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

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

Dear Professor Hamsten,

I would like to thank you for the opportunity to comment on the document submitted by Professor Gerdin of Uppsala University on the very serious matter of the charges of scientific misconduct levelled against me, my research team, and colleagues at the Karolinska Institutet (KI), Karolinska University Hospital and around the world (Assignment ref. 2-2184/2014). I refute these charges absolutely, and will in this document present new evidence to demonstrate that they are entirely unfounded.

The allegations in the original documents of 24th June and 18th August 2014 are extremely serious, and caused immense concern both to me and to the rest of my research team.

The allegations that I (and perhaps my co-authors and colleagues) had knowingly falsified or withheld important data with the aim of misleading the academic and clinical community, could very quickly destroy the professional reputation of my whole research team and their work, as well as undermining that of the Karolinska Institutet and Karolinska University Hospital. They even have implications for the trust of the academic community (not to mention the public at large) in the whole field of regenerative medicine – a field that has enormous potential for improving the wellbeing of future patients. The fact that they came from my own clinical co-authors will have given them extra credibility.

For these reasons I very much welcomed the KI's intention to address these matters thoroughly and also the appointment of an independent, external reviewer. I had hoped that an investigation accessing all data - including full medical records, biopsy records and laboratory notebooks that might not have been brought to my attention at the time of publication – would quickly reveal the truth behind this apparent divergence between published, and previously unpublished, records. However, Professor Gerdin has made it clear in the introduction to his Statement of Opinion that he has not been able to access such information, and that appears to have led to a potentially disastrous miscarriage of justice.

I repeat now that I have never, and would never, falsify or deliberately misrepresent results, or intentionally mislead readers about the details of my and my team's research. We work on the cutting edge of a very important area of science where reporting failures is as important as reporting successes so that progress can be made as quickly as possible – and, critically, with minimal risk to patients involved in early trials of the technology.

Professor Gerdin, in the concluding remarks of his report, alluded to the possible motivations behind co-authors of a paper suddenly making accusations about the data contained within it – which they themselves certified to the journal publishers was correct – 18 and 34 months after publication. Although he is, of course, absolutely correct in saying that these circumstances should not have any bearing on the careful analysis of the claims and their basis, I think it's important that the context of these allegations is known.

These accusations were prepared and submitted to the Karolinska Institutet very shortly after my colleague and co-author Dr Phillip Jungebluth made an official complaint against Dr Karl-Henrik Grinnemo (one of the complainants), which resulted in the latter being found guilty of plagiarism. This step appears to have initiated this series of counter-allegations (**Appendix 1**). We deeply regret that a previously fruitful academic partnership between my research group at the Karolinska Institutet, and the Department of Cardiothoracic Surgery at the Karolinska University Hospital appears to have not only broken down so irreparably, but that the result of the break down should have such serious repercussions for all concerned – a state of affairs that is bound to have nothing but a negative impact on patient welfare (including confidentiality), the reputation of both academic establishments, and the wider sphere of research.

Knowing that there is the potential for these accusations to have stemmed from a personal basis makes it particularly important for judgement of the case to be based on a comprehensive analysis of the situation. I will show that the complainants have put forward a powerful – and yet entirely false – picture of events by a selective use of evidence, but this requires an evaluation of the full patient records (not available to Professor Gerdin).

Moving on to my comments on the specifics of Professor Gerdin's report, there are several points that he has made with which I would agree.

Firstly, Professor Gerdin highlights the difficulties that sometimes arise in distinguishing between healthcare and research, and hence the legislative framework that surrounds particular procedures. I welcome the establishment of clearer legal guidelines that would ensure that all such research is done with clear oversight, to protect both patients and researchers in the future. I re-iterate that I and my colleagues have always attempted to ascertain that all ethical and legal permissions had been sought for the surgical operations and the research that we carried out, and believe that I have provided evidence of the assurances we received in response (**Appendices 2a & 2b**).

Secondly, the author statements that all of us signed, as a matter of routine, in some cases include confirmations that not one of us could truly stand by: namely that each of us had access to the full data on which the papers were based. In a large, multi-disciplinary team it is extremely unlikely that this would ever be the case. Although authors may often send each other summaries of their findings it is practically never the case that all authors would have had access to – let alone checked – all raw data collected. I admit that I, like all others, signed this statement despite the fact that sometimes I had not (and indeed could not due to the language barrier) read every bronchoscopy, biopsy, and patient report, nor inspected all the laboratory notebooks of my colleagues. Instead I often relied on verbal reports, written analyses and summaries of outcomes from trusted colleagues and co-authors, as well as my own assessments of patients when I saw them. However, as I will show, all the raw data that I have since accessed in order to investigate these allegations do entirely support the situations that I, and my co-authors, described in the papers.

Thirdly, it has sometimes been more difficult than it should be to obtain and demonstrate the precise sources for the clinical descriptions in the papers. This is clearly a less than ideal scenario but I believe it stems, not from negligent, malicious or unscientific behaviour, but instead of the difficulties of coordinating a new, large, international, and multidisciplinary team eager to be part of a new breakthrough in medical technology. The original written evidence documenting the patients' condition and results of tests at every stage are not only written in Swedish or Icelandic (two languages I have no knowledge of), but are (entirely correctly) kept confidential. I and my research team had no routine access to the clinical healthcare records.

However, I strongly disagree with the conclusions of Professor Gerdin regarding the accusations of scientific misconduct made against me. I was, in fact, deeply shocked to read them – knowing that I had not carried out the actions of which I am accused.

