Carbone Cancer Center
UNIVERSITY OF WISCONSIN
SCHOOL OF MEDICINE AND PUBLIC HEALTH

May 13, 2022

Thesis questions for
Mgr. Ondrej Uher
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From:
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1. The introduction is well written and compelling. There is one statement that needs clarification. "In humans, pancreatic adenocarcinoma is the most common cancer with a lethal prognosis. " As the number of deaths (at least in the USA) from lung cancer is approximately 3-fold higher than for pancreatic cancer (136,084 vs. 46.774 in 2020), some clarification or qualification of this statement is needed: https://www.cdc.gov/cancer/dcpc/research/update-on-cancer-deaths/index.htm#:~:text=Other%20cancers%20individually%20accounted%20for%20less%20than%205%25%20of%20cancer%20deaths.&text=136%2C084%20people%20died%20of%20lung,22%2C495%20females%20and%2024%2C279%20males) .

2. In Manuscript II, figure 7, thesis page 29 shows potent anti-tumor memory after MBTA for the pheo model. Is this tumor specific?

3. What is different about B16 vs. Panc02 or your pheo model, that requires anti-CD40 for the latter 2 but not the first? Do you have a hypothesis or data?

4. Manuscript-III, thesis page 47, you hypothesize combination therapy of radiotherapy with MBTA, suggesting giving radiation to distant sites of disease after the intratumoral MBTA regimen. Do you have data on the sequence of when to give radiation relative to the MBTA? If you need to give radiation to all distant sites of tumor, how might you be able to do this in the face of disseminated metastases, without causing immune-inhibitory immune suppression?

5. In Manuscript 4, page 55, Figure 2, it appears that CD4 cells are more important than CD8 cells in the prevention of outgrowth of Panc02? Do you have a hypothesis or data regarding how this may be working?

6. Manuscript 4, page 58, figure 2; in the dual combinations of MBTA with RT , might some variation of the timing between the MBTA and RT possibly give a different result?

7. Manuscript 5. Thesis page 64; what is different about the pheo model and the panc02 model, from the B16, to require CD4 cells as the primary mediators of memory, while

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CD8 is primary for the B16? How do you reconcile this with the important role of CD8 cells for the stabilization of metastatic growth for the Pheo noted in chapter 2 (as stated on page 96 in the summary)?

8. Manuscript 5, thesis page 73; why do the CD8+ mice in Figure 5, that are getting MBTA treatment, appear to have systemic dermatitis, compared to the CD4+ mice or control mice? Any data or hypotheses?

9. Manuscript 6, figure 1, thesis page 87. In figure 1A the untreated tumors grow faster in the aged mice than the young mice, yet the aged untreated mice show a slight advantage in survival. Any hypotheses or data to account for this?

10. The summary section on thesis pages 92 – 99 is written well and very helpful.

11. The future perspectives section on page 102, suggests MBTA therapy might be used as a "subcutaneous vaccine". As many patients may have cancer located in deeper, non-subcutaneous, locations that still may be injectable (ie: with radiological guidance), I think the correct term here might be "in situ vaccine" rather than subcutaneous vaccine. This may still be very translatable.

Sincerely,

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