Immune responses and immune memory to SARS-CoV-2 and COVID-19 vaccination: lessons for future vaccines

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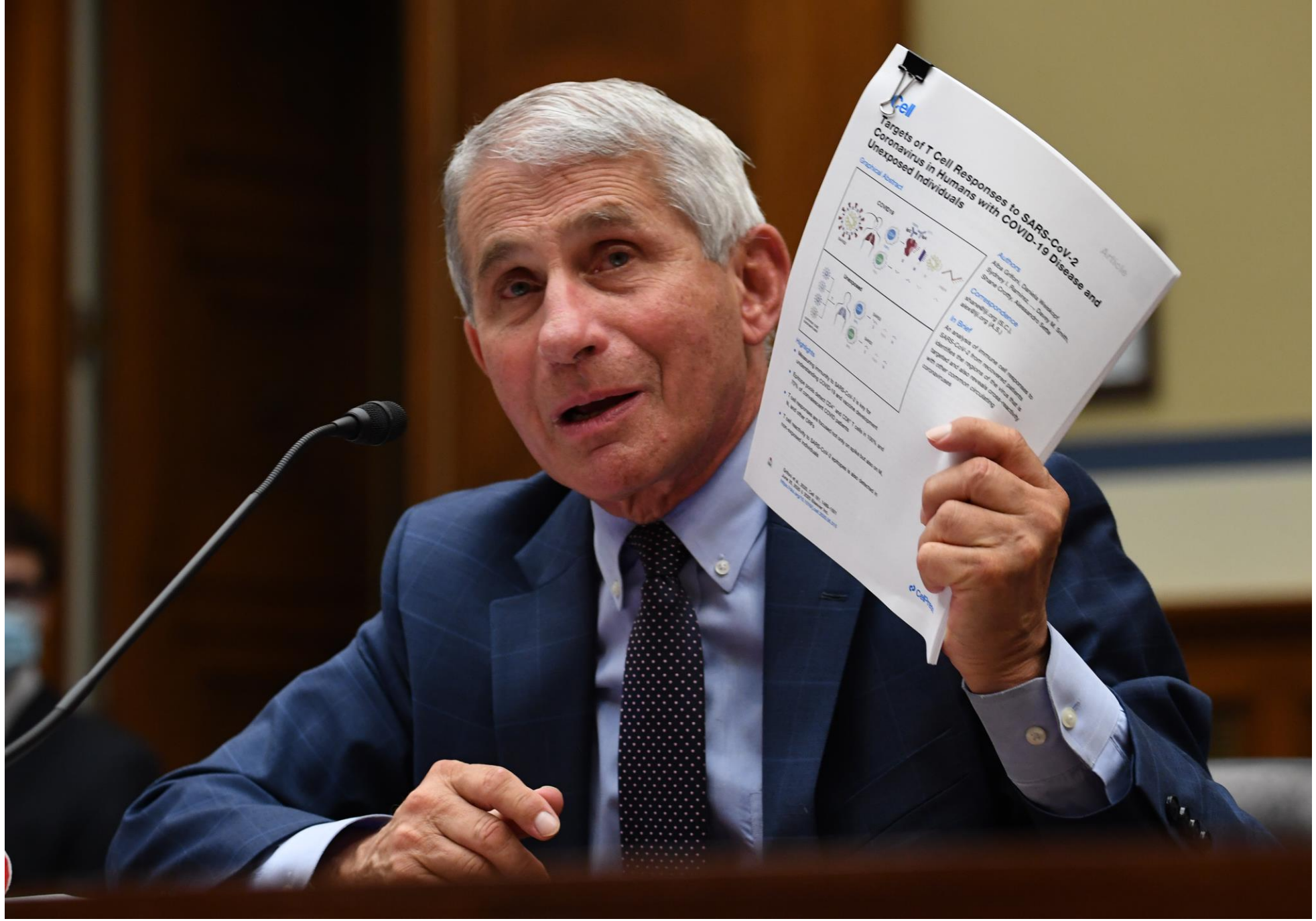
La Jolla Institute
FOR IMMUNOLOGY

UCSD School of Medicine
Dept. of Medicine

COVID-19 has killed more Americans than all the wars of the 20th century combined

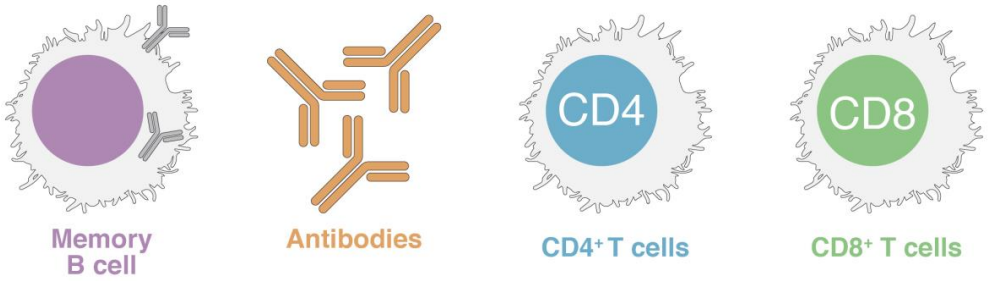


Tony Fauci. Congress, July 31, 2020

Do people develop immune memory to COVID-19?

Shane Crotty & Alex Sette

La Jolla Institute FOR IMMUNOLOGY



Dan & Mateus & Kato et al. Science. Jan 2021

- 188 subjects.
- 41 subjects @ 6 to 8 months

RESEARCH ARTICLE SUMMARY

Science

CORONAVIRUS

Immunological memory to SARS-CoV-2 assessed for up to 8 months after infection

Jennifer M. Dan*, Jose Mateus*, Yu Kato*, Kathryn M. Hastie, Esther Dawen Yu, Caterina E. Faliti, Alba Grifoni, Sydney I. Ramirez, Sonya Haupt, April Frazier, Catherine Nakao, Vamseedhar Rayaprolu, Stephen A. Rawlings, Bjoern Peters, Florian Krammer, Viviana Simon, Erica Ollmann Saphire, Davey M. Smith, Daniela Weiskopf†, Alessandro Sette†, Shane Crotty†

INTRODUCTION: Immunological memory is the basis for durable protective immunity after infections or vaccinations. Duration of immunological memory after severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and COVID-19 is unclear. Immunological memory can consist of memory B cells, antibodies, memory $CD4^+$ T cells, and/or memory $CD8^+$ T cells. Knowledge of the kinetics and interrelationships among those four types of memory in humans is limited. Understanding immune memory to SARS-CoV-2 has implications for understanding protective immunity against COVID-19 and assessing the likely future course of the COVID-19 pandemic.

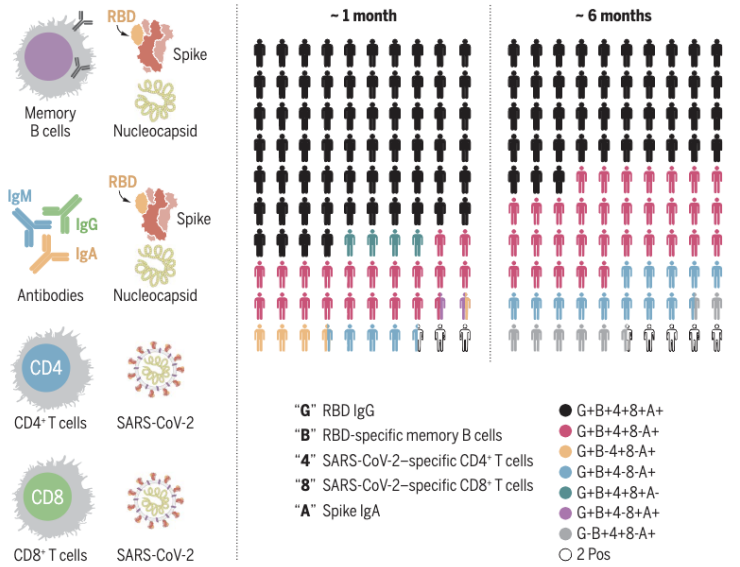
RATIONALE: Assessing virus-specific immune memory over at least a 6-month period is likely necessary to ascertain the durability of immune memory to SARS-CoV-2. Given the evidence that antibodies, $CD4^+$ T cells, and $CD8^+$ T cells can all participate in protective immunity to SARS-CoV-2, we measured antigen-specific antibodies, memory B cells, $CD4^+$ T cells, and $CD8^+$ T cells in the blood from subjects who recovered from COVID-19, up to 8 months after infection.

RESULTS: The study involved 254 samples from 188 COVID-19 cases, including 43 samples at 6 to 8 months after infection. Fifty-one subjects in the study provided longitudinal blood samples, allowing for both cross-sectional and longitudinal analyses of SARS-CoV-2–specific immune memory. Antibodies against SARS-CoV-2 spike and receptor binding domain (RBD) declined moderately over 8 months, comparable to several other reports. Memory B cells against SARS-CoV-2 spike actually increased between 1 month and 8 months after infection. Memory $CD8^+$ T cells and memory $CD4^+$ T cells declined with an initial half-life of 3 to 5 months. This is the largest antigen-specific study to date of the four major types of immune memory for any viral infection.

Among the antibody responses, spike immunoglobulin G (IgG), RBD IgG, and neutralizing antibody titers exhibited similar kinetics. Spike IgA was still present in the large majority of subjects at 6 to 8 months after infection. Among the memory B cell responses, IgG was the dominant isotype, with a minor population of IgA memory B cells. IgM memory B cells appeared to be short-lived. $CD8^+$ T cell and $CD4^+$ T cell memory was measured for all SARS-CoV-2 proteins. Although ~70% of individuals possessed detectable $CD8^+$ T cell memory at 1 month after infection, that proportion declined to ~50% by 6 to 8 months after infection. For $CD4^+$ T cell memory, 93% of subjects had detectable SARS-CoV-2 memory at 1 month after infection, and the proportion of subjects positive for $CD4^+$ T cells (92%) remained high at 6 to 8 months after infection. SARS-CoV-2 spike-specific memory $CD4^+$ T cells with the specialized capacity to help B cells [T follicular helper (T_{FH}) cells] were also maintained.

The different types of immune memory each had distinct kinetics, resulting in complex interrelationships between the abundance of T cell, B cell, and antibody immune memory over time. Additionally, substantially heterogeneity in memory to SARS-CoV-2 was observed.

CONCLUSION: Substantial immune memory is generated after COVID-19, involving all four major types of immune memory. About 95% of subjects retained immune memory at ~6 months after infection. Circulating antibody titers were not predictive of T cell memory. Thus, simple serological tests for SARS-CoV-2 antibodies do not reflect the richness and durability of immune memory to SARS-CoV-2. This work expands our understanding of immune memory in humans. These results have implications for protective immunity against SARS-CoV-2 and recurrent COVID-19. ■



Immunological memory consists of antibodies, memory B cells, memory $CD8^+$ T cells, and memory $CD4^+$ T cells. This study examined all of the types of virus-specific immune memory against SARS-CoV-2 in COVID-19 subjects. Robust immune memory was observed in most individuals.

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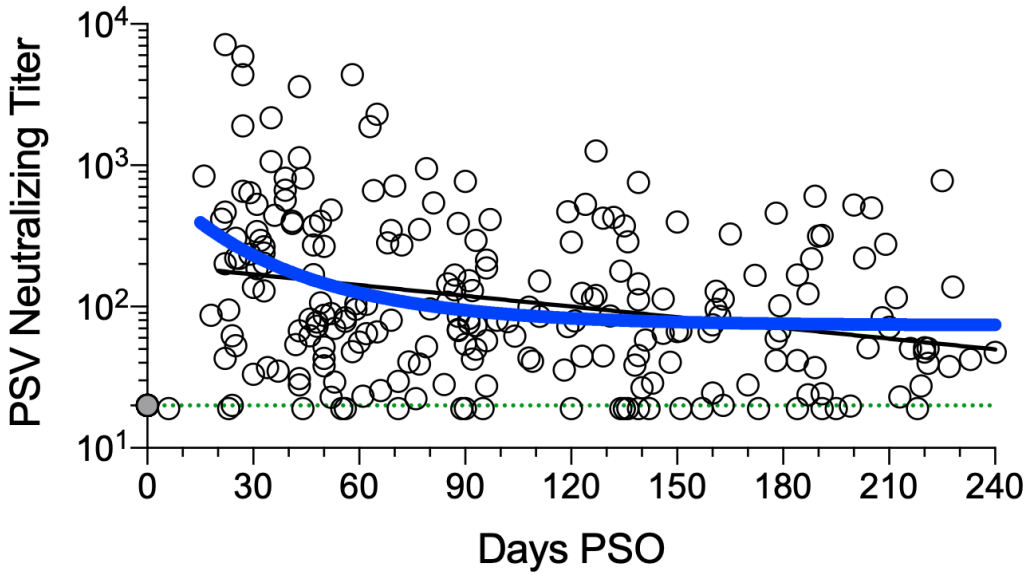
READ THE FULL ARTICLE AT https://doi.org/10.1126/science.abf4063

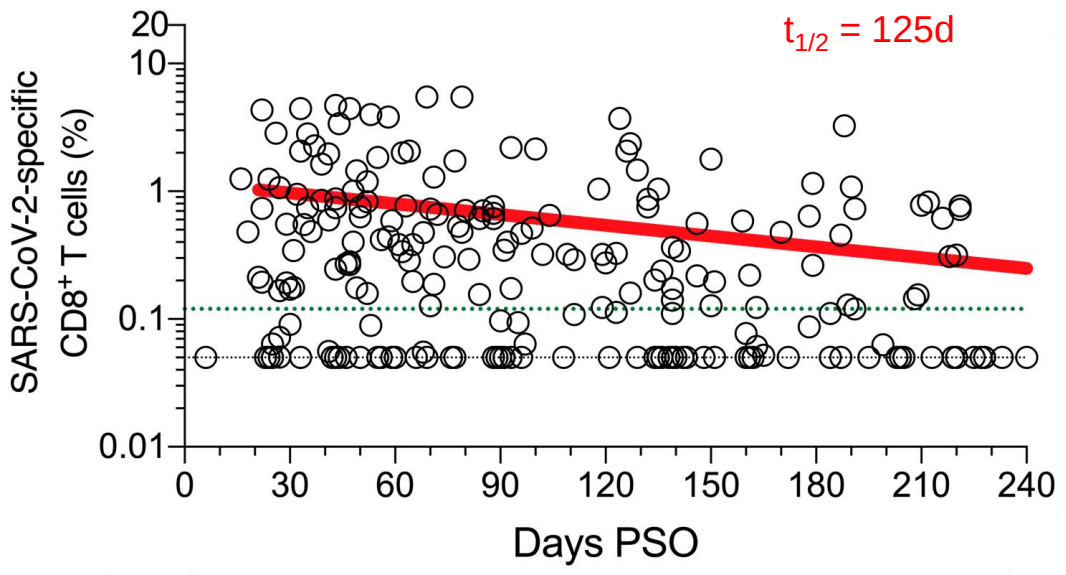
How long does immunological memory to SARS-CoV-2 last?

