Pages 2-76
Final report concerning allegations of research misconduct

Pages 77-82
The Weinberg Group investigational new drug (IND) assessment

THE OHIO STATE UNIVERSITY

Final Report of the College of Pharmacy Investigation Committee Concerning Allegations of Misconduct in Research under the University Policy and Procedures Concerning Research Misconduct

September 12, 2017

Introduction

The College of Pharmacy Investigation Committee (the "Committee") was formed on February 15, 2017 under the University Policy and Procedures Concerning Research Misconduct to address allegations made against University Professor and Lucius A. Wing Chair of Cancer Research and Therapy, Dr. Ching-Shih Chen, Department of Medicinal Chemistry and Pharmacognosy, College of Pharmacy (Respondent) by an anonymous complainant. Pursuant to the Policy, the Committee conducted a formal investigation under University Rule 3335-5-04 with respect to the allegations of falsification of research made against Ching-Shih Chen (Respondent) by an anonymous complainant emailed to the Ohio State University Office of Research. The allegations noted irregularities in figures contained in six (6) manuscripts indicating potential fabrication and falsification of research by image manipulation in the referenced manuscripts published during the time period between 2010 and 2014, supported by funding agencies as noted below:

1. Guh *et al.*, J Med Chem 2010. 53, 2552–2561

Jih-Hwa Guh, Wei-Ling Chang, Jian Yang, Su-Lin Lee, Shuo Wei, Dasheng Wang, Samuel K. Kulp, and Ching-Shih Chen (2010). Development of Novel Adenosine Monophosphate-Activated Protein Kinase Activators. J. Med. Chem. 2010, 53, 2552–2561.

Funding: National Institute of Health National Institute CA112250 and the Lucius A. Wing Endowed Chair Fund

2. Lee *et al.*, PLOS ONE 2013. 8; 6, e67149

Su-Lin Lee, Chih-Chien Chou, Hsiao-Ching Chuang, En-Chi Hsu, Po-Chen Chiu, Samuel K. Kulp, John C. Byrd, Ching-Shih Chen (2013). Functional Role of mTORC2 versus Integrin-Linked Kinase in Mediating Ser473-Akt Phosphorylation in PTEN Negative Prostate and Breast Cancer Cell Lines. PLOS ONE, Volume 8, Issue 6, e67149

Funding: National Cancer Institute (NCI) R01CA112250, the Stefanie Spielman Fund for Breast Cancer Research (to C.S.C), and a Specialized Center of Research grant from the Leukemia and Lymphoma Society (to C.S.C. and J.C.B.)

3. Chu *et al.*, Carcinogenesis 2013. 34; 12, 2694–2705

Po-Chen Chu, Samuel K. Kulp, and ChingShih Chen (2013). Insulin-like growth factor-I receptor is suppressed through transcriptional repression and mRNA destabilization by a novel energy restriction-mimetic agent. Carcinogenesis vol.34 no.12 pp.2694–2705

Funding: National Institutes of Health R01CA112250 (to C.-S.C.)

4. Lai *et al.*, Carcinogenesis 2014. 35;10, 2203–2213

I-Lu Lai, Chih-Chien Chou, Po-Ting Lai, Chun-Sheng Fang, Lawrence A.Shirley, Ribai Yan, Xiaokui Mo, Mark Bloomston, Samuel K. Kulp, Tanios Bekaii-Saab, and Ching-Shih Chen* (2014). Targeting the Warburg effect with a novel glucose transporter inhibitor to overcome gemcitabine resistance in pancreatic cancer cells. Carcinogenesis vol.35 no.10 pp.2203–2213.

Funding: National Institutes of Health (R01CA112250 to C.-S.C.); The Lucius A. Wing Chair of Cancer Research and Therapy (to C.-S.C.); OSUCCC Pancreas Cancer Research Program grant (to T.B.-S.); Pelotonia Fellowship Program (to I.-L.L.)

5. Chou *et al.*, Cancer Res 2014. 74; 17, 4783–4795

Chih-Chien Chou, Kuen-Haur Lee, I-Lu Lai, Dasheng Wang, Xiaokui Mo, Samuel K. Kulp, Charles L. Shapiro, and Ching-Shih Chen (2014). AMPK Reverses the Mesenchymal Phenotype of Cancer Cells by Targeting the Akt–MDM2–Foxo3a Signaling Axis. Cancer Res 74; 4783.

Funding: NIH grants R01 CA112250 and R21 158807, the Stefanie Spielman Fund for Breast Cancer Research, and the Lucius A. Wing Endowed Chair Fund at The Ohio State University Medical Center (C.-S. C.), and a Pelotonia Postdoctoral Fellowship (The Ohio State University Comprehensive Cancer Center; I.-L. Lai)

[redacted]

Preliminary Assessment Summary[1]

During the Preliminary Assessment on March 1, 2016, it was determined that the allegations regarding Manuscripts #1-#5 may indicate possible research misconduct. Therefore, it was recommended the Institution proceed to a Committee of Initial Inquiry. At this time, it was noted that Dr. Chen was a middle author on Manuscript #6, [redacted], and was the only author with an Ohio State affiliation (past or present). Dr. Chen stated that his involvement in the publication was limited to the design of the HDAC inhibitor being studied in the publication. Dr. Chen stated that he made no contribution to the design of the experiments and played no part in generating data or figures for the paper. As such, the investigation of possible research misconduct associated with this manuscript was determined to not be under the purview of The Ohio State University and was excluded from the scope of all future proceedings.

Sequestration of Data Summary[2]

Directly following the notification of the allegations to Dr. Chen on March 9, 2016, Dr. Jennifer Yucel and Ms. Courtney Mankowski went with Dr. Chen to his laboratory to sequester all relevant research records. Dr. Yucel reported that original research records for many of the images were not present in the lab. Dr. Chen indicated that most members of the lab took their records with them when they left the lab. In some cases, Dr. Chen indicated that there were no laboratory notebooks kept by members of the lab, rather individuals only had weekly progress reports and no daily records of the experiments they conducted. Dr. Yucel did sequester some physical records belonging to former lab members [redacted], [redacted], and [redacted]. During the sequestration, Dr. Chen contacted a number of previous lab members requesting that they send any data that they have relating to the figures to the university. Dr. Chen did forward a number of electronic data files to Dr. Yucel on March 9 and March 10 received from previous lab members no

[1] ATT 1 - 20160329 - Preliminary Assessment – Chen.pdf
[2] ATT 2 - 20160309 - Data Sequestration Sheet.docx

longer at the university.[3] With the assistance of the College IT group, reviews of the college server and desktop computers within the lab space confirmed the absence of any relevant saved records of Dr. Chen's laboratory staff. The College IT director did find electronic files for [redacted] and Dr. Chen on the college's file server and a forensic image of those files was obtained. In addition, Dr. Chen's personal laptop was forensically imaged along with an external backup drive used by Dr. Chen.

Committee of Initial Inquiry Summary[4]

A Committee of Initial Inquiry ("Committee") was formed on April 4, 2016. During their inquiry, they reviewed manuscripts #1-#5 as listed above, interviewed Dr. Chen and Dr. I-Lu Lai, co-author on manuscripts #4 and #5. During the interview, Dr. Chen stated repeatedly that the images were provided to him by students or postdoctoral researchers and that he simply arranged them into the final figures. On November 14, 2016, the Committee of Initial Inquiry found under the preponderance of evidence standard, by a unanimous vote, that the allegations of Research Misconduct (falsification/fabrication) against Dr. Chen had sufficient substance to warrant investigation under the Policy. The allegations were:

> **1. Guh *et al.,* J Med Chem 2010. 53, 2552–2561**: Duplicate images used in Fig 6C for the Western blots of AMPK, lanes 3 and 5, and p70S6K, lanes 2-4 and 5-7.
>
> **2. Lee *et al.,* PLOS ONE 2013. 8; 6, e67149:** Duplicate images used in Fig 3A for the Western blots of MK2 (lanes for Scr and ILK (rotated 180 degrees); Rictor and Pak1 (rotated 180 degrees) and for the Pak1 western blot (lanes for Scr and ILK (rotated 180 degrees), Rictor and DNA-PK, ATM and PKCBII).
>
> **3. Chu *et al.,* Carcinogenesis 2013. 34; 12, 2694–2705:** Duplicate images used in Fig 1A for the Western blots for p-473Ser-Akt, 2DG (mM), 48hr 10uM and Glucose Starvation 72 hr samples; duplicate images used in the Western blots for SP1 in Fig 2A and Fig 2F; and possible splicing of data into Fig 8A for the anti-FLAG Western blot lanes 4 and 5.
>
> **4. Lai *et al.,* Carcinogenesis 2014. 35; 10, 2203–2213:** Duplicate images used in Fig 1D for the Western blots lanes 1 and lane 6; irregular background and/or

[3] ATT 3 - Summary_Manuscripts 3&4_Email v. Sequestered Files
[4] ATT 4 - 20161114 - CII Final Report – Chen.pdf

possible duplicate images used in Fig 5A for the Western blots for pAKT, lanes 5 and 7.3 uM CG-5, and gamma-H2AX, lanes 5 and 7 uM CG-5.

5. Chou *et al.,* Cancer Res 2014. 74; 17, 4783–4795: Duplicate images used in Fig 3B for the RT-PCR gels representing Snail (MDA-MB-231), YB-1 (PC-3) and E-Cadherin (PC-3) rotated 180 degrees from the other two images

College of Pharmacy Investigation Committee

The College of Pharmacy Investigation Committee reviewing the matter regarding Dr. Chen included the following Ohio State University faculty:

- Dr. Alex Sparreboom (Chair), Professor, Pharmaceutics and Pharmaceutical Chemistry, College of Pharmacy
- Dr. Rajgopal Govindarajan, Associate Professor, Pharmaceutics and Pharmaceutical Chemistry, College of Pharmacy
- Dr. Karin Musier-Forsyth, Ohio Eminent Scholar, Professor, Chemistry and Biochemistry, College of Arts and Sciences

College of Pharmacy Investigation Committee Meetings:

The Investigation Committee met for meetings on the following dates:

- **03/29/17:** Dr. Behnfeldt presented "Forensic Image Analysis-Chen-JB.ppt", "Forensic Image Analysis Introduction.ppt", and "Hard Drive Exhibit Summary-Chen". The chair of the committee was determined (Alex Sparreboom). Dr. Yucel discussed the process and timeline of the investigation.
- **04/11/17:** Dr. Behnfeldt presented "Hard Drive Exhibit Summary 2-Chen.ppt" Committee discussed each member reviewing specific figures and then meeting with ORC team members to discuss their own independent findings and to look at the sequestered raw data.
- **04/25/17:** Investigation Committee members only meeting to independently review the sequestered data.
- **05/01/17:** Investigation Committee members only meeting to independently review the sequestered data. The members requested additional forensic analysis.
- **05/08/17:** Dr. Behnfeldt presented "Committee Requested Forensics 5.1.17.ppt" The committee discussed new allegations discovered during the review and the process of informing the Respondent of the new allegations.

- **05/17/17:** Dr. Behnfeldt and Dr. Yucel discussed new allegation written memo to be delivered to Dr. Chen (on 05/19/17). The Investigation Committee prepped for the interview with Dr. Chen, scheduled for 06/01/17.
- **06/01/17:** Dr. Chen, his counsel, Mr. David Ball, Dr. Yucel, Dr. Behnfeldt and Ms. Emily Schriver met for a court-transcribed statement that the Respondent requested in lieu of the interview. The Investigation Committee was not present.
- **06/22/17:** The Investigation Committee reviewed the statement given by Dr. Chen on 06/01/2017 and discussed the next steps in the process with Dr. Yucel and Dr. Behnfeldt.
- **08/02/17:** The Investigation Committee reviewed the new allegations for Manuscripts #7-#14 and reviewed responses provided by Dr. Chen on August 2, 2017 and August 3, 2017.
- **09/08/17:** The Investigation Committee met to review and discuss Dr. Chen's response to the Preliminary Report on September 1, 2017.

Research Records and Evidence

All research records generated for the manuscripts in question, located at The Ohio State University, were sequestered as described on March 9, 2016 or March 10, 2016.[5]

Dr. Chen provided the additional data via email on the dates listed below:

December 23, 2016[6]:

1. "Corrected Fig 1D.tif"
2. "Corrected Fig 5A.tif"
3. "Corrigendum Lai et al Carcinogenesis 35(10) 2203-2213, 2014.pdf"
4. "WB images for corrected Fig. 1D.pdf"
5. "WB images of corrected Fig. 5A.pdf"

January 1, 2017[7]:

1. "[redacted]

May 30, 2017[8] **(previously sent March 9, 2016):**

1. "Fig.1A 2-DG & glucose starvation p-Ser473-Akt.tiff"

[5] ATT 1- 20160329 - Preliminary Assessment – Chen.pdf
[6] ATT 5- 20161223 - Email Chen to RIO - corrigendum manuscript #4.pdf
[7] ATT 6- 20170111 - Email Chen to RIO - Information for Investigation.pdf
[8] ATT 7- 20170530 - Email #2 Chen to RIO - allegation #5.pdf

2. "Fig.8A Lane1 - Lane5.tiff"
3. "Fig.8A Lane6-Lane7 (4 different conditions of PCR results to make sure the negative result of lane 6 and lane 7).tiff"

Dr. Julia Behnfeldt, Research Integrity Officer, performed an additional review of the sequestered lab notebook materials and laptop (232.03GB) belonging to Dr. Chen and provided the following original autoradiography Western blot films and copies of hard drive files to the Investigation Committee:

Autoradiography Western blot films added to the record:

1. [redacted] Exhibit 1I
2. [redacted] Exhibit 1J
3. [redacted] Exhibit 1K
4. [redacted] Exhibit 1L
5. [redacted] Exhibit 1M
6. [redacted] Exhibit 1N

Hard drive files added to the record:

Manuscript #1 - Guh *et al.,* J Med Chem 2010. 53, 2552–2561

1. "Cpd 1-60 Western blots.cdx (date 08/09/2009, time 10:28)
2. "Cdc 1-60 Western blots.cdx" (date 08/09/2009, time 11:06)
3. "xFig2.tiff" (date 10/30/2009)
4. "Fig.3.cdx" (date 11/30/09)
5. "Fig.6.cdx" (date 01/16/10)
6. "Cpd 53 p-AMP P-p70SK6.pdf" (date 10/28/09)
7. "Fig.5.tiff" (date 11/30/09)
8. "Fig.6.cdx" date 01/16/10)
9. "Fig.6.tif" date 01/23/10)
10. "Fig-Cachaxie dose n time dependent 2.jpg" (date 11/01/09)
11. "Fig.5.cdx" (date 11/1/09)
12. "Fig. 5.jpg" (date 11/30/09)

Manuscript #2 - Lee *et al.,* PLOS ONE 2013. 8; 6, e67149

1. "PDK2 Page 2.pdf (date 11/10/11 9:39pm)"
2. "PDK2 Page 2.jpg (date 11/10/11 10:02pm)"
3. "081612 progress report.ppt" (date 08/16/12)
4. "siRNA knockdown PDK2.jpg" (date 07/25/12)
5. "Fig.3.tiff" (date 12/04/12)
6. "PDK Page 5.pdf" (date 11/10/11 7:53pm)

7. "PDF Page 5.jpg" (date 11/10/11 8:53pm)

Manuscript #3 - Chu *et al.,* Carcinogenesis 2013. 34; 12, 2694–2705

1. "Fig-1-merged.jpg" (date 10/30/11)
2. "Summary of Po-Chen data.ppt" slide 2, (date 6/5/12)
3. "IGF-IR P13K Akt Western PCR data.jpg" (date 6/6/12)
4. "xFig.1cdx (date 9/10/2012)
5. "Summary of Po-Chen data.ppt" slide 1,2,3 (date 06/05/2012)
6. "Fig. 4D Hur RRM 123 IGF-1R 3' UTR-5 RNA-IP.jpg" (date 9/9/12)
7. "Hur deletion RRM RNA IP TR-PCR 2.tif" (date 12/15/2012)
8. "Fig.8.pdf" (date 7/3/2013)

Manuscript #4 - Lai *et al.,* Carcinogenesis 2014. 35;10, 2203–2213

1. "RRM2 data.ppt" (date 2/3/12)
2. "Akt data [1].ppt" (date 2/6/12)
3. "Akt data-Akt.pdf" (2/6/12)
4. "NTUH 010412.ppt" (date 1/3/12)
5. "Fig.1.pdf" (date 1/16/14)
6. "H2Ax in panc1.pdf" (date 2/10/12)
7. "H2Ax in panc1.jpg (date 2/14/16)

The Investigation Committee performed an independent review of the sequestered lab notebooks and added the following original autoradiography Western blot films to the record:

1. [redacted] Exhibit 1G
2. [redacted] Exhibit 1H

Notification of Additional Allegations[9]:

The College Investigation Committee, through their review of the data and case materials, identified seven (7) new additional allegations of potential research misconduct, not present in the original allegations, nor identified in the inquiry phase. On the basis of the College Investigation Committee's review, they concluded that the new allegations may indicate possible Research Misconduct as defined in Section III of the Policy and added them and/or expanded them to/within the eight (8) allegations outlined in the CII Final Report, dated 11/14/2016, bringing the total number of alleged manipulated figures to thirteen (13).

[9] ATT 8- 20170519- Notification of New Allegations-DIO 6144.pdf

On May 19, 2017, Dr. Chen was notified of the additional allegations of possible research misconduct in a written notice per 42 C.F.R. § 93.310 (c), which are listed below:

Manuscript #1 – Guh *et al.,* J Med Chem 2010. 53, 2552–2561

- New Additional Allegation #1 – Western blot data were falsified by replacing two bands (for compounds labeled 8 and 49) of the p-AMPK and p-p70S6K blots of Figure 4A with unidentified, darker bands (p-AMPK) or lighter bands (p-p70S6K) when compared to the original research record.
- New Additional Allegation #2 – Western blot data were falsified by falsely labeling the p-p70S6K blot of Figure 7C as being treated with compound 53 when compared to the original research record.

Manuscript #2 – Lee *et al.,* PLOS ONE 2013. 8; 6, e67149

- New Additional Allegation #3 – Western blot data were falsified by replacing the p70S6K blot and β-actin blot with unidentified blots and by falsely labeling the Akt blot of Figure 1B when compared to the original research record.
- New Additional Allegation #4 – Western blot data were falsified by falsely labeling the p308-T-Akt, ILK, Akt and β-actin blots as being treated with or without Ku-0063794 and/or ILK siRNA of Figure 3B when compared to the original research record.

Manuscript #3 – Chu *et al.,* Carcinogenesis 2013. 34; 12, 2694–2705

- New Additional Allegation #5 – In addition to previously noted allegedly falsified Western blot data, the PCR data were also falsified and/or fabricated in Figure 8A when compared to the original research record.

Manuscript #4 – Lai *et al.,* Carcinogenesis 2014. 35; 10, 2203–2213

- New Additional Allegation #6 – Western blot data were falsified by falsely labeling the experiment conditions of the entire composite figure, falsely labeling the E2F1 and RRM2 blots and splicing together single bands from different experimental conditions to generate the p-Akt and gamma-H2AX blots of Figure 5A when compared to the original research record.

