May 7, 2014

To: Ryoji Noyori, RIKEN President

Research Paper Investigative Committee
Jun Watanabe, Chair
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Report on Review of Appeal of STAP Cell Research Paper Investigation Results

This report concerns the results of a review, made in response to an April 9, 2014 request from RIKEN, of the validity of an appeal lodged against the findings of the STAP Cell Research Paper Investigative Committee (“the Committee”).

Investigation result
The Committee concludes that further investigation of the findings set out in the “Report on STAP Cell Research Paper Investigation” of March 31, 2014 (“Investigation Report”) is unnecessary, having considered the purport of the appeal and its reasons, as well as the submitted Supplementary Document 1 (supplementary document to the Appeal Document dated April 20, 2014) and Supplementary Document 2 (supplementary document to the Appeal Document dated May 4, 2014).

Reasons
Reason 1: Falsification

1. Definition of “falsification” in the Regulations on the Prevention of Research Misconduct, September 13, 2012, Regulation No. 61 (“the Regulations”)

1) On “falsification”
Article 2, Paragraph 2 of the Regulations defines “research misconduct” as “the occurrence of any of the following in the course of research activities. Inadvertent or unintentional errors and differences of opinion are not regarded as research misconduct,” and lists three types of research misconduct, i.e., fabrication, falsification, and plagiarism. Of the three, the Regulations define falsification as “manipulating research materials, equipment, or processes, or changing or omitting data or results such that the research is not accurately represented in the research record.”

Accordingly, research records that are not authentic as a result of manipulation of research materials, changing data, etc., fall under the category of falsification.

2) On the question of intent (akui)
The Regulations use the term akui, meaning “with deliberate intent”, as a measure to determine whether an action can be considered research misconduct. The defining factor, therefore, for judgment of fabrication, falsification, and plagiarism, is whether or not there was deliberate intent, in both objective and extraneous terms. Accordingly, the Regulations can be interpreted to mean that any [of the three types of research misconduct] are defined as such when it is determined that there was deliberate intent.
If we are to interpret “deliberate intent” as the intent to cause harm, i.e., a strong intention or purpose to cause harm, the Regulations would only apply when such strong intent is present, but it is evident this is contrary to the purpose of the Regulations which is to ensure the credibility of research papers, etc. Therefore, we interpret “deliberate intent” or *akui* as it is defined in Japanese legal contexts as meaning “with knowledge or knowingly”, and synonymous with “intentional”. We note that the appellant uses the word “intentionally” herself, in her appeal when she states, “I mistook the images. I did not intentionally submit different images” (Appeal Document, p. 17).

3) Given that the Regulations comply with the guidelines, released on August 8, 2006, for dealing with research misconduct prepared by a special committee on research misconduct belonging to the Council for Science and Technology Policy in the Ministry of Education, Culture, Sports, Science and Technology (MEXT), the Committee will base its conclusions on fabrication, falsification, and plagiarism, as well as the term “deliberate intent,” as they are defined in the Regulations.

2. Can the conduct in question be judged to be falsification

1) The appellant argues as follows:
   a) Falsification is to change or omit data to create the impression that data showing positive results exist when in fact they do not. The essence of falsification is making up data that appear to show a positive result.
   b) Even when “manipulating research materials, equipment, or processes, or changing or omitting data or results” has taken place, it cannot be considered falsification if the research results have not been manipulated to show something false.
   c) Since data showing positive results do exist with regard to the matter under investigation, the actions of the appellant do not qualify as falsification.

Consequently, the appellant argues that manipulation of research materials to make positive control more obvious does not affect the results per se (see Appeal Document 2-1, 2-2, and Supplementary Document 1-2.)

2) As discussed in 1. 1) above, falsification is defined as “manipulating research materials, equipment, or processes, or changing or omitting data or results such that the research is not accurately represented in the research record.” In the matter under investigation, the key question is whether the research result shown in Figure 1i has been manipulated, changed, or otherwise processed such that it is no longer authentic. While the appellant’s assertions that falsification is “to change or omit data to create the impression that data showing positive results exist when in fact they do not” or “make up data that appear to show a positive result” do indeed represent classic cases of research misconduct, it is nevertheless clear that if Figure 1i has been manipulated, changed, or otherwise processed such that the figure is no longer authentic, this still qualifies as falsification even if data showing positive results do exist.

Our response to the appellant’s argument that manipulation to better show positive control does not affect the results per se, is as follows.

A. Regarding the insertion of lane 3
   i) The appellant argues (Appeal Document 2-3, 2-4, and Supplementary Document 1-2) as follows:
      a) The phenomenon of DNA becoming shorter in the process of T cell maturation has been observed. Therefore, pulsed-field electrophoresis was carried out to test whether mature
T cells were found (cells with T-cell receptor rearrangement were found), i.e., whether the phenomenon of DNA shortening could be observed in sorted-Oct4+ cells.

b) The test result found shorter DNA in sorted-Oct4+ cells, i.e., they showed T-cell receptor rearrangement.

c) The result of DNA shortening, i.e., sorted-Oct4+ cells showing T-cell receptor rearrangement, is not affected by the manipulation of the two gel photographs obtained as a result of the test to make the image more visible for publication in Paper 1 (i.e., manipulation to make positive control more visible).

d) Accordingly, this action does not falsify the research record, nor manipulate it into something inauthentic.

ii) The appellant inserted lane 3, which shows positive control of T-cell receptor gene rearrangements from gel 2 by enlarging gel 1 using a different aspect ratio, because the mobility of the standard DNA size marker in the photograph of gel 1 is roughly 1/1.6 of gel 2. However, gels 1 and 2 do not have a linear relationship in terms of the electrophoresis.

