

Vice-Chancellor Anders Hamsten
Karolinska Institutet
SE-171 77 Stockholm

Assignment ref: 2-2184/2014

Having been tasked with issuing a statement of opinion on seven papers with principal or co-authors from Karolinska Institutet (KI) concerning indications of scientific misconduct or other irregularities, I hereby submit the following observations.

Uppsala 13 May 2015

Bengt Gerdin Professor emeritus

Statement of opinion on assignment ref. 2-2184/2014

Assignment

This assignment has, with the support of chap.1 section 16 of the Higher Education Ordinance, been initiated as a response to two complaints requesting an investigation of scientific misconduct submitted to the Vice-Chancellor of Karolinska Institutet (KI). The assignment (ref. 2-2184/2014), which is reproduced in its entirety in the appendix, involves issuing a special statement of opinion in which it shall be judged whether or not scientific misconduct has occurred.

According to the written assignment description, this investigation was occasioned by the complaint that was made to the Vice-Chancellor on 24 June 2014. After conversations with the Vice-Chancellor and with KI's legal department, it was also made clear that it also includes an investigation of suspected misconduct described in the complaint dated 18 August. The investigation has therefore been conducted accordingly.

In January 2015, lawyer Christian Olofsson was asked to assist the inquiry on the juridical aspects of judging the claims of scientific misconduct and related issues.

The process of the investigation is described in the appendix.

The two complaints

The first complaint

was submitted by Oscar E Simonson, Matthias Corbascio and Karl-Henrik Grinnemo, is dated 24 June 2014 and concerns scientific misconduct as regards the following paper:

Sebastian Sjöqvist, Philipp Jungebluth, Mei Ling Lim, Johannes C Haag, Ylva Gustafsson, Greg Lemon, Silvia Baiguera, Miguel Angel Burguillos, Constantino Del Gaudio, Antonio Beltran Rodriguez, Alexander Sotnichenko, Karolina Kublickiene, Henrik Ullman, Heike Kielstein, Peter Damberg, Alessandra Bianco, Rainer Heuchel, Ying Zhao, Domenico Ribatti, Cristian Ibarra, Bertrand Joseph, Doris A Taylor and Paolo. Macchiarini (2014). Experimental orthotopic transplantation of a tissue-engineered oesophagus in rats." Nature Communications 5: 3562.

This paper is henceforth referred to as Sjöqvist et al.

The second complaint

was submitted by Matthias Corbascio, Thomas Fux, Karl-Henrik Grinnemo and Oscar Simonson, is dated 18 August 2014, with an addendum dated 24 September 2014, and concerns scientific misconduct as regards the following six papers:

The first of these is:

Philipp Jungebluth, Evren Alici, Silvia Baiguera, Katarina Le Blanc, Pontus Blomberg, Béla Bozóky, Claire Crowley, Oskar Einarsson, Karl-Henrik Grinnemo, Tomas Gudbjartsson, Sylvie Le Guyader, Gert Henriksson, Ola Hermanson, Jan Erik Juto, Bertil Leidner, Tobias Lilja, Jan Liska, Tom Luedde, Vanessa Lundin, Guido Moll, Bo Nilsson, Christoph Roderburg, Staffan Strömblad, Tolga Sutlu, Ana Isabel Teixeira, Emma Watz, Alexander Seifalian and Paolo. Macchiarini (2011). "Tracheobronchial transplantation with a stem-cell-seeded bioartificial nanocomposite: a proof-of-concept study." Lancet 378(9808): 1997-2004.

This paper is henceforth referred to as paper 1, in keeping with the numbering used by the complainants.

The second is:

Stephen F Badylak, Daniel J Weiss, Arthur Caplan and Paolo. Macchiarini (2012). "Engineered whole organs and complex tissues." Lancet 379(9819): 943-952.

This paper is henceforth referred to as paper 2, in keeping with the numbering used by the complainants.

The third is:

Philipp Jungebluth, Johannes C Haag, Mei Lim Lim, Greg Lemon, Sebastian Sjöqvist, Ylva Gustafsson, Fatemeh Ajalloueian, Irina Gilevich, Oscar E Simonson, Karl H Grinnemo, Matthias Corbascio, Silvia Baiguera, Constantino Del Gaudio, Staffan Strömblad and Paolo. Macchiarini (2013). "Verification of cell viability in bioengineered tissues and organs before clinical transplantation." Biomaterials 34(16): 4057-4067.

This paper is henceforth referred to as paper 3, in keeping with the numbering used by the complainants.

The fourth is:

Constantino Del Gaudio, Silvia Baiguera, Fatemeh Ajalloueian, Alessandra Bianco and Paolo. Macchiarini (2014). "Are synthetic scaffolds suitable for the development of clinical tissue-engineered tubular organs?" J Biomed Mater Res A 102(7): 2427-2447.

This paper is henceforth referred to as paper 4, in keeping with the numbering used by the complainants.

The fifth is:

Philipp Jungebluth and Paolo. Macchiarini (2014). "Airway transplantation." Thorac Surg Clin 24(1): 97-106.

This paper is henceforth referred to as paper 5, in keeping with the numbering used by the complainants.

The sixth is:

Fatemeh Ajalloueian, Mei Ling Lim, Greg Lemon, Johannes C Haag, Ylva Gustafsson, Sebastian Sjoqvist, Antonio Beltran-Rodriguez, Constantino Del Gaudio, Silvia Baiguera, Alessandra Bianco, Philipp Jungebluth and Paolo. Macchiarini (2014). "Biomechanical and biocompatibility characteristics of electrospun polymeric tracheal scaffolds." Biomaterials 35(20): 5307-5315.

This paper is henceforth referred to as paper 6, in keeping with the numbering used by the complainants.

Both the terms “graft” and “prosthesis” appear in the papers and the complaints. The investigator has opted to use the word prosthesis to denote the artificial, synthetic structure used to replace the trachea and the oesophagus in the different papers.

Assessment documents and process

Chap.1 section 16 of the Higher Education Ordinance provides that “a higher education institution that receives a complaint or becomes aware in some other way of suspected misconduct in research, artistic research or development work at the higher education institution shall investigate the suspicions”.

KI has received two such complaints. The first was submitted by Oscar E Simonson, doctoral student at KI and physician at Karolinska University Hospital (herein under referred to as “Karolinska”), Matthias Corbascio, docent at KI and physician at Karolinska, and Karl-Henrik Grinnemo, researcher at KI and physician at Karolinska.

The second complaint was submitted by Matthias Corbascio, Thomas Fux, doctoral student at KI and physician at Karolinska, Karl-Henrik Grinnemo and Oscar Simonson.

The person accused of scientific misconduct is Paolo Macchiarini, who on 1 December 2010 began a three-year temporary post as visiting professor of regenerative surgery at the Department of Clinical Sciences, Intervention and Technology (CLINTEC) at KI combined with the position of senior physician. The post was renewed by decision of the Vice-Chancellor on 1 December 2013, ending 30 November 2015.

As source documentation for this assessment, the investigator has had access to the seven papers, with online supplements when necessary. The investigator has also had access to the following material.

With respect to the first complaint:

“*Formal appeal...*” dated 24 June 2014, addressed to the Vice-Chancellor of KI, and signed by Oscar Simonson, Matthias Corbascio and Karl-Henrik Grinnemo.

Reply from Paolo Macchiarini, undated as far as the investigator can judge, sent to KI after the first complaint and before 3 August 2014.

Digital photographs relating to the controversial CT scan, laboratory records used by Sebastian Sjöqvist in the original, and data on the weight changes in the animals, the results of which have been challenged.

With respect to the second complaint:

“*Formal appeal...*” dated 18 August 2014, addressed to the Vice-Chancellor of KI, and signed by Matthias Corbascio, Thomas Fux, Karl-Henrik Grinnemo and Oscar Simonson.

“Analysis of clinical outcome of Synthetic Tracheal Transplantation Compared to results published in 6 articles by Macchiarini et al.” dated August 2014 and signed by Matthias Corbascio, Thomas Fux, Karl-Henrik Grinnemo and Oscar Simonson.

“Amendment to the formal appeal for an investigation...” dated 24 September 2014 and signed by Matthias Corbascio, Thomas Fux, Karl-Henrik Grinnemo and Oscar Simonson.

Statements from senior physician Richard Kuylenstierna, Karolinska, dated 30 November 2014 and 4 February 2015 and a text titled “Case 3”.

Paper copies of medical records (case books) from Karolinska. The investigator requested, via KI, access to all medical records for the three patients concerned, proposing that the digital records be read in the presence of staff from Karolinska in order to assure the investigator that all material could be identified, which would also entail having access to all laboratory tests, referrals, referral statements and other scanned material. Consent to this was not given, leaving the investigator to work on the assumption that the paper copies of the medical records provided are complete. A specific request was to obtain access to all test results available from Karolinska’s pathology-anatomy laboratory.

Paolo Macchiarini was asked, via his head of department, on 14 January to hand over those parts of the source material on which the relevant studies are based (see appendix). Paolo Macchiarini’s reply is dated 6 April 2015.

The investigator also had access to letters from the Medical Products Agency (LMV) to the head of the Ear Nose and Throat unit at Karolinska dated 16 April 2015 (ref. 6.3-2015-03429) concerning the treatment of patients with a stem cell-modified synthetic trachea.

The assignment issued by the Vice-Chancellor is to judge on the basis of an article review and all other documents whether scientific misconduct has occurred. The assignment is thus, in the first instance, to support KI’s own investigation into the suspicions of misconduct that have been presented. Since the research being questioned has been published in papers with several authors, the assignment also includes ascertaining the extent to which the various co-authors can be held to account for any such misconduct.

No detailed review has been made of all original material on which the publications in question are based and which has not been included in the complaint.

The basic purpose of the assignment does not entail assessing other possible irregularities, such as regarding the medical appropriateness of specific medical interventions or the subsequent care provided. It has not, however, been possible to avoid such matters. Since the complaints contain a good deal of information that potentially influence the assessment of scientific misconduct but that might also reflect shortcomings in the care provided and/or violations of pharmaceuticals legislation or legislation concerning “research involving humans”, the investigator has opted to also mention such incidents and in certain cases propose means for their investigation.

During the investigation a question arose on whether Paolo Macchiarini had been collaborating with, or had financial interests in companies that he was duty bound to declare in connection with the publication of the papers. The investigator has not had the necessary documentation to judge whether Paolo Macchiarini has had an interest that ought to have been declared.

The assignment has required, up to a point, a detailed analysis of how certain research data has been used and interpreted. The sections in the text below, which analyses certain studies and findings in more detail, expound upon this.

The investigator has based his assessment of whether or not scientific misconduct has occurred on the following:

1. The European Code of Conduct for Research Integrity, www.esf.org, www.allea.org
2. Accepted Scientific Practice: Swedish Research Council report series 1:2011
3. The Act concerning the Ethical Review of Research Involving Humans (hereinunder referred to as the Ethical Review Act) (SFS 2003:460)
4. <http://codex.vr.se>
5. The Committee on Publication Ethics (COPE), <http://publicationethics.org>

The text of the investigation has been largely written by the investigator personally. Lawyer Christian Olofsson has read the entire text and consulted with the investigator on the parts that are decisive in respect of the legal interpretation of whether scientific misconduct has occurred.

The ethical perspective

Since this investigation concerns scientific misconduct, there is reason to establish whether that which has been questioned by the complainants can even be considered “research” in the first place. This is particularly important because several statements submitted to this investigation express a view that certain aspects of what has been questioned by the complainants are not covered by the specific regulations that pertain to “research involving humans”.

The law

Research involving humans is regulated in the Ethical Review Act, section 1 of which reads:

This statute contains regulations concerning the ethical vetting of research concerning humans and biological material from humans. It also contains regulations concerning consent to such research. The purpose of the act is to protect individuals and human dignity when research is conducted.

Section 2 of the Ethical Review Act reads:

In this statute “research” refers to: scientific, experimental or theoretical work to obtain new knowledge and developmental work on a scientific basis, with the exception of that which is carried out as part of a programme of study at an institute of higher education at a basic or advanced level.

