VET TECH
Empowering Livestock Health

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Institute of Virology and Immunology IVI

The Immune System: A Blueprint for Animal Health

Professor Artur Summerfield

University of Bern, Institute of Virology and Immunology, Switzerland

- 2-3 of December 2025, Riyadh

وزارة البيئة والمياه والزراعة
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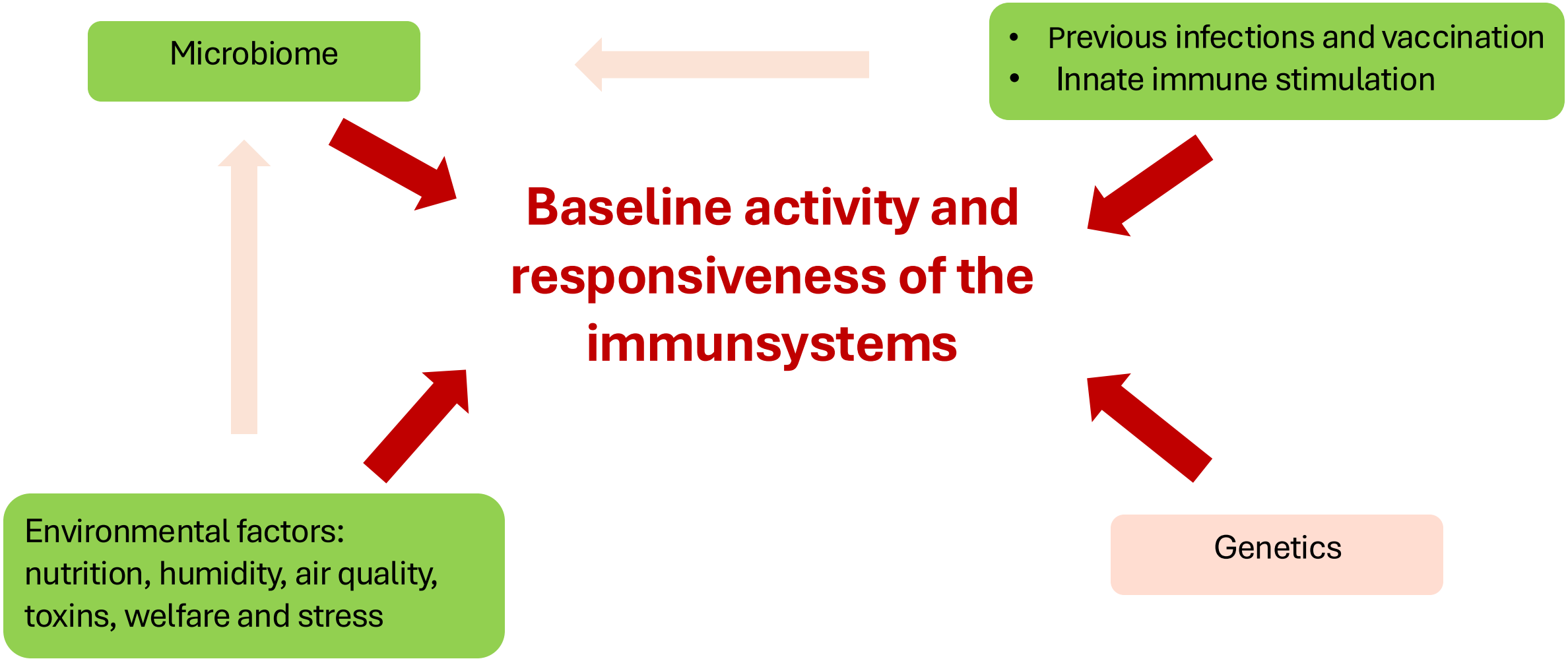
NATIONAL LIVESTOCK & FISHERIES D. P.

What could explain variations in responses to infections?



Problem addressed and possible solutions

Probiotics & prebiotics

- Vaccinations
- immunotherapeutics
- Improved hygiene

- Improved nutrition & husbandry
- Reduce stress and improve animal welfare

Breeding, genetic manipulation

Trained immunity concept

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RESEARCH

REVIEW

INNATE IMMUNITY

Trained immunity: A program of innate immune memory in health and disease

Mihai G. Netea,[1*] Leo A. B. Joosten,[1] Eicke Latz,[2,3,4] Kingston H. G. Mills,[5] Gioacchino Natoli,[6] Hendrik G. Stunnenberg,[7] Luke A. J. O'Neill,[5] Ramnik J. Xavier[8,9]

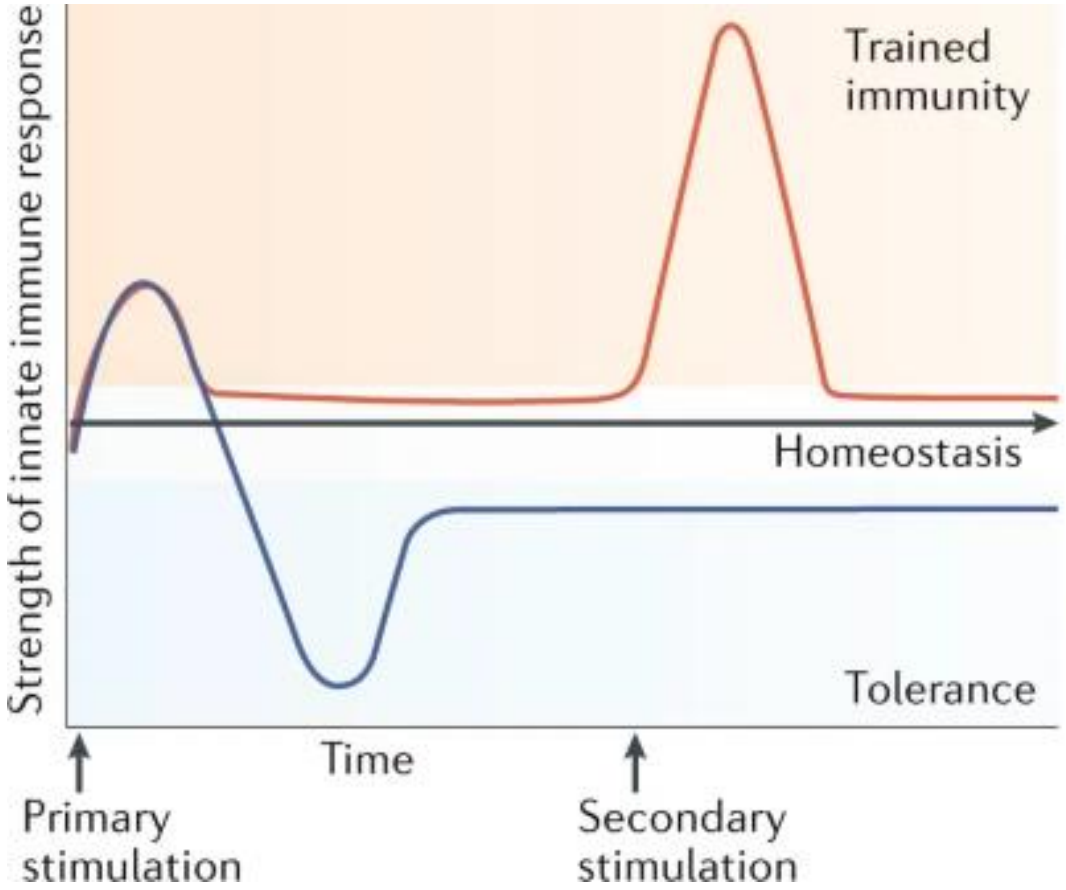
Review

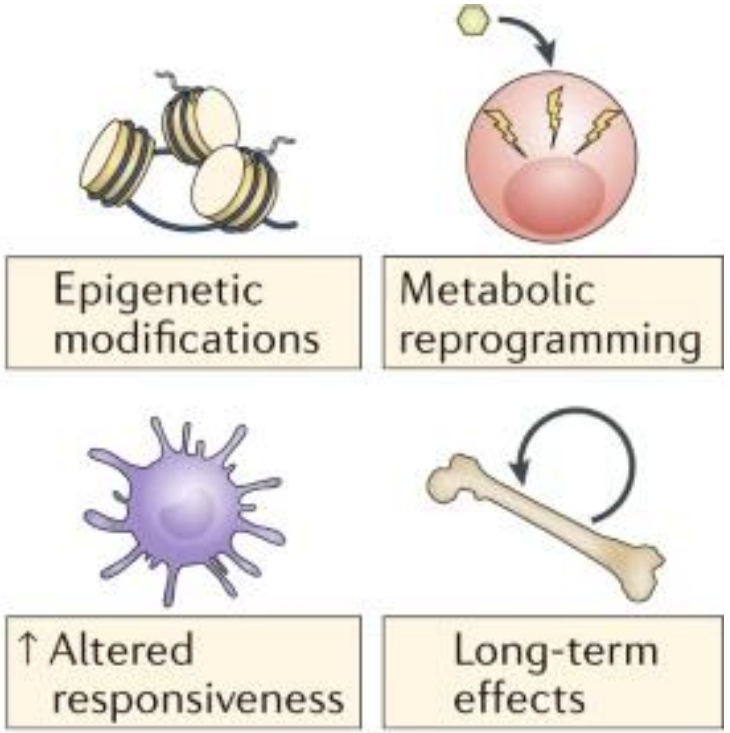
Cell PRESS

A small jab – a big effect: nonspecific immunomodulation by vaccines

Christine S. Benn[1], Mihai G. Netea[2], Liisa K. Selin[3], and Peter Aaby[4]

