A platform of CDK4/6 inhibitor-resistant patient-derived breast cancer organoids illuminates mechanisms of resistance and therapeutic vulnerabilities

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**Introduction**

- CDK4/6 inhibitors (palbociclib, ribociclib, abemaciclib) + antihormones have revolutionized the treatment of metastatic ER+ breast cancer.
- However, tumors eventually acquire resistance. Patients with resistant cancers are left with limited treatment options.
- Mechanisms of CDK4/6 resistance are quite heterogeneous. Potential resistance-conferring alterations include: RB1, FATT, PTEN, ARID1A, FGFR1/2, ERBB2, CCNE1/2, AURKA, and KRAS.
- Models of CDK4/6 resistance are needed to capture the heterogeneity of resistance mechanisms and identify novel therapeutic strategies for CDK4/6-resistant tumors.
- Patient-derived organoids (PDOs) provide a rapid, robust, and reliable platform that recapitulates intra-tumor heterogeneity, partially mimics the cancer microenvironment, and accurately predicts drug responses.

**Objective:** To generate and characterize a platform of CDK4/6-resistant breast cancer PDOs to serve as models for understanding acquired resistance to CDK4/6 + antihormones and identifying therapies to overcome resistance.

**PDOs established from metastatic biopsies of ER+ breast cancer patients progressing on CDK4/6 + antihormones**

**A subset of CDK4/6-resistant PDOs retain sensitivity to PI3K pathway and/or G2/M inhibitors**

**Conclusion**

- PDOs can be successfully established and cultured long-term from metastatic ER+ breast cancer biopsies.
- PDOs from patients progressing on CDK4/6 inhibit retain resistance in culture.
- Mutations in PDOs are concordant with clinical reports from biopsies and recapitulate alterations that have previously been associated with resistance to CDK4/6 and/or antihormones.
- CDK4/6-resistant PDOs fail to suppress proliferation to second-generation PI3K inhibitors.
- CDK4/6-resistant organoids are vulnerable to inhibitors of cell cycle proteins and/or PI3K/AKT pathway inhibitors.
- CDK4/6-resistant PDOs represent a valuable model to understand and explore diverse mechanisms of drug resistance and therapeutic vulnerabilities.