Section 4 of the Ethical Review Act reads:

*This statute is to be applicable to research that
...involves a physical intervention affecting a person who is participating in the research
...concerns studies of biological material that has been taken from a living person and that can be traced back to that person.*

Section 6 of the Ethical Review Act reads:

Research that is referred to [above] may only be conducted if it has been approved subsequent to an ethical vetting.

The Ethical Review Act does not cover the healthcare sector specifically, except in one respect, that which could be referred to as the “development work on a scientific basis” done therein (section 2).

Research or mere healthcare?

The statements to this investigation, which will be mentioned later, demonstrate that the line between research and healthcare can appear rather vague at times. Healthcare is characterised by the treatment of individual patients and is required by the Health and Medical Services Act (HSL) to be of “good quality”. The development of the healthcare sector is based on scientific activity and is defined as “research”; this can also be reworded as “research forms the basis of healthcare development”. This is supported by the definition in the Ethical Review Act, which provides an overall definition of research as *scientific, experimental or theoretical work to obtain new knowledge and developmental work on a scientific basis*.

A fundamental principle of research is the publication of its results in scientific journals or corresponding media. Conversely, it can also be said that all original material published in a scientific journal after peer review and intended to disseminate knowledge is research in one form or another.

In healthcare there is no explicit legislation demanding written consent from the patients prior to different treatments; on the other hand, the law pertaining to “research involving humans” demands in effect such consent before participation in a research project. The form this consent takes is an important aspect of an ethical review and is decided in the licensing process on a project-by-project basis.

The concept of misconduct

While the Higher Education Ordinance and the ordinance with instructions for the Central Ethical Review Board used the term “misconduct in research”, the Swedish Research Council also uses the synonymous “scientific misconduct”. This term has an inherent ambiguity as regards definitions and gravity, upon which the investigator would first like to comment. In its “Accepted Scientific Practice: Swedish Research Council report series 1:2011”, the Swedish Research Council’s expert committee for ethics has developed the concept of misconduct more generally and chosen, for Sweden, a narrow definition, which reads:

Scientific misconduct denotes actions or failures to act related to research that, deliberately or out of negligence, lead to false or distorted results, or that give misleading information about a person’s contribution to the research project (investigator’s emphasis).

The European Code of Conduct for Research Integrity published in March 2011 and adopted by a) the European Research Foundation (ESF), with the Swedish Research Council (VR), the Swedish Research Council for Environment, Agricultural Sciences and Spatial Planning (FORMAS), the Swedish Council for Working Life and Social Research (FAS) and the Bank of Sweden Tercentenary Foundation as members, and b) the All European Academies (ALLEA), with the Royal Swedish Academy of Sciences as member, takes a broader perspective, as evidenced by the following extract:

Both the definition of scientific misconduct and the specification for proper scientific practice are based upon principles of scientific integrity. These are principles that all scientific and scholarly researchers and practitioners should observe individually, among each other and toward the outside world. These principles include the following:

- *Honesty* in presenting research goals and intentions, in precise and nuanced reporting on research methods and procedures, and in conveying valid interpretations and justifiable claims with respect to possible applications of research results.
- *Reliability* in performing research (meticulous, careful and attentive to detail), and in communication of the results (fair and full and unbiased reporting).
- *Objectivity*: interpretations and conclusions must be founded on facts and data capable of proof and secondary review; there should be transparency in the collection, analysis and interpretation of data, and verifiability of the scientific reasoning.
- *Impartiality* and *independence* from commissioning or interested parties, from ideological or political pressure groups, and from economic or financial interests.
- *Open communication*, in discussing the work with other scientists, in contributing to public knowledge through publication of the findings, in honest communication to the general public. This openness presupposes a proper storage and availability of data, and accessibility for interested colleagues.
- *Duty of care* for participants in and the subjects of research, be they human beings, animals, the environment or cultural objects. Research on human subjects and animals should always rest on the principles of respect and duty of care.
- *Fairness*, in providing proper references and giving due credits to the work of others, in treating colleagues with integrity and honesty.
- *Responsibility for future science generations*. The education of young scientists and scholars requires binding standards for mentorship and supervision.

The European Code of Conduct for Research Integrity; section 2.2.3 Integrity in science and scholarship: principles

Violation of these overarching standards constitutes scientific misconduct. This perspective means that the definition of misconduct is wider than that offered by VR, and includes

“Other forms of misconduct include failure to meet clear ethical and legal requirements such as misrepresentation of interests, breach of confidentiality, lack of informed consent and abuse of research subjects or materials. Misconduct also includes improper dealing with infringements, such as attempts to cover up misconduct and reprisals on whistleblowers;”

VR’s narrow definition of scientific misconduct does not therefore cover certain censurable research-related behaviour as is included in the definition given by the European Code of Conduct for Research Integrity, such as breach of confidentiality, violation of drug laws, or violation of the Ethical Review Act. This is not based on the idea that such behaviour is less censurable but on the fact that it is regulated by other legislation and entails criminal liability.

This investigation is based on VR’s narrow definition of scientific misconduct. We have, however, also pointed out that certain actions might constitute a breach of healthcare and pharmaceuticals legislation and the Ethical Review Act.

VR’s narrow definition of scientific misconduct thus talks of actions or failures to act related to research (investigator’s emphasis). In reality, however, suspicions of misconduct arise after a reading of the text that is submitted for publication or that has been published, i.e. primarily with respect to the selection, analysis and presentation of research results. The definition also, however, encompasses quality deficiencies during the actual conducting of the research; the European Code of Conduct for Research Integrity states that the work is to be “*meticulous, careful and attentive to detail*”. It should be noted that the authors’ scientific interpretation of the data presented (i.e. the authors’ personal opinions) is not judged to constitute misconduct. Insofar as these interpretations go beyond what the results would warrant, this is expected to

be pointed out in the peer reviews conducted by the journals' Editorial Boards and reviewers. On the other hand, the concept of misconduct does cover the deliberate, even careless selection of certain data that support a particular interpretation and the omission of other received data that contradict it.

The concept of scientific misconduct does not presume that the actions or omissions are deliberate, but also covers careless conduct, such as result error caused by negligence or ignorance. VR says "deliberately or out of negligence" and The European Code of Conduct for Research Integrity uses the phrase "*intentionally, knowingly or recklessly*". In this investigation, we have, however, wherever possible, endeavoured to find circumstances that might indicate if any misconduct that might have been committed is a consequence of deliberate action or carelessness. This in order to facilitate any decisions that need to be made on sanctions. Concerning this point, VR (Accepted Scientific Practice: Swedish Research Council report series 1:201; p. 114) says:

The sanctions must naturally be in proportion to the degree of misconduct committed. Repeated or more extensive scientific misconduct is more serious than an isolated incident concerning one particular detail.

VR, thus, uses the term "degree of misconduct", which it associates with the action being "repeated" or "extensive". The investigator also deems the degree of severity to be determined by the extent to which the actions are deliberate and have no other intention than to give a different impression of reality than might objectively be considered to be the case. It is also determined by whether the actions concern results that are pivotal and fundamental to the scientific project and if this project depends entirely on the erroneous results presented.

A key question concerns the responsibility of the lead (primary/corresponding) author of a scientific paper. The investigator agrees with the general consensus of the scientific community that the lead author has more responsibility than the other authors for the content of a paper. Just how far this responsibility stretches is not self-evident. The investigator deems that the lead author has considerable responsibility but can not be held accountable for the results of each analysis contained within the scientific paper. The extent of the responsibility is clarified in the author declaration submitted to the different journals and is expressed in slightly different ways. If the lead author also has responsibility for the overriding research project, he must also ensure that research is conducted within the bounds of the law. He has personal responsibility to ensure that the necessary legal permits are in place for the research project he is conducting, in this case principally an ethical permit; that the data on which the paper is based are preserved and made accessible for reanalysis; and that each of his co-authors take responsibility for their parts of the paper's content. He also has responsibility for the overall impression the paper gives, i.e. the clarity and accuracy of the language. The journal *Nature* described the responsibilities of larger research constellations as follows:

Responsibilities of senior team members on multi-group collaborations.

Scientific Reports assume that at least one member of each collaboration, usually the most senior member of each submitting group or team, has accepted responsibility for the contributions to the manuscript from that team. This responsibility includes, but is not limited to: (1) ensuring that original data upon which the submission is based is preserved and retrievable for reanalysis; (2) approving data presentation as representative of the original data; and (3) foreseeing and minimizing obstacles to the sharing of data, materials, algorithms or reagents described in the work.

<http://www.nature.com/srep/policies/index.html>

The lead author also has shared responsibility with the journal in question to ensure that “*errata*” (corrections) are sent in to the journal if something should emerge to show that what has been presented is incorrect, or, if a paper contains serious errors, that a “retraction” is requested. If a disagreement arises amongst the group of authors after publication, each individual author has a moral duty to report to the journal whatever inaccuracies or errors he or she believes to exist.

The dominant journal publishers, including those responsible for the journals in which these seven papers have been published, are members of COPE (the Committee on Publication Ethics), which is a forum for editors and publishers that, amongst other things, gives guidance on all aspects of research publication ethics. COPE states in its publication guidelines that a journal shall consider the “retraction” of a publication if, for instance, it is the product of what is covered by the narrow definition of misconduct, but also if it is the product of unethical research. From a Swedish perspective, this latter term ought to include censorial behaviour in relation to research that is not covered by the narrow definition of misconduct but that is regulated in other legislation and may entail criminal liability.

Pharmaceuticals legislation

As mentioned above, The European Code of Conduct for Research Integrity includes in its definition of misconduct a failure to meet the requirements of other relevant legislation. Mention should be made here of pharmaceuticals legislation, for which LMV is the supervisory authority. This legislation regulates, amongst other things, “advanced therapy medicinal products”. In the Regulation of the European Parliament and of the Council (EC) no. 1394/2007 dated 13 November 2007 on pharmaceutical products for advanced therapy and on amendments to directive 2001/83/EC and regulation (EC) no. 726/2004, such a product is defined as “[one] that: – contains or consists of engineered cells or tissues, and – is presented as having properties for, or is used in or administered to human beings with a view to regenerating, repairing or replacing a human tissue” (article 2.1 b). Such products can be manufactured by an approved hospital laboratory for individual patients in accordance with separate regulations.

<https://www.lakemedelsverket.se/malgrupp/Halsosjukvard/Sjukhusundantagen/>

The “synthetic trachea” that has been manufactured in a bioincubator and that is one of the subjects of this investigation ought to constitute an “advanced therapy medicinal product” that is regulated by common EU law. This has recently been confirmed by the European Medicines Agency (EMA 328354/2014).

The complaint of 24 June 2014

Sjöqvist et al

This paper, which according to the journal website was received on 3 October 2013, was accepted on 5 March 2014 and published on 15 April 2014, describes the manufacture of a synthetic oesophageal prosthesis and the function of this prosthesis after grafting into a rat. The complaint concerns the description of the results in the paper as regards four specific points.

Point 1

The first complaint concerns the question of whether there is morphological support for the claim that the prosthesis was coated with an epithelium.

The questioned Figure 8 has the caption “*Imaging and functional assays of in vivo regenerated scaffold*” with sub-image 8a described as “*Contrast-enhanced computed tomography showed a smooth and patent oesophagus*”. According to the complainants, and as indirectly confirmed by Paolo Macchiarini, this study was conducted by Oscar Simonson, who was also the paper’s co-author when it was submitted and accepted for publication. Here it should be pointed out that the journal *Nature* does not demand that all authors sign a “Letter of submission”, but explicitly assumes that the author who had communicated with the journal can ensure “...that all the listed authors have agreed all of the contents.” When Simonson had seen the *proofs* of the paper, which according to the investigator ought to have been in later March or early April 2014, he asked to be removed from the list of authors. Simonson states in his complain that this was because he did not agree with the interpretation of the computer tomography image.

The paper contains no methodological description of how the study in question was carried out, at what point after the operation it was carried out, or if it was carried out on living or dead animals. Simonson has stated that the contrast agent was introduced via a tube that was inserted past the oesophageal prosthesis. On a direct request and as a part of this investigation, Simonson says that the study was carried out only five days after the operation, that the animal was alive when the study began but died during it, and that the tube used was probably an AgnTho’s 18G feeding catheter developed with an external diameter of 1.27 mm and an internal bore of 0.838 mm.

