Integration of clinical data and mechanistic model simulations highlights key parameters for design and selection of successful ADCs

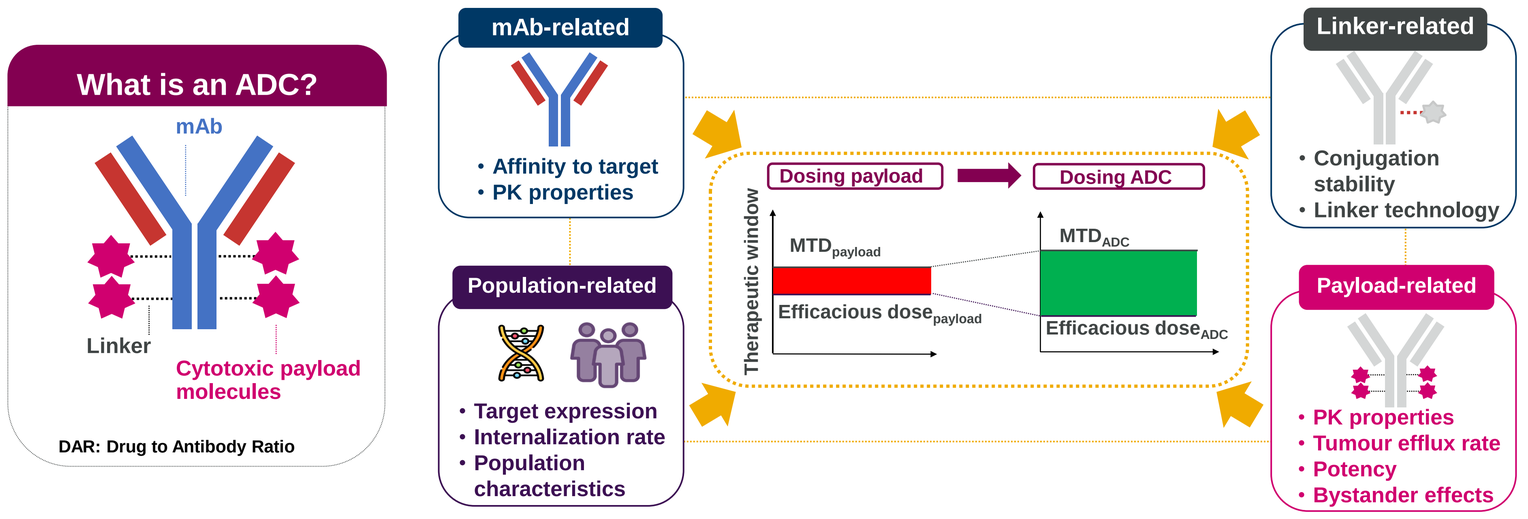
Adriana Savoca[1], Christina Vasalou[2], Cesar Pichardo-Almarza[3], Pavan Vajjah[4]

(1) Discovery Translational PKPD, Clinical Pharmacology and Quantitative Pharmacology, R&D Biopharmaceuticals, AstraZeneca, Cambridge, UK
(2) Discovery Translational PKPD, Clinical Pharmacology and Quantitative Pharmacology, R&D Biopharmaceuticals, AstraZeneca, Waltham, MA, US
(3) Systems Medicine, Clinical Pharmacology and Quantitative Pharmacology, R&D Biopharmaceuticals, AstraZeneca, Cambridge, UK
(4) Clinical Pharmacology and Quantitative Pharmacology, R&D Biopharmaceuticals, AstraZeneca, Cambridge, UK

Background & Introduction

- Antibody drug conjugates (**ADCs**) are designed to exploit the **targeted nature** of monoclonal antibodies (**mAbs**) to **selectively deliver highly cytotoxic drugs to tumour cells**.
- Despite the exciting "*magic bullet*" concept and 24 years since first approval, **only 12 ADCs have been FDA-approved to this day**. Several have been **discontinued**, because of limited efficacy or excessive toxicity.
- We have **integrated published clinical data with mechanistic modelling** to gain insight into **key designable parameters and their optimal ranges**, with the goal of identifying **learnings on what makes a clinically successful ADC.**

Design of a successful ADC requires a multiparametric approach to optimize therapeutic window