Manuscript #5 – Chou *et al.,* Cancer Res 2014. 74; 17, 4783–4795

- New Additional Allegation #7 – Western blot data were falsified by reusing and falsely relabeling the ACC blots in samples from MDA-MB-231 cells and those from PC-3 cells of Figure 2A when compared to the original research record.

Statement before the Office of Research Compliance

On May 30, 2017, Dr. Chen's counsel, Mr. David Ball, contacted Dr. Yucel, Dr. Behnfeldt and Ms. Emily Schriver, Associate General Counsel, Office of Legal Affairs, to indicate that Dr. Chen would like to give an admission statement on his involvement with the alleged research misconduct and discuss a possible Voluntary Settlement rather than proceed with the scheduled Investigation Committee Interview.[10] Following this email, Dr. Chen personally emailed to Dr. Yucel a document "Comments to CIC" containing his explanations for six (6) of the seven (7) new allegations.[11] Upon receipt and review, Dr. Yucel responded to Dr. Chen and explained that if Dr. Chen was "*not intending to provide an admission of intentional falsification of the figures contained in the entire set of allegations, then we will need to continue with the normal investigation process and we will proceed with conducting your interview with the investigation committee on Thursday."*[12]

In his response to Dr. Yucel, Dr. Chen clarified that the provided "Comments to CIC" document was not intended to be his basis for a voluntary settlement and confirmed

[10] ATT 9- 20170530 - Ball to RIO GC Statement.pdf
[11] ATT 10- 20170530 - Chen to RIO CIC Comments.pdf
[12] ATT 11- 20170530 - RIO to Chen Statement Requirements.pdf

he would "*discuss my role as to all the allegations*" in the statement meeting scheduled for Thursday, June 1, 2017.[13]

On June 1, 2017, Dr. Chen, his counsel Mr. David Ball, Dr. Yucel, Dr. Behnfeldt and Ms. Emily Schriver met for Dr. Chen's statement, which was court recorded and transcribed.[14] Dr. Chen presented his previously emailed "Comments to CIC." Prior to the start of the court recording it became apparent that Dr. Chen was not going to make a full admission statement. Therefore, Dr. Yucel and Dr. Behnfeldt presented Dr. Chen with the "ORC Slide Deck Full - 6.1.17" presentation, which included forensic analysis on each of the allegations and walked through the entire presentation.[15]

Overall, Dr. Chen stated that he was responsible for the falsification of "some" things but that he often just published what was sent to him from his students.[16]

> DR. CHEN: "*But as I pointed out, many of the allegations were not of my making either. So I'm responsible for the falsification for some of them, but in many other cases, I just followed what my group member presented to me."* (Page 76, lines 3-7)

Dr. Chen's specific response for each of the allegations can be found within the section, "Investigation Committee Analysis."

Notification of Additional Allegations #2[17]

During their review, the Office of Research Compliance (ORC) and the College Investigation Committee identified eight (8) new additional allegations of potential research misconduct in eight (8) new manuscripts, not present in the original allegations, nor identified in the inquiry phase, nor in the notification of new allegations memo sent

[13] ATT 12- 20170530 Chen to RIO Statement Confirmation
[14] ATT 13- 170601-OSU-Interview-JCB-PL CSC.pdf
[15] ATT 14- ORC Slide Deck Full - 6.1.17.pdf
[16] ATT 13- 170601-OSU-Interview-JCB-PL CSC
[17] ATT 15- 20170721- Notification #2 of new allegations.pdf

on May 19, 2017. On July 21, 2017, Dr. Chen was notified of the additional allegations of possible research misconduct in a written notice per 42 C.F.R. § 93.310 (c), which are listed below: (Note that manuscript numbering is sequential to previous manuscripts identified.)

Manuscript #7 – Kulp *et al.,* Clin Cancer Res 2006. 12; 17, 5199-5206
Samuel K. Kulp, Chang-Shi Chen, Da-Sheng Wang, Ching-Yu Chen, and Ching-Shih Chen (2006). Antitumor Effects of a Novel Phenylbutyrate-Based Histone Deacetylase Inhibitor, (S)-HDAC-42, in Prostate Cancer. Clinical Cancer Res 12(17):5199-5206.
Funding: CA94829 and CA112250, and by a grant from the William Randolph Hearst Foundation to C-S. Chen.

- *New Additional Allegation #1 - Western blot data were falsified by falsely labeling the concentration of (S)-HDAC-42 and the cell type in Figure 4A when compared to the original research record.*

Manuscript #8 – Wang *et al.,* J Med Chem 2012. 55, 3827-3835
Dasheng Wang, Po-Chen Chu, Chia-Ning Yang, Ribai Yan, Yu-Chung Chuang, Samuel K. Kulp, and Ching-Shih Chen (2012). Development of a Novel Class of Glucose Transporter Inhibitors. J Med Chem 55, 3827−3836.
Funding: CA112250 and Department of Defense Prostate Cancer Research Program Grant W81XWH-09-0198 (to C.-S.C.) and by Ministry of Economic Affairs (Taiwan) Grant 99-EC-17-A- 17-S1-152 (to C.-N.Y.).

- *New Additional Allegation #2 - Western blot data were falsified by falsely labeling the p-AMPK blot in Figure 4C when compared to the original research record.*

Manuscript #9 – Zhu *et al.,* Cancer Res 2004. 64, 4309-4318
Jiuxiang Zhu, Jui-Wen Huang, Ping-Hui Tseng, Ya-Ting Yang, Joseph Fowble, Chung-Wai Shiau, Yeng-Jeng Shaw, Samuel K. Kulp, and Ching-Shih Chen (2004). From the Cycloxygenase-2 Inhibitor Celeoxib to a Novel Class of 3-Phosphionositide-Dependent Protein Kinase-1 Inhibitors. Cancer Res 64, 4309-4318.
Funding: CA94829, Army Grant DAMD17-02-1-0117

- *New Additional Allegation #3 - Splice line in left panel (PC-3) cells Western blot between lanes 3 and 4 in Figure 7B*

Manuscript #10 – [redacted]

- *New Additional Allegation #4 - Splice lines between lanes 1 and 2 in the BIM blot and between lanes 3 and 4 in the GAPDH blot of Figure 4.*

Manuscript #11 – Weng *et al.*, Mol Cancer Ther 2008. 7, 800-808
Shu-Chuan Weng, Yoko Kashida, Samuel K. Kulp, Dasheng Wang, Robert W. Brueggemeier, Charles L. Shapiro, and Ching-Shih Chen (2008). Sensitizing estrogen receptor-negative breast cancer cells to tamoxifen with OSU-03012, a novel celecoxib-derived PDK-1/Akt signaling inhibitor. Mol. Cancer Ther 7, 800-808.
Funding: Susan G. Komen Foundation research grant BCTR0504187 (C-S. Chen)

- *New Additional Allegation #5 - Falsification/fabrication and falsely labeling of Figure 4A and 4B compared to the original research record.*

Manuscript #12 – Chen *et al.*, Cancer Res 2007. 76; 11, 5318-5327
Chang-Shi Chen, Yu-Chieh Wang, Hsiao-Ching Yang, Po-Hsien Huang, Samuel K. Kulp, Chih-Cheng Yang, Yen-Shen Lu, Shigemi Matsuyama, Ching-Yu Chen, and Ching-Shih Chen. (2007). Histone Deacetylase Inhibitors Sensitize Prostate Cancer Cells to Agents that Produce DNA Double-Strand Breaks by Targeting Ku70Acetylation. Cancer Res 67(11):5318-5327.
Funding: CA112250 and Department of Defense Prostate Cancer Research Program grant W81XWH-05-1-0089, William R. Hearst Foundation and Prostate Cancer Foundation awards

- *New Additional Allegation #6 - Falsification of two Western blots in Figure 2B and 2C by falsely labeling the dosage of HDAC42 used when compared to the original research record.*

Manuscript #13 – Lu *et al.*, Hepatology 2007. 46, 1119-1130
Yen-Shen Lu, Yoko Kashida, Samuel K. Kulp, Yu-Chieh Wang, Dasheng Wang, Jui-Hsiang Hung, Monica Tang, Zhong-Zhe Lin, Te-Jung Chen, Ann-Lii Cheng, and Ching-Shih Chen. (2007). Efficacy of a Novel Histone Deacetylase Inhibitor in Murine Models of Hepatocellular Carcinoma. Hepatology 46:1119-1130.
Funding: CA112250, grant from the William R. Hearst Foundation, and by the Lucius A. Wing Chair Fund of The Ohio State University Medical Center

- *New Additional Allegation #7- Falsification of a Western blot in Figure 4D by falsely labeling the protein examined when compared to the original research record.*

Manuscript #14 – [redacted]

- *New Additional Allegation #8 - Falsification of Western blot data in Figure 4 by the reuse of three (3) loading control beta-actin.*

On the basis of the College Investigation Committee's review, they concluded that the new allegations may indicate possible Research Misconduct as defined in Section III of the Policy and added them and/or expanded them to the eight (8) allegations previously outlined in the CII Final Report, dated November 14, 2016, and the seven (7) allegations previously outlined in the Notification Memo of New Allegations, dated May 19, 2017, bringing the total number of manuscripts to fourteen (14) and allegations to twenty-one (21). The files listed below were located on Dr. Chen's hard drive and directly relate to the new allegations and new manuscripts and were added to the record:

Manuscript #7 - Kulp et al Clin. Cancer Res. 2006 12(17):5199-5206
"HDACs in U87 and PC3.ppt", date (05/12/2005)
"pAkt-HDAC42&SAHA.tif", (date: 02/02/2006)
"(S)-HDAC-42 Summary Report.pdf", (date: 02/28/2007)

Manuscript #8 - Wang et al J Med Chem 2012 55, 3827−3836
"CG-5 CF3 48h western.tif" (date: 08/27/2011)
"xFig.4.pdf" (date 10/30/2011)

Manuscript #11 - Weng et al Mol Cancer Therapy 2008 7, 800-808
"Figures.ppt", (date: 12/26/2006)

Manuscript #12 - Chen et al Cancer Res 2007 67(11):5318-5327
"KU70 (05).ppt", (date: 08/04/2006)

Manuscript #13 - Lu et al Hepatology 2007 46:1119-30
"MS Figures.ppt", (date: 11/18/2006)

On July 24, 2017, Dr. Chen responded to Dr. Yucel stating that he was not the corresponding author on manuscripts #10 and #14. He wrote that he only provided reagents and did not do any of the experiments nor take part in the figure preparation on those manuscripts[18]. On July 26, 2017, Dr. Behnfeldt notified Dr. Chen that the memo sent on July 21, 2017 mistakenly had the total number of allegations listed at 23.[19] In actuality, the number of total allegations was 21.[20] Dr. Behnfeldt noted that all of the new allegations from the July 21, 2017 memo were still present; the only thing that had been revised was the total allegation number. The miscalculation of total allegation numbers was a result of the first additional allegations memo, sent on May 19, 2017, [21] expanding allegations on two of the figures already present in the original allegation from the anonymous Complainant.

Notification to Respondent –Information Release[22]

As a number of the new allegations identified to Dr. Chen on July 21, 2017 involved pre-clinical data generated for compound HDAC42/AR-42 currently in clinical trials, Dr. Yucel requested approval from Dr. Whitacre to contact and provide data related to the allegations to pertinent external parties and agencies involved in oversight and review of the clinical trials on HDAC42/AR-42.[23]

Under the "Policy":

[18] ATT 16- 20170724 - Chen to RIO New allegations
[19] ATT 17- 20170726 - Email RIO to Chen- Revised memo
[20] ATT 18- 20170726- Revised Notification #2
[21] ATT 8 - 20170519- Notification of New Allegations-DIO 6144.pdf
[22] ATT 15- 20170721- Notification #2 of new allegations.pdf
[23] ATT 19- 20170721 Email RIO to VP Release Request.pdf

Section I.D. – Confidentiality - "The goal of maintaining confidentiality shall not prohibit University officials from consulting, on a confidential basis and to the extent necessary, with persons outside the University community with relevant experience or expertise necessary to thoroughly investigate the allegations. The Vice President for Research shall be the University official responsible for determining when a release of information is necessary or appropriate. In any case in which release of information outside the University is deemed necessary, the person accused of research misconduct shall be so informed in advance of the release."

Dr. Caroline Whitacre, Senior Vice President for Research, approved Dr. Yucel's request to contact and release specific data to the Data Safety Monitoring Committee (DSMC), the Western Institutional Research Board (WIRB, the IRB of record) associated with AR-42 trials, the Food and Drug Administration (FDA), the U.S. Office for Human Research Protections (OHRP), the Ohio State University Innovation Foundation (OSIF), and Arno Therapeutics, the funding sponsor.[24] These parties were notified that potential data irregularities had been identified in the basic pre-clinical research within the specific manuscripts, IRB protocols and IND filings and that the University was suspending accrual to the one clinical trial currently open at the University.

These parties were provided with information regarding the irregularities to allow for their review, but no specific information regarding who may be a Respondent was provided.

Response to Additional Allegations #2

The Respondent provided a written response to the allegations on August 2, 2017.[25] Briefly, he stated that he was not the corresponding author for manuscripts #10 [redacted] or manuscript #14 [redacted] Importantly, Dr. Chen highlighted that an error had been made by ORC by

[24] ATT 20- 20170721 - SVPR to RIO Request Approval.pdf
[25] ATT 21- 20170802 - Responses to new allegations

misidentifying Figure 7A and 7B as the problematic figures instead of Figure 4A and 4B for the new additional allegation # 5 in manuscript #11 (Weng et al., Mol Cancer Ther 2008). ORC confirmed the error regarding the figure number and provided the corrected information to the committee members. In the same email correspondence, Dr. Chen provided the copies of files he referenced in his response document "(*Fig. 4 (tif file; dated June 24, 2007) of the original submission. 2. Please see page 3 in the attached for the revised p-Akt blot in response to reviewer 1's comments. Because the original ppt file is too large (22.6MB), I converted it to a pdf file with a reduced file size."* [26] Dr. Chen's specific response for each of the new additional allegations #2 can be found within the next section, "Investigation Committee Analysis."

On August 3, 2017, Dr. Chen emailed Dr. Yucel additional information relating to repeated experiments of alleged figures in Manuscripts #2 and #5.[27] The document contains information related to Dr. Chen's efforts to repeat the experiments in question for Manuscripts #2 and #5. The document was provided to the CIC for review.

[26] ATT 22- 20170802- Email RIO to Chen Request_Fig Number
[27] ATT 23- 20170803 – Email Chen to RIO RE:Repeated experiments of alleged figures in Manuscripts #2 and #5

Investigation Committee Analysis

Manuscript # 1 - Allegation #1 : Western blot data were falsified by replacing two bands (for compounds labeled 8, 49) of the p-AMPK and p-p70S6K blots of Figure 4A with unidentified, darker bands (p-AMPK) or lighter bands (p-p70S6K) when compared to the original research record in Guh *et al.,* J Med Chem 2010. 53, 2552–2561.
Finding of Fact: Allegation #1, Fig 4A, Guh *et al.,* J Med Chem 2010

1. Four different print outs of composite figures matching all of the published Figure 4A, except for bands for compounds labelled 8, 49 of the p-AMPK and p-p70S6K blots ([redacted] Exhibits 1K-1N) were found in [redacted], which was sequestered on March 9, 2016.
2. A figure found on Respondent's hard drive with the file name "Cpd 1-60 Western blots" date created 08/09/2009, time 10:28am, show p-AMPK/p-p70S6K bands for compounds 8 and 49 which match the data from the [redacted] ([redacted] Exhibits 1K-1N)
3. A figure found on Respondent's hard drive with the file name "Cpd 1-60 Western blots" date created 08/09/2009, time 11:06, show p-AMPK/p-p70S6K bands for compounds 8 and 49 which match the data from the [redacted] ([redacted] Exhibits 1K-1N). The file now has an additional unlabeled blot at the top of the page.
4. A figure found on the Respondent's hard drive with the file name "xFig2.tiff" date created 10/30/2009. The unlabeled blots matches the data from the [redacted] except for the compounds labeled 8, 49 of the p-AMPK and p-p70S6K blots.
5. A figure found on the Respondent's hard drive with the file name "Fig.3.cdx" date created 11/30/2009. The now labeled blots matches the data from the [redacted] except for the compounds labeled 8, 49 of the p-AMPK and p-p70S6K blots.
6. A figure found on the Respondent's hard drive with the file name "Fig.6.cdx" date created 01/16/2010 matches the data from the [redacted] except for the compounds labeled 8, 49 of the p-AMPK and p-p70S6K blots and appears in the same format as the published Figure 4A, Guh *et al.,* J Med Chem 2010.
7. As indicated by the statements in Finding of Fact #1-7, there were earlier versions of the figure found in the [redacted] ([redacted] Exhibits 1K-1N) that matched the earliest versions of the figure found on the Respondent's hard drive (Cpd 1-60 Western blots" date created 08/09/2009). The questioned parts of the figure (compounds labeled 8, 49 of the p-AMPK and p-p70S6K blots) only appear on the Respondent's hard drive at later dates (10/30/2009).
8. Through Adobe Photoshop analysis, the a forensic overlay of [redacted] Exhibit 1K with the published Figure 4A shows identical overlap of all bands expect for the bands for compounds labeled 8, 49 of the p-AMPK and p-p70S6K blots, indicating that the rest of the published Figure 4A contains data that is identical to the figures found in the [redacted] Exhibits 1K-1N. Only

the bands for compounds labeled 8, 49 of the p-AMPK and p-p70S6K blots are different.[28]

Knowledge and Intent: Allegation #1, Fig 4A, Guh *et al.,* J Med Chem 2010

1. The presence of a file on the Respondent's hard drive ("Cpd 1-60 Western blots" date created 08/09/2009) that matches the data found in the [redacted] lab notebook ([redacted] Exhibits 1K-1N) demonstrates that the Respondent received a version of the figure, [redacted], that did not contain any manipulations.
2. The presence of a later-dated file on the Respondent's personal hard drive ("xFig2.tiff" date created 10/30/2009) containing the alleged manipulations is indicative of him, [redacted], being the person responsible for the figure manipulation.
3. The goal of the compound screening experiment represented in Figure 4A was to identify compounds with certain "markers" i.e., activated AMPK (increased p-AMPK) and deactivated p70S6K (decreased p-p70S6K). For treatment with compound 8, the original research record ([redacted] Exhibit 1K)[29] showed data in the form of Western blot bands illustrating moderate p-AMPK activation and moderate p-p70S6K activation. The image manipulation and falsification replaced these bands to instead show increased p-AMPK activation and a greatly inhibited p-p70S6K. The same results were seen with compound 49 in the original research record and the same image manipulation and falsification of the bands was observed in the published Figure 4A. Therefore it is plausible that the manipulations were performed intentionally in order to increase the number of compounds identified in the screening experiment.
4. The act of cropping and pasting lanes into a blot so that it no longer matches or reflects the experimental data would cast doubt on these changes occurring through an honest error.

Respondent's Response: Allegation #1, Fig 4A, Guh *et al.,* J Med Chem 2010

DR. CHEN: *Actually, the blot for Number Compound 8 and Compound 49 were taken from a repeated experiment. Because the data here present the initial screening of 60 compound we synthesized. So we use AMPK, P70S6K, and Stat 3 as our markers.*
So we have this initial screening data. We found that there was some data were inconsistent with their ability to inhibit IO6 production. So I probably have asked [redacted] *to repeat the experiment with those compounds. And of course, the second set of*

[28] ATT 14 - ORC Slide Deck Full - 6.1.17, slide 7-8
[29] ATT 14- ORC Slide Deck Full - 6.1.17, slide 7-8

experiment must have shown this compound behaved differently from that initial screening. (Page 4, 11-24)[30]

DR. CHEN: *So I took those blot directly from the repeated experiment and insert in this initial screening data. So those were taken from another blot. We did not mention that there's a different set of experimental conditions for these two compound, and of course this result in the discrepancy between the published figure and this original initial screening data* (Page 5, 1-9).