Paolo Macchiarini claims in his statement from the summer of 2014 that he did not know that the tube was inserted with the tip below the prosthesis.

The digital material from the study in question has been supplied by Simonson in the form of DICOM images. A digital tag on the material shows that the study was conducted on 30 April 2013. The images have been analysed by the radiological unit of Akademiska Hospital with the former chief of staff and consultant in radiology, Per Liss, MD, PhD. Figure 1 below, the four parts of which depict exactly the same projections, shows in essence the observations that could be made. A collective assessment of all images and possible reconstructions show that a contrasting agent was injected via a tube that has a tip resembling a nipple, or an olive, that was inserted through the oesophagus with the said tip in line with the manubrium sterni. The agent primarily filled the lower oesophagus and partially backwards and upwards (i.e. in a retrograde direction). In Figure 1A, the contrast agent-filled area in line with the tube tip has a diameter of 2.3 mm. A few millimetres above it, there is a retrograde-filled area of 2.2 mm (Figure 1B). In the centre of this area the tube is visible as a highly attenuated area. Another few millimetres above this (proximally) is the tube only, the diameter of which has been measured here at 0.85 mm (Figure 1C, bottom left). Also visible in this image are traces of contrast agent outside the tube 1.93 cm above the nipple. With a change in brightness, only the position of the tube is visible (Figure 1D, bottom right).

Figure 2 shows our own image reconstruction of the same material, in which we have tried to obtain the same projection as in the figure published in Sjöqvist et al. It is clear that the contour that the authors interpret as the oesophageal wall is actually the contrast agent-filled tube, the tip of which (A) is in line with the upper part of the breast bone (manubrium). The bottom centimetres above it (B) reflect the contours of the oesophagus that was filled with

contrast agent in a retrograde direction. The image material does not reveal if this retrograde-filled area constitutes the prosthesis or a native oesophagus; it is, however, located lower down the throat than where the authors state that the prosthesis was sewn in, which is higher up the throat at the point of the grey-marked zone and bracket in Figure 2a. Figure 3 below shows the same image material projected in two ways and demonstrates even more clearly that the structure that is visible and has the same diameter from the buccal cavity downwards is the contrast agent-filled tube.

All in all, our study shows that the contour that the authors have interpreted to be “*a smooth and patent oesophagus*” is not that. All that the study shows is that it was possible to pass the prosthesis with the tube that was used five days after the operation.

The computer tomography image (Figure 8a in the paper) thus does not show “an oesophageal prosthesis with a soft inner surface”.

As regards this point of criticism, the investigator notes that none of the paper’s authors, judging by what is written under the heading “*Author contributions*”, has taken responsibility for the CT scan. This is a departure from the Vancouver declaration, which states that “*Any part of an article critical to its main conclusions must be the responsibility of at least one author*”. It is also a departure from *Nature*’s own rule that “*Corresponding authors have multiple responsibilities, but we now make it clearer that the author list should include all appropriate researchers and no others*”, which in this context carries the same meaning. However, two of the authors’ contributions to the paper were described in terms of being “involved” in the imaging process: “*R.H. and Y.Z. were involved with CT scan*”.

Since the paper lacks a description of how the CT scan was performed, it is not possible for a reader to interpret its results. The fact that it is not explicitly stated at what point after the operation the scan was done has the same consequence. The most natural interpretation for a reader is that it was done when the postoperative period had come to a end, which is given as be 14 days after surgery. Nowhere in the paper is it mentioned that one or more of all the experiments that were done were concluded after five days, i.e. the point in time at which Oscar Simonson claims that the computer tomography was performed.

The laboratory records supplied are not written clearly enough to ascertain exactly how many animals were studied using computer tomography, which makes it hard to generalise the observation that was made. A rough interpretation of what is written is that it is a question of a few, perhaps 2 to 4 animals.

The circumstances surrounding the CT scans need comment. It is not unique for a member of an *ad hoc* assembled research group to choose to leave without sharing the original data for the results he or she has obtained and without taking part in the intellectual discussion of these results. In this case, complainant Oscar Simonson chose not to be a co-author of the scientific paper and broke off contact with the lead author, Paolo Macchiarini. Paolo Macchiarini has made explicit in this investigation that Simonson, who specialised in the computer tomographical study of small animals, was the only person in possession of detailed information about how the study was done. To the investigator’s mind, this implies that no one else in the research group had sufficient information on the study and its interpretation for it to be credibly presented and interpreted in a scientific paper. Irrespective of which scientific or interpersonal mechanisms are at the root of this situation, the lead author, Paolo Macchiarini, has responsibility for ensuring that all necessary original data have been made

accessible, can be and have been analysed in a satisfactory way before the paper is published. If this was not possible in this situation, the only scientifically correct course of action would have been to omit the CT study from the manuscript since none of the authors could vouch for its proper interpretation and presentation. That this was not done was careless at the least.

Another aspect of this is that the individual researcher has “ownership” of his or her own scientific results. Thus, in this case, Oscar Simonson owns the result of this study and the figure describing the result. Until the time of his asking to be omitted from the list of authors, he consented to his results being used in the article. It has not emerged from the investigation that Simonson asked for his results to be removed from the source documentation when retracted his authorship. His consent to the figure being used in the paper therefore remained.

It may be questioned whether Simonson’s contribution to the study should have appeared in an *acknowledgement* stating that he carried out the CT study. See *The European Code of Conduct*, which says that “*Intellectual contributions of others should be acknowledged and correctly cited*”.

All in all, the central question interpreted from a perspective of misconduct is not what the CT image shows or does not show, but if the authors at the time of writing the paper deliberately or carelessly presented the research results that had been obtained by another researcher to support the main thesis of the paper, even though none of the authors had any knowledge of critical methodological or interpretive details. The investigator finds that this indeed is the case.

Figure 1. Analysis of the photographic material for Figure 8 in Sjöqvist et al. Each set of three images shows identical sagittal (upper left) and frontal projections (upper right). In each set, the purple line in the sagittal and frontal projections shows the level of the transversal projection in the lower left. The light green lines show the measurements that have been made. A) Diameter of the contrast agent-filled area in line with the catheter tip. B) The area filled with contrast agent in a retrograde direction a few mm above the tip. C) A few more mm up we see only the tube, filled with contrast agent and with an internal diameter measured at 0.85 mm. Small amounts of contrast agent can be discerned outside the tube up to 1.93 cm above the catheter tip. D) Shows the same measurement position as C), but with a different attenuation. For further explanation, see the text.

Figure 2. a) is Figure 8a from Sjöqvist et al; b) to f) represent different ways of handling the same image projection. The red line A marks the level of the manubrium – and the position of the catheter tip. The red bracket B shows the part of the oesophagus filled with contrast agent in a retrograde direction from the catheter olive. The grey zone marks the position of the prosthesis as marked by the authors within the bracket in Figure 8a.

Figure 3. The same image material as in Figure 2 presented in two projections to obtain a better free projection of the structure of the throat.

Point 2

It was questioned whether the weight change after the insertion of the oesophageal prosthesis is such that one can talk about the animals having a functional oesophagus.

It is written in the abstract that “*All animals survive the 14-day study period, with patent and functional grafts, and gain significantly more weight than sham-operated animals.*” This claim is erroneous since there was no “*weight gain*” at all in the experiment, which is obvious from the results reported in the paper (see e.g. Figure 7c). Since correct data are reported later

in the article, the investigator does not consider the information in the Abstract to be so false or distorted as to constitute scientific misconduct. An observant reviewer should, however, have flagged the error.

As regards the animals' weight gain, the authors write in the results section, instead, that *"Interestingly, the transplanted animals' weight curves were significantly better than those of the sham surgery group from day 4 onward"*. These results are thus found in Figure 7c of the paper, which presents the postoperative weight changes in the rats both with and without a grafted synthetic oesophageal prosthesis. The animals used in this experiment were described as eight-week old male Sprague-Dawley rats, which in my own experience and according to the literature and information from the breeder should weigh roughly 250 grams. The supplied weight data obtained from the laboratory show, however, that the animals weighed 400 grams, which means that they were twelve weeks old rather than eight. Nowhere is it made explicit how many animals were used. The impression gained from the method section of the paper is that there were ten animals in each group. (*"Adult Sprague-Dawley rats (n=10) were anaesthetized...midline, cervical incision was made... The oesophagus was bluntly dissected and mobilized....resected and replaced with a reseeded, decellularized scaffold."*). The department states, however, that the figure was only based on four animals, two of which were controls. The investigator's own figure based on the animal weights supplied by the department was identical to the one in the paper. Here the correspondence ends, and the significant difference in weight development between the groups as presented, and on which the functionality criteria of the prosthesis in part rests, can not be reproduced, which was expected given the fact that the statistics were based on only two animals in each group.

The fact is that both groups demonstrate pronounced weight loss of 124, 128, 170 and 191 grams, which shows that the food intake was not adequate for any of the four studied animals. This weight loss is to be compared with the weight gain of a healthy, unoperated rat weighing 400 grams of roughly four grams per day, or approximately 50 grams for the duration of the study. After a relatively major operation, a rat's weight drops over the ensuing days to stabilise after about a week and then rise again – provided that the surgical intervention has not caused a significant functional disturbance of some kind. If the operated rats in this study had had a properly functional oesophagus, their weight loss should have levelled off and their weight stabilised or even increased during the final days of the experiment. This was not the case, as both groups displayed a steady decrease in weight. These data show that neither group had a sufficient intake of food during the study.

A closer analysis of Figure 7c in the paper also shows that the difference in body weight that was recorded between the two experimental groups emerged already during the first six or seven days of the experiment. Figure 4 below shows the cumulative percentage weight difference between the groups over time. As can be clearly seen, the difference between the groups appeared before day seven, after which the rate of weight loss was comparable between the groups. Figure 7c also shows that absolute weight losses actually accelerated during the last days of the experiment. A reasonable interpretation of this is that the causes of the observed difference between the experimental groups should be sought in what happened during the first week after surgery and not in the functionality of the oesophagus during the latter part of the experiment.

The data reported in the paper do not therefore support the authors' interpretations. In the investigator's opinion, however, this is not such a departure from accepted scientific practice

as constitutes scientific misconduct; instead, it is a question of the type of quality flaw that should have been dealt with at the peer review stage prior to publication.

Figure 4. Cumulative difference in percentage weight loss between the two experimental groups. Positive values reflect a greater weight loss in the control group.

Point 3

It is claimed that there are CT images showing that the oesophagus was not functional and that the authors opted to omit these photographs/this information.

The submitted digital material includes a study dated 3 June 2013 that indeed presents “*a rat...show [-ing? – Translator’s note] food and hair mixed with contrast fluid lodged in the proximal part of the reseeded oesophagus*”. The question is whether this observation can be generalised beyond this single rat. Everyone who has worked to any great extent with experimental studies using small animals knows that there is a considerable variation in outcome from one animal to the next, something that is particularly evident when the experiment involves “technical” measures, as in this study. Moreover, it is not uncommon for “poor” results to be seen during a technical learning phase. A scientific interpretation can therefore only be done on group data and not on analyses of single animals.

Point 4

Here it is questioned whether there is morphological support for claiming that the prosthesis is coated with epithelium.

Figure 7a is said to show GFP-positive cells fused with the synthetic oesophageal prosthesis. The photograph is difficult to interpret and it cannot be seen how the specimen has been sectioned and thus which projection has been used. On the other hand, the degree of magnification is relatively low, with the scale bar representing 50 μm . Even if the investigator can see the cells that the complainants cannot see, he cannot judge if the photograph shows “GFP-positive cells fused with the synthetic oesophageal prosthesis”. All in all, it cannot be determined from the source material whether there is no support for this claim in the paper.

Other critical comments on Sjöqvist et al

In addition to these four criticisms from the complainants, there are other dubious or weak points to consider in this paper.

In the Abstract, the authors write “*All animals survive the 14-day study period, with patent and functional grafts.*” The laboratory books submitted show that this claim is false. Several animals died, largely due to problems related to the prosthesis. The claim is not explained in the paper either, which means that information in the paper as a whole is, in any case, misleading.

Figure 7 shows an immunohistochemical staining for desmin, where it is claimed that positivity in the specimen suggests arteriole ingrowth; instead, the figure rather suggests the presence of pericyte-like phenotypes, which appear earlier in regenerated tissues than arterioles.

