1. Background

(1) Outline

The University of Tokyo (UoT) Committee for the Code of Conduct for Research (CCCR) received anonymous claims on September 1, 2016, that one research group of the Institute of Molecular and Cellular Biosciences (IMCB) committed data fabrication and falsification in 7 published scientific articles. The CCCR established the Investigation Committee on September 20, 2016, and this Committee requested the Director of the IMCB to investigate the allegations on October 13 of the same year. The results of the internal investigation were reported to the Investigation Committee by the Director of the IMCB on January 25, 2017. Based on this report, the Investigation Committee carried out further fact-finding activities. Taking into account the review and discussion of the Investigation Committee, the CCCR issued its final adjudication of misconduct on May 31, 2017.

(2) Period and Scope of Investigation

Period of investigation: October 13, 2016 to May 31, 2017

Committee meetings:

    CCCR: five meetings from September 14, 2016 to May 31, 2017

    Investigation Committee: 15 meetings from October 13, 2016 to May 15, 2017

The scope of investigation included:

• Documents collected during internal investigations

• Documents presented by the article co-authors

• Response to the queries and requests of the Investigation Committee

• Questions sent to the publishers and their responses

• Face-to-face interviews with researchers, including those named in the allegations

2. Purpose of Investigation

The Investigation Committee investigated whether any of the alleged data fabrication or falsification took place. Suspicions of other incidents of data fabrication or falsification arising during the course of the investigation were also addressed.
3. Results of Investigation

(1) Complaints Received

The allegations included the following:

(A) Inappropriate image editing

Examples of complaints included the following:

• Images showing very similar results obtained from experiments conducted under different conditions (suggested that the same image was used to represent different experiments)
• Western blot images with uniform background noise level (suggesting excessive manipulation of the cutoff threshold or background image editing)
• Yeast plate images with discontinuous rims, suggesting assembly of parts of different dishes by copying and pasting
• Yeast plate images with partial intensity modification
• Maximum signal intensity altered in certain panels of a figure
• Image of a gel (used in western blotting, per the claim) showing a pair of artificial white lines above and below a band

(B) Inappropriate or incorrect graphs

Examples of complaints included the following:

• On two horizontal bar graphs with different dependent variable scales, the same results are wrongly indicated by bars of the same length
• The same fluorescence microscopy image is presented in separate figures, but its accompanying bar graphs show different SD values
• Bizarre and poorly constructed graphs
  
  To present similar values, the same bars and error bars were copied and pasted. What looks like a black painted box is actually a thick black line or a superimposition of multiple rectangles. Within one bar graph, error bar lines are presented in a variety of shapes: slightly oblique, in the upper direction only, or in both directions.
• Theoretically impossible SD values

(2) Figures Representing Misconduct

Based on the investigation of the allegations of fabrication and falsification explained in (1), the CCCR identified misconduct in image processing and other work, as explained below. In addition, the CCCR found additional figures containing fabrication or falsification. The article codes (e.g., “W-b”) in the sections to follow indicate the articles in which fabrication or falsification was identified. The reader is referred to the list in Section (4) for details.
(i) Graphs that present the results of nonexistent experiments (This case was not included in the set of claims received.)

The CCCR identified fabrication in one figure published in one article: Fig. 3A, Article W-c.

The figure contains 12 graphs, two of which showed results of nonexistent experiments. This is defined as fabrication, i.e., forgery of nonexistent data or other study results. One of the two graphs contains no visible data (Graph i), whereas the other apparently shows positive, though minimally noticeable, changes (Graph ii). In the Microsoft Excel file that contained the original data, no data corresponding to Graph i were found. Although the mean column contained data for Graph ii, despite the fact that the corresponding experiment was not conducted, the error column contained no data. The Investigation Committee could not determine who had entered the data. Dr. Yoshinori Watanabe reported to the Investigation Committee that he had failed to indicate ND (not determined) for Graph i. He believed that the experiment portrayed in Graph ii had been conducted.

