

UCD Case Number: 2014-SM003

ORI Case Number: DIO 5652

SUBJECT: Investigation Committee Report Regarding the Allegation of Misconduct in Research

Revised on 12.18.15 – based on feedback from Dr. Koul

FROM: Alison Lakin, Ph.D., Research Integrity Officer (RIO) and Assistant Vice Chancellor for Regulatory Compliance

Respondent: Hari K. Koul PhD
[REDACTED]

Complainant: Anonymous posting on PubPeer to UCD, LSU, NIH and ORI

Original Allegations: There were a number of figures labeled to represent different images that appeared to use the same image or a manipulated version of the image in three papers. These papers are detailed below as A, B and C.

Background:

Initial allegation received by e-mail from Pro Can on June 2, 2014. Also received letter from Dr. Garfinkel from ORI raising the same allegations. Both Drs Koul and [REDACTED] moved to Louisiana State University Health Science Center Shreveport (LSU) in February 2014. Dr. Koul took data files for active current projects and certain equipment in negotiation with CU. The CU laboratory was dismantled, and old computers cleaned. The only remaining material was stored on the CU server.

After discussions with the RIO at LSU and Dr. Garfinkel at ORI, it was decided that LSU would conduct the Inquiry Panel as they were already in the process of reviewing the allegation. RIO Lakin received notification of the findings of the LSU Inquiry on August 22nd 2014. A copy of the Inquiry Report and the responses from the Respondents were sent to Dr. Traystman, UCD's Deciding Official, for review. On August 22nd 2014, Dr. Traystman determined an investigation was warranted. A copy of the Inquiry Report and supporting documents was sent to the ORI with an accompanying letter dated September 22nd, 2014.

The Investigation Committee was charged on September 30th, 2014 in accordance with 42 CFR part 93 and the University of Colorado Policies and Procedures.

Investigation Committee:

[REDACTED] (Chair), Associate Professor, Webb-Waring Center, SOM
[REDACTED] PhD, Professor, Pharmacology, SOM

Conflict of Interest Screening:

Each member of the Investigation Committee stated that they were free of bias, conflicts of interest or conflicts of commitment that would impair their ability to render a fair and impartial judgment in this matter. RIO Lakin concurred in each instance.

Investigation was conducted under the following regulations:

The applicable regulations are Public Health Service requirements contained in 42 C.F.R. 93 and University of Colorado Policy.

Applicable considerations:

When it considers that its task has been completed, the Investigation Committee shall determine by majority vote whether the allegations of misconduct are supported by a **preponderance of evidence**.

The Investigation Committee shall reach one of the following decisions as to each allegation of research misconduct:

1. A finding of research misconduct;
2. A finding of no culpable research misconduct, but serious research error; or
3. A finding of no misconduct and no serious research error.

Misconduct in research includes the following and means:

1. **Fabrication, falsification, plagiarism** and other forms of misrepresentation of ideas, and other serious deviations from accepted practices in proposing, carrying out, reviewing, or reporting results from research.

The following definitions apply:

Fabrication is making up data or results and recording or reporting them;
Falsification is manipulating research materials, equipment, or processes, or changing or omitting data or results such that the research is not accurately represented in the research record;
Plagiarism is the appropriation of another person's ideas, processes, results, or words without giving appropriate credit

2. Failure to comply with established standards regarding author names on publications;
3. Retaliation of any kind against a person who, in good faith, reported or provided information about suspected or alleged research misconduct.

Research misconduct does not include honest error or honest differences in interpretations or judgments of data. However, where a person's conduct otherwise constitutes research misconduct, the burden of proof lies with that person to establish by a preponderance of the evidence that his or her conduct represents honest error or differences in interpretation.

Standard for Determination:

A finding of research misconduct requires that the Investigation Committee makes the following determinations finding that:

1. There is a **significant departure** from accepted practices of the relevant research community; and

2. The misconduct be **committed intentionally, knowingly, or recklessly**; and
3. The allegation be proven by a **preponderance of the evidence**.

Specifics of the Allegations:

- A. [REDACTED] and Hari K. Koul (2013). The transcription factor sterile alpha motif (SAM) pointed domain-containing ETS transcription factor (SPDEF) is required for E-cadherin expression in prostate cancer cells. *J. Biol. Chem* 28 (17) 12222-31 (manuscript has been retracted by PI).