Professor Gerdin states in his report that he had not been able to access materials other than that which had been submitted to him by the accusers (or myself in my original response to them), and therefore he had had to assume that these records were complete.

As a result, I felt it vital to halt all other work in which I am involved in order to devote the past few weeks entirely to assembling the evidence in order to demonstrate the truth: that the evidence submitted in the accusations was a selected subsample, chosen to give a particular view of the patients' situation throughout. I therefore submit below the results of my further investigations into the cases which will, I hope, lay these accusations to rest once and for all.

Dr. Paolo Macchiarini

26 June 15

Reply to:

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

By

Bengt Gerdin Professor Emeritus

Dated May 13, 2014 (Swedish version)

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Articles in question

1. **Experimental orthotopic transplantation of a tissue-engineered oesophagus in rats.** Sjöqvist S, Jungebluth J, Lim ML, Haag JC, Gustafsson Y, Lemon L, Baiguera S, Burguillos MA, Gaudio CD, Beltran AR, Sotnichenko A, Kublickiene K, Ullman H, Kielstein H, Damberg P, Bianco A, Heuchel R, Zhao Y, Ribatti D, Ibarra C, Joseph B, Taylor DA, Paolo Macchiarini. *Nat Comm* 5:3562, 2014.
   Submitted Oct 3, 2013. Published online Apr 15, 2014.

2. **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.

3. **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.

4. **Verification of cell viability in bioengineered tissues and organs before clinical transplantation.**
   Jungebluth P, Haag JC, Lim ML, Lemon G, Sjöqvist S, Gustafsson Y, Ajalloueian F, Gilevich I, Simonson OE, Grinnemo KH, Corbascio M, Baiguera S, Del Gaudio C, Strömblad S, Macchiarini P. *Biomaterials*. 2013 May; 34(16):4057 2013.02.057. Epub 2013 Mar 6.
   Submitted Feb 5, 2013, published online Mar 6, 2013.

5. ! **Are synthetic scaffolds suitable for the development of clinical tissue-engineered tubular organs?**Del Gaudio C, Baiguera S, Ajalloueian F, Bianco A, Macchiarini P. *J Biomed Mater Res A*. 2014 Jul;102(7):2427-47. Epub 2013 Aug 2. Review
   Submitted Mar 18, 2013, published online Aug 2, 2013.

6. **Airway transplantation.**
   Jungebluth P, Macchiarini P. *Thorac Surg Clin*. 2014 Feb; 24(1):97-106. Review.
   Submitted Aug, 2013, published online Feb 24, 2014.

7. **Biomechanical and biocompatibility characteristics of electrospun polymeric tracheal scaffolds.**
   Ajalloueian F, Lim ML, Lemon G, Haag JC, Gustafsson Y, Sjöqvist S, Beltrán-Rodríguez A, Del Gaudio C, Baiguera S, Bianco A, Jungebluth P, Macchiarini P. *Biomaterials*. 2014 Jul; 35(20):5307-15. Epub 2014 Apr 3.
   Submitted Jan 13, 2014, published online Apr 3, 2014.

Experimental orthotopic transplantation of a tissue-engineered oesophagus in rats.

Sjöqvist S, Jungebluth J, Lim ML, Haag JC, Gustafsson Y, Lemon L, Baiguera S, Burguillos MA, Gaudio CD, Beltran AR, Sotnichenko A, Kublickiene K, Ullman H, Kielstein H, Damberg P, Bianco A, Heuchel R, Zhao Y, Ribatti D, Ibarra C, Joseph B, Taylor DA, Paolo Macchiarini. **Nat Comm** 5:3562, 2014

Submitted Oct 3, 2013. Published online Apr 15, 2014.

Professor Gerdin, in his document, considers 4 allegations made about the presentation of results in this paper, and then adds his own criticisms of 'dubious or weak points'. He judges the journal's peer review process to be at fault in not picking up on these points. He also enquires about the question of 'ownership' of material in the published papers.

Members of the author team and I have already submitted very detailed responses to the initial accusations in 2014 (**Appendix 3a/b**), to which Professor Gerdin surprisingly makes no allusion, and have now also prepared further responses to Professor Gerdin's additional criticisms. These will be submitted to both the Karolinska Institutet, and the journal editors to enable them to consider another peer review of these points, should they deem this necessary, and hence judge if any errata or supplementary information should be published retrospectively (**Appendix 3c**).

Professor Gerdin, however, judges that one allegation qualifies as 'scientific misconduct' and that I, as the corresponding author, am guilty of it. I dispute this allegation wholeheartedly, and present my arguments for doing so below.

1. As regards Sjöqvist et al. the principally most outstanding fault is that the authors have decided to present research results for which none of them can take responsibility. This is inconsistent with accepted research practice and therefore qualifies as misconduct, and the lead author (or in Nature Communication's words "corresponding author") bears the blame for this.

To give the detail of the accusation, Professor Gerdin states (pg 13), "As regards this point of criticism, the investigator notes that none of the paper's authors, judging by what is written under the heading "Author contributions", has taken responsibility for the CT scan. This is a departure from the Vancouver declaration, which states that "Any part of an article critical to its main conclusions must be the responsibility of at least one author". It is also a departure from Nature's own rule that "Corresponding authors have multiple responsibilities, but we now make it clearer that the author list should include all appropriate researchers and no others", which in this context carries the same meaning. However, two of the authors' contributions to the paper were described in terms of being "involved" in the imaging process: "R.H. and Y.Z. were involved with CT scan" (Page 15, line 9).

