Npof.

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Decision on research misconduct

Decision

The Swedish National Board for Assessment of Research Misconduct ("the Board") finds [redacted] guilty of research misconduct.

The Board finds [redacted] not guilty of research misconduct.

Background

On 6 April 2021, Karolinska Institute (KI) referred a case concerning research misconduct to the Board. The referral took place in accordance with Section 6 of the Swedish Act (2019:504) on responsibility for good research practice and the examination of research misconduct.

The referral relates to suspicions of falsification eller fabrication of research results by [redacted], head of the research group to which [redacted] belongs, was the person who reported the matter to KI. [redacted] was employed as a postdoctoral researcher at KI in the period 2015–2019 and assistant professor in 2020–2021. [redacted] states that he began, in January 2021, to suspect that files with DNA sequence data had been manipulated. Thereafter, he discovered more suspect results in his in-depth review of the data.

The data and results to which the allegations relate were included in a manuscript (MS) entitled "AHCY is a tumour-suppressive enzyme responsible for methionine dependency in cancer cells". The authors of the MS were [redacted].

The MS was sent to the journal *Cancer Research*, and the journal's inspection prompted wishes for further analyses. The authors state that, at this time, they discovered that certain results were not possible to reproduce. The authors then withdrew the MS.

The allegations reported are as follows:

1. Manipulation of DNA sequence data. Files containing DNA sequence data for identification of cell lines used in the project are suspected of being falsified by plagiarism and modification of pre-existing data (Suspicion 1).
2. Microscopic images of cell cultures and colony formation assays (a method of measuring cells' ability to form tumours) are suspected of having been reused or replaced so as to make the results misleading (Suspicion 2).

3. Western blot images are suspected of having been reused or substituted in such a way as to make the results misleading (Suspicion 3).

4. Discrepancy with respect to overexpressing cell lines: for two cell lines produced by [redacted], new and independent experiments show that the cell lines do not match [redacted] documentation, which makes most of the results misleading (Suspicion 4).

5. Discrepancy with respect to experimental RT-PCR reagents: for an experiment intended to confirm gene expression in cell lines, the documentation specifies reagents (RT-PCR primers) that are incorrect. Such primers have never been purchased, which indicates that data from the experiment are misleading (Suspicion 5).

[redacted] admits in her statement to the Board that, regarding Suspicion 1, she manipulated DNA sequence data by using other results and giving them new file names. In her account, she states that the cell lines that were to be used in the experiment were destroyed because of problems with the nitrogen tank they were kept in, and she then had no more cell lines to sequence, verify and use in future experiments. The period in which this happened was, she relates, a highly stressful one for her since she had only a few weeks left on her employment contract. She states that this does not justify what she did, and she regrets it deeply.

Concerning the other suspicions, [redacted] asserts that she is not guilty of deliberate fabrication. She asserts that she performed all the experiments in the manner on which she and the research-group leader, [redacted], had agreed. Regarding suspicions 2 and 3, [redacted] says she no longer has access to the original images, which makes it hard for her to comment on the suspicions. She states that she showed the images from the experiments she performed, and thinks that she would therefore have had no reason to reuse previous pictures and give them new names. Summing up, she states that if errors were made in the images involved in Suspicions 2 and 3, they were unintentional. As for Suspicions 4 and 5, [redacted] describes how the experiments were done and the data managed. For Suspicion 4, she describes the situation in which this experiment, too, was affected by problems with the nitrogen tank: the fact that few cells survived, and she was obliged to culture them without antibiotics, with the result that they were unable to withstand antibiotic selection. Concerning Suspicion 5, [redacted] states that it was a relatively new experiment for her, and that she and [redacted] agreed on the protocol for the experiment; that she did not perform every part of the experiment; that another person was also involved; and that this person and she herself obtained comparable results in different systems.

Finally, [redacted] states that she had regular weekly meetings with [redacted], at which they discussed all the experiments, checks and anticipated results, and also which primers, plasmids and reagents should be purchased. [redacted] was, accordingly, aware of every aspect of the experiments. She writes that she spoke to him about how stressed she was, but nothing was done about the situation. She emphasises that the other co-authors were not involved in any way.

