Assessing DDI potential of Antibody-Drug Conjugates:

Points for consideration based on the IQ-sponsored ADC ADME working group discussions

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ADC ADME Working Group

- Working Group is sponsored by the International Consortium for Innovation and Quality in Pharmaceutical Development
- Group was launched in early 2014
- Team’s goal: Propose a strategy for addressing ADME of ADC
- White Paper is still in-preparation, so no specific recommendations can be presented today. Instead it will be an overview of potential “points for consideration” during the DDI assessment for ADCs
Diagram of Antibody-drug conjugate

- Also referred to as “payload”, “warhead”, or “toxin”.
- Compound which exerts the intended pharmacological effect of an ADC.
  - In the case of a cleavable linker, intact drug is released from the ADC.
  - In the case of non-cleavable linker, released from the ADC drug contains the linker and an amino acid fragment.

Chemical bridge which links the drug to the mAb

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Assessing DDI potential of an ADC

FIH clinical trials with ADCs are typically conducted in patients who also take multiple concomitant medications, rather than in healthy volunteers. DDI risk assessment is important to conduct at pre-clinical stage.

- In most cases, systemic concentrations of the released drug are extremely low, and, therefore, the likelihood of it causing DDI at clinically relevant doses is considered to be minimal.

- Liver might receive higher concentrations of the drug than those inferred from its systemic concentration because, as part of a normal IgG catabolic clearance, ADC will likely carry a large portion of the conjugated drug into the liver where it can be released.
Assessing DDI potential of an ADC

- In general, probability of a drug to be a DDI victim is higher
  - Drugs are typically highly potent (picomolar) cytotoxic molecules with narrow therapeutic margin
  - Potential induction of the enzymes metabolizing the drug in the tumor could result in a loss of efficacy.
  - Released drug can be eliminated unchanged or metabolized by enzymes such as the cytochrome P450.
- Direct renal or biliary elimination could potentially be a significant component of the overall drug’s clearance.

What information would help us assess DDI risk for a novel ADC?

*On the surface, it seems like it would be mostly similar to what we would do for a small molecule drug. Is it true?*

- Further metabolism of released drug (formation of potentially toxic and/or active metabolites)
- Enzymes and transporters involved in metabolism and transport of the drug
- Inhibition/induction of CYPs and UGTs by released drug
- Elimination routes of the released drug
- Mechanism of the drug release from the ADC
- ADC stability in blood (plasma)
- Impact of conjugation method and DAR on ADME properties of ADC
Is there a single *in vitro* system that can be used for characterization of both ADC and drug?

<table>
<thead>
<tr>
<th>Hepatocytes</th>
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<tbody>
<tr>
<td>Contain all relevant microsomal and cytosolic enzymes</td>
</tr>
<tr>
<td>Target protein is not expressed</td>
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<td>Drug may have limited permeability.</td>
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<table>
<thead>
<tr>
<th>Liver microsomes</th>
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<tbody>
<tr>
<td>Contain most relevant drug metabolizing enzymes</td>
</tr>
<tr>
<td>Not confounded by drug’s permeability or uptake</td>
</tr>
<tr>
<td>Lack the lysosomal enzymes responsible for release of drug from ADC molecule</td>
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<tr>
<th>Lysosomes</th>
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<tbody>
<tr>
<td>Mimic ADC degradation in the cell</td>
</tr>
<tr>
<td>Artificial system which does not contain drug-metabolizing enzymes</td>
</tr>
<tr>
<td>Uptake of ADC might be limited</td>
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<table>
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<tr>
<th>Liver S9 fraction</th>
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<tbody>
<tr>
<td>Contains the same drug metabolizing enzymes as hepatocytes.</td>
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<tr>
<td>Does not rely on drug’s permeability</td>
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<tr>
<td>Transporter independent</td>
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<tr>
<td>Can be used at either pH 7.4 (to study metabolism of the drug) or acidified to mimic lysosomal degradation of an ADC.</td>
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<tr>
<th>Cancer cells</th>
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<tbody>
<tr>
<td>Selection of cell line would depend on target expression,</td>
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<tr>
<td>Limited by the drug’s permeability</td>
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<tr>
<td>Drug metabolizing enzymes expressed by cancer cells are found in the liver</td>
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<td>Have been shown to up-regulate Phase II enzymes and down-regulate Phase I enzymes as compared to the liver</td>
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<thead>
<tr>
<th>Plasma</th>
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<tr>
<td>Contains proteases</td>
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Is there a single *in vitro* system that can be used for characterization of both ADC and drug?

Drug’s metabolic stability, reaction phenotyping, CYP/UGT inhibition

Liver microsomes
- Contain most relevant drug metabolizing enzymes
- Not confounded by drug’s permeability or uptake
- Lack the lysosomal enzymes responsible for release of drug from ADC molecule

Liver S9 fraction
- Contains the same drug metabolizing enzymes as hepatocytes.
- Does not rely on drug’s permeability
- Transporter independent
- Can be used at either pH 7.4 (to study metabolism of the drug) or acidified to mimic lysosomal degradation of an ADC.

Identification of metabolites formed from the drug

Plasma
- Contains proteases

Characterization of drug-containing species released from an ADC

Assessment of linker stability in the systemic circulation.
PPB of released drug
Summary

- Characterization of the DDI potential for an ADC is a complex process as it needs to take into account mAb and small molecule components of this modality.

- Selection of appropriate experimental system is important

- No standard “one fits all” approach can be applied to all ADCs, but general principles are similar

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