How Journals Treat Scientific Misconduct Allegations: Should Articles Be Retracted?

Evidence-based medicine is the basis for most of our clinical decisions. Innumerable researchers worldwide provide us with new data every day. Scientific results are presented at meetings, international conferences, and are published in peer-reviewed journals.

Most of our readers know this process from personal experience as an author, reviewer, editor, or associate editor.

In 2015, an article entitled “[Autologous Peripheral Blood Mononuclear Cells as Treatment in Refractory Acute Respiratory Distress Syndrome](#)” was submitted to this journal by a group of researchers. After an independent peer review process by different international reviewers and several revisions, the paper was accepted and published in the 6th issue of *Respiration* in 2015 [1].

At the end of January of this year, the journal received an email from the Karolinska Institutet in Sweden with the request to withdraw the article. Since 2016, the Karolinska Institute has examined several research projects from the aforementioned group and came to the decision that the research underpinning the article had been conducted without meeting the required ethical standards (Fig. 1). This decision is contrary to the assessment of the Central Ethical Review Board of Sweden, where an expert

group analyzed the research and concluded that it does not constitute grounds to determine scientific misconduct.

So, now it is up to the journal to decide on how to respond. First of all, the formal reviewing process followed all the standard international best practice guidelines. As usual, the responsible editor and the reviewers analyzed the available data and subsequently accepted the article. Should the journal and the publisher now withdraw the article? Shall we ignore the request? Or shall we give the authors the option to respond to the request?

After several internal discussions we decided to offer both parties the option of publishing a letter on the issue. We believe that, based on the evidence available to the journal, we are not in the position to make a judgement on the whether or not to retract this article.

Thus, we leave it up to our readers to decide how to treat the article in question and whether to accept its conclusions as valid. On the following pages, you can read the Karolinska Institutet's position as well as responses from Philipp Jungebluth, Paolo Macchiarini, and Bernhard Holzgraefe.

Felix J.F. Herth, June 29, 2018

Fig. 1. Karolinska Institutet's report of suspected scientific misconduct.

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Decision
2018-01-30

Dnr: 2-1764/2016
Sid: 1 / 12

Vice chancellor

NOTE! This is a translation of the Swedish version.
In the event of any discrepancy between the
versions, the Swedish version is the official decision
and the Swedish wording will prevail.

Suspected scientific misconduct

Decision

Karolinska Institutet finds that the research reported in the paper “*Autologous peripheral blood mononuclear cells as treatment in refractory acute respiratory distress syndrome*” published in the scientific journal *Respiration* (2015; 90:481-492) constitutes scientific misconduct.

Paolo Macchiarini, Philipp Jungebluth, Bernhard Holzgraefe and Håkan Kalzén are responsible for the scientific misconduct manifested in this paper.

No action in relation to labour law will be taken since none of the persons responsible are employed at Karolinska Institutet.

A formal request will be sent to the journal *Respiration* to immediately withdraw the article.

Karolinska University Hospital is being notified of this decision.

The case

On 13 April 2016 two researchers at Karolinska Institutet (KI) contacted acting pro-vice-chancellor Henrik Grönberg with misgivings about a paper titled “*Autologous peripheral blood mononuclear cells as treatment in refractory acute respiratory distress syndrome*”, published in the scientific journal *Respiration* (2015;90:481-492).

The paper was authored by Philipp Jungebluth, Bernhard Holzgraefe, Mei Ling Lim, Adil Doganay Duru, Vanessa Lundin, Nina Heldring, Oscar P.B. Wiklander, Joel Z. Nordin, Michael Chrobok, Christoph Roderburg, Sebastian Sjöqvist, Björn Anderstam, Antonio Beltrán Rodríguez, Johannes C. Haag, Ylva Gustafsson, Katharina G. Roddewig, Petra Jones, Matthew J.A. Wood, Tom Luedde, Ana I. Teixeira, Ola Hermanson, Ola Winqvist, Håkan Kalzén, Samir El Andaloussi, Evren Alici and Paolo Macchiarini.

