

# Shifting Paradigms in ADC Preclinical Development: From Pharmacology to Translational Research

**Xiangnan Qiang**

Head of Translational Biomarker Research,  
Biology, WuXi AppTec



# Milestone for ADC

Timeline depicting important events in the development and approval of ADC drugs over the past century since the “magic bullet” was proposed by Paul Ehrlich.



In 1913, Paul Ehrlich first proposed the concept of “magic bullets”  
1910

In 1967, ADC concept proposed  
1960

In 1958, MTX linked to antibody  
1950

In 1975, hybridoma technology  
1970

In 1988, humanized antibody reported  
1980

In 1993, BR96-DOX was on xenograft model; ADC conjugated to calicheamicin  
1990

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trastuzumab deruxtecan

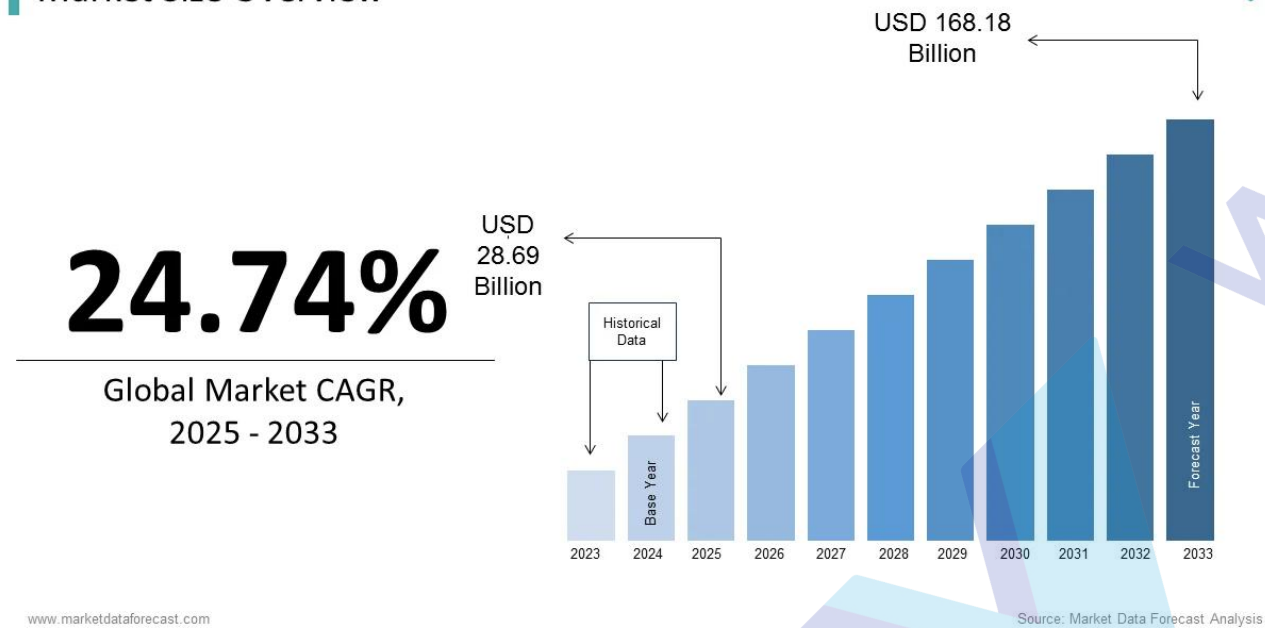
**BESPONSA®**  
inotuzumab ozogamicin

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gemtuzumab ozogamicin INJECTION FOR IV INFUSION

20 ADC drugs have been approved globally, with over 500 more currently in clinical trials.

# ADC Market Growth

## Global Antibody Drug Conjugates Market Market Size Overview



| Ranking | Name      | Target  | Company          | 2025 (Billion) | Growth rate % |
|---------|-----------|---------|------------------|----------------|---------------|
| 1       | Enhertu   | HER2    | Diachi Sanko/AZ  | 4.982          | 32.71         |
| 2       | Kadcyla   | HER2    | Roche            | 2.709          | 16.92         |
| 3       | Padcev    | Nectin4 | Astallas/Pfizer  | 2.306          | 45.21         |
| 4       | Polivy    | CD79b   | Roche            | 2.129          | 45.52         |
| 5       | Adcentris | CD30    | Takada/Roche     | 1.779          | -6.91         |
| 6       | Trodelvy  | Trop2   | Gilead           | 1.397          | 6.24          |
| 7       | Elahere   | FRa     | Abbvie           | 0.690          | 44.05         |
| 8       | Datroway  | Trop2   | Diachi Sanko/AZ  | 0.218          |               |
| 9       | Tivdak    | TF      | Pfizer           | 0.147          | 12.21         |
| 10      | Zynlonta  | CD19    | ADC therapeutics | 0.073          | 5.8           |

The global ADC technology market, valued at **USD 2.34 billion in 2025**, is projected to reach **USD 3.44 billion in 2026** and **USD 168.18 billion by 2033**, representing a 24.74% CAGR during the forecast period 2025 to 2033.

# A Dogma in Need of Revision

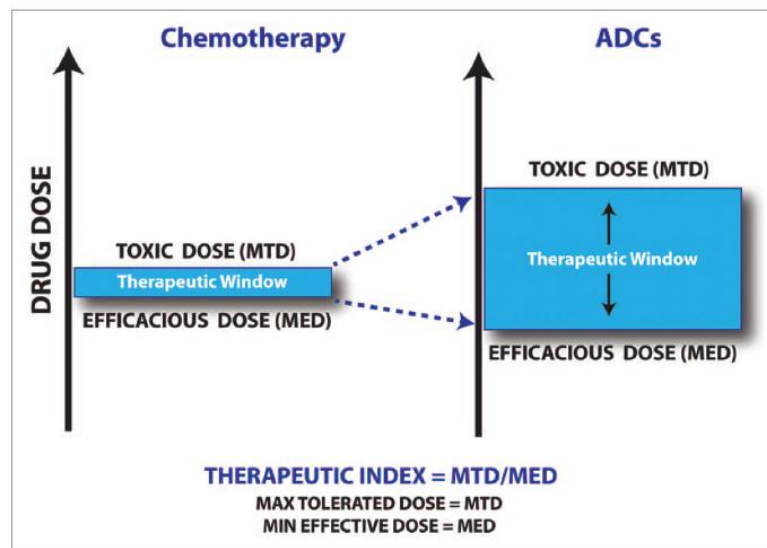
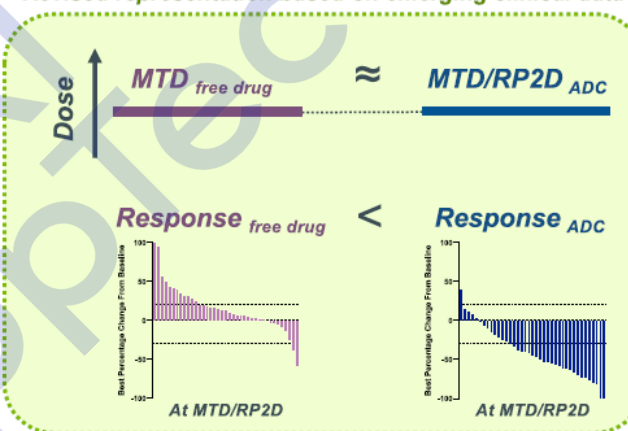


**Figure 1.** ADCs expand the therapeutic window. ADC therapeutics can increase efficacy and decrease toxicity in comparison to traditional chemotherapeutic cancer treatments. Select delivery of drugs to cancer cells increases the percent of dosed drug reaching the tumor, thus lowering the minimum effective dose (MED). The maximum tolerated dose (MTD) is increased, as less drug reaches normal, non-target tissue due to targeted delivery by the antibody. Taken together, the therapeutic window is improved by the use of ADCs.

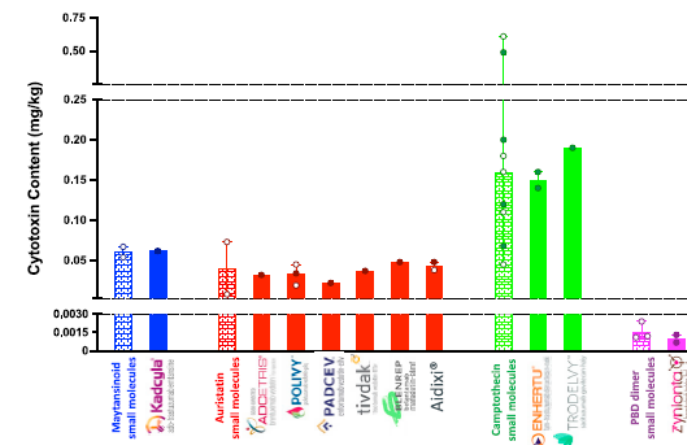
*Cancer Cell.* 2022;40(11):1255-1263

Observed preclinically in xenograft models but  
**NOT** determined in the clinical trials.

Revised representation based on emerging clinical data

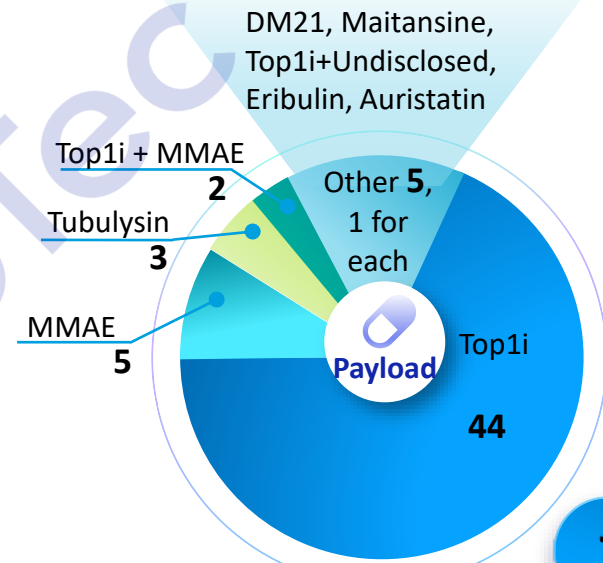
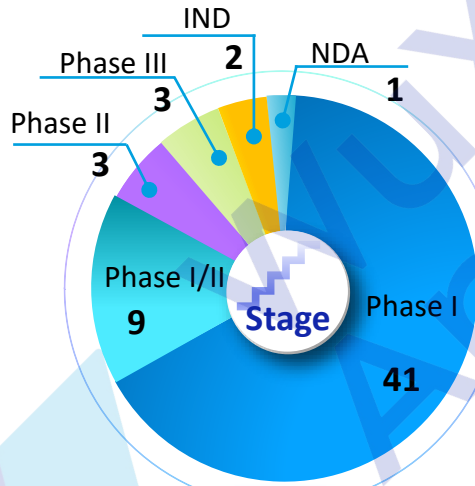
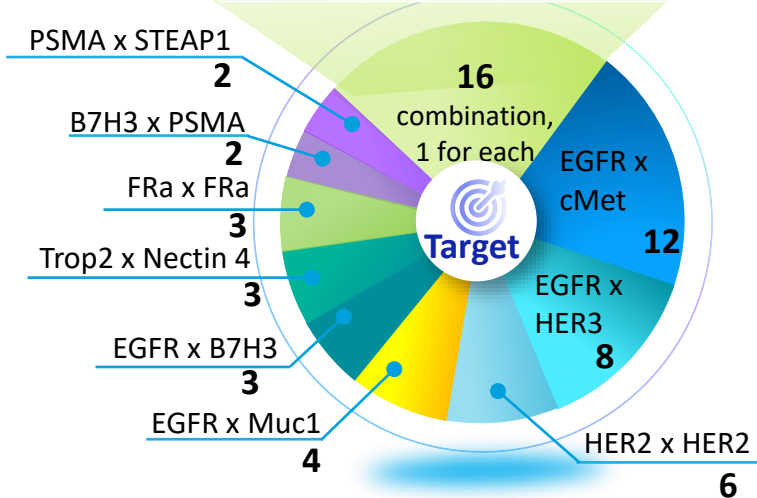