The investigator also notes a typographical error in line 2 of the second column of page 3, where it says: “...($E=0.12\pm 0.9$ and $E=0.15\pm 0.9$ for the native and decellularized oesophagus,

respectively, n=3; Fig. 2r,s) respectively.” The first margin of error should reasonably read 0.09, not 0.9. Moreover, it is meaningless to give the standard deviation for n=3.

It is not clear how the “*patency*” of the grafted oesophageal prosthesis has been calculated. This is described under the heading *Histological and functional graft evaluation post mortem* at the bottom of page 6. The method reference given is for a previous study by the main author conducted in 1995 in which the method was not used to calculate the “*patency*” of a rat oesophagus, but only that of grafted trachea in pigs. This was done using two perpendicular diameters. The measurement and analysis of the tracheal lumen is, of course, easy since the structure is “open” with a permanent lumen that is kept open by the tracheal rings. Furthermore, it ought to be possible to obtain relatively reproducible measures of these diameters on a much larger animal than a rat. In the study in question here, “*patency*” is “*expressed as a ratio between graft diameter and adjacent native oesophagus*”. It is plausible that one can measure two reproducible lumen diameters on the synthetic oesophageal prosthesis but how this is done for the adjacent oesophagus is hard to fathom, as it is normally in a collapsed state until a bolus passes through it, whereupon the one lumen diameter can approximate to zero. The investigator does not understand either how it is possible to obtain such precise measurements that the mean can be described in ten-thousandths, i.e. with an accuracy of 0.01%, as has been done here. Moreover, the measure for “*patency*” in the method’s reference section is given as a “*ratio*” between estimated cross-sections, and not a “*ratio between graft diameter and adjacent...*”.

Finally, the authors argue that the chosen postoperative period of 14 days is equivalent to a postoperative period of one year in humans. This temporal relativity might be true as regards age but not when it comes to basic biological processes. All healing processes do not go 26 times faster in rats than in humans simply because we live roughly 26 times longer. In the investigator’s opinion, however, this is not such a departure from accepted scientific practice as constitutes scientific misconduct; instead, it is a question of the type of quality flaw that should have been dealt with at the peer review stage prior to publication.

Over and above these comments, the investigator feels obliged to mention that the submitted laboratory records were poorly executed and lacked a good deal of information, and made it impossible to approach them in terms of traceability (i.e. the ability to follow an experiment from laboratory records to published paper, or vice versa). The investigator does not deem this to be such a departure from accepted scientific practice as constitutes scientific misconduct either.

General opinions

The main result of this study is, according to the paper’s discussion, “*...the successful development and transplantation of a decellularized donor oesophagus...that yields a functional graft in vivo...*” The assertion that the prosthesis works is thus a validation of the claim that the technical development work actually produced something that could be called a clinically usable prototype. Explicitly, this means that the functional results of the *in vivo* experiments in which the prosthesis was implanted into the right place (orthotropic transplantation) on the throat of the rat is critical to the paper’s scientific value. Even if the same quality requirements apply to all published science, it is the investigator’s view that the authors should show extra care with the results that actually support, or validate, the paper’s primary, or key message.

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 – in this case the CT study of an operated rat oesophagus – is a departure from accepted scientific practice. Further, the authors, due arguably to their lack of insight into how the study was conducted, 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 has responsibility for this circumstance, which constitutes scientific misconduct.

All other points raised by the complainants and examined by the investigator 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. The investigator lacks the grounds to state unequivocally that this evinces such disregard as constitutes a departure from accepted scientific practice. Since the faults are such that the readers of the paper risk misinterpreting the results presented, the journal should still be informed of them and of the circumstances described above.

The complaint of 18 August 2014, with amendment dated 24 September 2014

In this complaint, it is argued that papers 1 to 6 are instances of scientific misconduct. These papers concern operations and postoperative follow-ups of three patients at Karolinska who each received a synthetic tracheal prosthesis, referred to by the complainants as cases 1, 2 and 3. The investigator will refer to them here as patients 1, 2 and 3.

Roughly speaking, the criticism can be broken down into four parts. Firstly, there is the central question of research ethics – i.e. whether an ethical permit has been received as legally required for “research involving humans”. Secondly, there is the question of what knowledge the authors could be expected to have had about the clinical condition of the patient(s) when the paper was submitted for publication. Thirdly, there is the omission of important information about the patients' clinical condition, which has led to a false, embellished picture. And fourthly, there is the question of a violation of pharmaceuticals legislation.

Given that the complainants repeat certain critical opinions for multiple papers, the investigator has chosen to comment upon them in one context only – i.e. when dealing with the paper in which they were first made.

The three patients

Below is a brief summary of the three patients.

Patient 1

This patient is a 36-year-old man of Eritrean origin who was living on Iceland and who underwent a primary operation in Reykjavik in October 2009 for mucoepidermoid tracheal cancer localised in line with the carina. The operation became complicated with perforation of a bronchus, the azygos vein and a branch of the pulmonary artery. Postoperatively, the patient contracted a fungal infection and miliary tuberculosis. After a lengthy and complicated

postoperative process, he received a full dose of radiation, after which his condition improved. Early in 2011 a clinically suspicious recurrence in the form of a bronchial stricture was noticed on the right-hand side. This necessitated contact with Paolo Macchiarini and Karolinska. After an administrative process, he was operated on at Karolinska on 9 June 2011, upon which the bottom of the trachea and its subdivision into two main bronchi were removed and replaced by a synthetic tracheal prosthesis which had apparently been manufactured by University College, London, and then imported to Sweden for seeding with the patient's own stem cells in a bioreactor. A month following the operation, he was returned to Iceland for further observation. He returned regularly to Karolinska for check-ups, however, and for treatment of a growing fistula system that eventually developed into a life-threatening oesophago-tracheal fistula. Following increasingly aggressive attempts to operate, he died on 30 January 2014, 30 months after having received his synthetic tracheal prosthesis.

Patient 2

This patient is a 30-year-old American man from Maryland who was diagnosed in June 2011 with adenoid cystic tracheal cancer, which in the US was deemed inoperable. He was given radiation treatment for the tumour which caused it to shrink. After having done a search on the internet, the patient made contact with Paolo Macchiarini himself, who, on assessing the patient, referred him to Karolinska for the surgical removal of the tumour and replacement with a synthetic tracheal prosthesis made of another kind of plastic than that used for patient 1 5.3 months beforehand and that had not been used before. It was apparently not possible to operate on the patient in the USA as the material had not been licensed by the FDA for use. The operation was carried out on 17 November 2011 at Karolinska. The prosthesis was, as far as can be judged, manufactured by Harvard Bioscience Inc in Boston and imported to Sweden. The patient was sent home in January 2012, after which he said in interview with CBS and others on 16 January, *“Right now I am cancer free. I am happily cancer free, so now it's just the daily routine of getting stronger and getting back together.”* There is no formal information from the USA about what happened after this, but he was apparently rushed to hospital a little over a month later and died on 5 March 2012, 3.6 months after his operation at Karolinska and 49 days after the CBS interview. His parents have chosen not to publicise the cause of death.

Patient 3

This patient is a 22-year-old woman from Ordu in northern Turkey, who received iatrogenic tracheal damage in connection with surgery for palmar hypohydrosis, probably a thoracoscopic sympathectomy, and the attempts to repair the damage failed. Her doctor in Turkey contacted Paolo Macchiarini, who met the patient in the spring of 2012. A pre-operative examination was carried out, during which she had to wait four months for an operation. The complainants claim, with the support of her medical history, that her clinical condition was stable and did not deteriorate during this time. She was operated on at Karolinska on 24 July 2012, upon which her right lung was removed in order to prepare for the insertion of a synthetic tracheal prosthesis. On 7 August 2012, after having stabilised and been treated for infection, she was given a tracheal prosthesis made of the same or a similar material as that used for patient 2 (the investigator has been able to establish which), and manufactured by Nanofiber Solutions in Columbus, Ohio. Already two weeks after this operation, an oesophageal fistula appeared that was treated with a stent on several occasions. Owing to “material fatigue” and “collapse”, she was re-operated on 11 months later, on 9 July 2013, and given a new prosthesis of the same material. Following extensive postoperative fistula-related complications, she was put in intensive care at Karolinska, 2.5 years after the first operation, with serious respiratory problems.

Paper 1

Jungebluth P, Alici E, Baiguera S, Le Blanc K, Blomberg P, Bozoky B, et al. Tracheobronchial transplantation with a stem-cell-seeded bioartificial nanocomposite: a proof-of-concept study. *Lancet* 2011; 378: 1997-2004.

This paper, which features patient 1, reports on the result of the first transplantation of a synthetic trachea in a human. This paper is a key reference for the other papers.

The complainants state that the paper was submitted to *The Lancet* back on 11 October 2011 and refer to the direct contact that was had with its editorial assistant. Paolo Macchiarini has presented documentation to show that it was accepted on 7 November, that proofs were sent to the authors for approval on 8 November and that revised proofs were sent on 10 November. The paper was published online on 24 November and in print on 10 December 2011.

The investigator notes, initially, that one of the complainants, Karl-Henrik Grinnemo, is a co-author of, and thus partly responsible for this paper, which was submitted for publication 34 months before the report of scientific misconduct was made. The investigator also notes that all authors, according to *The Lancet's* authorship rules, signed the following declaration:

I agree with: the plan to submit to The Lancet; the contents of the manuscript; to being listed as an author; and to the conflicts of interest statement as summarised. I have had access to all the data in the study (for original research articles) and accept responsibility for its validity.

Below are the complainants' main arguments, itemised, and our interpretation of the alleged faults.

The authors write in the paper's summary that "*There were no major complications, and the patient was asymptomatic and tumour free 5 months after transplantation.*"

The paper was submitted, as already mentioned, to *The Lancet* on 11 October 2011, which was 124 days (or 4.1 months) after the operation, and accepted after extensive revision, according to the documents received from Paolo Macchiarini on 7 November, exactly five months after the operation. It is not impossible that on revision the follow-up time could be corrected to almost the stated "5 months".

Paolo Macchiarini states that Karl-Henrik Grinnemo sent a mail to author Jungebluth on 29 August, i.e. 2.7 months after the operation, containing the underlying text for the part of the paper dealing with the postoperative process in which he described a good clinical condition on discharge, which apparently took place on 8 July, a month after the operation. Paolo Macchiarini states that none of his clinical colleagues in the research group informed him that no change subsequently occurred. Paolo Macchiarini writes nothing to explicitly support the claim in the text that the patient's clinical condition five months after the operation was based on known facts at that time.

The underlying texts also reveal that the patient was treated on Iceland before and after the five-month stretch and re-admitted to Karolinska after about 5.5 months on 21 November, which was three days before the paper was published online. At this time, the patient was in a poor state, had lost 7 kg, and showed signs of a defective right lung. While the results of

the examinations carried out on Iceland before the patient was readmitted to Karolinska were not included in our investigation material, it is extremely likely that the patient was asymptomatic after five months, i.e. 14 days before re-admission to Karolinska. It should be noted here that while on Iceland, the patient should have been in the care of one of the paper's two Icelandic authors. It would have then been possible, even easy, to ensure the patient's correct clinical condition after five months.

All in all, there is no documentation to show on what the authors support their claim that "*...the patient was asymptomatic and tumour free 5 months after transplantation*".

Further, the authors write in the paper's summary that: "*...5 months after transplantation. The bioartificial nanocomposite has patent anastomoses, lined with a vascularised neomucosa, and was partly covered by nearly healthy epithelium.*" The complainants claim that there is nothing on record to back this up.

There is no support for this claim in the documents we have received. The paper states that "*Control endoscopies were done postoperatively daily for the first 7 days, for inspection of the graft and anastomoses. Bronchoscopies were then done once a week during admission to hospital, and once a month thereafter.*" The investigator finds that bronchoscopies were done on days 1, 7, 9, 10, 11, 12, 13, 21, 56, 61, 68 and 76 after the tracheal prosthetic graft. In the descriptions of most of these, there is no mention of the biopsies being taken. PAD from bronchoscopic material taken on 4, 16 and 24 August, i.e. 56 days (8 weeks), 68 days (10 weeks) and 76 days (11 weeks) after the operation, show results that are inconsistent with the "partly covered by nearly healthy epithelium" claim. The PAD description of a mucosa biopsy after eight weeks (i.e. two months) that is found in the records – "individual mesenchymal cells and no well-developed cell layer" – is inconsistent with the image given in Figure 2B v-vi, in which a respiratory epithelium is clearly visible. This discrepancy cannot be explained.

