

Reply to:

**Analysis of Clinical Outcome of Synthetic
Tracheal Transplantation Compared to Results
Published in 6 Articles by Macchiarini *et al.***

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Introduction

Matthias Corbascio, MD, PhD, Thomas Fux, MD, Karl-Henrik Grinnemo, MD, PhD, and Oscar Simonsson, MD have formally made significant accusations of scientific misconduct based upon 6 academic manuscripts in peer reviewed journals.

After a thorough review of their criticisms, we remain steadfast in our belief that no misinformation was knowingly reported in any of these publications and no misconduct occurred at any time.

In an effort to respond completely, included in this reply are the point-by-point responses to each accusation individually. Many of the accusations are similar for each manuscript, therefore we have tried to address them adequately and efficiently.

Articles in question

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.
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.
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, Strömblad S, Macchiarini P. *Biomaterials*. 2013 May; 34(16):4057-4067. Epub 2013 Mar 6.
 Submitted Feb 5, 2013, published online Mar 6, 2013.
4. [Are synthetic scaffolds suitable for the development of clinical tissue-engineered tubular organs?](#)
 Del Gaudio C, Baiguera S, Ajallouelian 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.
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. Review
6. [Biomechanical and biocompatibility characteristics of electrospun polymeric tracheal scaffolds.](#)
 Ajallouelian 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.

Article No. 1

Re: Allegations of scientific misconduct: Jungebluth, et al. [*Tracheobronchial transplantation with a stem-cell-seeded bioartificial nanocomposite: a proof-of-concept study.*](#) Submitted Oct 11, 2011, published online Nov 24, 2011. *Lancet* 378:1997-2004, 2011.

The *Lancet* manuscript entitled "Tracheobronchial transplantation with a stem-cell-seeded bioartificial nanocomposite: a proof-of-concept study" by Jungebluth *et al.* is the first of the manuscripts Drs. Karl-Henrik Grinnemo, Matthias Corbascio, Thomas Fux and Oscar Simonsson (here referred to as KHG, MC, TF and OS, respectively) have made scientific misconduct allegations about. These allegations claim that we proceeded without ethical permission and adequate patient consent, and that the manuscript contains major inconsistencies and omits clinical information.

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 1st December, 2010 until 30th 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.

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 11th 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 11th October, 2011. Of note, KHG et al.'s accusations have surfaced nearly 3 years after the publication of this manuscript.

Point-by-point response to the critique (allegations in blue, responses in black):

1. [Inquiries have been unable to identify any application for synthetic tracheal transplantation filed at the Regional Ethical Review Board.](#)

Response to 1: Please see the written statement of Dr. Richard Kuylenstierna, ENT, Karolinska University Hospital, Huddinge, who organized/supervised all ethical related issues, from 30th November, 2014, as well as an email transmission from Dr. Kuylenstierna (12th May, 2011) (**Appendices 2 & 3**), which directly address both allegations.

Reply to: Analysis of Clinical Outcome of Synthetic Tracheal Transplantation Compared to Results Published in 6 Articles by Macchiarini et al. By Matthias Corbascio, MD, PhD, Thomas Fux, MD, Karl-Henrik Grinnemo, MD, PhD Oscar Simonsson, MD

In summary, Dr. Kuylenstierna states the agencies approached for approval included the Medical Product Agency, the Ethical Approval Committee, the chief medical officer at the Karolinska University Hospital and the Swedish Research Council. In particular, prior to proceeding with the transplant, Dr. Kuylenstierna e-mailed the team on 12th May, 2011 and stated, *“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. This opinion was shared by Pierre LaFolie at the local ethical committee. However should research and clinical implication be furthered into a proper clinical project applications to the ethical committee as well as other authorities must be made. Finally I suggest that we have a proper airway conference on Thursday May 19th at 15:00 regarding the Icelandic patient with the intent to proceed with surgery the following week.”* After a thorough pre-operative evaluation and multidisciplinary conference, including six different subspecialties, the decision was made to proceed in an attempt to save the patient’s life, as no other conventional therapy would prolong his life.

2. Unapproved informed consent form signed 17 days after the transplantation.

Response to 2: Correctly informing the patient of the risks and the experimental nature of our work is of paramount importance to our team. As is stated by Dr. Kuylenstierna, *“The patient was informed prior to the surgery concerning opportunities and alternatives, risks and the nature of the operation. A “written consent” is not standard procedure in Sweden.”* Despite this lack of requirement by law, the patient was informed of the risks, potential benefits and possible complications of the procedure. This conversation was documented in the clinical chart and can be witnessed by PM, PJ and Prof. Jan Juto.

Article 5 of the European Convention on Human Rights and Biomedicine (<http://www.regeringen.se/content/1/c6/02/51/07/ab99d9ef.pdf>) states that medical interventions may be performed after the patient has given free and informed consent, based upon objective information given to them by the responsible health care professional regarding the purpose and nature of the intervention as well as its consequences and risks. Alternatives and their risks must also be discussed. This consent can be revoked at any time. *The consent may be verbal or written and the Article does not require any particular form.* Despite this, a written consent form, in compliance with all such requirements, was in fact signed by the patient prior to surgery (as indicated in the medical records).

As KHG, *et al.* points out: *“First, the main objection against this informed consent form is that it was signed on Jun 26, 2011, 17 days after the transplantation (Jun 9, 2011), which is a clear violation against the informed consent guidelines (The U.S Food and Drug Administration, among other Key organizations) which state that consent is to be documented before the planned intervention not after. Interestingly, the name of the scanned file of the consent form is labeled in the medical records “2011-05-26”.* Regarding the discrepancy in dates, regretfully, the date written on the consent form is not correct. However, based upon the date it was scanned into the medical record (26th May, 2011) - as pointed out by KHG, - it is obvious the consent was in fact obtained prior to the surgery (9th

June, 2011). This document was scanned into the medical record by an administrative staff member, independent of PM or PJ.

3. Serial fabrication and omission of biopsy findings.
4. Serial fabrication and omission of bronchoscopic findings.
5. Fabrication and omission of clinical status.

Response to 3-5: As previously mentioned, at no time did PM or PJ directly access the medical records, therefore dependence upon KHG for a clinical summary and detailed information, including that obtained by bronchoscopies and evaluations performed by other health-care providers was required. The apparent discrepancies between the statements made by KHG in August 2011 and the present accusations are both professionally and scientifically very concerning.

Based on the details provided below, the statements made in the published manuscript, *“...There were no major complications, and the patient¹ was asymptomatic and tumour free 5² months after transplantation. The bioartificial nanocomposite has patent anastomoses, lined with a vascularised neomucosa, and was partly covered by nearly healthy epithelium”*, were based upon a **direct statement** by KHG (**Appendices 4-6**) via a clinical summary submitted via e-mail by KHG to PJ on 29th August, 2011 at 11:11 AM, stating: *”To facilitate..... 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.”* along with bronchoscopy reports from Jan Juto (Karolinska Hospital) and information from Tomas Gudbjartsson (Iceland) (all co-authors of the manuscript). No member of the clinical team (including KHG) indicated any change from this clinical status between 29th August, 2011 and the time of publication (5 months).

Additional allegations:

Inconsistent and Omitted Clinical Information:

- a. The *Abstract in the Findings section* included the following statements: *“...There were no major complications, and the patient¹ was asymptomatic and tumour free 5² months after transplantation. The bioartificial nanocomposite has patent anastomoses, lined with a vascularised neomucosa, and was partly covered by nearly healthy epithelium. Postoperatively, we detected a mobilisation of peripheral cells displaying increased mesenchymal stromal cell phenotype, and upregulation of epoetin receptors, antiapoptotic genes, and miR-34 and miR-449 biomarkers. These findings, together with increased levels of regenerative-associated plasma factors, strongly suggest stem-*

cell homing and cell-mediated wound repair, extracellular matrix remodeling, and neovascularisation of the graft.”

¹Refers to Case 1 who was transplanted on Jun 9, 2011. The patient died at Karolinska on Jan 30, 2014.

²Approx. beginning of Nov 2011.

Concerning the stated “*asymptomatic*” patient: At readmission to Karolinska University Hospital on Nov 21, 2011, 5½ months after transplantation and 3 days before publication of the article on Nov 24, 2011, the medical records describe the clinical admission state of the patient as follows: “*looks a bit worn out*”, “*productive sputa*”, “*states that he has lost 7kg after the operation*”, “*no respiratory sounds on the right chest wall, relatively clear respiratory sound on the left side.*” (Nov 21, 2011, Clinical notes from admission Appendix 14).

Comments: The statement in the article that “*the patient was asymptomatic...5 months¹ after transplantation*” is contradicted by the medical records, which described a severely symptomatic patient at submission.