Specific Issues/Allegations:

Reuse of GAPDH bands from supposedly different blots (Fig 1C lanes 1-6 and Fig 2C lanes 1-6).
Numerous cases of both reuse and misrepresentation of images (Figs 6A, 6C, 7, 8A and 8C).

PHS Funding: NIH RO1 DK54084; RO1 CA161880; VA Merit Award BX001258,
University of Colorado

- B. [REDACTED] and Hari K Koul (2011). Potentiation of mitomycin C tumoricidal activity for the transitional cell carcinoma by histone deacetylase inhibitors *in vitro*. *J. Urol* 186(6): 2426-33.

Specific Issues/Allegations:

Beta actin bands "flipped" and reused (Figs 4C and 5B).
Possible pasting of experimental bands into figures (Figs 4c and 5b).

PHS Funding: None
Funding provided by University of Colorado School of Medicine and Novartis

- C. Lakshmi pathi Khandrika, Sweaty Koul, Randall B. Mechham, Hari K. Koul (2012). Kidney injury molecule-1 is upregulated in renal epithelial cells in response to oxalate *in vitro* and in renal tissues in response to hyperoxaluria *in vivo*. *PLoS One* 7(9): e44174.

Specific Issues/Allegations:

Possible pasting of bands in blot (Fig 3b).

PHS Funding: NIH RO1 DK54084

- D. [REDACTED] Hari K Koul (2010). p38 mitogen-activated protein

kinase-driven MAPKAPK2 regulates invasion of bladder cancer by modulation of MMP-2 and MMP-9 activity. *Cancer Res.* 70(2):832-41.

Specific Issues/Allegations:

Reuse and misidentification of microscopy images (Fig 2D and Fig 6B).

PHS Funding: None

Funding provided by The University of Colorado School of Medicine and Department of Surgery and Academic Enrichment Funds.

E.

[REDACTED] Hari K Koul (2009). Differential effects of valproic acid on growth, proliferation and metastasis in HTB5 and HTB9 bladder cancer cell lines. *Cancer Lett.* 281: 196-202.

Specific Issues/Allegations:

Bands on blot obscured or removed, apparent when the images are enhanced (Fig 4A p21 band "C" at 24hr, Fig 4B p21 band "C" at 24hr, and Fig 4B Cyclin A band "10" at 48 hr).

PHS Funding: None

Funding provided by The University of Colorado School of Medicine and Department of Surgery and Academic Enrichment Funds.

F.

[REDACTED] Hari K Koul (2010). Loss of PDEF, a prostate-derived Ets factor is associated with aggressive phenotype of prostate cancer: regulation of MMP 9 by PDEF. *Mol. Cancer* 9:148.

Specific Issues/Allegations:

Reuse of figure from a previous publication (Fig 4D first 4 bars and images appear identical to Fig 5E, [REDACTED] *Mol. Cancer Res.*, 2008;6:1639-1648).

Reuse of data from a previous publication (Fig 4D last 2 bars and images appear to be identical to Fig 5F 1st and last bars from [REDACTED] 2008)

Misrepresentation of data. In the present publication, the images above the last 2 bars are identified as PC3 cells whereas in the prior publication the same images in Fig 5F above the first and 4th bars are identified as DU145 cells.

PHS Funding: NIH/NCI-P20 CA103680-Schwartz/Byers Program PI's (H Koul, Pilot-Project PI) and the (Colorado) Department of Surgery, School of Medicine Academic Enrichment Funds.

G.

[REDACTED]
[REDACTED] Hari K Koul (2008). Primary culture and characterization of human renal inner medullary collecting duct epithelial cells. J. Urol. 179(5): 2057-2063.

Specific Issues/Allegations:

Misrepresentation of data. None of the "enlargements" are of the fields purported (Figs 2 and 6A).

PHS Funding: NIH R01 DK54084 and the University of Colorado at Denver Health Sciences Center School of Medicine and Department of Surgery Academic Enrichment Funds.

H.

[REDACTED] [REDACTED] Hari K Koul (2012). The transcription factor SPDEF suppresses prostate tumor metastasis. J. Biol. Chem. 287: 29968-29978.

Specific Issues/Allegations:

GAPDH bands appear to be reused in different blots (Figs 4B, 5F and 6).

