English translation of the statement from the expert group for misconduct in research at ÖNEP. Note! Only the original statement in Swedish is authorized and signed by the expert group.

Överklagandenämnden för etikprövning
ETHICS **REVIEW APPEALS BOARD**
EXPERT GROUP FOR MISCONDUCT IN RESEARCH

OPINION
10 June 2019 Ref no. O 7-2018

Institution that requested the opinion

University of Gothenburg
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SE-418 30 Gothenburg, Sweden.

Background

The University of Gothenburg submitted a written request for an opinion that arrived on 9 November 2018 from the Expert Group for Misconduct in Research at the Ethics Review Appeals Board. The document refers to accusations against Karin Dahlman-Wright, Vice-Chancellor at Karolinska Institutet. According to an agreement between Karolinska Institutet and the University of Gothenburg, the University is investigating the matter which concerns research activities at Karolinska Institutet.

The reports of misconduct in research concern suspicions of errors in images and suspicions of using incorrect images in eight scientific articles.

I. *Estrogen signalling and the metabolic syndrome: targeting the hepatic estrogen receptor Alpha action.* M Matic, G Bryzgalova, **H** Gao, P Antonson, P Humire, Y Omoto, N Portwood, C Pramfalk, S Efendic, P-0 Berggren, J-Å Gustafsson and K Dahlman-Wright, PLOS ONE (2013) pubmed: 23451233 doi: 10.1371/joumal.pone.0057458 issn: 1932-6203

2. *AP-1-mediated chromatin looping regulates ZEB2 transcription: new insights inta TNFa-induced epithelial-mesenchymal transition in triple-negative breast cancer.* Y Qiao, C-N Shiue, J Zhu, T Zhuang, P Jonsson, A P.H. Wright, C Zhao, K DahlmanWright. Oncotarget (2015) Pubmed: 25762639 doi: 10.18632/oncotarget.3158 issn: 1949-2553

3. *Estrogen receptor a promotes breast cancer by reprogramming choline metabolism.* M Jia, T Andreassen, L Jensen, T Frost Bathen, I Sinha, H Gao, C Zhao, L-A Haldosen, Y Cao, L Gimita, S A Moestue and K Dahlman-Wright. Cancer research (2016) pubmed: 27457520 doi: 10.1158/0008-5472.CAN-15-2910 issn: 1538-7445 issn: 0008-5472

4. *The atypical ubiquitin ligase RNF31 stabilizes estrogen receptor (J. and modulates estrogen-stimulated breast cancer cell proliferation.* J Zhu, C Zhao, A Kharman-Biz, T Zhuang, P Jonsson, N Liang, C Williams, C-Y Lin, Y Qiao, K Zendehdel, S Strömblad, E Treuter, K Dahlman-Wright. Oncogene (2014) pubmed: 24441041 doi: 10.1038/onc.2013.573 issn: 0950-9232 issn: 1476-5594

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5. *The genome landscape of ERalpha- and ERbeta-binding DNA regions.* Y Liu, H Gao, TT Marstrand, A Ström, E Valen, A Sandelin, J-Å Gustafsson, K Dahlman-Wright. Proceedings of the National Academy of Sciences of the United States of America (2008), pubmed: 18272478 doi: 10.1073/pnas.0712085105 issn: 1091-6490 issn: 0027-8424
6. *Estrogen receptor beta as a navel target of androgen receptor action in breast cancer cell lines.* P Rizza, I Barone, D Zito, F Giordano, M Lanzino, F D Amicis, L Mauro, D Sisci, S Catalano, K Dahlman-Wright, J-Å Gustafsson, S Ando. Breast cancer research: BCR (2014) pubmed: 24552459 doi: 10.1186/bcr3619 issn: 1465-542X
7. *The estrogen receptor {alpha}-selective agonist propyl pyrazole triol improves glucose tolerance in ob/ob mice; potential molecular mechanisms.* L Lundholm, G Bryzgalova, H Gao, N Portwood, S Fält, K D Berndt, A Dicker, D Galuska, J R Zierath, J-Å Gustafsson, S Efendic, K Dahlman-Wright, A Khan. Journal of endocrinology (2008) pubmed: 18757549 doi: 10.1677/JOE-08-0192 issn: 1479-6805 issn: 0022-0795
8. *Estrogen receptor specificity for the effects of estrogen in ovariectomized mice.* M K Lindberg, Z Weihua, N Andersson, S Moverare, H Gao, 0 Vidal, M Erlandsson, S Windahl, G Andersson, D B Lubahn, H Carlsten, K Dahlman-Wright, J-Å Gustafsson, C Ohlsson. The Journal of endocrinology (2002) pubmed: 12176656 issn: 0022-0795

