Comments and clarifications regarding the allegations against Jungebluth et al, Lancet, 2011.

I have been given the opportunity to give my comments and clarifications regarding the allegations against the above-mentioned publication in Lancet, and the investigation conducted by Bengt Gerdin, professor emeritus of Uppsala University, as I am one of the co-authors on this publication. I would like to first emphasize that I have not before been contacted by Gerdin or any other agency, press, media, or other institution, but this is the first time I have been given the chance to comment on the investigation and allegations.

I am a senior researcher/principal investigator in my sixth year according to Swedish career plans. I did my undergraduate studies on School of Medicine of Lund University 1987-90 and then continued my PhD studies at Linköping University, Sweden 1991 to 1997 when I graduated. I pursued my postdoctoral training in San Diego 1997-2002 before being recruited to Karolinska Institutet (KI) to start my independent lab 2002/3. I was given permanent position 2009 as so called senior researcher (equivalent to associate professor in the US system). My group primarily study neural stem cells, and how these can be steered/programmed to differentiate into functional neural cells through knowledge of epigenetic/transcriptional mechanisms. I also study stem cell-like cells in neural tumors, and am highly active in biomedical engineering for application in regenerative medicine.

In addition to my research I am highly active in many science-related areas. I have been a member of the Ethics council of KI since 2009-10 (of course not in this case where I am biased) and thus have acquired quite some experience in these type of investigations of accusations of scientific misconduct and carelessness. I was also for a time the “stem cell ombudsman” at KI and investigated the possibilities and hurdles in using human embryonic stem cells in clinical practice.

My role in the publication

I am a co-author of the publication referred to as “Essay #1” in the investigation of Gerdin, i.e. Jungebluth et al, Lancet, 2011.

In this publication me and Tobias Lilja, at the time a postdoctoral fellow in my lab, contributed with an analysis of protein modifications, more exactly histone modifications by chromatin immunoprecipitation of blood samples taken from the patient (from now referred to as patient AB). This analysis is represented in figure 3C in the publication and has not been criticized in the investigation.

However, the investigator, Professor Emeritus Bengt Gerdin, ends his main investigation with stating (my translation) "...none of the other authors, 28 in number in the most central publication, Essay #1, have questioned what has been presented but everyone has claimed to "...accept responsibility for its validity".

Since Gerdin has not contacted me or to the best of my knowledge any of the co-authors, I therefore would like to present the information we obtained and was given us and thus had by the time for publication.
I was contacted May 4th 2011 by Philipp Jungebluth after a lecture on how chromatin immunoprecipitation (ChIP) could be used for analysis, also of patients. The reason for him to contact me is/was that Jungebluth and Maccharini searched for improved methods of analysis of blood samples for the (many) patients they treated as the common information routinely obtained from blood samples (mostly protein levels and sedimentation rate) is not sufficient to investigate the health status of the patients after advanced and sophisticated surgery.

May 27th (2011) I received an email from Jungebluth who then tells me that there has been a major multidisciplinary video conference with all involved "heads" of the clinical departments, including anesthesia, intensive care, thorax surgery, ear-nose-throat etc, and that the surgery of the 1st patient to receive a bioartificial trachea is planned for June 9th. Me and Philipp meet and discuss how small/large volumes of blood that is required to perform an analysis with ChIP, and July 14, around a month after the surgery, Jungebluth writes to several if not most of the researchers that have offered to provide various methods to analyze the blood samples, and he then asks about the status on the analysis. After this, the analysis work is "rolling" and August 30, most of the to-become co-authors meet for a big and completely open and transparent walk-through of the results from the post-operative analyses of the blood samples and biopsies.

