CANCER RESEARCH

VHH *Nanobodies*

How nature's smallest antibody fragments could transform targeted cancer treatment, and what they might offer for glioblastoma, the deadliest brain cancer



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ABSTRACT

Camels, llamas and alpacas make unusually small antibodies whose target-binding fragment, the VHH domain, works on its own. This article explains how these nanobodies are produced, why their size, precision and stability make them promising for diagnosis, targeted drug delivery and immunotherapy, and what they might offer for glioblastoma, while noting that clinical testing in brain tumours is still largely ahead of us.

KEYWORDS Nanobodies · VHH · Cancer · Glioblastoma · Immunotherapy

THE STORY BEHIND NANOBODIES

Picture a camel at dawn, kneeling beside a desert well, as its ancestors have done for thousands of years while carrying people and goods across harsh land. Few would guess that its blood holds a medical secret: the VHH nanobody, an antibody fragment so small that it can slip into places where ordinary antibodies struggle to go.

Antibodies are natural defence molecules made by the immune system. They recognise targets such as viruses, bacteria and abnormal proteins. Antibody drugs have also become important in cancer treatment, but their large size can limit how well they reach certain tissues and tumour regions. This is where nanobodies may help.

A GIFT FROM THE CAMEL

The camel holds a special place in many cultures, including the Arab and wider Muslim world, and in the Quran, which invites people to reflect on how the camel was created (Surah Al-Ghashiyah, 88:17). Science has since found something remarkable in its blood. In 1993, Belgian researchers discovered that dromedary camels make a special type of antibody with only heavy chains and no light chains. (Most animals, including humans, have both.) Llamas and alpacas, close relatives, make them too.

The part that recognises the target, the VHH domain, works perfectly well on its own. It weighs only about 12– 15 kilodaltons (kDa), a measure of molecular size, against about 150 kDa for a conventional antibody, so a nanobody is roughly ten times smaller.

DID YOU KNOW?

Nanobodies are among the smallest antibody-based molecules able to recognise a specific target with high precision.

FROM CAMEL BLOOD TO THE LABORATORY

Making a nanobody starts with immunisation: a camel receives a harmless sample of the target, such as a tumour protein, and its immune system responds. Scientists then take a blood sample, extract genetic material from the immune cells, and copy the VHH genes.

These genes are placed into bacteria-infecting viruses called phages, creating a huge "library" of different nanobodies. Researchers fish out the phages whose nanobodies stick to the target. The chosen genes are then inserted into bacteria or yeast, which act as tiny factories, and the nanobodies are purified and tested.

WHY DO TINY ANTIBODIES MATTER?

Size is only part of the story. Nanobodies offer several attractive features:

- **Small size:** may reach tissues and tumour regions that larger molecules cannot.
- **High specificity:** can recognise particular disease-related molecules.
- **Good stability:** many tolerate heat and harsh conditions better than conventional antibodies.
- **Simple production:** can be made in bacteria or yeast, usually more easily than conventional antibodies.
- **Flexible design:** can be joined to drugs, imaging labels or other nanobodies.

Together, these traits make nanobodies promising for diagnosis, targeted treatment and immunotherapy.