The experiment was a polymerase chain reaction (PCR) assay conducted as outlined in the Methods section of Paper 1. Also, if there is a linear relationship between the gels, the calculated size of the T-cell receptor gene rearrangement band (which is estimated at around 180 base pairs from the genomic layout) is 262.0 base pairs for gel 1 (approximately 46% larger) and 284.8 base pairs (approximately 58% larger) for gel 2, with an 8.4% difference in calculated DNA size. There is also an 8.5% difference between gels 1 and 2 in the calculated size of the germ line (GL) band (not visible in lane 3 of Paper 1, but can be seen in gel 2 with contrast adjustment). However, such large differences are not found in the other bands visible in lane 3 (none are greater than 1%). Consistent with this observation is that positioning lane 3 as a positive control lane based on standard DNA size marker position information (as argued by the appellant) results in a clear discrepancy in the positioning of the standard DNA size marker bands, which should be approximately 180 base pairs. Conversely, there is also a clear discrepancy in the positioning of the standard DNA size marker bands of gels 1 and 2 when the positions of the T-cell receptor gene rearrangement bands are located. It is well known among researchers engaging in molecular biology experiments that differences between gels and electrophoresis conditions produce changes in the range of molecular weight that assures linearity between gels, and accordingly, the standard DNA size marker must be lined up for every electrophoresed gel. Thus even if lane 3 inserted from gel 2, with roughly 1.6 times difference in migration distance, can be pasted to show a similar pattern as in lanes 4 and 5 on the basis of visual confirmation, the auxiliary information of the calculated sizes of the bands show a clear disparity, and thus the presentation conceals this difference.

iii) The appellant argues that “the image shows a qualitative, not quantitative fact, and is not affected in any way by adjusting the contrast” (see Appeal Document 2-6).

If the size of the original band can be verified, its role as a positive control for rearrangement should be assured. However, it has to be said that its qualitiveness comes into doubt, because the image was altered in the way described above, resulting in the loss of accurate information regarding molecular weight needed to calculate the band that shows rearrangement.

B) On the insertion method and position

i) The appellant argues that the photograph of gel 2 has been shrunk and that there is no error in her description regarding the insertion position (see Appeal Document 2-6).
ii) Whether or not the image has been enlarged or shrunk depends on the assumption of which gel photograph is the original, but this is a relative issue, and the difference in assumption does not affect the conclusion.

A number of dust-like irregular spots can be found in gels 1 and 2. A study of their shape shows that in the composite image, the aspect ratio is not 1:1 for the part of the image derived from the photograph of gel 1, whereas no such change in the aspect ratio can be found in the part of the image derived from the photograph of gel 2. If the argument of the appellant is accurate, a change in the aspect ratio of lane 3 that is derived from gel 2 should be observed, but the aspect ratio is the same as in gel 2. This finding is not consistent with the appellant’s description of which gel photograph was enlarged/shrunk. Only by shrinking or enlarging the photograph of gel 1 horizontally do we obtain the image shown in Paper 1.

C) On the area of the DNA rearrangement bands
i) The appellant argues that, regarding the DNA rearrangement bands extending from the bottom of the GL band, the area above the GL band and area below the DNA rearrangement bands (with smaller molecular weight) are not important in the image under investigation, and that the image thus produced does not compromise the scientific relationship between mobility and DNA size (Appeal Document 2-6).

ii) However, plotting the standard DNA size markers and mobility of the two gels, we find differences in the range of molecular weight that assures linearity in the two electrophoresed gels. Moreover, as previously noted, the smallest in size (180 base pairs) and the GL band of the group of T-cell receptor gene rearrangement bands are outside the range of linearity. Consistent with this finding is that it is impossible to make all DNA size markers match for gels 1 and 2 regardless of how the aspect ratios are adjusted.

The area above the GL band and area below the DNA rearrangement bands are not the problem. The problem is claiming that something is the DNA rearrangement bands without providing the correct validating information.

D) On the argument that there is no discrepancy between the positions of the standard DNA size marker bands (issue of the two-degree incline)

i) The appellant argues that the photograph of gel 2 is inclined by approximately 2 degrees to the left, and that inclining the photograph of gel 2 by 2 degrees to the right perfectly matches up the standard DNA size marker band positions of the photographs of gel 1 and gel 2 (Appeal Document 2-6).

ii) It was the Committee that first identified the incline of gel 2, and its verification of the aspect ratio discussed in “B) On the insertion method and position” above took this into consideration. The existence of the two-degree incline has no bearing on our conclusion that perfect linearity associated with the migration of standard DNA size markers is not identical between gels 1 and 2. While it is possible, as the appellant argues, to match up the positive control lane in a way that appears identical on visual inspection, we reiterate that there is no scientific basis for the size of the reconstituted DNA band and our conclusion that the data lacks authenticity is unchanged.

E) From the foregoing, it is obvious that Figure 1i is not authentic, because the DNA rearrangement band was positioned by visual inspection instead of following scientific reasoning and processes.
The appellant argues that when she submitted a corrigendum draft at the request of Nature, she was asked to provide extra space to the right of lane 5 data, and while this resulted in an inappropriate presentation of the data, the change made is often used in qualitative analysis. However, as discussed above, this argument and request for a corrigendum disregard the fact that qualitiveness has been lost.

3. On whether or not this was done intentionally

1) The appellant argues that this was not done intentionally (Appeal Document 2-3, 2-4, etc.), because:
   a) She did not act with an awareness of the risk of inducing the reader to misinterpret the data.
   b) She did not act with an awareness that she was falsifying or with the intention to falsify the results.

2) However, as discussed above, the Regulations’ criteria for fabrication, falsification, and plagiarism is whether or not there was deliberate intent, in both objective and extraneous terms. We interpret “deliberate” or あくい as it is defined in Japanese legal contexts as meaning “with knowledge”, and synonymous with “intentional,” and we note that the appellant uses the word “intentionally” herself.

A) The appellant admits that her actions include positioning the DNA rearrangement bands by visual confirmation as discussed in detail in 2. 2) above.

On February 20, the appellant explained that she “superimposed the gel that presents a clean image of the band over the positive control of the original gel after ensuring that the band size matched perfectly.” On February 28, in answer to the question: “it appears that an image shrunk in a horizontal direction or enlarged in a vertical direction was superimposed on the original image, but did you in fact line them up using molecular markers (standard DNA markers)?”, the appellant commented: “I used molecular markers to adjust in a vertical direction.” Further, on March 1 she commented: “I believed it was better to show the band that was more visible,” and, despite having previously explained that she had carried out vertical linear alignment to produce a panel after verifying linearity of the electrophoresed gels, on March 23 she changed her statement. On being asked about the linearity associated with standard DNA size marker migration in the two gel photographs (“Do you still have diagrams or formulas that demonstrate linearity?”), she replied “I did not confirm linearity with a mathematical formula,” and to the question “does that mean you confirmed it visually?” she replied, “Yes.”