**B** Normalized human MTDs/RP2Ds of approved ADCs vs small molecules



# BsADC in clinic

|               |              |                  |
|---------------|--------------|------------------|
| HER3 x Trop2  | D7H3 x PMSA  | CDH17 x CLDN18.2 |
| EGFR x HER2   | MUC1 x Trop2 | ROR1 x ROR1      |
| PD L1 x Trop2 | 5T4 x 5T4    | B7H3 x PTK7      |
| B7H3 x PDL1   | PD L1 x VEGF | HER3 x cMet      |
| cMet x cMet   | PD L1 x αvβ6 | EGFR x Trop2     |
|               | ROR1 x B7H3  |                  |



Total: 59

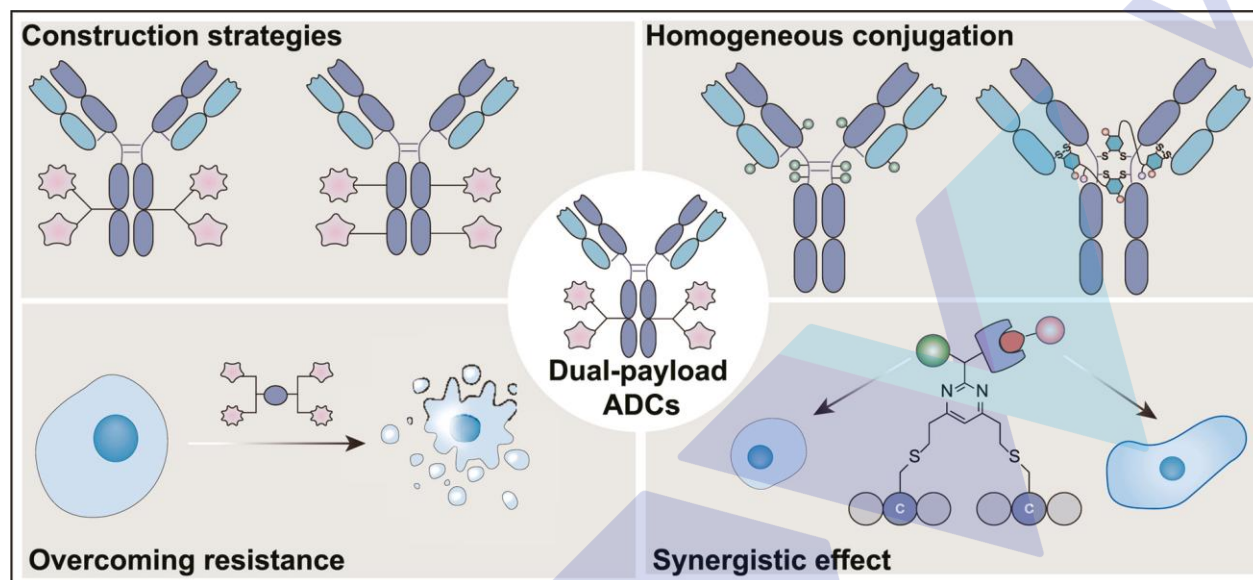
| No | Name     | Target          | Company     | Payload    | Stage      |
|----|----------|-----------------|-------------|------------|------------|
| 1  | BL-B01D1 | EGFR x HER3     | Bailli/BMS  | Top1i      | NDA        |
| 2  | JSKN003  | HER2 x HER2     | Alphamab    | Top1i      | Phase III  |
| 3  | JSKN016  | HER3 x Trop2    | Alphamab    | Top1i      | Phase III  |
| 4  | TOB2102  | HER2 x HER2     | Chiatai     | Top1i      | Phase III  |
| 5  | ZW-49    | HER2 x HER2     | Zymeworks   | Auristatin | Phase II   |
| 6  | M114     | cMet x cMet     | Regeneron   | Maitansine | Phase II   |
| 7  | IMGN151  | FRa x FRa       | Abbvie      | DM21       | Phase II   |
| 8  | SKB571   | EGFR x cMet     | Kelun       | Top1i      | Phase I/II |
| 9  | DB-1419  | B7H3 x PDL1     | Duality     | Top1i      | Phase I/II |
| 10 | Pro1286  | EGFR x cMet     | Profound    | Top1i      | Phase I/II |
| 11 | KY0301   | EGFR x cMet     | Novatim     | MMAE       | Phase I/II |
| 12 | TQ6411   | EGFR x cMet     | Chiatai     | Top1i      | Phase I/II |
| 13 | VBC103   | Trop2 x Nectin4 | VelaVego    | Top1i      | Phase I/II |
| 14 | DB-1418  | EGFR x HER3     | Duality     | Top1i      | Phase I/II |
| 15 | JK06     | 5T4 x 5T4       | Salubris    | MMAE       | Phase I/II |
| 16 | PM1300   | EGFR x HER3     | Biotheus    | Top1i      | Phase I/II |
| 17 | MED4426  | HER2 x HER2     | AstraZeneca | tubulysin  | Phase I    |
| 18 | M1231    | EGFR x Muc1     | Sutro/Merck | tubulysin  | Phase I    |
| 19 | Abby-969 | PMSA x STEAP1   | Abbvie      | Top1i      | Phase I    |
| 20 | AZ-9592  | EGFR x cMet     | AstraZeneca | Top1i      | Phase I    |

| No | Name     | Target           | Company    | Payload      | Stage   |
|----|----------|------------------|------------|--------------|---------|
| 21 | IBI-3001 | EGFR x B7H3      | Innovent   | Top1i        | Phase I |
| 22 | DM001    | EGFR x Trop2     | Doma       | Top1i        | Phase I |
| 23 | DM005    | EGFR x cMet      | Doma       | Top1i        | Phase I |
| 24 | DM002    | EGFR x Muc1      | Doma       | Top1i        | Phase I |
| 25 | BL-B16D1 | EGFR x HER3      | Bailli     | MMAE         | Phase I |
| 26 | IBI-3005 | EGFR x HER3      | Innovent   | Top1i        | Phase I |
| 27 | BR111    | ROR1 x ROR1      | Bioray     | Eribulin     | Phase I |
| 28 | JS212    | EGFR x HER3      | Jushi      | Top1i        | Phase I |
| 29 | TJ101    | EGFR x B7H3      | Phrontline | Top1i        | Phase I |
| 30 | VBC101   | EGFR x HER3      | VelaVego   | Top1i        | Phase I |
| 31 | BCG034   | B7H3 x PTK7      | Biocytogen | Top1i        | Phase I |
| 32 | PM1080   | EGFR x cMet      | Biotheus   | Top1i        | Phase I |
| 33 | IBI3028  | EGFR x cMet      | Innovent   | Top1i + MMAE | Phase I |
| 34 | SIM-0610 | EGFR x cMet      | Sincere    | Top1i        | Phase I |
| 35 | IBI-0314 | PD L1 x Trop2    | Innovent   | Top1i        | Phase I |
| 36 | IBI-0310 | FRa x FRa        | Innovent   | Top1i        | Phase I |
| 37 | DAC014   | D7H3 x PMSA      | DAC        | Top1i        | Phase I |
| 38 | VBC108   | CDH17 x CLDN18.2 | VelaVego   | Top1i        | Phase I |
| 39 | FH-006   | EGFR x B7H3      | Hengrui    | MMAE         | Phase I |
| 40 | SHR-1681 | HER3 x cMet      | Hengrui    | Top1i        | Phase I |

| No | Name      | Target          | Company  | Payload           | Stage   |
|----|-----------|-----------------|----------|-------------------|---------|
| 41 | SHR-A2102 | EGFR x Muc1     | Hengrui  | Top1i             | Phase I |
| 42 | SDP01873  | EGFR x cMet     | Hengrui  | Top1i             | Phase I |
| 43 | GenSci139 | EGFR x HER2     | GenSci   | Top1i             | Phase I |
| 44 | GenSci140 | FRa x FRa       | GenSci   | Top1i             | Phase I |
| 45 | GenSci143 | B7H3 x PMSA     | GenSci   | Top1i             | Phase I |
| 46 | AK139/140 | Trop2 x Nectin4 | Akeso    | Top1i             | Phase I |
| 47 | JSKN021   | EGFR x HER3     | Alphamab | Top1i + MMAE      | Phase I |
| 48 | JSKN022   | PD L1 x αvβ6    | Alphamab | Top1i             | Phase I |
| 49 | AK146D1   | Trop2 x Nectin4 | Akeso    | Top1i             | Phase I |
| 50 | JSKN027   | PD L1 x VEGF    | Alphamab | Top1i             | Phase I |
| 51 | NEOK001   | ROR1 x B7H3     | NEOK Bio | Top1i             | Phase I |
| 52 | NEOK002   | EGFR x MUC1     | NEOK Bio | Top1i             | Phase I |
| 53 | SHR-1049  | MUC1 x Trop2    | Hengrui  | Top1i             | Phase I |
| 54 | QLS-5316  | EGFR x cMet     | Qilu     | Top1i             | Phase I |
| 55 | ALK202    | EGFR x cMet     | AlinkBio | Top1i             | Phase I |
| 56 | KM501     | HER2 x HER2     | XuanZhu  | MMAE              | Phase I |
| 57 | DAC-008   | PMSA x STEAP1   | DAC      | Tubulysin         | Phase I |
| 58 | RC288     | B7H3 x PMSA     | Remegen  | Top1i             | IND     |
| 59 | DAC-018   | HER2 x HER2     | DAC      | Top1i+Undisclosed | IND     |

# Dual-payload ADC Evaluation

**Dual-payload ADCs** typically incorporate two different types of toxins, such as Topo inhibitor plus tubulin inhibitor, Topo inhibitor plus PARP inhibitor. This design can help avoid resistance that may arise from a single toxin mechanism. Additionally, the two different toxins often exhibit synergistic effects, thereby enhancing each other's activity