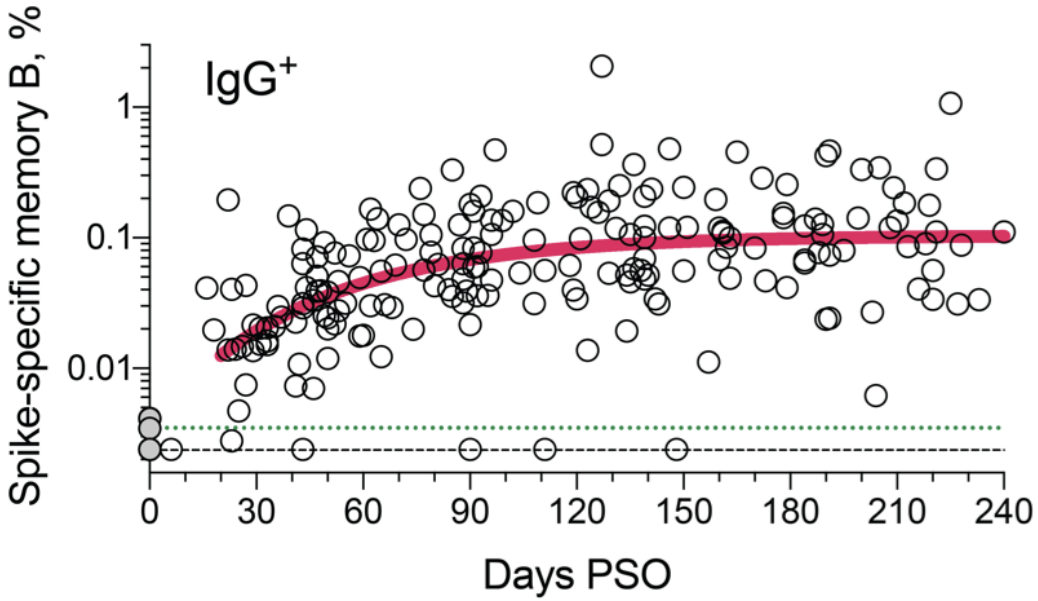
Antibodies

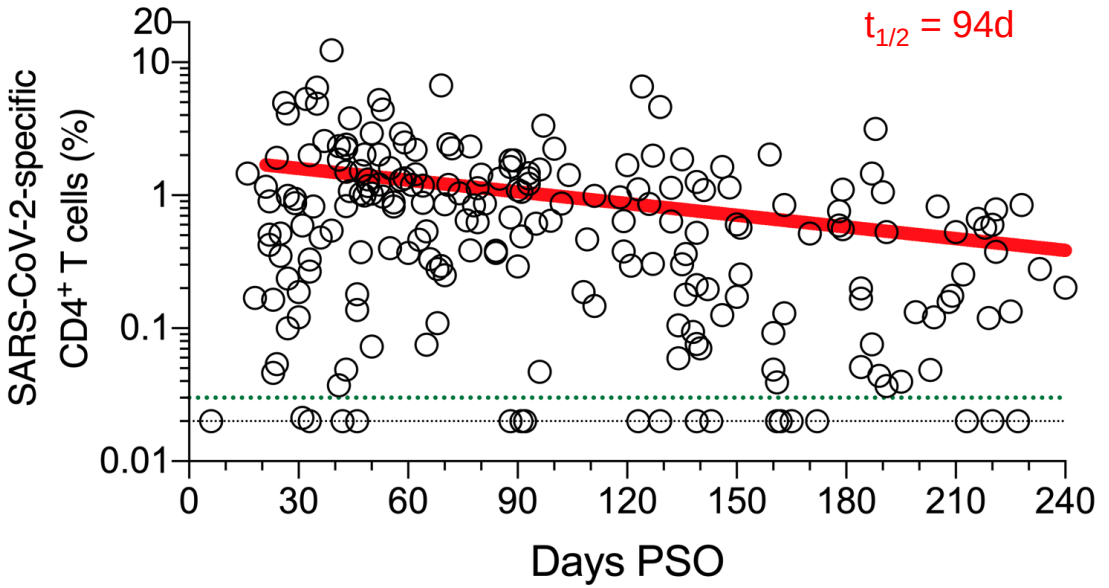
CD4⁺ T cells

CD8⁺ T cells

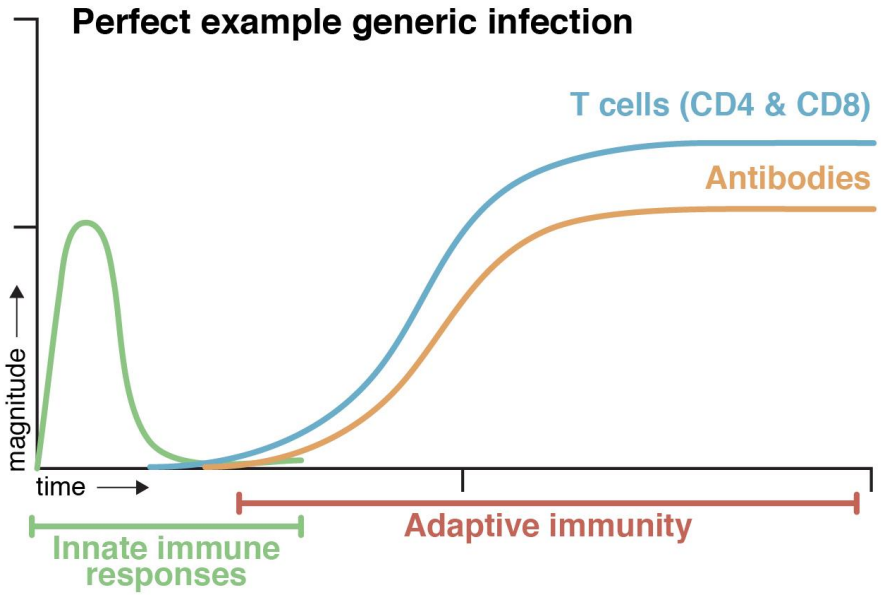


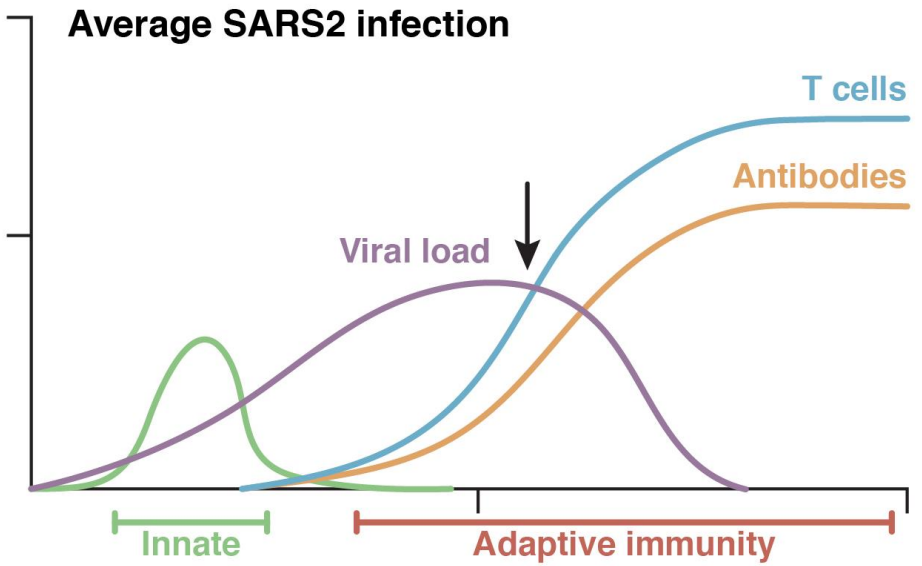


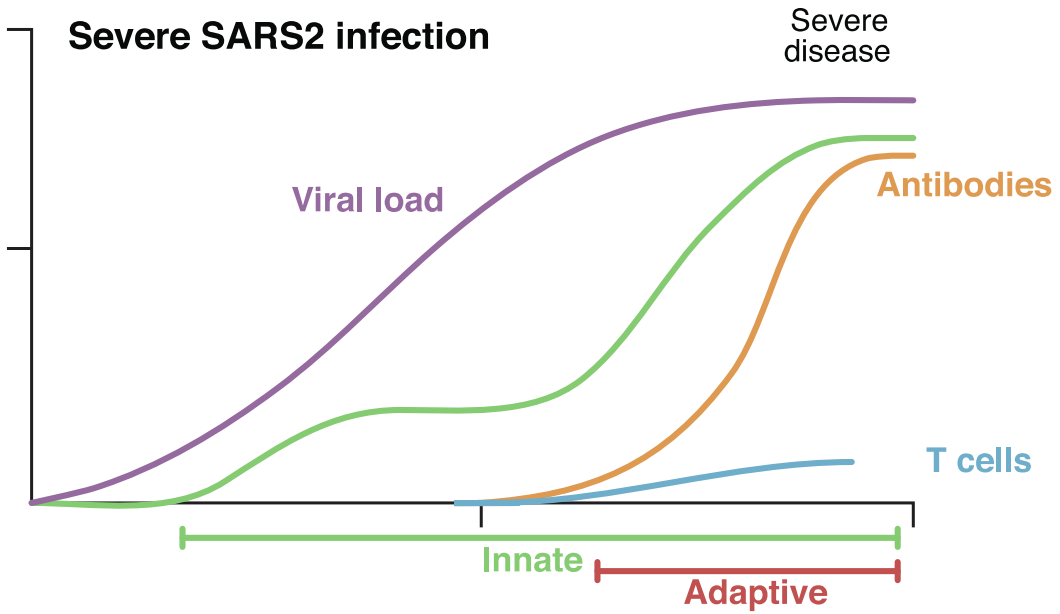




Immune response trajectories in COVID-19





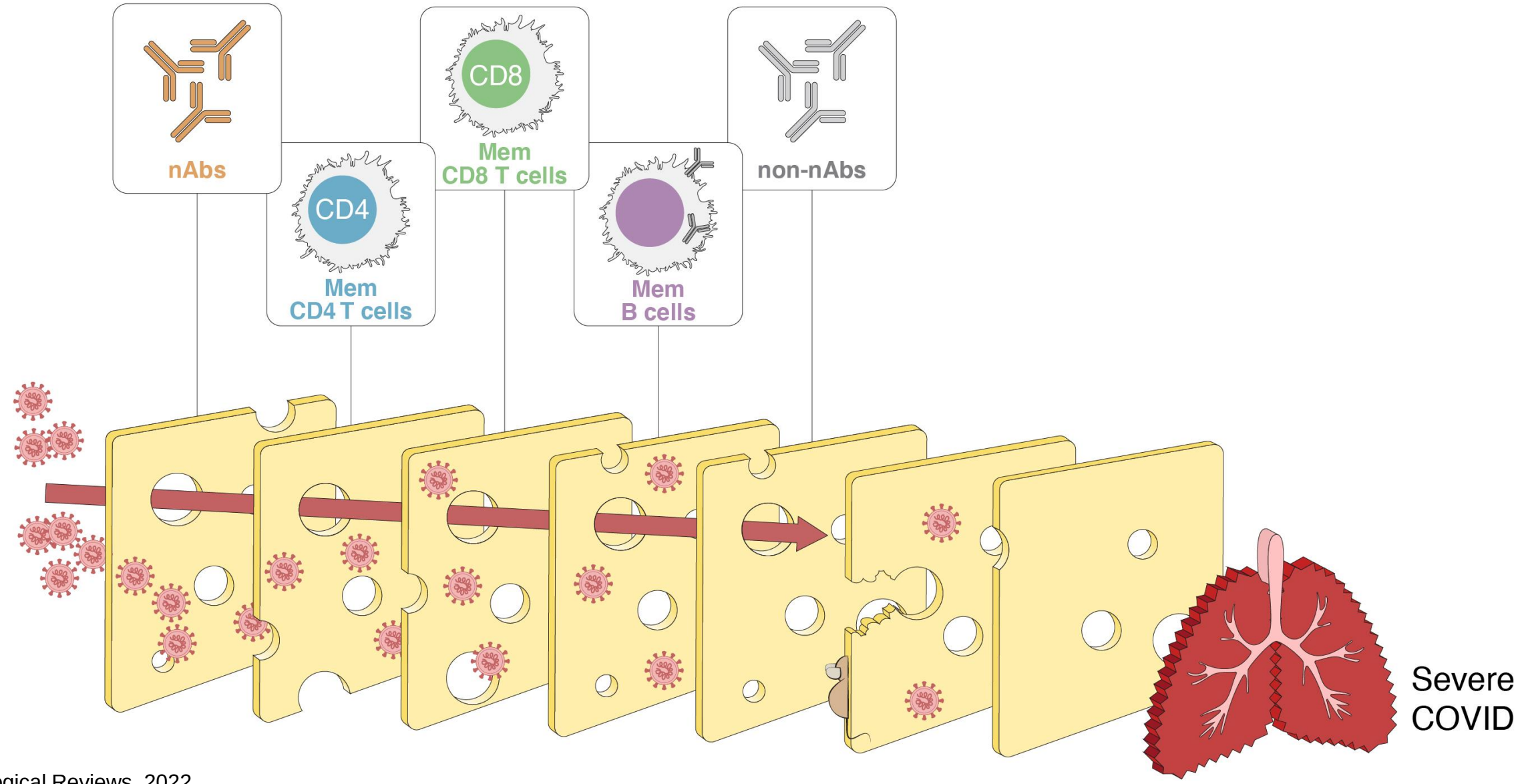


* “Innate” = innate immune response plasma signature

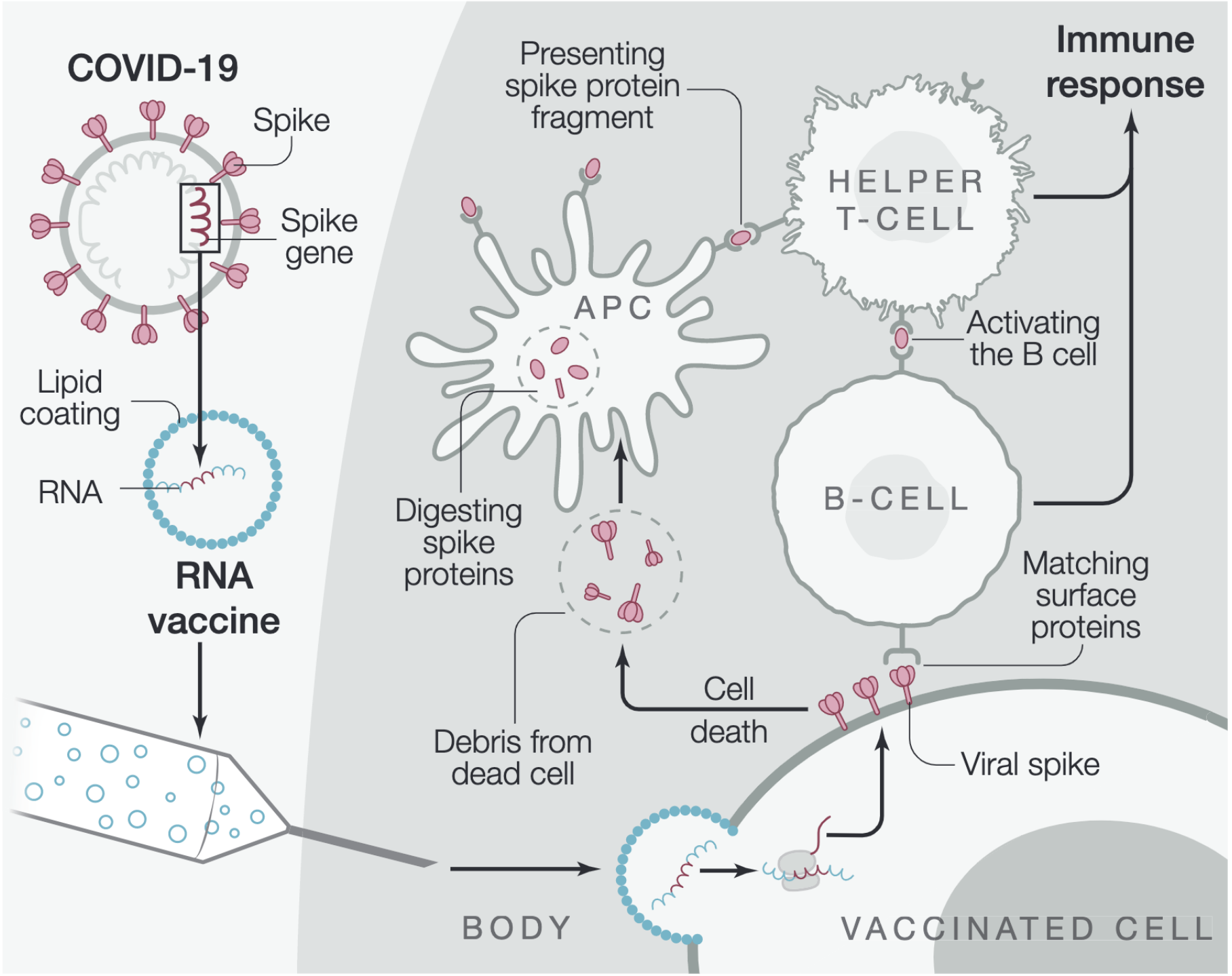
Sette and Crotty, Cell 2021

Layered defenses

Or the swiss cheese model of immunity

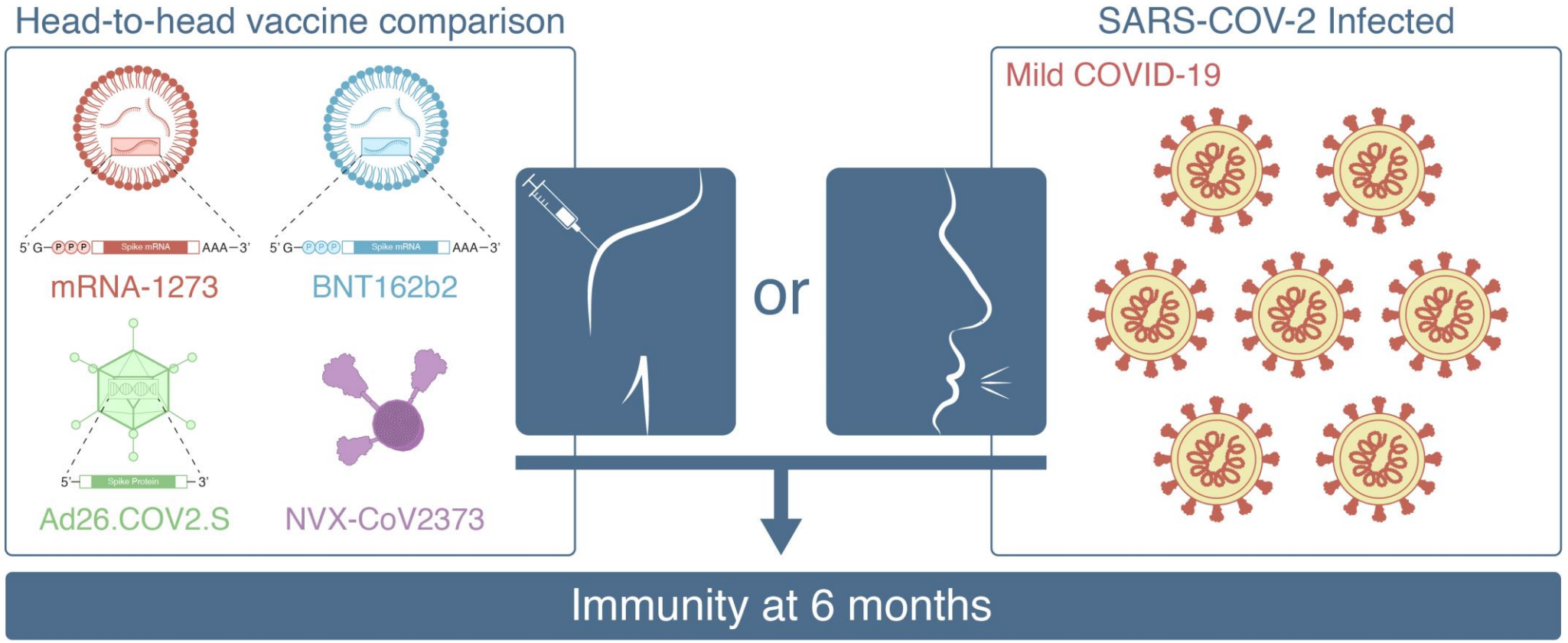


Immunological Reviews, 2022

