Title: Metabolic phenotype of methylmalonic acidemia in mice and humans: the role of skeletal muscle

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Author’s response to reviews: see over
June 25, 2007

Dear Members of the Editorial Board,

We appreciate the thorough review of the manuscript “Metabolic phenotype of methylmalonic acidemia in mice and humans: the role of skeletal muscle” and have addressed the reviewer and editorial comments as follows.

Major Compulsory Revisions

1. The statistical analysis methods are presented in a section of the methods titled statistics (page 10). Each experiment was re-analyzed by first applying the f-test and then using these results to direct the calculation of p-values using the student t-statistic. Significant p-values are indicated in the graphs. The values obtained are listed in the figure legends and significant results are designated with an asterisk.

2. Comments regarding the transplantation parameters and limitations of the studies have been added in the results and discussion section of the manuscript. Specifically, we have stated that the patients were not evaluated in a manner that allowed the determination of MMA output previously and more importantly, before renal insufficiency ensued (page 15) …….“Minimal biochemical data was available on the transplant patients when they had preserved renal function and precluded a direct comparison to the effect of combined organ transplantation in each patient.” Brief clinical histories on these patients have been published in references 25 and 26. As the reviewers may realize, there is no consensus opinion about when to evaluate MMA patients for renal disease. Because renal filtration (the GFR) is related to plasma MMA levels (reference Walter et al, Chronic renal failure in methylmalonic acidaemia (1989) Eur J Pediatr 148: 344-8), MMA output calculations need to be adjusted for renal function as does extent of metabolic correction post transplantation. We have also added a paragraph to the discussion (page 16) stating that “Direct comparison to the pre-transplant state in solid organ transplant patients was not possible because they had not been evaluated when renal function was intact nor in the same fashion described in this report. For this reason, the transplant patients were compared to a group of untransplanted patients with the same enzymatic phenotype who had been treated with low protein, high-energy diets. Future efforts to characterize the metabolic
parameters in MMA solid organ transplant recipients might benefit from standardized pre- and post-operative regimens to measure these parameters in all patients. Clearly, this will be an important clinical and research problem to address, especially since the number of MMA transplant recipients in the world is small.”

Minor Essential Revisions

1. The graphs and text have been standardized throughout and the units have clearly indicated.
2. Three references (14, 24 and 38) were added to the manuscript.

Thank you very much for considering this report,

Sincerely yours,

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