Peer Review File

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Responses to Reviewer A comments:

General Comments: (*The authors properly summarize comprehensive data of PROTAC technology for prostate cancer therapy. However, some sentences are out of context and need reorganization. This reviewer recommends English editing. Additionally, some points need to be supplemented or fixed.*)

Response to comment: Thank you very much for your attention on our paper. We polished the manuscript with a professional assistance in writing, thoroughly.

Comment 1: *(Although authors introduce several AR-PROTACs, there is not much information regarding their structural differences, potency, and routes of administration in the manuscript. This information is important to understand each PROTAC's pros and cons. Another option would be arranging them on a table.)*

Reply 1: Special thanks to you for this comment, we have now summarized the basic properties of the AR and CDK4/6 degraders described in this manuscript in **Table 1** and depicted in **Figure 1**.

Changes in the text: "The basic properties of the compounds described above are listed in **Table 1** and are depicted in **Figure 1**" has been added to line 264-265. **Table 1** has been added.

Comment 2: (*In line 171, "BRD4 degraders" is a better word than "BRD4 inhibitor coupled with PROTACs" for readers.)*

Reply 2: We accept your suggestion, and modification has been made on line 170-171.

Changes in the text: On line 170-171, modification has been made.

Comment 3: *(In line 139-140, the reference is missing.)*

Reply 3: Based on your suggestion, we added the missing reference.

Changes in the text: On line 140, modification has been made.

Comment 4: *(It would be better to include data from the latest papers for completeness (PMID: 32736229, PMID: 32928363, PMID: 32961381).)*

Reply 4: Thanks very much for your valuable comments. We added the related references to the revised manuscript. In line with these changes, we also re-wrote the description on line 233-235.

Changes in the text: On line 272 and line 235, modification has been made.

"ARD-61 overcomes the existing resistance process to anti-hormone therapies by directly depleting the AR protein in both PCa and breast cancer cell lines with AR-positive features." has been added to replace the previous text on line 233-235.

Responses to Reviewer B comments:

General Comments: (*The authors provide an interesting overview on PROTACs as possible future drugs for prostate cancer treatment.*)

Response to comment: Thank you very much for your attention on our paper.

Comment 1: *(At page 5, ER-PROTACs are mentioned, but it need to be clarified that these are estrogen receptor-addressing degrader molecules, of which linkers can cause a certain gap between the target protein binding site and the E3 ubiquitin ligase and ER150 PROTACs have the highest degradation effects.)*

Reply 1: Thank you for the instructive suggestion. We are sorry for not clearly describing the estrogen receptor (ER) degrader. We have rewritten and further discussed ER-PROTACs in this section.

Changes in the text: On line 147-150, modification has been made.

"Taking estrogen receptor-targeted PROTACs as an example, when the linker causes a certain gap between the target protein binding site and the E3 ubiquitin ligase, PROTACs with 16 atom chains of the linker have the highest degradation effects." has been added to replace the previous text on line 147-150.

Comment 2: *(ARCC4 (Salami et al, ref 45) is an enzalutamide-based PROTAC with a VHL ligand as ligase addressing part. The chemical structure should be drawn.)*

Reply 2: Based on you and other reviewers' suggestions, we summarized the basic properties of the AR degraders described in this manuscript in **Table 1** and depicted in **Figure 1**.

Changes in the text: "Figure 1 (A) Chemical structures of ARCC-4." has been added to the Figure Legend section.

Comment 3: *(ARD-69 (Han et al. ref 46) and ARD-61 (Kregel et al. ref 47) are aminocyclobutane-derived degraders with a special spacer structure and a differently linked VHL ligand. Their chemical structures should be provided as well. Please also consider to mention two further publications with respect to ARD-61 (Zhao et al. Neoplasia, 2020, 22, 522-532 and Han et al. J. Med Chem. 2019, 62, 11218-11231).)*

Reply 3: We summarized the basic properties of these two AR degraders described in this manuscript in **Table 1** and depicted in **Figure 1 (B, C)**. We added the related references in the revised manuscript.

Changes in the text: On line 235, modification has been made.

"Figure 1 (B) Chemical structures of ARD69. (C) Chemical structures of ARD61." has been added to the Figure Legend section.

Comment 4: *(For the treatment of castrate-resistant prostate cancer, CDK4/6 inhibitors have advanced the field of estrogen receptor positive breast cancer treatment and are being investigated in prostate cancer. Response to CDK4/6 inhibitors may be predicted by the tumors' genomic profile and may give insight into combinatory therapy with CDK4/6 inhibitors in order to delay resistance or provide synergistic effects. The authors should add a review on CDK4/6 inhibition and prostate cancer (Kase et al. Onco. Targets Ther. 2020, 13, 10499-10513).)*

Reply 4: As you suggested, CDK4/6 inhibitors should be monitored. We really agree with this viewpoint. We discussed the mechanisms of CDK4/6 function and CDK4/6 inhibitors in prostate cancer on line 249-260.

Changes in the text: On line 249-260, modification has been made.

"The mammalian cyclin-dependent kinases (CDKs) contain a cell cycle related sub-family (CDK1, CDK2, CDK4, CDK6). In clinics, CDK4/6 inhibitors have emerged as a powerful class of agents for estrogen receptor positive breast cancer treatment. Targeting the cell cycle represents a core attack on a defining feature of cancer, given the effects of AR signaling on the cell cycle in PCa. This is a key component of the treatment of cancer. Given the importance of CDK4 and CDK6, we propose that CDK4/6 inhibitors and novel strategic combinatorial therapies have the potential to improve patients' overall survival and quality of life. Steinebach et al. designed a VHL-based PROTAC (CST620) exhibiting dual activity against CDK4 and CDK6, and showed potent and long-lasting degrading activity in human and mouse cells and inhibited proliferation of several leukemia, myeloma and breast cancer cell lines. This attractive approach for targeted degradation of CDK4/6 may be further tested in PCa." has been added to line 249-260.

Comment 5: *(Efficient CDK4/6-adressing PROTACs have recently been reported. Hence, this work (Steinebach et al. Chem. Sci. 2020, 11, 3474-3486) needs to be mentioned and added to the list of references. The chemical structure of one representative, CST620 (compound 27) should be included next to the other chemical structures noted above.)*

Reply 5: We added the related reference to the revised manuscript. We summarized the basic properties of this CDK4/6 degrader (CST620) described in this manuscript in **Table 1** and depicted in **Figure 1 (D)**.

Changes in the text: On line 256-259, modification has been made.

"Figure 1 (D) Chemical structures of CST60." has been added to the Figure Legend section.