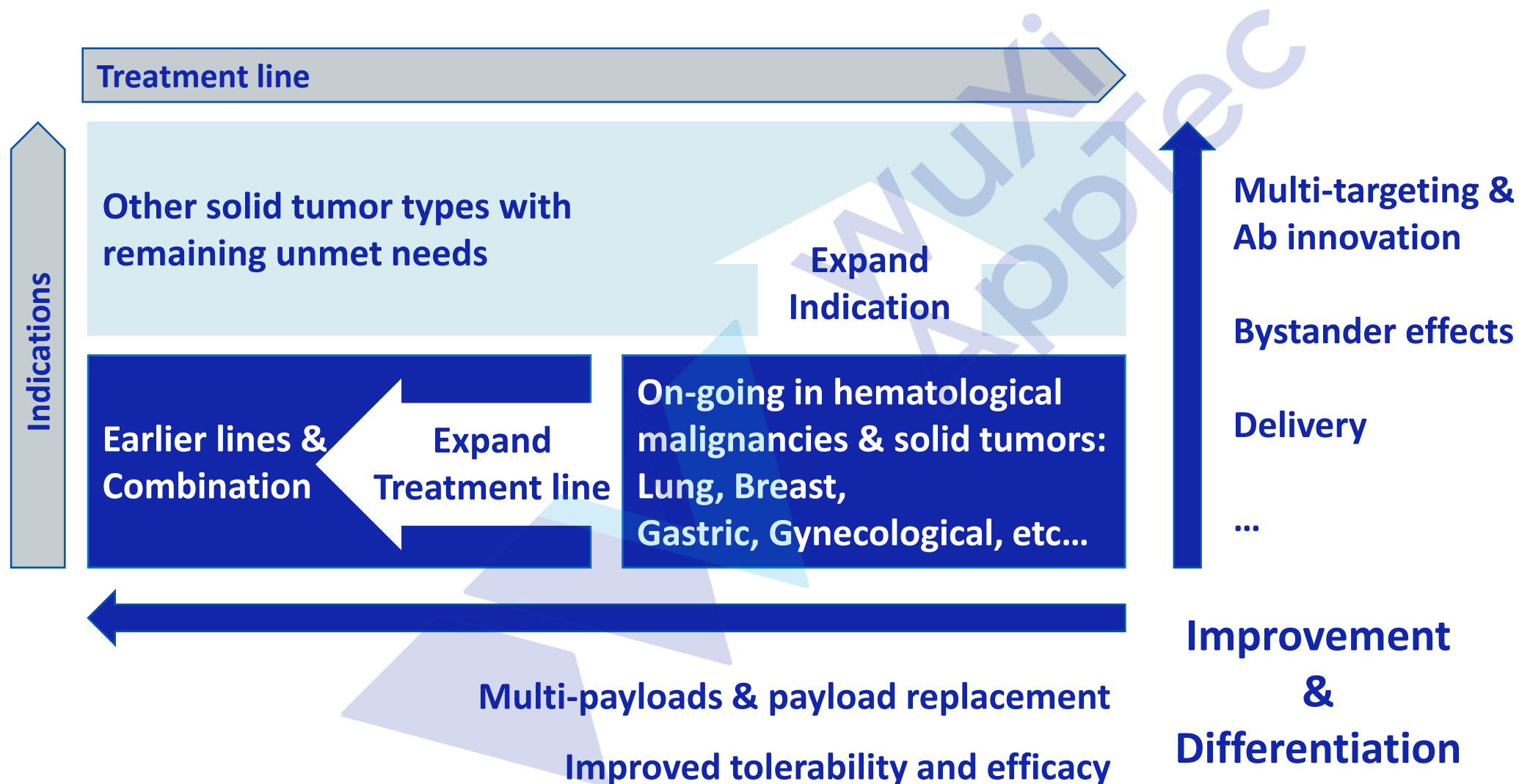


Junjie Tao, 2025

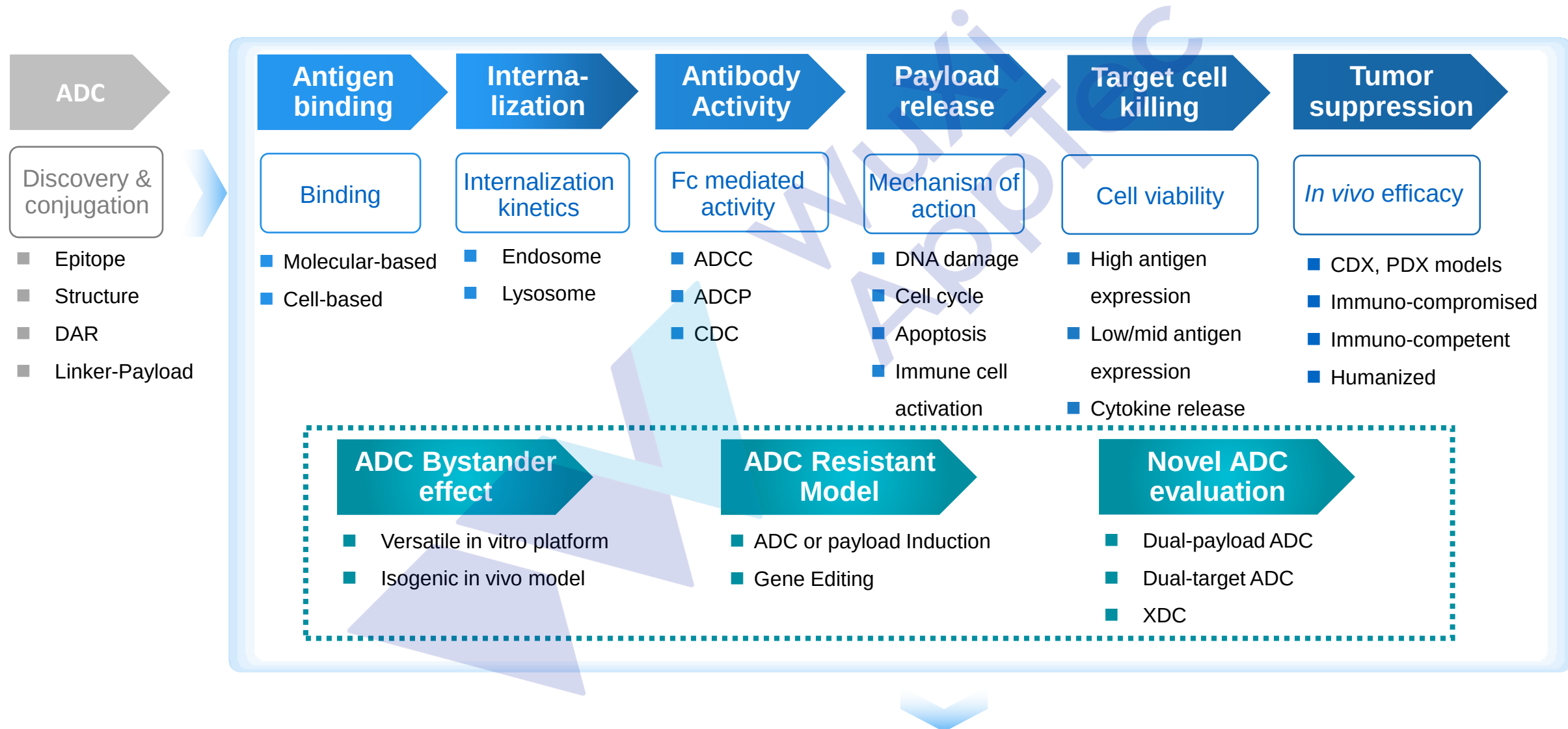
The following points need special attention in the evaluation of dual payload ADC:

- Payload ratio optimization for dual-payload ADCs
- Mechanistic investigation of payload–payload synergy
- Comparative potency of dual-payload ADC versus single-payload ADC
- Evaluation of dual-payload ADC to overcome resistance in resistant cell lines

# A Typical Translational Strategy of ADC Preclinical Development

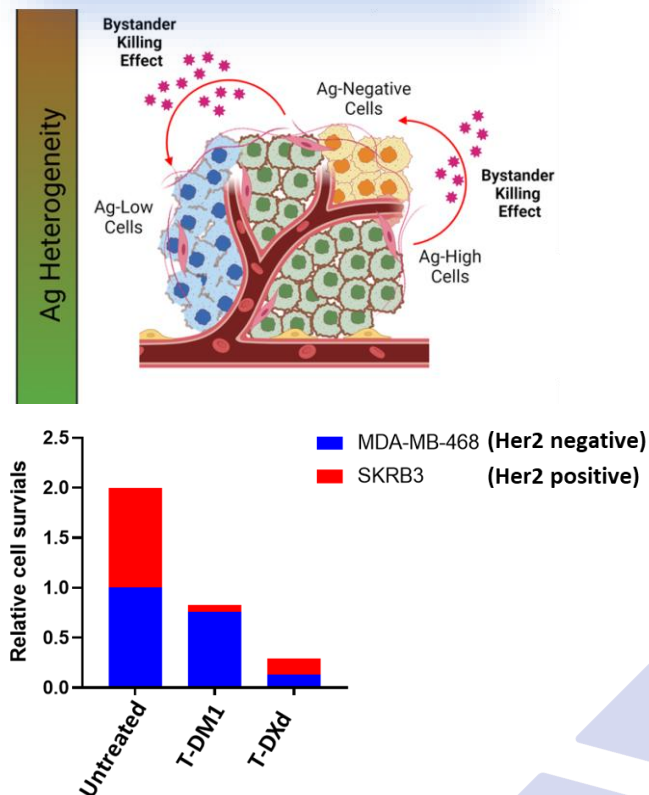


# Comprehensive ADC Pharmacological Evaluation



# Bystander Effect Evaluation

## FACS



- ✓ Co-cultured SKRB3 and MDA-MB-468 treated with anti-Her2 ADC T-DM1 or T-DXd
- ✓ T-DXd kills both Her2+ and Her2- breast cancer cells, unlike T-DM1 which only targets Her2+ cells.
- ✓ T-DXd's effect on Her2- cells is via bystander killing enabled by its cleavable linker and cell-permeable payload.

## IncuCyte

- HER2 negative MCF7\* (OEx TdTomato/Nluc) co-cultured with SKBR3

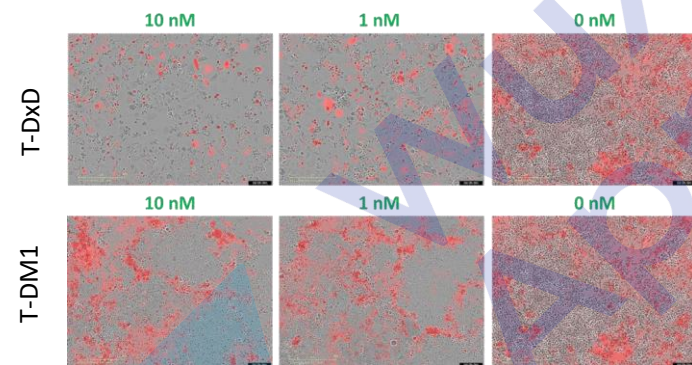
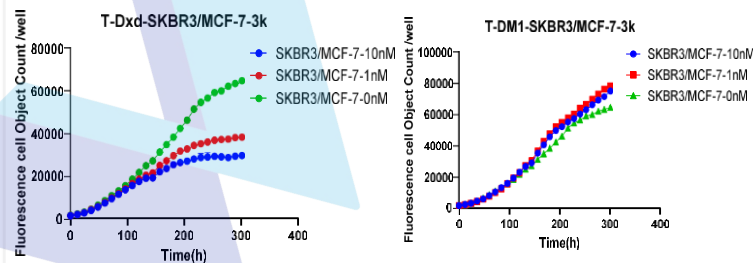


Image was captured at 300h

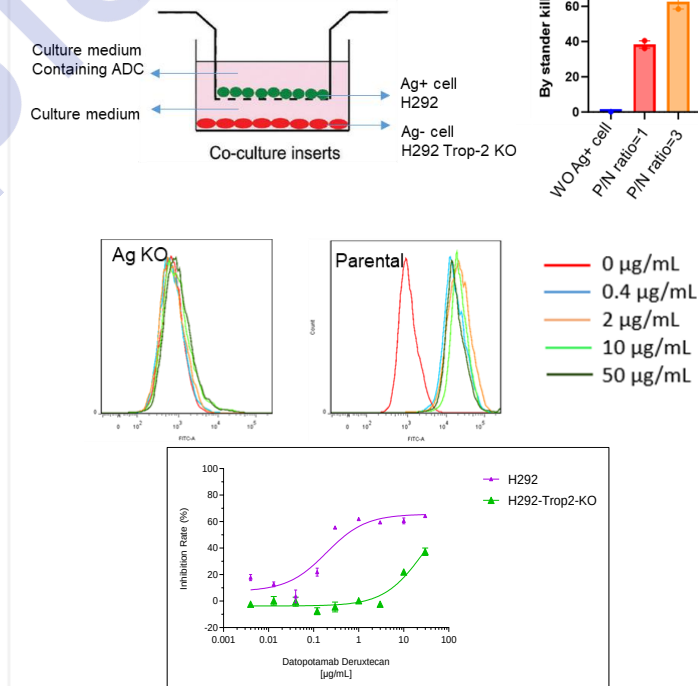


**SKBR3: HER2+**  
**MCF7\* (MCF7-Nluc-Tdtomato): HER2 negative**

- ✓ By IncuCyte kinetic killing assessment of TdTomato-labelled HER2 negative cell line (MCF7), T-DXd showed more obvious bystander effect compared to T-DM1.

