

Subject: JBC/2010/178640 -- Manuscript Decision

From: ktrisler@asbmb.org

Date: 9/21/10, 3:51 PM

To: Ilyas Washington <iw2101@columbia.edu>

MS ID#: JBC/2010/178640

Title: Deuterium enrichment of vitamin a at the C20 position prevents the formation of detrimental vitamin a dimers in wild-type rodents

Dear Dr. Washington:

Your manuscript entitled "Deuterium enrichment of vitamin a at the C20 position prevents the formation of detrimental vitamin a dimers in wild-type rodents" (JBC/2010/178640) 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 recommended acceptance with minor revision. The Reviewing Editor was concerned whether replacement of retinyl esters in the liver by C20-D3-vitamin A was sufficient to provide long term protection against retinaldehyde dimerization in vivo. Our other Reviewing Editor considered the paper sound and potentially worthy of appearance in JBC but cited a number of problems in presentation that need to be addressed.

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.

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.

In addition, do not abbreviate in the Summary if an abbreviation is not used again. Please provide spectral evidence of purity etc. in a Supplemental Data section, e.g. NMR, MS. Use periods for the abbreviations of journal names in your reference list. Define all non-standard abbreviations in a single footnote. Table 1 does not appear to be formatted correctly—separate from the figure legends. In the HPLC figures, use A445 on the y-axis and provide values (at least for a range).

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 is an innovative paper on the use of deuterated vitamin A to provide a significant kinetic isotope effect to slow down the rate of dimerization of retinaldehyde that can lead to the production of ATR dimers that precedes the onset of macular degeneration. The authors synthesize the C20-deuterated derivative and quantify dimer formation by LC-APCI-MS in vivo and in vitro in mice and rats. The authors show that this agent is as effective as fenretinide and TDH, two agents that are not used long term for macular degeneration due to associated toxicities. The authors also show that C20D3-vitamin A can be used to exchange the retinyl ester pool in the liver. The authors should address the following concerns:

1. They indicate that about 50% of the retinyl ester pool can be exchanged in diets containing C20D3-vitamin A for 30 days. Is this sufficient to maintain a long term reduction in vitamin A dimerization in the retina?
2. Once the C20D3-vitamin A is incorporated into the retinyl ester pool, what is the half-life of the enriched pool?

Reviewer 2

COMMENTS FOR THE AUTHOR:

The results and interpretation seem to be sound, but insufficient care was taken in preparation of the manuscript. The following problems made it challenging to understand the paper.

- 1) Almost all the figures are misnumbered in the text. Figure 4 is called Figure 1. Figure 6 is called Figure 3. Figure 7 is called Scheme 1. Figure 8 is called Figure 4. The data showing replacement of liver stores upon IP injection of C20-D3-vitamin A are not shown. Why not?
- 2) In addition, there are a number of grammatical errors.
 - a) Abstract: Either "the intrinsic rate of dimerization is less", or "dimerization is slower." The rate can't be slower.
 - b) p. 2, left column, third paragraph: MS is "mass spectrometry"
 - c) p. 2, left column, fourth paragraph: "...to give final concentrations..." (delete "a")
 - d) p. 2, right column, second and third full paragraphs: The last sentences in these two paragraphs lack proper parallel structure.
 - e) p. 4, left column, second paragraph: "...twelve times more slowly (or less rapidly)..."
 - f) p. 6, left column, second paragraph: comma after "in vivo" in line 2 of paragraph. Then "Mice given C20-D3-vitamin A had less A2E than control animals given normal vitamin A..."
 - g) p. 6, left column, bottom: I couldn't find where RPE65 had been defined.
 - h) The abbreviation "ca." should be used for dates. The symbol "~" means approximately equal to and should be used throughout the manuscript in place of ca.
 - i) p. 7, right column, line 2: I assume the authors mean "adult human" here, but they should specify this because adult can be an adjective modifying almost any higher organism

j) p. 7, right column, bottom of first paragraph: "...might drastically accelerate the time required for C20-D3-vitamin A to accumulate..." is logically incorrect. Either accumulation is accelerated or the time for accumulation is diminished.

k) p. 8, left column: comma in line 4 after the citations and the "or" in line 6 should be "and"

l) p. 8, right column: "data" in line 4 is a plural noun so verb form should be "elucidate". Then comma after lipofuscin in line 11.

Sent on: September 21, 2010