²Approx. beginning of Nov 2011.

Response: Please see the above statement regarding the source of clinical information, namely KHG, Jan Juto (Karolinska Hospital) and Tomas Gudbjartsson (Iceland) (all co-authors of the manuscript). Indeed, according to KHG, et al.’s own accusations, the “**patient was asymptomatic... 5 months after transplantation**”. He did not suffer clinical complications until 5 ½ months post transplantation, therefore the statement in the manuscript is correct by all accounts. Although we recognize the patient’s readmission 3 days **before** the publication of the manuscript (**at 5 ½ months post transplant**), this additional information does not invalidate the clinical picture at 5 months, which is based upon the above e-mail transmission from KHG. Furthermore, at the time of the patient’s readmission, the final manuscript was in the process of publication and contained no misleading clinical information. The final version of the manuscript was accepted on **7th November, 2011** after in-depth revision (**Appendices 7 & 8**) (original date publicly available from *The Lancet*, **Appendix 9**). The PDF for proof read was sent to us on 8th November, 2011 (Lancet: “That proof should be corrected and returned within 48 hours”) and returned to *The Lancet* on 10th November, 2011 (**Appendix 10**). Therefore the clinical status on **21st November, 2011** could not be included in this manuscript. The clinical changes on 21st of November 2011 were not concerning enough for any of the co-authors, including KHG, to consider halting or withdrawing the publication as they did not negate the findings reported in the publication. It is also worth noting that none of the co-authors, including KHG, raised concerns about the content and publication of the manuscript at the time, immediately afterwards, or in the intervening 3 years.

Allegation:

Concerning the statement in the article: “*...5 months after transplantation. The bioartificial nanocomposite has patent anastomoses, lined with a vascularised neomucosa, and was*

partly covered by nearly healthy epithelium” the bronchoscopy findings registered in the Karolinska medical records reveals the following:

- a. Bronchoscopy on Nov 21, 2011 (on the date of re-admission) 5½ months after transplantation and 3 days *before* publication of the article on Nov 24, 2011, describes:

4th line: *“there are distal granulations on the distal graft endings on both the right and left side. Starting by inspecting that there is a passage down in the left main bronchus which is stenosed but not more than to maybe 20%.”*

8th line: *“I first go down and recess the granulations on the right side in the main bronchus. It is possible to reduce them. They bleed fairly easily but it is possible to reduce the masses, it is not possible to clearly identify the branching of the upper lobe.”*

14th line: *“Decide to implant a stent...”* (Right main bronchus).

19th line: *“One can suspect a small opening at 1 o’clock position, in other words inside medially in front exactly at the edge of the graft. Implant even here a stent...”* (Left main bronchus).

(Nov 21, 2011, Bronchoscopy report, Appendix 15).

(Nov 21, 2011, Bronchoscopy Film 1 on the USB device).

- b. Bronchoscopy was repeated the next day on Nov 22, 2011, with the following findings:

4th line: *“...the right bronchus is filled with pus. It looks better on the left side. Sucking clean. It fills up all the time from down below on the right side.”*

12th line: *“...serous fluid is entering through the anastomosis between graft and bronchus at 6-7 o’clock position, right side.”*

15th line: *“...inserting a new stent...”* (Right main bronchus).

23rd line: *“See fistulation which lies medially and at the edge of the graft, on this side at 2-3 o’clock position.”* (Left main bronchus).

24th line: *“Finish by pulling the stent up again so that I achieve a nice cover in applied and treated surfaces.”* (Left sided stent).

(Nov 22, 2011, Bronchoscopy report, Appendix 17).

(Nov 22, 2011, Bronchoscopy Film 2 on the USB device).

Comments:

The bronchoscopy findings from Nov 21-22, 2011 with significant granulations in the anastomotic regions, verified fistulation, need for stent implantation and stent repositioning totally contradict the statements in the article of *“patent anastomoses...”* Prof Macchiarini was present at the ENT-Department according to the medical records of Nov 21, 2011, and must thereby have been fully aware of the clinical status and the bronchoscopic findings and the subsequent need for intervention.

(Nov 21, 2011, Medical record note, Appendix 16).

Response: The final version of the manuscript was accepted on 7th November, 2011. At this time (5 months post transplant) no stent had been placed, therefore the given passage in question from the manuscript **is indeed correct** (*“5 months after transplantation, the patient is asymptomatic, breathes normally, is tumour free, and has an almost normal airway (figure 2C) and improved lung function compared with preoperatively*). The findings reported here, after acceptance of the manuscript, do not invalidate the information provided

in the manuscript at the time point recorded.

Allegation:

Concerning the statement in the article that the transplant was “*lined with a vascularised neomucosa, and was partly covered by nearly healthy epithelium*”: There are no biopsies recorded in the Karolinska University medical records that confirm biopsy analyses at the stated “*5 months after transplantation*”. The temporally nearest biopsies registered in the Karolinska medical records were taken on Dec 20, 2011 (which is 6½ months *after transplantation*, 2½ months *after submission* of the article on Oct 11, 2011 and 4 weeks *after publishing* of the article on Nov 24, 2011) with the following findings:

Biopsy report from Dec 20, 2011 (6½ months after transplantation), describes:

The nature of the sample: “mucus membrane/granulation from the trachea”

Diagnostic Query: “*granulation? ca?*”

Description of the findings:

“Material from trachea, containing granulation tissue with richly vascularised uncompact stroma and abundant presence of plasma cells but also acute inflammatory cells. No signs of malignancy in the analyzed material. In conclusion, the picture is consistent with granulation tissue.”

(Dec 20, 2011, Biopsy report, Appendix 18).

(Dec 20, 2011, Bronchoscopy Film 3 on the USB device).

Comments:

The statement of a bioartificial nanocomposite “*lined with a vascularised neomucosa, and was partly covered by nearly healthy epithelium*” are not supported by the biopsy findings of abundant presence of plasma cells, acute inflammatory cells and a picture consistent with granulation tissue. Lack of a vascularised neomucosa and healthy epithelium at 6 ½ months makes the presence of such at 5 months unlikely.

Response: We have not claimed in the manuscript that the comments in contention, “*lined with a vascularised neomucosa, and was partly covered by nearly healthy epithelium*” were based upon biopsy findings. Instead, again, they were based upon a clinical summary written by KHG to PJ via e-mail on 29th August, 2011 (**Appendices 4-6**); “*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.*” This clinical report was verbally confirmed by KHG prior to publication. Moreover, the only biopsy findings presented in the Results section are clearly from the **1 week** (“*1 week after surgery.... The obtained biopsy samples showed the presence of necrotic connective tissue associated with fungi contamination and neoformed vessels (Fig. 2B)*”) and **2 months** time points (“*The biopsy sample 2 months after transplantation showed large granulation areas with initial signs of significant epithelialization and more organized vessel formations, and no bacterial or fungi contamination (Fig. 2B)*”). The accusations regarding the lack of vascularized mucosa at 6 ½ months do not apply to this manuscript, as they were taken after its publication and after any time point reported in the publication.

Allegation:

In the last sentence in the *Methods section* under the title *The Recipient* on p. 1998 the following statement is made: “*We obtained written informed consent from the patient, and the transplant procedure was approved by the local scientific ethics committee.*”

Comments:

Inquires have been unable to identify any application for synthetic tracheal transplantation filed at the Regional Ethical Review Board, which if confirmed, indicates that the above mentioned statement is a fabrication and potential violation against Swedish Law and the Helsinki Declaration of Ethical Principles for Medical Research Involving Human Subjects (see General Comments).

Response: As described above, Dr. Richard Kuylenstierna approached the Medical Products Agency, the Ethical Approval Committee, the chief medical officer at the Karolinska University Hospital and the Swedish Research Council. More detailed information can be found in the above section (and **Appendices 2 & 3**). For further information please contact Dr. Richard Kuylenstierna in the ENT Department at Karolinska University.

Allegation:

In the *Result section* on p. 1999 the following statements can be found:

“1 week after surgery, the bronchoscopy (webvideo 3, figure 2A) showed a normal and patent airway bleeding from its inner layer at the contact with the scope; the obtained biopsy samples showed the presence of necrotic connective tissue associated with fungi contamination and neoformed vessels (figure 2B). The temporary tracheotomy cannula was removed 18 days later. The patient was then transferred to a normal ward and discharged to the referral hospital 1 month after surgery. 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 (figure 2B). The patient was discharged from the referring hospital to start rehabilitation and later resumed his university studies. 5 months after transplantation, the patient is asymptomatic, breathes normally, is tumour free, and has an almost normal airway (figure 2C) and improved lung function compared with preoperatively.”

