Case Number: ORI 2013-003 (formerly DIO5517)

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

Respondent: [redacted]

Complainant: [redacted]

Complainant 2: [redacted]

Background:
On December 2, 2013, RIO Lakin, Ph.D. received an e-mail from [redacted] expressing concern that a reader had recently brought to the attention of the journal that there were several figure anomalies in a 2012 JCI publication (Equilibrative nucleoside transporter 1 (ENT1) regulates postischemic blood flow during acute kidney injury in mice, [redacted] The Journal of Clinical Investigation (hereafter JCI) 122: 693-710, 2012.

Prior to institutional involvement or evaluation, [redacted] wrote to the JCI on December 2, 2013 admitting that several errors in histologic images had been made but asserted that this was due to a lack of attention to detail during the final manuscript preparation. This response was sent to the journal without any consultation or involvement with the administration of the University.

On December 6, 2013, Dr. Lakin discussed the allegation from JCI with Dr. John Repine (Chair of the Research Ethics Committee, UCD) and Dr. Richard Traystman (Vice-Chancellor for Research, UCD). Most of the errors were in sections from "control" mice displaying normal renal histology but one section also involved different experimental groups (ischemic kidneys) being duplicated. Both Dr. Traystman and Dr. Repine found the number of errors concerning and agreed that this number of errors was significant enough to potentially place the scientific integrity of the paper into question, a finding consistent with the concern of the JCI.

Meeting with [redacted]: Dr. Lakin invited [redacted] to meet and provide an explanation for these errors before she made a final decision on whether an inquiry was warranted. Before such a meeting occurred, [redacted] came to Dr. Lakin's office on December 6, 2013 at 1 pm in the company of [redacted] to discuss the JCI article. [redacted] could not provide an explanation for how the duplication of images occurred and he expressed concern about the broader integrity of the manuscript. He also indicated that he had discussed the issue with [redacted] and she was at home reviewing the data.

Meeting with [redacted]: During her meeting with [redacted] on December 6, 2013 Dr. Lakin requested that [redacted] contact [redacted] and ask her to come to Dr. Lakin's office with her laptop and any other data

relevant to the manuscript that may be at her home. [redacted] arrived at 3pm that afternoon and gave Dr. Lakin her laptop and other materials that were then sequestered. [redacted] was unable to provide an explanation for how this error occurred except that [redacted] It was determined that Dr. Lakin would sequester relevant data immediately.

Additional allegations raised by Complainant 2:
After the initial allegation, on January 27th, 2014, Dr. Lakin was contacted by Complainant 2 who brought forward additional errors that he believed may be misconduct.
Complainant 2 reported several suspected errors (the full citations for these published papers is provided below):

1. Nature Immunology in figure 2c the authors try to provide evidence that NTN1 is transcriptionally induced by Hypoxia-inducible factor 1 alpha. One of the key aspects is the demonstration in figure 2c by ChIP. Lane 4 (from left) appears to have been falsified.
2. Hepatology: Figure 6b and figure 6f show identical panels for different treatments;
3. PNAS: Figure 2a and figure 2d show identical images for different genotypes;
4. Journal of Immunology: Figure 3b and figure 3e show identical images for different genotypes

Recommendation of Inquiry:
On February 5th, 2014 an Inquiry Committee was convened to review the allegations and they subsequently concluded that an Investigation was warranted. The Inquiry Committee Report dated 6/4/14 was reviewed by the deciding official, Dean of the School of Medicine Richard Krugman and sent back for additional information. An amended Inquiry Committee Report was submitted for consideration and Dean Krugman determined on 10/1/14 that the allegations should move forward to investigation.

Investigation Committee Members:
[redacted]

The Investigation Committee was charged by Dr. Lakin on Oct 23, 2014 with Christopher Puckett, Associate General Counsel also present.

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. [redacted] declared that he was listed as a co-author on a paper with the respondents but only provided the histology images. The committee determined that this limited relationship would not potentially bias the proceedings. Dr. Lakin concurred.

Investigation was conducted under the following regulations:
The applicable regulations are Public Health Service requirements contained in 42 CFR 93 and University of Colorado Policy.

Investigation Committee
The committee members and Dr. Lakin met a total of 18 times, in most cases joined by Associate General Counsel, Chris Puckett. They interviewed 10 individuals, 9 in person and 1 by telephone. They read and considered the information contained in the interview transcripts, laboratory notebooks, computer files, and the exhibits provided by each Respondent via their attorneys. The committee met individually with [redacted] The committee requested explanations of the inconsistencies in the publications and each respondent was asked to provide the primary research data that supported their results and conclusions.

ORI extensions provided during this investigation:
The committee was initially charged on 10/23/14 and granted extensions by ORI on 1/20/15, 6/30/15, 11/3/15 and 1/8/16 with an expiration date of 4/8/16.

Published papers under review.

1. [redacted] Journal of Clinical Investigation (hereafter JCI-2012), 122:693-710, 2012.
2. [redacted] 2013. Hepatology, 58:1766-1778, 2013.
3. [redacted] Proceedings of the National Academy of Sciences, USA. 110:12012-12017, 2013.
4. [redacted] Journal of Immunology 189:4566-4573, 2012.
5. [redacted] Nature Immunology, 10:195-202, 2009. Erratum in: Nature Immunology. 16:544, 2015.

Applicable considerations:
In accord with university policy and ORI regulations, 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 under 42 CFR 93.103 is defined as:

Research misconduct means fabrication, falsification or plagiarism in proposing, performing or reviewing research or in reporting research results.

a) Fabrication is making up data or results and recording or reporting them.

b) 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.

c) Plagiarism is the appropriation of another person's ideas, processes, results, or words without giving appropriate credit.

d) Research misconduct does not include honest error or differences of opinion.

Misconduct in research under University of Colorado policy is defined as:

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.
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.

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

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. (42 CFR 93.106)

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.

Investigation Process:

Documents and data sequestered: by Dr. Lakin accompanied by Sean Clark (Head, Information Technology-Security)

On Friday, December 6, 2013:

[redacted] laptop computer drive
3 lab books from [redacted]office
4 lab books from the lab
5 boxes of histology slides
CPU hard drive
Western blot hard drive
Microscope hard drive
HPSN: hard drive
Plate reader hard drive

On December 10, 2013:

[redacted] provided an external hard drive from her home computer.

Additional documents and data sequestered:

[redacted] laptop computer drive, 11 notebooks.
laptop computer drive and histology slides
additional lab notebooks
laptop computer drive

All of the documents and data described above were retained in locked drawers within locked offices, W1124 and C1013, in Building 500 on the UC-AMC campus. Physical evidence transferred between individuals involved in the case was verified via signature on a UC-AMC Chain of Evidence Custody form. Computer disks were imaged by Applied Trust, Boulder CO and examined with Encase Forensic Software, version 7.09.

Additional documentation provided:
Although [redacted] refused to provide a forensic copy of [redacted] home computer or make a pst copy available for the committee to review all pertinent e-mails, [redacted] did provide selected e-mails. in German with an English translation.

Interviews conducted by the Investigation Committee:
[redacted]

Data Analyzed:

I. Figures from the July 2, 2011 version of the JCI manuscript marked "final" that was emailed to a number of coauthors (before submission) and figures from the original version submitted to JCI on July 28, 2011 termed RG1 by the journal.
II. Figures from the original version of the manuscript submitted to JCI (RG1) and figures from the revised manuscript dated 10/14/2011 termed RV2.
III. Figures from the original submitted version of the Hepatology 2013 manuscript (1/2/13) and figures from the final revision (4/26/13).
IV. Computer files from the sequestered laboratory data.
V. Available laboratory notebooks and high-quality histology image files.

