

May 7, 2015

**Re: 2-2184/2014 Allegations of Scientific Misconduct against Professor Paolo Macchiarini, Karolinska Institutet**

To the President of Karolinska Institutet

Dear Professor Hamsten,

We have now reviewed Prof Macchiarini's answers to our allegations and would like to comment upon them in a concise manner. Our main conclusions will be listed directly below followed by a separate analysis of the text. The response by Prof Macchiarini did not in any way diminish our concerns over the treatment to which these patients were subject to, but instead reaffirmed the impression that the scientific basis of this therapy and the publications that it has yielded, rests on fabricated or manipulated data. Although the response by Prof Macchiarini is great in length, it failed to address some of the most important allegations and also confirmed deficiencies that we previously only suspected. The response provided by Prof Macchiarini has only addressed the content of first part of our appeal for an investigation and does not mention any of the allegations found in the document titled Amendment to the Appeal for an Investigation submitted to Karolinska Institutet on September 24, 2014. Our main conclusions and comments are as follows:

- Prof Macchiarini was employed as a Senior Consultant at the Department of Ear, Nose and Throat, Karolinska University Hospital, Huddinge and a Visiting Professor at Karolinska Institutet. As the principle investigator and senior scientist leading these scientific investigations, he has the main responsibility for the content of all scientific work he produces, as well as ensuring that all ethical and legal obligations are fulfilled. Any attempt to interject plausible deniability is not credible.
- At the time that these procedures were performed on the three patients at Karolinska, there existed no scientific data in small or large animals to support the feasibility of implanting a synthetic trachea reconstituted with bone marrow-derived cells. Extrapolating results obtained from decellularised allograft trachea transplantation to synthetic trachea transplantation is logically flawed. One is biological in origin, the other is made of plastic.
- Application for ethical permission with the local ethical review board (Etikprövningsnämnden) and registration with the Swedish Medical Products Agency (Läkemedelsverket) would have revealed the lack of scientific data supporting the feasibility of these procedures. By circumventing this process, proper oversight of the procedures never occurred and the paucity of scientific data was never revealed.

- The written informed consent constitutes a vital part of an application to the ethics review board when the aim is to conduct research in human beings. Consequently, a principal investigator cannot author this document on one's own initiative and then distribute to patients for signature. One of the functions of the ethics committee is to review the content in order to avoid formulations, which could exert pressure or coerce the patient. To use formulations like *"this is my only chance for survival"*, which can be found in the form produced by Prof Macchiarini, would probably not have passed a review by the local ethics committee. We can never be certain of this since Prof Macchiarini has not applied for ethical permission. Instead Prof Macchiarini has relied on the opinion of a private person, stated in a single e-mail correspondence, before proceeding with novel high-risk experimental surgery in human beings.
- At the end of the methods section of the first article published in the *Lancet* it is stated that *'the transplant procedure was approved by the local scientific ethics committee'*. This is not true and stating this in an article when it is not, is not only misleading to all of the co-authors but is also in our opinion, grounds for retraction.
- Three different synthetic tracheae manufactured from three different types of material were implanted to 3 patients during a time span of 2 years. None of these synthetic tracheae have been registered with the Swedish Medicinal Products Agency. It is our opinion that each implantation of a new unregistered medical device is a breach of Swedish law governing the use of medicinal products (LVFS, Läkemedelslag 1992:859).
- There exists no scientific data supporting the use of a *'regenerative boosting therapy'* in the medical literature. It remains unclear on what evidence this therapy was designed. Furthermore, patients were exposed to TGF- $\beta$ 3, acquired from a lab product supplier (R&D Systems, Minneapolis, MN, USA) and which is not approved for use in either animals or humans. All three patients were treated with unapproved high doses of erythropoietin and Granulocyte Colony Stimulating Factor (G-CSF) and all patients suffered from life-threatening thromboembolic complications. Lack of registration of this administration of drugs for a new indication as well as neglecting to report adverse events is in our opinion not reconcilable with Swedish law governing medicinal products.
- All implantations of synthetic tracheae were electively planned procedures in stable patients who were not threatened with impending affixation or death. On the contrary these patients were in stable clinical status allowing them to fly to Sweden using standard international airline transportation. A review of all three patient's medical records will demonstrate this conclusively and beyond doubt. Consequently, the utilization of a *'compassionate use'* clause is in our opinion invalid and an attempt to coerce external parties into the

belief that application for ethical permission and registration with the Swedish Medical Products Agency would have been superfluous.

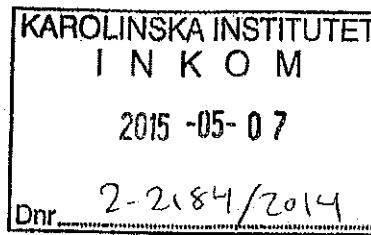
- Reoccurrence of the primary malignancy, which was postulated to be the indication for tracheal transplantation in the first patient, was never confirmed. Radiological examinations gave indication of malignancy but all biopsies were negative and the native trachea was never examined by a pathologist. It is our opinion that this event in and of itself justifies grounds for investigation by The Health and Social Care Inspectorate (Inspektionen för Vård och Omsorg).
- Histological analyses of the transplanted synthetic trachea presented in the *Lancet* do not correspond to the biopsy reports in the patient's medical records. Prof Macchiarini does not deny this, but instead blames his co-authors for delivering incorrect data. Consequently, this implies that the data in the *Lancet* article is incorrect and therefore it is our opinion that the articles published in the *Lancet* should be retracted independently of any other deficiencies that maybe unearthed.

The response supplied by Prof Macchiarini has not mitigated the seriousness of allegations, but has instead underscored the fraudulent means utilized in his scientific endeavors. It is our opinion that Prof Macchiarini in his response has revealed further evidence of misconduct and negligence, which increases the impetus for retraction of these articles from the medical literature. It is our ambition that this analysis of Prof Macchiarini's response will provide you and the external reviewer sufficient clarity and the evidence necessary to proceed with confidence in the direction that your discretion deems appropriate.