CHAIRPERSON YUCEL: *And do you recognize that that act of bringing in data from a different experimental set of conditions and pasting it into a figure for the initial screening is considered falsification of the research data?* (Page 5, 10-14)

DR. CHEN: *Well, at that time, probably I did not have the idea of falsification. I justthought that, well, since this experiment show that, then we just combine them together. I think this was a mistake. And we retrospectively, yes, this may constitute falsification. But those data were taken from another experiment. Unfortunately, I could not find the blot for this dose. But as you can see from there, there's no similarity of this blot with other blot, so that they are taken from another experiment.* (Page 5, 15-24; Page 6, 1)

Significance: Allegation #1, Fig 4A, Guh *et al.,* J Med Chem 2010

The Committee has determined that the falsification in Allegation #1 was performed by the Respondent. In his testimony, the Respondent admitted combining data from another experiment and representing it as a single experiment in Figure 4A. The original data that were combined with the original 60-compound screen were not found by the Respondent. The falsified data were likely used in Figure 4A to support the hypothesis that compounds possessing largely shared structural motifs with variations in substituents produced the highest potency (as stated on page 2555 of Guh et al, J. Med Chem 2010).

[30] ATT 13- 170601-OSU-Interview-JCB-PL CSC

Committee Conclusion:

By a preponderance of the evidence, the Committee finds by a vote of 3 in favor and 0 against, that the Respondent intentionally fabricated or falsified the data in Figure 4A related to compounds 8 and 49 and this act constitutes Research Misconduct as described in the Policy III. A and 42 C.F.R. § 93.103 (b).

By clear and convincing evidence, the Committee finds by a vote of 3 in favor and 0 against, that the Respondent intentionally fabricated or falsified the data in Figure 4A related to compounds 8 and 49 and this act constitutes Research Misconduct as described in the Policy III. A and 42 C.F.R. § 93.103 (b).

Manuscript # 1 - Allegation #2: Western blot data was falsified by replacing bands in the p70S6K (lanes 5-7) and AMPK blots (lanes 1, 3, 6 and 7) in Figure 6C of Guh *et al.,* J Med Chem 2010. 53, 2552–2561, when compared to the original research record.

Finding of Fact: Allegation #2, Fig 6C, Guh *et al.,* J Med Chem 2010

1. Autoradiography Western blot films partially matching the published Figure 6C were found in the [redacted] ([redacted] Exhibit 1A). The blots were labeled AMPK and p70S6K, which was sequestered on March 9, 2016.
2. A [redacted] ([redacted] Exhibit 1I) perfectly matching the autoradiography films ([redacted] Exhibit 1A) was found in the [redacted].
3. A figure found on the Respondent's hard drive with the file name "Cpd 53 p-AMPK p-P70SK6" date created 10/28/2009 perfectly matches the [redacted] Exhibit 1I) and the autoradiography films ([redacted] Exhibit 1A).
4. A figure found on the Respondent's hard drive with the file name "Fig.5" date created 11/30/2009 now contains the alleged manipulations present in the published Figure 6C.
5. A figure found of the Respondent's hard drive with the file name "Fig.6" date created 01/16/2010 contains the alleged manipulations and matches the format and layout of the published Figure 6C of Guh *et al.,* J Med Chem 2010.
6. Through Adobe Photoshop analysis, a forensic overlay indicates that the published lanes 1-4 of p70S6K blot in Figure 6C originate from lanes 2-5 of the

raw autoradiography Western blot film ([redacted] Exhibit 1A) for the p70S6K blot. [31]

7. Through Adobe Photoshop analysis, a forensic overlay indicates that the entire blot for AMPK in the [redacted] Exhibit 1I) shows a perfect overlay with the raw autoradiography Western blot film ([redacted] Exhibit 1A) for the AMPK blot.[32]
8. Through Adobe Photoshop analysis, a forensic overlay indicates that lanes 2,4, and 5 in the published Figure 6C match those lanes in the raw autoradiography Western blot film ([redacted] Exhibit 1A) for the AMPK blot, however the rest of the lanes (1,3,6, and 7) do not show a perfect overlay and indicate that they have been manipulated. [33]

Knowledge and Intent: Allegation #2, Fig 6C, Guh *et al.,* J Med Chem 2010

1. The presence of a composite figure print-off in the [redacted] lab notebook that shows the same data that is found on the autoradiography Western blot film also found in the [redacted] ([redacted] Exhibit 1A) indicates that the [redacted] was creating figures that accurately represented the raw experimental data.
2. The presence of a file on the Respondent's hard drive "Cpd 53 p-AMPK p-P70SK6" date created 10/28/2009 that matches the raw data found in the [redacted] and [redacted] demonstrates that the Respondent received a version of the figure, [redacted], that did not contain any manipulations and matched original raw experimental data.
3. The presence of a later-dated file on the Respondent's personal hard drive ("Fig.5.tiff" date created 11/30/2009) that contains the alleged manipulations is indicative of him, [redacted], being the person responsible for the figure manipulation.
4. Both AMPK and p70S6K are internal controls in the experiment represented in Figure 6C and therefore should remain a constant and equal expression with treatment. However, the fact that the experimental results showed decreasing expression (p70S6K) and unequal expression (AMPK) may have been motivation to manipulate the data so that it showed a constant and equal protein expression.
5. The act of cropping and pasting lanes into a blot so that it no longer matches or reflects the experimental data would cast doubt on these changes occurring through an honest error.

Respondent's Response: Allegation #2, Fig 6C, Guh *et al.,* J Med Chem 2010

DR. CHEN: *Well, for this changes, you know, this is long time ago, but I -- I try to answer as much as possible. P70S6K is internal control. Right? And, of course, the*

[31] ATT 14- ORC Slide Deck Full - 6.1.17, slide 14
[32] ATT 14- ORC Slide Deck Full – 6.1.17, slide 15
[33] ATT 14- ORC Slide Deck Full – 6.1.17, slide 15

relative intensity could be changed with -- with a different statin, right? So, yeah, in this case, falsification was made by inserting another set of experiment. (Page 16, lines 16-23)[34]

CHAIRPERSON YUCEL: *Okay. And you had mentioned previously, when we had met with you, that you were the person who created the figures. I think that was a statement that you had made, you know, from the very beginning of the case, and that you were the person who did all of the ChemDraw composite.* (Page 16, line 24; Page 17, lines 1-6)

DR. CHEN: *Most of them*. (Page 17, line 7)

CHAIRPERSON YUCEL: *Okay. So from the evidence that we have to date, it looks like these changes that are being made are happening as data is transiting through ChemDraw on your computer. Is there any explanation for that other than you are the person that is creating those changes?* (Page 17, lines 8-13)

DR. CHEN: *Well, I think in this case, I'm the person that's creating this change.* (Page 17, lines 14-15)

CHAIRPERSON YUCEL: *Okay. Is it* – (Page 17, line 16)

MS. SCHRIVER: *For the P707S6K?* (Page 17, line 17)

DR. CHEN: *For the P70S6K* (Page 17, line 18)

On the AMPK blots

DR. CHEN: *You know, to be honest, I don't have a good explanation for that* (Page 18, lines 14-15)

Significance: Allegation #2, Fig 6C, Guh *et al.,* J Med Chem 2010

The Committee has determined that the falsification in Allegation #2 was performed by the Respondent. In his testimony, the Respondent admitted the falsification of the p70S6K data and that he was the one who manipulated the ChemDraw files on his computer. The Respondent did not provide an explanation for the AMPK blot data changes. Both AMPK and p70S6K are internal controls in the experiment represented in

[34] ATT 13- 170601-OSU-Interview-JCB-PL CSC

Figure 6C and therefore should remain a constant and equal expression with treatment. However, the fact that the experimental results showed decreasing expression (p70S6K) and unequal expression (AMPK) likely motivated the Respondent to manipulate the data so that it showed a constant and equal protein expression.

Committee Conclusion:

By a preponderance of the evidence, the Committee finds by a vote of 3 in favor and 0 against, that the Respondent intentionally falsified the data in Figure 6C (AMPK and p70S6K blots) and this act constitutes Research Misconduct as described in the Policy III. A and 42 C.F.R. § 93.103 (b).

By clear and convincing evidence, the Committee finds by a vote of 3 in favor and 0 against, that the Respondent intentionally falsified the data in Figure 6C (AMPK and p70S6K blots) and this act constitutes Research Misconduct as described in the Policy III. A and 42 C.F.R. § 93.103 (b).

Manuscript # 1 - Allegation #3: Western blot data were falsified by falsely labeling the p-p70S6K blot of Figure 7C of Guh *et al.,* J Med Chem 2010. 53, 2552–2561, as being treated with compound 53 when compared to the original research record.

Finding of Fact: Allegation #3, Fig 7C, Guh *et al.,* J Med Chem 2010

1. A [redacted] Exhibit 1J) was found in the [redacted]. The figure shows treatment with Cpd53 and Cpd54 in a dose and time dependent manner.
2. A figure found in a file on the Respondent's hard drive "Fig Cachaxia dose n time dependent 2" date created 11/01/09 perfectly matches the [redacted] Exhibit 1J).
3. A figure found in a file on the Respondent's hard drive "Fig.5" date created 11/01/09 now only shows treatment with Cpd 53. Despite the labeling, the blots in the figure for p-p70S6K actually come from treatment with Cpd54 as shown in [redacted] Exhibit 1J.
4. A new version of the figure described above (#3) was found in a file on the Respondent's hard drive with the same title "Fig.5" but a later date created of 11/30/09 and only shows treatment with Cpd 53. Despite the labeling, the blots in

the figure for p-p70S6K actually come from treatment with Cpd54 as shown in [redacted] Exhibit 1J.

5. Through Adobe Photoshop analysis, a forensic overlay shows that the blots for p-p70S6K in the published Figure 7C labeled as being treated with Cpd 53 actually are p-p70S6K blots from cells treated with Cpd54.[35]
6. As shown by the original research record ([redacted] Exhibit 1J), the experiment purported in Figure 7C was actually performed, and shows that Cpd53 treatment decreases p-p70S6K expression in both a time and dose dependent manner.

Knowledge and Intent: Allegation #3, Fig 7C, Guh *et al.,* J Med Chem 2010

1. The presence of a file on the Respondent's hard drive "Fig Cachaxia dose n time dependent 2" date created 11/01/09 that matches the [redacted] ([redacted] Exhibit 1J) demonstrates that the Respondent received a version of the figure, likely from [redacted], that did not contain any manipulations and matched original raw experimental data.
2. As the experiment purported in Figure 7C was performed, as shown in [redacted] Exhibit 1J), with the results of Cpd53 and Cpd54 treatment both showing a decrease of p-p70S6K expression in both a time and dose dependent manner, it is possible that this was an unintentional error made by the Respondent.

Respondent's Response: Allegation #3, Fig 7C, Guh *et al.,* J Med Chem 2010

DR. CHEN: *Well, in this case, I must say, this is a careless honest mistake I made duringthe transfer of data. Because, you know, we deal with lots of blot to be transferred during the -- during the manuscript preparation. And from the -- from the original data, you can see that this two set of data are very similar. So, you know, to be honest, it's likely that, you know, I -- an honest error was made from that transfer of data. Because these two set looks so alike. And you know, I -- I think we all make mistake when we are fatigued, and then mistake were made when we transferred the data. And as you can see here, all the data are consistent. And when I transferred the blot from -- from there, it could be a mistake. You can see that these two set of data are very, very similar* (Page 23, lines 8-24; Page 24, line 1)[36]

CHAIRPERSON YUCEL: *Okay.* (Page 24, line 2)
DR. CHEN: *And there's no other advantage for me to use a different blot to show the result, because these two result are virtually -- I would not say virtually; very, very similar to each other. I would say that this is just a honest error while transferring the data. Because, again, there's no advantage form me to gain in this -- in this mistake. So I will say that this is just a honest error when I transferred the data.* (Page 24, lines 3-12)

[35] ATT 14- ORC Slide Deck Full - 6.1.17, slide 21
[36] ATT 13- 170601-OSU-Interview-JCB-PL CSC

Significance: Allegation #3, Fig 7C, Guh *et al.,* J Med Chem 2010

The Committee has determined that while data for a different compound were used in Figure 7C, the Respondent likely made an honest error and did not falsify the data in this figure. The data for compounds 54 and 53 were virtually identical according to the original research record and there would be no advantage gained by deliberately making this substitution.

Committee Conclusion:

By a preponderance of the evidence, the Committee finds by a vote of 0 in favor and 3 against, that the Respondent intentionally, knowingly, and/or recklessly fabricated or falsified the data in Figure 7C and this act does not constitute Research Misconduct as described in the Policy III. A and 42 C.F.R. § 93.103 (b).

By clear and convincing evidence, the Committee finds by a vote of 0 in favor and 3 against, that the Respondent intentionally, knowingly, and/or recklessly fabricated or falsified the data in Figure 7C and this act does not constitute Research Misconduct as described in the Policy III. A and 42 C.F.R. § 93.103 (b).

Manuscript #2 - Allegation #4: Western blot data were falsified by replacing the p70S6K blot and β-actin blot with unidentified blots and by falsely labeling the Akt blots of Figure 1B of Lee *et al.,* PLOS ONE 2013. 8; 6, e67149 when compared to the original research record.

Finding of Fact: Allegation #4, Fig 1B, Lee *et al.,* PLOS ONE 2013

1. A figure found on the Respondent's hard drive from the file "PDK2 Page 2.pdf" date created 11/10/11 time 9:39PM shows treatment of two different cell lines (LNCap and PC-3) with increasing amounts of KU-006794 and with or without T315 treatment.
2. A figure found on the Respondent's hard drive from the file "PDK2 Page 2.jpg" date created 11/10/11 time 10:02PM shows the same figure described above but certain blots (p473SAkt) have been cropped and pasted together while an additional unlabeled blot appears at the bottom of the figure.

3. Through Adobe Photoshop analysis, a forensic overlay shows that the published Akt blot described as only being treated as KU-006794 actually comes from an experiment with both KU-006794 and T315 treatment, which is present in both the above listed file figures.[37]
4. Published Figure 1B has three blots matching the blots found and identically described as in the above file figures, while the other two blots were from unidentified sources (p70S6K, β-actin), and not taken from the above file figures.

Knowledge and Intent: Allegation #4, Fig 1B, Lee *et al.,* PLOS ONE 2013

1. The timing between the date created on the above two files (11/10/11 at 9:39PM versus 11/10/11 at 10:02PM), both found on the Respondent's hard drive and the fact the file at 10:02PM showed figure manipulation in progress (cropping of blots, adding in another blot) strongly indicate that it was likely the Respondent generating the falsifications.

Respondent's Response: Allegation #4, Fig 1B, Lee *et al.,* PLOS ONE 2013

MR. BALL: *I think I have an understanding, and I'm not sure if you have it, so let me try this out, if I may. Is it true, Dr. Chen, you suspected falsification by* [redacted]*, and so you tried to figure out how* [redacted] *might have done it, and so then you manipulated data in a way that you think* [redacted] *must have done?* (Page 31, lines 17-24)[38]

DR. CHEN: *That's one way to put it, yes.* (Page 32, line 1)

CHAIRPERSON YUCEL: *So you would like us to believe -- can you forward to the next – that the -- that you did those edits. So what you're claiming is that the edits that were made in ChemDraw in the 11/10/2011 file was your attempt to try to mimic a falsification you thought* [redacted] *had done, and that you did that thinking it was falsified and then proceeded to publish the manipulated image? Is that what you are claiming?* (Page 32, lines 11-19)

DR. CHEN: *Unfortunately, yes. I did not confront* [redacted]. (Page 32, lines 20-21)

CHAIRPERSON YUCEL: *So you understand that that is still intentional falsification and research misconduct by you? That you published -- you knowingly published a falsified image?* (Page 32, lines 22-24; Page 33, line 1)

DR. CHEN: *Well, for the P70S6K, and the beta Actin, right, they must have been generated somewhere.* (Page 33, lines 2-4)

MR. BALL: *It's a yes-or-no question.* (Page 33, line 5)

[37] ATT 14- ORC Slide Deck Full - 6.1.17, slide 26
[38] ATT 13- 170601-OSU-Interview-JCB-PL CSC

DR. CHEN: *Yes, I agree, me. But I'm here to fully cooperate and tell you what I think.* (Page 33, lines 6-7)

Significance: Allegation #4, Fig 1B, Lee *et al.,* PLOS ONE 2013

The Committee has determined that the falsification in Allegation #4 was performed by the Respondent as determined by forensic analysis and his testimony. The falsified data changed the reported results by showing equal levels of p70S6K instead of unequal levels in original research records. AKT levels were increased with KU-006794 treatment, but another AKT blot (with both KU-006794 and T315 treatments) was used in the published figure, which shows no change in AKT levels. The falsified figure was used in the publication to support the hypothesis that the differential sensitivity to KU-0063794 induced cytotoxicity is attributable to differences in AKT phosphorylation status (as stated on page 4 of Lee et al, PLOS ONE 2013).

Committee Conclusion:

By a preponderance of the evidence, the Committee finds by a vote of 3 in favor to 0 against, that the Respondent intentionally falsified the data in Figure 1B and this act constitutes Research Misconduct as described in the Policy III. A and 42 C.F.R. § 93.103 (b).

By clear and convincing evidence, the Committee finds by a vote of 3 in favor to 0 against, that the Respondent intentionally falsified the data in Figure 1B and this act constitutes Research Misconduct as described in the Policy III. A and 42 C.F.R. § 93.103 (b).

Manuscript # 2 - Allegation #5: Western blot data was falsified by replacing and falsely relabeling single bands in the MK2 blot (lanes 1, 3) the PAK1 blot (lanes 1,3, 8) of

Figure 3A of Lee *et al.,* PLOS ONE 2013. 8; 6, e67149 when compared to the original research record.

