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RE: 2-723/2016 Suspicion of Scientific Misconduct

Karolinska Institutet postulates that new pivotal evidence of scientific misconduct on the part of Dr Macchiarini et al. has surfaced concerning the previously reported articles. This new information is incremental in scope compared with what has already been revealed by our earlier report from August 2014 (1), which was later also confirmed in the report by the external reviewer Prof Gerdin on May 13, 2015 (2). The purpose of trying to introduce the discovery of new information is to provide the leadership of Karolinska Institutet with absolution for earlier shortcomings in the handling of Dr Macchiarini's transgressions.

We can only conclude that this new information is one of a multitude of instances in which Dr Macchiarini's group has systematically misrepresented, forged or manipulated data in order to gain publication in high impact medical journals. Instead of repeating the investigation of the already analyzed articles, all other articles published by this group during the time of their affiliation with Karolinska Institutet that have not been previously analyzed, should be investigated in detail. There should also be an investigation of this group's earlier work and contacts should be made with the corresponding universities. At the time of our submission for an appeal for an investigation of scientific misconduct by Dr Macchiarini on August 18, 2014 (1) it became obvious that more than the seven articles that we had analyzed contained manipulated data, but because of time constraints we had to limit the scope of that report. For instance, an analysis of the rat trachea implantations carried out late in 2012 and early 2013, after the patients had been transplanted, will reveal that synthetic trachea implantation is a failure with the development of chronic inflammation and infection and finally graft occlusion. Dr Simonson performed these experiments for Dr Macchiarini's group. He reported these findings and was subsequently removed from the project. Dr Macchiarini *et al.* went on to publish the article in *Nature Protocols* (3) where the transplants are described as a success based on confabulated results.

Prof Hamsten, along with the leadership of Karolinska Institutet and Karolinska University Hospital, freed Dr Macchiarini of suspicion of research misconduct in the face of an insurmountable body of evidence. The acquittal was engineered by taking only into account the testimony of the entirety of Dr Macchiarini loyalists (Appendix 1), produced after the judgment of the external reviewer (4). The content of this biased testimony did not contain any factual information that could revoke the conclusions of the external reviewer, but nonetheless, its sheer volume was employed by Karolinska Institutet as an indicator of innocence. Prof Hamsten certainly stated that he had "*almost completely misjudged*" Dr Macchiarini (5) but we cannot accept that Prof Hamsten consciously relied on the prejudiced opinion of several Professors including Lendahl, Tsai-Felländer, Cardell, Carlstedt-Duke, Kuylenstierna and Hermanson. These key individuals all had a vested interest in Dr Macchiarini's fortunes and would have succeeded in undermining the review process if the monumental catastrophe of Dr Macchiarini's work had not been revealed by the Swedish Television documentary "Experimenten".

To now be contacted by Prof Carlstedt-Duke, one of the main authors of last years decision to free Dr Macchiarini, asking for more evidence of research fraud is just plain absurd. Last

year no amount of evidence was sufficient to pronounce Dr Macchiarini guilty. Now Karolinska Institutet is desperately searching for any and all signs of misconduct so that a guilty sentence can be handed down, but only based on what Profs Hamsten and Carlstedt-Duke describe as “completely new information” (5) and “Karolinska Institutet has got new information concerning the first patients time after the operation on Island” (6).

In our primary appeal for an investigation from Aug 18, 2014 (1), evidence was provided that showed that the articles in *Biomaterials* (7,8) should be retracted and was confirmed by Prof Gerdin. However, in last year’s decision by Karolinska Institutet (9), the *Biomaterials* articles and the transgressions there in, were not even mentioned and the articles were allowed to persist in the medical literature.

Sweden’s largest daily paper, *Dagens Nyheter*, reported on February 13, 2016, that the duplication of pictures in *Biomaterials* was the final straw that broke Hamsten’s back (10). This wouldn’t warrant comment if it had not been purported in such an important media outlet. The general public may believe that this was the decisive point but anyone with research experience knows that the head of internationally renowned institute does not resign because a research group has been caught double publishing pictures (11). What this story reveals is that the Karolinska Institutet is suffering from a culture of chronic media manipulation that reflexively tries to cover-up one batch of lies with another.

The coercion continues further with what has been designated as new information (12) concerning biopsies found in *The Lancet* “proof-of-concept” article (13) from 2011. In our appeal for an investigation from August 18, 2014 it is clearly stated that the biopsies depicted as regenerated tracheal mucosa after 7 days do not exist in the medical records at Karolinska University Hospital. We were incapable of finding this biopsy (14) as was the external reviewer Prof Gerdin (15), the pathologist and even Dr Macchiarini (16) who also did not register any biopsy at this date in his time line which was attached to his respond to the external reviewer on June 26, 2015 (17).

Prof Kuylenstierna has now produced an affidavit confirming that he did take a biopsy when performing a bronchoscopic examination of the first patient on the June 16, 2011. However, review of the patient’s medical files reveals that Prof Kuylenstierna has not mentioned the acquisition of a biopsy in the surgical notes describing the procedure. This is contrary to standard routine as acquisition of a biopsy is invasive and can be conducive to complications and thereby should always be stated in the procedural notes. Furthermore, there is no referral to the pathologist so there is no record of the biopsy ever having taken place. Dr Jungebluth has also now produced an affidavit confirming the receipt of the biopsy. Since there is no ethical permission to perform research on this patient, then this alleged biopsy has been procured under illegal circumstances.

