Suspected scientific misconduct in the case of Professor Paolo Macchiarini

Background

Two complaints of scientific misconduct were submitted on 18 August (annex 1) and 24 September 2014 (annex 2) 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 (herein under referred to as the complainants) concerning six scientific papers (herein under referred to as papers 1-6):


Papers 1, 3 and 6 are original articles that report new scientific findings, while papers 2, 4 and 5 are reviews that mainly summarise and comment upon previously published data, the latter generated either by the authors or by other researchers. The focus of both complaints and the ensuing inquiry is located in paper 1 and the patient case on which it is based, since some of the flaws concerning this article, according to the complainants, are also present in a similar form in the other papers.

The papers (1–6) describe the transplantation of a synthetic prosthesis (also referred to as the transplant or graft) to three patients with diseases of the trachea that were considered inoperable using established techniques. Paper 1 reports the first transplantation of a synthetic trachea into a human (patient 1) in which the prosthesis was coated in vitro with autologous, bone-marrow derived stromal cells using a bioreactor, and conditioned with certain drugs.

Paper 2 (the first review article) is based on the operation described by paper 1 and includes data from the follow-up of patient 1 up to eight months postoperatively.

Paper 3 describes a new technique for verifying cell viability in synthetic organs and tissues. Observations from the operation on patient 3 are also included as examples of the application of the technique.

Paper 4 (the second review article) refers to patient 1 and adds new information about the patient’s clinical condition up to twelve months after surgery.

Paper 5 (the third review article) summarises the progress of the patients who had received different tracheal prostheses.

Paper 6 reports a new technique for evaluating the biocompatibility of the synthetic polymeric tracheal prostheses used by the group. It also refers to clinical data relating to patient 1.

The complainants challenge several components of the published papers and thus also the conclusions drawn about the functionality of the tracheal prosthesis. The first complaint, which was received by Karolinska Institutet on 18 August 2014, makes the point that the actual clinical progress of the three operated patients does not concur with the results published in the six papers, as the authors have neglected to report peroperative and long-term postoperative complications. The complainants claim that the assertions in the papers that a synthetic tracheal graft can develop into a functioning trachea lack evidence, given the results of biopsies and bronchoscopic examinations that are presented in the patients’ medical records. The complainants also claim that all six papers either contain forged data or that they negligently omit or lack important information and that studies of the synthetic prosthesis in question should have been
conducted using animal models, with a longitudinal follow-up of function, before being used on humans.

Another main component of the complaint concerns the absence of an ethical permit for conducting research on humans. Since all three patients, according to the complainants, were operated on electively after months of planning, the operation cannot be classified as having been performed on the basis of a vital indication (use for humanitarian reasons – “compassionate use” or “hospital exemption”). They also note that the patients, despite the absence of ethical permits, signed a form (of which some of the wording is also challenged by the complainants) giving their informed consent to the operation. This procedure can have been misleading as it could have given the impression that the surgical intervention had been approved by the relevant authorities.

A third central part of the complaint concerns the absence of a permit from the Medical Products Agency (LMV) for the use of synthetic tracheal prostheses on humans. Moreover, three substances, two drugs and a chemical designed for laboratory use (TGF-β3 [transforming growth factor-β3, from R&D Systems], G-CSF [granulocyte colony stimulating factor, from Amgen Europe BV] and a synthetic erythropoietin analogue [Epoetin beta, from Roche]), had been used in situations for which no authorisation had been given.

The second complementary complaint, which was received by Karolinska Institutet on 24 September 2014, concerns the complainants’ opinion that there are no definitive findings suggesting a tumour recidive in patient 1 as well as other aspects of the use of three substances that were also addressed by the first complaint. The complainants maintain that no indication of malignancy was given by a preoperative CT scan, a tracheal biopsy or a bone marrow biopsy in patient 1, while a PET examination (PET-DT with 18F-FDG) did produce an image consistent with the presence of tumour tissue. Neither did inspection during the operation and cryosections of a peroperative biopsy detect any suspect tumour tissue. Despite all this, the trachea was still replaced with a synthetic prosthesis. The complainants also note that no documentation of a postoperative histological analysis of patient 1’s own trachea can be found in the medical records. All in all, the complainants maintain that patient 1 underwent major experimental surgery without clear pre-, per- and postoperative indications of any tumour disease.

