Stockholm Aug 18, 2014

Formal Appeal for an Investigation of Scientific Misconduct

To the President of Karolinska Institutet

RE: Prof Paolo Macchiarini, CLINTEC

Dear Prof Hamsten,

We would like to hereby make a request for a formal investigation of Prof Paolo Macchiarini, CLINTEC, Karolinska Institutet, on the grounds of scientific misconduct. Having been involved in the treatment and care of three patients who have undergone implantation of synthetic tracheal grafts, and subsequently acquainted with the clinical outcome of these procedures, it has become apparent that the results published by Prof Macchiarini do not correlate with the patients' actual clinical outcome. We have conducted an analysis of the medical records of the patients transplanted with synthetic tracheae and compared them to the outcomes published by Prof Macchiarini.

In the six articles listed below, the implantation of synthetic tracheal grafts is depicted as a viable treatment option for patients with non-resectable tracheal pathologies and is associated with negligible complications. The three patients who have undergone synthetic tracheal implantation at Karolinska University Hospital have all suffered from serious complications which have not been reported in these six publications. It is our opinion that these six articles neglect to address the morbidity associated with these procedures and omit the majority of complications which these patients have endured. Furthermore, the claim in these six articles that a synthetic trachea transplant can develop into a functional airway is unsubstantiated by the findings in the patients' medical records. During the analysis of the six articles listed below, we have found that all six articles contain falsified data or that crucial data has been omitted or neglected.

Other experts in the field have started to call into question the results that Prof Macchiarini has published in the medical literature (Appendix 1), as well as the ethical justification of implanting synthetic tracheae in humans when this procedure has not been tested in a large animal model (Appendix 1, 2a, b). Decellularised trachea have been successfully been transplanted in pigs, but these results cannot be extrapolated to a synthetic trachea (Appendix 3). The prerequisite milestone of first studying the synthetic trachea in an orthotopic implantation in large animals, and then observing the long-term outcome in that model, seems to have been deemed superfluous.

These questions should have been addressed at the time of application for ethical permission to perform medical research on human subjects. However, inquires we have made to the Regional Ethical Review Board have revealed that no such application has been applied for or approved. Had such an application been filed, then it is questionable if ethical permission would have been granted because of the lack of evidence in a large animal model. Furthermore, the tracheal transplant procedures cannot be considered to be examples of immediate or compassionate use since all three patients were operated electively and the procedures were planned months in advance.

Despite the lack of ethical permission to perform synthetic trachea transplantation, the patients have signed a consent form. This is, in of itself, a transgression since the patients have been asked to sign an informed consent form which has not been reviewed and approved by an ethics committee. This can also be a form of coercion, since the patients could have been mislead into believing that, since there is a consent form for a procedure,

then that procedure has been vetted and approved by the correct authorities. Furthermore, the consent form contains statements which are of a questionable nature. For example the prosthesis is claimed to be biocompatible although the prosthesis has never been tested in animals or in humans.

Inquiries to the Swedish Medical Products Agency (Läkemedelsverket) have not yielded any evidence that the synthetic trachea has been approved for clinical implantation. Furthermore, the patients were treated with "*regenerative doses"* of TGF-beta, G-CSF, and erythropoietin, which is a usage of these drugs which falls outside of their approved indications. Utilization of drugs for non-approved indications during a scientific investigation requires approval from the Swedish Medical Products Agency. Furthermore, usage of high doses of recombinant growth factors may have pro-oncogenic effects and can be deleterious to patients with already established malignancies. This issue has never come to light since discussions with the Swedish Medical Products Agency have never taken place.

In the article; **Tracheobronchial transplantation with a stem-cell-seeded bioartificial nanocomposite: a proof-of-concept study.** Jungebluth P et al. *Lancet* Vol. 378 Dec 10, 2011 (Appendix 4) which is a five-month follow-up of a 36 year-old man from Iceland transplanted at Karolinska University Hospital in June 2011, it is stated that biopsies performed in the early follow up demonstrate evidence of regeneration of the mucosal lining of the trachea. However, in the patient's medical records there is no evidence of regeneration of the airway mucosa and actually just the opposite is found. Biopsies analysed by different pathologists and taken at different times all show a chronically necrotic and infected airway. This is further corroborated by bronchoscopic findings which are included in this analysis on a USB memory storage device.

In our opinion, the biopsy results in the *Lancet* article from 2011 seem to be fabricated. The other five articles analysed use the *Lancet* article of 2011 as their primary reference and serve to perpetuate the fabrications of this initial publication. Please find the other five articles listed below, as well as an analysis of all six of the articles and documentation of their divergence from the patients' medical records.

Our inquires have revealed inconsistencies which we feel are of sufficient significance to warrant an investigation of Prof Macchiarini by Karolinska Institutet. If these misgivings are confirmed, it behooves the Karolinska Institutet to contact the Central Ethical Review Board, the Swedish Medical Products Agency and the National Board of Health and Welfare and inform them of any delinquencies which have been unearthed, as well as the *Lancet* so that the articles can be retracted from the medical literature.

The implications of these transgressions are not limited to the three patients transplanted at Karolinska University Hospital. We suspect that the findings presented in the *Lancet* article from 2011 were used as a primary reference when an application was filed with the US Food and Drug Administration. If this article was used as a pivotal reference when approval was granted for transplantation of a two-year old patient in the USA (who died in July 2013, 3 months after synthetic tracheal implantation), then that approval may have been attained by fraudulent means. This implies that federal laws and statues can have been breached and therefore subject to prosecution under US federal law. Since the content of the FDA application is not public, it is not possible for external parties to ascertain which eventual infringements have occurred during that process. Subsequently, it may also be prudent to inform the FDA so that they may determine if any infractions of US federal law have transpired.

Sincerely,

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