

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



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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 2C 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

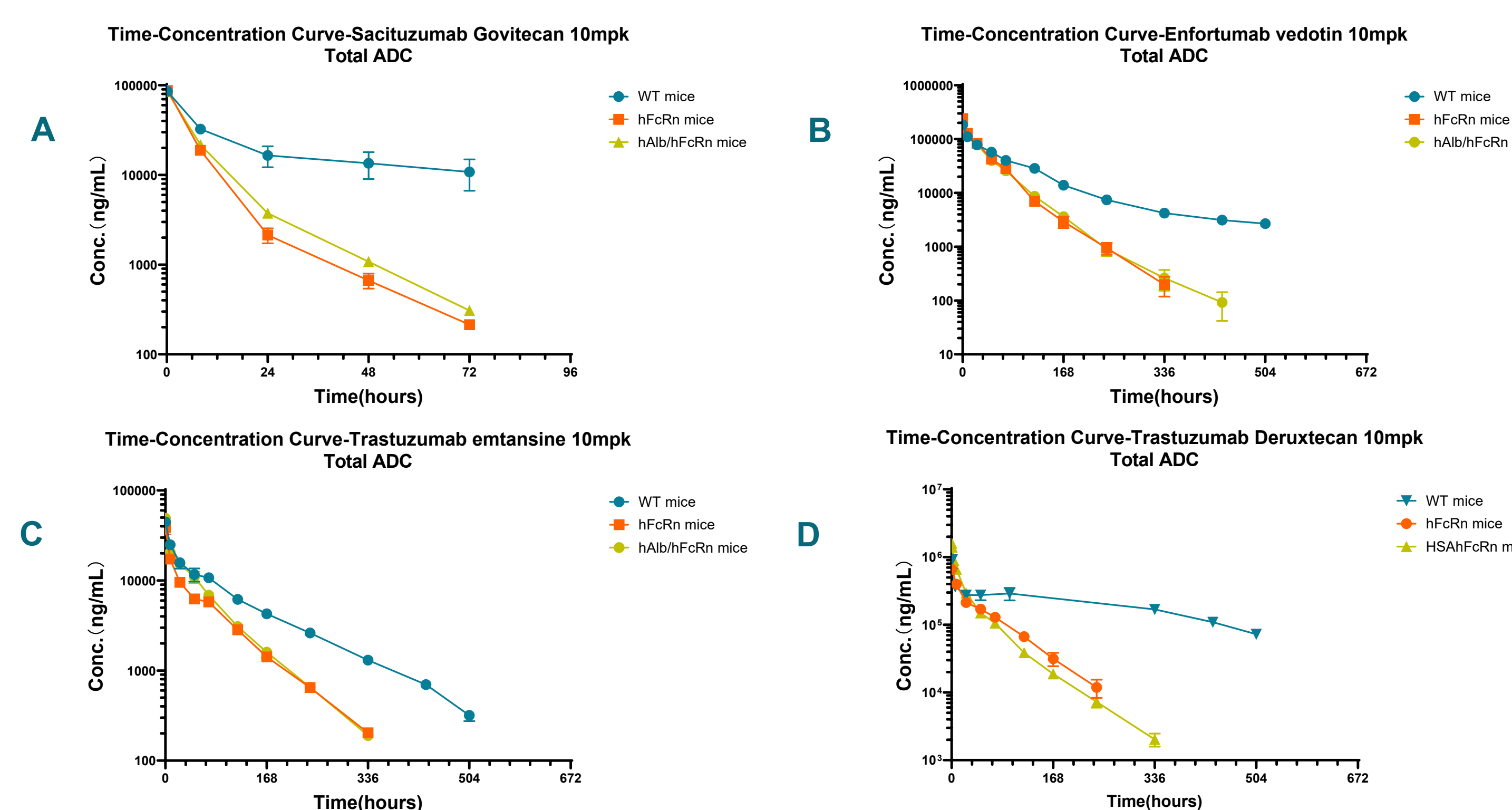


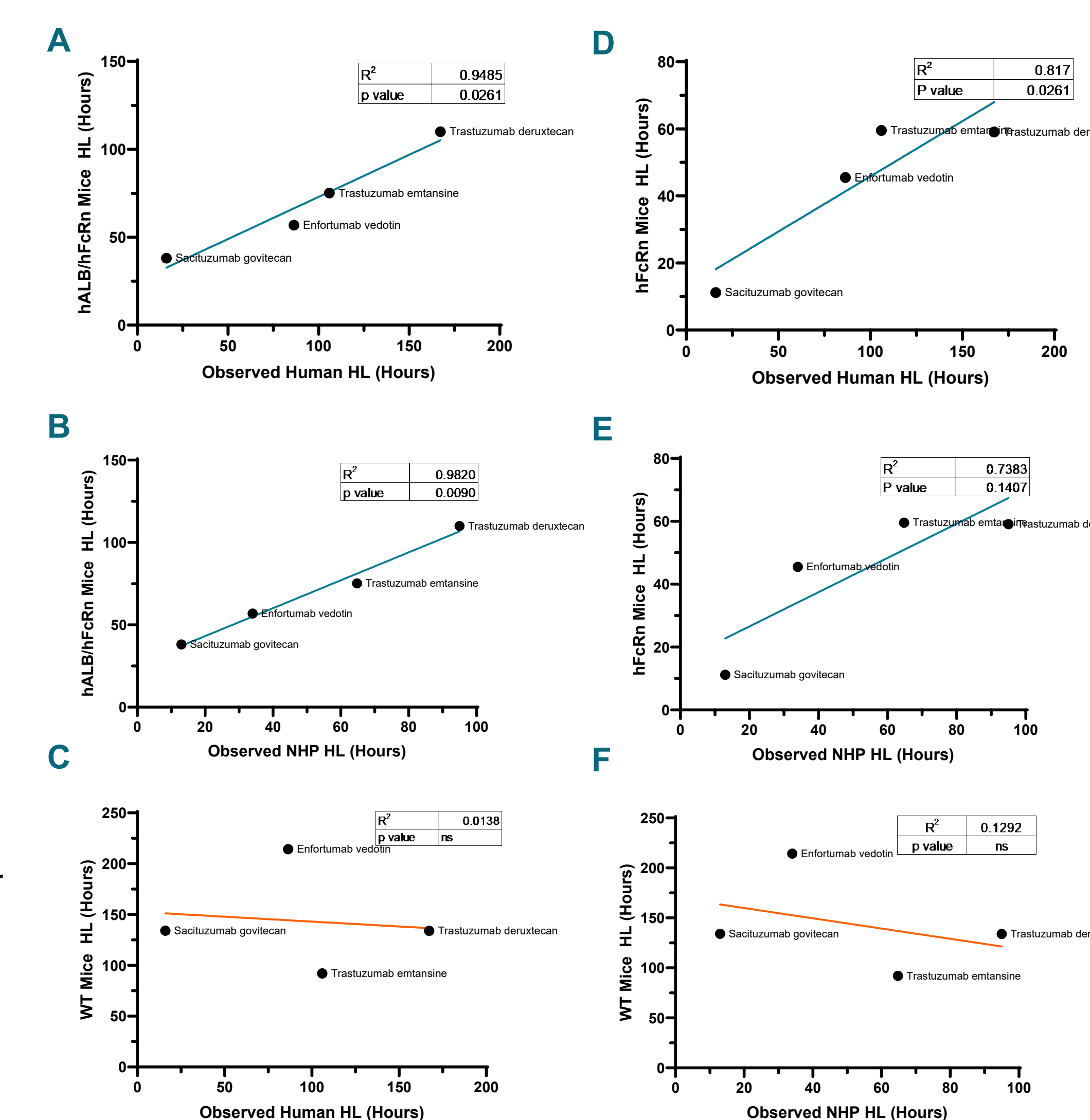
Table 3. Half-Life Comparison of ADCs PK in hFcRn Model vs Human and NHP

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

See our [Poster 1814](#) for our comprehensive *in vitro* / *in vivo* DMPK bioanalytical platform to accelerate ADC drug development

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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