As regards the three substances, one of which is not approved for use on humans, the complainants maintain that there is no scientific support for their use in “supratherapeutic” doses, according to the protocol described in paper 1. They also note that two of the operated patients had a known cancer diagnosis, which makes the use of growth factors risky, and that all three patients suffered potentially life-threatening postoperative thromboembolic complications, possibly related to the administration of the three substances.

A previous complaint of suspected scientific misconduct had been received by Karolinska Institutet on 24 June 2014 by Oscar Simonson, Matthias Corbascio and
Karl-Henrik Grinnemo concerning another original scientific paper based on experimental studies on rats (annex 3). This first complaint is not covered by this decision and 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. After the first complaint was received by Karolinska Institutet on 24 June 2014, 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. After the two additional complaints concerning the six clinical studies 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 seven 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. As part of Gerdin’s inquiry, Macchiarini submitted his response to the two complaints and Gerdin’s own questions on 6 April 2015 (annex 4). On receipt of Gerdin’s statement of opinion on 13 May 2015 (annex 5) 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, twenty-four (24) of which pertain to the complaint dealt with in this decision (annexes 6–29).

Objections of a conflict of interest have been raised against Gerdin. His methods and the result of his work have also been criticised, as well as the fact that he was the sole external investigator.

**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. Interviews were not conducted with the people involved, and, according to Gerdin, would not have made any difference to the assessment of the issues relevant to the matter of scientific misconduct.

Gerdin bases his assessment of the severity of suspected scientific misconduct on the term “degree of misconduct” as employed by the Swedish Research Council, which it associates with censurable conduct that is “repeated” or “extensive”. Gerdin’s view of severity also includes an assessment of whether the actions (i) were intentional, (ii) were taken for reasons other than distorting objectivity and (iii) concern results that are essential and fundamental to the scientific thesis.
Gerdin also notes that the Swedish Research Council’s definition of scientific misconduct does not cover certain forms of unacceptable behaviour, such as contravening the Ethical Review Act or the Medicinal Products Act, since violations of their provisions are regulated by different legislation and can result in criminal liability.

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 also works on the assumption that original findings, when published in a scientific journal following a peer review, must be considered research results.

Points made by Gerdin in his statement include the following:

**Paper 1:** Gerdin judges it unlikely that patient 1, as described in the paper, was asymptomatic five months after the operation. He also is of the opinion that there is nothing in the documents made available to him to support the paper’s claim that the tracheal prosthesis at this time had preserved anastomoses lined with vascular neomucosa and partly coated by epithelium of an almost normal appearance. Available PAD results from bronchoscopic biopsies taken eight, ten and eleven weeks after the operation are, according to Gerdin, not compatible with the authors’ claim that the prosthesis is partly covered by nearly healthy epithelium. A biopsy result, taken one week after the operation according to the paper, can not be found in Karolinska University Hospital’s medical records system. The paper also makes assertions about circumstances observed within four months of the operation, despite any such information being noted in the patient’s records.

As regards the matter of ethical permits, Gerdin notes that no approval was given by the local ethics committee. The claim in the paper that the transplant procedure was “approved by the local scientific ethics committee” is thus, he concludes, false.

The complainants question whether patient 1 de facto suffered a tumour recidive despite clinical suspicions of this being the case. Gerdin’s conclusion regarding this matter is that one must suspect that patient 1 did not have an active tumour recidive and that the issue is so serious that the healthcare principal should consider opening its own investigation.

As regards the use of the three substances included in the protocol given in the paper, Gerdin believes that it should be investigated by the LMV.

**Paper 2:** The complaint about this review article mainly concerns the claim it makes that the tracheal prosthesis given to patient 1 was functional, well-vascularised and lined with a well-developed healthy mucosa eight months after transplantation. This claim Gerdin finds to be unsubstantiated by both the available patient records and by Macchiarini’s response to the complainants’ criticisms.

**Paper 3:** This paper, which primarily reports on a new technique for assessing cell viability in synthetic organs and tissues, presents results from the surgery performed on patient 3. The complainants question whether there was an immediate need for the
intervention and challenge the description of certain characteristic features of the transplanted tracheal prosthesis at one week and five months after the operation.

Gerdin concludes that the description given in the paper is incomplete with respect to the presence of significant problems, and is therefore an embellishment.

