

This is an English translation of an e-mail from Professor Bengt Gerdin to Vice Chancellor Anders Hamsten on December 21, 2015. Karolinska Institutet is abbreviated “KI”, and Karolinska University Hospital is abbreviated “KS”. In the event of any discrepancy in interpretation the Swedish document has preferential interpretation.

Från: Bengt Gerdin

Skickat: den 21 december 2015 14:35

Till: 'Anders Hamsten'

Ämne: Utredningen - nu har jag läst allt - nästan

Dear Anders,

You will find my concluding perspective on our shared endeavour below. I will then consign it to a corner of my memory amongst other professional experiences. I had actually thought to do so earlier but, at any rate, all the attention from the media subsequently caused me to choose to read all of the statements of opinion which were sent to you after my report became public. There are two reasons why I will gladly conclude my role in this story in this way. First of all, the media has asked me on several occasions if you knew my views regarding the new “evidence” which was submitted in the form of all of the statements. I then responded that I would, in due time, communicate a final opinion to you when I had managed to read through everything and had also arranged it all intellectually. Secondly, I am now much more certain of my perspective given that the legal experts who have spoken up on the matter in various media now appear to have the same view that I do.

Best regards and a Merry Christmas

Bengt

You will get all perspectives below. I also include an appendix in PDF form in case you wish to use the text internally in some way. Since my comments are personal in character, I will indulge myself the use of slightly more unrestrained language than I would if this was part of a formal investigative process. I will attempt to divide up the perspectives into natural sections.

I do not really know how to begin, but I will take a stab at the written engagement I received from you.

My formal engagement only entails reviewing the experimental article in *Nature Communications* and, on the basis of other documents in the matter, determining whether any misconduct has occurred. In the basis for decision you write that “The procedure employed by Gerdin has involved analysis of the written material available at the beginning of the investigation ...”, but it is not apparent that it was precisely this to which the engagement related. During our conversations, both before and after I was formally retained in writing, it was crystal-clear that it also included an assessment of the six clinical articles in the same way.

At the outset, the investigation appeared quite straightforward – for the most part. Some “complainants” claimed that someone, Paolo Macchiarini (hereinafter “PM”), had described research results incorrectly in an article and described the clinical condition and other information pertaining to several patients in an erroneous way in several other articles. I then took the only proper course, or so I believed, and requested that the Institute ensure that all existing documented research material relating to the complainants’ claims of misconduct were supplied to the investigator. This occurred within the so-called line of authority, i.e. via the head of the department where he was employed, Professor Li Tsai. This proceeded first via Lisen Samuelsson, and thereafter in the form of follow-up telephone conversations with Li Tsai. Since I reached the conclusion that it was important to be very clear about what the Department was to deliver and to what PM would respond, I also sent the

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following fairly long, but definitely clear, text in an e-mail which would constitute the basis for the Institute’s provision of all material:

Hi Li,

Just corresponded with Lisen by e-mail. We agreed that I would contact you and clarify what was wanted. In order to be entirely certain that we are on the same page, I will perhaps reiterate what Lisen wrote. In any case, this increases certainty and perhaps helps us gain a little time.

There are two starting points for the request sent to the Institute:

The original material is to be secured by the investigation, and the accused is to be given a sporting chance to be able to point precisely to the original material supporting the claims which are questioned in the published works.

This brings us to two things:

First: The accused shall have access to the following three separate groups of text.

- 1 The first report, dated 24 June 2014 – it was sent by Karin Jakobsson as early as 7 July.
- 2 The second report, dated 18 August 2014 – it was to have been sent to you the other week.
- 2b Appendices to the second report which are entitled: “Analysis of clinical outcome of Synthetic Tracheal Transplantation Compared to results published in 6 articles by Macchiarini *et al.*” dated August 2014 (totalling 54 appendices). They were to have been included in the material you received the other evening. These are compiled in a file entitled: Formal appeal 18 Aug with appendices .pdf. It is a total of 15 MB in size.
- 3a Amendment to the second report dated 24 September – it was to have been sent to you the other week.
- 3b Appendices to the submitted amendment to the second report dated 24 September (totalling 2 tables and 19 appendices). They were to have been included in material you received the other evening. These are compiled in a file entitled: “Formal amendment to appeal dated Sept 24 with appendices .pdf.” It is a total of 10 MB in size.

PM has previously submitted his position on report number 1, but not regarding the two parts of the second report.

Thereafter

Since an investigation of this type entails a review of the entire foundation of the published works, the lead researcher’s personal response is insufficient but, rather, the investigation requires access to the original material, or those parts of the original material which are desired, i.e. parts of the material which, according to the rules and regulations, are to be preserved and saved by the Institute for 10 years following publication. Only then can an impartial assessment be made of the facts. Accordingly, the investigation wishes to have the following in original:

1 With respect to the first report, i.e. the Sjöquist *et al.*, 2014 article, a request is made for all of the laboratory books covering all trials in which artificial oesophagi are transplanted in rats. This is to include all examinations which were conducted; not only those reported in the work. Information regarding all post-operative computed tomographic investigations shall be reported, like all post-operative follow-ups, including daily weight of all animals. Data for all animals operated on as part of a control group shall be reported in the same way. It shall be possible to evaluate which animals were operated on without being included in the study, and which animals are included in the follow-up reported in table 7c of the work. I will get the original files from the disputed computed tomographies in DICOM form from Lisen.

