Combination monoclonal antibodies and alternate formats

Increasingly, researchers are testing combinations of monoclonal antibodies (mAbs) to address the emergence of drug-resistant strains or escape mechanisms for many diseases, including HIV, rabies and cancer. Monoclonal antibody combinations can increase the breadth of functional activity and improve response rates[1]. However, there are additional challenges in developing and manufacturing combination mAb products, some of which could be addressed by exploring alternate mAb formats.

There are several different types of antibody formats being developed: antibody-drug conjugates (ADCs) or antibody-protein/peptide conjugates, multispecific formats, antibody fragments, and single-chain antibodies (see figure on next page). All of these can expand the therapeutic potential of mAbs for multiple disease types, strains and targets[2–4]. Yet each of the different formats also has their unique advantages and limitations.

ADCs are designed to bind specifically to cell-surface targets and then deliver cytotoxic drugs to improve the efficiency of cell killing and reduce the non-specific side effects of chemotherapy. There are currently eight ADCs approved in the US, all for cancer treatment, and in 2019, there were approximately 175 ADCs (mostly for cancer) in clinical testing[5].

By comparison, there is limited investment in ADCs or antibody-protein/peptide conjugates for infectious diseases, although this approach is currently being tested to enhance killing of drug-resistant bacteria[6,7]. ADCs may be a promising way to treat drug-resistant infections, but developing and manufacturing them is typically more complex and costly.

Multispecific mAb antibody formats (e.g. bi- and trispecifics) incorporate regions from multiple antibodies into a single antibody product that can bind to distinct epitopes on the same or different antigen(s). Multispecific mAb products are potentially less costly than manufacturing and delivering combination mAb products and also have other advantages. Bispecific antibodies have been designed to promote cell killing – one arm of the antibody binds specifically to cell-surface antigens on tumors and the second arm binds to immune effector cells to redirect them to kill tumors. Significant advances in protein engineering platforms are enabling the design and manufacturing of stable multispecifics, including single-chain variable fragments (scFv) and full-length immunoglobulin G (IgG) with multiple variable domains (see figure on next page).

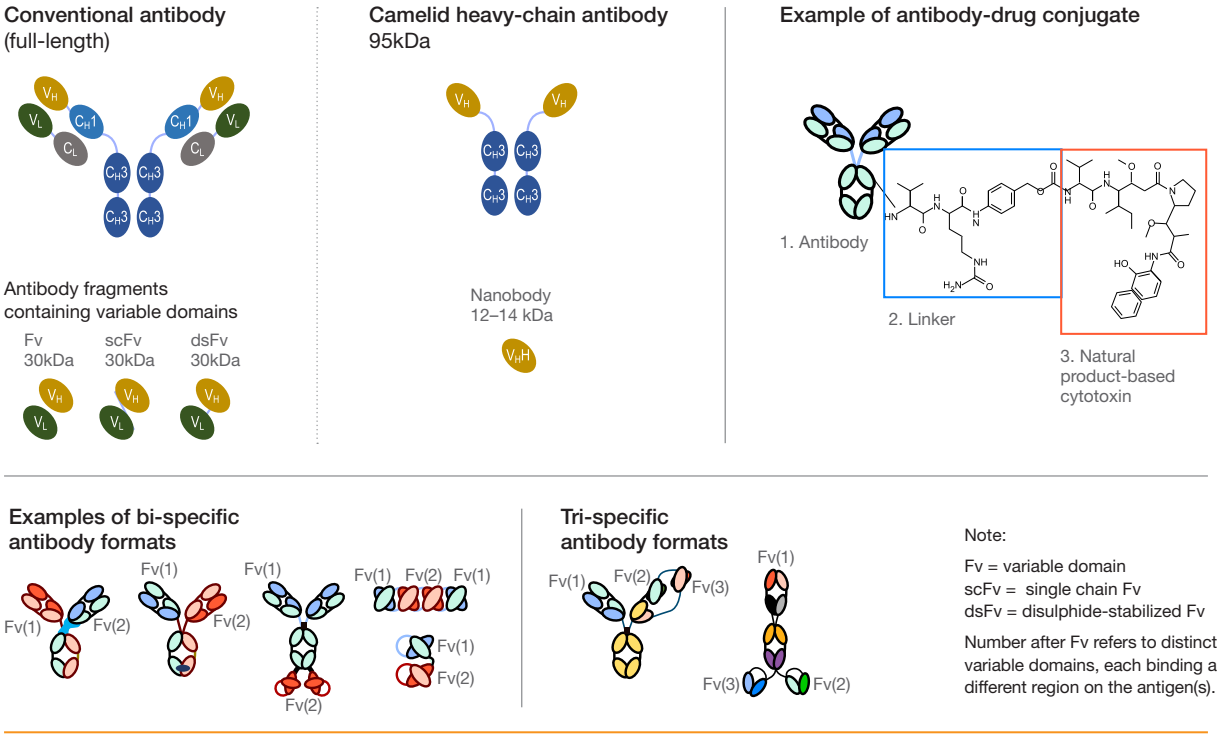
To date, there are two bispecific mAbs (blinatumomab and emicizumab) on the market for cancer and hemophilia respectively. More than half of the 132 multispecific mAbs in clinical development target cancer[3,8].

For infectious diseases, clinical development is limited to phase I/II studies with bi- and trispecific HIV broadly neutralising antibodies and a phase II study with a bispecific mAb to treat the bacterial pathogen *Pseudomonas aeruginosa*. There is, however, a growing number of multispecific mAbs in preclinical development for infectious and neglected diseases[9,10].

Given that engineered antibody formats are significantly different from naturally occurring human proteins, evaluation of their safety and immunogenicity will need to be carefully evaluated throughout the clinical development process[11,12]. Draft guidance from the U.S. Food and Drug Administration (USFDA) dictates that a clinical study comparing the bispecific antibody to the approved monospecific product(s) may be required[13]. For now, the European Medicines Agency (EMA) continues to evaluate bispecific mAb formats on a case-by-case basis.

There is also a growing pipeline of antibody fragments to treat cancers, enteric, infectious and neurodegenerative diseases[14–16]. Most of the mAbs in development are full-length IgGs, but small antibody fragments, including single-domain nanobodies derived from camelid antibodies, can more efficiently

Different types of antibody formats/fragments



penetrate tissues and access intracellular targets (see figure). Nanobodies are also more thermostable, resistant to extreme pH and soluble, which enables alternate routes of administration, including oral and pulmonary delivery. For example, nanobodies are being engineered and formulated to be resistant to intestinal proteases for treatment of enteric diseases[17,18].

Smaller-sized antibodies are also more easily expressed in microbial systems in large quantities, which should enable low-cost manufacturing. Antibody fragments, however, have significantly shorter half-lives than full-length antibodies (average of 2-3 days for nanobodies versus 14-21 days for full-length antibodies).

The first EMA- and USFDA-approved 28-kDa nanobody is the bivalent caplacizumab for treatment of thrombotic thrombocytopenic purpura. A 42-kDa trivalent nanobody (ALX-0171) targeting respiratory syncytial virus is currently in development, via pulmonary administration, to enable rapid drug delivery to the site of infection[19].

Alternate antibody formats have the potential to be game changers – not only do they expand the repertoire of diseases that can be treated by antibody-based products, but also offer the promise of lower-cost products in comparison to traditional antibodies. As more clinical data is obtained on these engineered and alternate antibody formats, these technologies could pave the way for broader access pathways to life-altering mAb therapies.

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