From these explanations, it is clear that the appellant had some awareness of the result of carrying out the above manipulations such as confirming linearity by visual inspection.

B) The appellant argues that she did not act with an awareness of risk of inducing the reader to misinterpret the data or with the intention of falsifying the results.

As discussed above, a strong intention akin to the intention to cause harm is not a necessary condition in determining that there was “deliberate intent”. However, we are forced to conclude that the appellant had awareness of the risk of inducing the reader to misinterpret the data based on the way the data was manipulated.

C) The following facts were confirmed in the process of the investigation.
i) When the appellant, after the 2012 Paper submitted to Nature in April 2012 was rejected, submitted a paper with similar content (the 2012 Paper with the addition of electrophoresis photographs to demonstrate T cell receptor rearrangement [Supplemental Figure 6]) to Science in July, she received the following comment from the reviewer: “Moreover, this figure has been reconstructed. It is normal practice to insert thin white lines between the lanes taken from different gels (lanes 3 and 6 are spliced in). Also I find the leading edge of the GL band suspiciously sharp in #2–#5.” It is possible to suspect that the “lane 3” in the comment is the same as lane 3 in Figure 1i of Paper 1, but regardless, is reasonable to assume that the appellant was aware that she needed to submit authentic data in August 2012, because she had to distinguish lane 3 (derived from two different gels) from other lanes.

Regarding the reviewer’s comment, the appellant stated that she had not reviewed it in detail and was not aware of the specific content; she had not considered the matter, because the theme of the research paper submitted to Science was different from that of Paper 1; that the Science Paper was unrelated to Paper 1 (i.e., it had a different theme) and it had no relevance to a review to determine whether or not to reinvestigate, and she had refrained from producing it for the investigation, because it was a rejected, unpublished paper.

However, the theme of the Science Paper is almost identical to that of Paper 1, and is the same as Paper 1 in the way it uses the T-cell receptor DNA rearrangement band (which was not in the 2012 Paper) as evidence for its argument that pluripotent cells can be reprogrammed by subjecting T-lymphocytes to acid stress. The appellant had prepared a paper in December 2012 that can be regarded as a revised version of the Science Paper because of its filename of “revised-1211”. Although both the 2012 Paper and the Science Paper were rejected, unpublished papers, the appellant submitted the former to the Committee, but says she was reluctant to submit the latter. If we are to believe the explanation given by the appellant, she should have submitted the Science Paper without delay, because it confirms her explanation. By refusing to submit it, we can only assume that the appellant abandoned the opportunity to explain her position. Also, with regard to the “revised-1211” file, the Committee requested that the appellant submit her copy of the “revised-1211” file to check for any differences between it and the version obtained by the Committee, but the appellant has failed to do so.

From the foregoing facts, we conclude that the explanation by the appellant that she did not read the reviewer’s comments, is not reasonable.

ii) If a researcher receives a comment as outlined in i) above and wishes to submit the paper to Nature, he or she would confirm the rules for the handling of images such as the gel photographs specified by the publisher, and take steps such as making a distinction between lanes 1 and 2 (derived from different gels) and lanes 3, 4, and 5 in compliance with these rules. However, the appellant submitted to Nature as Figure 1i of Paper 1 the data under investigation in March 2013, only seven months after receiving the above comment, without confirming the publication’s rules regarding the handling of images. Thus it is clear that the appellant acted intentionally, even if we are to assume that she did not know Nature’s rules regarding the handling of images at the time of submitting Paper 1.

4. On the argument that the appellant has not received sufficient opportunity to explain and defend her position

1) The appellant argues that she was not given sufficient opportunity to explain and defend her position, because the investigation was conducted in a short time, taking only two weeks or so between the Preliminary Inquiry Report and the Investigation Report; that the Committee did
2) However, as discussed above, it is clear that the appellant was given an opportunity to explain her position after the Preliminary Inquiry Report, and she used the opportunity to explain the reason for adding the number of lanes, the insertion method used, and the method used to confirm that there was positive linearity between the log-scale values of molecular weight and separation distances of the standard DNA size markers for gel 1 and gel 2. The Committee reached its conclusions based on these explanations.

Reason 2: Fabrication

1. On the definition of “fabrication” in the Regulations
   1) On the definition of “fabrication”
   Article 2, Paragraph 2 of the Regulations defines “fabrication” as “making up data or results and recording or reporting them.”
   Accordingly, in the context of the paper under investigation, the judgment of fabrication depends on whether the data in question was actually derived under the experiment conditions recorded in the paper, regardless of whether the data in question is authentic data obtained under other conditions, or whether other data obtained under the same conditions as the experiment recorded in the paper does exist.

2) On the question of intent
   See Reason 1, 1. 1) above regarding our interpretation of “deliberate intent”.

2. On whether the appellant’s actions qualify as fabrication
   1) The appellant argues as follows (Appeal Document 1-1, 2-3, etc.).
   a) The Investigation Report concludes that the paper under investigation includes “research misconduct” on a totally different level from the perspective of whether or not it fulfills the conditions of “research misconduct” set out in Article 2, Paragraph 2 of the Regulations, and the conclusion is therefore unreasonable. The appellant did not engage in the fabrication of data or research results that do not exist; her only error was to use the incorrect image in the paper. The Committee’s conclusion that research misconduct took place is unreasonable, because it confuses these two issues.
   b) The appellant did not engage in presenting non-facts as if they were facts, nor did she fabricate nonexistent data or research results.