2 As regards the second report of 18 August and the amendment of 24 September (i.e. the articles, Jungebluth *et al.*, Lancet, 2011; Badylak *et al.*, Lancet, 2012, Jungebluth *et al.* Biomaterials, 2013; Del Gaudio *et al.*, J Biomed Mater Res A, 2014; Jungebluth and Macchiarini, Thorac Surg Clin, 2014 and Ajalloueian *et al.*, Biomaterials, 2014).

- a. In the event the research group in its clinical studies prepared any type of CRF (Case Record Forms) for each of the patients included, these are requested in the original.
- b. In addition, or in the event such data is not included in those CRFs, the provision of all documentation pertaining to the alleged misconduct is requested. This means that the research group, in respect of each point in which the complainants are critical, shall be able to provide those parts of the research documentation which support the claims made in the article, and/or which

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oppose the criticism which was otherwise asserted.

c. A list of all communications, and dates of such, and the content thereof which the authors had with the relevant journals – everything from orientation contacts, via sending of the first manuscript, different revisions, and acceptances. Presumably, everything is in the form of e-mail communications. This list is to cover all journals and all articles.

I am also sending a copy to Lisen.
I hope this works out in some way.
Regards,
Bengt
/My underlining; double underlining shows that my request pertains to the research group, and not specifically PM.

I cannot see how the language could have been used any more clearly. The request was thus not sent explicitly to PM but, rather, to the Department and via the Department to the entire research group. The purpose was to ensure a collected and complete foundation for the determination of whether scientific misconduct occurred. The uncomplicated aspect of the request, that all original material was to be provided, was based upon the provision in the rules and regulations according to which all data forming the basis of published works shall be available and stored at the relevant university institute for a period of ten years following publication. KI otherwise has a very well-formulated documentation regime for clinical research (https://internwebben.ki.se/sites/default/files/null/klinisk_en.pdf) in which it clearly states what is to be documented. A researcher who complies with this can supply all background material for public review within seconds.

Now that I have compared my request for the documentation which was by and by actually provided by the research group via PM, and what was subsequently referred to in various statements, I see that a significant amount of original material was not provided. This includes all communication with Iceland regarding the condition of the patient, or regarding the investigations which were carried out and in which the material was sent to PM or Philipp Jungebluth for examination, including all documentation regarding the pathological anatomical material which obviously, at least in part, is in the possession of the pathologist, Béla Bozóky.

In any case, in response to my request via the head of department, PM submitted explanations and documentation on 6 April 2015. Therein he explicitly writes the following:

*Please find enclosed the requested documents. There was no CRF because the transplantations done were not within a clinical trial.
We have, however, all necessary and requested documentations regarding the allegations involving the six manuscripts, including.../Emphasis mine/*

I found no reason to suspect that PM did not do what was requested by the investigator, i.e. provide “all documentation relating to the alleged misconduct”. The whole of my interpretation was thus based upon that which existed, and with the belief that the department head ensured that PM actually understood that everything was to be provided. I find PM’s withholding of the original material from the investigation remarkable and grave and, furthermore, that this deed as such *de facto* sabotaged the investigation. Keeping in mind the very clear language which, as an investigator, I used in my request, I cannot interpret the withholding in any manner other than as being intentional.

In comparing my perspective with what you, in KI’s intranet in October, considered to be the reason why the investigation did not receive all material, there is very little that corresponds. You say nothing about the fact that I asked the Department, i.e. not PM, to obtain all material applicable to the alleged misconduct, but this did not happen. Nor do you mention the fact that PM responded to my

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request by saying that he delivered everything. Below, I will show that he had access to additional information.

Comments on the process as such

I will also take the opportunity to briefly comment on the process. There is no clear set of rules about how it is to be carried out, and KI’s internal routine (Journal no. 1-551/2014) offers little. The risk of something going wrong in a complex situation is thus quite high. In retrospect, certain deficiencies arose which could be learned from and which have actually affected the credibility of the investigation.

The greatest shortcoming is that, after the independent, impartial investigator carried out his task, the investigation was supplied with large quantities of “evidentiary material” which, for explicable reasons, mainly supported the person who is suspected of misconduct. This material was not evaluated by any impartial person who was independent of KI before you used it as the basis for your decision. This methodology entails specifically that the investigation promoted behaviour in which the person who was suspected of misconduct could elect to not provide more material than was necessary to the external, impartial investigator and thereby, in the next stage of the investigation, supply new material which could not then be evaluated in the same unbiased way.

The dearth of care in ensuring that the investigative material which would form the basis of your decision could be assessed in the same cautious and impartial way became very clear. The original investigative material was thus reviewed by me and commented upon at a detailed level in which I made the assessment that there had been scientific misconduct. Any reader can see what I considered to be wrong, point by point, and compare this with the accusations which led to the investigation which are now *de facto* public on the Internet. It is not apparent in your grounds for the decision that the new information provided had been reviewed at the same detailed level.

