



# Antibody Drug Conjugates: A New Era in Personalized Medicine and Targeted Cancer Therapy

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## Abstract

The challenges in discovery and development of small molecule drug has led to the emergence of antibody drug conjugates (ADCs) as an alternative for targeted cancer therapy. Over the past two decades, several antigens that have selective over expression on cancer cell surface have been identified and they have been exploited for tumor specific cargo delivery. Specific antibodies can be engineered to function as small molecule targeting ligand that can bind tightly to tumor cell's over expressing the target antigen. The potential of ADCs represents a novel class of cancer cell specific antigen targeted chemotherapy agent. ADCs thus represent a significant step forward in the war against cancer and personalized medicine.

**Keywords:** Antibody drug conjugates (ADCs); Antibody; Drug conjugates; Criteria for ADCs; Over expressed antigen; Personalized cancer therapy; Personalized medicine

## Components and Criteria of ADCs

An ADC comprises main of three components: (a) a monoclonal antibody (mAb), [1] which has tight binding ability to tumor antigen, such as the FDA approved HER-2 targeting "Kadcyla" with an *in vitro* binding affinity (K<sub>d</sub>) of 0.14 nM for HER2-positive cancer cell [2]; (b) a therapeutic payload, which can kill cancer cell population, such as the FDA licensed CD30 targeting "Adectris" which contains a antimitotic agent, monomethyl auristatin E, as the cytotoxic payload; and (c) a linker between the antibody and the drug. The linker determines the circulation stability and release of drugs in tumor lesions. For instance, low pH cleavable hydrazone linker is used in Mylotarg<sup>®</sup>, and cathepsin cleavable dipeptide (Citruilline-Valine) is used in Adectris<sup>®</sup> [3,4]. Upon treatment with ADC, the antigen binds with the ADC to form the ADC-antigen complex that subsequently gets internalized into the target cell by endocytosis. On its entry into the cell, in cytoplasmic conditions (acidic pH, proteases, glutathione etc.) the ADC releases the cytotoxic drug to elicit the required pharmacological/therapeutic effect. The fundamental criteria for the success of ADC includes (I) high expression of the target antigen in tumor cells compared to normal cells; (II) the antigen should be internalized through endocytosis; and (III) there should be less tumor heterogeneity [3]. Until recently, three ADCs have been approved for clinical use and two ADS are in phase III clinical trials. There are several ADC candidates in Phase I/II trials [4]. It is predicted that the global market for ADCs will reach more than \$3 billion by 2018.

## Success and Challenges

Due to tumor heterogeneity and shedding of antigen, the success rate of ADCs in solid tumors has not very prominent as it can be noted from the fact that the first two FDA-approved ADCs, namely, Mylotarg<sup>®</sup> and Adectris<sup>®</sup> are approved for non-solid tumors. However, expression level of antigen and internalization of ADC can also determine the success of ADC in solid tumors. A case in point is Kadcyla<sup>®</sup> for treating patients with HER-2 positive tumor. Although Kadcyla<sup>®</sup> is useful for only 20% of total breast cancer patients its success is achieved due to significant high expression of antigen and limited heterogeneity across the HER-2 positive tumor, with low expression in normal tissues [4].

Beside the success story of ADCs, the first FDA approved agent, Mylotarg<sup>®</sup> was withdrawn from the market after 10 years of approval. The treatment with Mylotarg<sup>®</sup> showed serious side effects of myelosuppression (or suppression of the bone marrow activity) in 98% of patients, tumor lysis syndrome, respiratory problems including death. The main reason for the side effects were attributed to the unstable hydrazone linker, resulting in premature cytotoxic payload release [5].

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Kadcyla<sup>®</sup> showed thrombocytopenia in 4.7% to 12.9% of patients due to off target toxicity. The major side effect of Kadcyla<sup>®</sup> in clinical development was the cardiotoxicity due to the antibody component, trastuzumab, which nonspecifically binds to highly abundant HER-2 positive cardiac tissues [5].

## Conclusion

The current trend in cancer therapy is shifting towards antibody drugs and therefore many ADCs are being developed in the war against cancer. More than 45 clinical trials are ongoing and among them, ABT-414, and CMC-544 are in phase III clinical trials [6-8]. Beside the success of ADCs in cancer therapy, many antibody-conjugated diagnostic agents are already marketed for early detection of solid tumors. In this regard, about 15 antibody-conjugated diagnostic agents are already in clinical trials and more than 5 have been FDA approved. The success of antimetabolic DNA-targeting payloads in ADCs helps better understand the target requirements of ADC design. With the advances in conjugation chemistries and better understanding of mechanism of action, ADCs are geared to play a pivotal role in personalized cancer therapy with limited side effects.

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