Innate immune memory concept

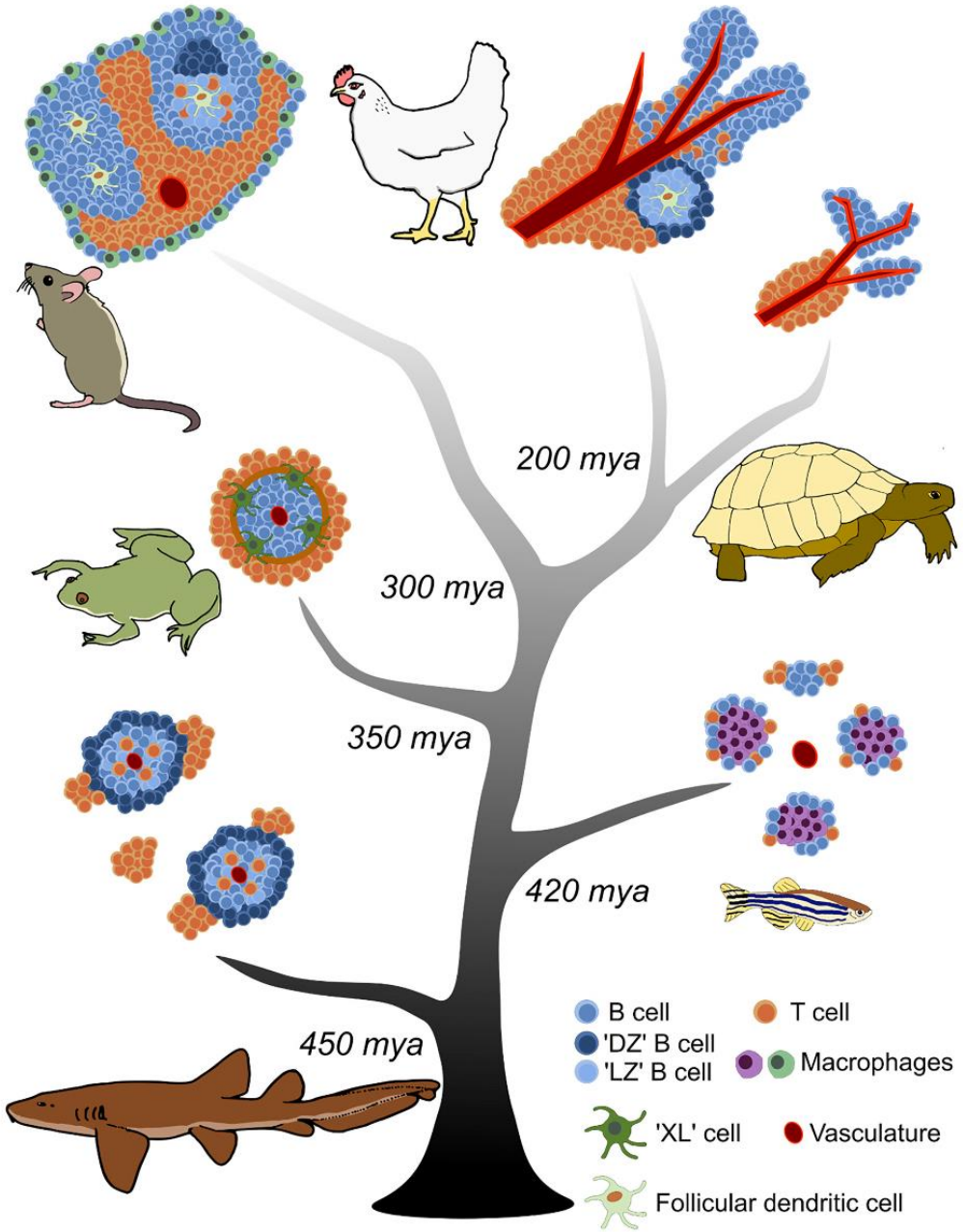




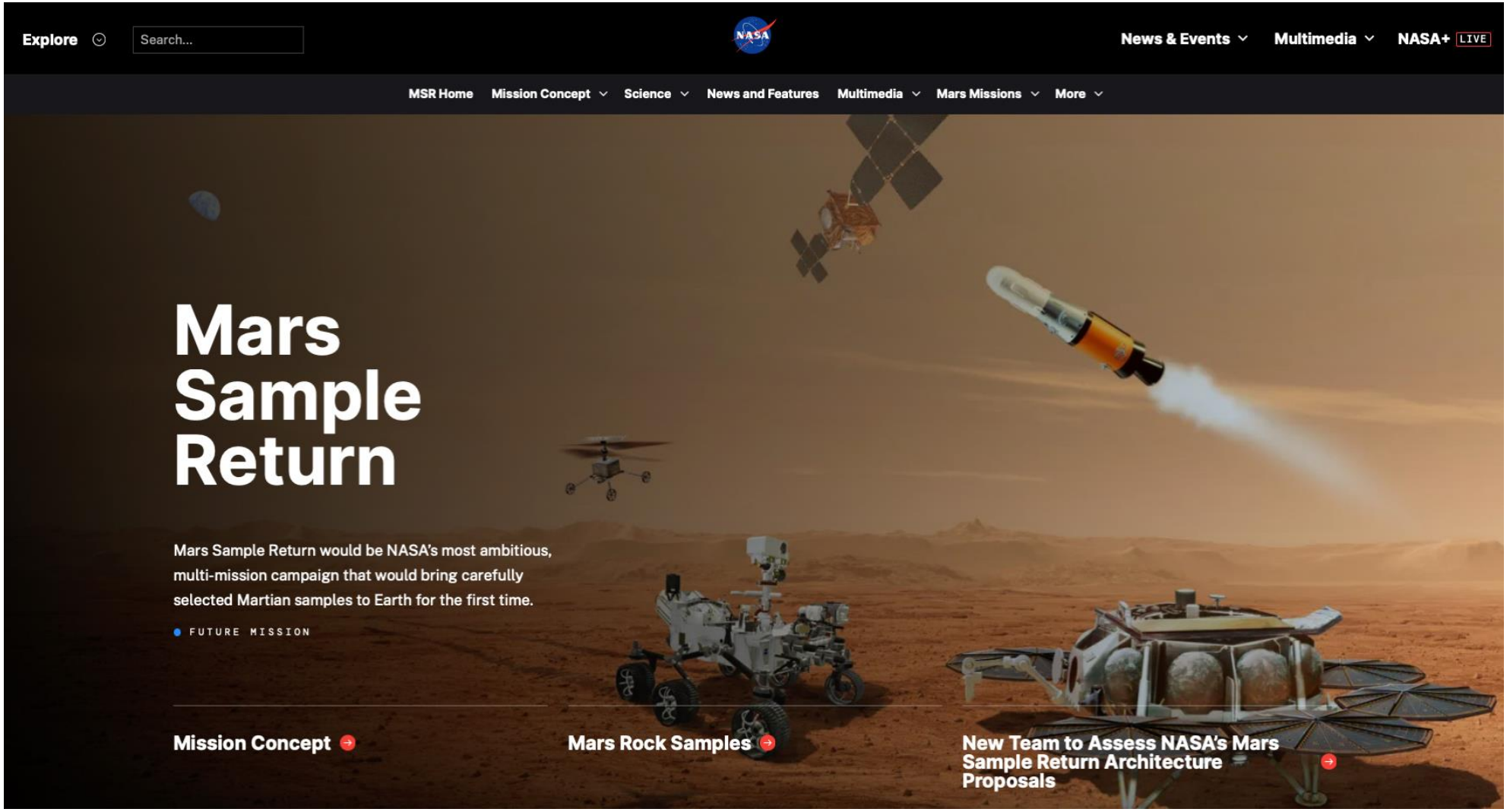
doi.org/10.1038/s41577-020-0285-6

450 Million years of evolution of the adaptive immune system

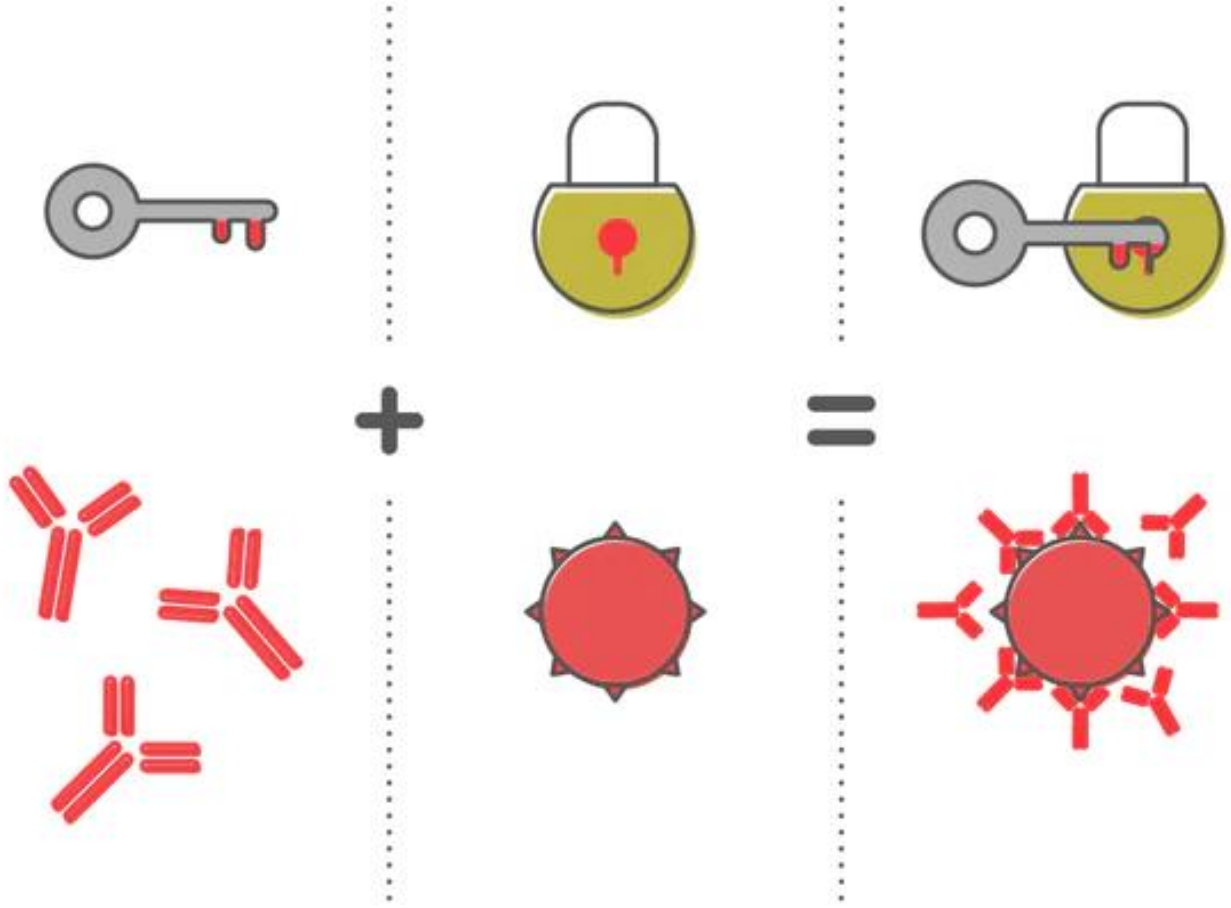
All those animals have B- and T-cells



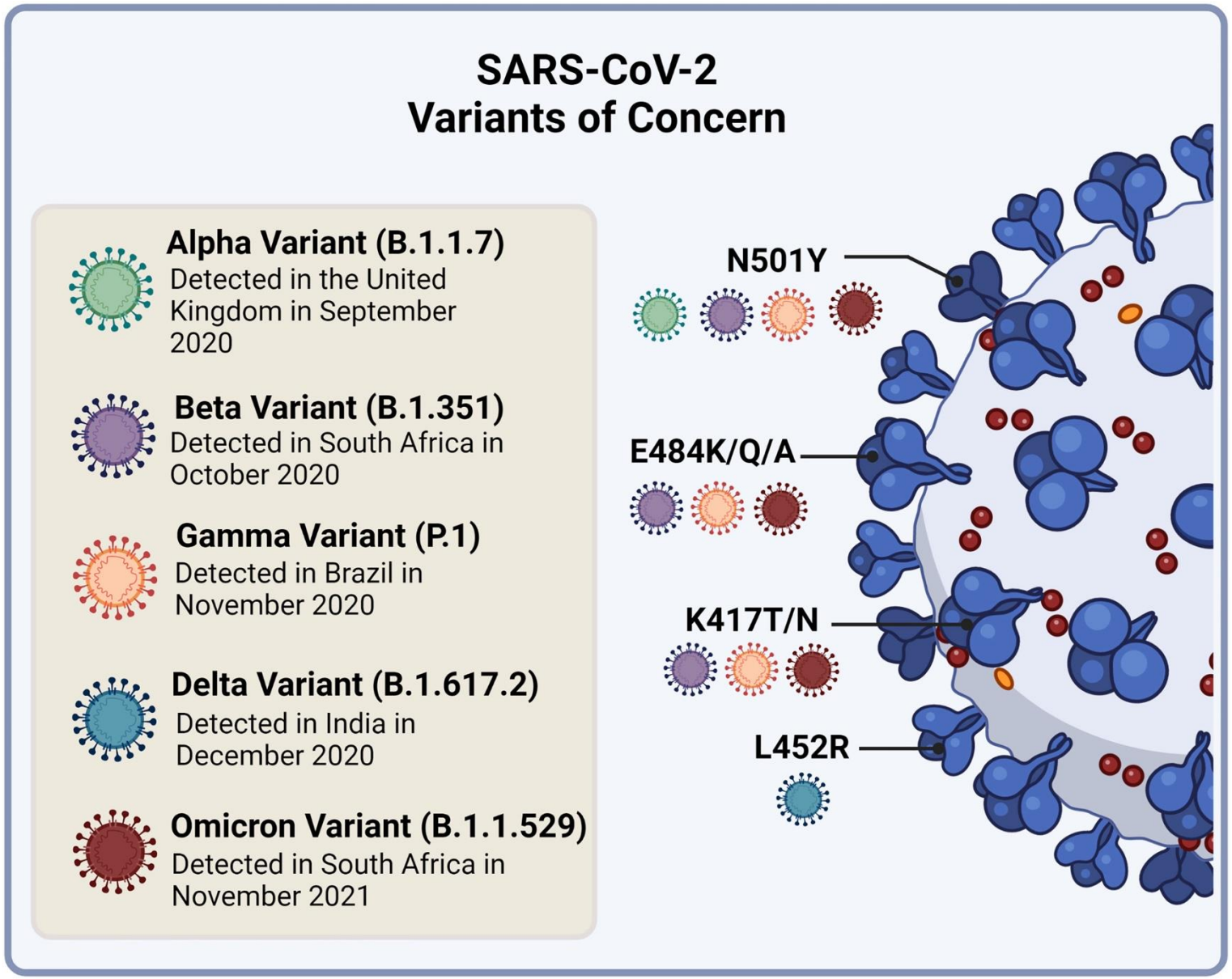
Can our immune system recognize structures it has never seen?



The adaptive immune system is highly specific: an antibody will only bind to well defined antigen on the pathogen



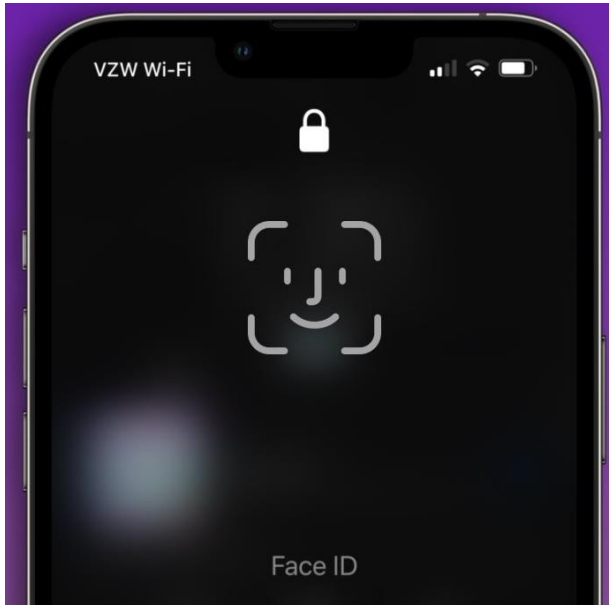
Examples on the level of specificity



10.3389/fimmu.2021.809244

What does the immunsystem have in common with a cell phone?

Find the two incorrect answers!



1. Both have the ability to learn
2. Only a cell phone can differentiate “**self**” from “**non-self**”
3. Both are trained to recognize “**non-self**”
4. Both are trained to recognize “**self**”

The mammalian immunsystem can make 100 000 000 000 (10^{11}) different antibodies potentially reacting with 10^{11} different antigens.

HOW DOES THIS WORK?

1. You inherit the genetic information for this diversity from your parents.
2. You acquire this diversity yourself over the course of your life through contact with many infections or vaccinations.
3. The diversity of antibodies is independent of contact with antigens.

