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Enhancing the Predictability of Human Pharmacokinetics for Antibody-Drug Conjugates Using Human FcRn Transgenic Mice

CROWN BIOSCIENCE

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Introduction

Accurate prediction of human pharmacokinetics (PK) remains a pivotal challenge in the preclinical development of Antibody-Drug Conjugates (ADCs). A primary determinant of ADC clearance is the interaction between the IgG Fc domain and the neonatal Fc receptor (FcRn), which governs antibody recycling and half-life. However, the species-specificity of this interaction means that wild-type (WT) mouse models often fail to recapitulate human FcRn binding and recycling and thus provide poor predictions of human PK, complicating first-in-human (FIH) dose estimation [1]. As demonstrated in foundational studies, transgenic mouse models expressing human FcRn (hFcRn) provide a more physiologically relevant system, showing better correlation with human PK for monoclonal antibodies [2][3]. However, the predictive value of this model for the more complex ADC PK/PD, which is influenced by additional factors such as linker stability and payload properties, remains less defined. This study investigates the utility of the hFcRn and hAlb/hFcRn transgenic mouse model for predicting the human PK of a diverse panel of approved ADCs, establishing its value as a core component of Crown Bioscience translational ADC DMPK platform.

Methods

A comprehensive *in vivo* PK study was conducted for four clinically approved ADCs: Trastuzumab Deruxtecan (T-DXd), Trastuzumab Emtansine (T-DM1), Sacituzumab Govitecan (SG), and Enfortumab Vedotin (EV). Each ADC was administered as a single intravenous dose (10 mg/kg) to three distinct mouse models (study design in **Table 1**).

Table 1. Study Design *of In Vivo* PK in WT Mice, hFcRn and hAlb/hFcRn Model

Group	Treatment	N of Mice	Treatment	Dose level (mg/kg)	ROA	Frequency
1	WT Mice	3	ADC	10	i.v.	single
2	hFcRn	3	ADC	10	i.v.	single
3	hAlb/hFcRn	3	ADC	10	i.v.	single

Blood samples were serially collected at 10 timepoints from 15 minutes to 28 days post-dosing. The concentrations of total ADC in plasma were quantified using ligand-binding assays (LBA), while released free payloads were measured via LC-MS/MS. Non-compartmental analysis was used to derive PK parameters, with a focus on terminal half-life. The half-lives obtained from each mouse model were then systematically compared with the reported clinical half-lives in human and non-human primate (NHP) from well-validated and reported data.

Results

The PK profiles of all four ADCs were markedly different across the mouse models. As anticipated, the WT mice consistently exhibited prolonged half-lives for total ADC, failing to reflect the faster clearance observed in humans. In contrast, the hFcRn and hAlb/hFcRn transgenic mice showed significantly shorter and more comparable half-lives, aligning more closely with known clinical data (**Table 2**).

For instance, the half-lives of T-Dxd was 134 hours in WT mice, while 59.07 hours in hFcRn mice and 110 hours in hAlb/hFcRn mice compared with 167.3 hours in human as reported (**Figure 1D**),. Meanwhile, SG showed a near-human half-life in hFcRn mice (11.2 hours vs. 16 hours in human), whereas WT mice significantly overestimated exposure (134.1 hours) (**Figure 1A**). EV and T-DM1 also displayed similar trends, with hFcRn-based models yielding half-lives (45.5 hours and 59.5 hours, respectively) that were substantially more predictive than those from WT mice (214.4 hours and 92.0 hours), closely matching clinical observations (81.6 and 93.6 hours) (**Figure 1B and 1C**).

Results Continued

Notably, our statistical analysis of the correlation between mouse model and clinical data revealed a compelling outcome: the half-lives in hAlb HSA/hFcRn transgenic mice demonstrated an excellent correlation with reported values in both human ($r^2 = 0.9485$, $p < 0.05$) (**Figure 2A**) and NHP ($r^2 = 0.9820$, $p < 0.01$) (**Figure 2D**)**;** the half-lives in hFcRn transgenic mice demonstrated a very good correlation with reported values in both human ($r^2 = 0.8170$, $p < 0.05$) (**Figure 2B**) and NHP ($r^2 = 0.7383$, $p = 0.1407$) (**Figure 2E**). Conversely, no significant correlation was observed between the half-lives in WT mice and those in either humans or NHPs (**Figure C and F**), underscoring the limited predictive power of the conventional model. Furthermore, the platform successfully differentiated the stability characteristics between ADCs with stable (e.g., T-DXd) and more labile (e.g., EV) linkers, providing insights into ADC structure complexity and PK relationships.

