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Decision regarding research misconduct

Decision

The National Board for Assessment of Research Misconduct (“the Board”) finds Myriam Aouadi, Valerio Azzimato, Laura Levi, and Cecilia Morgantini guilty of research misconduct.

The Board finds Emelie Barreby, Niklas Björkström, Jeremie Boucher, Ping Chen, Ewa Ellis, Kjell Hultenby, Tracey Hurrell, Claudia Kutter, Volker Lauschke, Xidan Li, Erik Näslund, Mikael Rydén, Joanne Shen, Sara Straniero, André Sulen and Anders Thorell not guilty of research misconduct.

Background

On March 25, 2022, Karolinska institutet (KI) submitted a case of alleged research misconduct to the Board. The submission took place pursuant to Section 6 of the Swedish Act (2019:504) on responsibility for good research practice and the examination of research misconduct.

The research concerns liver disease in overweight individuals with pre-stage or developed type 2 diabetes. It has been conducted at the Integrated Cardio Metabolic Centre, ICMC, which is a research center jointly founded by KI and AstraZeneca. The submission concerns suspicions of falsification and fabrication of data underlying three articles.

The submission relates to allegations of fabrication and/or falsification in the following:

- Article 1 - Azzimato, V., Chen, P., Barreby, E., Morgantini, C., Levi, L., Vankova, A., Jager, J., Sulen, A., Diotallevi, M., Shen, J. X., Miller, A., Ellis, E., Rydén, M., Näslund, E., Thorell, A., Lauschke, V. M., Channon, K. M., Crabtree, M. J., Haschemi, A., Craige, S. M., Mori, M., Spallotta, F., Aouadi, M. (2021). Hepatic miR-144 Drives Fumarase Activity Preventing NRF2 Activation During Obesity. *Gastroenterology*, 161(6), 1982–1997.e11. <https://doi.org/10.1053/j.gastro.2021.08.030>
- i. Figure 1F should show panels with images from Western blot (WB) experiments presented in the article, which are intended to

demonstrate the presence of the proteins IRG1 and beta-actin. The figure panels are allegedly duplicated from previous articles and do not show the results from the correct experiment.

- ii. The proteins KEAP1 and NRF2p(S40) are allegedly inaccurately identified in Figure 6H. Beta-actin is shown as a loading control for the experiment, but at the same time, the identification is stated to be done using a method (immunoprecipitation, IP) that excludes the use of beta-actin as a loading control. This leads to suspicions of falsification and/or fabrication of the beta-actin results as well.
 - iii. The error bars presented in figures 2-6 allegedly appear too small and to not correspond to what would be expected from the methods and results presented in the article.
- Article 2 – Azzimato, V., Jager, J., Chen, P., Morgantini, C., Levi, L., Barreby, E., Sulen, A., Oses, C., Willerbrords, J., Xu, C., Li, X., Shen, J. X., Akbar, N., Haag, L., Ellis, E., Wälhen, K., Näslund, E., Thorell, A., Choudhury, R. P., Lauschke, V. M., Rydén, M., Craige, S. M., Aouadi, M. (2020). Liver macrophages inhibit the endogenous antioxidant response in obesity-associated insulin resistance. *Science translational medicine*, 12(532), eaaw9709. <https://doi.org/10.1126/scitranslmed.aaw9709>
 - i. The data presented in figure 3B and F, 4G, 5A and B are not correct. The data are the molecular weights shown in different wb-panels, intensity ratios between individual western blot images, and in some cases, the allegations are that the wb images presented are not the correct ones.
 - ii. Figure 2A, 4L and 5C do not show what they are claimed to show in the article.

The same article has previously been tried by the Board in case 3.1-20/0059. The Board will therefore not try the article again.

- Article 3 – Morgantini, C., Jager, J., Li, X., Levi, L., Azzimato, V., Sulen, A., Barreby, E., Xu, C., Tencerova, M., Näslund, E., Kumar, C., Verdeguer, F., Straniero, S., Hultenby, K., Björkström, N. K., Ellis, E., Rydén, M., Kutter, C., Hurrell, T., Lauschke, V. M., Boucher, J., Tomčala, A., Krejčová, G., Bajgar, A., Aouadi, M. (2019). Liver macrophages regulate systemic metabolism through non-inflammatory factors. *Nature metabolism*, 1(4), 445–459. <https://doi.org/10.1038/s42255-019-0044-9>
 - i. The wb-image panels for AKT and Actin have changed places in figure 5D so that the panels claimed to be showing AKT are in fact showing Actin, and the opposite.
 - ii. Figures 5C, 5F, 5G, 5I, 5K, S2A, S5C does not show what they are claimed to be showing. Proteins are allegedly falsely identified and western blot images are erroneously claimed to be from the same gels.