Concerning the “1 week¹ after surgery”-findings:

No histological analyses are documented “1 week after surgery” in the Karolinska University Hospital medical records. According to the medical records the first biopsy is registered on Aug 4, 2011 (8 weeks after transplantation). There is no information in the Karolinska University Hospital medical records regarding analyses performed outside Karolinska and, if this is the case, where or by whom they were analyzed.

¹Approx. Jun 16, 2011.

Subsequently, the statement referring to the biopsy findings 1 week after surgery is inconsistent since no biopsy has been performed at this time point.

Concerning biopsy findings supporting the stated “2 months² after transplantation”, the following biopsies have been registered in the Karolinska University Hospital medical records:

²Approx. Aug 9, 2011.

Biopsy report from Aug 4, 2011 (8 weeks after transplantation) describes:

The nature of the sample: “*Synthetic trachea with cultured autologic cells*”

Diagnostic Query: “*Structural overview of the synthetic graft, extracellular matrix proteins? Engrafted cells?*”

The biopsy report describes:

“*In the sections from the three samples of the synthetic trachea which represent the left bronchus, right bronchus and trachea a similar picture of non-stainable porous material with double refractory characteristics. On the surface of this synthetic material only a few thin mesenchymal cells can be suspected. No well-developed cell layer could be identified.*” (Aug 4, 2011, Biopsy report 8 weeks after transplantation, Appendix 7).

Comments:

No signs of initial epithelialization and vessel formation are mentioned in the medical records.

New Biopsies were taken again 12 days later on Aug 16, 2011 (10 weeks after transplantation) and revealed:

The nature of the sample: “*Three biopsies from a transplanted trachea*”

Diagnostic Query: “*A frozen block shall be sliced and analyzed. The two other blocks shall just be sliced and stored at -80 Celsius.*”

“*These biopsies are from the same graft (synthetic trachea) which was implanted in the patient in June this year.*”

The biopsy report describes:

“*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.*”

(Aug 16, 2011, Biopsy report, 10 weeks after transplantation, Appendix 8a).

The pathologist then performed a complementary examination on Aug 16, 2011 on two other frozen biopsies taken at the same time with the following description:

“*The other two frozen biopsies are also fixated and sectioned. One of them shows a similar picture of necrotic connective tissue with detectable fungal hypha 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.*”

(26 Aug, 2011, Complementary Biopsy report, Appendix 8b).

Comments:

Advanced degeneration-necrosis, granulocytic reaction and the presence of fungi and bacteria contradicts the authors stated findings of “*initial signs of epithelialization and more organised vessel formations, and no bacterial or fungi contamination*”.

Response: 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.

Allegation:

Additional Biopsies were repeated 8 days later on Aug 24, 2011 (11 weeks after transplantation) and revealed:

The nature of the sample: “*Synthetic tracheal graft*”

Diagnostic Query: “*Cell ingrowth? Extracellular matrix structure?*”

The biopsy report describes:

“*In the sections from the four delivered small tissue samples a porous foreign material of synthetic graft can be identified. Detectable cellular components or matrix structures are not seen.*”

(Aug 24, 2011, Biopsy report, 11 weeks after transplantation, Appendix 19).

Comments:

This contradicts the described “*initial signs of epithelialization and more organised vessel formations.*”

Response: Please see our previous response. Again, it must be noted that these biopsies were not done by PM or PJ, they were completed by members of the clinical team (KHG and others). The technique of the bronchoscopy and biopsy greatly affects its diagnostic value, especially regarding adequacy of tissue.

Allegation:

In the Results section on p. 1999 the following statement can be found:

“*The patient was discharged from the referring hospital to start rehabilitation and later resumed his university studies. 5 months¹ 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.*”

¹²Approx. beginning of Nov 2011.

Comments:

There are no records of any biopsies performed at the 5 month time point in the Karolinska University Hospital medical records but the biopsy findings from Aug 4, 16, and 24 (Appendix 7, 8a, 19) and the findings from Dec 20, 2011 (Appendix 20), all show a

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pathological and not an “almost normal airway” 2, 3 and 6½ months after transplantation, respectively. These essential findings should have been immediately reported to the Lancet Editor in order to correct the manuscript as the bronchoscopy findings were known before publication.

Response: The sentence in question: “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.

Allegation:

In the *Discussion section* on p. 2002 it is stated:

“In this report, an avascularised, Y-shaped nanocomposite was implanted and the initial fungal infection had resolved within 4 months¹ from transplantation; later the endoluminal surface was partly lined with respiratory mucosa, at which we noted nearly healthy epithelium and proliferating endothelium. This finding provides evidence that a bioengineered synthetic tracheobronchial nanocomposite can be recellularised in vivo with site-specific cells to become a living and functional scaffold completely integrated into the adjacent tissues. The measured levels of miR-34/449 micro-RNAs, which have been proposed as potential biomarkers of terminal differentiation of airway epithelium,¹⁰ suggest the presence of postoperative airway epithelial differentiation in the patient.”

¹ Approximately beginning of Oct 2011.

Comments:

There are no “4 months”-findings recorded in the Karolinska University Hospital medical records that can verify this statement. A “endoluminal surface partly lined with respiratory mucosa” or “healthy epithelium and proliferating endothelium” was not found in any of the biopsies performed 2-2½ months (Aug 4, 16 and 24, 2011) or at 6½ months (Dec 20, 2011, Appendix 20) after transplantation. The statement is also contradicted by the bronchoscopic findings 5½ months after transplantation (Nov 21 and 22, 2011, Appendix 16, 17 and Bronchoscopic Films 1 and 2 on the USB device).

Subsequently, the statement referring to the findings at “4 months from transplantation...” must until further be recognized as inconsistent with the information registered in the Karolinska University Hospital medical records.

Response: 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 29th 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 (29th 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.

Allegation:

Further down in the *Discussion section* the following conclusions are drawn on p. 2002: *“This finding provides evidence that a bioengineered synthetic tracheobronchial nanocomposite can be recellularised in vivo with site-specific cells to become a living and functional scaffold completely integrated into the adjacent tissues.”*

Comments: This conclusion is not supported by any bronchoscopic or biopsy data registered in the medical records. The information in the biopsy reports, the bronchoscopic findings and the clinical patient status must without any doubt have been fully known by the main author (Prof Macchiarini) *before* publication of the article on Nov 24, 2011, since he was present at the ENT-Department at that time (according to the medical records Nov 21, 2011, Appendix 16). In summary, in the registered data there is no evidence that the synthetic trachea is *“a living and functional scaffold”* at the time of publication. On the contrary, the bronchoscopic and biopsy findings indicate instead crucial and significant pathology as pointed out above.

Response: This allegation is merely a summary of all the previous ones, and we refer to our previous responses. We additionally restate that the final version of the manuscript had been accepted for publication on 7th November, 2011. Therefore, new data obtained 14 days after the acceptance of publication is beyond the scope of this manuscript. Most importantly, this conclusion was largely based upon dialogue concerning the clinical postoperative course (i.e. clinical findings, health status and histological findings) provided by KHG (**Appendices 4-6**).

Allegation:

Towards the end of the *Discussion section* the following conclusion is drawn on p.2003: *“Taken together, these results provide evidence that a successful organ regeneration strategy has been accomplished (panel). The successful overall clinical outcome of this first-in-man bioengineered artificial tracheobronchial transplantation provides ongoing proof of the viability of this approach, in which a cell-seeded synthetic graft is fabricated to patient-specific anatomical requirements and incubated to maturity within the environment of a bioreactor.”*

Comments:

Reply to: Analysis of Clinical Outcome of Synthetic Tracheal Transplantation Compared to Results Published in 6 Articles by Macchiarini et al. By Matthias Corbascio, MD, PhD, Thomas Fux, MD, Karl-Henrik Grinnemo, MD, PhD Oscar Simonsson, MD

The bronchoscopic, biopsy and clinical admission data in the Karolinska medical records do not support this conclusion. The patient was readmitted with productive sputa, no respiratory sounds on the right chest wall, anastomotic granulations and a fistulation requiring bilateral stenting therapy (left and right main bronchus) *before* the article was published Nov 24, 2011.

Response: Please refer to the previous responses to similar allegations.

Allegations:

General Comments:

1. The most severe inconsistency is that *no application for synthetic tracheal transplantation has been filed at the Regional Ethical Review Board* despite what the authors state in the article in the section titled The Recipient p. 1998.

