**Response to the Reviewers:**

1. *Confocal part of the study requires a much more detailed description of the used methodology. It remains unclear how the green signals from the Decoy and Live cell stain were distinguished from each other. Were both stains analysed in 3D? simultaneously?*

This assay was performed on separate tissues and not simultaneously. The images show that the culture was intact and that there were few dead cells; therefore, one can only speculate that Decoy would have been incorporated into the living cells. This explanation is added to the manuscript.

1. *All figure legends should be self-explanatory. N numbers should be described in full - biological or technical replicates? Which values were used for the statistical analysis? Large error bars in some figures suggest the presence of possible outliers. Therefore the graphs should be redone displaying all individual points as well as average values.*

All “N” numbers have been rewritten as biological replicates. To clarify “biological replication” in the manuscript, we have stated that the expression N = 9 involves 3 batches which are in triplicate for the experiments with rabbit cells. In the experiment with human tissue, N=4 patients was added for clarification. Only ELISA MMP3 was used for the analysis of N=5 patients in the experiment using hNSCs; other assays could not be performed due to contamination. For consistency, the N of MMP3 was set to 4. This allowed modification of the graphs and statistics, but it did not alter the results. In addition, all graphs are now displayed with individual points. Error bars have been changed from SD to SE, as this more accurately displays the variability of the data.

1. *There remains a concern regarding an unusually high proportion of very old literature in the reference list (>30 years old), which appears to be related to the techniques used. The authors should justify the use of these techniques in Discussion and replace (when possible) with more recent references or reviews.*

The reviewer is likely referring to the PG synthesis and PG turnover assay and indicated that this assay method is listed among old literature. This methodology continues to be used as gold standard for the sulfated GAG synthesis and turnover assay.More recent techniques, such as gene expression or Western blots/Dye assays would only detect the content and they cannot reveal the rate of turnover. The authors believe the reliability of these methods warrant their use in this study and in the references. An explanation for the justification of this method has been added to the discussion section. In addition, we have taken the advice from the reviewer and have replaced some of the references with more current ones whenever possible. Our references which are older than 30 years represent 13/56, or approximately 23% of the reference section. Many of these cited papers fall into the category as “landmark methodology publications” and “original source”; therefore, we find it necessary to include them in our reference section rather than citing secondary papers.

We thank the reviewers for their time and effort in our manuscript submission.

Sincerely yours,

Dr. Hitoshi Nemoto

Dr. Daisuke Sakai

Dr. Deborah Watson

Dr. Koichi Masuda