Paper 4: Paper 4 (the second review article) adds new information about the clinical condition of patient 1 up to twelve months after the operation. The main concern over this paper is the authors’ description of the patient’s clinical condition after twelve months, where they note, amongst other things, that the patient exhibited a normal trachea and improved pulmonary function. Gerdin finds that the authors’ version of the patient’s postoperative progress for the first year (observations reported in the paper at one week, two months and one year after surgery) is “highly embellished”.

Paper 5: The complainants’ criticism of this review article, which discusses the need for tracheal transplants, developments in the field and future perspectives, is centred on the contents of a table that presents the outcomes for the patients who had so far received a tracheal prosthesis, amongst them eight using a synthetic scaffold. Gerdin judges here that the progress of the patients operated on by the lead author is described in an unbalanced manner, in that it does not include complications that had developed in two of the patients and that required active remedying.

Paper 6: This paper primarily reports on a new technique for evaluating biocompatibility in synthetic, polymeric tracheal prostheses, and is fiercely criticised by Gerdin for the way the authors describe the result for patient 1, who died shortly after the manuscript was submitted for publication, but a good month or so before it was accepted. The description of what Gerdin describes as a long and painful death he considers to be an embellishment in that important details about complications had been withheld. Gerdin is particularly critical of the way patient 1 is described as if still alive and merely troubled by a chronic fistula in the distal anastomotic sites of the left main bronchus, which required endoscopic interventions.

Gerdin’s other comments

In a separate section of his report, Gerdin gives his perspective on the situation that existed at the time of the three operations concerning deliberations over permit requirements and related contact with the relevant authorities. He also discusses the concept of “compassionate use”.

He concludes, amongst other things, that such experimental surgical therapy must be considered clinical research and that a large number of analyses performed on tissue samples taken during such therapy must be classified as “research involving humans” and thus subject to ethical review. As to whether the clinical activity examined was conducted within the bounds of the prevailing laws – if it is to be considered a clinical drug trial or falls under the hospital exemption – Gerdin concludes that unclear communication between the three institutions involved – Karolinska University Hospital/Karolinska Institutet and LMV – might have contributed to the situation. He further notes that the term “compassionate use” exists in Europe only with respect to the use of certain non-registered drugs, and consequently the interventions performed on these patients are not covered by this concept.
Gerdin also notes that one of the complainants, Karl-Henrik Grinnemo, is a co-author of, and thus partly responsible for paper 1, and that he, like all the other co-authors, signed a declaration to the effect that they had access to all the data generated by the study and that they accept responsibility for its validity. Further, Oscar Simonson, Matthias Corbascio and Karl-Henrik Grinnemo are co-authors of paper 3, and in this capacity confirmed with their signatures that permits had been given by the relevant institutions for the study on which it is based. This, argues Gerdin, means that the circumstances pointed out by the complainants regarding papers 1 and 3 should have been known to them when the papers were written and published. Gerdin also concludes that “what once appeared to be, in certain respects, a coherent research structure has since split apart and that this split in one way or another is linked to the complaint about suspected misconduct.”

All in all, Gerdin finds there to be departures from accepted scientific practice in all six papers, that the lead author Macchiarini should have been aware that clinical circumstances had been described erroneously and that important information had been withheld, and that he is therefore guilty of scientific misconduct.

Macchiarini’s response to the complaints received by Karolinska Institutet on 18 August and 24 September 2014 and his comments to Gerdin’s statement of opinion

Macchiarini dismisses categorically all allegations against him regarding scientific misconduct. He states that Gerdin’s inquiry is not based on all available documents of relevance to the six papers, which, in turn, influenced his statement of opinion. He also says that after Gerdin issued his statement, he personally and systematically read through certain relevant background documents that were written either by his co-authors or by the hospital and thus not made immediately available to him. Further, he states that for language reasons he had not read this material previously but had it presented to him in the form of textual summaries or diagrams, which unfortunately meant that his initial response to the complainants allegations and Gerdin’s questions were, in some respects, incomplete.

Macchiarini also notes that the two complaints were submitted at around the same time as his colleague Philipp Jungebluth submitted his own complaint against Karl-Henrik Grinnemo for suspected scientific misconduct, which later resulted in a guilty verdict against him for plagiarism (Karolinska Institutet ref. no. 2-1309/2014).