- iii. The data presented in the table in figure 2G are incorrectly rounded. The method used to calculate the data in the table is not presented in the article which leads to allegations of falsification.

The authors whose names are underlined conducted the research at a Swedish entity responsible for research.

Respondents' statements with respect to the allegations

The statements of the respondents are presented below, article by article, starting with the first and last author's statements. Then, the statements of the other co-authors are summarized very briefly, focusing on whether they differ in any significant way from the first or last author's statement.

Article 1

Valerio Azzimato's statement

Valerio Azzimato is the first author of article 1. In his statement to the Board, he explains that his contributions were to formulate the scientific idea behind the article, conduct most of the experiments, interpret the results, and write the article. He disputes the allegations of falsification/fabrication, arguing that the allegations stated in the complaint largely consist of misunderstandings or misinterpretations of the scientific method and technology used. He points out that the articles have passed the journal review processes and that the results have been confirmed by other laboratories.

To address the allegations regarding Figure 1F, Valerio Azzimato has provided lab notes and images that he believes demonstrate that the measurements of IRG1 were conducted in conjunction with the work on the article and were not inaccurately duplicated from previous articles. He admits that the blots intended to show the presence of beta-actin in Figure 1F are not from the measurement that should be shown. The authors have issued an erratum to correct this.

Figure 6H displays western blot images of the proteins CUL3, KEAP1, NRF2p(S40), and beta-actin after different treatments. Valerio Azzimato explains that the immunoprecipitation (IP) technique was performed on KEAP1 along with CUL3. Subsequently, WB was conducted on the remaining sample to examine the presence of NRF2p(S40), and beta-actin was used as a loading control. Therefore, a WB panel of beta-actin is shown despite stating that the measurements were made after IP. He has provided images of original data and refers to literature indicating significant uncertainty regarding the molecular weight of NRF2p, which he believes demonstrates that the protein is correctly identified.

Regarding the allegations that the statistical results shown in Figures 2-6 are inaccurate, Valerio Azzimato has attached raw data that he believes demonstrate that the calculations were performed correctly. He also argues that the results shown in the figures have been reproduced in independent measurements.

Myriam Aouadi's statement

Myriam Aouadi is the last author of article 1. She states that she is the most academically senior lead author of the articles and explains that she therefore considers

herself ultimately responsible for the content of the articles. After reading the complaint, she has gone through all the original data, laboratory notebooks, computers, and other equipment to check the material the articles are based on. She believes that the allegations of falsification/fabrication largely stem from the complainant having different opinions regarding which techniques are most appropriate and how data should be interpreted. She admits that some mistakes have been made but does not believe they have affected the conclusions drawn in the article. Regarding these mistakes, she points out that the authors have published errata as soon as they became aware of the errors. She mentions that she is deeply involved in the work in her laboratory and regularly discusses raw data and good research practices with her colleagues. She also notes that the article has been reviewed by at least three reviewers prior to publication, and that they did not detect the errors.

The remaining authors' statements

Emelie Barreby, Ping Chen, Ewa Ellis, Volker Lauschke, Laura Levi, Cecilia Morgantini, Erik Näslund, Mikael Rydén, Joanne Shen, André Sulen, Anders Thorell, and Ana Vankova are co-authors of article 1. All of them have submitted statements to the Board. Erik Näslund, Mikael Rydén, and Anders Thorell have provided a joint statement. Volker Lauschke and Joanne Shen have also done so.

Emelie Barreby and Ping Chen state that they conducted experiments other than WB and lack sufficient expertise to assess the allegations. Ping Chen expresses that she perceives that Myriam Aouadi and her research group prioritizes scientific rigor.

Laura Levi is the laboratory manager where the experiments were conducted. She states that both she and Cecilia Morgantini partially conducted the experiments subject to the allegations. Both certify that the experiments were conducted with scientific integrity. Both dismiss the allegations of falsification/fabrication.

