



ETHICS COUNCIL

To Vice-Chancellor Anders Hamsten

The Ethics Council has been asked to scrutinise a letter from Professor Pierre Delaere and examine whether or not Professor Paolo Macchiarini at Karolinska Institutet has been guilty of scientific misconduct regarding his work within regenerative medicine.

The Ethics Council has examined the allegations presented by Professor Delaere. When discussing the factual aspects about what adult stem cells can and cannot do, the Ethics Council has consulted an expert in stem cells research, Professor Ernest Arenas at the Department of Medical Biochemistry and Biophysics, Karolinska Institutet.

In the subsequent text the Ethics Council will answer or comment on Professor Pierre Delaere's questions and concerns regarding Professor Paolo Macchiarini's work. Professor Paolo Macchiarini has responded to Professor Delaere's allegations. The Ethics Council has condensed Professor Delaere's questions into the following ten issues:

1. Professor Delaere maintains that adult stem cells do not function as embryonal (pluripotent) stem cells. Professor Delaere states that in contrast to lizards and worms, human beings are not enabled to regenerate new organs. These facts, according to Professor Delaere, make it theoretically impossible to regenerate a new windpipe from a human being's own stem cells. Furthermore, according to Professor Delaere, the structure of the windpipe is so complicated that it is not possible to regenerate it – not even the mucosa.

Professor Macchiarini argues that humans can regenerate certain organs e.g. liver and skin.

The Ethics Council agrees that adult human stem cells (e.g. from the bone marrow) do not function as embryonal stem cells, but the Ethics Council finds that the word 'regenerative' might bring about a kind of miscommunication between Professor Delaere and Professor Macchiarini. The Ethics Council understands that while some organs such as liver and skin can regenerate, others may not be able to do so. However, it is possible to generate new cells from stem cells and assemble them by means of biomaterials, scaffolds and bioreactors in order to generate cell layers, which imitate the function of mucosa cell layers of e.g. the windpipe. This field of research, which combines cells and biomaterials, is also known as tissue engineering and as such is considered a branch of regenerative medicine, even if the final goal is not to regenerate the organ but rather to use cells to construct an artificial organ or organ mimetic.

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Accordingly, the Ethics Council concludes that this is not an issue of misconduct but rather one of miscommunication.

2. A second reason why Professor Delaere finds it impossible for mucosa cells to be built, is the lack of blood supply. According to Professor Delaere, revascularisation of the windpipe is impossible, given the current state of medical knowledge.

According to Professor Macchiarini, the blood supply to the thin layer of cells/mucosa tissue can be explained by neoangiogenesis.

According to the Ethics Council, the issue of revascularisation is an empirical question (rather than a theoretical one) and current evidence indicates that it is actually working. Neoangiogenesis might be a plausible explanation. However, another problem in this context is how to manage anastomosis and blood supply to whole organs. This problem has yet to be solved. Professor Macchiarini and his co-workers do not claim to have solved it. Accordingly, the Ethics Council does not find that Professor Macchiarini has acted in a dubious or fraudulent way.

3. With reference to arguments presented in points 1 and 2 above, Professor Delaere points out that claims of existing tissue regeneration are misleading and create unrealistic expectations among the patients concerned and among research councils which financially support such research.

According to the Ethics Council, patients' expectations of new medical technologies and treatments are problematic – particularly if those expectations are unrealistic. The press and media are interested in medical novelties and also read scientific journals. The universities and medical journals concerned provide press releases about published novelties – also publications based on case-reports. But according to the Ethics Council this is a general problem and nothing Professor Macchiarini should be blamed or considered responsible for.

The Ethics Council is aware that those who financially support medical research might also be influenced by expectations and wishful thinking towards potential new treatments. This might result in an unrealistic interest (hype) and the allocation of funding to such areas – thus taking them from other areas in need of financial support. This is a problem, but again it is a general issue and nothing Professor Macchiarini solely should be blamed or considered responsible for.

4. Professor Delaere states that the use of the 'bioreactor' and how it functions is unclear.

The bioreactor is a device used in order to stimulate stem-cells to proliferate. The device is under development, and might be used in different ways and versions as well as in different situations. *The Ethics Council* finds nothing suspicious in the manner Professor Macchiarini and his co-workers have described the use of the bioreactor in different situations.