So, the crucial question is, who took responsibility for the 'research results' of the CT study?

Although Dr. Oscar Simonson (OS) was the technician who performed the CT scan in question, Dr. Sebastian Sjöqvist (SS) and Dr. Johannes Haag (JH) attended the entire experiment as can be proven by a photocopy of the animal house log book (**Appendix 4**). OS showed SS the procedures on how to perform the scans, so that he could reproduce it in the future.

OS gave feedback on the manuscript throughout its preparation (and verbally approved its submission), so there was no question that the rest of the author team were not well enough supplied with the technical information required to correctly interpret the scans, and OS was apparently initially happy to improve the description of the method and the interpretation of the scans.

As we showed in our initial reply to the complainant's allegations submitted on Aug 3, 2014: "The email

from Dr. Simonson requesting his name be omitted from the author list on March 13th, 2014 stated "Thank you for the manuscript. I have now read the manuscript and since I have not contributed scientifically to the paper I can not be a co-author on the paper." (**Appendix 5**).

Professor Gerdin states (pg 13): "*Paolo Macchiarini has made explicit in this investigation that Simonson, who specialised in the computer tomographical study of small animals, was the only person in possession of detailed information about how the study was done. To the investigator's mind, this implies that no one else in the research group had sufficient information on the study and its interpretation for it to be credibly presented and interpreted in a scientific paper."*

I have never claimed that I did not take responsibility for the interpretation of the CT scan, just that I did not perform the CT scan. Our detailed initial response to the allegations, including very careful forensic analysis of the scan in question, (**Appendix 3a, pgs. 1-4, and 3b**) should reassure anyone that the authors of the paper are able to interpret such scans accurately.

I therefore entirely refute the claim that we have presented scientific data for which none of the authors can take responsibility, and therefore deny any charge of scientific misconduct.

To turn more briefly then to the question raised by Professor Gerdin of why no credit was given specifically for the CT scan in the detailed author contribution section of the manuscript (since it relates to his accusation of scientific misconduct).

Nature's author policy states: "*The author list should include all appropriate researchers and no others. Authorship provides credit for a researcher's contributions to a study and carries accountability. The Nature journals do not prescribe the kinds of contributions that warrant authorship but encourage transparency by publishing author contributions statements. Nature journals editors are not in a position to investigate or adjudicate authorship disputes before or after publication. Such disagreements if they cannot be resolved amongst authors should be brought up to the relevant institutional authority*." (Nature's full editorial policy can be found at http://www.nature.com/authors/gta.pdf and Nature's authorship policy can be found at http://www.nature.com/authors/policies/authorship.html).

As previously mentioned, OS wrote to say that he felt he had not contributed scientifically to the paper and therefore did not qualify as an author. (In line with Nature's policy, "*Any changes to the author list after submission, such as a change in the order of the authors, or the deletion or addition of authors, needs to be approved by a letter signed by every author*.", all authors were asked to approve the change in the author list (**Appendix 6**)).

Nature's policy is that: "*Authors are required to include a statement of responsibility in the manuscript that specifies the contribution of every author. The level of detail varies; some disciplines produce manuscripts that comprise discrete efforts readily articulated in detail, whereas other fields operate as group efforts at all stages*."

Since OS, the Doctor involved in the scanning, was no longer an author, his contribution was not included in this section.

Similarly, Nature's authorship guidelines do not state that every image or statement in the article be "assigned" to an author.

Therefore, I must re-iterate, there are no research results presented which are not the responsibility of the authors, only images that were obtained by someone who did not feel that these presented a great enough scientific contribution to the paper to demand authorship. This is entirely in line with Nature's authorship policy, and therefore **does not constitute scientific misconduct.**

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.

This paper, describing the post-operative development of a stem-cell seeded synthetic trachea, is the work of a multidisciplinary international group of collaborators, including more than 15 senior clinical consultants from the Karolinska University Hospital representing several departments; laboratory work done in Germany and the UK as well as at the stem cell preparation laboratory VECURA (http://www.vecura.se); clinical work in Iceland as well as at many departments, including the Cardiothoracic Department and the Department of Haematology of the Karolinska University Hospital. The data presented, therefore, comes from many different sources, and a great many health-care providers were involved in the preparation for, and later academic case presentation of, this complex surgical procedure.

The retrospective allegations from the clinical group at the Cardiothoracic Department of the Karolinska Hospital who were involved in this work were particularly shocking.

As I have previously acknowledged, I did not have direct access to all the raw data from these multiple sources, although I was completely confident that my colleagues were providing correct summaries in English, accurate figures and captions throughout. Nothing that I saw personally of the patient's condition and progress has ever made me doubt the veracity of those data.

As I have also acknowledged, it has taken me longer than I would have liked to trace all the relevant raw information in Swedish in order to put together a complete picture of the patient's progress at each particular time point. Unlike Professor Gerdin, I have now been able to speak to all the relevant co-authors and collaborators, and in many cases to make copies of their records in Swedish, which have previously not been viewed or considered in this investigation.

I have put together a timeline of the patient's care (**Appendix 7**), and have retained copies of most of these relevant records (or can point to where they may be viewed). This patient's confidentiality has already been extensively breached as a result of these allegations and therefore I do not attach the records themselves as Appendices, but will lodge them with the authorities at the KI to be viewed as required.

