Inhibition of CDK7 overcomes resistance to CDK4/6 inhibitors in hormone receptor positive breast cancer cells.

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INTRODUCTION

• CDK7 inhibitors have emerged as effective treatments in hormone receptor positive (HR+) breast cancer (BC) patients. 
• Despite the efficacy of the combination of endocrine therapy (TAM) and targeted drugs (such as HER2 inhibitors), patients eventually acquire resistance to these drugs.

• The loss of Rb is one of the mechanisms of resistance in HR+ BC patients.

• In the T47D cells, the loss of Rb was observed (among the top regulated genes) in T47D PDS and PDR (c).

• 20 genes that are significantly positively selected (among these genes were CDK7, CDK1, CKS1B, and MYC).

• A significantly enriched set of genes that are Down-regulated in T47D PDR is due to the deletion of the exon 1 of Rb1.

• The loss of Rb in T47D PDR is due to a deletion in the exon 1 of Rb1.

• Identification of T47D PDR vulnerabilities

• Genome-wide ChiPseq-CARD knockout screen in T47D PDS and PDR

• Surviving HR+/HER2+ breast cancer drug-resistant (PalR) model was developed by exposing HR+ BC sensitive (PalS) cells to Palbociclib 1 µM treated with escalating doses of fulvestrant and SY1365 (d, e).

• The THZ1 was equally effective in T47D PDS and PDR (b, e).

• The CDK7 inhibitor SY1365 was confirmed in MCF7 HR+ BC palbociclib sensitive (PalS) and resistant (PalR) cells (c, e).

• The loss of Rb in T47D cells (T47D RB1_KO) doesn’t regulate CDK7 expression level of CDK7 inhibitor targets in palbociclib resistant T47D cells, cyclin D1, CDK4 and CDK6 are not essential for cell growth in palbociclib resistant cells of breast cancer (a).

• In vitro drug response matrix (% inhibition)

• T47D PDR with palbociclib 1µM treated with escalating doses of Fulvestrant and SY1365 (c).

Fulvestrant and SY1365 combination studies

• T47D PDS and PDR growth and cell cycle analysis with palbociclib and SY1365

• SY1365 was equally effective in T47D PDS and PDR (d, e). SY1365 was significantly more potent in T47D PDS than PDR.

• SY1365 and fulvestrant in T47D PDR show synergistic activity (positive synergy score) at low drugs concentrations.

• T47D PDS and PDR growth and cell cycle analysis with palbociclib and SY1365

• SY1365 was equally effective in T47D PDS and PDR (a, e).

• SY1365 was significantly more potent in T47D PDS than PDR.

• SY1365 and fulvestrant in T47D PDR show synergistic activity (positive synergy score) at low drugs concentrations.

• SY1365 significantly enriches T47D PDR, growth.

• SY1365 and fulvestrant in T47D PDR show synergistic activity (positive synergy score) at low drugs concentrations.

CONCLUSIONS

1. In this palbociclib-resistant T47D cells, cycle 01, CDK7 and CDK19 are not essential for in vitro cell growth.

2. SY1365 and SY1365 are significant essential genes for in vitro cell growth in palbociclib-sensitive and palbociclib-resistant T47D cells.

3. The CDK7 inhibitor SY1365 arrests the cell cycle progression in 48/421 phase, and reduces the expression level of CDK7 enhancer targets in palbociclib-resistant resistant T47D cells.

4. In palbociclib-resistant T47D cells, the CDK7 inhibitor SY1365 and fulvestrant have synergistic activity (positive synergy score). SY1365 is a new therapeutic target for the treatment of breast cancer-resistant HR+/HER2- BC, and support the ongoing clinical investigation of SY1365 (NCT03134638) in combination with Fulvestrant in HR+ BC patients who have progressed through CDK4/6 inhibitors.