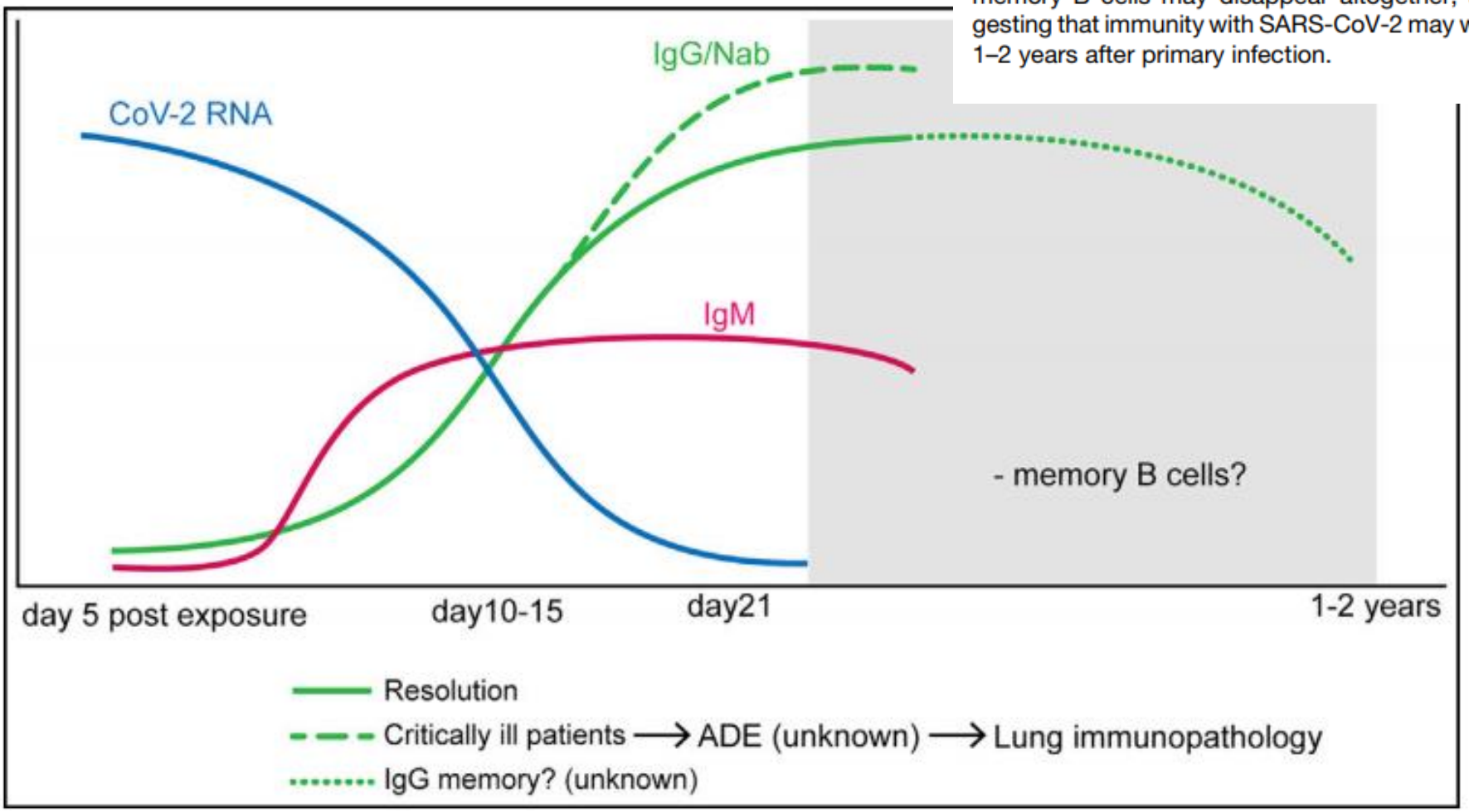
Highlights

- Single-cell transcriptomic analysis of >100,000 SARS-CoV-2-reactive CD4⁺ T cells
- Strong cytotoxic T_{FH} response in hospitalized patients early in the illness
- Reduced proportions of regulatory CD4⁺ T cells in hospitalized patients
- Substantial heterogeneity in the molecular profile of viral-reactive CD4⁺ T cells

SARS Antibody and Memory B cells are short lived (1-2 years)

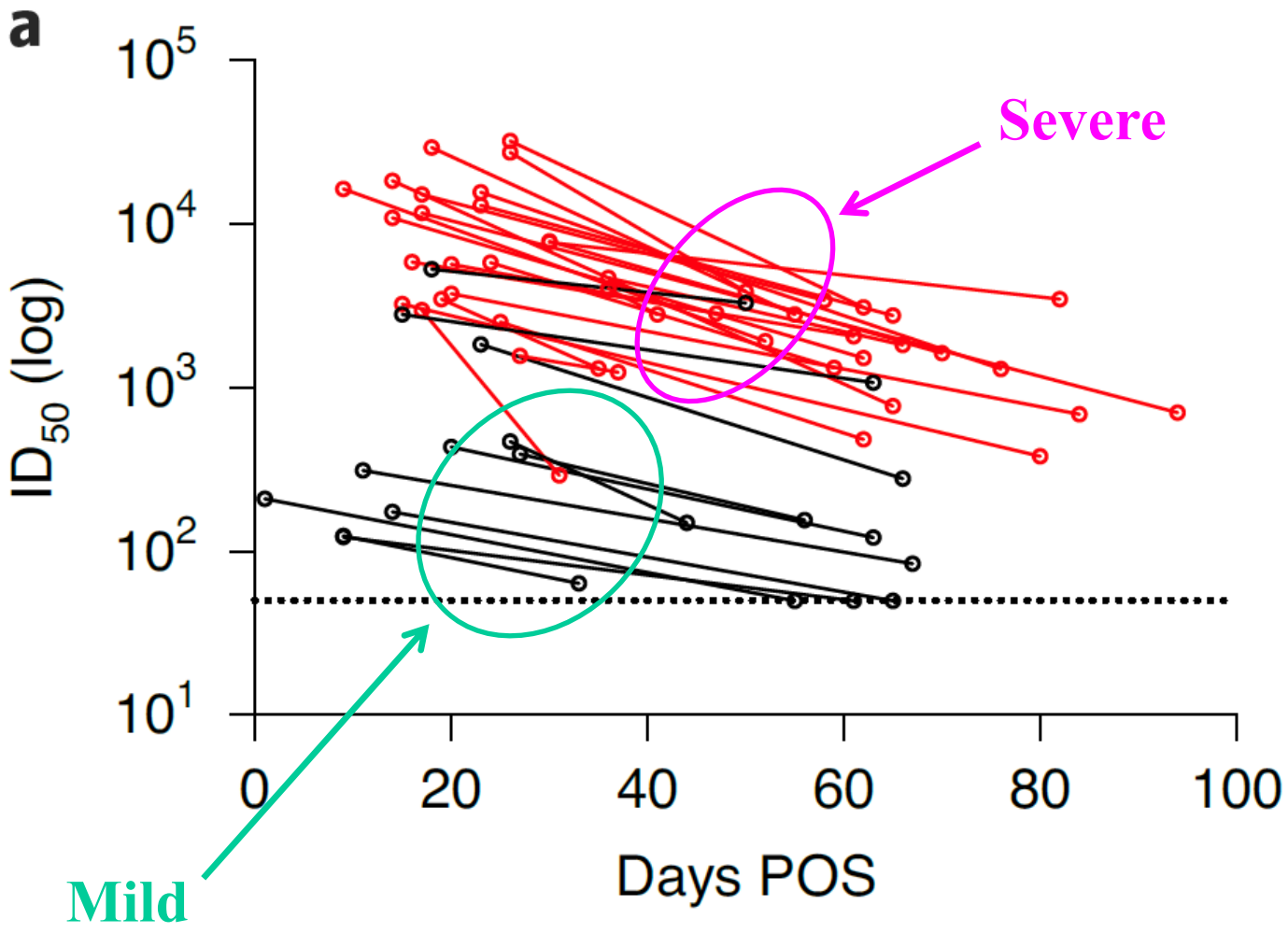
Figure 4. Antibody-Mediated Immunity in SARS-CoV-2

Virus-specific IgM and IgG are detectable in serum between 7 and 14 days after the onset of symptoms. Viral RNA is inversely correlated with neutralizing antibody titers. Higher titers have been observed in critically ill patients, but it is unknown whether antibody responses somehow contribute to pulmonary pathology. The SARS-CoV-1 humoral response is relatively short lived, and memory B cells may disappear altogether, suggesting that immunity with SARS-CoV-2 may wane 1–2 years after primary infection.



