Author's response to reviews

Title: Elevation of Bombina variegata peptide 8 in mice with collagen-induced arthritis

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Response to Dr. Rolf Braeuer

Major
1. The method of inducing arthritis using collagen was described in detail. The reference in question was corrected.
2. The reviewer’s comments are much appreciated. The data obtained from mice on all experimental days were incorporated into the results shown in Fig. 1d in the original manuscript. Histological examination was performed on days 28 and 35, and not on every experimental day. It was an overstatement to assert a correlation between the level of Bv8 expression and the severity of arthritis without histologically scoring arthritis. Therefore, this statement was deleted from the revised manuscript. Fig. 1d in the original manuscript was also omitted from the revised version.
3. We appreciate your comments. We are considering further analysis regarding this point using the suggested method. To show more detailed data on this, Fig. 4 was added.

Minor
4. Corrections were made as suggested.
5. We analyzed the distal tibia in this study. This site was examined in many mice, and the results are shown in low-power photomicrographs in the newly added Fig. 3.
Response to Dr. Kutty Selva Nandakumar

1. A description was added as suggested by the reviewer. Groups of 5 mice were used in the experiments, the results of which are shown in Fig. 1. The experiments were performed twice, and the reproducibility was confirmed. Each group of mice was housed in the same cage. Non-immunized mice were used as controls.

2. The method of inducing arthritis was described in the text. The reference in question was corrected.

3. Histological examination was performed on days 28 and 35 in groups of 5 mice. Representative results are shown.

4. Each group consisted of 5 mice, and their respective mRNA was analyzed. Please refer to Fig. 1b. Using the remaining RNA, VEGF expression was analyzed, and the results were added to Fig. 1d. There was no RNA sample remaining, and so we could not analyze VEGF expression on day 42. Since the level of Bv8 mRNA expression that was previously shown could not be compared with that of VEGF expression at this time, it was not included in Fig. 1. However, we believe that the significance of the results remains essentially intact.

5. We appreciate the reviewer’s suggestions. We are considering further analysis regarding this point. To show more detailed data on this, Fig. 3 was added.

6. We appreciate the reviewer’s suggestions. We will extend our
future studies according to them.