## Transwell Assay

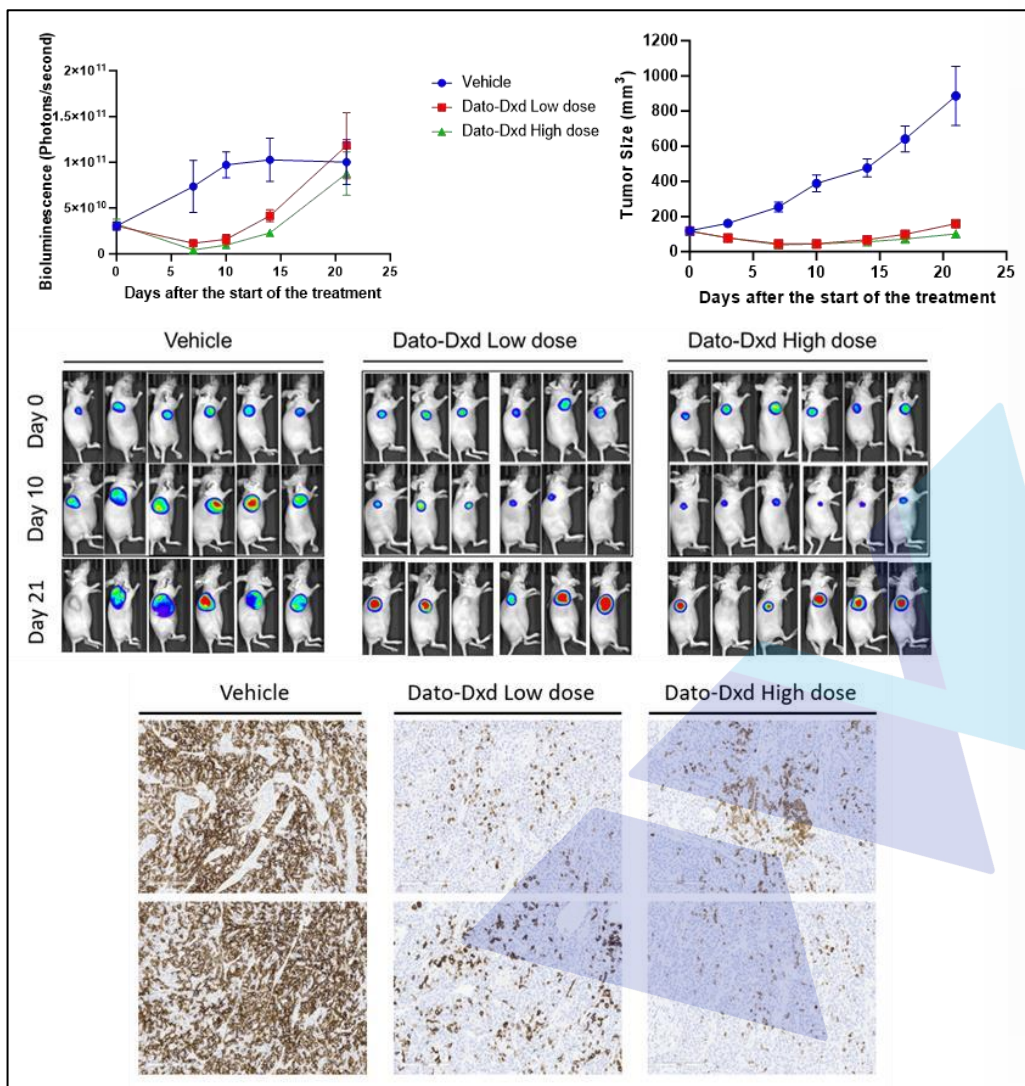
- Bystander killing *in vitro*



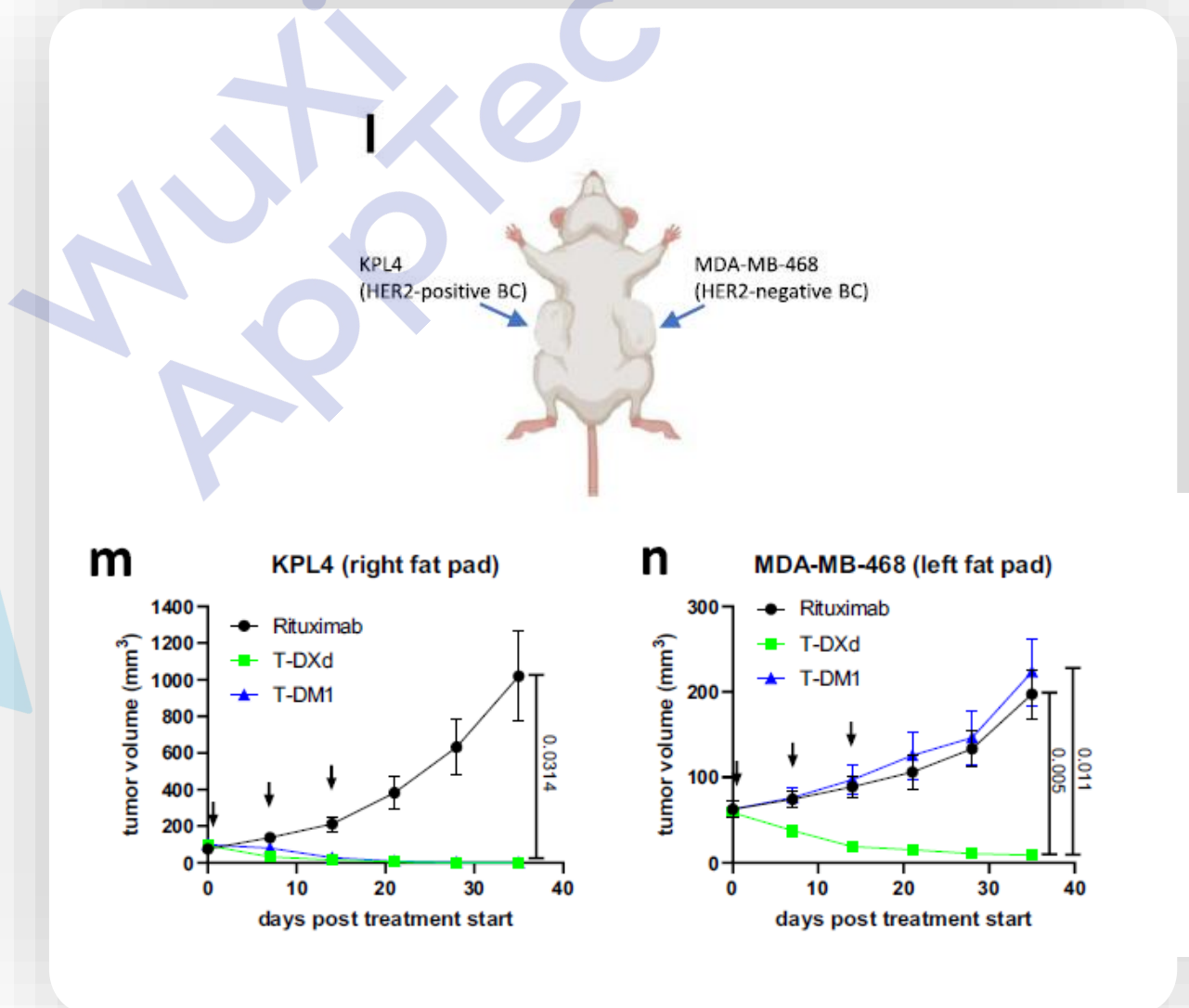
- ✓ The top layer (green cells) represent Ag+ target cells, the bottom (red) represents neighboring cells.
- ✓ This setup is used to study the bystander effect, where the drug impacts not only the target cells but also the surrounding ones.

# ADC Bystander Effect in vivo

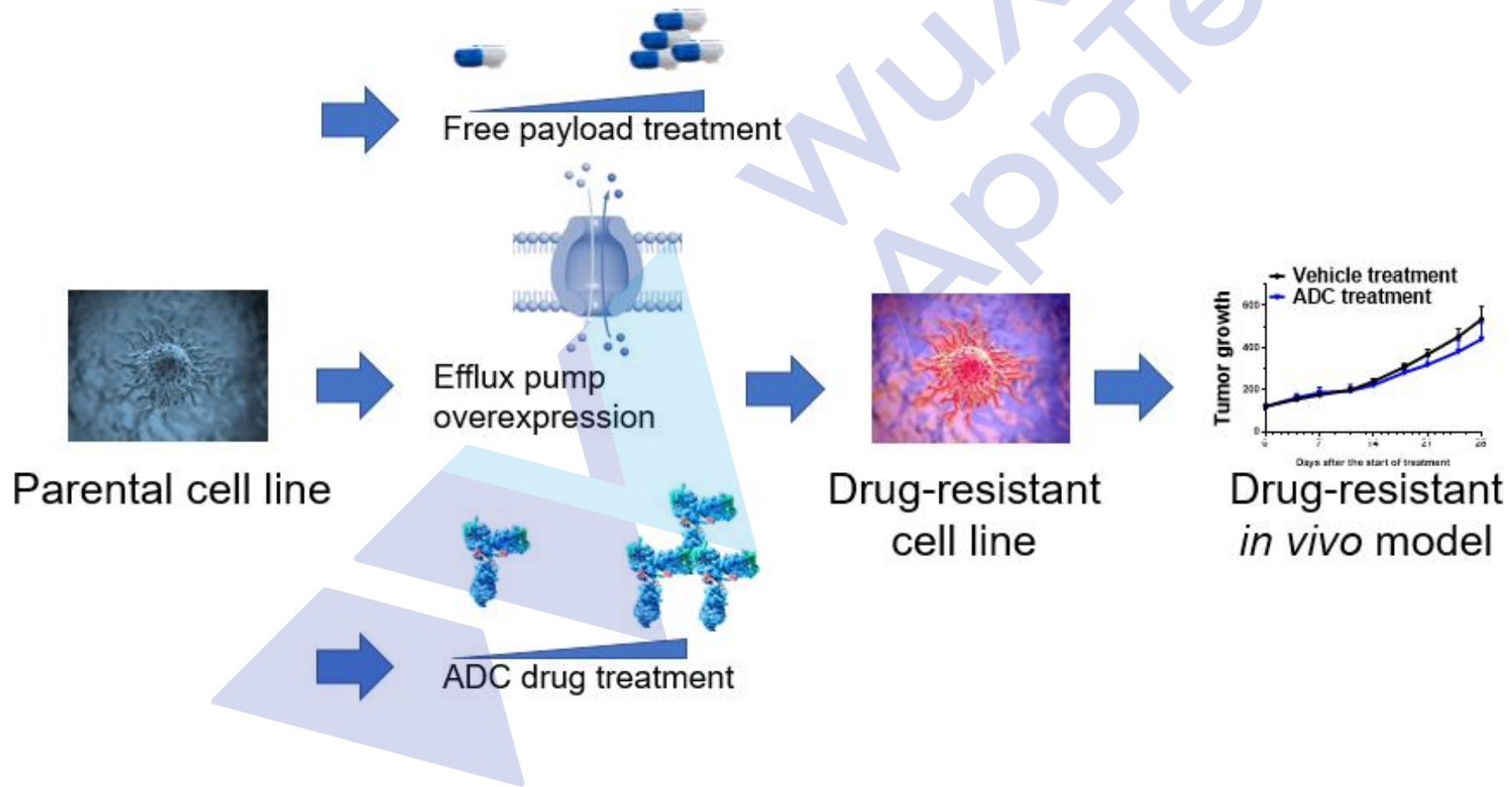
## Bystander killing in vivo (Co-inoculation)



