Unique Breast Cancer CDX panels for KAT6, ER, and CDK4/6

Tianyu Pang, Haiting Dai, Ziwei Li, Wenbo Du, Wen-Jen Yu

ICE Bioscience, INC. Building 14, Yard 18, Kechuang 13th Street, Beijing, China 100176
youwz@ice-biosci.com

ICE Bioscience
Innovative CRO+Explorer

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Abstract

Estrogen receptor-positive (ER+) breast cancer accounts for approximately 75% of all breast cancers. Over-expression of lysine acetyltransferase 6A (KAT6A), a histone acetyltransferase (HAT), shared a proportion of 10-15% in breast cancer patients and increased the tumor growth through binding the promoter region to enhance ER expression level. Inhibitors of KAT6A were thought to be anti-tumorigenic by deregulation of ER expression. In addition, the cyclin-dependent kinases 4/6-cyclinD-Rb(CDK4/6-cyclinD-Rb) pathway is very important and crucial for ER downstream signaling in ER+ breast cancers. To accelerate the discovery of anti-ER+ breast cancer drugs through KAT6A and CDK4/6 pathways, we generated four specific CDX models which cover the most popular ER+/KAT6A cell lines (BT-474, ZR-75-1) and ER+/CDK4/6 cell lines (MCF-7, HCC1428) and revealed the efficacy of KAT6A inhibitor (PF-9363) or ER inhibitor (Fulvestrant) on these breast CDX models. The in vivo MOA of these inhibitors were also evaluated by Western Blotting and pathological examination.

Results

1.Cell Line IC50 test

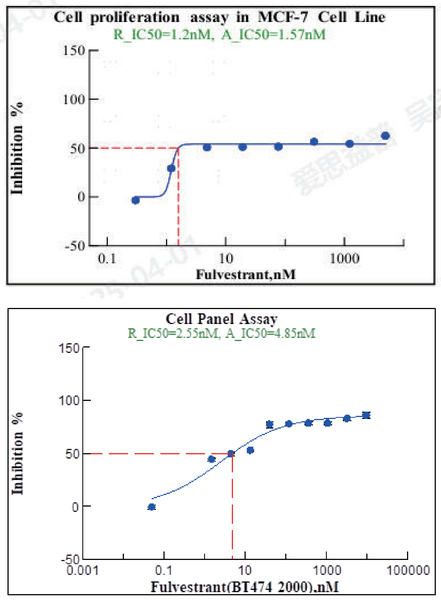
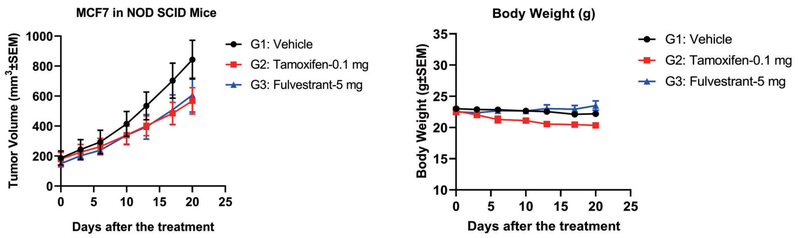


Figure 1. In vitro detection of MCF7 and BT-474 cell IC50 curve

The curve in the graph shows the trend of cell proliferation inhibition as the concentration of Fulvestrant increases. The rapid rise in the curve at lower concentrations indicates that the drug has a significant inhibitory effect on cell proliferation. Overall, the experimental results demonstrate that Fulvestrant has a strong inhibitory effect on the proliferation of the MCF7 and BT-474 cell line, and this effect is evident at relatively low drug concentrations.

2. In vivo Efficacy



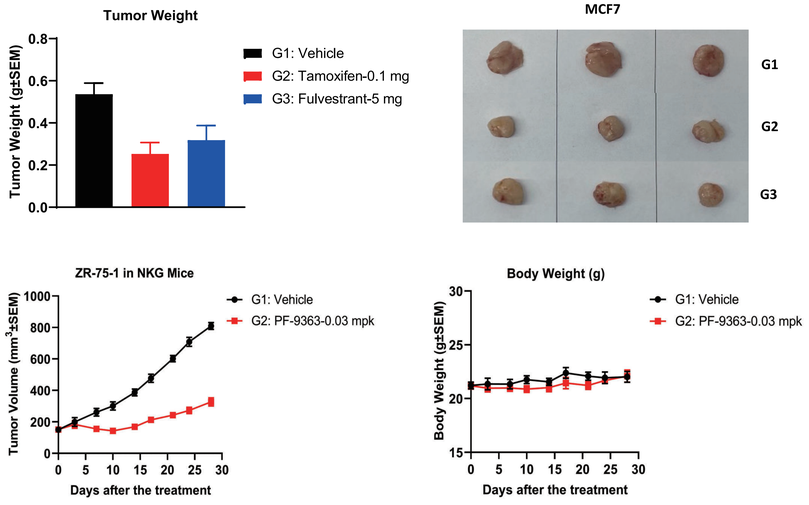


Figure 2. Tumor volume and body weight of MCF7, ZR-75-1, BT-474 and HCC1428 in vivo efficacy models.

