

President

NOTE! This is a translation of the Swedish version.
In the event of any discrepancy between the
versions, the Swedish version is the official decision
and the Swedish wording will prevail

Suspected scientific misconduct

Decision

Scientific misconduct

Given the amendment to Karolinska Institutet's decision of 7 April 2015 concerning case no. 2-2167/2014 and 28 August 2015 concerning the case no. 2-2184/2014, Karolinska Institutet finds that the research reported in all six examined papers constitutes scientific misconduct. The papers report over a four-year period (2011 to 2014) the clinical outcomes for any one of the three patients operated on at Karolinska University Hospital.

The six papers are

1. *Tracheobronchial transplantation with a stem-cell-seeded bioartificial nanocomposite: a proof-of-concept study*, published in *The Lancet* 2011; 378(9808): 1997-2004,

This paper details the first transplantation of a synthetic trachea with a stem-cell coating and reports on the clinical status of patient 1 at five months. The description is fabricated and is actually based on the patient's status on discharge from hospital some months earlier.

2. *Engineered whole organs and complex tissues*, published in *The Lancet* 2012; 379(9819): 943-952,

This paper deals with synthetic organs in general. It was written before paper 1 (*Lancet* 2011) and was submitted to the journal beforehand as well. It was published later, in February 2012. A short section of the article describes the same patient as in paper 1, this time with a status alleged to be recorded eight months after the operation. This fabricated status is based on the same status that was taken in summer of 2011 on discharge from hospital (i.e. the same status used in paper 1).

3. *Verification of cell viability in bioengineered tissues and organs before clinical transplantation*, published in *Biomaterials* 2013; 34(16): 4057-4067,

The paper discuss a method for determining cell viability in synthetic organs. It was published on 6 March 2013 and includes a brief clinical example using patient 3 and his

clinical status five months after the operation. It is claimed using fabricated data that there were unrestricted airways without sign of infection or inflammation.

4. *Are synthetic scaffolds suitable for the development of clinical tissue-engineered tubular organs?*, published in *the Journal of Biomedical Material Research* 2014; 102(7): 2427-2447,

The paper discusses whether synthetic scaffolds are suitable for developing tubular tissues and briefly describes the clinical status of patient 1 one year after the operation, claiming that the patient had almost normal respiratory passages and improved pulmonary function. These data are also fabricated.

5. *Airway transplantation*, published in *Thoracic Surgery Clinics* 2014; 24(1): 97-106,

The paper discusses different methods of tracheal transplantation. A table is presented at the end of the article in which patients 1, 2 and 3 can be identified, along with other patients studied by other researchers. The paper claims that several of the patients have well-functioning airways. Patient 2 had died before the article was submitted to the journal in the summer of 2013, and patient 1 died a month before the article was printed in February 2014. The fact that these patients have deceased are not discussed in the text or reported in the table.

6. *Biomechanical and biocompatibility characteristics of electrospun polymeric tracheal scaffolds*, published in *Biomaterials* 2014; 35(20): 5307-5315.

The paper deals with the characteristics of synthetic scaffolds, polymers, that could replace a trachea. One section discusses the graft received by patient 1, which is described as sub-standard. The patient died in January 2014. The article was published in April 2014 but does not mention this fact.

All in all there are no negative reports on adverse reactions until paper 6, which attributes the patient's suffering to the choice of material and claims that the development of the subsequent polymer mitigated the complications. This creates the impression of a systematic deceit deliberately intended to exaggerate the patients' condition in a positive manner using fabricated data. Repeatedly reporting on the transplantations over a period of years makes the method appear successful, which, in turn, can arouse false hopes and inspire similar clinical solutions. Building a chain of evidence on fabricated data in this manner is deemed by Karolinska Institutet to be a very serious form of scientific misconduct.

Author responsibility

In the judgement of these matters, author responsibility is divided into three levels: "responsible for scientific misconduct"; "blameworthy" (i.e. not beyond criticism); and "not responsible for scientific misconduct and not blameworthy."



Responsible for scientific misconduct

Paolo Macchiarini, Philipp Jungebluth, Karl-Henrik Grinnemo, Jan Erik Juto, Alexander Seifalian, Tomas Gudbjartsson and Katarina Le Blanc are responsible for scientific misconduct.

Blameworthy

Evren Alici, Tolga Sutlu, Silvia Baiguera, Guido Moll, Pontus Blomberg, Béla Bozóky, Sylvie Le Guyader, Staffan Strömblad, Oskar Einarsson, Jan Liska, Ola Hermanson, Tobias Lilja, Gert Henriksson, Bertil Leidner, Tom Luedde, Christoph Roderburg, Ana Isabel Teixeira, Vanessa Lundin, Emma Watz, Bo Nilsson, Johannes C Haag, Mei Ling Lim, Sebastian Sjöqvist, Ylva Gustafsson, Fatemeh Ajalloueian, Irina Gilevich, Oscar E Simonson, Matthias Corbascio, Constantino Del Gaudio, Alessandra Bianco and Antonio Beltrán-Rodríguez are, by dint of their involvement, blameworthy but not to an extent that constitutes scientific misconduct.

Not responsible for scientific misconduct and not blameworthy

Clarie Crowley, Stephan F Badylak, Daniel J Weiss, Arthur Caplan and Greg Lemon are not, by dint of their involvement, responsible for scientific misconduct and not blameworthy.

Notification to journals

The Lancet, *Biomaterials*, *The Journal of Biomedical Material Research* and *Thoracic Surgery Clinics* shall be notified of the decisions with a request for the immediate withdrawal of the papers.



The case

On 28 August 2015, Karolinska Institutet's (KI) then vice-chancellor (president), Anders Hamsten, took a decision on the matter of suspected scientific misconduct (ref. no. 2-2184/2014) concerning six papers reporting scientific findings on the transplantation of a prosthesis in the tracheae of three patients. Some of the papers were review articles summarising and commenting generally previously published data. His concluding decision was that Paolo Macchiarini was not guilty of scientific misconduct.

In January 2016 Swedish Television broadcast a three-part documentary titled *Experimenten*, triggering a rise in media criticism of Paolo Macchiarini, his research and the transplantations of synthetic tracheae that he had carried out. Professor Hamsten said that the media attention had brought to light fresh information that gave a different picture of the material available when the case was examined, and that the decision was therefore taken on incomplete grounds.

After Anders Hamsten's resignation, KI's new management decided to carry out a thorough investigation into the affair. To this end, both cases of suspected scientific misconduct were reopened.

KI has thus re-examined the research (current case no. 2-723/2016). The following report begins with a brief background of the investigation of case no. 2-2184/2014.

Background (former case no. 2-2184/2014)

Complaint

In a letter to KI dated 18 August 2014, with an addendum dated 24 September 2014, Matthias Corbascio, Thomas Fux, Karl-Henrik Grinnemo and Oscar Simonson made allegations of suspected scientific misconduct against six scientific papers, the authors of which, including leading author Paolo Macchiarini, were employed at KI. The six papers and the authors were:

Tracheobronchial transplantation with a stem-cell-seeded bioartificial nanocomposite: a proof-of-concept study, The Lancet 2011

Authors: 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.

Four authors have subsequently withdrawn their names from the paper: Bo Nilsson, Katarina Le Blanc, Ana Isabel Teixeira and Karl-Henrik Grinnemo.

Engineered whole organs and complex tissues, The Lancet 2012

Authors: Stephen F Badylak, Daniel J Weiss, Arthur Caplan and Paolo Macchiarini.

Verification of cell viability in bioengineered tissues and organs before clinical transplantation, Biomaterials, 2013

Authors: Philipp Jungebluth, Johannes C Haag, Mei Ling Lim, Greg Lemon, Sebastian Sjöqvist, Ylva Gustafsson, Fatemeh Ajalloueiian, Irina Gilevich, Oscar E Simonson, Karl-Henrik Grinnemo, Matthias Corbascio, Silvia Baiguera, Constantino Del Gaudio, Staffan Strömblad and Paolo Macchiarini.

Are synthetic scaffolds suitable for the development of clinical tissue-engineered tubular organs?, Journal of Biomedical Material Research A 2014

Authors: Constantino Del Gaudio, Silvia Baiguera, Fatemeh Ajalloueiian, Alessandra Bianco and Paolo Macchiarini.

Airway transplantation, Thoracic Surgery Clinics 2014

Authors: Philipp Jungebluth and Paolo Macchiarini

Biomechanical and biocompatibility characteristics of electrospun polymeric tracheal scaffolds, Biomaterials 2014

Authors: Fatemeh Ajalloueiian, Mei Ling Lim, Greg Lemon, Johannes C Haag, Ylva Gustafsson, Sebastian Sjöqvist, Antonio Beltrán-Rodríguez, Constantino Del Gaudio, Silvia Baiguera, Alessandra Bianco, Philipp Jungebluth and Paolo Macchiarini.

Investigation

In November 2014, Bengt Gerdin, professor emeritus at Uppsala University, was asked by KI to examine whether the censured papers constituted scientific misconduct. Lawyer Christian Olofsson at the former von Lode advokat AB was asked in January 2015 to assist him.

In his official pronouncement of 13 May 2015, Bengt Gerdin concluded that the research represented a departure from accepted scientific practice/good research ethics and that Paolo Macchiarini had acted in a fraudulent manner in all six published papers.

All authors were invited to comment on Bengt Gerdin's statement of opinion, and many of them responded.

On 28 August 2015 KI announced its conclusion that Paolo Macchiarini was not guilty of scientific misconduct. Certain circumstances that had come to light on Paolo



Macchiarini's work showed, however, that it had not reached KI's high quality standards in every respect. KI decided to take certain measures.

In December 2015 Bengt Gerdin volunteered his own comments on KI's decision in which he stood by his former conclusion.

Investigation of current case no. 2-723/2016

Earlier source material

The re-opened investigation includes the six papers in the original complaint of 18 August 2014 and the supplement of 24 September 2014. The investigation makes up the remaining part of case 2-723/2016 and concerns the issue of whether any of the six papers, which describe different aspects of the three patients who received transplantations at Karolinska University Hospital, constitute scientific misconduct. The investigation includes the complaints, the authors' comments to them, the expert inquiry made by Bengt Gerdin, the authors' comments to it, and the source data from the hospital's medical records.

The investigation also includes Professor Pierre Delaere's complaint of 25 June 2014 with supplementary mail correspondence, in which he expressed his suspicions of scientific misconduct and where KI announced, in its decision of 7 April 2015 (case no. 2-2167/2014), that Paolo Macchiarini was not guilty of scientific misconduct.

