AACR Annual meeting 2022

Evaluation of the efficacy of ADC *in vitro* and *in vivo*

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No. 5566

Abstract

Antibody drug conjugate (ADC) is a promising complex with therapeutic potential that aimed to the treatment of solid tumor and hematological malignancies. Compared with the therapeutic monoclonal antibody, ADCs-derived monoclonal antibody is conjugated with cytotoxic agents which can deliver potent cellular toxins to targeted cancer cells specifically. According to the specialization of ADCs, we have established the state-of-the-art platform to support the evaluation of the efficacy of ADC or the combination strategy of ADC and other anti-cancer therapy in the process of pre-clinical drug discovery, such as target validation, efficient internalization, cytotoxic effects and in vivo efficacy testing.

In order to explore the mechanism of action and the functional effects of ADC for supporting the application of investigational new drug. Our flow cytometry platform (BD LSRFortessa X20) supports to evaluate the target validation and the process of internalization in a quick, reliable and reproducible way. Also we are able to construct customized antigen-specific overexpression or KI cells used for the development of ADCs which target on the specific antigens theoretically. In terms of in vivo ADCs assessment, our abundant CDX and PDX resource facilitates the process of in vivo ADCs evaluation, and we have already assess the efficacy of ADC or the combination treatment of ADC and other anti-tumor drugs in several animal models.

Method

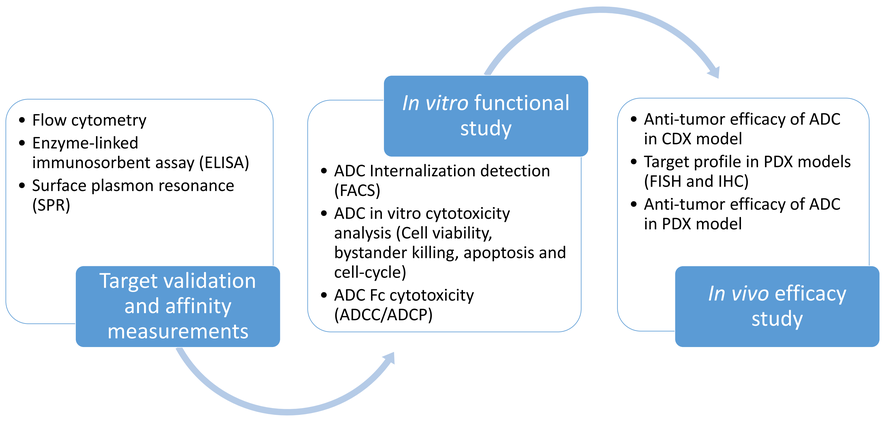

Fig 1. Methods for the evaluation of the efficacy of ADC *in vitro* and *in vivo*

Results

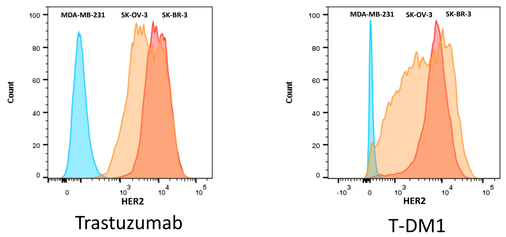

Fig 2. *In vitro* Target and affinity validation by flow cytometry
Trastuzumab and T-DM1 have higher binding affinity to SK-OV-3 and SK-BR-3 cell lines than MDA-MB-231 cell line. SK-OV-3 and SK-BR-3 have higher HER2 level than MDA-MB-231.

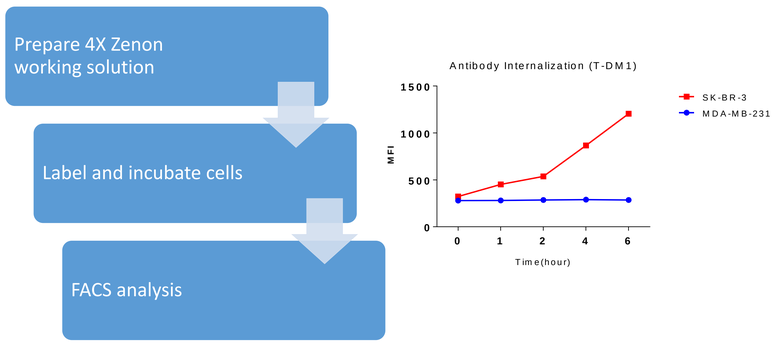

Fig 3. *In vitro* T-DM1 internalization assay in SK-BR-3 and MDA-MB-231 cells
The internalization signal of T-DM1 is increased in SK-BR-3 cells (HER2+), while there is no change in MDA-MB-231 cells (HER2-).

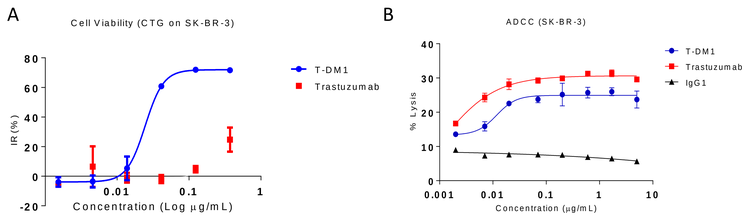

Fig 4. *In vitro* cell viability and ADCC assays in SK-BR-3 cells
A. T-DM1 displays the anti-proliferation effect on SK-BR-3 cells *in vitro*. B. T-DM1 and Trastuzumab stimulate the antibody dependent cellular cytotoxicity of NK cells on SK-BR-3 cells.

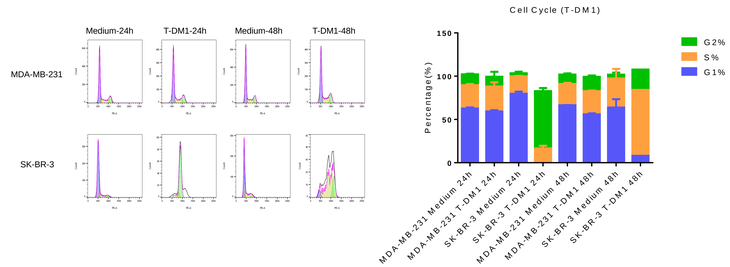

Fig 5. *In vitro* cell cycle assay on SK-BR-3 and MDA-MB-231
T-DM1 displays the effect to impact the cell cycle of SK-BR-3 (HER2+) at 24 and 48 hours, but no effect on MDA-MB-231 (HER2-) at the same time points.

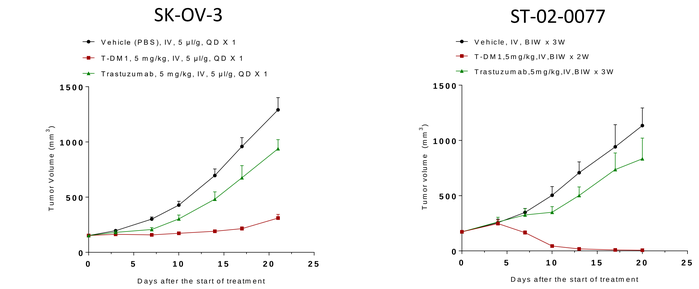

Fig 6. *In vivo* efficacy study of SK-OV-3 (CDX) and ST-02-0077 (PDX) models
T-DM1 shows anti-tumor efficacy in both SK-OV-3 (CDX) and ST-02-0077 (PDX) models.

Summary

- We have successfully established a series of *in vitro* assays and *in vivo* models to study the function and mechanism of action of ADC.
- In these assays or models, we also validated the efficacy of other drugs in the same or different mechanism.

Reference

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