The Investigation Committee inquired into creation of the graphs. Originally, two sets of graphs were created as a result of two experiments, but they were later combined into one figure. Consequently, the figure contained two panels for which no experimental data were available. According to the researcher who conducted the experiment, the graphs were combined on Dr. Watanabe’s instruction, which Dr. Watanabe denies. The researcher was then a graduate student (enrolled in the PhD program), suggesting that, according to the judgment of the Investigation Committee, Dr. Watanabe’s instruction carried weight. It is reasonable to believe that Dr. Watanabe was aware of the absence of experimentation under the conditions depicted in the two graphs. In addition, it is difficult to believe that Dr. Watanabe merely failed to indicate ND for Graph i, as he claims.

Dr. Watanabe was most probably aware that the graphs were false, and that no experimental results were available, when he submitted the manuscript. In the event that he simply failed to indicate ND despite knowing that the experiment had not been performed, he should still be held responsible for gross negligence.

(ii) A photographic image illustrates results from one yeast strain, whereas the corresponding figure shows quantification results from another strain. The absence of a specific mention of this fact misleads the reader to believe that the image and quantitation represent results from the same strain.

(This case was not included in the set of claims received.)

The CCCR identified fabrication in two figures published in one article: Figs. 2e and 3d, Article W-b.

The genetic background differed between the yeast strain reported for quantitation and the strain depicted in the fluorescence image. The use of a strain with different genetic characteristics constitutes a completely separate experiment. The act of presenting the results of one strain using data obtained from another constitutes fabrication of nonexistent study results.

The researcher who conducted the experiment was then a Master’s program student. Initially, the student conducted quantitative measurements using a yeast strain whose meiotic spindle is not visible in the absence of mCherry-atb2 (tubulin) (quantification strain). After the quantitative results were compiled, a separate strain expressing mCherry-atb1 (tubulin) was genetically engineered (second strain). For the sake of
visibility, Dr. Watanabe instructed the student to take a picture of the second strain and use it as an illustration in the article.

According to Dr. Watanabe, he assumed that the student had performed the quantitative measurement using the second strain. However, the Investigation Committee found no evidence substantiating that Dr. Watanabe instructed the student to conduct quantitative measurement of the second strain. The absence of clear instruction to the student and the failure to confirm the quantitative results of the second strain mean that Dr. Watanabe probably submitted the manuscript with full cognizance of the fact that different strains are shown in the photo and quantification. Even if Dr. Watanabe was not aware of this fact, he is still responsible for gross negligence, in that he failed to provide the student with specific instructions to quantitatively assay the second strain and confirm the results.

(iii) Samples were processed under different conditions, and images used for comparison were acquired under different conditions. (This case was not included in the set of claims received.)

The CCCR identified fabrication in three figures published in one article: Figs. 2C, S13C, and S15A, Article W-g.

Two to three pictures presented for comparison in the same figure in an article differed with respect to experimental conditions. The act of comparing and discussing the samples treated or photographed under different conditions without clearly indicating that fact is scientific misconduct. Dissimilar to the case of comparing samples collected under the same conditions, comparison of samples obtained under different conditions allows the author to make any conclusion he or she desires by craftily manipulating the conditions. A conclusion reached by such an approach is scientifically invalid. Publication of incorrect results as if they were obtained in a scientifically valid manner represents a betrayal of genuine scientific communication. This maneuver created results that could not otherwise be obtained, and thus represents forgery of nonexistent study results, i.e., fabrication.

Dr. Yuji Tanno conducted the quantitative measurement and created the representative image. Dr. Tanno was the first author of the article. He was an assistant professor when he wrote the manuscript, a scholarly position that requires sufficient knowledge of the ethics of article writing and image processing. The Investigation Committee judges that he committed fabrication.

The Investigation Committee could not clarify to what extent Dr. Watanabe was aware of the difference in image acquisition conditions. However, considering that he gave specific guidance and instructions to Dr. Tanno concerning image acquisition and other aspects of the experiment, the CCCR judges that he should also be held responsible for fabrication.