When the details are viewed as a whole and taken from all sources, it is clear that the picture of the patient's – and graft's – progress is entirely in line with the statements and facts of the manuscript in question (and with the subsequent papers that followed). As can be seen, over the first 3 weeks, regular (almost daily) bronchoscopies, show a picture of rapid healing and overgrowth of epithelium:

10 days post-op: "*There appears to be islands of respiratory epithelium in the graft which appears to be completely without mucus coverage. This is however limited parts but amongst others in the transition towards the intermedius bronchus, I believe that I can see such epithelium. It looks similar in the transition for the area of the trachea anastomosis*. Gert Henriksson 19/06/2011 13:04 (bronchoscopy recorded) (**Appendix 7** – entry 28)

12 days post-op: "*Reaching the graft wall which looks pink-shimmering and spotty. It appears to be signs of cellular ingrowth in the graft wall*." Gert Henriksson 21/06/2011 13:22 (**Appendix 7** – entry 33)

3 weeks post-op: *"upper anastomosis looked well healed, one starts to see indications of epithelial overgrowth from above the anastomosis onto the graft. This overgrowth is especially in the front wall where the epithelium is a little granulomatously thickened in the anastomosis border. Aspirating some brownish mucus which today appears less viscous than a week ago. Under the mucus there is some pink-red surface indicating cell infiltration. Focally, the mucus is more strongly adhering and you have to aspirate a few times before at least the superficial part is eliminated. Also down to the anastomoses left and right main bronchus, there are signs of epithelial overgrowth over the anastomosis border*." Gert Henriksson & Jakob Lien 30/06/2011 18:00 (**Appendix 7** – entry 43)

Shortly afterwards the patient returned to Iceland.

We have also identified the sources of the precise information cited in the paper, can strongly refute the original allegations that these findings were misrepresented in the manuscript, and will be submitting a detailed list of these particulars to the editors of the journal in question as well (**Appendix 8**)

However, here I respond in particular to the two allegations which Professor Gerdin judges to qualify as 'scientific misconduct' and of which, in his opinion, I am guilty.

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

Professor Gerdin explains that the examinations carried out in Iceland at this critical juncture "were not included in our [*i.e. his*] investigation material". As he points out "It should be noted that while on Iceland, the patient should have been in the care of one of the paper's two Icelandic authors. It would have then been possible, even easy, to ensure the patient's correct clinical condition after five months".

Indeed, the statements in the published manuscript were based on the patient's clinical condition at that time, as approved by the paper's Icelandic authors who were his health care providers and were 'conducting examinations of the patient'. They will be submitting their own evidence to support this.

However, it should be reassuring to read that on the patient's return to the Karolinska in November (5.5 months postop) – just before publication of this manuscript - Jan-Erik Juto and Gert Henriksson carried out a bronchoscopy in which they reported: "*do a biopsy in the middle of the graft and you can see a circulation…… then out to the plastic graft, i.e. there is epithelisation of some sort on the inside of the graft*." Jan-Erik Juto & Gert Henriksson 21st November 2011 12:09 (**Appendix 7** – entry 51)

The patient's notes from Dr. Jan Juto upon admission state how he had been medication-free for 2 months (i.e. with no infections), and living "in his private house in Reykjavik where he stays with his wife and kids."

It is thus clear after review of the additional evidence presented, that the clinical picture of this patient throughout the 5 month post-operative period was indeed entirely as represented and documented in the paper in question. There is no question of misrepresentation of the facts or medical records. All the bronchoscopy reports which mention the state of the graft surface indicate a healthy growth of epithelium tissue, the patient maintained a steady but good recovery to the point where he was recovering at home with his family, and was taking no medication.

Dr. Bela Bozóky, the pathologist who analysed the biopsy samples taken from the patient will be

submitting his own response and evidence to the KI, but he has been happy to confirm to me that the biopsies cited in the papers are indeed correctly described, and that he is happy that the paper accurately reflects the development of the graft as he saw it from the samples provided to him (**Appendix 9**). It is worth noting that samples supplied directly to pathology from the KI team, and not through the Karolinska Hospital system, were not noted and dated on the system available either to the accusers or to Professor Gerdin, and so only Dr Bozóky is able to supply a full list of dated samples and their descriptions, which match those in the paper.

It is also very important to recognise that biopsy samples can vary enormously, depending on the bronchoscopist, the method by which they are taken, and the location from which they are sampled. This of course, leaves much room for 'false negative' results as the entire graft surface cannot be biopsied. A biopsy showing no epithelium cannot be taken as evidence that no epithelium exists, whilst one that shows an epithelium is proof positive that – at least in that area – epithelium does exist. Biopsies are done sparingly, to prevent damage to the graft and minimize possible complications such as perforation and pneumothorax.

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

As I have previously acknowledged, and Professor Gerdin pointed out himself in his introductory comments, the question of which ethical permissions were required – and therefore obtained – is extremely complex.

The paper specifically states "the **transplant procedure** was approved by the local scientific ethics committee" (emphasis my own). It is clear from this statement that the ethics sought was for the transplant procedure, and not for a research project. **I therefore categorically deny that the paper itself made a false claim, and hence any scientific misconduct.**

The bigger question remains as to whether further ethical approval from a regional board was needed for the research aspects of the case. I have already provided evidence that I, and my collaborators, had attempted to ascertain exactly what permissions were required:

Dr. Richard Kuylenstierna on May 12, 2011 (**Appendix 2b**): *"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*."