Immunity 2020; 52: 910

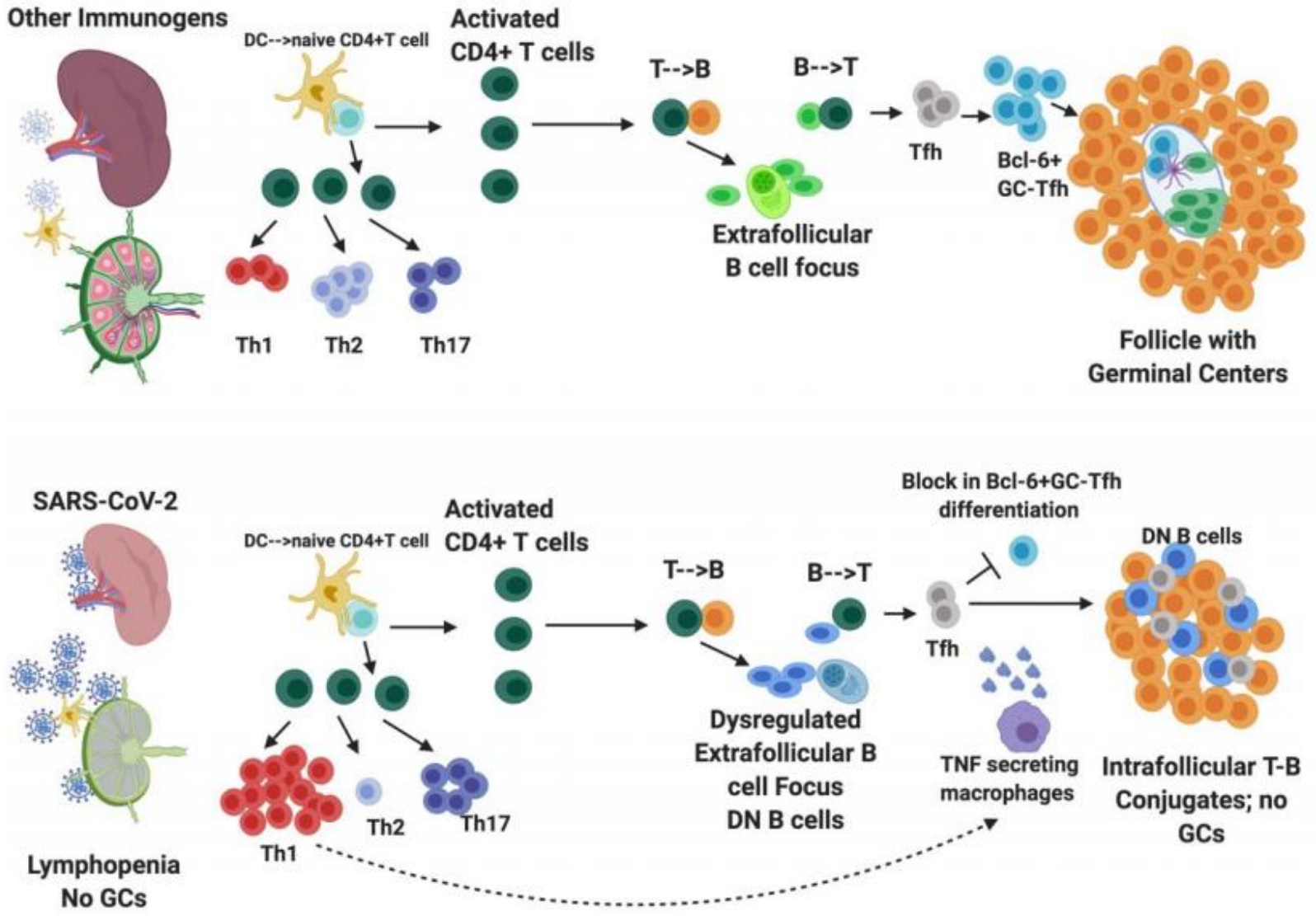
Longevity of the neutralizing antibody response



Post Onset of Symptoms

Nat Microbiol 2020 Oct 26. doi: 10.1038/s41564-020-00813-8

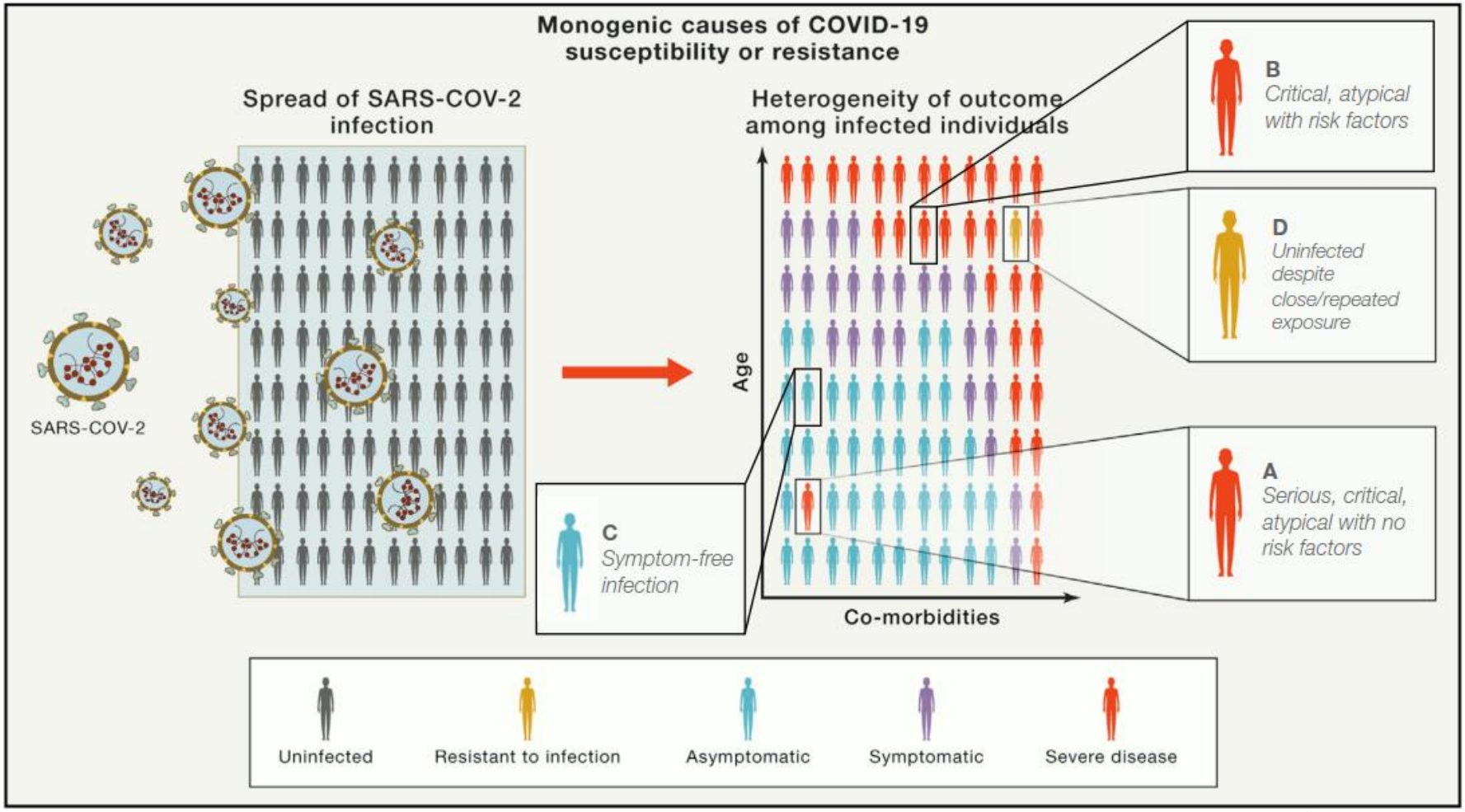
Why COVID-19 humoral immunity so short-lived?