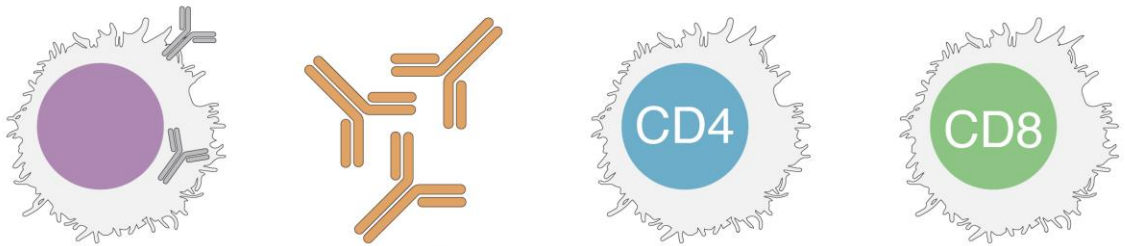


Eric Topol
Cell 2021

Head-to-head comparison of immune memory to four COVID-19 vaccines

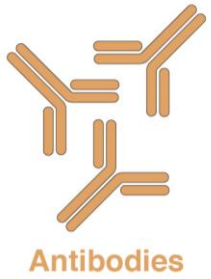


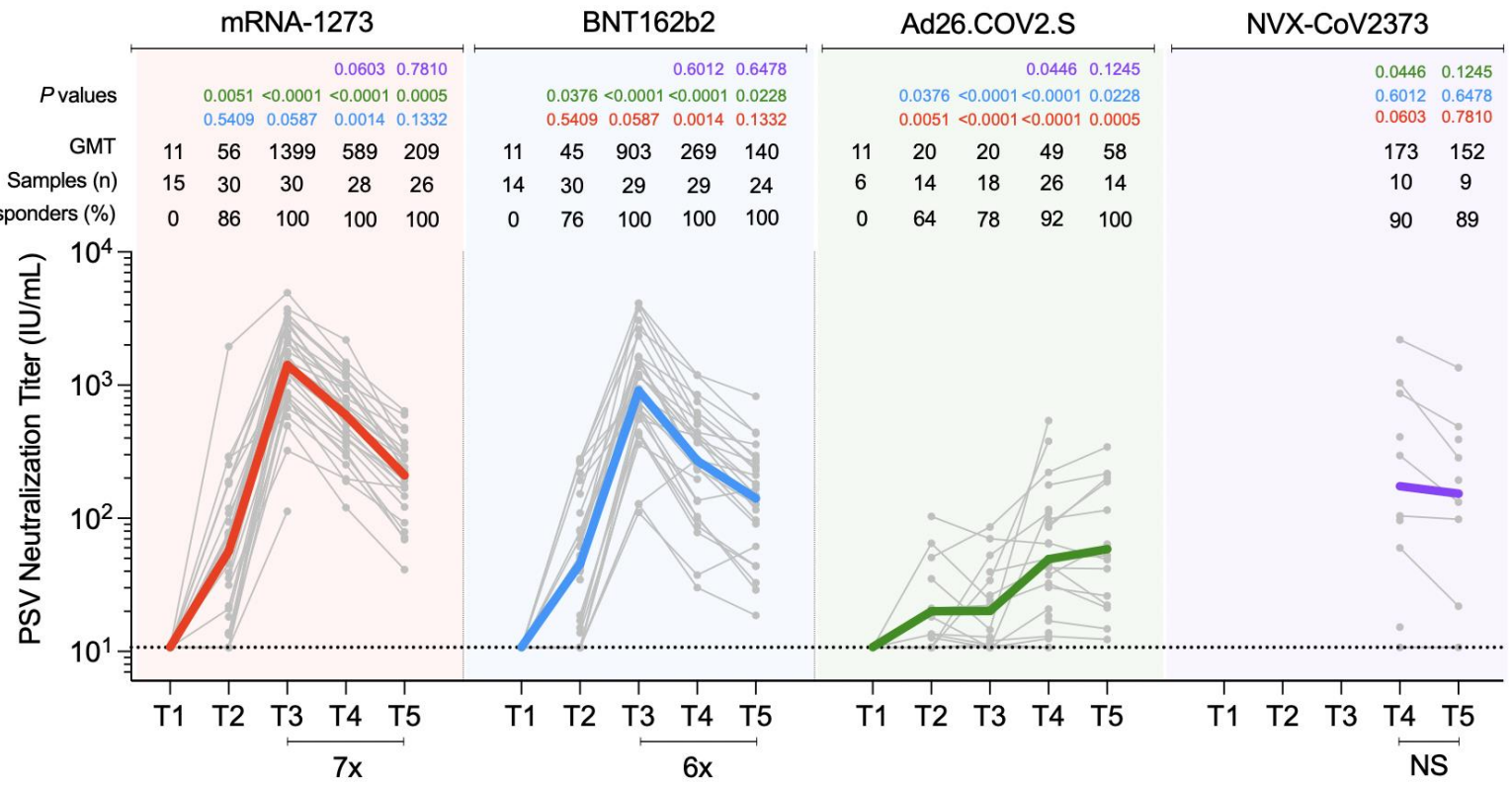
Prof. Daniela Weiskopf

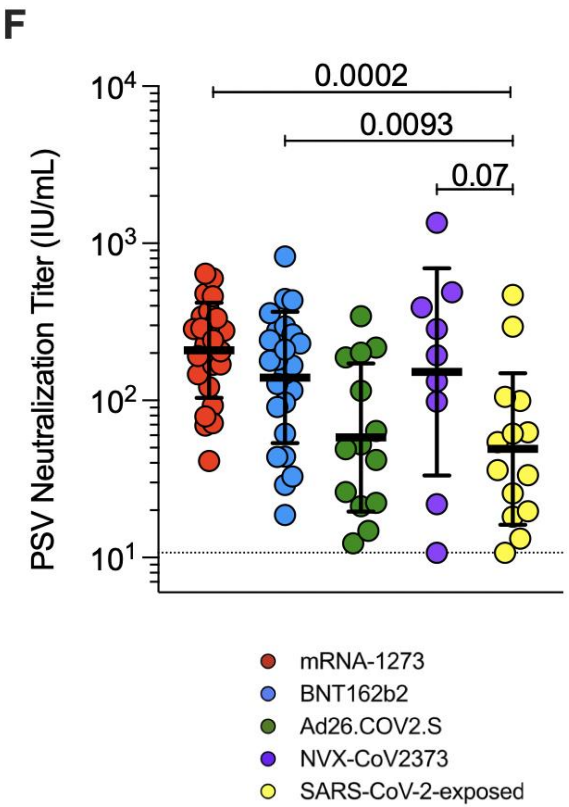


Zhang, Mateus, Coelho, Dan, Moderbacher et al . Cell 2022

Comparison of immune memory to four COVID-19 vaccines







Zeli Zhang, PhD

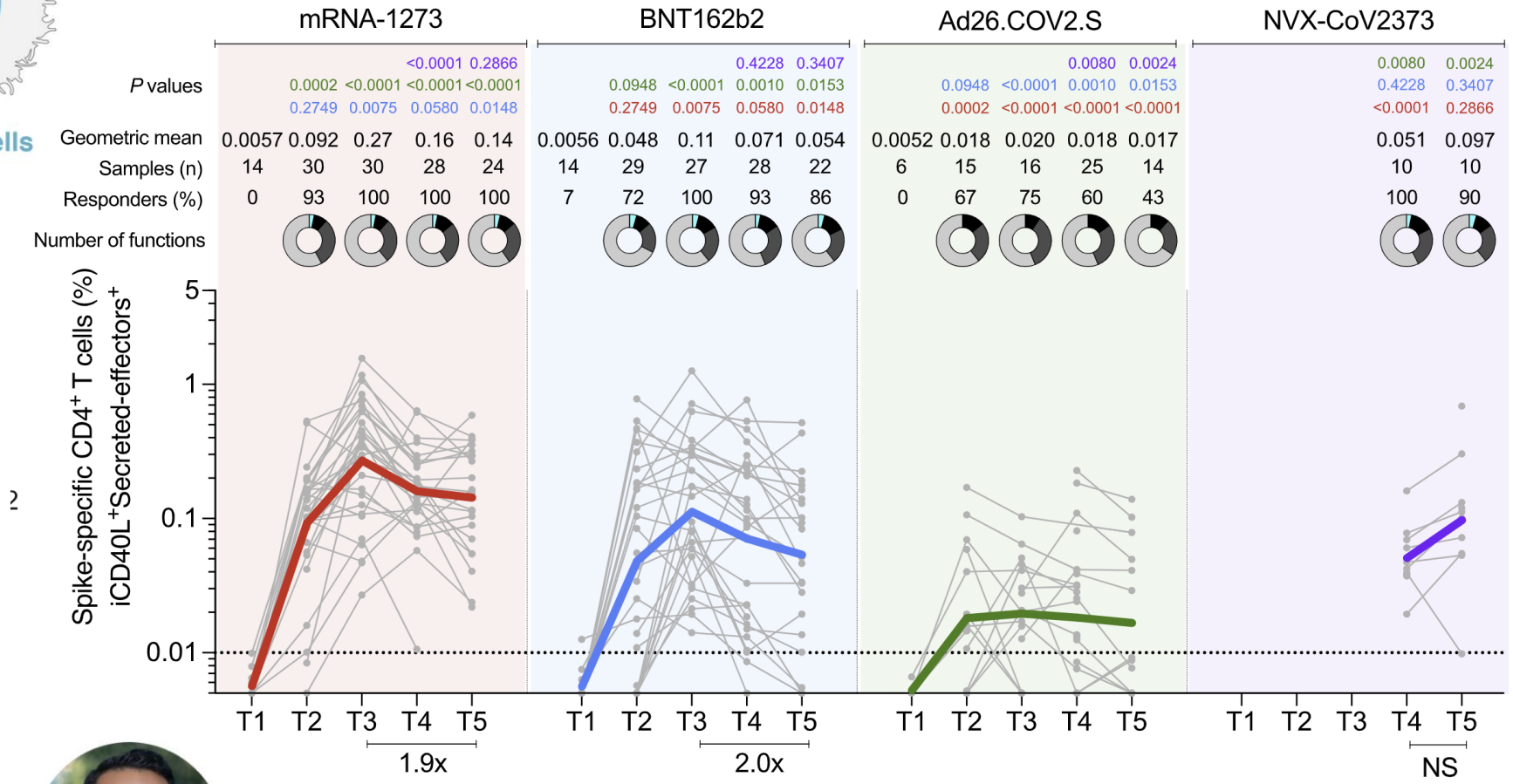
Jen Dan, MD/PhD

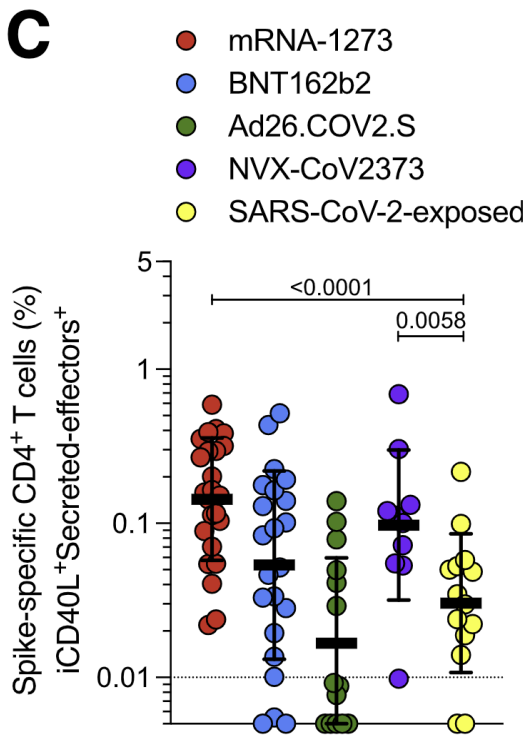
T1 = baseline
T2 = 14 days
T3 = 35-42 days
T4 = 3 months
T5 = 6 months