Supplemental Material:

S1. Side-by-side graphic comparison of 21 altered figure panels between the original submitted version (RG1) of the JCI 2012 paper (7/28/11) with the revised RV2 version (10/14/11).
S2 Side-by-side graphic comparison of 36 altered figure panels between the original submitted version (1/3/2013) of the Hepatology 2013 paper with the revised manuscript (4/26/2013)
S3. Graphic comparison of western blots of ENT1 and ENT2 protein levels in mice and in HK2 kidney cells from the 7/2/11 version sent to coauthors that was switched in the RG1, RV2 and published versions. Unswitched figures are shown for comparison and match the 7/2/11 pre-submission copy.
S4. An email from [redacted] to several coauthors (7/2/11) that included the "final" copy of the JCI 2012 manuscript. Also presented are email responses from some coauthors.
S5. All written correspondence from the respondents and their attorneys.
S6. Transcripts of Interviews.
S7 Forensic analysis of laboratory data computer files

Summary:
The Investigation Committee confirmed that there were 36 duplicated histology images from the 5 published papers in support of the conclusions of the Inquiry Committee. In addition, the Investigation Committee uncovered a number of new concerns from two of these papers that are documented in this report. The published papers (JCI 2012 and Hepatology 2013) are two of the 40 papers/reviews coauthored by [redacted] and [redacted] The committee requested the primary data for the 5 published papers however the respondents were unable to provide or identify where to locate the primary data for these papers to the Investigation Committee.

The respondents revised many figure panels with altered data that changed mean values and error bars, in 21 graphs presented in the JCI 2012 paper without informing the scientific reviewers, journal editors, and coauthors after the review process had commenced on July 28, 2011, following the submission of the manuscript by [redacted]. These changes were not asked for by the reviewers after their initial critique of the

manuscript. In addition, a pair of western blots for 2 equilibrative nucleoside transporters (ENT1 and 2) were switched prior to the original submission of the JCI paper and differ from their public presentation at several poster sessions. The switched protein bands were substituted after the final manuscript was sent to the coauthors for comments but prior to submitting the original manuscript to the JCI.

Interviews with at least two coauthors, [redacted] and [redacted], revealed they did not know what contributions they provided for the paper on which they were listed. [redacted] specifically stated that [redacted] was added as a coauthor by [redacted] so that [redacted] own upcoming paper would "look better if my name was on publications" (testimony page 9, lines 6-8). [redacted] testified that [redacted] did not contribute any technical data nor did [redacted] see the drafts of the JCI 2012 and PNAS 2013 papers (page 8, lines 1-6 and page 9, lines 1-4, 11/21/14).

In the [redacted] et al. Hepatology 2013 paper, there were changes in the error bars of the mean values in 36 conditions in the figures included in the original submission compared to those included in the final revision. There were also 23 instances of changes in statistical significance (p-value alterations) in the face of identical group means and sample sizes. The error bar discrepancy appears to be due to the careless graphing of standard deviation in the final revision instead of standard error of the mean, which was clearly stated in the methods section of both original and final versions of the paper.

Examination of [redacted] computer files using Encase Forensic software failed to locate the pzf files used to produce the graphs for either the original submission or the final revision of the Hepatology 2013 paper. Examination of [redacted] computer found 201 .pzf files from Aug 19, 2010 and Sept 2, 2011. None of these files were used to produce the graphs used in any versions of the Hepatology 2013 manuscript. The committee finds that the respondents and [redacted] (first author) have failed to supply this committee with the primary data that supports their hypotheses and conclusions. [redacted] testified that [redacted] produced all of the graphs (testimony page 10, lines 10-16, 12/1/2014) while he was mainly involved with liver surgeries, collection of samples for biochemical analyses and liver histology.

The inability of the respondents to provide the committee with the primary data for both the JCI and Hepatology publications demonstrates the poor oversight of both respondents with data generated at the University of Colorado and undermined the committee's ability to determine the accuracy and authenticity of the results and conclusions reached in the publications. These alterations involved at least 103 experiments and employed several hundred wild type and transgenic laboratory mice. Since the laboratory did not keep complete records of exactly which mice (eartag data) were included in each experiment, the committee could not verify that the control wildtype mice used in histology photos or group means were actually littermate controls as was specified in some of the figure legends.

The committee examined the primary data from two additional publications from that time period from the [redacted] laboratory and questioned [redacted], the designated first authors. These investigators produced the primary data to support their publications. The committee was completely satisfied with the ability of these investigators to provide all of the primary data in the publications on which they were the first author.

In addition, the committee heard testimony from a number of former members of the laboratory describing a strained work environment with pressure to produce data that conformed to the Principal Investigator's [redacted] general hypothesis.

The use of placeholders was prevalent in the laboratory at this time and reinforced by the PI, [redacted]. The practice went further with the PI requesting graphics representing the anticipated data set based upon the existing hypothesis. Former members of the laboratory testified that in future conversations with the research

team, [redacted] would not remember or identify that this data was merely a placeholder and put pressure on them to leave the placeholder data in the manuscript.

Section 1. Previous Allegations studied by the Inquiry Committee:
The allegations involved duplication of histology photos in 5 publications. Neither respondent challenged these findings.

a. Duplications in J Clin Investigation, 122:693-710, 2012. Sixteen histology panels were involved in image duplication. (Fig. 5H WT-I, 7D -Ischemia/-DIP, Fig. 7D -Ischemia/+DIP, Fig. 7D +Ischemia/+DIP, Fig. 7I -Ischemia/-DIP, Fig. 7I -Ischemia/+DIP, Fig. 7I +Ischemia/+DIP, Fig. 7N -Ischemia/-DIP, Fig. 7N -Ischemia/+DIP, Fig. 8D -Ischemia/-DIP, Fig. 8D -Ischemia/+DIP, Fig. 8I -Ischemia/-DIP, Fig. 8I -Ischemia/+DIP, Fig. 9D -Ischemia/-DIP, Fig. 9I -Ischemia/+DIP, and Fig. S8 Ent2-/- -Ischemia. In each case it appears that the same original photo was used for multiple images except that it was cropped differently for the different panels. Most instances where this occurred involved non-ischemic mice +/- pharmacologic treatment. [redacted] testified that the same photo was used for each histology image and that the data was not available at the time of submission (testimony of 6-11-2015: page 65, lines 18-25 and page 66, lines 5-10.

b. Duplications in Hepatology 58:1766-1778, 2013. Several duplicated histologic images were identified. (Fig 4C, WT –Ischemia, an exact duplication with Fig 5C ENT2 -/- -Ischemia, Fig. 6B +ZM-Ischemia is an exact duplication with Fig. 6F -PSB -Ischemia. Also there is one crossover duplication between this paper and the [redacted] et al. PNAS 2013 paper involving Fig. 3D –DIP –Ischemia (Hepatology 2013) with Fig. 3C Lysm Cre –I (PNAS 2013). Each image pair is the exact same photo.

c. Duplications in Proc Nat Acad Sci USA 110:12012-12017, 2013 (Fig 2A Adora1 -/- -Ischemia, is duplicated with Fig 2D Adora3 -/- -Ischemia and is the same photo but cut differently, Fig. 3B Adora2b flox/flox with Alb Cre –Ischemia is duplicated twice with Fig. S2B –PSB1115 –Ischemia and S3B –Bay –Ischemia, Fig 2A Adora1 -/- +Ischemia is duplicated with Fig. 2D Adora3 -/- +Ischemia, Fig. 3A Adora2b flox/flox VE-cadherin Cre –Ischemia is duplicated three times with Fig. 3B Adora2b Albumin Cre –Ischemia, Fig S2B +PSB1115 –Ischemia, and Fig. S3B +Bay – Ischemia. In the above examples the same photo was used but cropped differently. As specified above there was also a duplication of Fig 3C in this paper with Fig 3D of the Hepatology 2012 paper using the same photo.

d. Duplications in J Immunol 189:4566-4573, 2012. (Fig. 3B –Infliximab +Ischemia in a heterozygous Adora2b+/- mouse was duplicated with Fig. 3E –Infliximab +Ischemia in a heterozygous Adora2b+/- mouse.). The exact same image was used in both figures and this was confirmed by [redacted]

e. Duplication and questionable ChIP gel: [redacted]; Nature Immunology 10:195-202, 2009. (Fig. 5B is a histologic section of A2BAR -/- mice under control conditions, and is duplicated in Fig. 5A showing a wild type mouse under control conditions. The same photo was used in both figures. Fig. 2C may have been falsified in this Chromatin Immunoprecipitation assay. Lane 4 appears darker, with crisp margins to the neighboring lanes, which may have been manipulated. The original images have not been provided to the committee but this work was not conducted at the university.