The results of MCF7, ZR-75-1, BT-474 and HCC1428 CDX models showed the in vivo efficacy of Fulvestrant, Tamoxifen and PF-9363. In MCF7, the tumor growth rate in the Fulvestrant and Tamoxifen groups was significantly lower than that in the control group, demonstrating a strong anti-tumor effect. For the ZR-75-1 model, the tumor growth rate in the PF-9363 group was also significantly lower than that in the control group, indicating a strong anti-tumor effect. For the HCC1428 model, the tumor growth rate was somewhat reduced compared to the control group, showing a certain level of anti-tumor effect, but it was not as pronounced as the effect of Fulvestrant in the MCF7 model. In addition, the body weight of all the models showed no obvious change. There was no drug toxicity in Fulvestrant, Tamoxifen and PF-9363

3. Bioinformatic analysis

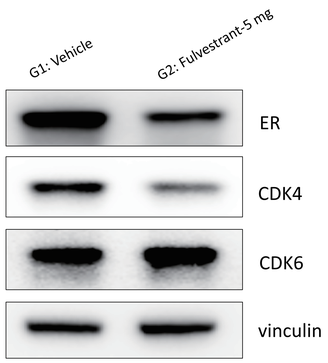


Figure 4: WB Results of HCC1428 Tumor Samples. G1: Vehicle. G2: Fulvestrant-25 mg.

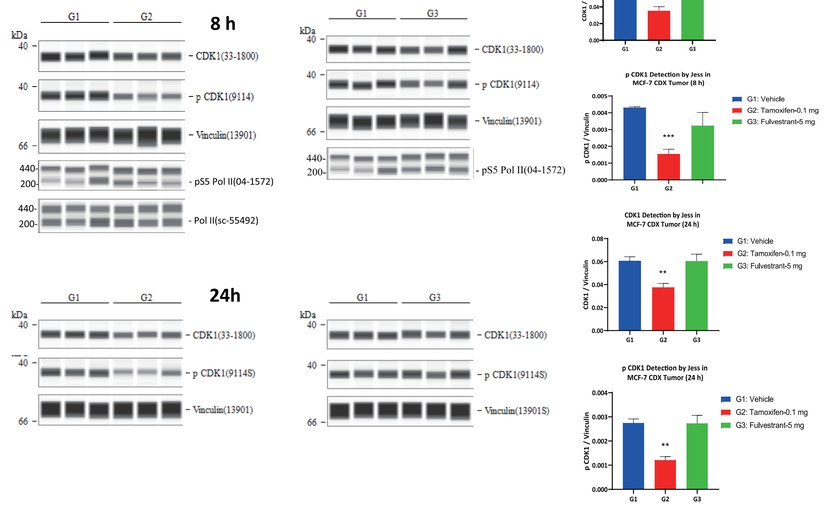


Figure 4: WB Results of MCF7 Tumor Samples. G1: Vehicle. G2: Tamoxifen-0.5 mg. G3: Fulvestrant-5 mg

The image shows the results of JESS conducted to detect the expression levels of CDK1, p CDK1, Vinculin, p55 Pol II, and Pol II proteins in the control group, Tamoxifen group and Fulvestrant group. For both the Tamoxifen and Fulvestrant groups, there were no significant differences in the expression levels of CDK1 (33-1800) and p CDK1 (9114) proteins.

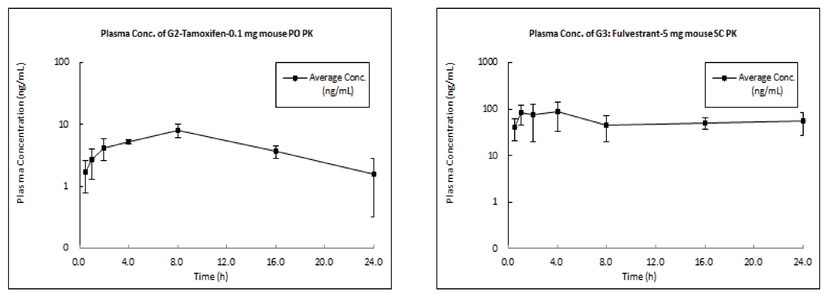


Figure 5: PK Results of MCF7 Plasma Samples. G2: Tamoxifen-0.5 mg. G3: Fulvestrant-5 mg.

The PK results of Tamoxifen and Fulvestrant in mice show that Tamoxifen's plasma concentration rapidly increases and reaches its peak after dosing, followed by a gradual decline. In contrast, Fulvestrant's plasma concentration decreases more slowly after reaching its peak and remains at a higher level over a more extended period.

Summary

ER, KAT6A, CDK4/6 inhibitors are crucial targets for the treatment of various cancers, especially hormone receptor-positive breast cancer. They play a significant role in cell growth and proliferation. Based on the results from four specific CDX models (BT-474, ZR-75-1, MCF-7, and HCC1428), which demonstrate the efficacy of Fulvestrant and Tamoxifen on these breast cancer models, we can offer the following insights:

1. The data provide an assessment of the compounds' potency and efficacy across various tumor types, which is crucial for evaluating potential therapeutic indications.

2. The findings offer insights into the effectiveness of these compounds against tumor resistance mechanisms.

3. The study delivers information on the selectivity of the compounds for different molecular pathways involved in cancer progression.