The Central Ethical Review Board's expert group for misconduct in research

On 23 June 2016, once the case had been re-opened in 2016, KI invited the Central Ethical Review Board's expert group for misconduct in research (the Expert Group) to comment on whether the content of the case material (i.e. the complaints and the investigation into cases 2-2167/2014 and 2-2184/2014) constituted scientific misconduct. On 18 March 2017, the Expert Group appointed professors Martin Björck (Uppsala) and Detlev Ganten (Berlin) as case experts. They submitted their report on 31 May 2017. The Expert Group gave the authors an opportunity to comment on this report, and responses were duly received from Arthur Caplan, Sylvie Le Guyader, Staffan Strömblad, Alessandra Bianco, Philipp Jungebluth, Sebastian Sjöqvist, Mei Ling Lim, Paolo Macchiarini, Tomas Gudbjartsson, Ola Hermanson, Karl-Henrik Grinnemo, Matthias Corbascio, Oscar E Simonson and Katarina Le Blanc. The experts were then given an opportunity to comment on the replies.

The expert group concluded in its pronouncement of 20 October 2017 that all six papers contained material that constituted scientific misconduct and that all authors were guilty of the same.

The authors and the complainants were asked to comment on the Expert Group's statement and several responded.



Other matters

The complainants have responded to the authors' comments on numerous occasions. KI has also accessed the English summary of the Icelandic commission's report on the referral of the Icelandic patient to Sweden for care and treatment.

In addition to his written submissions, Tomas Gudbjartsson met the acting vice-chancellor (vice president) and deputy university director in the summer of 2016, and submitted verbal information to KI at a meeting in June 2018 with the two rapporteurs.

On re-opening the investigation, KI wrote to all relevant journals about an Expression of Concern on 18 June 2016. The Lancet has published one such with regard to paper 1.

Separate decision regarding the duplication of illustrations in the Biomaterials paper

Following an anonymous complaint on 3 February 2016 on incorrect illustrations in the paper *Biomechanical and biocompatibility characteristics of electrospun polymeric tracheal scaffolds* published in Biomaterials 2014, KI decided to investigate the matter separately.

KI found that Paolo Macchiarini, with the support of his co-authors, immediately admitted the mistake and the mix-up of illustrations. The journal confirmed that it had received an email from Paolo Macchiarini but had been unable to open the attached file that Paolo Macchiarini said contained a request for rectification and the correct illustrations. The case could not, however, be investigated further as it could not be ascertained what the file did or did not contain. It was clear, however, that the journal had received material for amending the paper. In its decision of 7 June 2017 concerning case 2-723/2016 KI stated that Paolo Macchiarini deserved criticism for the mistake but that the mix-up did not constitute scientific misconduct.

Regulations concerning KI's duty to investigate and its case administration

Fundamental rules on the handling of misconduct cases are provided in the Higher Education Ordinance (1993:100). According to Chapter 1, section 16 a higher education institution that receives a complaint or becomes aware in some other way of suspected misconduct in research shall investigate the suspicions. Moreover, during its investigation the higher education institution may request an opinion from the expert panel on research misconduct at the Central Ethical Review Board.

KI's administrative procedures (ref. no. 1-551/2014) state that suspected scientific misconduct must be reported to the president, who is then to have the matter investigated by a specially appointed administrator in the university administration and, if appropriate, in consultation with the head of department and/or legal advisor. The president is to decide on the case either by taking no action or, should misconduct be found, by deciding on an appropriate sanction.



Division of responsibilities between Karolinska Institutet and Karolinska University Hospital

KI's mission as a public authority is stated in various regulations, primarily the Higher Education Act and the Higher Education Ordinance, and the government appropriation document, in accordance with which it is to pursue first, second and third-cycle education and research; to interact with the community; to publish information about its activities; and to ensure the utilisation of its research results. Karolinska University Hospital provides the care and treatment within the remit set by Stockholm County Council. The activities of the hospital are regulated by healthcare legislation, the Patient Data Act and the Patient Safety Act.

KI's activities are monitored by the Swedish Higher Education Authority (UKÄ) and the Central Ethical Review Board (CEPN) on matters concerning education and research. Karolinska University Hospital is run by the county council and the quality of its activities is evaluated by the Health and Social Care Inspectorate (IVO).

In practice, this means that KI has responsibility for medical research and Karolinska University Hospital has responsibility for medical care.

The three patients

The first patient to be operated on, in 2011, was a 36-year-old man who underwent a primary operation in Iceland in October 2009 for mucoepidermoid tracheal cancer localised at the level of the carina. Early in 2011 a clinically suspicious recidive was non-confirmed and contact was made with Paolo Macchiarini and Karolinska University Hospital, and he was operated on 9 June 2011 to remove part of the trachea and replace it with a synthetic tracheal prosthesis seeded with the patient's own stem cells. After discharge, the patient was monitored at home in Iceland, but returned to Karolinska University Hospital on 21 November 2011 for check-ups and examinations, since complications had appeared. A difficult-to-treat fistula between the oesophagus and trachea had developed and the patient suffered repeated infection. The patient died on 30 January 2014.

The second patient was a 30-year-old American man with inoperable adenoid cystic tracheal cancer, who made contact with Paolo Macchiarini himself. This time a synthetic tracheal prosthesis was used that was made of another kind of plastic than that used for patient 1. The operation was carried out on 17 November 2011. The patient was returned to the USA and died on 5 March 2012.

The third patient was a 22-year-old woman from Turkey, who received iatrogenic tracheal damage in connection with a thoracoscopic sympathectomy (sweat surgery). After attempts to repair the damage in Turkey failed, her doctors contacted Karolinska University Hospital and Paolo Macchiarini. A pre-operative examination was carried out at Karolinska University Hospital and a few months later she underwent surgery on 24



July 2012 to remove her right lung. On 7 August 2012, she was given a synthetic tracheal prosthesis. Two weeks after the operation, an oesophageal fistula appeared between her oesophagus and trachea. Her complications continued and after 11 months, on 9 July 2013, she was re-operated on and given a new synthetic trachea. She was put in post-operative intensive care at Karolinska University Hospital with extensive complications. She then left the hospital and travelled to the USA for further care. She died on 20 March 2017.

Judgement

Scientific misconduct (“oredlighet i forskning”)

There is no uniform definition of “oredlighet i forskning” in Sweden, and according to the prevailing statutes it is up to the universities themselves to decide on matters of suspected misconduct.

Chap. 2 section 3 of the Higher Education Act (1992:1434) states that in their activities the higher education institutions shall uphold scientific credibility and good research ethics. It is thus incumbent upon the university to ensure that good research ethics are maintained.

The term “good research ethics” refers to the ethical demands with which research ought to comply, such as being truthful about one’s research; consciously examining and openly stating the premises of one’s studies; openly reporting methods and results; keeping one’s research in order; and endeavouring to conduct research without harming other humans, animals or the environment. Certain serious departures from good research practice/ethics are normally termed “scientific misconduct”. In most Swedish and foreign definitions, the essence of the term is Falsification, Fabrication and Plagiarism (FFP).

Section 2 of the Act concerning the Ethical Review of Research Involving Humans (2003:460) defines research as scientifically experimental or theoretical work intended to result in new knowledge and development outcomes on a scientific basis, excluding work that is performed within the framework of higher education on the basic or advanced level. According to section 4, the law shall apply to research that involves physical intervention, is performed according to a method with the purpose of affecting a research person physically or mentally, or includes an apparent risk of injuring the research subject either physically or mentally, or relates to studies of biological material that has been taken from a living person, and can be traced to that person. Section 6 provides that the research covered by the law may only be conducted if it has been approved subsequent to an ethical vetting.

Chap. 7 section 9 of the Medicinal Products Act (2015:315), previously section 14 of the Medicinal Products Act (1992:859), provides that clinical drug trials may only be conducted when licence to do so have been granted by the Medical Products Agency.



The World Medical Association has issued recommendations for clinical research in the Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects. The declaration is a set of ethical guidelines designed to ensure that experiments involving humans are to be conducted as clinical research and in compliance with ethics-based rules, and that experimental medical research must safeguard the health, wellbeing and rights of research subjects.

The Declaration states that it is intended to be read as a whole and that no national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth therein (articles 1 and 10).

The Declaration also states that while the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects (article 8); that patients may only be involved in research to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects (article 14); that medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects (article 16); that all medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research and that risks must be continuously monitored, assessed and documented (article 17); and that medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation (article 21).

According to article 37 unproven intervention may be used under certain circumstances in the treatment of a patient if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering.

When the treatments in question were carried out, the 2008 version of the Declaration of Helsinki was in effect, the relevant article (35) of which read as follows:

"In the treatment of a patient, where proven interventions do not exist or have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, this intervention should be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information should be recorded and, where appropriate, made publicly available."

The Declaration of Helsinki has no legal status in Sweden. While much of the Ethical Review Act is based on the declaration, there is no provision corresponding to the present article 37 or the previous article 35. According to KI, this means that research on a human using an unproven method may not be conducted with the support of theoretical



data only. A solid knowledge-base derived from pre-clinical research must first be created to give physicians an understanding of the dangers and advantages before conducting the experiment.

The responsibilities of the corresponding author and co-authors

International professional-ethical guidelines

While there are no administrative provisions prescribing who can be held responsible for scientific misconduct, there are a number of professional-ethical guidelines.

The 2011 version of the Vancouver Convention, which embodies international regulations issued by the *International committee of medical journal editors* (ICMJE), states that “*Authorship credit should be based on 1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; 2) drafting the article or revising it critically for important intellectual content; and 3) final approval of the version to be published. Authors should meet conditions 1, 2 and 3. And also that “I have had access to all data in the study (for original) research articles and I accept responsibility for its validity.”*

The ICMJE published a revised version of the text in 2013, which reads: “*Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.*” A leader commentary to this new paragraph 4 on the ICMJE website clarifies the author’s obligation to be responsible for the content and the investigation of irregularities: “*Each author of a paper needs to understand the full scope of the work, know which co-authors are responsible for specific contributions, and have confidence in co-authors’ ability and integrity. When questions arise regarding any aspect of a study or paper, the onus is on all authors to investigate and ensure resolution of the issue.*”

The world-leading *Committee on publication ethics* (COPE) states in its 2010 document “*Responsible research publication: International standards for authors: A position statement*” that all authors are required to take joint responsibility for the scientific integrity of the work if there is no account given therein of who is responsible for what.

In 2011, the *All European Academies* (ALLEA) published “*The European code of conduct for research integrity*” which serves as a framework for self-regulation and is recognised as a general expression of research integrity. It states that “*All authors, unless otherwise specified, should be fully responsible for the content of publication*” and that investigations of suspected scientific misconduct must include an assessment of its degree of severity.