Sincerely,

Matthias Corbascio  
Thomas Fux  
Karl-Henrik Grinnemo  
Oscar Simonson

Department of Cardiothoracic Surgery and Anesthesiology  
Karolinska University Hospital, Solna  
171 76 Stockholm  
Sweden



May 7, 2015

## Considerations of Professor Paolo Macchiarini's Response to Allegations of Scientific Misconduct 2-2184/2014

Matthias Corbascio, Thomas Fux, Karl-Henrik Grinnemo, Oscar Simonson  
Department of Cardiothoracic Surgery and Anesthesiology, Karolinska University Hospital, Solna, Sweden.

---

The following is an analysis of Prof Macchiarini's response to our Appeal for an Investigation of Scientific Misconduct submitted to Karolinska Institutet on the 18<sup>th</sup> of August, 2014 and Amendment to the Appeal for an Investigation of Scientific Misconduct submitted on September 24, 2014, both with the reference number 2-2184/2014. The portions of Prof Macchiarini's response that we would like to comment on have been copied from his response and are shown in blue font and our analysis is shown thereafter in black. Because of time constraints and the multitude of potential issues we have chosen to concentrate on what we feel are the most important points.

### Article 1.

#### Tracheobronchial transplantation with a stem-cell-seeded bioartificial

nanocomposite: a proof-of-concept study. Jungebluth P, Alici E, Baiguera S, Le Blanc K, Blomberg P, Bozóky B, Crowley C, Einarsson O, Grinnemo KH, Gudbjartsson T, Le Guyader S, Henriksson G, Hermanson O, Juto JE, Leidner B, Lilja T, Liska J, Luedde T, Lundin V, Moll G, Nilsson B, Roderburg C, Strömblad S, Sutlu T, Teixeira AI, Watz E, Seifalian A, Macchiarini P. Lancet. 2011 Dec 10;378(9808):1997-2004.

Submitted Oct 11, 2011, published online Nov 24, 2011.

#### Comment 1:

On page 5 of Reply to Analysis Prof Macchiarini claims: *"Overall, it should be noted that KHG is a co-author of the manuscript in question as he was one of the primary Swedish physicians responsible for the entire clinical care of the patient and has access to the patient's medical record. Paolo Macchiarini (PM), as a visiting consultant, did hold a temporary Swedish medical license (from 1<sup>st</sup> December, 2010 until 30<sup>th</sup> November, 2014) and could theoretically have access to the patient's medical record. However, PM did not ever access the record as a non-Swedish speaking physician, as proven by the attached documentation (Appendix 1). Philipp*

*Jungebluth (PJ), as a researcher at Karolinska Institutet, has never had direct access to the patient's medical record. We therefore relied solely on the reports and clinical summary of KHG and other clinicians. A more detailed list of medical professionals who accessed the medical record of the patient(s) in question and when it was accessed is available upon request from Karolinska University Hospital."*

The response by Prof Macchiarini, the principal investigator of this research, starts with a disclaimer, which is repeated throughout the body of the response, that all clinical information has been given to him second hand. This implies that any inconsistencies found in the text could have been introduced by external agents and subsequently that Prof Macchiarini cannot attest to the veracity of the articles content. The responsibilities of being the senior scientist and principle investigator is to have the complete responsibility for the content of all scientific data produced and to insure that all ethical and legal standards are met in any and all scientific endeavors. To purport that other clinicians and co-authors are the source of these inconsistencies is far-fetched, approaching the ridiculous. Any attempt to push the burden of responsibility on to co-authors or other personnel is not credible.

The first patient received the totality of his medical care at the Department of Ear, Nose and Throat, Karolinska University Hospital, Huddinge. To accuse a physician working at another hospital campus at another department for all the misrepresentation and inaccuracies is a desperate act of denial. Prof Macchiarini was a senior consultant at the department where the patient was admitted and was designated as his responsible physician and the head surgeon during the implantation procedure. In his absence other consultants from that same department have taken over responsibility of the patient, which is evident when reviewing the patient's medical records. To place this responsibility on another physician at another department at another hospital campus is not a standard scenario in the current organizational structure, but an attempt to absolve oneself of responsibility as the patient's primary physician and as the principle investigator.

The fundamental basis of the five month follow-up, which is the first *Lancet* article (page 7, Reply to Analysis, Macchiarini), and the eight month follow-up, which is the second *Lancet* article (page 21, Reply to Analysis), is a one page summary provided by Dr Karl-Henrik Grinnemo describing the patient's clinical status at ***the time of discharge one month after transplantation*** (Appendix 5, Reply to Analysis, Macchiarini). The original discharge note was written by Dr Gert Henriksson from the Department of Ear, Nose and Throat on the 8<sup>th</sup> of July 2011 (see patient 1 medical records). The one page summary is a verbatim translation of Dr Henriksson discharge note. Prof Macchiarini argues that since none of the co-authors contacted him when the patient was readmitted and urged him to stop the publication of these articles, the publications were allowed to proceed. In our opinion this is not a credible

explanation. The patient was readmitted on November 21, 2011, to Prof Macchiarini's department where he was employed and indisputably present at the time and therefore the responsibility of stopping publication should fall solely on him.

What is more revealing and even more disturbing than trying to place responsibility on other doctors for the shortcomings of the first *Lancet* article, is that Prof Macchiarini has revealed that two articles in the *Lancet* are based on the discharge note at one month post-transplantation. This implies that Prof Macchiarini has not performed any follow-up in his two follow-up articles. Thereby, the principal investigator Prof Macchiarini has admitted that the content of both *Lancet* articles is built on misrepresented data and subsequently it is our opinion that the articles must be retracted. When clinical data became apparent which contradicted the main findings of the first *Lancet* article, demonstrated by the readmission notes and the disastrous finding of the bronchoscopies performed on the 21<sup>st</sup> and 22<sup>nd</sup> of November (Appendix 15, 17 Analysis of Clinical Outcome), he neglected to alert the *Lancet*. His presence at the Department of Ear, Nose and Throat is corroborated by the nurse's notes from the 21<sup>st</sup> of November where it is clearly stated that "*Dr. Juto or Dr Maccarina [as written by the nurse] will have to update the patient's medicine list the next morning*" (Appendix 16, Analysis of Clinical Outcome). Continuing to purport that the patient was still clinically asymptomatic at eight months after transplantation with a normal patent airway as depicted in the second *Lancet* article, is fabrication. These facts are in our opinion sufficient grounds for retraction of both of the articles from the *Lancet* as well tantamount to fraud.