2) As discussed in 1. 1) above, whether or not a research record qualifies as fabrication depends on whether the data in question was derived under the experiment conditions recorded in the paper.
   In Paper 1, the following data was obtained under conditions that are different from the experiment conditions recorded in the paper.
   a) Paper 1 states that the data was obtained under conditions of acid stress, but in fact the data was obtained under conditions of mechanical stress.
   b) Paper 1 states that the data was acquired using spleen cells, but in fact it was acquired using bone marrow cells.
   c) Paper 1 states that the data was acquired using one-week-old (baby) mice, but in fact it was acquired using mice aged 3-4 weeks (that have been weaned).
3. On arguments such as insufficient investigation, lack of “malicious” intent, etc.

1) The appellant argues as follows (see Appeal Document 1., 3., etc.).
   a) The investigation was rushed, taking only two weeks between the Preliminary Inquiry Report and the Investigation Report, and only one interview was conducted with the appellant.
   b) The image data under investigation is Image A2, which is part of a PowerPoint file. The Committee independently analyzed a PDF file version of the file and concluded that the appellant casually cut-and-pasted the image from her PhD dissertation.
   c) The Investigation Report ignores important evidence and contradicts empirical rules. The Committee acknowledges that the incorrect image may have been used as a result of oversight. The Committee has not questioned the appellant in detail about the conditions under which the images that it assumes the appellant used were kept.
   d) The Committee’s decision does not consider the appellant voluntarily reporting that she used image data from said PhD dissertation, the existence of Image B, or the appellant submitting Image C to Nature as a correction.
   e) The appellant used Image A2 (which is part of a PowerPoint file), mistaking it for Image B, which was obtained using the acid stress process. She mixed up the images, not the experiment conditions.

2) However, it is clear that the above arguments are groundless.
   A) Two interviews were conducted after the Preliminary Inquiry Report was submitted on March 13. The outcome of the two interviews is discussed in detail below. It is obvious that the explanations of the appellant were fully heard and the investigations necessary for the Committee to reach a conclusion were carried out.
   B) In the process of the investigation, the Committee found in analyzing the image data in Paper 1 that an image had been copied from a diagram with a similar layout as one in the PhD dissertation. The Committee thus concluded that image data copied from a diagram with a similar layout as one in the PhD dissertation had been used in Paper 1. It also concluded that the diagram with a similar layout that in the PhD dissertation came from a PowerPoint file. Even if the PowerPoint file is the same as the PowerPoint file associated with the appellant’s argument (Appeal Document, Reference 4), this does not contradict the Committee’s conclusion.
   C) The Committee concluded that the appellant had acted with deliberate intent, on the basis of its analyses of the images, the conditions under which they were stored and managed, and the conclusion of the initial Investigative Report that, “sloppy data management was observed, raising the possibility that data from an unconfirmed source that could not be tracked or verified scientifically was used in a paper submitted for publication.”
   D) The Committee’s conclusion that there was deliberate intent also took into consideration the appellant’s appeal that she had on her own discovered and voluntarily reported that she had used image data from the PhD dissertation, that she reported the existence of Image B, and that she had submitted Image C to Nature as a correction.
   E) The Committee’s specific responses to the appellant’s points made above are set forth below in item 4. The Committee’s conclusions.
F) Concerning disclosure, all necessary steps were taken. The appellant’s attorney checked and copied the laboratory notebooks, and copies of the materials submitted by the appellant with her appeal were sent to the attorney.

4. The Committee’s conclusions

1) On the management and use of data by the appellant

A) The appellant stated that her “data management was not well organized” (Appeal Document, p. 18), but that is quite an understatement. The sloppiness of the appellant’s data management is evident in her explanations on March 19 and March 23: “I could not find the teratoma and immunostaining photos anywhere among recent data when I checked the photos individually in mid-February and realized something was wrong. The images were composite images, making it difficult to find them. Going back as far as data from my student days, I found the photos in a folder of experiments conducted during my doctoral program stored in a hard disk that I used years ago. I initially thought that the image data had been obtained in experiments by the Genomic Reprogramming Research Team under Dr. Wakayama, but later realized that it had been obtained in experiments at Tokyo Women’s Medical University. I’m not sure how this mistake was made.” It is obvious that with such sloppy data management, it would be easy to use data from one experiment for another experiment, and it is inconceivable that the appellant was unaware of this risk.

B) Problems regarding the handling of the image data under investigation go beyond sloppy management.

As is obvious from the appellant’s explanations on March 19 and March 23, she gathered image data from the PhD dissertation and lab experiments, made composite images from them, and overwrote, stored, and used them as composite images: “I often gathered the data needed for writing research papers”; “I continued to produce Figures by overwriting [images] on PowerPoint”; “[I] made composites of six images at a time”; “I can’t remember if I used three or six images, but I probably used composite teratoma images for the Figure in the paper submitted to Nature”; “I don’t think the teratoma images were photographed individually; I should be aware of it if that had been the case”; and “I used a composite image when we submitted Paper 1, but subsequently replaced the image with another one”.

C) The above-mentioned data management allows for various interpretations of the composite data, because no explanation of the source of individual data is provided. It also carries the risk that data from the wrong experiment may be used because it is not specified which experiment the data came from. It is obvious that composite image data needs to be checked to confirm the original source of each individual image before using the image in a paper for publication because of the risk that image data from experiments conducted under different conditions to the one recorded in the paper may be used. Yet the appellant admits that she did not carry out any checks.

D) There was a nine-month interval between the submission of Paper 1 (March 2013) and its acceptance for publication (December 2013). The appellant had plenty of time to replace the images during this period.

E) Therefore, we are forced to conclude that the appellant ignored the abovementioned risks by failing to check the source of individual image data and reconciling experiment conditions,
with laboratory notes and image data, and as a result used the images under investigation, whose experiment conditions were different from those recorded in the paper.

2) The continued use of the image data under investigation not only in the 2012 Paper, but throughout the time up to the submission of Paper 1 as well
The appellant states that the 2012 Paper was written by her and was on converting spleen lymphocytes into pluripotent cells by subjecting them to acid stress. As discussed above, she used composite image data in the paper, and used the same data in Paper 1. Although she changed the text on the image data, she used the same image data for both papers. As discussed above, she did not check the source of the data despite having opportunities to do so, including submissions to Nature, Cell, and Science magazines in 2012. Her conduct clearly ignores the risk of using composite data without specifying the source of individual data.