**Concerning information regarding the patient’s status after August 2011**

The patient AB is recovering and during August returns to Iceland. After his departure, me and most of the senior co-authors receive several emails from Professor Tómas Gudbjartsson that inform us about the clinical exams and investigations, and recovery of the patient AB that has been done and (at the time) are being done on Iceland. Among other things, he tells us: 1) in an email dated September 4, 2011, AB is in a rehabilitation program and has recovered health enough to get back to his MSc studies that he was forced to interrupt before the surgery (*Supplementary file 1*; note that one of the complaints, K-H Grinnemo, is recipient of all the emails from Iceland that I refer to here), 2) in an email from October 7, 2011, a CT-scan has been performed October 6 that looks good and also here the positive development/recovery is confirmed (*Supplementary file 2*), and 3) in an email from October 18, 2011, tells us that investigations have been made continuously that looks good, and the next exam is to be performed October 20, around 4 ½ months after the surgery (*Supplementary file 3*). Soon hereafter the statement in the manuscript is updated to "five months after surgery" with authors consent, including Grinnemo, after the reports we received from Iceland. November 11, almost exactly 5 months after surgery, Professor Maccharini appropriately sends all the senior co-authors the "proofs" as should be done, and tells everybody, including Grinnemo, that this is the last chance to change or challenge the statements in the manuscript (*Supplementary file 4*). At this timepoint, the patient AB is according to both the MDs at Iceland as well as in his own words, doing significantly better than before the surgery – a time when he for example couldn’t pursue his studies in geophysics – and there was thus no reason to, as Gerdin phrases it, “question what was represented”.

Gerdin writes (my translation): "It should here be noted that the patient [AB] should have been under clinical care by some of the manuscript’s two Icelandic co-authors. It should thus have been possible, even without difficulty, to secure the patient’s correct clinical status after five months."
This is thus exactly what was done and the around 15 senior authors were informed, including Grinnemo.

It would of course have been my pleasure to provide this information to the investigator Gerdin if I would have been contacted [we are not allowed to contact the investigator during the investigation if not asked for as that could lead to attempts of inappropriate influences], and Gerdin should definitely have contacted the Icelandic MDs that participated in the post-operative care and analysis instead of making comments about the role of the co-authors.

Gerdin doesn’t seem to have contacted any of the co-authors more than some of the complainants, and his investigation therefore has severe and serious flaws in lack of information as well as expertise in regenerative medicine, stem cell biology, and biomaterials. His conclusion that there was no documentation that supports the statement “five months” is thus fundamentally erroneous, and the proposal that this should represent scientific misconduct is formally incorrect.

I comment on this and other formal errors in the investigation that has resulted in very serious complications below.

Concerning the sentence: “We obtained written informed consent from the patient, and the transplant procedure was approved by the local scientific ethics committee.”

There was of course a vivid discussion about which of the many aspects in this complicated surgery and treatment that required ethical approval and from where. Here we have lately seen in the press, along with the “haters” on the web and other “trolls” on more and less serious blogs and homepages, a series of extremely convinced opinions.

Virtually all discussions in any forum without any of the authors involved and allowed to contribute are after-constructions and revisionism.

The sentence regarding the ethical approval was re-written several times during the writing of the manuscript. A so called “proof-of-concept” study in Lancet, (see title) is very short and rather to be compared with a case report. The sentence was therefore created to summarize a number of various procedures included in the treatment, which all in one way or another were performed correctly according to rules and regulations 2011.

The actual surgery was approved by the Karolinska University Hospital after discussions with representatives of the National Medical Products Agency (Dr Lennart Åkerblom) and the local scientific ethics committee (Pierre LaFolie). This is clarified by an email from Richard Kuylenstierna (Supplementary file 5). Gerdin acknowledges that this covers the surgery itself.

I have further during the path of the investigation received a more comprehensive document where the communication between these instances is more complete, and where one of the leading experts in medical ethics, Professor Göran Hermerén, points towards paragraph 34 of the recommendations of ISSCR (International Society for Stem Cell Research), and thereby recommends that the result of the surgical treatment should result in a publication. This to optimize the transparency around new treatments involving stem cells. This document is 39
pages, mostly in Swedish, so I don’t attach it here for practical reasons, but I can complement with this if required. Gerdin has acknowledged that he has read this material.