## Bystander killing in vivo (Dual site inoculation)



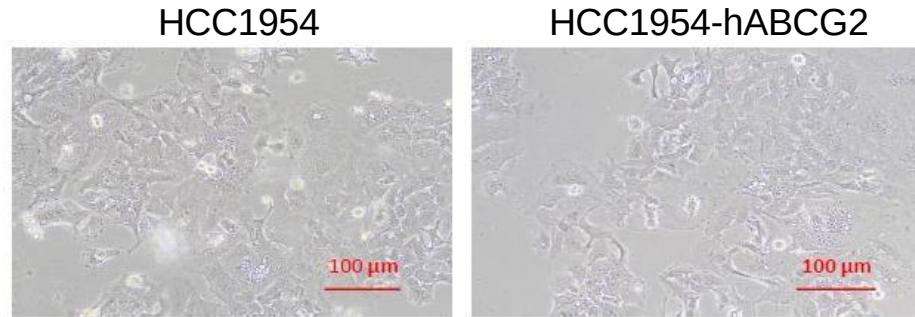
# Strategies Studying Acquired Resistance to ADC



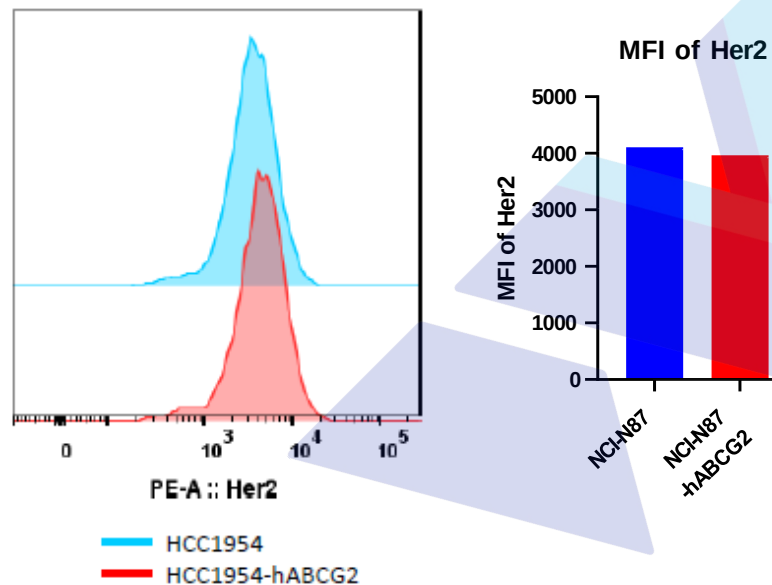
# Drug Pump Overexpressing Resistant Models

## ■ ABCG2 overexpression-mediated resistance to Dxd

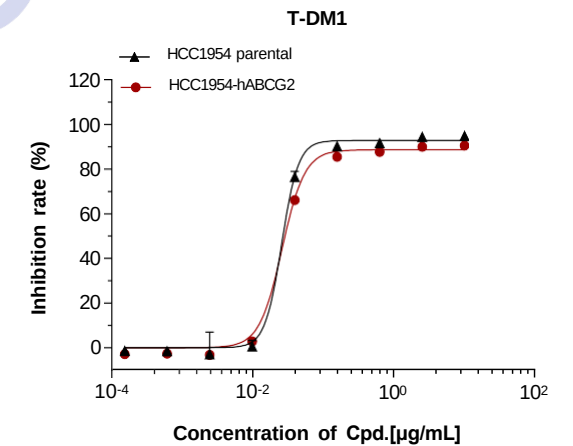
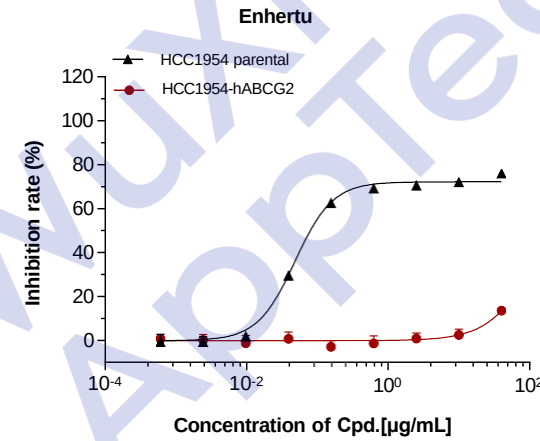
Cell  
Morphology



Flow  
Cytometry

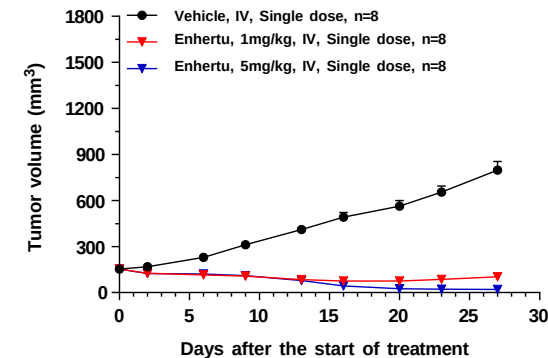


## In Vitro Cytotoxicity Validation

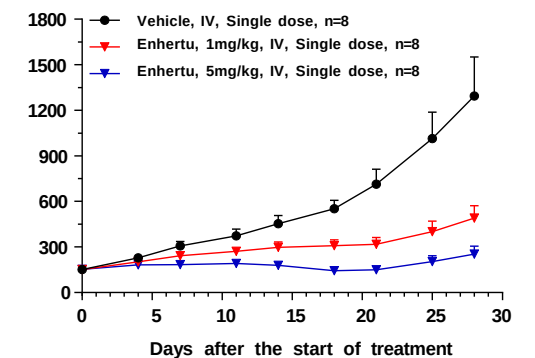


## In Vivo Efficacy Validation

### HCC1954



### HCC1954-hABCG2

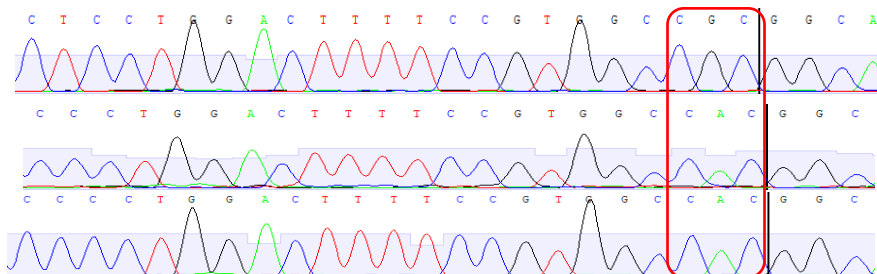


# TOP1 site mutation cell-lines

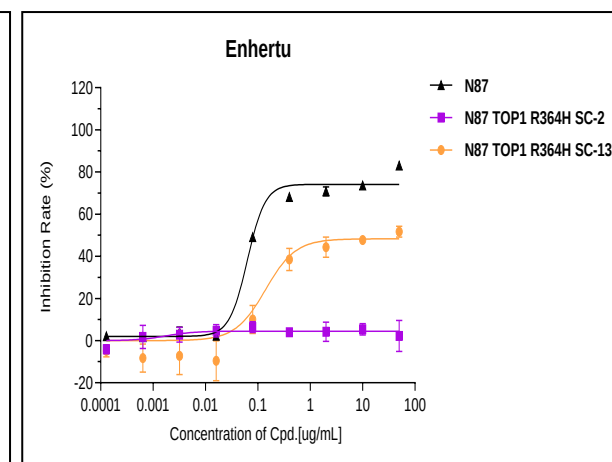
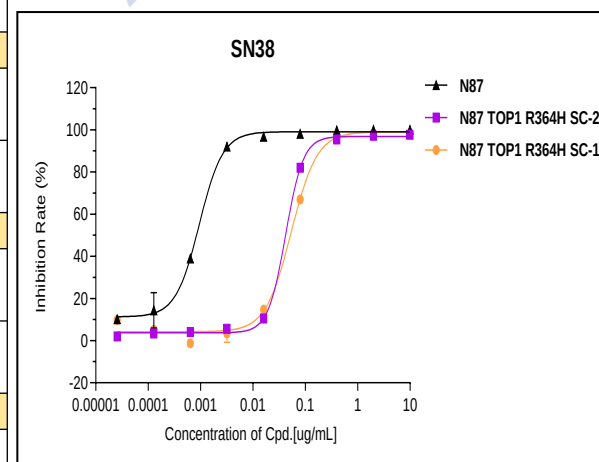
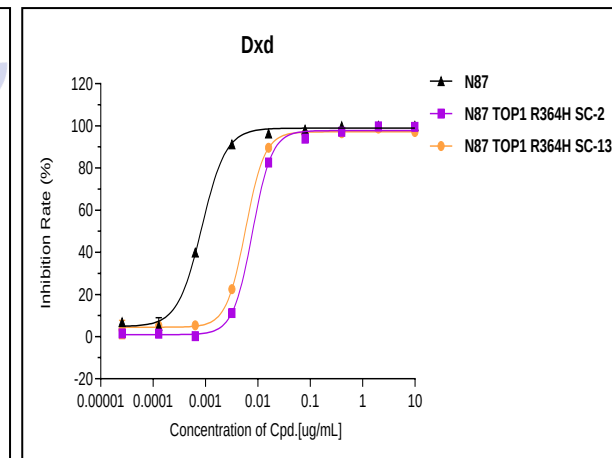
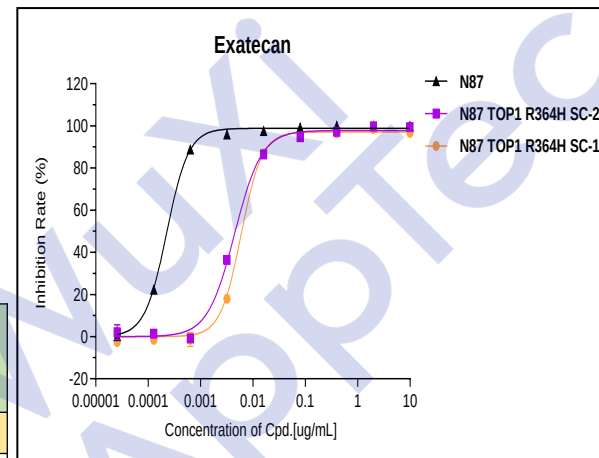
NCI-N87  
parental