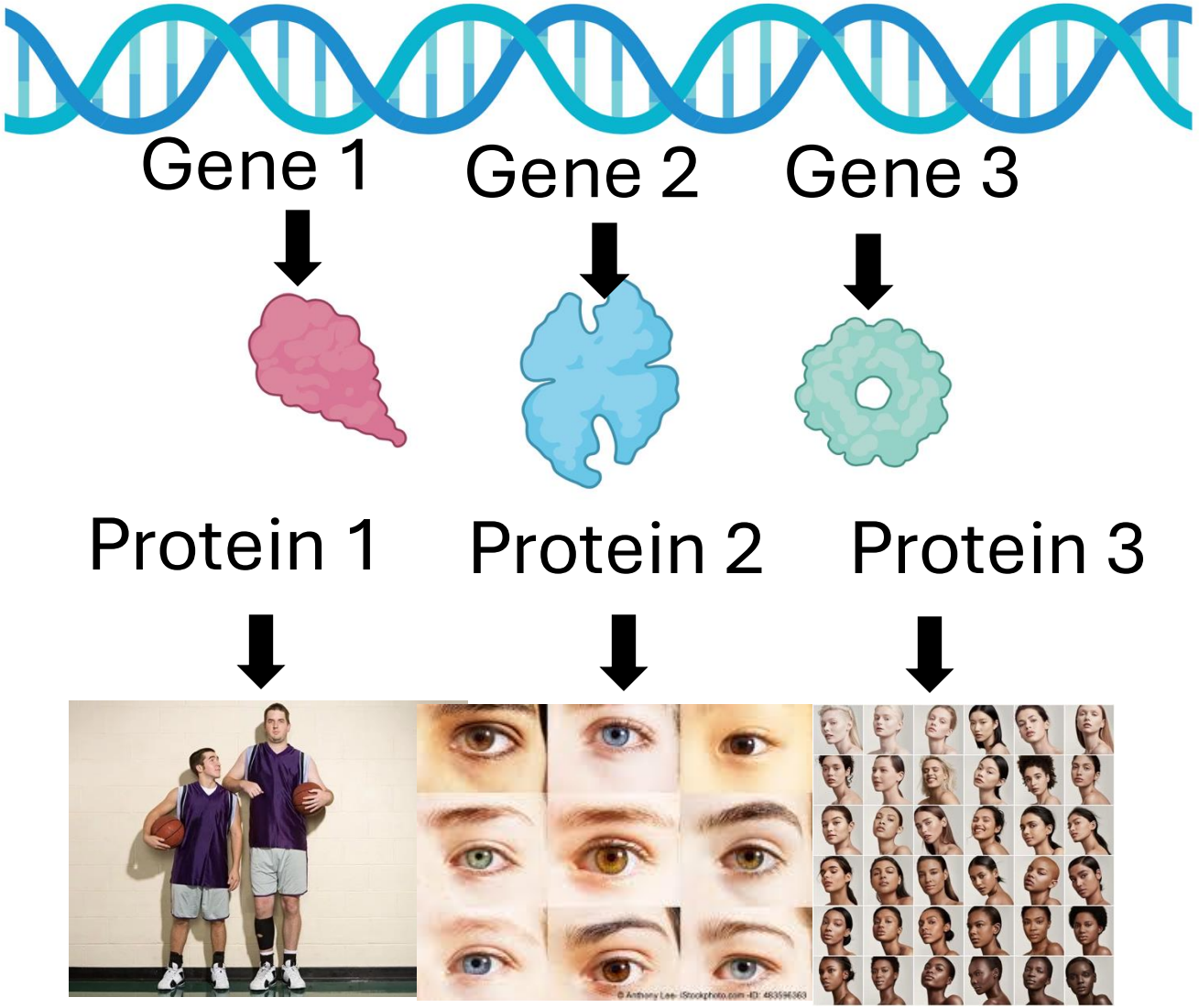
The answer is....

- „The immune system produces “keys” en masse without knowing the matching lock.
- In theory, any conceivable lock can be opened.
- You “only” have to find the right one among trillions of keys.

Next problem: 1 gene → 1 protein → 1 feature

Number of coding genes

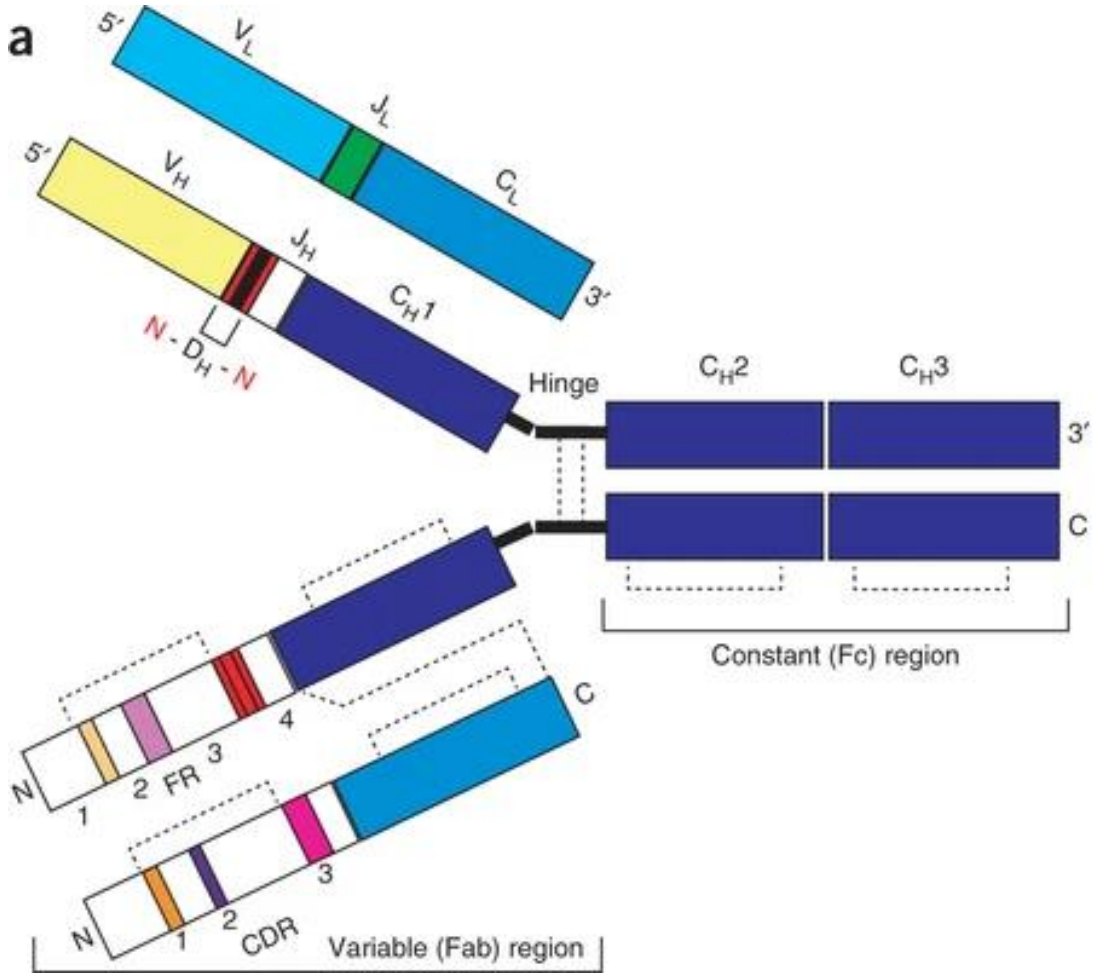
Human genome: 20’000
Camel: 21’000
Sheep: 21’000
Sanderia malayensis : 28’000