On page 5 Prof Macchiarini further claims: "*Paolo Macchiarini (PM), as a visiting consultant, did hold a temporary Swedish medical license (from 1<sup>st</sup> December, 2010 until 30<sup>th</sup> November, 2014) and could theoretically have access to the patient's medical record. However, PM did not ever access the record as a non-Swedish speaking physician, as proven by the attached documentation (Appendix 1).*"

Comment 2:

As stated above, Prof Macchiarini may not have entered into the electronic medical records of the patient, but he was physically present at the Department of Ear, Nose and Throat when the patient was readmitted. The admitting physician was Dr Juto (Appendix 14, Analysis of Clinical Outcome), who also performed the bronchoscopies on the 21<sup>st</sup> and 22<sup>nd</sup> of November, 2011 (Appendix 15, 17, Analysis of Clinical Outcome). It is highly unlikely that upon readmission of this very unique patient, that Dr Juto would not have informed Prof Macchiarini of the patient's presence or the terrible state of his airway.

Comment 3:

On page 5 it is claimed: *"We therefore relied solely on the reports and clinical summary of KHG and other clinicians. A more detailed list of medical professionals who accessed the medical record of the patient(s) in question and when it was accessed is available upon request from Karolinska University Hospital."*

In this portion of the response the principal investigator Prof Macchiarini directly contradicts his statement in the first article published in the *Lancet*. On page 1999 of the first *Lancet* article (Appendix 4, Analysis of Clinical Outcome) in the section titled *"Role of the funding source"* the second sentence states the following: *"The corresponding author had full access to all the data in the study and final responsibility to submit for publication."* Prof Macchiarini is the corresponding author as stated on page 1998 of that same article and he is correct in that as the main author he is responsible for its content. The inability to speak Swedish especially among fluent English speaking colleagues, does not absolve Prof Macchiarini of insuring that the content of the articles corresponds to the content of the medical records.

Comment 4:

On page 5 it is further claimed that: *"Additionally, all clinical data presented in the manuscript had been thoroughly discussed by the entire consortium of co-authors prior to submission to Lancet. The final version of the manuscript had been circulated to all co-authors prior to publication (online on 11<sup>th</sup> November, 2011) and approved by all co-authors (including KHG) through a written consent (available by request from The Lancet) prior to submission of the manuscript on 11<sup>th</sup> October, 2011. Of note, KHG et al.'s accusations have surfaced nearly 3 years after the publication of this manuscript."*

At the time of receiving the proofs of the first *Lancet* article on the 8<sup>th</sup> of November 2011, there was no reason to question the veracity of the content of the manuscript. The patient had not been readmitted to Karolinska since his release in July, so the co-authors would not have had any reason to question signing the consent form for publication. Furthermore, upon reading that the study had received ethical approval from the local ethics committee, they would have naturally assumed that this was true since it is the responsibility of the principle investigator, Prof Macchiarini, to insure that all ethical and legal issues have been resolved at the time of submission. Furthermore, it was the responsibility of Prof Macchiarini to stop the publication of the article when he was made aware of the findings of the bronchoscopies of the 21<sup>st</sup> and 22<sup>nd</sup> of November 2011 (Appendix 14-17, Analysis of Clinical Outcome). He did not alert the *Lancet* and publication proceeded.

As physicians practicing at the Department of Cardiothoracic Surgery and Anesthesiology, Karolinska University Hospital, Solna, we first became aware of the terrible state of the first patient when we were contacted in order to discuss the possibility of performing a right-sided pulmectomy to alleviate chronic dysfunction and infection of the entire right lung (see medical records of patient 1). This was in **the fall of 2013**. At this time the second patient had already been transplanted, returned home and died shortly thereafter, and the third patient had been in our department for over a year and was suffering from multiple debilitating complications (see medical records of patient 3). At this time it became clear that this procedure entailed disastrous complications for the patients subjected to it. This, together with the fact that Prof Macchiarini left his responsibility for the 3<sup>rd</sup> patient, lead us to start investigating the circumstances surrounding this procedure and ultimately to form our appeal for an investigation. Up until this time we never questioned the veracity of Prof Macchiarini's publications nor his competence as a scientist or physician.

Comment 5:

On page 5 Prof Macchiarini writes: *"Please see the written statement of Dr. Richard Kuylenstierna, ENT, Karolinska University Hospital, Huddinge, who organized/supervised all ethical related issues, from 30<sup>th</sup> November, 2014,..."*

Refers to a document written by Prof Kuylenstierna (*"To whom it may concern"* dated November 30, 2014) which starts up with the following sentence::

*"The patient was referred to Karolinska from abroad on the basis of previously published reports stating the success of a new technique in the field of airway reconstruction performed in Spain and in the UK. The patient had previously been treated surgically and received external irradiation in his...."*

The previously published reports stating the success of a new technique refers to the use of a **human decellularised tracheae from cadaveric donors**, one case in Spain 2008 and one case in the UK 2010 (1,2). The success achieved using a biologically based scaffold does not automatically translate into using a scaffold produced synthetically in plastic. Prof Kuylenstierna neglects to state this in his letter and has thereby given the impression that there exists scientific data to support the use of a synthetic trachea. This is misleading, since the material to be used had never been tested in either rodents or large animals. Consequently, it would be impossible to know anything about the outcome of transplanting a trachea made of plastic into a human being.

**1. Clinical transplantation of a tissue-engineered airway.** Macchiarini P, Jungebluth P, Go T, Asnaghi MA, Rees LE, Cogan TA, Dodson A, Martorell J, Bellini S, Parnigotto



PP, Dickinson SC, Hollander AP, Mantero S, Conconi MT, Birchall MA. Lancet. 2008 Dec 13;372(9655):2023-30.

2. **Stem-cell-based, tissue engineered tracheal replacement in a child: a 2-year follow-up study.** Elliott MJ, De Coppi P, Speggorin S, Roebuck D, Butler CR, Samuel E, Crowley C, McLaren C, Fierens A, Vondrys D, Cochrane L, Jephson C, Janes S, Beaumont NJ, Cogan T, Bader A, Seifalian AM, Hsuan JJ, Lowdell MW, Birchall MA. Lancet. 2012 Sept 15; 380 (9846):994-1000.

