Over 800! Establishment of an ADC Payload Efficacy Database Across Diverse Tumor Cell Lines: Foundation for Optimized In Vitro ADC Evaluation and Drug Development

KYINNO Biotechnology
Drug Discovery Service

Guoqian Wang, Yao Tang, Jingxiao Xu, Tingduo Lv, Jinying Ning, Feng Hao*

KYinno Biotechnology Co., Ltd. F2 Building, Yizhuang Biomedical Park, Beijing 101111 China. Correspondence: feng.hao@kyinno.com

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Abstract

Since the inaugural approval of the first antibody-drug conjugate (ADC), Mylotarg, in 2000, the landscape of oncology therapeutics has evolved dramatically. To date, the market has expanded to encompass 15 approved products, with a robust pipeline of over 210 candidates currently in clinical trials. This surge signifies that ADC development has entered a flourishing era. Notably, ADCs targeting molecules such as HER2, EGFR, Trop2, CLDN18.2, and Nectin-4 have demonstrated remarkable efficacy and manageable safety profiles, underscoring their vast therapeutic potential in cancer treatment.

Structurally, an ADC comprises three integral components: a monoclonal antibody, a chemical linker, and a cytotoxic payload. Among these, the payload is the cornerstone of the drug's potency. The payloads utilized in approved ADCs—such as MMAE/MMAF, calicheamicin, DM1/DM4, and SN38/Dxd—are characterized by high toxicity, often exceeding that of traditional chemotherapeutic agents by one to two orders of magnitude, with some exhibiting potency in the picomolar (pM) range. Current research categorizes the mechanisms of action for these payloads into four primary classes: DNA alkylating agents, DNA topoisomerase inhibitors, microtubule disruptors, and RNA polymerase II inhibitors.

To support this advancing field, we have established a comprehensive cell bank containing over 900 cell lines, including 800+ human and 100+ animal tumor lines, covering a broad spectrum of cancer types. Leveraging this extensive biological resource, we are constructing a state-of-the-art ADC screening platform. Through systematic profiling, we generate efficacy data for various payloads across these cell lines, which serves as a critical reference for selecting optimal models for in vitro ADC evaluation. To date, we have successfully characterized over 700 cell lines using benchmark payloads, including MMAE, SN38, Dxd, and exatecan.

As a large-scale strategic initiative, this ADC screening platform is poised to play a pivotal role in accelerating the discovery and rigorous evaluation of next-generation ADC therapeutics.

Payloads summary

Payload Class	Mechanism of Action	Representative Toxins	Representative ADC	Advantages	Limitations
Microtubule Inhibitors	Inhibit microtubule polymerization, block cell division, and arrest cell cycle (G2/M phase).	MMAE, MMAF, DM1, DM4	Adcetris® (MMAE), Kadcyla® (DM1)	Well-characterized mechanism; used in approved ADCs; high efficacy in rapidly dividing cells.	Limited to actively dividing cells; resistance common; neurotoxicity risks.
DNA-Damaging Agents	Induce DNA double-strand breaks or crosslinks via intercalation/alkylation.	Calicheamicin, PBD, Duocarmycin	Mylotarg® (calicheamicin), Besponsa® (calicheamicin derivative)	Ultra-potent (picomolar-level); effective against quiescent cells.	Narrow therapeutic window; off-target DNA damage risks.
Topoisomerase Inhibitors	Inhibit Topo I/II, causing DNA strand breaks during replication/ transcription.	DXd, SN-38	Enhertu® (DXd), Trodelvy® (SN-38)	Effective in dividing and non-dividing cells; bypasses microtubule resistance.	Instability in some payloads; reduced efficacy due to detox mechanisms.
RNA Polymerase II Inhibitors	Block mRNA synthesis by inhibiting RNA Pol II.	α-Amanitin	HDP-101 (α-Amanitin, preclinical)	Broad antitumor activity (including quiescent cells); overcomes resistance.	Extreme systemic toxicity; requires optimized linker design.
Novel-Mechanism Payloads	Non-classical mechanisms (e.g., protein degradation, immune activation).	Eribulin, STING agonists	HDP-101 (Eribulin, Phase I)	Potential to overcome resistance; expands targets (e.g., low-proliferation tumors).	Limited clinical data; complex mechanisms; safety under investigation.