The Investigation Committee found that Dr. Watanabe finalized several figures of other manuscripts, inappropriately editing them to make the conclusion more convincing. The Committee discovered that Dr. Watanabe made high-handed instructions regarding the research activities in his laboratory, including image data creation, and that the laboratory members could not dare to refuse his instructions or question his erroneous approach to image editing. Taking these findings into account, the CCCR believes that Dr. Watanabe is responsible for the fabrication in the article in question.
(iv) Inappropriate image editing

The CCCR identified falsification in seven figures published in four articles: Fig. 4a, Article W-b; Figs. 3e, 3g (CAP-H), 5a, S16 (Actin), Article W-e; Fig. 2A, Article W-f; and Fig. S8A, Article W-g.

Manuscript preparation allows for image editing, within certain acceptable limits. Acceptable editing work includes uniform enhancement of the density of a faint picture and image processing to increase readability. On the other hand, over-processing is considered an inappropriate operation by many publishers, as reflected in their instructions for authors, as well as among researchers.

It is technically challenging and sometimes controversial to draw a clear line between fraudulent retouching and inappropriate but permissible manipulation. Experts in this area argue that researchers may have a code of practice on authorship, but this is not equivalent to criteria for evaluating what constitutes deceptive and unfair editing.

Regarding the components constituting misconduct, the CCCR considered that (i) excessive retouching, such as elimination of a band, is falsification, because such a procedure aims to treat existing data as if they are non-existent. The CCCR also took note of the (ii) importance of taking into consideration a wide range of evidence, including the method, purpose, and scope of the editing; the extent and significance of the information lost; and the motive of the image editor (in particular, the intention inferred from the operation) before making a judgment in the absence of excessive editing.

Based on the above criteria for evaluating misconduct, the CCCR judged that data fabrication had taken place because certain bands, spots, or other features were removed from the non-microscopic images that were investigated (relevant to i). In addition, the CCCR located several figures that were processed inappropriately, but not in an abusive manner aimed at removing certain objects. The Committee judged that these images do not fall in the category of falsification.

Consequently, the CCCR identified falsification in seven figures published in four articles. Anecdotally, several pictures were edited in a two-step process: first, the image contrast was significantly enhanced, and then a certain level of background noise was applied to reduce its brightness.

Manipulation was identified in the following figures:

(A) Fig. 4a, Article W-b

In this figure, the image of HP1α was subjected to excessive contrast adjustment and subsequent background processing to reduce its brightness. As a result of such retouching, the faint bands in the IgG lane were almost completely erased, and were no longer visible. Removing an existing band is excessive editing and falsification, regardless of whether the vanished band does or does not impact the conclusion of the study. The Investigation Committee could not determine whether the experimenter or Dr. Watanabe performed the dishonest retouching.

Even if Dr. Watanabe did not alter the image in person, he was the supervisor of the Master’s student who conducted the experiment, as well as the corresponding author of the article in question. Dr. Watanabe’s loose sense of author responsibility and lack of ethical standards regarding image data processing underlie the
act of submitting falsified images for publication. The CCCR acknowledges Dr. Watanabe’s gross negligence as a researcher. In conclusion, the CCCR judges that Dr. Watanabe is responsible for falsification of the figure.

(B) Figs. 3e, 3g (CAP–H), 5a, S16 (Actin), Article W-e

These figures were processed with excessive contrast manipulation and background rendering so that faint bands seen in the original image were no longer visible. Removing an existing band is over-processing; it represents falsification, regardless of whether the vanished band does or does not impact the conclusion of the study.

For Figs. 3g and S16, the experimenter presented his progress at an internal laboratory meeting using images showing faint bands (his PowerPoint presentation files have been retained in the laboratory). This suggests that Dr. Watanabe eliminated the faint bands from the images used for publication.

For Figs. 3e and 5a, however, the experimenter removed faint bands when he created the laboratory presentation materials. These experimenters were both graduate students, one in the Master’s program and the other in the PhD program. These students cannot be regarded as having sufficient scholarly knowledge of manuscript preparation. They removed nonspecific bands based on an erroneous belief, which could probably be attributed to the guidance and education they received in this particular laboratory.