The paper is a case description of a patient with acute respiratory distress syndrome (ARDS) who received ECMO (extra corporeal membrane oxygenation) therapy at

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(Figure continued on next pages.)

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Karolinska University Hospital in 2011. After nine days of treatment an experimental treatment was tried without an ethical permit. The patient received a local lung intervention consisting of a suspension of mononuclear cells extracted from the patient's own blood. The treatment was carried out using repeated intratracheal instillations via bronchoscope.

On 22 April 2016 acting vice-chancellor Karin Dahlman-Wright decided to launch an investigation into suspected scientific misconduct.

The investigation

The authors' statements

The authors of the article in question were invited on 11 May 2016 to comment upon twelve issues concerning the paper and the treatment. Some of them have, however, not been possible to reach as KI does not have their addresses and they do not work at KI.

Johannes C. Haag, Nina Heldring, Ola Hermanson, Bernhard Holzgraefe, Philipp Jungebluth, Håkan Kalén and Paolo Macchiarini: The intervention was carried out on the patient not for the purposes of research but to commence a potentially life-saving treatment in a clinically desperate situation. The paper in question is a case study. Since the treatment was not initiated as a prospective study or a research study it cannot be considered research. The decision to commence the treatment without an ethical permit was made in accordance with article 37 of the Helsinki Declaration. There was ethical approval prior to the laboratory analyses and to the publication of the paper. All treatment was carried out in the patient's best interests. No additional bronchoscopic procedures to those considered necessary by the patient's doctor were performed. Blood tests were taken as part of routine care and to evaluate the care being given. What was reported in the paper is in line with the clinical developments and the fact that the initially positive development did not result in the patient's survival was pointed out.

Ana Teixeira: On 6 February 2012 she was asked by Philipp Jungebluth to perform blood analyses, which were done by a doctoral student in her lab and reported to Philipp Jungebluth on 1 May 2012. She told Philipp Jungebluth that her contribution did not constitute co-authorship and that she wished to be removed from the author list. On being informed by the journal that the paper had already been submitted, she took no further action. She was then notified by Philipp Jungebluth that the paper had been accepted. She is not a doctor and she was not involved in discussions on the treatment of the patient.

Samir El Andaloussi, Joel Z. Nordin and Oscar P.B. Wiklander: Their contribution was to isolate and analyse the effect of extracellular vesicles from pre-prepared media after the treatment was over. They were not involved in the treatment itself.

Eyren Altici, Michael Chrobok and Adil Doganay Duru: Their contribution consisted of analysing circulating cell populations using flow cytometry and they were not involved

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in the patient's treatment or the clinical decisions. Neither did they have access to the patient's medical records. They were informed by the clinical team that the patient was treated in 2011 and that no ethical permit was needed for the treatment as it was for humanitarian purposes. Ethical approval for the paper was received in 2012. The paper was drafted between 2013 and 2015 and published in 2015. The laboratory results reported within are correct.

Ola Hermanson and Nina Heldring: The questions and allegations do not relate to the analyses carried out in Ola Hermanson's laboratory (i.e. chromatin immunoprecipitation.)

Björn Anderstam: He was not involved in the study itself. His contribution involved analysing some inflammation markers in "blind" tests in 2013–2014. He told Philipp Jungebluth that according to KI's publication regulations his contribution should not constitute co-authorship.

Ethical application

On 5 September 2016, KI received information concerning an application for an ethical permit. The application, titled *Periferia stamceller och Enthrapoietin som behandling för teraprefraktär svår andningsvägssyndrom under pågående extrakorporal membranoxygenerering* and with Stockholm Council as the applicant and Bernhard Holzgraefe as main responsible, was approved on 23 January 2013 by the Regional Ethical Review Board in Stockholm.

Medical records

KI has viewed the patient's medical records from the ECMO Centre at Karolinska University Hospital covering the period 9 November–19 December 2011.

Investigation by the expert panel for scientific misconduct at the Central Ethical Review Board

On 25 October 2016, KI asked the expert panel for scientific misconduct at the Central Ethical Review Board (CEPN) (the Expert Panel) to issue an official statement about whether the content of the documents in the case potentially constituted scientific misconduct, paying particular attention to whether the action taken was a matter of healthcare or research.

