Author’s response to reviews

Title: Therapeutic Limitations in Tumor-specific CD8+ Memory T Cell Engraftment

Authors:

Dr Oliver F Bathe (bathe@ucalgary.ca)
Nava Dalyot-Herman (boaznava@hotmail.com)
Thomas R Malek (tmalek@med.miami.edu)

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Dear Editor:

We would like to thank the reviewers for their constructive review of our manuscript. We would like to take this opportunity to address any concerns the reviewers expressed.

Dr. Gillanders and Dr. Mackensen pointed out that the main weakness of this work is the lack of innovation and the fact that the conclusions will have a limited impact. Mechanism-driven information was not derived. We acknowledge that our findings are not entirely novel, except in that the context of the observations was in tumor-specific memory T cell engraftment. The fact that no new mechanisms of tumor resistance were described should not detract from the importance of our findings with respect to designing an immunotherapeutic strategy for cancer in humans. What is striking is the considerable magnitude of the obstacles to success. The model consists of tumor expressing antigen targeted by CD8+ T cells genetically engineered to recognize the (specific) tumor antigen. If 10$^9$ million optimally primed cytotoxic T lymphocytes (CTL) are required to engraft sufficient memory to prevent tumor in mice, then 1 – 10$^9$ billion such cells would be required for therapeutic success in humans. Generating this number of high quality CTL will be a major technical feat. In the same vein, while antigen loss variants have previously been described, the fact that selective pressures have limited therapeutic success in this idealized experimental system underscores what is an inevitability in immunotherapies directed at a single tumor antigen. Therefore, the importance of this work is not in its novelty, but in its identification of the issues that will severely limit our ability to translate what works in the lab to the clinic. Strategies must be developed to bypass these obstacles.

Dr. Mackensen did not agree with our assertion that our model simulated the clinical situation of a patient with minimal residual disease. It is likely that this clinical situation would be better simulated by performing an adoptive transfer in a mouse which underwent resection of an established tumor. Experimentally, this would have limited our ability to test how well CD8+ T cell memory was engrafted, as recurrence occurs in a random, unpredictable fashion. Therefore, since our previous data demonstrated that CTL had differentiated to memory cells by 35 days, tumor was induced in a standardized fashion at that interval. More accurately, our model represents tumor induction after memory engraftment. However, it is not clinically likely that tumor-specific CD8+ T cells will ever be administered to patients without any history of that tumor. Therefore,
we considered this model to also approximate the situation of minimal residual disease. We have acknowledged the imperfect approximation to the clinical situation of minimal residual disease in the Discussion section.

Dr. Mackensen pointed out that, in the Kaplan-Meier figure (Figure 1), the curve corresponding to the tumor-free survival for one group (“2M CTL”) did not drop to zero. This was an error in transferring our graphics file, and we have corrected this.

It was noted by Dr. Mackensen that an increase in the number of transferred T cells of 20-fold resulted in an increase in ³H-thymidine uptake of only 3 – 4 fold, in splenocytes stimulated with ovalbumin. One reason for this is that the number of cells that survived as memory cells increased to a lesser degree, as reflected in Figure 2. In addition, numerous other factors may affect the linear relationship between T cell number and proliferative response, including the state of the T cells (eg: whether they are effectors or memory cells), and the state/number of antigen presenting cells in the spleen. Regardless, we agree with Dr. Mackensen’s point that this experiment does not exclude the possibility that individual cells have been rendered anergic, and we have acknowledged this in the Results section of the manuscript. However, this possibility does not detract from the main conclusion of the paper, and so we have chosen not to perform intracellular cytokine stains at this time.

We agree with Dr. Mackensen that the emergence of antigen loss variants after immunotherapy is a product of the selection of clones with low levels of antigen expression.

Thank you very much for the opportunity to address the issues raised by your reviewers. We hope that these changes merit publication in BioMed Cancer.

Sincerely,

Oliver F. Bathe, MD, MSc, FRCSC