Finding of Fact: Allegation #5, Fig 3A, Lee *et al.,* PLOS ONE 2013

1. Autoradiography Western blot films partially matching the published Figure 6C were found in the [redacted] Exhibit 1A and [redacted] Exhibit 1B). The blots were labeled PAK1 and MAPKAPK2 (i.e., MK2), which was sequestered on March 9, 2016.
2. A figure found on the Respondent's hard drive within a PowerPoint presentation file name "081612 progress report" date created 08/16/2012, slide 25, shows a composite figure that contains blots for PAK1 and MAPKAPK2 (i.e., MK2), that matches the blots found on the autoradiography Western blot films ([redacted] Exhibit 1A and [redacted] Exhibit 1B).
3. A figure found on the Respondent's hard drive in a file named "siRNA knockdown PDK2" date created 07/25/12 now contains the falsified lanes in the PAK1 and MK2 blots. There are red dotted boxes around each siRNA treatment lane.
4. A figure found on the Respondent's hard drive in a file named "Fig 3" date created 12/04/12 matches the published Figure 3A and contains the falsifications in the MK2 and PAK1 blots.
5. Through Adobe Photoshop analysis, a forensic overlay shows that lanes 2, 4, 5,6,7,9 and 10 in published Figure 3A, PAK1 are identical to the same numbered lanes in the blot from [redacted] Exhibit 1A. Lanes 1, 3 and 8 in Figure 3A do not show a perfect overlay and appear to be flipped in relation to the lanes that do match the original research record indicating they have been replaced intentionally when compared to the original research record.[39]
6. Through Adobe Photoshop analysis, a forensic overlay shows that lanes 2, 4-10 published Figure 3A, MK2 are identical to the same numbered lanes in the blot from [redacted] Exhibit 1B. Lanes 1 and 3 in Figure 3A do not show a perfect overlay indicating they have been replaced when compared to the original research record.[40]

Knowledge and Intent: Allegation #5, Fig 3A, Lee *et al.,* PLOS ONE 2013

1. The presence of a file on the Respondent's hard drive within a PowerPoint presentation file name "081612 progress report" date created 08/16/2012, slide 25 that matches the original autoradiography Western blot films ([redacted] Exhibit 1A and 1B) demonstrates that the Respondent received a version of the figure, [redacted] that did not contain any manipulations and matched original raw experimental data.

[39] ATT 14- ORC Slide Deck Full - 6.1.17, slide 32
[40] ATT 14- ORC Slide Deck Full - 6.1.17, slide 33

2. The presence of a file on the Respondent's personal hard drive "siRNA knockdown PDK2" that contains the alleged manipulations and red dotted squares around the bands that were expected to show a decrease (those that were treated with various siRNAs) is indicative of him, [redacted] being the person responsible for the figure manipulation.
3. The lanes that were changed in the PAK1 blot showed a lighter expression and were those not treated with PAK1 siRNA so it is plausible that the falsification occurred in order for it to appear that the untreated samples all had the same expression level. The same is true for the bands changed in the MK2 blot.
4. The act of cropping, flipping, and pasting lanes into a blot so that it no longer matches or reflects the experimental data would cast doubt on it being honest error.

Respondent's Response: Allegation #5, Fig 3A, Lee *et al.,* PLOS ONE 2013

DR. CHEN: *This one very puzzling because -- well, first of all, I cannot explain why the difference is. And, again, I mentioned about motive. Motive is to make the data more convincing. But if you look at the original data, as relative to the published data, the published data did not look better than the original data. So I have -- I -- I cannot explain why there's a difference. And by -- if there's any alteration, really, I don't get anything from that. And the reason -- the question I -- that's puzzling, is why would I do that? So I cannot explain the difference, but I didn't have the motive to do this manipulation. I don't know what's happened, to be honest*. (Page 36, lines 13-24; Page 37, lines 1-3)[41]

CHAIRPERSON YUCEL: *Right, no, I understand what you're saying in terms of there's no actual change to the reported results. But are you saying that you are not responsible for the changes that were made to the data in the files that we are finding on your hard drive?* (Page 37, lines 7-12)

DR. CHEN: *Well, I -- to the best of my knowledge, I didn't make the change*. (Page 27, lines13-14)

CHAIRPERSON YUCEL: *And it is not changed, it matches the original research record. So what motive would* [redacted] *have to then send you another file with data that has now been changed?* (Page 38, lines 13-16)

DR. CHEN: *I don't know. I don't know. Probably not* [redacted] *Probably by* [redacted]*. But, you know, I cannot explain. And I don't have any advantage to gain by altering this data. Because, you know, they look -- although there are minor differences, they look exactly the same. And the original data actually look better than the published data.* (Page 38, lines 17-24)

[41] ATT 13- 170601-OSU-Interview-JCB-PL CSC

Significance: Allegation #5, Fig 3A, Lee *et al.,* PLOS ONE 2013

The Committee has determined that the falsification in Allegation #5 was performed by the Respondent based on the progressive line of evidence obtained from the Respondent's personal hard drive and lack of clarifications in his testimony. The falsified data changed the reported results by showing all the untreated samples had the same expression level, when in fact this was not the case in the original research record. The falsified figure was used in the publication to support the notion that si/shRNAs used in developing the Figure 3A were effective (more selective) in reducing the expression of respective targets (as stated on page 6 of Lee et al, PLOS ONE 2013).

Committee Conclusion:

By a preponderance of the evidence, the Committee finds by a vote of 3 in favor and 0 against, that the Respondent intentionally falsified the data in Figure 3A (MK2 and PAK1) and this act constitutes Research Misconduct as described in the Policy III. A and 42 C.F.R. § 93.103 (b).

By clear and convincing evidence, the Committee finds by a vote of 3 in favor and 0 against, that the Respondent intentionally falsified the data in Figure 3A (MK2 and PAK1) and this act constitutes Research Misconduct as described in the Policy III. A and 42 C.F.R. § 93.103 (b).

Manuscript # 2 - Allegation #6: Western blot data were falsified by falsely labeling the p308-T-Akt, ILK, Akt and β-actin blots as being treated with or without Ku-0063794 and/or ILK siRNA of Figure 3B Lee *et al.,* PLOS ONE 2013. 8; 6, e67149 when compared to the original research record.

Finding of Fact: Allegation #6, Fig 3B, Lee *et al.,* PLOS ONE 2013

1. A figure found on the Respondent's hard drive from the file "PDK2 Page 5.pdf" date created 11/10/11 time 7:53PM shows treatment of LNCaP with increasing amounts of shILK and with or without KU-0063794 treatment.
2. A figure found on the Respondent's hard drive from the file "PDK2 Page 5.jpg" date created 11/10/11 time 8:53PM shows the same figure described above but certain blots have been cropped and 7 unlabeled blots appears at the right of the figure.
3. Through Adobe Photoshop, forensic overlay shows that 5 of the unlabeled blots from the above mentioned file appear in the published Figure 3B as:[42]
    a. Blot 1 – labeled as ILK in Figure 3B
    b. Blot 2 – labeled as Akt in Figure 3B
    c. Blot 3 – labeled as p473S-Akt in Figure 3B
    d. Blot 6 – labeled as p308t-Akt in Figure 3B
    e. Blot 7 – labeled as beta-actin in Figure 3B
4. To be accurately represented according to the figure legend of published Figure 3B, all of the blots should contain lanes (1), (2, 3, 4 or 5) and (7, 8, 9 or 10) from the above images. Through Adobe Photoshop analysis, forensic overlay shows only one blot (Blot 3, p-473S-Akt) in published Figure 3B correctly has those lanes (lanes 1, 2 and 7). The rest of the published blots match bands from a variety of different lanes[43]:
    a. Blot 1 of "pdk2 page 5.jpg" = Lanes 5, 6, 7 of ILK Blot of "pdk2 page 5.pdf"
    b. Blot 2 of "pdk2 page 5.jpg" = Lanes 8, 9, 10 of AKT Blot of "pdk2 page 5.pdf"
    c. Blot 3 of "pdk2 page 5.jpg" = Lanes 1, 2, 7 of p473S-Akt Blot of "pdk2 page 5.pdf"
    d. Blot 6 of "pdk2 page 5.jpg" = Lanes 6, 7, 8 of GSK3B Blot of "pdk2 page 5.pdf".
    e. Blot 7 of "pdk2 page 5.jpg" = Lanes 6, 7, 8 of B-actin blot of "pdk2 page 5.pdf"
5. The act of cropping and pasting lanes into a blot so that it no longer matches or reflects the experimental data would cast doubt on this being honest error.

Knowledge and Intent: Allegation #6, Fig 3B, Lee *et al.,* PLOS ONE 2013

1. The timing between the date created on the above two files (11/10/11 at 7:53PM versus 11/10/11 at 8:53PM), both found on the Respondent's hard drive and the fact the file at 8:53PM showed figure manipulation in progress (cropping of blots, blots added to the side of the figure) strongly indicate that it was likely the Respondent generating the falsifications.

[42] ATT 14- ORC Slide Deck Full -6.1.17.pdf, slide 38
[43] ATT 14- ORC Slide Deck Full -6.1.17, slides 39-40

Respondent's Response: Allegation #6, Fig 3B, Lee *et al.,* PLOS ONE 2013

CHAIRPERSON YUCEL: *So it is your contention, then, that the manipulations that were made by you on your machine between November 10 at 7:53 -- 2011 at 7:53, and ten minutes later, the changes that we see in the documents were all your attempt to verify or determine what changes had been made by* [redacted]*, that is your contention?* (Page 41, lines 13-19)[44]

DR. CHEN: *That is a correct statement.* (Page 41, line 20)

CHAIRPERSON YUCEL: *And that you then, instead of correcting the research or asking for the data to be redone, you intentionally and knowingly published a falsified figure?* (Page 41, lines 21-24)

DR. CHEN: *I knowingly published the falsified figures* (Page 42, lines 1-2)

Significance: Allegation #6, Fig 3B, Lee *et al.,* PLOS ONE 2013

The Committee has determined that the falsification in Allegation #6 was performed by the Respondent based on his testimony and forensic analyses. A falsified figure was used to report the results, which showed that ILK knockdown had no effect in terms of pSer473AKT levels on untreated cells, but that phosphorylation decreased with KU-0063794 treatment along with ILK siRNA treatment. The committee believes that this falsified figure (Figure 3B) in the publication was used to support the lack of a role of ILK in mediating pSer473-AKT phosphorylation in LNCaP (as stated on page 6 of Lee et al, PLOS ONE 2013).

Committee Conclusion: Allegation #6, Fig 3B, Lee *et al.,* PLOS ONE 2013

By a preponderance of the evidence, the Committee finds by a vote of 3 in favor and 0 against, that the Respondent intentionally falsified the data in Figure 3B and this

[44] ATT 13- 170601-OSU-Interview-JCB-PL CSC

act constitutes Research Misconduct as described in the Policy III. A and 42 C.F.R. § 93.103 (b).

By clear and convincing evidence, the Committee finds by a vote of 3 in favor and 0 against, that the Respondent intentionally falsified the data in Figure 3B and this act constitutes Research Misconduct as described in the Policy III. A and 42 C.F.R. § 93.103 (b).

Manuscript # 3 - Allegation # 7: Western blot data was falsified by falsely relabeling the experimental conditions and by reusing, inverting and falsely labeling single unidentified, lighter bands in the p^{473}-Ser-Akt bands (lanes 10 and 14) treated with 10 mM 2-DG or glucose starvation for 72 hours in Figure 1A of Chu *et al.,* Carcinogenesis 2013. 34; 12, 2694–2705 when compared to the original research record.

Finding of Fact: Allegation #7, Fig 1A, Chu *et al.,* Carcinogenesis 2013

1. A figure found on the Respondent's hard drive labeled "Fig-1 merged" date created 10/30/2011 shows LNCaP cells treated with a variety of inhibitors including 2-DG (0,5,10,20,30 mM) and glucose starvation (0, 24, 48, 72 hrs). The blots for p^{473}- Ser-Akt for 2-DG and glucose starvation show a modest protein expression decrease.
2. The same figure as described above was found on the Respondent's hard drive in a PowerPoint presentation labeled "Summary of Po-Chen data", slide 2, date created 06/05/12. The blots for p^{473}- Ser-Akt for 2-DG and glucose starvation are identical to those in the above figure file.
3. An additional identical version of the figure was found on the Respondent's hard drive in a file labeled ""IGF-IR PI3K Akt Western PCR data" date created: 6/6/12. The blots for p^{473}- Ser-Akt for 2-DG and glucose starvation are identical to those in the above two figure files.
4. A version of the figure, that now shows manipulations in lanes 10 and 14, appears on the Respondent's hard drive in a file labeled "xFig.1" date created 09/10/12 Ser-Akt for 2-DG and glucose starvation show a drastic protein expression decrease in lanes 10 and 14, while the rest of the blot is identical.
5. Additionally, the figure found in the "xFig.1" now is labeled as 2-DG treatment at 0, 2.5, 5, 7.5 and 10 mM.

Knowledge and Intent: Allegation #7, Fig 1A, Chu *et al.,* Carcinogenesis 2013

1. The presence of three files showing identical labeled conditions and blots for Ser-Akt for 2-DG and glucose starvation on the Respondent's hard drive indicate that he received the data that had not been manipulated three times.

2. It is only in a later-dated file on the Respondent's hard drive (xFig.1, date created 09/10/12) that the manipulations appear, indicating that the Respondent is likely the person responsible for generating the falsification.

Respondent's Response: Allegation #7, Fig 1A, Chu *et al.,*Carcinogenesis 2013

DR. CHEN: *I have no explanation for this really. I don't know how it happened, to be honest. If I made mistake, I would say I did so. But in this case, I could not account for the difference.* (Page 44, lines 21-24; Page 45, line 1)[45]

CHAIRPERSON YUCEL: *And would it be possible that someone had access to your computer and could have manipulated these documents on your computer during this time frame?* (Page 45, lines 2-5)

DR. CHEN: *The other possibility is that there's another set of data given to me, that's the only explanation. But I don't know. I don't have evidence to support or refute my statement. And I really don't know*. (Page 45, lines 6-10)

Significance: Allegation #7, Fig 1A, Chu *et al.,* Carcinogenesis 2013

The Committee has determined that the falsification in Allegation #7 was performed by the Respondent based on forensic analyses and dating of retrieved files from the Respondent's hard drive. Falsified pSer473-AKT data for 2-DG and glucose starvation data in the figure were used to falsely substantiate the claim of concentration-dependent effects of 2-DG and time-dependent effects of glucose deprivation on treated prostate cancer cells occurring in parallel with observed effects on IGF-IR (as stated on page 2696 in Chu et al, Carcinogenesis 2013).

Committee Conclusion: Allegation #7, Fig 1A, Chu *et al.,* Carcinogenesis 2013

By a preponderance of the evidence, the Committee finds by a vote of 3 in favor and 0 against, that the Respondent intentionally falsified the data in Figure 1A (p-AKT blots) and this act constitutes Research Misconduct as described in the Policy III. A and 42 C.F.R. § 93.103 (b).

[45] ATT 13- 170601-OSU-Interview-JCB-PL CSC

By clear and convincing evidence, the Committee finds by a vote of 3 in favor and 0 against, that the Respondent intentionally falsified the data in Figure 1A (p-AKT blots) and this act constitutes Research Misconduct as described in the Policy III. A and 42 C.F.R. § 93.103 (b).

Manuscript # 3 - Allegation #8: Western blot data was falsified and/or fabricated by reusing and relabeling the entire Sp1 blots in samples treated with increasing doses of CG-5 or pCMV/CG-5 in Figure 2A and 2F of Chu *et al.,* Carcinogenesis 2013. 34; 12, 2694–2705 when compared to the original research record.

Finding of Fact: Allegation #8, Fig 2A/2F, Chu *et al.,* Carcinogenesis 2013

1. Figures found on the Respondent's hard drive in a PowerPoint presentation labeled "Summary of Po-Chen data" date created 06/05/12 has three slides (slides 1,2, and 3) that match partially to parts of published Figure 2A and 2F. In this PowerPoint there are no duplications of the Sp1 blots.
2. Through Adobe Photoshop, a forensic overlay shows that the Sp1 blots in Figure 2A and 2F show a perfect overlay indicating they are the same image.[46]
3. The Sp1 blots in Figure 2A and 2F were not rotated, flipped, or cropped.

Knowledge and Intent: Allegation #8, Fig 2A/2F, Chu *et al.,* Carcinogenesis 2013

1. The presence of a file on the Respondent's hard drive "Summary of Po-Chen data" date created 06/05/12 demonstrates that the Respondent received a version of the figure, likely from Po-Chen, which did not contain any duplications of the Sp1 blots.
1. In the correction, published by *Carcinogenesis* on 11/21/16 the authors state "*In the original Fig. 2, the image of the blot of Sp1 in Fig. 2A is the same as the Sp1 blot in the left panel of Fig. 2F, resulting from the unintentional incorporation of the same image in two different figure panels"* and therefore the authors do not dispute that the Sp1 blot was duplicated. However, the authors had no explanation for the error in their correction.
2. As the experiment purported in Figure 2A and 2F were both performed, as shown in "Summary of Po-Chen data", with the results showing a dramatic decrease for all Sp1 blots, and the blots in Figure 2A and 2F were presented in the same orientation it is possible that this was an unintentional error made by the Respondent.

[46] ATT 14- ORC Slide Deck Full - 6.1.17, slide 50

Respondent's Response: Allegation #8, Fig 2A/2F, Chu *et al.,* Carcinogenesis 2013

DR. CHEN: *Any statement is that -- again, this probably an honest error. As you can see, there are so many SP1 blots in this manuscript. So it is most likely that I made a human error, you know, by reuse the same blot. And we have corrected that in the -- in the -- in the core agenda because as you can see, you know, in this paper, I don't know how many SP1 blots there are. You know, over 80 figure, there's SP1 blot. So I would say this is just by accident, due to human error, that this SP1 blot where we used* (Page 47, lines 7-17)[47]

Significance: Allegation #8, Fig 2A/2F, Chu *et al.,* Carcinogenesis 2013

The Committee believes that the Respondent likely made an honest error and did not falsify the data in this figure. The original data for the Sp1 blots in the experiments presented in panels A and F were virtually identical with the original research records and it would not have been advantageous to deliberately re-use the information.

Committee Conclusion: Allegation #8, Fig 2A/2F, Chu *et al.,* Carcinogenesis 2013

By a preponderance of the evidence, the Committee finds by a vote of 0 in favor and 3 against, that the Respondent intentionally, knowingly, and/or recklessly falsified the data in Figures 2A and 2F (Sp1 blots) and this act does not constitute Research Misconduct as described in the Policy III. A and 42 C.F.R. § 93.103 (b).

By clear and convincing evidence, the Committee finds by a vote of 0 in favor and 3 against, that the Respondent intentionally, knowingly, and/or recklessly falsified the data in Figures 2A and 2F (Sp1 blots) and this act does not constitute Research Misconduct as described in the Policy III. A and 42 C.F.R. § 93.103 (b).

Manuscript # 3 - Allegation # 9: In addition to previously noted allegedly falsified Western blot data, the PCR data were also falsified and/or fabricated in Figure 8A of Chu *et al.,* Carcinogenesis 2013. 34; 12, 2694–2705 when compared to the original research record.

[47] ATT 13- 170601-OSU-Interview-JCB-PL CSC

Finding of Fact: Allegation #9, Fig 8A, Chu *et al.,* Carcinogenesis 2013

1. A figure found on the Respondent's hard drive in a file labeled "Fig. 4D HuR RRM 123 IGF-1R 3' UTR-5 RNA-IP", date created 09/09/12 shows the same experimental conditions as those reported in Figure 8A. The PCR portion of the figure is identical to the PCR portion of Figure 8A, but the Western blot is not the same.
2. A figure found on the Respondent's hard drive in a file labeled "HuR deletion RRM RNA IP RT-PCR 2", date created 12/15/12 has two lanes (lanes 2 and 4) of the PCR gel that match the published Figure 8A and the Western blot figure now matches the published Western blot in Figure 8A.
3. A figure found of the Respondent's hard drive in a file labeled "Fig.8", date created 07/30/13 is identical to the published Figure 8A.
4. Through Adobe Photoshop analysis, a forensic overlay shows that the PCR data is slightly modified (lane 5 in first file is removed in the second file but reappears in the third file) through the different versions of the figure.[48]

Knowledge and Intent: Allegation #9, Fig 8A, Chu *et al.,* Carcinogenesis 2013

1. The original allegation regarding Figure 8A was the presence of crop lines surrounding lanes 4 and 5 in the Western blot part of the figure.
2. In the correction, published by *Carcinogenesis* on 11/21/16 the authors state "*In the western blot panel of the immunoprecipitation experiment shown in the original Fig. 8A, an inconsistency between the background of the blot and the area surrounding the bands in lanes 4 and 5 was detected*." The authors had no explanation for the error in their correction.
3. With three different versions, both in the PCR and Western blot data, found on the Respondent's hard drive, the validity of the final Figure 8A is highly questionable.