Over 800 human cancer cell lines in Kyinno

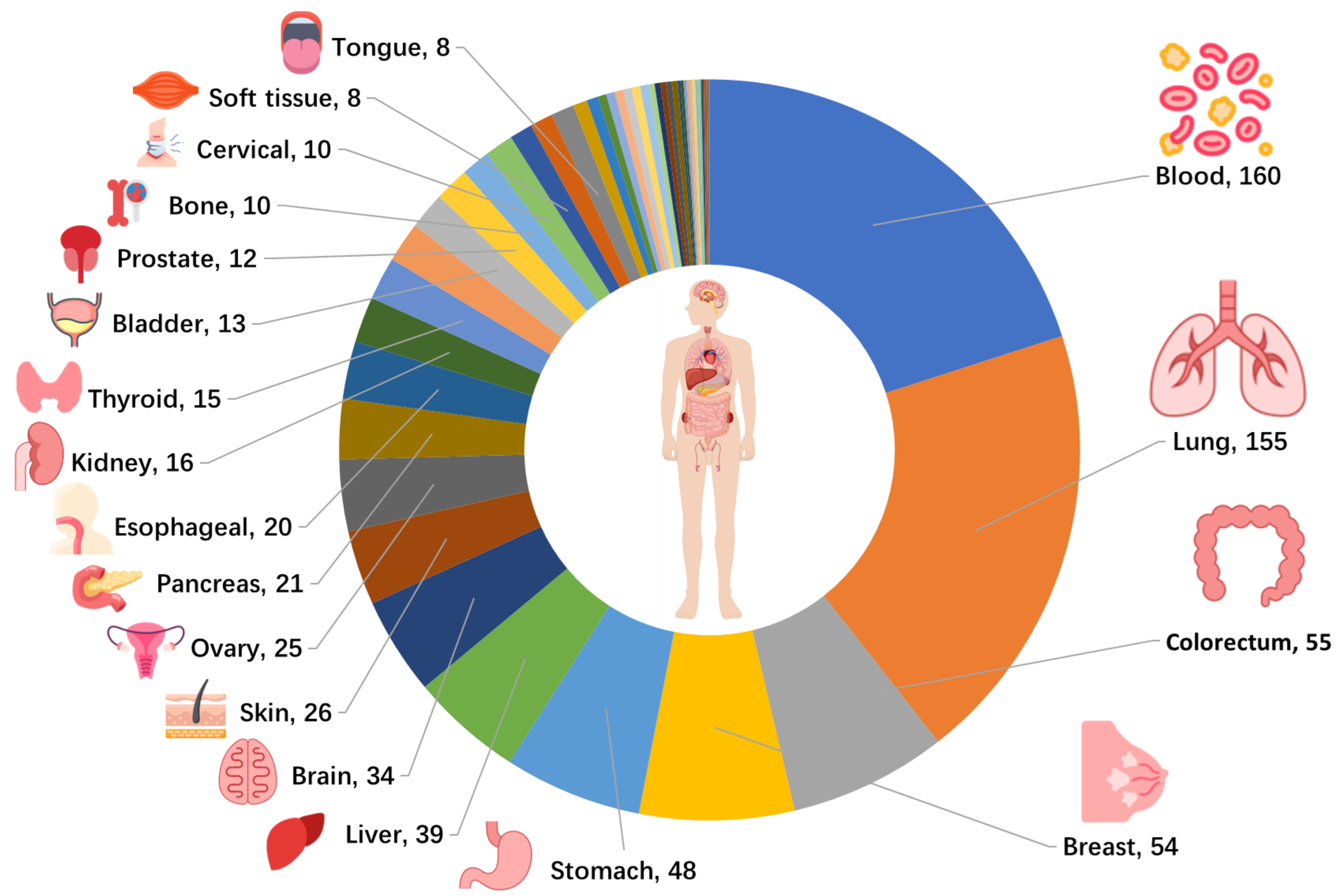


Figure 1: Overview of Tumor Cell Lines. Kyinno has established a cell bank containing over 800 human tumor cell lines, covering 44 types of cancer, which almost encompasses all known tumor types. The figure lists most cancer types and the corresponding number of cell lines available.