Section 1 Findings

The committee considered the following evidence in relation to the 16 duplicated histology slides in the JCI paper as defined in section 1a above:

Early versions of the JCI manuscript had clear place holders – designated by green boxes. For example, the version dated Feb 25, 2011 had green boxes for Figs 5A, 5F, 5K, 6E, 6F, 6G, and 7F while the version dated Mar 14, 2011 had green boxes for Figs 2J, 5D, 5I, 5L, 6R, 6F, 6H, 6I, 6K, and 6L. Placeholders were routinely used by this research team to develop manuscripts and [redacted] originally indicated that any duplications were a result of her failure to remove the placeholders before publication.

[redacted] testified that she had not performed the experiments to generate the histology slides when the first version of the paper was submitted to JCI for review. She testified on 6/11/2015 that: "I didn't have the control histologies" (page 65, lines 18-25); "We put placeholders in there to make it look like it would when we submitted it…I forgot about them" (page 66, lines 1-4 and 18-25).

The same histology slide was used for each image but the image was cropped differently making it easy to miss. No rational explanation was provided by [redacted] as to why this cropping took place nor why neither a green box nor the exact same photo was used as a placeholder. [redacted] indicated that [redacted] wanted to see how the paper appeared visually. However, the same visual appearance could have been achieved by using the same image or a green box.

[redacted] testified that she was the sole researcher responsible for creating the histology slides and taking the photos (Inquiry Committee testimony 8/12/13: page 38, lines 17-24 and page 42, lines 16). The committee noted that [redacted] but e-mail communication suggested that she was still actively involved in the lab before the first version was submitted and also provided the additional material requested after the paper was reviewed by JCI. However, the committee did not have full access to all e-mails in [redacted] possession to confirm the communication string between [redacted] [redacted] indicated in her response, (testimony: page 47 lines 9-21) that she asked for additional time to make sure that all the GFR data was verified to her satisfaction. She characterized [redacted] as "very challenging and he just wanted to get it submitted".

[redacted] indicated that she directed PRAs [redacted] and a postdoc [redacted] to complete studies asked for by reviewers. Her ongoing experiments on [redacted] studies would not allow much time to repeat previous studies in that same time period.

In her interview [redacted] said that she regretted some of her decisions. She testified: "I should have said no. [redacted] is very challenging. I was not in the physical condition to say no. I said yes" (page 47, lines 20-25). This came in response to a question about [redacted] pressure to complete the paper in 2011. The committee could not determine with certainty that [redacted] was aware of all discrepancies in the JCI paper and all its revisions, even though [redacted] testified that in her opinion, he knew about all of the changes. However, [redacted] was the one coauthor who received multiple versions of the derived plots and histology images as the respondents developed the paper. In general from discussions with many individuals in his lab, [redacted] appeared to micromanage his laboratory projects and he admits for 5 years he was intimately involved in the formulation of hypotheses and conclusions reached in the JCI publication. The committee cannot conclude that it is more likely than not that [redacted] knew about the lack of actual control histology images when the paper was originally submitted or that the placeholders were not replaced. The committee does conclude that [redacted]

[redacted] should have known and it was within the expectations for a principal co-author to ensure that experiments were completed and placeholders not used or removed.

The claim by [redacted] that some control histology slides were not done/available prior to submission demonstrated that they chose to submit a paper hurriedly before all the substantiating data was available. It is important to note that 12 other histology images were substituted (section 2B) after the coauthors received their final copy of the draft (on 7/2/11) and prior to the initial JCI submission (on 7/28/11). This demonstrates they were trying to include the best images that would correlate with renal function. Whether the respondents planned to add the missing data later in the revision process is unknown.

E-mail communication provided by [redacted] suggests that he was on vacation when the second version of the JCI manuscript was submitted and gave permission for [redacted] to submit on his behalf. The glass histology slides are now available but there is no supporting documentation to show when these slides were made and it is difficult to track the slides to the original experiments.

Findings made by the committee in relation to [redacted]

The 16 histology images detailed in section 1a above were fabricated and falsified. Falsified and fabricated images were intentionally inserted by [redacted] appeared in the publication in the JCI. Based on the preponderance of the evidence detailed above, this was not honest error, and it is a significant departure from accepted practices of the research community in this field.

The committee finds that [redacted] committed research misconduct in relation to the 16 histology images detailed in section 1a above.

The committee considered the following evidence in relation to the duplicated histology images in the Hepatology paper as defined in section 1b above:

- [redacted] testified that he was responsible for the creation of all histology images in the paper (testimony of [redacted] on 12/1/14, page 10, lines 2-6 and [redacted] Inquiry Committee testimony on 8/12/14, page 24, lines 12).
- [redacted] admitted that he was frequently working on the early drafts late at night after having been on clinical service.
- It was clear to the committee that [redacted] had little laboratory research experience and relied heavily on [redacted] for her expertise He wrote to Dr Lakin on 4/3/15: "The majority of the original data contributed by multiple collaborators including [redacted] was collected and incorporated into figures by [redacted] my contribution to each publication was limited to surgery, tissue histology, and liver enzymes.

Findings made by the committee in relation to section 1b:
The committee finds: no culpable research misconduct, but ***honest error*** in the duplication of the histology images on the part of [redacted] and/or the Respondents.

The committee considered the following evidence in relation to the duplicated histology images in the PNAS paper as defined in section 1c above:

- These consist of duplicating the same photo but cropping it differently.
- [redacted] testified that it was the same photo (Inquiry testimony of 8/12/2014: page 7, lines 14-17 and page 15, lines 7-19).

- [redacted] testified that he was responsible for all the histology images in the paper (testimony of [redacted] on 12-1-2014, page 10, lines 2-6).
- As with the Hepatology paper, [redacted] admitted that he was frequently working on the early drafts late at night after having been on clinical service. It was clear to the committee that [redacted] had little laboratory experience and relied heavily on [redacted] (testimony: page 5, lines 9-11) particularly to put together the data figures ([redacted] testimony, page 10, lines 8-18).

Findings made by the committee in relation to section 1c:
The committee finds: no culpable research misconduct, but honest error in the duplication of the histology images on the part of [redacted] and/or the Respondents. However, the committee has not been able to examine the original data to verify that there are no other errors in this paper.

The committee considered the following evidence in relation to the duplicated histology images in the Journal of Immunology paper as defined in section 1d above:

- The exact same photo was used in both figures and this was confirmed by [redacted] to the Inquiry Committee.
- [redacted] testified that [redacted] provided him with all the data and he used it to draft the manuscript. [redacted] did not see any of the original data and does not have access to the original data.
- [redacted] testified that [redacted] asked him to write the paper ([redacted] testimony, page 4, lines 20-25 and page 5, line 1).

Findings made by the committee in relation to section 1d:
The committee finds: ***no culpable research misconduct, but honest error*** in the duplication of the histology images on the part of [redacted] and/or the Respondents. However, the committee has not been able to examine the original data to verify that there are no other errors in this paper.

The committee considered the following evidence in relation to the duplicated histology images in the Nature Immunology paper as defined in section 1e above:
The experiments were performed in Germany, and the committee was not provided with the original electronic files of the chromatin immunoprecipitation experiments showing *in vivo* DNA occupancy. The committee could not confirm the first author's explanation and substitution of revised figures with the original electronic versions of the files). The first author has already made a correction to this paper. Erratum in: Nature Immunology. 16:544, 2015.

Section 2A. New Allegations: Inappropriate switching of two files for ENT1 vs. ENT2 protein levels in two western blots prior to the JCI 2012 submission.

