



Session MS.CH01.01 - Innovative Approaches in Drug Discovery: Novel Leads, Degraders, and AI-Driven Solutions

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3756 - Optimization of the LIPA targeting agent for the treatment of ovarian cancer

📅 April 28, 2025, 2:35 PM - 2:50 PM

📍 Room S100 A (Grand Ballroom A) - McCormick Place South (Level 1)

Presenter/Authors

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Disclosures

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Abstract

Background: Ovarian cancer (OCa) is the most lethal form of gynecologic cancer in the United States, with a five-year survival rate below 20%. Tumor resistance to chemotherapy and poor clinical outcomes are driven by intratumoral and intertumoral heterogeneity. There is a critical need for novel therapies to overcome these challenges. Recent findings indicate that elevated basal levels of endoplasmic reticulum stress (ERS) in OCa represent a significant vulnerability and identified LIPA as a novel target for inducing ERS in cancer cells with the oligobenzamide ERX-41. In this study, we have synthesized and tested several derivatives of ERX-41 for lead optimization, established ERX-208 as the optimized lead, validated its mechanism of action.

Methods: ERX-208 activity was validated in 17 OCa cell lines, representing five major histological subtypes.

Mechanistic studies involved Western blotting, IHC, RNA-seq, mutagenesis, docking, and CRISPR/Cas9 knockout. PK and toxicology studies were conducted in C57BL/6 mice, and preclinical assessments in cell line-derived xenograft (CDX), patient-derived xenograft (PDX), and patient-derived explant (PDE) models.

Results: After the screening of a curated oligobenzamide library derived from ERX-41, ERX-208 was identified as a more potent analog, by virtue of its ability to potently reduce the cell viability and promoting ERS in OCa cells. ERX-208 reduced the viability of 17 different OCa cell lines, with an IC₅₀ range of 50-100 nM, in comparison to ERX-41,

which showed an IC₅₀ around 500 nM. Importantly, ERX-208 had minimal impact on the viability of normal ovarian surface epithelial cells, indicating a selective action against cancerous cells. Treatment with ERX-208 resulted in a significant decrease in colony formation and induced apoptosis. Mechanistic studies, including RNA-seq, Western blot analysis, TEM, and RT-qPCR revealed the activation of ERS as early as five hours post-treatment, suggesting a rapid onset of action. These studies also identified LIPA as a potential therapeutic target, with the activity of ERX-208 being notably diminished when LIPA was knocked out or when specific amino acids involved in ERX-208 interaction were mutated, as determined through docking studies. Further pre-clinical studies, including dose-range, MTD and PK assessments, indicated that a 10 mg/kg was the minimal amount required to achieve 50% efficacy without causing toxicity. ERX-208 treatment effectively reduced tumor growth in OCa CDXs, PDXs, and PDEs models. IHC analyses revealed a marked decrease in tumor cell proliferation, as evidenced by Ki67 expression, and demonstrated an increase in ERS markers, including GRP78 and p-PERK.

Conclusions: These findings suggest that ERX-208 is a promising candidate as a therapeutic agent in OCa treatment. Since a related analog of ERX-208, ERX-315 is in clinical trials, these data strongly support the evaluation of ERX-208 in patients with OCa.