

October 15, 2014

## Research Internal Investigation Committee - Final Report

<b>Investigation Committee Members:</b>	Richard Weisel, MD, FRCSC, Research Integrity Advisor (Chair) Imogen Coe, Ph.D., Dean, Faculty of Science, Ryerson University Rod Bremner, Ph.D., Senior Investigator, Lunenfeld-Tanenbaum Research Institute, Mount Sinai Hospital
<b>Respondents:</b>	Shereen Ezzat, FRCPC, FACP, MD Sylvia L. Asa, MD, Ph.D.
<b>Complainants:</b>	'Clare Francis' <i>American Journal of Pathology (AJP)</i> <i>Journal of Clinical Investigation (JCI)</i>
<b>Allegations</b>	Allegations with respect to multiple publications include reuse and alteration of images that can be generally characterized as " <b>fabrication and/or falsification</b> ".

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Pursuant to the Policy (defined below), a draft version of the Research Internal Investigation Committee Report was provided to Drs. Ezzat and Asa for comment. This final version of the Report includes footnotes where Drs. Ezzat's and Asa's commentary warranted a response by the Committee directly in the Report. An addendum to the report provides more detailed responses to the comments provided to the Committee by Drs. Ezzat and Asa in their review of the draft Report.

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## Background

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Postings dated October 4, 2012 and November 8, 2012 on the now non-operational 'blog' website, "http://www.science-fraud.org/?p=973" (Science Fraud) identified multiple irregularities in images in six publications. Drs. Ezzat and Asa were listed as authors in each of those publications.

Subsequently, emails were sent from an individual claiming to be 'Clare Francis' to members of the research community including the University of Toronto and journal editors. These emails referenced the Science Fraud website and also alleged irregularities in these 6 and an additional 17 publications on which Drs. Ezzat and Asa shared authorship, and 1 on which Dr. Ezzat, but not Dr. Asa, is listed among the authors.

Concerns specific to two of these papers published in AJP and mentioned in the 'Clare Francis' emails were also raised to Dr. Ezzat by the *American Journal of Pathology* (AJP) on September 19, 2012. When the responses provided by Dr. Ezzat to the journal editor were determined to not sufficiently address AJP's concerns, allegations of image fabrication and/or falsification were forwarded by the journal editor to the University of Toronto for further investigation.

## Allegations

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Allegations with respect to multiple publications include reuse and alteration of images that can be generally characterized as fabrication and/or falsification. For the purposes of this report the term "Allegations" shall be used to describe the allegations made in relation to the subset of nine publications selected for initial review as described below, comprised of the seven articles listed in Table 1 and two additional articles listed under the 'Additional Irregularities' section in this report.

## Internal Inquiry Process

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Concerns were forwarded by the University of Toronto to UHN in accordance with the *University of Toronto Research Misconduct Framework Addendum: Procedures for Determining Jurisdiction in Complaints Involving Certain Non-University Institutions* (2009) and UHN assumed jurisdiction in the inquiry.

As per the UHN policy #40.90.001 *Responsible Conduct of Research* ("the Policy"), complaints of possible research misconduct are handled using a two-step approach. The first step is an internal inquiry to determine whether an investigation is warranted. If an investigation is warranted, then the case proceeds to the second step, which is an internal investigation.

As the allegations related to 24 publications, it was decided to conduct an initial review of images from a subset of 7 of the papers (Table 1), ranging in dates from 2002-2012 including 6 in which allegations were published on the public Science Fraud website. The seventh paper entitled *A Growth Hormone Receptor Mutation Impairs Growth Hormone Autofeedback Signaling in Pituitary Tumors*, referenced herein as 'Cancer Res 67(15)', received partial funding from a National Institutes of Health (NIH) grant through a collaborator and was included in the initial review group. In order to comply with NIH requirements including possible reporting to the US Office of Research Integrity (ORI), a review of the allegations related to this paper was prioritized and conducted first.

Primary data were retrieved for the images in question for the NIH funded paper. Dr. Richard Weisel, Research Integrity Advisor, reviewed the primary data and published images, supported by Mr. Thomas Goldthorpe, Senior Director of Research Information Systems and an internal UHN technical expert in image analysis. Dr. Weisel and Mr. Goldthorpe noted that the images in the published figure had undergone a number of digital processing steps, but confirmed that the published images could be reproduced from the primary data. In relation to this paper, Dr. Weisel determined that the allegations as presented by the complainant 'Clare Francis' were unfounded and no report to ORI was required. However, in analyzing the data, one additional irregularity concerning the control band for lysate was identified for further review.

**Table 1: Publications under review**

	<b>Publication</b>	<b>Funding</b>
1.	<b>Internal Reference: 'Cancer Res 68(10)'</b> <b>Ikaros Modulates Cholesterol Uptake: A Link between Tumor Suppression and Differentiation.</b> Siobhan Loeper, Sylvia L. Asa and Shereen Ezzat <i>Cancer Res</i> 2008, 68(10): 3715-23. Published online May 15, 2008.	CIHR (MOP-79340 to S.L Asa and S. Ezzat) Deutsche Forschungsgemeinschaft (LO 1178/1-1 to S. Loeper)
2.	<b>Internal Reference: 'Cancer Res 68(19)'</b> <b>The Melanoma-Associated Antigen A3 Mediates Fibronectin-Controlled Cancer Progression and Metastasis.</b> Wei Liu, Sonia Cheng, Sylvia L. Asa, and Shereen Ezzat <i>Cancer Res</i> 2008, 68(19): 8104-12. Published online September 30, 2008.	CIHR/CBCRA (MOP-86493) Rita Banach Thyroid Cancer Research Fund TML
3.	<b>Internal Reference: 'Cancer Res 72(8)'</b> <b>FGFR2 Isoforms Support Epithelial – Stromal Interactions in Thyroid Cancer Progression.</b> Miao Guo, Wei Liu, Stefano Serra, Sylvia L. Asa, and Shereen Ezzat <i>Cancer Res</i> 2012, 72(8): 2017-27. Published online February 17, 2012	CIHR (MOP-86493) OMHLTC
4.	<b>Internal Reference: 'Oncogene 31'</b> <b>The insulin resistance Grb 14 adaptor protein promotes thyroid cancer ret signaling and progression.</b> Balogh K, Asa SL, Zheng L, Cassol C, Cheng S, Ezzat S. <i>Oncogene</i> 2012, 31: 4012-21. Published online December 12, 2011	CIHR (MOP-86493) OMHLTC PMHF
5.	<b>Internal Reference: 'AJP 177(6)'</b> <b>Loss of heterozygosity and DNA methylation affect germline fibroblast growth factor receptor 4 polymorphism to direct allelic selection in breast cancer.</b> Xuegong Zhu, Lei Zheng, Sylvia L. Asa, and Shereen Ezzat. <i>Am J Pathol</i> 2010, 177(6): 2860-9. Published online October 29, 2010	CIHR (MOP-86493)
6.	<b>Internal Reference: 'AJP 176(5)'</b> <b>Genetic and epigenetic mechanisms down-regulate FGF receptor 2 to induce melanoma-associated antigen A in breast cancer.</b> Xuegong Zhu, Sylvia L. Asa, and Shereen Ezzat. <i>Am J Pathol</i> 2010, 176(5): 2333-43. Published online March 26, 2010	CIHR (MOP-86493) OMHLTC
7.	<b>Internal Reference: 'Cancer Res 67(15)'</b> <b>A Growth Hormone Receptor Mutation Impairs Growth Hormone Autocrine Signaling in Pituitary Tumors.</b> Sylvia L. Asa, Rebecca DiGiovanni, Jing Jiang, Megan L. Ward, Kimberly Loesch, Shozo Yamada, Toshiaki Sano, Katsuhiko Yoshimoto, Stuart J. Frank, and Shereen Ezzat <i>Cancer Res</i> 2007, 67(15): 7505-11. Published online August 1, 2007	CIHR (MOP-79340 to S.L. Asa) CIHR (MT-14404 to S. Ezzat) NIH (RO1-DK 58259 to S.J. Frank)

On November 15, 2012 at the onset of the inquiry process, Drs. Ezzat and Asa were informed of the allegations and the inquiry/investigation process in a meeting with Dr. Christopher Paige, Vice-president, Research and Dr. Charles Chan, Vice-president, Medical Affairs and Quality. Drs. Paige and Chan were subsequently informed on December 11, 2012 by Drs. Ezzat and Asa that they had engaged legal counsel to represent them in this process<sup>1</sup>.

An internal inquiry focused on the initial subset of seven papers was conducted by Dr. Richard Weisel, Research Integrity Advisor, and supported by the UHN Research Integrity Team ("Research Integrity Team"),

- Ms. Katie Roposa, Director Research Quality Integration
- Mr. Inshan Hosein, Research Integrity Associate

Dr. Weisel reviewed the complaint and relevant documents to determine whether there were reasonable grounds to proceed to an investigation into possible research misconduct.

Based on a review of the complaint and documentation at hand, Dr. Weisel determined that an internal investigation into the research conduct of Drs. Ezzat and Asa was warranted based on the fact that:

- There was nothing to suggest that the Allegations were frivolous and a preliminary review of the figures from the papers revealed irregularities
- The Allegations fall within the definition of research misconduct in the Policy

## Investigation Process

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By letters dated December 5, 2012 Drs. Ezzat and Asa were notified of the outcome of the internal inquiry and formally informed of the allegations. An Internal Investigation Committee ("the Committee") was struck to investigate the Allegations relating to 7 of the 24 publications and was comprised of the following members:

- Richard Weisel, MD FRCSC, Research Integrity Advisor (Chair)
- Rod Bremner, PhD, Senior Investigator, Lunenfeld-Tanenbaum Research Institute, Mount Sinai Hospital
- Imogen Coe, PhD, Dean, Faculty of Science, Ryerson University

In keeping with the Tri-agency Framework: *Responsible Conduct of Research*, an initial report dated January 16, 2013 was provided to the Secretariat for Responsible Conduct of Research describing the allegations received with respect to the publications that had acknowledged grant funding from the Canadian Institutes for Health Research (CIHR; see Appendix 1).

The Research Integrity Team facilitated the identification, scanning and review of the primary data along with support from the following expert resources:

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<sup>1</sup> The IIC accepts that, as stated in the respondents' response to the draft of the internal investigation report, Dr. Chan may have suggested Dr. Ezzat to seek legal counsel. However, even if true, this would not affect the accuracy of the statement made here.

