Developing Novel Resistant Models to Accelerate Next-Generation ADC Drug Discovery

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Introduction

In recent years, antibody-drug conjugates (ADCs) have demonstrated impressive therapeutic effects in cancer treatment, especially for solid tumors. Notably, DS-8201, an ADC targeting HER2, has been approved for multiple cancer treatments, showcasing remarkable efficacy. However, resistance to ADC therapy remains a significant challenge, limiting its long-term effectiveness. To address these challenges, we successfully developed various ADC-resistant cell lines through various methods including drug induction (using ADCs or free payloads) and efflux pump overexpression. The resistant properties of these models were validated both in vitro and in vivo. For some drug-induced resistant models, we identified potential resistance mechanisms. Notably, we found that in one of our ADC-induced models the surface marker of the target antigen did not change, while the metabolic status of the payload was altered. These drug-resistant models and comprehensive findings provide crucial tools that can significantly assist in the development and optimization of next-generation ADC drugs.



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Figure 2. Evaluation of ADC-induced resistant tumor cells. (A) CTG analysis of T-DM1-induced resistant HCC1954 cells. (B) Enhertu-induced resistant HCC1954 cells, (C) H2170 cells, and (D) N87 cells.



Construction Strategies



Figure 3. In vivo evaluation of Enhertu-resistant N87 model.



NCI-N87 NCI-N87-R



Figure 4. Mechanism of action of the Enhertu-resistant N87 model.

(A) IHC analysis of HER2 expression in tumors, (B) KEGG enrichment analysis, (C) Genes with differential levels of metabolism of xenobiotics by cytochrome P450 signal, (D) GSEA analysis of metabolism of xenobiotics by cytochrome P450 signal, (E) qPCR validation of changed genes, and (G) CTG analysis of combination MA (AKR1C inhibitor, Mefenamic acid) and Enhertu.

Summary of developed resistant models

Model name	Cancer type	Target	Validated resistance
Enhertu-R-N87	Gastric	HER2	Enhertu, Dxd
Enhertu-R-HCC1954	Breast	HER2	Enhertu, T-DM1, RC48
Enhertu-R-H2170	Lung	HER2	Enhertu, RC48
T-DM1-R-HCC1954	Breast	HER2	T-DM1
RC48-R-HCC1954	Breast	HER2	Enhertu, T-DM1, RC48
Dxd-R-HCC1806	Breast	TROP2	Dxd, Datroway
Dxd-R-HCC827	lung	TROP2	Dxd Datroway

Figure 1. Evaluation of payload-resistant tumor cells. (A) CTG analysis of Dxd-induced resistant HCC1806 cells, (B) Dxd-induced resistant HCC827 cells, (C) Dxd-induced resistant HCC4006 cells, (D) CTG analysis of ABCG2-overexpressed HCC1954 cells, (E) ABCG2-overexpressed N87 cells, and (F) ABCB1-overexpressed N87 cells.





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