Cell 2022

Comparison of immune memory to four COVID-19 vaccines

CD4⁺ T cells



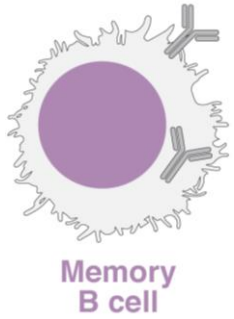


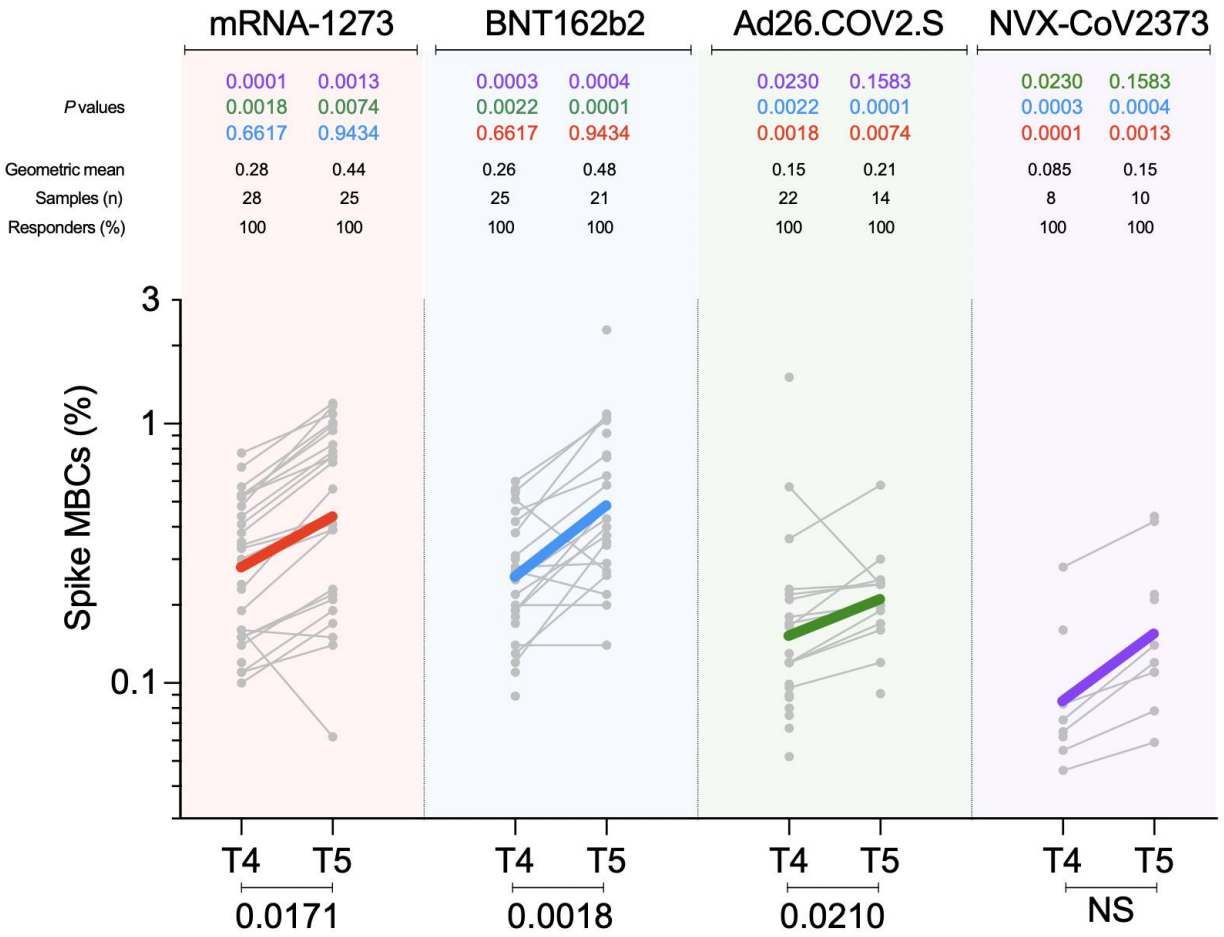
Carolyn Rydyznski Moderbacher, PhD

Jose Mateus, PhD

Cell 2022

Comparison of immune memory to four COVID-19 vaccines

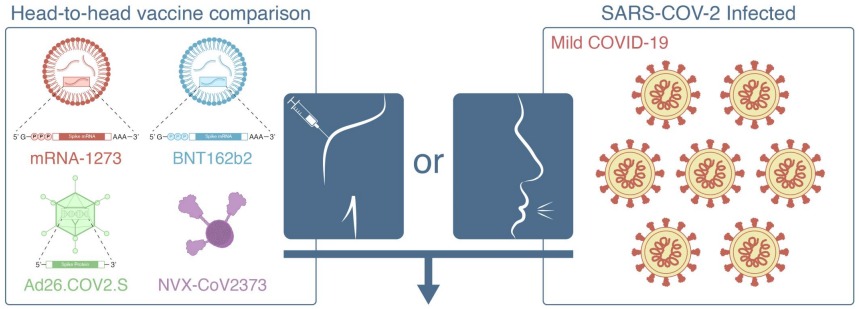




Camila Coelho, PhD

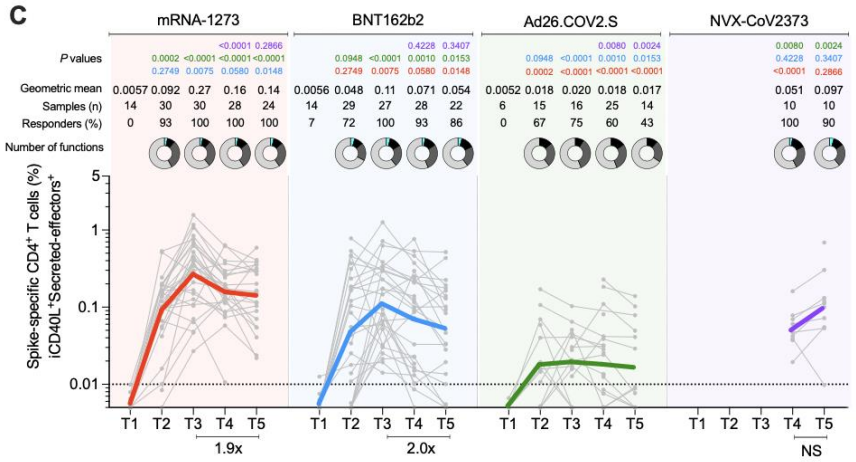
Cell 2022

Head-to-head comparison of immune memory to four COVID-19 vaccines



