Integrated Resistance Cell Panel Platform for ADC Profiling and Mechanism-Guided Payload Exploration

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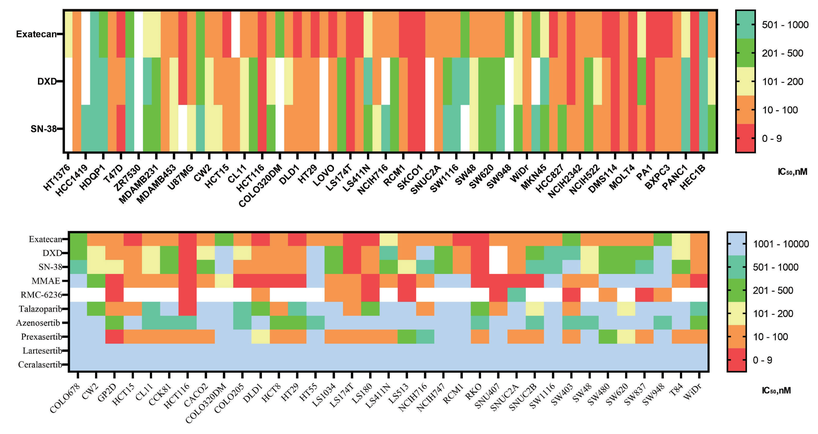
Part 1: ADC Parental Cell Panel Characterization



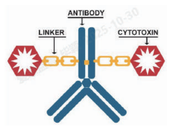
Heatmap of sensitivity to ADC, payload and small molecule inhibitors across parental cell lines

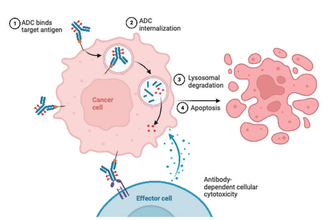
Part 2: Characteristics of 25 Established ADC-Resistant Cell Lines

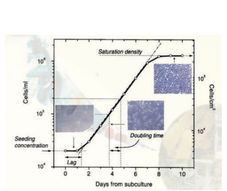
1. Procedure of In Vitro Drug-Induced Resistance

Multi-doses treat → RI ↑ → Stability Test → Growth Curve → MoA Study

- Set up resistance
- More resistance
- Sequential cell viability assay
- STR
- Growth curve (parental vs. resistant cells)
- RNA-seq
- WES







