Peer Review File

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Reviewer A

Mazza et al commented on a recent study by Jasper et al on IL-18-armoured CAR-T cell targeting DDL-3 in in vivo syngeneic and xenogenic models of SCLC. Presenting the results of the study, this commentary well explains why this therapeutic strategy is of interest.
The figure and the table are clear and appropriate.

In this reviewer opinion, this manuscript could be improved before acceptance and publication by reviewing of the following:

Major points

• It would be useful to give a short general introduction about CAR-T cells development, mechanism of action and types, with appropriate references. *We have modified our text as advised page 2, lines 25:33).*

• Lines 80-83 Given the peculiar toxicity of DLL-3 targeting strategies and novel immunotherapy strategies (Rova-T, tarlatamab, AMG119), which is still mitigating the enthusiasm around these undoubtedly promising therapies, it could be useful to dwell a little more into the expected toxicity due to the constitutively activity of IL-18. This could also be useful to put in frame the anti-DLL3 CAR-T approach and development in the scenario of emerging treatments for SCLC, with focus on other anti-DLL-3 approaches. *We have modified our text as advised, page 3 lines 59:72. Description of toxicity risks with constitutively active IL-18 are described in lines 101:102 and lines 172:177.*

• Line 132: I believe that "switching species" can be misleading to the reader as it gives the impression of treatment of human subjects, although clearly explained thereafter.
We have modified our text as advised.

• I would consider commenting on the potential for CAR-T retreatment given the persistence of DLL3+ expression on cells of tumors relapsing after response to SC16.8_mIL18. *We have revised our text and updated the literature as suggested, page 7 lines 158:163).*

• Please clarify that PD-L1 inhibition has been used in syngeneic SCLC models, while PD-1 blockade in xenogeneic ones and, if felt appropriate for the type of content, comment on potential implications – e.g., anti PD-L1 approved in the clinical setting in SCLC, while anti PD-1 have no current indication in the clinic. *We have revised our text, page 7 lines 156:157 and 161:162).*

Minor points

• line 35 Please quantify the unfavourable prognosis (mOS 12 months, 5-year OS <7%, etc). *We have revised our text and updated the literature as suggested, page 2 lines 39:42).*

• Line 40 no positive trial with the use of single-agent TKIs are reported in SCLC, emerging data with anlotinib combinations are promising – for clarity please reference properly or delete TKI. *We have made the necessary corrections to our text as advised, page 2 lines 46:48.*

• Line 43 3-year update of CASPIAN and the recently presented IMBRELLA A study suggest this % is no more than 10-12%. *We have revised our text and updated the literature as suggested, page 3 line 50.*

• Line 49 consider revising "on the cell surface of SCLC tumour cells" into "on the surface of SCLC cells ". *We have revised our text as advised, page 3 line 56.*

• Lines: 55-56 Please explain the role of 4-1BB as CAR-T co-stimulation domain – and specify in the text that the same domain has been used in the syngeneic models tested, but the CD28 one has been used in the xenogeneic models. *We have revised our text as advised, page 5 lines 106:109 and page 7 lines 150-151.*

Acknowledgement: Sara Stumpo, MD, and Maria Giovanna Formelli, MD, assisted me in the peer reviewing of this manuscript.

Reviewer B

This editorial is a well-written synopsis and the importance of the manuscript by Jasper et al (J Clin Invest. 2023 May 1;133(9): e166028. doi: 10.1172/JCI166028.). There are only two comments that can improve this work.

1) From lines 92 to 143 the go into too much detail about the work of the paper describing every experiment and its results. I suggest reducing this section to what is importance and its relevance to the field. *We have revised our text as advised.*

2) There are some abbreviations that need to be described, for instance "TRUCKs" which may not be common knowledge. *We have revised our text as advised, page 4 line 81-82).*