Ewa Ellis, Volker Lauschke, Erik Näslund, Mikael Rydén, Joanne Shen, André Sulen, Anders Thorell, and Ana Vankova state that they have not worked with the experiments or data which the allegations concern.

Article 3

Cecilia Morgantini's statement

Cecilia Morgantini is the first author of article 3. She states that her contributions were to formulate the scientific idea behind the article, conduct most of the experiments, interpret the results, and write the article. She argues that the allegations concern subjective opinions of the method and techniques used, except for the minor errors they have corrected in an erratum. She disputes the allegations of falsification/fabrication.

Regarding the allegations that the WB panels for the proteins AKT and Actin have been swapped in Figure 5D, Cecilia Morgantini admits that the images are in the wrong place in the figure. The authors have asked the journal to publish an erratum. She points out that the reported ratio between pAKT and AKT is correct because the measurements and calculations were performed on the right western-blot images.

Cecilia Morgantini states that Figure 5F shows what it is claimed to show and disputes that anything is incorrect. Regarding Figure 5G, she notes that the wrong images are displayed, and that they have published an erratum. Regarding Figure 5I, she states that the original data is shown in Figure S7 and disputes that the blots shown come from the same WB band as claimed in the complaint. She argues that the WB panels for p-AKT, AKT, and actin in Figure 5K are from the same membrane and that the blots for p-ERK and ERK are from the same membrane. Thus, she argues that it is correct to calculate the ratios p-AKT/AKT and p-ERK/ERK as reported in the article and shown in the figure. Regarding Figure S2A and S5C, she states that the experiments were conducted as described in the article and that the complainant's allegations are a matter for scientific discussion rather than evidence of misconduct. She admits that the actin blots in Figure S2A are displayed in the wrong order and states that they have included a correction for that error in the erratum.

Cecilia Morgantini notes that the numbers given in the table in Figure 2G are incorrectly rounded and explains that the errors occurred when they changed from presenting the relative number of patients as ratios to presenting them as percentages. To clarify this, the authors have updated the numbers in the table in an erratum, but Cecilia Morgantini points out that the change strengthens their conclusion. She explains that she discovered the one number in the table was incorrect when preparing the new table for the erratum.

Myriam Aouadi's statement

Myriam Aouadi is the last author of article 3. She has provided the same statement concerning article 3 as she did for article 1.

The remaining authors' statements

Valerio Azzimato, Emelie Barreby, Niklas Björkström, Jeremie Boucher, Ewa Ellis, Kjell Hultenby, Tracey Hurrell, Claudia Kutter, Volker Lauschke, Laura Levi, Xidan Li, Erik Näslund, Mikael Rydén, Sara Straniero, André Sulen, and Connie Xu are co-authors of article 3.

Valerio Azzimato disputes the allegations of falsification/fabrication and contends that they are unfounded. His contribution to the article has involved conducting some experiments and interpreting and discussing the results. He fully supports Cecilia Morgantini's statement.

Emelie Barreby, Ewa Ellis, Volker Lauschke, Laura Levi, Erik Näslund, Mikael Rydén, and André Sulen have provided the same statement as for article 1.

Connie Xu states that she has never participated in or witnessed any research misconduct during the work with the article.

Niklas Björkström, Kjell Hultenby, Tracey Hurrell, Xidan Li, and Sara Straniero state that they have not worked with the experiments or data subject to the allegations.

Claudia Kutter explains that she has assisted with calculations, analysis, and interpretation of data. She believes there are no grounds for allegations of research

misconduct. She feels that she and the other authors have fulfilled their responsibility by investigating and discussing the allegations and publishing errata in cases where errors have been detected.

Expert statement

The Board has obtained an expert opinion on the matter. The expert¹ has been tasked with assessing whether articles 1-3 contain falsification or fabrication according to the allegations described in the submission from KI, and if so, whether it constitutes a serious deviation from good research practice.