3) The appellant acknowledges that data obtained in an experiment conducted under different conditions to the experiment recorded in the paper had been used
The appellant gave the following explanations on March 19 and 23 regarding the use of data obtained under different experiment conditions from those recorded in Paper 1, admitting that she used the data even though it may have been obtained under different conditions from the experiment recorded in the paper.
   a) In answer to the question “were you aware on February 20 that the experiment in the dissertation was conducted under mechanical stress and the one in Paper 1 under acid stress?” she answered: “To be precise, the experiment in the dissertation used triturated stem cells and the one in the paper submitted to Nature used stem cells subjected to acid stress. From my perspective they are both STAP cells, but strictly speaking they are not.”
   b) On the data obtained from bone marrow cells recorded as being made from spleen cells: “It is an experiment I have conducted many times, and the results were always similar, so I used it with confidence that the data showed the correct phenomenon. It’s not that I believed it was acceptable to use data from spleen cell experiments as if the data had come from bone marrow cell experiments.”

4) On the awareness that the image data under investigation was derived from the said PhD dissertation
The appellant gave the following explanations on March 19 and 23: “It was champion data in a sense”; “such a clean teratoma photograph like the image under investigation was a rare occurrence in a doctoral program experiment”. Analysis of the image data under investigation found that changes, such as the superimposition of text on the image, had been made twice. The appellant commented on this on March 19 as follows: “to be honest, I had noticed the text.” On this basis, we are forced to conclude that the appellant was aware that the image data under investigation may have been derived from the PhD dissertation or from the data for another experiment.

   We are forced to conclude that not only did she ignore the risk of using composite image data without checking the sources of individual data, but also that she went ahead and used the image while being aware that the data may have been obtained in a different experiment from the one recorded in the paper. This [kind of action] threatens the very foundations of the credibility of data in the scientific research community.

5) The appellant’s arguments concerning the existence of image data B and C
The appellant argues that she used the image in the PowerPoint file (Image A2) by mistake, believing it was an image obtained from the acid stress experiment (Image B); that her mistake was
not that she mixed up the experiment conditions, but she got the images mixed up, i.e., that Image A2 appeared in Paper 1 due to an oversight (Appeal Document 3). She makes the following points:

a) She discovered and reported that she used image data from the PhD dissertation.
b) An image obtained from an experiment using acid stress conditions (Image B) does exist.

A) The appellant’s discovery and reporting of the use of data from the PhD dissertation

On February 20, at an interview attended by the appellant, Dr Sasai explained that the image data under investigation had been a simple case of mixing up experiments using cells taken from bone marrow and spleen cells. In a jointly signed document dated March 1, the appellant and Dr Sasai stated that they had mistakenly used data from bone marrow cells instead of data from spleen cells, but they made no reference to differences in experiment conditions. Further investigation revealed that the image data under investigation was taken from the PhD dissertation and obtained in an experiment that used mechanical stress.

The appellant explained for the first time in the March 23 interview that she had used data from an experiment conducted under different conditions from those recorded in the paper. Prior to that, she had given an explanation in person to committee members when they visited the RIKEN Center for Developmental Biology (CDB) to check materials, saying that there was something about her PhD dissertation that she wanted to explain. However, her explanation only covered her discussions with the PhD dissertation assessor about the image data mix-up and with university authorities about the future treatment of the PhD dissertation, with no mention of how data from experiments carried out under different conditions had come to be used. (We note that the Committee did not ask for an explanation on this matter on March 19, because it had decided to ask the appellant to explain how the data mix-up had occurred at the interview scheduled for March 23). The appellant had been instructed by Dr Sasai to explain to the Committee how she had come to use image data from the PhD dissertation.

This situation indicates that the appellant had no intention of speaking about how she had come to use image data from her PhD dissertation which had been obtained under different experiment conditions beyond the explanation she had given on February 20.

At this time, questions about Paper 1 had already been raised on the Internet and elsewhere, and there was clearly a possibility that the data mix-up would be identified (and indeed, comments appeared on the Internet and elsewhere thereafter). While we acknowledge that the appellant reported the oversight before it was commented on by others, the fact remains that she had been aware that the data in Paper 1 had been obtained under different experiment conditions to those recorded in the paper (or at least was aware of the possibility), yet did not say so, and explained it as a simple mix-up.

B) The composite teratoma image data derived from a PowerPoint file

i) The six composite teratoma images derived from a PowerPoint file had already been used as a Supplemental Figure in the 2012 Paper. Of these six images, the three hematoxylin and eosin (HE) stained images were replaced when the 2013 paper was submitted; different images were published in Paper 1 as Figure 2e (top panel). The three immunostained teratoma images (Image B) said to have been obtained in June 2012 were not used when Paper 1 was submitted, but of the composite teratoma images used in the 2012 Paper, the three remaining immunostained images were published in Paper 1 in Figure 2e (bottom panel). Image C is image data prepared by immunostaining a piece of stored teratoma to prevent any suspicion arising over the source of the teratoma, and did not exist at the time of the submission of the paper. This image data (Image C) was prepared from the same teratoma as the HE stained
image data in the top panel of Figure 2e in Paper 1, but it is unknown whether it was prepared from the same teratoma as Image B.

ii) On this point, the appellant says that she used the composite image that she had previously used instead of the immunostained teratoma prepared from spleen-derived STAP cells obtained in June 2012, because the immunostaining results were identical.

When comparing the image data under investigation with Image B, we have a considerably different impression of the corresponding immunostained images. We find the explanation by the appellant that the results were identical unconvincing. It would be extremely rare for identical immunostaining results to be obtained under different experiment conditions.

Even if we are to assume the image data under investigation and Image B are identical, it does not change the fact that the appellant decided to use the image data under investigation obtained from a different experiment to the one recorded in the paper without checking its source, nor did she check the source when replacing the image data; and that she submitted the paper despite being aware of the possibility that the composite images (including the image data under investigation) came from the PhD dissertation. We note that Image B is not a composite image.