In 2011, the Lancet declaration, which all authors signed, read as follows: “*I agree with: the plan to submit to Lancet; the contents of the manuscript; to being listed as an author, and to the conflicts of interest statements as summarised. I have had access to all data in the study (for original) research articles and I accept responsibility for its validity.*”



It is also worth mentioning here that the acknowledgements section of a scientific paper mentions people who have aided the work in different ways, be it personally, professionally, technically or financially.

KI's general considerations

Responsibility for established scientific misconduct must lie with the authors. KI bases its assessment of author responsibility on the relevant international and national regulations that were in force at the time of the research and its publication. Since the regulations are constantly changing, works from different years must be judged in part differently. Reference should also be made to the declaration that is individually signed on the submission of a manuscript. It is KI's opinion that the assessment of responsibility must be based on the regulations in force at the time of the suspected misconduct.

As regards assessing responsibility for the content of the scientific publications, KI holds that whoever puts his/her name to a scientific paper shares some of the responsibility. Of all the authors, the corresponding or lead author bears the main responsibility.

In accordance with the practice that is known to KI, only the leading author or a few of his/her co-authors have been judged guilty of misconduct in cases similar to that at hand. Two particularly high profile cases come to mind, namely from Copenhagen University (Milena Penkowa, 2012) and Oslo University (Jon Sudbø, 2006), in which only the leading author was deemed guilty of scientific misconduct.

KI holds that judging the responsibility for misconduct of an individual author depends on the degree and nature of the author's involvement. More experienced and senior researchers are much better placed than their junior colleagues to determine what may be demanded of their co-authors. If the person is a leading author or senior researcher who has responsibility for other colleagues in a position of dependency or who has been a driving force in or a major contributor to the research itself, he/she bears a greater responsibility. If the researcher has made a lesser contribution to the work, he/she may be considered criticized but not guilty of misconduct if the data he/she reports are correct. A researcher can also be considered blameworthy if he/she has not evaluated the data that other co-authors have contributed.

In assessing personal responsibility KI finds that three categories can reasonably be used to nuance the process: "responsible for scientific misconduct", "blameworthy", which means that the researcher is not responsible for scientific misconduct but is not beyond criticism and "not responsible for scientific misconduct and not blameworthy".

A key consideration of this investigation is that the status report that the 2011 Lancet paper mentions as having been made at five months had remained unchanged from earlier versions of the paper and was included in the pre-final manuscript (proofs) before this date had even passed. The same status text was, in fact, used throughout the autumn of 2011. The reason for this, according to Paolo Macchiarini, is that they received no



information about any change to the patient's status. Further, the authors who took part in the first attempt at publication in The New England Journal of Medicine (NEJM) bear a greater responsibility than those who joined later, since they were made aware of NEJM's rejection and did not rectify the manuscript before it was sent to the Lancet. The researchers who joined later, like the others, do bear responsibility, however, for having colluded in the scientific misconduct on the basis of the declaration they signed and sent to the Lancet.

Summary of KI's assessment criteria

It is vital to KI and to public confidence in research as a whole that the research conducted at KI maintains a high level of quality. This requires KI to provide the resources, education, leadership training and support that researchers need to do their work properly. The researchers also have a personal responsibility. All parties must live up to the demands imposed for ensuring research quality.

KI finds that there were definitions already in place in 2011 concerning the proper conduct of research, but definitions concerning the opposite (misconduct) varied, and that there were clear general guidelines for author responsibility, which were also included as a declaration to be signed and submitted to the journal with respect of papers 1 and 2. The assessment process used by KI with respect to the papers in the Lancet 2011 and 2012 is based on the rules that applied then.

The Expert Group finds all authors of the six papers responsible for scientific misconduct. In their statement to KI on 20 October 2017, they stated that it was not possible to investigate in greater detail to what extent the authors might have been misled about the content. However, if misled, authors should have reacted and asked for their name to be deleted when the publication became known to them. To refuse responsibility only if and when a paper is criticized is, according to the Expert group, not a reasonable course of action.

KI shares this conclusion, but not the Expert Group's view on collective author responsibility. KI therefore has examined the responsibility for each author, as far as it has been proved possible. It can be discussed to what extent each individual author can take on responsibility for each other's contributions for each article. The Expert Group finds that such responsibility lies with each contributing author. KI also considers that the authors has an obligation to familiarize themselves with co-authors research results, but that in highly specialized medical research it may be difficult to do this completely. In the end collaborative research must rely on confidence. The Vancouver rules were changed in this respect 2013.

All authors do, however, have a personal responsibility to check crucial data (e.g. whether the date of an examination falls after the publication date). As described by ALLEA back in 2011, the degree of severity of misconduct must also be evaluated. The reason for such an adjustment can, in KI's view, be the work the co-author contributed,



how much insight he/she has had to the work, and whether he/she has been in a position of dependency.

There are numerous aspects of the investigation that describe the clinical situation. The investigation that KI has now carried out is based on the research conducted, not the care provided or any medical errors that might have been made. Research has been defined here in accordance with the Ethical Review Act and the CEPN's precedent-setting decision, which base their definition on the premise that the difference between quality development in healthcare and research is determined by whether the intention exists to publish the work in a scientific context.

As regards research on humans, KI's view is that the manuscript must make clear that an ethical permit has been obtained, stating the relevant registration/reference number.

Paper 1 – Tracheobronchial transplantation with a stem-cell-seeded bioartificial nanocomposite: a proof-of-concept study, published in the Lancet 2011.

The paper was first sent to the NEJM, which had issues with flaws in the manuscript. Paolo Macchiarini wrote an email on 4 September 2011 urging his co-authors to submit supplementary material. NEJM did not accept the paper, rejecting publication in a missive dated 6 October 2011, with no opportunities for corrections to be made to the manuscript. The paper was then sent on 11 October 2011 to the Lancet, which accepted it on 7 November 2011 and a day later sent a proof, which was responded to by the authors on 10 November. The paper was published online on 24 November 2011 and in print on 10 December 2011.

It is KI's opinion that the paper is pivotal to the investigation of scientific misconduct as it provided the underlying material for decisions that were then passed on and was used in the later published papers under investigation.

Ethical permit

The paper claims that it received approval from the Regional Ethical Review Board and written informed consent from the patient/research person. KI can confirm that no application was submitted to the Regional Ethical Review Board (EPN) in Stockholm and that there can thus be no ethical permit or board-approved informed consent for the research to be carried out.

A cornerstone of research ethics is the concept of informed consent. The patient's medical records note such "informed consent" from the patient, written in the first person. The note addresses the medical care to be administered and describes the intended operation in detail. It does not mention any research aspect to it, only describes the surgical method as an opportunity to completely remove the patient's tumour with no mention of any alternatives to treatment. There is no mention of any adverse reactions or risks. The note also declares that the patient ("I") understands that the transplantation is the only chance of survival. Consent is also given for the handling of samples.



According to the Ethical Review Act, research on humans and informed consent are to be approved by the Ethical Review Board before research may commence. The law was written to protect the individual and is to be applied on research involving surgical intervention.

The external investigators share this view. Bengt Gerdin maintains that the paper claims that an ethical permit had been granted despite there not being one. According to experts Martin Björck and Detlev Ganten, the research as described in the paper is clearly of such a kind that requires review under the Ethical Review Act, which did not happen.

Permit from the Medical Products Agency

The Medicinal Products Act regulates advanced therapy, by which is meant gene therapy, cell therapy or a tissue engineering product (cf Regulation (EC) no. 1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products). Combined products (e.g. an engineering product that uses stem cells) are also covered by the regulations. Research is to be reviewed in accordance with Chapter 7 of the act as regards clinical trials. If the work is for the purpose not of research but treatment, the production process is to be inspected and approved by the Medical Products Agency as per the hospital exemption before the product can be given to the patient. In its investigation KI has not found that any permit for clinical drug trials or the use of the hospital exemption was received in this matter from the Medical Products Agency.

The clinical permit issue

On 30 November, former clinical manager at Karolinska University Hospital, Richard Kuylenstierna, reported on the permit that was obtained for the first transplantation. His submission describes conversations with representatives of the Medical Products Agency, the Ethical Review Board, the hospital's lead clinician, the Swedish Research Council and others. It is unclear on what ground the different people were contacted and what underlying material was presented. The procedure was an informal one and no legally-binding decision was given. He writes, for example, that the Medical Products Agency was contacted and it referred them to the hospital's rules since the patient's situation was acute.

The clinical impression presented to the authorities and others was of a seriously ill patients who could be offered no other treatment than surgery. This was also documented later in the clinical manager's declaration to the Medical Products Agency concerning inspection case no. 6.3-2015-013429, dated 17 February 2015, in which the patients intended for transplantation were described as "patients with breathing difficulties and dyspnoea".

The conclusion of Richard Kuylenstierna's investigation is that the first operation is to be performed on medical grounds for a vital indication, but that if it leads to research, an ethical application must be submitted.

The clinical status of patient 1

Paper 1 is an original paper that describes the course of the first transplantation up to five months later. It was published online in the Lancet on 24 November 2011.

The paper describes the patient on admission to hospital prior to surgery as having whistling breath, a cough and respiratory difficulties. The patient's medical records describe his general condition on arrival as good. He could move without hindrance and on physical examination on 24 May 2011, when the admission note was made, his lungs were described as "physically normal, although with occasional bronchial respiratory sounds and some audible stridor on both sides." He is stated to have been admitted due to a recidive cancer in the distal trachea. Pre-operative examinations with biopsies and computer tomography showed no definite tumour. An isotope scan (PET-CT) revealed a possible tumour with no spread and a diameter of 1.5 cm at the division of the two main bronchi. According to the patient's doctor, this uptake, along with lesser uptake around it, can also be due to damage caused by earlier radiotherapy of the patient's original tumour.

The paper states that the patient's condition at five months after operation (9 November 2011) is without complications, that he is symptom and tumour-free. At about the same time as the paper was published (24 November) the patient was readmitted (on 21 November) to Karolinska University Hospital owing to a deterioration of his condition. By this time, five and a half months had passed since the operation. The patient had lost seven kilos and showed signs of a failing right lung. His medical records of 21 November clinically describe his lungs as "no respiratory sounds on right side. Relatively clear respiratory sound on left side". Subsequent examinations show the patient's right lung to be non-functional.

The implant at five months is described in the paper as having preserved anastomoses lined with vascular neomucosa and partly coated by fresh epithelium. There is no evidence that a bronchoscopy was performed at this time. The last known bronchoscopy was in October 2011. In the bronchoscopy that was performed on 21 November 2011, five and a half months after the operation, no mention is made of any such findings as described in the paper. Instead, the bronchoscopy shows constrictions of the airways caused by extensive granulation where the transplant is attached to the trachea. Several stents, spring-loaded coils, were inserted in different locations in the bronchi to keep the airways open and, a little later, to close a hole (fistula) caused by the transplantation. A tissue sample now indicates the growth of cancer cells.