Additional e-mail communications demonstrate further contact between Dr. Kuylenstiema and Stefan Engqvist, who was in contact with Goran Hermerén, Chairman of the Ethics Committee of the Research Council stating: *"The problem is important and interesting and reminiscent of similar cases where treatments are not proven can still be defended. I was one of the authors of ISSCR (International Society for Stem Cell Research) Guidelines for the Clinical Translation of Stem Cell Research) (**Appendix 10**). We discussed this problem in one of our recommendations. The whole opinion is available online, but the recommendation is relevant is below - I hope it can be of some help and specify the conditions in which unproven treatments could be ethically justifiable."*

The recommendation in question is Recommendation 34 "*Clinician-scientists may provide unproven stem cell-based interventions to at most a very small number of patients outside the context of a formal clinical trial*" under certain conditions. The Karolinska Institutet and the Karolinska University Hospital

(**Appendix 11**) adhered strictly to those conditions (all contained in **Appendix 2b**), including the requirement to communicate outcomes to the scientific community through publications such as the manuscript in question.

In summary, as I have already stated, I welcome any Swedish legal clarification on what ethical framework applies in cases such as this. I believe that both I and my colleagues went to all reasonable lengths to ascertain and obtain the correct permissions required in this case, adhered to the guidelines laid down by the ISSCR, and therefore that no negligence occurred, and I absolutely do not accept that the paper contained any false statement, as put forward by Professor Gerdin.

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.

This is a review article which references the previous paper, and updates the record as far as 8 months post-operatively (the date at which this paper was finally accepted).

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

(Emphasis my own)

There are two aspects to this allegation. Firstly that the description of the healing of the mucosa over the prosthesis does not match the accounts given in the medical records.

As previously mentioned, it has taken longer than I would have liked to obtain the full bronchoscopy and biopsy reports of this patient, but I have now done so and am able to demonstrate the basis for the statements in the paper. I note that these were not apparently made available to Professor Gerdin, and apologise that they were also not available when I made my first response to the allegations.

In late November 2011, 5.5 months after surgery, a bronchoscopy of the middle of the graft showed: "….*do a biopsy in the middle of the graft and you can see a circulation… then out to the plastic graft, i.*e *there is epithelization of some sort on the internal side of the graft*." Jan-Erik Juto & Gert Henriksson, 21st November 2011 12:09 (**Appendix 7** – entry 51)

The presence of both circulation and epithelial tissue here, in the middle of the graft, is very significant. It allowed us to be confident of the healing of the mucosa over the graft. Other biopsies taken, and reported, were not taken from the graft but merely of removed granulation tissue in order to confirm that malignancy had not returned.

Because of the invasive and destructive nature of biopsies, we take them minimally in the graft area, especially once evidence of epithelial growth has been obtained as it is of a delicate nature and the risk of perforation of the graft is too great. We therefore have far more evidence of epithelial growth by subjective bronchoscopists' reports than by biopsy.

Our confidence in the successful healing appears to have been well-placed as a bronchoscopy report from 22nd May 2012 (nearly 12 months after transplant) also confirms that:

"We go down with a bronchoscope and see in the trachea and in the graft especially a cover which appears to be some sort of epithelium. Jan-Erik Juto & Fabian Pettersson 22nd May 2012 14:06 (bronchoscopy recorded) (**Appendix 7** – entry 61)

I therefore submit that our descriptions of the healing of the mucosa over the scaffold were entirely supported by documented clinical data.

The second part of the allegation concerns the updating of the record as far as 8 months.

After 8 months, in early February, the patient was still in Iceland, and his doctors there kept in regular contact with him – Dr. Tómas Guðbjartsson can report on his medical condition during this time in detail and will be submitting the evidence independently to the KI. The patient, as reported to me and the rest of the clinical team in Sweden, was breathing normally and was not admitted to hospital at any time apart from for routine check-ups. Please see the table in **Appendix 7** showing the timeline of this patient's care.

It is therefore entirely false to claim that we were not still following up with the patient and that the information supplied in the paper was unsubstantiated.

With these new pieces of evidence, I thereby prove the basis for my statement in this paper, and so show that I am not guilty of scientific misconduct.

Verification of cell viability in bioengineered tissues and organs before clinical transplantation.
Jungebluth P, Haag JC, Lim ML, Lemon G, Sjöqvist S, Gustafsson Y, Ajalloueian F, Gilevich I, Simonson OE, Grinnemo KH, Corbascio M, Baiguera S, Del Gaudio C, Strömblad S, Macchiarini P. *Biomaterials*. 2013 May; 34(16):4057 2013.02.057. Epub 2013 Mar 6.

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

This is a paper describing a technique to evaluate cell viability, which mentions the case of a transplanted patient (referred to as 'patient 3') as an example of an instance when the technique was used.

Professor Gerdin notes that the ethical permit referred to in the Methods section of the paper only referred to the animal work reported in the paper. This is indeed the case, as the Methods section was only describing the animal work, and as such this is entirely clear to all readers.

However, he makes the judgment that:

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

Professor Gerdin correctly states that the purpose of the paper was to detail a useful regenerative medicine assay to determine semi-quantitatively, cell viability on a synthetic scaffold. The field of regenerative medicine is in its infancy and such an assay may be of use to various practitioners around the world.

The phrase in question is stated as only one of the conclusions to a long paper on the new assay technique that is the entire focus of the manuscript reads:

"*The intermediate post-operative outcome (5 months) shows a patent and non-contaminated graft without any signs of inflammation*."

