UNIVERSITY OF CALIFORNIA, SAN FRANCISCO

BERKELEY • DAVIS • IRVINE • LOS ANGELES • RIVERSIDE • SAN DIEGO • SAN FRANCISCO • SANTA BARBARA • SANTA CRUZ

CARL GRUNFELD, MD, PHD
Professor of Medicine
University of California, San Francisco

Associate Chief of Staff for Research and Development
Chief, Metabolism & Endocrine Sections
Veterans Affairs Medical Center
4150 Clement Street (111F)
San Francisco, Ca. 94121
(415) 750-2005 FAX :(415) 750-6927

March 13, 2017

Keith T. Flaherty, MD
Editor In Chief
Clinical Cancer Research
American Association for Cancer Research
615 Chestnut Street
17th Floor
Philadelphia, PA 19106-4404
E-mail: ccr@aacr.org
kflaherty@partners.org

In re: **Data Fabrication and/or Falsification Constituting Research Misconduct in two papers**:

#1 “Polymorphisms of the CYP1B1 gene as risk factors for human renal cell cancer” by M. Sasaki, Y. Tanaka, S.T. Okino, M. Nomoto, S. Yonezawa, M. Nakagawa, Seiichiro Fujimoto, N. Sakuragi, and R. Dahiya. **Clinical Cancer Research** 10: 2015-9, 2004.

#2 “CYP1B1 gene polymorphisms have higher risk for endometrial cancer, and positive correlations with estrogen receptor α and estrogen receptor β expressions” by M. Sasaki, Y. Tanaka, S.T. Okino, M. Nomoto, S. Yonezawa, M. Nakagawa, Seiichiro Fujimoto, N. Sakuragi, and R. Dahiya. **Cancer Research** 63: 3913-3918, 2003.

Dear Dr. Flaherty:

An Investigation Committee on Scientific Misconduct of the Veterans Affairs Medical Center, San Francisco and the University of California, San Francisco has determined that **Figures 1b in each of the above cited papers** (also attached) have fabrication or falsification of data that constitutes Research Misconduct. The findings have been reviewed by the VA Office of Research Oversight (ORO) and in part by the UCSF Office of Research Integrity (ORI), who concur with the conclusions.

The two papers had some figures with the same panels used for both papers despite being experiments from two different cancers. The figures also have some panels repeated from and identical to an earlier paper studying a third type of cancer: #3 “Polymorphisms of the CYP1B1 gene have higher risk for prostate cancer”. Y. Tanaka, M. Sasaki, M. Kaneuchi, H. Shiina, M. Igawa and R. Dahiya. Biochemical and Biophysical Research Communications 296: 820–826, 2002.

"The Investigation Committee reviewed in detail the analytical methods and findings of the Inquiry Committee. It unanimously agreed that there were numerous similarities between the figures in question, including the location and shape of streak and spot artifacts, as well as band morphologies were noted. This was concluded by the Committee to support the allegation of data falsification or fabrication and research misconduct."

"It was determined by the Inquiry Committee that several of the figures in question, alleged to be manipulated images from the same source rearranged and relabeled in the two publications, were first published in a third publication, "Polymorphisms of the CYP1B1 gene have higher risk for prostate cancer", Biochemical and Biophysical Research Communications 296 (2002) 820–826, Authors, Y. Tanaka, M. Sasaki, M. Kaneuchi, H. Shiina, M. Igawa and R. Dahiya."

"It was also noted that while the 2002 paper, for which Dr. Tanaka was the first author, did not include a representation of 'Codon 453', which was apparently not present in the targeted population, the subsequent papers, which utilized the same population, included panels labeled 'codon 453'."

"Overall, the committee concluded that there was clear evidence of intentional manipulation and misrepresentation of the data, even though the figures were meant only to be illustrative of genotyping results. The above figures contained evidence of intentional data fabrication or falsification, and that this constituted instances of research misconduct."

The **Committee could not determine who was responsible for the fabrication or falsification of data**. The first author Dr. Masahiro Sasaki returned to Japan and was not reachable despite repeated attempts. Other co-authors stated that Dr. Sasaki was responsible for producing the figures. The laboratory could not provide any of the primary data. Therefore, the Committee did not make a definitive determination of who was responsible for the fabrication or falsification of data that constitutes Research Misconduct.

Based on these conclusions, we and the Committee recommend that both Clinical Cancer Research and Cancer Research **assess these papers for correction or retraction**. If you have further questions, do not hesitate to contact Dr. Grunfeld as above or by e-mail at carl.grunfeld@va.gov.