- Mr. Thomas Goldthorpe, MASC, Senior Director, Research Information Systems, UHN
- Dr. Helen Chan, PhD, Manager, Research Communications, UHN

A locked cabinet was placed in the laboratory office of Dr. Asa in order to facilitate the sequestration of the primary data in question. A specific list of the primary data required for investigative purposes was provided by the Research Integrity Team to Drs. Ezzat and Asa, who were then asked to produce and identify the primary data. The primary data identified by Drs. Ezzat and Asa were catalogued and locked in the cabinet. The cabinet key was kept by the Research Integrity Team, thereby ensuring that access to the primary data throughout the entire investigative process could only occur in the presence of both: 1) a member of the Research Integrity Team, and; 2) either Dr. Ezzat or Dr. Asa.

The Research Integrity Team subsequently returned to Dr. Asa's lab on multiple occasions during the following five months. The data identified by Drs. Ezzat and Asa were scanned by Mr. Thomas Goldthorpe, with the assistance of Dr. Helen Chan. The primary data were then returned to the original binders and lab notebooks before being returned to the locked cabinet.

## Image Analysis

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The Committee met and reviewed the relevant documentation including the published images and the available primary data. Written responses provided to the Committee by Drs. Ezzat and Asa were reviewed along with those responses submitted by Dr. Ezzat to the editor of AJP regarding the journal's September 19, 2012 inquiry into two papers: AJP 176(5) and AJP 177(6). The Committee was supported by Mr. Goldthorpe, who provided a detailed review of the images using various digital analysis techniques to assess for similarities, differences, artifacts, indications of erasures, cloning and/or alterations. In order to validate Mr. Goldthorpe's image analysis, an external forensic image analysis expert, Mr. George Reis, of *Imaging Forensics* was engaged to review selected images.

All told, the Committee reviewed 89 images from the 7 different publications. The Committee's observations were classified as follows:

<b>Observation</b>	<b>Number</b>
Primary data match published image	21
Primary data provided do not match published image	33
Primary data not provided	35

The Committee's detailed review identified many instances of image modification including alterations to resolution, contrast, filtering and stretching. Some of these alterations may have been intended to enhance or beautify the images for publication, but were not described in the figure legend according to the requirements outlined in the journal editorial policies. The Committee has not pursued or made findings regarding these relatively minor irregularities.

In an effort to streamline and focus the investigation, the Committee requested and obtained specific responses from Drs. Ezzat and Asa to 21 instances in which they found duplication of an image or part of an image, and those 8 instances in which radical alterations appeared to have been made in the 89 images under review.

The Committee met with Drs. Ezzat and Asa for further clarification on October 31, 2013. At this meeting, Drs. Ezzat and Asa were accompanied by legal counsel, Ms. Elizabeth Grace and Mr. Josh Koziobrocki. UHN General Counsel, Ms. Bella Martin, was also present. Drs. Ezzat and Asa provided an overview of their research and their perspective on the investigation to date. At their request, the Committee visited their lab space and observed the storage conditions of the sequestered primary data. Explanations for the image irregularities were not provided by Drs. Ezzat and Asa at this meeting.

The Committee requested that Drs. Ezzat and Asa continue preparation to review each image and related observation as previously requested by the Committee. Drs. Ezzat and Asa provided written responses and met with Committee members Dr. Coe (Acting Chair) and Dr. Bremner on December 19, 2013 for a detailed review of the images, observations and responses. Counsel was not present at this meeting.

## Additional Irregularities

Toward the end of the investigation, additional concerns were raised by the editor of the Journal of Clinical Investigation regarding apparent reuse of images within and across two publications. Drs. Ezzat and Asa were notified of these new allegations by letter dated April 29, 2014. As the Committee has now had the opportunity to review these images and Drs. Ezzat's and Asa's responses, they are included as part of the Allegations in this report:

	<b>Publication</b>	<b>Funding</b>
1.	<p><b>Internal Reference: 'JCI 109'</b>  <b>FGFR2 Isoforms Support Epithelial – Stromal Interactions in Thyroid Cancer Progression Targeted expression of a human pituitary tumor-derived isoform of FGF receptor-4 recapitulates pituitary tumorigenesis.</b>                      Shereen Ezzat, Lei Zheng, Xian-Feng Zhu, Gillian E. Wu, and Sylvia L. Asa  <i>J Clin Invest</i> 2002, 109: 69-78.</p>	<p>CIHR (MT-14404 to S. Ezzat)                      CIHR (MT-14464 to S.L. Asa)</p>
2.	<p><b>Internal Reference: 'AJP 163(3)'</b>  <b>Ikaros Isoforms in Human Pituitary Tumors.</b>                      Shereen Ezzat, Shunjiang Yu, and Sylvia L. Asa  <i>Am J Pathol</i> 2003,163(3):1177-84.                      Figure 2a showing the PKG-1 RT-PCR image in AJP-2003-163(3), Figure 1b PKG-1 RT PCR image and Figure 1c FGFR1 RT PCR image in JCI-2002-109 appear identical.</p>	<p>CIHR (MT-14404 to S. Ezzat and S.L. Asa)                      TML</p>

## Co-author Communication

In April and May, 2014 the Committee wrote to the co-authors of the publications in respect of which the Allegations had been made. Contact information could be obtained for 13 of the 18 co-authors. Detailed requests for information were sent to the co-authors. They were asked to provide information regarding routine lab practices in Dr. Ezzat's and Dr. Asa's labs, describe their own involvement with the publications and comment on the irregularities and annotated images highlighting the Committee's observations. Written responses were received from 12 of the 13 co-authors. A complete list of the co-authors who responded to the Committee's request for information is attached in Appendix 2. Responses included descriptions of the co-authors' involvement with the publications and routine

laboratory practices in Drs. Ezzat's and Asa's labs. Interviews were held with four of the co-authors to provide further clarification.

Of note, the Committee interviewed Dr. Xuegong Zhu, a former lab member with Dr. Ezzat, currently a Post-Doctoral Fellow at the University of Cincinnati. The Committee noted that a significant language barrier precluded comprehensive exploration of the issues, but, with the assistance of someone identified by Dr. Zhu as an interpreter throughout the interview process, Dr. Zhu described copying and pasting bands in multiple instances in the two papers on which he was first author: AJP 176(5), and; AJP 177(6). He did this, he said, out of "convenience" saying that he pasted bands in the same pattern as the experiment results. Dr. Zhu also said that use of "photoshop" was common in the lab.

Dr. Weisel, representing the Committee, subsequently interviewed three co-authors who are current UHN personnel:

- Dr. Wei Liu, Research Associate, Dr. Asa's lab
- Lei Zheng, Research Technician, Dr. Ezzat's lab
- Dr. Stefano Serra, Active Staff, Pathology

In one interview, Dr. Liu, a current member of Dr. Ezzat's lab, described a telephone conversation he had with former lab member, Miao Guo, first author of Cancer Res 72(8). Dr. Liu explained that Dr. Ezzat requested he contact Ms. Guo to help him find the primary data related to the Cancer Res 72(8) article. Dr. Liu said that Ms. Guo described pasting a band in an image, in order to enhance the appearance of the figure, after seeing Dr. Zhu do the same. Dr. Liu said he informed Dr. Ezzat<sup>2</sup> of Ms. Guo's comments. Multiple attempts by the Committee to contact Ms. Guo for clarification by email using the email address provided by Dr. Ezzat and Dr. Liu, by telephone using the contact number provided by Dr. Liu, and by written letter have been unsuccessful.

The following describes a summary of the written and verbal communications provided by the co-authors.

There was consensus in the co-author responses regarding the following lab practices:

- Photographs of gels are taken and then stored on hardware/software as well as being printed and pasted in lab notebooks. The original gels are then discarded.
- Images of gels are reused between experiments because running gels is expensive. The costs associated with running certain experiments have been emphasized by Dr. Ezzat in his discussions or interactions with lab personnel.
- Drs. Asa (sometimes) and Ezzat (always) review ongoing work in weekly lab meetings.

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<sup>2</sup> In their response to this report, Drs. Asa and Ezzat claim that "Dr. Ezzat is certain he was never told by Dr. Liu about his call with Dr. Guo," and instead "...Dr. Liu, after reflection, told them [Drs. Ezzat's and Asa's counsel] he had thought further about this and that it was Dr. Asa whom he told..." The IIC concludes that the coauthor communication section of the IIC report is an accurate reflection of the statements received from the coauthors. In the interest of fairness, we will include this footnote as an addition to Dr. Guo's statements. However, the IIC notes that it is not relevant to the investigation whether Dr. Liu told Dr. Ezzat or Dr. Asa about his conversation with Dr. Guo. Drs. Ezzat and Asa claim in their response that Dr. Asa instructed Dr. Liu to disclose the conversation he had with Dr. Guo to the IIC. It is unclear why Dr. Ezzat or Dr. Asa did not notify the IIC of this information directly. Regardless of the means in which this information was communicated, it is clear to the IIC that: 1) Dr. Guo notified Dr. Liu that she constructed figures under the apparent guidance of Dr. Zhu, and; 2) this information was relayed to either Dr. Ezzat or Dr. Asa, but was never mentioned to the IIC by either respondent.

- The first author of any given article is generally the one who drafts the manuscript and prepares the figures for publication.

Conflicting statements were provided by the co-authors for some areas of lab process. For example:

- Training:  
More senior lab members train new lab members on how to perform certain experiments vs.  
New lab members learn how to perform certain experiments by reading the available lab-specific protocols;  
Lab members are not instructed on how to perform experiments.
- Record keeping:  
Lab members are required to keep detailed notes of all lab work vs.  
According to an external collaborator, lab members are not required to keep records of the experiments that do not work.
- Experiment process:  
All lab members are required to repeat experiments multiple times vs.  
Lab members are only required to repeat experiments that are unsuccessful.
- Manuscript/figure review:  
Drs. Asa and Ezzat review all manuscripts/figures prior to publication vs.  
Figures are not reviewed by Drs. Asa and Ezzat prior to publication.  
One co-author noted that Dr. Ezzat used to review all manuscripts and figures prior to publication, but now he "has no time" to do so.

