Game over for viruses: how Pokémon-like nanobodies can defeat future pandemics

Àlex Müller Bort[1, 2]

[1]Department of Biotechnology and Biomedicine, Technical University of Denmark

[2]Faculty of Biology, University of Barcelona

Pokémon are known by almost everyone. Even those who haven't played their games, like Pokémon GO or the classical Nintendo versions, probably have heard of them before. The same can't be said for antibodies: although we all have them in our bodies, not many people know what they are or do. And even fewer have heard of nanobodies. But it might be time to get to know them, as they will be important in the fight against future pandemics.

Introduction: The Immune System's Pokémon Trainers

As a Gen Z-er, I've often played Pokémon GO. One of the main ways to win big rewards is to select six champions to fight against a boss. Each champion has a special ability, which works particularly well against a specific type of enemy. So, to win the fight, you don't necessarily need the biggest or fiercest champions, but rather those best suited to fight each opponent. In our bodies, something similar happens: our immune system is made up of millions of cells and molecules that defend us against a wide range of threats, ranging from viruses to cancer. However, the kind of cells and molecules responsible for keeping us healthy differ depending on the objective. Even the best champions effective against a virus almost certainly are powerless against a bacterial infection.

Antibodies are one type of molecules involved in the immune response. These large molecules can recognize and bind to specific proteins. Once an abnormal molecule is detected, for example a viral protein, multiple antibody variants are produced against it, each being slightly different. The body selects the ones that show the best binding to the target while simultaneously ensuring they do not attack our own body, which could lead to allergy or autoimmune diseases. After a long process, the antibodies are released into the bloodstream, where they navigate the body until they find the affected area. Once they bind to their target, they can work both as a GPS for other cells - guiding them to join the fight against the threat- or directly neutralize the target (1).

Fact Box – Recombinant heterologously expressed antibodies

- When antibodies are synthesized, they have a specific target. By using genetic engineering, scientists produce what's known as 'recombinant' antibodies—designed to hit exactly the spot we want.
- The term heterologously expressed means that the protein is produced in an organism that isn't the original one. For example, if yeast produce antibodies originally from humans.

During recent decades, recombinant antibodies have been widely used in the biomedical world for their characteristics. For example, they can bind to cancer cells and help direct immune cells to eliminate the tumor(2). Additionally, antibodies can be attached to a fluorescent marker, enabling the visualization of the exact location of a target protein within a cell (1).

The Evolution of Antibodies: V_HHs, the second-generation Pokémon

Just like Pokémon, antibodies can "evolve". This has happened in species from the Camelidae family (like camels and alpacas) and in sharks, which have structurally different antibodies in comparison to humans. Not only do they have conventional antibodies, but also heavy-chain-only antibodies, which are approximately half the size. From these, the binding domain can be isolated, and it can function independently. The result is a molecule with binding properties that is only approximately a tenth of the size of a human antibody. When it's produced recombinantly in the laboratory, it's called a recombinant V_HH, popularly known as nanobody (3).