PHS Funding: VA Merit Award 01BX001258, NIH R01 DK54084, and NIH/NCI R01 CA161880, University of Colorado.

Investigation Process:

Documents and data sequestered:

UCD made forensic copy of all data on the urology-surgery server.
No other material available as the laboratory had re-located to LSU.

LSU sequestered:

[REDACTED] laboratory notebook
Gel negatives that were retained by Dr. Koul with respect to the relevant publications relating to journal of Urology Paper and PLoS paper.
Electronic data from [REDACTED]
Electronic data from Dr. Koul relating to journal of Urology Paper and PLoS paper

Interviews conducted by the Investigation Committee:

Dr. Koul interviewed on 1/4/15

Written responses from:

Follow-up responses from Dr. Koul

[REDACTED] now in India
[REDACTED] now JHMS
[REDACTED] now in North Dakota

Review of Grants:

Based on the information provided in the journal articles in question, the majority of funding appears to have been internal to the University of Colorado Denver but the following NIH grants are also referenced:

- NIH R01 DK54084; RO1 CA161880; VA Merit Award BX001258, University of Colorado
- NIH R01 DK54084
- NIH/NCI-P20 CA103680-Schwartz/Byers Program PI's (H Koul, Pilot-Project PI)
- NIH R01 DK54084
- VA Merit Award 01BX001258, NIH R01 DK54084, and
- NIH/NCI R01 CA161880, University of Colorado.

Timeline for the Committee Review:

The Investigation Committee was scheduled to complete its work by 1/4/15. RIO Lakin requested extensions to the investigation due to the significant number of publications requiring review. ORI subsequently granted extensions, which changed the due date for the Investigation Committee report to 4/3/15, 8/3/15 then 11/6/15.

Conclusions:

- A. [REDACTED] and Hari K. Koul (2013) J. Biol. Chem 28 (17) 12222-31
(manuscript has been retracted by PI).

Specific Issues/Allegations:

Reuse of GAPDH bands from supposedly different blots (Fig 1C lanes 1-6 and Fig 2C lanes 1-6).

Numerous cases of both reuse and misrepresentation of images (Figs 6A, 6C, 7, 8A and 8C).

Finding: Correction made earlier by [REDACTED]. The investigation committee has not been able to contact [REDACTED] since he left LSU. The committee noted that he came forward when he found the mistake. He is not connected to any of the other papers.

- B. [REDACTED]
[REDACTED] and Hari K Koul (2011) J. Urol 186(6): 2426-33.

Specific Issues/Allegations:

Beta actin bands “flipped” and reused (Figs 4C and 5B).
Possible pasting of experimental bands into figures (Figs 4c and 5b).

Finding:

██████████ stated he helped with some of the experiments but that ██████████ did all the work on the figures and ██████████ wrote the paper. He believed that ██████████ did all the western blots. The committee has not been able to locate contact information for ██████████ since he returned to Egypt. None of the authors were able to produce the original data. The material saved on the server at CU were versions of the completed figure only but did not include the data that was used to compile the figure. The committee has significant concerns that the image appears to have been manipulated but the committee was unable to identify who created the image.

- C. Lakshmipathi Khandrika, Sweaty Koul, Randall B. Mechham, Hari K. Koul (2012) PLoS One 7(9): e44174.

Specific Issues/Allegations:

Possible pasting of bands in blot (Fig 3b).

Finding: Remains unclear from communication with ██████████ which bands were used and how the blot was done. The committee has significant concerns that the image appears to have been manipulated but the committee was unable to identify who created the image.

- D. ██████████ ██████████ ██████████ ██████████
██████████ Hari K Koul (2010) Cancer Res. 70(2):832-41.

Specific Issues/Allegations:

Reuse and misidentification of microscopy images (Fig 2D and Fig 6B).

Finding: Based on e-mail dated February 2, 2015, ██████████ admitted that the original control panel does not match the published article. He provided the original data for Figure 2D and requested permission to make a correction due to an error. The investigation committee agreed that there was an honest mistake in the construction of Figure 2D.

- E. ██████████ ██████████ ██████████ ██████████
██████████ Hari K Koul (2009) Cancer Lett. 281: 196-202.

Specific Issues/Allegations:

Bands on blot obscured or removed, apparent when the images are enhanced (Fig 4A p21 band “C” at 24hr, Fig 4B p21 band “C” at 24hr, and Fig 4B Cyclin A band “10” at 48 hr).