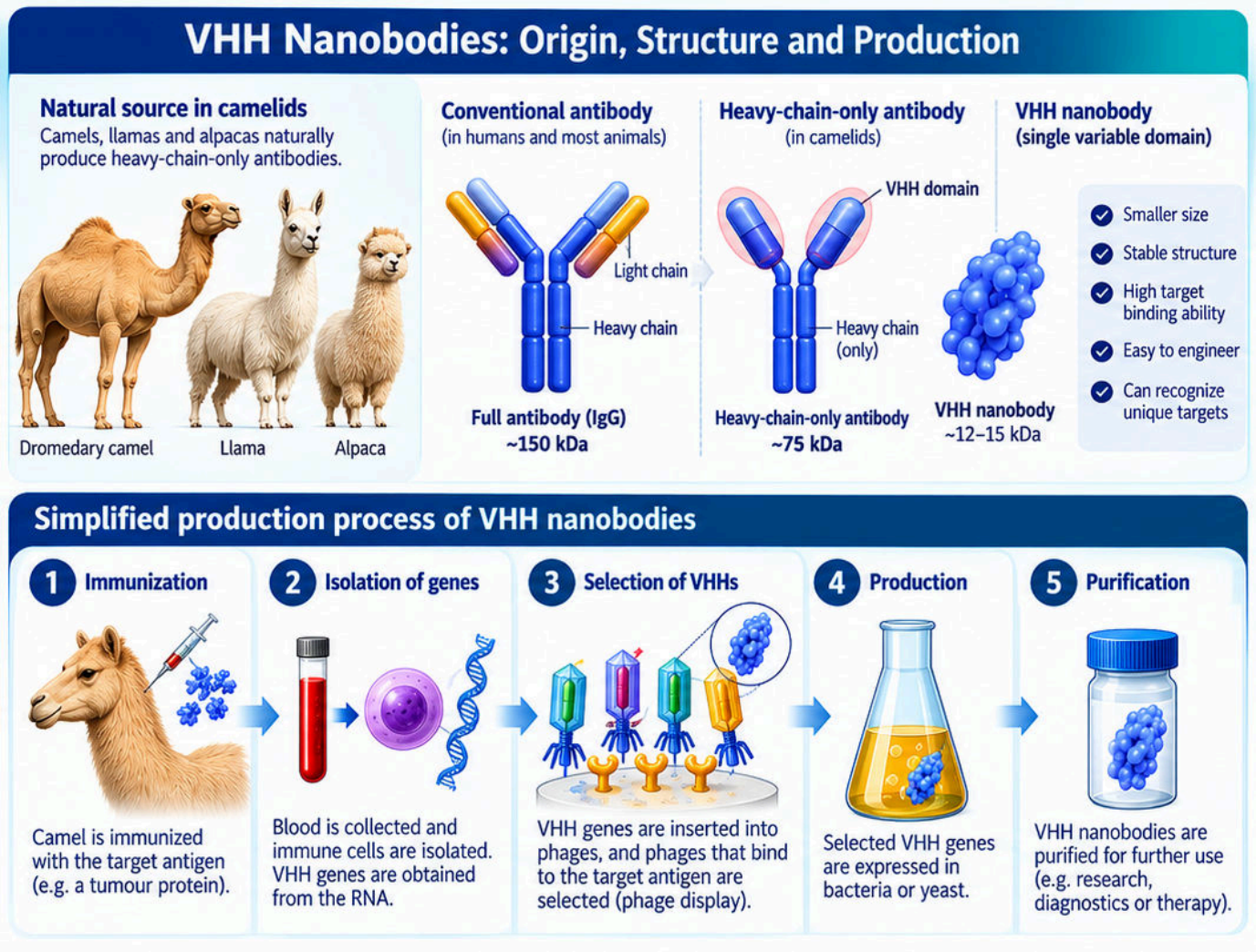


Figure 1. How VHH nanobodies are made. Camels, llamas and alpacas naturally produce heavy-chain-only antibodies. After a camel is immunised with a target such as a tumour protein, immune cells from its blood supply the VHH genes. These are screened using phage display, and the best candidates are produced in bacteria or yeast and purified.

FIGHTING CANCER WITH NANOBODIES

Cancer cells often carry particular proteins that help them grow, survive and hide from the immune system. Nanobodies can be designed to recognise these proteins and block their activity.

They can also act as guided carriers, delivering drugs or other therapeutic molecules to cancer cells. In immunotherapy, two-part nanobodies can work as bridges, holding a cancer cell and an immune cell, such as a T cell or natural killer (NK) cell, close together so the immune cell can attack. And when linked to fluores-

cent or radioactive labels, nanobodies can help doctors see tumours more precisely.

