

METAvivor Final Report

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Grant title: Identifying Therapeutic Vulnerabilities in *RBI*-negative, ER-positive Breast Cancers

Approximately 75% of all breast cancers are Estrogen Receptor (ER)-positive. CDK4/6 inhibitors, in combination with a hormone therapy, are the preferred treatment for ER-positive breast cancer patients with disseminated disease. While these treatments are quite effective in controlling the cancer initially, nearly all patients with disseminated breast cancer ultimately become unresponsive/resistant to these drugs. Treatment options for such patients are severely limited. Therefore, there is an urgent need to develop new treatments that overcome resistance to CDK4/6 inhibitors and improve survival in these patients.

In this study, we establish model systems to study how breast cancer patients develop resistance to CDK4/6 inhibitors. Using gene editing approaches we deleted *RBI*, a tumor suppressor gene, to establish a model of treatment-resistant breast cancer. Loss of *RBI* is a mechanism of treatment resistance in metastatic breast cancer patients treated with CDK4/6 inhibitors. Using this clinically-relevant model, we show that CDK4/6 inhibitor-resistant tumors undergo alterations in DNA repair pathways and gene regulatory networks. We also show the OTX015, a drug that targets bromodomain and extraterminal domain (BET) family of proteins, blocks such remodeling and overcomes resistance to CDK4/6 inhibitors, both in cell culture and animal models of breast cancer.

In summary, we introduce a new paradigm for treatment of metastatic, ER-positive breast cancer patients, who have become resistant to currently available targeted therapies. There are over 200,000 women living with metastatic breast cancer in the United States. Nearly 75% of these women harbor Estrogen Receptor (ER)-positive breast cancer. Nearly all ER-positive, metastatic breast cancer patients eventually develop resistance to CDK4/6 inhibitors. There are currently limited targeted therapy options for such patients. BET inhibitors such as OTX015, which overcome resistance to CDK4/6 inhibitors, have the potential to improve survival in patients with metastatic breast cancer.