Respondent's Response: Allegation #9, Fig 8A, Chu *et al.,* Carcinogenesis 2013

CHAIRPERSON YUCEL: *And then we go to the next file, and the Western blot matches, and the PCR matches, so this has been put together, it's been combined. The PCR from a different experiment and a Western from a different experiment have been combined to make the final figure.* (Page 51, lines 12-18)[49]

DR. CHEN: *Maybe that's what* [redacted] *has done*. (Page 51, lines 19-20)

CHAIRPERSON YUCEL: *So even though you have this file on your computer, and then you have a second file where now all of a sudden the things have been combined, and*

[48] ATT 14- ORC Slide Deck Full -6.1.17.pdf, slide 56
[49] ATT 13- 170601-OSU-Interview-JCB-PL CSC

then we have a published figure on your computer, your contention is that [redacted] *sent you the data in this format? And then again changed, and then you put that -- you used that to create the final figure?* (Page 51, lines 21-24; Page 52, lines 1-4)

DR. CHEN: [redacted] *has --* [redacted] *must have submitted the final form to me for the -- for the -- for the final figure*. (Page 52, lines 5-7)

CHAIRPERSON YUCEL: *And do you have any evidence to support the claim that it was* [redacted] *and not you creating that combination file?* (Page 52, lines 8-11)

DR. CHEN: *No, I didn't. But, you know, you can ask* [redacted]. (Page 52, lines 12-13)

Significance: Allegation #9, Fig 8A, Chu *et al.,* Carcinogenesis 2013

The Committee has determined that the falsification in Allegation #9 was performed by the Respondent based on forensic analyses and, in part, on his testimony. The falsified figure in the publication was likely used in order to rush to produce and publish highly significant data for cancer research.

Committee Conclusion: Allegation #9, Fig 8A, Chu *et al.,* Carcinogenesis 2013

By a preponderance of the evidence, the Committee finds by a vote of 3 in favor and 0 against, that the Respondent intentionally falsified the data in Figure 8A and this act constitutes Research Misconduct as described in the Policy III. A and 42 C.F.R. § 93.103 (b).

By clear and convincing evidence, the Committee finds by a vote of 3 in favor and 0 against, that the Respondent intentionally falsified the data in Figure 8A and this act constitutes Research Misconduct as described in the Policy III. A and 42 C.F.R. § 93.103 (b).

Manuscript # 4 - Allegation #10: Western blot data was falsified by reusing and falsely relabeling an Akt blot from an unrelated experiment as the Akt blot of Figure 1D of Lai *et al.,* Carcinogenesis 2014. 35; 10, 2203–2213.

Finding of Fact: Allegation #10, Fig 1D, of Lai *et al.,* Carcinogenesis 2014

1. A figure found on the Respondent's hard drive in a PowerPoint presentation labeled "RRM2 data", slide 1, date created 02/03/12 shows a figure that partially matches the published Figure 1D except it does not contain any phospho-Akt or Akt blots. The blots all contain 7 lanes and show three different cell lines with and without Gemcitabine treatment.
2. A figure found on the Respondent's hard drive in a PowerPoint presentation labeled "Akt data (1)" date created 02/06/12, time 8:45PM, contains blots from the above figure file and now contains two phospho-Akt blots (Ser473 and Ser308) with the same experimental conditions listed.
3. A figure found on the Respondent's hard drive in a file labeled "Akt data-Akt" date created 02/06/12 time 8:53PM, shows a single unlabeled blot with 13 lanes.
4. The single unlabeled blot matches an Akt blot for an experiment labeled "Kinase-targeted Focused Compound Library" from a PowerPoint presentation labeled "NTUH 010412", slide 14 date created 01/03/2012. The experiment shows Compounds 1-53 and their effect on Akt and phospho-Akt.
5. The PowerPoint presentation "NTUH 010412" was presented by Dr. Chen at the National Taiwan University Hospital.
6. Through Adobe Photoshop analysis, a forensic overlay shows that the Akt blot in published Figure 1D overlays perfectly with lanes 1-7 of the Akt blot from the "Akt-data-Akt" file and also the lanes 1-7 of the Akt blot from the unrelated experiment in the "NTUH 010412" file.[50]

Knowledge and Intent: Allegation #10, Fig 1D, of Lai *et al.,* Carcinogenesis 2014

1. The timing between the file "Akt-data(1)" file 8:45PM and the "Akt-data Akt" file 8:53PM brings the Respondent's explanation of that he viewed the first file and saw there was no Akt blot (8:45PM), emailed [redacted] asking for the Akt data and received the unlabeled Akt blot back (8:53PM) into question.
2. Additionally, with the source of the falsely labeled Akt blot being found on the Respondent's hard drive in a presentation he gave (title slide has his name and his positions at the university) strongly indicates that he was likely the person responsible for falsifying the Akt blot.

[50] ATT 14- ORC Slide Deck Full - 6.1.17, slide 64

Respondent's Response: Allegation #10, Fig 1D, of Lai *et al.,* Carcinogenesis 2014

DR. CHEN: *Well, you know, when I received the -- the AK -- phospho for AKT file, I immediately ask where the AKT comes from. And that was what I received. And, you know, again, I forgot who sent me the data, because in the interview with I-Lu Lai, she mentioned that she did part of the figure, and I don't know who did the other part. She mentioned about B -- and I forgot the -- this is what I got when I asked for AKT internal control.* (Page 57, lines 16-24; Page 58, line 1)[51]

Significance: Allegation #10, Fig 1D, Lai *et al.,* Carcinogenesis 2014

The Committee has determined that data for a completely different experiment found on the Respondent's hard drive were used in Figure 1D for the Akt blot. The falsification of the AKT blot was likely motivated by the fact that an internal control was missing from the original data provided to him by the student, and was needed for this experiment.

Committee Conclusion: Allegation #10, Fig 1D, Lai *et al.,* Carcinogenesis 2014

By a preponderance of the evidence, the Committee finds by a vote of 3 in favor and 0 against, that the Respondent intentionally falsified Figure 1D (Akt blot) and this act constitutes Research Misconduct as described in the Policy III. A and 42 C.F.R. § 93.103 (b).

By clear and convincing evidence, the Committee finds by a vote of 3 in favor and 0 against, that the Respondent intentionally falsified Figure 1D (Akt blot) and this act constitutes Research Misconduct as described in the Policy III. A and 42 C.F.R. § 93.103 (b).

[51] ATT 13- 170601-OSU-Interview-JCB-PL CSC

Manuscript # 4 - Allegation #11: Western blot data were falsified by falsely labeling the experiment conditions of the entire composite figure, falsely labeling the E2F1 and RRM2 blots and splicing together single bands from different experimental conditions to generate the p-Akt and gamma-H2AX blots of Figure 5A of Lai *et al.,* Carcinogenesis 2014. 34; 12, 2694–2705 when compared to the original research record.

Finding of Fact: Allegation #11, Fig 5A, Lai *et al.,* Carcinogenesis 2014

1. A figure found on the Respondent's hard drive in a file labeled "H2Ax in panc1" date created 02/10/12, shows the same experimental conditions as published Figure 5A.
2. A figure found on the Respondent's hard drive in a file labelled "H2Ax in panc1" date created 02/14/12, shows the same figure listed above except there are additional lanes cropped together and lined up next to the blot for H2A (i.e., H2AX). The RRM2 blot now shows a white bar over its entirety.
3. Through Adobe Photoshop analysis, a forensic overlay shows that the published γ-H2AX blot in Figure 5A is identical to the additional lanes cropped together and lines up in the "H2Ax in panc" file created on 02/14/12 and show an increasing expression of γ-H2AX with higher doses of OSU-CG30 while the actual original research record shows γ-H2AX varying expression with higher doses of OSU-CG30. [52]
4. Through Adobe Photoshop analysis, a forensic overlay shows that the published p-Akt blot in Figure 5A was created by cropping and flipping and pasting four bands from the original research record for p-Akt in order to falsely represent that p-Akt expression decreases upon OSU-CG30 treatment. The original research record shows varying expression for p-Akt upon OSU-CG30 treatment.[53]
   The E2F1 blot from the original research record was labeled as RRM2 in the published Figure 5A, while the RRM2 blot from the original research record was labeled as E2F1.

Knowledge and Intent: Allegation #11, Fig 5A, Lai *et al.,* Carcinogenesis 2014

1. The Respondent testified that he was the person responsible for creating the figure manipulations in Figure 5A and he did it because he was frustrated with how long it was taking [redacted] to produce the data.
2. Conversely, in his Response to the Final Report of the CII, sent on 11/21/2016, specifically in response to the CII conclusion that it appears there are splice lines in Figure 5A between lanes 4 and 5 the Respondent includes his own Adobe Photoshop forensic gradient map of Figure 5A and highlights a portion in the figure (by a yellow bracket) where the straight cropping line does not continue. He writes:

[52] ATT 14- ORC Slide Deck Full - 6.1.17, slide 72
[53] ATT 14- ORC Slide Deck Full - 6.1.17, slide 73

"*The yellow bracket and arrow indicate a discontinuity in the straight edge (i.e. the edge does not extend the entire width of the blot) that would not be expected if splicing had been done*." [54]

3. Since Adobe Photoshop analysis using forensic overlay shows that every band has been cropped and pasted in the published Figure 5A and the Respondent has testified that he was responsible for the manipulation and falsification, the question of why he originally wrote a response trying to discredit the falsification allegations based on the discontinuity of splice lines is hard to understand and raises serious concerns as to the credibility of Dr. Chen's statements.

Respondent's Response: Allegation #11, Fig 5A, Lai *et al.,* Carcinogenesis 2014

DR. CHEN: *Yes, I falsified the data. And you may ask me why? I think frustration took a better part of me.* (Page 64, lines 22-24)[55]

CHAIRPERSON YUCEL: *I'm sorry, can you say that again?* (Page 65, lines 1-2)

DR. CHEN: *Frustration took a better of me. That -- you know, I was confident in that this data could be reproduced. And indeed, you know, in the corrigendum we sent, this data was reproduced exactly. We were in a hurry to send the paper out. And we -- I -- we couldn't get the data from* [redacted] *quick enough. I made a mistake. And in this case, I admit my mistake. But in other cases, you know, I would attribute this to human errors.* (Page 65, lines 3-13)

Significance: Allegation #11, Fig 5A, Lai *et al.,* Carcinogenesis 2014

The committee has determined that the Respondent intentionally falsified data in Figure 5A. Out of frustration due to the rush to reproduce and publish highly significant data for cancer research, the Respondent admits to intentionally falsifying data on a compound (OSU-CG5) for which the specific end goal is to provide therapeutic strategies for pancreatic cancer in patients. Intentionally falsifying data on compounds (OSU-CG30) for which the specific end goal is to provide to patients is highly significant and incredibly dangerous.

[54] ATT 24- 20161121- Response to Final Report of the CII-CHEN.pdf, page 8, Figure 3
[55] ATT 13- 170601-OSU-Interview-JCB-PL CSC

Committee Conclusion: Allegation #11, Fig 5A, Lai *et al.,* Carcinogenesis 2014

By a preponderance of the evidence, the Committee finds by a vote of 3 in favor and 0 against, that the Respondent intentionally falsified the data in Figure 5A and this act constitutes Research Misconduct as described in the Policy III. A and 42 C.F.R. § 93.103 (b).

By clear and convincing evidence, the Committee finds by a vote of 3 in favor and 0 against, that the Respondent intentionally falsified the data in Figure 5A and this act constitutes Research Misconduct as described in the Policy III. A and 42 C.F.R. § 93.103 (b).

Manuscript # 5 - Allegation #12: Western blot data were falsified by reusing and falsely relabeling the ACC blots in samples from MDA-MB-231 cells and those from PC-3 cells of Figure 2A of Chou *et al.,* Cancer Res 2014. 74, 4788 when compared to the original research record.

Finding of Fact: Allegation #12, Fig 2A[56], Chou *et al.,* Cancer Res 2014

1. Original research record "[redacted] Exhibit 1G" contained numerous Western blots labeled as "ACC" and "p-ACC".
2. Through Adobe Photoshop analysis, the forensic overlay shows that the blot labeled "PC3 53D" is identical to the blot in Figure 2A labeled "ACC" from MDA-MB-231" and to an additional blot in Figure 2A labeled "ACC" from PC3 cells.[57]

Knowledge and Intent: Allegation #12, Fig 2A, Chou *et al.,* Cancer Res 2014

1. The original research record "[redacted] Exhibit 1G" does indicate that the experiment was performed for both PC3 cells and MDA-MB-231 cells.
2. In the "Comments to CIC" submitted by the Respondent on May 30, 2017, Dr. Chen included an image of an email chain between himself and [redacted]

[56] 20170912 CIC Final Report was mislabeled as " Finding of Fact: Allegation #12, Fig 3B, Chou et al., Cancer Res 2014" This revision shows the correction.
[57] ATT 14- ORC Slide Deck Full - 6.1.17, slide 77

3. In a response email from [redacted] on May 19, 2017, he states "Indeed the CC blots of PC-3 and 231 were reused by mistake. Please check the attached file that I marked for the correct ACC blots for PC-3 and 231." [58]

Respondent's Response: Allegation #12, Fig 2A, Chou *et al.,* Cancer Res 2014

DR. CHEN: *In this case, again, I follow exactly what was presented to me. And [redacted], send an e-mail saying that was a mistake [redacted] made. And I think this is, again, another human error. When you deal with so many pieces of data, it is likely that a mistake was made* (Page 70, lines 13-19)[59]

Significance: Allegation #12, Fig 2A, Chou *et al.,* Cancer Res 2014

The Committee has determined that the falsification in Allegation #12 was made recklessly by the Respondent by not adequately scrutinizing the data presented to him, which resulted in the reuse of ACC blots (for both PC-3 and MDA-MB-231 cell lines) in the published figure. The lack of proper research records did not allow the Committee to confirm whether the reported results are correct or whether there would be an advantage in making such a substitution.

Committee Conclusion: Allegation #12, Fig 2A, Chou *et al.,* Cancer Res 2014

By a preponderance of the evidence, the Committee finds by a vote of 2 in favor and 1 against, that the Respondent recklessly falsified the data in Figure 2A (ACC blots) and this act constitutes Research Misconduct as described in the Policy III. A and 42 C.F.R. § 93.103 (b).

By clear and convincing evidence, the Committee finds by a vote of 0 in favor and 3 against, that the Respondent recklessly falsified the data in Figure 2A (ACC blots) and this act does not constitute Research Misconduct as described in the Policy III. A and 42 C.F.R. § 93.103 (b).

[58] ATT 25- "Comments to CIC.doc" page 8, Figure 7
[59] ATT 13- 170601-OSU-Interview-JCB-PL CSC

Manuscript # 5 - Allegation #13: RT-PCR data was fabricated and/or falsified by reusing and falsely labeling a single image to represent SNAIL mRNA, YB-1 mRNA, and E-Cadherin mRNA expression in Figure 3B of Chou *et al.,* Cancer Res 2014. 74, 4783.

Finding of Fact: Allegation #13, Fig 3B, Chou *et al.,* Cancer Res 2014

1. Using Adobe Photoshop analysis, the forensic overlay shows that the gel image labeled as Snail is identical to the E-Cadherin gel image when it is flipped horizontally. [60]
2. The Respondent provided slides to the CII on 01/11/17 with the description "*Thus, I have asked* [redacted] *to use the image data of original full-length gels associated with the alleged Fig. 3B of manuscript #5 (listed in A27 Data files; 231 Snail.tif, PC-3 E-cad 3.tif, PC-3 YB-1 3.tif) as an example to do a step-by step illustration of how* [redacted] *cropped and processed these image data"*[61]
3. The same step-by-step cropping and processing of the images that was described in the above email was used to determine if the provided images were indeed the images published in Figure 3B of Cancer Res 2014.[62]
4. Using Adobe Photoshop analysis, a forensic overlay shows that the provided full-length gel Snail image is identical to the Snail gel image in Figure 3B.[63]
5. Using Adobe Photoshop analysis, a forensic overlay shows the provided full-length gel images for YB-1 and E-Cadherin are not identical to the published gel images for YB-1 and E-Cadherin in Figure 3B. [64]

Knowledge and Intent: Allegation #13, Fig 3B, Chou *et al.,* Cancer Res 2014

1. As it appears that the original research records [redacted] only match 1 of the 3 images in questions, it is unclear why the other images were reused.
2. The action of flipping a blot and reusing it suggests it was not a simple pasting error but rather an intent to obscure the similarity of the reused blot.

Respondent's Response: Allegation #13, Fig 3B, Chou *et al.,* Cancer Res 2014

DR. CHEN: *You know, basically, in this case, I just follow whatever* [redacted] [redacted]. *Identical, exactly. I didn't change anything* (Page 68, lines 16-18)[65]

[60] ATT 14- ORC Slide Deck Full - 6.1.17, slide 79
[61] ATT 26- "20170111 Email Chen to RIO.pdf"
[62] ATT 14- ORC Slide Deck Full - 6.1.17, slides 81-83
[63] ATT 14- ORC Slide Deck Full - 6.1.17, slide 81
[64] ATT 14- ORC Slide Deck Full - 6.1.17, slide 82-83
[65] ATT 13- 170601-OSU-Interview-JCB-PL CSC

Significance: Allegation #13, Fig 3B, Chou *et al.,* Cancer Res 2014

The committee has determined that no fabrication or falsification by the Respondent occurred in connection with Allegation 13. In particular, the Committee remains unanimously unconvinced that the forensic analyses point to misconduct or re-use of portions of the figure as alleged.

Committee Conclusion: Allegation #13, Fig 3B, Chou *et al.,* Cancer Res 2014

By a preponderance of the evidence, the Committee finds by a vote of 0 in favor and 3 against, that the Respondent intentionally, knowingly, and/or recklessly fabricated or falsified the data in Figure 3B and this act does not constitute Research Misconduct as described in the Policy III. A and 42 C.F.R. § 93.103 (b).

By clear and convincing evidence, the Committee finds by a vote of 0 in favor and 3 against, that the Respondent intentionally, knowingly, and/or recklessly fabricated or falsified the data in Figure 3B and this act does not constitute Research Misconduct as described in the Policy III. A and 42 C.F.R. § 93.103 (b).

