Antibody Therapeutics for Cancer: How good are the modern magic bullets?

By Vijay Shankar Balakrishnan, Ph.D.

"Magic bullets!" Everyone who thinks about targeted therapies and antibodies is reverberated with these words. This concept of magische Kugel (targeted therapies), proposed by Paul Ehrlich early in the 20th century, became closer to a reality when Georges Köhler and César Milstein first reported their discovery of monoclonal antibodies (mAbs) using hybridoma technology in 1975 [1]. mAbs are antibodies made by cells that are identical copies of each other; therefore the antibodies all recognize the exact same target and can be mass produced. Since then, wherever possible, targeted therapies have become an integral part of different treatment regimens. For example, in some cancers, mAb therapies can be an alternative to the widely used and (sometimes un-) popular cytotoxic chemotherapy. Yet, there are still several "if's and but's" that surround mAb therapies, most pertinently towards their fidelity (or lack thereof), their half-life in the blood stream, and their toxicity in patients.

Since Robert Weinberg's Boston lab's discovery of the neu oncogene in rat neuroblastoma cells early in the 1980s [2], other oncologists, including Jeffrey Drebin and Mark Greene, have tried attacking the neu protein with targeted antibodies. Since the product of the neu gene is a receptor protein that is over-expressed and potentially easily accessible on the surface of cancer cells, it is an attractive target for mAb therapies. However, the reality of using a therapeutic antibody against a cancer cell receptor remained elusive until Dennis Slamon, an oncologist from UCLA, found success in the late 1980s [3]. This happened shortly after the discovery of over-expressed HER2 by Genentech, which in convergence with that of the neu gene from Weinberg's lab led to the gene being thereafter frequently referred to as HER2/neu.

Engineering mAbs

The choice of mouse myeloma cells by Köhler and Milstien became the seed for continuous industrial production of monoclonal antibodies. Otherwise, due to the natural properties of the immune B-cells (particularly their short, polyclonal lives), it would be difficult to produce mAbs for a long time [4]. Overcoming technical hurdles, along with advances in recombinant and protein engineering technology, has now made it possible to abundantly produce antibodies that are target specific. Scientists and physicians accelerate murine, chimeric, humanized, and human mAbs development by leaps and bounds seemingly day-by-day. Targeted therapies like Roche's first generation therapy, Herceptin (trastuzumab), laid the groundwork; now we are in the second and futuristic generation of fusion-mAbs, antibody-like variants, and biosimilar versions of some of the first generation mAbs.

The therapeutic mAbs are like different buildings with the same foundational blue-print. For all the

antibody classes, immunoglobulin G (IgG) remains the skeleton, whereas the body of a mAb can be variably engineered in different regions where the target-antibody reaction takes place. The constant Fc-region initiates the immune-effecting cascade to elicit cell toxicity [5]. Goals for advancing the development of cancer-treating mAbs are improving fidelity, enhancing bio-availability, and minimizing side effects through fine-tuning newly developed antibodies according to lessons learned from the old ones. Thus far, there are 13 FDA-approved mAbs against various cancers – the lot consisting mostly of IgG1 and IgG2 sub-classes of IgG antibodies and antibody-drug conjugates (ADCs, where a powerful drug is attached to a mAb), plus a few next-generation mAbs in various stages of clinical trials [4, 5]. After a brief note on the therapeutic principles of mAb therapies for cancers, we'll discuss a few examples and then give a futuristic conclusion.

Therapeutic Principles

There are a variety of rapidly developing approaches in cancer immunotherapy that encompass both innate (non-specific) and adaptive (acquired/specific) immune responses [6-9]. One approach, for instance, targets vaccines against dendritic cells (DCs), whereas a second targets antibodies against a specific target (receptors), and a third involves ex vivo cell therapies (called adoptive cancer cell therapies). Of these, the target-specific approach is mAb therapy. Like HER2/neu, many tumor-expressed targets for therapeutic antibodies are growth factor receptors that are over-expressed in cancer cells and drive cancer cell growth. The design and development of antibodies and, in turn, the therapies are specific with respect to the cancer type and its microenvironment.

In principle, antibodies should bind to the receptors and block ligand binding, and/or perturb the signal transduction that promotes tumor growth. Trastuzumab, a mAb binding to the HER2/neu receptor, is often viewed as the best and first example of a therapeutic mAb. Rituxan (rituximab) is another mAb that targets the CD20 protein on the B-cells that cause lymphomas such as non-Hodgkin lymphoma (NHL) or chronic lymphocytic leukemia (CLL) [10]. The inhibitory effects of mAbs such as these is in addition to potentially inducing cancer cell suicide (apoptosis) or aiding any chemotherapeutic agent. Some mAbs may also be anti-metastatic, although trastuzumab, for example, only wipes out circulating cancer cells with the help of additional chemotherapeutic drugs [10]. In case of solid tumors, like in HER2-positive breast cancer treated with trastuzumab, mAbs may also curtail vascular development [10].