Comment 6:

Prof Kuylenstierna writes the following passage in his ethical justification of performing the procedures:

*"I have been in contact with the medical product agency (Lennart Åkerblom) whose opinion in this case is that the sole responsibility lies within the framework of the medical authorities (lege artis) in a case where the major indication is survival or not."*

The clinical state of the patient was not a question of "survival or not" (see medical records of patient 1 at the time of the first admission). There were other alternatives for the patient. The patient was not in a state of impending suffocation (see medical records of patient 1, clinical status at the first admission). The proper treatment for impending suffocation in this scenario, if this would have been the case, is stenting of the airway to relieve obstruction. At the time of admission the patient was nearly asymptomatic and was preoperatively free to come and go at will including given leave for an entire weekend (see medical records of patient 1, doctors and nurse's notes during the time before the first transplantation). This is not a sufficient level of monitoring for a patient suffering from impending suffocation. Furthermore, a proper diagnosis was never attained preoperatively. PET-CT demonstrates absorption at the site of prior surgery but a biopsy positive for malignancy was never produced (see medical records of patient 1, all biopsy reports).

Comment 7:

Prof Kuylenstierna continues his justification with:

*"This opinion was shared by Pierre LaFolie at the local ethical committee."*

The text that Prof Kuylenstierna is referring to is the following, which was written in an email by Pierre LaFolie (see ref number 32981/20 IVO, submitted 2015-02-18):

*"Bedömningen av vad som gäller ur ett forskningsetiskt perspektiv avgörs av huvudmannen för forskningen enligt etikprövningslagen EPL, dvs i detta fall av SLL om*

*det inte är delegerat till sjukhusdirektör/verksamhetschef. EPL säger också att förhandsbesked från etikprövningsnämnden ej kan ges."*

The last sentence states that *"preliminary decisions cannot be provided by the ethics committee"*, in other words a complete application for ethical approval must be submitted in order to attain approval.

*"Som vi diskuterade kan huvudmannen också överväga vad som står i Hälso- och sjukvårdslagens §26 vari det framgår att sjukvården ansvarar för att följa upp sina rutiner och insatser (kvalitetsutveckling) och utveckla metoder (forskning). I det som du tog upp i ditt samtal nämnde du att denna operation avses göras på vitalindikation, varav följer att det kanske är mer en medicinsk etisk fråga, än en forskningsetisk fråga."*

The last sentence states: *"According to what you brought up in your discussion, you stated that this operation was a question of life or death, subsequently it maybe more a question of medical ethics than a question of research ethics"*. In other words Prof Kuylenstierna has made the case that there are only two options, synthetic tracheal transplantation or death. This is untrue since the patient could have received a stent to alleviate any impending suffocation in order to provide time to make a definite diagnosis. Furthermore, it is unknown if the patient actually had a reoccurrence of his primary malignancy since histological verification was never found in the pre-transplant biopsies (see medical records of patient 1, all biopsy reports) and the removed trachea was never examined by a pathologist which in itself is a complete lapse from the well-established routines in cases with postulated malignancies undergoing surgical resection. Histological analysis of a postulated tumour and clarification of surgical radicality (if the resection sites are free from tumour cells) are the main cornerstones in cancer surgery and influences the prognosis and future care of the patient. Why this was not done can just be speculated upon.

Dr LaFolie ends his email with the following statement:

*"Jag vill understryka att detta svar är lämnat av mig som privatperson, och att i händelse av att ärendet kommer upp i EPN jag avser meddela jäv."*

The translation of this sentence is: *"I would like to emphasize that this answer which I have provided is by me as a private person, and if this case comes up for discussion at the Ethical Review Board then I will have to declare bias."*. In other words, this is not an official sanction by a member of the ethical review board but a judgment from a private person.

In Prof Kuylenstierna's email to Dr LaFolie he writes the following (see ref number

32981/20 IVO, submitted 2015-02-18):

*"XX har fått all konventionell behandling som extern radioterapi och kirurgi men har recidiverat lokalt i trakea med hotande hotande kvävning. XX enda chans till överlevnad är att tumören avlägsnas vilket kommer att kräva en rekonstruktion som aldrig prövats tidigare nämligen att defekten ersätts med ett artificiellt polymertransplantat som relinäs dels med stamcellsteknik men också med luftvägsslemhinna."*

The translation of this is: *"XX has received all forms of conventional treatment like external radiotherapy and surgery but has a reoccurrence locally in the trachea with threatening suffocation. XX only chance for survival is that the tumor is removed which will demand a reconstruction that has never been tried before, specifically that the defect is replaced with an artificial polymer transplant that has been reconstituted with stem cell technology and with airway mucosa."*

First of all, the patient was not suffering from impending suffocation. Review of the medical records depicts a patient hardly affected by the partial obstruction of the airway, with the ability to breathe normally and attain normal oxygen saturation of the blood on air. The admission notes describes the patient's general status as *"good and unaffected"* and as already described above, the patient was free to leave the hospital on social visits and even went on extended leave for the entire weekend before surgery. So the state of the patient as described to Dr LaFolie is not accurate. Furthermore, stating that his only chance for survival is a tracheal transplant is false. Whether the patient actually had a tumor had not been verified and the option of stenting the partial obstruction was still available. So the circumstances that were presented to Dr LaFolie were not accurate and therefore his response is not applicable.