There is/was also an “informed consent” (although this is not required in Sweden) signed by the patient. Gerdin also acknowledges that this is sufficient to cover the post-operative aspects of the surgical treatment.

In addition to this there were/are ethical approvals to aspirate cells from the bone marrow, and to expand those into so called multipotent stromal cells or more popular “mesenchymal stem cells” (MSCs) from the patient. This a common routinely performed procedure at the Karolinska University Hospital and is covered together with the transplantation [therapy] of MSCs by ethics approvals from the local scientific ethic committees and also approval from the National Medical Product Agency to Professor Katarina Le Blanc (see e.g., Moll et al., PLoS One, 2011; Le Blanc et al., Lancet, 2008; Le Blanc et al., Leukemia, 2007) as well as the activities of Vecura (Pontus Blomberg), see e.g.,:

http://www.vavnad.se/cms/sites/vavnadsradet/home/cellterapi/nationella-resurscentra/stockholm-vecura.html (also Supplementary file 6, in Swedish)

Professor Le Blanc has in her statement to KI confirmed that all aspects concerning her activities were performed in accordance with all ethical regulations.

To summarize all these procedures in a brief sentence, the phrasing “transplant procedure” was suggested in the end of the manuscript processing. If anyone with expertise in the stem cell field and regenerative medicine had been contacted at any stage of the investigation by Gerdin, this would have been solved immediately.

The interpretation of the sentence “We obtained…” has taken an unexpected and very disturbing development. We have seen numerous researchers and non-researchers completely lacking expertise in regenerative medicine that has been very outspoken in the press, other media, in emails, and on the web with extremely strong opinions. In reality, this is a difficult question with many points for discussion as regenerative medicine is a rapidly developing field (the ISSCR is the same week as the deadline for our responses, around June 26, publishing a preliminary set of new guidelines for commenting from the researchers and MDs), but it is obvious that in this case, regarding patient #1, the local and international rules, guidelines, and regulations of 2011 were respected and followed.

To be as transparent as possible and meet the questions from the revisionists and media, I suggest that a clarification could be published in Lancet where the approvals of the various procedures, from the surgery and the post-operative care, to bone marrow aspiration, stem cell expansion and transplantation are explained clear and in a pedagogic way to resolve the critique from non-experts in the field.

Also here it is clear that since Gerdin did not contact any co-authors, neither with experts in the fields of stem cells and regenerative medicine, the consequences of his assumptions have been very serious.

**Comments on the investigator and the complainants**
As a member of the Ethics council at KI the past years, I have organized and co-organized a number of lectures and symposia on how important it is to protect and govern investigators of scientific misconduct as well as “whistleblowers”. It hurts me profoundly that I must acknowledge a number of irregularities and doubts regarding both these entities in this particular case.

I do not question Ger din’s authority regarding surgery and epidemiology. It is however utterly damaging that such serious errors of fact have been made wholly because Ger din failed to contact main- or co-authors and let them be interviewed and get a chance to explain before submitting his investigation. It is further striking that no experts in regenerative medicine, stem cells, biomaterials etc have been consulted. The complaint was made by thor ax surgeons that clearly left out essential information in their documents (for example the contact with Iceland), and the discussion has therefore become completely one dimensional, if any dimension at all.

Ger din provides a very careful definition of how he defines scientific misconduct – in Swedish “oredlighet”. I welcome this, but couldn’t disagree more. The international view is that scientific misconduct is a specific term concerning “FFP”, hence “fabrication, falsification or plagiarism” and variations thereof. The term “oredlighet” in Swedish is highly debated and even under revision by the government, as it includes many kinds of “misbehavior”, including a main supervisor asking his/her PhD student to babysit or similar. The validity of Ger din’s way of defining “oredlighet” and thus “misconduct” is therefore questionable, and by coincidence a lecture on the definition of “oredlighet” was organized at KI just the days before Ger din submitted his investigation where the inadequacies of the older Swedish/Nordic interpretation of the word “oredlighet” was clearly explained by the Danish lawyer Jens Ravnkilde, and it is unfortunate that Ger din and others did not attend this lecture. I attach a relatively brief summary by Ravnkilde (in Danish; Supplementary file 7).

