

Reviewer's report

Title: Immunomodulation of murine collagen-induced arthritis by N, N-dimethylglycine and a preparation of Perna canaliculus

Version: 1 **Date:** 11 April 2007

Reviewer: Rene Toes

Reviewer's report:

General

This manuscript by Lawson et al describes the immunomodulatory properties of N,N-dimethylglycine (DMG) and extracts from the New Zealand green-lipped mussel Perna canaliculus (Perna). Although only "Perna" decreases, while DMG increases, LPS-induced TNF- α and IL-12p40 productions from the human monocytic cell line THP-1, prophylactic treatment with either of the compounds reduces the disease incidence and severity of CIA in rats. This is associated with decreased anti-collagen IgM, but not IgG antibodies in sera. More importantly, amelioration of CIA in mice is achieved following therapeutic administration of Perna, while DMG has no effect in this setting. Based on these observations, the authors speculate that Perna, and perhaps DMG, may be useful in the treatment of RA in humans.

Comments:

Although the clinical data on CIA-progression look convincing, this manuscript does not provide an explanation for the effects observed, especially not in light of the finding that clinical effects are not directly correlated with the findings made in vitro. Therefore, the impact of the manuscript would increase in case more mechanistic insight is provided. This could, for example, be achieved by addressing the following points:

1. Since TNF- α is very important in the pathogenesis of RA/CIA, the effect of these drugs on the TNF- α levels in the sera could be analysed?
2. As CIA is considered to be mediated mainly by T and B cells, Figure 1-3 may be eliminated because they are not closely related to the other data presented in the manuscript. Moreover, it is a bit confusing that the pro-inflammatory property of DMG on human monocytes (Figure 1) contrasts the in vivo anti-inflammatory effect on rat CIA, although this might be due to species-specific as mentioned by the authors. Alternatively, rat/murine cell lines should be included as well. More importantly, however, crucial controls are missing in these figures such as the exclusion of possible toxicity on cells, especially in the case of Perna (Figure 2 & 3).
3. To corroborate the beneficial effects of DMG and/or Perna on CIA, adding immunohistochemistry data demonstrating the structure and cell infiltration of the affected joints to table 1 and Figure 5 would be helpful.
4. In addition to the spleen (table 2), the percentages of T/B cells in the draining lymph nodes should be given as well? Is there any change concerning the phenotype and/or functions of these cells?

Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

Discretionary Revisions (which the author can choose to ignore)