Evaluating the Efficiency of Payload Delivery by ADCs Using a Minimal PBPK Model

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Objectives: Antibody drug conjugates (ADCs) aim to deliver a sufficient amount of payload (drug) into tumor cells whilst minimizing exposure of healthy tissues to the free payload. The amount of payload internalized into tumor cells depends on a number of factors including tumor capillary density, target antigen level, ADC internalization rate, target binding affinity, de-conjugation rate and extent of off-target binding. An integrated approach is needed to model the interplay of these multiple factors. For this purpose a minimal PBPK model was used to describe the disposition of ADCs in vivo and to evaluate the efficiency of payload delivery to a solid tumor.

Methods: A minimal PBPK model for monoclonal antibodies (mAb) [1] was adapted to describe each ADC species (defined by payload:mAb ratio) with payload release [2] leading to inter-conversion between ADC species (figure 1, upper panel). A tumor compartment was added to the model [3]. Target binding can occur at multiple sites and extended TMDD models allow multiple ADC species to compete for target binding. Payload is released following de-conjugation, target binding and internalization, and protein catabolism in tissue or plasma. The released payload (%ID) in the tumor is calculated.

Results: Both a high level of antigen with low internalization rate and a low level of antigen with high internalization rate can achieve a high payload delivery to the tumor (Figure 1(a)). For a given antigen level and internalization rate there is an optimal range of doses to achieve maximal efficiency of payload delivery (%ID). Figure 1(b) shows the impact of antigen level in normal tissue on the efficiency of payload delivery to the tumor compartment.

Conclusions: A mechanistic tumor model was incorporated into a minimal PBPK framework to model the efficiency of payload delivery to the tumor by ADCs.

References:
[1] Li et al. AAPS J. 2014; 16.
Drug release:
A. Target binding and consequent internalization
B. Deconjugation of ADC
C. Catabolism of ADC
D. Plasma clearance of ADC

Target binding:
1. Binding in tumor interstitial space
2. Binding in tissue interstitial space
3. Binding in plasma
4. Binding in lymph node

A – on-target toxicity  B,C,D – off-target toxicity

Figure 1. A schematic representation of a minimal PBPK model for ADCs (upper panel) and the simulation results: (a) the percentage of injected dose (payload) internalized into tumor cells (%ID) for a range of antigen concentrations with different internalization rates; (b) the impact of antigen expression levels in normal tissues on %ID. $Y_j$ – ADC species with DAR j.