Methods

Clinical Data

Data search and collection → **Data analysis**

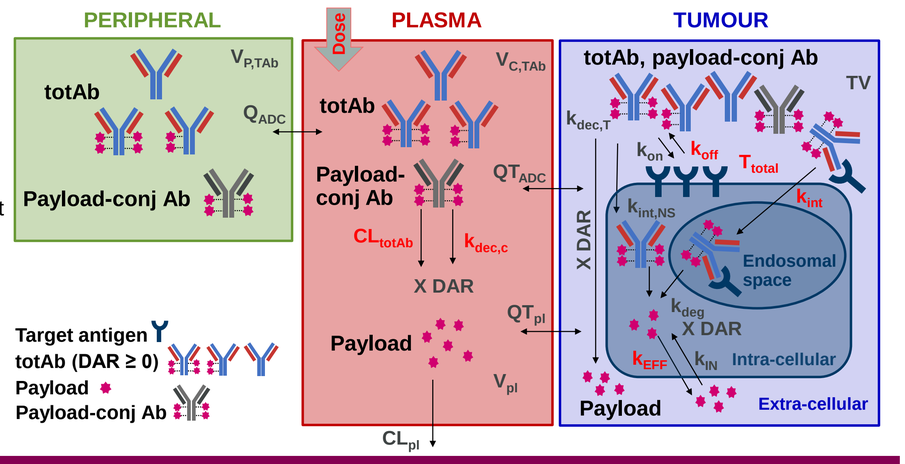
For approved and/or in-development and discontinued ADCs, we have gathered publicly available **clinical data** on

- **total antibody** (totAb) **and ADC exposures**
- **conjugation stability** (as ADC:totAb AUC ratio)
- **binding affinity to target**

Mechanistic model

A **published mechanistic model**[1] was adapted to describe **totAb**, **antibody-conjugated payload and free payload pharmacokinetics** in plasma, peripheral tissue and tumour. The ADC can enter tumour cells via nonspecific uptake or target-mediated internalization, then release the cytotoxic payload upon lysosomal degradation. The payload can drive cell killing in tumour and influx/efflux rates regulate its diffusion from intra-cellular to extra-cellular tumour space, from where it can extravasate back to plasma. Deconjugation associated to linker instability is also accounted for in the model. Simulations of **plasma and tumour payload exposure** allow comparing different scenarios of

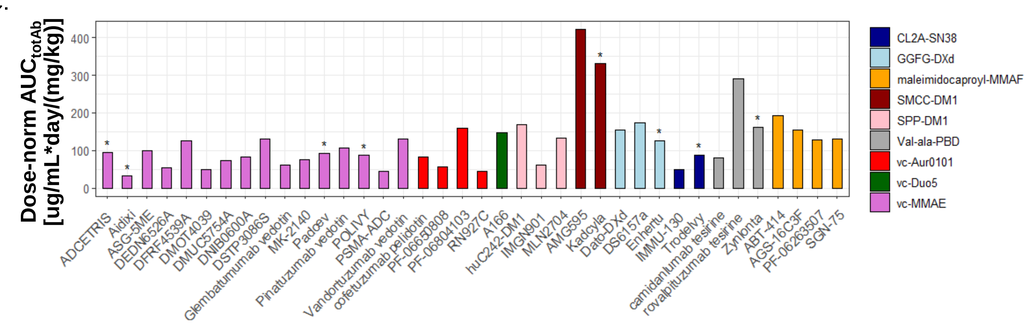
1) totAb clearance (CL_{totAb}) and conjugation stability (k_{dec});
2) binding affinity (K_d) for different target levels and internalization rate (k_{int});
3) payload efflux rate from tumour cells (k_{Eff})