If this is confirmed, it may be a violation of:

- a. Swedish Laws and Regulations on Ethical Vetting of Research Involving Humans (Ethical Review Act, Svensk Författningssamling 2003:460, Statute Jan 1, 2004, Amendment 2007/08:44, Statute Jun 1, 2008).
- b. Swedish Medical Devices and Pharmaceuticals Acts (Medical Product Agency, Läkemedelsverket).
- c. The Helsinki Declaration of Ethical Principles for Medical Research Involving Human Subjects.

Response: This has been extensively addressed earlier in the document (please see pages 5 & 6).

2. No ethical application seems to have been filed at the Ethical Review Board but there is an *informed consent form* dated Jun 26, 2011 (signed by the investigator and the patient) registered in the Karolinska Medical records (Appendix 5a, b).

Specific comments concerning the attached informed consent form from Jun 26, 2011:

- a. First, the main objection against this informed consent form is that it **was signed on Jun 26, 2011, 17 days after the transplantation (Jun 9, 2011)**, which is a clear violation against the informed consent guidelines (The U.S Food and Drug Administration, among other Key organizations) which states that consent is to be documented *before* the planned intervention not after. Interestingly, the name of the scanned file of the consent form is labeled in the medical records “2011-05-26”. (Surgical notes, June 9, 2011, Appendix 6)

Response: As stated in the accusation itself, the scanned file was labeled with a date of 26th May, 2011, **before** the procedure itself. Neither PM (**Appendix 1**), nor any member of his team, ever accessed the medical record(s) therefore could not have entered this information themselves. One can assume an independent, administrative party scanned the informed

consent with the supposition that this was indeed the date it was completed and signed. Please see the above statements regarding the informed consent accusations as well.

- b. Second, an informed consent form before a highly invasive procedure as in this proof-of-concept-study cannot replace or substitute an ethical vetting as the informed consent form also has to be approved as a part of the study to prohibit manipulation or coercion of a desperate patient.
- c. Third, in the unapproved but present informed consent form there are several violations against the established guidelines on how to write a informed consent form recommended by The Swedish Central Ethical Review Board (Etiska Prövningsnämnden, EPN), FDA and other Key organizations:

2nd part, 3rd line: “...its reconstruction with a synthetic polymer-based and completely biocompatible tracheal scaffold...”

Comments: “*Biocompatibility*” in this context can mislead the patient to believe that this synthetic material has been tested *in vivo* for this purpose and in this anatomical position, and thereby will be accepted by the surrounding native tissue. This was not scientifically proven at the time.

Response: 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 material has been extensively investigated for its biocompatibility properties by Prof. Seifalian (UCL, London, GB). The material was clinically approved at the time of the transplantation. For more detailed information, please see references #18 & 19 of the manuscript or contact Prof. Seifalian.

Allegation:

3rd part, 1st line: “*I have read as well the protocol of the transplant procedure, written in English and understand that this represents the only chance of survival I have.*”

Comments: This is a severe violation against the informed consent form guidelines stated by the FDA: “*Consent documents should not contain unproven claims of effectiveness or certainty of benefit, either explicit or implicit, that may unduly influence potential subjects. Overly optimistic representations are misleading and violate FDA regulations concerning the promotion of investigational drugs [21 CFR 312.7] or investigational devices [21 CFR 812.7(d)] as well as the requirement to minimize the possibility of coercion or undue influence [21 CFR 50.20].*”

It would have been more realistic and honest to inform the patient that this was a experimental intervention with a material used for the first time as a trachea in a human being with no previous presented *in-vivo* animal data.

No registered information is given about alternative interventions and no pros and cons are laid out as suggested in the guidelines by the FDA: “*...subjects should be aware of the full range of options available to them. Consent documents should briefly explain any pertinent alternatives to entering the study including, when appropriate, the alternative of supportive care with no additional disease-directed therapy.*”

The informed consent form is written in 1st person, which is clearly against the above mentioned FDA guidelines as:

“Although not prohibited by the FDA regulations, use of the wording, “I understand...” in informed consent documents may be inappropriate as many prospective subjects will not “understand” the scientific and medical significance of all the statements. Consent documents are more understandable if they are written just as the clinical investigator would give an oral explanation to the subject, that is, the subject is addressed as “you” and the clinical investigator as “I/we.” This second person writing style also helps to communicate that there is a choice to be made by the prospective subject. Use of first person may be interpreted as presumption of subject consent, i.e., the subject has no choice. Also, the tone of the first person “I understand” style seems to misplace emphasis on legal statements rather than on explanatory wording enhancing the subject’s comprehension.”

“Subjects are not in a position to judge whether the information provided is complete. Subjects may certify that they understand the statements in the consent document and are satisfied with the explanation provided by the consent process (e.g., “I understand the statements in this informed consent document).” They should not be required to certify completeness of disclosure (e.g., “This study has been fully explained to me,” or, “I fully understand the study.”)”

In conclusion, an incorrectly formulated and unapproved informed consent was signed 17 days after weeks after an invasive, unique and highly experimental intervention lacking ethical approval.

Response: Regarding the style of the patient consent, as KHG et al. correctly stated: *“Although not prohibited by the FDA regulations, use of the wording, “I understand...” in informed consent documents may be inappropriate as many prospective subjects will not “understand” the scientific and medical significance of all the statements.* The FDA clearly states that the style is not prohibited. Although the consent form may not be ideal by FDA standards, it is acceptable from a Swedish legal point of view. The pros and cons of surgery and its alternatives were extensively discussed with the patient prior transplantation, and witnessed by Prof. Juto. There is no legal need for a written consent in Sweden (see details above). However, it is the most proper and ethical thing for a clinician to do and document, which occurred in this case.

3. The “proof-of-concept study” is the most important of the articles reviewed in this analysis as it was the first one published (but not submitted) describing the “*first-in-man bioengineered artificial tracheobronchial transplantation*” and is used as a reference in the other articles that were published afterwards.
4. Three days *before* the online publication on Nov 24, 2011, the patient who is described as a success in the article, is readmitted looking “*a bit worn out*” with “*productive sputa*”, “*no respiratory sounds on the right chest wall*” and having “*lost 7kg after the operation*¹”. The two bronchoscopies performed on Nov 21 and 22, 2011, confirmed a left sided fistulation, anastomotic stenoses secondary to granulations causing the right bronchus to be “*filled with pus*”. The crucial bronchoscopic findings with need for interventions including insertion of 2 stents and no verification of transplant epithelialization are not consistent with the terminology “*asymptomatic*” and “*an almost*

normal airway.” At this point it would have been possible to retract or postpone and adjust the publication.

¹Refers to the transplantation on Jun 9, 2011.

Response: The manuscript describes the **5 months** follow-up but not the clinical status after this time period. Again, the clinical changes on 21st of November 2011 were not thought to be contradictory enough for any of the co-authors, including KHG, to halt or withdraw the publication as they did not negate the findings reported in the publication.

5. The bronchoscopy findings, stent interventions and clinical admission status must without any doubt have been known by Prof Macchiarini who was present at the ENT-Department at the time (according to the medical records from Nov 21, 2011, Appendix 16).

Response: PM received all clinical information *via* Jan Juto (co-author), Gert Henriksson (co-author) and Karl-Henrik Grinnemo (co-author) (**Appendices 4-6**).

6. The present article demonstrates systematic presentation of inconsistent or fabricated clinical, bronchoscopic and histological findings together with omission of well known and registered data in the Karolinska University Hospital medical records.

Response: There is no inconsistency between the information presented in the published article and the actual clinical status of the patient at the time points mentioned. Whether or not the clinical information provided by KHG, as a contribution to the published article, is consistent with the written medical records cannot be confirmed or denied by us, as we cannot read, nor have we accessed the medical records (**Appendix 1**). The attached emails (**Appendices 4-6**) clearly indicate the responsibility and role of KHG in this manuscript, namely, to provide the clinical data.

Conclusions:

1. PM and PJ cannot be held accountable for what has been written in the medical records by KHG and others, nor have they read the documentation firsthand.
2. Email conversations from KHG to PJ clearly indicate that the clinical information had been provided by KHG, a co-author on the final manuscript. KHG et al. had ample opportunity between the time of the clinical summary he emailed on 29th August and the submission of the manuscript to suggest modification to the manuscript, including the opportunity to edit the final draft and galley proofs.
3. It is surprising to us that KHG et al., who approved the final published version of the manuscript in 2011, have now, for the first time, nearly 3 years later, made so many accusations regarding information that he himself provided, and approved for publication. In fact, most accusations stem from clinical observations made after the

manuscript published in Lancet 2011 was submitted, accepted and even published. The statements in the article therefore remain correct.

4. The patient consent had been in place prior to the transplantation and with documentation in the clinical records, as stated by KHG, and can be approved by PM, PJ and Jan Juto. All ethical related issues have been organized/supervised by Dr. Richard Kuylenstierna prior the transplantation, and have been described in the letter provided.
5. 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.