5. Professor Delaere maintains that Professor Macchiarini and his co-workers are fabricating data.

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It is generally acknowledged that observations of empirical data might be influenced by theories and hypotheses and the expectations associated with the theories and hypotheses. This is a general problem for all empirical research, and it is also the reason why researchers try to use e.g. blinded procedures when making observations. When conducting studies involving surgical interventions on one or two patients, it might obviously be difficult to apply blinding procedures or other controlling strategies. In such studies there is an increased risk of presenting hypothesis-impregnated observations, and this risk should be acknowledged. But scientific journals are aware of such issues, and case-reports or series of cases accordingly have a special headline and are considered to have a fairly low evidential value. Nevertheless, case reports are valuable because they have a hypothesis-generating function. Critical scientists such as Professor Delaere are supposed to react and criticise if they find that results are unbelievable or run counter to current medical knowledge. However, we must accept that empirical findings might contradict current theories – otherwise we would not be able to make progress in e.g. the medical sciences.

The Ethics Council is aware that medical researchers might behave in a biased manner in order to obtain empirical support for their hypotheses, but we have found nothing in the data presented that supports the allegation that data are fabricated.

6. According to Professor Delaere, Professor Macchiarini is using uncontrolled (electron) microscopic images. This is also, according to Professor Delaere, part of the fabrication of data (see point 5).

The Ethics Council has tried to understand what is meant by ‘uncontrolled electron-microscopic images’, but even though we have asked Professor Delaere to specify, we have not succeeded.

7. According to Professor Delaere, the clinical outcome of the transplantation is poor.

According to *the Ethics Council*, what constitutes a good or successful outcome can be debated. Since the three patients who were transplanted were all in bad condition and transplantation was considered the last resort, the present survival rate can be perceived as not that bad. All three patients were transplanted on a compassionate basis. One patient survived half a year and died due to other causes. Another patient survived 2.5 years, and the third patient is still alive (after 2.5 years), although re-operated. Since these patients and other issues related to the clinical studies are the subject of a separate investigation, *the Ethics Council* will not comment any further on this issue.

8. Professor Delaere maintains that among the patients who were either re-operated or autopsied, no trace of the ‘regenerated tissue’ was found.

According to Professor Macchiarini, the graft was in one case totally destroyed due to different interventions (stenting, intubation and resuscitation). In another case, where the patient was born without a trachea, epithelisation and neovasculation were identified by the local pathologist.

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The Ethics Council finds it plausible that the transplanted tissue might have been destroyed by the different interventions. Furthermore, it has no reason to doubt that the local pathologist found epithelisation and neovasculation. Thus, the Ethics Council finds that Professor Delaere's claim is poorly supported.

9. According to Professor Delaere, Professor Macchiarini has opposed microscopic examination of the remaining part of the synthetic windpipe in connection with the patient who died in January 2014.

Professor Macchiarini has responded that it was the patient's relatives and not Professor Macchiarini who were against the post mortem microscopic examination.

The Ethics Council finds no reason to suppose that Professor Macchiarini impeded post mortem microscopic examinations in order to hide the non-existence of a prosthetic windpipe containing stem cell-generated tissue. Furthermore, a local pathologist (see point 8) identified microscopic traces of tissue epithelisation and revascularisation in another post mortem examination.

10. According to Professor Delaere, the review process of *The Lancet* has been conducted in an irresponsible manner contrary to the review process performed by *New England Journal of Medicine*, which refused the paper in the first place.

According to the Ethics Council, there is nothing dubious in resubmitting a paper to another scientific journal when the paper has been refused by the first one. Professor Macchiarini has allowed the Ethics Council to see the correspondence between the authors and *The Lancet*. The Ethics Council can confirm that the paper was critically reviewed by four reviewers in *The Lancet*. The authors revised the paper in accordance with the reviewers' comments. We have also seen the changes made in the original version. The Ethics Council's conclusion is that the review process has been correct.

The Ethics Council's general conclusion is that apart from the clinical outcome of the transplanted patients – whose medical records we have not examined and which are being examined in another investigation – we find that the issues raised by Professor Delaere are of a philosophy-of-science kind rather than of a research-ethical kind. Accordingly, the Ethics Council concludes that, on the backdrop of the examined issues, Professor Delaere's allegations of scientific misconduct are unfounded.

On behalf of the Ethics Council



Niels Lynøe

Chairperson