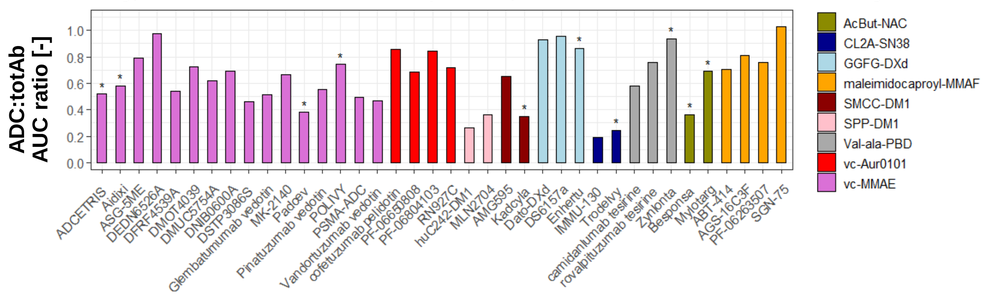
Results

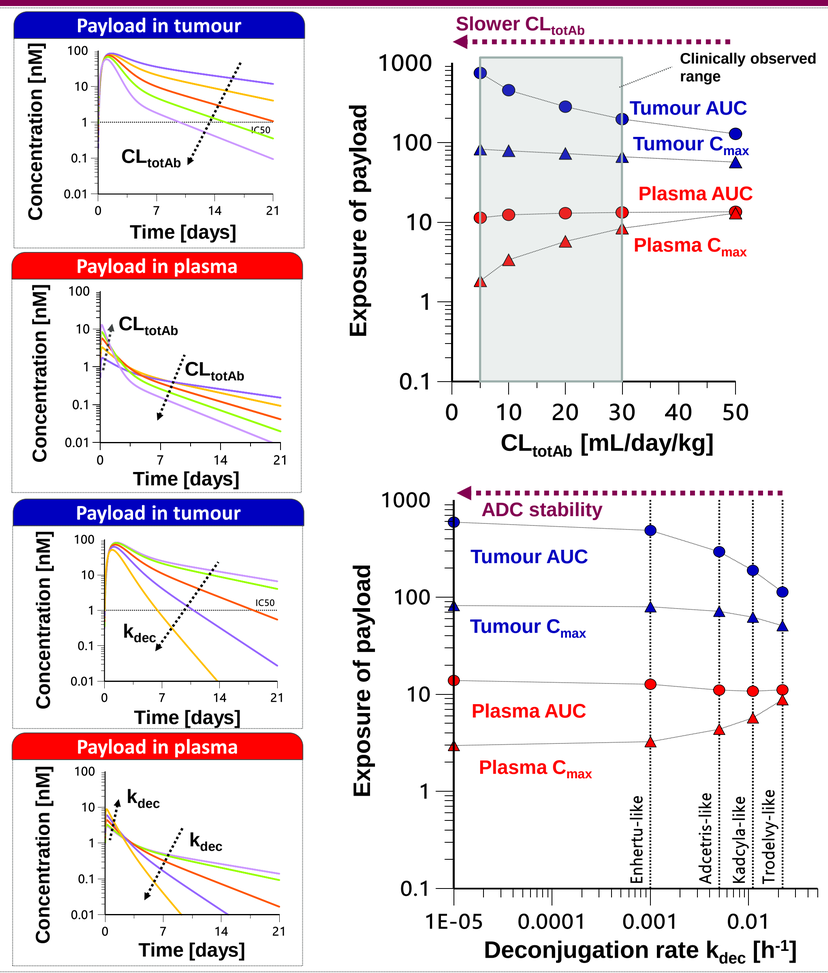
1. Clearance and conjugation stability

- Analysis of totAb AUC for **discontinued/in-development vs approved (*) ADCs does not indicate a clear threshold for success**. However, model simulations show that a **slower CL_{totAb} can enhance tumour exposure of released payload**, with limited impact on its plasma AUC.