The committee considered the following evidence:

- [redacted] sent the "final version" of the JCI paper to many coauthors on 7/2/2011 and asked for any changes/comments (see Supplemental Material). E-mails from several coauthors failed to comment on figures that were altered prior to submitting the paper first to Nature/Genetics (7/14/2011) and then to JCI (7/28/2011).
- In a visual comparison of the figures, it was noted that a number of panels differed between the July 2 (sent to coauthors) and July 28 versions. An initial discrepancy involved relative quantitation of two equilibrative nucleoside transporters: ENT1 and ENT2 from mice subjected to IP (ischemia-reperfusion) or HK2 kidney cells grown in low oxygen conditions. Comparisons of electronic files showed that the

ENT band reassignments were changed between 7/7/2011 and 7/14/2011 without informing the coauthors of the substitution. The switched version was submitted to Nature-Genetics on 7/14/11 (not reviewed) and then to J Clin Investig on 7/28/11.

- Specifically, files of two western blots for ENT1 and 2 proteins were switched, ENT1 for ENT2 and ENT2 for ENT1 in two different figures. The ENT1 and ENT2 protein bands on this blot were switched prior to submitting the paper for publication on 7/14 and 7/28 (J Clin Investig) respectively. There is no evidence that these changes were sent to coauthors to review before submission. A comparison of the Figure 2b (7/2/11) with revised Figure 3B (10/14/11) in mice (0-120 min) and Figure 2f (7/2/11) with revised Figure 3F (10/14/11) in HK2 cells (1% oxygen for 0-24 hr) clearly showed these inconsistencies.
- The unswitched bands were incorporated into all versions of the manuscript prior to July 2, 2011. The unswitched bands were also shown in two poster sessions at the American Society of Nephrology, 2009 (authors: [redacted]) and at the [redacted] (authors: [redacted]). Examination of electronic files of uncropped western blots in Fig. 2b agreed with versions prior to 7/2/11 and did not match what was submitted in the original JCI 2012 manuscript or the published paper. Copies of these two posters are shown in Supplementary Material, S3.
- The revised figures that were switched are identical with the proofs and the final publication. For Fig 2b (7/2/11), filenames on laboratory computers matched the 7/2/11 version of the manuscript and not the submitted or published versions. The original filenames found in [redacted] computer from 2008 matched the unswitched version shown in two poster sessions. Only [redacted] claimed in her lawyer's letter to the committee that they should have been switched. Neither of the two key coauthors, [redacted] (co-first author) nor [redacted] (corresponding author), confirmed [redacted] explanation. For example, [redacted] was sent an email by [redacted] on 7-2-2011 that requested her to: "Please find attached the final version of our ENT manuscript including figures, figure legend, supply, methods and figures." [redacted] communicated back to [redacted] with some minor changes but did not mention that the ENT western blots were wrong and needed to be switched (see Supplemental Material, S4).
- It was difficult for the committee to interpret the uncropped western blot of the mouse data (fig 2a) (7/2/11) as it contained numerous artefactual bands likely due to nonspecific binding of the primary or secondary antibodies (see Supplementary Material). The committee could not find uncropped western blots for Fig 2f among the files in the laboratory computers or in the sequestered notebooks. [redacted] did not produce the uncropped western blot or identify its location.
- The committee considers that the changes to the western blot detailed above more appropriately match the narrative that emphasizes the importance of ENT1 over ENT2. The switched blot shows that 30 min of ischemia results in much lower protein levels of ENT2 but not ENT1 (Fig 3B in paper). At 30 min of ischemia (Fig 1D) kidney function is improved when a nonspecific inhibitor of ENT is used. It's more consistent with the overall hypothesis if ENT1 protein is detectable and able to be inhibited by the drug DIP (bar 4 vs bar3). The unswitched version would put more focus on ENT2 and not ENT1, the latter showing low protein levels following 30 min of ischemia.
- On several occasions, the committee heard testimony that [redacted] would refuse to allow data to be published that did not correspond with his broader hypothesis (for example, [redacted] testified that he heard such allegations from several former lab members, testimony of 12/1/2014: page 50, lines 9-21 and page 78, lines 2-7).

Findings made by the committee concerning Section 2A in relation to [redacted] was responsible for the construction of the figures in the JCI paper. The figure initially contained the correct western blots in earlier versions of the manuscript. [redacted] only saw the unchanged version based on the e-mail communication found and her statement.

The committee finds: that [redacted] **intentionally falsified and fabricated** this data. It was not an honest error. This manipulation is a significant departure from accepted practices of this research community.

The committee finds that [redacted] committed research misconduct in relation to Figure 2a and Figure 2f detailed in section 2A above.

Section 2B. New Allegations: Changes made to additional histology figures prior to JCI 2012 submission. This allegation was a result of a more thorough analysis of the figures from multiple versions of the manuscript. Changes were made prior to submission of the paper to Nature-Genetics (7-14-2011) and then to JCI (7-28-2011). Histology changes were made in 12 photos. None of the figure duplications in Section 1A were changed at this time. Substituted histology photos were found in Figs. 1k, 4d, 4n, 4s, 5d, 5i, 5k, 5l, 5m, 6d, 6f, and 6h.

The committee considered the following evidence in relation to the additional changes made to additional histology figures prior to JCI 2012 submission:

- There is no evidence that these changes were sent to coauthors before submission, which does not align with the procedures outlined by [redacted] in [redacted] testimony.
- The committee agreed that it was appropriate for the research team to present their most representative and compelling histology photographs.
- No evidence was identified to suggest that these images do not represent the description detailed in the manuscript although the primary source data for these images cannot be tracked back to the original tissue and / or description of the experiment in laboratory notebooks. Neither [redacted] nor [redacted] were able to produce the original data or figures for these changes.

Findings made by the committee in relation to Section 2B:
The committee finds: **no culpable research misconduct, and no serious research error** by the Respondents relating to these changes.

The committee reminds [redacted] and [redacted] that it is not good practice to make changes to a manuscript without indicating the changes to the co-authors or the journal.

Section 3. New Evidence: Alterations to the JCI 2012 manuscript during the review process.
Detailed examination of numerous versions of the revised manuscript revealed that 21 figure panels contained improper modifications to group means and error bars without revealing these changes to reviewers, JCI editors, or coauthors after the review process commenced. There were 45 changes (multiple changes in some figures) to ischemic mice vs 9 on sham operated but hemi-nephrectomized control animals. [redacted] testified that GraphPad Prism (.pzf files) was used exclusively to plot the group means, error bars, and statistical significance. The committee was not able to locate the pzf files from these 21 figures. In the data folder there were over 3400 files in a folder IP_Niere (ischemia/reperfusion kidney) but it only contained 3 pzf files that related to experiments using bilateral kidney damage that was asked for by a reviewer. [redacted] claimed that the absence of these files on her hard drive was due to damage to the hard drive during the summer of 2012. The missing pzf files did not appear to be backed up on other devices even though other files relating to this manuscript were duplicated in several different computer locations. [redacted] did supply pdf copies of data points and graphs that were incorporated into Figure 7A and were contained in Exhibit D sent to the committee. When asked, [redacted] did not produce electronic files of this data. This section contains text descriptions of the alterations while a graphic comparison of the original vs final revision is shown in the Supplemental Material.

Section 3A: Text descriptions of discrepancies between the original submitted, and the published versions of the JCI 2012 paper.
Fig. 7A. - [redacted] submitted individual data points and resultant graphs to the committee on April 28, 2015 as

a pdf copy of two pzf files used to construct these plots for both the original and resubmitted/finalized manuscript (see Supplementary Material). The committee verified that the graphs were identical to those from both submissions by re-deriving plots from the supplied individual experiments. A comparative analysis of the graphs revealed that the graph present in the revision contained additional data points while other points were removed. In the Adora1 null mice, ischemia was tested in the absence/presence of DIP. Analysis showed a marked decrease in mean values only with the ischemia part of the study while ischemia enhanced the difference in both inhibitor treatments. These substitutions were not brought to the attention of the JCI reviewers, editors, and most coauthors. [redacted] was unable to provide documentation to support where these data points originated. The committee concluded that there was inappropriate inclusion of different data and suppression of valid data in the re-submitted version of the manuscript submitted to the JCI.