Dr. Watanabe himself erased certain bands in other images, thereby creating an atmosphere in his laboratory in which it was acceptable to remove nonspecific bands. He had the final responsibility for the manuscript that included Figs. 3e and 5a. The experimenters were graduate students. These facts indicate gross negligence on the part of Dr. Watanabe, regardless of whether he was aware of the experimenters eliminating certain bands. The CCCR concludes that Dr. Watanabe is responsible for the falsification of these figures.

(C) Fig. 2A, Article W-f

The panel showing eso1+/AcPsm3 was processed with obscuring and background shading algorithms. Consequently, the faint bands in the 2- and 6-hour lanes observed in the original image were eliminated, along with a significant signal reduction in the band in the 7-hour lane. In addition, the figure shown in the article was an artificial image created by rotating the original along its horizontal or vertical axis (i.e., top–bottom or right–left inversion). The excessive processing involving obscuring and background shading, by which the originally visible bands were rendered invisible, represents falsification according to the criteria described above, irrespective of whether the removed bands impact the conclusion of the study.

Dr. Watanabe edited this picture in person. The CCCR adjudicates that he is responsible for falsifying this figure.

(D) Fig. S8A, Article W-g

The original images contain faint spots that indicate reaction with anti-H3K9me3S10ph antibody. However,
they are no longer visible in the published figure, due to excessive contrast and density manipulations and background processing. Such editing represents falsification according to the criteria described above, regardless of whether the eliminated spots influence the conclusion of the study.

Dr. Tanno was undoubtedly involved in the editing work, but not in obscuring the image. The collected materials and interview statements cannot substantiate that he eliminated the spots by himself. However, Dr. Tanno was in charge of the experiment in question, and the first author of Article W-g. He was an assistant professor when he carried out the experiment. The CCCR assumes that he should have been aware of the disappearance of several spots from the images used for internal presentation and publication; if he was unaware, he should be held liable for gross negligence as a researcher.

For Dr. Watanabe, the collected materials and interview statements cannot substantiate that he removed the spots by himself. However, he admits having blurred the manuscript images, and he was the supervisor of Dr. Tanno’s work, providing guidance regarding image processing and other parts of the experiment. It is reasonable to presume that Dr. Watanabe was cognizant of the removal of the spots. Even if he was not, he should be held responsible for gross negligence as a researcher in submitting for publication a manuscript that contained falsified images. The CCCR concludes that Dr. Tanno and Dr. Watanabe are responsible for falsification of the figure.

(5) Fluorescence Microscopy Image Manipulation

The CCCR identified falsification of three figures published in an article: Figs. S11F, S12B, S8B, Article W-g. The published figures contain panels used for comparison, which depict a noteworthy difference in signal intensity between them. However, the original figures show no appreciable difference, indicating that the signal intensities were purposefully manipulated for publication. Publication of measurements of signal intensity or other parameters obtained under different conditions cannot immediately be considered misconduct. However, to do so without specifically mentioning that fact does represent misconduct. Unlike comparison of samples collected under the same conditions, comparison of samples obtained under different conditions allows the author to reach any conclusion that he or she wants. Such an act is likely to have a major impact on the study conclusion.

As far as the three figures in question are concerned, they allowed the author to reach a conclusion that he could not have reached by honest means. Therefore, this act represents image falsification. Figure S11F compares relative intensities between samples, and this comparison requires scientifically valid measurement and analysis in order to draw a legitimate conclusion. Figure S12B relates to an experiment about chromosome integrity, whose results were evaluated by comparison. In such a case, images must be processed by applying the same levels of brightness and intensity in order to make a valid conclusion. Figure S8B compares signal intensities, and this comparison makes no scientific sense if the intensities were processed in different manners.

Dr. Tanno took the representative photos and quantified the results. However, given the possibility that Dr. Watanabe was also involved in signal intensity correction and other image processing operations, it is not completely certain that Dr. Tanno performed all the observed falsifications alone. Nonetheless, Dr. Tanno was
the first author of this article, and he was an assistant professor when the manuscript was written, a scholarly position in which one is expected to possess sufficient knowledge of the code of ethics for article writing and image processing. Even if he did not edit all the images and included them in the manuscript he was writing, he should have verified them before accepting them. Based on the findings above, the CCCR believes that Dr. Tanno either committed image falsification or is responsible for gross negligence in submitting falsified photos for publication.