Loss of Bcl-6-expressing T follicular helper cells and germinal centers

Cell 2020

Genetic basis of severe COVID-19



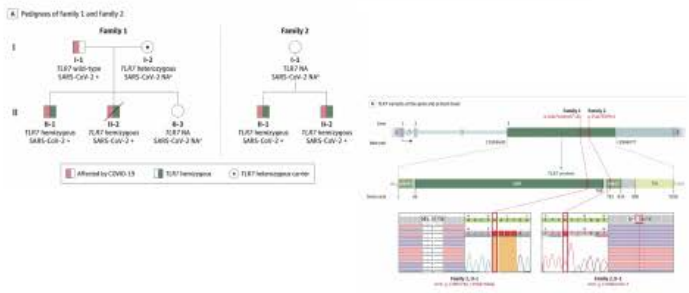
Cell 2020

TLR7

SOCS1

JAMA | Preliminary Communication

Presence of Genetic Variants Among Young Men With Severe COVID-19



THE JOURNAL OF Allergy AND Clinical Immunology

FULL LENGTH ARTICLE | ARTICLES IN PRESS

Immune dysregulation and Multisystem Inflammatory Syndrome in Children (MIS-C) in individuals with haploinsufficiency of *SOCS1*

Pui Y. Lee, MD, PhD * • Craig D. Platt, MD, PhD * • Sabrina Weeks, BA • ...
Douglas R. McDonald, MD, PhD • Raif S. Geha, MD ** • Janet Chou, MD ** • Show all authors •
Show footnotes

Published: August 24, 2020 • DOI: https://doi.org/10.1016/j.jaci.2020.07.033

RESEARCH

RESEARCH ARTICLE

CORONAVIRUS

Autoantibodies against type I IFNs in patients with life-threatening COVID-19

Paul Bastard[1,2,3*†], Lindsey B. Rosen[4†], Qian Zhang[3†], Eleftherios Michailidis[5†], Hans-Heinrich Hoffmann[5†],

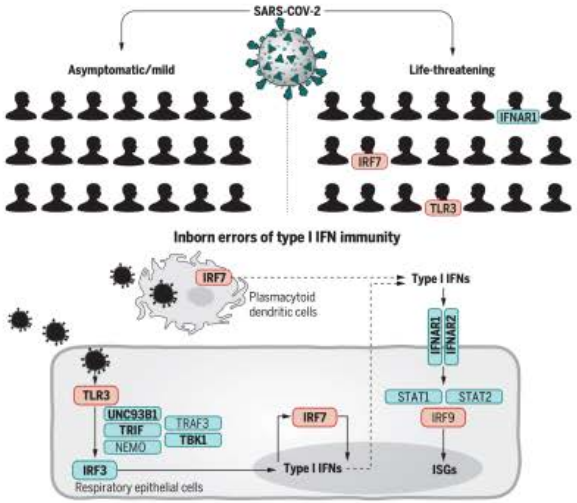
RESEARCH

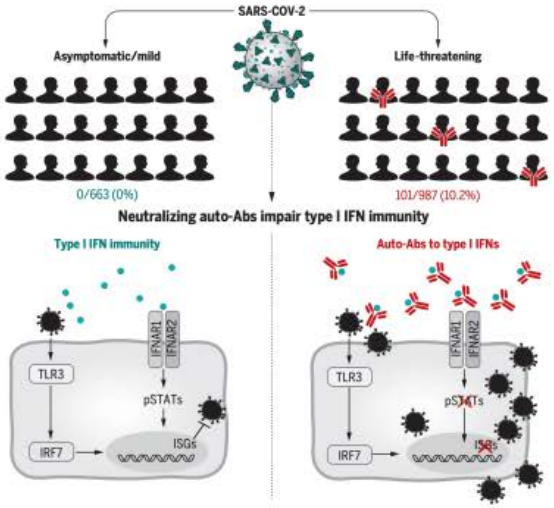
RESEARCH ARTICLE

CORONAVIRUS

Inborn errors of type I IFN immunity in patients with life-threatening COVID-19

Qian Zhang[1], Paul Bastard[2,3*], Zhiyong Liu[1*], Jérémie Le Pen[4*], Marcela Moncada-Velez[1*], Jie Chen[1*],





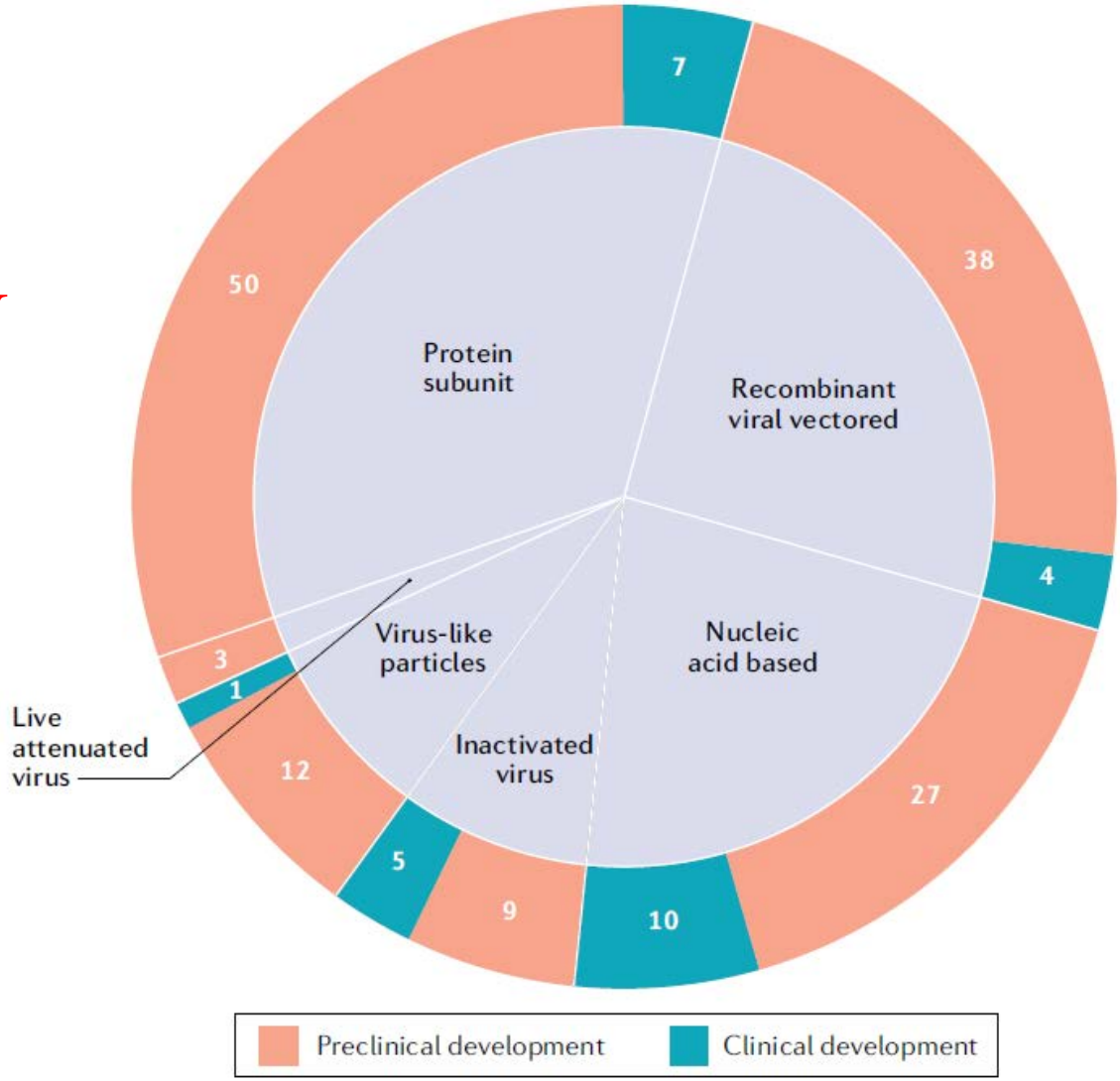
JAMA 2020 | Science 2020 | Science 2020 | J Allergy Clin Immunol 2020

Outline

- **SARS-CoV2 & Host immune response**
- **Vaccine platform & design**
- **Leading candidates & Future**

Six COVID-19 Vaccine Platforms

BCG

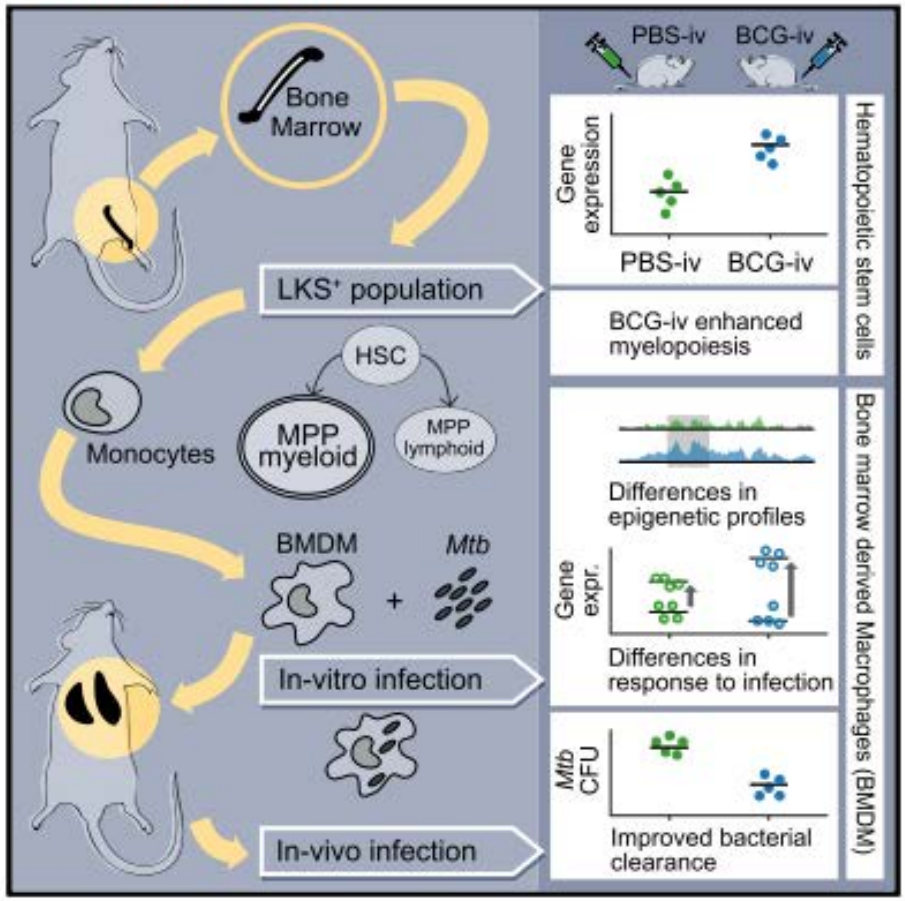


Nature Reviews in Immunology 2020;20:615

Cell

BCG Educates Hematopoietic Stem Cells to Generate Protective Innate Immunity against Tuberculosis

Graphical Abstract



In Brief

BCG induces trained immunity through education of hematopoietic stem cells.