Individual co-authors provided the following comments:

- Dr. Ezzat emphasizes importance of good note taking.
- Representative gels are chosen for publication.
- Images of PCR gels were "photocomposed" for publication using software.
- The use of "photoshop" is common practice in the lab.

A common theme was evident in the written responses and discussions; the focus of the responses was on the scientific results indicated by the presence or absence of bands in each experiment, rather than on the images themselves or their preparation for publication.

## Journal Communication

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Drs. Ezzat and Asa provided responses directly to three journal editors (*American Journal of Pathology*, *Oncogene* and *Cancer Research*), in some cases providing primary data scans and in others alternate images or explanations. The Committee noted that in some cases the primary data provided to the Committee were different from those provided to the journals.

### *American Journal of Pathology*

AJP raised concerns to Dr. Ezzat regarding two publications: AJP 176(5), and; AJP 177(6). Dr. Ezzat provided a written response, including scans of primary data. After requesting further clarifications, a subsequent response provided to AJP by Dr. Ezzat on December 21, 2012 was deemed insufficient by AJP editors. AJP wrote a letter dated March 13, 2013 to Dr. Paul Young, Vice-president, Research at the University of Toronto requesting a formal investigation into the allegations of fabrication and falsification of images in these two publications.



### ***Oncogene***

The Committee was not able to provide a comprehensive review as no primary data were provided to the Committee. Drs. Ezzat and Asa explained that the bands in question were realigned to remove a blank control lane because it was not run in both samples. The explanation provided by Drs. Ezzat and Asa to the journal editor was accepted. Accordingly, the Committee considered the matter closed.

### ***Cancer Research***

A voluntary figure correction was submitted to the editor by Dr. Ezzat for *Cancer Research* 72(8) Figure 3, before the investigation began. The journal editor explained to the Committee that the correction had not been printed as the responses provided by Dr. Ezzat to specific questions raised by the journal regarding this publication were deemed insufficient. Thus, outstanding issues remained to be resolved. *Cancer Research* has indicated that their internal investigation, which includes this and other publications, is ongoing.

## **Summary of Observations Related to the 29 Images**

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The Committee has identified numerous instances of image reuse and editing that were not described in the figure legends. In most cases, Drs. Ezzat and Asa were not able to provide a satisfactory explanation. In multiple instances Drs. Ezzat and Asa told the Committee they were not able to locate the primary data. Details of the Committee's observations and responses provided by Drs. Ezzat and Asa for each of the images reviewed are as follows:

### **1. Ikaros Modulates Cholesterol Uptake: A Link between Tumor Suppression and Differentiation**

Siobhan Loeper, Sylvia L. Asa, and Shereen Ezzat

*Cancer Research* 2008, 68(10): 3715-23.

**NOTE:** The Committee notes that the first author of this paper, Dr. Loeper, has relocated to Germany. Drs. Ezzat and Asa informed the Committee that they had been in contact with Dr. Loeper and that she had sent them what primary data she had with her in Germany. Dr. Loeper provided a brief response to the Committee's request for information, stating she is unable to provide a detailed response as she is on a personal leave.

<b>IMAGE</b>	
2A/2D	<p><b><u>Observation</u></b></p> <ul style="list-style-type: none"><li>Actin panels are identical. The reuse of images was not disclosed in the figure legend.</li></ul> <p><b><u>Response</u></b></p> <ul style="list-style-type: none"><li>Drs. Ezzat and Asa have explained that the replication was intentional, as the actin panels represent the same experiment using the same cells. Protein from this experiment was run for LDL-R (figure A) then for Ikaros (figure D) and the same actin should have been used for both pieces of data.</li></ul> <p><b><u>Conclusion</u></b></p> <ul style="list-style-type: none"><li>The reuse of images has been explained to the Committee, but was not disclosed in the figure legend.</li></ul>

**CONTINUED**

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2A/2D (continued)	<p><b><u>Observation</u></b></p> <ul style="list-style-type: none"><li>• 2A- LDL-R (120kDa): Erasures are evident at Ik6.</li></ul> <p><b><u>Response</u></b></p> <ul style="list-style-type: none"><li>• Primary data were provided on June 19th 2014.</li></ul> <p><b><u>Conclusion</u></b></p> <ul style="list-style-type: none"><li>• Analysis of the alleged erasures using this primary data was inconclusive as the image quality was poor. It is not clear why the lanes marked "Pc" in the primary data were not those reported in the publication. Rather, adjacent lanes in the primary data, relabeled with the letters "Pc", were used instead.</li></ul> <p><b><u>Observation</u></b></p> <ul style="list-style-type: none"><li>• 2D- Ik1 (57kDa) and Ik6 (36kDa): Primary data do not match published image.</li></ul> <p><b><u>Response</u></b></p> <ul style="list-style-type: none"><li>• Primary data have been provided.</li></ul> <p><b><u>Conclusion</u></b></p> <ul style="list-style-type: none"><li>• Primary data provided are a partial match for the published image, in that some of the bands are a match, however, some of the labels used in the published image do not appear to match the labels in the primary data for Ik1 (57kDa) at pcDNA and Ik6.</li><li>• A satisfactory explanation for these irregularities has not been provided.</li></ul>
3C-ChIP1&2	<p><b><u>Observation</u></b></p> <ul style="list-style-type: none"><li>• The primary data provided from the lab notebook demonstrate the presence of faint bands in CHIP1 at Ik6, and pcDNA. These bands do not appear in the published image. The published image shows evidence of erasures of multiple lanes.</li></ul> <p><b><u>Response</u></b></p> <ul style="list-style-type: none"><li>• Drs. Ezzat and Asa indicated that missing bands in the published image is a reflection of the poor quality of scan used to capture the primary data. They were unable to confirm whether these were the exact primary data used in the published image. No alternate primary data were provided to match the published image.</li></ul> <p><b><u>Conclusion</u></b></p> <ul style="list-style-type: none"><li>• A satisfactory explanation for these irregularities has not been provided.</li></ul>
3C-Input2	<p><b><u>Observation</u></b></p> <ul style="list-style-type: none"><li>• The primary data provided shows 8 lanes (marker +7), while the published image shows 9 lanes (marker + 8).</li><li>• In the published image, lanes 4, 5, 6 (pcD1, pcD2, Ik1) are identical to lanes 7, 8, 9 (Ik2, Ik61, Ik62).</li></ul>

**CONTINUED**

1. **Ikaros Modulates Cholesterol Uptake: A Link between Tumor Suppression and Differentiation**  
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*Cancer Research* 2008, 68(10): 3715-23.

3C-Input2 (continued)	<p><b><u>Response</u></b></p> <ul style="list-style-type: none"><li>• Drs. Ezzat and Asa said that the primary data were not available, and provided a “replicate experiment” that allegedly demonstrated the same pattern of results. However, forensic imaging analysis revealed that the primary data provided were actually a match for the published image. Nonetheless, Drs. Ezzat and Asa did not provide any specific response with regards to the nine bands that appear in the published image, even though only eight bands exist in the primary data. They also made no comment on the apparent duplication of lanes 4, 5 and 6 in lanes 7, 8 and 9.</li></ul> <p><b><u>Conclusion</u></b></p> <ul style="list-style-type: none"><li>• Examination of the published images demonstrates cut lines, erasures, and alteration of the backgrounds around the reused bands.</li><li>• Image analysis has confirmed that the published image was created from the primary data provided, with the marker lane and lanes 2-6 (wt1, wt2, pcD1, pcD2, lk1) in the published image matching the primary data. Lanes 7 and 8 in the primary data are not seen in the published image, instead lanes 4, 5, 6 (pcD1, pcD2, lk1) have been reused and labeled in lanes 7, 8, 9 as lk2, lk61, lk62.</li><li>• A satisfactory explanation for these irregularities has not been provided.</li></ul>
4C/4D	<p><b><u>Observation</u></b></p> <ul style="list-style-type: none"><li>• Input 4C (ACh3) and 4D (ACh4) are identical, but have different levels of exposure.</li></ul> <p><b><u>Response</u></b></p> <ul style="list-style-type: none"><li>• Drs. Ezzat and Asa agree that the images are identical, but state that “the scientific impact is nil”. They explained that a manuscript reviewer requested that the same inputs be shown for Ach3 and Ach4.</li></ul> <p><b><u>Conclusion</u></b></p> <ul style="list-style-type: none"><li>• The reuse of images has been explained to the Committee, but was not disclosed in the figure legend.</li></ul> <p><b><u>Observation</u></b></p> <ul style="list-style-type: none"><li>• The bands in Input 4B for pcDNA, lk1 and lk6 are identical to those seen in 4C and 4D, but in 4B they are flipped horizontally, and with grayness adjustment/exposure change. The control band from 4C and 4D is not duplicated in 4B. The control band in the published image in 4B is seen in the primary data adjacent to the band indicated as pcDNA.</li></ul> <p><b><u>Response</u></b></p> <ul style="list-style-type: none"><li>• Drs. Ezzat and Asa agree that the inputs are identical and in the case of 4B, part of the image is flipped.</li></ul> <p><b><u>Conclusion</u></b></p> <ul style="list-style-type: none"><li>• A satisfactory explanation for these irregularities has not been provided.</li></ul>

2. **The Melanoma-Associated Antigen A3 Mediates Fibronectin-Controlled Cancer Progression and Metastasis**

Wei Liu, Sonia Cheng, Sylvia L. Asa, and Shereen Ezzat  
*Cancer Research* 2008, 68(19): 8104-12.

