Opinion

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Improvements in drug delivery and monitoring of diseases in biotherapeutics

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Monoclonal antibodies tagged with therapeutic drugs are invaluable delivery devices that specifically target diseased cells in pathological tissues. This improves the efficacy of therapeutic treatments and minimizes toxic side effects of these drugs on normal cells also resident in the tissues. However, the immunoglobulin-G (IgG) or pentameric immunoglobulin-M (IgM) which target cell surface glycan epitopes are relatively large proteins (150-750 kDa) that poorly penetrate dense tissues for therapeutic drug delivery. Nanobodies are single variable heavy chain fragments (VHH) of IgG with a small molecular weight (15 kDa) (Figure 1).

Nanobodies retain antigen epitope binding properties and their modular characteristics are amenable to incorporation into constructs containing therapeutic drugs in a way not possible with IgG or IgM. VHH nanobodies were discovered almost 25 years ago and have been used to specifically target cells in cancer therapy and to develop novel antimicrobials.[1–4] Nanobodies, recombinant, antigen-specific, single-domain, variable Ig fragments of Camelid (*Camelus dromarius, Camelus bactrianus, Lama glama, Lama pacos, Lama guanicoe and Lama vicugna*) heavy chain-only antibodies are affinity bioreagents that have been produced in high yield in a broad range of expression systems.[1–3] The ability of nanobodies to specifically target unique epitopes with subnanomolar affinity, and to penetrate dense solid tumours make them a powerful tool in medical therapeutic procedures and in tumour pathobiology.[2,5–7]

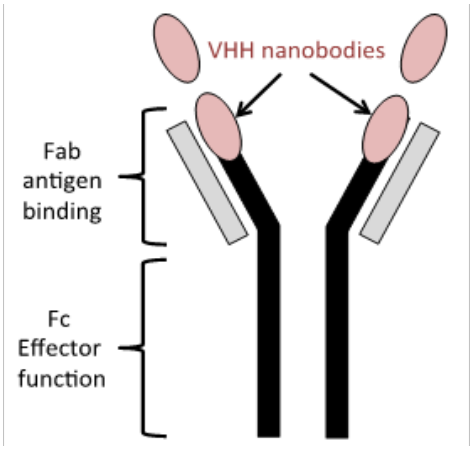

Figure 1 Diagrammatic representation of an Immunoglobulin molecule showing the VHH nanobody fragment derived from the Fab antigen binding region.

Nanobodies have been used to combat diseases/pathologies by inhibiting ligand–receptor interactions to block thrombosis,[8] to combat the inflammatory properties of TNFα in the treatment of rheumatoid arthritis[9] and to block epidermal growth factor-epidermal growth factor receptor interactions in cancer.[10] The small size of nanobodies facilitates their penetration into dense tissues[11] to specifically target cell populations in solid tumours. Lentiviruses,[12] microbubble,[13] nano gold and albumin particle,[7,14] nanocapsule,[15] and polymeric micellar delivery systems have all been employed using nanobodies[16,17] to improve therapeutic procedures. Chimeric antigen receptor (CAR T) cell therapy, is a new form of immunotherapy that uses specially altered T cells to directly and precisely target cancer cells.[18] CAR-T cells have been developed that secrete VHH nanobodies improving the efficacy of these cells in cancer treatment strategies.[18,19] Thus nanobodies offer a significant improvement in drug delivery in therapeutic procedures and are powerful examples of how nanotechnology can also be applied to improve therapeutic repair procedures. Some examples of the improved efficacy afforded by the use of nanobodies are listed[8–11] thus nanobodies will be useful in the future development of drug incorporated affinity reagents for the specific targeting of tumour cells and will be widely effective and applicable to many areas of repair medicine. The use of nanobodies in bio-sensor development is a particularly interesting novel application, it is envisaged that nanobodies will continue to find application in varied biosensor platforms for the detection and monitoring of disease processes at strategic locations in the human body or the detection of exposure to noxious chemicals.[20–23] Nanobodies thus represent a new generation multifunctional affinity bio reagent with broad application in biotherapeutics delivering significant improvements in therapeutic repair biology.

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Author contributions

JM composed, wrote and edited the manuscript in entirety.

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