If that were the only statement made about the patient's condition in a clinical case study manuscript, then of course I would agree that it would be an inadequate level of detail for that purpose. However, I would urge all readers to consult this paper for themselves **(Appendix 12)** and judge whether, in their opinion, it would have been more appropriate to detail further clinical complications *in this context*. For example, a detailed description of minor areas of dehiscence or exuberant granulation tissue at the anastomotic sites requiring stent placement were not pertinent elements in a paper on a novel laboratory assay technique. Importantly, the addition of this level of detail would also not have changed the central conclusions of this manuscript

I accept that the complainants themselves may have genuinely-held concerns about the clinical status of the patient, and that the bringing of this case may be their way of seeking an opportunity to air their opinions on the subject. I would welcome an open discussion about this very difficult, ground breaking case, as it was extremely medically and surgically complex in all 3 phases of care: pre-, intra- and post-operatively, and required the unique experiences of several senior physicians – scientists representing several departments. In my previous surgical experience with similar types of cases (amenable to complicated conventional surgical techniques), postoperative complications – many arising from the dire situation of the patient pre-operatively – were to be expected, and none were relevant to the paper's conclusions.

I would have been happy to discuss the unsurprisingly less than perfect performance of the implanted neotrachea, if for no other reason than to highlight that much work is still needed in the regenerative

medicine field and that our new technique for determining cell viability prior to transplant may result in better results with future implants. However, in the context of this paper, it seemed inappropriate to do so.

In conclusion, there was absolutely no attempt whatsoever to "deliberately dress up" the results of our trachea implant experience, and thus I deny any charge of scientific misconduct in this case. I do appreciate that this conclusion is a matter of personal judgment, and – as I said - I do urge all readers to read the original paper to make their own mind up.

Also, as previously stated, I am very happy to discuss the care of this patient further, with full medical details, in an environment where those records can be kept confidential.

Are synthetic scaffolds suitable for the development of clinical tissue-engineered tubular organs?

Del Gaudio C, Baiguera S, Ajalloueian F, Bianco A, Macchiarini P. *J Biomed Mater Res A*. 2014 Jul;102(7):2427-47. Epub 2013 Aug 2. Review

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

This review paper again mentions 'Patient 1', this time updating the clinical picture to 12 months, stating: "*After 12 months, an almost normal airway and improved lung function were assessed*"

The complainants discussed many of the post-operative complications and argued that this picture was inconsistent with the medical records.

Professor Gerdin judged:

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

I accept that my previous written response to the original accusations was inadequate in this case, as I did not give specific references and medical cases in order to justify the statement at that time. I have now accessed, apart from the English summaries provided by the respective co-authors, a far greater range of the patient's Swedish reports than were available to Professor Gerdin during the preparation of his statement, including from the patient's follow-up visits in Sweden, and have re-confirmed the facts with the patient's health-care providers in Iceland, who were the primary care-givers for much of the relevant time period in the run-up to this publication. These confirm the basis for the published statement, as outlined below.

Prior to the manuscript submission, the patient had had an extended period of time after transplantation with a very "good result" - this patient would otherwise certainly have otherwise asphyxiated in this time period from his growing carinal tumour had the transplantation not taken place. During this extended period, the patient was not intubated, breathing without supplemental oxygen, had good quality of life, and had an "almost normal" airway. He had returned to and completed his academic studies with enough strength to graduate. As previously mentioned, his Icelandic doctors were predominantly in charge of his care during much of this time, and will be submitting their own statements as well as being able to provide evidence to support it if necessary.

Stents had been placed to help control granulation tissue formation at the anastomotic sites and then a fistula. At the time of this manuscript submission, the patient was newly readmitted with ongoing clinical problems that were being assessed and managed. There was an issue of a thrombus related to a vascular graft that had necessarily been placed during the initial implant to reconstruct the right pulmonary artery which required resection with the tumour specimen. The subsequent thromboembolic events, which were unrelated to placement of the implant itself, but again, necessary for complete tumour resection, were likely responsible for the progressive failure of his right lung function and subsequent ventilatory-perfusion mismatch. These events were not connected to the graft itself. In short, this was a very complicated patient with many issues related and unrelated to his neotrachea, many of which were precipitated by his underlying condition and tumour anatomy prior to transplant.

However, as can be seen from email correspondence with Dr. Tómas Guðbjartsson in late May 2012 (available in confidence, on request only), he was 'better again' and indeed to mark the 12 month anniversary, I was present at a conference in Iceland and was celebrating the anniversary with the patient

himself on stage and at dinner. See hyperlink to **Appendix 13**: Video), which includes an interview with the patient himself from this date, as well as clinicians involved in his care. I hope it is clear to anyone reading the full timeline of care and detailed clinical course of this patient in the first year following transplantation that he could in no way be described as being in an 'extremely serious condition' (especially compared with his pre-operative state), and that we had full grounds for optimism about his future recovery.
I believe that it cannot be denied that the initial implant was a success, and that the clinical picture also at this point was still promising in terms of the graft's performance.

I do not believe that the readers of this paper, interested in learning the pros and cons of the various types of synthetic scaffolds and comparing them to our experience with recellularized natural scaffolds, would have benefited from a more detailed description of one patient's post-operative complications. **I therefore disagree strongly that not including this discussion constitutes scientific misconduct.**

I note also that Professor Gerdin points out that a second transplant patient had died, and that the third had recently had a new tracheal graft. The death of the second patient was entirely unrelated to the trachea implant, and as such, has no relevance to this case (the details of that patient's death are confidential, by request of the family, but I am happy to discuss it in strict confidence if absolutely required). I re-iterate that in no part of the manuscript do we present data on these patients or express a view that regenerated synthetic tracheas were ready for clinical acceptance, or were superior to other methods described, but specifically state that much additional clinical study was (and indeed still is) required. The fact that we are in the early stages of such research, and as such are constantly learning and refining our techniques, is something I never shy away from, and therefore would never 'dress up' results to sound more positive than they actually are.

