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Foreword

Novel methods in bioanalysis and characterization of antibody–drug conjugates

Boris Gorovits & Stacy Shord

Antibody–drug conjugates (ADCs) represent an important and emerging class of biotherapeutics. Although the idea of targeted delivery of small molecular weight drugs for treatment of cancer was proposed several decades ago, the development of these targeted drug products has taken significant time. Only two ADCs are currently available in the USA.

ADCs contain three components: a monoclonal antibody (mAb) as a delivery vehicle, a linker to join the antibody to the small molecule drug and permit timely release of the drug in the tumor and a small molecular anti-cancer drug as the cytotoxic payload. The individual characteristics of each of these components will influence the pharmacokinetics, clinical activity and toxicity properties of an ADC. As an example, the conjugation chemistry, such as random lysine residues and site-specific conjugation, can influence drug:antibody ratio and ADC clearance based on data from nonclinical models.

Numerous combinations of mAbs, linkers and drugs can be imagined, suggesting that early *in vitro* analytical assessment of an ADC is important to guide further development. Importantly, a ‘smart linker’ should ideally release drug within the targeted cell and avoid premature release of the cytotoxic drug in the circulation in humans. Therefore, early understanding of ADC stability *in vivo* is critical to the ability to predict the pharmacokinetics, activity and tolerability of an ADC. For example, ADCs that shed their small molecule drug when in circulation should cause more toxicity and reduce clinical activity. As another example, the change in the drug:antibody

ratio during *in vivo* circulation could influence the pharmacokinetics, clinical activity and tolerability, as well.

To reasonably describe the complexity of an ADC, a multianalyte approach is needed to appreciate the pharmacokinetics, activity and tolerability. Various analytical platforms are being applied, including ligand binding and LC/MS/MS methods. The current industry position along with regulatory expectations suggests that multiple analytes should be measured to adequately explore the relationship between exposure and clinical activity and safety. A selective and strategic approach for selecting the analytical methods for an ADC during early discovery evaluation is therefore critically important. A careful analysis that includes the pharmacokinetic assessment of multi-analytes is particularly challenging during late clinical development.

The potential for an immunogenicity response to ADC compounds should also be considered when developing relevant bioanalytical methods. A solid strategic approach to investigate the development of binding and neutralizing antitherapeutic antibodies is required.

In summary, the development of ADCs is quickly moving forward with many compounds in nonclinical and clinical development. The diversity of the linkers and small molecular drug payloads continues to expand. It is likely that the components used to create an ADC compound will continue to evolve going forward, as the understanding of the influence of the chemistry on the pharmacokinetics, clinical activity and tolerability continues to grow. Time is still needed to identify the most critical elements that identify an ADC that is likely to demonstrate a meaningful risk:benefit ratio.

In this book, the reader will find important information from several key opinion leaders including industry researchers and regulators, who are intimately involved in the development of ADC compounds. The various challenges outlined above together with case studies are discussed.

Financial & competing interests disclosure

Stacy Shord is employed by the US FDA. Boris Gorovits is employed by Pfizer and is involved in development of compounds relevant to those discussed in this manuscript and receives salary and equity based remuneration. The editors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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