Points made by Macchiarini in his response include the following:

Regarding paper 1:

An examination of the patient records and conversations with clinical colleagues in Sweden and Iceland, who have access to material not available to the lead author, the complainants and Gerdin, parts of which can be found in their separate statements, have now been held. According to Macchiarini, this examination corroborates the descriptions given in the paper of patient 1’s clinical condition and the anastomoses and epithelialisation of the tracheal prosthesis. Specifically, there is information about the patient’s clinical status from the patient’s Icelandic doctors. Macchiarini also points out
that the complainants selectively quote the patient’s medical records from admission to Karolinska University Hospital 5.5 months after the operation. The fact that patient 1 was fully mobile, lived with his wife and children in his own house and was off medication for two months is not mentioned in the complaint. At this time, patient 1 had been readmitted to hospital to remove some granulation tissue and had absolutely no serious symptoms. As shown by repeated bronchoscopies and biopsies, including the one carried out a week after the operation, the prosthesis exhibited clear signs of epithelialisation. One observandum, according to Macchiarini, is that one of the biopsies that the complainants call “negative” and thus contradicted the paper’s conclusion, derives from a preoperative examination, and that all biopsy results are not available in Karolinska University Hospital’s medical records system. The pathologist responsible, Dr Béla Bozóky, who also submitted his own statement, testifies that the descriptions of the biopsy findings in his records agree with what is reported in the paper in question.

As regards the matter of ethical permits, Macchiarini maintains that representatives of Karolinska University Hospital made inquiries with the relevant authorities and decision-makers and that the necessary permits for performing transplantation surgery were issued. It was his understanding that it had been established that the operation would be assessed in medical terms on the basis of the permit decision taken by Karolinska University Hospital’s ethics committee (annex 30), and that the guidelines drawn up by the International Society for Stem Cell Research (ISSCR) allow operations on individual patients without it being considered a clinical study (annex 31). Macchiarini and the clinicians that were involved in the decision to operate on patient 1 thus met the criteria issued by the ISSCR in recommendation 34. Macchiarini therefore concludes that the complainants and Gerdin are wrong when they claim that no permits had been issued for the operation and states that the wording of the criticised paper is sufficient. As regards the question of the informed consent given in writing for the operation, Macchiarini claims that such written informed consent is not required in Sweden, but that this procedure was followed because the ISSCR guidelines include obtaining documented evidence that the patient has understood and consented to the operation.

The complainants and Gerdin question if patient 1 de facto suffered a tumour recidive despite clinical suspicions of this being the case. Macchiarini challenges this conclusion, maintaining that delegates at a multidisciplinary patient conference at Karolinska University Hospital as well as the response to the request for a second opinion from Harvard University judged a tumour recidive to be the most likely diagnosis and that surgery was necessary for preventing the already dyspnoeic patient 1 from suffocating to death. Supporting this assessment is the fact that the malignant tumour was only excised partially during the original operation in Iceland in 2009. Further, when patient 1 was admitted to Karolinska University Hospital, a non-conventional intervention was required, regardless of whether the tumour was malignant or not, owing to the way in which it had progressively grown into the tracheal lumen. Macchiarini also states that the peroperative biopsy was, for several reasons, taken deliberately outside the visual zone of tumour spread, mainly because the previous surgery had been complicated by massive and almost fatal haemorrhaging appearing in connection with a tumour biopsy, and because the PAD results of a biopsy of the tumour would not affect the subsequent surgery. He also notes that the resected sample, as indicated in the patient’s medical
records, was sent to the pathology unit for immediate examination. Over and above the oral notification given to the surgeon by the participating head anaesthesiologist that the entire tumour had been removed, Macchiarini, like the complainants and Gerdin, has not been able to locate the PAD results for the tumour itself.

Since Macchiarini finds that Gerdin makes no personal comments about the use of the three substances included in the protocol described in the paper other than that he believes it should be the subject of investigation by LMV, he states only that he and his colleagues consider all aspects of their work to have been performed in accordance with Swedish and International law and other regulations.

Regarding paper 2: Macchiarini holds that the description in this review article of the length of the follow-up and the function and appearance of the tracheal prosthesis in patient 1 concurs with documented clinical data. He also states in this context that not all bronchoscopy and PAD results were accessible to him when he submitted his initial response to the allegations against him or to the complainants and Gerdin.