The Expert Panel appointed Professor Emeritus Dag Lundberg, Lund University, as case expert.

In his report dated 14 February 2017, Dag Lundberg adduces that the actions taken in the case are to be regarded more as research than pure healthcare and that the case, despite some mitigating circumstances, can be considered one of scientific misconduct. He maintains that the study can be designated as a clinical innovation in that it uses a

previously unproven method to supplement a normal treatment in order to cure or give relief to an individual patient. According to customary research ethics, for the use of an innovative method to be ethically justified it has to have theoretical patient-benefit potential based on published results from relevant animal experiments and/or previous human studies. The conclusion that the measures taken in the case constitute research is based on an entry in the medicinal record made on 18 November 2011 to the effect that a decision was taken to treat the patient in the form of a study; moreover, it was not clear that the patient's condition was so alarming as to warrant humanitarian life-saving treatment or that there was any vital indication, and so there was time for informal contract to be made with the Regional Ethical Review Board. There was also a dual purpose of the innovative treatment: to save the patient's life and to generate new molecular-biological and immunological knowledge. Dag Lundberg also states that the facts, firstly, that the laboratory part of the study cannot be dealt with separately since it requires the completed innovative clinical treatment and, secondly, that 26 researchers put their names to the case description suggest that they considered the study research.

Dag Lundberg believes that the researchers responsible are guilty of scientific misconduct in that they neglected to document a risk/benefit analysis and detailed ethical considerations prior to the decision to commence the innovative treatment; that they neglected to contact the Regional Ethical Review Board before action was taken despite there reasonably being the necessary time for an informal consultation; that they exploited a severely sick patient without an ethical permit as a means of advanced preclinical research; that they carried out the innovative treatment despite its fragile theoretical basis; and that they omitted to report in the paper concurrent conventional clinical treatment and discuss the possibilities that it could explain the temporary improvement. Further, he believes that it indicates scientific misconduct that the researchers responsible grossly exaggerated the significance of the achieved results, neglected prevailing ethical practice for publications by including 26 authors, and renounced all ethical responsibility in their statement to KI. He adds that he is also unable to completely overlook certain possibly mitigating work environment-related circumstances.

The Expert Panel gave the authors opportunity to comment on Dag Lundberg's report.

Håkan Karlén. He was specialist physician at the ECMO Centre, but was not part of the decision to start the treatment, and was not in a position of medical seniority during the period in question. He participated in the daily care of the patient, the severity of whose condition was unique. The multiple bronchoscopic procedures were not primarily indicated by the additional stem cell therapy but by the gradually disintegrating bronchial mucosa. Not reporting unique therapy experiments he considers unequivocally unethical, as follows from the Helsinki Declaration. The application of clinical regulations at Karolinska University Hospital and KI was made considerably stricter in 2016 but this should not be taken into consideration in the assessment of this case, which relates to practice applied at an earlier time, in this instance from 2011.

Bernhard Holzgräfe. The patient had very serious corrosive damage to the airways and needed ECMO owing to life-threatening anoxia. The patient's chances of survival were judged to be extremely low. Paolo Macchiarini and his group were contacted to discuss the case and to find out if they knew of any treatment that could help save the patient's life. In their opinion, the attempt to regenerate the patient's mucosa and tissue in the proximal and distal airways was reasonable under the circumstances. The purpose of the treatment was to save the patient's life and not to conduct a study on a seriously ill patient. The information gained from the notes gives an incomplete picture of the patient's situation. After the treatment was concluded, the decision was taken to compile a case description, since the case was extremely unusual. To make sure that everything was handled correctly, he contacted the CEPN to ensure that publication of the treatment given did not contravene any ethical rules. Following the reply he received from the CEPN, he decided to go ahead with publication, which he also felt obliged to do by article 37 of the Declaration of Helsinki. It is not uncommon for extended analyses to be done after the end of treatment, and they had applied for an ethical permit to do just this retrospectively. He fully accepts that he has an ethical responsibility and had never sought to renounce it.

