

## Peer Review

# Review of: "The Development of Differentiation-Based Therapy for Breast Cancer Using EDAR and XEDAR Signalling Pathways: A Conceptual Framework"

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The two-phase therapeutic strategy of epigenetic restoration of XEDAR expression, followed by pathway activation with synthetic ligands, offers a novel and promising approach with potential clinical benefits, such as reduced toxicity and resistance. The manuscript is well-structured and grounded in robust biological and clinical insights, but several areas require improvement. The discussion of challenges, such as the off-target effects of epigenetic agents and the immunogenicity of synthetic ligands, would benefit from more specific and actionable solutions. The clarity and detail of the figures should be enhanced, with improved captions to aid understanding. Additionally, the section on biomarkers for therapy monitoring could expand on how these could be integrated into clinical practice. Addressing minor language issues and ensuring all claims are well-supported by references will also strengthen the manuscript. Overall, this is a well-conceived and relevant study recommended for **acceptance with minor revisions**, particularly focusing on refining these critical aspects.

- What specific solutions can you suggest for minimizing off-target effects and the immunogenicity of the proposed therapy?
- Can you provide examples of how biomarkers could be practically implemented in clinical settings for therapy monitoring?

## **Declarations**

**Potential competing interests:** No potential competing interests to declare.