Airway transplantation.

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

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

This is a review article containing a table summarising the outcomes of various synthetic materials used in tracheal transplants so far. The complainants argue that this table misrepresents the outcomes for these patients.

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

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

He therefore concludes:

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

Firstly, I would like to point out that Professor Gerdin was mistaken in his assumptions about the patients referenced in the table. The left hand column of the lower portion of the table (dividing cases into 'malignant' or 'benign') is not meant to be read as aligned with the right hand column of the table (listing a series of outcomes). Thus the conclusion that 'Of the two patients operated on for their malignant disease, only one is stated to have died' is incorrect. We do not specify which of the deaths related to cases with malignant or benign origins. Also:

- The patient with benign disease who received a synthetic scaffold implant and later died of an unrelated cause is a patient not mentioned in the investigator's review and who was operated on in the US and died in July 2013.
- Patient 1 is described in the table as having malignant disease, who received a synthetic scaffold and is described in the table as: "To date, all patients are alive (only the POSS/PCU scaffold requires stent treatment because of abnormal granulation tissue and fistula formation)". Again, this patient was alive at the time of submission and online publication, but we clearly referenced the problems with fistula formation.

Patient 3 is described as having benign disease and received a synthetic scaffold which required stent treatment. Although this description does not describe the need for a second transplant, it does accurately describe the stenting needed in the post-operative period and for what indication and that the patient is still alive.

It is a matter of personal judgment ('*in the investigator's view*...') that the omission of this one piece of information in this review article counts as 'information being withheld' as described in the **main text** of Professor Gerdin's document. I would certainly dispute, however, the wording used in the **final judgment conclusion** that it was '*active* withholding of information'. And the term 'dressing up of results' certainly cannot be maintained, given that our conclusion in the manuscript very clearly made reference to the complications and failures we have encountered:

"Trachea transplantation remains a highly challenging procedure and, so far, no ultimate solution has been discovered. For many decades, physicians and researchers made immense efforts to overcome the hurdles of replacing a simple connection between the larynx and the lungs. It turned out to be much more difficult and, in particular, more complex than previously assumed. Various purely surgical techniques have been evaluated; however, because of technical challenges, they have not proven their clinical feasibility. In addition, conventional allogenic transplantation requires lifelong immunosuppressive medication and is associated with negative side effects. 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). Progress has been made in investigating underlying mechanisms and pathways of cell–surface interactions, cell migration, and differentiation; however, we are far from fully understanding the complexity of tracheal tissue regeneration. TE is a step in the right direction but only the future will elucidate the real impact of this technology on tracheal replacement."

There is clearly in this paper no attempt to 'dress up results', making the techniques sound more successful than they were. Instead, just the opposite is true, through the by acknowledgement of the 'highly challenging procedure' which has 'turned out to be much more difficult and, in particular, more complex as previously assumed'.

I would be happy to discuss the possibility of issuing an errata to the table with the journal publishers to include the fact that Patient 3 received a second graft, **but maintain absolutely that this omission was neither a deliberate nor a misleading act, and that it therefore does not qualify as scientific misconduct.**

Biomechanical and biocompatibility characteristics of electrospun polymeric tracheal scaffolds.

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

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

This is a paper describing the biomechanical characteristics of various synthetic scaffolds that we have used, and as such, includes a description of the biomechanical properties as discovered in the case of Patient 1.

The description given in the paper was: *"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."*

Professor Gerdin states that: *"The investigator deems the description of the outcome of this patient to be an embellishment in that important information was withheld. When the manuscript was submitted in January 2014, the patient was in a very poor condition and the surgical report from 10 December, i.e. 34 days before the paper was submitted to the journal, states that there were signs that the tracheal prosthesis had become loose both proximally and distally."*

He therefore concludes:

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

The post-operative complications of Patient 1 were described in the introduction of this paper as a way to prove that this particular scaffold was not ideal for use in clinical tracheal replacements. Professor Gerdin certainly cites more detailed, morbid terms from the patient's confidential health records, but our description of the abnormal granulation and chronic fistula are chosen specifically to highlight the aspects of the patient's condition that we believed specifically related to the stiffness of the scaffold to which we were referring. Even if we had given further details of the problems from which the patient suffered, the conclusion drawn after the description of his postoperative course is the same *i.e.*: "*The need to improve the biomechanical properties of the scaffold and our willing(ness) to mimic the native tracheal extracellular matrix (ECM), led to fabrication of the next generation of scaffolds to include FDA approved polymers like polyethylene terephthalate (PET) and polyurethane*." (page 1-2 of original manuscript).

Providing further details of "really major problems that led to the operated patient's death" would have led the reader to exactly the same conclusion. **I therefore assert that there is no basis for the claim of "false embellishment of the results", and thus refute the claim that this is a case of scientific misconduct.**

Additional points

Professor Gerdin makes mention of, but does not pass judgment on, two additional, very serious allegations.

1) The confirmation of the recurrence of the tumour in patient 1.

As Professor Gerdin states: "*in an amendment dated 24 September 2014, the complainants question whether the patient actually had a tumour recurrence*", and that "*these issues are so serious that the healthcare principal should consider opening its own investigation*".

This is indeed a very serious question. However, there is abundant evidence that the tumour was indeed a recurrence, and that the surgery was absolutely required to save the patient's life.