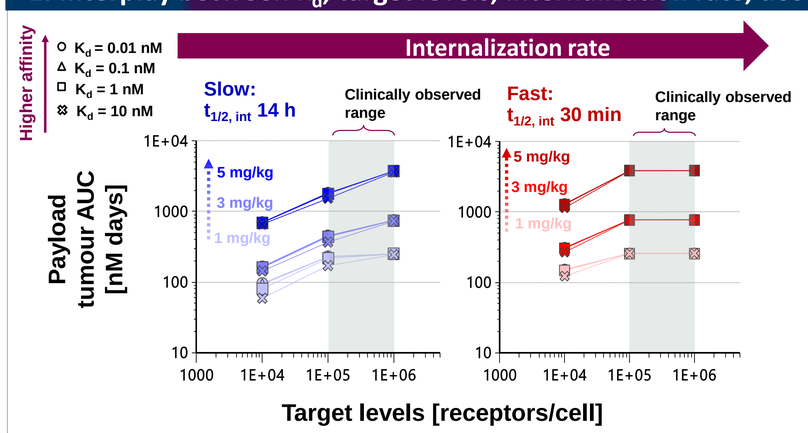


- Simulations show that **lower stability levels can be detrimental on payload tumour exposure** and **increase plasma C_{max}**, with potential concerns on **C_{max}-driven toxicity**. However, **improving stability over a certain threshold** (~0.85-0.9 ADC:totAb AUC ratio) **brings minimal benefit** to released payload tumour exposure. Clinical data show that stability of approved **(*)** ADCs is quite varied, and similar for approved vs in development/discontinued ADCs. This suggests that, **while conjugation stability is critical to enhance payload tumour delivery, other mechanisms can compensate, and drive observed clinical efficacy.**





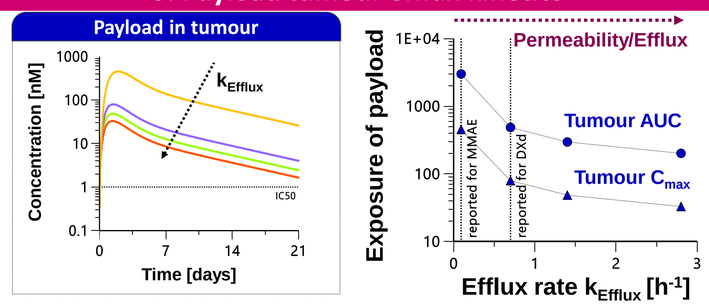
2. Interplay between K_d, target levels, internalization rate, dose



- **Affinity range** of approved ADCs in **solid tumour** indications, where target levels spans 10^5-10^6 recept/cells, is **26 pM to ~5 nM**.
- Simulations show that **higher affinity is favourable for lower target levels, slower internalization rates, and low doses**.

ADC	Target	K_d [nM]	Source
Padcev	Nectin4	4.94	Patent (WO2021213434)
Tivdak	TF	3.1	BLA, FDA , n. 761208. 21
Aidexi	HER2	0.044	Patent (WO2020042941A1)
Kadcyla	HER2	1.08	EMA label, Procedure No.EMEA/H/C/002389/0000. 2013
Enhertu	HER2	0.047	EMA label, Procedure No.EMEA/H/C/005124/0000. 2020
Trodelvy	TROP2	0.026	2014 Goldenberg et al. JCO
Elahere	Fr-alfa	0.2	BLA, FDA , n. 761310. 022.

3. Payload tumour efflux kinetics



- **Payloads** approved in **solid tumour** indications have **potency** ranging from **high** (10^{-10}-10^{-9} M, auristatins and maytansinoids) to **mid-high** (10^{-9} - 10^{-8} M, TOP1is). Majority of them are reported to have **bystander effects**[2].
- Simulations suggest **enhanced tumour exposure can be obtained by optimizing physicochemical properties and compensate for a lower cytotoxic potency**, reducing probability of adverse effects.
- **Efflux rates reported for MMAE**[3] **and DXd**[4] **can be used as benchmarks** for balancing extent of payload retention in tumour cells, necessary to achieve **target-positive cells killing**, with capability of diffusing across tumour tissue and drive **killing of bystander target-negative cells**.

MMAE = Monomethyl Auristatin E; DXd = Dexruxtecan

Conclusions

- By combining available clinical data with mechanistic model simulations, we have shed light on **ranges of designable parameters for approved ADCs**, their interaction with population-related parameters, and their **effect on tumour and plasma payload kinetics**, which can be correlated to **clinically observed efficacy and toxicity**.
- The analysis presented here on the various clinical compounds can **inform decision-making in ADC discovery and development programs** and improve probability of clinical success, with reported ranges functioning as **benchmarks to build confidence in the candidates**.

References

1. Singh et al. (2016). The AAPS journal, 18, 861-875.
2. Khera et al. (2018). Molec Sys Design & Eng, 3(1), 73-88.
3. Bussing et al. (2021). AAPS J. , 23(3):56.
4. Vasalou et al. (2024). Pharmacometrics Syst Pharmacol.