Table 2. PK Profiles of 4 ADCs in Different Mouse Models

Parameters	Mouse Model	Sacituzumab Govitecan	Enfortumab Vedotin	Trastuzumab Emtansine	Trastuzumab Deruxtecan
Half-life(hour)	WT C57BL/6	134.14	214.35	91.98	133.99
	hFcRn	11.17	45.50	59.54	66.65
	hAlb/hFcRn	38.08	56.81	75.12	110.13
Cl(mL/hour/kg)	WT C57BL/6	418.70	157.65	4.16	0.13
	hFcRn	156.71	64.76	8.56	0.30
	hAlb/hFcRn	0.92	0.52	0.43	0.13
AUClast(day*ug/mL)	WT C57BL/6	169.69	411.24	99.22	2658.00
	hFcRn	21.95	271.77	48.28	1344.78
	hAlb/hFcRn	450.81	794.01	910.08	469.48

Figure 1. *In Vivo* PK Profiles of 4 ADCs (10 mpk) in Wild-Type, hFcRn, hAlb/hFcRn Mouse Models
(A) Sacituzumab Govitecan (B) Enfortumab Vedotin (C) Trastuzumab Emtansine (D) Trastuzumab Deruxtecan

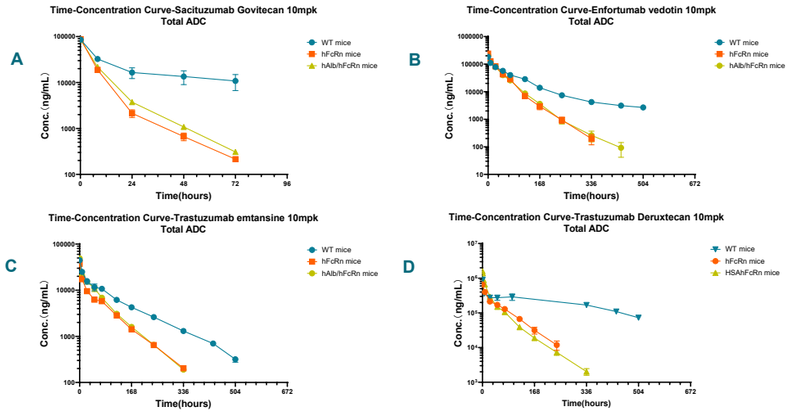

Table 3. Half-Life Comparison of ADCs PK in hFcRn Model vs Human and NHP

ADC	Target	Linker	Payload	Half-life in individual species (Hours)				
				hAlb/hFcRn	hFcRn	WT mice	Human	Cyno Monkey
Sacituzumab govitecan	Trop-2	Acid-cleavable linker (CL2A)	SN-38	38.08	11.17	134.14	16.00	13.00
Enfortumab vedotin	Nectin-4	Protease-cleavable linker (MC-VC)	MMAE	56.81	45.50	214.35	81.60	34.00
Trastuzumab emtansine	HER2	Non-cleavable (thioether)	DM-1	75.12	59.54	91.98	93.60	64.80
Trastuzumab deruxtecan	HER2	Cleavable tetrapeptide linker (GGFG)	DXD	110.00	59.07	134.00	167.28	95.00

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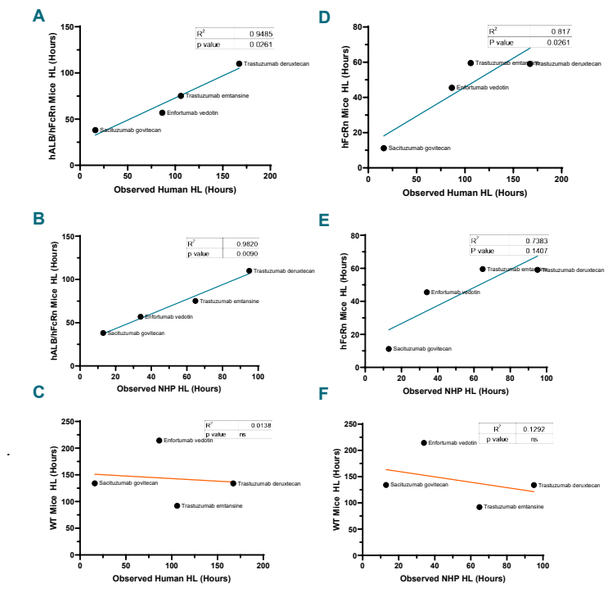
Results Continued

Figure 2. Correlation Analysis of Half-life for 4 ADCs in hFcRn Model vs Human and NHP (A) hAlb/hFcRn Model vs Human (B) hFcRn Model vs Human (C) WT Model vs Human (D) hAlb/hFcRn Model vs NHP (E) hFcRn Model vs NHP (F) WT Model vs NHP



Conclusion

This study provides validation of the hFcRn transgenic mouse model as a clinically predictive system for ADC pharmacokinetic assessment. Our data demonstrate that this model recapitulates more closely human-relevant PK profiles, addressing a major limitation of conventional WT mouse models.

This platform improves the reliability of human PK predictions and supports FIH trial design, reducing risk throughout ADC development. Through data-driven candidate selection and enhanced translational confidence, it minimizes NHP study dependency and accelerates the progression of promising ADC therapeutics toward clinical evaluation.

References

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