Highlights

- Access of BCG to the bone marrow expands HSCs and promotes myelopoiesis
- BCG educates HSCs to generate trained monocytes/macrophages
- BCG induces a unique epigenetic and transcriptomic signature in macrophages
- BCG-trained macrophages are highly protective against pulmonary *M. tuberculosis* infection

Cell 11 January 2018: 172:176

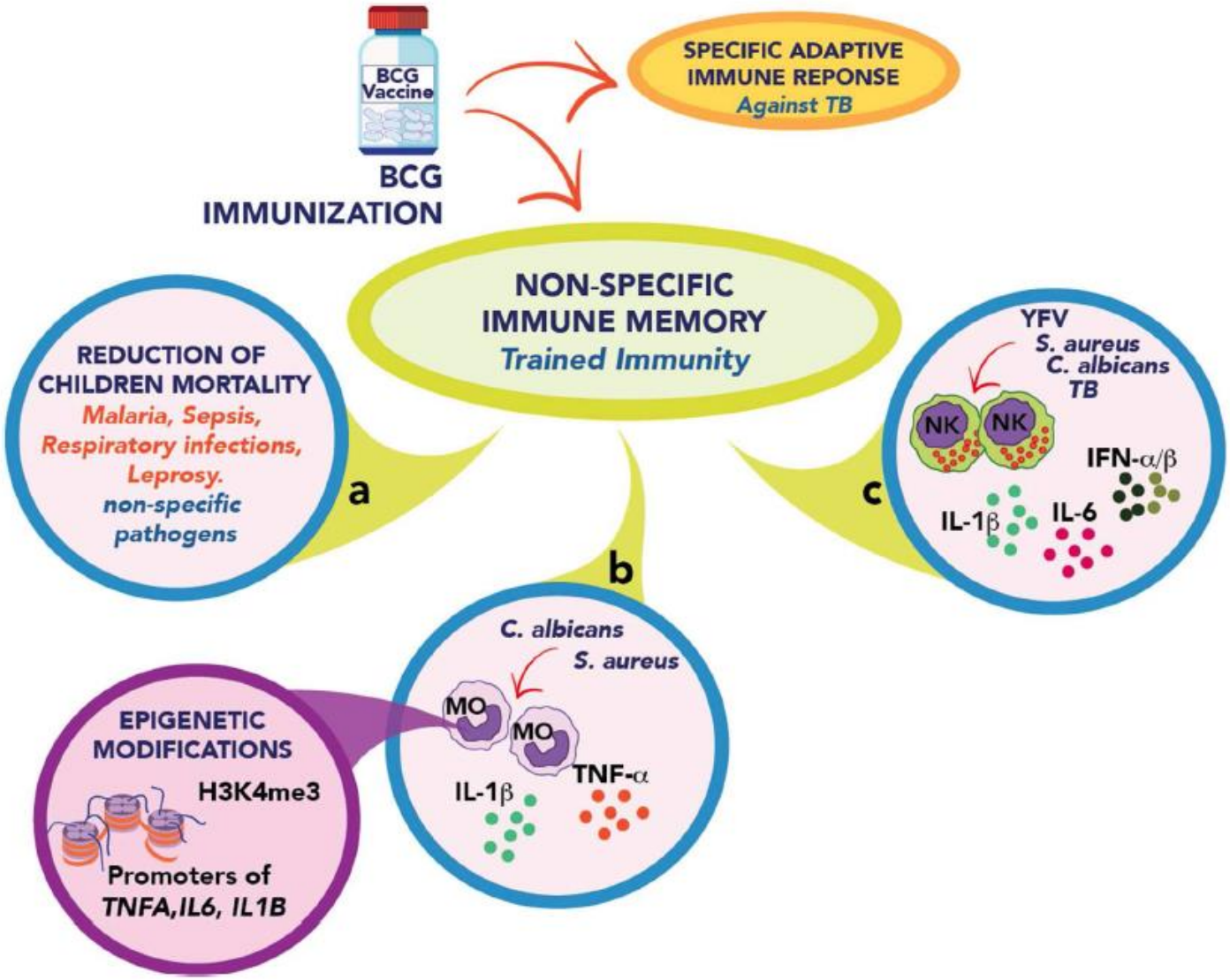
Trained immunity as a potential COVID-19 vaccine strategy

- **BCG vaccination endows circulating monocytes with characteristics of trained immunity through epigenetic and metabolic rewiring of myeloid progenitors in the bone marrow**

- **These trained monocytes enhance protection against heterologous infections, including respiratory viral infection**

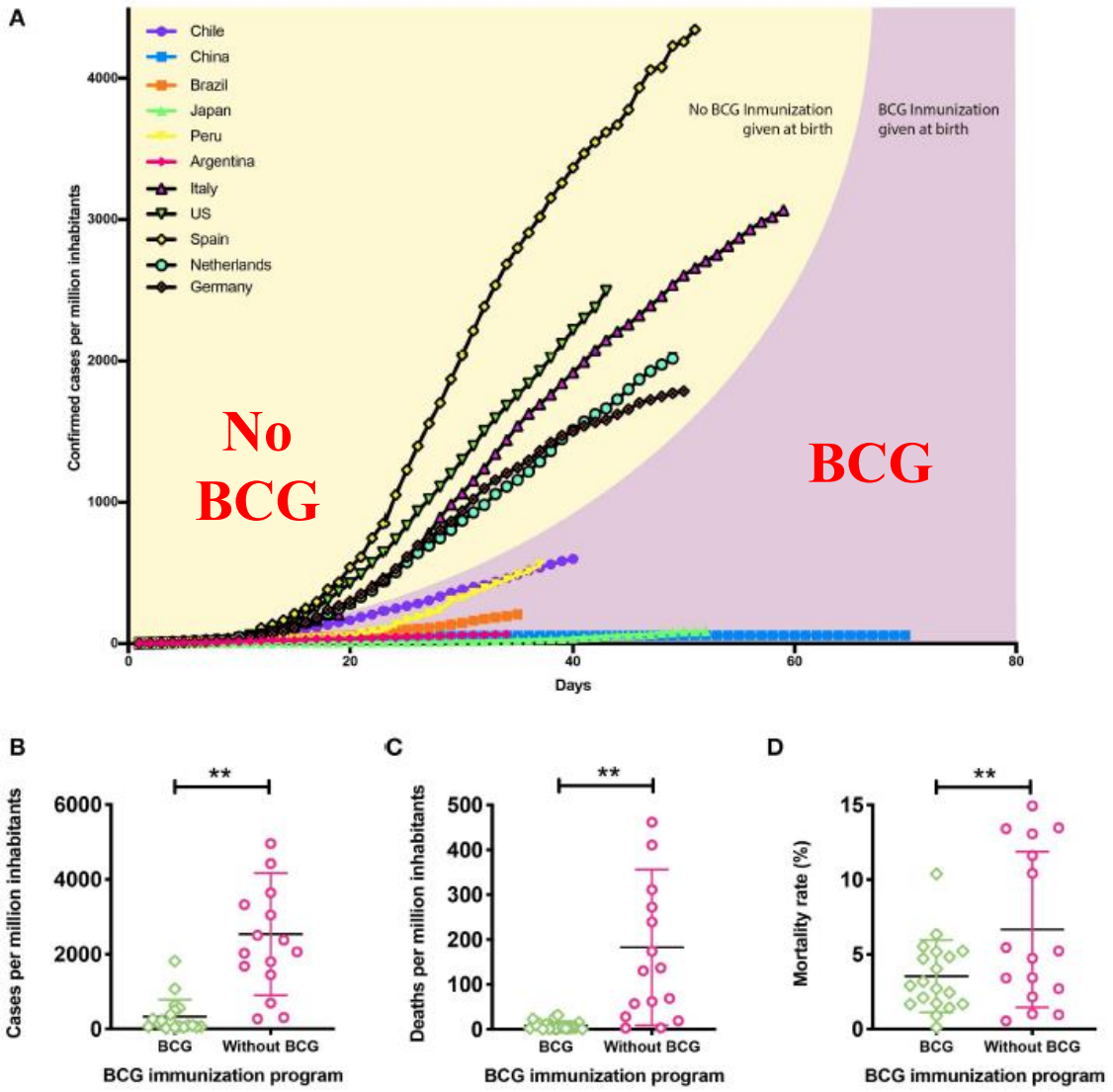
Nature Reviews in Immunology 2020;20:615