IMAGE	
3C/3D	<p><b>Observation</b></p> <ul style="list-style-type: none"><li>• MAGE-A3 in 3C and 3D are identical but scaled by a factor of 1.3 in the y axis.</li><li>• p21 in 3C and 3D are identical but scaled by a factor of 1.27 in the y axis.</li><li>• Actin in 3C and 3D are identical but scaled by a factor of 1.43 in the y axis and a factor of 1.04 in the x axis.</li></ul> <p><b>Response</b></p> <ul style="list-style-type: none"><li>• Drs. Ezzat and Asa explained that the replication of the MAGE-A3, p21, and actin was intentional, and done to demonstrate their relationship with the other cell components. They note that there was no indication or intention that these were separate experiments. Dr. Liu explained the same two clones were used for the whole experiment and the figure was constructed with repeated images to provide a comparison for the reader. Dr. Liu also explained that the editor had requested the labels as shown in the published image.</li><li>• He added that the resizing of the bands was unintentional during the figure preparation using "powerpoint".</li></ul> <p><b>Conclusion</b></p> <ul style="list-style-type: none"><li>• The presentation of these images is unclear, as the images appear to be from two separate experiments. It is unclear why, if the duplication was intentional, the images are scaled and not exact copies of each other. The reuse of images has been explained to the Committee, but was not disclosed in the figure legend.</li><li>• A satisfactory explanation has not been provided.</li></ul>

3. **The Insulin Resistance Grb 14 Adaptor Protein Promotes Thyroid Cancer Ret Signaling and Progression**

Katalin Balogh, Sylvia L. Asa, Lei Zheng, Clarissa Cassol, Sonia Cheng, and Shereen Ezzat  
*Oncogene* 2012, 31: 4012-21.

IMAGE	
1A	<p><b>Observation</b></p> <ul style="list-style-type: none"><li>• Published image PGK-1 demonstrates a clean cut line, suggesting alteration of the control lane. Primary data were not provided.</li></ul> <p><b>Response</b></p> <ul style="list-style-type: none"><li>• Dr. Ezzat and Asa explained that the bands were realigned to remove a blank control lane because it was not run in both samples. This explanation was provided to the journal editor and was accepted. The Committee did not pursue this Allegation further.</li></ul> <p><b>Conclusion</b></p> <ul style="list-style-type: none"><li>• Based on the journal editor's acceptance of Drs. Ezzat and Asa's response, it was determined that no further investigation would be undertaken.</li></ul>

4. FGFR2 Isoforms Support Epithelial – Stromal Interactions in Thyroid Cancer Progression

Miao Guo, Wei Liu, Stefano Serra, Sylvia L. Asa, and Shereen Ezzat  
*Cancer Research* 2012, 72(8): 2017-27.

IMAGE	
p-MAPK- 1B & left	<p><b>Observation</b></p> <ul style="list-style-type: none"><li>• WRO- FGFR2-IIb control and FGF4 appear identical.</li></ul> <p><b>Response</b></p> <ul style="list-style-type: none"><li>• Drs. Ezzat and Asa state that these images represent two different experiments on different cell lines showing similar results. Primary data for the WRO cells have not been provided<sup>3</sup>.</li></ul> <p><b>Conclusion</b></p> <ul style="list-style-type: none"><li>• A satisfactory explanation for these irregularities has not been provided.</li></ul>
1D- 3T3-left	<p><b>Observation</b></p> <ul style="list-style-type: none"><li>• There is evidence to suggest that a band was pasted into the 3T3 lane.</li></ul> <p><b>Response</b></p> <ul style="list-style-type: none"><li>• Drs. Ezzat and Asa presented this image in a meeting with the Committee October 31, 2013, where they indicated that 'multiple versions of this are in the book' and 'the most likely one to be missing is the one that was removed for scanning.'</li><li>• Dr. Liu informed the Committee that he had telephone contact with Miao Guo at the request of Dr. Ezzat. Dr. Liu stated that Ms. Guo told him she had pasted the 3T3 band over.</li></ul> <p><b>Conclusion</b></p> <ul style="list-style-type: none"><li>• With the application of a variant grading map, the 3T3 lane demonstrates digital alteration with distinct lines and background inconsistencies around the 3T3 band.</li><li>• Primary data were identified by Drs. Ezzat and Asa, with a note '1D' in the image scanned. These primary data do not match published image.</li><li>• A satisfactory explanation for these irregularities has not been provided.</li></ul>
3A/3B	<p><b>Observation</b></p> <ul style="list-style-type: none"><li>• The images used for the migration assay in figures 3A and 3B appeared to be identical although the cell types are different.</li><li>• A comparison of images offered to the Committee purported to be 'Actual' as sent to the journal, show that the WRO cells appear to be magnifications of sections of those in the respective TPC-1 cells.</li></ul> <p><b>Response</b></p> <ul style="list-style-type: none"><li>• Drs. Ezzat and Asa described an apparent error in figure preparation made at the imaging facility. Images provided to the Committee labeled 'actual' and 'after sending' were offered as a demonstration of typesetting changes made by the journal prior to publication. When asked to provide the primary data, Drs. Ezzat and Asa identified a box filled with numerous slides...</li></ul>

<sup>3</sup> Drs. Asa and Ezzat have pointed out an error in the draft report. They did provide data to the IIC for analysis. The IIC acknowledges this mistake and have amended this report accordingly. This oversight notwithstanding, the IIC has reviewed the data provided and still believes that a satisfactory explanation for the irregularity has not been provided. The two bands are identical and neither matches the primary data that were provided.

**CONTINUED**

**4. FGFR2 Isoforms Support Epithelial – Stromal Interactions in Thyroid Cancer Progression**

Miao Guo, Wei Liu, Stefano Serra, Sylvia L. Asa, and Shereen Ezzat

*Cancer Research* 2012, 72(8): 2017-27.

<b>IMAGE</b>	
3A/3B (continued)	<ul style="list-style-type: none"><li>• ...and told the Committee that the slides had been mislabeled, which “made it impossible to determine which slides represented which experiment”. As such, although the primary data may have technically been ‘provided’, the primary data were not identified in a way to make it possible for the Committee to review.</li><li>• The Committee was informed that corrected images had been provided to the journal editor. However, the correction has not been published.</li><li>• No response was provided regarding the magnifications of the sections of the TPC-1 cells.</li></ul> <p><b><u>Conclusion</u></b></p> <ul style="list-style-type: none"><li>• A satisfactory explanation for these irregularities has not been provided.</li></ul>
3C	<p><b><u>Observation</u></b></p> <ul style="list-style-type: none"><li>• The images used in the control and FGR2-IIIb panels of the migration assay appear to be horizontally flipped versions of each other.</li></ul> <p><b><u>Response</u></b></p> <ul style="list-style-type: none"><li>• Drs. Ezzat and Asa described a typesetting error that had occurred after the images were submitted for publication.</li><li>• When asked to provide the primary data, Drs. Ezzat and Asa identified a box filled with numerous slides, and told the Committee that the slides had been mislabeled, which “made it impossible to determine which slides represented which experiment”. As such, although the primary data may have technically been ‘provided’, the primary data were not identified in a way to make it possible for the Committee to review.</li><li>• The Committee was informed that corrected images had been provided to the journal editor. However, the correction has not been published.</li></ul> <p><b><u>Conclusion</u></b></p> <ul style="list-style-type: none"><li>• A satisfactory explanation for these irregularities has not been provided.</li></ul>
5A	<p><b><u>Observation</u></b></p> <ul style="list-style-type: none"><li>• All three Rb panels are identical.</li></ul> <p><b><u>Response</u></b></p> <ul style="list-style-type: none"><li>• Drs. Ezzat and Asa indicate that the Rb bands in each panel are identical and that the duplication was intentional, done at the request of a manuscript reviewer. Reuse of Rb data was not noted in the figure legend.</li></ul> <p><b><u>Conclusion</u></b></p> <ul style="list-style-type: none"><li>• Primary data identified by Drs. Ezzat and Asa and scanned by the Research Integrity Team on June 19<sup>th</sup> 2014 are a match for all three Rb panels.</li><li>• The reuse of images has been explained but was not disclosed in the figure legend.</li></ul>

**CONTINUED**

**4. FGFR2 Isoforms Support Epithelial – Stromal Interactions in Thyroid Cancer Progression**

Miao Guo, Wei Liu, Stefano Serra, Sylvia L. Asa, and Shereen Ezzat

*Cancer Research* 2012, 72(8): 2017-27.

5A (continued)	<p><b><u>Observation</u></b></p> <ul style="list-style-type: none"><li>• Panel 780, 795 and 807/811 are identical and all match primary data labeled 795 11-12/1/2010.</li></ul> <p><b><u>Response</u></b></p> <ul style="list-style-type: none"><li>• Primary data was subsequently identified by Drs. Ezzat and Asa and scanned by the Research Integrity Team on June 18<sup>th</sup> and 19<sup>th</sup> 2014.</li></ul> <p><b><u>Conclusion</u></b></p> <ul style="list-style-type: none"><li>• The primary data provided to support 780 and 807/811 do not match the published images. Panel 780, 795 and 807/811 all match primary data labeled 795 11-12/1/2010.</li><li>• A satisfactory explanation for these irregularities has not been provided.</li></ul>
5B-actin middle	<p><b><u>Observation</u></b></p> <ul style="list-style-type: none"><li>• Keratin panel on primary data provided does not match published image.</li><li>• Fibronectin actin panel and n-cadherin actin panel are identical. Reuse of actin was not noted in the publication legend.</li></ul> <p><b><u>Response</u></b></p> <ul style="list-style-type: none"><li>• Drs. Ezzat and Asa note that the original keratin blot scanned for the published image is missing.</li><li>• Drs. Ezzat and Asa note that the actin bands are identical and that the duplication is intentional.</li></ul> <p><b><u>Conclusion</u></b></p> <ul style="list-style-type: none"><li>• Actin panel for keratin in the published image matches primary data 11-12/1/2011. However, keratin panel on that primary data gel does not match the keratin in the published image.</li><li>• The reuse of the actin panels has been explained but was not disclosed in the figure legend.</li><li>• Primary data supporting the keratin panel are not available to validate the image.</li><li>• A satisfactory explanation for these irregularities has not been provided.</li></ul>

**5. Loss of Heterozygosity and DNA Methylation Affect Germline Fibroblast Growth Factor Receptor 4 Polymorphism to Direct Allelic Selection in Breast Cancer**

Xuegong Zhu, Lei Zheng, Sylvia L. Asa, and Shereen Ezzat

*Am J Pathol* 2010, 177(6): 2860-9.

