



Vice-Chancellor

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Suspected scientific misconduct in the case of Professor Paolo Macchiarini

Background

On 24 June 2014, Karolinska Institutet received a report of suspected scientific misconduct from Dr Oscar Simonson, doctoral student at Karolinska Institutet and physician at Karolinska University Hospital; Dr Matthias Corbascio, docent at Karolinska Institutet and physician at Karolinska University Hospital; and Dr Karl-Henrik Grinnemo, researcher at Karolinska Institutet and physician at Karolinska University Hospital (herein under referred to as the complainants) concerning the original scientific paper titled "Experimental orthotopic transplantation of a tissue-engineered oesophagus in rats", authored by Sebastian Sjöqvist, Philipp Jungebluth, Mei Ling Lim, Johannes C Haag, Ylva Gustafsson, Greg Lemon, Silvia Baiguera, Miguel Angel Burguillos, Constantino Del Gaudio, Antonio Beltrán Rodríguez, Alexander Sotnichenko, Karolina Kublickiene, Henrik Ullman, Heike Kielstein, Peter Damberg, Alessandra Bianco, Rainer Heuchel, Ying Zhao, Domenico Ribatti, Cristián Ibarra, Bertrand Joseph, Doris A Taylor and Paolo Macchiarini and published in the journal Nature Communications (2014; 5:3562) (herein under referred to as the paper).

The paper describes the manufacture of a synthetic oesophageal prosthesis and the function of this prosthesis after grafting into a rat. The complainants question the description of the results in the paper as regards several specific points and thus also the conclusions drawn about a functional oesophageal prosthesis. One of the points concerns a CT scan and its interpretation, and whether there is morphological support for the claim that the prosthesis was coated with an epithelium. The complainants also question that the change in weight and general condition of the animals after the implantation of the synthetic oesophageal prosthesis are such that the animals demonstrate a functional oesophagus. They also question the longer term functionality of the transplant and claim that there are CT images showing that the oesophagus is not functional, and they also raise doubts whether or not all the illustrations in the paper show a synthetic or normal oesophageal prosthesis (annex 1).

Further reports of suspected scientific misconduct were subsequently submitted on 18 August and 24 September 2014 by Dr Matthias Corbascio, docent at Karolinska Institutet and physician at Karolinska University Hospital; Dr Thomas Fux, doctoral student at Karolinska Institutet and physician at Karolinska University Hospital;

Dr Karl-Henrik Grinnemo, researcher at Karolinska Institutet and physician at Karolinska University Hospital; and Dr Oscar Simonson, doctoral student at Karolinska Institutet and physician at Karolinska University Hospital. These complaints concern six other scientific papers and as they are not covered by this decision will be decided upon separately.

Procedure

Pursuant to Chap. 1 para. 16 of the Higher Education Ordinance (1993:100), Karolinska Institutet has investigated this case of suspected scientific misconduct. Concerning the first complaint, the Vice-Chancellor's inquiry began on 7 July 2014 with a letter to Professor Paolo Macchiarini (herein under referred to as Macchiarini) inviting him to comment. Macchiarini submitted his statement to Karolinska Institutet on 3 August 2014 (annex 2). After the two additional complaints were received, Karolinska Institutet sought out an independent, external, Swedish-speaking expert with experience of experimental and clinical patient-orientated research and without ties to the researchers involved, who would be able to accept the task of judging whether the criticised papers qualified as scientific misconduct. The decision to task Bengt Gerdin, professor emeritus at Uppsala University (herein under referred to as Gerdin), with issuing a statement of opinion on the matter was made on 25 November 2014. Lawyer Christian Olofsson was asked in January 2015 to assist Gerdin with the juridical aspects of judging the claims of scientific misconduct. On receipt of this statement of opinion on 13 May 2015 (annex 3) Karolinska Institutet gave all authors of the seven criticised papers an opportunity to comment on its content. Thirty-one (31) such comments had been received by Karolinska Institutet by 24 June 2015, fourteen (14) of which pertain to the complaint dealt with in this decision (annexes 4–17).

Objections of a conflict of interest have been raised against Gerdin.

Macchiarini's comments to the complaint received by Karolinska Institutet on 24 June 2014

In his response to the first point raised by the complainants, Macchiarini repudiates on the basis of the re-examination of raw data (the images obtained and the probe) the complainants' claim that the probe used for the CT scan completely fills out the volume of the graft. He also maintains that the CT results are not essential to the challenged conclusion. As regards the complainants' comments on the animals' weight change, there is no discrepancy in Macchiarini's own understanding of the observations. However, he maintains in this context too that the conclusions drawn by the study concerning the functionality of the graft were not based on differences in weight reduction between the two studied groups of rats. He also dismisses the significance of the discovery of hair in the oesophagus and evidence of pneumonia in an animal as an expression of a dysfunctional oesophagus. Further, Macchiarini dismisses the complainants' description of and comments on certain details of study design.

Gerdin's statement of opinion

Gerdin's method involved analysing the written material available to him at the start of the inquiry, and additional written material subsequently requested by him. This method was judged by Gerdin to be sufficient for answering the main question of whether scientific misconduct as defined for Swedish circumstances by the Swedish Research Council had been committed. According to Gerdin, interviewing the people involved would not have made any difference to the assessment of the issues relevant to the matter of scientific misconduct.