It is particularly important that the new material which was provided through statements from persons who were involved should be examined in detail by the impartial investigator since this material was provided to the investigation by persons all of whom, in their role as co-authors of one or several articles, are naturally self-serving in their statements. At the end of this text, I will show the result of the deficient examination of detail by pointing out a number of factual errors in the articles which could not be refuted and which are not commented upon in your basis for the decision.

The chosen methodology for conducting the investigation actually renders it meaningless to retain an outside investigator.

I have perceived some additional shortcomings which could be addressed in new internal instructions. **One such shortcoming** is the definition of to whom the “suspicion of misconduct applies”. In the relevant case, the report of suspected misconduct applied to only one person, PM. In principle, this would not have prevented KI/the Vice-Chancellor from considering also whether other persons might be suspected. When suspicion arises, it is *a priori* not so that it is clear who might have acted inappropriately in a complicated research structure, something which experience from other investigations has demonstrated. There are many examples at <https://ori.hhs.gov/>. The duty to investigate suspected misconduct does not mean that the investigation is to be directed at a particular person, even if the report formally focuses on such a person. Here, it was clear early on that PM played such a dominant role in what had occurred, and his responsibility was also explicitly expressed in the presentation of authors in the articles, that any negligence on the part of other parties was obscured. As referred to above, the request I made to the Department was not, in any case for formal reasons, directed only at PM but, rather, I requested that all relevant material from the entire research group be provided. PM, however, authored the reply which was received in April.

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A third shortcoming applies to the fact that, during the earlier phase of the investigation, it was obviously not clear to what extent PM would be provided with the allegations against him in the report with respect to suspected misconduct in the clinical work. In a telephone call with his head of department on 21 January this year, he had not had access to the complaint material which was received by the Vice Chancellor in August and supplemented in September 2014. At that time, I sent an e-mail to attorney Lisen Samuelsson as follows:

I just spoke with Li Tsai. She explained that she had only received the first pages of the report from August and supplement from September, but not all underlying data containing the detailed complaints. She – and Paolo Macchiarini – must be formally provided with these in order to be able to respond. These have certainly been subjected to confidentiality, but it only means that they may not leave the authority, KI. In addition, there is actually no general interest in protection since all material is available on retractionwatch – even the newspapers have disclosed that it’s available on the net!!

Only after this contact was PM afforded access to the report against him. My interpretation is that the uncertainty surrounding also this type of procedure reflects that routines for how an investigation of this type is carried out must be honed.

This was everything of importance about the process which, properly conducted, could have fortified confidence in how legal principles were handled internally at KI.

Some perspective on the ethical issues

After having read your basis for the decision, I am of the opinion that there are major errors in thinking with respect to how KI, and KS, view the ethical rules. You write that the question “...whether applicable permits were granted ...” was not included in your assessment. I think that this approach was wrong since this question is to be matched against the truth of the assertion in the article that the research ethics committee granted permission. The permit issue certainly relates to possible violations of ethics legislation, but the issue of whether the assertion in the article is untruthful definitely relates to the issue of whether misconduct occurred.

In the “key article” the authors explicitly state that an ethics permit was granted. The words are “...*the transplant procedure was approved by the local scientific ethics committee.*” I see no analysis in your basis for the decision that can defend this statement made in the article. It is certainly stated that the decision to operate was to have involved an internal review at KS by its ethics committee, but you simultaneously state that the research aspects were not covered by this review. KS’s internal ethics committee has no mission within Swedish research ethics legislation but, rather, is only an internal advisor in respect of precisely “medical ethics”. The term, “*scientific ethics committee,*” in Sweden can linguistically and actually only correspond to the “committee” which addresses “research ethics” and “research ethics issues”. “Research ethics” and “medical ethics” are actually two different terms. Briefly stated, there is nothing in your basis for the decision which supports the assertion that a “research ethics group” was involved and “approved” all of this. The research ethics legislation, the goal of which is to protect individual persons and the respect for human value in research, views such breaches of the law so seriously that fines or terms of imprisonment not exceeding six months may follow. My interpretation is that this reflects a general legal position which makes the duty of care in research on humans high. To falsely write that there is approval from “*the local scientific ethics committee,*” can thus not be said to reflect anything other than a very high degree of carelessness and, from my perspective, misconduct.

Furthermore, the reference to the Helsinki Declaration, section 32 (my comment: last paragraph in an earlier version of the declaration), is clearly no excuse for violating Swedish legislation regarding Swedish ethics. It is based, among other things, on precisely the Helsinki Declaration, and the general

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moral standard enhancement of all research ethics which took place in the 1950’s and forward. A straightforward read-through of all points of the Helsinki Declaration, rather than an excerpt of one of its articles outside its context, shows this to be crystal clear. Actually, the Helsinki declaration should be read in an integrated context as stated in its paragraph 1, which states that “..The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs”. The entire declaration is found on: <http://www.wma.net/en/30publications/10policies/b3/>

The Helsinki Declaration thus provides no support whatsoever for that which has transpired, something obviously claimed by PM.