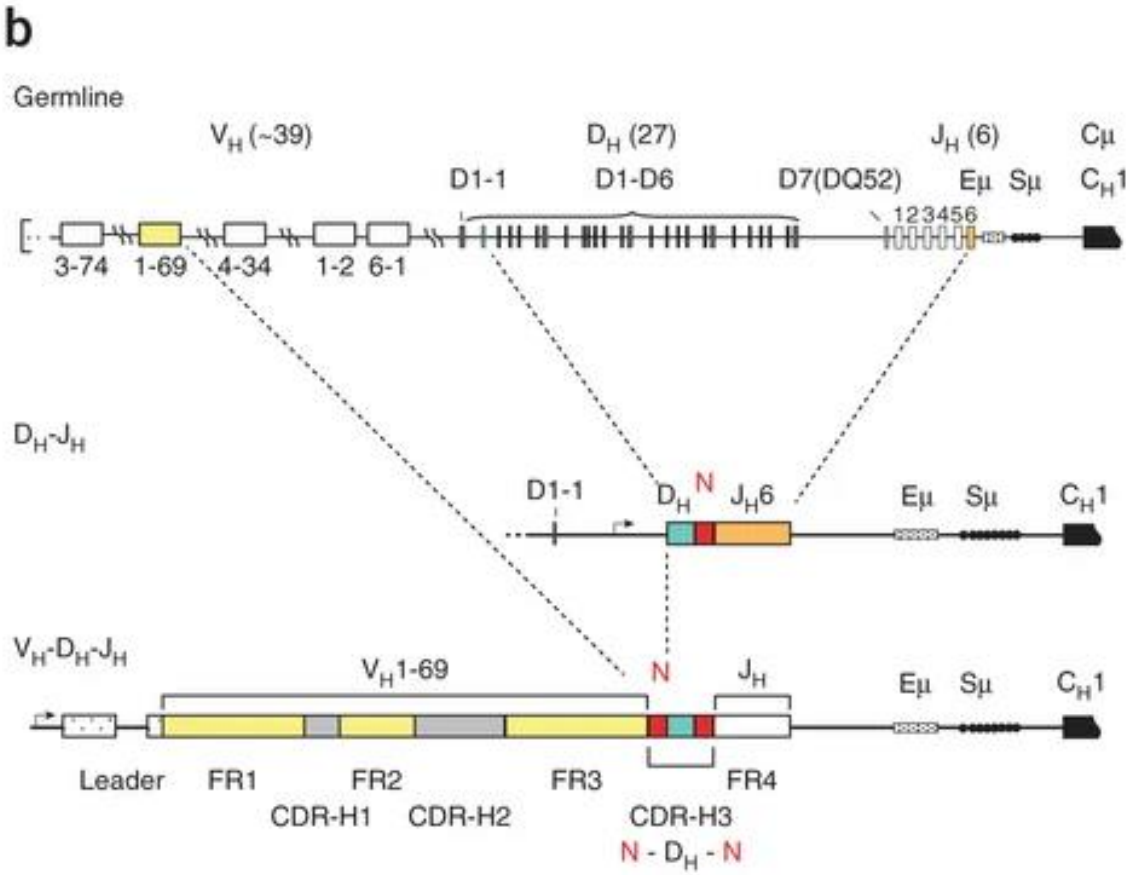


Created with BioRender.com

The lego trick

VDJ recombination fo germline sequences





Nature Biotechnology volume 32, pages 158–168 (2014)

Theoretical diversity of 10^{11}

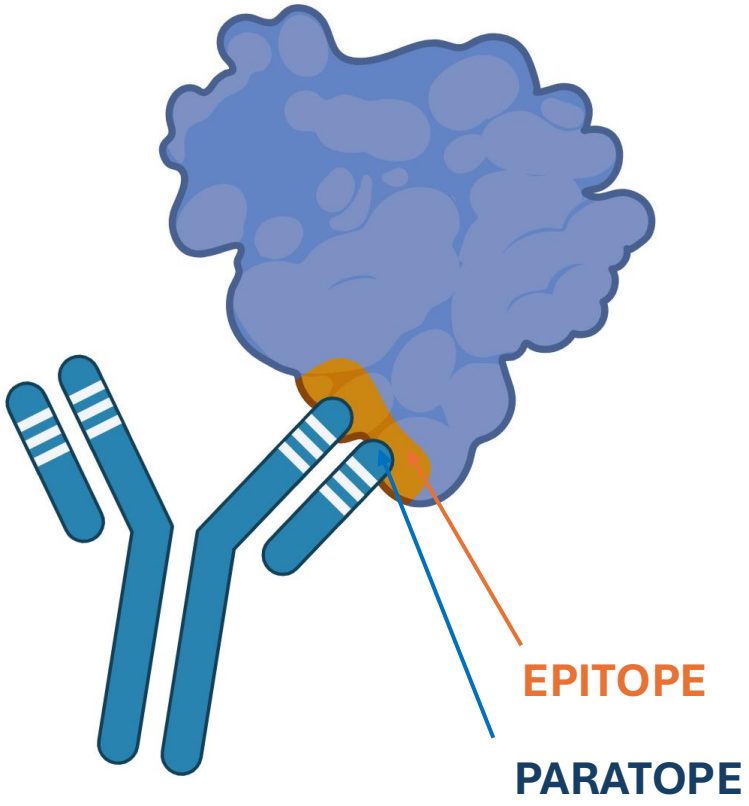
Virus evolution and the adaptive immune system

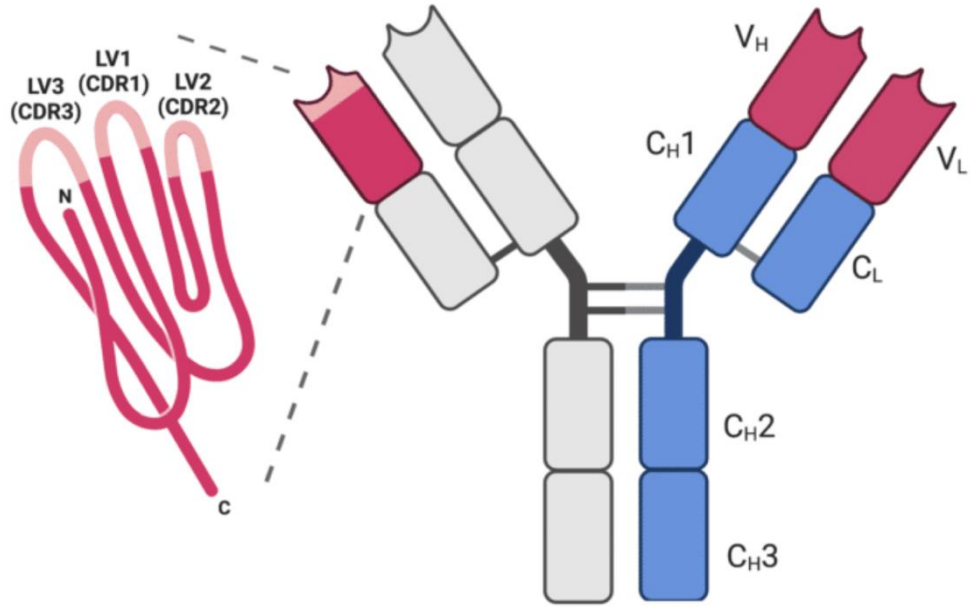
- RNA Viren have a very high mutation rate
- Calculation example for FMDV
  - mutation per replicated genome copy: 1
  - infectious viruses per FMDV lesion: 10^{10}

→ So these are 10 billion theoretical mutations per lesion

→ There is definitively a race between the immune system and the virus

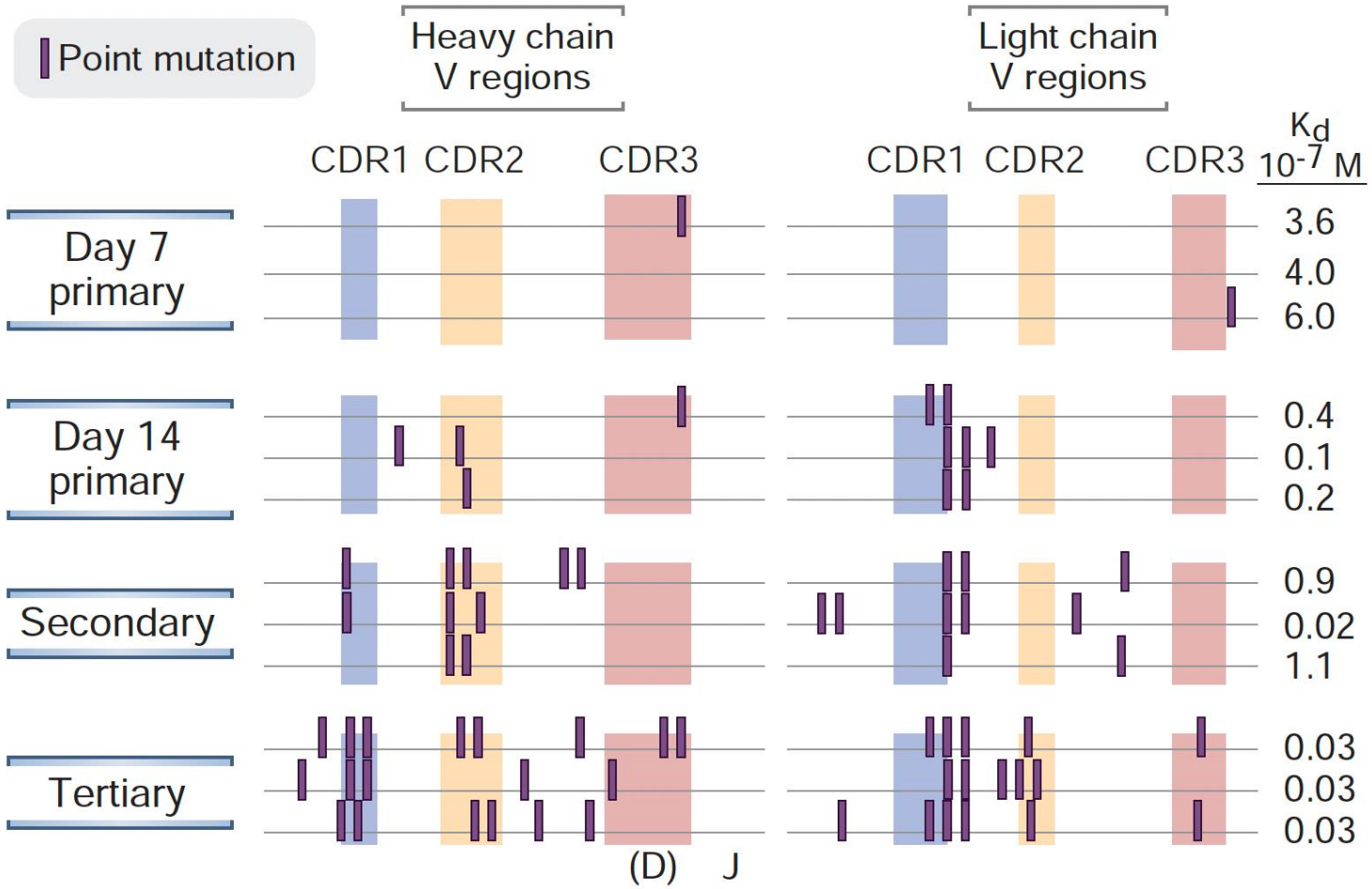
The antigen binding site (paratope) of the antibody formed by the complementary determining regions (CDRs)





