Reviewer's report

Title: Opera music induced prolongation of cardiac allograft survival and generation of regulatory CD4+CD25+ cells in a murine model

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Reviewer: Wolfgang Jungraithmayr

Reviewer's report:

The article from Uchiyama et al. describes the effect of classical (opera) music from La Traviata transplanted heart grafts. Although the exact mechanisms remain unclear how this kind of music leads to the observed results, the beneficial effect of classical music on health and disease is unequivocal. This is a very carefully performed piece of work and has a high level of originality. However, no mechanistics are shown. The authors are not urged to show, however it would be very interesting and at least subject to further studies.

The most exciting issue would be to explore the mechanistic that links the e.g. increase IL-10 and regT cells to the effect of the graft amelioration. I can think of neurogenic perception via hormone or other mediator release that finally leads to the beneficial IL milieu or cell generation. Moreover, classical music is a heterogenous field of music/medium. Operas, or most parts of it except for the majority of arias, belong to a rather hectic and rough kind of music genre that rather causes stress while e.g. Brahms Violin concert, 2nd movement or Bach’s Air from the Suite D major has all features of a calming, relaxing music. Differences of effects would be expected here to be be even more pronounced.

Specific comments (major)

- Page (P) 9, discussion, Line (L) 7: the link music – generation of regT cells is not a possible mechanism, what is the rationale from music to the generation of regT cells? Please re-formulate and balance the statement. The authors mentioned a first possible mechanism in P 10, L 4: as the authors state, I also see a possible link between the perception of music -> release of mediators such as hormones that directly or indirectly influence the levels Interleukins or the number of cell types. The second possible mechanism is the reduction of stress and thus less stress mediators. Though I don’t think the authors need to show those mediators of interest in this paper, it would be the key mechanistic link.
- Don’t repeat too often your results in the discussion section that you have listed already in the result section.
- Fig. 1: the difference between treated and non treated animals is immense. Aren’t there any other explanation that lead to such a prolongation of heart function?
- Fig. 2D: the immunohistochemistry is a too small magnification to detect real
differences, also, what exactly should be stained? The figure legend does not tell.

**Level of interest:** An article of outstanding merit and interest in its field

**Quality of written English:** Not suitable for publication unless extensively edited

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

no competing interests.