

ANTIBODY–DRUG CONJUGATES: RECENT ADVANCES & CURRENT LIMITATIONS

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INTRODUCTION

Antibody–drug conjugates (ADCs) combine the tumor-targeting specificity of a monoclonal antibody with an extremely potent cytotoxic agent. As a conjugated pair, the therapeutic window of each respective component may ideally be widened. ADCs have gained considerable traction in the clinic over the past decade, as evidenced by the recent FDA approval of Adcetris (2011, Hodgkin lymphoma) and Kadcyla (2013, HER2 (+) metastatic breast cancer). Despite significant advancements relating to each of the three components in recent years, however, the initial promise of ADCs as the ‘magic bullet’ for cancer therapy has not yet been realized. This report highlights a number of challenges that have hindered ADCs in the clinic and select developments that have recently been offered as potential solutions.

ANTIBODY

A critical flaw of most current ADCs (including Adcetris and Kadcyla) is that they are produced as heterogeneous mixtures. The drug-to-antibody ratio (DAR) varies depending on the method used for antibody-linker conjugation, which can significantly impact drug efficacy, pharmacokinetics, and toxicity in human patients.

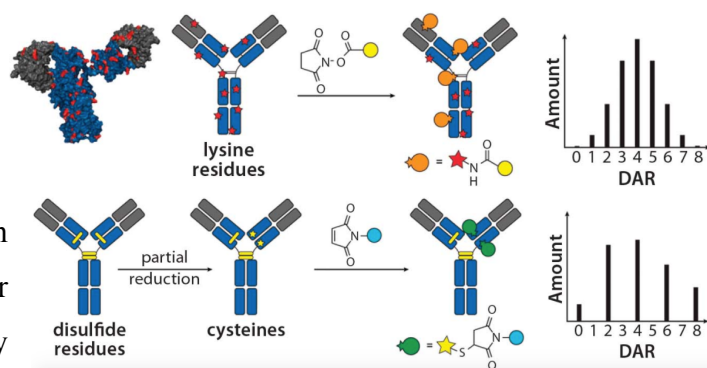


Figure 1: Current conjugation strategies lead to heterogeneous drug-antibody ratios

However, several new strategies utilize site-specific conjugation to establish homogeneous ADCs with reproducible, unambiguous DARs. One approach incorporates engineered cysteine residues into the non-essential regions of an antibody and selectively links them to the linker moiety. This led to homogeneous ADCs with DARs of two that subsequently showed similar efficacy but better pharmacokinetics than heterogeneous ADCs.¹

LINKER

It is essential that the linking unit of an ADC be stable during formulation and circulation, but labile within tumor tissue. Linker instability and subsequent loss of free drug remains one of

the primary causes for dose-limiting toxicities in the clinic. Although contemporary ADCs utilize stronger linkers (dipeptides and non-cleavable cycloalkanes) than first-generation ADCs (hydrazones), conjugation of reactive thiols through a maleimide moiety is still prevalent. However, the thiosuccinimide linkage is inherently reversible, particularly over the prolonged duration of ADC circulation, which has been shown to lead to free drug release over time. A new strategy has been developed which introduces a self-hydrolyzing maleimide linkage to ADCs that led to improved tolerability *in vivo*.²

DRUG

ADCs have generally been limited to a select few cytotoxins due to favorable functionality for conjugation and the retention of activity upon attachment to an antibody. A novel strategy, however, permits the conjugation of tertiary and heteroaryl amines to ADCs, which dramatically broadens the scope of amine-containing drugs that may be used. The conjugation occurs through *p*-aminobenzyl quaternary ammonium salts, which were shown to have good activity *in vivo*.³

ANTIBODY–DRUG CONJUGATES AGAINST SOLID TUMORS

A primary deficiency of ADCs is their efficacy against solid tumors. To date, there is minimal clinical evidence that appending an antibody to a small-molecule drug leads to greater efficacy in human patients. In fact, a head-to-head study comparing Kadcyla to Herceptin, its antibody counterpart, found no significant difference in the survival of breast cancer patients.⁴ A primary explanation may be due to the poor penetration of antibodies past the periphery of solid tumors. This phenomenon helps to explain the ineffectiveness of conjugating less potent toxins to antibodies, and instead requires exceptionally potent small-molecules, which creates more susceptibility to off-target side effects.

CONCLUSION

The intrigue surrounding the promise of antibody-drug conjugates as ‘magic bullets’ has escalated dramatically with the approval of Adcetris and Kadcyla. Nevertheless, the promise of a dramatically widened therapeutic window has not yet been fulfilled. Efforts are certainly ongoing, however, as more than sixty unique ADCs are currently in various stages of clinical trials.

REFERENCES

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