The bronchoscopic discovery of both vascularisation and epithelium in the middle of the prosthesis after 5.5 months is, according to Macchiarini, of particular significance as it inspired confidence about the healing of the mucosa over the prosthesis. It is also important to be aware that certain biopsies were deliberately not taken from the prosthesis but from the granulation tissue in order partly to discover any tumour recidives and partly to avoid the danger of perforating the prosthesis. For this reason there are more visual than PAD-based assessments of epithelialisation. Macchiarini also feels it worth pointing out that bronchoscopy after twelve months also reveals an epithelial coating over the prosthesis.

The criticism of how the authors describe the patient’s condition during the follow-up period is completely repudiated by Macchiarini, who refers to the regular check-ups that took place with the patient’s doctors on Iceland and the separate report they submitted. The overall description conveyed to their colleagues in Stockholm was that the patient was evincing normal respiration and only visited hospital for routine check-ups.

Regarding paper 3: Macchiarini denies that the description of the actual experiences of the surgery performed on patient 3 was an embellishment in this paper, which describes a new technique for verifying cell viability in synthetic organs and tissues. The complainants question whether there was an “immediate” need for the performed surgery, and the description of certain characteristics of the transplanted tracheal prosthesis at one week and five months after the operation. The former is judged by Gerdin to be incomplete with regard to the development of significant postoperative problems and thus an embellishment.

As regards the condition of patient 3 at the time of surgery, Karolinska University Hospital’s evaluation of a previous evaluation made in the patient’s home country by local medical specialists (annex 32) is confirmed. Macchiarini also questions the relevance to the description of a new analytical method of a more detailed description of the current clinical and prosthesis-related status of patient 3. Besides, postoperative complications, many of which were related to the patient’s serious preoperative situation, were expected in this medically and surgically highly complex patient and in all cases
irrelevant to the paper’s conclusions. He does acknowledge, however, that this opinion need not be shared by all readers.

Regarding paper 4: Macchiarini challenges the opinion that a more detailed description of the postoperative complications in patient 1 would have been particularly valuable in a review article discussing the pros and cons of different types of synthetic prostheses and comparing these and the authors’ experience of recellularised natural prostheses. He therefore dismisses Gerdin’s opinion that the omission of a more detailed discussion of patient 1 constituted scientific misconduct as well as his and the complainants’ opinion that the description given in the paper of patient 1’s condition up to and at twelve months, in which the authors note (amongst other things) that the patient exhibited a normal trachea and improved pulmonary function, was inconsistent with the information on the patient contained in the medical records and thus an embellishment. At the same time, Macchiarini admits that his original response to the submitted complaints was inadequate, since specific references and medical records had not been made available at that juncture. On the basis of more records than were likely available to Gerdin and after contact with patient 1’s doctors in Iceland, Macchiarini claims that a picture emerges of a medical condition for the patient that corresponds to that given in the paper.

In sum, according to Macchiarini, patient 1, who without the tracheal implant would have died of suffocation over the ensuing years, enjoyed a good quality of life for a long time before the completion of the paper. He was not intubated, could breathe without an extra oxygen supply, and was able to complete his academic studies. Stents had been used to prevent the formation of granulation tissue. By the time the manuscript was ready, the function of the patient’s right lung was very poor owing to blood clots in the right pulmonary artery, a complication associated with the initial tumour surgery that called for a reconstruction of the right pulmonary artery. This complication, according to Macchiarini, can not be considered related to the tracheal transplant per se, but was connected to the patient’s basic disease and tumour anatomy. Patient 1 also took part in the one-year anniversary of the operation, at which time he agreed, like the responsible doctors, to be interviewed.

In light of this, Macchiarini asserts that patient 1’s clinical status at that time could not, as Gerdin put it, have been “extremely serious”, and that the tracheal graft has to be seen as successful and the function of the prosthesis as promising.

Regarding paper 5: The complainants’ criticism of this review article focuses on the content of a table that summarises the progress of the patients with tracheal prosthesis implants. Gerdin’s opinion is that the progress of the patients operated on by the lead author has been described in an unbalanced manner, in that it does not include complications that had developed in two of the patients (patient 1 and patient 3) and that required active remedying. Macchiarini argues here that Gerdin must have misinterpreted the table, of which the lower left column is unconnected to the right-hand column listing patient progress. Gerdin’s conclusion about the way in which the two patients with a malignant disease who had been operated on by Macchiarini are presented in the table is thus incorrect. As regards patient 3, Macchiarini admits that the description does not include the fact that this patient had needed a second graft and says that he is prepared to discuss the possibility of submitting an erratum to the journal to this effect. He does,
however, take issue with Gerdin’s opinion that he actively withheld information and embellished the results and is thus guilty of scientific misconduct. To support his version of the presentation of the results obtained he cites a passage in the paper that relates to the conclusions drawn and, as he sees it, clearly refers to the complications and setbacks experienced.