Trained immunity elicited by BCG immunization



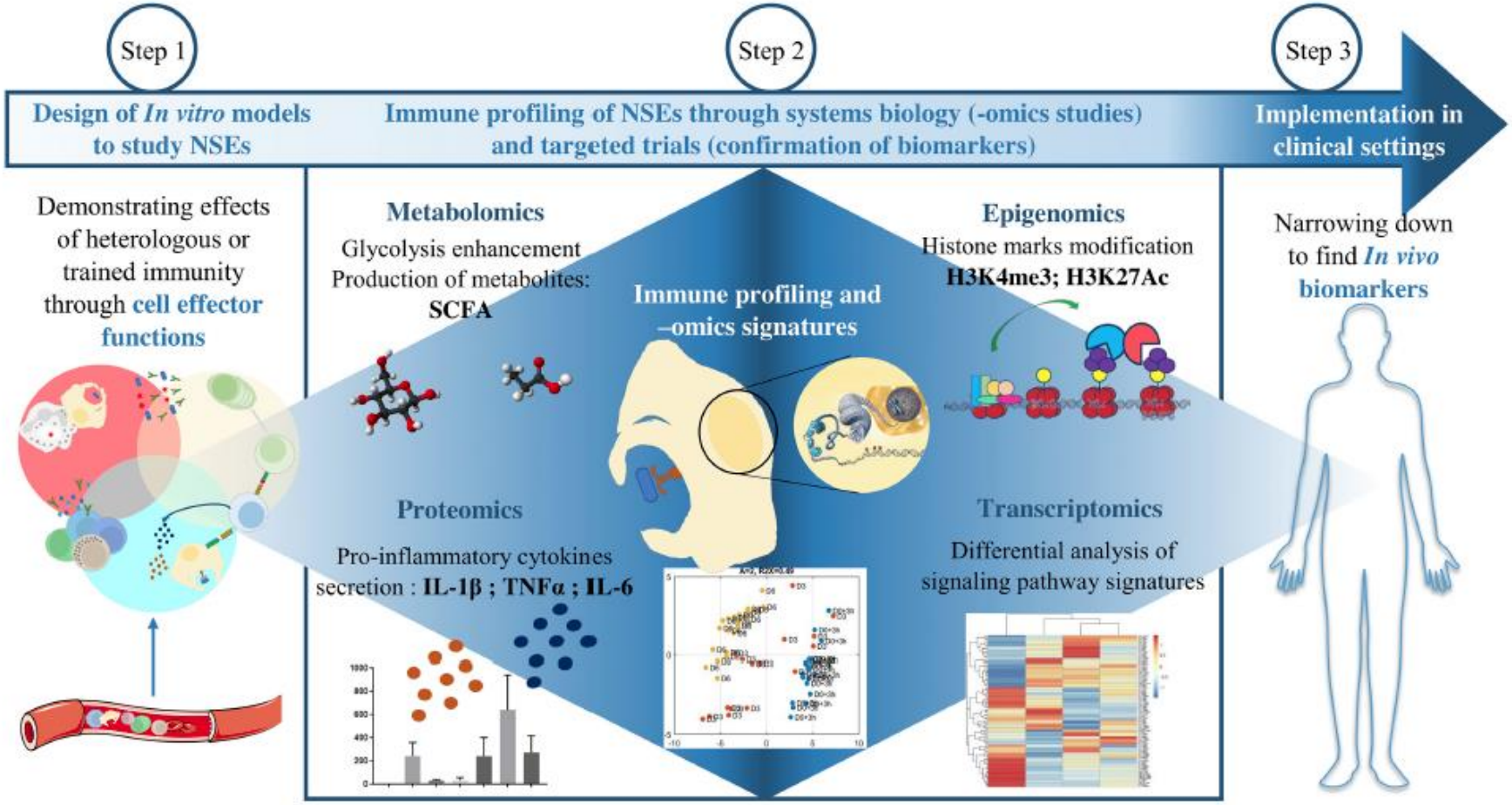
Frontiers in Immunology 2020; 11:970

Protective role of BCG in SARS-CoV-2 infection



Frontiers in Immunology 2020; 11:970

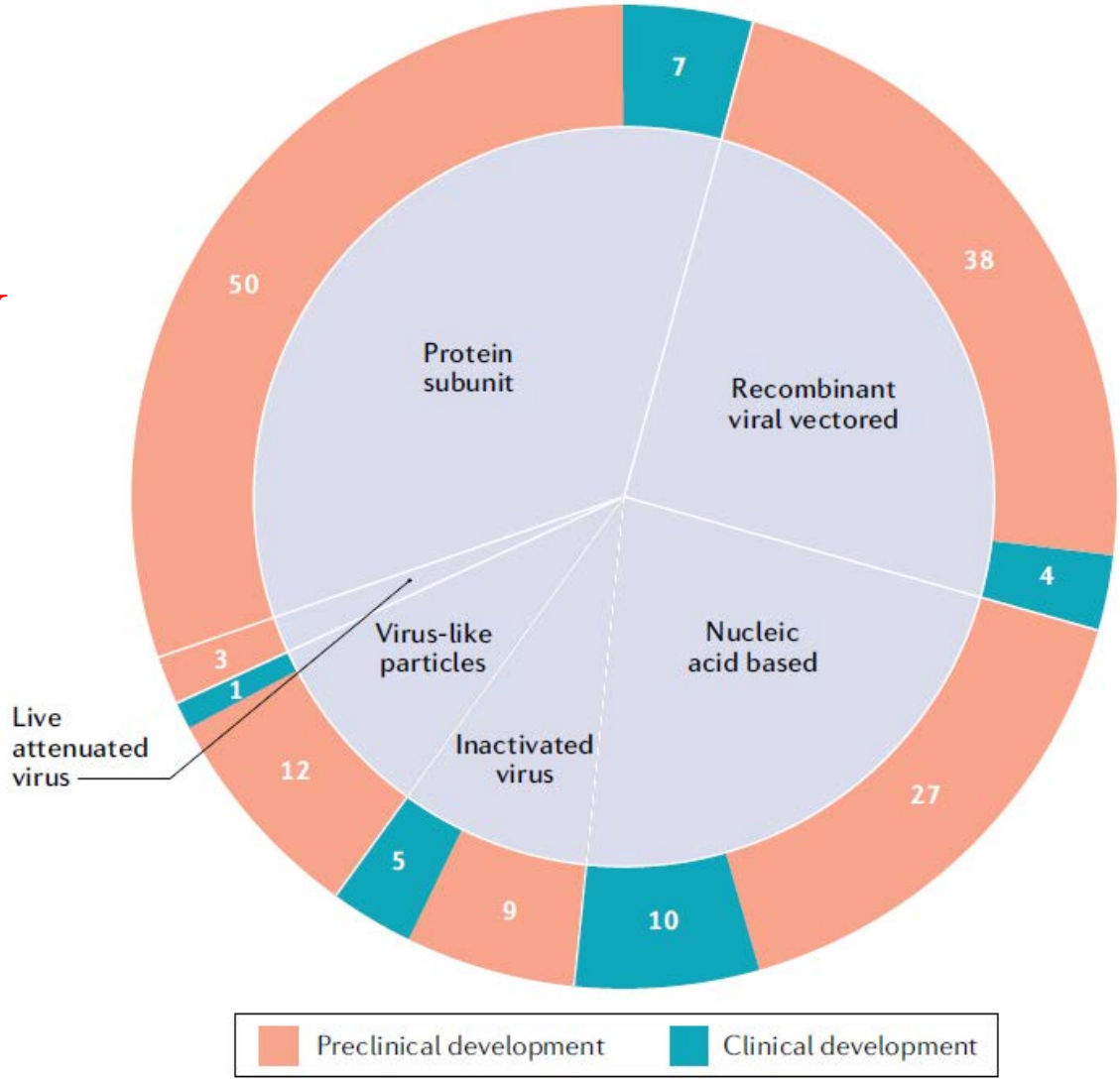
Approaches to investigate BCG NSEs



Frontiers in Immunology 2018; 9:2869

Six COVID-19 Vaccine Platforms

BCG

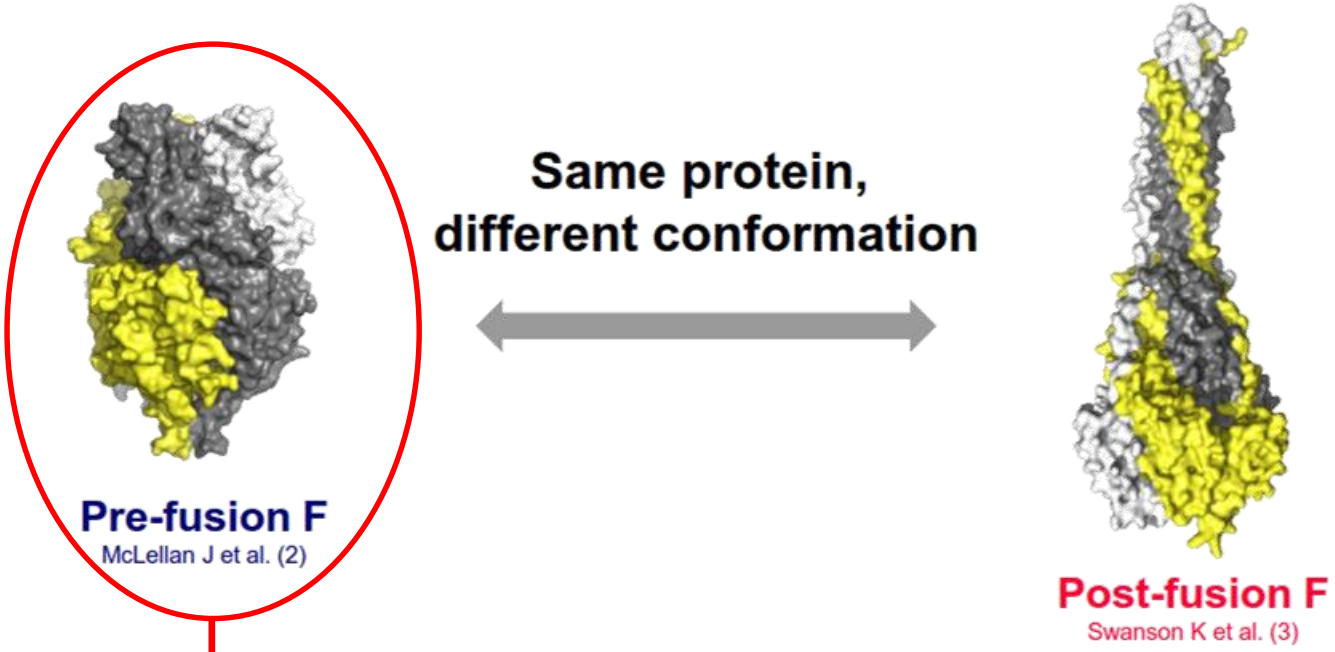


Nature Reviews in Immunology 2020;20:615

Structural Vaccinology

Example 2 (Respiratory Syncytial Virus, RSV)

- Can now use 3D knowledge of protein structure to design new vaccine antigens with optimized biological and immunogical features[1]
- E.g. design of RSV F antigen engineered as stable pre-fusion conformation[2]

