

**(1) Scientific Quality**

We thank the reviewers for their valuable time taken in assessing our manuscript 'MicroRNA sequences modulating inflammation and lipid accumulation in macrophage 'foam' cells: implications for atherosclerosis'. Our detailed responses to their comments can be found below;

**Reviewer #1**

**1.1 The reviewer asks us to rewrite the manuscript according to the PRIZMA guideline for review/meta-analysis, and to limit the number of references to 50.**

We feel that the reviewer perhaps has not understood our intent in producing this manuscript, which follows the narrative style we have adopted in a number of our recently published review articles:

Martin *et al* (2018) Clin Sci (Lond) 132(15):1629-164. doi:10.1042/CS20171483 [Impact factor: 5.237].

Soffientini and Graham (2016) Clin Sci (Lond) 130(21): 1843-59. doi:10.1042/CS20160339 [IF 5.237].

Graham (2015) Free Radic Biol Med 89:982-9. doi:10.1016/j.freeradbiomed.2015.08.010 [Impact factor: 5.376].

Graham *et al* (2015) World J Cardiol 7(5):277-286. doi:10.4330/wjc.v7.i5.277 [IF 1.53].

Our goal was to fill an un-met need in the literature: an assessment of microRNA sequences implicated in foam cell formation, fully contextualised by an in-depth introduction to the lipid metabolism and inflammatory responses under consideration. We have taken great care to utilise primary literature supporting the original findings of the studies cited, and to ensure that all of the microRNA sequences discussed in Table 1, have been contextualised in the Introduction. This means that individuals who perhaps are not fully familiar with the interface between inflammation and lipid metabolism should now be able to recognize and discuss the role(s) of each microRNA sequence described in Table 1, before focusing on new developments in the field.

To clarify this, we have included an explicit opening statement (Introduction; paragraph 1) to set out our goal, and to indicate why it should be of interest to researchers and clinicians working in this field.

We also note that the comments of the other two reviewers, and of the editorial staff, also ask us to expand (not reduce) the review article, and/or to include more self-citations. These responses seem mutually conflicting with the advice given above, limiting our ability to respond constructively to this reviewer.

**1.2 The reviewer asks for more meaningful legends to the figures (sic. Animations) presented.**

We have now expanded the description to each legend (highlighted) to provide additional information on the pathways described.

**Reviewer #2**

We thank the reviewer for their highly positive review, and assessment of our presentation.

**2.1 The reviewer asks us to correct the (rare) typos and grammar errors throughout the manuscript**

We have made a number of corrections (highlighted) in the attached manuscript.

**2.2 The reviewer asks us to emphasize the novelty of the paper within the topic we have analysed.**

We have now included an opening statement (Introduction; paragraph 1; highlighted) to indicate the scope of the article, and to indicate its novelty and target audience (#Reviewer 3). The therapeutic section has now been updated (highlighted) to make the clinical relevance of the review article more explicit.

**Reviewer #3**

We thank the reviewer for their very positive comments on the manuscript, and their recognition of the depth and comprehension of our article.

**3.1 The reviewer suggests that the section 'Therapeutic options: clinical applications of microRNA' should be extended before acceptance, and that we indicate the target audience more clearly in which this novel approach might be useful.**

We have now extended this section (highlighted) to include consideration of human clinical trials, targeted delivery of miRNA sequences, and the individuals who might benefit from this type of therapy, compared with more conventional drug therapies.

## Responses to Editorial Office's comments

### **(1) Science Editor**

1. *In addition to the reviewers' comments (above) the Editor requests that we provide the conflict-of-interest disclosure form*

This form is now included in the uploaded documents.

### **(2) Editorial Office Director**

1. *In addition to the reviewers' comments (above), the Director suggests that we cite our own research work, include the grant application form, and provide editable figures*

We have now included some of our own work (Caruso *et al*, 2010<sup>[237]</sup>; Caruso *et al*, 2012<sup>[238]</sup>), highlighted in the bibliography. The grant application form is included, and the figures have now been uploaded as Powerpoint files which can be modified and edited. Please note that, due to the complexity of Figure 1, the editor must 'Zoom out' to see it in its complete form.

### **(3) Company Editor-in-Chief**

1. *In addition to the reviewers' comments (above) the Editor-in-Chief requests correct ethics documents.*

We have now uploaded the conflict-of-interest disclosure form.

### **(2) Language quality**

The manuscript has been corrected for minor typographical and grammatical errors (please see point 2.1 above); all authors are native English speakers (United Kingdom).

### **(3) Special requirements for figures**

The figures have now been submitted in an editable form, in Powerpoint. Please note that, due to the complexity of Figure 1, the editor must 'Zoom out' to see it in its complete form.

### **(4) Special requirements for tables**

Table 1 has been reviewed for missing or multiple spaces, and special words and letters appropriately italicized, as required. Spaces between the reference brackets and the preceding word have been removed; minor changes to the text have been made to improve clarity, and the text reviewed using 'Spelling and Grammar' check (Windows 10, Word).

### **(5) Special requirements for references**

The PubMed numbers (PMID: highlighted) have been added to the DOI citation numbers, and all authors of references are listed. The references are cited in Arabic numerals, superscripted in the text, and the numbering order is correct. The space between the bracket and the preceding word has been removed throughout. The author names cited in the text are consistent with the first author's surname in the corresponding reference list.

### **(6) Special requirements for article highlights**

Not applicable

### **(7) Ethical documents**

The conflict of interest form has been uploaded; as a review article, no other ethical permissions are required.

### **(8) Approved grant application forms**

The grant award letter (hard copy only) is currently in lockdown in the corresponding author's office, 100 miles away; travel in Scotland and access to the University is prohibited at present. Instead, we provide the final report on the grant award (confidential), which makes reference to this submitted review, and also has the contact details for our funder.