The paper states that: "*1 week after surgery, the bronchoscopy (webvideo 3, figure 2A) showed a normal and patent airway bleeding from its inner layer at the contact with the scope; the obtained biopsy samples showed the presence of necrotic connective tissue associated with fungi contamination and neoformed vessels (figure 2B).*"

The complainants state that there is no information in Karolinska's medical records system to show that the alleged biopsy was taken and/or analysed. The investigators have not found this biopsy in the records received from Karolinska either. There are thus no grounds on which this claim can be verified.

The paper states that: "*The biopsy sample 2 months after transplantation showed large granulation areas with initial signs of epithelialisation and more organised vessel formations, and no bacterial or fungi contamination (figure 2B).*"

The complainants claim that the first documented biopsy was taken on 4 August 2011, i.e. eight weeks after the operation. The investigators have examined the PAD result for this biopsy in the records from Karolinska's pathology unit. The content of the PAD result does not support the claim made in the paper.

The paper states that: "*5 months after transplantation, the patient is asymptomatic, breathes normally, is tumour free, and has an almost normal airway.*"

This claim is addressed above and nowhere has the investigator found any material to support it.

The paper states that: *“The initial fungal infection had resolved within 4 months from transplantation; later the endoluminal surface was partly lined with respiratory mucosa, at which we noted nearly healthy epithelium and proliferating endothelium.”*

According to the complainants, there is no information about the circumstances after four months in Karolinska’s records system. Paolo Macchiarini says in his reply that the paper says “within 4 months” and that everything is based on information from Karl-Henrik Grinnemo, who described the patient’s status on discharge in a mail of 29 August 2011, i.e. 2.7 months after the operation. This description implies that there were no signs of “active infection” at the time of the patient’s discharge.

The paper states that: *“Taken together, these results provide evidence that a successful organ regeneration strategy has been accomplished (panel). The successful overall clinical outcome of this first-in-man bioengineered artificial tracheobronchial transplantation provides ongoing proof of the viability of this approach.”*

The complainants maintain that this claim lacks support. The passage refers to observations made after four months. In the investigator’s view, it is an exaggerated and unscientific use of language to use phrases such as *“successful overall clinical outcome”* and *“successful organ regeneration strategy”* based only on the circumstances for the first four months after transplantation of the tracheal prosthesis, during which the authors were not able to show any convincing results showing that any regeneration at all had occurred. It is, however, difficult to take a stance on the question of whether this reflects a deliberate error or simply exaggerated uncritical optimism.

The paper (p. 1,998, column 1) also states: *“We obtained written informed consent from the patient, and the transplant procedure was approved by the local scientific ethics committee.”* The complainants maintain that both these statements are false.

In answer to KI’s question, the Regional Ethical Review Board states that there is no application for the research project in question.

The complainants have submitted an *“informed consent”*, which is in Karolinska’s records system and dated 26 June, i.e. 17 days after the operation. Paolo Macchiarini claims that the month is a typing error, and that “June” should really be “May”, and supported this by noting that the document was scanned in the digital computer system on 26 May. Karolinska has confirmed that the document was in fact scanned on 26 May 2011. The investigator therefore deems it ascertained that the document had been signed before the operation. On the other hand, this *informed consent* is so worded as to cover only the “healthcare” measures themselves – i.e. the planned surgery – and in no sense the patient’s participation in research. The investigator therefore sees no reason to, with the odd exception, comment on the wording of this *informed consent* in detail.

It is worth mentioning in this context that a letter from the referring doctor in Reykjavik dated 3 August 2013 states that ethical approval had been given, although the source of this information remains undeclared.

Paolo Macchiarini defends the claim of ethical approval with reference to a statement from senior physician Richard Kuylenstierna from 30 November 2014 that describes his contact with LMV, the research ethics committee and chief physicians at Karolinska. The investigator finds that this statement only tries to shed light on the medical ethical problem that the operation itself entailed and does not take up the research ethical aspect.

All in all, there is no approval from “the local scientific ethics committee”. The claim in the paper is thus false.

In an amendment dated 24 September 2014, the complainants question whether the patient actually had a tumour recurrence. There was a clear clinical suspicion of such, but the complainants say that it had not been PAD-verified before re-operation was proposed and then performed, or verified after the operation either. This is relevant to this investigation only as regards the truth of the paper’s claim that the patient actually had “*recurrence*” of his tumour disease at the time of the operation.

The investigator notes here that a bronchoscopic examination was carried out on Iceland on 11 February 2011 and showed a bronchial stricture on the right-hand side. A tracheal biopsy of good quality showed only granuloma. On 18 May 2011, six days before the patient was admitted to Karolinska, a referral was issued for a PET/CT scan with the information: “Now recurrence of... .. We plan a tracheal graft (never performed before in Sw)... ..judge as soon as possible if the tumour is disseminated”. On 19 May, five days before the patient was admitted to Karolinska, a referral was issued for CT with the following information: “Now recurrence of tumour... ..The patient is planned for radical surgery on 7/6...with reconstruction of airways.” These two examinations were conducted on 24 and 25 May respectively. CT showed an expansivity that was less than 10 mm³ and several “soft tissue masses” which were thought to be possible lymph glands or to be related to the previous dose of radiotherapy. PET/CT with ¹⁸F-FDG confirmed that there was an area of increased uptake, which the referral statement describes as “the known tumour recurrence”. On 26 May, PAD from two biopsies taken 1 and 2 cm respectively above the tumour shows normal respiratory mucosa only.

Despite the extended preoperative investigation, there was therefore still no PAD-verified diagnosis before the major, life-threatening operation was carried out. Cryosections taken during the operations did not reveal any tumour either. The operative specimen, which would give a definitive answer about the presence of a recurrence was clearly not examined, as no information about this can be found in Karolinska’s databases. Nor is there any information in the operation report about whether the operative specimen was even sent for pathological-anatomical examination, something that is *lege artis* in tumour surgery. How this came to be is inexplicable.

Taken together, all this raises suspicions that the patient did not actually have an active tumour recurrence, a question that the complainants also raise. On this ground, the complainants thus question the medical purpose of the surgery performed, whether the preoperative examination procedure was carried out correctly, and whether it is *lege artis* to not have a suspected tumour PAD-verified in a resection specimen. These issues are so serious that the healthcare principal should consider opening its own investigation.

In the amendment of 24 September, the complainants also state that the postoperative treatment involved the incorrect administration of three drugs to achieve “*regenerative boosting therapy*”. The first, recombinant transforming-growth factor β 3 (TGF- β 3), manufactured by R&D Systems, is actually not a drug but a normal chemical intended for laboratory use and does not fulfil the safety requirements for use on humans. The second is Neupogen® (filgrastim) from Amgen, which is registered for a different indication. The third is NeoRecormon® from Roche, which is indicated for stimulating the formation of red blood cells. They have all been used in what the authors call “supratherapeutic doses”.

This circumstance is serious enough to warrant an investigation by LMV. In this respect, it transpires that on 16 April 2015, LMV delivered its opinion on the matter in its reply to a letter from Karolinska that the activity as such probably classifies as a clinical drugs trial or falls under what is called the “hospital exemption”. It has also been brought to the investigator’s attention that LMV has decided to report the incident to the police as a suspected violation of the pharmaceuticals legislation. The investigator lacks information, however, on whether LMV has access to the same background material as this investigation.

It can, moreover, be noted that the medical records confirm the administering of Neupogen and NeoRecormon, but do not identify where/when/how/if recombinant TGF- β 3 was given.

It should be mentioned here that in the *informed consent*, it is written that this drug treatment is without “side effects”, which is a seriously false claim.

In this context, it is pertinent to point out a claim from paper 6 (see below), which describes the prosthesis implanted in patient 1:

The need to improve the biomechanical properties of the scaffold and our willing [sic – translator] to mimic the native tracheal extracellular matrix (ECM), led to fabrication of the next generation of scaffolds to include FDA approved polymers like polyethylene terephthalate (PET) and polyurethane (PU).

This description of the need to improve the prosthesis used in patient 1 shows that the research group was unhappy with its biomechanical properties. The new type of tracheal prosthesis was planned for use in patient 2 just five months after patient 1 was operated on. This means that the flaws that occasioned the material development must have already been well known to the authors when paper 1 was submitted. However, this paper lacks any details suggesting that the material was not optimal.

Finally, the investigator notes that Paolo Macchiarini was the lead author who described his role thus: “*Paolo Macchiarini was the primary investigator and leading author of the report, indicated how to built [sic – translator] the three-dimensional nanocomposite, was leading surgeon and was responsible for the preoperative and postoperative course, and oversaw the review process.*”

Paper 2

Badylak SF, Weiss DJ, Caplan A, Macchiarini P. Engineered whole organs and complex tissues. *Lancet* 2012; 379: 943-952.

The complainants state that the paper had been submitted to *The Lancet* already on 12 August 2011, 64 days after the operation on the patient whose 8-month data was reported in the paper, and refer to the direct contact made with the journal's editorial assistant. This means that it was submitted before paper 1, and was available online on 8 March 2012.

This is a review article that does not report its own data. It does, however, refer to the patient on whom paper 1 was based (i.e. patient 1) and who was operated on in Stockholm on 9 June 2011.

The paper states that: "*The artificial scaffold, which was seeded ex vivo with autologous bone marrow-derived stromal cells (in a bioreactor) and conditioned with pharmacological therapy, was implanted into a patient with a primary recurrent tracheobronchial tumour. The graft was patent, well vascularised, and lined with a well-developed healthy mucosa 8 months after transplantation*⁴⁹."

The complainants claim that this is an erroneous description of the healing of the mucosa and that the reference (reference no. 49 is Paper 1 in this investigation) only contains information about the mucosa five months after the operation, the veracity of which the complainants consider dubious. See above.

The complainants also claim that the only bronchoscopic examination that was carried out eight months after the operation date from 14 February 2012. This was done after two stents had been inserted into the tracheal/bronchial lumen to ensure the free passage of air. On this examination there was a suspected fistula that had also been described on previous examinations, and biopsies revealed extensive granulation tissue and only parts of an eroded epithelium. Brushed material from the graft surface produced no detected epithelial cells.

Paolo Macchiarini argues that "*All these criticisms relate to a single sentence within a 10-page review article*" and refers to a bronchoscopy carried out on 14 February 2012, the visual impression of which was the basis of the statement in the text. On the other hand, a copy of the email correspondence that Paolo Macchiarini had had with *The Lancet* shows that proofs of the paper were sent to the authors already on 1 February and returned on 5 February. Clearly, the information from the bronchoscopy from 14 February cannot have been the basis of the statement made in the paper.

The investigator also notes that the medical records referred to by the complainants show everything but that the prosthesis is "*lined with a well-developed healthy mucosa*". Amongst other things, there is already a fistula that was treated with a stent. What the paper claims is thus unsupported, and has not been corroborated by Paolo Macchiarini since either.

Since there is no original data in this paper, it ought not to qualify as misconduct that no scientific ethical review was conducted.

The investigator notes that Paolo Macchiarini was the main author and in that role has the main responsibility for the content of the publication. It was in addition noted that he was the only of the authors who had his scientific workplace in Sweden, and who reasonably had any knowledge about the postoperative results that were presented.

Paper 3

Jungebluth P, Haag JC, Lim ML, Lemon G, Sjoqvist S, Gustafsson Y, et al. Verification of cell viability in bioengineered tissues and organs before clinical transplantation. *Biomaterials* 2013; **34**: 4057-4067.

This paper was received on 5 February 2013, accepted on 20 February 2013 and was available online on 6 March 2013. This was, respectively, 6, 6.65 and 6.9 months after patient 3, who is referred to in the text, was operated on.