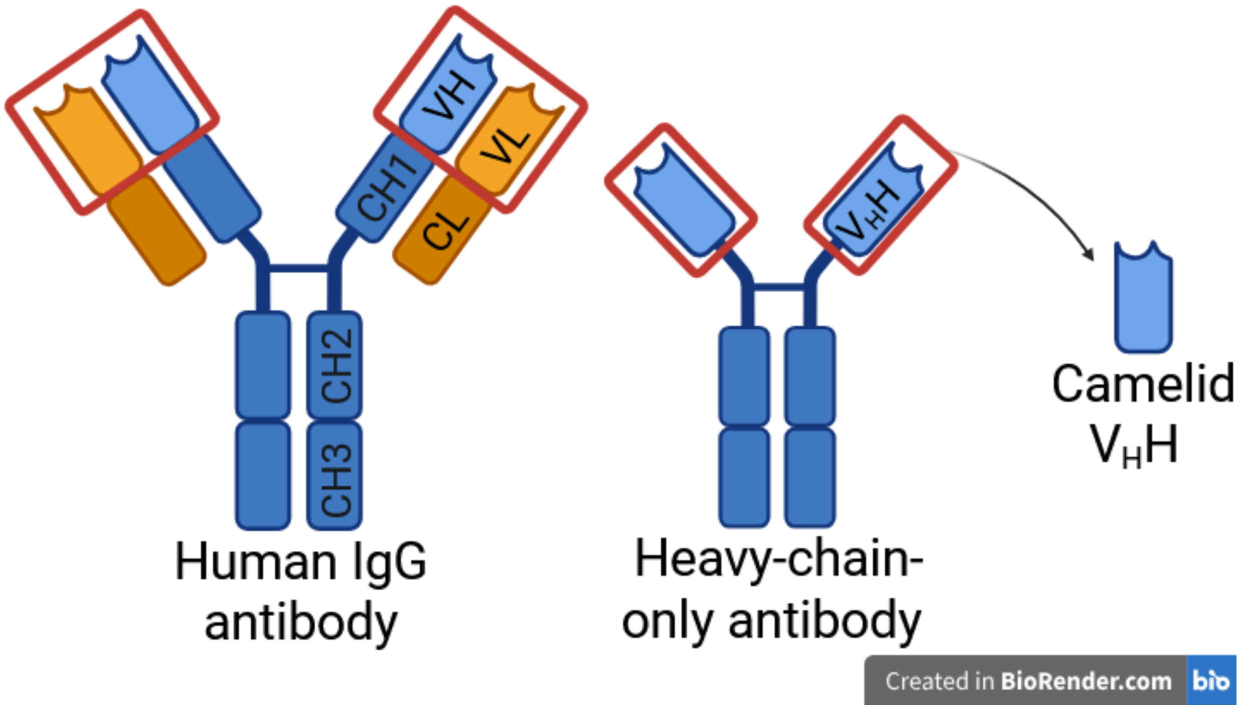

Figure 1: Size and characteristics comparison between antibodies and nanobodies. On the left, we see a common IgG human antibody, made of two heavy chains (in blue) and two light chains (in orange). Both types have constant regions: 3 in the case of the heavy IgG chain (named CH1, CH2, CH3), and only one region in the case of the light chain (CL). Both chains have a variable domain (VH and VL), which are the binding domains (red squares; regions that bind to the target). In comparison, the camelid heavy-chain-only antibody only has two heavy chains, composed of one variable domain (V_HH) and two constants. The V_HH of the heavy-chain-only antibody can be separated and attach to proteins on its own.

This small size makes them perfect for squeezing into small spaces. V_HHs are not only smaller but also more stable: they can withstand boiling up to 90 degrees (4). Both size and stability, while maintaining a high affinity, make nanobodies strong candidates for achieving tasks that conventional antibodies cannot. Furthermore, nanobodies have better tissue penetration and can reach proteins that can't be detected with antibodies. Lastly, they are also easier to produce in the laboratory and in larger scale, which makes them even more valuable (5).

One of the most exciting uses of nanobodies is the fight against pathogens. Those troublemakers have always been a serious threat, but new and more devious microbes continue to emerge. The last one was the coronavirus, and although it caused irreversible damage, it also pushed biomedical research forward. The most known and important milestone is the production of mRNA vaccines, but there was also a focus on producing a "cure" against COVID once one got infected.