In addition, the committee found the following:

- Fig. 1D. Glomerular filtration rate (GFR) following 30 min renal ischemia (I) and 1 hr reperfusion. All mean values have been altered suggesting different data points in the graphs contained in the original compared to the final version of the manuscript. Minus I group - the nonspecific ENT inhibitor DIP increased while the -I+DIP mean value decreased. Both +I -/+DIP have decreased means. Respondents did not produce the raw data to verify either of the graphs.

- Fig. 1G. RT-PCR of IL6 RNA levels after 30 min Ischemia and 2 hr reperfusion. The mean value of the +I, -DIP increased as did the error bar, while the +I, +DIP decreased and had a smaller error bar. This supports an interpretation of an increase in the inflammatory response as measured by the level of IL6 transcription, in response to ischemia. This interpretation supports the the favored hypotheses, however the respondents were unable to produce the raw data to verify the graphs.

- Fig. 2A. Levels of the neutrophil marker MPO following 30 min of ischemia and 1 hr reperfusion. With ischemia, -DIP or +DIP, mean values were both modestly elevated revealing a larger response toward the favored hypothesis of more damage with ischemia. Both error bars are smaller. Respondents did not produce the raw data to verify the graphs.

- Figure 5C. GFR following 30 min Ischemia and 24 hr reperfusion. Three of 4 means were altered. The wt mice -I mean increased with a smaller error bar. Wt +I mean decreased while the Ent-/- +I increased with an increased error bar. This shows more of a difference between mouse strains when ischemia is tested. Respondents did not produce the raw data to verify the graphs.

- Fig. 5F. IL6 transcript levels following 30 min ischemia and 2 hr reperfusion determined by RT-PCR. Ent-/- -I mean decreased. Wt +I increased mean with an increased error bar and the Ent-/- +I slightly increased with an increased error bar. Shows an increased ischemic response more in wt mice than the Ent1 null mice. Respondents did not produce the raw data to verify the graphs.

- Fig. 5G. MPO levels after 30 min ischemia and 24 hr reperfusion. Vertical scales are altered. The magnitude of MPO mean levels increase with ischemia are altered from 3.5 fold to over 8 fold in wt mice and from 2 fold to 5 fold in Ent1 null mice. Error bars in the ischemia treated mice decreased. Respondents did not produce the raw data to verify the graphs.

- Fig. 6A. GFR assessments in Ent1 bone marrow chimeric mice or in Ent1-/- reconstituted with human ENT1. Mean levels for reconstituted bone marrows for wt to wt and wt to KO show are decreased. Respondents did not produce the raw data to verify the graphs.

- Fig. 6B. Serum creatinine levels in Ent1 bone marrow chimeric mice or in Ent1-/- reconstituted with

human ENT1. Ischemia was for 30 min with 24 hr reperfusion. The mean value of the reconstituted bone marrow for wt to KO was decreased. Respondents did not produce the raw data to verify the graphs.

- Fig. 6G. Serum GFR levels in Ent1-/- mice reconstituted with human ENT1 via a lentivirus or a control lentivirus. Ischemia was for 30 min with 1hr reperfusion. The mean value GFR using a control lentivirus increased while the hENT lentivirus treatment had a decreased mean in the absence of ischemia. Both mean GFR values decreased with either lentivirus treatment in the presence of ischemia. Data shows a result directed toward the preferred ischemic hypothesis. Respondents did not produce the raw data to verify the graphs.

- Fig. 6I. MPO levels in Ent1-/- mice reconstituted with human ENT1 via a lentivirus or a control lentivirus. Ischemia was for 30 min with 24 hour reperfusion. Under ischemic conditions there were altered means with both lentiviral vectors, evident with the hENT1 reconstitution that shows an increased effect over what was originally submitted and not disclosed to reviewers, JCI editors, or most coauthors. Respondents did not produce the raw data to verify the graphs.

- Fig. 7A. Discussed in detail at beginning of this section. [redacted] submitted individual data points and resultant graphs as a pdf file to the committee used to produce this figure in both the Original submission and resubmitted and finalized manuscript. The graphs were identical to those in both submissions. Analysis shows addition of new data points while older ones were removed. These substitutions were not brought to the attention of JCI reviewers, editors, and most coauthors nor explained.

- Fig. 7B. Testing of Adora1 null mice on creatinine levels (measure of kidney dysfunction) following 30 min ischemia and 1 hr reperfusion in the absence or presence of the ENT inhibitor, DIP. Altered means slightly decreased in presence of ischemia +/- DIP. Any change shows data has been altered. Respondents did not produce the raw data to verify the graphs.

- Fig. 7K. Testing of Adora3 null mice on GFR levels following 30 min ischemia and 1 hr reperfusion in the absence or presence of DIP. The -DIP + ischemia mean was lowered leading to the most detrimental combination experiment. Respondents did not produce the raw data to verify the graphs.

- Fig. 7L. Testing of Adora3 null mice on GFR levels following 30 min ischemia and 24 hr reperfusion in absence or presence of DIP. Both error bars were decreased only in the ischemic group +/- DIP. Respondents did not produce the raw data to verify the graphs.

- Fig. 8A. Role of pretreatment with DIP in Adora2b null mice. There was a slight increase in the mean GFR levels in this mouse strain following 30 min ischemia and 1 hr reperfusion. Error bars were altered. Respondents did not produce the raw data to verify the graphs.

- Fig. 8F. Adora2b null mice pretreated with the antagonist PSB1115 and/or DIP; effect on GFR following 30 min ischemia and 1 hr reperfusion. The means of the +Ischemia groups have been decreased in both +/- DIP. This results in a larger response after ischemia, in line with their favored hypothesis involving this adenosine receptor. Respondents did not produce the raw data to verify the graphs.

- Fig. 9A. Conditional Adora2b mice with a deletion of the receptor in mice using a kidney tubule expressed CRE recombinase directed by the PEPCK promoter. Results compared GFR levels following pretreatment with DIP and 30 min ischemia followed by 1 hr reperfusion. The –DIP mean was slightly

reduced following ischemia. The respondents did not produce the raw data to verify the graphs.

- Fig. 9B. Conditional Adora2b mice with a deletion of the receptor in mice using a kidney tubule CRE directed by the PEPCK promoter. Results compared serum creatinine levels following pretreatment with DIP and 30 min ischemia followed by 24 hr reperfusion. The +DIP mean was decreased following ischemia. The error bar of the –DIP mean following ischemia was reduced. Respondents did not produce the raw data to verify the graphs.

- Fig. 9C. Conditional Adora2b mice with a deletion of the receptor in mice using a kidney tubular CRE directed by the PEPCK promoter. Results compared MPO levels following pretreatment with DIP and 30 min ischemia followed by 24 hr reperfusion. The mean values in both +/- DIP groups were increased. The Respondents did not produce the raw data to verify the graphs.

- Fig. 9F. Conditional Adora2b mice with a deletion of the receptor in mice using a vascular endothelial CRE directed by the VE-cadherin promoter. Results compared GFR levels following pretreatment with DIP and 30 min ischemia followed by 1 hr reperfusion. Mean of +DIP + ischemia mice were inappropriately increased. Respondents did not produce the raw data to verify the graphs.

- Fig. Suppl 4 (original), Suppl 6 (final). Renal adenosine content in wt vs Ent2 null mice following 30 min ischemia and 0 hr reperfusion. Mean adenosine values were decreased in Ent2 null mice in the absence of ischemia and mean values were also decreased in both wt and Ent2 null mice in the presence of ischemia. Error bars of the latter group were also decreased. Respondents did not produce the raw data to verify the graphs.

The committee considered the following evidence in relation to the alterations to the JCI 2012 manuscript during the review process in relation to section 3A above:

- The respondents could not provide the original data that was used to make either the original figures used in the first draft of the manuscript submitted to the JCI or used to make the altered figures present in the final version of the manuscript.
- Any data provided was not labelled in a way that could be identified or tracked back to the source of the data.
- Among the sequestered material the committee could not identify any Graph Pad Prism Pro files that contained the data s used to make the figures in either the original or the final version of the manuscript submitted to the JCI.
- The best interpretation is that the figures included in one version of the manuscript is not correct but the respondents were unable to provide any data supporting either version of the figures.
- [redacted] testified that she was responsible for producing all the figures in the papers but could not produce the data or the files used to make the graphics ([redacted] letter to committee 4/28/2015, page 6, paragraph 5).
- At the time the data was sequested, [redacted] did not indicate that one of her computers with significant portions of data relating to this paper had crashed. In later correspondence (letter dated April 28, 2015) she indicated that the computer crashed in the summer of 2012. She indicated that she no longer has the computer and no one else who was in the laboratory at that time remembered [redacted] reporting a computer crash.
- [redacted] testified that she told [redacted] that she could not stand behind the data used to produce the figures in the original version of the JCI paper. [redacted] denied that any such communication occurred.