<b>IMAGE</b>	
1C	<p><b><u>Observation</u></b></p> <ul style="list-style-type: none"><li>• Bands in #1N, #24 N and #24T are identical.</li><li>• Bands in #1T and #24M are identical.</li></ul> <p><b><u>Response</u></b></p> <ul style="list-style-type: none"><li>• Drs. Ezzat and Asa have indicated that the primary data were lost in a hardware failure. They assert that the images are not identical and that the sequencing data provided in the published image demonstrate differences in nucleotide composition.</li><li>• Dr. Zhu has admitted to copying and pasting bands when preparing this figure.</li></ul>

**CONTINUED**

**5. Loss of Heterozygosity and DNA Methylation Affect Germline Fibroblast Growth Factor Receptor 4 Polymorphism to Direct Allelic Selection in Breast Cancer**

Xuegong Zhu, Lei Zheng, Sylvia L. Asa, and Shereen Ezzat

*Am J Pathol* 2010, 177(6): 2860-9.

1C (continued)	<p><b><u>Conclusion</u></b></p> <ul style="list-style-type: none"><li>• The Committee notes that these data are not supported by the identical gel images. Primary data are not available for review.</li><li>• Dr. Zhu has informed the Committee that these images are identical as he copied and pasted in the preparation of this image.</li></ul>
4B/5B/5D	<p><b><u>Observation</u></b></p> <ul style="list-style-type: none"><li>• Bands in 4B #17N, 5B MCF7- and 5D control appear identical. These bands all appear to match band BT20 in 5D primary data.</li><li>• MCF7+ in 5B and MCF7- in 5D appear identical. These bands appear to match MCF 7- in 5D primary data.</li><li>• Bands in the control lane in 5B appear to match the lane labeled T30 in primary data scan 5D, but with space between bands removed.</li></ul> <p><b><u>Response</u></b></p> <ul style="list-style-type: none"><li>• Drs. Ezzat and Asa assert the gels representing 4B and 5B are 'clearly very different'.</li><li>• Drs. Ezzat and Asa have indicated that the primary data for 5B were lost in a hardware failure. Primary data was retrieved from back-up files by UHN Research Information Systems.</li><li>• The first author, Dr. Zhu, has admitted copying and pasting bands in the preparation of this figure.</li></ul> <p><b><u>Conclusion</u></b></p> <ul style="list-style-type: none"><li>• Irregularities are present in the tiff files as submitted to AJP for publication, and provided to the Committee by AJP for review.</li><li>• Dr. Zhu has informed the Committee that he copied and pasted bands in the preparation of this image.</li></ul>
5C	<p><b><u>Observation</u></b></p> <ul style="list-style-type: none"><li>• MCF 7 GAPDH and MDA 453 GAPDH appear identical, despite being different cell types.</li></ul> <p><b><u>Response</u></b></p> <ul style="list-style-type: none"><li>• Drs. Ezzat and Asa do not agree that the images are identical. Drs. Ezzat and Asa have indicated that the primary data were lost in a hardware failure. Primary data were retrieved from back-up files by UHN Research Information.</li><li>• Dr. Zhu stated the images are identical and has admitted copying and pasting in the preparation of this figure.</li></ul> <p><b><u>Conclusion</u></b></p> <ul style="list-style-type: none"><li>• Dr. Zhu has informed the Committee that he copied and pasted bands in the preparation of this image.</li></ul>



6. Genetic and Epigenetic Mechanisms Down-Regulate FGF Receptor 2 to Induce Melanoma-Associated Antigen A in Breast Cancer

Xuegong Zhu, Sylvia L. Asa, and Shereen Ezzat

*Am J Pathol* 2010, 176(5): 2333-43.

IMAGE	
1D	<p><b><u>Observation</u></b></p> <ul style="list-style-type: none"><li>• FGFR2 bands in 6, 7, 8 are identical. The 'n &amp; t' pair used cannot be identified in the primary data provided.</li></ul> <p><b><u>Response</u></b></p> <ul style="list-style-type: none"><li>• Drs. Ezzat and Asa provided a response and correction to AJP acknowledging error by trainee.</li></ul> <p><b><u>Conclusion</u></b></p> <ul style="list-style-type: none"><li>• No further investigation required.</li></ul>
2C-top	<p><b><u>Observation</u></b></p> <ul style="list-style-type: none"><li>• 4n, 5n, 21n appear identical</li><li>• 1t and 22t appear identical</li></ul> <p><b><u>Response</u></b></p> <ul style="list-style-type: none"><li>• Drs. Ezzat and Asa have indicated that the primary data were lost in a hardware failure.</li><li>• The first author, Dr. Zhu, has admitted copying and pasting bands in the preparation of this figure.</li></ul> <p><b><u>Conclusion</u></b></p> <ul style="list-style-type: none"><li>• Dr. Zhu has informed the Committee that he copied and pasted bands in the preparation of this image.</li></ul>
2C-bottom	<p><b><u>Observation</u></b></p> <ul style="list-style-type: none"><li>• 11n, 23n, 28n, 28t, and 30n appear identical.</li><li>• 8n, 8t and 12n appear identical.</li><li>• Double bands present in the primary data are not seen in the published image.</li></ul> <p><b><u>Response</u></b></p> <ul style="list-style-type: none"><li>• Drs. Ezzat and Asa disagree that the primary data do not match the published image, explaining that missing bands in the published image is a reflection of the lower quality of the scan used to capture the primary data. Dr. Zhu forwarded email correspondence to the Committee which he had sent to Dr. Ezzat in September 2012. The scan of the primary data attached to that email clearly shows these double bands.</li><li>• The first author, Dr. Zhu, has admitted copying and pasting bands in the preparation of this figure.</li></ul>

**CONTINUED**

**6. Genetic and Epigenetic Mechanisms Down-Regulate FGF Receptor 2 to Induce Melanoma-Associated Antigen A in Breast Cancer**

Xuegong Zhu, Sylvia L. Asa, and Shereen Ezzat

*Am J Pathol* 2010, 176(5): 2333-43.

2C-bottom  
(continued)

**Conclusion**

- Primary data provided to AJP in response to their query do not match the published image artifact and lane spacing does not align.
- The primary data provided labeled as 'COBRA R2' from the lab notebook are a partial match to the published image. Multiple artifact and blot spacing demonstrate that these are the primary data used in this published image. However, double bands present in the primary data are not seen in the published image. These double bands occur in the primary data at the points where the 'identical' bands noted above appear in the published image.
- The Committee notes an email exchange dated Sept 27, 2012, from Dr. Zhu to Dr. Ezzat in which Dr. Zhu told Dr. Ezzat that the COBRA2 image was "merged from different gels".
- Dr. Zhu has informed the Committee that he copied and pasted bands in the preparation of this image.

4A

**Observation**

- ESRP2- Bands present in MDA436 and BT 549 in primary data are not present in published image.

**Response**

- Drs. Ezzat and Asa disagree with the observation, stating that the bands are identical.
- The response provided to AJP by Drs. Ezzat and Asa dated October 4, 2012 included an image of the primary data and a note stating only "published data are confirmed". On this image, a blue box was drawn around the bands denoting the area in question.
- The first author, Dr. Zhu, has confirmed that because the bands in question were "non-specific" they were cropped out of the figure.

**Conclusion**

- Review confirms that the bands present in the primary data are not present in the published image, where relative spacing to other bands present would indicate that they should be visible. The cropping out of these bands was not disclosed in the figure legend.
- In a follow-up communication from AJP dated December 21, 2012, the reviewer noted a 'higher band that is nearly obscured by blue box in lane for BT549'. The primary data reviewed by the Committee, without the blue box demonstrated the two bands were present and had been obscured by the blue box.
- It is noted that these 'non-specific bands' of incorrect size appear only where ESRP2 is not expressed. The possible significance of this is unclear.

**CONTINUED**

**6. Genetic and Epigenetic Mechanisms Down-Regulate FGF Receptor 2 to Induce Melanoma-Associated Antigen A in Breast Cancer**

Xuegong Zhu, Sylvia L. Asa, and Shereen Ezzat  
*Am J Pathol* 2010, 176(5): 2333-43.

4A (continued)	<p><b><u>Observation</u></b></p> <ul style="list-style-type: none"><li>• MAGE-A – the band shown in the published image at BT549 is not present in the primary data.</li></ul> <p><b><u>Response</u></b></p> <ul style="list-style-type: none"><li>• Drs. Ezzat and Asa explained that the missing band in the primary data is a reflection of the length of exposure used to capture the primary data. However, the first author, Dr. Zhu, has admitted copying and pasting this band in the preparation of this figure.</li></ul> <p><b><u>Conclusion</u></b></p> <ul style="list-style-type: none"><li>• Dr. Zhu has informed the Committee that he copied and pasted in the preparation of this image.</li></ul> <p><b><u>Observation</u></b></p> <ul style="list-style-type: none"><li>• FGFR2-IIIb- Band present at MDA 436 in the primary data, as provided by Dr. Ezzat to AJP, is not present in the published image where relative spacing to other bands present would indicate that it should be visible.</li></ul> <p><b><u>Response</u></b></p> <ul style="list-style-type: none"><li>• Drs. Ezzat and Asa explained that the larger band present in MDA436 is a faint, non-specific PCR product of the wrong size. It was 'not included in the published data that usually shows only the bands of the correct size.' The first author, Dr. Zhu, has confirmed that because the bands were 'non-specific' they were cropped out of the figure.</li></ul> <p><b><u>Conclusion</u></b></p> <p>Dr. Zhu has informed the Committee that he cropped the bands out in preparation of this image. This was not disclosed in the figure legend.</p>
4C	<p><b><u>Observation</u></b></p> <ul style="list-style-type: none"><li>• Published image MCF10A is missing faint bands in '-' lane that are seen in the primary data.</li><li>• Published image MDA 453 is missing faint bands in '-' lane that are seen in the primary data.</li><li>• In published image, lane 1 in PGK-1 and PGK-4 appear identical.</li><li>• In published image, lane 1 in PGK-2 and PGK-3 appear identical.</li></ul> <p><b><u>Response</u></b></p> <ul style="list-style-type: none"><li>• Drs. Ezzat and Asa explained that 'experiments in multiple cell Lines: MCF-10A, MCF-7, BT20, and 453 all show MAGE induction in response to AZC treatment. There is no impact of AZC on the housekeeping gene.' No explanation was provided for the irregularities.</li><li>• No primary data were provided for PGK.</li></ul> <p><b><u>Conclusion</u></b></p> <p>A satisfactory explanation for these irregularities has not been provided.</p>

**CONTINUED**

**6. Genetic and Epigenetic Mechanisms Down-Regulate FGF Receptor 2 to Induce Melanoma-Associated Antigen A in Breast Cancer**

Xuegong Zhu, Sylvia L. Asa, and Shereen Ezzat  
*Am J Pathol* 2010, 176(5): 2333-43.