Regarding paper 6: Macchiaiini denies that the authors have embellished the description of the progress of patient 1 and that they are thus guilty of scientific misconduct. The information given in the introduction to the paper was intended to indicate that the rigidity of the prosthesis (the scaffold material) used in the patient was not ideal for a tracheal transplant. The data concerning the abnormal formation of granulation tissue and chronic fistulation presented in the paper were judged to be directly related to the rigidity. Adding a description of further complications affecting patient 1, which were also probably related to the biomechanical properties of the prosthesis, would not have made any difference to the conclusion of the paper, namely that the biochemical properties of tracheal prostheses must be improved.

Macchiaiini’s concluding comments

In his concluding comments to Gerdin’s statement of opinion, Macchiaiini admits the presence of certain shortcomings in the study and the publications that have been examined in detail in the two complaints and the subsequent statements and comments. The submission of an erratum could therefore be appropriate.

Comments by the other co-authors on the inquiry

Points made by the other co-authors in the comments on the criticised papers include the following:

The co-authors that commented on the criticism levelled against Macchiaiini give unanimous support to his response both to the complainants and to Gerdin’s statement of opinion. The other authors limit their comments to a description of their own contributions to the papers in which they were involved. Support is also given to Macchiaiini’s point that there were no discussions on the quality of the data or the allegations of scientific misconduct during their work on the papers in question, including the two on which representatives of the complainants participated. The matter of scientific misconduct was only raised after the aforementioned complaint from Dr Philipp Jungebluth concerning Dr Karl-Henrik Grinnemo had been submitted to Karolinska Institutet (ref. no. 2-1309/2014).

Important complementary documents, enclosed as annexes to several of the submitted comments, include the documentation received concerning the process and assessment ahead of the operation of patient 1; docent Richard Kuylenstierna’s summing up is essential in this respect. These documents make it clear that the decision to operate was taken by the healthcare authority after a transparent process at Karolinska University Hospital based on patient 1’s condition and the lack of alternative therapeutic options. Before patient 1 underwent surgery, Karolinska University Hospital’s medical ethics committee and an external ethics expert from the Swedish Research Council’s Ethics Committee were consulted.
As regards especially important specific comments, Tómas Gudbjartsson and Óskar Einarsson, the patient’s doctors in Iceland, give an account of the clinical controls and bronchoscopic examinations conducted of patient 1 there. No evidence emerges from this that the patient would not have been feeling well in mid-November 2011, which is to say five months after the operation. They maintain that the operation performed in Iceland in October 2009 is not to be seen as primary cancer surgery but as an acute, life-saving intervention to stop a massive haemorrhage that occurred in connection with a biopsy of the tumour, during which the said tumour was only partially excised. After radiotherapy, the tumour mass reduced as did the clinical symptoms from which patient 1 had been suffering. In early 2011, the patient developed right-side chest pain, dyspnoea and stridor, at the same time as tissue was observed to have expanded into the tracheal lumen at exactly the same place where the patient’s tumour had been discovered in October 2009. In April and May 2011, the patient deteriorated markedly, especially as regards the stridor and expectorating cough, upon which it was noted that the tumour that has expanded into the trachea had expanded further (as mentioned in the statement by Professor Jan-Erik Juto). In connection with this, a specialist was consulted at Harvard University, who confirmed that a tumour recidive was the likely diagnosis and that the tumour was inoperable. Since patient 1 had already had a full dose of radiotherapy, palliative care was the only form of conventional therapy available. In summary, the comments from the Icelandic doctors confirm completely the authors’ description of the clinical events for patient 1.

Regarding other central issues, Dr Mei Ling Lim and Dr Johannes Haag testify that brushed samples from a bronchoscopy procedure conducted a week after the operation on patient 3 had been sent for analysis to the Advanced Center for Translational Regenerative Medicine (ACTREM) laboratory at Karolinska University Hospital in Huddinge.

Dr Ola Hermanson argues in his comments that paper 1 is to be considered a case report and that, as such, does not constitute a research paper.