In the basis for the decision, you have addressed the issue of whether the surgical procedure constituted a part of research or only constituted medical care provided in a hopeless clinical situation. This is naturally an important question since a conclusion according to which that which has transpired was not research has rendered the entire merry-go-round meaningless. If KI, during an orientation stage, understood that this very thing was a key issue, it should have been better clarified before the investigative assignment was given. Now, the analysis by the investigation is overshadowed by how you and KS interpret this issue.

As regards the point at issue, in any event I do not understand the interpretation according to which the surgical procedure *per se* constituted medical care and not a part of research. The formulation of the question is otherwise linguistic hair-splitting since a measure carried out on a patient is always care even if its indication, execution or result entails that it is part of research. You yourself state that the prosthesis constituted a “research tool” and that “research methodology” was applied for the follow-up.” Is this not an admission that that which was done was, in reality, precisely research? I am sorry to say it, but to me an attempt to force another interpretation is a smokescreen. To be abundantly clear, I see the false dichotomy between care and research as one of the errors in thinking in the interpretation. There is a borderland, but this borderland is common ground and not a demarcation. The Helsinki Declaration addresses precisely this shared grey area which is relevant. It is worth a read!

If one looks at what actually occurred, any smoke begins to dissipate. In the Icelandic statement, it is apparent that PM explicitly did not want the documents regarding examinations conducted after discharge from KI to Iceland on 8 July 2012 to be sent to KS where care was provided but, rather, to KI where “the research methodology” was used, and then directly to his laboratory. This relates, for example, to the biopsies which were taken during the post-operative bronchoscopic examinations in Iceland. This cannot be interpreted to reflect anything other than precisely a matter of research. Let us say that PM only used “research methodology” to follow up on the post-operative clinical course as part of the patient’s care, and not as part of research. If so, all of these documents would naturally be incorporated in the patient’s journal at KS. This was obviously not done in spite of the fact that the clinical follow-up protocol explicitly states that follow-up shall take place at KS.

I have further comments regarding this. Where research comes into play while an individual patient is being cared for continuously varies and, in principle, is determined by the clinical researcher’s actions in real time. If tests are taken or examinations are conducted which are not primarily presumed to benefit the relevant patient, this constitutes research irrespective of whether they are taken or conducted as part of the actual care of the patient. In this case, In this particular case, the body of postoperative analyses and investigations done, and which are no included in the patient records were obviously not intended specifically to benefit the relevant patient but, rather, constituted a basis for the continued development within a research area.

An additional perspective is that the ethics committee was not involved at all notwithstanding that this should have been the case. There is no value in informally contacting a member (who is not primarily an ethicist) before surgery is done. The Ordinance on Ethical Review states that the ethics committee

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can provide advisory statements in the event the research does not appear to be covered by the Act. This reflects, among other things, that there is a grey zone for the application of the Act and, in practice, that the ethics committee may be instrumental in the interpretation of this grey zone. This occurs by doing what we, usually describe as “ticking the box” as we normally do in the application when we apply for an ethical review. One might wonder why this was not done. It would have been to raise the bar from an ethics perspective.

The analysis which was presented in your basis otherwise applies only to patient 1. Patient 2 was operated on after 5 months! Was the same “rigorous” ethical process pursued, or was it the opinion that the principle which was banged out for patient 1 would apply here, i.e. a last-resort situation which could be justified since the patient would die if something was not tried. Thereafter a patient number 3. Was this also considered to be medical care – only?? I can see that much of the weight of the argument in your basis for decision pertains to patient 1, but I do not see that there is anything compelling as regards the other 2 patients.

Finally, a pure credibility issue. How credible is it to claim that scientific work involving as many as 16 authors from KI, of which only 3 belong to KS and a total of only 6 authors from KS, does not constitute research which was carried out at KI?

Surgically resected preparation which simply disappears

Another question which sends shivers up the spine of a retired surgeon is that a perioperative excised surgical specimen from a patient with a suspected recurrent carcinoma is allowed to simply disappear. This issue is somewhat to the side of the main issue in the investigation, but pertains to the formal definition of what is deemed to be “cancer” and not, i.e. what appears in the article. I am certainly not a specialist in thoracic conditions, as a consequence of which I express myself with particular reservation, but it appears doubtful to me that one can be absolutely certain that what one perceives in a wide-spread fibrotic mass within a hilar region of the mediastinum, in which a complicated surgical measure has been previously carried, and which was subsequently given heavy radiation therapy, and in addition followed by flaring tuberculosis, is actually a recurring tumour. Here, if ever, a pathological anatomical diagnosis from the specimen should be a prerequisite to expressing oneself on the issue with certainty. Briefly stated, a suspected tumour in this area certainly cannot be anything more than just “a suspected tumour” in the absence of a pathological anatomical diagnosis. I truly hope that it is an extremely unlucky coincidence that such an extremely unique operation as this one was followed by an event so unique as a critical surgical specimen just vanishing. Furthermore, the sample must have disappeared before it reached the pathologist since it is obviously not in the pathologist’s database from which I have requested all information.