5B-top#1

**Observation**

- 1n band present in primary data is missing in published image.

**Response**

- Drs. Ezzat and Asa agree that the band in #1N is 'less obvious' in the published image.

**Conclusion**

- When the published image is viewed at 400%, the band present in 1n in the primary data is not visible, while other bands of similar shade/darkness are visible.
- A satisfactory explanation for these irregularities has not been provided.

**7. A Growth Hormone Receptor Mutation Impairs Growth Hormone Autofeedback Signaling in Pituitary Tumors**

Sylvia L. Asa, Rebecca DiGiovanni, Jing Jiang, Megan L. Ward, Kimberly Loesch, Shozo Yamada, Toshiaki Sano, Katsuhiko Yoshimoto, Stuart J. Frank, and Shereen Ezzat  
*Cancer Research* 2007, 67(15): 7505-11.

**IMAGE**

5B-lysate

**Observation**

- Control band in lysate primary data does not match published image.

**Response**

- Primary data have been provided.
- Drs. Ezzat and Asa claim they have already addressed these concerns to UHN's satisfaction on April 11, 2013.

**Conclusion**

- The original concern presented involved possible cloning of bands. Image analysis demonstrated that although the images have undergone a number of digital processing steps, the published images can be reproduced from the primary data. However, the control band for lysate does not match the primary data.
- While the initial concern had been addressed, a satisfactory explanation for the additional irregularity relating to the control band has not been provided.

8. **FGFR2 Isoforms Support Epithelial – Stromal Interactions in Thyroid Cancer Progression Targeted Expression of a Human Pituitary Tumor-Derived Isoform of FGF Receptor-4 Recapitulates Pituitary Tumorigenesis.**

Shereen Ezzat, Lei Zheng, Xian-Feng Zhu, Gillian E. Wu and Sylvia L. Asa  
*J Clin Invest* 2002, 109: 69-78.

9. **Ikaros Isoforms in Human Pituitary Tumors.**

Shereen Ezzat, Shunjiang Yu and Sylvia L. Asa  
*Am J Pathol* 2003, 163(3):1177-84.

IMAGE	
AJP 2A & JCI 1B/1C	<p><b><u>Observation</u></b></p> <ul style="list-style-type: none"><li>• Figure 2a showing the PKG-1 RT-PCR image in AJP-2003-163(3), Figure 1b PKG-1 RT PCR image and Figure 1c FGFR1 RT PCR image in JCI-2002-109 appear identical.</li></ul> <p><b><u>Response</u></b></p> <ul style="list-style-type: none"><li>• Drs. Ezzat and Asa were unable to provide primary data for these images, stating that the work had been completed in 1995-96.</li><li>• Despite reviewing the report of the forensic expert confirming that these images are from the same source, Drs. Ezzat and Asa claim these gels cannot be the same because there is a larger gap present between the ladder and lanes in Figure 1b and 1c from JCI 109.</li><li>• Drs. Ezzat and Asa later identified 'primary data' for Figure 1b PKG-1 RT PCR image and Figure 1c FGFR1 RT PCR image in JCI-2002-109. They state that these data had been removed from the lab notebook and used in a poster presentation, and only recently uncovered. They assert that these newly uncovered images demonstrate that the published figure was composed of several distinct gels.</li></ul> <p><b><u>Conclusion</u></b></p> <ul style="list-style-type: none"><li>• Initial analysis of blot spacing, width, size and shape and artifact, has demonstrated that these images are identical; all three images are from an identical source. In JCI Figure 1b, there is no space between lanes 1 and 2, while in JCI 1c and AJP 2a, a space exists. Analysis reveals that the part of the image bordered just around the entire row of bands has been cut and shifted to the right, creating a space between lanes 1 &amp; 2.</li><li>• Forensic imaging analysis demonstrated that this 'primary data' identified and scanned June 19<sup>th</sup> was not an image of an original gel, but was a print out of the same images used in the publication. These printouts contained the same irregularities as in the publication. If the printouts were of an original gel, the alterations would not have been present. Both the PKG-1 and the FGFR1 images are identical to each other and to the published images, including the alterations as described above.</li><li>• A satisfactory explanation for these irregularities has not been provided.</li></ul>

## Discussion

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The Committee identified numerous instances of image reuse and alteration for which Drs. Ezzat and Asa were not able to provide satisfactory explanations. In many instances primary data were not provided to the Committee for review. In addition, the Committee noted several inconsistencies and misinformation in the responses of Drs. Ezzat and Asa to the Committee and to the journal editors.

### *Inconsistencies/misinformation*

- **AJP 176(5), Figure 4A:** In a review of AJP 176(5) Figure 4A, (specifically the MAGE-A) Drs. Ezzat and Asa provided primary data to the journal in response to their query regarding a band present in the published image that was not visible in the primary data. Drs. Ezzat and Asa state in a written response to the Committee dated December 17, 2013 that 'The original response provided to the journal was a shorter exposure that did not show the weaker band, but a longer exposure was subsequently provided and accepted by AJP.' The Committee noted that the primary data provided to the journal are not the same as that provided to the Committee and that the response submitted to the journal by Drs. Ezzat and Asa was not actually 'accepted'. Concerns over the 'MAGE-A' image have not been resolved; the AJP editor has included this irregularity in the letter of allegations to the University of Toronto.
- **AJP 176(5), Figure 4A, ESRP2:** A concern was raised regarding bands present in the primary data that were not visible in the published image. The response provided to the journal by Drs. Ezzat and Asa dated October 4, 2012 included an image of the primary data and a note stating only 'published data are confirmed'. On this image, a blue box was drawn around the bands denoting the area under review. In a follow-up from AJP dated December 21, 2012 the reviewer noted a 'higher band that is nearly obscured by blue box in lane for BT549'. The primary data scanned from the lab notebook by the Integrity Team and reviewed by the Committee (without the blue box) demonstrated that two bands were present.
- **Cancer Res 72(8):** In a letter to Dr. Weisel dated May 15, 2014 Drs. Ezzat and Asa stated that they have "provided the Committee with the original slides" supporting the migration assays. While boxes of slides were provided, no specific slides were identified by Drs. Ezzat and Asa for the Committee to review. A corrected figure was provided to the journal, but was not published. According to Drs. Ezzat and Asa "it appears that they have chosen not to publish it since it is inconsequential". Communication with the journal on behalf of the Committee indicated that the journal's investigation is continuing, therefore no correction has been published to date.

In response to the Allegations regarding Figure 3, images labeled 'actual' and 'after sending' were offered as a demonstration of the typesetting changes made by the journal prior to publication. A comparison of images purported to be 'actual', as sent to the journal by Drs. Ezzat and Asa, demonstrates that the 'actual' images of WRO cells appear to be magnifications of sections of the respective TPC-1 cells. This concern was identified to Drs. Ezzat and Asa in a letter dated April 29, 2014. Their response dated May 6, 2014 included no explanation for the enlargement of the corner of the images in Figure 3.

The editor of Cancer Research also noted that the journal wrote to Dr. Ezzat with questions regarding multiple papers, and that his responses were deemed insufficient. Thus the journal's investigation continues. Drs. Ezzat and Asa did not disclose this communication.

### ***Responses not provided***

In their responses to the Committee, some of the Allegations were not addressed in that no comment or explanation was offered. For example:

- **Cancer Res 68(10), Figure 3C, Input 2:** When analysis demonstrated that the primary data did not match the published image, Drs. Ezzat and Asa did not provide comment concerning the existence of nine bands in the published image, while there was only eight bands in the primary data. Drs. Ezzat and Asa did not respond to the observation that lanes 4, 5, and 6 appeared to be duplicated in lanes 7, 8, and 9.
- **Cancer Res 72(8), Figure 3:** A comparison of images offered to the Committee purported to be 'Actual' as sent to the journal show that the WRO cells appear to be magnifications of sections of those in the respective TPC-1 cells. No comment or explanation was offered.
- **AJP 176(5), Figure 4C:** Drs. Ezzat and Asa explained that "experiments in multiple cell Lines: MCF-10A, MCF-7, BT20, and 453 all show MAGE induction in response to AZC treatment". Further, "There is no impact of AZC on the housekeeping gene". No explanation was provided for the irregularities.
- **Cancer Res 67(15), Figure 5B, Lysate:** The original concern presented to the respondents involved possible cloning of bands. Image analysis demonstrated that although the images have undergone a number of digital processing steps, the published images, except for the control band for lysate, can be reproduced from the primary data. The control band for lysate does not match the primary data. While Drs. Ezzat and Asa have responded to some of the Allegations, they never responded to the concern regarding the lysate control band.

### ***Primary data availability/review***

In their response to AJP dated Oct 4, 2012 concerning questions raised by the journal editor, Drs. Ezzat and Asa state "Drs. Lei Zheng, Sylvia Asa and I [Dr. Ezzat] have carried out a full review of the data that were retained in our laboratory as notes in the work books and in the electronic files of Dr. Zhu". They go on to say "We have been able to retrieve the original documentation of gels/blots and based on annotations in the lab notebook, we have verified that the data presented are valid and correct". However, the written response to the Committee states that in multiple instances in these two papers, "the primary data are no longer available as they were only on Dr. Zhu's computer when it crashed and could not be retrieved by RIS". It is unclear how the primary data were available for review in preparing the response to AJP in Sept 2012, and not when requested by the Committee in 2013. Dr. Zhu noted in his email correspondence to Dr. Ezzat dated September 27, 2012 that he had changed his computer in the beginning of 2009. It is unclear if this is the hard drive failure referenced by Drs. Ezzat and Asa.

In a subsequent letter to Dr. Weisel dated May 15, 2014 Drs. Ezzat and Asa state in reference to the Allegations "We have full and complete documentation of the original primary data". However, the Committee notes that in many instances, primary data requested were not provided to the Committee for review.