NCI-  
N87\_TOP1\_R364H  
\_SC-2

NCI-  
N87\_TOP1\_R364H\_  
SC-13



| Compound | Cell line            | Absolute IC50 (µg/mL) | Relative IC50 (µg/mL) | Min (%) | Max (%) | Note | Absolute resistant index | Relative resistant index |
|----------|----------------------|-----------------------|-----------------------|---------|---------|------|--------------------------|--------------------------|
| Exatecan | N87                  | 0.0002                | 0.0002                | 0.21    | 99.93   | 2D   |                          |                          |
|          | N87 TOP1 R364H SC-2  | 0.0046                | 0.0045                | -0.79   | 99.77   | 2D   | 20.10                    | 19.80                    |
|          | N87 TOP1 R364H SC-13 | 0.0061                | 0.0060                | -2.51   | 98.51   | 2D   | 26.77                    | 26.35                    |
| Dxd      | N87                  | 0.0008                | 0.0009                | 5.14    | 100.01  | 2D   |                          |                          |
|          | N87 TOP1 R364H SC-2  | 0.0080                | 0.0079                | 0.25    | 99.75   | 2D   | 9.74                     | 9.24                     |
|          | N87 TOP1 R364H SC-13 | 0.0057                | 0.0058                | 3.38    | 98.65   | 2D   | 7.01                     | 6.83                     |
| SN38     | N87                  | 0.0008                | 0.0009                | 10.16   | 100.02  | 2D   |                          |                          |
|          | N87 TOP1 R364H SC-2  | 0.0421                | 0.0423                | 1.95    | 97.63   | 2D   | 50.16                    | 44.59                    |
|          | N87 TOP1 R364H SC-13 | 0.0521                | 0.0541                | -1.26   | 98.52   | 2D   | 62.05                    | 57.08                    |
| Enhertu  | N87                  | 0.0825                | 0.0630                | 1.61    | 83.13   | 2D   |                          |                          |
|          | N87 TOP1 R364H SC-2  | > 50                  | 0.0018                | -4.03   | 6.42    | 2D   | /                        | /                        |
|          | N87 TOP1 R364H SC-13 | > 50                  | 0.1401                | -9.58   | 51.65   | 2D   | /                        | /                        |



# ADC-induced Payload-specific Resistance (Enhertu in N87)

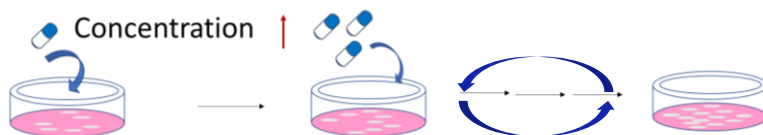
Enhertu  
in vitro inducement

Sensitive  
(parental)

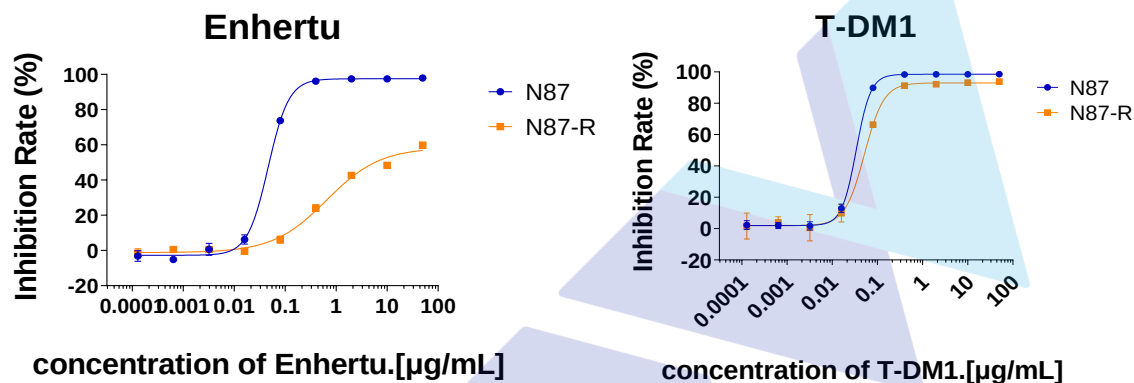
Resistant  
Cell line

Mouse  
model

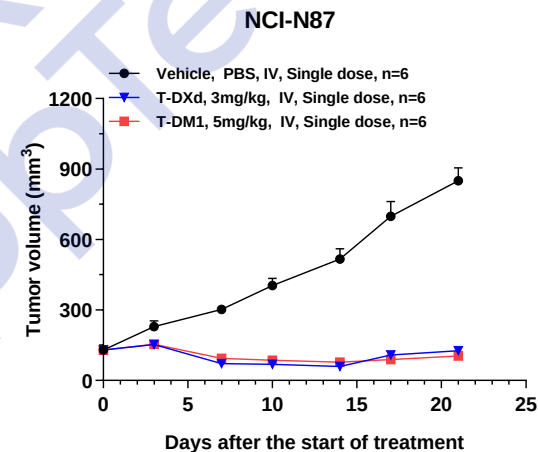
Mouse model generation



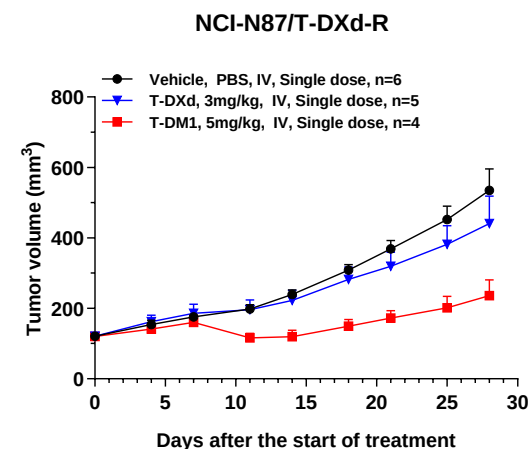
Resistant phenotype by in vitro CTG assay



Acquired resistant phenotype to T-DXd NOT T-DM1



Parental

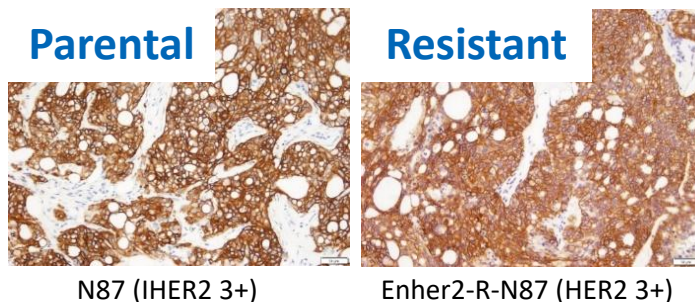


Resistant

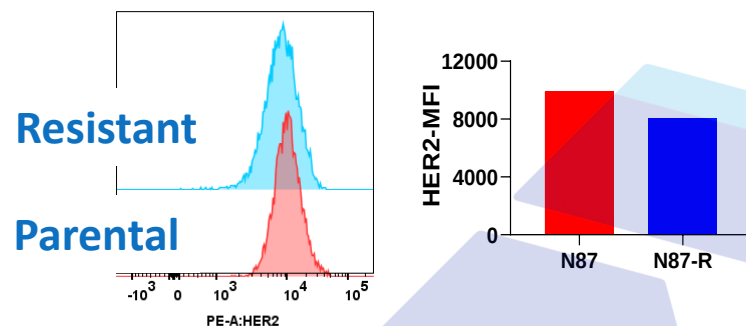
# ADC-induced Payload-specific Resistance (Enhertu in N87)

Mechanism of resistance exploration into Ag/Ab or payload aspects

## HER2 expression in tumor

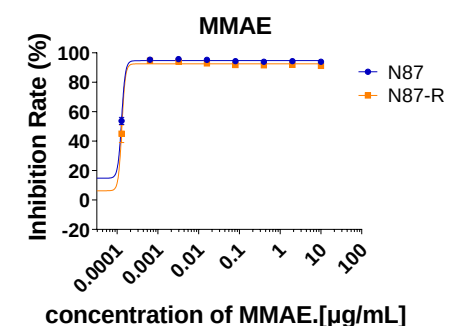
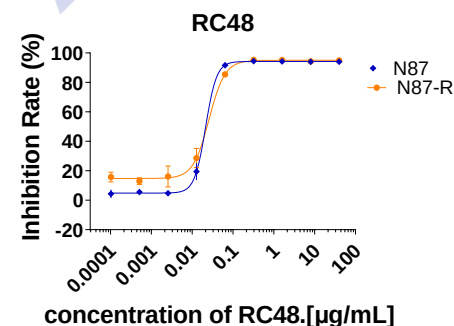
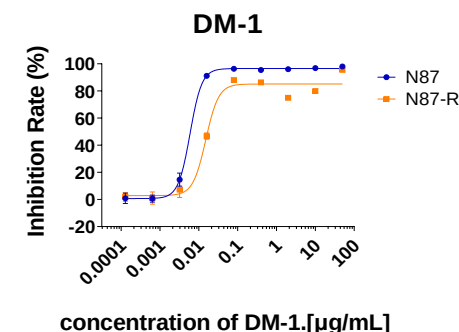
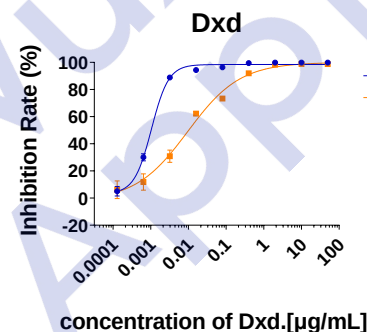


## HER2 binding in cell line



NO loss on HER2 Ag expression or Ab binding affinity

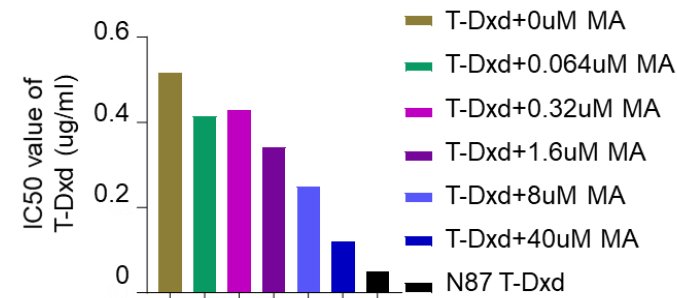
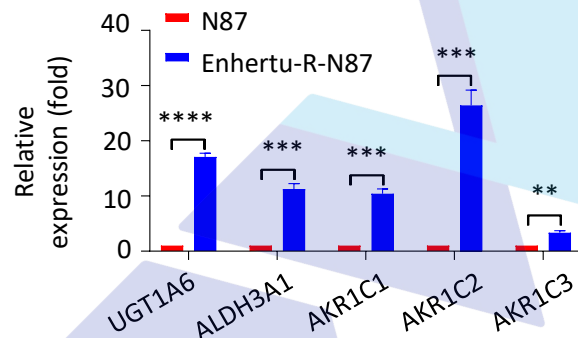
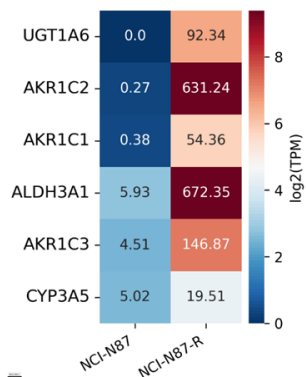
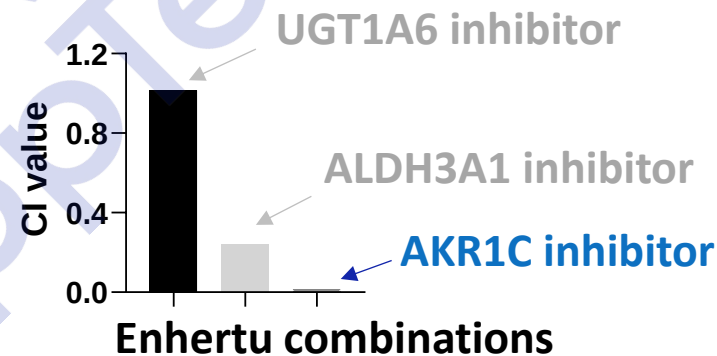
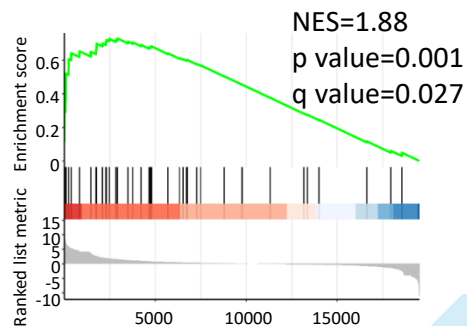
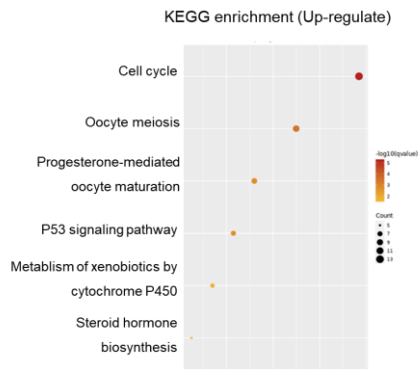
## Payload specificity



