Epigenetic Reactivation of estrogen receptor beta Enhances Antitumor Activity of a Novel estrogen receptor beta agonist CIDD-0149897 in Triple-Negative Breast Cancer

: U. Pratap1 , M. Mahajan1 , K. Nassar1 , T. Adeniran1 , N. Karinel2 , G. Sareddy1 , N. Mukherjee1 , S. Viswanadhapalli1 , S. McHardy2 , A. Brenner1 , R. Vadlamudi1 ; 1OBGYN, UT Health San Antonio, San Antonio, TX, 2OBGYN, UTSA, San Antonio, TX.

Abstract

Breast cancer (BC) is the most common cancer in women with approximately 40,000 deaths in the USA. Among the different sub-types of BC, 60-70% are estrogen receptor (ER) positive, and 15-24% are triple negative breast cancer (TNBC). TNBC is more aggressive and represents a disproportional share of the BC mortality. TNBC lacks expression of estrogen receptor alpha (ERα), progesterone receptor, and HER2. However, it uniquely expresses estrogen receptor beta (ERβ), which functions as a tumor suppressor. Despite this, therapeutic activation of ERβ is currently underexplored due to the lack of selective and potent ERβ agonists and challenges posed by epigenetic silencing of ERβ in advanced TNBC. ***There is a critical need for rationally designed therapies for TNBC.*** . We recently identified indanone and tetralone-keto oximes as promising ERb agonists. The **objective** of this proposal is to test whether HDACi enhance the expression of ERβ and the utility of ERβ agonist for the treatment of TNBC.

Materials and Methods

c

CIDD-0149897 was evaluated in seven TNBC cell lines (SUM159, BT549, MDA-MB-468, HCC1806, HCC70, MDA-MB-231, E0771). ERb expression was measured by RT-qPCR and Western blot. Functional assays included cell proliferation, colony formation, invasion, and apoptosis following treatment with CIDD0149897, HDACi, or combination therapy. Mechanistic studies involved RNA sequencing, reporter assays, immunohistochemistry, and pathway analysis. In vivo efficacy was assessed using TNBC xenograft and syngeneic mouse models.

Key Highlights

1. ERβ is variably expressed but functionally targetable across TNBC models.
2. CIDD-0149897 activates ERβ signaling and induces potent anti-tumor effects.
3. HDAC inhibitors epigenetically restore ERβ expression and enhance pathway activation.
4. Combination of CIDD-0149897 + HDACi yields synergistic anti-cancer activity.
5. Combination therapy demonstrates superior in vivo efficacy and immune modulation.

Conclusion: These findings demonstrate that CIDD-0149897, in combination with HDAC inhibition, effectively reactivates ERb signaling and modulates the tumor microenvironment. This combinatorial strategy offers promising therapeutic potential for TNBC and provides critical insights that may guide the development of more effective, targeted treatments.

This study was supported by the NCI grant 1R01CA269866-01A1 (R.K.V., S.M., A.B.)