The expert's assessment is that there are no grounds for any of the allegations of falsification and fabrication. She summarizes that there are some mistakes in the articles, but they are minor and have had no, or very little, impact on the results. The allegations point to some well-known challenges associated with WB analysis, and although she believes that there could have been good reasons to further attempt to verify the results, she does not consider this cause for allegations of research misconduct but rather a matter for scientific discussion. She also argues that the authors have provided credible explanations and responses to the allegations. Regarding the WB panels that the complainant claims have been inaccurately reused, the expert believes that it cannot be known for certain without further image analysis but points out that there is no apparent motivation to reuse WB panels in the alleged manner and that quantitative data, not the images displayed, have been used in the analysis. Therefore, she considers further image analysis unnecessary.

Respondents' comments on expert statement

Myriam Aouadi, Valerio Azzimato, Claudia Kutter, Laura Levi, and Cecilia Morgantini have submitted final statements to the Board that do not contain any additional information affecting the Board's assessment of whether research misconduct has occurred.

Legal regulation

Under the Act (2019:504) on responsibility for good research practice and the examination of research misconduct ("the Act"), the Board is tasked to investigate issues of research misconduct.

Section 2 of the Act defines research misconduct as a serious breach of good research practice in the form of fabrication, falsification or plagiarism, committed with intent or through gross negligence, in the planning, conduct or reporting of research.

The Board's assessment takes place in stages, pursuant to the above provision.

¹ Professor Tuulia Hyötyläinen, Örebro University

Grounds for decision

Researchers

Under Section 4 of the Act, researchers are responsible for complying with good research practice in their work.

People who count as researchers are those who are attending or have completed research education and are participating in research. Other individuals taking part in research activities, such as students at basic (first-cycle, bachelor's) or advanced (second-cycle, master's) level and technical and administrative staff, should not count as researchers.

The Board finds that Myriam Aouadi, Valerio Azzimato, Emelie Barreby, Niklas Björkström, Jeremie Boucher, Ping Chen, Ewa Ellis, Kjell Hultenby, Tracey Hurrell, Claudia Kutter, Volker Lauschke, Laura Levi, Xidan Li, Cecilia Morgantini, Erik Näslund, Mikael Rydén, Joanne Shen, Sara Straniero, André Sulen, and Anders Thorell are researchers and are therefore subject to investigation by the Board.

Ana Vankova and Connie Xu have worked as laboratory assistants and have not started a doctoral education. The Board assesses that they are not researchers and therefore should not be subject to investigation by the Board.

Research covered

Section 3 of the Act covers research conducted by higher education institutions that have the Swedish state as the entity responsible for their research, and that are subject to the Swedish Higher Education Act (1992:1434), other government agencies, municipalities and regions and certain other specified activities.

Myriam Aouadi, Valerio Azzimato, Emelie Barreby, Niklas Björkström, Jeremie Boucher, Ping Chen, Ewa Ellis, Kjell Hultenby, Tracey Hurrell, Claudia Kutter, Volker Lauschke, Laura Levi, Xidan Li, Cecilia Morgantini, Erik Näslund, Mikael Rydén, Joanne Shen, Sara Straniero, André Sulen and Anders Thorell made their contributions to the research (on which allegations were reported) at a Swedish entity responsible for research that is subject to Section 3 and, accordingly, to investigation by the Board.

Naveed Akbar, Bajgar, A., Keith Channon, Robin Choudhury, Mark Crabtree, Siobhan Craige, Marina Diotallevi, Arvand Haschemi, Jennifer Jager, Gabriela Krejčová, Anne Miller, Mattia Mori, Francesco Spallotta, Michaela Tencerova, Aleš Tomčala and Francisco Verdeguer conducted their part of the research at a foreign research entity. As such, they are not subject to Section 3 and not investigated by the Board.

Chanchal Kumar is a co-author of article 3 and was affiliated with both KI and AstraZenica according to the article, however, he did not have a formal agreement with KI but was only employed by AstraZeneca. Chanchal Kumar's contribution to the research at AstraZeneca is not subject to Section 3 and not investigated by the Board.

Planning, conduct or reporting of research

As defined in Section 2 of the Act, breaches of good research practice that may constitute research misconduct must have been committed during the planning, conduct or reporting of research. This means that the term “misconduct” refers to breaches throughout the research process². “Reporting” refers both to publication and to other types of disclosure.³

The Board considers that the case relates to reporting of research because the allegations concern articles published in scientific journals.

Fabrication, falsification, or plagiarism

The Board’s remit is to investigate three forms of research misconduct: fabrication, falsification and plagiarism. These terms are not defined by law, but the preparatory work for the Act refers to the fact that they are described in codes (codices) and guidelines on research ethics, such as The European Code of Conduct for Research Integrity^{4,5}.