Drug treatment

The complainants have pointed out that various approved drugs with a growth-factor effect were given to the patient in very high doses. The use of these approved drugs is stated in the patient's medical records. That the drug use is outside approved indications and doses cannot be judged from a research misconduct perspective. The complainants also state that a cell-growth agent intended solely for laboratory use was applied direct to the patient's trachea. No support in the medical records has been found for such a claim so it has no impact on the judgement of scientific misconduct.

Statement from the pathologist regarding biopsies

Biopsies obtained from the patient at Iceland, spring 2011, showed no cancer. On the patient's admission to Karolinska University Hospital new biopsies were taken, and they too indicated no cancer. Normally, samples taken during an operation are sent for pathological diagnosis but the source data contain no details of such an examination and its results. Information recorded from the operation states that a lymph gland was sent to the pathology unit at the hospital for an opinion. The results did not indicate any malignity. The paper mentions a result that forms the basis of illustration 2B. The sample was taken seven days after the operation and is claimed to show early signs of vascular growth on the transplant. No basis for this illustration can be found in the source data, however. The paper describes a biopsy taken after two months (i.e. around 9 August). The source data include a biopsy that was sent for examination on 4 August. The results state that three tubes containing synthetic tracheae were sent to the pathologist, according to whom no well-developed cell layer can be seen in any of them. Three new tissue samples were sent on 17 August to the pathologist having allegedly been taken the day before. Subsequent investigation has shown that these samples came from Tomas Gudbjartsson on Iceland and that he also included a biopsy of healthy tissue in the material. Preliminary results for these samples from 17 and 22 August suggest necrotic tissue with bacteria and fungi. A definitive report on these samples was written on 26 August, which states that the remaining two tissue samples have now been analysed and that one of them, like in the first analysis, showed necrotic connective tissue with fungi and bacteria. The third sample is described as capillary-rich granulation tissue with respiratory epithelial coating and squameous epithelial metaplasia.

Meanwhile another biopsy containing four tissue samples was sent to the pathologist on 24 August, and arrived the following day. The statement, dated 26 August but signed 2 September by Béla Bozóky identifies "...porous foreign material of synthetic graft... No detectable cell components or matrix structures are seen". The sites from which the sample were taken are not indicated in the referrals. Illustrations 2B iii-viii, which supposedly show the condition of the synthetic trachea two months after operation, thus lack support in the source data. In one of many examinations tissue was observed that possibly resembles illustration 2B while a new examination just a week or so later gives the same result as before without findings of any cellular components. The individual illustration of more normal tissue included in these samples is a control biopsy of a non-transplanted trachea that Tomas Gudbjartsson had submitted. This is not made clear in



the referrals or the paper. In each case it was Karl-Henrik Grinnemo who sent the referrals to the pathologist.

The issue of whether the description of the patient was deliberately embellished

The patient's physical condition was better prior to surgery than the paper describes. No cancer could be reliably identified before or after the operation. According to his medical records, the condition of the patient five months after the operation was far worse than the paper describes. Biopsies then indicated tumour growth, at the same time as the patient is described in the paper as "tumour free". When the patient was admitted to Karolinska University Hospital in November 2011 the paper had just been published online but not yet in the physical journal. It would, in other words, have been possible to stop publication had the authors so wished.

Publication in another journal

The investigation has had access to the mail correspondence between the authors and NEJM. The manuscript was submitted first to NEJM, before being sent to the Lancet, where it was later published. NEJM appointed two reviewers, who went through the manuscript. In an email from 4 September 2011, Paolo Macchiarini urged his co-authors to submit supplementary material. NEJM rejected the paper on 6 October without giving any opportunity for corrections to be made. Amongst the stated reasons for NEJM's refusal is that reviewer 1 would have liked to see animal data allowing translation to research on humans, while reviewer 2 questions some of the datasets used for the illustrations.

The rejection from NEJM was sent to Paolo Macchiarini, who then forwarded it to the then research group, which comprised of Philipp Jungebluth, Evren Alici, Katarina Le Blanc, Pontus Blomberg, Karl-Henrik Grinnemo, Tomas Gudbjartsson, Sylvie Le Guyader, Ola Hermanson, Jan Erik Juto, Bertil Leidner, Tom Luedde, Staffan Larsson, Guido Moll, Tolga Sutlu, Ana Isabel Teixeira, Emma Watz and Alexander Seifalian. This author list is slightly shorter than the one that appeared in the Lancet, which also included Silvia Baiguera, Béla Bozóky, Claire Crowley, Oskar Einarsson, Gert Henriksson, Tobias Lilja, Jan Liska, Vanessa Lundin, Bo Nilsson, Christophe Roderburg and Staffan Strömblad. One of the original authors, or more correctly perhaps addressees, Staffan Larsson, is missing from the final publication. KI has found no evidence that any substantial changes were made to the paper (e.g. to address the NEJM reviewers' objections) before it was sent to the Lancet.

The referral from Iceland

The Icelandic investigation was launched by the University of Iceland and Landspítali University Hospital in October 2016 into the care of the patient and his referral from Iceland to Karolinska University Hospital, and Tomas Gudbjartsson's responsibility in the matter. One of the chapters in the commission's report sums up the investigation in English. Here it is written (p. 241) that Paolo Macchiarini asked Tomas Gudbjartsson in



an email dated 12 May 2011 to change his description of the patient's status in the referral to Karolinska University Hospital and to confirm that there was actually no other alternative treatment for the patient. This change was made the same day (12 May 2011) upon which the text came to describe surgery, with or without transplantation, as the only possible recourse for the patient. The Icelandic investigation shows that before the decision was taken the defraying Icelandic authority requested a statement from a doctor in Boston, who replied that, given the patient's situation, laser treatment would be the most appropriate course of action.

In another email from the same day, Paolo Macchiarini asked Tomas Gudbjartsson to replace the sentence "Is surgery a possible treatment modality for this patient?" with "This patient has already exhausted every possible medical treatment and his only hope of survival and cure is, given that the tumour is only locally invasive and has no regional or systemic metastasis, the resection of the tumour with a safe construction, either via standard airway surgery or using a transplant. I kindly ask you to help us in this difficult case." This means it must have been absolutely clear to Paolo Macchiarini when he read Tomas Gudbjartsson's email that the patient's condition was too good to be considered for an explorative, unproven method.

Concluding verdict on scientific misconduct with respect to paper 1

The patient information is untrue and does not meet the requirements of the Ethical Review Act. It is subjective, tendentious, misleading and gives no account of risk other than stating that surgery is the only treatment option for the patient if he wants to survive.

The leading author Paolo Macchiarini suggested changes to the referral letter from Iceland, these changes made the patient seem in a worse condition than he actually was.

There was no evidence to suggest that there was a vital indication for the treatment, which was one of the necessary conditions for performing the operation. The clinical description of the patient's pre-surgical condition given in the paper does not tally with the source data. There was no evidence of any reactivated cancer at either admission to hospital or at the time of the operation, contrary to what the paper claims.

The clinical description of the patient's condition at five months after surgery does not tally with the source data.

One of many negative tracheal tissue samples showed a well-developed cell layer. This sample was taken on the patient at Iceland and according to Tomas Gudbjartsson was labelled as a control sample from an intact part of the trachea above the transplant. This label was lost en route, a fact that is not mentioned in the referral letter. This led to erroneous conclusion of successful growth of mucosa in the transplant.

The paper mainly describes positive effects, which do not correspond to the actual situation. This is a distortion of the data, a view that is also supported by the statements of Bengt Gerdin, the experts and the Expert Group.



It is KI's view that the critical comments from NEJM were of a particularly serious nature as they pointed to a lack of translational data that must precede and can safeguard research on humans. Despite this, it can not be shown that after the rejection of the first version of the manuscript that was sent to NEJM the authors took the consequences of this criticism by demanding amendments to the paper or by renouncing their authorship.

The Icelandic investigation suggests that another treatment was possible (laser debulking) and that the alternatives open to the patient had not been exhausted, as the paper claims they had. It has also emerged that the leading author put pressure on the Icelandic doctor to make the patient seem worse than he was in his letter of referral.

None of the authors seems to have reacted to the lack of dated and registered ethical permits when the paper, which must have been regarded as a research project by everyone, was initially composed.

It is obvious to KI that the main authors deliberately resorted to deception to improve the paper's impact. Through its publication, the authors have endangered the lives not only of their own patients but also other patients at other hospitals, where doctors might have been inspired to perform similar operations. The main authors also acted dishonestly when claiming to have had ethical approval when this was not the case.

KI finds that the research described in the paper constitutes scientific misconduct. These conclusions are shared by the external reviewers.

It is KI's opinion that the paper must therefore be withdrawn and will be contacting the Lancet to request that this be done without delay.

Who is included in the investigation

All participating authors are part of the investigation. Some authors who were included on the original publication have since been removed from the author list at their own request. They are: Karl-Henrik Grinnemo (erratum 5 March 2016) and Bo Nilsson, Ana Isabel Teixeira and Katarina Le Blanc (erratum 26 March 2016). One of the authors, Karl-Henrik Grinnemo, is one of the original complainants. In KI's view, the simple fact of removing one's name from the paper after publication does not mean that one may evade investigation and be cleared of any responsibility.

Further, it has been argued that a complainant (whistle-blower) should not be found guilty of misconduct since it would deter other whistle-blowers from speaking out. It is essential that whistle-blowers report such irregularities and all credit must go to the four whistle-blowers who submitted this very thoroughly grounded complaint and thus triggered this investigation. However, it is KI's firm opinion that a whistle-blower who has participated in a study and contributed as author to a published scientific paper, in spite of the official complaint he or she lodged, can not avoid investigation and be cleared of any responsibility for scientific misconduct.



All named authors in the Lancet publication have had opportunity to reflect upon the fact that the paper refers to a point in time in its status report that still lay in the future (five months after 9 June is 9 November 2011 – and the final manuscript reached the Lancet on 8 November).

The first author group, which received the rejection from NEJM, should, after having read the comments of the two reviewers and the absolute rejection with no possibility of amendment, which is normal, have realised that the criticism voiced was very serious and either requested changes to the manuscript or withdrawn their participation.