Finding:

██████████ stated that most of the work on this paper had already been done when he joined the laboratory to work with ██████████. ██████████ did some of the mass spectrometry but ██████████ should have had all the original data for the manuscript. ██████████ stated that there was a rush to finish the manuscript as ██████████ was leaving and the blots were not labeled well. Dr. Koul does not have any contact information for ██████████ who returned to South Korea. None of the authors were able to produce the original data. The committee has significant concerns that the image appears to have been manipulated but the committee was unable to identify who created the image.

F. ██████████

██████████ Hari K Koul (2010) Mol. Cancer 9:148.

Specific Issues/Allegations:

Reuse of figure from a previous publication (Fig 4D first 4 bars and images appear identical to Fig 5E, ██████████ Mol. Cancer Res., 2008;6:1639-1648).

Reuse of data from a previous publication (Fig 4D last 2 bars and images appear to be identical to Fig 5F 1st and last bars from ██████████ 2008)

Misrepresentation of data. In the present publication, the images above the last 2 bars are identified as PC3 cells whereas in the prior publication the same images in Fig 5F above the first and 4th bars are identified as DU145 cells.

Finding:

██████████ indicated that his role in this paper was limited and he did not have any role in the figures in question. He stated that ██████████ was in a rush and that he did not always label his blots well.

Based on communication between Dr. Koul and ██████████ it seems that there were numerous versions of the figures so it is difficult to identify the original data.

Based on e-mail communication between ██████████ and Dr. Koul, it seems unclear if there is data for DU145 cells, which leads to concern as to the veracity of data published in Figure 5F that is identified as DU145 cells in ██████████ Mol. Cancer Res., 2008;6:1639-1648.

Dr. Koul stated ██████████ compiled the data for the manuscript (e-mail dated September 26th, 2014 9:35am). Dr. Koul admitted that some of the data had been previously published without being appropriately cited or permission obtained from other journal (e-mail dated September 26th, 2014 10:51am).

No contact information is available for ██████████ since he retired.

The authors could not produce the original data although examples of some of the images were found on the CU server. The committee has significant concerns that the image appears to have been manipulated but the committee was unable to identify who created the image.

The committee recommends that both journals be contacted to inform them that there is a concern with the figures and the original data is not available to affirm the figure in either paper is correct.

G. [REDACTED]

[REDACTED] Hari K Koul (2008) J. Urol. 179(5): 2057-2063.

Specific Issues/Allegations:

Misrepresentation of data. None of the "enlargements" are of the fields purported (Figs 2 and 6A).

Finding:

[REDACTED] does not have the original images and in his response dated February 1, 2015 stated that he could not explain why the blown up images did not match the areas highlighted in the 10x image but he stated that "The ultimate decision about the contents of the manuscript and the representation of the results rested with Dr. Koul."

The original data as well as the final figures were saved on the server in a folder under [REDACTED] name. It is not clear if someone other than him was involved in making these figures.

H. [REDACTED] Hari K Koul (2012) J. Biol. Chem. 287: 29968-29978.

Specific Issues/Allegations:

GAPDH bands appear to be reused in different blots (Figs 4B, 5F and 6).

Finding: E-mail communication from [REDACTED] dated January 28th, 2015 where he admitted an error in Figure 6 in that the blue boxed and red boxed bands should have been flip-flopped. The blue box represents cell lysates (used in Fig. 4B and should have been the left column of Fig. 6). The red box represents tumor lysates (used in Fig. 5F and should have been on the right column of Fig. 6). [REDACTED] admitted that he made the error in constructing the figure.

[REDACTED] also stated that the green box referenced on the right side of figure 4B is not the same band as encircled in Figure 5F and Fig. 6. Asserted that these bands came from a different PCR run and GAPDH band.

The investigation committee agreed that there was an honest mistake in the figure construction of Figure 6. The same bands were not re-used in Figures 4B, 5F and 6.

Other evidence:

██████████ stated in e-mail dated February 1, 2015 that:

- There was no pressure to produce but there was limited oversight of the experiments.
- Dr. Koul did not review the raw data or the compiling of the manuscript. The final manuscript was not pre-reviewed by other authors.
- There were no designated lab notebooks everyone had their own method of documentation.

Dr. Koul stated on 11.18.15:

(These statements are self-serving and some of the statements are completely incorrect.