Paolo Macchiarini. He was contacted for a consultation because of his clinical expertise on patients with diseases in the final stages and organ failure and because of his background in translational medicine and stem cell therapy. The responsible doctors said that they could see no possible alternative standard therapy. He described his earlier unpublished experience in Italy with tracheal regeneration and preclinical rat trials with intratracheal injections of mesenchymal stem cells in a pulmonary hypertension model, and suggested this experimental method. He and the responsible doctors spoke to the patient's parents and explained the risks associated with the treatment. He discussed the issue of ethical approval with the head of the intensive care unit to make sure that the local regulations were being complied with. The head of the unit explained that it was a matter of healthcare and that he was sure that the use of stem cells in the context was in accordance with the prevailing rules. The CEPN later, ahead of the paper's publication, confirmed that ethical approval or consultation was not required prior to treatment. It was consistent with accepted practice to collect all available data. Ethical approval had been obtained for the gathering, storage, analysis and publication of data. The treatment of an individual patient cannot be considered a study. He does not know what was written in the patient's records.

Petra Jones and Ola Winqvist. They worked with Bernhard Holzgräfe at the ECMO centre at Karolinska University Hospital, where they analysed blood samples. They did not take part in any clinical decisions. They received a draft of the case study by email, where they appeared as co-authors. The paper contained no data or statistics from their analyses but they assumed that they had been included as they contributed to the general understanding of the case.

Ola Hermanson and Nina Hedding. The results they contributed were generated in the autumn of 2013 and compiled in November 2013. On presenting the manuscript in 2014 they were told that the patient's relatives had given their permission for treatment and

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that the cells could be used for later analyses, that the cells had been correctly deposited in KI's biobank and that approval from the Regional Ethical Review Board to analyse these cells had been received. They were also told that the treatment of the patient had been carried out because there was no other alternative and that it was preceded by a care conference. They later found out that the CEPN had stated in writing that the initial treatment was to be regarded as healthcare. Since the patient never regained consciousness the doctors wanted to investigate if there were any signs of positive (or no) effects of the administered cell therapy and therefore contacted a number of non-clinical researchers.

Mei Ling Lim: She was not involved in the patient's treatment. Regulations on how scientific misconduct is to be dealt with are lacking and term scientific misconduct is not defined. The Swedish National Council on Medical Ethics' report "Ethiska bedömmingar i gränslandet mellan hälso- och sjukvård och forskning och Vetenskapsrådets- och UHR:s Codexregler" was not published until after the study had been concluded.

Eyren Alci: He was not part of the clinical decisions and became involved about two years after the patient's treatment. He carried out no experiments before communicating with the CEPN and there were relevant permits for the laboratory experiments. A non-clinical researcher cannot be held responsible for the clinical treatment.

Dag Lundberg submitted his final comments to the Expert Panel on 11 April 2017.

The Expert Panel's statement

The gist of the Expert Panel's statement of 2 June 2017 is as follows: As regards the question of whether the action taken constitutes healthcare or research, it is obvious that it is solely a case of healthcare when the patient is admitted, and solely a case of research when the case study is prepared and finally published. However, at what point and at what stage the research commenced is impossible to ascertain. The faults pointed out by Dag Lundberg fall in all essentials under healthcare rather than research. It is also impossible to establish that the 23 bronchoscopies were carried out as research. If this has been done for the purposes of scientific study, it can be criticised and possibly constitutes scientific misconduct. Given the circumstances of the case, it cannot be ruled out that it was done in order to examine the effect of the experimental treatment. Notes were also made to the effect that action was taken for the purposes of a study and that several hypothetical assessments provided a basis for the action taken. This can also indicate that the conceivable benefit was chiefly one of knowledge rather than healthcare. It cannot, however, be taken as certain that this was not done to study the progress of a patient with life-threatening injuries for which there is no known treatment. In light of these circumstances, it cannot be established that the action taken was within the boundaries of research. All that remains of the aspects of the case that without doubt constitutes research is the actual publication of the case study. The Expert Panel establishes that the authors applied for and received an ethical permit for the ensuing analyses and publication, and that there are no grounds to pass a verdict of scientific misconduct.

