Author's response to reviews

Title: ACE2 Gene Expression is Up-regulated in the Human Failing Heart

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PDF covering letter
Re: MS: 1249940712238591

Dear Dr Gadd,

Thank you for your recent correspondence. I have read with interest both reviewer’s reports. The reviewers raise valid points that I have tried to address as follows.

Both referees make the valid point that the study would have been strengthened by immunohistochemistry and/or western blotting to determine the localisation of the ACE2 protein and to qualitatively confirm the results of the gene expression studies by demonstrating that ACE2 is also upregulated at the protein level. We have also recognised this limitation in the Discussion (Page 11, line 15-19). At the point when this study was carried out (approximately two years ago), we were keen to attempt such investigations, however, at that time no commercial antibody was available for ACE2. Two years on, we are no longer researching this target, many of the samples are no longer available for retrospective evaluations and as a commercial organisation, our focus has now moved on to other therapeutic targets. Thus, we hope that the referees will understand that it is now very difficult for us to return to this research topic and complete additional studies. However, we do believe that the results, as they stand, make a contribution to the literature on ACE2, especially since they are human tissue based, and, therefore, hopefully will provide a basis for others to study changes in ACE2 protein expression and localisation in the failing heart.

Similarly, Dr. Tikellis makes the valid point that a receptor for Ang 1-7 has been uncovered in the past year. We agree that it would indeed be interesting to determine if this receptor is differentially regulated in the failing heart, however, we hope Dr. Tikellis will understand why it is difficult for us to now return to this research area and that others may be better placed to take up the challenge. In recognition of Dr. Tikellis’ point, however, we have updated the Discussion (Page 11, lines 7-10).

Dr. Penninger raised the points that sex and or age and previous treatments may have affected the study outcome. These points have been addressed along with the study limitations in the Discussion (Pages 11-12 lines 20-23, 1-2).

Of the remaining minor points raised by Dr Tikellis, the scale on the y-axis (Figure 1) has been clarified as a log scale and the legend for the figure has been changed to reflect this. The point regarding ACE2 mRNA being more highly expressed in non-failing ventricle than ACE has been discussed in greater detail in the discussion (Pages 9-10 lines 19-21, 1-8) and an
additional reference added to reflect our view that the relative expression levels of ACE:ACE2 are likely to be both tissue and species dependent.

Once again, we appreciate the constructive comments of the referees and hope that with these modifications they will now find the manuscript suitable for publication.

Kind regards
Andrew Goulter