Reviewer's report

Title: Indoxyl sulfate, a uremic toxin, downregulates renal expression of Nrf2 through activation of NF-kappaB

Version: 1 Date: 29 November 2012

Reviewer: Scott A Reisman

Reviewer's report:

This article describes the effects of indoxyl sulfate, a uremic toxin, on Nrf2. The experimental design was exceptional and provides novel data in nephrology. I have some minor comments below, which the authors should address or comment further prior to publication.

1. In the results, it should be clarified whether the western blots are whole cell or tissue lysates or nuclear fractions. If they were whole cell lysates, why were nuclear fractions not investigated. The subcellular location of Nrf2 could be very informative in regards to Nrf2 regulation in this model.

2. It would be easier to review the serum levels of indoxyl sulfate in tabular form instead of simply reporting in the text.

3. Please clarify the subheadings within the results section with bolded or italicized text.

4. There are better Nrf2 target genes than HO-1. The article would be greatly improved with the addition of others, such as Nqo1, sulfiredoxin 1, etc.

5. The article would be improved with the addition of NFkB targets.

6. The article would benefit greatly with grammatical revisions.

Specific grammatical comments:

Abstract:

Page 2:

Line 4: "is downregulated" should be "are downregulated"
Line 4: No comma after "sulfate" is needed.
Line 6: No comma after "kidneys" is needed.
Line 9: Should be "the following animals"
Line 17: No comma after "dithiocarbamate) is needed.

Page 3:

Line 4: Add comma after "sulfate."
Line 5: Add comma after "hypertension."
Line 6: No comma after "HO-1" is needed.

Introduction:

Page 4:

Line 2: No comma after "proteins" is needed
Line 8: No comma after "senescence" is needed.

Page 5:

Line 4: Add reference
Lines 6 and 7: Nrf2 is not actually released from Keap1. The correct model of the relationship between Nrf2 and Keap1 should be discussed. Please see Li Wenge, Mol Carcinog, 2009, 48: 91-104.
Lines 8-10: Awkward, please rephrase

Results:

Page 11:

Line 7: Instead of "inhibits," the word "decreased" or "diminished" would be more appropriate

Page 12:

Lines 15-16: Add comma after "sulfate" and after "hypertension.

Discussion:

Page 14:

Last line: "regulation" should be "regulatory"

Level of interest: An article of outstanding merit and interest in its field

Quality of written English: Needs some language corrections before being published

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

I am employed by and have a financial interested in Reata Pharmaceuticals, Inc.