Manuscript # 7 - Allegation #14 - Western blot data were falsified by falsely labeling the concentration of (S)-HDAC-42 used and the cell type used when compared to the original research record in Figure 4A of Kulp *et al.,* Clin Cancer Res 2006. 12; 17, 5199-5206

Finding of Fact: Allegation #14, Fig 4A, Kulp *et al.,* Clin Cancer Res 2006

1. A PowerPoint presentation located on the Respondent's hard drive in a file labeled "HDACs in U87 and PC3.ppt", date created 05/12/05, contained two slides that show composite Western blot figures with identical p-AKT Ser 473 and Thr 308 blots to the published Figure 4A. The rest of the blots do not match and the concentration of (S)-HDAC-42 used is labeled at 0.5, 2.5, 5.0 µM. Two different cell lines (U87MG and PC3) were used. [66]
2. [redacted]"HDACs in U87 and PC3.ppt", date created 05/12/05, PowerPoint presentation is [redacted] of "Chen CS, Weng SC,

[66] ATT 27- 20170802 ORC Slide Deck 2, slide 2-3

Tseng PH, Lin HP, Chen CS. Histone acetylation-independent effect of histone deacetylase inhibitors on Akt through the reshuffling of protein phosphatase 1 complexes. J Biol Chem. 2005 Nov 18; 280(46):38879-87." (see point 3)

3. The figures in the file "HDACs in U87 and PC3.ppt" were published in their entirety (all blots in the composite figure) as Fig 1A of Chen *et al.,* J Biol Chem. 2005 Nov 18; 280(46):38879-87. Using Adobe Photoshop, a forensic overlay analysis shows perfect overlay of the two blots for p-AktSer473 and p-AktThr308.[67]
4. A file located on the Respondent's hard drive labeled "pAkt-HDAC42&SAHA.tif", date created 02/02/2006, shows an unlabeled image in the process of being pieced together. The blots in the file appear to match the blots from the U87MG cell line p-^{473}Ser-Akt and p-^{308}Thr-Akt blots in Fig 1A of Chen J Biol Chem 2005. 280(46):38879-87.[68]
5. A file located on the Respondent's hard drive labeled "(S)-HDAC-42 Summary Report.pdf", date created 02/28/2007, shows a figure (Fig 2) with both cell lines and the concentration of HDAC-42 matching the original labeling of the PowerPoint file "HDACs in U87 and PC3.ppt", date created 05/12/05, and Fig 1A of Chen *et al.,* J Biol Chem. 2005 Nov 18; 280(46):38879-87.[69]
6. Using Adobe Photoshop, a forensic overlay analysis shows that the p-^{473}Ser-Akt and p-^{308}Thr-Akt blots labeled as PC3 cells and (S)-HDAC-42 concentration of 0.25, 1, 2.5 µM in the questioned Fig 4 of Clin Cancer Res 2006 are identical to the p-^{473}Ser-Akt and p-^{308}Thr-Akt blots labeled as U87MG and HDAC-42 concentration of 0.5, 2.5, 5 µM of Fig 1A of Chen *et al.,* J Biol Chem. 2005 Nov 18; 280(46):38879-87.[70]

Knowledge and Intent: Allegation #14, Fig 4A, Kulp *et al.,* Clin Cancer Res 2006

1. The presence of a PowerPoint presentation file, [redacted] of Chen *et al.,* J Biol Chem. 2005 Nov 18; 280(46):38879-87, that contains a figure that is identical to the published Fig 1A of Chen *et al.,* J Biol Chem. 2005 Nov 18; 280(46):38879-87 indicates that the Respondent was receiving data that was not originally manipulated.
2. At a later date (02/02/2006) on the Respondent's hard drive the figure now appears to be in the process being manipulated (file "pAkt-HDAC42&SAHA.tif") In this file, crop lines and pasting actions are obvious, suggesting that the Respondent was responsible for the intentional falsification of Fig 4 by mislabeling the concentration of HDAC-42 and cell type used in the experiment.
3. The act of cropping and pasting lanes into a blot so that it no longer matches or reflects the experimental data would cast doubt on these changes occurring through an honest error.

[67] ATT 27- 20170802 ORC Slide Deck 2, slide 4
[68] ATT 27- 20170802 ORC Slide Deck 2, slide 5
[69] ATT 27- 20170802 ORC Slide Deck 2, slide 6
[70] ATT 27- 20170802 ORC Slide Deck 2, slide 7, 10

Respondent's Response: Allegation #14, Fig 4A, Kulp *et al.,* Clin Cancer Res 2006

"Please note that the concentration range of (S)-HDAC-42 used in all Western blot analyses throughout this manuscript (0.25-2.5 μM) was lower than that used for the other HDAC inhibitor to which it was being compared (0.5-5 μM). This was done due to the higher potency of (S)-HDAC-42 relative to the other agents, and was the approach used for the experiments in this manuscript. In light of this experimental approach, I believe that the observed discrepancy between the research record and the published figure in the labeling of concentrations reflects an attempt to correct a typographical error. However, this article was published more than a decade ago, thus I cannot recall specifically when and how this change was made. As is the practice in our group, I believe that the direct source data for this figure was provided by one of the authors which I used to prepare the figure for publication. Moreover, I believe that the use of data from the U87MG cell line, instead of the intended cell type (PC-3), was a mistake. These two cell lines were tested at the same time, and as shown, these two sets of data bear a high degree of similarity, which might have caused this unintentional mistake. Again, I believe that the direct source data for this figure was provided by one of the authors which I used to prepare the figure for publication". [71]

Significance: Allegation #14, Fig 4A, Kulp *et al.,* Clin Cancer Res 2006

Manipulating data on compounds (HDAC-42) for which the specific end goal is to be tested in human clinical trials is highly significant and incredibly dangerous. The hypothesis of the research was that HDAC42 has stronger drug effects at lower concentrations than the first FDA-approved deacetylase inhibitor, suberoylanilide hydroxamic acid (SAHA, Vorinostat). By showing Western blot figures where the concentration of SAHA used is labeled as [0.5, 2.5, 5.0 μM] while the concentration of HDAC42 used is labeled [0.25, 1.0, 5 μM] it suggests an intent to support the conclusion that HDAC42 was more efficacious than SAHA. Based on the data files found on the Respondent's computer (in three different versions), it appears that both drugs were actually used at [0.5, 2.5, 5.0 μM] concentrations. The data reviewed do support the conclusion that HDAC42 has the reported effects, but they have been exaggerated by misrepresentation of the concentration of drug used to show those effects.

[71] ATT 28- 20170802-Responses to new allegations page 2

The Committee has determined that the falsification in Allegation #14 was performed by the Respondent based on forensic analyses and dating of retrieved files from the Respondent's hard drive. The falsification in the figure was used to falsely substantiate the claim that HDAC-42 is more efficacious than SAHA and to falsely provide pre-clinical support for the clinical exploration of HDAC-42.

Committee Conclusion: Allegation #14, Fig 4A, Kulp *et al.,* Clin Cancer Res 2006

By a preponderance of the evidence, the Committee finds by a vote of 3 in favor and 0 against, that the Respondent intentionally falsified the data in Figure 4A and this act constitutes Research Misconduct as described in the Policy III. A and 42 C.F.R. § 93.103 (b).

By clear and convincing evidence, the Committee finds by a vote of 3 in favor and 0 against, that the Respondent intentionally falsified the data in Figure 4A and this act constitutes Research Misconduct as described in the Policy III. A and 42 C.F.R. § 93.103 (b).

Manuscript # 8 - Allegation #15 - Western blot data were falsified by falsely labeling the p-AMPK blot when compared to the original research record in Figure 4C of Wang *et al.,* J Med Chem 2012. 55, 3827-3835.

Finding of Fact: Allegation #15, Fig 4C, Wang *et al.,* J Med Chem 2012

1. A figure located on the Respondent's hard drive in a file labeled "CG-5 CF3 48h western.tif", date created 08/27/2011, shows two panels of a composite Western blot with the labels of "CG-5" and "CF-3".
2. The p-AMK blot in the "CF3" panel shows a characteristic background artifact between lanes 5 and 6.[72]
3. Another figure located on the Respondent's hard drive in a file labeled "xFig.4.pdf", date created 10/30/2011, shows three panels of a composite Western blot with the labels of "Cpd 5", "Cpd 28", and "Cpd 30." (Note "Compound" = "Cpd".)

[72] ATT 27- 20170802 ORC Slide Deck 2, slide 13

4. Based on the characteristic background artifact seen between lanes 5 and 6 of the "CF3" p-AMK blot in the "CG-5 CF3 48h western.tif" figure, it appears that the p-AMK blot of the "Cpd 30" of "xFig.4.pdf" is identical.
5. All of the "CG-5" blots from "CG-5 CF3 48h western.tif", date created 08/27/2011, match the "Cpd 5" blots of the "xFig.4.pdf" figure. In contrast, all of the "CF3" blots from "CG-5 CF3 48h western.tif" date created 08/27/2011, except for p-AMKP, appear to match the "Cpd 28" blots of xFig.4.pdf" figure.
6. The "CF3" p-AMPK blot from "CG-5 CF3 48h western.tif", date created 08/27/2011, now appears as "Cpd30" in "xFig.4.pdf". The rest of the blots comprising the composite panel for "Cpd 30" in xFig.4.pdf come from unknown sources.
7. Using Adobe Photoshop, a forensic overlay analysis shows that lanes 1, and 3-6 of the p-AMPK blot "Cpd-30" blot of "xFig.4.pdf" are identical to lanes 1, and 3-6 of the p-AMPK blot of Fig 4C; however, lane 2 of the p-AMPK blot of "Cpd-30" blot of "xFig.4.pdf shows very low expression, lane 2 of p-AMPK blot of Fig 4C shows a much darker band that appears to have been cropped and pasted into the published Fig 4C.[73]
8. The source of the lane 2 in the published Fig 4C is unknown.

Knowledge and Intent: Allegation #15, Fig 4C, Wang *et al.,* J Med Chem 2012

1. While the precise relationship between CF3, compound 28, and compound 30 is unknown, it is the Committee's understanding that compound 28 and compound 30 represent different modifications of Compound 5 and therefore should not have blots (images) coming from an experiment originally labeled as experimental results from testing CF3. It is possible that CF3 is being used to indicate 'compound 30'. If true, then part of the data in "xFig.4.pdf" may be valid but regardless, it can't be correct for both compound 30 and compound 28.
2. The act of cropping and pasting lanes into a blot so that it no longer matches or reflects the experimental data would cast doubt on these changes occurring through an honest error.
3. The Respondent's response on August 2, 2017 does not explain how a single blot, easily identified by a unique background artifact, appears in two computer files – labeled with different compound names, and then appears in a published figure but only partially (only lanes 1, 2-4) and with lane 2 having a different data pasted in. New data from a repeated experiment provided by the Respondent would not have the same unique background artifact.

Respondent's Response: Allegation #15, Fig 4C, Wang *et al.,* J Med Chem 2012

"Figures were prepared via different stages during the preparation of a manuscript, and when new data were provided, these new data would replace the original data to make a new version of the figure. It is likely that I was provided with the new p-AMPK blot

[73] ATT 27- 20170802 ORC Slide Deck 2, slide 16

during the preparation of the final Fig. 4 for publication, which is different from xFig. 4. Manuscripts and figures were distributed to all authors for review, but these discrepancies were not brought to my attention. Thus, these discrepancies were not addressed"[74]

Significance: Allegation #15, Fig 4C, Wang *et al.,* J Med Chem 2012

Manipulating data on compounds for which the specific end goal is to provide to the compounds to be tested in human clinical trials is highly significant and incredibly dangerous. The Committee has determined that the falsification in Allegation #15 was performed by the Respondent based on forensic analyses and dating of retrieved files from the Respondent's hard drive. The falsification in the figure was presumably performed to present desired or anticipated findings for compounds that were not in existence.

Committee Conclusion: Allegation #15, Fig 4C, Wang *et al.,* J Med Chem 2012

By a preponderance of the evidence, the Committee finds by a vote of 3 in favor and 0 against, that the Respondent intentionally falsified the data in Figure 4C and this act constitutes Research Misconduct as described in the Policy III. A and 42 C.F.R. § 93.103 (b).

By clear and convincing evidence, the Committee finds by a vote of 3 in favor and 0 against, that the Respondent intentionally falsified the data in Figure 4C and this act constitutes Research Misconduct as described in the Policy III. A and 42 C.F.R. § 93.103 (b).

[74] ATT 28- 20170802-Responses to new allegations page 3

Manuscript # 9 - Allegation #16 - Splice line in left panel (PC-3) cells of Western blot between lanes 3 and 4 in Figure 7B of Zhu *et al.,* Cancer Res 2004. 64, 4309-4318

Finding of Fact: Allegation #16, Fig 7B, Zhu *et al.,* Cancer Res 2004

1. Using Adobe Photoshop analysis, there appears to be a splice line between lanes 3 and 4 in Figure 7B.
2. At this time no original research records have been identified in which to compare published data.

Knowledge and Intent: Allegation #16, Fig 7B, Zhu *et al.,* Cancer Res 2004

1. The act of cropping and pasting lanes into a blot so that it no longer matches or reflects the experimental data would cast doubt on these changes occurring through an honest error.

Respondent's Response: Allegation #16, Fig 7B, Zhu *et al.,* Cancer Res 2004
"Consistent with the process by which we have prepared figures for publication, I am certain that I was provided with the western blot data included in this figure by one of the co-authors. Because this manuscript was from 2004, I could not recall what had happened, and the original blot could not be located to verify this figure." [75]

Significance: Allegation #16, Fig 7B, Zhu *et al.,* Cancer Res 2004

The Committee has not been able to definitively determine that the apparent falsification in Allegation #16 was performed by the Respondent, due to the lack of supporting forensic analyses and the unavailability of additional electronic files from the Respondent's hard drive as well as original records. The falsification in the figure was used to falsely provide preclinical support for the clinical exploration of OSU-03012[76].

Committee Conclusion: Allegation #16, Fig 7B, Zhu *et al.,* Cancer Res 2004

The Committee did conclude that the image had been manipulated, however the lack of any research records made it impossible for the Committee to determine if the manipulations constituted Research Misconduct. Under the federal regulations, *"The*

[75] ATT 28- 20170802-Responses to new allegations page 4
[76] The 20170912 CIC Final Report was mislabeled as "The falsification in the figure was used to falsely substantiate the claim that HDAC-42 is more efficacious than SAHA and to falsely provide preclinical support for the clinical exploration of HDAC-42." This revision shows the correction.

destruction, absence of, or respondent's failure to provide research records adequately documenting the questioned research is evidence of research misconduct where the institution or HHS establishes by a preponderance of the evidence that the respondent intentionally, knowingly, or recklessly had research records and destroyed them, had the opportunity to maintain the records but did not do so, or maintained the records and failed to produce them in a timely manner and that the respondent's conduct constitutes a significant departure from accepted practices of the relevant research community." 42 C.F.R. §93.106(b)(1). As Manuscript #9 was published in 2004, the lack of research records in 2017 was not considered by the Committee to be evidence of deliberate destruction of research records or an unwillingness to retain such records. Therefore, by a preponderance of the evidence, the Committee finds by a vote of 0 in favor and 3 against, that the Respondent intentionally, knowingly, and/or recklessly falsified the data in Figure 7B and this act does not constitute Research Misconduct as described in the Policy III. A and 42 C.F.R. § 93.103 (b).

By clear and convincing evidence, the Committee finds by a vote of 0 in favor and 3 against, that the Respondent intentionally, knowingly, and/or recklessly falsified the data in Figure 7B and this act does not constitute Research Misconduct as described in the Policy III. A and 42 C.F.R. § 93.103 (b).

Manuscript # 10 - Allegation #17 - Splice lines between lanes 1 and 2 in the BIM blot and between lanes 3 and 4 in the GAPDH blot in Figure 4 [redacted]

Finding of Fact: Allegation #17, Fig 4, [redacted]

1. Splice lines in Fig 4 are apparent by visual examination between lanes 1 and 2 in the BIM blot and between lanes 3 and 4 in the GAPHD blot.
2. At this time no original research records have been identified in which to compare published data.
3. Using Adobe Photoshop analysis, the splice lines are confirmed in the published figure.

Knowledge and Intent: Allegation #17, Fig 4, [redacted]

1. As there are not consistent splice lines between all lanes 1 and 2 or lanes 3 and 4 within all the blots in the published composite Fig 4 it is unlikely that the splice lines were due to poor experimental set up (e.g., all of the samples for lane 2 and 3 being run on a different gel so that they had to be added into a final figure).
2. The act of cropping and pasting lanes into a blot so would cast doubt on these changes occurring through an honest error.

Respondent's Response: Allegation #17, Fig 4, [redacted]
Dr. Chen's written response*: "I collaborated with* [redacted] *, on this project, but my role was limited to providing OSU- 03012 and my expertise on this agent. I was not involved in doing any of the experiments, nor did I take part in preparing the manuscript or any of the figures."*[78]

Significance: Allegation #17, Fig 4, [redacted]

The committee has not been able to conclusively determine that fabrication or falsification by the Respondent occurred in connection with Allegation #17. Whereas the Adobe photoshop analysis confirmed the presence of splice lines, suggesting the act of cropping and pasting lanes into the blot shown in Fig. 4, there is no evidence that the Respondent prepared any of the figures for this manuscript on his computer. As stated in his written response, this work was a collaboration [redacted] and, according to his unverified testimony, the Respondent's only role was to provide OSU-03012.

[77] [redacted]
[78] ATT 28- 20170802-Responses to new allegations, page 1

Committee Conclusion: Allegation #17, Fig 4, [redacted]

By a preponderance of the evidence, the Committee finds by a vote of 0 in favor and 3 against, that the Respondent intentionally, knowingly, and/or recklessly falsified the data in Figure 4 and this act does not constitute Research Misconduct as described in the Policy III. A and 42 C.F.R. § 93.103 (b).

By clear and convincing evidence, the Committee finds by a vote of 0 in favor and 3 against, that the Respondent intentionally, knowingly, and/or recklessly falsified the data in Figure 4 and this act does not constitute Research Misconduct as described in the Policy III. A and 42 C.F.R. § 93.103 (b).

Manuscript #11 - Allegation #18 - Falsification/fabrication and falsely labeling of Western blot data when compared to the original research record in Figures 4A and 4B of Weng *et al.,* Mol Cancer Ther 2008. 7, 800-808.

Finding of Fact: Allegation #18, Fig 4A, Fig 4B, Weng *et al.,* Mol Cancer Ther 2008

Figure 4A

1. In a PowerPoint Presentation labeled "Figures.ppt", date created 12/26/2006, located on the Respondent's hard drive, there is a slide (7) showing a Western blot representing the same experiment as Fig 4A.
2. All of the blots from the "Figures.ppt" Western blot are identical to the blots in the published Fig 4A, except for the p-Akt blots for the MDA-MB-231 samples.
3. For the p-Akt blots for the MDA-MB-231 samples, the actin loading sample from the original record "Figures.ppt" are used in the published Fig 4A, but the experimental p-Akt blots are not used.

Figure 4B

1. In a PowerPoint presentation labeled "Figures", date created 12/26/2006, located on the Respondent's hard drive, there is a slide (8) containing Western blots representing the same experiment performed in both MCF-7 and MDA-MB-231 cell lines.
2. When Fig 4B, purported to represent data for MDA-MB-231cells only, is compared to the Western blots described above, it is apparent that certain portions of the figure represent data obtained in experiments using the MCF-7 cell line while other portions were taken from experiments using the MDA-MB-231 cell line. Specifically:

a. Blots for p-AKT, p-p38, Pp-27, and actin come from experiments using MDA-MB-231 cells
b. Blots for total AKT, p-GSK3α/β, and PARP come from experiments using the MCF-7 cells

3. The last lane of the p-p38 and PARP blots of Fig 4B do not match the original research record, while the first seven lanes in both blots do match perfectly.