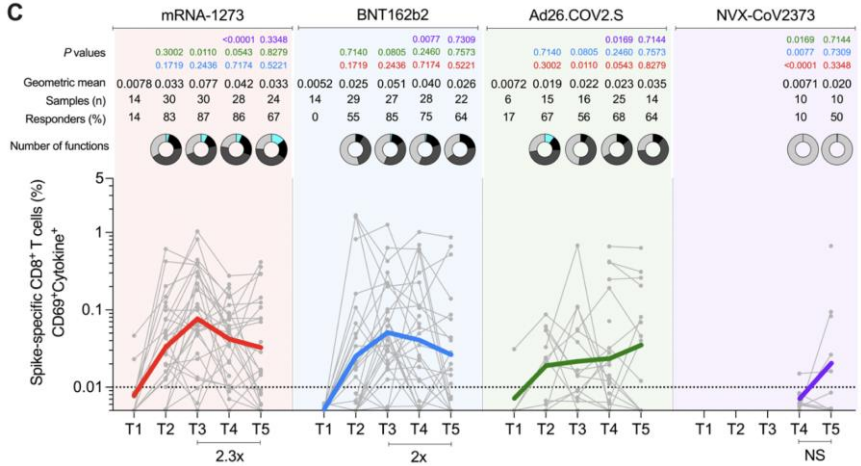
CD4

CD4⁺ T cells

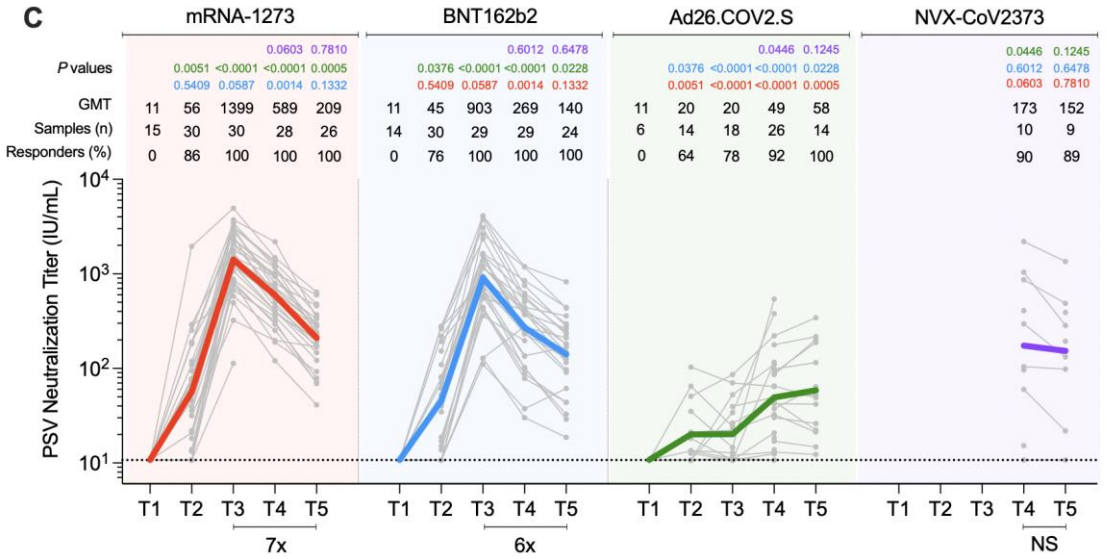


CD8

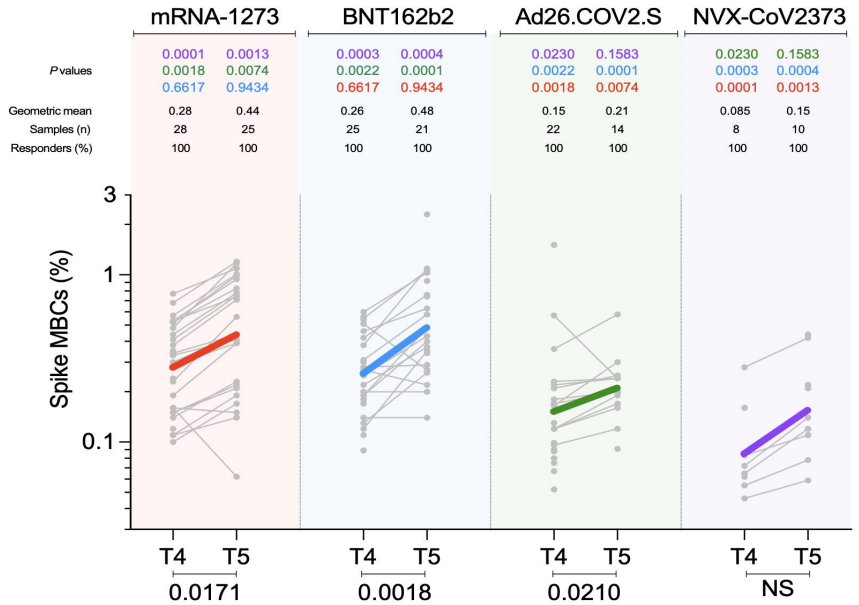
CD8⁺ T cells



Antibodies

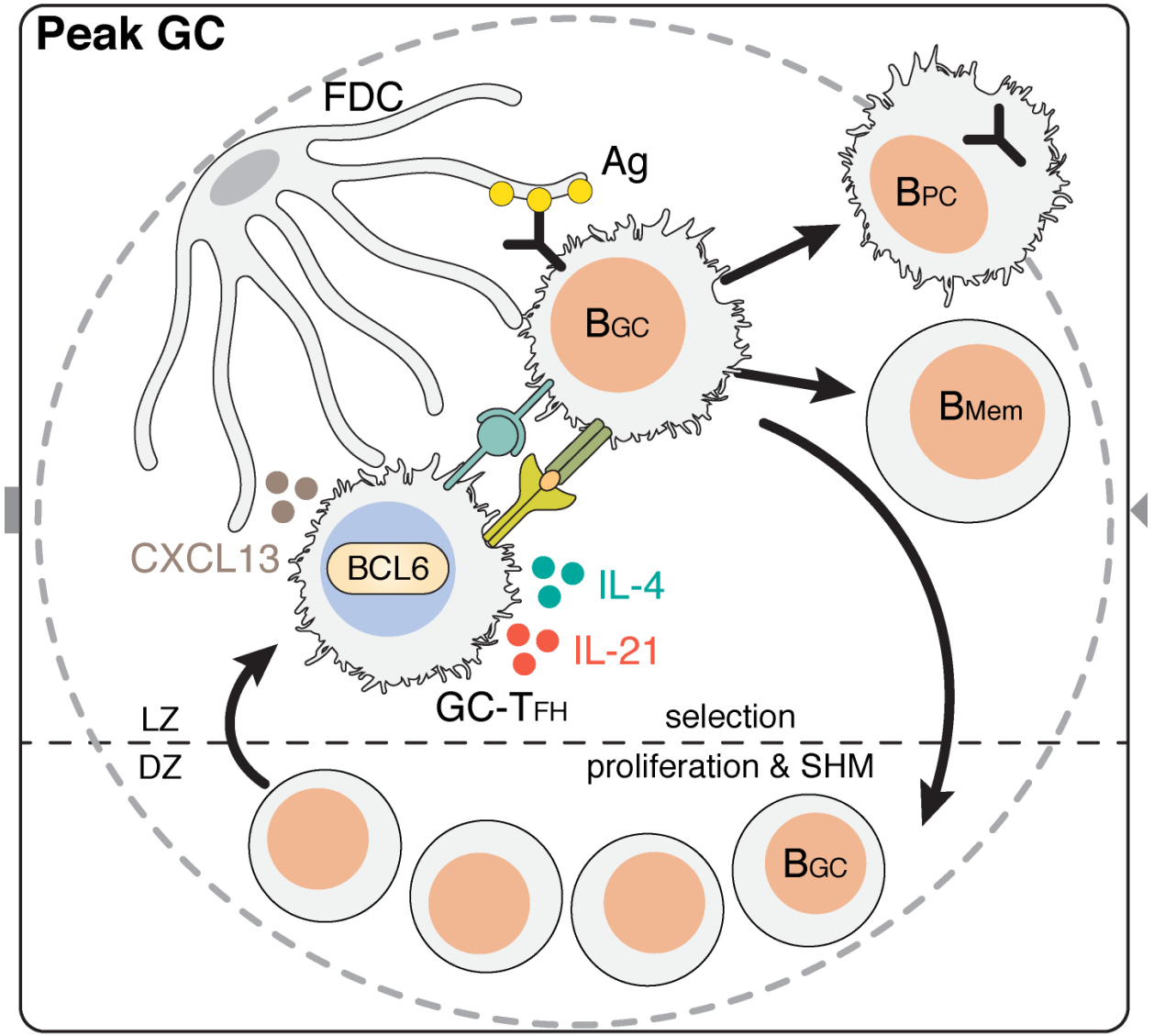


Memory B cell



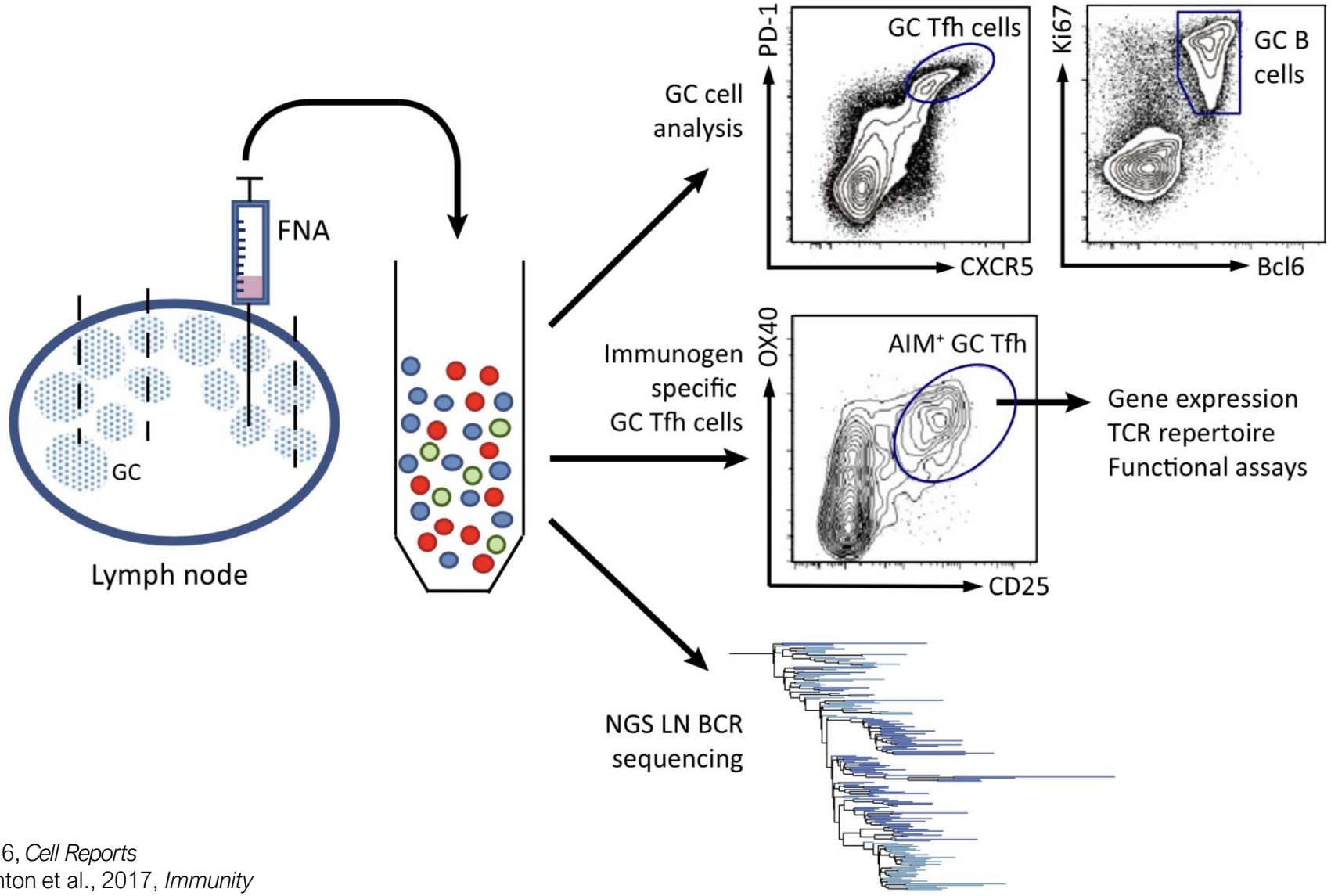
Cell 2022

Germinal centers



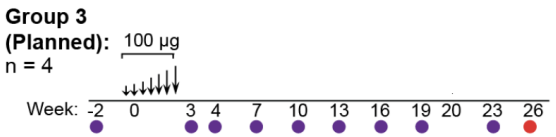
Immunity 2019

Lymph node fine needle aspirates (LN FNAs) allow for sampling of the lymph node longitudinally