Article No. 2

Re: Allegations of scientific misconduct: Badylak et al. *Engineered whole organs and complex tissues*. Lancet. 10; 379(9819): 943-52. Review, 2012

The Lancet review article entitled "[Engineered whole organs and complex tissues](#)." by Badylak *et al.* is one of the manuscripts Drs. Karl-Henrik Grinnemo, Matthias Corbascio, Thomas Fux and Oscar Simonsson (here referred to as KHG, MG, TF and OS, respectively) have made scientific misconduct allegations about. These allegations claim that we have reported major inconsistencies and omitted clinical information.

Overall, it should be noted that this manuscript is a **review article** that provides an overview of the entire field of tissue engineering of whole organs and tissues, **without intentions to provide detailed clinical results of any particular method**. The article references the previous article in the Lancet (Article 1) and hence KHG et al. have repeated many of their criticisms of that article again. The only actual new allegation concerns the same patient's status at 8 months post-transplant.

Point-by-point response to the allegations (allegations in blue, responses in black):

1. [Inquiries have been unable to identify any application for synthetic tracheal transplantation filed at the Regional Ethical Review Board.](#)
2. [Unapproved informed consent form signed 17 days after the transplantation.](#)

Response to 1 and 2: These have both been discussed in detail elsewhere in this response. Please see **pages 5 & 6** of the reply to the allegations of scientific misconduct regarding the manuscript by Jungebluth, et al. entitled [Tracheobronchial transplantation with a stem-cell-seeded bioartificial nanocomposite: a proof-of-concept study](#). Lancet 2011; 378:1997-2004.

3. [Fabrication and omission of biopsy findings.](#)

[Fabrication and omission of bronchoscopic findings.](#)In the section [Organ-specific examples](#) under the section [Respiratory system](#) on p. 946 of the manuscript, it is stated:” *The artificial scaffold, which was seeded ex vivo with autologous bone marrow-derived stromal cells (in a bioreactor) and conditioned with pharmacological therapy, was implanted into a patient¹ with a primary recurrent tracheobronchial tumour. The graft was patent, well vascularised, and lined with a well-developed healthy mucosa 8 months² after transplantation.³*”

¹Refers to Case 1 who was transplanted on Jun 9, 2011 and died at Karolinska on Jan 30, 2014.

²Approx. beginning of Feb 2012.

³Refers to the article: [Tracheobronchial transplantation with a stem-cell-seeded bioartificial nanocomposite: a proof-of-concept study](#). Jungebluth P, Macchiarini P et al. *Lancet*. 2011 378:1997-2004. Epub 2011 Nov 24.

Comments:

Reply to: Analysis of Clinical Outcome of Synthetic Tracheal Transplantation Compared to Results Published in 6 Articles by Macchiarini et al. By Matthias Corbascio, MD, PhD, Thomas Fux, MD, Karl-Henrik Grinnemo, MD, PhD Oscar Simonsson, MD

The statement above refers to the *Lancet* article “*Tracheobronchial transplantation with a stem-cell-seeded bioartificial nanocomposite: a proof-of-concept study*”, Jungebluth P, Macchiarini P et al. published Nov 24, 2011, where “5 months after transplantation data” is presented (p. 1999). Using the “proof-of-concept study” which presents 5 months data as a reference to present 8 months data is an incorrect utilization of a reference and gives the impression of a longer follow-up than actually can be stated. It has also to be pointed out that the 5 months data referred to in the “proof-of-concept study” do not correlate to the registered findings in the medical records at the time. To be precise, the presented 5 months data referred to in the “proof-of-concept-study” should also more correctly have been presented as 4 months data considering the time interval from transplantation on Jun 9 and submission of the “proof-of-concept-study” on Oct 11, 2011.

Furthermore, despite the above mentioned inconsistencies regarding the actual follow-up times the author uses the time point “8 months” in this publication omitting data that obviously became apparent *after* the publication of the “proof-of-concept study” on Nov 24, 2011.

This way of referencing gives the impression of the same “positive” outcome in the present “Engineered whole organs”-article as in the previous “proof-of-concept”-reference article, despite the crucial and negative findings that were diagnosed and treated *before* submission (Nov 21-22, 2011, Appendix 14, 15, 17) as well as *after* (Dec 20, 2011, Appendix 20) the publication of the “proof-of-concept-study” on Nov 24, 2011. Importantly, these results were well known and documented *before* the publication of the “Engineered whole organs”-article on Mar 10, 2012.

According to the *Lancet* (Editorial Assistant H. Baker on Jul 9, 2014) the reference article “proof-of-concept study” was submitted on Oct 11, 2011 but the “Engineered whole organs”-article was submitted on Aug 12, 2011, 9 weeks *before* the “proof-of-concept study”. According to the same *Lancet* Editorial Assistant (Jul 9, 2014) that was because the “proof-of-concept study” was handled as a “fast-track-publication”-article which resulted in an online publication already on Nov 24, 2011, just 2 months after submission. That was not the case with the “Engineered whole organs”-article, which took until Mar 10, 2012 to be published, 7 months after submission on Aug 14, 2011. This would give the following time plan:

- a. “Engineered whole organs”-article is submitted on Aug 12, 2012.
- b. The “proof-of-concept study” is submitted 2 months later on Oct 11, 2011.
- c. The “proof-of-concept study” is published on Nov 24, 2011 presenting “5 months after transplantation”-data (which as mentioned above, should have been presented as 4 months data as the transplantation took place on Jun 9, 2011 and the submission date was 4 months later on Oct 11, 2011). The clinical and transplant tracheal graft deteriorates with visualization of fistulation and need for bilateral stenting on Nov 21-22, 2011, which is 3 days before the online publication of the “proof-of-concept study” on Nov 24, 2011. The main author (Prof Macchiarini) was present at the ENT-department (according to the medical records Nov 21, 2011, Appendix 16) and must thereby have been fully informed about these crucial findings, however, no supplemental information was communicated to the *Lancet* regarding these important pre-publication findings.

- d. “Engineered whole organs”-article is then published on Mar 10, 2012, 3½ months after the publication of the “proof-of-concept study” on Nov 24, 2011, stating the “*graft was patent, well vascularised, and lined with a well-developed healthy mucosa 8 months after transplantation*”.

Response 3-4: All these criticisms relate to a single sentence within a 10-page *review article* concerning a reference to the clinical case that was published previously (Jungebluth et al. 2011). The “way of referencing” is the style required by the journal – to reference all supporting information at the end of the final sentence of the passage, allowing readers to find further detailed information on the subject. The case study manuscript thus referenced clearly indicates at what time point the clinical parameters are reported. Our previous “proof-of-concept study” was initially submitted on 11th October, 2011 but ultimately accepted with final modifications on 7th November, 2011 hence there is no discrepancy regarding the period of 5 months follow-up. For more detail, please see responses to Article 1.

When reading the full review paper under scrutiny, it is immediately apparent that including such detailed clinical data on a single case study as KHG et al. suggest “have been omitted” would be in no way appropriate for such an overview of the broad subject.

4. Fabrication and omission of clinical status.

Response to 5. Regarding the clinical data: “*The graft was patent, well vascularised, and lined with a well-developed healthy mucosa 8 months after transplantation*”.

All information (“patent, well-vascularized and lined with a well-developed mucosa”) referred to here are based upon the bronchoscopist’s subjective visual assessment (please refer to Prof. Jan Juto) and not histological data. Nowhere in the manuscript is this claimed to be based upon histologic data. Additionally, biopsy results without mention of epithelium should not be taken as definitive evidence of the absence of healthy epithelium. As mentioned above, these results are directly dependent upon the quality of the bronchoscopist’s evaluation and sampling. From the bronchoscopy of 14th February, 2012 (KHG et al.’s Appendix 54), it is clear that the description given is accurate. The entirety of the graft was constantly patent. The obstruction the authors imply is actually granulation tissue which occurred at the native trachea-graft anastomosis, not within the graft itself. The definition for a patent airway is an airway that is unobstructed and able to support the inhalation of oxygen and exhalation of carbon dioxide. **“A patent airway is essential for adequate oxygenation and ventilation, and protection of the airway against aspiration of gastric contents is vital.** The conscious, alert patient uses the musculature of the upper airway and various protective reflexes to maintain a patent airway and to protect against the aspiration of foreign substances, gastric contents, or secretions. **The ability of the patient to phonate with a clear, unobstructed voice is strong evidence of both airway patency and protection”** (Walls, et al. *Manual of emergency airway management*. Ron Walls, Michael Murphy, eds. — 3rd ed., Lippincott Williams & Wilkins, Philadelphia, USA, pp 267-268, 2008; ISBN 978-0-7817-8494-8). The statement in question does not imply that

the patient is completely free of dyspnea or the use of adjunctive measures (i.e. nasal cannula oxygen, face mask oxygen, nebulized medications), rather, that oxygen can be administered without the use of surgically reconstructed airway. A patient who is alert and able to phonate has a patent, unobstructed airway.