**Karolinska Institutet’s deliberations and judgement**

Karolinska Institutet finds that the matter can be decided upon the basis of existing material, such as the reports of scientific misconduct dated 18 August and 24 September 2014, Macchiariini’s response to these complaints, relevant passages from Gerdin’s statement of opinion and the comments submitted by Macchiariini 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 extensive inquiry contribute new material that was not examined by Gerdin and that is critical to how the complaint is assessed. The statement from the Icelandic doctors, for example, has been particularly valuable for understanding the clinical process and the preoperative evaluation of patient 1, and for obtaining a complete picture of the checks and tests that were conducted on the patient after the operation.
Karolinska Institutet’s deliberations and judgement do not include the question of whether the appropriate permits had been issued for the operations on which the papers are based, since the Swedish Research Council’s definition of scientific misconduct does not cover breaches of the Ethical Review Act or the Medicinal Products Act. Violations of their provisions are regulated by different legislation and can result in criminal liability. Furthermore, a preliminary inquiry is being conducted by a prosecutor concerning breaches of both the Ethical Review Act and the Medicinal Products Act.

Regardless of the above, Karolinska Institutet notes that it is unclear how the applicable regulations are to be interpreted. Like Gerdin, the university notes that the grafting of a synthetic tracheal prosthesis raises obvious problems of delimitation regarding both drug use and the development of medicotechnical products and stem cell grafts. Karolinska Institutet also shares Gerdin’s opinion that “it is reasonable to suppose that unclear communication between Karolinska University Hospital/Karolinska Institutet and LMV might in practice have created the conditions for the problems to arise.” As noted by Gerdin, the term “compassionate use” exists in Europe only with respect to the use of certain non-registered drugs, and consequently the interventions performed on these patients are not covered by this concept.

Karolinska Institutet also notes, however, that the decision to operate in the case in question was taken following a transparent process including assessment by Karolinska University Hospital’s ethics committee, in which research aspects of the case were not considered. The decision was made solely by the healthcare authority on the basis of patient 1’s medical condition and the lack of alternative therapeutic options. In line with this, the patient’s informed consent was obtained to the planned surgery rather than to participation in a research project. Macchiarini and his colleagues have, on the other hand, used research tools, such as the synthetic prosthesis, during the operations in question and thereafter applied research methods to follow the patients’ clinical progress in accordance with the source material supplied to the hospital management for its decision whether or not to operate on patient 1 (annex 33). Before this operation, the hospital’s medical ethics committee was consulted and an external ethics expert from the Swedish Research Council’s Ethics Committee.

Publication of the experiences gained has followed ISSCR guidelines, in which it is particularly stressed that the results of advanced surgical interventions are to be published. This procedure stands in contrast to Gerdin’s assertion that publication of the results of the three operations is required by the Ethical Review Act to undergo prior ethical review. As regards the publication of primary data in the review articles (of relevance here for patients 1 and 3), Karolinska Institutet notes that this is expected to take place to a very limited extent, in accordance with the design of the three review articles examined in this case.

In his statement of opinion, Gerdin concludes that his inquiry has demonstrated that all examined papers, to varying degrees, contain passages, mainly in the form of descriptions of scientific findings and the patients’ general condition, that constitute scientific misconduct. However, the statements submitted by Macchiarini and many of his co-authors convincingly contest the essentials of the complainants’ criticisms and
Gerdin’s assessments of the key issues that form the basis of his conclusion that scientific misconduct has been committed.

As regards the other issues discussed by Gerdin, most of which are repudiated by Macchiarini, Karolinska Institutet agrees in general with Gerdin that they should not be considered as scientific misconduct.

It is noted that the complainants have not included certain significant clinical data in their two complaints and other submitted documents on the preoperative condition and postoperative progress of two of the patients (according to letters from referring doctors Professor Cengiz Gebitekin [patient 3], and statements from profs. Tómas Gudbjartsson and Öskar Einarsson [patient 1]). Neither do they mention the fact that patient 3 underwent resuscitation on two occasions after a cardiac arrest; the first during the right-side pulmonary resection, the other eighteen (18) days after the transplantation and four days before the discovery of the fistulation between the trachea and oesophagus.

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.