Fabrication means that the researcher invents results and documents them as if they were genuine.

Falsification refers to manipulation of research material, equipment or processes or unjustified alteration, omission or suppression of data or results.

The Board’s assessment of the allegations of falsification/fabrication is presented article by article.

Article 1

Figure 1F

Figure 1F allegedly shows something other than what it is claimed to show, which indicates that it is falsified/fabricated. According to the submission from KI, the WB image panels intended to show IRG1 and beta-actin are incorrectly duplicated from previous measurements and thus do not show results from the experiments described in the article. The submission includes evidence showing that the WB panels for IRG1 exactly match results from previous experiments to detect the protein DMT1 and thus do not show the correct protein.

The first author admits that the beta-actin blots in the figure are incorrectly duplicated and do not show the experiments they are claimed to show. For the protein IRG1, he has provided notes and images that he claims demonstrate that the experiments were

² Prop. 2018/19:58, p. 100.

³ Prop. 2018/19:58, p. 49.

⁴ Den europeiska kodexen för forskningens integritet. Reviderad utgåva. Berlin: All European Academies (ALLEA); 2018, kap. 3.1.

⁵ Prop. 2018/19:58, p. 45, 100.

conducted as described in the article and that the results are shown in the figure. The co-authors who have worked together with the first author in the laboratory; Myriam Aouadi, Laura Levi, and Cecilia Morgantini support the statement of the first author. The other co-authors have stated that they have not had the opportunity or sufficient insight to know how the experiments were conducted.

The expert thinks that the authors have provided sufficient evidence to show that the WB panels for IRG1 have been produced later than the previous experiments were performed and therefore can be considered to have been conducted as claimed in the article. She also points out that the conclusions drawn from Figure 1 agree with the measurement results that the first author has provided in his statement to the Board.

Concerning the beta-actin, it is undisputed that the image is incorrectly duplicated, as the first author has admitted that the wrong WB panel is displayed. Concerning the panel intended to show IRG1, the Board has received additional evidence, after receiving the expert's assessment, which supports the allegations. The evidence shows exactly the same WB results from measurements of another protein conducted no later than 2017, which contradicts the first author's explanation that the images come from experiments conducted later. Therefore, the Board finds that the panel displayed as IRG1 in the figure, is incorrectly duplicated from previous measurements. This means that data and results have been altered and omitted without justification. This means that Figure 1F contains falsification according to the definition above.

Figure 6H

Figure 6H allegedly shows something other than what it is claimed to show, which indicates that it is falsified/fabricated. The submission from KI states that at least one of the proteins KEAP1 and NRP2p(S40) is incorrectly identified in the figure. It is also noted that it is incorrect to show a loading control with beta-actin since the experiments were performed using a method (immunoprecipitation, IP) which means that there is no beta-actin left in the sample.

The respondents explain that IP was performed on the proteins KEAP1 together with CUL3, and WB was performed on the entire sample for NRP2p before IP, and that was when beta-actin was used as a loading control.

The expert believes that there is a risk that one or more proteins are misidentified in the figure but argues that this is part of the interpretation of the results and is not a matter of falsification or fabrication.

In the figure caption for Figure 6H, it is stated that the figure shows WB on CUL3, KEAP1, and NRP2p(S40) after IP. If this description is correct, beta-actin cannot be present in the sample, and should not be detected in a WB experiment as the figure shows. The first author contradicts this in his statement where he explains that only CUL3 and KEAP1 were identified with IP. If this is the case, the figure caption is incorrect because it states that all three proteins were identified with IP. The Board assesses that it is unlikely that the experiments were conducted in the manner described by the first author, among other reasons because it contradicts what is shown in Figure 6G, namely that CUL3, KEAP1, and NRP2p(S40) bind to each other inside the cell.

Regardless of whether it is the figure or the figure caption for Figure 6H that is incorrect, the figure does not show what it is claimed to show. This means that data and results have been altered without justification, and therefore, the Board finds that Figure 6H contains falsification.