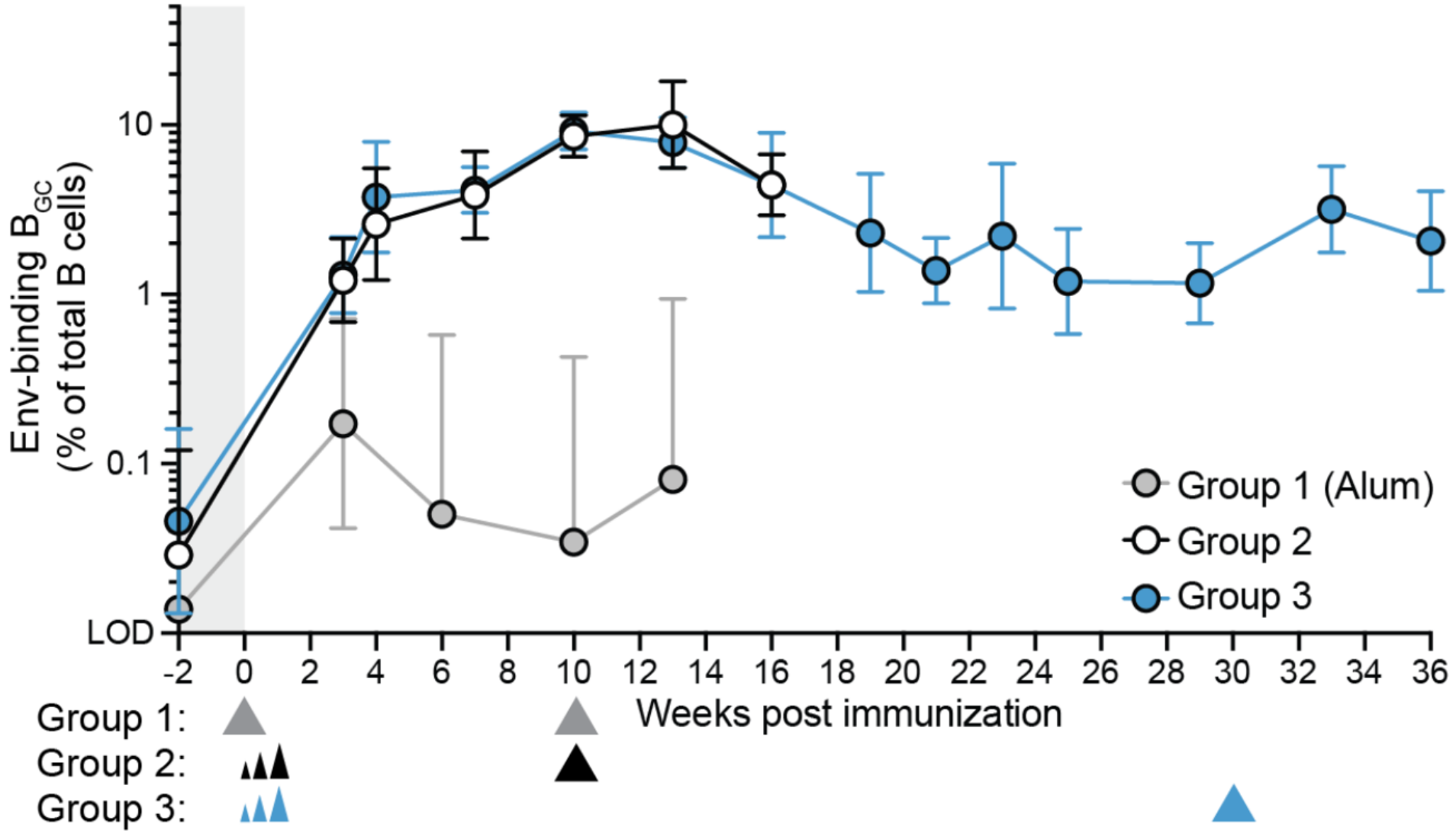
Havenar-Daughton, et al. 2016, *Cell Reports*
Pauthner and Havenar-Daughton et al., 2017, *Immunity*

Looooong-lasting germinal centers to a priming immunization



HIV Env trimer + SMNP adjuvant

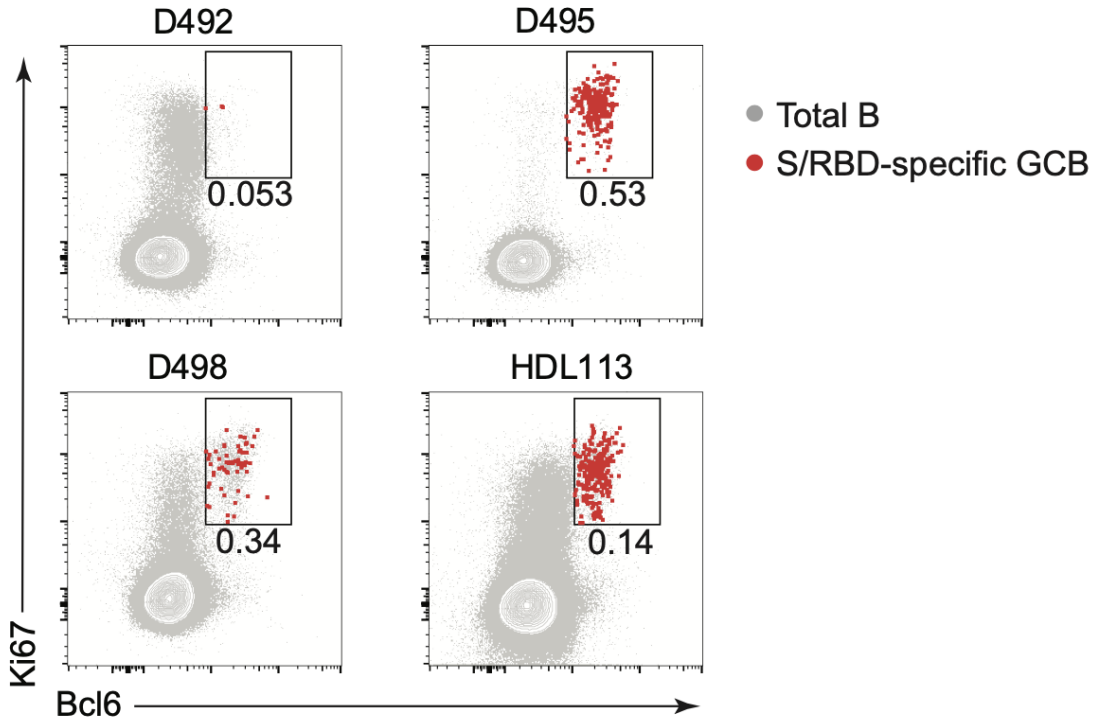
via 12-day escalating dose slow delivery

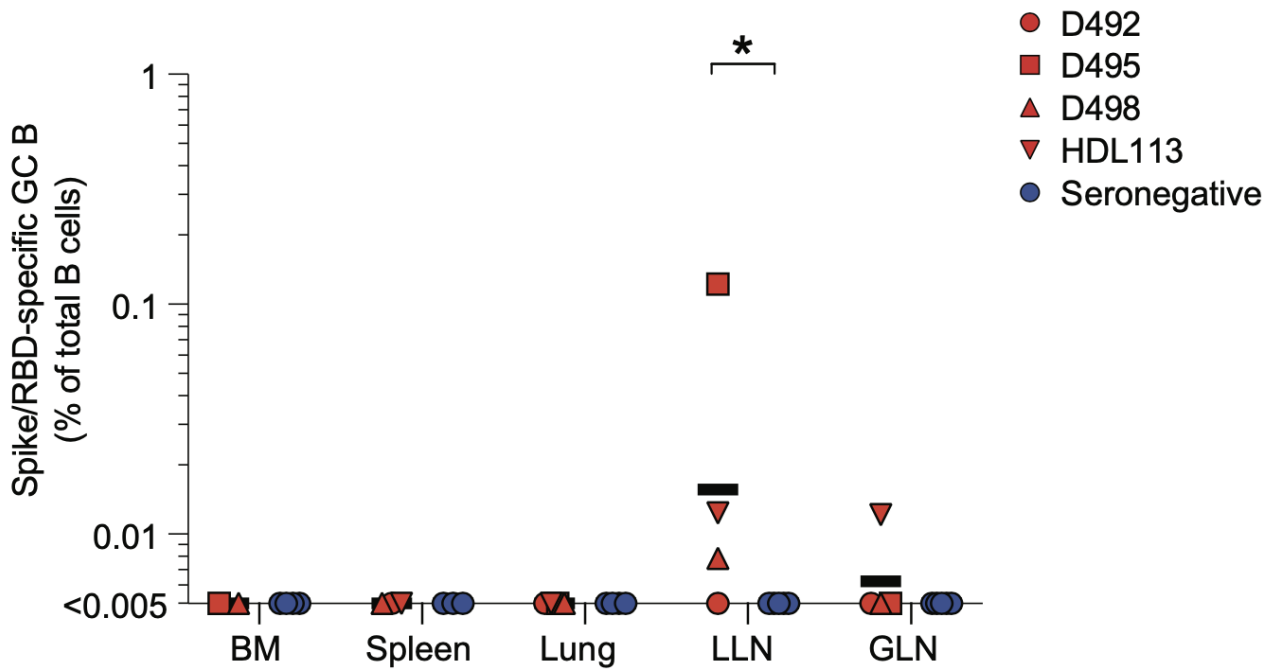


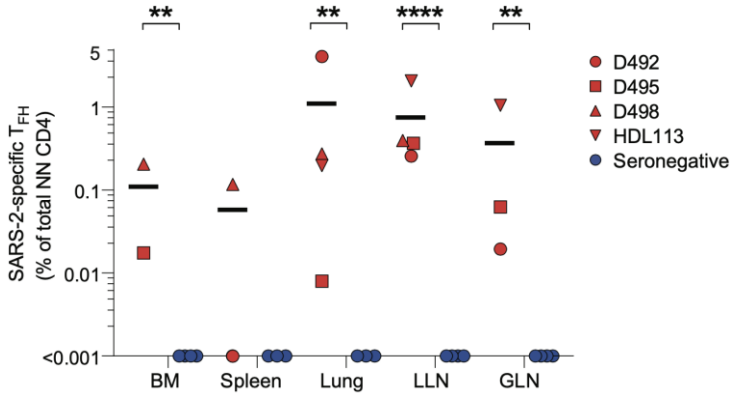
Lee & Sutton et al. Nature 2022

- Germinal centers can last for > 6 months after an optimized priming immunization.
- Dramatically larger and more durable germinal centers than conventional alum-based

Long-lasting virus-specific germinal centers

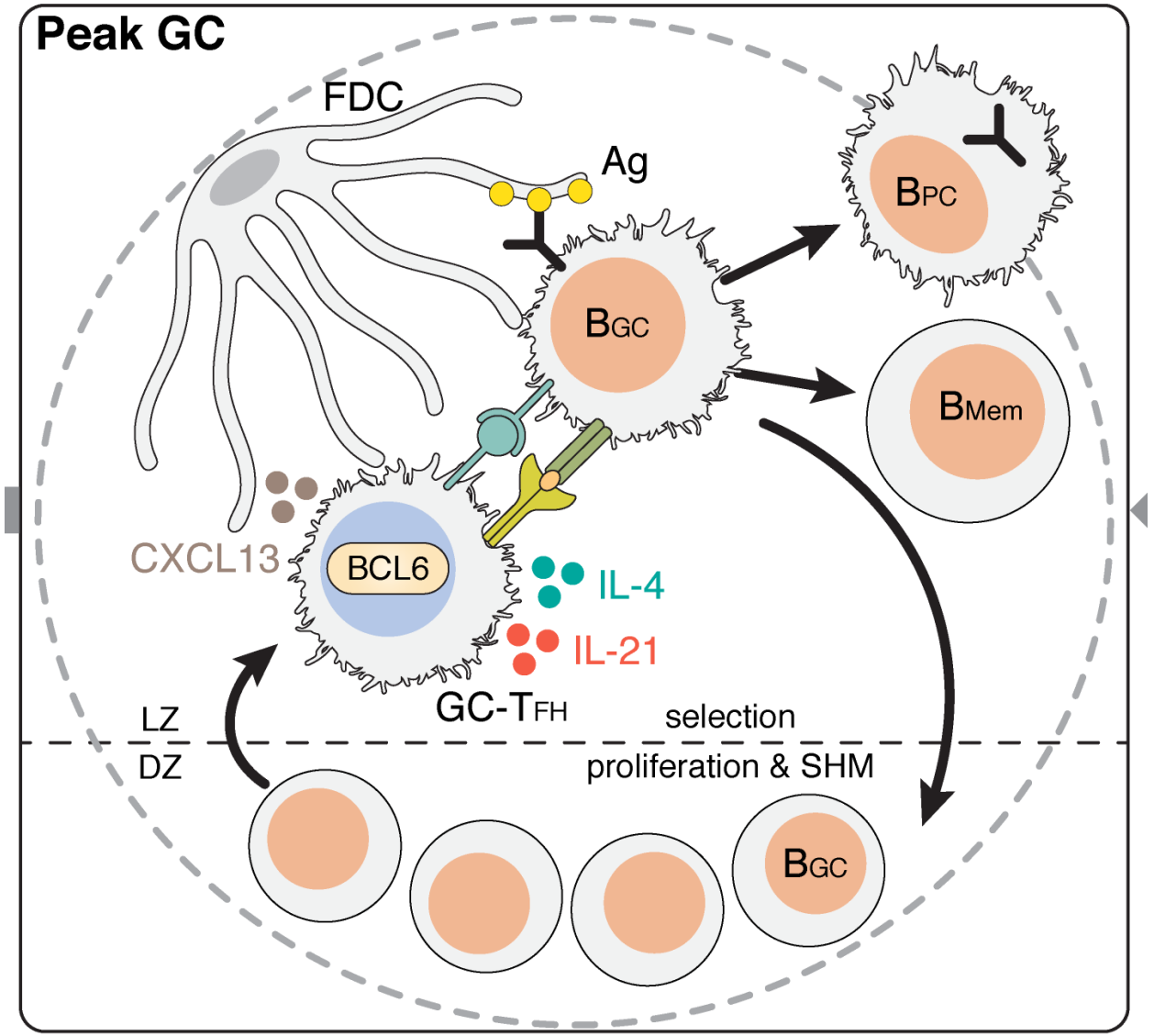






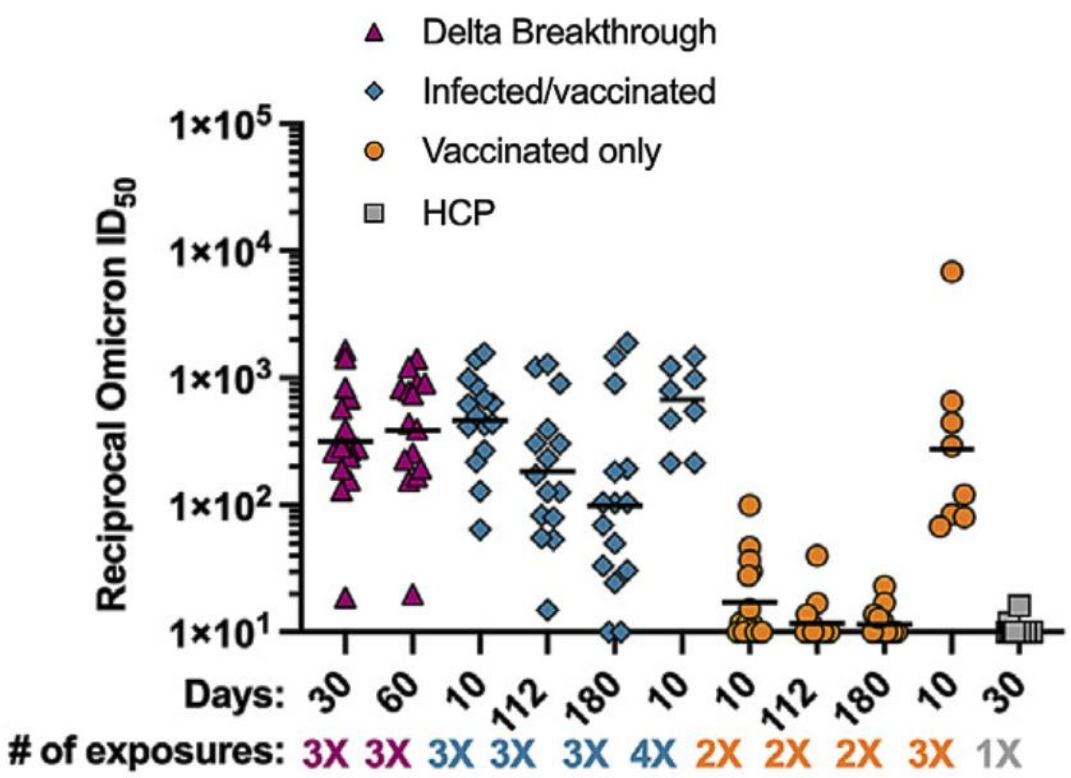
Farber and Crotty labs.
Science Immunology 2021

