LETTER

Reply to Cauwels et al.: Of men, not mice, and inflammation

We appreciate the comments of Cauwels et al. (1) regarding our recent publication (2). Cauwels et al. cite the use of anti-TNF treatment for rheumatoid arthritis and inflammatory bowel disease and the failure of nitric oxide (NO) synthases in sepsis as examples of the successful use of mouse models. Ironically, these examples could in fact be used to illustrate the differences between mice and humans. Anti-TNF treatment was developed for the treatment of sepsis because it protected mice in models of sepsis (3). However, anti-TNF failed in human trials of sepsis (4). It was only later that anti-TNF was shown to be helpful for rheumatoid arthritis and inflammatory bowel disease. In the case of NO, it should be noted that although mouse macrophages readily produce NO in vitro, human macrophages do not (5). The many trials for sepsis in which drugs protected in mice but failed in humans suggest that ability of mouse efficacy models to predict human inflammatory diseases is close to random, and therefore it should not be surprising that occasionally there is a correlation. However, for such a model to be helpful, it needs to prospectively predict the human condition. In this case, mouse models appear to perform very poorly indeed.

Cauwels et al. (1) question the use of blood cells in contrast to parenchymal cells to study pathology. We believe that this opinion has not been well established. The evidence cited by Cauwels et al. is based upon NO release in mice after massive doses of LPS. This design, as with all similar studies using mouse models, cannot reliably inform on human inflammation, especially given that human macrophages do not make NO in vitro.

Cauwels et al. (1) question whether the appropriate dose of LPS was used in our mouse model and suggest that a larger dose would have better mimicked severely ill patients. This situation was a comparison of LPS response in the two species. In our study, we used the maximum dosage allowed for this LPS in humans and sought an LPS dosage in the mice to induce an equivalent plasma concentration of IL-6, a well-established proinflammatory biomarker in mouse and human. The comments of Cauwels et al. are further notable because they highlight not only the tremendous disparity between the species in the dose needed to induce pathology (10^6), but also the disparity between the doses required to induce IL-6 and shock responses within each species (15-fold in humans, and 1,000- to 10,000-fold in mice) (1).

Cauwels et al. (1) point out that mice may be helpful to gain mechanistic insights in mice and we certainly agree. However, overwhelming amounts of data suggest that mice fail to mimic complex inflammatory human diseases with respect to efficacy. This finding is certainly true for sepsis. Rather than clinging to models that have had limited benefit in the past, it seems time for the scientific community to address this reality directly and work together to find creative solutions moving forward.

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1 Cauwels A, Vandendriessche B, Brouckaert P (2013) Of mice, men, and inflammation. *Proc Natl Acad Sci USA* 110:E3150.

2 Seok J, et al.; Inflammation and Host Response to Injury, Large Scale Collaborative Research Program (2013) Genomic responses in mouse models poorly mimic human inflammatory diseases. *Proc Natl Acad Sci USA* 110(9):3507–3512.

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The authors declare no conflict of interest.

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