https://www.rapidnovor.com/identifying-cdrs-antibody-sequencing/

The response to mutation by the virus is mutation in the CDRs

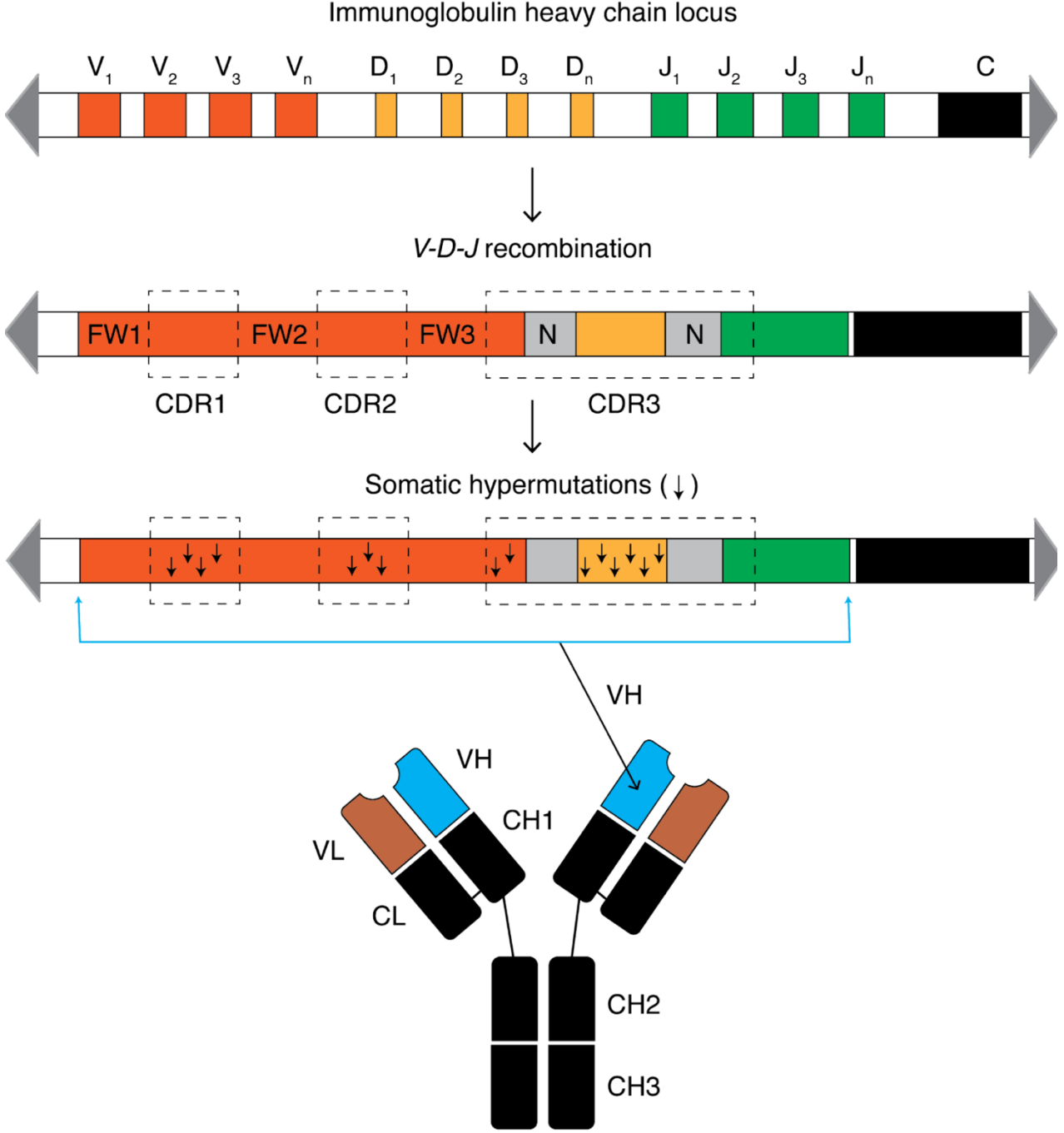


Large species differences in the possible Ig diversity based on VDJ recombination

TABLE 1 | Number of biologically functional (and total) gene segments in different species*.

Species	Vκ IGKV	Jκ IGKJ	Vλ IGLV	Jλ IGLJ	V_H IGHV	D_H IGHD	J_H IGHJ
Mice	**80** (>100)	**4** (5)	**2** (2)	**4** (4)	**>100** (>100)	**16** (31)	**3** (4)
Rats	**>100** (>100)	**5** (6)	**8** (10)	**2** (3)	**>100** (>100)	**25** (35)	**4** (4)
Humans	**44** (>100)	**5** (5)	**32** (>100)	**4** (6)	**45** (130)	**27** (30)	**6** (9)
Pigs	**10** (14)	**2** (5)	**10** (23)	**2** (4)	**10** (25)	**2** (4)	**1** (5)
Goats	**6** (15)	**1** (4)	**25** (63)	**1** (2)	**4** (34)	**2** (4)	**1** (6)
Horses	**19** (60)	**4** (5)	**27** (144)	**4** (6)	**4** (50)	**35** (40)	**8** (8)
Sheep	**8** (13)	**1-NC?**[#] (3)	**14** (43)	**1** (2)	**6** (10)	**4** (2)	**2** (6)
Cattle	**6** (25)	**1-NC**[#] (4)	**24** (63)	**5** (8)	**10** (36)	**9** (23)	**2** (4)
Marsupials	**37** (122)	**2** (2)	**35** (64)	**8** (8)	**21** (25)	**3?** (3)	**2** (6)
Chickens (birds)?	**0**	**0**	**1**[$] (200)	**1** (1)	**1**[$] (100)	**16** (16)	**1** (1)