It is of utmost importance to note that the intention of the manuscript in question was to introduce tissue engineering of organs and complex tissue. The minimum amount of clinical data reported in this paper is provided solely to illustrate the concept's translational feasibility, NOT as a case report or report of clinical success or failure.

Article No. 3

Re: Allegations of scientific misconduct: Jungebluth *et al.* *Verification of cell viability in bioengineered tissues and organs before clinical transplantation.* *Biomaterials*, 34(16): 4057-67, 2013.

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. PM, as a visiting consultant, did hold a temporary Swedish medical license (from 1st December 2010 till 30th 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**). 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.

This article describes a laboratory technique developed for bioengineered transplants, and mentions one clinical case as context for this description. KHG et al. have criticisms regarding two sentences in this 11 page manuscript, along with raising the issues of ethical and patient consent, as previously.

Point-by-point response to the critique (allegations in blue, responses in black):

1. *Inquiries have been unable to identify any application for synthetic tracheal transplantation filed at the Regional Ethical Review Board*

Response to 1: In further detail to the responses to the same allegation above, PM has, from his first day of employment at the Karolinska Hospital until 31st December, 2014, a temporary contract as visiting consultant in the Division of Ear, Nose and Throat Diseases (ENT) of the Department of Clinical Science, Intervention and Technology (CLINTEC), Huddinge and as visiting Professor at the Karolinska Institutet (affiliated with the same Division and Department) as the Director of the Advanced Center for Translational Regenerative Medicine (ACTREM). 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.

PM had utmost concern regarding the appropriate ethical permissions for each tracheal transplantation and verbally asked the doctors responsible for the patient in question (including KHG and others) multiple times regarding its status and approval. He did not

receive any negative feedback (written or verbal) in regards to these matters therefore the first surgery (a right pneumonectomy) and subsequent tracheal transplantation took place under the assumption they had secured appropriate consents.

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). 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.

2. No informed consent form has been found in the medical records.

Response to 2: We would like to refer to the letter written on 18th August, 2014 by Drs. MG, KHG, OS and TF to Prof. Hamsten, President of the Karolsinka Institutet. In particular, the 5th paragraph states: *“Despite the lack of ethical permission to perform synthetic trachea transplantation, the patients have signed a consent form. This is, in of itself, a transgression since the patients have been asked to sign an informed consent form which has not been reviewed and approved by an ethics committee. This can also be a form of coercion, since the patients could have been mislead into believing that, since there is a consent form for a procedure, then that procedure has been vetted and approved by the correct authorities. Furthermore, the consent form contains statements which are of a questionable nature.....”*.

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.

In detail, on 5th December, 2012, Dr. Philipp Jungebluth wrote Dr. Thomas Fux the attached email exchange requesting that Dr. Fux ask the patient (or rather the patient’s father, his designated healthcare decision maker) to sign the informed consent form, giving permission to obtain samples for analysis and future publication (**Appendices 12 & 13**).

One hour and 28 minutes later, Dr. Fux replied, stating that obtaining the signature would not be a problem and that he would ensure this happened. He then asks if it can be signed and send back by the next Monday. A few days later, Dr. Jungebluth was called by Dr. Fux and informed that the document was signed and provided to KHG and MC, who were solely responsible for the clinical care of the patient. Of note, Dr. Jungebluth is a well-trained and honest general thoracic surgical resident and now fellow. At the time of this research, he had extensive knowledge regarding the patient’s pathophysiology and the research informed consent process, given his medical training in Germany. However, he did not have a

Swedish medical license, clinical privileges at the Thorax Clinic, nor access to the patient's confidential medical record and data, therefore he was dependent upon the clinical authors of this manuscript (KHG and MC) responsible for these matters. 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.

The patient in question is a Turkish citizen. She was hospitalized at the Thorax Clinic in Solna, Karolinska Hospital, only after financial approval and a signed contract issued by Stockholm Care. Please refer to Ms. Birgitta Thellman Beck, MBA, MA, acting CEO, of Stockholm Care and The Tobias Registry (birgitta.thellman.beck@stockholmcare.se).

In this contract, point 3 states: *The HCR (Health Care Recipient) hereby acknowledges and confirms that the Health Care Services to be provided under this agreement are complex and that the HCR has duly considered all risks associated with the Health Care Services, including, but not limited to, side effects and other complications that may arise in conjunction therewith....etc.* No patient coming from outside Sweden can be hospitalized without this contract which represents informed consent for treatment. It should be noted that the physician is not involved in this administrative process, rather it is a contract between Stockholm Care and hospital administrative personnel.

Furthermore, we would like to acknowledge the letter written by the representatives of the Turkish Ministry of Health, Prof. Cengiz Gebitekin, MD, EBCTS and Dr. Adnan Sayar, MD (**Appendix 14**). This letter, clearly and without doubt, confirms that the patient and her biological father were adequately informed, in their native language, about all matters concerning the surgical treatment and consented to such treatment.

3. Fabrication and omission of biopsy findings

Response to 3: In the submitted version of the manuscript, references to clinical data, for which KHG, OS and MC were primarily responsible, include:

- a. *“The early clinical evaluation revealed an initial graft epithelialization as judged from the 1-week post-operative brushing (Fig. 7)”*.

As per the accusations from KHG, OS and MC, a member of the clinical care team documents, in the medical record, on 14th August, 2012 (one week after initial tracheal transplantation): *“Bronchoscopy by Dr. Macchiarini who thinks that it looks very good in the graft and also down below. Little bit of mucous but no large amounts. Cultures are taken.”*

Their comments in the accusation document include: *“A subjective visual evaluation through a bronchoscope without biopsies does not objectively (histologically) confirm there is initial graft epithelialization.”*

Of note, the above statements in the medical record illustrate the absence of medical documentation from PM, who did not ever access the patient's chart (**Appendix 1**). The official documentation is a subjective account of the author of the statement, rather than

PM himself.

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.

Unfortunately, the cultures taken during this bronchoscopy and their subsequent analysis have not been obtained by our group without access to the medical record and were never provided to us by KHG, OS and MC.

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 1st 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 of the tracheal graft.

The original manuscript was submitted for publication to *Science Translational Medicine* (STM) on 24th January, 2013 after unanimous approval of the final version of the manuscript by all authors, including KHG, OS and MC. The manuscript was not considered for publication in STM, which we were informed about on 30th January, 2013. The manuscript was then submitted on 5th February, 2013, to *Biomaterials*, after minimal modification and restructuring to conform to *Biomaterials* guidelines. In particular, KHG himself (as witnessed by Drs. Mei Ling Lim, Sebastian Sjöqvist, Johannes Haag, and Philipp Jungebluth) suggested inclusion of the sentence:

Reply to: Analysis of Clinical Outcome of Synthetic Tracheal Transplantation Compared to Results Published in 6 Articles by Macchiarini et al. By Matthias Corbascio, MD, PhD, Thomas Fux, MD, Karl-Henrik Grinnemo, MD, PhD Oscar Simonsson, MD

“Patient’s consent was given for all analytical evaluations and publication” because, based on his verbal statement, *this would be important for a reliable publication.* (Again, this self-contradicts statements made by KHG, OS and MC regarding informed consent in point 2.)

At the time of the manuscript’s submission and acceptance in *Biomaterials*, there was no reason to doubt any of the above contributions made by KHG, OS or MC, therefore, written proof of any of their actions was not requested, as would be the case with any professional relationship.

All three individuals approved submission of the final version of the manuscript, both in writing and verbally. In his email, KHG stated: “Very nice manuscript and thank you for putting me on it.” (**Appendices 15 & 16**) Additionally, all three authors separately received a confirmation email from *Science Translational Medicine*:

Manuscript Number: 3005781

Dear Dr. (author’s name) You are listed as a coauthor on the above manuscript, which has recently been submitted to Science Translational Medicine. According to the journal’s policies, all authors must have seen and approved the submission of their manuscript. If you have seen the manuscript and approved its submission, no action is necessary. If you have not read this paper and do not approve its submission to Science Translational Medicine, please let us know as soon as possible.

The editorial office of STM has attested that this email has been sent to the re-verified email addresses of the above mentioned authors (for further information please contact: Phone: 202-326-6501, the original email can be provided as well).