Comment 8:

On page 11 and 12 of Reply to Analysis, Prof Macchiarini discusses the biopsy findings in the first *Lancet* article. In the results section of that article the following sentence can be found: *"The biopsy sample 2 months after transplantation showed large granulation areas with initial signs of epithelialization and more organised vessel formations, and no bacterial or fungi contamination..."*

However the pathologist writes in his report the following (Appendix 8a, Analysis of Clinical Outcome):

*"In the sections from the submitted samples can be found a cylinder of tissue that is composed of eosinophilic material similar to degenerated connective tissue with granulocytic reaction at the edge of the biopsy. Using double refractory microscopy,*

*collagen fibers can be detected. Even trichrome staining shows collagen fibers. **No intact nuclear staining, which implies advanced degeneration-necrosis.** Focally, basophilic granulocytic material can be identified. This can represent dystrophic calcification. Trichrome staining shows erythrocytes partially in seemingly shadow formations of vascular structures partially assumed in the interstitium. PAS staining identifies fungal hypha. Gram-staining shows bacteria colonization.”*

The pathologist then amends his report ten days later with the following statement (Appendix 8b, Analysis of Clinical Outcome):

*“The other two frozen biopsies are also fixated and sectioned. One of them shows a similar picture of necrotic connective tissue with **detectable fungal hyfa** like the one above. The other one consists of capillary rich granulation, partially with an ulcerated surface, partially with recognizable epithelial lining showing squamous epithelial metaplasia.”Final diagnosis: “Biopsies from transplanted trachea with necrotic connective tissue with **fungus and bacteria** and capillary rich granulation.”*

Prof Macchiarini’s answer to this is the following (page 13, Reply to Analysis):

*“All medical data and information have been provided and approved by the Swedish medical doctors that are co-authors on the manuscript (please find attached emails by KHG, (Appendices 4-6, 11). The manuscript had been circulated and approved by all co-authors (written approval on request at The Lancet). The notes in the medical record and biopsy results cannot be personally confirmed or denied by us because we do not speak the language and have therefore never accessed the medical recording system at any stage during data collection or submission of the discussed manuscript. As mentioned above, at the time of publication of this manuscript, we had no reason to question the accuracy of the clinical information provided by the clinical medical providers in this case (KHG included), therefore written proof was never requested.”*

In other words, it is the fault of the **co-authors** that the biopsy description in the *Lancet* article is different than the results in the medical records. The co-authors should according to Prof Macchiarini have alerted him of the discrepancies. Prof Macchiarini is incorrect. It is the responsibility of the senior author and principle investigator to insure that the content in the submitted manuscript is correct. Furthermore, if he or Dr Jungebluth never looked at the medical records as they attest, then from where did the incorrect cited biopsy results originate? This line of defense also provides direct evidence that the principal investigator Prof Macchiarini has either fabricated the clinical results or is the victim of a conspiracy involving a number of clinicians.

More importantly, in the passage above, Prof Macchiarini does **not deny** that the

findings in the article are incorrect. He only states that he cannot be held responsible. The conclusion of this reasoning is that the results in the first *Lancet* article are false. If Prof Macchiarini could have produced a series of biopsies, which depicted something other than what is found in the medical records then he could have argued that the content of the first *Lancet* article was true. He has not done so. He admits that the information is not correct and that his co-authors have failed him, implying a rather surreal conspiracy as the co-authors accused by Prof Macchiarini in his reply were not informed about the patient's current status or that he was re-admitted. The direct implication of this is that the article should be retracted, no matter who has entered the incorrect data, the data is still false.

Comment 9:

The sentence in question on page 14 in Prof Macchiarini's response: *"5 months after transplantation, the patient is asymptomatic, breathes normally, is tumor free, and has an almost normal airway (figure 2C) and improved lung function compared with preoperatively."* **does not mention any histological findings.** The statements were instead, again, based on a clinical summary provided by KGH (**Appendices 4-6**). Comments regarding histologic findings from bronchoscopies in December or other time points are irrelevant in this context.

In this passage Prof Macchiarini freely admits that he is using the information from the **one-month post-transplant discharge note** to make claims about the patient's status at **five months** of follow-up. Furthermore, he is admitting that he never reviewed the patient's medical records, which would have demonstrated pathological findings on the biopsy. Therefore the data presented in the article is false and consequently it is our opinion that the articles are retracted.

Further down on page 14 Prof Macchiarini under the last section Response claims:

*"We do not state that at the exact time point of 4 months postoperatively the fungal infection had been resolved but instead state within 4 months. Because we have not accessed the patient's medical record, we cannot verify with negative cultures, the absence of infection, at the time of discharge. This information, again, was a re-statement of an e-mail authored by one of the primary physicians on this case, KHG, addressed to PJ on 29<sup>th</sup> August, 2011 (Appendices 4-6), which states, "....The patient was transferred to the normal ward twenty-one days after surgery and was discharged to the referral hospital one month after surgery. At the time of discharge, endoscopy demonstrated signs of vascularization and overgrowth of bronchial epithelium on the upper part of the synthetic tracheal implant. His respiratory status had also strikingly improved and chest x-ray showed improved ventilation of both lungs with less atelectasis in the right upper and lower lobes. The patient had no signs of active infection at the time of discharge." The clinical team, including KHG,*

*did not report any significant clinical changes between their clinical summary (29<sup>th</sup> August 2011) and the time of publication. This includes prime opportunities to raise concerns when the final draft of the manuscript was sent for authors' approval and, once accepted by The Lancet, at the time the manuscript proofs were again sent for approval. We must refer to previous statements regarding our error in judgment to trust these statements without insisting on laboratory proof."*

Proper follow-up would have entailed contacting the physicians at the referral hospital who see the patient on a regular basis to inquire on the status of the patient. Again, Prof Macchiarini freely admits that the follow-up is based on the discharge note written **one-month after transplantation**. He does not deny that the graft is chronically infected, which is **not** what is stated in the article. The findings in the article are thereby incorrect. The basis for the conclusions of the article is thereby flawed and subsequently the article should be retracted.

Comment 10:

On page 17 Prof Macchiarini responds: *"In contrast to the alleged statements of KHG et al, the term "biocompatibility" does not include in vivo testing neither for the actual purpose nor the anatomical position. In contrast, biocompatibility is a term from the in vitro testing using assays and ex vivo experimental settings."*

The word *"biocompatibility"* is used in the consent form signed by the first patient. The Merriam-Webster Dictionary defines biocompatibility as: ***"compatibility with living tissue or a living system by not being toxic, injurious, or physiologically reactive and not causing immunological rejection"***. This definition is different than the definition provided by Prof Macchiarini. Most people would probably understand the word to mean compatible with in a living organism. The use of this word in the consent form could have led the patient to believe that the synthetic trachea had been tested in a living organism. This was not the case and this misunderstanding demonstrates the importance of submitting the informed consent form with the ethical review application. Had the consent form been reviewed by external experts, then they may have questioned on what basis this synthetic trachea was biocompatible. Thereby they would have been informed that it actually had never been implanted in any organism, but that this statement was based on *ex vivo* testing. Not only would the consent forms wording have been refuted, but the proposed experiment probably outright rejected.