10.3389/fimmu.2022.823145



Two essential pillars of antibody diversity

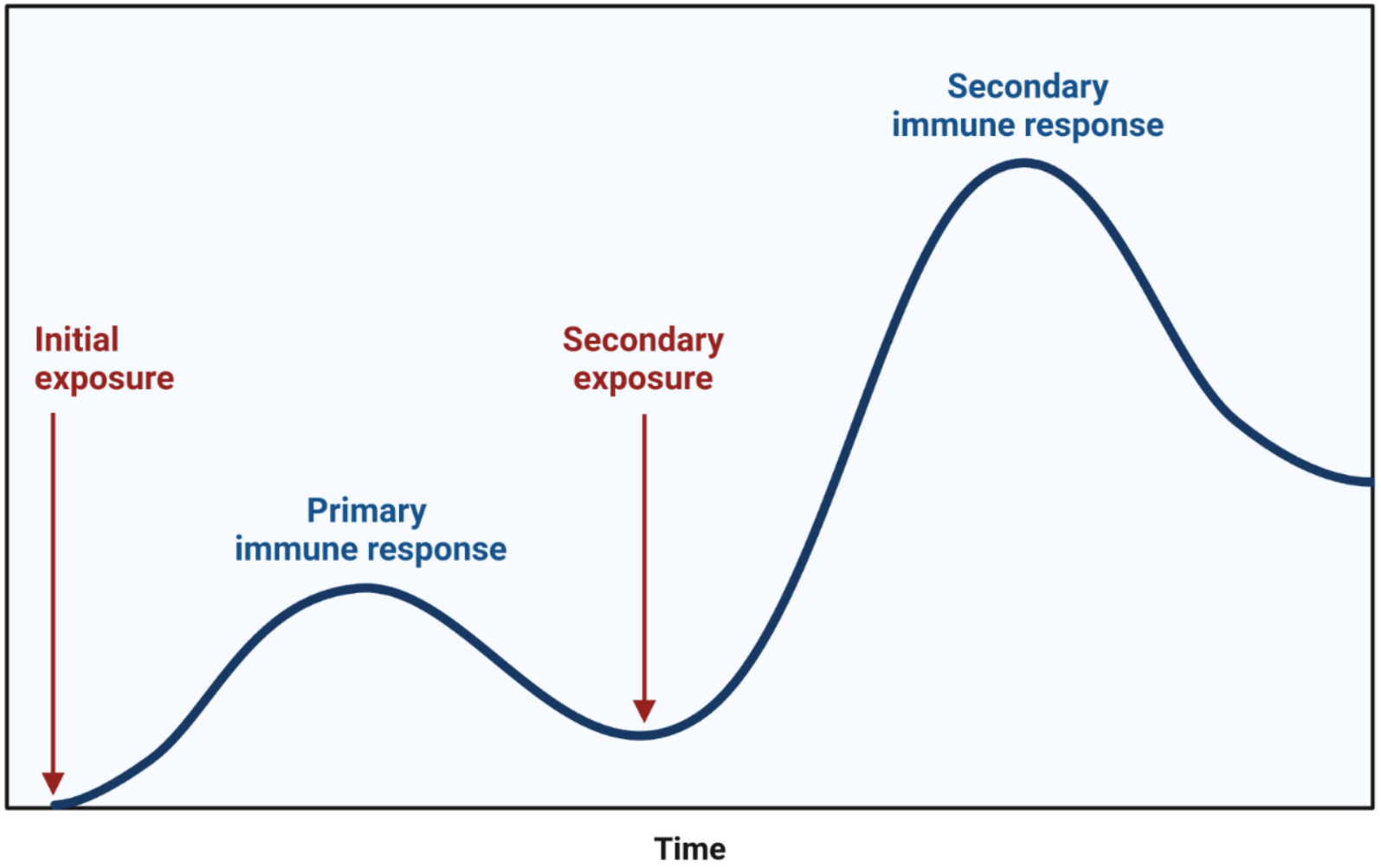
VDJ recombination

+

Somatic hypermutation

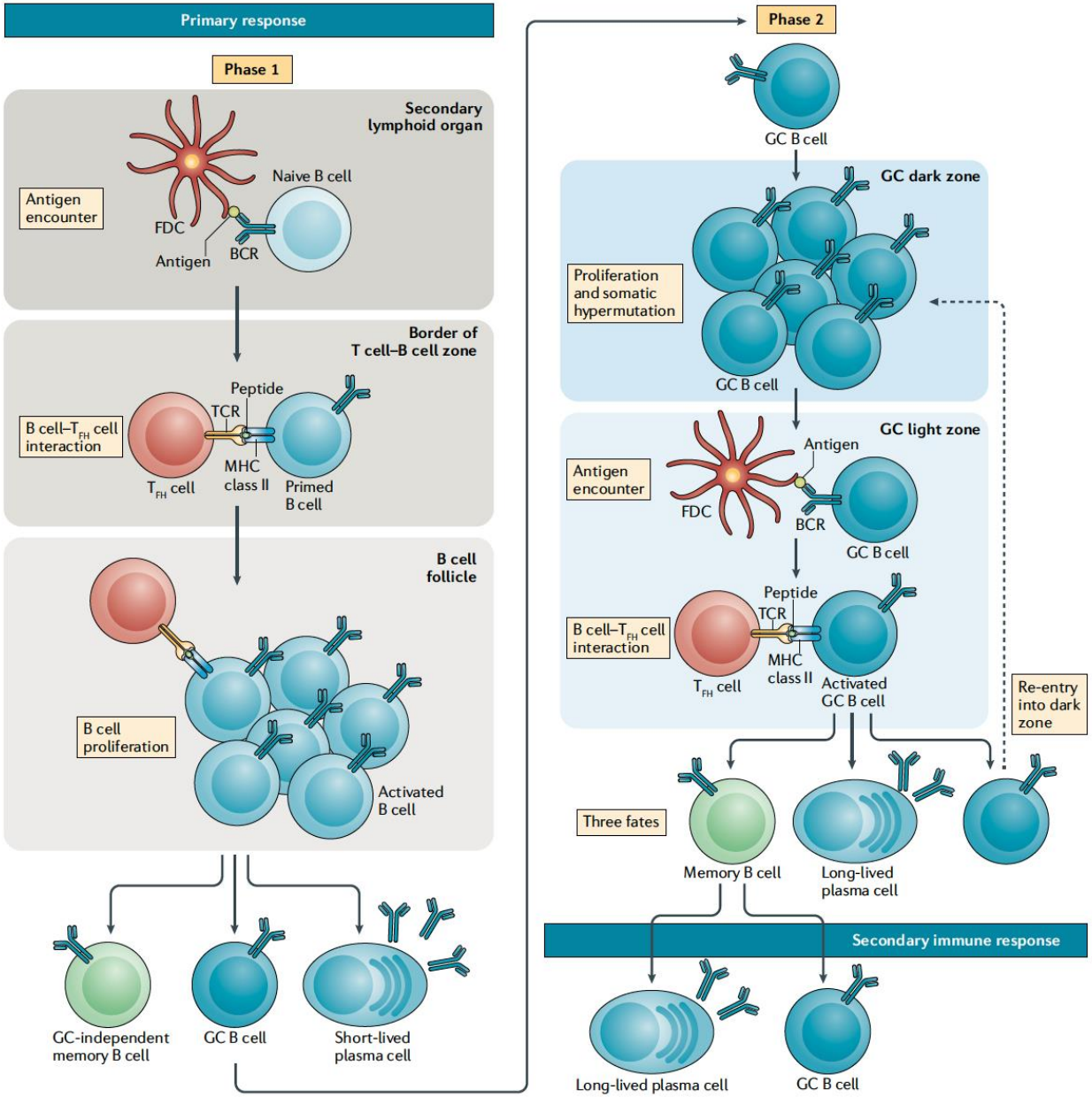
https://en.wikipedia.org/wiki/Somatic_hypermutation

Importance of booster vaccinations



Booster vaccination not only enhance antibody levels...

....But also promote



1. Affinity maturation
2. Generation of long-lived plasma cells
3. Generation of memory cells

- In the secondary immune response, B cells return to the dark zone of the B cell follicle for proliferation.
- Then they move to the light zone for another “round” of stimulation by **T helper cells**

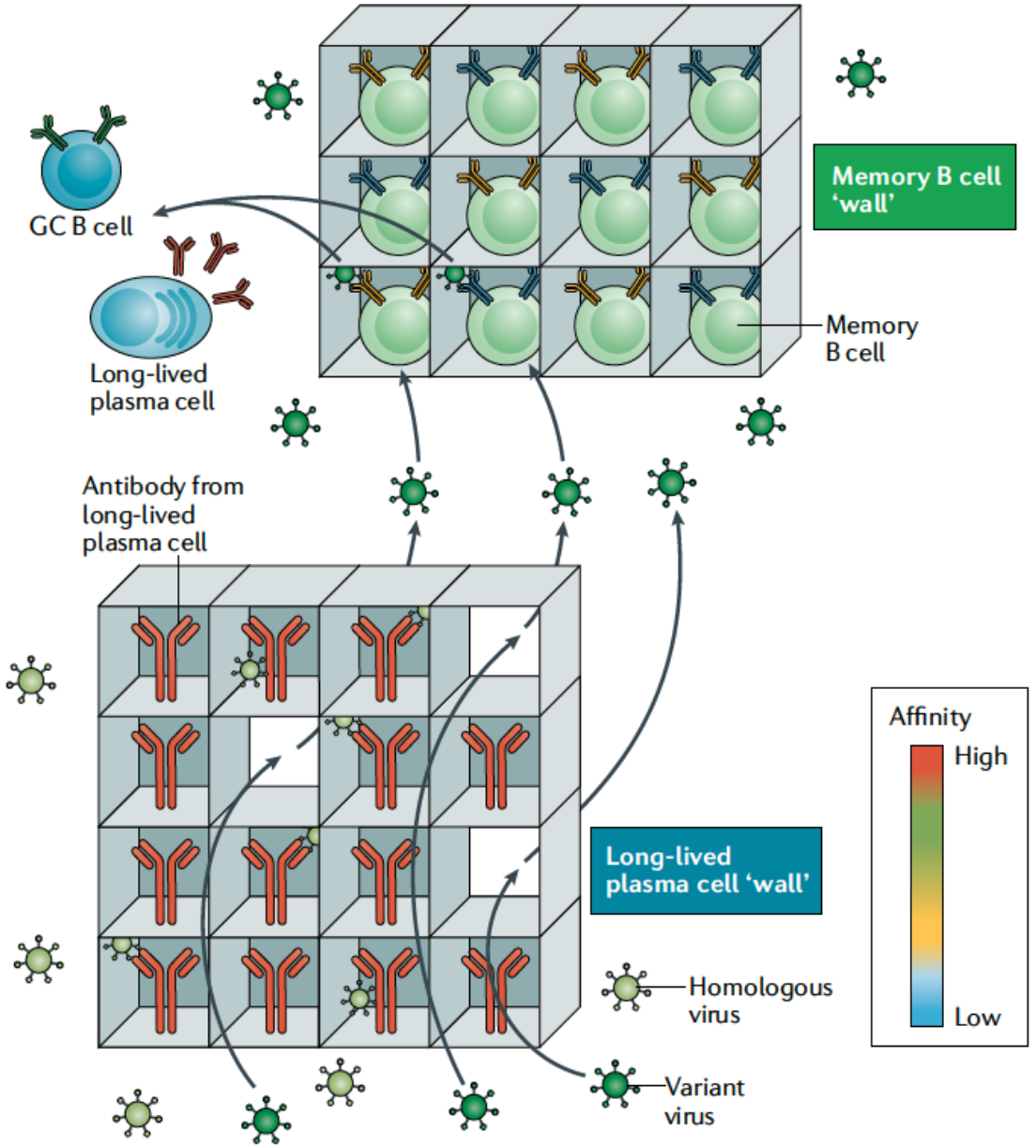
Importance of memory B cells

Antibody “escape” virus mutants arise that can no longer be neutralized.