The University of Gothenburg is requesting an opinion on whether incorrect calculations, if any, or the use of incorrect images can be considered to be mistakes that affected the reported results in the relevant articles. If the Expert Group finds that the errors have affected the reported results in the articles, the Expert Group has been requested to determine whether this has been done for the purpose of e.g. improving or changing the results. In addition, the Expert Group has been requested to determine whether images have been manipulated, or whether incorrect images have been systematically used in the articles. Moreover, an assessment has been requested to determine whether misconduct in research can be considered to have occurred and if so, to which individual or individuals this misconduct can be attributed.

The University of Gothenburg has conducted a limited investigation and obtained statements from Karin Dahlman-Wright, as well as from one of the complainants, Johan Thyberg, among others.

On 29 November 2018 the Expert Group decided to appoint Professor Nils Billestrup, Panum Institute, Copenhagen University, to serve as an expert to review the case. Nils Billestrup submitted his report on 8 March 2019. Of the 68 different co-authors, 58 were given the opportunity to comment on Nils Billestrup's report. The Expert Group was unable to find the contact details for ten of the co-authors. Replies were received from 15 co-authors. Nils Billestrup then submitted comments on the replies that were received.

Nils Billestrup attended the Expert Group meeting on 8 April 2019.

The Expert Group's assessment

Karin Dahlman-Wright pointed out that some of the reported articles were written a long time ago and that these articles, according to the law that is proposed to come into force commencing on 1 January 2020, should be considered to be subject to the statute of limitations. Today, there is no legislation that regulates deviations from good research practice. Under the provisions of the regulation (2007: 1068) with instructions for the Ethics Review Appeals Board, the Expert Group, at the request of a university or university college that has the State as its principal and that is subject to the Higher Education Act

(1992: 1434) shall comment on matters concerning investigations of suspicions of misconduct in research, artistic research and development work. The Expert Group is therefore prevented from rejecting requests for opinions with reference to legislation that has not yet entered into force.

The Expert Group concludes that the case has been carefully and meticulously analysed by the expert, Nils Billestrup. The Expert Group has thoroughly reviewed the observations and conclusions that were made by Nils Billestrup and concludes that the review is logical and comprehensive. The Expert Group essentially shares Nils Billestrup's conclusions regarding the errors in the articles. In all essential regards, the authors in question have also attested to these errors.

Nils Billestrup has found that doubts can be raised concerning six of the eight reported articles and that the errors in three of them are such that they deserve serious criticism: articles 3, 5 and 7. Nils Billestrup considers the errors that occur in these three articles to be of such a nature that they could possibly have affected the conclusions of the articles. However, Nils Billestrup leaves it up to the Expert Group to determine whether the errors are serious enough to be considered to be misconduct in research. The Expert Group assesses each of the eight articles separately below.

In article 1, sections of the same image were used to illustrate two different experiments in Figure 2. This is admitted by the accused authors, who state that it occurred by mistake. According to Nils Billestrup, it cannot be determined whether the mistake was intentional or unintentional. However, Nils Billestrup criticises shortcomings in safety and security controls and in data handling. The same assessment and conclusion apply to article 2. The Expert Group shares this assessment.

Article 4 shows a duplication of images that were intended to represent different proteins in Figures 6C and 6E. In other words, the same image was used to represent different experiments. The accused authors have admitted this and the mistake has been remedied by sending a correction to the periodical. The Expert Group shares Nils Billestrup's opinion that even if the mistakes should have been discovered by the corresponding author, it cannot be determined that they were made intentionally or through gross negligence.

In articles 6 and 8, no evidence was found for accusations of errors.

