Answers to Reviewer 2

We thank the reviewer for his valuable comments and suggestions who helps us to improve our manuscript. Please Find below a point-by-point to your comments and suggestions.

Reviewer 2

Comments and Suggestions for Authors

This manuscript entitled "Hydrocarbon-stapled peptide based-nanoparticles for siRNA delivery" reports the design and synthesis of stapled peptides that promote uptake of siRNA. The delivery of siRNA to specific tissues and subsequently into the cells of those tissues remains a challenging hurdle for the development of siRNA-based therapeutics. This manuscript reports a method to overcome the latter.

Minor comments:

1. In the materials and methods, the sequence of the anti-firefly luciferase is reported. As written, this is not a standard siRNA 19+2 format as there is an extra C on the 5' end of the sense strand. If this is a mistake, it should be corrected. If not, it should be explained.

   Many thanks for this remark, it's a mistake. A guanine (G) is missing at the 3' end of the anti-sense strand which is now added. The correction is highlighted in yellow in the text.

2. The different bands (siRNA and siRNA/peptide complex) should be labeled in figure 3a.

   As requested by the reviewer, the different bands were now labelled in figure 3a.

3. The changes in cell morphology in figure 4 require comment and explanation. The cells treated with siRNA complexed with JMV6580 look much healthier than those treated with siRNA complexed with either JMV 6582 or JMV6583.

   We agree with the reviewer and for this we changed the figure 4 by providing better and higher resolution confocal images where the treated cells look much healthier than in the previous images.

4. Discussion as to the lack of correlation of activity presented in figure 5 to uptake shown in figure 2b is missing.

   This point is now added and discussed (Lines 333-337, page 8).