- [redacted] testified that the policy of the laboratory was to back all data up to the Department of Anesthesiology server. No explanation could be provided by either respondent as to why [redacted] did not follow policy.
- The committee heard testimony from other members of the laboratory that standard lab procedures did not apply to [redacted] and that she and [redacted] worked closely as a team.
- [redacted] was, at that time, an Assistant Professor with significant research experience.
- There is no documentation to indicate that the co-authors or JCI editors were informed of changes in the figures included in the different versions of the manuscript.
- There does not seem to be a clear rationale for making the changes between versions but a number of the changes do serve to better illustrate the hypothesis of the paper.

Findings made by the committee concerning section 3A above in relation to [redacted]:
The committee understands that sometimes select data points are omitted however there must be justified on the basis of a clear experimental rationale and accompanied by a noted explanation. In contrast, wholesale manipulation of figures and graphs is not an acceptable practice and appears to have been done with intent and a lack of transparency. Even though the impact on the conclusions of the paper were not major in scope, there was a clear suppression/omission of some of the data points, as evidenced by the changes made in Figure 7A. Many of the alterations magnified the differences between the means of the groups and were slanted to be consistent with a favored hypothesis. The lack of any primary data impedes the committee's ability to determine the authenticity of the results and conclusions for the remaining figure panels.

The committee determines that the changes made to numerous figures detailed in section 3 above were fabricated and/or falsified figures that were intentionally inserted by [redacted] into the published version of the JCI paper. This was not honest error based on the preponderance of the evidence detailed above and it is a significant departure from accepted practices of the research community in this field.

The committee finds that Dr. Grenz committed research misconduct in relation to the 21 figures detailed in section 3A above.

Section 3B:
NIH Grants – use of figure panels lacking the primary data to support them. The Investigation Committee determined that #123612Title: Purinergic Signaling during Acute Kidney Injury. P.I. [redacted] used 12 figures from the *JCI* paper in the supporting manuscripts section.

The application was submitted 6/1/2012. Period: 4/1/2013-3/31/2018. RO1 DK098337-01. Key people: [redacted]

Findings: There were 12 figure panels including graphical results and histology images shown on pp. 92-93 of the grant submission that are linked to a paper that has been examined by the committee. The authors were not able to produce the primary data that supports their results and conclusions.

- Figures involved include (Figure numbers - JCI paper) 10 panels Figure 9, [redacted] et al., JCI 2012. This consisted of figure panels A, B, C, D, E, F, G, H, I and J from Figure 9 and figures 12 D and E. The authors could not supply the primary data to support their results and conclusions.
- Several mean values and error bars were modified but not disclosed to reviewers or JCI editors. The figures were on pp. 92-93 in the submission application.

Findings made by the committee concerning section 3B above in relation to [redacted]:
NIH Grant RO1 DK098337-01 included figures that were falsified and/or fabricated in the JCI paper.

The committee determines that the changes made to same figures detailed in the grant were also fabricated and/or falsified figures that were intentionally inserted by [redacted] into the NIH grant submission. This was not honest error based on the preponderance of the evidence detailed above and it is a significant departure from accepted practices of the research community in this field.

The committee finds that Dr. Grenz committed research misconduct in relation to the 12 figures detailed in section 3B above.

Section 4. New Evidence: Erroneous use of error bars and alterations to statistical significance in the Hepatology 2013 publication.

A comparison of the graphs contained in the original submitted manuscript (1-2-2013) with the final revision (4-26-2013) revealed in 36 figure panels, error bars that were much larger in the final version (see Supplemental Material). These changes could be easily seen by visual comparison. By inspection, the group means did not change in any of these figures. In the methods of both versions of the manuscript the authors cited that the graphs used standard error of the mean and not standard deviation to depict the error bars. The committee was not able to find nor was anyone able to produce the original data points for all the figures and so could not determine the mean values exactly. There were two types of errors that noted. One had to do with alterations in error bars between both versions and the second consisted of changes in statistical significance with identical mean values.

Section 4A. Figures with much larger error bars (Figure number relates to the final revision): Fig 1B left, Fig. 1B right, Fig 1E left, Fig 1E right, Figure 3B, Fig 3C left, Fig 3C right, Fig 3E left, Fig 3E right, Fig 4A, Fig 4B left, Fig 4B right, Fig 4D left, Fig 4D right, Fig 4D mid, Fig 4E left, Fig 4E right, Fig 4E mid, Fig 4F left, Fig 4F right, Fig 5A, Fig 5B left, Fig 5B right, Fig 5D left, Fig 5D right, Fig 5D mid, Fig 5E left, Fig 5E right, Fig 5E mid, Fig 5E right, Fig 5E mid, Fig 5F left, Fig 5F right, Fig 6A left, Fig 6A right, Fig 6C left, Fig 6C right, Fig 6E left.

[redacted] sent the committee an exhibit (exhibit G) containing a pdf file with real time polymerase chain reaction (RT-PCR) measurements of liver mRNA levels for ENT1 or 2 on 4-28-2015 (see Supplemental Material). Each of four panels from Fig. 1 included the plots from the paper (original version numbering), 5 individual data points per experiment, and the words "mean +/- SEM" for the original version or mean +/- SD for the final revision. SEM = SD/square root n. The panels included data from Figures 1B left, 1B right, 1E left, and 1E right from the original submission (1-2-2013) and final revisions (4-10-2013). In contrast to the JCI paper, none of the data points or sample size changed between versions; confirming that the mean values were identical. Extrapolated from this example it appears that something similar occurred for the other indicated figure panels.

[redacted] however, did not supply the committee with the original electronic files of these figure panels even after repeated requests.

Section 4A findings:

It appears that the respondents switched from use of standard error of the mean (SEM) in the original submission to standard deviation (SD) in the final revision. This appears to be a case of careless misuse of error bar calculations. In each case someone had to alter the original files from SEM to SD but did not change the text of the Methods section. ***The committee finds that this mistake was an honest error by [redacted] and/or the Respondents.***

Section 4B. New Evidence: Alterations in "p value" determinations of statistical significance between group means in the Hepatology paper.

Even though the group means of the graph panels identified in Section 4A were not altered, there were 23 instances of p value changes of statistical differences between group means. These will be described as follows and shown in Supplemental Material:

Fig. 3B. Comparison of liver adenosine immediately after 45 min ischemia. The means for bars 1 (-Ischemia, -DIP) and 3 (+Ischemia, -DIP) changed the p-value from <0.01 to <0.05. The p-value for bars 2 (-Ischemia, +DIP) and 4 (+Ishemia, +DIP) changed from <0.1 to <0.05.

Fig 3C left. Comparison of plasma aspartate aminotransferase (AST) levels for 45 min Ischemia, 2 hr reperfusion. The means for bars 3 (+Ischemia, -DIP) and 4 (+Ischemia, +DIP) changed the p-value from 0.01 to 0.05. The p-value for bars 2 (-Ischemia, +DIP) vs 4 (+Ischemia, +DIP) changed from not significant (n.s.) to <0.05.

Fig. 3E left. Comparison of AST levels for 45 min Ischemia, 24 hr reperfusion. The means for bars 1 (-Ischemia, -DIP) and 3 (+Ischemia, -DIP) changed the p-value from <0.01 to <0.001. The p-value for bars 2 (-Ischemia, +DIP) vs 4 (+Ischemia, +DIP) changed from <0.05 to <0.01. The p-value for bars 3 (+Ischemia, -DIP) vs 4 (+Ischemia, +DIP) changed from <0.05 to <0.01. P-values in all three alterations showed more statistical significance between the group means.