Specific resistance to Dxd payload

# ADC-induced Payload-specific Resistance (Enhertu in N87)

## Transcriptomics based mechanism research



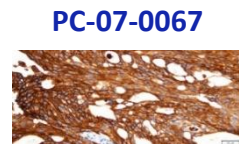
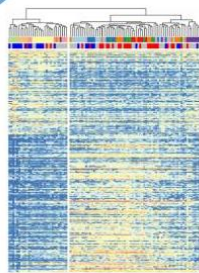
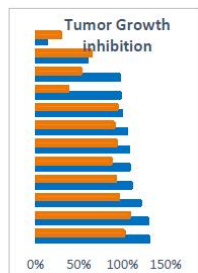
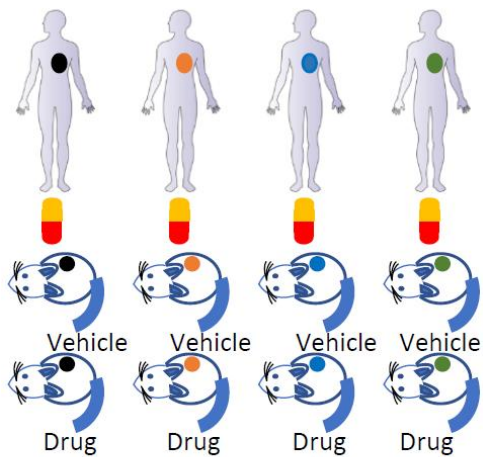
Drug metabolism and detoxification signals  
were activated in the resistant line

AKR1C inhibition recovered  
Enhertu drug sensitivity

# De novo Resistance of ADC in PDX Mouse Trial

## PDX selection and 'enrollment' based on Trop2 expression for Trodelvy efficacy

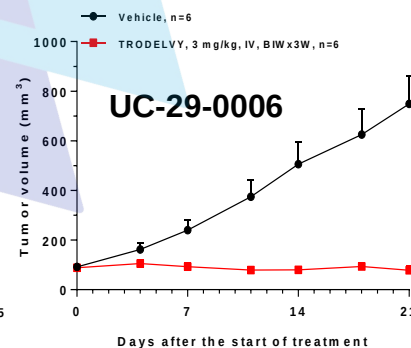
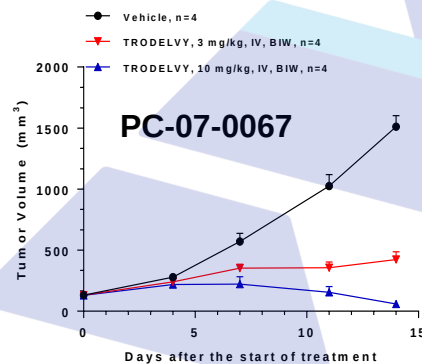
### PDX trial outline



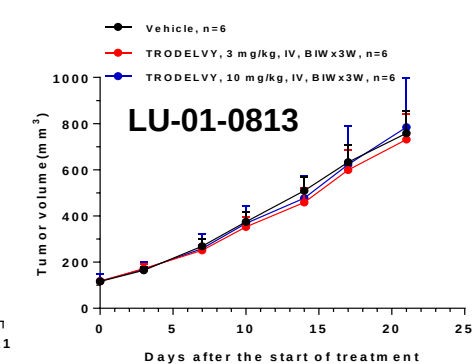
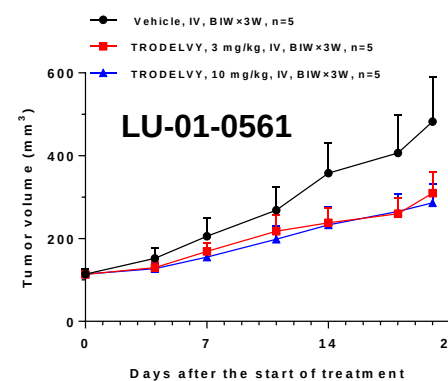
| Model      | Cancer type | Trop2 H-score |
|------------|-------------|---------------|
| PC-07-0067 | Pancreatic  | 230           |
| UC-29-0006 | Urothelial  | 245           |
| LU-01-0561 | Lung        | 280           |
| LU-01-0813 | Lung        | 260           |

## Trodelvy efficacy differentiated across models

### Responders



### Non-responders



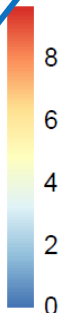
# Exploration of Resistant Mechanisms

Drug metabolism activated  
in non-responders

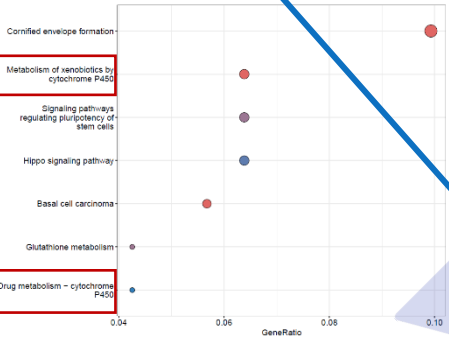
Responders

Non-responders

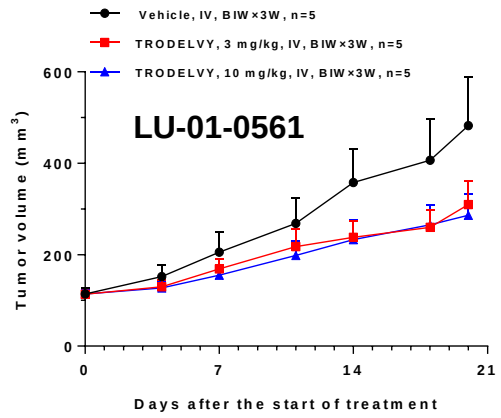
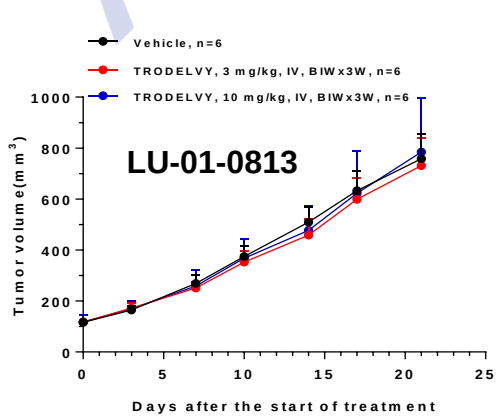
|      |      |      |      |         |
|------|------|------|------|---------|
| 0.16 | 0.42 | 7.06 | 8.77 | ADH7    |
| 3.52 | 1.08 | 9.42 | 9.64 | ALDH3A1 |
| 0.23 | 0.69 | 4.39 | 3.33 | UGT1A7  |
| 0.50 | 1.26 | 4.77 | 4.36 | GSTA4   |
| 2.32 | 0.00 | 6.05 | 6.24 | GSTA1   |
| 1.13 | 0.45 | 3.00 | 4.09 | CYP2E1  |



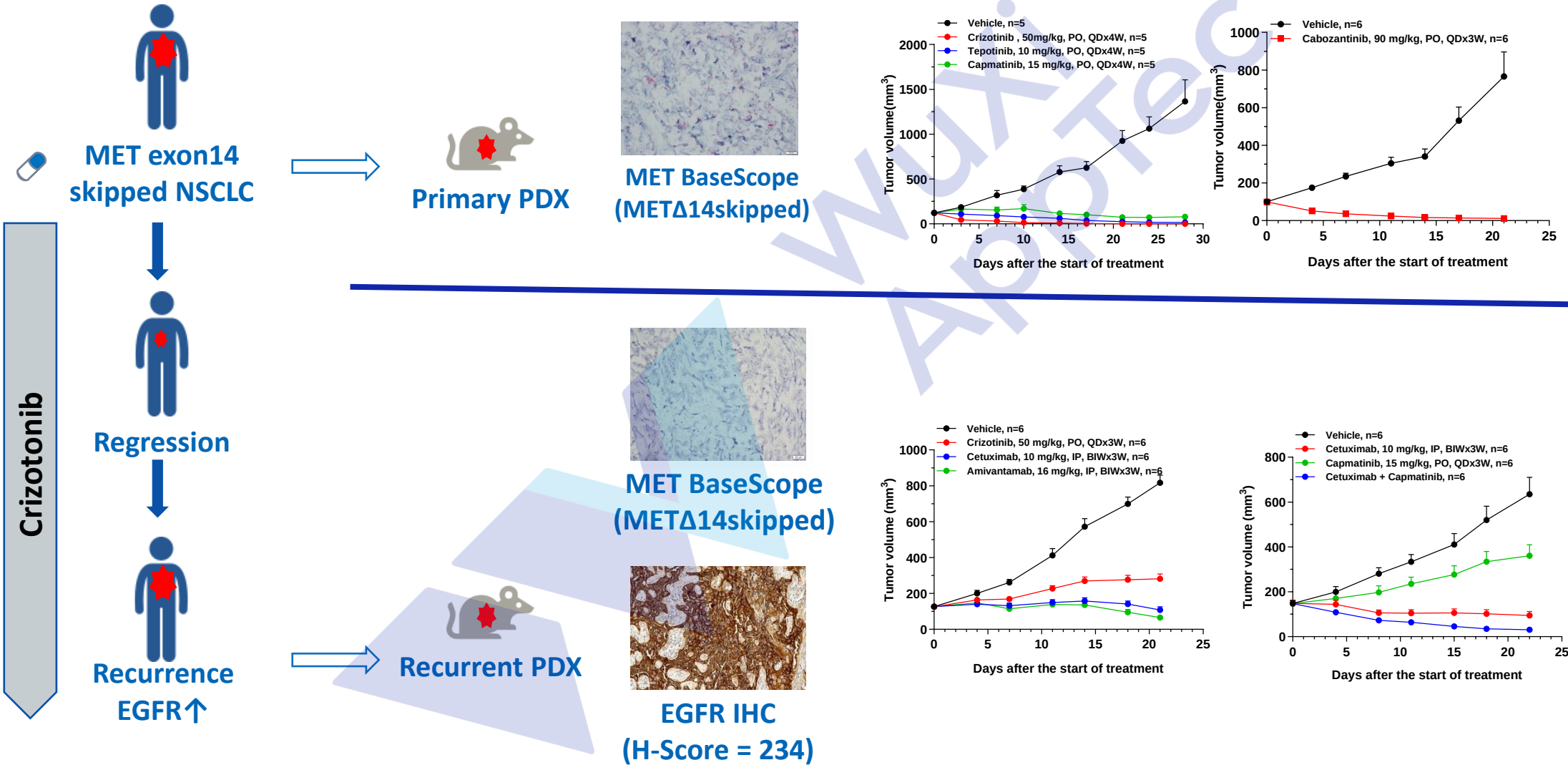
PC-07-0067  
UC-29-0006  
LU-01-0813  
LU-01-0561