ISSCR Guidelines

We are also not in agreement here. Interpreting ISSCR recommendations (Recommendation 34) as you did, i.e. as a principal legalisation of certain untested stem cell activities in the form of a parallel medico-legal process as what otherwise applies to research on humans in accordance with applicable law, is not in keeping with the Swedish legal tradition. There is nothing in this Recommendation regarding “advanced interventions”, which is the term you use. It mentions “unproven stem cell-based interventions”, and that there must be a plan to communicate the results.

This formulation is part of a recommendation the primary purpose of which is to emphasise that the evaluation of certain “unproven” stem cell treatments on individual patients may be carried out without conducting a formal “clinical trial”. This does not mean that this can occur in the absence of customary ethics reviews. The proposed interpretation according to which, in the relevant context, it could occur without an ethics review is frightening and lacks a basis in other provisions of the

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Guidelines. The fact is that the ISSCR’s recommendation language contains a solid ethical perspective and, elsewhere amongst the 34 Recommendations, it is clear that it is desirable that everything which transpires shall be used for “research” and shall be subject to ethical review. I cannot refrain from inserting a small piece of text from the commentary to recommendation 2:

Regardless of the recommendations encompassed in this document, scientists and clinicians should comply with local policies and adhere to local, national, and international guidelines relevant to research.

Your words that publication pursuant to ISSCR’s Recommendations is contrary to my perspective according to which publication presupposes a preceding ethical review is thus so incorrectly interpreted that I have concluded that someone other than you must have been the author at that time. The person who authored those lines is obviously completely ignorant of the important perspective in the Guidelines.

I will take the opportunity, if not as a warning then to stir reflection, to quote the following ethical moral text in the Guidelines as sub-text to precisely Recommendation 34. This takes up the desperate hopes of patients:

Not following such standards may exploit desperate patients, undermine public trust in stem cell research, and unnecessarily delay better designed clinical trials. Many who provide stem cell-based therapies may claim that they offer innovative medical care not available in other medical institutions because of the conservative nature of medical care. Strict application of the above criteria to many clinical interventions offered outside of a formal clinical trial will identify significant shortcomings that should call into question the legitimacy of the purported attempts at medical innovation.

In order to wrap up this part of the perspective, the provisions of ISSCR’s Recommendation 34 are actually wholly uninteresting. ISSCR’s Guidelines apply only to stem cells. It does not apply to organ matrices manufactured with foreign plastic materials which are wholly untested in animal trials. Raising ISSCR’s Recommendation 34 as part of the argument in your basis for decision is, for this reason, also so half-baked that I have reached the conclusion that someone else must have also written this. Otherwise, as we both see, the use of the mesenchymal stem cells does not *per se* entail any ethical problem but, rather, it is precisely the use of the synthetic trachea which are foreign to the species and which have not been subjected to animal trials.

Some perspectives on the most important statements

These include PM’s statement, pathologist Béla Bozóky’s statement and the statement which came in from Iceland.

Thus, PM states in his reply that my investigation was not based on complete material. This is correct and is due only to the fact that, as I wrote earlier, PM and his department did not deliver all of the material I requested as early as January 23. In his reply in April, he said that this had taken place and that he did not have any information regarding the patients but, rather, “relied on his clinical colleagues”. What he writes there relates to what the Icelandic colleagues wrote in their later statement according to which PM had explicitly stated that all information from Iceland was to go directly to him or to Philipp Jungebluth. Setting aside this discrepancy on the relevant point, PM’s way of selectively choosing when he will submit his views on the matter to the Vice Chancellor’s investigation means that he, consciously or not, misled the investigation.

The submission which came in from Reykjavik mentions that there were several contacts with PM regarding the health of the patient. Contact was also made with Philipp Jungebluth, who was

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employed not at KS as a doctor but, rather, as a researcher at KI. The suggested explanation is that the information which was provided to him is perhaps not in the KS patient records.

The submission from the co-author, pathologist Béla Bozóky, is interesting. Here it is stated that he, within clinical pathology at KS, has information which shows that what is written in the articles is correct. Notwithstanding that I have explicitly requested all information available within clinical pathology regarding the patient, this has not reached me. Nor has this been entered into the patient record. As I understand it, Béla Bozóky’s statement that he has samples which support the articles’ statements have not been validated in your internal process. This issue is, of course, important since the information which the pathology department at KS submitted to the patient record regarding what was seen in certain samples and at certain times differ from what is said in the articles.

As regards other statements, my overall impression is that most things need not have been written if the Department and PM had submitted all of the supporting materials which I requested in January 2015. Most of those who answered are satisfied with describing their part of the investigation. Some suggest that I should have checked with Iceland. Some co-authors raise the hurdle of lead authorship and the responsibility that follows. Those whose opinion differs from mine with respect to responsibility and roles are advised to read what PM himself has written in his description of his role in the various articles under scrutiny.