Comment 11:

On page 18 Prof Macchiarini states: *"Although the consent form may not be ideal by FDA standards, it is acceptable from a Swedish legal point of view."*

This is not correct. A consent form according to Swedish law must be submitted to an ethical review board and approved to insure that no false statements or misrepresentations are contained in the text. Since there was no ethical permission approved or applied for, the presence of a consent form is worse than if there had been no consent form at all because the consent form gives the impression to the patient that the procedure has been vetted by the proper external authorities. In this particular case, not only is the language contained in the consent form coercive, the existence of it is a form of coercion.

Comment 12:

On page 20 Prof Macchiarini claims that: *"It is unrealistic that a novel procedure with such high media and medical/surgical stakes would have been approved at the Karolinska University Hospital on a normal working day in an open operation room, with so many professionals of various medical and surgical disciplines involved, without the required documents in place and without appropriate consensus to proceed with the procedure in an attempt to save a man's life."*

Everyone in the operating room would automatically assume that the proper ethical permission and registration with the Medicinal Products Agency were in place by the principal investigator, researcher and the head surgeon responsible for the procedure, as well as that this had been tested in vivo in an large animal model and followed long-term before initiating serial research experiments in humans.

**Article 2.**

**Engineered whole organs and complex tissues.** Badylak SF, Weiss DJ, Caplan A, Macchiarini P. *Lancet*. 2012 Mar 10; 379(9819):943-52. Review.

Submitted Aug 12, 2011, published online Mar 10, 2012.

Comment 13:

The first patient was transplanted on June 9, 2011. Article no. 2 was **submitted on August 12, 2011**. This is **two months and 3 days after transplantation**. On page 23 Prof Macchiarini defends his in the article postulated sentence: :

*"The graft was patent, well vascularised, and lined with a well-developed healthy mucosa 8 months after transplantation."*

It is important to point out that Prof Macchiarini is presenting **eight month** follow-up

data already **two months after transplantation**. An examination of the patient's medical records up until 8 months after transplantation would have revealed that the patient had undergone multiple episodes of stenting and surgical interventions to relieve granulation formation and was suffering from fistulation of the airway. This is hardly what would be expected by the statement of a patency (Appendix 21, Analysis of Clinical Outcome). Granuloma obstructed the right main bronchus and the bronchus to the right upper lobe was completely occluded resulting in secondary infection (see patient 1 medical records, Nov 24, 2011). The graft maybe patent but at the site of anastomosis there is fistulation and granuloma. To argue that the description is correct by claiming that it only relates to the graft itself and not to the points of connection in the rest of the airway is semantic subterfuge.

*"Further down on page 23 Prof Macchiarini claims: "Additionally, biopsy results without mention of epithelium should not be taken as definitive evidence of the absence of healthy epithelium."*

The biopsy description from the pathologist is quite specific in describing an absence of normal airway mucosa (Biopsy report February 17, 2012, Appendix 21, Analysis of Clinical Outcome). Inspection of the bronchoscopy films from Nov 21, Nov 22, Dec 20, 2011 and Feb 14, 2012 (Bronchoscopy Film 1-4 included on USB in Analysis of Clinical Outcome) all demonstrates a severely pathological and stented airway without vascularization or healthy mucosa and extensive granuloma and fistulation.

### Article 3.

**Verification of cell viability in bioengineered tissues and organs before clinical transplantation.** Jungebluth P, Haag JC, Lim ML, Lemon G, Sjöqvist S, Gustafsson Y, Ajallouelian F, Gilevich I, Simonson OE, Grinnemo KH, Corbascio M, Baiguera S, Del Gaudio C, Strömlad S, Macchiarini P. *Biomaterials*. 2013 May; 34(16):4057-4067. doi: 10.1016/j.biomaterials.2013.02.057.

Submitted Feb 5, 2013, published online Mar 6, 2013.

### Comment 14:

On page 25 Prof Macchiarini claims: *"It should be noted that KHG, MC and OS (again) are co-authors of the manuscript in question as they were the primary Swedish physicians responsible for the **entire clinical care** of the patient and had/have access to the patient's medical record."*

OS has never been involved in the clinical care of patient 3. KHG and MC only became involved in the care of patient 3 when the patient required surgical



intervention for complications. Prof Macchiarini was the primary surgeon and principle investigator responsible for the care of the patient. He was in regular and frequent contact with the department's Head, surgical consultants and intensive care specialists to direct all major planning (held multiple therapy conferences) in all aspects of her care. At the time of submission of the article we had no reason to question the veracity of Prof Macchiarini's scientific work, nor his competence as a physician. We assumed that Prof Macchiarini had consulted the patient's medical records when writing the article.

Further down on page 25 Prof Macchiarini states: *"After the first transplantation in 2011 at the Karolinska Hospital Huddinge, the Karolinska Hospital administration determined all further transplantations were to be done at the Thoracic Clinic in Solna, directed by Dr. Ulf Lockowandt. PM was to act only as a visiting consultant belonging to the ENT Division and be "clinically available" for consultation. As the previous letter from Dr. Richard Kuylenstierna demonstrates, he was not responsible for any administrative hospital tasks related to tracheal transplantation, as stated in his contract (Appendix 2). These were the responsibilities of the doctors at the Thoracic Clinic under Dr. Ulf Lockowandt. In addition, The ENT Department preferred to rely on the previous administrative experience of Dr. Richard Kuylenstierna in regards to the paperwork related to this type of transplant.*

This is a fabrication. The patient was operated at the Department of Cardiothoracic Surgery and Anesthesiology because of the eventual need for cardiopulmonary bypass. Prof Macchiarini was the senior scientist and principle investigator in charge of this research. As such he was responsible for all legal, ethical and clinical decisions.

On the next page 26 Prof Macchiarini continues with the following response: *"Although PM personally informed the patient and family of the risks, benefits and alternatives of the tracheal transplantation, answered all questions, and obtained verbal consent to perform the transplant, he was not the responsible party for the administrative approvals from the Regional Ethical Review Board (as per the above).*

Again, Prof Macchiarini was the senior scientist and principle investigator in charge of this research. As such he was responsible for all legal, ethical and clinical decisions.