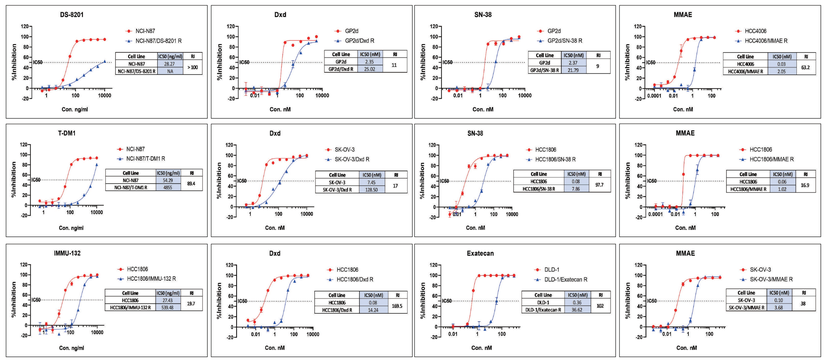
2. Procedure of Genetic Editing

Edited Cells Generation → Functional/Phenotypic Validation → Stability Test

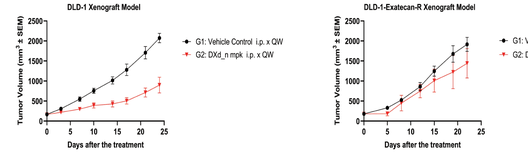
No.	Drug Resistant Cells	Status	RI#	STR	RNA-seq	WES	Drug	Drug Type	Target	Cancer Type	Method
1	NCI-N87/DS8201R	In vitro validated	>100	√	√	√	DS-8201	ADC	HER2,Topoisomerase I	Gastric	In Vitro Drug-Induced Resistance
2	NCI-N87/T-DM1R	In vitro validated	>10	√	√	√	T-DM1	ADC	HER2, Tubulin	Gastric	In Vitro Drug-Induced Resistance
3	HCC1954/T-DM1R	In vitro validated	>20	√	√	√	T-DM1	ADC	HER2, Tubulin	Breast	In Vitro Drug-Induced Resistance
4	HCC1806/IMMU-132 R	In vitro validated	>10	√	√	√	IMMU-132	ADC	TROP2,Topoisomerase I	Breast	In Vitro Drug-Induced Resistance
5	DLD-1/Exatecan R	In vitro validated	>100	√	√	√	Exatecan	payload	Topoisomerase I	Colorectal	In Vitro Drug-Induced Resistance
6	SK-OV-3/Dxd R	In vitro validated	>10	√	√	√	Dxd	payload	Topoisomerase I	Ovarian	In Vitro Drug-Induced Resistance
7	GP2d/Dxd R	In vitro validated	>10	√	√	√	Dxd	payload	Topoisomerase I	Colorectal	In Vitro Drug-Induced Resistance
8	HCC1806/Dxd R	In vitro validated	>50	√	√	√	Dxd	payload	Topoisomerase I	Breast	In Vitro Drug-Induced Resistance
9	GP2d/SN-38 R	In vitro validated	>5	√	√	√	SN-38	payload	Topoisomerase I	Colorectal	In Vitro Drug-Induced Resistance
10	HCC1806/SN-38 R	In vitro validated	>20	√	√	√	SN-38	payload	Topoisomerase I	Breast	In Vitro Drug-Induced Resistance
11	NCI-N87/ZD06519 R	In vitro validated	>20	√	Ongoing	Ongoing	ZD06519	payload	Topoisomerase I	Gastric	In Vitro Drug-Induced Resistance
12	NUGC-4/MMAE R	In vitro validated	>10	√	√	√	MMAE	payload	Tubulin	Gastric	In Vitro Drug-Induced Resistance
13	OVCAR3/MMAE R	In vitro validated	>5	√	√	√	MMAE	payload	Tubulin	Ovarian	In Vitro Drug-Induced Resistance
14	HCC1806/MMAE R	In vitro validated	>10	√	√	√	MMAE	payload	Tubulin	Breast	In Vitro Drug-Induced Resistance
15	SK-OV-3/MMAE R	In vitro validated	>10	√	√	√	MMAE	payload	Tubulin	Ovarian	In Vitro Drug-Induced Resistance
16	HCC4006/MMAE R	In vitro validated	>50	√	√	√	MMAE	payload	Tubulin	Lung	In Vitro Drug-Induced Resistance
17	OVCAR3-ABCB1-OE	In vitro validated	MMAE > 20	√	√	/	/	ADC/payload	ABCB1	Ovarian	Genetic Editing
18	OVCAR3-ABCG2-OE	In vitro validated	Dxd > 10	√	√	/	/	ADC/payload	ABCG2	Ovarian	Genetic Editing
19	NCI-N87-ABCB1-OE	In vitro validated	MMAE> 20	√	√	/	/	ADC/payload	ABCB1	Gastric	Genetic Editing
20	NCI-N87-ABCG2-OE	In vitro validated	Dxd > 10	√	√	/	/	ADC/payload	ABCG2	Gastric	Genetic Editing
21	JIMT-1-ABCB1-OE	In vitro validated	MMAE>100	√	√	/	/	ADC/payload	ABCB1	Breast	Genetic Editing
22	JIMT-1-ABCG2-OE	In vitro validated	Dxd >10	√	√	/	/	ADC/payload	ABCG2	Breast	Genetic Editing
23	SK-BR-3-ABCB1-OE	In vitro validated	MMAE>100	√	√	/	/	ADC/payload	ABCB1	Breast	Genetic Editing
24	SK-BR-3-ABCG2-OE	In vitro validated	Dxd > 10	√	√	/	/	ADC/payload	ABCG2	Breast	Genetic Editing
25	HCT116-TOP1-R364H	In vitro validated	Dxd > 20	√	√	√	/	ADC/payload	Topoisomerase I	Colorectal	Genetic Editing

RI#: fold increase in IC50 (resistant vs parental)