As regards judging responsibility for the content of the scientific publication, Gerdin ascribes primary responsibility to the lead author over all the other co-authors. He also maintains that this person's responsibility is not defined in the same way in all scientific contexts and that it varies from one journal to another, for example, and depends on whether he or she is also ultimately responsible for the entire research project.

Gerdin concludes the following in his statement:

There is at least one significant departure from accepted scientific practice and a number of basic scientific flaws in this paper. The use of research results that a researcher other than one of the authors has produced and of which the quality and origins none of them can take responsibility for is a departure from accepted scientific practice. Further, the authors have presented the results in an incorrect manner that gives ungrounded support to the paper's main thesis. This is, in any case, careless; the lead author (Macchiarini) has responsibility for this circumstance, which constitutes scientific misconduct. All other points raised by the complainants (numbers 2–4 in their complaint) and examined by Gerdin reflect scientific defects that should have been handled by this highly reputed journal's review system. This can be put down to inattentiveness or haste or ignorance or carelessness. Gerdin lacks the grounds to state unequivocally that this evinces such disregard as constitutes a departure from accepted scientific practice. Gerdin goes on to say that the faults are such that the readers of the paper risk misinterpreting the results presented, and the lead author (Macchiarini) bears responsibility for this too. Gerdin also noted that the study protocol sent to him for examination was sorely lacking and incomplete.

Comments on Gerdin's statement by Macchiarini and his co-authors

Macchiarini's comments include the following (annex 4):

Macchiarini challenges Gerdin's judgement that none of the co-authors had been involved in the CT scan and that none of the authors were familiar with the method. He maintains that Sebastian Sjöqvist and Johannes Haag were both present, which can be verified in the animal house logbook. Further, he claims that Oscar Simonson had demonstrated the technique to Sebastian Sjöqvist (and to Johannes Haag, see below) so that he would be able to repeat the study in the future. Oscar Simonson was also involved in the wording of the manuscripts, so it is incorrect to claim that the authors lacked access to the technical information they needed to interpret the CT images. Macchiarini also denies having previously said that he did not take responsibility for the interpretation of the CT images, and that only Oscar Simonson possessed detailed knowledge of how

the study had been conducted. Consequently he challenges the claim that the authors presented data for which none of them could take responsibility and that he is therefore guilty of scientific misconduct.

Macchiarini also dismisses most of the other criticisms that Gerdin levels at the paper and that he describes as scientific flaws.

The co-authors' comments include the following:

The comments received support Macchiarini's version of events, especially his description of the procedures surrounding the CT scan (Philipp Jungebluth, Johannes Haag). Besides Sebastian Sjöqvist and Johannes Haag, Ying Zhao and Rainer Heuchel, both co-authors, have also worked with the CT technique. Additional support is lent to Macchiarini's remark that there were no discussions during the writing of the paper on the quality of the data or accusations of scientific misconduct. This latter only occurred after a complaint of such had been submitted to Karolinska Institutet by Dr Philipp Jungebluth regarding Dr Karl-Henrik Grinnemo, a complaint that subsequently led to a guilty verdict against Dr Grinnemo for plagiarism (Karolinska Institutet's ref. no. 2-1309/2014). Oscar Simonson was thus an active co-author of the paper when the first version was submitted to Nature Medicine for review in July 2013 and of the revised version that was later submitted to Nature Communications in December that same year. He was still listed as a co-author when the paper was accepted for publication on 5 March 2014 and when the proof was returned five days later on 10 March. There is thus documentary evidence that there was a co-author with responsibility for the CT scan when the paper was accepted and when the proof was sent to be printed. Throughout this part of the publication process, Oscar Simonson expressed no reservations about the image or the description of the CT results. It was not until 13 March 2014 that he notified Sebastian Sjöqvist by email that he no longer wished to be listed as a co-author of the paper, since in his own opinion he had made no scientific contribution to the study. The email made no mention of any reservations about the CT image or the interpretation of the result, nor did Oscar Simonson request that the image be withdrawn. This did not happen until a month later when Karl-Henrik Grinnemo and his colleagues sent a letter to the editor of Nature Communications.

Karolinska Institutet's deliberations and judgement

Karolinska Institutet finds that the matter can be decided upon the basis of existing material, such as the report of scientific misconduct dated 24 June 2014, Macchiarini's response to the complaint, relevant passages from Gerdin's statement of opinion and the comments submitted by Macchiarini and the other authors of the criticised paper and all other documents related to the case.

Karolinska Institutet finds that there is no circumstance to suggest that Gerdin has a conflict of interest in the matter.

Karolinska Institutet notes that the authors' comments on the external inquiry contribute new material that was not examined by Gerdin and that is critical to how the complaint is assessed.

Gerdin notes in his comment on the paper titled “Experimental orthotopic transplantation of a tissue-engineered oesophagus in rats” that the use of research results that a researcher other than one of the authors has produced and of which the quality and origins none of them can take responsibility for is a departure from accepted scientific practice. Karolinska Institutet shares this principle understanding and the opinion that it is Macchiarini who is responsible for ensuring that the authors together possess all the necessary competence to present and interpret all data included in the paper correctly.