[redacted], head of the research group and last author of the manuscript, states that he was unaware — and had no suspicions — of any allegations of misconduct until, in January 2021, he discovered that data with DNA sequences must have been fabricated. After that, he detected further errors. Although, jointly with [redacted], he had been through the data and images several times — as she asserts in her statements — it would, in his opinion, have been impossible for him to know where the data had come from. This applied, for example, to the actual cell line, the antibodies that had been used and the fact that data were manipulated. He states that, just as everyone in the field does when they are collaborating with trusted colleagues, he had assumed that the data were authentic.

[redacted] states further that [redacted] as a senior postdoctoral researcher and subsequently assistant professor, largely worked independently and that he had extremely little scope for overviewing her day-to-day experimental work. He repeats that he now, in retrospect, considers that he should have examined [redacted] work and documentation of the research at an earlier stage. He also asserts that there had not been anything wrong with the nitrogen tank as such; instead, he believes many of the cell lines were destroyed because a rack of them may have been left out at room temperature. [redacted] states that it is vital to mention that the other co-authors of the unpublished manuscript were not involved in the suspected experiments and in no way could have known that anything might be wrong with the cell lines supplied to them.

[redacted] have sent in a joint statement, asserting that they participated in the experiment that was performed on mice. They write that, noting evident morphological differences among the cell lines, they sent pictures to [redacted] to double-check whether the appearance of the cells was healthy and similar to when she was culturing them. Further, they describe how [redacted] and [redacted] prepared the figures and wrote the manuscript, which they all read and commented on. They state that they had no indications that anything might be wrong. Nor —in line with usual practice — did they see or have access to raw data. They state that the manuscript had been returned after the review with a stated wish to see further experiments. [redacted] had then left the lab and the consequential experiments were conducted by other members of [redacted] lab. In addition, they describe how it was during this period that [redacted] contacted them, and they learnt that the results were not reproducible, and that the manuscript had to be withdrawn.

The Board has obtained an expert's statement on the matter. In connection with Suspicion 1, the expert's[1] assessment is that files containing DNA sequence data had been given new names. These were said to show other experiments, and falsification of data was thus involved.

Regarding Suspicion 2, the expert states that the cell lines studied were created in 2018 and 2019, but that some of the images used by [redacted] to support her claims about methionine dependence for these cell lines are identical with images created before 2018 — that is, before the creation of the cell lines being studied. He says these images created before 2018 had clearly been duplicated and used in the

[1] Fredrik Mertens, professor at the Division of Clinical Genetics, Lund University.

experiments on methionine dependence to support key assertions. The expert's assessment is that falsification is involved. He considers it unlikely that this took place by mistake and that, rather, it happened because the experiments did not turn out as expected. He states that his conclusion is supported by the fact that there are many examples of duplicated images with various names among the alleged offender's files, and this suggests that file names were changed deliberately.

With respect to Suspicion 3, the expert states that western blot images said to have been produced in 2019 are identical with images produced in 2017 — that is, before the cell lines included in the current experiment were supposed to have been produced. The expert's assessment is therefore that these western blot images have been duplicated; that file names have been changed; and that falsification has been involved. The expert states that it is probable that these things have been done intentionally because the experiments have not turned out as expected.

Regarding Suspicion 4, the expert says that the matter is more complex and difficult to settle than the other suspicions, since [redacted] provides the majority of explanations that, to some extent, describe why it is difficult to re-create the results. The expert refers to the fact that, in her statement, [redacted] assertions include saying that there was a shortage of space at the lab, and that samples were kept temporarily and therefore not registered in the correct manner, which might explain why documentation was lacking. Another example is her assertion that, owing to various problems with the cells, she cultured some without antibiotics. This might explain why [redacted], in checks after the suspicions had arisen, was unable to find cells able to survive antibiotic selection. The expert also writes that, in the opinion of the company from which the plasmid vector is said to have been ordered, the vector is unusable for the purpose it is said to have been used for. The expert states that, overall, he finds it most probable that the cells were never produced, and the data were thus fabricated.

In connection with Suspicion 5, the expert thinks that the primers said to have been used are not compatible with any human gene, and therefore cannot have provided information about gene expression. He writes that he is unable to argue with absolute certainty against [redacted] explanations, and that she may have acted in good faith. He maintains that, as first author, [redacted] should have verified whether the primer sequences were correct or not. The expert's assessment is thus that fabrication was involved, but that he is not sure whether it took place out of carelessness or ignorance, or with intent.