It is further very serious that the investigator Ger din directly after submitting his investigation in Swedish and before Macchiarini and Jungebluth, who don’t speak Swedish, even knew what they were to reply to, let himself be interviewed by National and international press, including NY Times. It is obvious that this behavior is highly irrational and unethical.

Sadly, it has also come to be known that there is a suspicion of bias (in Swedish “delikatessjäv”). Ger din is a personal friend of the head (“divisionprefekt”) of the main complainant Grinnemo, Professor Anders Ekbom, and they (Ger din and Ekbom) have been in touch during the time of investigation even if this contact is claimed to be private (Supplementary file 8). I have the deepest respect for Professor Ekbom and know him as a person with flawless integrity and ethical knowledge, but I must here express my concern for that the result of a one-man-investigation of such importance can be jeopardized by a relatively typical case of personal bias.

It is further well known that Grinnemo collaborates with the department [surgery] that Ger din belonged to when he was active. In my mind, an investigation of this weight should have been conducted by a group consisting of several MDs, researchers, and ethics experts, preferably international, with expertise in a number of various areas.
Whistleblowers play a very important role in research as they must be allowed and encouraged to step forward and report on problems and suspected misconduct and other deviations from good research practice when such occur or have occurred, and the Ethics council at KI has organized numerous lectures and symposia on how important it is to protect whistleblowers and protect and govern these.

Unfortunately, it is my strong opinion that this group of complainants has abused this role and thereby aggravated the situation for whistleblowers in the future.

For example, Grinnemo, Simonson and Corbasco in 2012 started the company IsletOne Therapeutics with a direct interest to sell therapies based on stem cell treatments (with MSCs; Supplementary file 9) and a series of patents around these activities exist, for example placed in Canada. It is noted that the company reports that they have already treated two patients with life-threatening diseases 2014 with “remarkable, life-saving outcomes” and other dramatic expressions (Supplementary file 9). Thus there is here a quite typical “conflict of interest” concerning transplantations and use of these stem cells/progenitors (MSCs) therapeutically. It is serious that this “COI” has been unnoted and unmentioned by the many who has expressed opinions about this case. There are reasons to investigate the question regarding the fundamental reason for the conflict between Grinnemo and Macchiarini.

An unusually active role has been played by the press and the in particular a reporter at a major Swedish newspaper, Svenska Dagbladet, Jani Pirttisalo. In spite of being obviously ignorant regarding care and research, he has in a series of tendentious articles with imprecise expressions not only accused but convicted Macchiarini for misconduct. In the edition of June 24, 2015, he writes for example (my translation): “...there has been misconduct in the science reporting from the transplantations.” (Supplementary file 10; in Swedish)

When this is written (June 24) none has been found guilty for scientific misconduct and no article of those included in the complaint has been retracted or even corrected. The newspaper thus states something that is factually wrong and that should be noted and reported to the correct institution irrespective of the decision of the vice chancellor of KI. Also the Swedish television news, Aktuellt, has acted questionably when they broadcasted the author-list of the Lancet publication from 2011, with among others my name in center (since we were listed in alphabetical order) without giving me or any of my colleagues the opportunity to comment (this is against Swedish regulations, so called “replikrätt”).

Also the acting of the agencies of IVO and in particular the Swedish research council, VR, is arguably guilty of abuse of authority (“myndighetsmissbruk”) as they without hearing the defendant have published press-releases of negative decisions. In a true Kafkaesque style these agencies have charged and convicted without hearing the defendant. This behavior raises serious questions of the legal certainty in Sweden.

Comments on research versus care and cure versus treatment

It belongs to the basic course of research studies to distinguish between scientific research versus surveys and analysis in healthcare, including case reports. It is therefore astonishing to
see how many [non-experts in regenerative medicine] have declared these transplantations to be scientific research. The only rational explanation for this is that no one has actually read the publications and review articles in the investigation.