There is a dispute in Article 3 concerning whether the images of the bands in Figures 4A and 6A were duplicated. In her reply, Min Jia claimed that new experiments confirmed the original conclusions. According to Nils Billestrup, there is no support for this assertion. The use of duplicated bands contributes to raising doubt regarding the results presented in the article. Meanwhile, Karin Dahlman-Wright claims that when she reviewed the proofs she focused on technical details, for which reason she did not discover the changes in Figure 4. The Expert Group shares Nils Billestrup's assessment that all aspects must be taken into account when reviewing a manuscript that is ready for print and that one of the most important quality controls is specifically the integrity of the various figures. However, the study is an analysis of a variety of different gene expressions and according to the Expert Group's assessment, with respect to Figures 4A and 6A the figures in question hold no significance for the overall conclusion of the study, which Nils Billestrup also states. The results related to Figure 4A have to some extent been repeated in regard to greater membrane expression, but not completely so in regard to the cytosol portion. In addition, the authors have conceded that the wrong images were used in a couple of cases. However, the Expert Group holds that the errors have not had any crucial significance for the overall conclusion of the study. According to the Expert Group's assessment it is also difficult to determine that the errors occurred intentionally or through gross negligence. There is no reason to assume that anyone would falsify a subtotal that does not have any great significance for the overall conclusion of the study. Although serious criticism should be directed against the authors, especially the first and last author, for carelessness with archiving and use

of image material, as well as for shortcomings during proofreading, the Expert Group does not find the errors to be of such a serious nature that they constitute misconduct in research.

In article 5, according to Nils Billestrup there is no question that the images in Figures 1 A and 1 C have been manipulated. Nils Billestrup holds that the errors in Figures 1 A and 1 B lack significance for the results of the study, while the error in Figure 1 C could possibly affect the results of the study. Image 1 C was part of the basis for the assertion that the LBD antibody reacted with oestrogen receptor beta. Evidence for this was also found in images 1 A and 1 B and, perhaps even more importantly, in image 10, which was carried out on the prepared material that was also used in conjunction with DNA binding studies. According to the Expert Group, it therefore is not clarified that the errors had any crucial significance for the results of the study. This also means that there are no strong reasons to assume that the errors were committed intentionally. Regarding article 5 there is also reason to strongly criticise the carelessness in research, but not to such a degree that it represents misconduct in research.

In article 7, the image in Figure 10a was manipulated in that different parts of the original film were cut and pasted. Thus, the band that represents data from one mouse shows bands from several mice. This approach means that the conclusions of the article can be called into question. One submitted reply claims that the mistake was corrected and that the results in principle show the same results as previously. Nils Billestrup expresses doubt regarding this conclusion, especially because of the change in the level of significance. Even if the Expert Group shares this doubt, as was also expressed in the answers, it is the quantitative calculations visualised in Figure 10b, not in the images in Figure 10a, that carry the greatest weight in relation to the conclusions of the article. As with Articles 3 and 5, the incorrect figures and incorrect calculations in Article 7 can be seriously criticised. However, the Expert Group does not see any strong reasons to question the main conclusions of the study, and therefore there is no reason to assume that the errors were committed intentionally or through gross negligence. According to the Expert Group, support for misconduct in research can thus not be found in relation to article 7 either.

In summary, the Expert Group concludes that even if several of the errors and mistakes from which the articles suffer deserve serious criticism, it cannot be considered to be established that the shortcomings are such that they comprise misconduct in research.

The Expert Group notes that the overall impression is that good research practices did not seem to be the norm in the research environment, where responsibility is taken to introduce new researchers to all aspects of a sound scientific approach. The inadequate procedures noted in conjunction with the review of the case were likely a contributing factor to the carelessness that occurred. Even if several of the errors that were noted were difficult to detect, blaming them on a generally stressful situation, as Karin Dahlman-Wright does, is noteworthy. It bears witness to a nonchalant approach to the important task of the research leader.

The case is thus closed on the part of the Expert Group.

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This opinion has been adopted by Jerry Eriksson (dissenting), chairman, Aleksander Giwercman, Lena Halldenius, Holger Luthman, Jack Lysholm, Elisabeth Rachlew (dissenting) and Göran Sandberg. The final processing of the case was also attended by substitutes Per Carlbring, Sofia Feltzing and Björn Petersson, administrative director Jörgen Sviden, and administrative secretary Eva Kaaman Modig.

On behalf of the Expert Group for Misconduct in Research

Jerry Eriksson

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Dissenting opinion

Jerry Eriksson and Elisabeth Rachlew had a dissenting opinion and cite the following:

We made a different assessment from that of the majority of the Expert Group regarding articles 3, 5 and 7 and therefore reached a different conclusion regarding the matter of misconduct in research. Our assessment can be seen below.