The investigator notes that the three complainants, Oscar E Simonson, Matthias Corbascio and Karl-Henrik Grinnemo, are co-authors of this paper placed 9-11 in the list of 15 authors. Likewise, it is noted that all authors, in accordance with the journal's rules, accepted by their signatures their co-authorship and the manuscript as such. The investigator also notes that in signing the authors also "*confirm that any aspect of the work covered in this manuscript that has involved either experimental animals or human patients has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript.*" Finally, it is noted that this paper was submitted for publication 1.5 years before the three co-authors, Oscar Simonson, Matthias Corbascio and Karl-Henrik Grinnemo reported Paolo Macchiarini for scientific misconduct.

The paper cites the results from patient 3 as an example of how the technique that had been developed for studying the viability of cells on biotechnologically manufactured organs and tissues can be used.

The complainants question whether it is truthful to describe the need for surgery in patient 3 as "immediate", citing as support the clinical status which, according to the patient's anamnesis in the medical records, was relatively stable for the four months that the patient had to wait for the operation.

The paper presents tracheal brush biopsy data taken a week after the operation when the patient received a synthetic tracheal prosthesis. According to the complainants, the medical records lack information on whether such a biopsy was taken, as well as its results. Paolo Macchiarini argues that this brush biopsy was not done at Karolinska but at the research group's laboratory at KI. The results of the brush biopsy are described as follows: "*The early clinical evaluation revealed an initial graft epithelialization as judged from the 1-week post-operative brushing.*" The results were visualised in the paper's Figure 7C.

The paper describes the results after five months as "*a patent and non-contaminated graft without any signs of inflammation*".

According to the complainants – who refer to a bronchoscopy that was done after 4.5 months – there was considerable granulation, a previously performed stenting, and an established fistula. This is confirmed by the medical records, which show that the patient was infected both before and after surgery.

The complainants also refer to a large number of additional bronchoscopies that were done within five months that do not support the described results after five months.

Paolo Macchiarini maintains that he has had not access to results of bacteriological analyses from Karolinska's records system and that the three clinical co-authors did not tell him about

them. He also maintains that the fistula and the need for a stent were related to previous surgery.

Irrespective of whether Paolo Macchiarini was explicitly informed by his co-authors about all the postoperative studies done on the patient, the wording of the paper is intended to create the impression that the paper gives a correct and well-founded account of the circumstances that prevailed at five months. The investigator finds that the description is incomplete as regards the presence of extremely disturbing postoperative problems of which Paolo Macchiarini could hardly have been ignorant, and that therefore the impression that reader receives is false positive, even taking into account that the paper's primary objective is not clinical.

The investigator also notes that no ethical permit was issued for the part of the study that concerned the operated patient; the ethical permit referred to in the paper's method section applies solely to the animal experiments.

The investigator notes that Paolo Macchiarini was the lead author and as such had primary responsibility for the paper's content.

Paper 4

Del Gaudio C, Baiguera S, Ajallouelian F, Bianco A, Macchiarini P. Are synthetic scaffolds suitable for the development of clinical tissue-engineered tubular organs? *J Biomed Mater Res A* 2014; 102:2427-2447.

The paper was received on 13 March 2013, again in revised form on 11 July 2013 and accepted on 17 July 2013. It was received by the journal 21 months after patient 1 had been operated on, and submitted in revised form and accepted 25 months after this operation.

This is a review article that does not report its own data, with one exception. It refers to the patient on whom paper 1 was based (i.e. patient 1) and gives information different to that in paper 1. Here mention is made of the clinical condition at 12 months, which it describes in positive terms:

“After 12 months, an almost normal airway and improved lung function were assessed.”

Paolo Macchiarini does not deny the existence of the postoperative complications cited by the complainants, but describes that he was *“not present for a majority of the clinical decision making”* and did not have access to the patient records at Karolinska. The investigator finds that this claim differs diametrically from how Paolo Macchiarini describes his role in the operation of patient 1 in the author description in paper 1: *“PM...was leading surgeon and was responsible for the preoperative and postoperative course...”* Paolo Macchiarini also maintains that in expressing himself as above he meant to say: *“Additionally, the use of the term “airway” in the manuscript was meant in a nonspecific manner and only to emphasize the absence of tumor recurrence in the patient’s airway (the initial presenting problem)”*. Paolo Macchiarini does not believe that the claim is false seen from the described perspective.

In the investigator's view, the used phrase is the third of three consecutive sentences that describe in detail the patient as a clinical example of the course of events after the replacement of a trachea with a synthetic prosthesis. In this context, the only interpretation the

reader can make is that “*airway*” means “the operated airway”. The interpretation Paolo Macchiarini says he intended is difficult to reconcile with the wording and context of the text.

The investigator thus finds that the authors’ description gives a highly dressed-up impression of the course of events over the first year after the implantation of the synthetic tracheal prosthesis. During this time the patient’s airways had had to be stented repeatedly owing to progressive occlusion in the operated area and suspected anastomosis failure and fistula formation. These problems had deteriorated up until the time of submission of the paper, at which points a tracheoesophageal fistula had established itself and defied all attempts to treat it.

The embellished picture is partly a consequence of the authors’ choice to only provide information on the three observation times (a week, two months and one year) after the operation and deselected information on all the problems that arise in the intervals – or afterwards.

It should be pointed out that when this paper was submitted patient 2 had already died and patient 3 was in a critical condition and had had a regraft the days before the revised version of the article was submitted.

The investigator notes that Paolo Macchiarini was the paper’s lead author and as such primarily responsible for the paper’s content. It is also noted that he was the only one of the authors who had a scientific workplace in Sweden and who could be expected to have knowledge of the postoperative results presented.

Paper 5

Philipp Jungebluth and Paolo Macchiarini (2014). Airway transplantation. *Thorac Surg Clin* 24(1): 97-106

The complainants state that this paper was submitted on 4 August 2013. It was available online on 27 November 2013 and in print in February 2014. It is a review of the clinical need to replace the main airways with a graft, of developments up to that point, and of what the authors deem to be promising paths of development. The complainants claim that the authors omitted to report their biopsy findings, bronchoscopic observations and other clinical observations in the three reported cases operated on at Karolinska, which would make the patients’ postoperative developments appear in a better light than the text in the paper makes out.

The investigator notes that the criticism levelled by the complainants focuses on the content of a table – Table 3 – which presents an overview of the “outcomes” for 17 patients who received a tracheal prosthesis, amongst them eight using a synthetic scaffold. Three of these patients were those who were operated on at Karolinska. The table presents a general summary and does not state the source of the data, which makes it impossible for the reader to validate them. However, it is stated that two of eight patients given a synthetic prosthesis had died, one with a benign disease who died from a “non-related cause”, and one with a malignant disease who died from “*severe gastrointestinal bleeding*”. The latter is probably patient 2 in this complaint.

Of the two patients operated on for their malignant disease, only one is stated to have died, apparently patient 2, but it is not mentioned that the other patient, who must be patient 1, had a very problematic oesophagotracheal fistula that had defied all constructive treatment attempts. On the other hand, it is stated that a patient with a benign disease needs “*stent treatment*”, obviously patient 3. There is no mention that patient 3 was also re-operated with a new prosthesis owing to “material fatigue” and subsequently needed stenting on account of fistula formation.

In the investigator’s view, the course of events for these patients is described in a simple manner and information was withheld that would have given a more balanced view of the outcome. However, the paper is an overview and so the demand for detail can be set lower than for an original article. This aside, the investigator judges it to be inconsistent with accepted scientific practice and thus finds the omission of information about the incomplete results for patients 1 and 3, who were both operated on by the lead author, to qualify as scientific misconduct.

The investigator notes that Paolo Macchiarini was the paper’s lead author and as such primarily responsible for the paper’s content.

Paper 6

Ajallouelian F, Lim ML, Lemon G, Haag JC, Gustafsson Y, Sjoqvist S, et al. Biomechanical and biocompatibility characteristics of electrospun polymeric tracheal scaffolds. *Biomaterials* 2014; 35:5307-5315.

The paper was received by the journal on 13 January 2014, accepted on 7 March, and was available on 3 April 2014. Patient 1, who is mentioned in the text, died on 30 January 2014, i.e. before the paper was accepted, after a prolonged period of pain that defied all attempts to treat it.

This paper gives an account of a new technique for evaluating the biocompatibility of synthetic polymer tracheal prostheses. The introduction, states that patient 1 has been operated on, with the outcome described thus:

However, due to the stiffness of the scaffold, an abnormal granulation tissue formation developed within the post-operative course. Moreover, it led to chronic fistula at the distal anastomotic sites of the left main bronchus, which required endoscopic interventions.

The investigator deems the description of the outcome of this patient to be an embellishment in that important information was withheld. When the manuscript was submitted in January 2014, the patient was in a very poor condition and the surgical report from 10 December, i.e. 34 days before the paper was submitted to the journal, states that there were signs that the tracheal prosthesis had become loose both proximally and distally. This was followed by an accelerating chain of complications, and he died 17 days after the manuscript’s submission, but a full 36 days before the paper was actually accepted. The autopsy report from 7 February 2014 showed, amongst other things, that the tracheal prosthesis had achieved insignificant integration and was lying loose in an area of pussy liquid and dead tissue with only about 10% of the proximal anastomosis healed in place.

The investigator observes that the patient is described in terms that definitely imply that he was alive and in an enticingly good condition when the paper was completed and submitted. It is censurable to describe the patient's condition in this way even if he had been alive when the paper was accepted, and a breach of accepted scientific practice to describe a patient's condition in this way when it is known that the patient's outcome was not only a "*...chronic fistula at the distal anastomotic sites of the left main bronchus, which required endoscopic interventions...*", but death as a result of this condition.

The investigator notes that Paolo Macchiarini was the paper's lead author and as such primarily responsible for the paper's content, and, based on the above, the most informed of the 12 authors about the patient in question and his condition.

Perspectives on the current research situation

When patient 1, who underwent surgery on Iceland for a tracheal tumour, developed a clinically suspect recurrence in February 2011, he was referred to Paolo Macchiarini at Karolinska for an assessment of the possibility of another operation to replace the trachea with a synthetic prosthesis. This plan is clearly described in the referral to PET/CT which was written already six days before the patient was admitted to Karolinska. The patient came to Sweden on a regular flight, had no manifest pain at rest and had a relatively normal respiratory sound. In his statement to this investigation, senior physician Richard Kuylenstierna states that the ethical aspects were considered and that contact was made with LMV and the Regional Ethical Review Board in Stockholm, as well as chief physician at Karolinska. Kuylenstierna states that the authorities contacted put the responsibility for performing the planned surgery on healthcare representatives. Kuylenstierna uses the phrase "*...the present situation constituted a medical care ethical question rather than a scientific one.*" As regards his thoughts about whether or not to perform the operation, he also writes: "*In this assessment can also be added the necessary urgency connected in this particular case suffocation pending.*"

After the operation on this first patient, another two globally recruited patients were received who were also described as being in a life-threatening condition and who subsequently underwent surgery. In this context, the investigators would like to highlight five aspects.

Firstly, this investigation only deals with the matter of scientific misconduct, and so the question of there being any ethical impediments to perform the surgery does not form part of the investigator's assignment. What is included, however, is an assessment of whether the scientific paper, in which the medical interventions are described and in which the results of a number of laboratory studies of patient material and of the continuing clinical progress of the patients are presented in a scientific journal, is covered by the legislation concerning "research involving humans".

Secondly, the investigator would like to point out the fact that there was a vision at KI, and with Karolinska as a partner, even before patient 1 made his appearance, of expanded practice with the aim of being able to perform these very operations within the near future. The source material written on 4 June 2010 and sent to KI's recruitment committee regarding the proposal to employ Paolo Macchiarini included the following passage:

“With the recruitment of Professor Macchiarini, a growing European network collaboration will very quickly blossom. We expect to be performing regenerative tracheal transplantations by no later than three months after his establishment at the ENT clinic at Karolinska University Hospital. It is likely that we will be able to recruit patients ahead of the new year on a national basis and a little later from across Europe.”

Paolo Macchiarini was employed on 1 November 2010 and patient 1 was operated on 9 June 2011.

