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Bispecific antibodies and ADCs
Once and future kings?

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The malleability and versatility of antibodies present both promise and challenges for researchers developing the molecules as therapeutics. The potential for introducing new functionality by engineering two different antigen binding sites or conjugating drugs to antibodies, was realized decades ago, but development of marketed products based on these formats proved challenging. Obstacles relating to design, engineering, manufacturing and preclinical and clinical evaluation of these products have gradually been overcome and, as of 2011, most major pharmaceutical companies and a plethora of biotechnology firms are developing bispecific antibodies or antibody-drug conjugates (ADCs), or both.

Bispecific antibodies, with their inherent ability to bring two different targets into proximity, have been evaluated primarily in cancer patients, with HER2/neu, EpCAM, CEA and CD30 frequently selected as a tumor-associated antigen. A design challenge of the bispecific antibodies has been the selection of the second target. Bispecific antibodies began entering clinical study in the early 1990s; the focus then was on enabling cell-killing functionality by utilizing CD64 or CD16 as the second target of the molecules. However, the bispecific antibodies that entered clinical study in that period were ultimately terminated due to a variety of factors, including the complexity of the biology, production issues and competition from conventional IgG antibodies targeting the same tumor-associated antigens that were also in development at the same time.

The combination of knowledge gained from past experiences, improvements in protein engineering and manufacturing methods, expansion of the traditional pharmaceutical industry pipeline to include large molecule development, as well as the realization of the limitations of conventional IgGs, has led to a notable revival of interest in bispecific formats. In 2009, one therapeutic bispecific antibody, anti-EpCAMxCD3 catumaxomab, was approved in Europe, although none of the other new bispecific antibody formats have been evaluated in Phase 3 clinical studies. Numerous pairs of targets have now been clinically validated and bispecific molecules that might show enhanced efficacy compared with conventional IgGs are now entering clinical study in increasing numbers. The bispecific T-cell engager (BiTE) antibodies from Micromet are an excellent example of innovative bispecific therapeutics. These molecules target CD3 on T cells as well as tumor-associated antigens. Encouraging Phase 2 clinical results have been reported for blinatumomab, which targets CD3 and CD19 and is undergoing evaluation in patients with B-precursor acute lymphoblastic leukemia and non-Hodgkin lymphoma.

The intense focus by researchers on bispecific antibodies has led to the development of a wide variety of bispecific formats. For the most part, the underlying approaches rely on company-specific technologies. Patrick Baeuerle and colleagues at Micromet have identified over 35 unique formats for construction of bispecific antibodies. Several classes of these are IgG-like molecules, but others incorporate combinations of antigen binding fragments. Approaches involving oligoclonal antibodies and bispecific non-immunoglobulin protein scaffolds are also being investigated as treatments for a variety of indications, including inflammatory diseases. The scientific creativity and dedication of substantial resources to the development of these innovative molecules is laudable; however, it may be difficult to compare preclinical results from the molecules to determine the pros and cons of each because of differences in the formats. As has been found with the well-known IgG format, small changes in the molecules can lead to unexpected biological outcomes; therefore, knowledge gained about the stability, immunogenicity and biological activity of one type of bispecific antibody may not inform development of others. Nevertheless, the increased functionality of bispecifics relative to IgGs makes them attractive for development as therapeutic products.

As was the case with bispecific antibodies, ADCs as a product class also underwent a long period of research and development prior to the approval of a product. Utilizing antibodies as a means to guide drugs to a specific target was envisioned long ago and explored in depth over the course of the past 30 years, but the development of approved ADC therapeutics proved difficult. One ADC, gemtuzumab ozogamicin (Mylotarg®), was approved in the US in 2000 via the accelerated approval mechanism as a treatment for acute myeloid leukemia, but was withdrawn in 2010 when the drug failed to demonstrate an improvement in clinical benefit in a confirmatory trial and new safety concerns were raised.

Like bispecifics, ADCs add functionality to classical antibodies, e.g., a new mode of cell-killing activity, but also add complexity. With ADCs, the linker and the drug as well as the target and the antibody must be carefully selected. The linker must be stable in circulation and selectively release biologically active drug after internalization; the drug must

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be stable in circulation and lysosomes, potent and have a relevant mode of action. It is also desirable for the addition of the linker/drug to be site-directed so as to limit the heterogeneity of the final product.

Advances in the knowledge of linker and drug properties and antibody engineering, design and selection, have enabled the development of a new generation of ADCs that are demonstrating promising clinical results. Brentuximab vedotin (Seattle Genetics), an anti-CD30 chimeric antibody conjugated to monomethyl auristatin E, is undergoing review by the US Food and Drug Administration (FDA) as a treatment for Hodgkin and systemic anaplastic large cell lymphomas. The FDA is expected to act on the application by August 30, 2011. Other ADCs that might reach the market within the next 1–3 years are trastuzumab emtansine (ImmunoGen/Genentech; humanized anti-HER2/neu antibody conjugated to DM1), which is undergoing evaluation in Phase 3 studies of breast cancer patients and inotuzumab ozogamicin (Pfizer; humanized anti-CD22 antibody conjugated to calicheamicin), which is in a Phase 3 study as a treatment for follicular non-Hodgkin lymphoma. In addition, more than a dozen ADCs are currently in early stage clinical studies.

The innovative research on bispecific antibodies and ADCs, as well as bispecific antibodies that are themselves ADCs, holds great promise for the future development of therapeutics for a variety of diseases. However, these potential products will be derived from a variety of company-specific technologies that are difficult to compare. Clinical development of candidates from every platform would require substantial investments; it remains to be seen how the industry will allocate its resources. Despite this, it is clear that progress has been made and new antibody products based on bispecific and ADC approaches will be marketed in increasing numbers in the future.