Firstly, the initial operation in Iceland in 2009 only partially excised the tumour (see description published in Am J Resp and Crit Care Med 2011, 183, 681-682, **Appendix 14**). The tumour material was at that point confirmed as malignant, and as it had only been partially excised, its return was expected. The return was indeed reported in the above article ("Control bronchoscopy 7 months after the operation revealed a small residual tumour").

Bronchoscopies, CT and PET scans all confirmed the presence of a mass in exactly the same position as the original tumour, with a strong signal. A multidisciplinary conference on 27th May 2011 attended by more than 15 senior physicians (notes in **Appendix 7** – entries 8 & 9), as well as a second opinion obtained from Harvard University both concluded that a recurrence of the tumour was the most likely diagnosis, and that surgical intervention was required to prevent asphyxiation of the patient, who was already suffering dyspnea from its intrusion into the airway. The need for a non-conventional surgical procedure would have been the case whether the mass was malignant or not, given its progressive growth into the airway.

The biopsies taken for PAD testing on the 27th May were specifically taken outside of the margins of the mass in order to ascertain the size of complete resection needed, and to manufacture the bioengineered scaffold to the exact length and shape required. As such, a negative result on those was hoped for, and expected. A biopsy of the suspected tumour was not taken at this point, as the previous surgery on the tumour had cause unexpected massive and near-fatal bleeding, which necessitated intra-operative initiation of veno-arterial extra corporeal membrane oxygenation to keep the patient alive. The risk of this complication re-occurring outweighed the benefit of a biopsy of a mass which needed resection no matter the results of the biopsy.

Surgery was planned, and the surgical notes by Dr. Jan Liska of 9th June 2011 (**Appendix 7** – entry 10) reveal that the surgical specimen was indeed sent to the pathology lab for biopsy from the operating theatre. Like Professor Gerdin, however, we have no notes of the result of analysis of the suspected tumour itself, only confirmation by Dr. Anna Januszkiewicz, the anesthetist responsible of the operation, to the surgeon (myself) that the entire mass had been successfully resected (**Appendix 7** – entry 11).

2) Allegations of financial impropriety concerning my relationship with Harvard Bioscience.

I have no financial relationship with Harvard Bioscience and in fact gave away my patents to them for commercial development with the hope that my scientific credibility would not be questioned on the basis of personal greed. I switched to their product purely because our research supports that it was superior to the other products previously used. I have opened up all my accounts and dealings with the company – as well as all other aspects of my affiliations to academic and commercial agencies - to scrutiny by the KI in the hope that this will put the issue to rest once and for all.

Finally, Professor Gerdin also mentions additional allegations concerning the use of certain drugs during the trial. He does not express an opinion on this matter. As ever, my team and I would be happy to provide any evidence required to provide reassurance that all our work is carried out in strict accordance with Swedish and international law and regulations.

Conclusions

As I stated at the beginning of this response, I have never – and would never – falsify, embellish or in any way knowingly misrepresent the findings of my (and my collaborators') research. To be accused of having done such is the greatest attack I can imagine to my honour and scientific integrity.

I hope that I have shown in this document that such accusations are without basis.

The definition of 'scientific misconduct' (version as of May 8, 2014 - which can be found at http://www.codex.vr.se/en/etik6.shtml) reads: "…, a person must have performed the misconduct intentionally or shown great negligence." (We note that this is a more recent definition than that used by Professor Gerdin – previously the word 'great' in front of negligence was omitted). I must adamantly continue to deny this is the case here.

As a result of the amount of work that has gone into the preparation of these accusations, and the various responses to them, certain things have been made apparent that could be improved in our future work, or that might warrant an errata note to past publications. Few of these imperfections, however, are unusual in such cutting-edge and international research groups, and none of them show "intentional misconduct" or "great negligence".

The complaints argue that I could have been more detailed and inclusive in the descriptions of the various patients that we implanted with tissue engineered tracheas. Taken to an illogical extreme, I could have prepared detailed Kaplan-Meier survival curves depicting the current status of the implantation of regenerated tracheas. This in fact might be an instructive endeavour as the survival curves would most closely resemble the early attempts of chemotherapy for leukemia or the clinical failure and success of early liver transplantation. Regenerative medicine is in its early clinical development stage and our initial results with tracheal regeneration and implantation may remind the world of the early controversies of these and other innovative therapies that have had a transformative effect on patient care.

These accusations of scientific misconduct are so serious, and have such wide implications, that they deserve a full investigation and decision based on all possible evidence.

It is vitally important to establish the truth in these matters, not simply to restore my own personal integrity and academic credibility but also the legitimacy of my entire research group (including young scientists whose promising careers could be seriously affected by such allegations), the reputation of the Karolinska Institutet and the Karolinska University Hospital, and the whole field of regenerative medicine.

Not only that, but where patients are involved, we have a duty to them, their families, and their clinical caregivers to show that they received the very best treatment possible at the Karolinska Hospital, and that this treatment was carried out with all the thought, care and oversight that every patient deserves.

In conclusion, it is deeply regrettable that the current situation has arisen. It is also regrettable that the external assessment of Professor Gerdin has not examined all the evidence necessary to clear the matter up.

I would like to make available to the Karolinska Institutet, and any independent assessors whom the Institutet should appoint, all the extra evidence that I have obtained – as well as any more that they should request – in order to establish once and for all the integrity of my research team's work so that we can resume our place at the forefront of the field and concentrate our efforts on the challenges at hand to save patients' lives.

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