Karolinska Institutet thus finds that Gerdin’s statement of opinion has been of great value to the inquiry process and that it has drawn attention to deficiencies in the activities on which the six papers are based. However, the main issues addressed and criticised by both the complainants and Gerdin have been satisfactorily countered by Macchiarini and his co-authors, and so there is nothing to support the complainants’ suspicions of scientific misconduct. The question of whether an author other than the lead author is guilty of carelessness or scientific misconduct falls outside the scope of this inquiry, which was conducted in response to the allegations levelled against Macchiarini.

Finally, Karolinska Institutet notes that Gerdin’s inquiry addresses a number of issues that must be dealt with at a general level to develop a more thorough set of rules for the translation of research and development of new therapies in the field of regenerative medicine.

Decision

All things considered, Karolinska Institutet finds that Professor Paolo Macchiarini is not guilty of scientific misconduct. Certain circumstances that have arisen during the inquiry concerning Professor Macchiarini’s work show, however, that it does not meet the university’s high quality standards in every respect.

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

- 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.
- Karolinska Institutet is to review its procedures, rules and support structures for clinical studies, clinical therapy research and clinical trials with a mind to
improving coordination between the two institutions involved – the university (Karolinska Institutet) and academic healthcare (Karolinska University Hospital). Karolinska Institutet should also investigate the need for a greater degree of centralisation of activities concerning experimental and clinical therapy research on humans, and experimental therapy for seriously ill patients.

- The concept of "vital indication" as grounds for the use of novel therapy should be further investigated in consultation with representatives of Karolinska University Hospital and national/international experts in order that clear guidelines and procedures for central decisions on vital indication can be established.

- Karolinska Institutet’s experiences from this now concluded inquiry are to be communicated to ongoing national investigations into how suspicions of scientific misconduct should henceforth be managed and investigated.

- The division between clinical application and research as regards experimental therapy is to be defined and formulated though clear guidelines for the university hospital and university.

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:

2. Complaint to Karolinska Institutet, submitted 24 September 2014 by Matthias Corbascio, Thomas Fux, Karl-Henrik Grinnemo and Oscar Simonson
3. Complaint to Karolinska Institutet, submitted 24 June 2014 by Oscar Simonson, Matthias Corbascio and Karl-Henrik Grinnemo
4. Comments on the complaint by Paolo Macchiariini, submitted 6 April 2015
6. Paolo Macchiarini’s comments on the statement of opinion, submitted 24 June 2015
7. Comment on the statement of opinion by Evren Alici
8. Comment on the statement of opinion by Antonio Beltrán Rodríguez
9. Comment on the statement of opinion by Pontus Blomberg
10. Comment on the statement of opinion by Béla Bozóky
11. Comment on the statement of opinion by Matthias Corbascio, Thomas Fux, Karl-Henrik Grinnemo and Oscar Simonson
12. Comment on the statement of opinion by Claire Crowley
13. Comment on the statement of opinion by Tómas Guðbjartsson and Óskar Einarsson
14. Comment on the statement of opinion by Johannes Haag
15. Comment on the statement of opinion by Gert Henriksson
16. Comment on the statement of opinion by Ola Hermanson
17. Comment on the statement of opinion by Philipp Jungebluth
18. Comment on the statement of opinion by Jan-Erik Juto
19. Comment on the statement of opinion by Sylvie Le Guyader
20. Comment on the statement of opinion by Bertil Leidner
21. Comment on the statement of opinion by Greg Lemon
22. Comment on the statement of opinion by Mei Lim Ling
23. Comment on the statement of opinion by Mei Ling Lim, Philipp Jungebluth, Johannes Haag and Sebastian Sjöqvist, and the complaint of COI directed against Professor Emeritus Bengt Gerdin
24. Comment on the statement of opinion by Guido Moll, Katarina Le Blanc and Bo Nilsson
25. Comment on the statement of opinion by Sebastian Sjöqvist
26. Comment on the statement of opinion by Staffan Strömblad
27. Comment on the statement of opinion by Tolga Sutlu
28. Comment on the statement of opinion by Ana Isabel Teixeira
29. Comment on the statement of opinion by Daniel J Weiss, Stephen Badylak and Arthur Caplan
30. Official note regarding permits from the local ethics committee
31. Guidelines issued by the International Society for Stem Cell Research (ISSCR)
32. Letter from Cengiz Gebitekin and Adnan Sayar
33. Source material for decision by Karolinska University Hospital, supplied by Paolo Macchiarini