Regarding Dr. Watanabe, the Investigation Committee could not reveal to what extent he was aware of the difference in imaging conditions. However, the Committee found that he had discussions with, and provided specific guidance and instructions to, Dr. Tanno regarding imaging and other experimental conditions. Based on these findings, the CCCR considers it likely that Dr. Watanabe was involved in falsification. In submitting falsified images for publication, he should at least be held responsible for gross negligence as the corresponding author. The Investigation Committee found that Dr. Watanabe finalized several figures of other manuscripts, and inappropriately edited them to make them appear more supportive of the conclusion. In addition, the Committee discovered that Dr. Watanabe made forceful instructions about the research activities in his laboratory, including image data creation, and that the laboratory members could not dare to refuse his instructions or question his erroneous approach to image editing. Considering these findings, the CCCR believes that Dr. Watanabe is also responsible for the falsification of the figures in question. Thus, CCCR concludes that Dr. Tanno and Dr. Watanabe are responsible for falsifying the figures.

(3) Other Claims

(i) Image Processing

The CCCR found no other images that fall in the category of falsification, other than those described in (2) above.

(ii) Graph Presentation

The CCCR identified several graphs that do not correctly reflect the original data, as pointed out in the claims received. Original numeric data were available for each of the identified graphs, and the Investigation Committee examined the extent of and causes of the inaccuracies. As a result, the CCCR found no evidence of purposeful manipulation, and the inaccuracies were attributable to the limitations of the drawing software programs or inadvertent errors in tracing the template images. This conclusion was shared by the investigation of the Graduate School of Medicine and Faculty of Medicine.

Inadvertent errors in graph creation may represent falsification through gross negligence, if the author fails to recognize that a graph contains significant flaws. However, the Investigation Committee found that none of the inaccuracies presented in the graphs were grave, which foreclosed the likelihood of gross negligence. The CCCR adjudicates that the graphs mentioned in the claims involve no falsification.
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<th>Article No.</th>
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<td>W-c</td>
<td>Two histone marks establish the inner centromere and chromosome bi-orientation. <em>Science.</em> 2010;330(6001):239–43.</td>
<td>Fig. 3A</td>
<td>Yoshinori Watanabe (corresponding author)</td>
<td>IMCB</td>
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<td>Same as above</td>
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**IMCB** indicates Institute of Molecular and Cellular Biosciences, The University of Tokyo; **JSPS**, Japan Society for the Promotion of Science.
(5) Characteristics of Identified Misconduct

The CCCR adjudicates that the following researchers of the IMCB have committed scientific misconduct: Dr. Yoshinori Watanabe and Dr. Yuji Tanno. Dr. Tanno (an assistant professor at the time when the articles in question were published) was a researcher at the laboratory led by Dr. Watanabe. The research activities at Dr. Watanabe’s laboratory had the following characteristics, which could have served as the background of the misconduct:

(i) Inappropriate Notebook-Keeping Practice

Researchers at Dr. Watanabe’s laboratory did not engage in the standard practice of writing and keeping a laboratory notebook. To report research progress at the once-weekly internal laboratory meeting, entitled the “Work Seminar,” they prepared documents (in PowerPoint format, which were sometimes referred to as “laboratory presentation files” or “work seminar files”). They considered these documents as their laboratory notebooks, and the laboratory filed their printouts. Sometimes, the researchers included processed images and other visual materials in the file for laboratory presentation. Dr. Watanabe’s laboratory implemented poor documentation efforts that were incompatible with common laboratory practice.

(ii) Image Manipulation Commonly Performed at the Laboratory

Dr. Watanabe often edited images inappropriately by himself, and instructed his staff members to make their studies more convincing and appealing to the reader by manipulating image data. The researchers in Dr. Watanabe's laboratory felt uncomfortable with such instructions when they began working in his laboratory. However, they gradually lost their moral conscience, and persuaded themselves that they should be subordinate to their leader as long as they were part of the laboratory. To have their draft manuscripts approved by the professor, there was no other way but to prepare figures according to his guidance. In such a laboratory environment, some researchers voluntarily edited their images according to Dr. Watanabe’s way of thinking in order to obtain approval from the professor.