Either way, we are forced to conclude that she used the data ignoring the risk of a data mix-up.

C) The existence of image B
   i) With regard to image B, the appellant argues in Supplementary Document 1 that the teratoma on which Image B is based (which she argues is correct, based on p. 75 of the laboratory notes) was extracted on January 24, 2012.

   ii) However, p. 75 of the laboratory notes is not dated. The closest dated pages are p. 73 (marked “6/28”), p. 76 (either “2/29” or “2/19”; impossible to decipher), and p. 81 (“October”), and none of them say which year the entry was made. We therefore cannot confirm whether the experiment recorded on p. 75 was conducted on January 24, 2012. As well, the entry on p.75 does not say what type of cells or method was used to produce the teratoma.

   iii) The appellant argues that Image B (which she argues is correct, based on p. 117 of the laboratory notes) was photographed on June 9, 2012 (Supplementary Document 1, 3.-3, 3.-4, etc.) However, p. 117 is not dated and merely has the entry “(Differentiation assay) (ES colony)”, and does not say how the staining was conducted using which antibody. Differentiation assay usually refers to an experiment that examines differentiation potential of the test cells; in the Methods section of Paper 1, there is a paragraph on in-vitro differentiation assay in which immunostaining is conducted by changing the culturing conditions of STAP cells to induce differentiation into different germ layers. Paper 1 also contains a paragraph on in-vivo differentiation assay. In this experiment, STAP cells are transplanted subcutaneously into mice with an immune deficiency to form a teratoma. The entry “Differentiation assay” on p. 117 could mean in-vitro differentiation assay, because of the entry “ES colony” beside it, but it is unclear whether it refers to in-vitro or in-vivo differentiation assay. The appellant says she has carried out other immunostaining experiments believed to involve teratomas, but their origin is unclear, as is their relationship with Image B.

   iv) The usual practice is to carry out analysis such as immunostaining immediately after extracting the teratoma, because proteins may break down or degenerate while the sample is stored,
causing the loss or reduction of antibody reactivity. We are thus skeptical of the appellant’s explanation that she extracted the teratoma on January 24, 2012, and carried out immunostaining analysis on June 9, 2012. Between these two dates, the appellant submitted papers on this research subject to Nature (the 2012 Paper) in April, to Cell in June, and to Science in July. Given the importance of teratoma analysis in this study, we find it inexplicable that she did not use the teratoma Image B (prepared on June 9, 2012), which was derived from STAP cells made from spleen cells of a one-week-old mouse, in the papers submitted to Cell and Science.

v) The appellant argues that, based on the entry on p. 99 of the laboratory notes, it is likely that the teratoma immunostaining experiment was conducted on February 27, 2012, and Image B’ (similar to Image B) was photographed in early March 2012 (Supplementary Document 1, 3. and 4). This argument indicates that the appellant herself is unable to specify from the laboratory notes the date that the experiment took place.

vi) The laboratory notebook is a primary source showing what kind of experiments were conducted and when they were conducted. However, it is scientifically impossible to verify from the submitted laboratory notebooks how image B, which is claimed to be the correct image, was acquired.

vii) The appellant does not appear to have considered the data obtained from the experiments in detail. Her attention was fixated on the so-called champion data (“champion data” refers to data from an experiment that is not carried out frequently, but happens to turn out well. This data, which the appellant calls champion data, was used from the time of submission of the 2012 Paper).

D) Our conclusion, from the foregoing and from the fact that the appellant discovered and reported the use of image data from the PhD dissertation and the existence of Image B and Image C, that the use of data from the PhD dissertation, which was obtained under different experiment conditions, in Paper 1 was not due to oversight, but was an attempt to rectify after the fact a predictable situation stemming from taking action with the knowledge of the possible risk of data mix-up. We therefore believe there is no need to change our decision that the actions were intentional.

6) The PowerPoint files and changing themes of the papers
A) The appellant explains that: “the image data used in Paper 1 is an image used in the PhD dissertation with the color and position of the text adjusted for use in a PowerPoint file. The PowerPoint file was prepared as reference material for reporting to Professor Wakayama and others in November 2011 and the PowerPoint file demonstrates ‘in the context of research from the perspective of stress treatment that STAP cells can be produced from various cells such as bone marrow and spleen-derived cells by applying stimuli such as physical and acid stress’” (Appeal Document 3.-1). Further, the appellant says she changed the theme of her PowerPoint file and papers (2012 Paper and Paper 1), and explains that she mixed up the photographs through carelessness in the process; that the original theme was “conversion of cells into stem cells by applying stress” (as in the PowerPoint file), but that it was revised to “chimera formed from somatic cell by applying stress” (2012 Paper), and finally to “properties of stem cells produced by acid stress” (Paper 1) (Supplementary Document 1, 3.-6 and Supplementary Document 1, Statement).
B) In making the abovementioned report, it is unclear whether the PowerPoint file was used as
data obtained in the acid stress experiment or in the mechanical stress experiment, or whether
it was used without distinguishing between the two.

The appellant explains that she submitted the 2012 Paper on the understanding that it
was about “teratomas from cells produced by applying stress.”

Even if we assume this is the case, the paper was written by the appellant and contains
the following sentences. “Consequently, we focused on exposure to low pH as the stress
treatment of choice for the remainder of the study.” “To expose the mature cells to a physio-
logical stress, they were treated with low pH (pH5.5) solution.” This draws our attention to ac-
id stress, and the image data from the PowerPoint file is used to demonstrate this point. The
2012 Paper submitted by the appellant and the paper sent to Professor Wakayama on the day
before it was due to be submitted have slight differences in wording, but the two sentences
quoted above are identical, as are the two images. The appellant has avoided referring to these
entries.

During the March 23 interview, the appellant answered “yes” to the question: “I want to
check this point very carefully. Did you believe that the data used in the 2012 Paper was stem
cell data produced by acid stress?” Thus she admitted that she thought that the data used when
she submitted the 2012 Paper was stem cell data produced by acid stress. She had no alterna-
tive given the theme of the 2012 Paper.