I also note that some are unaware of the Swedish terms and limits of the principal of free access to public documents. After my investigation became public, I have been interviewed regarding the contents of the investigation but, in conjunction with these interviews, I have in no respect gone one millimetre outside what I wrote in the investigation, i.e. only brought up that which was publicly available and which was otherwise already available to those who interviewed me via KI.

Finally, I do not intend to polemicize with those who wrote statements, even if this could be easily done *in extensio*, but nonetheless cannot avoid drawing attention to the fact that certain statements contain absolute factual errors, many, while others are extremely verbose and jumbled without strictly addressing the issue at hand, whether certain assertions in the articles are unfounded or not.

Contents of the patient journals

As for what is said in the patient records, it is word against word. Some of the persons who have given statements say, for example, that the journal documents contain explanatory information which I missed. I strongly doubt it, even after having read through and checked the most important parts some weeks ago, but I am naturally nonetheless troubled. Of course, I may have missed something notwithstanding very careful searches amongst the several thousand pages of paper print-outs from the digital journals released by KS to KI. Browsing through large bundles of paper documents which someone else has obtained from the computer is always more uncertain than sitting down and reading through the complete documentation digitally. The digital journal should contain various types of search functions which make it easier to specifically search for desired information. As you know, this was my foremost wish which KS denied for reasons which are unclear to me. This refusal definitely made my job more difficult. Accordingly, I received thousands of pages of print-outs, most of which were not relevant since they concerned patient number 3 who had been under care for a long period of time after the relevant period of time. On the other hand, I cannot be sure that all information in patient records, other KS databases and pathology systems were included. In any case, I take it for granted that what some claim I missed and which is said to support PM has been evaluated in detail in your process, even if it has not been commented upon in detail.

I was recently able to go through parts of the records journals once more, and certain important pages which I had hoped to obtain eventually, as you know, are missing. I also considered reading these but, quite likely, there is nothing which affects what I have written here.

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Specific comments regarding the statements regarding what I found to be misconduct

You will, finally, get some perspective on my current position in respect of what I previously regarded as misconduct. Before I go into the details, I wish to say that, generally speaking, I have not found anything pointing to an error on my part in my overall conclusions. To the extent some of what I wrote previously falls to the wayside, it is a direct consequence of the fact that PM did not give me the material I needed in January but, rather, provided it to you later in.

Let us begin with the pre-clinical article in *Nature Communications*.

In his submission from April 2015, PM wrote the following, among other things, in his own words:

No person from ACTREM (our laboratory) has access to the appropriate CT scanner needed for this imaging (this can be independently confirmed by Professor Moustapha Hassan, Department of Laboratory Medicine). Therefore we asked for the assistance of Dr Simonson, who had access to, and experience with, the necessary hard- and software. Since we did not have the software or expertise to create 3D-renderings ourselves, we used the image that Dr. Simonson gave us ...trusting him as a scientific collaborator to have given us all raw data used for the 3D-rendering.

I was of the opinion then, as I am now, that what was written cannot be interpreted in any manner other than that no one other than Simonsson had the knowledge or resources to dynamically and critically be able to create the 3D pictures which were necessary for an adequate and certain interpretation. In the submitted statements, in which attempts were made to emphasise the fact that several co-authors participated in or, rather, were present in conjunction with, the actual computed tomographic examination of a rat, I could not see that any of them actually had the knowledge by which they could take scientific responsibility for the images or even create and evaluate the images. No one has explicitly stated that they had access to the software necessary in order to review DICOM pictures. No one has explicitly stated that they placed the DICOM images in a viewer and rotated the 3D pictures back and forth in order to attempt to understand what is depicted and which forms the basis for rendering representative 2D pictures for publication. What thus remains is that the research group could not take responsibility for the results they chose to include in their article.

As regards Simonsson’s election to refrain from authorship, several interesting puzzle pieces are included in the statements which I could not get previously. They reflect that the circumstances and cooperative relationship between the various persons involved seems to have been very special, which obviously prevented the conversations regarding the completion of the article from being steered by rational forces. My personal perspective is that it is dishonest – and inappropriate – to write a scientific work in respect of which one cannot take responsibility for ensuring that what is written is correct, but it is also dishonest to slow down a shared work by withdrawing from it at the last second and claim scientific reasons if the reason is something else. Notwithstanding this, I have not found anything which shows that my conclusion in the investigation was incorrect.

Let us now have a look at what the submitted statements mean for the interpretation of the other articles

In article 1 it is stated that there is approval from “*scientific ethics committee*”. I have commented on this above and have shown that the assertion is false. This untruth entails misconduct.

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In article 1 it says: *“There were no major complications, and the patient was asymptomatic and tumour free 5 months after transplantation”*, and, furthermore, *“5 months after transplantation. The bioartificial nanocomposite has patent anastomoses, lined with a vascularised neomucosa, and was partly covered by nearly healthy epithelium.”* The Icelandic statement explicitly states that the last bronchoscopy on Iceland was conducted on 20 October 2011, after 4.5 months, and no biopsies were taken from the graft at that time. On the other hand, biopsies were taken from other sites. This means that the assertion is not validated and thereby groundless. Accordingly, my criticism remains.