Germinal centers



Immunity 2019

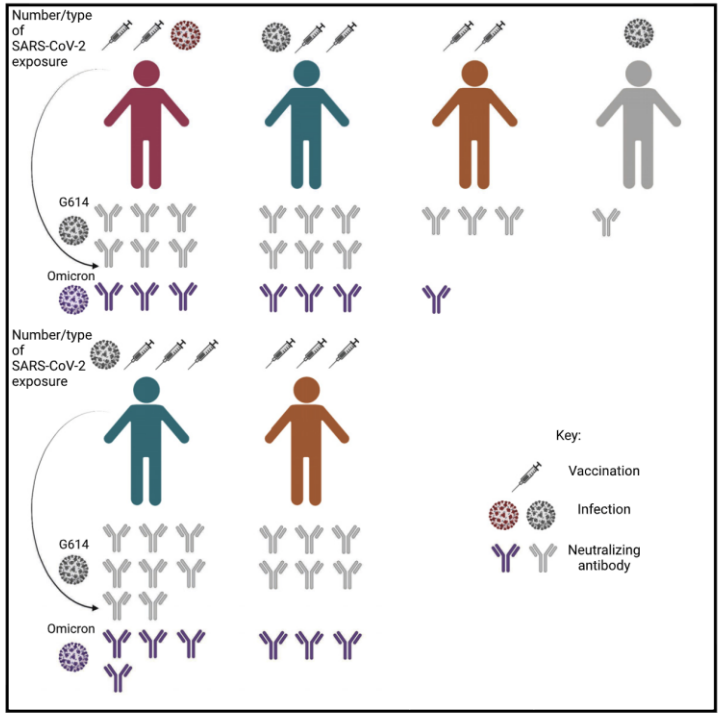
Hybrid immunity results in potent neutralizing antibody breadth, also with breakthrough infections



Cell

SARS-CoV-2 breakthrough infections elicit potent, broad, and durable neutralizing antibody responses

Graphical abstract



Authors

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In brief

Individuals with breakthrough COVID-19 infections, previously infected/vaccinated individuals, and those vaccinated thrice have potent serum-binding and -neutralizing antibody responses against variants of concern, including Omicron. Neutralization of SARS-CoV, however, was moderate, thus urging the need for developing broad vaccines for pandemic preparedness.

Highlights

- Breakthrough infections induce potent neutralizing antibody responses
- Number of exposures (infection or vaccination) correlates with potency and breadth
- Three-dose vaccination improves neutralization of the SARS-CoV-2 Omicron variant
- SARS-CoV-2 infection or vaccination elicit moderate neutralization of SARS-CoV

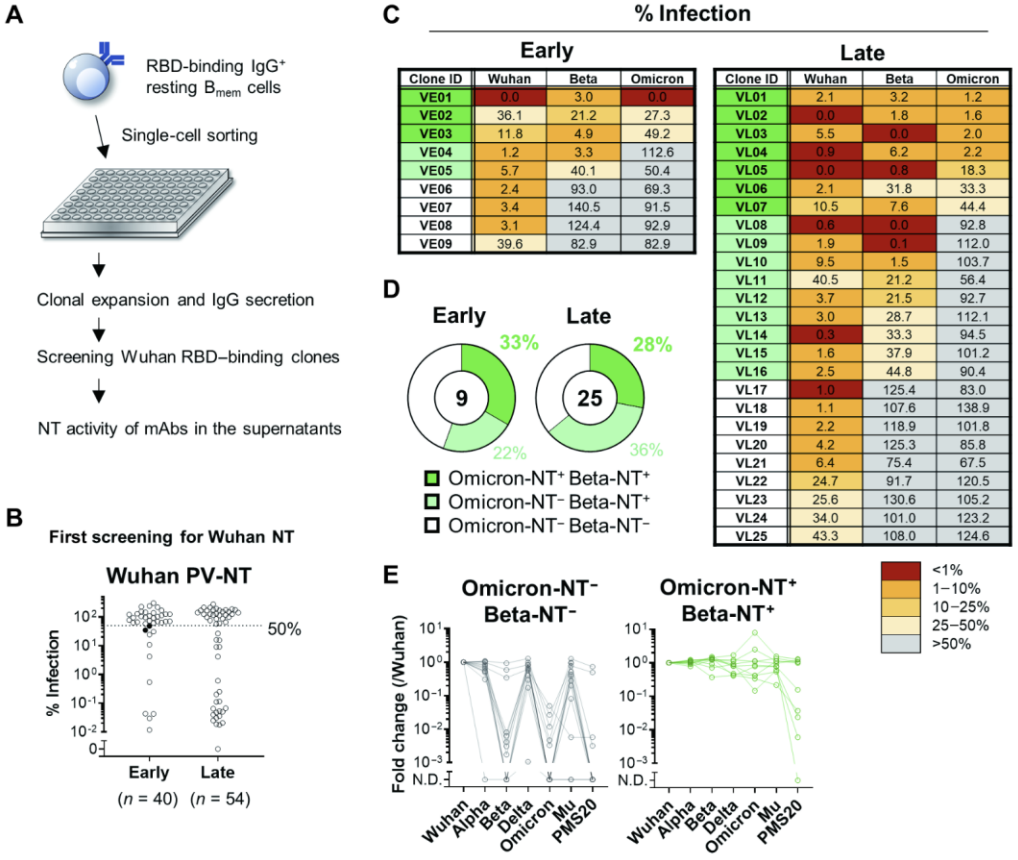
Omicron and memory B cells

SCIENCE IMMUNOLOGY | REPORT

CORONAVIRUS

SARS-CoV-2 Omicron-neutralizing memory B cells are elicited by two doses of BNT162b2 mRNA vaccine

Ryutaro Kotaki[1]†, Yu Adachi[1]†, Saya Moriyama[1]†, Taishi Onodera[1]†, Shuetsu Fukushi[2], Takaki Nagakura[1], Keisuke Tonouchi[1], Kazutaka Terahara[1], Lin Sun[1], Tomohiro Takano[1], Ayae Nishiyama[1], Masaharu Shinkai[3], Kunihiro Oba[4], Fukumi Nakamura-Uchiyama[5], Hidefumi Shimizu[6], Tadaki Suzuki[7], Takayuki Matsumura[1], Masanori Isogawa[1], Yoshimasa Takahashi[1]*



Article

Increased memory B cell potency and breadth after a SARS-CoV-2 mRNA boost

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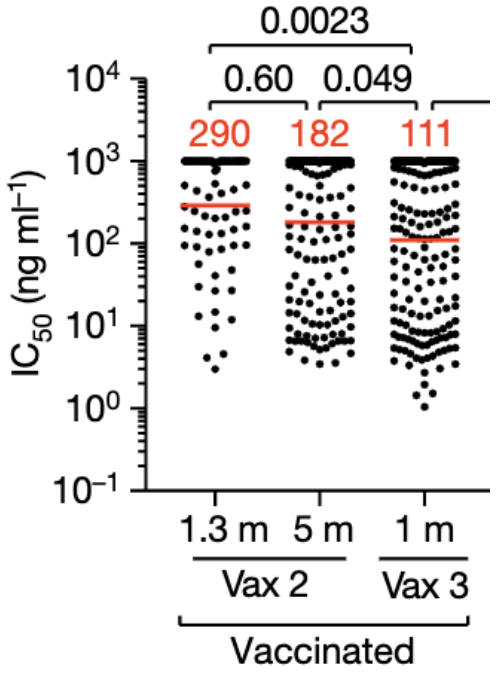
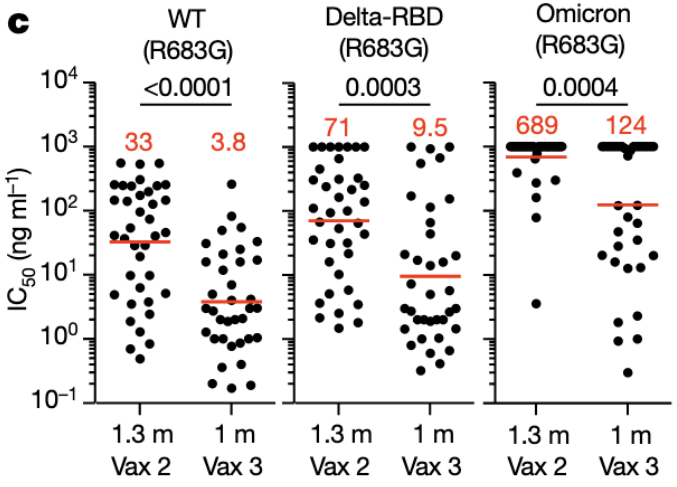
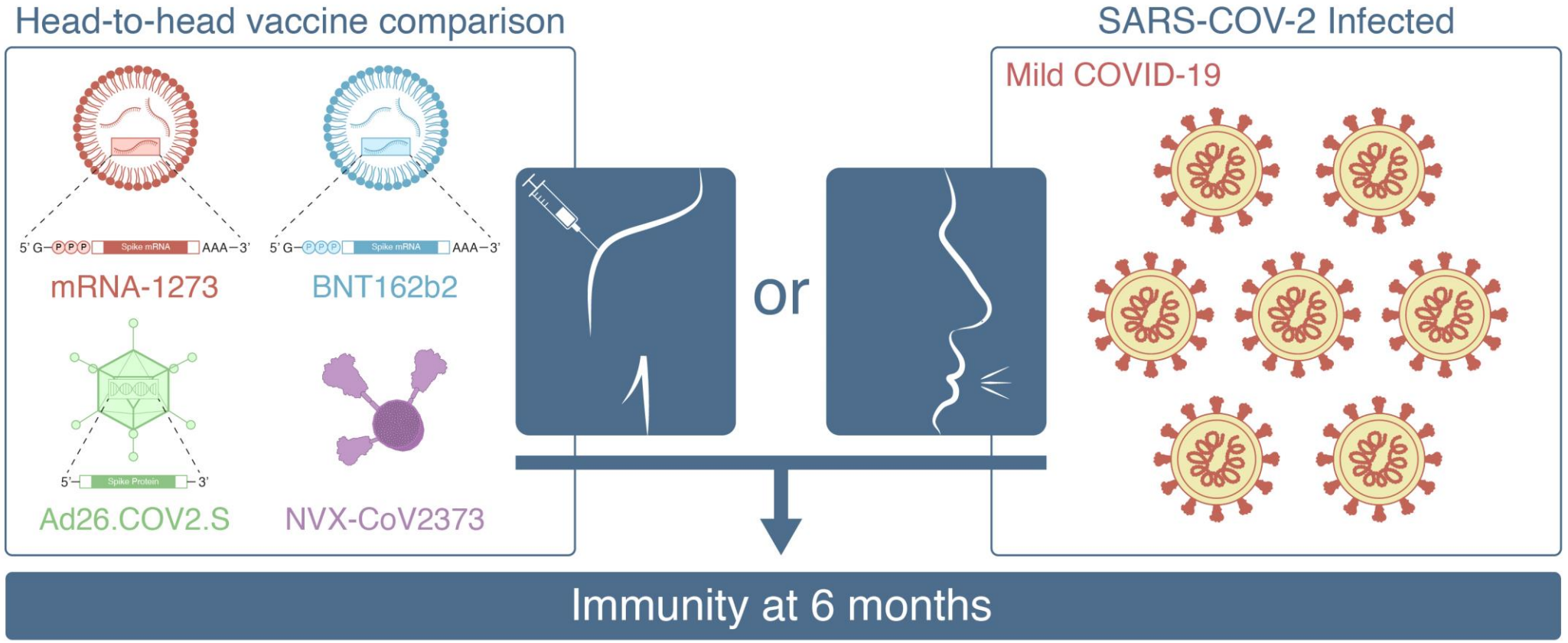
Frauke Muecksch[1,4], Zijun Wang[2,4], Alice Cho[2,4], Christian Gaebler[2], Tarek Ben Tanfous[2], Justin DaSilva[1], Eva Bednarski[1], Victor Ramos[2], Shuai Zong[2], Brianna Johnson[2], Raphael Raspe[2], Dennis Schaefer-Babajew[2], Irina Shimeliovich[2], Mridushi Daga[2], Kai-Hui Yao[2], Fabian Schmidt[1], Katrina G. Millard[2], Martina Turroja[2], Mila Jankovic[2], Thiago Y. Oliveira[2], Anna Gazumyan[2], Marina Caskey[2], Theodora Hatziioannou[1]✉, Paul D. Bieniasz[1,3]✉ & Michel C. Nussenzweig[2,3]✉