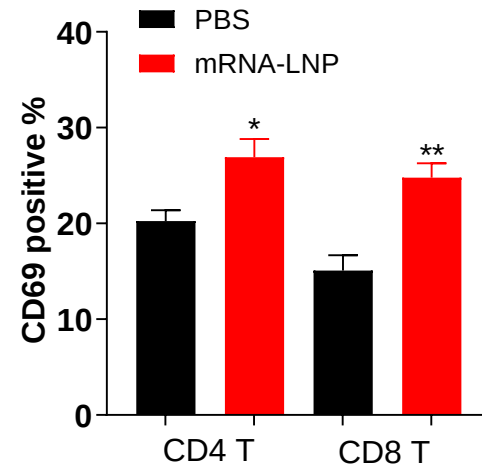
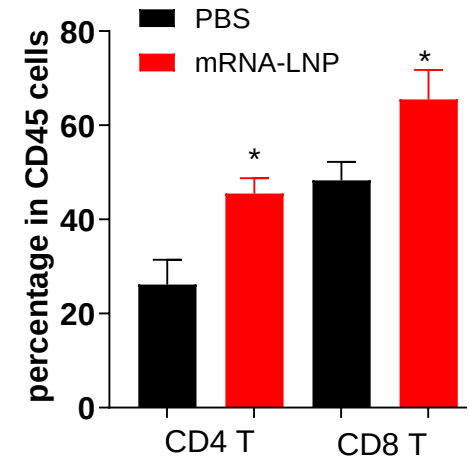
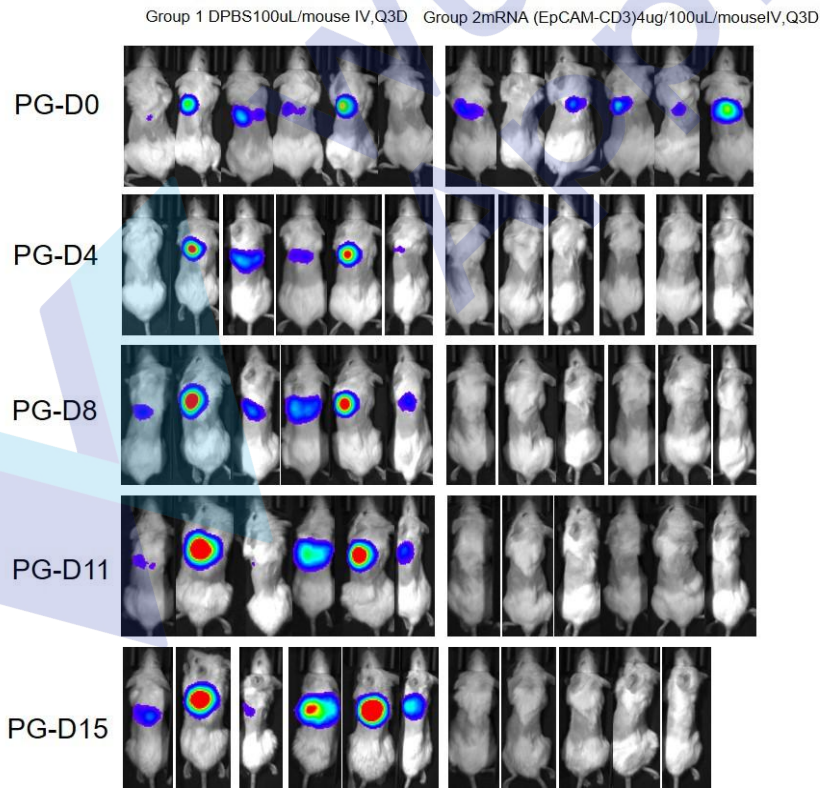
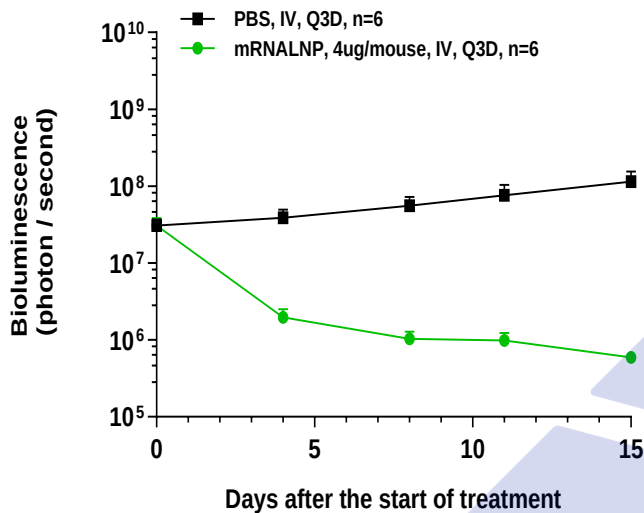
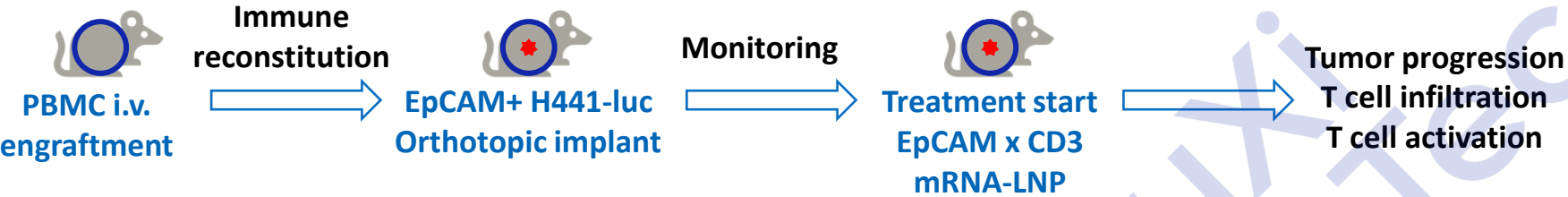
| Model            | LU-01-0813 | LU-01-0561 |
|------------------|------------|------------|
| ABCG2 expression | 2.82       | 0.15       |
| HRD score        | 25         | 44         |
| HRD status       | Negative   | Positive   |



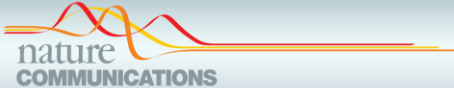
# Clinical Relevant PDX Enabling the Development of Bispecifics



# Humanized Models Enabling the Development of Bispecifics



# Exploration of Potential Resistance and Combination Mechanisms

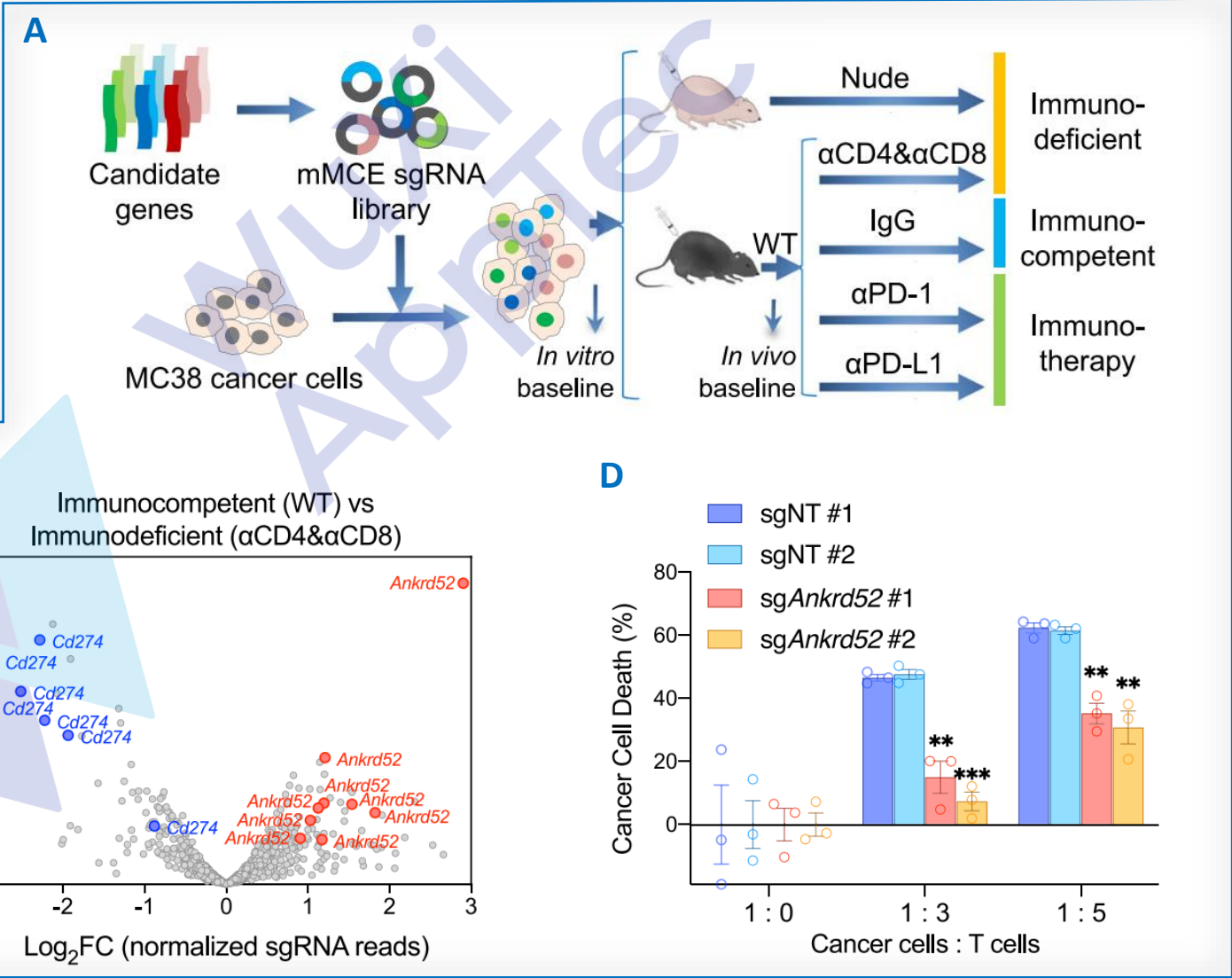


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<https://doi.org/10.1038/s41467-021-27331-3> OPEN

Tumor evolution selectively inactivates the core microRNA machinery for immune evasion

Tian-Yu Song<sup>1,2,3,6</sup>, Min Long<sup>1,3,6</sup>, Hai-Xin Zhao<sup>4,6</sup>, Miao-Wen Zou<sup>1</sup>, Hong-Jie Fan<sup>1,5</sup>, Yang Liu<sup>1</sup>, Chen-Lu Geng<sup>1,3</sup>, Min-Fang Song<sup>1,2,5</sup>, Yu-Feng Liu<sup>1</sup>, Jun-Yi Chen<sup>1</sup>, Yu-Lin Yang<sup>4</sup>, Wen-Rong Zhou<sup>4</sup>, Da-Wei Huang<sup>4</sup>, Bo Peng<sup>1</sup>, Zhen-Gang Peng<sup>4</sup> & Yong Cang<sup>1</sup>✉



# Comprehensive ADC Pharmacological Evaluation

