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"Targeting CISD1 to Overcome Endocrine Resistance in Breast Cancer"

Breast cancer is the second most common cancer type in American women, affecting about 1 in every 8 females, or about 13% of the female population in the country. Estrogen Receptor Positive breast cancer (**EPBC)** is the most common subtype, comprising ~70% of breast cancer cases. These tumors are dependent on the estrogen receptor (**ERα**), and modulating **ERα** activity through endocrine therapy (ET) is a current treatment approach. Targeted treatment with selective estrogen receptor modulators (**SERMs**; e.g., Tamoxifen) and selective estrogen receptor degraders (**SERDs**; e.g., Fulvestrant) has been an effective approach for some cases. However, prolonged therapeutic use often causes resistance via multiple mechanisms, including mutation or loss of **ERα**, metabolic rewiring, or upregulation of alternative pathways (HER2, MAPK, AKT, etc.), often leading to cancer relapse. Of the 70% of ER+ breast cancer patients, about 40% of this population ultimately develop drug resistance. When including the rare ~15% of BC cases that are triple-negative and ~15% that are ER negative, ~70% of all breast cancer patients remain without any effective targeted therapeutic treatment.

CISD1, also known as mitoNEET, is an iron-sulfur cluster protein bound to the outer mitochondrial membrane that is responsible for maintaining iron homeostasis, possesses enzymatic redox functions, and is often overexpressed in cancers, including EPBC. Increasing evidence suggests that aberrant CISD1 overexpression promotes cancer cell survival and enhances energy metabolism to sustain rapid proliferation. The abundance of overexpression in tumor cells, as well as destructive cellular effects upon its suppression, highlights CISD1 as a potential cancer biomarker and therapeutic target.

Based on these findings, we hypothesize that targeted inhibition of CISD1 will effectively inhibit the growth and proliferation of wild-type and tamoxifen-resistant EPBC cells *in vitro* and will synergize with antihormonal therapies to overcome resistance to SERMs.
To test this hypothesis, we employed bioinformatics approaches, cell viability assays (MTT), and immunoblotting. We found that CISD1 mRNA and protein expression are negatively correlated with ESR1/ERα expression in wild-type and Tamoxifen-resistant EPBC cells. We also found that exogenous overexpression of CISD1 significantly decreases sensitivity to both 4-OH Tamoxifen and Fulvestrant, and that CISD1 inhibition enhances Tamoxifen-resistant MCF-7 cells' sensitivity to Tamoxifen.