There was no reply to that letter by KHG, MC or OS. This can be confirmed by the editorial office of STM.

4. Fabrication and omission of clinical status

Response to 4: See details provided above. It is of utmost importance to note that the intention of the manuscript in question was to introduce a new standard operative procedure to verify cell viability on bioengineered tissue before implantation. The minor amount of clinical data reported in this paper is provided solely to illustrate the concept’s translational feasibility, NOT as a case report or report of clinical success or failure. KHG et al. go to great lengths in their document to emphasize the difficulties that this particular patient has suffered during her illness and treatment. These are of no relevance to the two sentences of clinical information given in this manuscript, but we are happy to discuss the patient's treatment and outcome in a different context. The welfare of all patients is our primary concern, and we have taken every step possible to try to save her life, and improve her quality of life since she came into our care.

Article No. 4

Re: Allegations of scientific misconduct: Del Gaudio et al, *Are synthetic scaffolds suitable for the development of clinical tissue-engineered tubular organs?* J Biomed Mater Res Part A, 102A: 2427–2447, 2014. Review.

The *J Biomed Mater Res A* manuscript entitled "Are synthetic scaffolds suitable for the development of clinical tissue-engineered tubular organs?" by Del Gaudio *et al.* is one of the manuscripts Drs. Karl-Henrik Grinnemo, Matthias Corbascio, Thomas Fux and Oscar Simonsson (here referred to as KHG, MC, TF and OS, respectively) have made scientific misconduct allegations about. These allegations claim we have reported major inconsistencies and omitted clinical information. KHG et al.'s criticisms concern 3 disputed sentences in a 21-page review article which, once again, references the actual clinical case that was published previously (Jungebluth et al. 2011).

Point-by-point response to the critique (allegations in blue, responses in black):

1. Inquiries have been unable to identify any application for synthetic tracheal transplantation filed at the Regional Ethical Review Board.
2. Unapproved informed consent form signed 17 days after the transplantation;

Response to 1 and 2: These allegations have been extensively addressed in a former section of this document. Please see: **Re: Allegations of scientific misconduct (Jungebluth et al. Verification of cell viability in bioengineered tissues and organs before clinical transplantation. *Biomaterials*, 34(16):4057-67, 2013.) and Appendices 2 & 3.**

3. Serial fabrication and omission of biopsy findings
4. Serial fabrication and omission of bronchoscopic findings
5. Fabrication and omission of clinical status.

Response to 3- 5: The manuscript in question is a peer reviewed **review article** addressing whether synthetic scaffolds are suitable for the development of clinical tissue-engineered tubular organs and is not a manuscript detailing a case report, reporting clinical status, reporting new information or describing any particular clinical outcome. Its purpose was solely to summarize previously reported data (e.g. Jungebluth et al. 2011). No clinical data is referenced other than that which has already been published, and to a lesser extent, including: a) originally published in 2011 in the *Lancet* by Jungebluth et al. ("is asymptomatic, breathes normally, is tumor free") is now stated as "an almost normal airway and improved lung function"; b) due to the timing of the manuscript, the follow up was extended from 5-months to 12-months. This new date of 12 months follow up is the only criticism of this manuscript by KHG et al. that we have not previously addressed.

Reply to: Analysis of Clinical Outcome of Synthetic Tracheal Transplantation Compared to Results Published in 6 Articles by Macchiarini et al. By Matthias Corbascio, MD, PhD, Thomas Fux, MD, Karl-Henrik Grinnemo, MD, PhD Oscar Simonsson, MD

Specific post-operative complications of this transplantation were not detailed in this article, as that was **not this article's intended purpose**. 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. It requires emphasis that PM was not present for a majority of the clinical decision making, nor the procedures, and has not accessed the medical record, therefore, cannot comment on many of their conclusions. More specifically, we cannot address the bronchoscopic or biopsy findings, as we have not accessed these reports and most importantly, did not observe where the biopsy specimens were obtained from specifically.

Additionally, the use of the term “airway” in the manuscript was meant in a nonspecific manner and only to emphasize the absence of tumor recurrence in the patient’s airway (the initial presenting problem). If our purpose would have been to describe the implanted graft specifically or exclusively, a more specific term such as *neo-trachea*, *engineered trachea* or *implanted graft* would have been used.

Notably, surgical complications aside, at 12 months post-transplant, the patient had returned to his home residence in Iceland and was well enough to have graduated from the University of Iceland. His University celebrated together with the key healthcare providers his “one-year-anniversary” in Iceland (http://english.hi.is/frettir/one_year_anniversary_first_artificial_trachea_transplant). On that occasion, he declared in front of the media and local audience, that he would positively reconsider such a transplantation again and that he feels better than prior the transplantation (<http://www.visir.is/einstok-adgerd-bjargadi-lifi/article/2012706099969>). This indication of quality of life was the basis behind the subjective account of a “normal” airway and “improved lung function” as compared to prior to the procedure.

Please recall that this procedure has only been offered to patients in whom no conventional corrective surgical procedure exists. These patients have previously endured all traditional medical and surgical therapies, without improvement, prior to being offered an experimental airway transplant. Possible post-operative complications have always been discussed with each and every patient and their family, prior to transplantation. Many of these complications can be expected due to the patient’s previous surgeries in the thorax and their pre-existing and serious co-morbidities. Due to their dismal life expectancy at the time of transplant, this procedure offers months to years more than they likely would have experienced without it. These particular details are also not discussed in the manuscript(s) as it is not their intended purpose.

Article No. 5

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

The review article in Thoracic Surgery Clinics entitled "Airway transplantation" by Jungebluth *et al.* is one of the manuscripts Drs. Karl-Henrik Grinnemo, Matthias Corbascio, Thomas Fux and Oscar Simonsson (here referred to as KHG, MC, TF and OS, respectively) have made scientific misconduct allegations about. This article is a review of techniques in the field of airway transplantation. KHG et al. have made criticisms of a Table within the paper giving an overview of clinical cases.

Point-by-point response to the critique (allegations in blue, responses in black):

1. Omission of biopsy findings.
2. Omission of bronchoscopic findings.

Response to 1 and 2: This is an *invited peer review article* discussing the *pros* and *cons* of various technologies available for airway transplantation, and there is no discussion of clinical findings in the text but only a table showing the numerical outcome of our experience to date. Therefore, it is entirely appropriate that there are no biopsy or bronchoscopic findings presented or discussed in the referenced article.

3. Omission of clinical status and outcome data.

Response to 3: This manuscript is an overview of all methods of tracheal transplantation and is **in no way intended to provide detailed clinical results of any particular method**. The only reference to clinical or outcome data is a table (referenced as: "*Recently, early clinical achievements in tissue engineered trachea provide clinical evidence that this method might be the next promising therapeutic alternative in tracheal replacement (Table 3)*"), which summarizes our overall experience with biologic and bioartificial tracheal transplantations. Despite this, KHG et al. claim we have omitted clinical status and outcome, as follows:

- a. *In Table 3 on p. 104 under the section Synthetic-based Trachea (2011-2013) under Outcome the statement is made: "1 (out of 6) patient died of unrelated causes". Before submission of this article on Aug 4, 2014, oral information was given by the research group of Prof Macchiarini that Case 2, who is referred to as dead, died in his resident country (USA) due to a fatal bleeding secondary to fistulation of the tracheal transplant, which led to aspiration of blood and suffocation. No documentation concerning cause of death is available in his Karolinska University Hospital medical records. No autopsy was performed according to the same research group. It is not*

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possible to draw the conclusion or to prove that the patient died of “unrelated causes” 3½ months after a major surgical airway intervention involving implantation of a unique synthetic tracheal scaffold as an autopsy was never performed. On the contrary, it must be more reasonable to suspect that a previous major operation in the central airways involving vascular surgery of the large vessels to be a main factor involved in an acute massive and fatal airway bleeding 3½ months later (arterial-tracheo fistulation?).

Response: The information “1 (out of 6) patient died of unrelated causes” refers to a patient who was transplanted and then died in the United States, is in fact entirely correct. The cause of death was not related to the tracheal graft itself. Further information can be found in the official autopsy report in the US medical record. It should be noted that not only was the FDA made aware of the outcomes of all previous tracheal transplants performed by our team prior to the approval of the procedure in the US but additionally, all FDA adverse event reporting procedures were followed after the death of the US patient, including disclosure of the circumstances surrounding the patient's death and full autopsy report.