Karolinska Institutet also notes that a contrast-enhanced CT scan of the oesophagus was conducted by Oscar Simonson, who left the group of authors before publication of the paper, but at a time when it had already been accepted for publication and proofed. There was thus a co-author who was responsible for the study and interpretation of the image when the paper was accepted for publication and when the proof was returned to the journal. The proof also showed that Oscar Simonson had joint responsibility for the CT scan with co-authors Rainer Heuchel and Ying Zhao. The article text as published however (in the “Author contributions” section), as Gerdin also observes, gives the impression that none of the authors takes responsibility for this part of the study.

The comments submitted by Macchiarini and some of his co-authors present a convincing case against Gerdin’s remarks that none of the co-authors had been involved in the CT scan and had any knowledge of the method. It is also important to note that Oscar Simonson left the writing process in the capacity of co-author after the manuscript had been accepted and proofed. It is also the case that he requested no changes to the manuscript at this time.

As regards the issue of weight change in the animals, Karolinska Institutet notes that that observed in the transplanted animals had been just as good as in the sham-operated animals. Further, a video sequence was published with the paper in Nature Communications showing that the experimental animals could move freely, eat and groom – i.e. behaved normally.

As regards the other scientific flaws discussed by Gerdin, most of which are, however, dismissed by Macchiarini, Karolinska Institutet concurs with Gerdin that they do not represent unequivocal departures from accepted scientific practice but are the result of inattentiveness, haste, ignorance or carelessness. These circumstances are, however, a reflection of quality deficiencies in the research process and the way in which the research and its results have been presented.

Karolinska Institutet also notes that what had initially been a unified and effective research environment (Advanced Center for Translational Regenerative Medicine [ACTREM]) had gradually disintegrated, and that this aggravated the situation.

In conclusion, Karolinska Institutet finds that Macchiarini, in certain respects, acted without due care in the process that gave rise to the original scientific paper published in Nature Communications, in that, for example, the paper contained incomplete information, particularly concerning the details of the animal experiments. However, it does not deem the circumstances to constitute scientific misconduct as it has emerged that one of the complainants was a co-author and responsible for the part of the study that involved the published CT scan in the version of the paper that had been accepted for



publication, and that several of its co-authors had been involved in and possess knowledge of the CT technique.

Decision

All things considered, Karolinska Institutet finds that while Professor Paolo Macchiarini has acted carelessly, he is not guilty of scientific misconduct.

In light of the university's express desire to safeguard scientific credibility and good scientific practice, the Vice-Chancellor has decided on the following:

- Karolinska Institutet finds that certain circumstances surrounding Professor Paolo Macchiarini's research do not meet its high quality standards.
- Paolo Macchiarini is to ensure that an erratum is sent to the journal based on the critical observations noted in the inquiry that could not be satisfactorily countered in the comments submitted by the authors.
- A meeting is to be held between the Vice-Chancellor, the head of the Department of Clinical Science, Intervention and Technology (CLINTEC), the director of CLINTEC's Ear, Nose and Throat unit and Professor Paolo Macchiarini in order to go through the current circumstances and measures decided upon.
- It falls to the head of CLINTEC to decide whether this decision will have consequences for Professor Paolo Macchiarini and other authors of the paper in question.

The decision on this matter has been taken by the Vice-Chancellor in the presence of University Director Per Bengtsson after presentation by legal advisor Lisen Samuelsson. Also present was Deputy University Director Marie Tell and the vice-chairperson of the Medical Students' Union, Andrea Montano Montes. Dean of Research Professor Hans-Gustaf Ljunggren and senior advisor to the Vice-Chancellor Professor Jan Carlstedt-Duke were involved in the final administration of the case.

Anders Hamsten

Lisen Samuelsson



Annexes:

1. Complaint to Karolinska Institutet, submitted 24 June 2014 by Oscar Simonson, Matthias Corbascio and Karl-Henrik Grinnemo
2. Comments on the complaint by Paolo Macchiarini, submitted 3 August 2014
3. Statement of opinion from Bengt Gerdin, submitted 13 May 2015
4. Paolo Macchiarini's comments on the statement of opinion, submitted 24 June 2015
5. Comment on the statement of opinion by Antonio Beltrán Rodríguez
6. Comment on the statement of opinion by Miguel Burguillos
7. Comment on the statement of opinion by Peter Damberg
8. Comment on the statement of opinion by Johannes Haag
9. Comment on the statement of opinion by Rainer Heuchel
10. Comment on the statement of opinion by Cristián Ibarra
11. Comment on the statement of opinion by Bertrand Joseph
12. Comment on the statement of opinion by Philipp Jungebluth
13. Comment on the statement of opinion by Karolina Kublickiene
14. Comment on the statement of opinion by Greg Lemon
15. Comment on the statement of opinion by Mei Lim Ling
16. Comment on the statement of opinion by Sebastian Sjöqvist
17. Comment on the statement of opinion by Ying Zhao