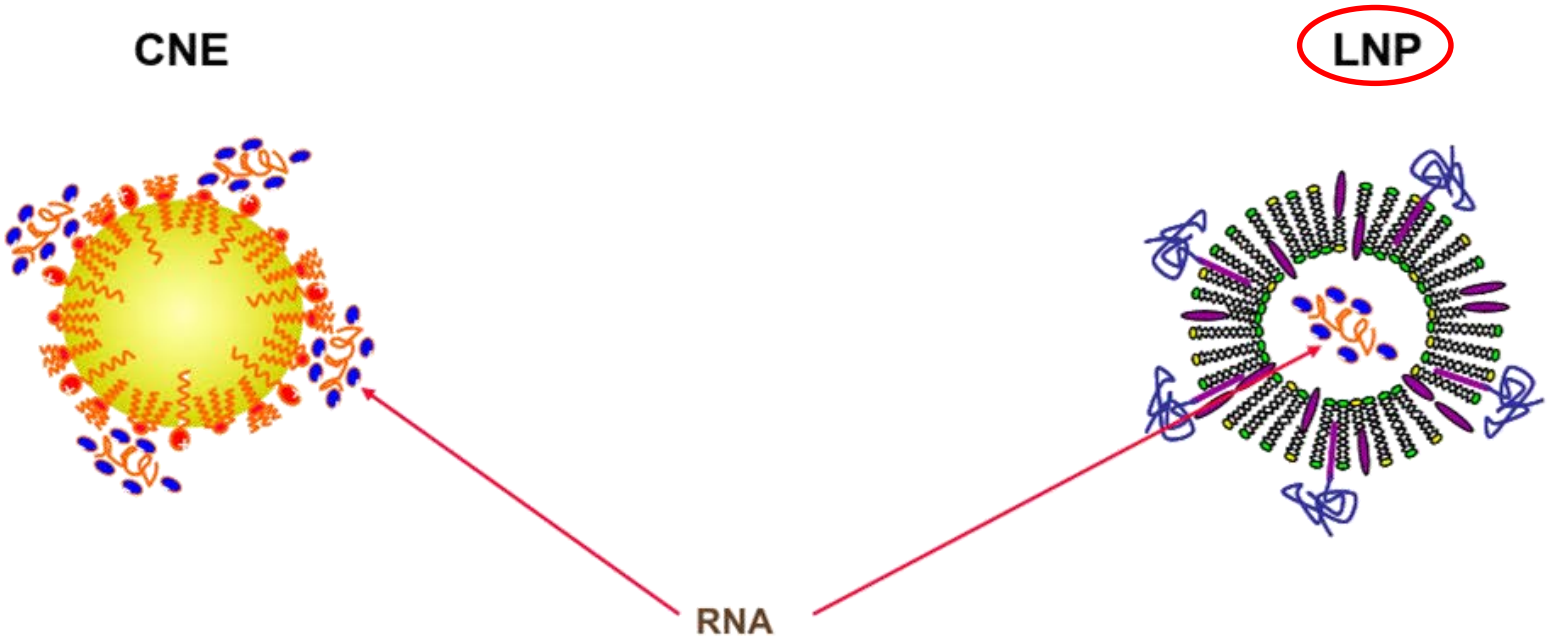


Dormitzer PR et al. Nat Rev Microbiol; 2012;10:807-813. 2. McLellan J et al. Science. 2013;342;592-598. 3. Swanson K et al. PNAS. 2011;108:9619-9624.

Pre-fusion S protein for COVID-19 vaccine

Courtesy of Dr. Philippine Buchy

Non-viral delivery of self-amplifying mRNA vaccines



LNP: lipid nanoparticle (zwitterionic lipid 10%, cationic lipid 40%, cholesterol 48%, PEGylated lipid 2%)
CNE: cationic nanoemulsion (buffer and Tween 80 with an oil phase containing Span 85, DOTAP [1,2-dioleoyl-sn-glycero-3-phosphocholine], and squalene)

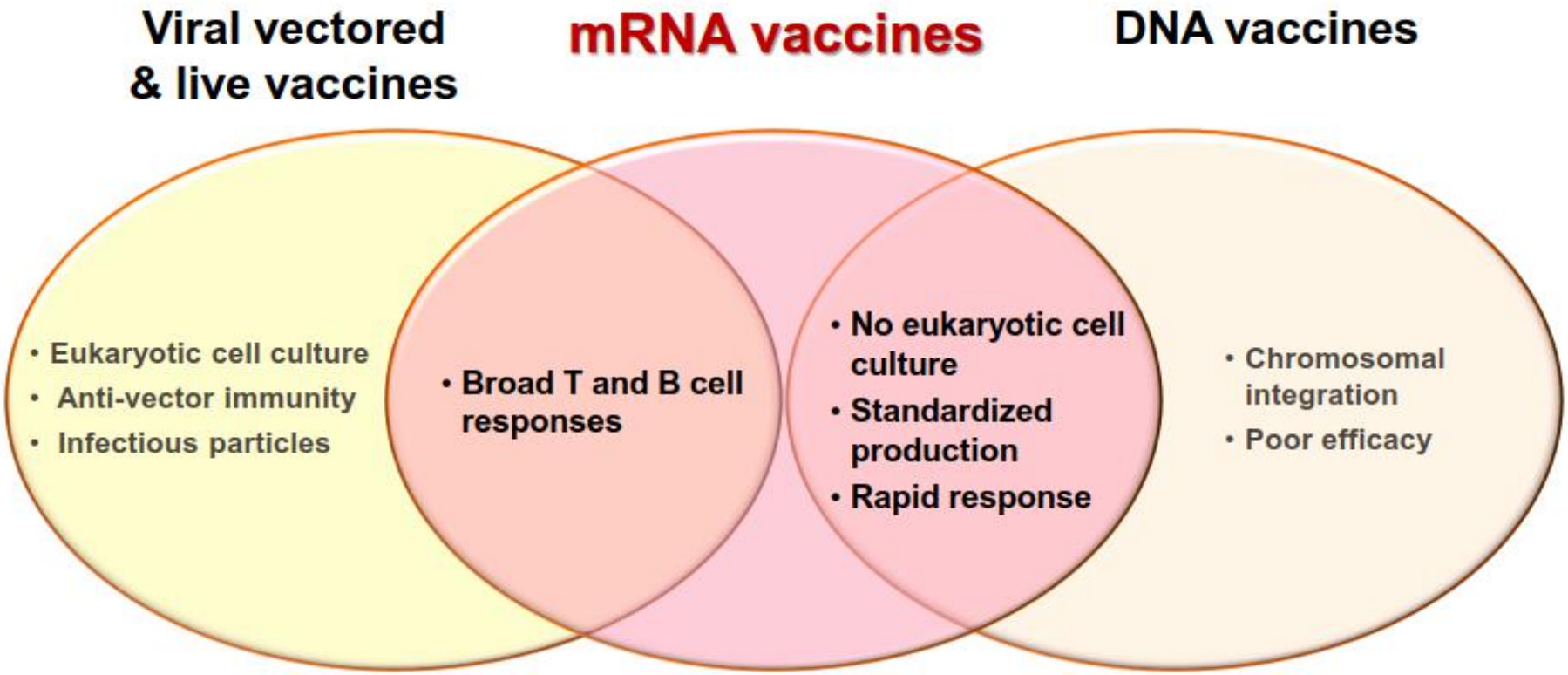
Geall AJ et al. Proc Natl Acad Sci USA 2012; 109: 14604-14609, Brito LA et al. Mol Ther 2014; 22: 2118-29,