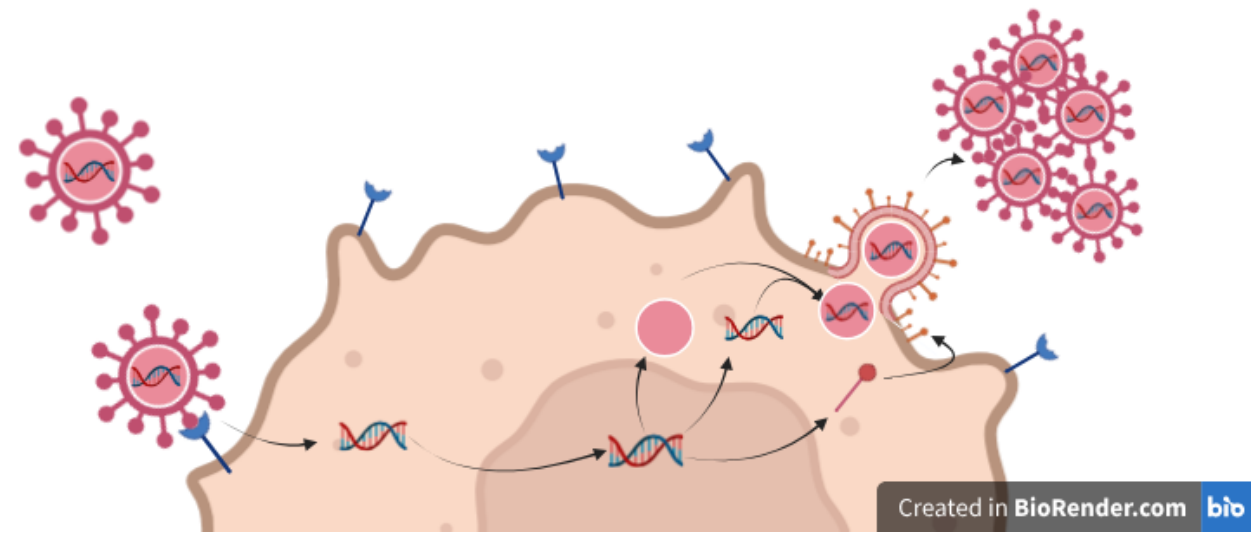

Figure 2: Viruses need to enter a host cell in order to reproduce. The spike protein (in red) is what enables the coronavirus to enter human cells. It attaches to the human protein ACE2 (in blue), located in cells from the lungs, blood vessels and others, guiding the virus to enter the cell to make new coronavirus particles that can further infect new cells (6).

One of the products ended up being a nose spray made with nanobodies. Once in the body, they start binding to the spike protein from the coronavirus. That blocks the virus from attaching to the human cell, making it impossible for the virus to enter it. The nanobodies hinder the replication of the virus and eventually lead to the recovery of the patient (6).

Final Showdown: Divalent Nanobodies against the Mutating Virus

Viruses have mastered the art of evasion via mutations. In the case of coronavirus, the mutations occur especially in the spike protein. When such changes are substantial, nanobodies that were previously effective might not recognize the new variant, losing their protective properties. Luckily, nanobodies can be shaped to fight against multiple variants at the same time.

Imagine that now you can battle with two allied Pokémons at the same time in order to defeat the boss. This is what divalent nanobodies do, combine the specificity, neutralization and power of two nanobodies. That's because they are "simply" two nanobodies united with a small linker. Each nanobody in the construct can unite to a different protein, but in our case, it detects two different variants of the spike protein. That way, you could be protected from the omicron and the beta coronavirus variants at the same time (6).

This technique has gained popularity during the last few years, as it has been used in various fields, including as a scorpion antivenom or with other viruses like HIV (7,8). In the future, it may be key to fight against other pandemics. A broad spectrum of activity, high stability, low costs, as well as very high efficiency make it perfect for fighting against the COVID 2.0.

Conclusion: Evolving Our Defences

Nanobodies could be the future of biomedicine. Just like unlocking a secret attack in a game, nanobodies are redefining the gameplay against viruses. But the fight doesn't stop here. Divalent nanobodies are an innovative solution in a game that is being constantly updated. Maybe in a few years, a newer and better defence mechanism will appear and revolute the world again. Or the production of nanobodies will be so optimized that there is no need for conventional antibodies. Either way, only time will tell. But if newer outbreaks occur, even with upgraded bosses, remember that Pokémon-nanobodies could have a cure against it.

1. Jenni Punt, Sharon Stranford, Patricia Jones, Judy Owen. Kuby Immunology 8e [Internet]. 2018 [cited 2025 Apr 23]. Available from: http://archive.org/details/kied8

2. Paul S, Konig MF, Pardoll DM, Bettegowda C, Papadopoulos N, Wright KM, et al. Cancer therapy with antibodies. Nat Rev Cancer. 2024 Jun;24(6):399–426.

3. Muyldermans S. Nanobodies: Natural Single-Domain Antibodies. Annual Review of Biochemistry. 2013 Jun 2;82(Volume 82, 2013):775–97.

4. Kinoshita S, Nakakido M, Mori C, Kuroda D, Caaveiro JMM, Tsumoto K. Molecular basis for thermal stability and affinity in a VHH: Contribution of the framework region and its influence in the conformation of the CDR3. Protein Sci. 2022 Nov;31(11): e4450.

5. Jin B kyung, Odongo S, Radwanska M, Magez S. NANOBODIES®: A Review of Diagnostic and Therapeutic Applications. International Journal of Molecular Sciences. 2023 Jan;24(6):5994.

6. Koenig PA, Das H, Liu H, Kümmerer BM, Gohr FN, Jenster LM, et al. Structure-guided multivalent nanobodies block SARS-CoV-2 infection and suppress mutational escape. Science. 2021 Feb 12;371(6530):eabe6230.

7. Hmila I, Saerens D, Ben Abderrazek R, Vincke C, Abidi N, Benlasfar Z, et al. A bispecific nanobody to provide full protection against lethal scorpion envenoming. FASEB J. 2010 Sep;24(9):3479–89.

8. Montefiori DC. Bispecific Antibodies Against HIV. Cell. 2016 Jun 16;165(7):1563–4.