A description of the authors' contribution to the paper

According to the paper, after the above errata, the authors presented the following information. “**Philipp Jungebluth** was responsible for the bioreactor-based cell seeding; assisted the surgery and with collection of secondary data; and wrote corresponding methods, results, and interpretation sections. **Evren Alici** and **Tolga Sutlu** undertook all flow cytometry characterisation of the cells, interpreted the results, and wrote corresponding methods. **Silvia Baiguera** provided preclinical data for human tracheal biomechanics and helped to write the report. **Guido Moll** designed, undertook, and assessed the multiplex analyses and wrote corresponding methods. **Pontus Blomberg** organised and supervised standards at the good manufacturing practice facility. **Béla Bozóky** did histological evaluation. **Claire Crowley** and **Alexander Seifalian** designed and developed the three-dimensional nanocomposite trachea and wrote corresponding methods. **Oskar Einarsson** and **Tomas Gudbjartsson** are responsible for the clinical follow-up of the patient and provided biopsy material and blood samples; Tomas Gudbjartsson also participated in the surgery and wrote corresponding methods. **Jan Liska** assisted the surgery. **Sylvie Le Guyader** and **Staffan Strömblad** did all cell imaging and wrote corresponding methods. **Ola Hermanson** and **Tobias Lilja** undertook and assessed all epigenetic analyses and wrote corresponding methods. **Jan Erik Juto** and **Gert Henriksson** assisted in the preoperative and postoperative care. **Bertil Leidner** did all radiological imaging, interpretation, and three-dimensional reconstruction, and wrote corresponding methods. **Tom Luedde** and **Christoph Roderburg** undertook and assessed the miRNA-studies and wrote corresponding methods. **Vanessa Lundin** and **Ana Isabel Teixeira** undertook and analysed gene expression experiments and wrote corresponding methods. **Emma Watz** isolated the mononuclear cells. **Paolo Macchiarini** was the primary investigator and leading author of the report, indicated how to build the three-dimensional nanocomposite, was the leading surgeon and was responsible for the preoperative and postoperative course, and oversaw the review process. All authors provided primary data for modelling scenarios and assisted with interpretation of results and report revision.”

The original paper, prior to the errata, also states the work done by **Karl-Henrik Grinnemo**, **Bo Nilsson** and **Katarina Le Blanc**: “KLB and BN designed, undertook, and assessed the multiplex analyses and wrote corresponding methods. KLB undertook the bone marrow isolation.” “KHG assisted the surgery.”



KI bases its judgement on these accounts about who did what and takes them as an expression of mutual agreement between the authors about their individual responsibilities.

The authors' individual responsibilities

As one of the principal authors **Philipp Jungebluth** bears considerable responsibility for the established misconduct. He was one of the drivers of the project and had detailed knowledge of the research and he is the one who subsequently received, stored and sent tissue samples for analysis, one of which indicated almost normal conditions. This was a sample that Tomas Gudbjartsson had sent and that according to him was labelled as a sample from healthy tracheal mucosa, information that is absent from the pathology referral written by Karl-Henrik Grinnemo. Philipp Jungebluth also claims that in the final version of the paper, the same clinical status was used as that which Karl-Henrik Grinnemo submitted to the first version of the paper (that of 29 August 2011). This two-month status was also used for the five-month report, since nothing had been heard from any of the clinicians in the author group to the effect that the patient's condition had changed. As one of the principal authors he did not make contact with any of the clinicians to obtain a status update ahead of publication. Philipp Jungebluth believes that the lack of information on the patient means that he was complication-free up to five and a half months after surgery. It was therefore right to use this status from August in November too. There is no medical examination from this time to corroborate his claim. Further, he had received NEJM's statement but remained on the author list without making sure that the paper had been revised. Philipp Jungebluth is responsible for scientific misconduct.

Evren Alici and **Tolga Sutlu** did laboratory studies (flow cytometry) in the project. Evren Alici was supervisor for Tolga Sutlu, who was a doctoral student. There is nothing to suggest that their studies were carried out in a way that involved the manipulation of data. They were both included in the first group of authors and should have demanded that steps be taken to address the views of the reviewers or withdrawn their authorship. They ought to have demanded greater insight into the project and reacted to the patently erroneous five-month status reported in the paper. They are both blameworthy in this respect but not to an extent that would constitute scientific misconduct.

Silvia Baiguera, **Claire Crowley** and **Alexander Seifalian** were responsible in various ways for the development of the synthetic trachea. The model used in paper 1 had not been fully tested and lacked reported animal data. Subsequent bronchoscopies show how the synthetic trachea was coming away from the living tissue, that there were lightly bleeding granulations around the anastomosis, that the airways were collapsing, that there was an air leakage to the diaphragm from the start, and that a fistula into the oesophagus was developing where the synthetic trachea had damaged the oesophageal tissue. All this cannot be explained by new tumour growth alone. Given the knowledge these developers must have had regarding good manufacturing practice (GMP), manufacturing approval from the regulatory authorities and the lack of animal tests with



the intended synthetic trachea, KI's view is that they should have curtailed their collaboration in the project, and even questioned the entire endeavour. Neither have they reacted to the patently erroneous five-month status reported in the paper. *Claire Crowley* joined the author group in the final month as a student. Granted, she too should have reacted to the patently erroneous five-month status reported in the paper, but in that she became involved at such a late stage and was a student, KI finds that she is not responsible for scientific misconduct and not blameworthy. *Silvia Baiguera* was also not in the first author group but necessarily deserves criticism for being involved in a project that must have appeared extraordinary to her, despite many years' experience in the research field, and for not requesting clarification of the clearly incorrect clinical status reported in the paper as she should have. *Silvia Baiguera* is blameworthy but not to an extent that constitutes scientific misconduct. As ultimately responsible for the synthetic trachea, *Alexander Seifalian* necessarily deserves criticism for non-compliance with the Medicinal Products Act's quality GMP-criteria in, and the lack of Medical Products Agency permit for its manufacture. He was also a member of the first author group and should have demanded that steps be taken to address the views of the reviewers. *Alexander Seifalian* is therefore responsible for scientific misconduct.

Guido Moll did multiplex analyses (with Bo Nilsson and Katarina Le Blanc, see below). There is no reason to believe that his contribution to these analyses was made to deceive. He did not react to the patently erroneous five-month status reported in the paper. He was a member of the first author group and should have demanded that steps be taken to address the views of the reviewers. He is therefore blameworthy but not to an extent that constitutes scientific misconduct.

Pontus Blomberg was responsible for the GMP- facility. He did not react to the patently erroneous five-month status reported in the paper. He was a member of the first author group and should have demanded that steps be taken to address the views of the reviewers. As the only author in charge of the GMP unity, he should have requested more data, especially after receiving the report of the NEJM reviewers. He is therefore blameworthy but not to an extent that would constitute scientific misconduct.

Béla Bozóky was the pathologist that examined many of the pivotal biopsies taken, some of which cannot today be found. This in itself is censurable but it cannot be claimed that this was Béla Bozóky's responsibility. He is responsible for the only statement that, after a long series of negative outcomes, both before and after this particular sample (taken by Tomas Gudbjartsson on 16 August 2011), demonstrated a vascularised epithelial growth, that is, a finding that suggested a successful transplantation. However, he cannot be blamed for his statement, since it was not made clear where in the trachea the sample, which had been sent from Philipp Jungebluth with a referral from Karl-Henrik Grinnemo, had been taken. The label that Tomas Gudbjartsson attached to the sample, i.e. the information that the sample had been taken from a non-transplanted part of the trachea as a control, did not reach him. He was not a member of the first author group. Béla Bozóky did not react to the patently erroneous five-month status reported in the paper. He is blameworthy but not to an extent that would constitute scientific misconduct.



Sylvie Le Guyader and **Staffan Strömblad** did cell studies. In a written declaration to KI *Sylvie Le Guyader* has claimed that she did not conduct her studies to deceive and that she had no opportunity to check other authors' data. She was a member of the first author group and should have demanded that steps be taken to address the views of the reviewers. She did not react to the patently erroneous five-month status reported in the paper. She is blameworthy but not to an extent that would constitute scientific misconduct. *Staffan Strömblad* joined the author group in connection with the submission of the paper to the *Lancet* and in his statement to KI stated that he did confocal analyses and other cell studies. He did not react to the patently erroneous five-month status reported in the paper. He is blameworthy but not to an extent that would constitute scientific misconduct.

Oskar Einarsson and **Tomas Gudbjartsson** participated in the clinical care of the patient, mainly on Iceland; Tomas Gudbjartsson also participated in the operation performed at Karolinska University Hospital. They had good insight into the patient's circumstances and gave their approval to publication of the paper in November 2011 in which the patient's five-month status was reported. Oskar Einarsson was not a member of the first author group, and was added before submission to the *Lancet*. Tomas Gudbjartsson had a more senior role. He claims that he tried to describe the patient's complications in the paper, but that this part of the text was deleted by Paolo Macchiarini on the grounds that it took up too much space. He also states that he had no reason to suspect that there was no ethical permit for the study, as the manuscript made it clear that the study had obtained one.

The patient's condition was relatively good during the postoperative period until the fourth month (i.e. October 2011). During this period, the patient was active, studied and had no pronounced respiratory difficulties. After four months his condition deteriorated. The biopsies were taken at the request of Karolinska University Hospital on 12 and 21 July, 16 August and 20 October 2011. On 16 August biopsies were taken from both the upper section of the transplant and of normal tracheal tissue and were sent by courier straight to Philipp Jungebluth. According to the investigation *Tomas Gudbjartsson* initiated care of the patient at the hospital in order that the patient could receive symptomatic treatment in the form of a reduction in tumour mass (debulking) using a laser. He then amended the referral to the Swedish doctors as instructed by Paolo Macchiarini to the effect that the patient's status appeared worse than it actually was. The patient thus qualified for a tracheal transplantation, despite the procedure being unknown and unproven. In KI's view, it cannot be ruled out that the customary treatment could have kept the disease in check for a while longer, based on the fact that the tumour could not be confirmed before the transplantation or in the material obtained during surgery. There is thus no reason to believe that there was a vital indication for surgery. Tomas Gudbjartsson was a member of the first author group and should have demanded that steps be taken to address the views of the reviewers. He is therefore responsible for scientific misconduct. Oskar Einarsson was a member of the author group recruited after the *NEJM* rejection. He did not react to the patently erroneous five-month status reported



in the paper. *Oskar Einarsson* is blameworthy but not to an extent that would constitute scientific misconduct.

Jan Liska participated in the operation and in the care of the patient. He did not react to the patently erroneous five-month status reported in the paper. He was not a member of the first author group. He is blameworthy but not to an extent that would constitute scientific misconduct.

Ola Hermanson and **Tobias Lilja** were responsible for the epigenetic studies. There is nothing to suggest that these studies are in themselves to be judged as dishonest in either execution or outcome. *Ola Hermanson* was a member of the first author group and should have demanded that steps be taken to address the views of the reviewers. *Tobias Lilja* joined the author group after submission to the *Lancet*. Neither *Ola Hermanson* nor *Tobias Lilja* reacted to the patently erroneous five-month status reported in the paper. They are blameworthy but not to an extent that would constitute scientific misconduct.