Knowledge and Intent: Allegation #18, Fig 4A, Fig 4B, Weng *et al.,* Mol Cancer Ther 2008

Figure 4A

1. For 4A, original research records match all of the published data, including the loading controls, with the exception of the p-Akt blots for MDA-MB-231, bringing into question the authenticity of the p-Akt blots in the published image.
2. In order for a different experiment to provide the p-AKT blots for the published image, a separate specific loading control blot would be required for scientific accuracy.

Figure 4B

1. The act of cropping and pasting lanes into a blot so that it no longer matches or reflects the experimental data would cast doubt on these changes occurring through an honest error.

Respondent's Response: Allegation #18, Fig 4A, Fig 4B, Weng *et al.,* Mol Cancer Ther 2008

"The manuscript was published after a major revision. In the original submission, Fig. 4A was identical to that shown in Slide 7 (see figure from original submission below). However, Reviewer 1 commented, "The bottom panel of Figure 4A showing a western blot of MDA-MB-231 in response to Tamoxifen is not acceptable in its present form. Immunoblot signals pertaining to phosphor-Akt in panel B is much better than the one in panel A for the same cell line." Therefore, the same cell lysates were used to repeat the western blot, which was used in the resubmission (please see Tam+ OSU revision.ppt, and image provided below). As for Fig. 4B, it is likely that I was provided with the data during the preparation of the final figure for publication. I suspect that there was an unintentional mix-up of blots from both cell lines due to similarities between these two sets of data. Similarly, the manuscript and figures were distributed to all authors for review, but these discrepancies were not brought to my attention. Thus, these discrepancies were not addressed." [79]

Significance: Allegation #18, Fig 4A, Fig 4B, Weng *et al.,* Mol Cancer Ther 2008

The Committee has determined that the Respondent intentionally falsified data in Figure 4A. As indicated in the Respondent's response, the Western blot for p-Akt of

[79] ATT 28- 20170802-Responses to new allegations, page 5,6

MDA-MB-231 was repeated in response to a reviewer's comment that the original blot was not acceptable. The Respondent then used a different p-Akt blot with the same actin control blots as in the original data. It is likely that this substitution was made because the data in Figure 4A more convincingly support the conclusion that phosphorylation of Akt is only transiently upregulated in response to tamoxifen.

The Committee has determined that the Respondent also intentionally falsified data in Figure 4B. Based on figures found on the Respondent's hard drive, it is clear that data from two different cell lines were used for the data represented as from MDA-MB-231 in Figure 4B. In addition, bands were cut and paste from an unidentified source into the final OSU-03012 lane. These manipulations were likely performed to strengthen the conclusions of the experiments (as stated on page 806-807 of *Mol. Cancer Ther* 2008) including: (1) OSU-0312 interacted with tamoxifen to reduce in a dose-dependent manner the phosphorylation of Ser21/Ser9-GSK3α/β, and (2) the level of phosphorylated Thr180/Tyr182-p38 MAPK remained unaltered in drug-treated cells. In addition, the Akt blot was substituted to show that the total Akt control was uniform under all conditions.

Committee Conclusion: Allegation #18, Fig 4A, Fig 4B, Weng *et al.,* Mol Cancer Ther 2008

By a preponderance of the evidence, the Committee finds by a vote of 3 in favor and 0 against, that the Respondent intentionally falsified the data in Figures 4A and 4B and this act constitutes Research Misconduct as described in the Policy III. A and 42 C.F.R. § 93.103 (b).

By clear and convincing evidence, the Committee finds by a vote of 3 in favor and 0 against, that the Respondent intentionally falsified the data in Figures 4A and 4B

and this act constitutes Research Misconduct as described in the Policy III. A and 42 C.F.R. § 93.103 (b).

Manuscript #12 - Allegation #19 - Falsification of two Western blots by falsely labeling the dosage of HDAC42 used when compared to the original research record in Figures 2B and 2C of Chen *et al.,* Cancer Res 2007. 76; 11, 5318-5327.

Finding of Fact: Allegation #19, Fig 2B, Fig 2C, Chen *et al.,* Cancer Res 2007

Figure 2B

1. A PowerPoint presentation "KU70 (05).ppt", date created 08/04/2006, was located on the Respondent's hard drive. Slide 3 from the presentation shows a Western blot of Ku-70 protein expression after 0.5 or 5.0 μM treatment of HDAC-42S and other drug treatments.
2. Using Adobe Photoshop, a forensic overlay analysis shows that the Ac-Lys blot from published Fig 2B is identical to the AC-K (Ac-Ku-70) Western blot from the presentation. However in published Fig 2B, the concentration of HDAC42 is labeled as 0.25 and 1 μM.
3. Notably, the other drug treatments (SAHA, MS-275 and TSA) are correctly labeled in Fig 2B when compared to the "KU70 (05).ppt" Western blot.

Figure 2C

1. A PowerPoint presentation "KU70 (05).ppt", date created 08/04/2006, was located on the Respondent's hard drive. Slide 4 from the presentation shows a Western blot of Ku-70 protein expression after 0.1, 0.5 or 1.0 μM treatment of HDAC-42S or MS-275 treatments
2. Using Adobe Photoshop, a forensic overlay analysis shows that the Ku-70 blot lanes 2-5 from published Fig 2C are identical to lanes 2-5 of above described Ku-70 blot in "KU70 (05).ppt" presentation.
3. Using Adobe Photoshop, a forensic overlay analysis shows that the Ku-70 blot lanes 1 (DMSO) and 6 (MS-275, 5 μM) of Fig 2C do not match lanes 1 and 6 of the original research record.
4. Additionally, in Fig 2C, the concentration of HDAC42 treatment is labeled as 0.25, 0.5 and 1 μM, which is inconsistent with the original research record

Knowledge and Intent: Allegation #19, Fig 2B, Fig 2C, Chen *et al.,* Cancer Res 2007

Figure 2B

1. The fact that all other compounds are correctly labeled in the figure with the exception of HDAC42, would cast doubt that the mislabeling occurred through an honest error.
2. Mislabeling the concentration of HDAC42 in the published figure would misled readers about the effects of HDAC42 treatment.

Figure 2C

1. The act of cropping and pasting lanes into a blot would cast doubt on these changes occurring through an honest error.
2. Unlike what is seen in Figure 2B, in Figure 2C it appears that the mislabeling of the concentration of HDAC42 was misreported at 2.5X higher than what was actually used in the original research record. Out of the three concentrations used in the original research record, only the lowest concentration was mislabeled in the published Figure 2C.

Respondent's Response: Allegation #19, Fig 2B, Fig 2C, Chen *et al.,* Cancer Res 2007
"*The identified differences in the labels for the HDAC-42S concentrations are most likely the result of typographical errors (either in the original data or the published figures), which, however, were not identified by co-authors in the course of preparing the manuscript. In the case of Fig. 4B, the situation is like that identified in Fig. 4A in Manuscript #7 in which a lower concentration range was typically used for the more potent HDAC-42."*[80]

Significance: Allegation #19, Fig 2B, Fig 2C, Chen *et al.,* Cancer Res 2007

The Committee has determined that the Respondent intentionally falsified data in Figure 2B. Based on figures found on the Respondent's hard drive, lower concentrations of HDAC42 were reported in the paper than were actually used in the experiment. This was likely done to show increased potency of HDAC42 compared to inhibitors SAHA and MS-275. In addition, the Ku70 and Ku80 blots were likely falsified to support the conclusion that acetylation of Ku70 did not affect complex formation with Ku80 as the ratio of these two proteins in the immunoprecipitates remained unchanged, as stated on page 5321 of Chen *et al., Cancer Res* 2007.

In the case of Figure 2C, the Committee remains unconvinced, based on the available evidence and in the absence of formal forensic analyses, that the blots in the 20170718 AR42 Assessment for COPIC ppt (slide 2) are the same (smile lines and many smears do not appear to match). Even if they match, the Committee considered it unlikely

[80] ATT 28- 20170802-Responses to new allegations, page 6

that changes to the figure could have been made intentionally, as Figure 2C reports a higher concentration of HDAC42 than in the hard drive data slide.

Committee Conclusion: Allegation #19, Fig 2B, Fig 2C, Chen *et al.,* Cancer Res 2007

By a preponderance of the evidence, the Committee finds by a vote of 3 in favor and 0 against, that the Respondent intentionally falsified the data in Figure 2B (but not Figure 2C) and this act constitutes Research Misconduct as described in the Policy III. A and 42 C.F.R. § 93.103 (b).

By clear and convincing evidence, the Committee finds by a vote of 3 in favor and 0 against, that the Respondent intentionally falsified the data in Figure 2B (but not Figure 2C) and this act constitutes Research Misconduct as described in the Policy III. A and 42 C.F.R. § 93.103 (b).

Manuscript #13 - Allegation #20 - Falsification of a Western blot by falsely labeling the protein examined when compared to the original research record in Figure 4D of Lu *et al.,* Hepatology 2007. 46, 1119-1130.

Finding of Fact: Allegation #20, Fig 4D, Lu *et al.,* Hepatology 2007

1. In a figure found in a file on the Respondent's hard drive labeled "MS Figures", date created 11/18/2006, there is an identical composite Western blot to published Figure 4D.
2. Of the five proteins represented in the figure, four of them (Ac=H3, Ac-tubulin, Bcl-Xl, beta-actin) match the published labeling. However, in the "MS Figures" file, the data for the fourth panel is labeled as cIAP-1, while the published fourth panel is labeled as cIAP-2.

Knowledge and Intent: Allegation #20, Fig 4D, Lu *et al.,* Hepatology 2007

1. The figure legend for published Figure 4D states “cIAP-1” so there is a strong possibility that the mislabeling of the figure could be the result of an honest error occurring during the preparation of the figure.

Respondent's Response: Allegation #20, Fig 4D, Lu *et al.,* Hepatology 2007
"This mislabeling was attributable to a typographical error. Please note that the legend of Fig. 4D identifies the use of cIAP-1 as a biomarker (underlined in red). Moreover, in this manuscript, we have tested the effect of HDAC42 on the expression of both cIAP-1 and cIAP-2 (Fig. 3A as shown below). Thus, I am certain that the blot was unintentionally mislabeled as cIAP-2, instead of cIAP-1, an error that was not identified by co-authors in the course of manuscript preparation."[81]

Significance: Allegation #20, Fig 4D, Lu *et al.,* Hepatology 2007

The Committee has determined that no fabrication or falsification by the Respondent occurred in connection with Allegation #20. The committee has determined that the Respondent likely made an honest error during the figure preparation, which led to a misreporting in Figure 4D that states 'cIAP-2' instead of 'cIAP-1'. The legend in the same figure stating the blot as cIAP-1 and not cIAP-2 supports the Respondent's claim, and additionally, the effect of HDAC42 on the expression of both cIAP-1 and cIAP-2 is reported elsewhere in the same manuscript. Thus, the Committee considers there would be no advantage in intentionally making such an alleged substitution.

Committee Conclusion: Allegation #20, Fig 4D, Lu *et al.,* Hepatology 2007

By a preponderance of the evidence, the Committee finds by a vote of 0 in favor and 3 against, that the Respondent intentionally, knowingly, and/or recklessly falsified the data in Figure 4D and this act does not constitute Research Misconduct as described in the Policy III. A and 42 C.F.R. § 93.103 (b).

By clear and convincing evidence, the Committee finds by a vote of 0 in favor and 3 against, that the Respondent intentionally, knowingly, and/or recklessly falsified the data in Figure 4D and this act does not constitute Research Misconduct as described in the Policy III. A and 42 C.F.R. § 93.103 (b).

[81] ATT 28- 20170802-Responses to new allegations, page 7

Manuscript # 14 - Allegation #21 - Falsification of Western blot data by the reuse of three (3) loading control beta-actin in Figure 4 [redacted]

Finding of Fact: Allegation #21, Fig 4, [redacted]

1. Using Adobe Photoshop, a forensic overlay analysis shows that Figure 3H actin blot is identical the left-most actin blot of Figure 4B; Figure 3F actin blot when flipped over is identical to the middle actin blot of Figure 4B; and Figure 3A actin blot is identical to the right-most actin blot of Figure 4B.
2. At this time no original research records have been identified in which to compare published data.

Knowledge and Intent: Allegation #21, Fig 4, [redacted]

Respondent's Response: Allegation #21, Fig 4, [redacted] Dr. Chen's written response: "[redacted] *My role was limited to providing AR-42 and other agents and my expertise on histone deacetylases. I was not involved in doing any of the experiments, nor did I take part in preparing the manuscript or any of the figures."*[82]

Significance: Allegation #21, Fig 4, [redacted]

The Committee has not been able to definitively determine that the Respondent conducted falsification in connection with Allegation #21. Despite the deliberate reuse of the same β-actin blots in Figure 3 and Figure 4B, there is no evidence that the Respondent prepared any of the figures in this manuscript [redacted]. In addition, the Respondent testifies his participating role as to only providing AR-42 (and other agents) to the research team and sharing his expertise on histone deacetylases and not conducting any of the experiments or preparing figures. Additionally, [redacted] does not publish individual author contributions that do not permit understanding the role of co-authors.

[82] ATT 28- 20170802-Responses to new allegations, page 1

Committee Conclusion: Allegation #21, Fig 4, [redacted]

By a preponderance of the evidence, the Committee finds by a vote of 0 in favor and 3 against, that the Respondent intentionally, knowingly, and/or recklessly falsified the data in Figures 3 and 4B and this act does not constitute Research Misconduct as described in the Policy III. A and 42 C.F.R. § 93.103 (b).

By clear and convincing evidence, the Committee finds by a vote of 0 in favor and 3 against, that the Respondent intentionally, knowingly, and/or recklessly falsified the data in Figures 3 and 4B and this act does not constitute Research Misconduct as described in the Policy III. A and 42 C.F.R. § 93.103 (b).

Corrections/Retractions

Chu *et al.*, Carcinogenesis 2013. 34; 12, 2694–2705
Correction posted on November 21, 2016[83]

"The authors of the manuscript referenced above wish to inform readers of corrections to Figs. 2A, 2F, and 8A in response to issues recently brought to the attention of the authors. In the original Fig. 2, the image of the blot of Sp1 in Fig. 2A is the same as the Sp1 blot in the left panel of Fig. 2F, resulting from the unintentional incorporation of the same image in two different figure panels. In the western blot panel of the immunoprecipitation experiment shown in the original Fig. 8A, an inconsistency between the background of the blot and the area surrounding the bands in lanes 4 and 5 was detected. Attempts to identify the correct Sp1 blot for each of the figure panels in Fig. 2 and to verify the data in Fig. 8 were unsuccessful as the original films of these blots could not be located. Consequently, the experiments were repeated by an individual in the corresponding author's laboratory who was not involved in the conduct of the experiments reported in the original article. The new results are essentially identical to those acquired previously and lead to the same conclusions reported in the original article. The corrected figure panels containing this new data are shown below.

The authors regret the error in Fig. 2A and the anomaly in Fig. 8A, which they cannot explain, and apologize for not identifying these issues earlier in the publication process. The authors appreciate and acknowledge the contribution of Dr. Hsiao-Ching Chuang, who repeated the experiments."

[83] ATT 29- Correction-Carcinogenesis 2013.pdf

Culpability of Co-Authors

Based on the evidence reviewed by the Investigation Committee, including statements made by Dr. Chen and other co-authors, the Investigation Committee believes that for the papers on which Dr. Chen was the corresponding author (manuscripts #1-5, #7-9, #11-13), Dr. Chen was solely responsible for the Research Misconduct identified. The Investigation Committee found no evidence of any intentional, knowing, or reckless behavior by any of the other co-authors to indicate a potential role by anyone other than Dr. Chen in the misconduct. Further, during the course of the proceedings, Dr. Chen did not provide any credible evidence that any of the other co-authors were involved in or were aware of the Research Misconduct and therefore, the Investigation Committee believes that none of the other co-authors should be named formal Respondents.

The Investigation Committee did note [redacted]

[84] ATT 47 - [redacted]

[redacted]

Respondent's Response to Preliminary Report

As required under the Policy, the Investigation Committee's Preliminary Report[86] was provided to Dr. Chen on August 11, 2017, along with all referenced materials, and Dr. Chen was given thirty (30) days to review and provide written comments. On September 1, 2017, Dr. Chen provided his response via email to Dr. Yucel and the Investigation Committee.[87,88] In his response, Dr. Chen did not deny or dispute any of the findings of the Investigation Committee. Dr. Chen requested only that the Investigation Committee consider allowing corrections to be submitted for manuscripts #2, #3, and #4

[85] ATT 46- 20160725-Chen CII Interview
[86] ATT 41 - 20170811 - CIC Preliminary Report - Chen
[87] ATT 42- 20170901- Email Chen to RIO Response to report
[88] ATT 43- 20170901 - Chen Response to CIC report

rather than requiring full retraction of those articles. Dr. Chen's response included images of what he indicated were recently conducted repeat experiments for many of the falsified images. Dr. Chen noted in his response that the results obtained were "*essentially identical to those published previously and lead to the same conclusions reported in the original article."* [89]

On September 8, 2017, the Investigation Committee met to review Dr. Chen's written response and consider any changes that might be needed to the report based on Dr. Chen's response. Following review and discussion, the Investigation Committee stands by their original conclusions and recommended actions relating to Dr. Chen and the disposition of the manuscripts. The Investigation Committee feels strongly that for manuscripts where it has been determined that there was intentional Research Misconduct, the only appropriate action is retraction rather than correction of those manuscripts. Therefore, no changes have been made to the Investigation Committee's conclusions or recommended actions with the exception of the addition of a requirement that the College of Pharmacy put in place a data oversight committee to review and approve all data generated by the Chen laboratory in any current or future proposals or manuscript submissions.

Summary of Investigation Committee Conclusions

Regarding an allegation of Research Misconduct by falsification of research, as defined under the University's Policy and Procedures Concerning Research Misconduct, "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

[89] ATT 43- 20170901 - Chen Response to CIC report

research record." Further, a finding of Research Misconduct requires that there is a significant departure from accepted practices of the relevant research community, that the misconduct be committed intentionally, knowingly, or recklessly, and that the allegation be proved by a "Preponderance of the Evidence" under the federal regulations and by "Clear and Convincing Evidence" under the University Policy for faculty members.

Based on the federal requirements, the College Investigation Committee determined that for fourteen (14) of the twenty-one (21) allegations, Dr. Chen committed Research Misconduct by deviating from the accepted practices of image handling and figure generation and intentionally falsified data in [Manuscript #1 (Figs 4A, 6C); Manuscript #2 (Figs 1B, 3A, 3B); Manuscript #3 (Figs 1A, 8A); Manuscript #4 (Figs 1D, 5A); Manuscript #7 (Fig 4A); Manuscript #8 (Fig 4C); Manuscript #11 (Figs 4A, 4B); and Manuscript #12 (Fig 2B)]. For Manuscript #5 (Fig 2A), the committee found that Dr. Chen committed Research Misconduct by deviating from the accepted practices of figure generation and acting "recklessly" by not reviewing or scrutinizing the data provided to him leading to the inappropriate reuse of data (Falsification).

The Committee determined that for three (3) of the twenty-one (21) allegations [Manuscript #1 (Fig 7C), Manuscript #3 (Fig 2F) and Manuscript #13 (Fig 4D)], the data irregularities identified were the result of 'honest error' by the Respondent during the generation of the figures.