Fig. 3E right. Comparison of alanine aminotransferase (ALT) levels for 45 min Ischemia, 24 hr reperfusion. The means for bars 2 (-Ischemia, -DIP) and 4 (+Ischemia, +DIP) changed the p-value from n.s. to <0.01. This altered value now shows a rather large statistical significance with DIP treatment, a much different outcome than originally presented to reviewers.

Fig. 4A. Comparison of liver adenosine content following 45 min Ischemia in ENT1 null vs wt mice. The y-axis scale for the original submission is pmol/mg liver weight and the scale for the final version is nmol/g liver weight. These should be the same since there are 1000 pmol in a nmol and 1000 mg in a gram, yet the values for the bars are quite different (see Supplemental Material). The means of bars 1 (-Ischemia, wt) and 3 (+Ischemia, ENT1 null) changed the p-value <0.01 to <0.05. The p-value for bars 2 (-Ischemia, ENT1 null) and 4 (+Ischemia, ENT1 null) has been changed from <0.01 to <0.05. The p-value for bars 3 (+Ischemia, wt) and 4 (+Ischemia, ENT1 null) have changed from <0.05 to n.s. Each of these shows less of a statistical significance with these comparisons.

Fig. 4B right. Comparison of ALT levels in ENT1 null vs wt mice following 45 min liver ischemia followed by 2 hr reperfusion. The means for bars 3 (+Ischemia, wt) and 4 (+Ischemia, ENT1 null) changed the p value from <0.05 to <0.01. This results in a larger statistical difference than the graph seen by reviewers in the original submission.

Fig. 4E mid. Comparison of pulmonary myeloperoxidase MPO levels in ENT1 null vs wt mice after 45 min liver ischemia followed by 2 hr reperfusion. The means for bars 3 (+Ischemia, wt) and 4 (+Ischemia, ENT1 null) changed the p-value from <0.05 to <0.01. This change results in a larger statistical difference than the graph submitted to reviewers initially.

Fig. 4F left. Comparison of liver AST levels in ENT1 null vs wt mice after 45 min liver ischemia followed by 24 hr reperfusion. The means for bars 1 (-Ischemia, wt) and 3 (+Ischemia, wt) changed the p-value from <0.01 to <0.001. The means for bars 3 (+Ischemia, wt) and 4 (+ Ischemia, ENT1 null) changed the p-value from <0.05 to <0.001. Both of these alterations resulted in larger statistical differences of 10 fold to 50 fold over the initial submission.

Fig. 4F right. Comparison of liver ALT levels in ENT1 null vs wt mice after 45 min liver ischemia followed by 24 hr reperfusion. The means for bars 3 (+Ischemia, wt) and 4 (+ Ischemia, ENT1 null) changed the p-value from <0.05 to <0.01. This change results in a 5 fold increase in statistical significance than was shown initially to reviewers.

Fig. 5A. Comparison of liver adenosine content in ENT2 null vs wt mice measured immediately after 45 min ischemia. The means for bars 2 (-Ischemia, ENT2 null) and 4 (+Ischemia, ENT2 null) changed the p-value from <0.01 to <0.05. This result is a decrease in statistical significance.

Fig. 5E left. Comparison of pulmonary IFNγ content in ENT2 null vs wt mice after 45 min liver ischemia followed by 2 hr reperfusion. The means for bars 1 (-Ischemia, wt) and 2 (-Ischemia, ENT2 null) changed the p-value from <0.05 to n.s. The result is a decrease in statistical significance that now shows no difference between these genetically different groups of mice in the absence of ischemia.

Fig. 5E right. Comparison of pulmonary IL6 content in ENT2 null vs wt mice after 45 min liver ischemia followed by 2 hr reperfusion. The means for bars 2 (-Ischemia, ENT2 null) and 4 (+Ischemia, ENT2 null) changed the p-value from n.s. to <0.05. The means for bars 3 (+Ischemia, wt) and 4 (+Ischemia, ENT2 null) changed the p-value from 0.05 to n.s. One result increases the other decreases statistical significance.

Fig. 5F left. Comparison of AST levels in ENT2 null vs wt mice after 45 min liver Ischemia and 24 hr reperfusion. The means for bars 2 (-Ischemia, ENT2 null) and 4 (+ischemia, ENT2 null) changed the p-value from <0.001 to <0.01. This result decreases the statistical difference in the ENT2 null mice before and after ischemia. This is similar to the result in Fig 5A.

Fig. 6A left. Comparison of AST levels in ENT1 null treated with an Adora2a specific antagonist, ZM241385 after 45 min ischemia followed by 24 hr reperfusion. The means for bars 1 (-Ischemia, ENT1 null – ZM241385) and 3 (+Ischemia, ENT1 null -ZM241385) changed the p-value from <0.001 to <0.01. This decreases the statistical significance with ischemia in ENT1 null mice treated with the Adora2 antagonist.

Fig. 6A right. Comparison of ALT levels in ENT1 null treated with an Adora2a specific antagonist, ZM241385 after 45 min ischemia followed by 24 hr reperfusion. The means for bars 2 (-Ischemia, ENT1 null +ZM241385) and 4 (+Ischemia, ENT1 null +ZM24138) changed the p-value from n.s. to <0.05. This results in the presence of a statistical difference due to ischemia from no significance.

Fig 6C left. Comparison of AST levels in ENT1 null treated with an Adora2b specific antagonist, PSB1115 after 45 min ischemia followed by 2 hr reperfusion. The means for bars 1 (-Ischemia, ENT1 null – PSB1115) and 3 (+Ischemia, ENT1 null – PSB1115) changed the p-value from n.s. to <0.05. This results in the presence of a statistical difference due to ischemia from no significance.

The committee considered the following evidence in relation to the statistical changes in the Hepatology paper as defined in section 4B above:

- Testimony from [redacted] indicated that he was responsible for the histology images (testimony 11/21/2014: page 8, lines 3-10). He did some of the initial figures but [redacted] re-did them using graph prizm pro (testimony: page 32, lines 12-14).
- Review of [redacted] computer indicated that he stored TIF and JPG images of liver histology but no pzf files for this paper, which supports his assertion.
- [redacted] confirmed that she did end up creating a number of the figures for the paper (testimony of 6/11/2015: page 72, lines 24-25 and page 73, lines 1-3).

Section 4B findings relating to the Hepatology paper:
If the means and sample numbers between 2 groups does not change, statistical differences should not change because of a shift from standard error of the mean to standard deviation. There were 23 instances of this occurring in this manuscript. Regardless, 13 instances of the significance appearing to increase and 10 instances of it decreasing; none should have changed.

The committee makes a finding of no culpable research misconduct, but serious research error by [redacted] and/or the Respondents.

Conclusion:

The committee finds Dr. Grenz to have engaged in research misconduct with regard to falsification and/or fabrication relating to the JCI paper only.

Mitigating factors:

- The JCI paper used data collected over a significant period of time and the laboratory did not have good policies and procedures for the storage of data.
- Experimental protocols detailing how an experiment is to be conducted were poor or did not exist.
- There was no clear policy or expectation of how data was to be stored or analyzed.
- [redacted] was in her [redacted] at the time that the JCI was being submitted and was [redacted] at the time of the manuscript revisions.
- There was poor data management or version control for figures.
- The Principal Investigator was more concerned to ensure that data was aligned with his hypothesis.
- The Principal Investigator was out of the country at the time the paper was submitted and [redacted] submitted on his behalf but under his name.

Recommendations based on the findings of Research Misconduct by [redacted]
The Investigation Committee considers that the level of fabrication and falsification identified is substantive in the JCI paper but taking into account the mitigating factors detailed above makes the following recommendations:

1. [redacted] and all members of her current laboratory must undergo extensive training in the responsible conduct of research and this training should be updated every three years. The training program must include in-person training and any proposed training program must be approved and reviewed by the RIO.
2. An independent oversight committee, which should include at least one biostatistician, should be established to review all original data and corresponding lab notebooks to ensure that it has been analyzed appropriately and the figures appropriately labelled before a manuscript is submitted for publication by [redacted]. Any changes to the manuscript must also be reviewed by this committee as well as all co-authors. A similar review of data should be conducted by this independent oversight committee prior to any grants being submitted from [redacted] laboratory to any funding agency. The oversight committee that is appointed should provide written confirmation to the Dean of the School that they have verified the validity of all the data included in manuscript and grant submissions on which [redacted] is an author or co-author. This oversight committee should perform these roles for at least three years.