Figure 2-6

Figures 2-6 show results from measurements as bar plots with error bars. According to the submission from KI, the variation between repeated measurements is unexpectedly small. This leads to the allegations that the authors incorrectly treated technical replicates (when a measurement is repeated on the same sample) as biological replicates (when a measurement is repeated on different samples), which would constitute falsification as it does not agree with how the authors describe that the experiments were conducted in the article.

The authors state that the measurements and statistical calculations were performed as described in the article.

The expert does not find that sufficient evidence has been provided to claim that the statistical calculations were performed incorrectly.

The Board notes that results from individual measurements are presented in the bar plots along with averages, and the spread between the individual measurements agrees with the error bars presented. Since the results from each individual measurement are shown, and the method is described, readers can easily assess whether the results are reasonable or not. Therefore, the Board finds that there are no grounds for the allegation that the statistical calculations have been falsified.

In summary, the Board finds that Figure 1F and 6H in article 1 are falsified, but not Figures 2-6.

Article 3

Figure 5D

Figure 5D allegedly does not show what it is claimed to show, which indicates that it is falsified or fabricated. According to the submission from KI, the WB panels for the proteins AKT and actin have switched places in the figure.

The respondents acknowledge that there is an error in the figure but argue that it does not change the conclusions drawn in the article.

The expert confirms that the respondents have admitted that the WB panels are displayed in the wrong place in the figure.

The Board finds that Figure 5D contains falsification, as the WB panels for AKT and actin have been incorrectly switched, resulting in that data and results have been altered without justification.

Figures 5C, 5F, 5I, and S5C

According to the submission from KI, the proteins shown in the figures are incorrectly identified, which indicates that the figures are falsified or fabricated.

The respondents argue that the figures show what they are claimed to show.

The expert thinks that the best methods for protein identification with WB is a matter for scientific discussion and not a question of research misconduct. She explains that it would have been appropriate to confirm several of the identifications with additional experiments but does not think that the lack of further support for that the correct protein has been identified means the figures are falsified.

The Board agrees with the expert that WB experiments have associated uncertainties that warrant confirming protein identification with additional experiments. Regarding figures 5C, 5F, 5I, and S5C, the Board thinks that there are several reasons to question some of the choices made by the authors when deciding which WB panels indicate the presence of the IGFBP7 protein. Among other things, the choice of the size at which IGFBP7 is expected to be found in the WB experiments. According to the first author, IGFBP7 is expected to be bound to a larger protein during the experiments, and this explains why IGFBP7 is found at a much larger weight than expected. This may be correct if the proteins are inside the cell but not after the sample has been prepared for WB experiments. Additionally, the molecular weight at which IGFBP7 can be found is allowed to vary in the article within a range much larger than the expected uncertainty of the measurements, for example, in figure 5C. The authors explain that they have relied on the specificity of the antibody to bind to the protein of interest primarily and on the molecular weight secondarily. However, in figure S5C, they have chosen to only show an empty panel at the larger assumed weight, despite the antibody binding to a protein detected at the lower expected weight. In summary, the Board finds that the identification of the IGFBP7 protein using WB is characterized by contradictory and unjustified choices, leading the Board to conclude that the wrong protein is shown where IGFBP7 should have been shown in figures 5C, 5F, 5I, and S5C. Thus, the data and results have been altered without justification, and the figures are falsified.

Figure 5G

According to the submission from KI, the blots in figure 5G do not match the quantitative data presented in a bar plot in the same figure, and therefore the figure is allegedly falsified.

The respondents admit that the wrong blot images are shown in the figure.

The expert notes that the authors have admitted that there are errors in the figure.

Since incorrect images are shown in the figure, the Board finds that data and results have been altered and omitted, and that figure 5G is falsified.

Figure 5K

In figure 5K, ratios between the WB image panels for the proteins pAKT and AKT, and pERK and ERK, are displayed. According to the submission from KI, the blots for

the proteins and their phosphorylated counterparts (pAKT and pERK) do not come from the same gels and therefore they cannot be compared in the way that is done according to the figure.

The respondents argue that AKT and pAKT are run on the same gel, while ERK and pERK are run on a different gel.

The expert does not find that there is sufficient evidence to support the claim that the blots come from different gels.