Sincerely,

Carl Grunfeld, MD, PhD
Associate Chief of Staff for Research & Development

Robert Nissenson, PhD
Research Integrity Officer

UNIVERSITY OF CALIFORNIA, SAN FRANCISCO

BERKELEY • DAVIS • IRVINE • LOS ANGELES • RIVERSIDE • SAN DIEGO • SAN FRANCISCO • SANTA BARBARA • SANTA CRUZ

CARL GRUNFELD, MD, PHD
Professor of Medicine
University of California, San Francisco

Associate Chief of Staff for Research and Development
Chief, Metabolism & Endocrine Sections
Veterans Affairs Medical Center
4150 Clement Street (111F)
San Francisco, Ca. 94121
(415) 750-2005 FAX :(415) 750-6927

March 13, 2017

Professor Dr. Peter Lichter
Editor In Chief
International Journal of Cancer
C/o Managing Editor: Sherryl Sundell
s.sundell@dkfz.de
peter.lichter@dkfz.de

In re: **Data Fabrication and/or Falsification Constituting Research Misconduct** in "Genistein mediated histone acetylation and demethylation activates tumor suppressor genes in prostate cancer cells" by Nobuyuki Kikuno, Hiroaki Shiina, Shinji Urakami, Ken Kawamoto, Hiroshi Hirata, Yuichiro Tanaka, Shahana Majid, Mikio Igawa and Rajvir Dahiya. In the **International Journal of Cancer** 123: 552-560), 2008

Dear Professor Dr. Lichter:

An Investigation Committee on Scientific Misconduct of the Veterans Affairs Medical Center, San Francisco and the University of California, San Francisco has determined that **Figures 3a, 4a, 4b, 4e, and/or 5b** in the above cited paper (also attached) have fabrication or falsification of data that constitutes Research Misconduct. The findings have been reviewed by the VA Office of Research Oversight (ORO) and in part by the UCSF Office of Research Integrity (ORI) who concur with the conclusions.

"The Committee examined the figures directly and using Fiji-ImageJ. In Fig 3A, showing RT-PCR results, it appeared that mirror images of the first and second lanes in the PC3 panel (CYLD treatment) were used to represent lanes 3 and 4 in that panel. Similarly it appeared that mirror images of the first and second lanes in the LNCaP panel (PTEN treatment) were used to represent lanes 3 and 4 in that panel. For the row labeled GAPDH, the same image appeared to have been used to represent two different cell lines (LNCaP and PC-3). Further image analysis of the CYLD row, PC-3 panel, in which bands were grayscale inverted, flipped horizontally and overlaid on the original image, found that the two images were entirely superimposable, indicating that that data from two experimental conditions with PC-3 cells had been used to represent data from two additional conditions. In addition, the Committee noted that the image for the PTEN treatment (LNCaP cells) appeared to be similar to the image in the CYLD row, PC3 panel. Image analytic examination of with grayscale inversion and overlaying on the original image for the PTEN treatment (LNCaP cells) found again that the images were superimposable, indicating that data from two experimental conditions with different cell lines had been used to represent data from two additional conditions. The Committee also reviewed four lanes in GAPDH row LNCaP cells; by overlaying the relevant image panels it was concluded that different exposures of the

same GAPDH blot were likely used to represent two different cell lines. Regarding figures 4a and 4b, using Image J, the Committee examined an inverted image of the SIRT1 PC-3 panel (Fig. 4a) overlain on both the SIRT1 image LNCaP panel (Fig. 4b) and the SIRT1 image PC-3 panel (Fig 4b). This provided good evidence that the three images were derived from the same blot and thus did not represent different experimental origins. In review of figure 4e, the same image appeared to have been used to represent experiments from two different cell lines (PC-3 and LNCaP). Enlargement and false colorization of the images revealed striking commonalities, such as the shape of the protein bands and features of the surrounding backgrounds in the two pairs of bands in question; lanes 3 and 4 eIF1α blot, left panel (PC-3 cell line) appear to have been duplicated as lanes 1 and 2 of the eIF1α blot, right panel (LNCaP cell line). Regarding figure 5b the Committee examined enlarged and false colored versions of o the PTEN and CYLD images, revealing multiple striking similarities in the shapes and internal characteristics of the DNA bands and backgrounds. The Committee concluded that the PTEN and CYLD promoter panels in the INP column are likely to have been derived from a single source.

Based on these findings, the Committee unanimously agreed that these figures contain clear evidence of manipulation and misrepresentation of the data. Given the number of such events, as well as their type (e.g., the flipping of bands), the evidence strongly indicates that these manipulations were done intentionally."

The **Committee could not determine who was responsible for the fabrication or falsification of data**. The first author Dr. Noboyuki Kikuno returned to Japan and was not reachable despite repeated attempts. Other co-authors stated that Dr. Kikuno was responsible for producing the figures. The laboratory could not provide any of the primary data. Therefore, the Committee did not make a definitive determination of who was responsible for the fabrication or falsification of data that constitutes Research Misconduct.

Based on these conclusions, we and the Committee recommend that the International Journal of Cancer **assess this paper for correction or retraction**. We understand that you may have previously been contacted on this matter, but ask that you assess the paper again based on the Investigation Committee's findings. If you have further questions, do not hesitate to contact Dr. Grunfeld as above or by e-mail at carl.grunfeld@va.gov.

Sincerely,

Carl Grunfeld, MD, PhD
Associate Chief of Staff for Research & Development

Robert Nissenson, PhD
Research Integrity Officer