

Subject: JBC/2010/178657 -- Manuscript Decision

From: ktrisler@asbmb.org

Date: 9/24/10, 4:09 PM

To: Ilyas Washington <iw2101@columbia.edu>

MS ID#: JBC/2010/178657

Title: Prevention of lipofuscin deposition in a mouse model of stargardt disease

Dear Dr. Washington:

Your manuscript entitled "Prevention of lipofuscin deposition in a mouse model of stargardt disease" (JBC/2010/178657) has been reviewed by two members of the Editorial Board and the reviews are appended below. As you will see, the Reviewing Editors found your work to be of potential interest to our readers. However, several issues will have to be addressed before a final decision is made regarding your manuscript.

One of the Reviewing Editors is of the opinion that there are important elements to the manuscript and that it addresses an important topic. The novelty of using a deuterated version of vitamin A is also considered quite novel. The other Reviewing Editor appreciated the potential importance of this work, but felt that the study was largely descriptive and lacking in sufficient mechanistic insight to warrant publication in the Journal.

If you believe that you can address all of the issues raised in the reviews, please address all of the concerns of the Reviewing Editors, modify the manuscript appropriately, and submit your revised manuscript via the JBC Electronic Submission site (<http://submit.jbc.org>). The manuscript will need to be accompanied by a cover letter that includes a point-by-point response to all of the issues raised in the reviews. You will need to provide the cover letter separate from the manuscript during on-line submission of your revision.

In your reference list, please use periods for the abbreviations of journal names. Also you should present analytical data (spectra) on your synthetic chemicals in a Supplementary Data section. Ref. 14 can only be used as a reference if accepted for publication. All non-standard abbreviations need to be defined in a single footnote.

Title and Summary: It is important that the major findings of your study are intelligible to all JBC readers, including those who are not specialists in the field. Please review your title and summary to make sure they convey your essential points succinctly and clearly, and do not contain undefined abbreviations or specialized terms. If acronyms or abbreviations are used, then the name/term should be first indicated in full followed by the short form (e.g., Visualization of Polarized Membrane Type 1 Matrix Metalloproteinase (MT1-MMP) Activity in Live Cells by Fluorescence Resonance Energy Transfer (FRET) Imaging. A full name is not required for the most common biochemical abbreviations e.g. ATP.

It is critical that you review the revised version of your manuscript very carefully before submission. If the new version of your paper is accepted, we will publish the manuscript version as a JBC Papers in Press on the day of acceptance. This date is considered the date of publication.

Please note the instructions on preparation of the manuscript requiring text in two columns, single space format (<http://www.jbc.org/misc/ifora.xhtml>). You can also see a sample of what the manuscript should look like by clicking on the link that says "example of the manuscript's format" under the "initial manuscript submission" section or clicking on this link: http://www.jbc.org/misc/ms_sample.pdf. A description of the JBC Papers in Press program can be found at the JBC On-line web site (<http://www.jbc.org>).

Source files (Word for text, TIFF or EPS for figures) will be required when the manuscript is accepted for publication and will be submitted directly to Cadmus Professional Communications via their FTP site. Specific instructions will follow acceptance of the manuscript. See <http://www.jbc.org/misc/ifora.xhtml> for additional information.

Please note that the revised manuscript must be submitted within 120 days of the date of the decision letter or it will be assigned a new manuscript number.

Thank you for the opportunity to consider your manuscript for publication in the Journal of Biological Chemistry.

Sincerely yours,

F. Guengerich
Associate Editor

Reviewer 1

COMMENTS FOR THE AUTHOR:

This manuscript examines the effect of long-term administration of C20-D3-vitamin A on RPE lipofuscin deposition and eye function in a murine model of Stargardt's disease. This disease is the most prevalent form of inherited blindness and there is currently no cure. Vitamin A dimerization may underlie the disease as a result of mutation in ABCA4. The strategy here is to interfere with dimerization of endogenous vitamin A, thereby relieving lipofuscin formation and retinal cell death. Evidence in support of this model includes the inhibition of A2E and ATR dimer biosynthesis in the eyes of ABCA4 mutant mice. In addition, C20-D3-vitamin replaces endogenous vitamin and reduce RPE autofluorescence. Consistent with the model, treated mice show lower levels of lipofuscin deposits and show slowed loss of eye function. The authors conclude that C20-D3-vitamin A administration may prove effective in the treatment of Stargardt's disease.

Concerns: The data presented are interesting and supportive of the authors' conclusion. The work, however, is largely descriptive and focused almost entirely on the pharmacological potential of C20-D3-vitamin. The mechanistic insights provided by the paper are interesting but not developed fully enough to warrant publication in the Journal. Additional mechanistic insight could strengthen the manuscript and add considerably to pharmacological interest.

Reviewer 2

COMMENTS FOR THE AUTHOR:

This manuscript describes the effect of feeding a deuterated version of vitamin A to mice carrying a mutation that predisposes them to developing Stargardt's disease. There is great interest in this disorder and it is of significant clinical importance. The use of a C20-D3-vitamin A is quite novel and interesting.

While much of the manuscript is well done and quite interesting, several points should be addressed:

1. It is not clear that the level of ATR dimer can be accurately measured from the chromatogram shown in Figure 1 because it does not appear to be well resolved from compounds that have a similar mobility. The authors should address this issue.
2. An experiment in which a mixture of vitamin A and C20-D3 vitamin A seems essential and may reveal other effects of C20-D3 vitamin A other than its effect on chemical dimerization. Could there be some other pharmacological effect?
3. The level of lipofuscin in figure 4 does appear to be reduced, but this change should be quantified.
4. The data on inflammatory proteins is interesting, but the reproducibility of the data is not indicated. Some of the differences noted in the text may be due to errors that are expected when so many markers are measured simultaneously. A statistical analysis is needed.
5. The change in C4b is hard to interpret. It is not clear that one would expect message to predict protein in this case. At least some of the markers that are said to change should be independently tested using a different method.
6. It is not clear that the individual data points are shown in Figure 3A.
7. The paper would be strengthened if the authors were to include a behavioral test of vision, and this should be added.
8. The conclusions drawn seem to be rather strongly stated and more reserved conclusions would

better represent the data. Is Lipofuscin deposition completely 'prevented'? Is vision loss truly 'halted'? Is it clear that the effect that are observed are due exclusively to aberrant reactivity of Vitamin A or might other mechanism play a role? These issues should be modified or that authors should better justify their choice of words.

9. It is not clear that the summary figure is warranted. If the authors can argue it is justified, the discussion of the summary figure (which is now in the Discussion section of the paper) should be incorporated into the legend of that figure and the legend should be modified to indicate that this is a hypothesized model.

Sent on: September 24, 2010