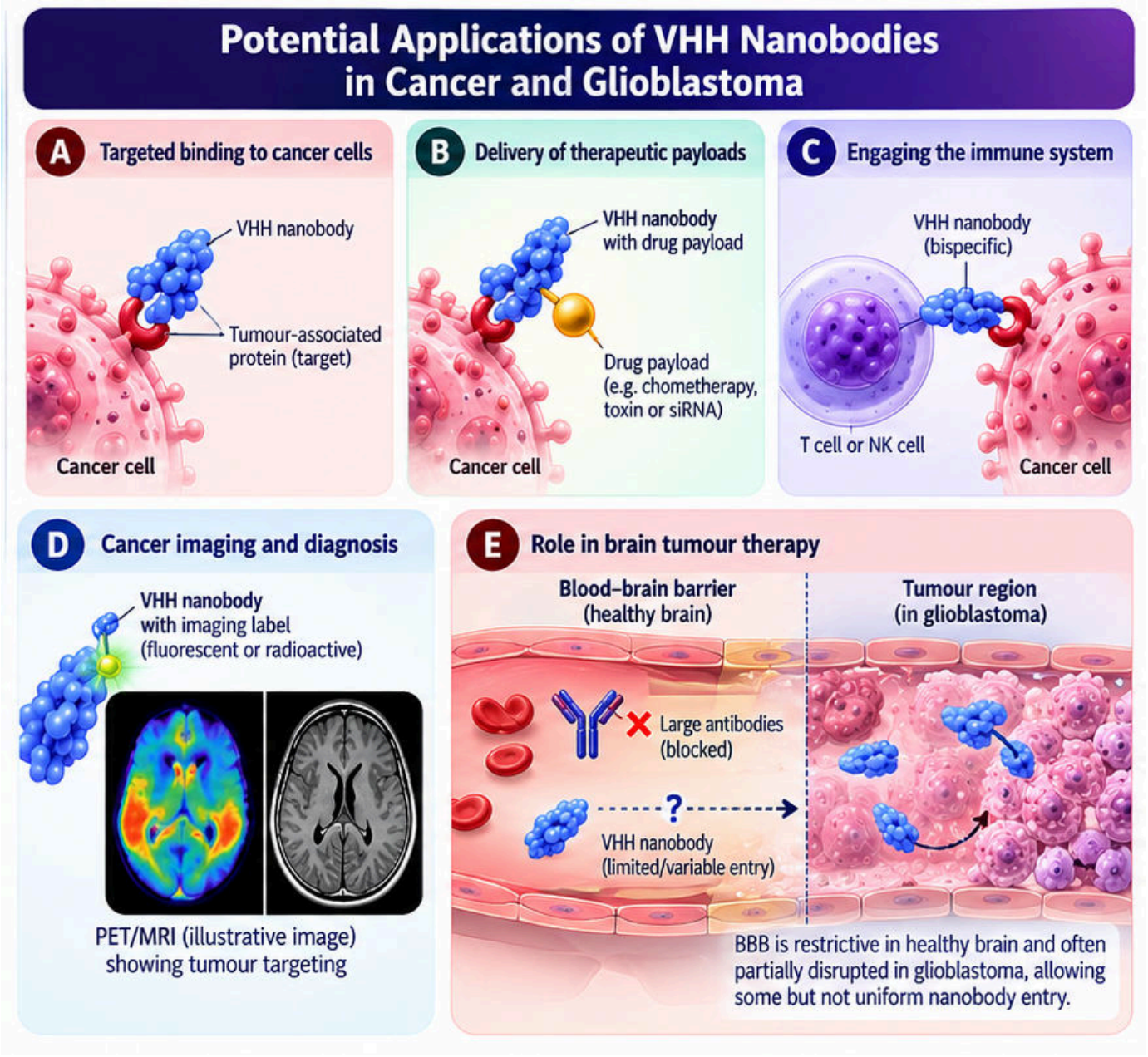


Figure 2. Possible uses of VHH nanobodies in cancer and brain tumours. They can bind proteins that are abundant on cancer cells (A), carry drugs (B), bring immune cells close to tumours (C), and carry imaging labels (D). Whether they can cross the blood–brain barrier in glioblastoma has yet to be shown (E).

THE BRAIN TUMOUR CHALLENGE

Glioblastoma is one of the most aggressive brain cancers. It is hard to treat and often returns. A major obstacle is the blood–brain barrier, a tightly controlled lining of blood vessels that protects the brain by limiting what passes from the bloodstream into brain tissue. Essential as it is, it also blocks many large antibodies and anticancer drugs.

Because of their size, nanobodies are being explored as a way around this barrier. Some may reach brain tissue more easily, and others are being engineered to use the body's natural transport routes across it. But smaller does not automatically mean better delivery. In glioblastoma, the barrier is disrupted only in places, and much of the evidence so far comes from laboratory studies rather than patients.

NEW POSSIBILITIES FOR GLIOBLASTOMA

Researchers are exploring nanobodies to:

- **Recognise** proteins found on glioblastoma cells.
- **Deliver** drugs directly to tumour cells.
- **Engage** the immune system to attack the tumour.
- **Image** the tumour by carrying visible labels.
- **Combine** with chemotherapy, nanoparticles and other emerging treatments.

FROM THE LABORATORY TO THE CLINIC

Nanobody medicines are no longer theoretical. Caplacizumab, approved in Europe in 2018 and the United States in 2019 for a rare blood-clotting disorder, was the first. Ozoralizumab, for rheumatoid arthritis, followed in Japan in 2022.

In cancer, several candidates have reached human trials. KN046 joins single-domain antibodies against PD-L1 and CTLA-4, two "checkpoint" proteins that tumours use to switch off immune attacks, and has been tested in lung and other cancers. DR30303, which targets Claudin 18.2, a protein found in stomach and pancreatic cancers, entered a Phase I trial in 2022, although the sponsor later ended that study for strategic reasons.

The newest example is GTB-5550, whose first patient was dosed in a Phase I trial in May 2026. It combines camel-derived nanobodies that grab B7-H3 on tumour cells and CD16 on NK cells with IL-15, a signal that helps NK cells multiply, to draw these immune cells to the tumour. Phase I trials mainly test safety, so results are early, and this one focuses on solid tumours such as prostate cancer, not brain tumours.

Testing VHH-based treatments in glioblastoma patients is still largely ahead of us.

LOOKING AHEAD

Nanobodies face real hurdles. They are cleared from the body quickly, so they may need modification to last longer. Because they originate in animals, they can trigger immune reactions unless carefully engineered. Reaching some tissues, including the brain, also remains difficult.

> *The future of cancer treatment may depend not only on more powerful drugs, but on smarter ways of delivering them.*
>
> DR. MOHAMMED HASEEB KHAN

With their small size, precision and flexible design, nanobodies could help create a new generation of targeted therapies, particularly for difficult cancers such as glioblastoma.

Sometimes, the smallest biological tools may open the biggest doors in medicine. ■

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