If we have a closer look at the publication in Lancet 2011, we see in figure 1 the transplantation procedure being described, namely the surgery and the stem cell incubator. In figure 2 histological exams are shown, a standard analysis, and measurements from the blood samples of the patient. Note that these measurements completely lack error bars, there are thus no controls or additional duplicates [from hypothetical additional patients]. And in the last original figure, figure 3, we again see measurements from the blood samples demonstrating which cell types that could be found in the blood, levels of some protein precursors (mRNA) along with our analysis of protein (histone) modifications.

Link to the article: http://www.sciencedirect.com/science/article/pii/S014067361637157#

There are no error bars, there are no controls, there are no cohorts, there are no reproduced experiments [which had required additional patients], and there are no hypothesis or similar that are the basis to refer to this to scientific medical research. This is a translational case report with a new stem cell based surgical technique (proof-of-concept) and a more sophisticated analysis of the blood samples rather than “sedimentation rate” or other.

This publication is thus not to refer to as medical research formally. If this in the future are to be referred to as science, all MDs that try a new treatment, combination, or variant, perhaps in emergency, and then take blood samples afterwards, can be reported, and everybody who makes a single observation can call themselves scientists.

Another issue that has been mixed up during the discussion is the difference between cure and treatment. This procedure was/is a development for an improved treatment of tracheal cancer, it was not claimed to cure all patients with this important disease.

If we look at the three patients [that were treated at the Karolinska University Hospital] including the two patients not included in the Lancet-publication and for whom the transplant procedure and molecular analysis have not been published more than anecdotal mentioning in basic research publications and review articles (and thus further proves that it [the transplant procedure] is not research), it looks like follows:

The development for the first patient, named AB, was clearly positive 5 months after the surgery according to the reports we got from Iceland and the patient’s own words. Even if additional actions had to be made after almost 6 months, AB told Icelandic press a year after the surgery that he was very positive and would redo it (http://www.hi.is/fretir/vel_heppnud_malthing_um_timamotaadgerd). This is a substantial time for a new treatment of a disease with >90% lethality where many times one (1) month is a limit for whether the treatment was successful or not (see e.g., http://www.dagensmedicin.se/artiklar/2015/04/29/3d-printat-luftvagsstod-tyktes-hjalpa-barn-med-sallsynt-sjukdom).

I have seen sarcastic formulations speculating whether the patient AB was seriously sick or not. It is actually disgusting to read. My own father died at the day 34 years ago, June 24 1981,
by cancer, and he was in good shape until around 3-4 days before his death when he got sepsis and died quickly. The patient AB had a [tumor like a] golf ball in his throat that grew back after the first attempts of surgical resections so he had a hard time to breathe and became powerless. In Swedish care, human dignity comes first and it is as described above [and elsewhere] clear that AB was in better shape after the surgery than before. But it is a serious disease and it is thus still a long way to a general cure.

Considering patient 2, this patient left the hospital in Stockholm in very good shape around a month after the surgery, his condition is documented. Tragically, he died around six months after surgery from reasons not related to his transplantation. Some of us know more about the reasons for his death but has promised [Macchiarini and] the patient's family not to make this official. I can if necessary meet the vice-chancellor and communicate the information I have been given.

The 3rd patient was the responsibility of the thoracic division entirely, including the complainants, and they should be questioned regarding the circumstances of the surgery and which standards of care ethics and conditions they practiced. The 3rd patient is still alive.

**Conclusion**

As the investigator Bengt Gerdin failed to talk to or contact any of the main authors or any of the co-authors, there are serious flaws and formal errors in the investigation. Concerning the two main points regarding the Jungebluth et al. publication in Lancet 2011, 1) there were continuous investigations on Iceland of the status of the patient that were made transparent through regular emails to the co-authors, and 2) ethical approvals for the stem cell part of the aspiration [of bone marrow], expansion [of MSCs] and transplantation were in place, the hospital granted the surgery, and the post-operative care and analysis was cleared by an informed consent.

The accusations of scientific misconduct are thus completely unwarranted.

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