In article 1 it also states *“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).”* Furthermore, it states *“The biopsy sample 2 months after transplantation showed large granulation areas with initial signs of epithelialisation and more organised vessel formations, and no bacterial or fungi contamination (figure 2B).”* PM comments here that pathologist Béla Bozóky has information regarding all biopsies.

If you now return to the patient record, it states that Béla Bozóky examined the biopsy samples obtained in Iceland on 16 August, i.e. 2.2 months after the operation. They are the only ones which, as is apparent from the Icelandic statement, which were taken at all during the relevant period of time. Bozóky describes the findings in the patient record (Reg no. T13253-11) the following:

*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 may 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 bacterial colonization.***

In a supplemental statement in the journal, he states the following:

“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.”

He thus states as the final diagnosis:

“Biopsies from transplanted trachea with necrotic connective tissue with fungi and bacteria and capillary rich granulation.”

In the samples which constitute the basis for both the text in the patient record and in the article there are thus fungi and bacteria. As set forth above, this fact is explicitly denied in the article. The article also says: *“more organised vessel formations”*, and the patient record states *“partially in seemingly shadow formations of vascular structures partially assumed in the interstitium.”*

I continue to assert that the text of the article is not formulated with the intention of providing a true description of the pathological-anatomical findings. Can this be anything other than misconduct? How can you interpret this as *“so there is no support for ... suspicions regarding misconduct in research”*?

In article 1 it is also stated: *5 months after transplantation, the patient is asymptomatic, breathes normally, is tumour free, and has an almost normal airway.* There is nothing in the Icelandic statement which actually contradicts this assertion in the article. This statement describes only that he,

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at this time, came in for “non-specific complaint” and was treated with antibiotics. On the other side, no clinical examination was conducted of the patient in Iceland in September, October or November 2011, i.e. in broad terms, 3 – 5.5 months after the operation, which would have been required for a scientifically based claim that breathing was objectively normal and that his airway was almost normal.

In article 1 it is also stated: *“the initial fungal infection had resolved within 4 months from transplantation; later the endoluminal surface was partly lined with respiratory mucosa, at which we noted nearly healthy epithelium and proliferating endothelium.”* This must thus be based on an interpretation of the bronchoscopy which was conducted on October 20, when no biopsy was taken. There was nothing in the Icelandic statement which supports the assertion in the article. In addition, one cannot make a statement regarding “proliferating endothelium” without microscopic examination of the sample and staining for proliferation markers. I am surprised that no-one in the group of authors questioned this.

In article 1 it is also stated: *“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,”* Since the facts upon which the assertion is based have no support, this assertion is also false.

In article 2 it says: *“The artificial scaffold, which was seeded ex vivo with autologous bone marrow-derived stromal cells (in a bioreactor) and conditioned with pharmacological therapy, was implanted into a patient with a primary recurrent tracheobronchial tumour. The graft was patent, well vascularised, and lined with a well-developed healthy mucosa 8 months after transplantation ⁴⁹.”* The examination which took place closest to eight months after the operation was carried out on 14 February 2012, which is equal to 8 months and 5 days, and was carried out at KS by Juto and PM and is also described in PM’s own submission (section 57 of Appendix 7, page 23). Here there is nothing said about the fact that the graft was *“well vascularised, and lined with a well-developed healthy mucosa”*. It is noteworthy, furthermore, that, in the brush centrifuge from the graft area which was taken at the time of the examination, they did not find *“any considerable epithelial material”*. During the examination, several biopsies were taken which were explicitly described in the referral to the pathologist to be from the anastomotic areas. Furthermore, the pathology report found in the patient record do not confirm the assertion in the article. This states:

“a lot of granulation tissue with some plasmocyte infiltration. The surface epithelium consists partially of squamous epithelium which is eroded by granulocytic attack, partially completely rejected with scab formation, and focally single atypical squamous epithelial cells are seen but these seem to be mostly of a reactive character.”

An entirely different matter is that PM actually denies that the patient was cared for at all at KS during the relevant period and that he did not know how the patient was doing – surprisingly notwithstanding that he had actually bronchoscoped the patient! On page 13 of his statement he writes the following:

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. Tomas Gudbjartsson 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 article was unsubstantiated.

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

What he says here is demonstrably wholly incorrect. How did you succeed in interpreting this in such a way that PM had responded to the criticism “satisfactorily”? And how can you even interpret this as “so there is no support for ... suspicions regarding misconduct in research”.

In article 3 it is written: “*The early clinical evaluation revealed an initial graft epithelialization as judged from the 1-week post-operative brushing.*” It is said that this brush biopsy is examined at their own research laboratory. Notwithstanding this, there is no information regarding it in the journal, which is a requirement if it was taken as part of the patient’s medical care.

In article 3 it is written about the result five months in: “*a patent and non-contaminated graft without any signs of inflammation*”. I maintain that this brief assertion is incorrect and leads the reader to believe that “all is well” at five months – which it definitely was not! PM leaves it to the reader to decide whether there was reason in this article, which above all has an experimental feature in which this assertion was a subordinate clause, to develop the assertion further. Irrespective thereof, the assertion is false.