Jan Erik Juto and **Gert Henriksson** participated in the pre- and postoperative care of the patient. *Jan Erik Juto*, but not *Gert Henriksson*, were a member of the first author group and should have demanded that steps be taken to address the views of the reviewers. It should have been evident to them that the results as described in the paper were untrue as the patient had not yet had his five-month evaluation when the final proposed paper appeared. *Jan Erik Juto* had a more prominent part to play here as he had met the patient already at his admission to hospital in May 2011 and obviously noted that he was not as sick as had been assumed. Both participated in different bronchoscopies and operations during the patient's time in care. *Jan Erik Juto* states that the patient lived for another three years, two of which he regards as being of good quality, albeit with recurring infection, and argues that this would hardly have been the case, given the patient's cancer relapse, if he had not undergone surgery. As a senior member of the author group, *Jan Erik Juto* had good knowledge of the patient's care and was in a position to demand changes to address the views of the reviewers after submission to *NEJM*. He could also have easily established that the status as presented in the paper was not based on relevant clinical data. *Jan Erik Juto* is therefore responsible for scientific misconduct. *Gert Henriksson* is blameworthy but not to an extent that would constitute scientific misconduct.

Bertil Leidner did the radiological studies and assessments, the conclusions of which were subsequently criticised and challenged. However, it cannot be ascertained whether they were done to deceive. He was a member of the first author group and should have demanded that steps be taken to address the views of the reviewers. He did not react to the patently erroneous five-month status reported in the paper. He is blameworthy but not to an extent that would constitute scientific misconduct.

Tom Luedde and **Christoph Roderburg** did and assessed the miRNA studies. The investigation finds no evidence that they were done to deceive. *Tom Luedde* was a member of the first author group and should have demanded that steps be taken to address the views of the reviewers. Neither of them reacted to the patently erroneous



five-month status reported in the paper. Both Tom Luedde and Christoph Roderburg are blameworthy but not to an extent that would constitute scientific misconduct.

Vanessa Lundin and **Ana Isabel Teixeira** did and analysed the gene expression studies. There is no reason to claim that they were done to deceive. Neither of them reacted to the patently erroneous five-month status reported in the paper. *Ana Isabel Teixeira* was a member of the first author group and should have demanded that steps be taken to address the views of the reviewers. She is blameworthy but not to an extent that would constitute scientific misconduct. *Vanessa Lundin* joined the author group just before submission to the *Lancet* and had a subordinate role in the work. She is blameworthy but not to an extent that would constitute scientific misconduct.

Emma Watz did the studies on mononuclear cells. The investigation finds no evidence that they were done in a dishonest manner. She did not react to the patently erroneous five-month status reported in the paper. She was a member of the first author group and should have demanded that steps be taken to address the views of the reviewers. She is blameworthy but not to an extent that would constitute scientific misconduct.

Bo Nilsson and **Katarina Le Blanc** participated in various analyses. *Katarina Le Blanc* also undertook the bone-marrow isolation to obtain stem cells with which to coat the synthetic trachea. Neither of them reacted to the patently erroneous five-month status reported in the paper. Katarina Le Blanc had in this regard greater responsibility by virtue of her seniority and her responsibility for the production of the stem cells that made the project possible. Katarina Le Blanc has submitted a statement to KI on her own, Guido Moll's and Bo Nilsson's behalf claiming that they contributed their own part to the work, that their contribution was not done to deceive, and that they cannot be blamed for errors/wrongdoings committed by others beyond their control and influence. Katarina Le Blanc appended an email from clinical manager Richard Kuylenstierna dated 12 May 2011 where he writes that he has been in contact with the Medical Products Agency and the Ethical Review Board and that these authorities stated that if the primary indication is survival or death, the case must be treated as clinical. However, if the project entails research, approval must be obtained from both authorities. KI interprets this to mean that she was aware that the project was no longer one of pure care and treatment but that it had become research since the intention was to publish at least one scientific paper, and that she had, given her experience, thus realised that it was now a scientific project.

At this time, 2011, the Central Ethical Review Board (CEPN) had introduced the practice (2008) that medical research projects on humans constitutes research, not healthcare, if the intention is to publish it scientifically. Over the years, case reports have been scientifically published in different medical disciplines without their having first been approved by ethical review boards or the Medical Products Agency because they fell under healthcare. It was thus probably not surprising for these researchers that this project would also fall under healthcare rather than research ethics/science. However, for decades it had been a given within the medical profession that completely unproven techniques must not be tried on humans without prior animal data describing its effect

and safety and with reasonable expectations that similar data can be obtained in studies on humans. At the time the paper was written, the researchers knew of only isolated animal data on the intended method of transplantation. The data were, however, irrelevant to the technique that was used and, especially, the synthetic trachea was unproven. It is KI's view that Katarina Le Blanc must have been aware that the underlying material on which this first transplantation was based was flawed.

Katarina Le Blanc's clinical immunology unit has had a long-standing and close partnership with Vecura, Stockholm County Council's unit for the production of stem cells and vectors. Vecura manufactures these drugs in compliance with GMP and so there are good grounds for assuming that Katarina Le Blanc disregarded the GMP requirements for research involving humans in participating in this study since she could hardly have been unaware of the fact that the plastic tracheae that were used had not been manufactured by Vecura or even in accordance with GMP. The reference that usually appears to have been used to support this first transplantation is a tracheal transplant performed in Barcelona using a decellularised human trachea, a technique that differs significantly from the synthetic trachea that was used in this case at Karolinska University Hospital. She was a member of the first author group and should have demanded that steps be taken to address the views of the reviewers. She should also have realised that the patient's status as given in the paper could not be correct since five months had not passed since the operation when the print-ready original from the Lancet was presented. *Katarina Le Blanc* is responsible for scientific misconduct. Bo Nilsson had a subordinate role and was only recruited as a co-author ahead of submission to the Lancet. *Bo Nilsson* is blameworthy but not to an extent that would constitute scientific misconduct.

Karl-Henrik Grinnemo was one of the surgeons who participated in the transplantation and who wrote the biopsy referrals during the work reported in the paper. He has confirmed that the clinical status he sent to Paolo Macchiarini was based on an epicrisis written by the patient's doctor in early August 2011. This clinical summary, which was completed on 29 August, then accompanied the different versions of the paper over the ensuing months. Karl-Henrik Grinnemo reasons that since he was working at the thoracic surgery clinic and that during this time the patient belonged to the ear, nose and throat clinic, he was unable to access the patient's clinical development. The source data show that the last clinical bronchoscopy and biopsy examination was done on day 76, roughly eleven weeks after the operation. Karl-Henrik Grinnemo thus had every opportunity to understand that even before the paper was submitted to NEJM at the end of August it did not describe the patient's actual condition, since these biopsies taken by the hospital and on Iceland did not provide any underlying data for the cell status at seven days and two months as reported in the paper. He claims that he knew nothing about the patient's clinical development since after his operation he was cared for at another clinic. This raises questions about how he could accept his co-authorship. Since it was such an unusual operation, it is unlikely that he did not even make private contact with the relevant clinics to find out how things went for the patient. Karl-Henrik Grinnemo is one of the authors who had direct knowledge that the patient's status as described in the paper cannot have reflected the actual situation at five months. Karl-Henrik Grinnemo



was a member of the first author group and should have demanded that steps be taken to address the views of the NEJM reviewers. The evidence found no evidence that he tried to update his clinical description in the prefinal manuscript to the Lancet in early November, that he actively tried to block publication at this time, that he tried to withdraw his authorship or that he tried to update the description of the patient's status in the paper during the interval between publication online on 24 November and its printing on 10 December, by which time the patient had already (in November) been re-admitted to Karolinska University Hospital.

This played out during the summer and autumn of 2011. His and the three other complaints' report was made in August 2014, i.e. three years later. The complainants have said that they did not realise how the patient had fared until they were later brought in to take care of patient 3, when they realised the scale of the clinical problem. This is, however, of less relevance to the judgement of Karl-Henrik Grinnemo's responsibility since according to KI he appears to be the author who knew most about how the clinical report for patient 1 was prepared and who had authorial responsibility to make sure that it was reproduced correctly in the paper.

As KI has already made clear, a researcher may not evade investigation or be cleared of any guilt of suspected scientific misconduct concerning research in which he or she has participated simply because he or she is a whistle-blower. All credit must go, however, to the four whistle-blowers for submitting a very thoroughly grounded complaint and thus triggering this investigation. As regards Karl-Henrik Grinnemo, he was a key clinician with insight into the clinical data, and was one of the principal authors of the paper. He did nothing to ensure that his and other people's contributions to the scientific description of the patient reflected the actual situation. He is responsible for scientific misconduct.

The leading principal investigator was **Paolo Macchiarini**. The concept of principal investigator includes taking responsibility for financing and initiating research, having overall control, taking responsibility for all data and bearing overall responsibility for the final scientific paper. He is identified in the project description as the leading researcher, the leading author, the one who described how the synthetic trachea was to be designed, the leading surgeon, the one responsible for the pre- and postoperative care, and the one who led the review of the paper that was required on different occasions.

The investigation found that Paolo Macchiarini had taken the initiative already during the introductory phase to deceive on the matter of the patient's status when he persuaded Tomas Gudbjartsson to change the referral text so that the patient would appear more sick than he actually was. Paolo Macchiarini thus acted in a deliberately deceitful manner from the very start without concern for the patient's situation. As the senior investigator he must have been aware of the national and international regulations in effect at this time regarding research and development surrounding medical technology, for research with stem cells and comparable drugs, and that translational research requires preceding preclinical data and the establishment of high-quality manufacturing processes. With this in mind, conducting research despite being aware of the methodological and



administrative shortcomings appears almost amateurish or possibly fraudulent. Further there is a decision from the clinical manager at Karolinska University Hospital, Richard Kuylensstierna, that the work constituted healthcare but that a permit had to be applied for when it shifted to research. In light of this, an ethical permit and other relevant permits should have been obtained back at the time the paper was being planned. Paolo Macchiarini claims that he was aware that the clinical report on the patient's status was written in August and that it was impossible to foresee that the patient's clinical status would change during the postoperative phase. Since he was part of an experimental and preclinical unit, he was, by his own account, unable to check the patient's status himself in the hospital's medical records. He therefore assumed that the patient's status was unchanged since he had heard nothing from the responsible clinicians. KI finds that there was nothing to stop him, as the leading author, asking the clinicians or co-authors about the patient's current status before the final manuscript to the Lancet. It is KI's view that Paolo Macchiarini is responsible for scientific misconduct.