Prof Macchiarini goes on by claiming: *"Similarly, it would not be appropriate for him or a member of the research team to obtain informed consent for obtaining tissue for study. This is the responsibility of an independent party, familiar with the research, in order to avoid issues of potential bias or coercion."*

Prof Macchiarini reveals that he does not understand the responsibilities of what it entails to be the principle investigator in this experimental research setting. Just the

opposite is true. It is his responsibility of the principle investigator to insure that informed consent is obtained, either by himself or by proxy.

Prof Macchiarini further down on page 26: *"This statement, whose official copy can be requested at the Lawyer's office of the Karolinska Institutet, [Ms. Lisen Samuelsson, Jurist Ledningskansliet, (lisen.samuelsson@ki.se)] self-contradicts the allegations of lack of informed consent in the medical records and the above comments regarding ethical permissions. KHG, et al. state the patient did indeed sign a consent form (for which they were administratively responsible), but now contend this document cannot be found. As the primary health care practitioners responsible for the patient's care, these statements are distressing. Additionally, this contraindication suggests the authors' capacity to make purposely misleading and inconsistent statements in their allegations."*

KHG, MC, TF or OS had no involvement with the patient before the first experimental transplantation. Our first encounter with the patient was after the transplantation. To place responsibility on us for attaining the informed consent form is a ridiculous statement. In our analysis, we assumed that this patient had signed consent and that Ethical approval was obtained since the first patient had signed one. We have never seen or been asked to attain patient consent for any of the two experimental transplant procedures (transplantation August 2012 and re-transplantation July 2013) planned and performed by Prof Macchiarini. This is not to be confused with a separate consent for blood samples which Dr Jungebluth asked for 4 (!) months after the primary transplant. At that time TF was not aware that the consent form that he asked the patient to sign had not been approved by the local ethics committee.

Prof Macchiarini: *"Dr. Jungebluth was verbally reassured several times by KHG and MC that the signed consent document was stored at the Thorax Clinic in Solna and therefore, the manuscript could be submitted."*

This is a fabrication. This conversation has never taken place. MC or KHG never meet the patient preoperatively and only first became involved in the patient care in order to treat multiple complications.

On page 27 Prof Macchiarini argues on by stating: *"No patient coming from outside Sweden can be hospitalized without this contract, which represents informed consent for treatment."*

A contract from Stockholm Care, which helps patients from foreign countries receive medical care at Karolinska, does not suffice as a form of informed consent for experimental surgery. There is no correlation between a contract for financing medical treatment and informed consent. The contract from Stockholm Care has not been approved by the regional ethical review board. Prof Macchiarini reveals a

paucity of knowledge in the ethics of performing research in humans.

On page 28 Prof Macchiarini states that: *"Indeed, the submitted figure (Fig 7 in the manuscript) was based on a brushing taken during this bronchoscopy at the Thoracic Clinic one week post-operatively and processed in our lab at Karolinska Institutet. Our group still has the original slide from which the figure was made and, if deemed necessary, can be used to analyze the genome content to confirm that it is from the patient in question. This sample was used to visually analyze the cells, and nowhere is it claimed in the manuscript that histological analysis was completed, as KHG, OS and MC suggest. Therefore, the above mentioned submitted and unaltered figure supports the statement made in the manuscript."*

Taking samples from patients and analyzing in a research lab without ethical approval is not legal. This is an unregistered scientific sample, which is illegal to store in the lab without permission. Again, Prof Macchiarini reveals a paucity of knowledge in the ethics of performing research in humans.

Further down on the same page: *"b. "The intermediate post-operative outcome (5 months) has shown a patent and non-contaminated graft without any signs of inflammation."*

*The accusations are again partially self-contradictory here. They state: "There are no biopsies or bronchoscopies registered in the medical records after 5 months that support the statement in the article that "The intermediate post-operative outcome (5 months) has shown a patent and non-contaminated graft without any signs of inflammation..." but there are bronchoscopies recorded in Dec, 2012 (4 months after the 1<sup>st</sup> transplantation) which document significant granulations, presence of stents and a fully established fistula."*

*As stated in the allegations, 4 months after the first transplantation, the tracheal graft was patent, albeit with the assistance of a tracheal stent, placed by the clinical team (KHG, OS and MC). This tracheal stent placement was necessary due to the compressive effects of a previously placed over-sized esophageal stent (placed by the clinical team without Dr. Macchiarini present) to treat the development of an esophageal fistula which developed 7 days post-transplantation. This fistula was likely a result of the numerous previous surgeries done in Turkey, extensive mediastinal dissection that took place during the emergency removal of the right lung and tracheobronchial dissection and subsequent median sternotomy necessary to gain access to the left main bronchus during the transplantation. This early post-operative complication does not represent a primary failure."*

If the transplant required stenting after four months then it can hardly be called patent with the stent in place at five months. Furthermore, a review of the patient's

medical records clearly state that the graft was infected. This is direct evidence of fabrication. Therefore the article should be retracted. KHG, OS and MC had no involvement in the day to day care of the patient and certainly not in the esophageal stenting. This is also a complete fabrication which the medical records clearly demonstrate.

#### Article 4.

**Are synthetic scaffolds suitable for the development of clinical tissue-engineered tubular organs?** Del Gaudio C, Baiguera S, Ajalloueian F, Bianco A, Macchiarini P. *J Biomed Mater Res A*. 2014 Jul;102(7):2427-47. Epub 2013 Aug 2. Review

Submitted Mar 18, 2013, published online Aug 2, 2013.

#### Comment 15:

Concerning the statement by Prof Macchiarini in the article on page 11: *"an almost normal airway and improved lung function"* which he defends on page 30 in his respond.

It is impossible to reconcile the formulation *"an almost normal airway"* with a patient that has undergone multiple stenting procedures, has no evidence of normal airway epithelium in the synthetic scaffold, has fistulas to the mediastinum and partially obstructed main bronchi, secondary to significant scaffold associated granulations (chronic inflammation) (see Bronchoscopic films 1,2,3,4,11 attached to the Appeal for an Investigation of Scientific Misconduct Aug 18, 2014). This is direct evidence of fabrication and an attempt to perpetuate the concept that synthetic tracheal transplantation is a viable option for patients with advanced tracheal pathology.