### ***Communication with Dr. Zhu***

Drs. Ezzat and Asa indicated to the Committee that they could not produce the primary data because they had been unable to contact Dr. Zhu, stating in a letter to Dr. Weisel dated May 15, 2014 that they "are particularly pleased that the UHN has been able to locate Dr. Zhu who has not responded to multiple emails that we have sent". However, when the Committee contacted Dr. Zhu, he provided a total of 13 emails exchanged between himself and Dr. Ezzat

during September, 2012<sup>4</sup>. These emails included eight attachments of primary data files, containing dozens of images. In one email exchange dated September 27, 2012 Dr. Ezzat requested Dr. Zhu to “keep checking” for the primary data for AJP 176(5), figure 2C; upper (COBRA). Dr. Zhu replied that he “remembered the uper [sic] COBRA gel was merged from diffrents [sic] gels, you may try to find them one by one from the gel we have now”. In his response to the Committee, Dr. Zhu has admitted to pasting bands into this image. The appearance of identical bands was not addressed in Drs. Ezzat’s and Asa’s response to the Committee. Instead they only offered to provide a “different experiment using the same samples that show the same patterns for all but one of the samples that was not run in this experiment”.

#### ***Communication with co-author Miao Guo***

According to Dr. Liu, a Research Associate in Dr. Asa’s lab, Dr. Ezzat had requested that he contact Miao Guo, first author on Cancer Res 72(8), to inquire regarding the apparent alteration of an image in Figure 1D. Dr. Liu telephoned Ms. Guo, who told him she had pasted a band in the image. Dr. Liu advised the Committee he had passed this information to Dr. Ezzat. Dr. Ezzat did not disclose this finding to the Committee.

#### ***‘Science’ vs. ‘images’***

In their letter to Dr. Weisel on May 15, 2014 Drs. Ezzat and Asa state that they are “...disappointed that some of the images in these publications appear to be altered to some degree when the work behind them remains scientifically valid. We remain concerned that the investigation is focusing only on the images and that there has been less interest in examining and determining the scientific validity of the work”.

In multiple instances, Drs. Ezzat’s and Asa’s written explanations minimize the importance of the images and instead highlight the scientific validity of the results and conclusions that were drawn from those images. In the letter to Dr. Weisel dated May 15, 2014 they note that “Data differs from images” and that “A researcher may create a perfect image, but what is most significant in publishing images is whether the material used to create that image was accurate or able to reproduce the intended result”.

The Committee agrees with Drs. Ezzat and Asa that “The images in these scientific publications are intended to be representative of the data, meaning illustrations of representative results of experiments that were performed more than one time to ensure reproducibility and performed with accurate materials”. However, the applicable standards require that images appearing in publications must be actual images of the experiment as performed, and that any changes made during preparation must be explicitly described in a manner that is consistent with the journal publication policy as well as the standards of the scientific community.

For example, in their response to the Committee dated December 17, 2013 Drs. Ezzat and Asa note that:

- “There were errors that were created during figure preparation by the imaging facility but they are of no consequence as the data are in the bar graphs”
- “...data are all identical so the scientific impact is nil”.
- “...we have other examples of the same data”
- “The point of this image is to show that the product is digested into the smaller bands below ...Please refer to Table 1 for data reporting of all sample pairs...”.

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<sup>4</sup> This correspondence was not disclosed to the Committee and was only acknowledged by Drs. Ezzat and Asa to exist after the draft Report was provided to them for comment.



In another letter dated May 6, 2014, in response to the Allegations regarding the alteration and reuse of an image in AJP 163(3) and JCI 109, Drs. Ezzat and Asa state that "In all of these examples, the data show the status of housekeeping genes that were shown only to prove the integrity of the RNA in cases of negative findings. These are not significant data that would alter the interpretation of the actual data".

During interviews with Dr. Weisel, lab personnel explained the image irregularities in a similar fashion, focusing on the science and the purpose of the figure, rather than the composition of the image. They described reusing images of control gels; that images of housekeeping gels were run and kept for future use.

### **Supervision**

Drs. Ezzat and Asa acknowledge in their letter dated May 15, 2014 that "As Principle [sic] Investigators, we are responsible for oversight of the laboratory. We have provided evidence that we have significant oversight of the day-to-day activities of the people who work in our labs, that we regularly review their material individually and in group lab meetings, and that we regularly evaluate the results of experiments as they evolve". In describing their responsibility for oversight, they state "However, the final preparation of the images for publication is the responsibility of the person doing this work" and that their responsibility as Principal Investigators is to "...ensure that it accurately reflected the 'data', i.e. the scientific information obtained in their replicate experiments...". The Committee noted that it is the responsibility of the Principal Investigator to ensure that the published image is an accurate demonstration of the experiment as it was performed, and that it is prepared and presented according to the standards prescribed by the journal and research community.

### **Decision**

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The Committee evaluated the Allegations before it, guided by the Policy, established and administered as per Section 4.3 of the *Tri-agency Framework: Responsible Conduct of Research*. The Policy defines "Research Misconduct" as: "Any research practice that deviates materially from the commonly accepted ethics/integrity standards or practices of the relevant research community and includes, but is not limited to:

- Intentional fabrication
- Falsification
- Plagiarism
- Material non-compliance with accepted standards and regulations

'**Falsification**' is defined in the Policy as: "manipulating, changing or omitting research materials, equipment, processes, data or results, including graphs and images without proper acknowledgement such that the research is not accurately represented in the research findings, conclusions or records".

'**Fabrication**' is defined in the Policy as making up data, source material, methodologies, findings or results, including graphs and images, and recording or reporting them.

'**Material non-compliance with accepted standards and regulations**' ("Material Non-Compliance") is defined in the Policy as including a "...material failure to conform with accepted professional and academic standards and practices with respect to scientific rigour, accountability, honesty, fairness and professional integrity".

The Committee considers the intentional manipulation of images by any form of enhancement that removes or adds data, resulting in the misrepresentation of the primary data, as well as the inaccurate labelling of images (all of which are described in this report) to constitute Falsification. Specifically, any irregularity that prohibits the primary data from being accurately represented was considered by the Committee to be Falsification.

The Committee also considers the intentional and undisclosed addition and removal of bands in images, the repurpose or reuse of controls and experimental bands to construct "new" composite figures as well as the relabeling of data such that they no longer represent the original experiment or now represent a part of an experiment to which they did not belong to constitute Fabrication. Specifically, the construction of new material that cannot be replicated, regardless of the validity of the source data used to construct that new material, was considered by the Committee to be Fabrication.

The images published must be actual images of the experiment as performed, with alterations disclosed in the figure legend, and limited to those accepted by the journal publication policy and according to the standards of the scientific community. The Committee considers the repeated failure of Drs. Ezzat and Asa to comply with these standards for manuscript preparation, including the inability to provide the primary data to match published images and the failure to disclose alterations according to the journal authorship policies to constitute Material Non-Compliance under the Policy.

The Committee also considers the instances of inconsistencies and misinformation in responses provided by Drs. Ezzat and Asa during the investigation process to constitute material failure to comply with accepted professional and accountability standards.

In these publications reviewed, the Committee notes that multiple instances of falsification, fabrication, and material non-compliance occurred between 2002 through 2012. Further, Dr. Ezzat was the only author that contributed to all of these publications, while Dr. Asa contributed to all but one of these publications. The evidence available to the Committee does not permit it to make a determination about how all of the identified irregularities occurred or who in particular caused them to occur. It is also not clear whether, or to what extent, these irregularities arose as a result of inadequate supervision by the authors or other research staff (such as Dr. Zhu) who were involved in preparing the images in question. Despite the Committee's inability to determine who was responsible for creating each of the identified irregularities in the images, the fact that such irregularities persisted over a 10-year period during which time there were changes in personnel working in Drs. Ezzat's and Asa's labs suggests that there are systemic flaws in the way their laboratories are run, managed and supervised.

On the basis of the evidence it has reviewed, the Committee has concluded that Research Misconduct within the meaning of the Policy has occurred, and specifically, that Falsification, Fabrication and Material Non-Compliance have occurred.

Although Drs. Ezzat and Asa insist that the identified irregularities do not affect the validity of the scientific conclusions in the papers containing the images, the Committee has not reached any conclusion, nor is it necessary for it to do so, concerning whether and to what extent the identified irregularities in the images affect the findings and

**Confidential  
Research-related Record**

**Reference: 2012-003**

conclusions of the papers in which the images appear. The Policy does not require that there be any such connection between Research Misconduct and the validity or outcomes of the research in respect of which the Research Misconduct has occurred.

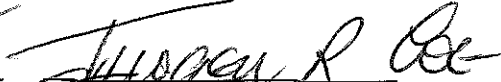
Respectfully submitted,



Richard Weisel, MD, FRCSC,  
Research Integrity Advisor (Chair)



Rod Bremner, Ph.D.  
Senior Investigator,  
Lunenfeld-Tanenbaum  
Research Institute,  
Mount Sinai Hospital