Courtesy of Dr. Philippine Buchy

Advantages of mRNA vaccines over other nucleic acid-based vaccines

ChAdOx1

BNT/Pfizer
Moderna



Courtesy of Dr. Philippine Buchy

COVID vaccine design

1. **Selection of SARS-CoV2 antigens**
   - **For SARS-CoV, only antibodies directed to S protein can neutralize virus**
   - **All vaccines in development include at least a portion of S, such as S1 or RBD**
   - **Inclusion of other antigens, such as N protein and/or other non-structural proteins may help create a balanced response involving both B and T CMI, (especially the highly conserved function proteins may target emerging viral strains)**

Nature Review Immunology 2020; 20:633

COVID vaccine design

2. Vaccine platforms

- **6 platforms**
- **Vaccine require 2 components:**

  Antigens of SARS-CoV2

  Infection signal (PAMP, DAMP)
- **For non-viral vaccine platform, will need adjuvants as infection signal and may need multiple doses**

Nature Review Immunology 2020; 20:633

COVID vaccine design

3. Vaccination routes and regimens

- **IM route gives rise to protective IgG and can appear at respiratory mucosa, but not effective to induce mucosal IgA or lung tissue-resident memory T cells (TRM)**
- **Inactivated virus, protein subunit and nucleic acid vaccines cannot be delivered by respiratory mucosal route as they need adjuvants which may be unsafe for such route**
- **Human serotype 5 adenovirus (Ad5) or chimpanzee derived adenovirus (ChAd) safe and effective for mucosal route**

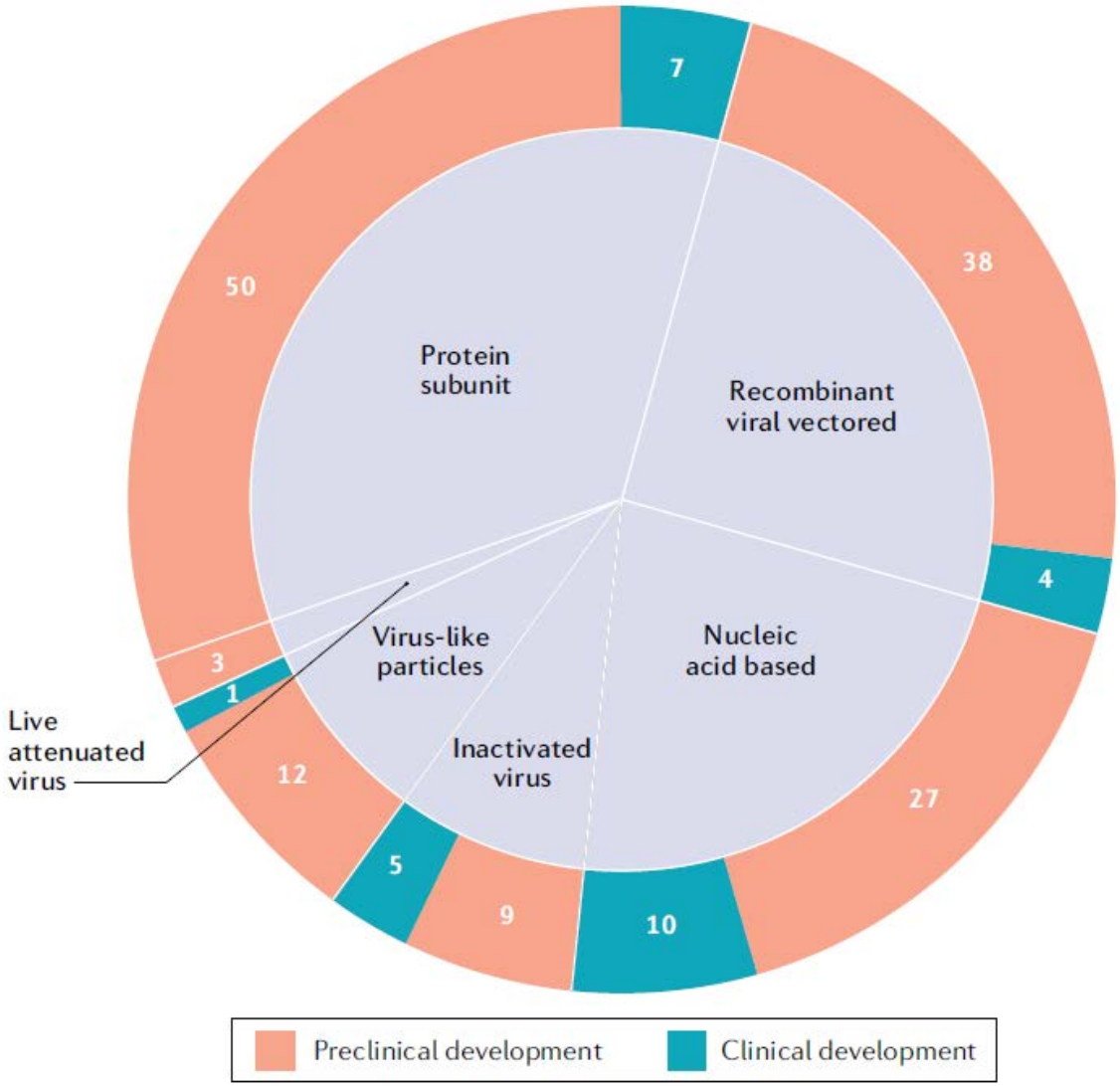
Nature Review Immunology 2020; 20:633

Vaccine-associated enhancement of respiratory diseases (VAERD)

- VAERD observed in children received whole-inactivated measles & RSV in 1960's
- Antibody-mediated (non-neutralising)
- T helper 2 biased response

Science 2020; 368:945

Six COVID-19 Vaccine Platforms



- **High neutralising antibody titers**
- **T helper 1 response**

Nature Reviews in Immunology 2020;20:615

Outline

- **SARS-CoV2 & Host immune response**
- **Vaccine platform & design**
- **Leading candidates & Future**