In summary, the expert writes that the accusations against [redacted] are well founded and that she had a leading part in planning the experiments, performing the analyses and summarising the results. The expert also states his opinion that the suspicions relate to an attempt to compensate for the lack of actual data by falsifying and fabricating results for the purpose of enabling the study to give a better impression, and that this involved serious breaches of good research practice.

Grounds for decision

Legal regulation

The Board's remit is to examine issues of research misconduct under the Swedish

Act (2019:504) on responsibility for good research practice and the examination of research misconduct ("the Act"). Section 2 of the Act defines research misconduct as a serious deviation from 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.

Research covered by the Act

The research that is subject to Section 3 of the Act includes research conducted by higher education institutions (HEIs) for which the Swedish state is the responsible entity, and which are covered by the Higher Education Act (1992:1434).

Three of the co-authors of the manuscript — [redacted] — were affiliated to an HEI in the United States. These co-authors are therefore not included in the Board's investigation.

Researchers' responsibility to follow good research practice

Under Section 4 of the Act, researchers are responsible for complying with good research practice in their work. "Researcher" is neither a protected occupational title nor defined in the Act. However, the preparatory work shows that people who count as researchers are those attending, or who have attended, research training and who are taking part in research. Other research participants, such as students at basic or advanced level and technical and administrative staff, should not count as researchers.[2] The preparatory work states that two implications of researchers' responsibility to follow good research practice under Section 4 are that they are honest and do not contravene laws and recognised norms of research ethics.

One of the manuscript's co-authors, [redacted] worked as a laboratory technician on the project for three months. He cannot be regarded as a researcher and is therefore not covered by the Board's investigation.

The authors included in the Board's assessment are those listed on the manuscript as affiliated to KI: [redacted]

Planning, implementation and reporting of research

The breaches that may constitute research misconduct must, according to the definition in Section 2 of the Act, have been committed in the planning, implementation or reporting of research. This formulation means, according to the preparatory work, that the notion of misconduct relates to deviations throughout the research process.[3] Reporting relates both to publication and to other forms of disclosure to the public.[4]

The suspicions relate to research summarised in a manuscript and sent to an academic journal for scrutiny. This may be regarded as part of the procedure for reporting of research and, accordingly, must be examined by the Board.

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[2] Swedish Government Bill 2018/19:58, pp. 32–33.
[3] Swedish Government Bill 2018/19:58, p. 100.
[4] Swedish Government Bill 2018/19:58, p. 49.

Fabrication, falsification or plagiarism

The Board's remit is to examine three forms of misconduct: fabrication, falsification and plagiarism. Th Act does not define these terms, but its preparatory legislative work 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* (ALLEA).[5,6] The principles are also explained in the Swedish Research Council's publication *Good Research Practice*.[7] According to the preparatory legislative work, "fabrication" is often described as inventing results and documenting 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. Lastly, the description of plagiarism is a researcher's use of others' texts, ideas or works without due acknowledgement of the original source.[8]

The suspicions in the case concern whether data that formed the basis for the submitted manuscript has been falsified and/or fabricated.

Regarding Suspicion 1, [redacted] has admitted that she manipulated files containing DNA sequence data. The expert's assessment is that data were falsified. For Suspicions 2 and 3, the expert judges that files have been replaced and renamed in order to represent other results, and that data have been manipulated — actions that constitute falsification. The Board has reached the same assessment and considers that regarding Suspicions 1–3, falsification is indeed involved.

Concerning Suspicion 4, the expert deems it most likely that cell lines were never produced and, accordingly, that the results were fabricated. Several factors, such as the vector being unable to function with the virus, that primers were not ordered until after the cells were supposed to have been produced and that raw data are lacking, support such a conclusion. The Board deems that, regarding Suspicion 4, it is not possible to state with sufficient certainty that data have been fabricated.

For Suspicion 5, the expert's assessment is that the primers that are said to have been used cannot have generated the results that were reported, and that fabrication is, accordingly, involved. The Board's assessment is the same and it thus considers that, for Suspicion 5, fabrication of data is involved.

