Author's response to reviews

Title: Ancestral DDT Exposures Promote Epigenetic Transgenerational Inheritance of Obesity

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Author's response to reviews: see over
September 11, 2013

Dr. Lin Lee, PhD
Senior Editor
BMC Medicine

Dear Dr. Lee:

The enclosed second revised manuscript MS#: 3183211929952274 entitled “Ancestral DDT Exposures Promote Epigenetic Transgenerational Inheritance of Obesity” is a submission for consideration for publication as an Article in BMC Medicine.

All the comments of the editor and reviewers were addressed with revisions and outlined in the Discussion of Revisions enclosed. We feel the manuscript has been improved by responding to the reviewers comments.

The manuscript was submitted electronically as requested by BMC Medicine. Supplementary information is also submitted and required for review. We look forward to your comments and hope the manuscript is now suitable for publication in BMC Medicine. Thank you for considering the manuscript and please let me know if any additional information would be useful.

Sincerely

Michael K. Skinner
Professor
Epigenetic Transgenerational Inheritance of Obesity

Transgenerational Obesity

Transgenerational Sperm Epimutations
Discussion of Revisions

Editor –

1) Concern on use of the term obesity.

We feel it would be misleading not to refer to obesity, but appreciate the complexity of defining this disease. The revised Method and Discussion sections now includes a discussion of a consensus report on the definition of obesity and criteria to consider. The criteria they have outlined are present in the data presented. Therefore, we can support from the literature our definition and use of the term obesity. The revised Discussion section now includes and references this information.

Reviewer 1 –

We appreciate the positive comments regarding the study and acceptance of the paper with no further comments.

Reviewer 2 –

1) Concern on dose of DDT used.

The dose used is within the anticipated human exposure dose and this is now referenced in the revised Discussion section. The issue is the mode of administration, IP injection vs. oral administration. We appreciate the reviewers bias for risk assessment and endocrine disruptors, and would have liked to run more variables regarding dose and mode of administration. However, the cost and time for these studies, as an initial study on the topic, simply are not possible for any type of environmental study. This study provides the first DDT transgenerational study and required the selection of optimal conditions to see if an effect could be observed. The observations are presented and transgenerational obesity was not expected. Future studies can now use this information to do risk assessment and more thorough analysis of obesity. Therefore, we feel this study is a very significant contribution, and the experiments suggested are simply beyond the scope of any initial study on a new topic. Due to this concern, we have further expanded this discussion in the revised Discussion section and qualified the study by clarifying these limitations.

2) As requested, a new reference is presented and discussed in the revised Method and Discussion sections from a consensus report that defines obesity physiological characteristics. The characteristics of weight gain, severe abdominal adiposity, and association of several known correlated diseases by definition constitutes obesity. Although more detailed analysis of some of the associated pathology such as metabolic disease would strengthen this observation, this report indicates the use of the term is appropriate. In regards to rat versus human disease, the scientific literature has routinely indicated over the past 100 years that the basic physiology and abnormal physiologies between mammalian species are far more similar than different. Humans do not have a unique physiology or disease condition. As the consensus report indicates and now discussed the rat obesity condition observed is similar to what is observed in
humans. In response to this concern the revised Discussion section now more thoroughly addresses and references this issue.

Reviewer 3 –

1) Request for logistic regression details.

As requested, the revised Methods now presents the details and references. The variables are clarified and the n-value is clarified in each figure legend. The model fit is also now stated in the revised Methods statistics section.

2) Describe statistics methods.

As requested, the revised Methods section now presents an expanded description of all the statistics methods used.

3) Clarification of Figure 1 statistics.

As requested, the statistics test used for Figure 1 and all figures now is stated in the figure legends. The t-test, n-value and p-value are now clarified in the Figure 1 legend. No multiple comparison made as now stated in the revised Methods statistics section. The symbol/labeling for the various p-value are now clarified in the Figure 1 legend as requested.

4) Clarification of Figure 3 & 4 legends.

As requested, the same details and clarifications made for Figure 1 legend are now provided for the Figure 3 and 4 legends, as well as Supplemental Figure legends.