It was very likely that “a patient 1” would turn up sooner or later to be appraised for possible participation in the ongoing development project, and when this happened, an acute need for surgery would be expected. This is because one of the clinical arguments for developing synthetic transplants is that the patients who are to undergo this type of care will have a “semi-emergency need”. In that there was a long-term development project/research programme underway, it is reasonable to think that the expected patients would form the basis of clinical activities that would then be regulated in all respects by the Ethical Review Act. It is also reasonable to foresee a form for the expected practice that would be heavily influenced by the pharmaceuticals legislation, especially that pertaining to advanced therapy medicinal products.

So when Paolo Macchiarini was contacted from Iceland about patient 1 evincing the clinical symptoms that were the case, and with the prospects of a short remaining life without surgery, it was completely expected. The patient’s expected short life and a described threat of very likely airway obstruction were the reasons for the decision to perform emergency surgery on this patient. This fact does not, however, allow an interpretation of the law that would mean that this patient could be incorporated into the research activities going on at KI without the customary ethical assessment being made. A conceivable possibility in the described emergency situation would have been, given the “present situation”, to apply for an ethical permit for a research project that entailed the right to follow up an “unconventionally operated patient” with available methods, and to argue in the application that there was a clear and great scientific need to perform such a follow-up, and that this in itself is ethically relatively unproblematic.

A few months after patient 1’s operation, patient 2 was also accepted for surgery after having been informed online in the US about Paolo Macchiarini’s work. He underwent surgery on 17 November 2011, a little over five months after patient 1. It is the investigator’s opinion that the operation performed on this patient was not deemed to form part of a research project either, since no application for an ethical review was submitted. The investigator can find no information in the documents stating that anyone even considered the need for it. Patient 3, in turn, arrived a few months later and underwent surgery on 7 August 2012, 14 months after patient 1 and almost nine months after patient 2. No ethical permit was applied for in this case either, nor can the investigator find any evidence that any such action was even considered.

Given these three consecutive scenarios, one can say that it is definitely contrary to the intention of the law to establish a development activity based on the global recruitment of seriously ill patients facing relatively imminent death due to the lack of effective treatment onto an experimental therapy programme without this being considered clinical research.

Thirdly, and this is partly a development of the above point, the investigator would like to draw attention to the fact that KI expected Paolo Macchiarini to advance the university’s

clinical and scientific positions within the field of regenerative medicine. These visions are clearly evident in the above-mentioned material with which KI's Recruitment Committee was furnished regarding the proposal to employ Paolo Macchiarini:

Professor Macchiarini has initiated with the framework of a European collaboration a possible paradigm shift in regenerative medicine. By combining biomaterial, in the example of the airways [a] decellularised bronchial wall with the seeding of different stem cells, he has created a regenerative situation in which the recipient's own stem cells obtain a matrix for the regeneration of fresh tissue. It is possible that this paradigm will be developable for other organs, such as heart valves, bone, cartilage, vocal cords, heart muscle and lung. In recruiting Professor Macchiarini KI would thus obtain an innovative force of international calibre with the development of clinical regeneration based on biomaterial – an area which is currently very weak.

As can be seen, a “paradigm shift” was expected in an area in which the clinical application of scientific progress includes uncommonly many ethical dimensions and pharmaceutical-legal problems. Nothing has emerged during this investigation to show that KI had predicted or taken precautions to deal with these problems when they arose in connection with Paolo Macchiarini's work. It cannot be ruled out that this is one reason for the shortcomings that manifested themselves in the handling of the scientific-ethical issues.

Fourthly, it is clear, particularly in paper 1, in which an entire online appendix comprises a highly detailed analysis of cellular descriptions, that a large number of analyses had been performed of a type that indisputably can be classified as “research involving humans”. It is also clear that biopsy material had been taken from the Karolinska's pathology laboratory to the research laboratory. That Paolo Macchiarini explicitly understood that the work did actually qualify as “research involving humans” is also evident a) in the documents submitted to the investigation, including copies of emails in which a member of the research group gives reassurance that the patient was asked to consent to the use of imaging material for future publication, and b) in the description that biological material had been taken care of for analysis in the research group's own laboratory at KI and not at Karolinska's own laboratory.

Fifthly, nothing has emerged from this investigation to support the claim that formal contact was made with LMV during the group's work regarding, for example, procedural issues related to the awarding of permits or to definitions and delimitations for developing it within the bounds of the prevailing laws. The implantation of a synthetic tracheal prosthesis involves obvious boundary-drawing problems as regards the use of drugs and the development and manufacture of active medical technical products and as regards stem cell grafts. In the above-mentioned letter from LMV dated 16 April 2015, however, LMV says that a statement from Karolinska from 17 February does not alter its opinion that the work being done is probably classifiable as a clinical drugs trial or, alternatively, falls under the “hospital exemption” (see the Pharmaceuticals legislation section). This implies that there had been previous contact, in which LMV stated that what was being planned/done or had been done was classifiable as clinical drug trials – and thus research. The investigator does not have any information, however, about the nature of this contact. Regardless, it is reasonable to suppose that unclear communication between Karolinska/KI and LMV might in practice have created the conditions for the problems to arise.

The investigator has also been informed that LMV opened a supervisory case against Karolinska (ref. 6.3.-2015-013429) which has since been closed in that no further operations

were planned. LMV has also decided to report the interventions performed for being a possible breach of the Medicinal Products Act (1992:859) to the Police Authority in Stockholm (case no. 5000-K446303-15). In this context, the investigator would also like to draw attention to the meaning of the term “compassionate use” given Paolo Macchiarini’s claim in several documents that the care interventions were performed under the terms of what he describes as “compassionate use”. This means that patients with an extremely poor prognosis can be given “last resort” care with the support of certain legal provisions. However, the term “compassionate use” exists formerly in Europe only with respect to the use of certain non-registered drugs and is strictly regulated in the Regulation of the European Parliament and of the Council (EC) no. 726/2004 of 31 March 2004 on the Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency. The FDA also has a compassionate use programme, which also includes different kinds of device. It is important to point out that the term “compassionate use” is not something that the individual doctor may use at his or her discretion, but is based on official permission granted by the relevant authority. The interventions performed on these patients are not covered by this concept.

Conclusions

Following a detailed analysis of all available material, an extremely complex picture emerges where much of what has occurred has not been clarifiable in detail. Even though the investigator has been focused on the main matter of alleged scientific misconduct, it is impossible not to comment on the fact 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. The correspondence that has come into the investigator’s possession thus shows that one of the researchers who signed his name to the complaint alleging scientific misconduct to the Vice-Chancellor, Karl-Henrik Grinnemo, is a co-author of, and in that capacity also responsible for two of the questioned papers (1 and 3) that were submitted for publication in October 2011 and February 2013 respectively. It is made explicit that he contributed a detailed description of the patient’s condition in paper 1, which is critical to this investigation. Two other complainants of the four are co-authors of paper 3. The complaint in question, in which the results of these papers are described, was submitted to the Vice-Chancellor 34 and 18 months, respectively, after the papers had been submitted for publication. The investigator cannot interpret this to mean anything but that the original team of researchers, which included the complainants, split up at some point after paper 3 was submitted, and that the complainants thereafter decided to ask the Vice-Chancellor to investigate the matter of scientific misconduct. Certain aspects of the circumstances that they point out in their complaint should already have been known to them in connection with the writing and publication of the papers.

The investigator cannot take the above circumstances into account in his assessment of the matter of alleged scientific misconduct. At the same time, it is impossible not to bear in mind when assessing which scientific information that different people/co-authors, in particular the complainants, contributed to the papers. This last matter is related to the question of how obliged the lead authors of a paper are to check the various parts of its content. The complaints contain a great deal of reasoning and facts to support the idea that the papers in question contain falsehoods, omissions or else claims that give evidence of scientific misconduct. The investigator has shown that there have been many detailed deviations from what is defined as accepted scientific practice. Some of these can be independently seen as not very or moderately censurable, but combined they reflect a scientific process that has departed from accepted scientific practice. Some of the anomalies noted are not covered by

the narrow definition of misconduct as laid out in VR's "Accepted Scientific Practice" (see above) but instead by the healthcare and pharmaceuticals legislation or by the legislation on "research involving humans". One matter that must be cleared up is where, in this case, the line is between research and healthcare. In the investigator's view, the medical interventions performed on the three patients fell under the definition of research at that moment someone reflected upon and planned to disseminate and use the information scientifically. This includes some kind of description of what had been done and what results it produced, as well as all handling of material for analysis over and above what was required for the patients' care. From this perspective, the investigator deems that the scientific publication of the results of the performed operations entails "research involving humans" and as such therefore falls under the jurisdiction of the Ethical Review Act. An important question is how seriously one is to look upon the omission to describe in detail certain phenomena regarding the clinical results in the papers that are to be regarded as "reviews" or that have other points of inquiry than purely patient-related ones. In the situation in question, the investigator finds that all activities dealt with by the papers support in one way or another the clinical development of the research field that constituted KI's motives for recruiting Paolo Macchiarini. The investigator deems that what may be judged as misconduct, or a departure for accepted scientific practice, shall *an sich* be seen equally serious in all the papers that form the basis of this investigation. The investigator therefore pays no heed to Paolo Macchiarini's apologetic comments on one of the papers that the criticism only referred "*to a single sentence within a 10-page review article.*"

The investigator finds that the errors about which the complaints have been made in these papers concern descriptions of very patient-related circumstances and outcomes of the patients operated on by Paolo Macchiarini and colleagues, and the outcome of which is central to Paolo Macchiarini's clinical research. Regardless of the conflicts that have apparently arisen amongst the authors, the lead author, Paolo Macchiarini, has responsibility above all for ensuring that the data underpinning the content of the papers is checked and reported correctly. It seems altogether unreasonable here to think that Paolo Macchiarini had been in a state of ignorance about the results of the studies that had been done postoperatively, the genuinity of which has been thrown into question by the complainants. As pointed out above under the heading Paper 1, Paolo Macchiarini also claims that he "*was leading surgeon and was responsible for the preoperative and postoperative course...*". The investigator therefore does not find that Paolo Macchiarini's explanations and the shifting of some of the burden of responsibility onto other authors has no bearing on this judgement. The principal responsibility for the departures from accepted scientific practice that have been observed must therefore be Paolo Macchiarini's and his alone.

In the investigator's view, there have been departures from accepted scientific practice in seven mutually independent papers, all of which share a common feature of being related to Paolo Macchiarini's main research field. The type of departure that takes the form of a false description of clinical circumstance and the active withholding of information that contradicts the papers' primary thesis strongly suggests that the resulting selection of information was deliberate. Both these circumstances, the restatement and selection of information, is a strong indication that lead author Paolo Macchiarini was aware that what had been written did not meet scientific requirements on correctness.

As regards Sjöqvist et al. the principally most outstanding fault is that the authors have decided to present research results for which none of them can take responsibility. This is inconsistent with accepted research practice and therefore qualifies as misconduct, and the

lead author (or in *Nature Communication*'s words "*corresponding author*") bears the blame for this. The paper also contains a number of other weaknesses/faults in the presentation of the animal experiments that had been conducted. These experiments are presented so vaguely that it is surprising that a journal of *Nature Communication*'s calibre accepted the paper without demanding extensive clarifications, which should have been dealt with in an effective referee-process.

As regards paper 1-6 many of the claims that the complainants have made can only be interpreted as evidence of irregularities either in the care that has been provided or in the papers published and that have been based on the research data presented. The following must be considered clear infringements:

To describe a clinical result after five months without conducting any examination of the patient at this point in time is significant; it is inconsistent with accepted scientific practice and therefore qualifies as misconduct (Paper 1).

To explicitly state that an ethical permit exists despite the absence of one is a false claim that affects the reliability of the research; this is a serious departure from accepted scientific practice and therefore qualifies as misconduct (Paper 1) .

To refer to paper 1 and make out that it accounts for a longer follow-up than actually was the case is false. This also applies to the actual description of the healing of the mucosa over the prosthesis, which in no way matches the accounts given in the medical records. In any case, it is an act of carelessness and a departure from accepted scientific practice and therefore qualifies as misconduct (Paper 2).

To describe the postoperative condition of a patient in such a way that leaves readers unable to make any other interpretation than that the postoperative conditions are good when in reality the patient has serious problems is to deliberately dress up the results. This is inconsistent with accepted scientific practice and therefore qualifies as misconduct, regardless of the fact that the paper's main purpose is not purely clinical (Paper 3).

