1310 SUPPORTING DOSE DECISIONS FOR ANTIBODY DRUG CONJUGATES (ADC) THROUGH COMBINED EFFICACY AND TOXICITY MODELING

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Background Antibody Drug Conjugate (ADCs) therapies combine targeted antibodies with potent drugs. However, systemic toxicities often limit their effectiveness and narrow their therapeutic index (TI).[1] While there are methods to predict the initial dose for ADCs based on efficacy,[2] predicting toxicities that determine the maximum tolerated dose (MTD) remains a challenge. However, Inability to identify the MTD can lead to drug discontinuation.[3 4]

ADC programs face major challenges in selecting the right components, inferring human dose from preclinical data, and improving the TI. To address these challenges, we developed a mechanistic model. Here, we present two case studies: 1) How to select the appropriate payload based on cancer type? and 2) Deriving the dose for First-In-Human (FIH) trials while considering efficacy and toxicity. We also propose a framework for predicting MTD based on information from approved ADCs.

Methods We built an mPBPK model with detailed mechanisms for ADC internalization (figure 1). In case study 1, we compared Dxd and DM1 payloads[5–7] based on their cell killing potential, bystander effect, and dose sensitivity. Case study 2 involved predicting the FIH dose for Lonca and comparing it to clinical data.[8 9] We relied on published data for both case studies. For MTD prediction, we hypothesized that the plasma Cmax of the payload at MTD ($PCmax_{PL}$) should be similar for ADCs sharing the same payload (figure 2). Here we present the observations from 6 ADCs sharing MMAE payload.

Results We observed that Dxd and DM1 had similar potency, but Dxd exhibited a stronger bystander effect, making it suitable for heterogeneous lesions. DM1 was more sensitive to dose, but at high doses, its response was comparable to Dxd (figure 3A). Our model accurately predicted the FIH dose for Lonca, aligning with clinical recommendations (figure 3B). Consistency in $PCmax_{PL}$ values (3–8 ng/mL) was observed for selected ADCs sharing the MMAE payload,[10–15] supporting our hypothesis.

Conclusions ADCs require customization for specific cancer types and populations. Payload selection should consider factors beyond potency, including bystander effect and systemic toxicity. Our mechanistic ADC model reliably predicts the FIH dose based on preclinical data and the consistency in clinical $PCmax_{PL}$ aids in predicting MTD for novel ADCs, enhancing FIH dosing recommendations.

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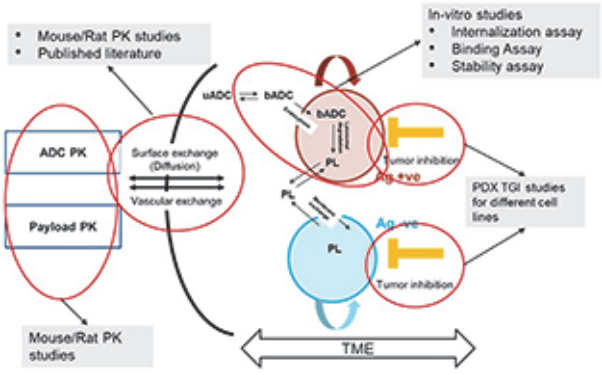
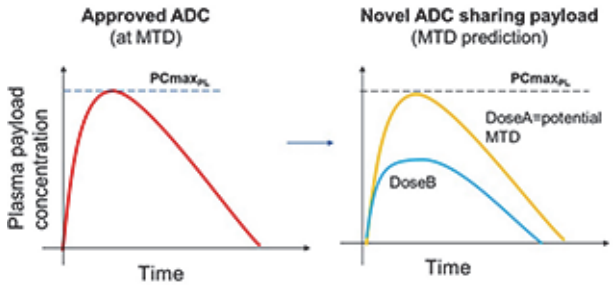
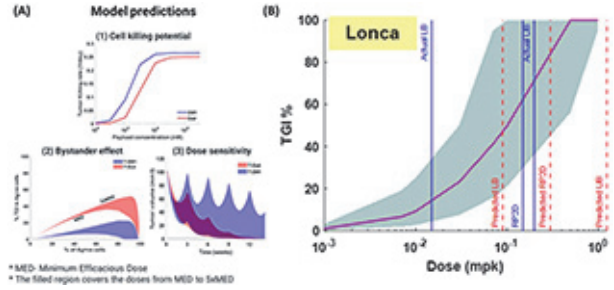


Abstract 1310 Figure 1 Model components and the data informing them. uADC - Unbound ADC, bADC - bound ADC, PL - Payload, Ag — Antigen



Abstract 1310 Figure 2 Depiction of MTD prediction for novel ADC using data from approved ADCs



Abstract 1310 Figure 3 Results from case study 1 (A) and case study 2 (B)

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