The Committee determined that for one (1) of the twenty-one (21) allegations [Manuscript #5 (Fig 3B)], the allegation regarding possible falsification of the figure was not substantiated as they did not believe that the forensic analysis of the figure demonstrated that data had been reused. The Committee also determined that Figure 2C,

in Manuscript #5 (a subpart of allegation #12) was not substantiated as they did not believe that the forensic analysis of the figure demonstrated that data had been reused.

The Committee determined for the last three (3) of the twenty-one (21) allegations [Manuscript #9 (Fig 7B), Manuscript #10 (Fig 4), Manuscript #14 (Fig 4)], the figures in question did appear to have been Falsified in some manner, however due to the lack of evidence and research records it was not possible for the Committee to determine clearly what had been done, the source of the data used, and who had committed the actions in question. Additionally, in the case of Manuscripts #10 and #14, Dr. Chen was not the corresponding author of the manuscripts and Dr. Chen has stated that he did not provide the figures or data in question. Without access to the original research records there is no way for the Committee to verify or refute Dr. Chen's statement.

Based on University requirements dictated by Senate Rule 3335-5-04, the College Investigation Committee has made the identical determinations, as outlined above for the federal requirements, with one exception. In the case of Manuscript #5 (Fig 2A), the Committee does not find that the evidence meets the Clear and Convincing standard and would therefore not constitute Research Misconduct for that allegation.

Recommended Actions

Under the University Policy and Procedures Concerning Research Misconduct, section IV.F.5, the Committee shall include recommended sanctions in cases where allegations of Research Misconduct are substantiated. Given the serious nature and scope of the Research Misconduct findings against Dr. Chen, the committee recommends that the following sanctions be imposed:

1. Immediate termination of employment.

2. RETRACTIONS - Dr. Chen be required to work with the Institution and the other co-authors in contacting the following journals requesting the immediate retraction of the following manuscripts:

    a. Manuscript #1 - Guh et al., J Med Chem 2010. 53, 2552–2561

    b. Manuscript #2 - Lee et al., PLoS One 2013. 8; 6, e67149

    c. Manuscript #3 - Chu et al., Carcinogenesis 2013. 34; 12, 2694–2705

    d. Manuscript #4 - Lai et al., Carcinogenesis 2014. 35;10, 2203–2213

    e. Manuscript # 7 - Kulp et al., Clin Cancer Res 2006. 12; 17, 5199-5206

    f. Manuscript # 8 - Wang et al., J Med Chem 2012. 55, 3827-3835

    g. Manuscript # 11 - Weng et al., Mol Cancer Ther 2008. 7, 800-808

    h. Manuscript # 12 - Chen et al., Cancer Res 2007. 76; 11, 5318-5327

3. CORRECTIONS - Dr. Chen be required to work with the Institution and the other co-authors in contacting the following journals to process corrections for the following manuscripts. In the event that figures cannot be corrected with verified original research records, then retractions will be required:

    a. Manuscript # 5 - Chou et al., Cancer Res 2014. 74; 17, 4783–4795, correction of Figure 2A

    b. Manuscript #9 - Zhu et al., Cancer Res 2004. 64, 4309-4318, correction of Figure 7B

    c. Manuscript # 13 - Lu et al., Hepatology 2007. 46, 1119-1130, correction of Figure 4D

4. OTHER NOTIFICATIONS - The Institution, with the assistance of Dr. Chen, to contact the corresponding authors of the following manuscripts and take the appropriate actions to process corrections of the identified figures. In the event that the figures cannot be corrected with verified original research records, then retractions will be required:

    a. Manuscript #10 - [redacted], correction of Figure 4. [redacted]

    b. Manuscript #14 – [redacted] correction of Figures 3 and 4. [redacted]

    c. Notification of allegations of possible Research Misconduct to home Institutions listed for Manuscript # 6 – [redacted]

    d. Notifications to all co-authors on all corrected or retracted manuscripts.

5. College of Pharmacy Oversight Committee – The College of Pharmacy will put in place a faculty committee with appropriate scientific expertise to review and approve all data prior to submission for all current and future manuscripts or proposals containing data generated by the Chen laboratory to ensure the integrity of the data and the reported results.

Length of Proceedings

The hearings and report took longer to complete due to the extensive nature of the allegations, spanning a large number or manuscripts containing many questioned figures. The Ohio State University Office of Research Compliance obtained the appropriate extensions to the deadline from the Office of Research Integrity during this process.[90,91,92,93,94]

[90] ATT 30- 20170605 - Email RIO to ORI Extension Request
[91] ATT 31- 20170605 - ORI extension request
[92] ATT 32- 20170605 - Email ORI to RIO granting extension
[93] ATT 44- 20170905 - ORI extension request
[94] ATT 45- 20170906 - Email ORI to RIO Extension Approval

Appendix

Complainant:

Anonymous

Respondent:

Dr. Ching-Shih Chen, University Professor and Lucius A. Wing Chair of Cancer Research and Therapy, Dr. Ching-Shih Chen, Department of Medicinal Chemistry and Pharmacognosy, College of Pharmacy

Respondent's Counsel:
David T. Ball, Esq., Rosenberg & Ball Co., LPA, 395 North Pearl St., Granville, OH 43023

Known PHS Federal Research Support:

National Institute of Health National Cancer Institute 1 R01 CA112250 – Closed as of 2/8/2017. Cited as funding support in Manuscripts 1, 2, 3, 4, 5, 7, 8, 12, 13

National Institute of Health 1 R21 CA158807 – Closed, funding from 2011-2012. Cited in Manuscript #5 as funding support. ORC reviewed and found that Figure 2C in grant proposal version 01 (submitted 6/16/2010) is same as Fig 6C in Manuscript #1 that has been determined to be falsified. Falsified figure did not appear in grant proposal version 01A1, submitted 03/16/2011 (funded version).
National Institute of Health 1 R01 CA172576-01A1 – Current Active Grant – ORC reviewed 01 and 01A1 versions and Progress Reports submitted in 2015 and 2016. None of the falsified images identified in this report were used in the Progress Reports, no evidence of manipulated figures.

National Institute of Health 1 R01 CA094829-01 – Closed, funding from 2001-2005. Cited as funding support for Manuscripts #7 and #9. ORC Reviewed Progress Reports from 2002 – 2006. None of the falsified images identified in this report were used in the Progress Reports. ORC did not have access to funded 01 version from 6/11/2001 so it was not reviewed.

NCI R01CA197944 (Chen is Co-PI) – not yet reviewed
NIAID R01AI116917 (Chen is Co-PI) – not yet reviewed

1 R21 AI135336-01 (PENDING) – Reviewed by ORC, None of the falsified images identified in this report were used in the proposal. Proposal does cite Manuscripts #7 and #13 in 'Contributions to Science' session but citation is not to specific data. Pending IRG review.

1 S10 OD012724-01 (WITHDRAWN) – ORC reviewed version 01, none of the falsified images identified in this report were used in the proposal. No evidence of manipulated figures.

1 R21 CA173502-01 (WITHDRAWN) – ORC reviewed version 01, Figure 2 in the proposal is the same as falsified Fig 1D in Manuscript #4. Figure 5B in the proposal is the same as falsified Fig 5A in Manuscript #4.

1 R21 CA188974-01 (WITHDRAWN) – ORC reviewed version 01, none of the falsified images identified in this report were used in the proposal. No evidence of manipulated figures.

1 R01 CA190620-01 (WITHDRAWN) - ORC reviewed version 01, none of the falsified images identified in this report were used in the proposal. No evidence of manipulated figures.

1 R01 CA208397 (WITHDRAWN/ NOT DISCUSSED) – ORC reviewed both version 01 and 01A1, none of the falsified images identified in this report were used in the proposal. No evidence of manipulated figures.

Committee Members:

- Dr. Alex Sparreboom (Chair), Professor, Pharmaceutics and Pharmaceutical Chemistry, College of Pharmacy
- Dr. Rajgopal Govindarajan, Associate Professor, Pharmaceutics and Pharmaceutical Chemistry, College of Pharmacy
- Dr. Karin Musier-Forsyth, Ohio Eminent Scholar, Professor, Chemistry and Biochemistry, College of Arts and Sciences

OSU Research Integrity Officers/Office of Research Compliance Staff:

- Dr. Jennifer K. Yucel, Associate Vice President & Research Integrity Officer, Office of Research Compliance
- Dr. Julia Behnfeldt, Associate Director & Research Integrity Officer, Office of Research Compliance
- Courtney Mankowski, Research Integrity and Compliance Manager, Office of Research Compliance

OSU Office of Legal Affairs:

- Emily Schriver, Associate General Counsel, Office of Legal Affairs

Correspondence:

20170508 - Email from Chen to RIO with an attached point-by-point response to the CII report. [95,96]

20170511 - Email from Chen to RIO showing his lab members and his completed CITI training.[97,98]

20170519 - Email from RIO to Chen with notification memo of new allegations[99,100,101]

20170525 - Email from RIO to Chen with list of files used in new allegations[102,103]

20170530 - Email from Ball to RIO to confirm that Respondent would like to give a statement instead of proceed with the CII interview.[104]

20170530 - Email from Chen to RIO with responses to new allegations and CIC Comments[105]

20170530 - Email from RIO to Chen stating the requirements for a possible voluntary settlement with the Institution and the ORI.[106]

20170530 - Email from Chen to RIO stating his previous email was not intended as the basis for the settlement statement meeting.[107]

20170530 - Email from Chen to RIO forwarding an email chain regarding allegation #5, Fig 8A for Carcinogenesis 8A, previously sent to the RIO on March 9, 2016. [108]

20170721 - Email from RIO to Chen with new allegations #2.[109]

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[95] ATT 33- 20170508 Chen to RIO Response Email.pdf
[96] ATT 34- Point-by-Points Responses to CII Reports.pdf
[97] ATT 35- 20170511 Email Chen to RIO CITI
[98] ATT 36- Appendix II. CITI Training on Responsible Conduct Research
[99] ATT 37- 20170519 Email RIO to Chen New Allegations.pdf
[100] ATT 8- 20170519- Notification of New Allegations-DIO 6144
[101] ATT 38- DIO 6144 - New Allegations 20170519
[102] ATT 39- 20170525 -RIO to Chen List of Files
[103] ATT 40- 20170525 - List of data files to Chen
[104] ATT 9- 20170530 - Ball to RIO GC Statement
[105] ATT 10- 20170530 - Chen to RIO CIC Comments
[106] ATT 11- 20170530 -RIO to Chen Statement Requirements
[107] ATT 12- 20170530 Chen to RIO Statement Confirmation
[108] ATT 7- 20170530 - Email #2 Chen to RIO - allegation #5

20170724 -Email from Chen to RIO regarding manuscripts #10 and #14[110]

20170726 - Email from RIO to Chen stating the correction of the number of allegations listed in the 07/21/2017 notification memo. [111]

20170802 - Email from Chen to RIO with a written response to the new allegations[112]

20170803 - Email from Chen to RIO with additional information regarding allegations in manuscripts #2 and #5[113]

20170901 - Email from Chen to Yucel with response to Investigation Committee Preliminary Report[114]

20170905 - Extension request from Behnfeldt to ORI for extension[115]

20170906 - Email from ORI to Behnfeldt approving extension request approved by ORI[116]

[redacted]

[109] ATT 15- 20170721- Notification #2 of new allegations.pdf
[110] ATT 16- 20170724 - Chen to RIO New allegations
[111] ATT 17- 20170726 - Email RIO to Chen- Revised memo
[112] ATT 21- 20170802-Responses to new allegations
[113] ATT 23- 20170803 – Email Chen to RIO RE:Repeated experiments of alleged figures in Manuscripts #2 and #5
[114] ATT 43-20170901 – Email Chen to Yucel response to COPIC report
[115] ATT 44 – 20170905 – Extension Request OSU to ORI
[116] ATT 45 – 20170906 – Email ORI to OSU granting extension
[117] [redacted]

IND Assessment
for
AR-42

Prepared for:

The Ohio State University

December 13, 2017

TABLE OF CONTENTS

1. OBJECTIVE

1.1. Scope of Work

The Ohio State University ("OSU") has asked The Weinberg Group to evaluate the continued viability of several INDs related to a novel compound, AR-42, if some of the supporting publications included in the INDs are retracted and to evaluate the impact that analysis will have on a currently suspended clinical trial.

1.2. Information Provided by OSU

OSU provided The Weinberg Group access to several development documents. These documents include:

- Original IND 103279,
- Documents related to IND 115832 (including the 2014 and 2015 Annual Report, Phase 1 protocol, Investigator's Brochure, and Response to Clinical Hold letter),
- Documents related to IND 127486 (including Clinical Trial Suspension Notice to FDA, 2017 Annual Report, Phase 1b protocol, Investigator's Brochure, FDA Information Requests, and IND Study May Proceed Letter), and
- Probable corrective actions related to the retraction of four publications: Kulp et al. 2006, Chen et al. 2007, Lu et al. 2007, Kissberth et al. 2008.

Additionally, The Weinberg Group conducted a teleconference with OSU on September 15, 2017. The Weinberg Group reviewed all regulatory documents provided by OSU, with a specific focus on the areas of the INDs supported by the publications in question.

2. BACKGROUND

2.1. Situation Background

A novel cancer treatment compound, histone deacetylase inhibitor AR-42, has been in development by Arno Therapeutics (Arno) and OSU, with several IND applications filed with the FDA for development of this compound. The treatment regimens are either monotherapy or in combination with other cancer chemotherapeutics. One of these programs, IND 103279 for the treatment of solid tumors and hematologic malignancies, will be assigned back to OSU from Arno. Upon transfer of the IND, OSU will accept responsibility for all data included in the IND.

Background research on AR-42, including investigations of its biological activity as an inhibitor of an important cancer-related protein which modulates gene regulation in tumor cells, was conducted by researchers at OSU. Other development work was conducted by Arno or outsourced to third-party commercial organizations. However, irregularities were identified within some of the published pharmacology data for AR-42 contained in four publications (Kulp et al. 2006, Chen et al. 2007, Lu et al. 2007, and Kissberth et al. 2008). Upon initiation of an investigation by OSU, clinical activities for IND 127486 (Phase 1b trial OSU-15004 of AR-42 in

combination with pomalidomide in relapsed multiple myeloma) were suspended in June 2017, pending further evaluation of the impact of these irregularities.

2.2. Product Background

AR-42 is an orally bioavailable, small molecule, broad spectrum histone deacetylase (HDAC) inhibitor that also deacetylates non-histone proteins (pan-DAC inhibitor). AR-42 targets multiple signal transduction pathways of cancer cell survival, including protein kinase B (Akt) signaling, mitochondrial integrity, and caspase activity. AR-42 is currently being studied for monotherapy or combination therapy as part of three INDs:

Table 1: Approved AR-42 INDs

IND	Compound(s)	Indication	Date Opened
IND 115832	AR-42 and Decitabine	Acute Myeloid Leukemia (AML)	August 2012
IND 127486	AR-42 and Pomalidomide	Relapsed Multiple Myeloma	September 2015
IND 103279	AR-42	Solid Tumors and Hematologic Malignancies	March 2009

3. REGULATORY CONSIDERATIONS

3.1. The Weinberg Group Approach

The worst-case scenario for OSU would be to withdraw all four publications that were identified and no longer use them to support any of the INDs referenced in Table 1. Therefore, The Weinberg Group reviewed how these publications were cited and used to support the safety and efficacy of AR-42; specifically, how removal of the publications would impact the IND.

The Weinberg Group reviewed the provided comparison of western blot presentations from the noted publications (Chen et al. 2007, Kulp et al. 2006, Lu et al. 2007 and Kisseberth et al. 2008) versus blots from the researcher's notebooks. The INDs were reviewed to determine whether western blot presentations, if present, were based on lab notebook or published sources. The Weinberg Group then assessed the importance of any irregularities to OSU's development programs for AR-42.

3.2. Regulatory Assessment

No nonclinical western blot data were presented in the IND materials provided for either IND 115832 or IND 127486. However, these INDs did reference IND 103279. Blots provided in IND 103279 were based on blots shown in some or all of Chen et al. 2007, Kulp et al. 2006, Lu et al. 2007 and Kisseberth et al. 2008.

The differences between western blots from the researcher's notebook and their corollary blots from the publications contained inconsistencies in AR-42 dose concentrations evaluated in the blot experiments and/or cell types evaluated.

The conclusions from the western blots present in both the publications or the lab notebooks are that AR-42 produces dose-dependent effects on a number of cellular biomarkers known to be associated with histone acetylation and cell apoptosis. Incorrect labeling of the AR-42 concentrations evaluated does not impact these conclusions related to the pharmacologic mechanism of action. They do, however, mistakenly show the relative potency of AR-42 versus the comparator histone deacetylase inhibitor SAHA. Incorrect labeling of cell lines, possible substitution of PC-3 for U87MG, is not of great importance since PC-3 is a human prostate cancer cell line and research records show effects in this line. At most, the research results suggest that AR-42 is not entirely specific for prostate cancer since U87MG is a cell line from a different cancer type. However, this has no impact on the AR-42 development program.

The INDs provide other evidence for AR-42 biological activity to induce apoptosis and produce anti-tumor effects in live animal models. These experimental data fully support the presumption that AR-42 might prove useful in patients with prostate cancer.

Not directly related to the discrepancies of interest in our evaluation, the INDs show very appropriate animal toxicology results for AR-42 from studies conducted by an independent third party. These data are relevant to the safety of AR-42 and support its evaluation in human trials, whereas the western blot information is simply support for the mechanism of action and/or proof of concept.

Western blot results in the INDs, with likely mislabeling of AR-42 concentrations tested and/or the cell line evaluated, have no impact on the safety evaluation of AR-42 for human subjects. Studies that were relied upon to establish drug safety were conducted independent of the research presented in the publications that were reviewed. Safety conclusions from these studies would not be impacted by the performance or reporting of western blot data. Any such abnormalities in western blot data, relevant only to details related to mechanism of action and/or proof of concept, have no impact on further development of AR-42. Without the four publications in question, the INDs would still be scientifically valid and within FDA compliance.

3.3. Implications on Current Clinical Trial

As discussed in Section 3.2, the noted abnormalities in the publications are of minor importance to the safety of AR-42 and do not warrant continued suspension of the Phase 1b, OSU-15004 trial, nor do they hold up human development of AR-42 in any of the INDs listed in Table 1. The Weinberg Group believes it is appropriate to continue the OSU-15004 trial without the support of the four identified publications.

4. CONCLUSION

The Weinberg Group analyzed the implications of retracting four publications that were used to support several INDs for the novel compound, AR-42. In addition, The Weinberg Group reviewed the impact of removing these studies on a currently suspended clinical trial, OSU-

15004. The publications in question were primarily used to support the mechanism of action and/or proof of concept. The western blot findings from the publications have limited impact on conclusions regarding potential efficacy of AR-42, and have no influence on the evidence that AR-42 is safe to be studied in humans. The INDs contain other information, including toxicology studies conducted by an independent party that provide ample safety evidence and potential for efficacy in the chosen indication for AR-42. Therefore, the INDs listed in Table 1 are scientifically valid without supportive western blot evidence from Kulp et al. 2006, Chen et al. 2007, Lu et al. 2007, and Kissberth et al 2008. The suspended OSU-15004 may be resumed without any risk to patients associated with the removed publications.