Paper 2 – Engineered whole organs and complex tissues, published in the Lancet 2012

The complainants state that this paper was submitted to the Lancet on 12 August 2011, that is *before* paper 1 was submitted to the same journal. The reason for the different times leading up to publication is that paper 1 was given high priority. The paper, a review article of different methods of creating new organs, was published online on 8 March 2012. The section on respiratory difficulties mentions a successful transplantation of a synthetic trachea, with the patient feeling well after eight months. Reference is made to paper 1, which corresponds in time to 9 February for patient 1. According to the paper, the transplant – eight months after surgery – exhibits open airways and an interior surface coated with well-developed, healthy mucosa. At this time, the status of the patient's airways, according to the surgical report for a bronchoscopy performed on 14 February 2012 (i.e. a few days later) was as follows: ... “granulations to the right and left...a stent has migrated upwards and is covering the opening into the right bronchus ...suspected fistula at 3–4 o'clock...the bronchus of the right superior lobe is slightly pinched, biopsy and brush sample taken”. The pathological diagnosis states: “No appreciable epithelial material in the rinse fluid.” The biopsies show: “An abundance of granulation tissue, surface epithelium comprises squamous epithelial cells, in places eroded, in places rejected with ulceration.” From this, KI concludes that the description the paper gives of the patient after eight months cannot be true. Since the clinical part of the paper concerns patient 1, on whom research was done without the approval of the Ethical Review Board, this report also lacks ethical approval.

Stephen F Badylak, Daniel J Weiss and Arthur Caplan have written a joint statement to KI claiming that this review article does not present any new data and that it is not clear how the study can affect publication. KI finds that none of them is responsible for scientific misconduct or blameworthy.

Paolo Macchiarini mentions in his statement that epithelia was visually confirmed by the bronchoscopist and that biopsies were ideally to be avoided. This contradicts a statement by Jan-Erik Juto, who describes patient 1's respiratory passages as being



covered in dried and viscous mucous that made it hard to probe and inspect the cell layer. Further, it takes advanced methodology to ascertain the degree of viability, cell growth and epithelialisation. The issue is so complex that it forms the subject of a separate paper (paper 3). This means that visual inspection is not enough to determine the presence of epithelialisation. The clinical pathologist's report also provides no evidence that there is a functioning layer of mucosa at this time. KI finds that Paolo Macchiarini used the paper to spread the idea that patient 1's transplantation was successful. Since no adverse reactions or problems were raised by the paper it is un-nuanced. KI finds that Paolo Macchiarini is responsible for scientific misconduct.

Generally speaking, the paper does give a valuable overview of the area, but the section on patient 1, the information about Paolo Macchiarini as author and all references to KI mean that the paper must be withdrawn.

Paper 3 – Verification of cell viability in bioengineered tissues and organs before clinical transplantation, published in Biomaterials 2013

This paper was submitted to the journal on 5 February 2013, was accepted on 20 February and published online on 6 March. It describes a method of estimating cell viability in a tracheal graft. A brief clinical example is given from patient 3, with reference to a brush sample taken a week after surgery. Patient 3 was had two transplants, the first on 7 August. Already after just over a fortnight the first complication appeared – a fistula between the trachea and oesophagus. At five months after surgery, the paper states that there are open airways with no signs of infection or inflammation. There is nothing in the medical records that this was so at the five-month mark (i.e. the beginning of January 2013). No examination was performed at this time. The previously most recent one was a bronchoscopy performed four and a half months after surgery, which shows considerable granulation, a formerly inserted stent, and a fistula. The paper states that an ethical permit had been obtained, which turns out later to be for the animals used. There is thus no research-ethical approval for the research on humans that the paper reports on. The paper states that the patient needed an immediate transplant. In the source data, an entry in the patient's medical records from 25 June 2014, it is noted that the patient says that she felt relatively fine before the first operation: she could walk 200–300 m at a brisk pace, climb two steps without difficulty and manage her own hygiene. Her greatest problem was the two or three daily coughing fits. This implies that the indication for performing the transplantation (dyspnoea, respiratory distress) can be questioned.

Philipp Jungebluth explains in his statement that this is a presentation of a new procedure to determine cell viability in manufactured biomaterial. Even if examples are given with clinical data, it is not the purpose of the paper. A bronchoscopy was performed a week after the operation, in which a brush rather than a biopsy sample was taken. This was not noted in the medical records, but the samples were sent at Philipp Jungebluth's laboratory, where staining was done. Philipp Jungebluth claims that since so little was done with the human tissue, no ethical permit was needed. This statement contravenes both the Biobank Act and the Ethical Review Act. He also writes that any



ethical permit was not his responsibility, but the clinicians'. KI finds that Philipp Jungebluth evidently received material that is not traceable as it was neither registered in the patient's medical records nor sent to a pathological laboratory, nor was it registered in any other way in traceable channels or biobanks. The research report also lacked an ethical permit and approval from the local biobank. Philipp Jungebluth is responsible for scientific misconduct.

Johannes C Haag states that the focus of the work was the development of the new calculation model. KI finds that Johannes C Haag, with the composition of the scientific paper and the report on scientific human data it contains, should have realised that it concerned research that lacked an ethical permit. He is therefore blameworthy but not to an extent that would constitute scientific misconduct.

Mei Ling Lim explains in her statement that even though it was not registered in the patient's medical records, a bronchoscopy was performed with brushing and that this sample was transported to Philipp Jungebluth's laboratory. The paper was intended to present a method and was not a clinical report. She collected samples, analysed data, prepared the underlying documentation and commented on the manuscript. Mei Ling Lim should therefore have realised that the work being done was research, not healthcare. She is blameworthy but not to a degree that renders her guilty of scientific misconduct.

Greg Lemon states that he is a mathematician and that his role in the paper was to produce a method to calculate cell coverage over the synthetic organ seeded with stem cells. This was done using a method that measures the depth of staining of crystals attached to the synthetic organ. He was unable to determine if the data the paper presented were relevant or not. He also helped to check the language of the paper, as he has done for other papers. Greg Lemon is neither responsible for scientific misconduct nor blameworthy.

Sebastian Sjöqvist reasons that he cannot be held responsible for the clinical description since he was prevented by the Patient Data Act from opening the patient's medical records. He does not think that the paper should be withdrawn and that an erratum would suffice. He did, however, deliberately help write the paper, which presents research on humans that was conducted without prior ethical review. Sebastian Sjöqvist is therefore blameworthy but not to an extent that would constitute scientific misconduct.

As for **Ylva Gustafsson** there is no detailed data on her contribution to the paper. She was, however, clearly involved in writing a paper that presents research on humans that was conducted without prior ethical review. She is therefore blameworthy but not to an extent that would constitute scientific misconduct.

Fatemeh Ajallouecian writes that she is not a doctor and that she did not have access to the patient's medical records. She believes that all presented in-vitro data are correct and replicable. She was involved in writing a paper that presents research on humans that was



conducted without ethical review. She is therefore blameworthy but not to an extent that would constitute scientific misconduct.

Irina Gilevich is named as a co-author of the study but it is not clear exactly how or what she contributed to it. She was, however, involved in writing a paper that presents research on humans that was conducted without human ethical review. She is therefore blameworthy but not to an extent that would constitute scientific misconduct.

Oscar Simonson, Karl-Henrik Grinnemo and Matthias Corbascio have submitted a joint statement. They do not see how collective responsibility for the contributions of other authors can be reasonable and argue that in raising the alarm about irregularities in a research study – albeit after publication – they fulfilled their responsibilities as co-authors. Oscar Simonson was not working at Karolinska University Hospital (Thorax clinic) at this time and does not know about the clinical development of patient 3. His contribution to the research concerned the animal operations. Karl-Henrik Grinnemo and Matthias Corbascio add another consideration. Oscar Simonson, Karl-Henrik Grinnemo and Matthias Corbascio were involved in a paper that presents human data from research conducted without prior ethical review. As KI made clear earlier, being a whistle-blower does not mean that one can evade investigation and possible responsibility for scientific misconduct. KI therefore finds that all three are therefore blameworthy but not to an extent that would constitute scientific misconduct.

Silvia Baiguera helped to manufacture the synthetic trachea. She was, however, involved in writing a paper that presents research on humans that was conducted without prior ethical review. She is therefore blameworthy but not to an extent that would constitute scientific misconduct.

Constantino Del Gaudio is a materials expert and worked with the manufacture of the synthetic trachea as part of this group. He was involved in writing a paper that presents research on humans that was conducted without prior ethical review. He is therefore blameworthy but not to an extent that would constitute scientific misconduct.

Staffan Strömblad objects in his statement to KI the treatment of author responsibility as a collective responsibility. He believes he can not be held responsible for the actions of the principal authors, especially as he could not access the patient's medical records without breaking the law. He was involved in writing a paper that presents research on humans that was conducted without prior ethical review. He is therefore blameworthy but not to an extent that would constitute scientific misconduct.

Paolo Macchiarini claims that he had an ethical permit for research on animals and a permit from the patient. The paper describes only the cell coating and it was good a week after transplantation. He does not believe that a more thorough clinical description of the patient's condition, with large granulations that required stents at the join between the tissue and the transplant, would have contributed to the scientific discussion on the determination of cell viability, which was what the paper was about. KI finds that the clinical information given in the paper can delude the reader into believing that the



method as such can contribute to a post-operative development, especially if this information is weighed up with other similar publications from Paolo Macchiarini and his group. It is KI's view, then, that the paper lacks balance as it does not report complications and adverse reactions. Paolo Macchiarini is therefore responsible for scientific misconduct.

KI finds that the paper is largely based on patient material obtained without prior ethical review. In making no reference to the patient's actual clinical condition and only to the cell coating on the graft, the reader is denied important information for judging the benefit of the proposed method in a clinical context. The impression given of the patient's airways five months after operation is also untrue. Even if the research field is valuable, the report on the patient bears significantly on the benefits of the results presented. KI therefore finds that the paper must be withdrawn.

Paper 4 – Are synthetic scaffolds suitable for the development of clinical tissue-engineered tubular organs?, published in Journal of Biomedical Material Research A 2014

The paper discusses different tracheal grafts and states that patient 1's condition at twelve months is good, with almost normal airways and improved pulmonary function. There is no documented examination of the patient noted in his medical records 12 months after surgery, the most recent previous examination being a bronchoscopy performed in May 2012, eleven months after surgery. The bronchoscopy shows slightly bleeding granulations around the anastomosis between the graft and the tissue on the left side, where there is copious secretion blocking the opening to the right main bronchus. There is bubbling in the fistula between the trachea and the oesophagus. Exposed bronchial rings are visible. There is severe granulation causing a blockage a little way down the right bronchus through which only the narrowest suction catheter (2 mm) is able to penetrate. A suture has come free at its right-hand lower connection with the tissue, which means that the description of the patient's condition given in the paper is false.

