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Peer Review

Review of: "Phosphatidylserine (PS)-Targeting Chimeric Interferon (IFN) Fusion Proteins for Anti-Tumour Applications"

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Review of: ***Phosphatidylserine (PS)-Targeting Chimeric Interferon (IFN) Fusion Proteins for Anti-Tumour Therapy***

This manuscript addresses an important area of immunotherapy by developing and characterizing PS-targeting chimeric IFN fusion proteins for anti-tumor applications. The authors present a compelling rationale for targeting exposed phosphatidylserine (PS) on tumor cells and the tumor microenvironment, integrating interferon-based immune activation in a novel delivery format.

Strengths

- The approach of combining PS-targeting with IFN-based immunostimulation is new and overcomes drawbacks of systemic IFN treatment.
- Experimental design is sound in general, and data are presented clearly.
- Figures are informative, and quantitative analyses support the main conclusions.

Points for Improvement

1. Mechanistic Explanation

Although the central idea is novel, the manuscript would be strengthened by more in-depth consideration of downstream immune signaling induced by the fusion protein. Inclusion of pathway-specific assays—e.g., STAT1/2 phosphorylation, ISRE-luciferase reporter assays, or qPCR for ISGs (OAS1, MX1, IFIT1)—would significantly enhance mechanistic understanding.

doi.org/10.32388/24JP7A

2. In Vivo Validation

The manuscript would be greatly improved by in vivo efficacy data in a syngeneic tumor model (e.g., B16-F10 or MC38 in C57BL/6 mice). Such models would enable immune modulation and anti-tumor activity to be assessed in an immunocompetent context. If not possible, a clear discussion of current limitations and future in vivo plans is suggested.

3. Safety and Immunogenicity

In light of the clinical limitations of systemic IFN therapies, the immunogenicity or toxicity of the chimeric construct can be commented on, however preliminary.

4. PS-Targeting Specificity

The specificity and affinity of the PS-binding domain need to be better characterized or referred to. The inclusion of quantitative binding assays (e.g., Annexin V competition, lipid dot blots, or SPR for KD values) would strengthen the targeting claims. Placing the approach in the context of earlier agents such as bavituximab would emphasize the novelty.

Minor Comments

- Standardize terms (e.g., use "chimeric IFN" consistently instead of "IFN fusion protein").
- Make sure all figure legends describe conditions and define abbreviations. Consider including a graphical or schematic abstract representing the mechanism of action.

Conclusion

This is a good and well-planned study. The chimeric fusion approach has translational potential, yet more mechanistic and in vivo data (or further discussion) would greatly strengthen its significance and credibility. I suggest revision to cover the above issues.

Declarations

Potential competing interests: No potential competing interests to declare.