Peer-Review Report

Peer Review of “Localized Immune Cascade Programming in Desmoplastic Tumors: In Silico Modeling and Validation Study”

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This is the peer-review report for “Localized Immune Cascade Programming in Desmoplastic Tumors: In Silico Modeling and Validation Study.”

Round 1 Review

General Comments

This paper [1] presents a conceptual framework for a sequential, localized immune cascade (“Second Breath”) aimed at reprogramming “immune-cold” desmoplastic tumors to enhance immunotherapy responsiveness. It is positioned as a preclinical concept paper, relying entirely on literature synthesis and in silico modeling without generating new experimental data. While the integration of immunology, biochemistry, and systems biology concepts is ambitious and potentially innovative, the work has significant limitations.

Specific Comments

Major Comments

1. The abstract does not require reference citations. Please remove the citations in the abstract. If reference citations are deemed really necessary, please start with 1 instead of 4. Also, please go on in ascending order instead of skipping references, like [4,5,6,7,32,33].
2. The main text instead should be backed up by reference citations to increase its value. However, the same principle also applies to starting from 1 and continuing in ascending order, but not starting in the middle and skipping references. Also, the references need to be cited in a uniform format. The following needs to be revised in the Introduction: “...(ECM) [6,7,32,33]....(ICIs) [13,14,15]....exposure [1,2,4,5,9,10,11].....Therapy for a Sustainable Outcome’ (M. Novruzov, 2025),...” The same format of reference citations should be used, thus “(M. Novruzov, 2025)” should be cited as per others: “[n].” Please revise.
3. The references are drawn from reputable sources, but the synthesis appears biased toward supportive evidence. For example, citations for bacterial priming (eg, Clostridium novyi-NT) highlight antitumor responses but downplay failures in clinical trials, such as high toxicity or limited efficacy in advanced tumors. Similarly, extracellular matrix (ECM) modulation via collagenase/hyaluronidase is presented positively but ignores biochemical drawbacks like enzyme instability in vivo, nonspecific proteolysis leading to tissue damage, or rebound ECM deposition. It is unclear how the authors reconciled conflicting literature. For example, the Wnt pathway enrichment is noted as dominant, but its protumorigenic role in desmoplastic tumors (eg, promoting fibrosis via β-catenin) is only briefly mentioned in the Discussion without quantitative risk assessment. Please add in a more balanced view and references.
4. The framework proposes a 10-stage sequence, gated by biomarkers like interferon (IFN)–γ signature or interstitial fluid pressure reduction. However, this complexity introduces numerous failure points without clear prioritization. Biochemically, the “IL-12 → IFN-γ → TNF-α axis” assumes linear signaling, ignoring feedback loops (eg, tumor necrosis factor α [TNF-α]–induced apoptosis resistance via NF-κB) or crosstalk with immunosuppressive pathways (eg, transforming growth factor β in desmoplastic stroma). The “Warmth Readiness Index (WRI)” is mentioned but undefined quantitatively. How is it calculated? What thresholds were derived from it? This vagueness makes the model hard to falsify, as the “prediction matrix” relies on

qualitative outcomes rather than measurable biochemical end points. Please revise and supplement.

5. The go/no-go criteria (eg, "≥2-fold fold increase in CXCL9/10/11") are arbitrary; please justify them from literature or simulations.

Round 2 Review

General Comments

This paper has undergone revisions and looks much better.

Specific Comments

Major Comments

1. The references do not appear in ascending order upon a citation in the main text. The first citation that showed up was "[6-7,32-33]," followed by "[13-15]," and then "[1-2,4-5,9-11]."

The authors also addressed this in their rebuttal letter, showing their difficulties in rearranging the list of references, because such an adjustment would require rewriting the article from scratch, which is beyond the scope of the current revision. They are open to discussion on an alternative option for formatting references that would preserve the structure of the work. I think the editorial office or I can help rearrange the reference numbers.

Conflicts of Interest

None declared.

References

1. Novruzov M, Mammadova M, Raval K, Khan WU, Shiraliyeva U. Localized immune cascade programming in desmoplastic tumors: in silico modeling and validation study. JMIRx Bio. 2026;4:e85507. [doi: 10.2196/85507]

Abbreviations

ECM: extracellular matrix
IFN: interferon
TNF-α: tumor necrosis factor α

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