There is a dispute in Article 3 concerning whether the images of the bands in Figures 4A and 6A were duplicated. In her reply, Min Jia claimed that new experiments confirmed the original conclusions. According to Nils Billestrup, there is no support for this assertion. The use of duplicated bands strongly contributes to putting the results presented in the article in significant question. Meanwhile, Karin Dahlman-Wright claims that when she reviewed the proofs she focused on technical details, for which reason she only saw the changes in Figure 4. We share Nils Billestrup's assessment that all aspects must be taken into account when reviewing a manuscript that is ready for print and that one of the most important quality controls is specifically the integrity of the various figures. The authors have conceded that the wrong images were used in a couple of cases. We hold that the lack of crucial significance of these errors to the overall conclusion of the study is unrelated to the issue of misconduct. Bands have been duplicated and this mistake is so severe that it may be considered to be misconduct in research. It is clear from both the statement of Nils Billestrup and from the replies of the involved researchers that there have been shortcomings in the researcher environment, resulting in inadequate procedures. This has contributed to carelessness. Regarding the issue of whether the duplication was intentional or due to carelessness, Nils Billestrup states that "it is less likely to be caused by honest mistake". If it therefore cannot be determined that the duplication occurred intentionally, with reference to what has emerged regarding shortcomings in the researcher environment, it can still be concluded that the question of carelessness rises to a level that can be considered to be gross negligence. The duplication thus represents, in our opinion, misconduct in research according to the Expert Group definition.

In article 5, Nils Billestrup concludes there is no question that the images in Figures 1 A and 1 C have been manipulated. There is no reason to assume that this occurred by mistake since, among other things, it may have had a favourable effect on the results of the study. No explanation has been given for this in the article, either. According to our assessment, this is such a serious error that it can constitute misconduct in research. Regarding the matter of whether the mistake was intentional or due to gross negligence, our assessment is the same as for article 3.

In article 7, the image in Figure 10a was manipulated in that different parts of the original film were cut and pasted. Thus, the band that represents data from one mouse shows bands from several mice. This action means that the conclusions of the article can strongly be called into question. The reply submitted by Lovisa Lundhold claims that the mistake was corrected and that the results in principle show the same results as previously. Nils Billestrup expresses doubt regarding this conclusion, especially because of the change in the level of significance. We share this doubt. Even if, as the majority of the Expert Group cites, there is no reason to question the main conclusions of the study, we hold that the method used to manipulate the image is such a serious departure from good research practices that it constitutes misconduct in research. The method used also means that it cannot be a question of anything other than intentional manipulation of the image. By manipulating images as was done in the article, the authors are guilty of misconduct in research.

In summary, we hold that such serious deviations from good research practice have occurred in three of the reported articles – articles 3, 5 and 7 – that a conclusion of misconduct in research must be reached.

What we must determine next is which individual or individuals can be considered to be responsible for the scientific misconduct. We make the following assessment regarding this question.

In earlier decisions, the Expert Group has cited that it may be considered to be good scientific practice that the authors who approved the manuscript without any reservation assume collective responsibility for this. All European Academies (ALLEA) also holds this position (European Code of Conduct for Research Integrity). If a scientific article is considered to be burdened with such serious shortcomings that scientific misconduct can be ascertained, in such cases the responsibility falls to all co-authors. We share this assessment.

Even if all co-authors share responsibility for any irregularities in an article, the burden of responsibility varies among the authors.

In article 3, Min Jia and Karin Dahlman-Wright have a higher level of responsibility as corresponding authors. Trygve Andreassen, Tone Frost Bathen, Indranil Sinha, Hui Gao, Chunyan Zhao, Lars-Arne Haldorsen, Leonard Girnita and Siver Andreas Moestue, who along with Min Jia and Karin Dahlman-Wright are responsible for writing, reviewing and/or revision of the manuscript, may also be considered to have a high level of responsibility.

Article 5 lacks a detailed description of the individual contributions of each author, for which reason the responsibility should be shared by all participating authors. As corresponding author, Karin Dahlman-Wright has a particularly high responsibility. The same assessment applies to article 7, where Karin Dahlman-Wright bears a higher level of responsibility as the final author.

In conclusion, we agree with what the majority states in the final paragraph on the overall impression of the relevant research environment and the nonchalant attitude.