Imogen Coe, Ph.D.  
Dean, Faculty of Science,  
Ryerson University

**Appendix 1: Publications Under Review**

**Note: publications currently under review include # 1-6, 11, 25 and 26.**

	<b>Publication</b>	<b>Funding</b>
1	<b>Ikaros Modulates Cholesterol Uptake: A Link between Tumor Suppression and Differentiation</b> Siobhan Loeper, Sylvia L. Asa and Shereen Ezzat <i>Cancer Res</i> 2008, 68(10): 3715-23. Published online May 15, 2008.	CIHR/MOP-79340 Deutsche Forschungsgemeinschaft (LO 1178/1-1)
2	<b>The Melanoma-Associated Antigen A3 Mediates Fibronectin-Controlled Cancer Progression and Metastasis</b> Wei Liu, Sonia Cheng, Sylvia L. Asa, and Shereen Ezzat <i>Cancer Res</i> 2008, 68(19): 8104-12. Published online September 30, 2008.	CIHR/CBCRA (MOP-86493) Rita Banach Thyroid Cancer Research Fund TML
3	<b>FGFR2 Isoforms Support Epithelial – Stromal Interactions in Thyroid Cancer Progression</b> Miao Guo, Wei Liu, Stefano Serra, Sylvia L. Asa, and Shereen Ezzat <i>Cancer Res</i> 2012, 72(8): 2017-27. April 15, 2012	CIHR (MOP-86493) OMHLTC
4	<b>The insulin resistance Grb 14 adaptor protein promotes thyroid cancer ret signaling and progression</b> Balogh K, Asa SL, Zheng L, Cassol C, Cheng S, Ezzat S. <i>Oncogene</i> 2012, 31: 4012-21. Published online December 12, 2011	CIHR (MOP-86493) OMHLTC PMHF
5	<b>Loss of heterozygosity and DNA methylation affect germline fibroblast growth factor receptor 4 polymorphism to direct allelic selection in breast cancer.</b> Xuegong Zhu, Lei Zheng, Sylvia L. Asa, and Shereen Ezzat. <i>Am J Pathol</i> (2010), 177(6): 2860-9.	CIHR (MOP-86493)
6	<b>Genetic and epigenetic mechanisms down-regulate FGF receptor 2 to induce melanoma-associated antigen A in breast cancer.</b> Xuegong Zhu, Sylvia L. Asa, and Shereen Ezzat. <i>Am J Pathol</i> 2010, 176(5): 2333-43.	CIHR (MOP-86493) OMHLTC
7	<b>Dual Inhibition of RET and FGFR4 Restrains Medullary Thyroid Cancer Cell Growth</b> Shereen Ezzat, Ping Huang, Alan Dackiw, Sylvia Asa <i>Clin Cancer Res</i> 2005,11(3): 1336-41.	CIHR (MT-14404) Cancer Research Society TML
8	<b>Sp1-Mediated Transcriptional Control of Fibroblast Growth Factor Receptor 4 in Sarcomas of Skeletal Muscle Lineage</b> Shun Jiang Yu, Lei Zheng, Marc Ladanyi, Sylvia L. Asa, and Shereen Ezzat <i>Clin Cancer Res</i> 2004, 10(19): 6750-8.	CIHR (MT-14404) Cancer Research Society TML
9	<b>Fibroblast growth factor 2 and estrogen control the balance of histone 3 modifications targeting MAGE-A3 in pituitary neoplasia</b> Zhu X, Asa SL, Ezzat S. <i>Clin Cancer Res</i> 2008, 14(7): 1984-96.	CIHR (MT-14404) TML

	<b>Publication (continued)</b>	<b>Funding</b>
11	<p><b>A Growth Hormone Receptor Mutation Impairs Growth Hormone Autofeedback Signaling in Pituitary Tumors</b> Sylvia L. Asa, Rebecca DiGiovanni, Jing Jiang, Megan L. Ward, Kimberly Loesch, Shozo Yamada, Toshiaki Sano, Katsuhiko Yoshimoto, Stuart J. Frank, and Shereen Ezzat <i>Cancer Res</i> 2007, 67(15): 7505-11. Published online August 1, 2007.</p>	<p>CIHR (MOP-79340 to S.L. Asa) CIHR (MT-14404 to S. Ezzat) NIH (RO1-DK 58259 to S.J. Frank)</p>
12	<p><b>Epigenetically Controlled Fibroblast Growth Factor receptor 2 Signaling Imposes on the RAS/BRAF/Mitogen-Activated Protein Kinase Pathway to Modulate Thyroid Cancer Progression</b> Tetsuo Knodo, Lei Zheng, Wei Liu, Junichi Kurebayashi, Sylvia L. Asa, and Shereen Ezzat <i>Cancer Res</i> 2007, 67(11): 5461-70. Published online June 1, 2007.</p>	<p>CIHR (MT-14404) TML Ministry of Education, Culture, Sports, Science and Technology, Japan grant (16-KAI-194 to T. Kondo)</p>
13	<p><b>Inhibition of the Sodium Potassium Adenosine Triphosphatase Pump Sensitizes Cancer Cells to Anoikis and Prevents Distant Tumor Formation</b> Craig D. Simpson, Imtiaz A. Mawji, Kika Anyiwe, Moyo A. Williams, Xiaoming Wang, Amudha L. Venugopal, Marcela Gronda, Rose Hurren, Sonia Cheng, Stefano Serra, Reza Beheshti Zavareh, Alessandro Datti, Jeffrey L. Wrana, Shereen Ezzat, and Aaron D. Schimmer <i>Cancer Res</i> 2009, 69: 2739-47. Published online March 17, 2009.</p>	<p>Canadian Cancer Society Ontario Institute for Cancer Research CIHR Banting &amp; Best Fellowship (awarded to C.D. Simpson)</p>
14	<p><b>Histone-Acetylated Control of Fibroblast Growth Factor Receptor 2 Intron 2 Polymorphism and Isoform Splicing in Breast Cancer</b> Xuegong Zhu, Sylvia L. Asa, and Shereen Ezzat. <i>Molecular Endocrinology</i> 2009, 23(9): 1397-1405.</p>	<p>CIHR (MOP-86493)</p>
15	<p><b>Deoxyribonucleic Acid Methyltransferase 3B Promotes Epigenetic Silencing through Histone 3 Chromatin Modifications in Pituitary Cells</b> Xuegong Zhu, Xinliang Mao, Rose Hurren, Aaron D. Schimmer, Shereen Ezzat, and Sylvia L. Asa <i>J Clin Endocrinol Metab</i> 2008, 93(9): 3610-17.</p>	<p>CIHR (MOP-79340) TML</p>
16	<p><b>Fibroblast growth factor receptor 4 is a target for the zinc-finger transcription factor Ikaros in the pituitary.</b> Yu S, Asa SL, Ezzat S. <i>Molecular Endocrinology</i> 2002, 16(5): 1069-78.</p>	<p>CIHR (MT-14404)</p>
17	<p><b>The Zinc Finger Ikaros Transcription Factor Regulates Pituitary Growth Hormone and Prolactin Gene Expression through Distinct Effects on Chromatin Accessibility</b> Shereen Ezzat, Shunjiang Yu, and Sylvia L. Asa <i>Molecular Endocrinology</i> 2005, 19(4): 1004-11.</p>	<p>CIHR (MT-14404) TML</p>
18	<p><b>Fibroblast growth factor receptor 4 (FGFR4) mediates signaling to the prolactin but not the FGFR4 promoter</b> Yu, Shunjiang, Lei Zheng, Sylvia L. Asa, and Shereen Ezzat <i>Am J Physiol Endocrinol Metab</i> 2002, 283: E490-E495.</p>	<p>CIHR (MT-14404)</p>

	<i>Publication (continued)</i>	<i>Funding</i>
19	<p><b>Pituitary Tumor AP-2a Recognizes a Cryptic Promoter in Intron 4 of Fibroblast Growth Factor Receptor 4</b> ShunJiang Yu, Sylvia L. Asa, Ronald J. Weigel, and Shereen Ezzat <i>J Biol Chem</i> 2003, 278(22): 19597-602.</p>	<p>CIHR (MT-14404) TML</p>
20	<p><b>Analysis of ret/PTC Gene Rearrangements Refines the Fine Needle Aspiration Diagnosis of Thyroid Cancer</b> Carol C. Cheung, Bessie Carydis, Shereen Ezzat, Yvan C. Bedard, and Sylvia L. Asa <i>J Clin Endocrinol Metab</i> 2001, 86(5): 2187-90.</p>	<p>Not listed</p>
21	<p><b>Molecular Basis of Hurthle Cell Papillary Thyroid Carcinoma</b> Carol C. Cheung, Shereen Ezzat, Lily Ramyar, Jeremy L. Freeman, and Sylvia L. Asa <i>J Clin Endocrinol Metab</i> 2000, 85(2): 878-82.</p>	<p>Temi Latner/Dynacare Saul A. Silverman Family Foundation</p>
22	<p><b>Distinct Multiple RET/PTC Gene Rearrangements in Multifocal Papillary Thyroid Neoplasia</b> Sonia L. Sugg, Shereen Ezzat, Irving B. Rosen, Jeremy L. Freeman, and Sylvia L. Asa <i>J Clin Endocrinol Metab</i> 1998, 83(11): 4116-22.</p>	<p>MIPPS Research Fund Saul A. Silverman Family Foundation Temmy Latner/Dynacare</p>
23	<p><b>CEACAM1 impedes thyroid cancer growth but promotes invasiveness: a putative mechanism for early metastases.</b> W Liu, W Wei, D Winer, A-M Bamberger, C Bamberger, C Wagener, S Ezzat and SL Asa <i>Oncogene</i> 2007, 26: 2747-58. Published online 23 October 2006.</p>	<p>TML Rita Banach Thyroid Cancer Research Fund</p>
24	<p><b>Vitamin D inhibits CEACAM1 to promote insulin/IGF-I receptor signaling without compromising anti-proliferative action</b> Wei Liu, Miao Guo, Shereen Ezzat and Sylvia Asa <i>Laboratory Investigation</i> 2011, 91: 147-156. Published online 16 August 2010.</p>	<p>Rita Banach Thyroid Cancer Research Fund</p>
25	<p><b>Ikaros Isoforms in Human Pituitary Tumors Distinct Localization, Histone Acetylation, and Activation of the 5_ Fibroblast Growth Factor Receptor-4 Promoter</b> Shereen Ezzat, Shunjiang Yu, and Sylvia L. Asa <i>Am J Pathol</i> 2003, 163(3): 1177-84.</p>	<p>CIHR(MT-14404) TML</p>
26	<p><b>Targeted expression of a human pituitary tumor-derived isoform of FGF receptor-4 recapitulates pituitary tumorigenesis</b> Shereen Ezzat, Lei Zheng, Xian-Feng Zhu, Gillian E. Wu, and Sylvia L. Asa <i>J. Clin. Invest</i> 2002, 109: 69-78.</p>	<p>CIHR (MT-14404) CIHR (MT-14464)</p>

**Appendix 2: Co-author Responses**

Co-author name	Publication
Siobhan Loeper	Cancer Res 68(10)
Wei Liu	Cancer Res 68(19) Cancer Res 72(8)
Sonia Cheng	Cancer Res 68(19)
Stefano Serra	Cancer Res 72(8)
Xuegong Zhu	AJP 176(5) AJP 177(6)
Lei Zheng	AJP 177(6) JCI 109 Oncogene 31*
Jing Jiang	Cancer Res 67(15)
Kimberly Loesch	Cancer Res 67(15)
Shozo Yamada	Cancer Res 67(15)
Katsuhiko Yoshimoto	Cancer Res 67(15)
Stuart J. Frank	Cancer Res 67(15)
Gillian Wu	JCI 109

***\*The Allegations related to this publication were not forwarded to the co-authors. Because the journal had accepted the response provided by Drs. Ezzat and Asa, the Committee considered the matter closed.***