→ Plasma cell wall will no longer be effective

→ Memory B cells will undergo another round of affinity maturation, allowing them to generate newly adapted plasma cells.

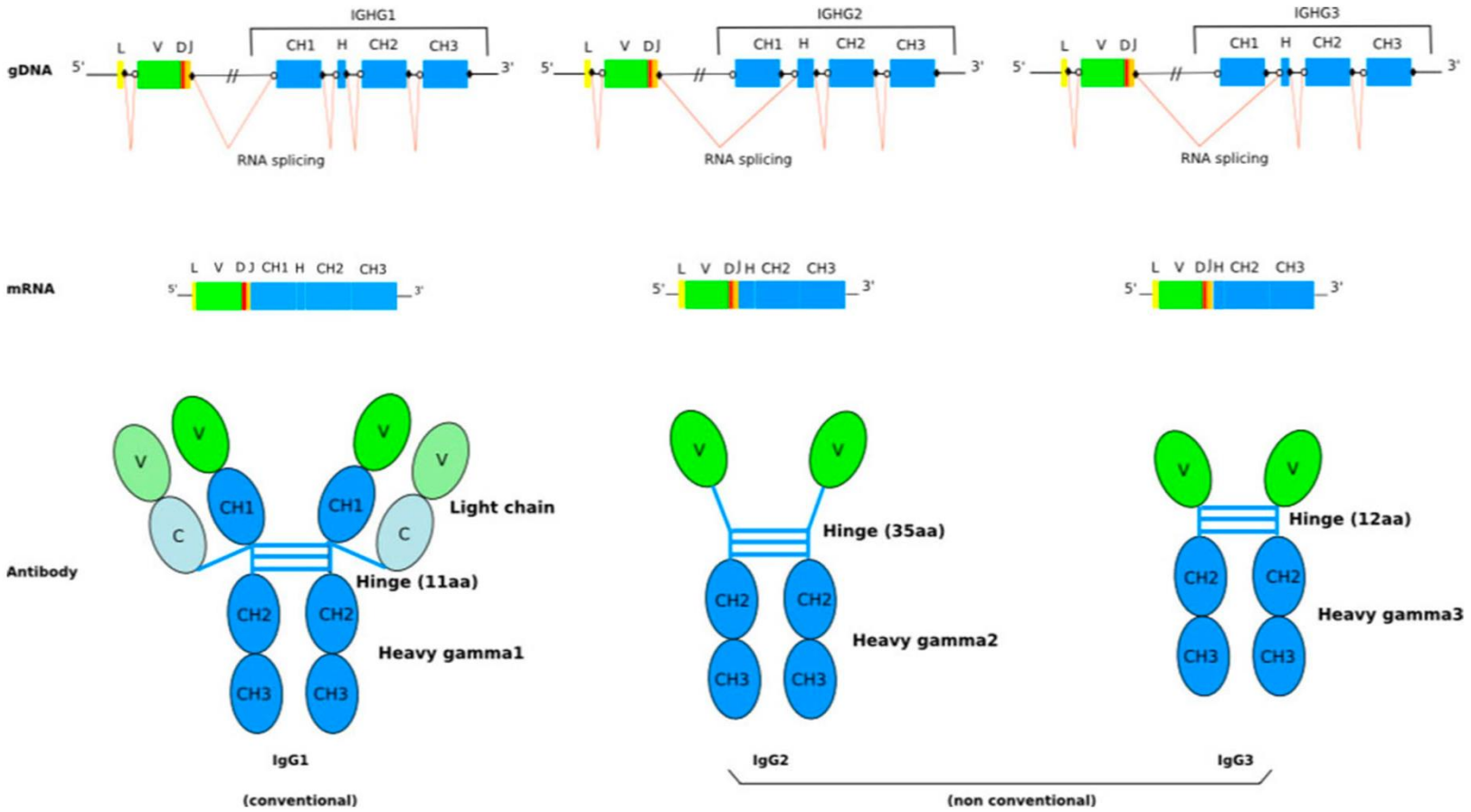
Thus, memory B cells form a second barrier.



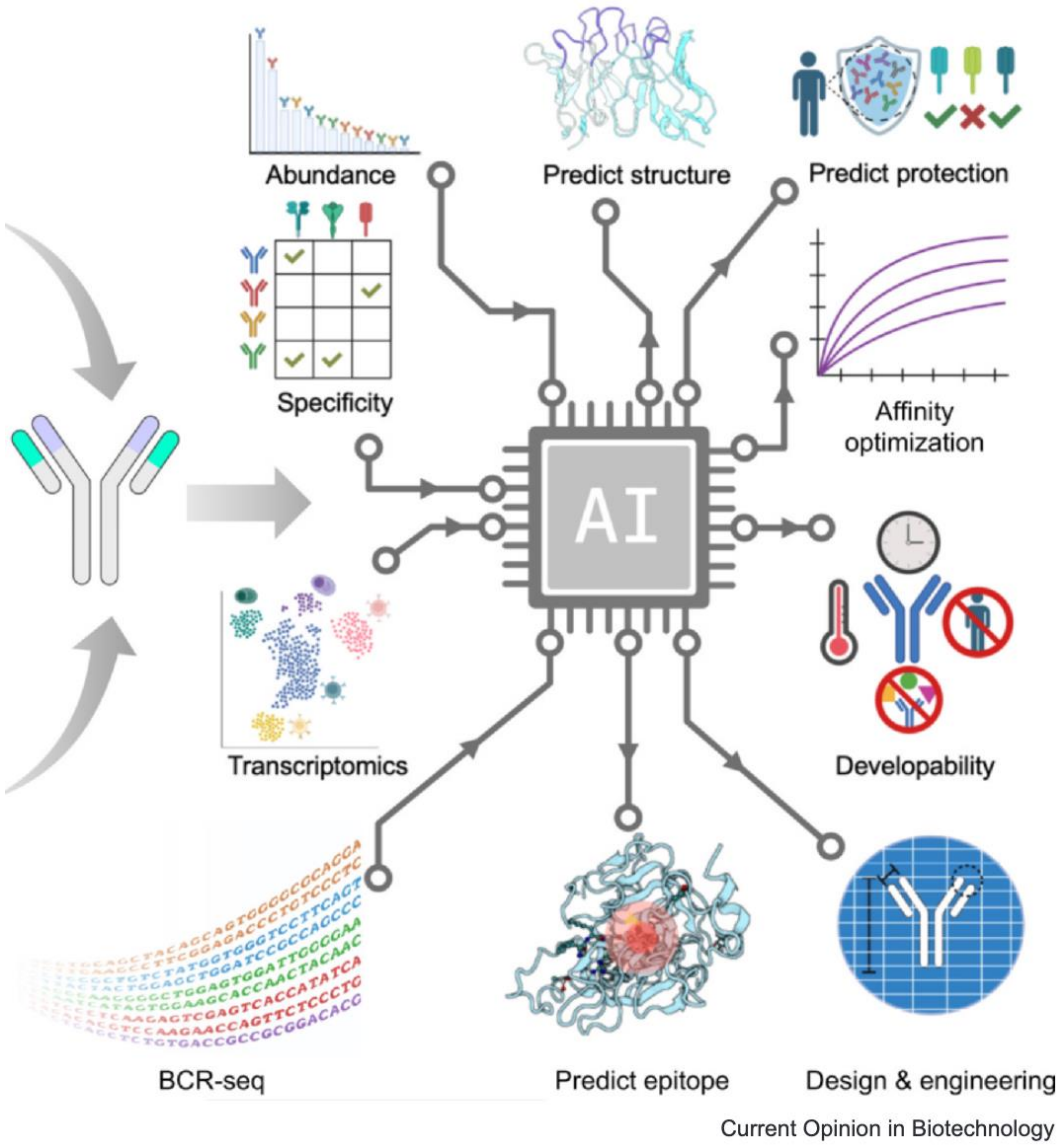
Nat. Immunol 2020; https://doi.org/10.1038/ s41577-019-0244-2

https://www.chemistryworld.com/features/the-incredible-antibodies-of-sharks-llamas-and-camels/4015629.article

Camelid antibodies



New technologies are changing immunology and creating new possibilities



→ Predict antibody structure
→ Predict epitope
→ Develop vaccine
→ Engineer high affinity antibodies

Adapted from Current Opinion in Biotechnology 2024, 86:103082.

Conclusions

- Enhancing resilience against infections should apply a holistic approach using vaccination, improved husbandry, innate immune training, microbiome targeting, and genetics.
- During embryogenesis and early life, adaptive immune receptors are made in such as variety that they can recognize almost every antigen. The mechanism of generating diversity is species dependent.
- Second rounds of B-cell stimulation are required for generation of long-lived plasma cells, affinity maturation and memory B cells. The latter are important for duration of immunity and protection against escape mutants.
- There are considerable differences in antibody biology amongst veterinary species which may impact vaccination and diagnostic tests.
- In future, next generation sequencing of adaptive immune repertoires together with AI tools will enabling exiting possibilities to develop new diagnostics, vaccines and treatment options. But we need to invest in veterinary species.