Peer-Review Report

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

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**Keywords:** oncology; tumor microenvironment; cancer microenvironment; immunology; immune-cold tumors; intratumoral immunotherapy; extracellular matrix remodeling

*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*

In this paper [1], overall, there is a clear scientific narrative defining “second breath” as a testable conceptual framework for converting immune-cold tumors to a more responsive state. The graphical representation of the model and the concise logical sequence make the manuscript more appealing to read. The Introduction highlights key biological barriers like low T-cell infiltration, dense extracellular matrix, and stromal resistance that justify the need for a localized immune therapy. The overall study framework is clearly articulated, well-structured, and presented in a concise and accessible manner. The citations are well integrated and support the key arguments effectively. The abstract is informative, but the functional role of β-catenin/Wnt–linked programs in the cascade requires more clarity. The Results section highlighting Wnt signaling dominance is contradictory to the existing literature and the Discussion section of the manuscript, which requires further supporting evidence with human-specific models.

### *Specific Comments*

#### Major Comments

1. Wnt-signaling dominance in the Results section: It is known that APC, CTNNB1, and AXIN1 gene mutations of the canonical Wnt/β-catenin pathway give rise to cancers. Inappropriate activation of the Wnt/β-catenin pathway is believed to be involved in carcinogenesis. Specifically, there are multiple genetic abnormalities involved in the activation of the Wnt/β-catenin pathway; nonetheless, the CTNNB1 mutation is a typical driver mutation that is found in approximately 30% of hepatocellular carcinoma cases. In 2015, Spranger et al [2] reported that the Wnt/β-catenin pathway activation inhibits cytotoxic T-cell infiltration in the immune microenvironment of malignant melanoma, resulting in resistance to immune checkpoint inhibitors. Wnt/β-catenin signaling was shown to inhibit this dendritic cell invasion into the tumor. However, the manuscript has reported dominance of Wnt signaling in the pathway enrichment analysis, which is contradictory. Provide more clarity by offering more predictive insights into human-specific responses. The Discussion raises important safety concerns, and so to strengthen practical relevance, propose any mitigation strategies or alternative approaches.

#### Minor Comments

1. Although it is stated in the manuscript that “Second breath” represents a novel preclinical approach for antitumor immunity, kindly clarify the novelty by elaborating on how the model is better than existing intratumoral immunotherapy strategies (like immunostimulatory antibodies, gene therapy, and combination therapy) while both are aimed at limiting systemic toxicities. A strong statement is needed emphasizing how the model can be translated into a therapeutic approach.
2. While the sequential representation in the Materials section is clear and logically structured, the overall writing tends to be overly repetitive and unnecessarily elaborate, which makes it difficult to follow and

detracts from readability. I'd suggest streamlining the content of the Materials and Methods section.

# Round 2 Review

## General Comments

Overall, the authors have made commendable efforts to address the majority of the primary comments in the revised submission. Nonetheless, the Discussion section remains problematic due to conflicting interpretations of the literature and insufficient data to address potential safety concerns.

## Specific Comments

### Major Comments

1. Add more references to paragraph 3 of the Discussion section: As the proposed model is entirely in silico and derived from literature synthesis without experimental validation, the Discussion requires greater precision and depth. To enhance its rigor, the author should incorporate additional references that present experimental data or propose concrete mitigation strategies to address the model's limitations and potential toxicities. Moreover, the Discussion would benefit from supporting evidence derived from human-specific models to strengthen the translational relevance of the findings. Provide more clarity by offering more predictive insights into human-specific responses. The Discussion raises important safety concerns and needs to strengthen its practical relevance. The paradox of Wnt enrichment versus fibrosis/immunosuppression is noted but left unresolved.
2. The Introduction could be confusing for readers. Earlier in the Introduction, the conceptual framework is proposed to consist of five modules, but later in the text, it expands into a 7-stage framework. This discrepancy could confuse readers. Consider harmonizing the framework (define stages clearly and keep it consistent).

# Round 3 Review

## General Comments

The authors have undertaken considerable revisions in response to the comments, and the incorporation of additional references has notably reinforced the model's scientific grounding and its "testable" framework. These revisions substantially enhance the clarity, rigor, and coherence of the manuscript. Inclusion of additional references strengthens the Discussion by addressing the Wnt/β-catenin paradox. The Introduction looks more refined now with harmonization of the framework nomenclature. Presenting the 10 sequential intervention stages within five functional modules creates a consistent organizational structure that will help readers navigate the conceptual workflow without ambiguity.

Overall, these revisions significantly elevate the manuscript's scientific robustness, and they position the work more effectively within the current landscape of tumor microenvironment research to provide effective antitumor immunity.

### 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]
2. Spranger S, Bao R, Gajewski TF. Melanoma-intrinsic β-catenin signalling prevents anti-tumour immunity. Nature New Biol. Jul 9, 2015;523(7559):231-235. [doi: 10.1038/nature14404] [Medline: 25970248]

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