C) As discussed above, the appellant explained the differences in experiment conditions as fol-
 lows. “To be more precise, the experiment in the dissertation used triturated stem cells and the
one in the paper submitted to Nature used stem cells bathed in acid. From my perspective they
are both STAP cells, but strictly speaking they are not.” The Committee noted in its report its
understanding that the appellant was not fully aware of the differences in experiment condi-
tions. The Committee concluded that the core message of Paper 1 is that a highly versatile
method called acid stress had been developed (i.e., under different experiment conditions from
the PhD dissertation) and accordingly it is unlikely that the appellant was unaware of the dif-
ference in experiment conditions in preparing the image data.

However, the appellant argues in Supplementary Document 1 that she did not make such
an explanation and that she was fully aware of the differences in experiment conditions.

This argument is consistent with the Committee’s understanding. We conclude that the
appellant did not use the image data with an awareness of the risk that image data obtained
under different experiment conditions might be being used in the 2012 Paper and Paper 1, but
rather that she used image data from the PowerPoint file while fully aware of the differences
in experiment conditions.

D) Experiment data used in academic papers are sometimes changed, e.g., the author may start
out using bone marrow-derived data, but later switch to using spleen-derived data. Assuming
the author is asked to confirm the source of the data at the time of submission, it is not incon-
ceivable that the author may forget that the initial bone marrow-derived data was later re-
placed with spleen-derived data.

However, the most important theme of Paper 1 is the formation of STAP cells from ma-
ture spleen lymphocytes by applying acid stress, and the image data under investigation is
critical for demonstrating this point. The appellant is clearly well aware of this.

Even if we assume that the appellant had forgotten that the image data used in Paper 1 at
the time of submission was from the PhD dissertation and obtained under different experiment
conditions, the fact remains that she decided to use the data in the 2012 Paper and Paper 1 without confirming the source of the data by cross-checking with the original data, despite being aware of the risk of using image data obtained under different experiment conditions, and continued to use this data thereafter. As a consequence, she used data obtained under different experiment conditions in a paper submitted for publication. This course of action arising from the events outlined above cannot be seen as accidental carelessness.

7) Our review of the Supplementary Document 2 dated May 4 submitted by the appellant
A) The appellant submitted materials relating to an August 29, 2013 case heard by the Sendai District Court (Hanrei Jiho No. 2211). She argues that the decision on research misconduct should be based on the judicial interpretation shown in this case, i.e., the judicial interpretation of “fabrication” and “falsification” set out in the MEXT guidelines that combining several photographs into one photograph does not qualify as fabrication or falsification unless data that does not exist was created, or data was deliberately processed into inauthentic data.

It goes without saying that under the above guidelines, these actions do not constitute fabrication or falsification as long as it is done unintentionally, and this is the same as in the RIKEN Regulations, which stipulate that such action does not qualify as fabrication or falsification if done unintentionally.

The court ruling cited by the appellant concerns a defamation case. The court concluded that the paper did not contain fabrication or falsification for the following reasons. “The sectional photo ended up with almost 8% difference in the aspect ratio compared with the original photo, because the plaintiff neglected to fix the aspect ratio in the process of pasting the image data into the document file of the paper.” “The photograph used in the paper does not involve the creation of data that does not exist nor data processed into inauthentic data, and thus, in light of the MEXT guidelines and the university’s guidelines, we cannot conclude that the paper contains fabrication or falsification, although we cannot deny that it contains an inaccurate sectional photograph” (pages 104 and 105, Hanrei Jiho No. 2211). The court concludes that “the sectional photo ended up with almost 8% difference in the aspect ratio compared with the original photo” by error, not intent, and that the photograph that was published in the paper does not qualify as data that does not exist being created or data processed into inauthentic data with intent.

B) The appellant argues that the Committee’s conclusion should take into consideration how the image mix-up occurred, i.e.,

a) The appellant’s working environment, experimental methods, and approach to writing papers underwent various changes in the period between March 2011 and March 2013. The paper was written in a short period of time under extraordinary circumstances. These factors have a strong impact on how the image mix-up should be regarded. The Committee’s findings and conclusion, which do not take these factors into consideration and overlooks them, are inappropriate.

b) As background to the image mix-up, the appellant changed affiliations from Harvard University to RIKEN, her research supervisor changed from Professor Wakayama to Professor Sasai, the stress applied to the cells changed from physical stress to acid stress, and her concept of the study changed from the 2012 Paper to Paper 1, all in the period leading up to the submission of Paper 1. The appellant forgot to replace the teratoma immunostaining image as a result of this combination of extraordinary circumstances (Supplementary Document 2, Statement 2).
However, to reiterate, the appellant wrote her papers from the 2012 Paper onward with acid stress as the main experiment method, and the structure of her papers is consistent between this paper and the paper submitted to Cell, the Science Paper, and Paper 1. Thus, she should have been aware of the need to replace the teratoma image derived from cells exposed to physical stress from the time of submitting the 2012 Paper onward. There was also plenty of opportunity to replace the image during the nine-month period between March 2013, when Paper 1 was submitted, and December 2013, when it was approved for publication. Thus the special circumstances at the time of submitting Paper 1 need not be taken into account.

We note that the 2012 Paper comments that the teratoma data is supplemental and no detailed account is provided. While the teratoma data is clearly presented as supplemental data [in this paper] and only presented as data for the paper itself from Paper 1 onward, the teratoma formation experiment is an important one in demonstrating the pluripotency of cells, and it is obvious that the appellant presented teratoma data as supplemental data with the expectation that it would have such an effect, even without a detailed account.

C) The appellant argues that Article 15, Paragraph 5 of the Regulations stipulates that “the investigative committee may, if it considers it necessary, instruct the subject of the allegations to replicate experiments or may approve a request made by the informant to have the experiments replicated” to guarantee an opportunity for the said person to clear his or her name of research misconduct by providing them the chance to replicate the experiment. In the case under investigation, a successful teratoma formation experiment under the conditions recorded in the paper under investigation would clearly demonstrate that the appellant had genuinely carried out the teratoma formation experiment, from which she had obtained the teratoma image. Given that RIKEN launched a project to verify the STAP phenomenon in April, one of whose objectives is to examine the reproducibility of the method recorded in the paper, the actions of the appellant cannot be ruled as research misconduct and the decision on whether or not research misconduct took place should not be made before the results of the verification experiment.

