Peer Review File

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Reviewer A

Comment 1: *The review lacks any novelty and impact to the field. there are many reviews in this field. Paper should benefit more from illustrative issues in the field of 3D modelling of tissue.*

Reply 1: We sincerely appreciate your valuable suggestions. We fully understand the significance of your comments and have therefore delved deeper into the latest advancements in 3D in vitro models relevant to this study. Specifically, we have expanded our discussion on 3D-printed tumor models, covering their development, their role in elucidating the cancer cell cycle, their importance in drug screening, the establishment and distribution of vascular and lymphatic networks, and their future applications. This additional analysis aims to provide a more comprehensive perspective on the topic.

Changes in the text: We have modified our text as advised (see Page 7, line 213-234, Page 8, line 256-285, line 298-310, Page 11, line 485-510)

Reviewer B

Comment 1: *Can 3D bioprinting models provide a platform for parameterizing the interaction between cells and cellular materials, including all components present in TME? What other processes or plans are needed to achieve this condition? Suggest adding relevant content.*

Reply 1: We fully comprehend your invaluable suggestions. It has been noted that 3D bioprinted Cancer-on-a-chip can provide a parameterized platform for the interactions between cells and cellular materials. However, at present, there is still a lack of specific parameters regarding the cell composition, mechanical structure, cell-matrix components, and vascular distribution in standardized in vitro tumor models. It is also pointed out that this will require further refinement through high-throughput in vitro experiments.

Changes in the text: We have modified our text as advised (see Page 9, line 298-310)

Comment 2: *How will the development of in vitro models promote our understanding of the progression of metastasis? How to capture the significant features of cancer biology more comprehensively? Suggest adding relevant content.*

Reply 2: We sincerely appreciate your valuable comments and fully understand them.

In response, we have incorporated manifestations of tumor-metastasis-related mechanisms in *in-vitro* models. Additionally, we have added research on tumor-metastasis-related mechanisms to each of the three in-vitro tumor models mentioned in the article. This enables a more effective simulation of the tumor microenvironment and a more comprehensive capture of tumor-biology-related characteristics.
Changes in the text: We have modified our text as advised (see Page 8, line 256-276, Page 11, line 378-384, Page 13, line 437-444)

Comment 3: *Suggest increasing discussions on considerations and limitations related to 3D printing and emphasizing how to utilize these advancements to better simulate transfer.*
Reply 3: We express our sincere gratitude for your valuable feedback. In the article, we have expanded on the current limitations of 3D bioprinting. Concurrently, we have further elaborated on its prospects, elucidating how to leverage these aspects to better simulate tumor metastasis in vitro.
Changes in the text: We have modified our text as advised (see Page 15, line 485-510)

Comment 4: *Suggest discussing the research progress of bioprinting for single-cell, multicellular, and personalized tumor models, and summarizing the comprehensive application of bioprinting in preclinical drug screening and innovative treatments.*
Reply 4: We fully understand your suggestions. Accordingly, we have added research and case studies related to the bioprinting of single-cell, multi-cell, and personalized tumor models. We have also summarized their applications in pre-clinical drug use respectively.
Changes in the text: We have modified our text as advised (see Page 7, line 213-234)

Comment 5: *How to accurately control the structure, uniform size and shape, minimal batch variation, and more realistic TME model through 3D bioprinting technology? Suggest adding relevant content.*
Reply 5: We fully understand your suggestions. In the article, we have added content regarding how to more accurately control the structure, dimensions, and shape of the printed objects through multi-layer, concentric, and co-axial nozzles. Meanwhile, we have also included information on minimizing batch-to-batch variations.
Changes in the text: We have modified our text as advised (see Page 15, line 492-501)

Comment 6: *Suggest increasing the application of 3D bioprinting models in understanding cancer cell cycle and evaluating and improving solid tumor immunotherapy.*
Reply 6: We fully understand your valuable suggestions. In the article, we have added

the latest research on the relationship between 3D bioprinted models and the cell cycle of tumor cells, pointing out that most chemotherapeutic drugs affect the cell cycle. Meanwhile, we have also added the latest applications of 3D printing technology in the evaluation and improvement of immunotherapy for solid tumors.

Changes in the text: We have modified our text as advised (see Page 9, line 279-285)