COVID-19 vaccine candidates in clinical trials

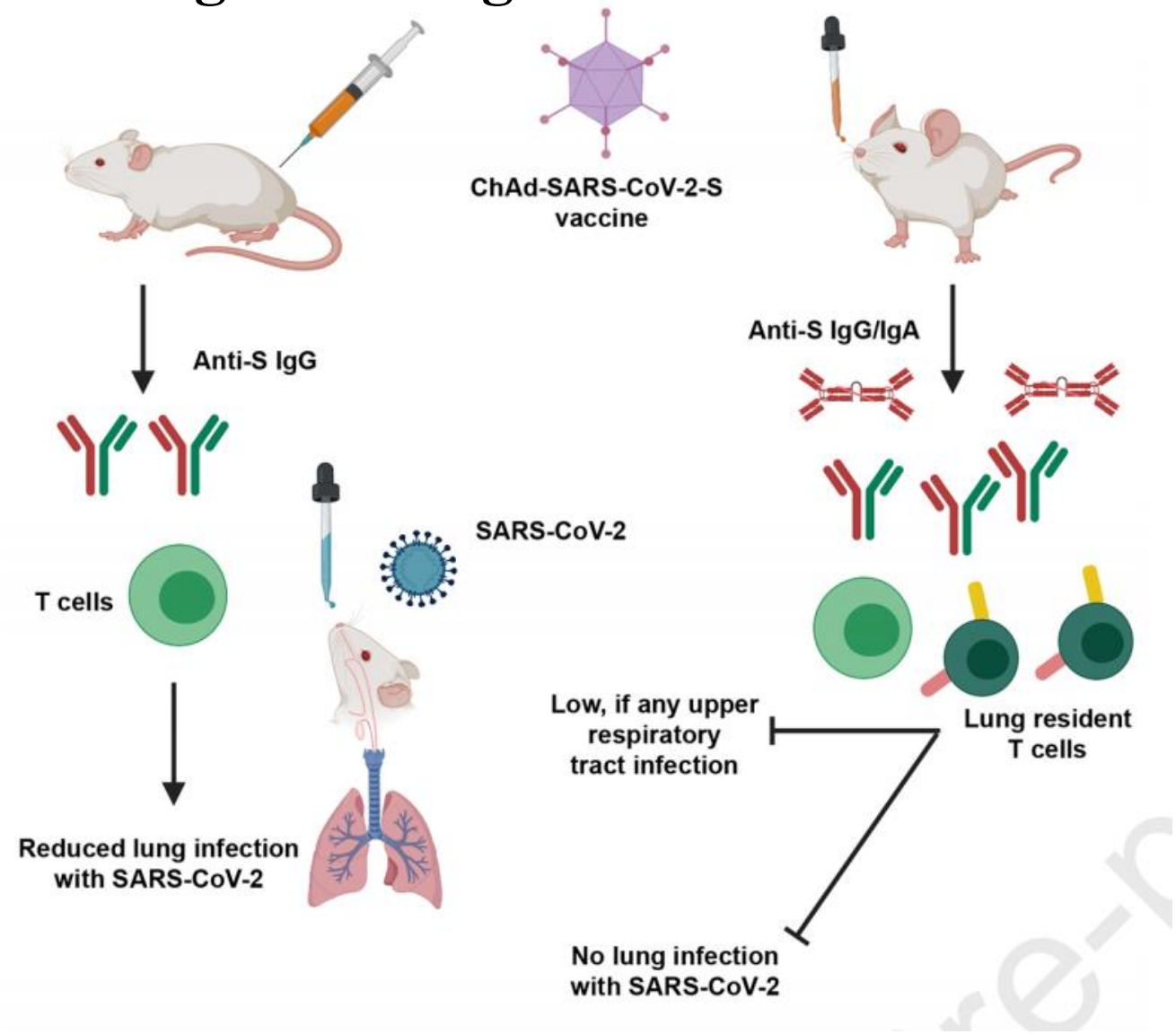
Vaccine	Platform	Developer	Clinical trial phase	Immunization attributes	Preclinical data	Clinical data
BNT162b1[a]	Lipid nanoparticle–mRNA	BioNTech, Pfizer, Fosun Pharma	Phases I–III; dose- and candidate-finding in Germany, USA and China	RBD of S protein; two repeated doses of IM injection	Published data from mouse model showing strong antibody and T cell responses	Submitted report indicating safety, high neutralizing antibody titres and T_H1 cell-type $CD4^+$ and $CD8^+$ T cell responses
ChAdOx1 nCov-19 (AZD-1222)[a]	ChAd-vectored, non-replicating	University of Oxford, AstraZeneca	Phases I–III in UK, South Africa, USA and Brazil	Expressing S protein; single dose or two repeated doses of IM injection	Published data showing prevention of pneumonia but not transmission in NHPs	Published data showing safety and good induction of neutralizing antibodies and T cell activation in >90% of vaccinees
PiCoVacc	Inactivated SARS-CoV-2	Sinovac Biotech	Phases I–III; phase III in China and Brazil	Multiple viral antigens; two repeated doses of IM injection	Published data from NHP model showing protection	Interim phase I/II information released to indicate safety and immunogenicity
NVX-CoV2373[a]	Protein subunit	Novavax	Phases I and II in Australia	Recombinant S protein; two repeated doses of IM injection	Unpublished information indicates high levels of S-specific neutralizing antibodies	NA

Nature Reviews in Immunology 2020;20:615

Preliminary Phase 3 trials result

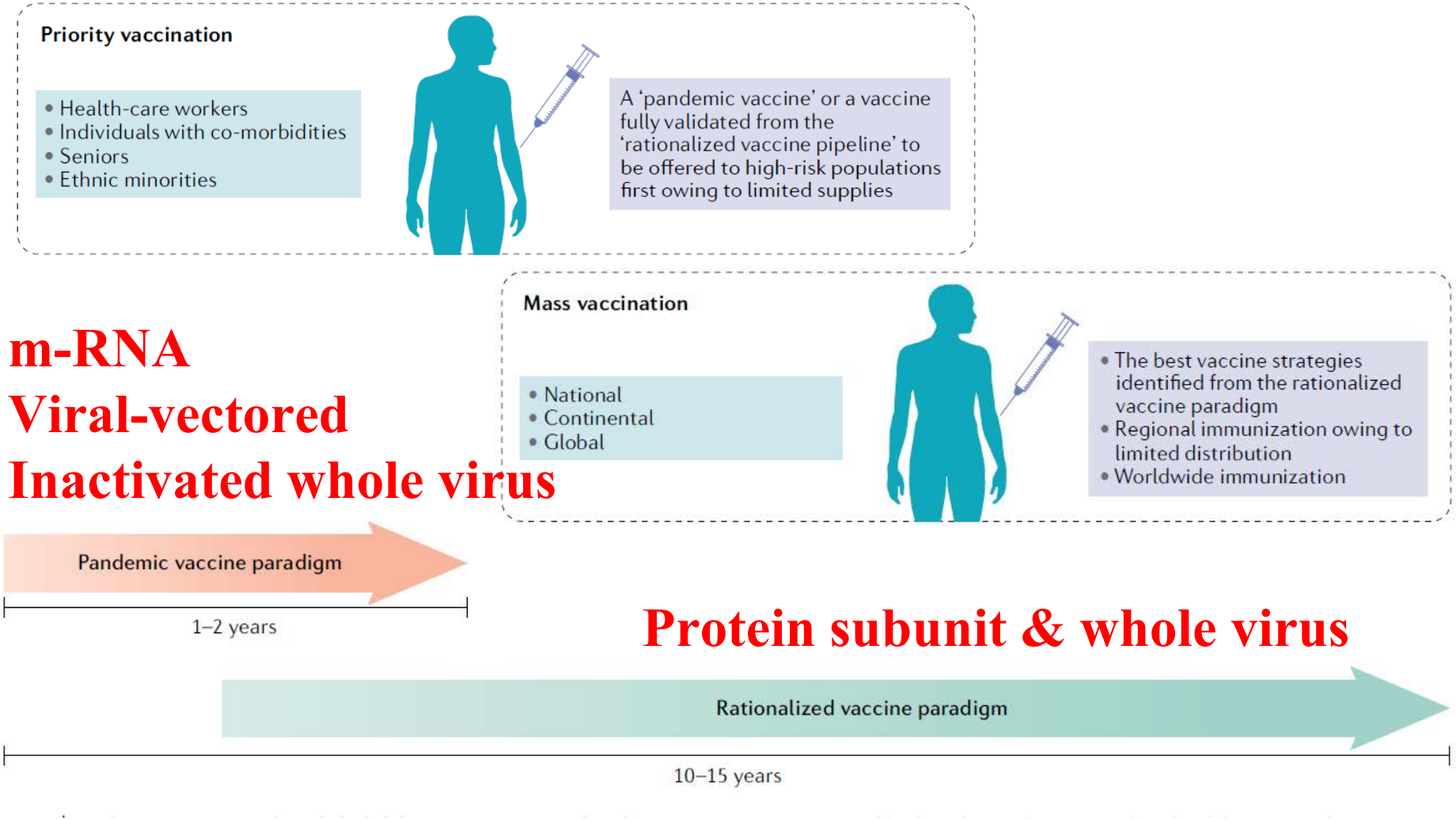
- For both mRNA candidate vaccines from BNT/Pfizer & Moderna, 95% & 94.5% efficacy after 2 doses
- For ChAd candidate vaccine from Oxford U/AstraZeneca, 62 to 90% efficacy after 2 doses
- Only short term and summary data known through press release
- These vaccines NEVER used in large scale in human
- Implementation issues, such as equity cost & storage
- Durability of B&T cell memory
- Monitor of rare SAEs

Intranasal route better to generate IgA & Lung resident T cells



Cell doi.org/10.1016 /j.cell.2020.08.026

Phased implementation of COVID-19 vaccine



Nature Reviews in Immunology 2020;20:615

兒童癌病基金
Children's Cancer Foundation

The Children's Cancer Foundation Peter Nash Paediatric Oncology Research Grant (Hong Kong)

The Society for the Relief of Disabled Children

UGC 大學教育資助委員會 University Grants Committee

The Shun Tak District Min Yuen Tong

Research Fund Secretariat
Food and Health Bureau
The Government of the Hong Kong Special Administrative Region

Jeffrey Modell Foundation
Curing PI. Worldwide.

Health and Medical Research Fund (HMRF)