(iii) Neglect of Research Ethics

The IMCB frequently hosted research ethics seminars to provide the faculty and staff members with education and guidance on typical problems of excessive image processing. However, Dr. Watanabe did not pay attention to the seminar teachings.

(iv) Strong Leadership of Dr. Watanabe

The researcher other than Dr. Watanabe who was judged to be responsible for misconduct can be viewed as a victim of the professor’s misdirected guidance and instructions. However, given that he was an assistant professor at the time that he was conducting the studies in question, he was already
an independent researcher and cannot evade the responsibility for his misconduct. However, the likelihood that the influence of Dr. Watanabe from his post-graduate days interfered with his adherence to a strict framework of research ethics places more weight on the responsibility of his mentor.

4. Measures for Preventing Misconduct

(1) Previous Actions

Following the alleged research misconduct at the laboratory of former professor Kato, The UoT launched the Research Ethics Action Plan in March 2014. Based on this plan, a variety of activities aimed to foster ethics consciousness have been implemented, including awareness campaigns and education programs for students and staff members. In January 2016, The UoT promulgated the Rules for the Prevention of Research Misconduct, which defined the misconduct management structure including the duties and responsibilities of the President, Executive Vice-President for Research, and the Director in charge of individual research projects. The UoT also issued the Guidelines for Storage of Research Materials, etc. These guidelines require that documentation, such as records, numeric, image, and other data must be retained for 10 years, whereas samples, specimens, and other laboratory materials must be maintained for 5 years.

Starting in academic year 2013, the IMCB has hosted three research ethics seminars per year, which all researchers are obliged to attend. Since January 2014, the IMCB has implemented misconduct prevention measures, which require authors to register raw data used in their manuscript, fill out a submission checklist, and submit the filled-out form. The submission checklist has been revised as necessary.

The actions that The UoT and IMCB took in the aftermath of the fraud incident in the former Kato Laboratory were not tailored to address researchers that are not ethically minded or ethically motivated. The CCCR recommends that The UoT and IMCB should review the present incident and put forward new misconduct prevention measures aimed at regaining public trust in scholarly research.

(2) Proposed Program for Misconduct Prevention

Based on its review of the present incident, the IMCB has proposed new misconduct prevention measures as follows:

I. Reinforcing Anti-Misconduct Measures by the Creation of the Research Promotion Office

The Research Misconduct Office* will be reorganized into the Research Promotion Office, which will be staffed by several full-time university research administrators, as well as a faculty member at the assistant professor–level and technical staff members well-trained in research misconduct issues. This office will provide services to prevent author misconduct by objectively reviewing the
experimental data. Specifically, this office will:

1. Examine the agreement between raw data and data presented in the manuscript.
2. Scan the image data used in the manuscript using special software, and evaluate and comment on the appropriateness of the image processing work.
3. Provide consultation regarding data analysis, data quality, and other research-related topics (in particular, assistance concerning information processing and statistical analysis).
4. Organize training courses on statistical analysis and quantitative experimental methods.

*The Research Misconduct Office was established in April 2013 following the alleged misconduct incident of former professor Shigeaki Kato. The Office, staffed with six members, was charged with the following responsibilities: (i) reception of, reporting of, and consultation concerning, research misconduct; (ii) an educational campaign aimed at raising awareness of misconduct; (iii) storage and maintenance of raw data processed for publication (e.g., data registry management and creation of submission checklist); (iv) review of the internal conditions leading to misconduct, and development and management of prevention plans; and (v) hosting interdisciplinary networking and project presentation opportunities.

II. Improving Operational Management by Input from an Independent Advisory Body

The IMCB will launch a new consultative panel (“IMCB Advisory Council”) consisting of four renowned scientists from overseas and three from Japan. The purpose of this Council will be to make recommendations and suggestions on the operations of the IMCB (e.g., misconduct risk management and surveillance).