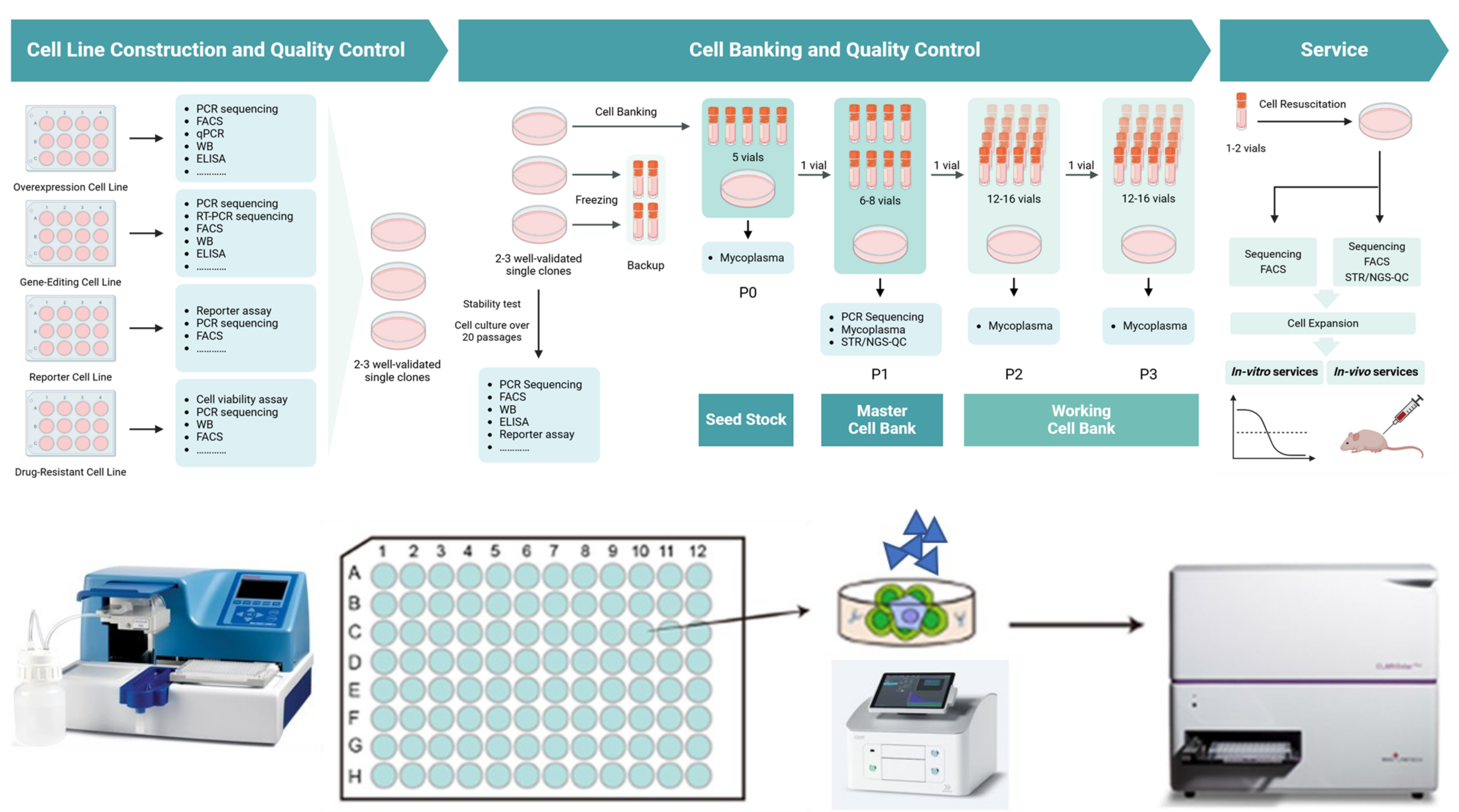
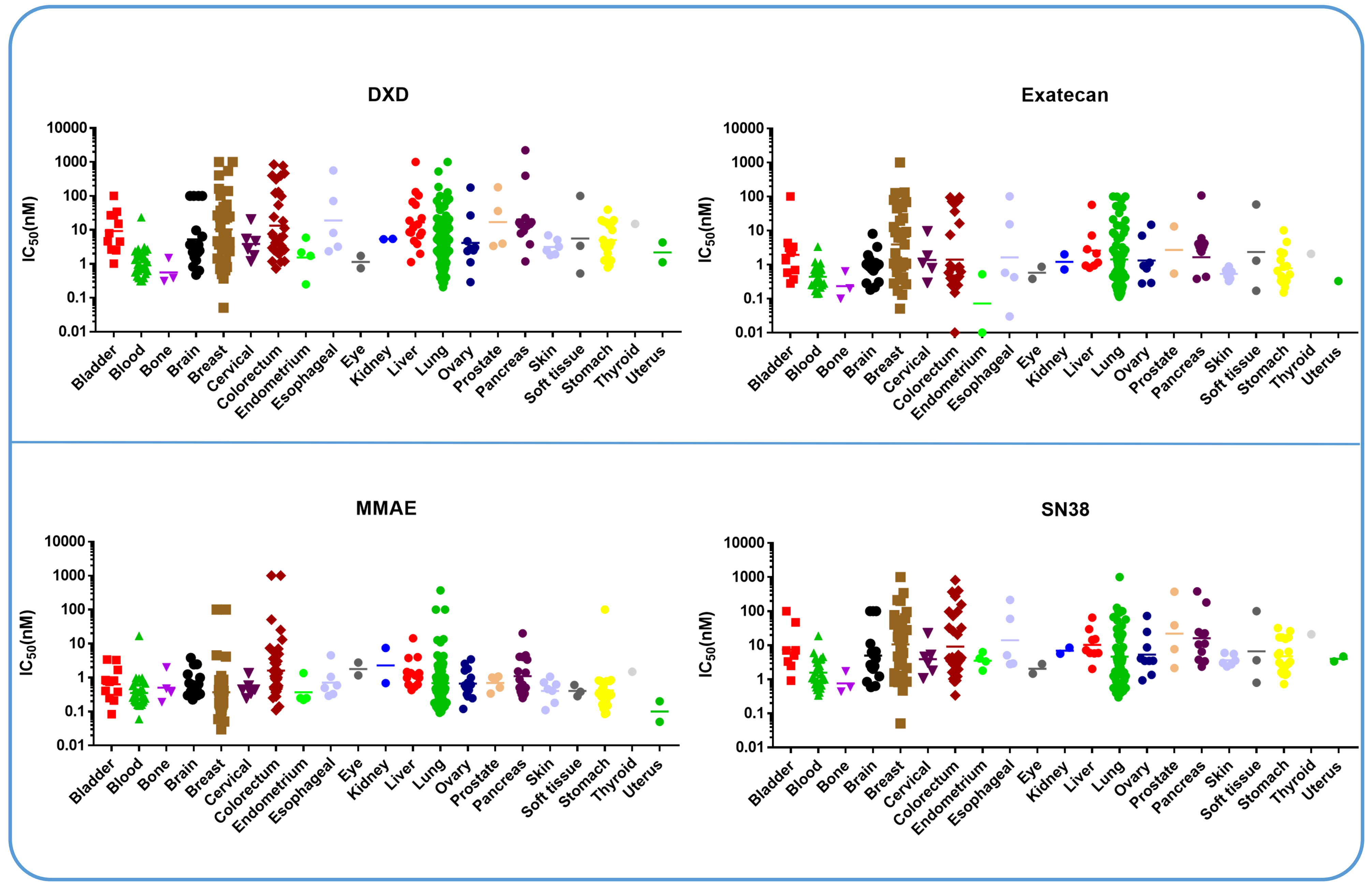


Figure 2: Schematic of Cell Banking QC and HTS Screening. This figure shows how we perform cell quality control and cell library banking quality control to ensure the accuracy and consistency of the cells used in *in vitro* and *in vivo* tests. Additionally, during the MegaScreen process, we have completely adopted automated instruments to replace manual operations in order to enhance the consistency and accuracy of the tests.

IC_{50} summary of payloads cross cancer cell lines



MegaScreen Services

Unwavering quality: Stringent QC: STR, mycoplasma, cell growth curve；Validated control compounds

Customized solutions: Services tailored to your specific research needs, including testing time points, cell densities, and others

Bioinformatic analysis: Omics data from Depmap, Sanger's Cell Model Passport, and in-house profiling; Drug similarity analysis; Univariate and multivariate biomarker discovery

Summary

- Kyinno has established a cell bank comprising more than 800 human tumor cell lines covering 44 cancer types.
- Through comprehensive profiling, we generated efficacy data for diverse ADC payloads across a broad panel of cell lines. Combined with bioinformatic analysis, these data enable rational selection of appropriate cell lines for the in vitro evaluation of ADCs.

Contact: Dr. Feng Hao, Email: Feng.hao@kyinno.com
Website: http://www.kyinno.com
Database：http://innopedia.kyinno.com