Author’s response to reviews

Title: The Therapeutic Effects of MicroRNAs in Preclinical Studies of Acute Kidney Injury: A Systematic Review Protocol

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The Therapeutic Effects of MicroRNAs in Preclinical Studies of Acute Kidney Injury: A Systematic Review Protocol

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Response to Reviewers

We would like to thank the Editors and the reviewers for the positive review of our manuscript, and for the helpful comments and suggestions. Our responses are provided below.

Reviewer #1:

Minor comments: “I am skeptical that there will be enough non-biased studies in animal models that will allow for robust meta-analysis. Also, I am worried that the heterogeneity and lack of transparency in many pre-clinical studies will make it very difficult to draw meaningful conclusions. However, I think the authors should attempt this analysis and should proceed.”

Response: We agree with the reviewer that there may be insufficient numbers of non-biased studies (as determined by the risk of bias tool) to conduct a meta-analysis. Nonetheless, we consider that conducting this systematic review will be important to determine the current state of the field, and to report study limitations associated with use of animal models of acute kidney
injury (AKI). The review will thereby serve to highlight the importance of rigorous efforts to limit bias in future pre-clinical research.

There are likely to be a number of sources of heterogeneity, including the particular miRNA(s) selected for interventional study in each manuscript. While several candidate miRNAs implicated in the pathogenesis of AKI have already been identified, it is important to recognize that miRNAs may target multiple messenger RNAs, and there may be homogeneity in pathways that are affected by distinct miRNA species. Thus, there is potential value in the proposed systematic review in attempting to identify common pathogenic mechanisms of action.

We agree with the comment regarding the potential for lack of transparency in many pre-clinical studies. However, it is only by conducting this systematic review that we can assess if these studies are free of selective outcome reporting and presence of confounding bias. In this regard, the SYRCLE’s risk of bias tool will guide us to evaluate if methods, analysis or data subsets are reported in good faith. Thus, the strength of our conclusions and recommendations will be based on the quality of evidence and likelihood of bias found in those studies. This information can inform the optimal conduct of future pre-clinical studies aimed at therapeutic interventions in AKI.

In the revised manuscript, we have addressed these limitations of our study (Discussion, p. 14, lines 323-334).

Reviewer #2:

1. “The authors outlined several sources of heterogeneity in experimental AKI research but one that was not well emphasized was the timing/duration of administration of the miRNAs (or alternatives) in relation to the onset of injury (e.g., before, immediately after, 1-2 days after, etc.). The timing/duration of administration may be considered as part of the planned sub-group analyses.

Response: We agree with the reviewer’s excellent suggestion. Certainly, timing and duration of administration of miRNAs will be a critical aspect to inform the design of translational trials in humans. This is particularly relevant since in humans, the diagnosis of AKI often occurs after significant delay beyond the time of initial injury/insult. In the revised manuscript, we have included additional emphasis on timing and duration of therapy, and proposed sub-group analyses that addresses this aspect (revision, p. 10, lines 230-234).
2. “The authors should briefly outline the possible mechanisms of candidate miRNAs (or alternatives) for ameliorating AKI or promoting kidney recovery/repair. A summary Table may enhance this report and benefit the scientific community.”

Response: We thank the reviewer for this suggestion. In the revision, we briefly discuss possible mechanisms for miRNA action in AKI, and present a Figure depicting points in pathways where miRNAs have been implicated in the prevention, protection, or exacerbation of AKI in pre-clinical studies. We have avoided providing a list of particular candidate miRNAs for each mechanism, since indeed this information will be generated from our systematic review (see revision, p. 5, lines 123-126, and Figure 1, with legend [lines 521-525]).

3. “If the main purpose of this work is to contribute and accelerate the translation of miRNAs therapies into trials in human AKI, the authors should consider adding to their protocol the examination of clinical data on miRNAs measures in human AKI. This may help identify windows of administration of these potential drugs in humans. Despite the authors clearly pointed out that current human data of miRNAs in AKI are purely observational, the scientific community may benefit from systematic reporting and summary of these data, which may also contribute to future interventional studies in humans”.

Response: We fully agree with the reviewer on the importance and merits of examining current observational data on miRNA studies in AKI in humans, to link to the systematic review of pre-clinical studies, and thereby guide design and conduct of interventional trials. However, inclusion of clinical data in our proposed systematic review is beyond our principle objective, and would create an abundance of information that will be difficult to separate, analyze and integrate into one study. Rather, in the revised manuscript we propose to conduct a separate scoping review upon completion of the systematic review of pre-clinical studies, with a different methodological approach. This review will involve knowledge synthesis aimed at mapping key concepts relevant to the clinical utility of miRNA delivery in humans with AKI, and will be guided by our findings from the pre-clinical literature. The scoping review will examine the potential for conduct of a formal systematic review of human observational studies (dependent on numbers and quality of publications), summarize the current state of the literature, identify gaps in knowledge, and make recommendations for future research directions. Building on the review of pre-clinical studies, such a scoping review could inform optimal timing and duration of administration of miRNAs to humans with AKI, and identify most promising miRNA species for clinical trials. We have included a brief presentation of our plans to conduct this scoping review in the revised Discussion (lines 335-348).