Serious breach

Only serious breaches of good research practice constitute research misconduct and fall within the scope of investigation by the Board. Other breaches are, instead, dealt with by the entities responsible for the research (the HEIs), pursuant to Chapter 1, Section 17 of the Swedish Higher Education Ordinance (1993:100). In the preparatory legislative work on the Act, it is stated that fabrication and falsification are always, in principle, serious breaches of good research practice. In certain cases,

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[5] *The European Code of Conduct for Research Integrity*, revised edition. Berlin: All European Academies (ALLEA); 2018, Section 3.1.
[6] Swedish Government Bill 2018/19:58, pp. 45, 100.
[7] *Good Research Practice*. Stockholm: Swedish Research Council, 2017, Chapter 8.
[8] Swedish Government Bill 2018/19:58, pp. 45, 100.

for example concerning a minor infraction on a single occasion, plagiarism should not be considered a serious breach of good research practice.[9]

The premise for the Board's investigation of this aspect is that falsification and fabrication are, in principle, serious breaches of good research practice. No reason to deviate from the premise stated in the preparatory work has emerged in the case. The Board's conclusion is therefore that the deviations are serious.

Intent or gross negligence

Under Section 2 of the Act, the serious breach of good research practice must have been committed with intent or through gross negligence to be considered research misconduct. "Intent" means, according to the preparatory legislative work on the Act, that the researcher understands what (s)he has done, while "negligence" means that this should, in any case, have been understood by the researcher. For "gross negligence", the conduct must stand out as particularly serious or reprehensible. Oversights, carelessness or misunderstanding should not, as a rule, be regarded as gross negligence according to the preparatory legislative work.[10]

Since 1 January 2020, researchers' responsibility to comply with good research practice in their work has been subject to statutory regulation under Section 4. How far-reaching this responsibility may or should be in each individual case must be investigated and assessed.

[redacted] admits that she deliberately falsified data in the manner specified in Suspicion 1. The Board's assessment is that it is clearly established that [redacted] conducted falsification with intent.

As for the other suspicions, she denies intentionally falsifying or manipulating data.

Where Suspicions 2 and 3 are concerned, the Board deems [redacted] explanations to be unconvincing. Since these cases relate to files of cell lines and western blot images being repeatedly duplicated from other experiments, the Board's assessment is that this could not have taken place as a result of carelessness, and this makes it particularly reprehensible. In light of the expert's assessment and the other findings that have emerged in the case, the Board judges that [redacted] conduct was indeed intentional, or in any case grossly negligent.

Regarding Suspicion 5, the research-group leader [redacted] states that he is unable to find any documentation supporting the claim that the primers said to have been used were purchased. The expert asserts that [redacted] may have acted in good faith but that in any case, as first author of the manuscript, she should have ensured that the sequences were correct. Given what has emerged in the case, the Board's assessment is that it is not entirely possible to establish, first, what happened and accordingly, second, that [redacted] acted with intent or out of gross negligence.

When it comes to responsibility for the other co-authors included in the Board's investigation, ALLEA's *European Code of Conduct for Research Integrity* states

[9] Swedish Government Bill 2018/19:58, p. 100.
[10] Swedish Government Bill 2018/19:58, pp. 50–51, 100.

that all the collaborating partners must take responsibility for the integrity of the research. The Code also states that all co-authors bear full responsibility for the content of their publication unless it specifies otherwise.[11] The manuscript does not specify any division of responsibility. However, the author group have on their own initiative, since they were unable to repeat the experiments again during the review process, requested withdrawal of the manuscript prior to publication.

[redacted], who was named as the last author of the withdrawn manuscript, asserts in his statement that he trusted [redacted] until he discovered that files containing DNA sequence data had been manipulated. [redacted] also states that he lacked the kind of detailed grasp of [redacted] work that would have enabled him to grasp that the origins of the images or analyses she showed him were incorrect. Both [redacted] and [redacted] testify that the other co-authors included in the investigation had no cause to suspect that anything might be wrong with the experiments they were involved in. These authors have stated that they participated in only a limited proportion of the experiments. They say that they posed certain verifying questions to [redacted] about the cells they were provided with, but that they otherwise had no indications that anything was wrong. It was also [redacted] who reported the research misconduct case at KI.

In light of what has emerged in the case, the Board finds that there are no grounds for suspecting intent or gross negligence on the part of [redacted] or the other co-authors included in the investigation.

In summary, the Board finds [redacted] guilty of research misconduct. The Board does not find [redacted] guilty of research misconduct. [redacted] were not included in the Board's investigation.

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The Board has decided in this case following its presentation by caseworker Dorota Green.

Thomas Bull
Chair

Dorota Green
Caseworker

[11] *The European Code of Conduct for Research Integrity*, revised edition. Berlin: All European Academies (ALLEA); 2018. See sections 2.6 and 2.7.