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 (cytotoxic 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 target antigen level, ADC internalization rate, target binding affinity, de-conjugation rate, and number of off-target binding, etc. An integrated approach is needed to model the interplay of these multiple factors. For this purpose a minimal PBPK model for ADCs coupled with a full PBPK model for released payload 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, i.e., DAR) with payload release [2] leading to interconversion between ADC species (figure 1). A tumor model with the same structural basis as tissue was added into the PBPK framework; this is an extension of the solid tumor model developed by Thurber et al [3]. For solid tumor, in contrast to normal tissue diffusion rather than convection is the primary mechanism for transport of ADC species across the blood vessel wall. The diffusion process is mainly characterized by the average radius of tumor tissue surrounding each blood vessel representing the density of tumor blood vessels [3]. Full, quasi-steady state, and Michaelis-Menten models for target-mediated drug disposition (TMD) were extended to allow multiple ADC species to compete for binding to a single target, with the additional possibility that target binding can occur at multiple sites. Mass fluxes from all possible routes of drug release (including non-specific catatasis in tissue and plasma, de conjugation in plasma via specific and tissue catatasis via target binding and subsequent internalization) were tracked and summated. These fluxes are fed into the full PBPK model for small molecule drugs, see figure 2.

RESULTS Figure 3 shows typical outputs from the model. The kinetics of the payload show typical formation-limitation metabolites profile. Rates of declining conjugated Ab, conjugated drug, and released payload are converging as time progresses, see figure 3B. In addition, the model shows a good sensitivity of the averaged DAR profile on deconjugation rates (k_d) see figure 3D.

CONCLUSION A minimal PBPK model is developed for ADCs, which also incorporates a mechanistic tumor model to allow the study of payload delivery to the tumor. The percentage of injected drug (payload) being internalized into tumor cells was used to assess the efficiency of payload delivery. In this simulation study, it is shown that a high efficiency of payload delivery can be achieved either by a high level of antigen with a low internalization rate or a low level of antigen with a high internalization rate, but was also dependent on several other factors, such as dose, binding affinities to target and FcRn, and the density of tumor blood vessels. This complex interplay of multiple factors exemplifies the need for an integrated modelling and simulation approach to understand the disposition of ADCs.

REFERENCES