Prof Macchiarini on page 31: *"We cannot confirm nor deny many of the procedures carried out by and subjective reported findings of KHG, MC, TF and OS as they were the primary physicians in these procedures and the authors of the procedure notes referenced in the allegations."*

The patient was not admitted to the Department of Cardiothoracic Surgery and Anesthesiology, Karolinska University Hospital, Solna but was admitted to the Department of Ear, Nose and Throat, Karolinska University Hospital, Huddinge, a department where Prof Macchiarini was employed. He had ample opportunity to check the status of the patient and it is highly unlikely that his colleges did not make him aware of the condition of the patient's airway. This is not a credible excuse.

Furthermore, Prof Macchiarini freely admits that he did not check the status of the patient and thereby has fabricated the sentence since it has no basis in the actual clinical status of the patient at one year after transplantation.

**Article 5.**

**Airway transplantation.** Jungebluth P, Macchiarini P. *Thorac Surg Clin.* 2014 Feb; 24(1):97-106. Review.

Submitted Aug, 2013, published online Feb 24, 2014.

**Comment 16:**

Concerning the statement by Prof Macchiarini in the article on page 104: *"Recently, early clinical achievements in tissue engineered trachea provide clinical evidence that this method might be the next promising therapeutic alternative in tracheal replacement."*

An objective review of the clinical outcome of synthetic tracheal transplantation would conclusively demonstrate that this method is intimately associated with disastrous complications. It is highly unlikely that the principal investigator and main surgeon, Prof Macchiarini was not well aware about these findings in these high-profile and very unique patients. The lack of feasibility would have been apparent at an earlier stage if the procedure was first tested in an animal model. However, this step was deemed superfluous and instead first tested in humans. A simple database analysis of synthetic tracheal transplantation will show that this method had not been attempted in animals until Prof Macchiarini's group published this in Nature Protocols in rats in 2014.

*On page 33 Prof Macchiarini goes on by stating: "Therefore, one needs to call into question where they received the information on which to base their allegations."*

We received this information verbally from Dr. Jungebluth shortly after the patient's death.

*Concerning the stated "No other patients had both granulation and fistula at the same time."*

This is incorrect. Patient 1 and 3 had fistulation and granuloma formation (and airway stents) requiring surgical intervention both at the same time. Patient 2 had granulation and fistula formation as demonstrated by CT scan performed before discharge. It is again highly unlikely and not believable that the principal investigator

and main surgeon Prof Macchiarini was not well aware of all of these findings in these high profile patients that he had recruited, operated and clinically responsible for. The article was also published 3 weeks after the 1<sup>st</sup> patient died secondary to a totally dehiscent and dysfunctional synthetic scaffold after 8 months of hospitalization whereof the last months in the same hospital were Prof Macchiarini was employed. This article is yet another example of false advertising for a method that is an absolute disaster.

#### Article 6.

**Biomechanical and biocompatibility characteristics of electrospun polymeric tracheal scaffolds.** Ajalloueian F, Lim ML, Lemon G, Haag JC, Gustafsson Y, Sjöqvist S, Beltrán- Rodríguez A, Del Gaudio C, Baiguera S, Bianco A, Jungebluth P, Macchiarini P. *Biomaterials*. 2014 Jul; 35(20):5307-15. Epub 2014 Apr 3.

Submitted Jan 13, 2014, published online Apr 3, 2014.

#### Comment 17:

Our main problem with this article is that the reader is left with the impression that there is some granuloma formation that required intervention to alleviate after synthetic trachea transplantation. This is a misrepresentation of the actual clinical status of the patient who in reality suffered from a plethora of complications, which were not amenable to any treatment and eventually lead to his death. At autopsy the transplant was completely disconnected from the native airway and with chronic mediastinitis present. The right lung was completely dysfunctional and chronically infected. To only mention the formation of granuloma and a partial collapse of the graft is a blatant understatement of the patient's status and disrespect to his suffering. Any review of the patient's medical records will demonstrate this beyond doubt.

Table 1  
Patient and Transplant Characteristics, Authorizations

PATIENTS	CASE 1	CASE 2	CASE 3
[REDACTED]			
[REDACTED]			
PRIMARY TRACHEAL TRANSPLANTATION	SYNTHETIC TRACHEA	SYNTHETIC TRACHEA	PULMONECTOMY SYNTHETIC TRACHEA

[REDACTED]			
[REDACTED]			

SECONDARY TRACHEAL TRANSPLANTATION (RE-TRANSPLANTATION)

RE-TRANSPLANTATION SYNTHETIC TRACHEA



**Table 2**  
**Etiology of Tracheal Disorder and Transplantation-associated Drugs**

PATIENTS	CASE 1 Transplantation Jun 9, 2011	CASE 2 Transplantation Nov 17, 2011	CASE 3 1 <sup>st</sup> Transplantation Aug 7, 2012	CASE 3 2 <sup>nd</sup> Transplantation Jul 9, 2013
----------	--	---	--	--

[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
			[REDACTED]	[REDACTED]

TRANSPLANTATION ASSOCIATED DRUGS	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
----------------------------------	------------	------------	------------	------------

[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
			[REDACTED]	[REDACTED]

COMPLICATIONS	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
---------------	------------	------------	------------	------------

[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
			[REDACTED]	[REDACTED]

[Redacted]

[Redacted]

**LONG TERM COMPLICATIONS**

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

Table 3  
Transplant-related and General Complications, Final outcome

TRACHEAL SCAFFOLD RELATED COMPLICATIONS	CASE 1	CASE 2	CASE 3
---	--------	--------	--------

[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
------------	------------	------------	------------

GENERAL COMPLICATIONS	CASE 1	CASE 2	CASE 3
-----------------------	--------	--------	--------

[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
------------	------------	------------	------------

POST-TRANSPLANT INTERVENTIONS/THERAPY	CASE 1	CASE 2	CASE 3
---------------------------------------	--------	--------	--------

[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
------------	------------	------------	------------

FINAL OUTCOME