To state that the circumstances 12 months after the operation were good despite the patient being in an extremely serious clinical condition and to claim by way of excuse that no check was made of the patient's status in the hospital records is significant; it is inconsistent with accepted scientific practice and therefore qualifies as misconduct (Paper 4).

To omit to mention that one of the reported patients had to undergo a new operation because of material failure was an active withholding of information and a dressing-up of the results. Such withholding of information is inconsistent with accepted scientific practice and therefore qualifies as misconduct (Paper 5).

To selectively describe certain minor postoperative problems while omitting the really major problems that led to the operated patient's death is a false embellishment of the results. This constitutes active withholding of information, which is inconsistent with accepted scientific practice and therefore qualifies as misconduct (Paper 6).

In closing, it must be mentioned that the assignment given by the Vice-Chancellor concerns the investigation of misconduct per se. Whenever misconduct has occurred, the investigator interprets his charge to also entail identifying the researcher(s) who acted in this way. The

investigator finds that the results that have been questioned are so essential to the research line pursued by Paolo Macchiarini that he, in his capacity as “*principal investigator*” and lead author of the papers in question, cannot have been unaware of them. The investigator therefore deems it obvious that he bears the main responsibility for the publication of false or incomplete information in several papers, and is therefore guilty of scientific misconduct. In view of the documents presented and without an extremely detailed investigation it cannot be ascertained in detail the extent to which other authors had knowledge of these faults and were thus bound to expose them. The investigator does find, however, that co-author Karl-Henrik Grinnemo, given his close participation in the care of patient 1, should have had some knowledge of the defects of paper 1. The investigator also finds that co-authors Oscar E Simonson, Matthias Corbascio and Karl-Henrik Grinnemo should similarly have known about some of the defects of paper 3. Given the nature of these faults, they should have had known about them by the time the paper was submitted for publication. In general, the investigator observes that none of the other authors, who total 28 in the most important work (paper 1), have questioned what has been presented, all having claimed to “*accept responsibility for its validity*”.

Appendix

Investigation assignment

Vice-Chancellor

Preparation of case concerning alleged scientific misconduct – request pronouncement from expert

On 24 June 2014 Karolinska Institutet received a complaint of alleged scientific misconduct from Dr Oscar E Simonson, Dr Matthias Corbascio and Dr Karl-Henrik Grinnemo. The complaint concerns, amongst other things, an article in *Nature Communications* titled “Experimental orthotopic transplantation of a tissue-engineered oesophagus in rats”. The complainants are of the view that the paper contains inconsistencies, distortions and examples of scientific misconduct (Appendix 1). The complaint was supplemented in August 2014 with additional documents.

The complaint was sent to Professor Paolo Macchiarini on 7 July 2014 for comment. He submitted his statement to Karolinska Institutet on 3 August 2014 (Appendix 2).

Chap.1 section 16 of the Higher Education Ordinance (1993:100) requires a higher education institution that receives a complaint or becomes aware in some other way of suspected misconduct in (e.g.) research at the higher education institution to investigate the suspicions.

Proposal for how to proceed

In compliance with the procedural regulations concerning scientific misconduct, Karolinska Institutet is to task Professor Emeritus Bengt Gerdin with making a pronouncement on the matter.

The assignment entails examining the paper and other relevant documents and judging whether or not scientific misconduct has occurred.

Professor Emeritus Bengt Gerdin’s findings will be reported to Karolinska Institutet on 15 January 2015.

Enclosed:

Appendix 1. The complaint

Appendix 2. Professor Paolo Macchiarini’s comments

Investigative procedure

All communication with KI has been mediated by legal expert Lisen Samuelsson unless otherwise stated.

| | | | Mail | |
|------------|----|---|-------|---------|
| | | | To KI | From KI |
| 2014-11-19 | W | Assignment request from Vice-Chancellor. | | |
| 2014-11-25 | Tu | Vice-Chancellor's decision. | | |
| 2014-11-26 | W | | x | |
| 2014-11-28 | F | Receipt of written source documents. Initial reading for orientation. | x | x |
| 2014-12-01 | M | | x | x |
| 2014-12-04 | Th | | x | x |
| 2014-12-08 | M | | x | x |
| 2014-12-09 | Tu | | x | x |
| 2014-12-15 | M | | x | x |
| 2014-12-16 | Tu | | x | x |
| 2014-12-17 | W | | x | x |
| 2014-12-18 | Th | | x | x |
| 2014-12-19 | F | | x | x |
| 2014-12-28 | Su | | x | x |
| 2015-01-07 | W | | x | x |
| 2015-01-08 | Th | Meeting with Vice-Chancellor. Informed of preliminary assessment based on fragmentary material. Requested KI to requisition all medical records from Karolinska/Stockholm County Council on the three patients, and all documents from the department concerning the research in question. Suggest that a legal expert take part. Sent proposal for the wording of request for the material requisition. Conversation with senior physician Dr Per Liss, radiology, Akademiska Hospital regarding help with DICOM images. | x | x |
| 2015-01-09 | F | Completion of proposed letter to the department. Confirmed involvement of legal expert. Wish expressed to discuss the matter with a legal expert with experience of ethical reviews. | x | x |
| 2015-01-10 | Sa | | x | |
| 2015-01-13 | Tu | | x | x |
| 2015-01-14 | W | Request for material to have been sent to the department. | x | x |
| 2015-01-15 | Th | Meeting with lawyer Christian Olofsson. | | |
| 2015-01-16 | F | Mail from KI to head of department with detailed request for material. | x | x |
| 2015-01-20 | Tu | Meeting with legal expert Erik Lempert, chair of the Regional Ethical Review Board in Uppsala to obtain a better perspective on procedural matters in ethics boards. Phone call with Professor Kerstin Westermark, LMV, on LMV procedures. | x | x |
| 2015-01-21 | W | Telephone call with head of department Li Tsai, KI, to clarify the request for material that had been sent to the department. Mail to KI to ask about the deadline for receiving requested material from the department. | x | |
| 2015-01-22 | Th | | x | x |
| 2015-01-23 | F | Explanatory mail to head of dept. Li Tsai. Received DICOM images from CT scan. | x | x |
| 2015-01-26 | M | | | x |
| 2015-01-28 | W | Suggest that I be allowed to read all medical records supplied by Karolinska in digital form on a computer at Karolinska and in the presence of Karolinska staff. | x | x |
| 2015-01-29 | Th | | | x |
| 2015-02-03 | Tu | Conversation and analysis of DICOM images in radiology unit, Akademiska Hospital. | | |
| 2015-02-05 | Th | | | x |
| 2015-02-06 | F | | x | |
| 2015-02-11 | W | Mail to KI owing to delay in receipt of documents. | x | x |
| 2015-02-12 | Th | | | x |
| 2015-02-17 | Tu | Mail from KI that material from Karolinska will arrive in a day or so. | | x |
| 2015-02-20 | F | Mail from KI: documents are available. | | x |
| 2015-02-23 | M | | | x |
| 2015-02-24 | Tu | KI all day. Read Karolinska's material. | | |
| 2015-03-08 | Su | Mail to KI: request for missing material from Karolinska. | x | |
| 2015-03-09 | M | | | x |
| 2015-03-23 | M | | x | x |
| 2015-03-26 | Th | | x | |
| 2015-04-06 | M | PM's reply received by KI; Some missing material from Karolinska also there. | | |
| 2015-04-08 | W | Read PM's material at KI; mail to KI: still missing pathology results from Karolinska. | x | |
| 2015-04-09 | Th | | x | x |
| 2015-04-10 | F | | | x |
| 2015-04-12 | Su | Mail to Ola Hermansson, KI, asking if PM has really understood. Question asked owing to missing material. | | |
| 2015-04-13 | M | Requested medical records received by KI. | | |
| 2015-04-14 | Tu | Read medical records and pathology results at KI. | | |
| 2015-04-15 | Th | | | x |
| 2015-04-17 | F | Material to lawyer Christian Olofsson . | | x |
| 2015-04-24 | F | | x | x |
| 2015-04-27 | M | Meeting with Vice-Chancellor; information on results of investigation; draft written. | x | x |
| 2015-05-04 | M | | x | x |

| | | | | |
|------------|----|--|---|---|
| 2015-05-06 | W | Analysis of text with lawyer Christian Olofsson. | | |
| 2015-05-07 | Th | Analysis of text with lawyer Christian Olofsson. | x | x |
| 2015-05-08 | F | Analysis of text with lawyer Christian Olofsson. | x | x |
| 2015-05-11 | M | Analysis of text with lawyer Christian Olofsson. | | |
| 2015-05-12 | Tu | Final review of text. | | |
| 2015-05-13 | W | Submission of investigation report to Vice-Chancellor. | | |

Request for primary material from the department

The request was sent to head of department Li Tsai in a mail from Lisen Samuelsson and as an explanatory mail from the investigator on 23 January. It reads as follows:

Dear Li

I have just been in email correspondence with Lisen, and we agreed that I should contact you and explain what is needed. To make sure that we are speaking the same language, I might repeat what Lisen has already written. This will make things safer and help us gain a little time.

There are two points on which the request for information that has been sent to the department rests:

The original material is to be secured by the investigation and the person identified is to be given a sporting chance to indicate the parts of the original material that support the claims that have been questioned in the published papers.

This leads to two things:

First: The identified person is to have access to the three separate text groups below.

- 1 The first complaint, dated 24 June 2014 – sent by Karin Jakobsson already on 7 July.
- 2a The second complaint, dated 18 August 2014 – ought to have been sent to you the other week.
- 2b Appendices to the second complain with the heading: *Analysis of clinical outcome of Synthetic Tracheal Transplantation Compared to results published in 6 articles by Macchiarini et al* dated August 2014 (total 54 appendices). Ought to have been included in the material you received the other evening. These are collected in a file named “Formal appeal 18 Aug with appendices.pdf.” This file is a full 15 MB.
- 3a Amendment to the second complaint dated 24 September – ought to have been sent to you the other week.
- 3b Appendices to the submitted amendment to the second complaint dated 24 September (total 2 tables and 19 appendices). Ought to have been included in the material you received the other evening. These are collected in a file named “Formal amendment to appeal dated Sept 24 with appendices.pdf.” This file is a full 10 MB.

PM has previously stated his opinion about complaint no. 1, but not about the two parts of the second complaint.

Then

Since an investigation of this type entails an analysis of the entire basis upon which the published works rest, it needs access to the original material or the requested parts of the original material, i.e. parts of the material that are required by the regulations to be archived at the department for ten years after publication, as the personal reply of the principal investigator is insufficient. Without it there can be no impartial assessment of the facts.

Consequently, the investigation requests the following original documents:

1. With respect to the first complaint, i.e. Sjöqvist et al, 2014, all the laboratory records covering all research involving the grafting of an artificial oesophagus into a rat. These are to include all studies made, not just those reported in the paper. Information on all postoperative CT scans is to be accounted for, as well as all postoperative follow-ups, including the daily weights of all animals. Data for all animals operated on as part of the control group is to be accounted for in the same way. It must be possible to evaluate which animals had been

operated on without recourse to the study, and which animals are included in the follow-up described in table 7c of the paper. I will receive the original files from the disputed CT in DICOM form via Lisen.

2. With respect to the second complaint of 18 August and amendment of 24 September (i.e. the papers Jungebluth et al, Lancet , 2011; Badylak et al, Lancet, 2012; Jungebluth et al, Biomaterials, 2013; Del Gaudio et al, J Biomed Mater Res A, 2014; Jungebluth and Macchiarini, Thorac Surg Clin, 2014, and Ajalloueian et al, Biomaterials, 2014).

a. Any CRFs (Case Record Forms) drawn up for each patient included in the research group's clinical studies, in the original.

b. In addition, should such data not be given in such CRFs, all documentation relating to the alleged misconduct. By this is meant that the research group must, for each point of criticism raised by the complainants, be able to submit the parts of the research documentation that support the claims in the paper and/or that disprove the criticism that has otherwise been put forward.

c. A list of all communication, including dates and content, that the authors have had with the journals in question – everything from feelers, through submission of first manuscript, various revisions to acceptance. Everything probably exists in email format. This list is to cover all journals and all papers.

I am also sending a copy to Lisen.

I hope this can be sorted out somehow.

All the best

Bengt

Appendix