Some mAbs At Work

The earliest mAbs had their origin in mouse myeloma or hybridoma cells (a fusion of an antibody-producing B cell with a myeloma cell), and thus they induced an immune response in patients. Through antibody engineering (protein engineering) and recombinant methods, humanized mAbs (mAbs developed to be able to be used in humans) began to be produced along with chimeric mAbs (a combination of antibody regions 'cut' from both mouse and human and 'pasted' suitably). Although fully human mAbs for cancer, such as cixutumumab do exist, their production is challenged by the lack of appropriate human myeloma cells that can produce stable mAbs for long time. However, efforts are underway for more successful ones [4]. With that said, there are still several approved mAb therapies under post-marketing surveillance in addition to several more in clinical trials. Four different successful mAbs from that list are discussed in more detail below [4, 5].

Pertuzumab (Perjeta) is a second-generation version of trastuzumab that results in tumor cell apoptosis by discouraging the dimerization of HER2/neu, which is an important cellular event that encourages tumor growth in breast cancers. This mAb was developed by Genentech and was recently

approved for clinical use in many countries. It is prescribed in combination with trastuzumab and docatexel for patients with HER2/neu-positive breast cancers who have not received any antibody or anti-metastatic therapy. The Clinical Evaluation of Pertuzumab and Trastuzumab (CLEOPATRA) trial demonstrated its competence in boosting the efficacy of Herceptin [11]. However, the side effects are significant. Pertuzumab use and a following pregnancy may result in embryo-fetal death and birth defects [4]. In such circumstances, it is likely that patients will be advised to use contraception.

Brentuximab vedotin, or Adcetris is a recently approved ADC produced by Seattle Genetics that targets CD30 on B-cells. It is used to treat patients with Hodgkin Lymphoma, usually either after a failure of at least two rounds of chemotherapy, or those who failed autologous stem cell transplant (ASCT). It is also prescribed for patients with systemic anaplastic large cell lymphoma (sALCL) if they fail one round of chemotherapy. This ADC is comprised of the chemically synthesized microtubule-disrupting agent monomethyl auristatin E (MMAE) and a protease-cleavable linker that attaches MMAE to the mAb, plus the mAb itself. The most severe adverse effect may be progressive leukoencephalitis, a rare, potentially fatal inflammation of white matter in the brain that can result from John Cunningham (JC) virus infection [4, 5].

Ipilumumab, or Yervoy, is a rather unique mAb in oncology. Developed by Bristol-Meyers Squib, it is a recombinant, fully human IgG1-kappa mAb that targets the cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4). While brentuximab vedotin targets B-cell surface receptors, ipilumumab targets the T-cell receptor CTLA-4, which then cross-presents to B-cells. Ipilumumab is used in patients with unresectable (surgically impossible to remove) tumors or metastatic melanoma. Treatment using ipilumumab is considered rather indirect, most likely due to the T-cell route it takes. Despite the benefits, ipilumumab elicits several severe and potentially fatal side effects that, due to the T-cell mediated immune response, are possible in any organ system. As these adversities present themselves during treatment, ipilumumab often must permanently be discontinued [4, 5].

Trastuzumab emtansine (Kadcyla), from Genentech/Roche, is an ADC of the chemotherapy drug mertansine linked to the trastuzumab monoclonal antibody. This combination delivers chemotherapy directly to HER2/neu positive cells. As this article was going to press, results of the phase 3 TH3RESA trial were published, demonstrating that trastuzumab emtansine could significantly improve progression-free survival with reduced toxicity compared to other regimens ('physician's choice'). The most common serious side effects included neutropenia (reduced neutrophils and therefore potentially increased susceptibility to infection) and diarrhea [12].

To Wrap Up

Perhaps because mAbs are engineered, in spite of their excellent therapeutic properties, they are highly immunogenic in patients. Cancer therapy regimens using mAbs are indeed useful, yet the patients must be under strict medical advice and surveillance. In this case, the advancement in clinics is accountable at each stage to patients and their safety. That said, it can be assumed that developers of therapeutic mAbs for cancer are likely being careful, given the complex nature of mAbs and the unpredictability of the immune system. Scientists, physicians, and regulatory bodies are revising strategies at every step including target identification and validation, lead optimization, correct engineering of the lead, pre-clinical toxicology studies, clinical trials and post-administration surveillance.

Technologically speaking, there is plenty of room for development in terms of patient safety with existing and pipeline mAbs. A few current goals include improving the pharmaceutical properties of mAbs, making bi-specific mAbs that target two epitopes or antigens, and engineering new protein scaffolds with better pharmacodynamic properties. Surprisingly, recombinant poly- or oligo-clonal antibodies are also under development [13]. To help address the cost of therapies, biosimilar ("bio-generic") versions of some mAbs are under development, such as the approved Reditux, a biosimilar of rituximab, produced by Dr. Reddy's Laborataries in India. Thus, as can be seen from several angles, antibody therapeutics is progressing exponentially, and the hope is that the future will be better for patients too!

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