Peer Review File

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Review Comments

Reviewer A

Excellent initiative to review microRNA therapeutics. The methods section doesn't provide details of the strategy to search for articles to be included in this narrative review. It is important to provide search terms and to indicate how many articles were retrieved (how many articles were selected/discarded for this review). A grammar check is also needed.

Reply 1: Thanks for reviewer's nice comment. We have modified the manuscript.

Changes in the text: Page 4, Line 98-99.

Reviewer B

This is a well-written review which highlights some of the challenges in translating microRNA for therapy. Comments have been added to the PDF document.

Comment 1: Line29, Mammalians should be "mammals". However, microRNAs are present in worms, flies, etc.. not just mammals.

Reply 1: Thanks for reviewer's nice comment. We have modified our text as advised.

Changes in the text: Page 2, Line 31.

Comment 2: What does "suitable for signal transduction" mean?

Reply 2: Thanks for reviewer's nice comment. The stem-loop structure of microRNAs gives them stability and thus microRNAs can act as signaling molecules.

Changes in the text: None.

Comment 3: I assume the preclinical animal models were immune compromised? Can the authors comment on how this might have given a false sense of safety for MRX34?

Reply 3: Thanks for reviewer's nice comment. The preclinical animal model here should be preclinical toxicology animal models. We are sorry for the mistake and corrected the description in the manuscript.

Changes in the text: Page 6, Line 150.

Comment 4: Define PD here.

Reply 4: PD indicates "progressive disease". We have added the full name of PD in the manuscript.

Changes in the text: Page7, Line 179.

Comment 5: Miravirsen is to treat existing hepatitis C infection, not block infection.

Reply 5: Thanks for reviewer's nice comment. We have corrected the description in the manuscript.

Changes in the text: Page 8, Line 213.

Comment 6: Tumors do have leaky vessels. Isn't this expected to facilitate drug penetration?

Reply 6: Thanks for reviewer's nice comment. Although tumors have leaky vessels, the delivery of nanoparticles to solid tumors is inefficient as about 0.7% nanoparticles can reach the tumor sites (1). The major obstacle of efficient delivery is the interstitial extracellular matrix of tumor cells (2), which suggests the solid tumor do not have large space for entry of nanoparticles.

Changes in the text: None.