With regard to the patient transplanted at the Karolinska University Hospital who died of severe gastrointestinal bleeding in the US (according to the US death certificate, no autopsy), KHG et al. allege that “fistulation of the tracheal transplant, which led to aspiration of blood and suffocation”. This allegation is self-contradictory. KHG et al. themselves state that “No documentation concerning cause of death is available in his Karolinska University Hospital medical records. No autopsy was performed...” therefore, one needs to call into question where they received the information on which to base their allegations.

b. *In Table 3 on p. 104 under the section Synthetic-based Trachea (2011-2013) under Outcome it is further stated that: “To date all patients are alive (only the POSS/PCU scaffold requires stent treatment because of abnormal granulation tissue and fistula formation)”.*

In two (Case 1 and Case 3 as referred to in the table above) of the three patients transplanted at Karolinska University Hospital, extensive and repeated airway stenting has been necessary. In Case 3 the previous tracheal transplant as well as the current (re-transplanted on 9 Jul, 2013, due to material fatigue and severe anastomotic fistulation) trachea transplant, have required repetitive and extensive stenting. In all that makes three synthetic scaffolds in need of extensive stenting, not one. The extensive need for stenting was known before submission of this article on Aug 4, 2013.

(Nov 22, 2012, CT scans of Case 1, Left and right main bronchi are both stented. Upper right lobe shows signs of extensive consolidation, Appendix 43). (Sep 6, 2012, CT scans of Case 3 with a stented synthetic trachea and a stent in the esophagus in an attempt to treat the tracheo-esophageal fistulation, CT scan was performed before the loop esophagostomy on Apr 9, 2013 and the later transhiatal esophagectomy which was performed on Aug 6, 2013. The submission of this article on Aug 4, 2013 was 11 months after the CT scan with visualized the double stenting and accordingly fully known by the authors at submission, Appendix 44).

Reply to: Analysis of Clinical Outcome of Synthetic Tracheal Transplantation Compared to Results Published in 6 Articles by Macchiarini et al. By Matthias Corbascio, MD, PhD, Thomas Fux, MD, Karl-Henrik Grinnemo, MD, PhD Oscar Simonsson, MD

Response: The information “*To date all patients are alive (only the POSS/PCU scaffold requires stent treatment because of abnormal granulation tissue and fistula formation)*” is entirely correct. At the time of submission of the review, all patients in this section were alive (aside from the two patients that are listed in the table) and only the POSS/PCU scaffold required stent because of abnormal granulation and fistula formation. No other patients had both granulation and fistula at the same time.

General Comments: Regarding all further allegations and comments in this section (“General Comments”) we emphasize again that this paper was not an appropriate forum to discuss detailed clinical data. The text referring to the single table summarizing many years of clinical work states that “*we are far from fully understanding the complexity of tracheal tissue regeneration*”, and the article discusses the pros and cons of every approach. At no time is it claimed that any one technique has approached clinical success. We therefore entirely refute the accusations that the brevity of the clinical data, presented in a single table within a broad review paper, is in any way a demonstration of 'omission of known and registered data of crucial importance'.

Article No. 6

Re: Allegations of scientific misconduct: Ajalloueian et al. *Biomechanical and biocompatibility characteristics of electrospun polymeric tracheal scaffolds*. *Biomaterials*. 5308-5315, 2014.

The *Biomaterials* manuscript entitled "Biomechanical and biocompatibility characteristics of electrospun polymeric tracheal scaffolds" by Ajalloueian *et al* is one of the manuscripts Drs. Karl-Henrik Grinnemo, Matthias Corbascio, Thomas Fux and Oscar Simonsson (here referred to as KHG, MC, TF and OS, respectively) have made scientific misconduct allegations about. These allegations claim we have reported major inconsistencies and omitted clinical information.

Point-by-point response to the critique (allegations in blue, responses in black):

1. Inquires have been unable to identify any application for synthetic tracheal transplantation filed at the Regional Ethical Review Board.
2. Unapproved informed consent form signed 17 days after the transplantation.

Response to 1 and 2: These allegations have been extensively addressed in a former section of this document. Please see: **Re: Allegations of scientific misconduct (Jungebluth et al. Verification of cell viability in bioengineered tissues and organs before clinical transplantation. *Biomaterials*, 34(16):4057-67, 2013.) and Appendices 2 & 3.**

3. Omission of biopsy findings.
4. Omission of bronchoscopic findings.
5. Omission of clinical status and outcome.

Response to 3 to 5: The intention of the manuscript in question was to characterize a newly developed electrospun polymeric tracheal scaffold and to present an optimized *in vitro* testing concept for cell seeded scaffolds, and the paragraph at which KHG et al. level their criticisms is a very brief summary in the opening introduction to the paper. In no way was the manuscript intended as a case study or clinical description, rather, to describe data obtained from *in vitro studies* and an *in vivo* rodent animal model. The critical comments "The present article demonstrates the most severe form of omission of the vast clinical, bronchoscopic and histological pathological findings found registered in the Karolinska University Hospital medical records" and "The author chooses to present the clinical outcome in just 2 short sentences, thereby consciously omitting the major part of the continued and complex airway deterioration..." are entirely unjustified. The appropriately short summary clearly outlines the major complications and acknowledges that scaffold design was a shortcoming.

Based on KHG *et al*'s accusations (“... it has become apparent that the results published by Prof Macchiarini do not correlate with the patients’ actual clinical outcome.” and “.... neglect to address the morbidity associated with these procedures and omit the majority of complications which these patients have endured.”), we would like to reiterate the following passages reported in the published manuscript:

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

The above statement in the manuscript was meant as a short summary of the patient’s post-operative course and accurately reflects not only a morbidity of the transplant but also the general clinical outcome. We explicitly acknowledge the chronic fistula at the distal anastomosis of native-to-graft left main bronchus as well as granulation tissue, hence there is no discrepancy between the manuscript and the patient’s clinical status.

Additionally, this clinical description was included only to demonstrate that the previously used scaffold was suboptimal and to make the conclusion: “need to improve the biomechanical properties of the scaffold and our willing to mimic the native tracheal extracellular matrix” (page 1, last sentence).

- *However, we noted that this scaffold showed partial collapse one year post transplantation which may be due to the degradation of applied PU.*

Again, we feel this reported statement is a direct and accurate description of the patient’s clinical status and a morbidity associated with the transplant. This statement was intended to provide general information based upon our experience gained from patients who have been transplanted with PU-based scaffolds. The scope of the manuscript (to discuss the properties of different possible materials for tracheal scaffolds) did not require or allow a full clinical history of the patient, and the accusation that it is a "gross example of omission of important clinical findings" is wholly false.

Overall Conclusions

The accusations from Matthias Corbascio, MD, PhD, Thomas Fux, MD, Karl-Henrik Grinnemo, MD, PhD, and Oscar Simonsson, MD are deeply troubling, and we have taken time to examine them in as much detail as is possible.

Although leveled against 6 individual manuscripts and extending into many pages and appendices, the criticisms appear to fall into three main complaints:

1. That ethical permissions were not sought, or that the patient was not asked to give consent in the correct form before two of the transplant surgeries carried out in Sweden.

* In response, I hope that we have been able to show clearly that informed consent for each case was obtained prior to the performance of each surgery. Additionally, permissions from the appropriate agencies were obtained prior to proceeding.

2. That clinical data, such as biopsy, bronchoscopy and clinical status data was either omitted or 'fabricated' in two papers detailing transplantation case studies.

* In response, we have provided evidence that KHG, et al themselves supplied the clinical information published in these two manuscripts, and on which they were co-authors. As co-authors, they had ample opportunity to raise concerns at any time prior to the article's submission, and indeed, by contrast, expressed their contentedness with the wording. In addition, they did not raise any concerns with the publication at any time in the past 3 years since publication of the first of these papers, either formally or informally, and have continued to work with other members of the research team. In fact, KHG has even utilized and cited his contribution to the first transplantation on several occasions such as grant application and career achievement (**Appendix 17**).

3. That subsequent papers referencing the clinical case studies omitted 'vital clinical data'.

* These remaining criticized articles either directly reference the same information as cited in the two clinical papers, or are reviews describing the state of regenerative medicine, describing various aspects of new techniques, addressing the limited success of the new technology and describing some of the obstacles left to overcome. Detailing the ongoing clinical challenges would have been inappropriate in these settings. We have, however, addressed specific points as raised by KHG et al. about information contained within these articles. Although we appreciate and welcome collegial scientific and scholarly critique of our research we feel Matthias Corbascio, MD, PhD, Thomas Fux, MD, Karl-Henrik Grinnemo, MD, PhD, and Oscar Simonsson, MD's accusations based upon these 6 manuscripts are largely irrelevant or false.

After our in-depth evaluation of our published manuscripts, we remain adamant that no misinformation was knowingly reported in any manuscript by our team and no misconduct occurred at any time.

We appreciate you taking time to review this information and are available to answer questions or concerns at any time.



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