3. The Investigation Committee is concerned and seeks assurances from [redacted] that she develop detailed policies and procedures that outline how data is stored in her laboratory. In addition, [redacted] should develop protocols for specific experiments and any deviations from that procedure documented. [redacted] should work with a biostatistician to ensure that all her experiments have an appropriate data analysis plan.
4. The Investigation Committee recommends that [redacted] not be permitted to employ or supervise any graduate or post-doctoral students in her laboratory for a period of 3 years.
5. The Investigative Committee recommends that [redacted] and her laboratory members include all relevant mouse identification data in laboratory notebooks and in computer files used to analyze and present laboratory results. Furthermore, the committee recommends that every identified mouse in future experiments be linked to each data point or histology image included in the results section of published papers or grant applications. Data should include eartag numbers (if provided), birth dates, sex, genetic strain information of transgenic or wild type mice, dates of surgery, and any problems that may have occurred during the procedure. Data points considered outliers should have a justifiable valid reason for their exclusion.

Recommendations relating to publications:

[redacted], *Journal of Clinical Investigation* (hereafter JCI-2012), 122:693-710, 2012. - recommended for **retraction**

[redacted] and [redacted] 2013. *Hepatology* 58:1766-1778, 2013. - recommended for **retraction**

[redacted] *Proceedings of the National Academy of Sciences* USA. 110L12012-12017, 2013. - recommended for **correction**

[redacted] *Journal of Immunology* 189:4566-4573, 2012. – recommended for **correction or retraction** in consultation with the corresponding author.

[redacted] *Nature Immunology*. 10:195-202, 2009. This paper was not under the jurisdiction of this committee as all the data was collected external to the University of Colorado Denver. A correction was requested and granted by the journal as an Erratum published in: Nature Immunology. 16:544, 2015.

Recommendations relating to grants:

1. JCI 2012:

   The research was conducted under:
   NIH grant support: DK081646 to [redacted]
   DFG (Deutsche Forschungsgemeinschaft) Research Fellowship grant (GR2121/1-1) to [redacted]
   American Heart Association grant to [redacted]
   National Heart Institute grants RO1-HL092188, RO1-DK083385, RO1-HL098294 to [redacted]
   Grant from the Crohn's and Colitis Foundation of America (CCFA) to [redacted]

   The committee determined that the funded NIH grant (R01 DK098337): Purinergic Signaling during Acute Kidney Injury., P.I. [redacted], used 12 figures from the [redacted] et al., 2012 paper. The primary data used for the results and conclusions could not be verified by the committee. (See Appendix D).

   Each of the funding agencies should be contacted to advise them of the findings of this

investigation.

2. Hepatology 2013:
The research was conducted under NIH grant support: Mentored Clinical Scientist Development Award to [redacted] KO8HL103900-01;
National Health Institute Grants RO1 DK097075, RO1-HL0921, RO1-DK083385, RO1-HL098294, and POIHL114457-01; and a grant by the Crohn's and Colitis Foundation of America to [redacted]. Funding from the Juvenile Diabetes Foundation and an American Heart Association to [redacted]

Each of the funding agencies should be contacted to advise them of the findings of this investigation.

3. PNAS 2013:
The research was conducted under NIH grant support: Mentored Clinical Scientist Development Award to [redacted] KO8HL103900-01;
National Health Institute Grants RO1 DK097075, RO1-HL0921, RO1-DK083385, RO1-HL098294, and POIHL114457-01; and a grant by the Crohn's and Colitis Foundation of America to [redacted]

Funding agencies do not need to be contacted regarding the work conducting in relation to this paper.

4. Journal of Immunology 2012:
The research was conducted under NIH grant support: National Heart Institute grants RO1-HL092188, RO1-DK083385, RO1-HL098294; and a grant from the Crohn's and Colitis Foundation of America (CCFA) to [redacted]
Funding from the Juvenile Diabetes Foundation and the American Heart Association to [redacted]

Funding agencies do not need to be contacted regarding the work conducted in relation to this paper.

5. Nature Immunology 2009.
The research was conducted using funding support from the University of Tubingen Fortune grants 1639-0-0 to [redacted] and 1778-0-0 to [redacted], Deutsche Forschungsgemeinschaft (FL 274/2-1 to [redacted] and EL 274/2-1 and RO3671/2-1 to [redacted] and Foundation for Anesthesia Education and Research to [redacted]

Funding agencies do not need to be contacted regarding the work conducted in relation to this paper.

Additional information relating to the forensic analysis of data:

Appendix A – Side by side comparison of JCI figures

Appendix B – Side by side comparison of Zimmerman et al. Hepatology 2013

Appendix C – American Society of Nephrology poster

Appendix D – NIH Grant RO1 DK098337-01

Review of the Respondent's response to the draft investigation report:

[redacted] received the draft report and supporting evidence on July 22nd, 2016. Her lawyer requested an extension that Dean Reilly, the Deciding Official, [redacted] On 9/24/16, [redacted] responded to the draft investigation report. This response was sent to the committee members on 9/25/16 for their consideration.

On 10/10/16, the Investigation Committee met to consider the response by [redacted]

1. The committee considered the material that [redacted] provided but noted that there was no new scientific data provided. The committee was concerned that the e-mail exchanges provided in the various exhibits to this response were not on any of the computers sequestered by the RIO at the beginning of the inquiry, nor provided to the committee when previously requested. It is highly unusual and concerning that emails/documents regarding this case are only now provided nearly three years after this process began.
2. The committee also noted that the e-mail exchange (Exhibit E) indicated that [redacted] requested that a manuscript folder be established. This email was not previously provided and this information was not previously shared. After numerous inquiries and searches by the committee, this alleged folder was never located or even referenced by anyone in their testimony. It is apparent that no one in the lab complied with this request. It was also noted that [redacted] did not follow up to ensure compliance with the request.
3. The committee discussed [redacted] concern that the JCI paper was held to a different standard than the other papers. The committee was able to identify that [redacted] did have a role in the Hepatology, PNAS and Journal of Immunology paper but because neither she nor any other person in the lab was able to produce the data, it was not possible to establish who was actually responsible for the changes of concern or to determine if the data was manipulated. While the actual finding regarding these publications was honest error, the investigation committee is extremely concerned at the lack of data. This inability for anyone to provide or identify the underlying data supporting these papers led to the recommendation of retraction.
4. [redacted] was asked to provide additional information in an e-mail dated 2/23/15 in which she was asked to address discrepancies identified based on a comparison of figures identified by the investigation committee between the initial and final draft of the manuscripts sent to the JCI. A formal response by [redacted] was received on April 1, 2015 to these concerns. Consequently, the committee does not find [redacted] allegations that she was unaware that the committee was reviewing additional issues in the JCI paper to be credible.
5. The response from the attorney for [redacted] did not address the comments made to the committee by [redacted] when she admitted (6/11/2015) that she submitted the manuscript to the JCI knowing that the parallel control experiments for the histology figures in question in the JCI paper had not be performed, and the images were not available, so she substituted images from another source. (page 65, lines 18-25).

Conclusion:

The Investigation Committee determined that the information provided by [redacted] did not change any of the findings outlined in the initial draft report dated 5/16/16. Therefore, the findings outlined above become the final findings and recommendations of the committee to Dean Reilly, Deciding Official for this case.

Chair, Investigation Committee, affirms the accuracy of this report:

Signed by: [redacted] **Date:** 10/17/16

Also Affirmed by the additional members of the Investigation Committee:

Signed by: [redacted] **Date:** 10/18/16

Signed by: [redacted] **Date:** 10/18/2016

Signed by: [redacted] **Date:** 10/24/2016

Signed by: [redacted] **Date:** 10/24/2016