Part 3: Dose-Response Curves in Parental and Resistant Cell lines

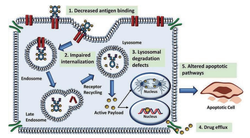


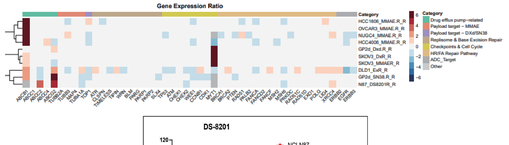
Part 4: In Vivo Evaluation of Exatecan-Resistant DLD1 Model



Part 5: Bioinformatics Analysis

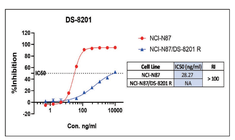
The identified possible causes of resistance





DS-8201 (Trastuzumab Deruxtecan) – Enhertu®

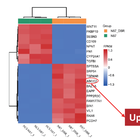
Molecule Type	Antibody-Drug Conjugate (ADC)
Target	HER2 (Human Epidermal Growth Factor Receptor 2)
Payload	Dxd (Topoisomerase I inhibitor)
Phase & Indications	**Approved globally for:** **Breast Cancer:** HER2-positive & HER2-low metastatic. **Gastric Cancer:** HER2-positive metastatic. **Lung Cancer:** HER2-mutant non-small cell (NSCLC). **In Clinical Trials:** For other HER2-expressing solid tumors.



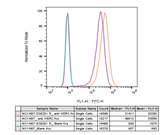
Resistant Cell Lines	Resistance Index (RI)	Status	Method	Cancer Type
NCI-N87/ DS-8201 R	> 100	MoA Study*	Natural Resistance (in vitro)	Gastric tubular adenocarcinoma

*Note: The MoA study combines flow-cytometry–based target detection with transcriptomic (RNA-seq) and genomic (WES) profiling.

RNA-seq result: NCI-N87/NCI-N87-DS-8201-R



HER2 expression in N87 (R)



Downregulation of HER2

Compound ID	N87			NCI-N87-DS8201-R		
	R_IC$_{50}$, nM	A_IC$_{50}$, nM	Max Inhibition%	R_IC$_{50}$, nM	A_IC$_{50}$, nM	Max Inhibition%
TROP2-Top1i(4)& Prexasertib(4)	0.85	1.41	78.1	>100	>100	7.32
TROP2-Prexasertib(DAR4)	>100	>100	19.31	>100	>100	9.02
DS-1062(TROP2-DXd, DAR4)	2.77	6.79	69.78	>100	>100	9.2
TROP2-Top1i(4)	0.77	1.08	81.59	>100	>100	5.13
TROP2-Prexasertib(DAR4) combine with TROP2-Top1i(4)	2.47	5.58	67.18	>100	>100	8.13
DXD	2.22	2.14	99.81	26.25	28.5	93.24
DS-8201	0.31	0.31	95.78	>100	>100	49.74
Staurosporine	0.54	0.65	99.94	3.21	3.08	99.94

Integrated mechanistic analysis of ADC resistance. Resistance mechanism schematic (upper left, Adapted from Dean et al., MAbs 2021); paired transcriptomic profiling with log2 R/WT matrices (upper right); NCI-N87/DS-8201R case study with ABCG2 upregulation and HER2 downregulation (middle); cytotoxicity profile of TROP2-ADCs with distinct payloads in parental vs. NCI-N87/DS-8201R cells (table below), demonstrating cross-resistance and informing dual-payload design strategies.

Part 6: Conclusion & Future Directions

Key Conclusions

- **Platform:** Established a comprehensive ADC-resistant cell panel comprising 25 RI-characterized models with multi-omics profiling (WES/RNA-seq), enabling systematic evaluation of ADC efficacy and resistance mechanisms
- **Mechanisms:** Identified convergent and lineage-specific resistance drivers including efflux activation, target loss, and DNA repair upregulation, informing next-generation ADC design
- **Application:** Established a scalable framework for ADC optimization by leveraging the cell panel to construct customized resistant models, enabling prospective assessment of ADC potency and resistance liability, identification of resistance-overcoming candidates, and rational design of dual-payload ADCs with improved durability.