In the figure, only one WB image panel for betaactin is shown. The first author has stated that AKT and ERK, along with their phosphorylated counterparts, come from separate gels, leading to an uncertainty as to which gel the betaactin WB image panel belongs to. If the intention is to measure the ratios between the proteins and their phosphorylated counterparts through measurements on the same gel, the loading control betaactin becomes irrelevant. However, since only one WB panel for betaactin is shown, this implies that all the measurements were done using a single gel, which then contradicts the authors' statements. If the measurements were done on two gels, it means that a misleading depiction of how the experiments were conducted is shown in the figure. Therefore, the Board finds that data have been altered and omitted without justification in figure 5K, which constitutes falsification.

Figure S2A

According to the submission from KI, the protein IGFBP7 in figure S2A is allegedly misidentified, and the figure is falsified.

The respondents argue that they used a specific antibody for IGFBP7 and that even though the molecular weight of the protein differs slightly from the expected value, they had no reason to suspect that the WB panel did not correspond to IGFBP7. They state that the actin band is horizontally flipped.

The expert explains that it would have been appropriate to confirm the identification through additional measurements but does not find that there is sufficient evidence to claim that the identification of IGFBP7 is incorrect.

The WB panel for the protein betaactin is undisputedly flipped, meaning that data have been altered without justification. Therefore, the Board finds that figure S2A is falsified.

Figure 2G

In Figure 2G, a table is presented, and according to the submission from KI, the values in the table are incorrectly rounded, leading to allegations of data fabrication. The submission also states that important information is missing in the article regarding how the values presented in the table were calculated.

The respondents explain that a rounding error occurred when they switched between presenting the results as ratios and whole percentage values. The errors have been corrected in an erratum.

The expert believes that it is clear what is being presented in the table and therefore, it does not constitute fabrication or falsification.

The Board finds that data have been rounded to a lower precision than warranted, but this does not imply that data has been altered, omitted, or suppressed. It also does not imply that data have been invented. Therefore, what is presented in the table does not constitute falsification or fabrication.

In summary, the Board concludes that figures 5C, 5D, 5F, 5G, 5I, 5K, S2A, and S5C in article 3 are falsified.

Serious breach of good research practice

Only serious breaches of good research practice can constitute research misconduct.

In principle, fabrication and falsification are always serious breaches of good research practice.

The Board finds that figures 1F and 6H in article 1, and figures 5C, 5D, 5F, 5G, 5I, 5K, S2A, and S5C in article 3 are falsified.

The premise of the Board's assessment is that falsification is, in principle, always a serious breach of good research practice. No reason to deviate from this premise has emerged in the case. Accordingly, the Board's conclusion is that the breaches constitute serious breaches of good research practice.

Intent or gross negligence

Since 1 January 2020, researchers' responsibility to comply with good research practice in their work has been subject to statutory regulation under Section 4. The potential or required extent of such responsibility must be examined and assessed in each individual case.

Under Section 2 of the Act, for research misconduct to be found, the serious breach of good research practice must have been committed with intent or through gross negligence.

"Intent" means that the researcher understood what (s)he was doing, while "negligence" means that the researcher, in any case, should have understood this.

"Gross negligence" requires the conduct to stand out as particularly serious or reprehensible. According to the preparatory work⁶, oversights, carelessness or misunderstandings should not, as a rule, be regarded as gross negligence.

According to international guidelines^{7,8}, all parties involved in a collaboration are responsible for the integrity of the research. It is also stated that all authors bear full

⁶ Prop. 2018/19:58, p. 50-51, 100.

responsibility for the content of the publication unless otherwise specified. Swedish law is based on this international regulation. Both articles reviewed in the case contain information about the various authors' contributions to the research that aligns with what the authors have stated to the Board. Myriam Aouadi is the corresponding author for both articles.

Article 1

In figure 1F of article 1, the blots intended to show different proteins (IRG1 and betaactin) are incorrectly duplicated from previous research, which constitutes serious deviations from good research practice in the form of falsification. The first author, Valerio Azzimato, has admitted that the western-blot panel for betaactin is incorrect but disputes that the panel for IRG1 is.

The corresponding author, Myriam Aouadi, has attested that she has worked closely with her group members, held regular meetings where raw data has been discussed, and considers herself responsible for what is presented in the article. Laura Levi and Cecilia Morgantini have worked closely with the first and corresponding authors in the laboratory and had access to raw data during the article's preparation. Other authors have contributed to other parts of the research underlying the article.