We find this whole scenario implausible and give little credence to the affidavit produced by Prof Kuylenstierna and even less to that of Dr Jungebluth. Prof Kuylenstierna has been one of the main facilitators of Dr Macchiarini’s endeavors at Karolinska and is responsible for the “attainment” of “ethical approval” under fraudulent forms. He is one of the several involved key players affiliated with these acts of medical abuse and consequently his word is of little worth.

A more likely explanation is the following:

In an email from Dr Macchiarini from August 3, 2011 to Prof Gudbjartsson, the first patients referring doctor on Iceland (18) it is stated: “To increase the chances to get it accepted (*The Lancet* proof of concept article, our note), we would need the blood samples and biopsies samples listed in the attached file. We would need to have them by the end of next week. Is this please possible?” where after the biopsy samples asked for are specified: “Biopsies from the native bronchi and graft: Cover with Tissue Tec and freeze with liquid nitrogen. Send please on

dry ice (Federal Express) to Stockholm, (address as mentioned) Address: Philipp Jungebluth, Karolinska Institutet, Hjärtlab, KFC, Novum floor 6, exp. 614/Huddinge, SE-141 86 Stockholm, Sweden”.

After the above given instructions four biopsies were taken during a bronchoscopy performed on Iceland on August 16, 2011 (19) which was recorded on film (20,21), 10 weeks after the implantation of the synthetic trachea. Three of these biopsies were from the tracheal implant and one from (N.B) the native trachea according to Dr Macchiarini’s specifications (18). The samples were shipped by Prof Gudbjartsson on the same date from Iceland directly to and received by Dr Jungebluth at Karolinska Institutet. This act is in and of itself illegal, as biopsies sent for healthcare purposes should only be sent directly between hospitals. Biopsies sent from a hospital to a laboratory can be allowed for research purposes but only after ethical approval, which in this case was lacking.

The biopsies were then delivered to Dr Bozoky at the Department of Pathology who described severely diseased findings (22), which in no way correlated to the photos in figure 2B (iv-viii) in *The Lancet proof-of-concept* article (13). Most likely Dr Jungebluth has used the biopsy from the native trachea taken on Iceland at ten weeks (August 16, 2011) after implantation in *The Lancet proof-of-concept* article and called it a day 7 biopsy proving that a new mucosa has been generated on the plastic scaffold after only one week. Dr Bozoky has certified (23) that the photo in the article corresponds to the biopsy that he analyzed. However, he cannot guarantee from when, where or even from whom the sample was taken since the biopsies have been handled outside of the official referral system. There is no official record of any biopsy taken on June 16, 2011 or at any time around that date except that of the affidavits from two individuals produced under duress four years after the supposed occurrence. The bronchoscopic film performed on August 16, 2011 on Iceland shows no signs of a normal mucosa on the implanted graft at two and a half months after implantation but instead a completely exposed plastic surface. This implies that the presence of a functioning mucosa already at one week is impossible.

It should also be noted that two other biopsies from the first patient that have been registered in the medical records on August 4 and 24, 2011 were acquired at the time of the first tracheal transplantation on June 9, 2011, immediately before the actual implantation of the synthetic trachea graft. The biopsy samples were taken from the synthetic scaffold and showed *“no developed cell layer could be detected”* and *“no detectable cell components or matrix structures can be found”* (24,25). This means that the patient received a naked plastic trachea without any cell layer covering it. This could never have resulted in anything except chronic infection and a death sentence for the patient.

This key information did not stop Dr Macchiarini and his team from performing the next synthetic trachea implantation three months later on November 17, 2011. In total three young patients at the Karolinska and an unknown number of patients outside of Sweden underwent the same experimental procedure resulting in unnecessary suffering and death. Furthermore, these biopsy findings completely disavow Dr Macchiarini’s claims that a two day incubation with bone marrow derived cells can yield a cellular coverage of the plastic trachea necessary to prevent bacterial contamination and generation of a functional mucosa. The implication of these biopsy findings is that the full thickness respiratory mucosa, with a completely developed underlying supportive tissue, would have to have developed after seven days from an evidently naked plastic graft. Dr Macchiarini describes the futility of the experiment best himself in an article published in 2004 (26):

“...It is well known that a tissue-engineered cellular graft of larger than 0.8 mm in diameter needs vascularization to maintain viability after implantation into the host. However, the revascularization process usually begins within the first 2 weeks and flourishes within the eighth week of implantation. One might therefore speculate that an implantation time of 1 week is almost certainly too short for sufficient revascularization of small-diameter grafts.”

"So, what can we learn from this and what implications does this study have for the current and future state of the art of tracheal transplantation? Surgically placed porous prostheses (with and without epithelialization) have been unsuccessful in human use basically because they are exposed to a contaminated interface between air, chronically repairing connective tissue, and epithelium. It is time to acknowledge that they are biologically incompatible, in contrast to vascular conduits placed in potentially sterile mesenchymal tissue."

Dr Macchiarini's superiors and facilitators at Karolinska Institutet should be quarantined from positions of influence, as should the Karolinska Ethics Committee, who in an act of ethical somersaults freed Dr Macchiarini of any wrong doing when it was well known that his patients were either dead or dying. These people will continue to poison the waters in order to maintain their status at the expense of our institution. It would be cathartic to immediately retract the seven articles already deemed to be fraudulent from the medical literature without having to go through the charade of a new investigation. Anything shy of retracting these articles risks perpetuating Karolinska Institutet to a reputation as a safe haven for charlatans and fraudsters.

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