Constantino Del Gaudio is a materials expert and worked with the manufacture of the synthetic trachea. He was involved in writing a paper that presents research on humans that was conducted without prior ethical review. KI finds that he is therefore blameworthy but not to an extent that would constitute scientific misconduct.

Silvia Baiguera helped to manufacture the synthetic trachea. She was involved in writing a paper that presents research on humans that was conducted without prior ethical review. KI finds that she is blameworthy but not to an extent that would constitute scientific misconduct.

Fatemeh Ajallouei writes that she is not a doctor and that she did not have access to the patient's medical records. She believes that all presented in-vitro data are correct and replicable. She was involved in writing a paper that presents research on humans that was



conducted without ethical review. She is therefore blameworthy but not to an extent that would constitute scientific misconduct.

Alessandra Bianco states that she cannot be held accountable for the study's shortcomings as regards the lack of ethical review and the patient's condition, something that she cannot judge given that she is not a doctor. Her contributions to the paper cannot be considered dishonest. KI finds that she was involved in writing a paper that presents research on humans that was conducted without ethical review. She is therefore blameworthy but not to an extent that would constitute scientific misconduct.

Paolo Macchiarini asserts that the declaration that the patient felt well was based on what he had heard from the responsible clinics. Since he met the patient himself at roughly this time on Iceland, he had no reason to question the patient's status. He attributed the patient's persistent breathing difficulties to vascular complications after the right pulmonary artery was damaged during surgery. He also states that the patient's clinical status was not the main concern of the paper. KI finds that Paolo Macchiarini used the paper to publicise the claim that there were long-term benefits of the technique presented by his research group in paper 1. KI finds that Paolo Macchiarini is responsible for scientific misconduct.

The paper gives a false, unbalanced and un-nuanced presentation of alleged long-term benefits of this type of surgery. These benefits are, however, fabrications. Even if the paper could be retained, other parts of it are so serious in this regard that it has to be withdrawn to avoid the technique gaining wider spread before having been developed in pre-clinical studies.

Paper 5 – Airway transplantation, published in Thoracic Surgery Clinics 2014

The paper is a review of different methods that can be used for tracheal transplantation. There is a table of cases at the end, including patients 1, 2 and 3. No more details of the patients are given. The authors say that more development is needed but that many of the patients had well-functioning airways at the time the paper was written. Patient 1 died on 30 January 2014, i.e. before the publication came into print in February 2014. The complainants say that just after the paper was submitted to the journal in August 2013, Paolo Macchiarini announced that patient 2 had died from, as he claimed, a gastrointestinal haemorrhage. However there was no autopsy report available. Patient 3 had her second transplant on 9 July 2013, which the paper does not mention. The paper was submitted to the journal, according to the previous investigation, on 4 August 2013. It was published online on 27 November 2013 and in print on 11 February 2014.

Philipp Jungebluth writes in his statement to KI that the criticised table (3) contains a column that does not relate to the other columns and that the table does not claim to be complete as regards the patients' backgrounds. KI finds that this is an unbalanced publication of clinical cases in which complications and negative consequences are not presented thoroughly enough for the reader to be able to evaluate the clinical



information. In KI's view, therefore, Philipp Jungebluth is responsible for scientific misconduct.

Paolo Macchiarini states that the columns of the table do not correspond to each other. In his opinion, patient 1 was described as well as was possible and that there was not enough time to update the paper with the patient's death since it had already been published online when the death occurred. He also believes that patient 3 was described correctly and points at the need for post-operative stents and their indication. Paolo Macchiarini was involved in the unbalanced and uncritical publication of the clinical cases and the use of patients in research that had not been subjected to prior ethical review. KI finds that Paolo Macchiarini is responsible for scientific misconduct.

According to KI, the paper shows mainly positive results, even if the results make up only a small part of it. Further, it does not adequately describe the risks and negative consequences for the patients, which can give the reader an erroneously optimistic view of the methods' usefulness. The paper must therefore be withdrawn.

Paper 6 – Biomechanical and biocompatibility characteristics of electrospun polymeric tracheal scaffolds, published in Biomaterials 2014

The paper is a review and describes different types of tracheal grafts that the research group has used. It makes particular mention of the graft that was used in patient 1 and the experiences gleaned from this. The previous investigation pointed out that the paper was submitted to the journal on 13 January 2014, was accepted on 7 March and published on 3 April 2014. The paper describes the synthetic trachea as giving rise to large granulations and chronic fistulae, attributing this to its lack of flexibility. The paper does not report that patient 1 was operated on 10 December 2013 in order to move up part of the large intestine to replace part of the oesophagus damaged by the trachea. It was noted during this operation that the graft had become detached from the lung tissue at all three points. The patient died a short while afterwards on 30 January 2014, two weeks after the paper was submitted. In KI's view it would not have been particularly difficult for the authors to amend the clinical description before publication if they had so wished. As mentioned earlier, the paper has already been the object of investigation as far as concerns errors in the illustrations. Here the authors admitted the mistake (case 2-723/2016, decision on 7 June 2017).

Fatemeh Ajalloueian writes that she is not a doctor and that she did not have access to the patient's medical records. She believes that all presented in-vitro data are correct and replicable, and that the paper's description of a 2D model for describing the cell's prospective 3D configuration makes a significant contribution, with a bearing that extends far beyond the scientific field. KI finds that she was involved in writing a paper that presents research on humans that was conducted without ethical review. She is therefore blameworthy but not to an extent that would constitute scientific misconduct.

Mei Ling Lim writes in her statement to KI that she monitored in-vitro studies, including the experimental concept and design, statistics and the dynamic seeding of



cells, the estimation of the number of adherent cells and the MTT analysis. She also made comments on the manuscript. She believes the paper to be important and that it should remain once a suitable erratum has been inserted. She writes that the purpose of the paper is to discuss a novel technique. Describing patient 1 as "...definitely imply that he was alive and in an enticingly good condition..." when he had actually died is a pure misunderstanding. She also states that material development must be allowed to continue and that the material that patient 1 received was the best available at the time. KI finds that she was involved in writing a paper that presents research on humans that was conducted without ethical review. Mei Ling Lim has also demonstrated a lack of scientific ethics in not taking account in her argument the basic rules of research on humans. She is blameworthy but not to an extent that would constitute scientific misconduct.

Greg Lemon states that he is a mathematician and was not able to determine if the data in the paper were relevant or not. He also helped to check the language of the paper, as he has done for other papers. Greg Lemon is neither responsible for scientific misconduct or blameworthy.

Johannes C Haag says that this is a technical paper that makes no claim to report clinical findings. KI finds that he was involved in writing a paper that presents research on humans that was conducted without ethical review. He is therefore blameworthy but not to an extent that would constitute scientific misconduct.

Ylva Gustafsson was involved in writing a paper that presents research on humans that was conducted without ethical review. She is blameworthy but not to an extent that would constitute scientific misconduct.

Sebastian Sjöqvist writes in his statement to KI that the purpose of the paper is to study the mechanical properties of the prostheses and their biocompatibility in vitro. In his view, the paper describes the clinical intervention relatively carefully and states that synthetic prosthetics could be the next solution. The patients are described as having abnormal granulation tissue, chronic fistulas and prosthetic collapse. As he understands it, patient 1 died after the manuscript had been submitted to the journal but before it was published. In his view, the journal should have been informed of the patient's death before publication so that the paper could have been updated immediately. He does not think that the paper should be withdrawn but updated with information about the patient's death. The paper contains numerous illustrations, and some of those mentioned by Sebastian Sjöqvist have already been the subject of a separate investigation, on which Sebastian Sjöqvist also had an opportunity to comment. The paper contains an acknowledged confusion of illustrations, duplicated with several mistakes. He was involved in research on humans that was conducted without ethical review. He is therefore blameworthy but not to an extent that would constitute scientific misconduct.

Antonio Beltrán-Rodríguez says that he did not meet with any of the investigators or was asked any specific questions, a fact he considers important. He was involved in different ways in the research and thinks that even though there were faults with some of



the illustrations, data from morphological and physiological experiments give similar results. KI finds Antonio Beltrán-Rodríguez blameworthy but not to an extent that would constitute scientific misconduct.

Constantino Del Gaudio is a materials expert and worked with the manufacture of the synthetic trachea. He was involved in research on humans that was conducted without prior ethical review. KI finds that he is therefore blameworthy but not to an extent that would constitute scientific misconduct.

Silvia Baiguera helped to manufacture the synthetic trachea. She was involved in writing a paper that presents research on humans that was conducted without prior ethical review. KI finds that she is blameworthy but not to an extent that would constitute scientific misconduct.

Alessandra Bianco states that she cannot be held accountable for the study's shortcomings as regards the lack of ethical review and the patient's condition, something that she cannot judge given that she is not a doctor. Her contributions to the paper cannot be considered dishonest. Further, she did not know about paper 6 until it appeared online, and was not asked about her contribution. KI finds that she was involved in writing a paper that presents research on humans that was conducted without ethical review. It is remarkable that she did not react publically to having been included as a co-author without her knowledge. Alessandro Bianco is therefore blameworthy but not to an extent that would constitute scientific misconduct.

Philipp Jungebluth states that the paper focuses on synthetic tracheae made of "electrospun" or PET/PU. Patient 1 had a graft made of POSS/PCU, which is not discussed in the paper, and this is why the problems for patient 1 were not mentioned before. He also writes that they were not legally obliged to apply for an ethical permit. As with previous papers, Philipp Jungebluth was one of the driving principal authors. KI finds that Philipp Jungebluth is responsible for scientific misconduct.

Paolo Macchiarini believes that the paper describes the situation well and addresses the granulation that the graft caused as well as the fistula that developed. He writes that such experiences prompted the further development of the material. KI finds that as with previous papers Paolo Macchiarini was one of the project's drivers and leader. He is accountable for the shortcomings in terms of scientific competence, knowledge of the rules, coordination and communication that led to the flaws in this work also. Paolo Macchiarini bears considerable responsibility for the deceit inherent in this paper caused by his deliberately misleading colleagues, patients and relatives. KI finds Paolo Macchiarini responsible for scientific misconduct.

Even though the paper points to some of the problems that arose with this type of transplantation, it concentrates more on the material than on the use of a technique that repeatedly caused fistulas, serious complications and death. It is therefore, despite this angle, misleading and could motivate further experiments in the field, with the possible injury to patients it entails. KI therefore finds that the paper must be withdrawn.



**Karolinska
Institutet**

The decision on this matter has been taken by President Ole Petter Ottersen after presentation by docent Pierre Lafolie and legal counsel Mats Gustavsson. Also participating in the final handling of the case was head of the Legal Office Helén Törnqvist.

Ole Petter Ottersen

Pierre Lafolie

Mats Gustavsson