All the members of the laboratory met each week on Thursdays for 2-4 h. The laboratory members presented their original data generated during the week and received input from their colleagues and I chaired these meetings and provided constructive criticism and scientific direction. All the data was electronically saved by laboratory members on their individual assigned computers. I however, did not review the raw data at the time the fellows compiled the manuscripts.

The committee concluded that there was not a laboratory standard for where data should be stored. Based on the limited data stored on the CU server, the committee assumes that data was also stored on the local computer. Oversight of data and manuscripts produced by fellows was insufficient, leading to errors.

Findings of Scientific Misconduct

The committee struggled to conduct a thorough investigation of these allegations due to the poor record keeping within the laboratory at that time. The situation was further impeded by the relocation of the laboratory.

In some instances, the investigation committee determined that the discrepancies were due to honest error.

But in other instances, detailed above, the investigation committee determined that it was more likely than not that the image had been manipulated indicating a level of falsification and / or fabrication. The manipulation was a significant departure from accepted practice and may have been conducted with intent. However, there is insufficient evidence to determine who conducted this manipulation due to the poor record keeping and minimal oversight in the laboratory at the time. The committee, therefore, determined that there was no culpable research misconduct but there was serious research error.

Recommendations based on the findings of the Investigation Committee:**Recommendations to funding agencies:**

The Investigation Committee did not make any findings of research misconduct and so it does not feel it would be appropriate to report to any of the funding agencies.

Recommendations relating to publications:

[REDACTED] and Hari K. Koul (2013). The transcription factor sterile alpha motif (SAM) pointed domain-containing ETS transcription factor (SPDEF) is required for E-cadherin expression in prostate cancer cells. *J. Biol. Chem* 28 (17) 12222-31 - manuscript has already been retracted by PI.

[REDACTED] and Hari K Koul (2011). Potentiation of mitomycin C tumoricidal activity for the transitional cell carcinoma by histone deacetylase inhibitors *in vitro*. *J. Urol* 186(6): 2426-33. – the journal should be informed that the date is not available. A correction should be made after the experiment has been repeated or the paper should be retracted

Lakshmipathi Khandrika, Sweaty Koul, Randall B. Mechham, Hari K. Koul (2012). Kidney injury molecule-1 is upregulated in renal epithelial cells in response to oxalate *in vitro* and in renal tissues in response to hyperoxaluria *in vivo*. *PLoS One* 7(9): e44174 – journal should be informed that the data is not available. A correction should be made after the experiment has been repeated or the paper should be retracted

[REDACTED] Hari K Koul (2010). p38 mitogen-activated protein kinase-driven MAPKAPK2 regulates invasion of bladder cancer by modulation of MMP-2 and MMP-9 activity. *Cancer Res.* 70(2):832-41 – the journal should be contacted with request to correct the error.

[REDACTED] Hari K Koul (2009). Differential effects of valproic acid on growth, proliferation and metastasis in HTB5 and HTB9 bladder cancer cell lines. *Cancer Lett.* 281: 196-202. – the journal should be informed that the date is not available. A correction should be made after the experiment has been repeated or the paper should be retracted.

[REDACTED] Hari K Koul (2010). Loss of PDEF, a prostate-derived Ets factor is associated with aggressive phenotype of prostate cancer: regulation of MMP 9 by PDEF. *Mol. Cancer* 9:148 – the journal should be informed of the errors and the committee recommends retraction.

[REDACTED] Koul HK. (2008): Focal adhesion kinase controls aggressive phenotype of androgen-independent prostate cancer. *Mol. Cancer Res.*; 6:1639-1648– the journal should be informed of the errors and that the committee recommends retraction.

[REDACTED]
[REDACTED] Hari K Koul (2008). Primary culture and characterization of human renal inner medullary collecting duct epithelial cells. J. Urol. 179(5): 2057-2063 – the journal should be informed that the original data for this figure cannot be found and the figure is not accurate. The committee recommends retraction of this article.

[REDACTED] Hari K Koul (2012). The transcription factor SPDEF suppresses prostate tumor metastasis. J. Biol. Chem. 287: 29968-29978 – the journal should be contacted with a request to correct Figure 6.

Investigation Committee signatures for case DIO 5652

Signed by:

[REDACTED]

Date:

1/14/16

Chair of Investigation Committee