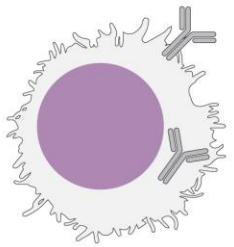


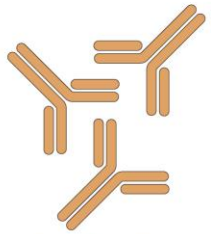


Head-to-head comparison of immune memory to four COVID-19 vaccines



Prof. Daniela Weiskopf


Memory B cell


Antibodies

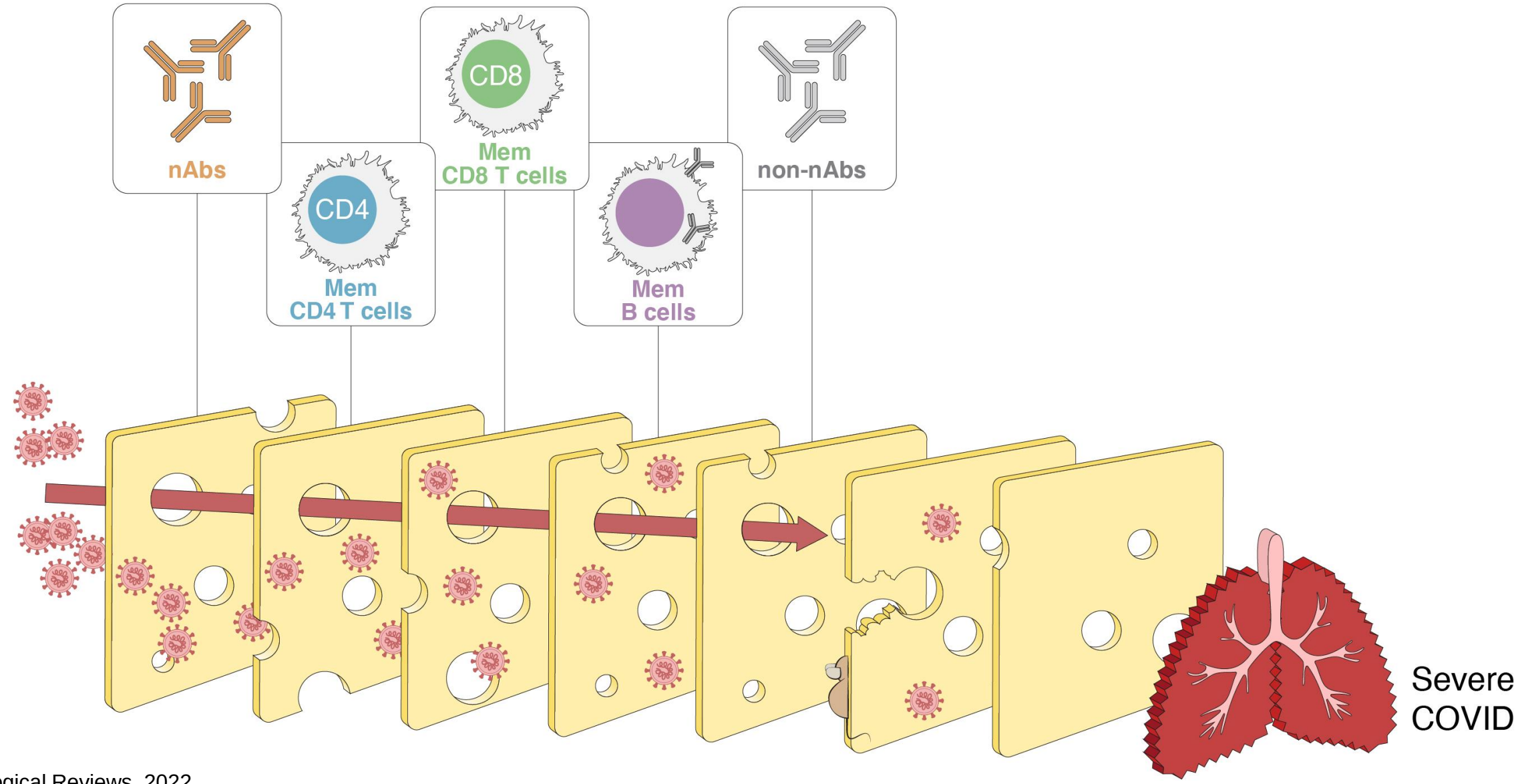
CD4⁺ T cells

CD8⁺ T cells

Zhang, Mateus, Coelho, Dan, Moderbacher et al . Cell 2022

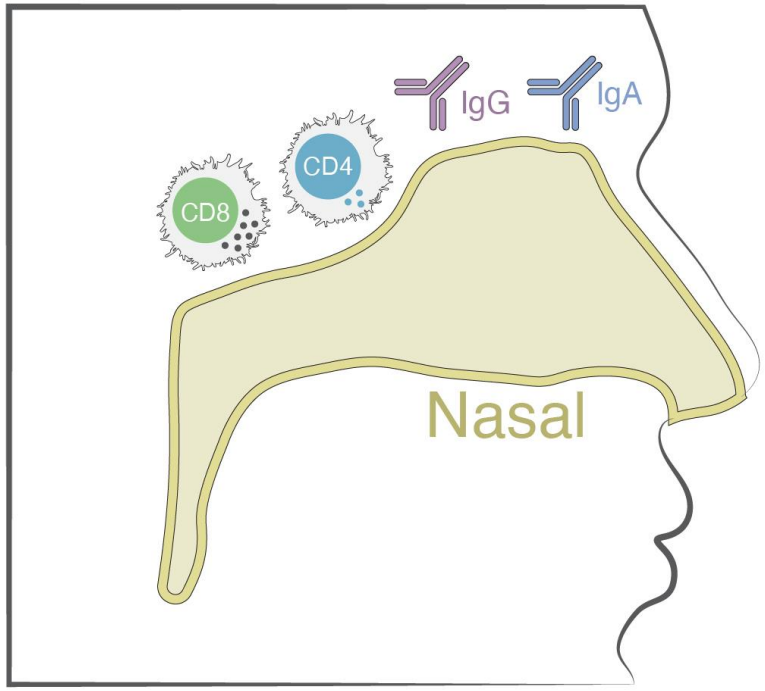
Layered defenses

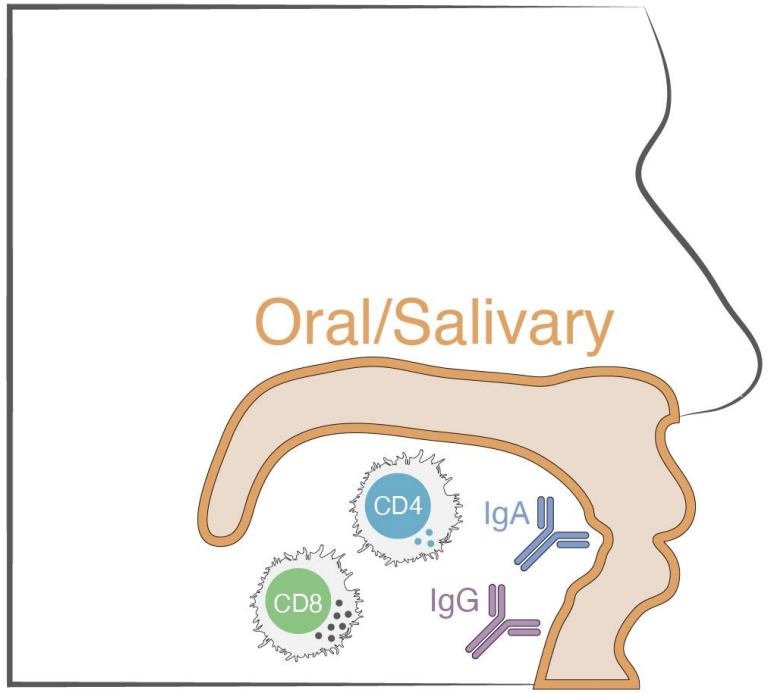
Or the swiss cheese model of immunity

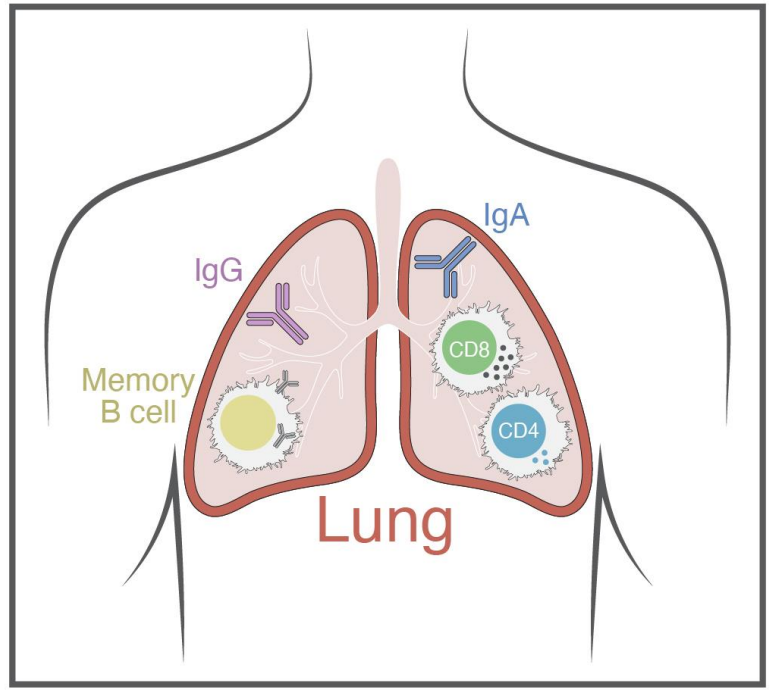


Immunological Reviews, 2022

Anatomy of immunity to SARS-CoV-2





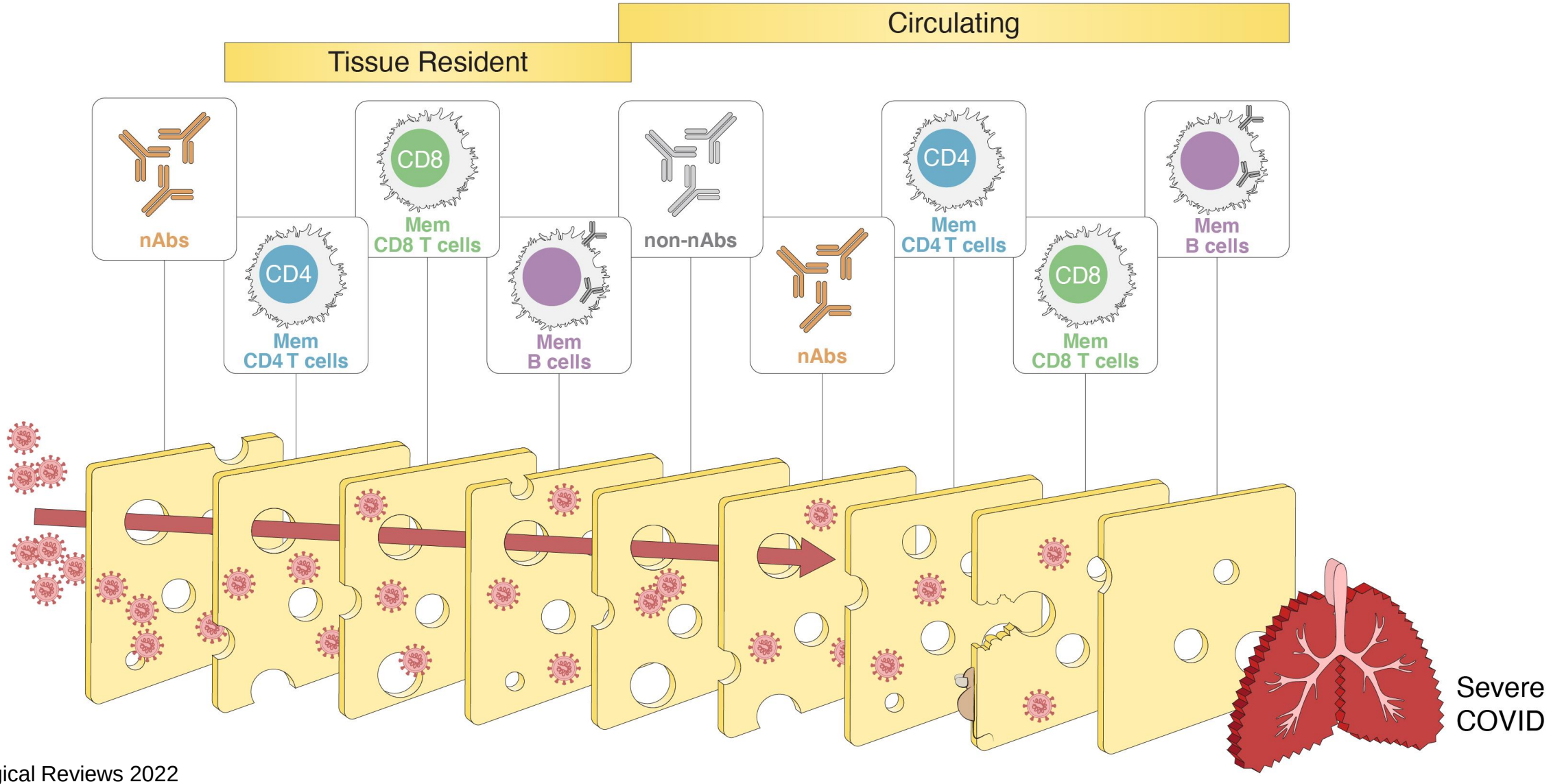


It is all a race

A race between the virus and your immune system.
Memory change the race. You then have the headstart instead of the virus.

Layered defenses

Or the swiss cheese model of immunity



Immunological Reviews 2022

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