My perspective on this is the same as before. At the relevant point in time, there was a fistula which was interpreted as suture dehiscence which was stented on multiple occasions, and was unburdened by PEG, and also recurrent granulomas at the site of the anastomosis. Describing the result as was done suggests to me that the intention was not honest in describing the clinical overall truth regarding the chain of events, but a selective truth in which the words themselves were chosen so as not to be able to be called into question. The obligation to write the truth has nothing to do with the number of words it is expressed in, something that PM attempts to persuade us to believe. I see that you, and those who judged the content of the statements with you, have a different view than mine, also with respect to this part of that which is said against PM.

In article 4 it is said: “*After 12 months, an almost normal airway and improved lung function were assessed.*” Here, PM has not replied satisfactorily in any respect. I refer to my previous opinion and to the complete patient record which contains detailed information from the time point 11.5 months after surgery, i.e. on May 22, 2012. In reality there was nearly a total occlusion of the right main bronchus which was expanded with a stent and, furthermore, a fistula. I developed this more in my first report, and I am steadfast in the same position today as I was then. There are facts in the patient records, which state that the patient was in a bad way. The article says something different! I am sorry, but I truly do not understand how this can be explained away, and how Macchiarini’s response may be said to be “satisfactory”. To generalize, the inconsistencies which I have described earlier in this report are of two types, elements in the written text which were without basis in the patient records, and elements which are completely contrary to the actual data that exists and which are in the records. It is the second type of inconsistency which appears in this article. As regards to these, it is logical, if the article is correct, that the patient record is wrong. The latter is highly improbable since what is written in the patient record is done in real time and describes the current clinical picture which dictates the patient care at that time. This is why a patient record always has a high degree of credibility. Thus, the article is incorrect.

Another aspect of this pertains to the grave circumstance, which I did not develop in my previous opinion, namely that the authors actually had access to the information regarding the patient’s condition far beyond the 12 months’ observation point reported, up to 2 years after the operation, since the article was sent in 21 months later, and in revised form 25 months later. Commencing some month after the first anniversary, a progressive fistula problem was diagnosed which led to PEG and oesophageal stenting. Then it was possible to actually see that things were starting to go downhill. To refrain from presenting the best possible description of the chain of events all the way until the completion of the article is dishonest in my view. I wish to draw a parallel with a known case of misconduct within your speciality, the infamous VIGOR study, which was published in NEJM, in which the authors knew that the data on the publication date was worse than at the time of follow-up which was selected to appear in the article. In my view, what

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is present here is not, in principle, of lesser magnitude than that which occurred in the VIGOR study. Do you?

As regards article 5, I note that PM was prepared to submit an *amendment* in order to facilitate the interpretation of the table. However, I maintain that I interpreted the table correctly – such as it is written. I also maintain that the course of events for patients 1 and 3 were so superficially described that they do not provide a correct impression of the degree of gravity of the actual clinical condition. It is misconduct. Furthermore, I cannot interpret it in any manner other than that patient 2 is the patient with the malignant illness who died due to gastro-intestinal bleeding, but in respect of which PM in other contexts did not choose to state the cause of death. PM doesn’t comment on this.

In article 6, it is written that: *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.* PM defends the erroneous description. Irrespective thereof, my criticism remains. It is not reasonable, by means of linguistic virtuosity, to avoid the actual facts by selectively stating that one is describing “only a small part of the whole”. The purpose of language, even within this part of science, is to communicate the overall truth rather than a small, selected puzzle piece. Otherwise, the requirement of truthfulness is equally great irrespective of whether one is explaining something peripheral or regarding the main course/main result of a project. What is written in the article is not at all intended to provide a correct description of the state of things. When the article was accepted, the patient had been dead for 5 weeks, but 2 weeks after it was sent in!

In summary, as opposed to what you write in the KI intranet, the statements have only marginally changed the picture of what occurred, at least as regards the issue of misconduct. An important new piece of information is certainly that there was good control of the first patient’s care in Iceland, which was not clear in the initial documentation. Another valuable new piece of information is that information from Iceland regarding the condition of the patient, like the fact that the results of examinations and material from examinations in Iceland was sent at PM’s request directly to Philipp Jungebluth at KI, and not to KS, and therefore was available to PM’s research group, which PM reasonably should have had knowledge about. Since the picture has only been affected marginally, I cannot subscribe to substantial parts of the argumentation in the basis for your decision under the heading, “Karolinska Institutet’s deliberations and judgment”. Above all, I cannot subscribe to the interpretation that “*The main issues to which attention has been drawn and which have been criticised could, in a satisfactory way, be addressed by Macchiarini and co-authors,*” and that “*so there is no support for the complainants’ suspicions regarding misconduct in research*”. I am sad to need to say it, but the logical consequence is thus that nothing has come forward which affects my position of the principal matter. Thus, there has been misconduct in the writing of the articles which I show by pointing out some uncontested facts as support for this; facts which are so impossible to overturn that I cannot understand how it is possible to manoeuvre around them while maintaining any credibility at all.