The Board finds it unlikely that the western-blot panels that should have been shown in figure 1F were inadvertently replaced with results from previous measurements without the intention of the first author, Valerio Azzimato, who must have deliberately replaced the images when constructing the figure. The researchers who worked with him during the experiments and had continuous access to, and the opportunity to check the raw data, Myriam Aouadi, Laura Levi, and Cecilia Morgantini, are found to have acted with gross negligence by not realizing that the blots shown in the figure are incorrect.

Figure 6H contains serious deviations from good research practice in the form of falsification. The Board believes that the figure and its caption do not accurately reflect the results or how the experiments were conducted. The first author, Valerio Azzimato, has provided an explanation that does not comply with what is shown in the image. The Board finds that it is grossly negligent for those who participated in and had insight into the work in the laboratory where the western blot experiments were conducted; Valerio Azzimato, Myriam Aouadi, Laura Levi, and Cecilia Morgantini, not to have noticed that what is shown in the figure does not agree with the methods they have used.

Emelie Barreby, Ping Chen, Ewa Ellis, Volker Lauschke, Erik Näslund, Mikael Rydén, Joanne Shen, André Sulen, and Anders Thorell have been responsible for other parts of

⁷ Den europeiska kodexen för forskningens integritet. Reviderad utgåva. Berlin: All European Academies (ALLEA); 2018, 2023 kap. 2.6.

⁸ Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly work in Medical Journals. Updated May 2022, International Committee of Medical Journal Editors. <http://www.icmje.org/recommendations>.

the research and did not have access to raw data from the western blot experiments during the work. The Board finds that they did not act negligently when they did not detect the errors in figure 1F. The images presented in figure 6H contradict how the experiments are described in the figure caption. The Board concludes that the co-authors acted negligently, but not grossly negligently, when they did not detect the errors in figure 6H.

Article 3

Figure 5C, 5D, 5F, 5G, 5I, 5K, S2A, and S5C contain serious deviations from good research practice in the form of falsification. The first author, Cecilia Morgantini, admits that blots have been mixed up in figures 5D and 5G and that the betaactin band is incorrectly oriented in figure S2A. Apart from that, the authors dispute the allegations. The Board finds that it is grossly negligent of those who participated in and had insight into the work in the laboratory; Cecilia Morgantini, Myriam Aouadi, Laura Levi, and Valerio Azzimato, that a large number of mixed up and incorrect blots have been included in the article.

Emelie Barreby, Niklas Björkström, Jeremie Boucher, Ewa Ellis, Kjell Hultenby, Tracey Hurrell, Claudia Kutter, Volker Lauschke, Xidan Li, Erik Näslund, Mikael Rydén, Sara Straniero, and André Sulen have been responsible for other parts of the research and did not have access to raw data from the western-blot experiments during the work. The Board finds that they did not act negligently when they did not detect the errors in figures 5C, 5D, 5F, 5G, 5I, S2A, and S5C. Regarding figure 5K, the Board finds that it is evident that the western-blot panels shown in the figure cannot come from the same gel, and therefore it was negligent, but not grossly negligent, of the co-authors not to detect the errors in figure 5K.

Summary of the decision

In summary, the Board finds that Myriam Aouadi, Valerio Azzimato, Laura Levi, and Cecilia Morgantini have committed research misconduct in articles 1 and 3. The Board concludes that Emelie Barreby, Niklas Björkström, Jeremie Boucher, Ping Chen, Ewa Ellis, Kjell Hultenby, Tracey Hurrell, Claudia Kutter, Volker Lauschke, Xidan Li, Erik Näslund, Mikael Rydén, Joanne Shen, Sara Straniero, André Sulen, and Anders Thorell have not committed research misconduct.

The Board has reached a decision in this matter following a presentation by Sofia Bergström, case officer. In the final handling of the case, the case officer Magnus Eklund has also participated.

Thomas Bull
Chair

Sofia Bergström
Case officer

How to appeal

A decision pursuant to an investigation of research misconduct may be appealed to a general administrative court. An appeal must be in writing and must reach the Board for Assessment of Research Misconduct (NPOF) no later than three (3) weeks after you were notified of the decision. If the appeal is received by NPOF within the prescribed period, the matter is referred to the Administrative Court in Uppsala.

The appeal should preferably be sent by email or letter post.

Email

registrator@npof.se

Postal adress

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