However, it is clear that research misconduct in the form of fabrication and falsification by the appellant is evident in Paper 1, and the case does not require instruction or permission to replicate an experiment (nor has the appellant requested one). We thus see no reason to await the results of a verification experiment before reaching our conclusions.

Reason 3: Conclusions
From the foregoing, the results of the Committee’s investigation remain unchanged from those of the Investigative Report of March 31, 2014, and we conclude there is no need for further investigation.

In Supplementary Document 1, the appellant asks for a two-week postponement of the review (see below).

1. According to the Regulations, “a RIKEN researcher who is suspected of research misconduct has a responsibility to explain the facts of the case to RIKEN” (Article 5); “in refuting the allegations, the subject of the allegations must provide scientific evidence that the research in question was carried out with appropriate scientific methods and reported on appropriately in published research papers” (Article 15, Paragraph 4); and “RIKEN shall require the individual appealing the case to submit materials that will provide grounds for overturning the inquiry decision… and will request other forms of cooperation as necessary for a speedy resolution of
the case” (Article 19, Paragraph 5). The appellant received a copy of the Regulations on February 21 and is required to comply.

2. In this context, the steps taken by the Committee with regard to the review and the response of the appellant to these steps are provided below for the record.

   i) On April 10, the Committee informed the appellant’s attorney as follows:
      a) If there was anything the appellant had not explained sufficiently or she wished to add regarding her appeal, she should send it in writing to the Committee, which would accept a record of an interview by an attorney.
      b) The Committee asks the appellant to include in the above document more details about her reference to “something I want you to understand about the so-called fabricated image” in the April 9 press conference, as well as explaining whether other laboratory notes other than those submitted to RIKEN were related to the image, and if so, to submit the relevant laboratory notes.

   ii) On April 15, the Committee informed the appellant’s attorney that if it was difficult to compile the supplementary information in a document, it could be in the form of an audio or video recording.

   iii) On April 20, the attorney submitted Supplementary Document 1. Supplementary Document 1 contains an argument based on an interview of the appellant by the attorney, and came with supplementary materials such as a statement by the appellant and materials she prepared.


However, we note the following:

   a) Of the materials that the attorney claims that they did not have enough time to go through, many related to disclosure are materials prepared and submitted by the appellant, or submitted jointly with Professor Sasai.
   b) The hard disk, which the attorney says he obtained a copy of on April 17 and needed time to go through, is one that the appellant used in the past. The Committee asked her to submit the disk for the investigation, because it contained the original image data from the dissertation. She refused to submit the disk because it contains personal data, instead submitting a copy of the original image data from the dissertation. This suggests that she had checked the content of the disk at the time, and should have been able to inform the attorney what the disk contained.
   c) In her Statement, the appellant argues that the images became mixed up as a result of several changes to the theme of her papers, but the themes of the papers were those the Committee already knew (to reiterate, the theme and entries in the 2012 Paper contradict her explanation).
   d) In Supplementary Document 1, the attorney records a summary of the teratoma experiment as an interview of the appellant. Looking at the content, it appears that the appellant is recalling her laboratory notes and experiment conditions, quoting from the laboratory note entries to explain the content in detail.
iv) On April 27, the Committee informed the appellant’s attorney that it would conduct an interview, if the appellant requested one, on either April 28 or 29, and if an interview were to be held, the Committee would send materials relevant to the questions it wished to ask. The Committee sent the papers submitted to Cell and Science, and the reply from Science (including the editor’s and reviewer’s comments), and asked the attorney to confirm the materials and submit them. The Committee also clearly marked sections of the materials that it planned to ask questions about.

The appellant responded as follows on the same day:

i) She would not attend an interview unless the Committee specified the document(s) and question topics.

ii) She would need at least a week’s notice before attending an interview because of ill health.

iii) She would submit a doctor’s certificate if required by the Committee.

v) On April 30, the appellant submitted a list of questions to the Committee to clarify the Committee’s interpretation of fabrication and falsification. The Committee answered on the same day that it had given careful consideration [to the meaning] of the terms of falsification, etc., and that it would make this clear in the review results.

vi) On May 1, the appellant sent a document explaining the reply from Science (including the editor’s and reviewer’s comments) as stated in d) above, and stating that she would not submit the Science Paper. The details of the exchange are as outlined above. We believe the paper should be submitted without delay because, according to the appellant’s explanation, the paper provides materials that back up her argument. She appears to have voluntarily abandoned an opportunity to explain her position.

vii) On May 4, the appellant submitted Supplementary Document 2. Supplementary Document 2 records in approximately four pages her argument obtained from an interview. It contains a chronological table broken down by month with the appellant’s affiliations, her views on the Oct4+ cells, teratoma, theories discussed in her papers, images, etc., and comes with a Statement by the appellant of approximately five pages as a supplementary document. (The results of our review are as set out above).

viii) Other items such as a request for an interview, checking and submitting laboratory notes and remaining materials, and the opinion of a legal expert have not been submitted. A doctor’s certificate has not been submitted either.

Supplementary information
The following terms have been used in this document.

<table>
<thead>
<tr>
<th>Committee</th>
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<tr>
<td>Regulations</td>
<td>Regulations on the Prevention of Research Misconduct, September 13, 2012 Regulation No. 61, Effective October 1, 2012</td>
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<td>Attorney</td>
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<table>
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<tr>
<th>Document Type</th>
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<tr>
<td>Appeal Document</td>
<td>“Appeal Document” dated April 8 submitted by the appellant</td>
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<tr>
<td>Supplementary Document 1</td>
<td>“Supplementary Document 1 concerning the reasons for the appeal” dated April 20 submitted by the appellant</td>
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<tr>
<td>Supplementary Document 2</td>
<td>“Supplementary Document 2 concerning the reasons for the appeal” dated May 4 submitted by the appellant</td>
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