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The authors' comments on the Expert Panel's statement

The authors were invited to comment on the Expert Panel's statement. Ola Hermansson, Nina Heldring and Bernhard Holzgräfe commented and referred largely to their statements to the Expert Panel.

The prevailing rules and international guidelines

Chapter 1 section 16 of the Higher Education Ordinance (SFS 1993:100) provides that a higher education institution that receives a complaint or becomes aware in some other way of suspected misconduct in research shall investigate the suspicions. During its investigation the higher education institution may request an opinion from the expert panel on research misconduct at the Central Ethical Review Board.

The Health and Medical Service Act (SFS 1982:763) defines healthcare as medical action designed to prevent, investigate and treat diseases and injuries. The aim of healthcare is to ensure the health and equal care of the entire population. Healthcare operators are required by the act to meet the conditions of good healthcare (para. 1–2). According to the healthcare and medical service bill (1981/82:97 p. 23) effective healthcare requires the care invention to be based on empirical knowledge and proven experience and related to various quality standards.

The Patient Safety Act (SFS 2010:659) requires all healthcare providers to work in accordance with the empirical and experience-based principle. A patient is to be given expert and thorough healthcare that meets this requirement and that is designed, as far as possible, in consultation with the patient. The patient is to be shown consideration and respect (chapter 6, para. 1).

The purpose of the Act concerning the Ethical Review of Research Involving Humans (SFS 2003:460) (the Ethical Review Act) is to protect individuals and human dignity when research is conducted. Human rights and fundamental liberties must always be taken into account during ethical vetting, while at the same time giving consideration to the fact that there can be a growth of knowledge as a result of research. The welfare of people should always be given precedence over the needs of society and science. The Act defines research as scientifically experimental or theoretical work intended to result in new knowledge and development outcomes on a scientific basis, excluding work that is performed within the framework of higher education on the basic or advanced level. The Act applies, inter alia, to research that subjects a research subject to a physical intervention or is performed according to a method with the purpose of affecting a research person physically or mentally or includes an apparent risk of injuring the research subject either physically or mentally. Further, research that is referred to above may only be conducted if it has been approved subsequent to an ethical vetting. (1, 2, 4 and 6 §§).

World Medical Association has issued recommendations for clinical research in the Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects. The declaration is a crucial set of ethical guidelines and provides that experiments involving humans are to be conducted as clinical research and must comply with ethical rules, and that patient safety must be safeguarded during experimental and medical procedures.

The WMA states that the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects and that physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries (articles 1 and 10).

The declaration also states that while the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects (article 8). Patients should be involved in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects (article 14). Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects (article 16). All medical research must be preceded by a careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation; and the risks must be continuously monitored, assessed and documented (article 17). Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, adequate laboratory and, as appropriate, animal experimentation (article 21). Article 37 provides that under certain circumstances an unproven intervention may be used if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering.

At the time of the intervention, the 2008 version of the declaration was in effect. Then, the relevant article (35) read as follows:

"In the treatment of a patient, where proven interventions do not exist or have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, this intervention should be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information should be recorded and, where appropriate, made publicly available."

The Declaration of Helsinki has no legal status in Sweden. And while it informs much of the Ethical Review Act, there is no clause corresponding to article 37 (or the earlier article 35).

The criteria for authorship set out in the "Vancouver Convention", which contains international regulations for scholarly works in medical journals, state that a person shall be held responsible for all aspects of his/her paper by guaranteeing that questions of accuracy are investigated and resolved in an appropriate manner. This means that co-authors are obliged to assist in the event of an investigation into a paper's alleged lack of clarity or precision.

Conclusion

Healthcare or research

The definition of research in the Ethical Review Act is general, and to judge whether an event constitutes research, a comprehensive assessment must be made and many circumstances weighed up against each other.

The requirement that healthcare intervention is to be based on science and proven experience does not rule out a certain element of clinical development. The difficult balancing exercise is to both cater for the patient's need for protection while in hospital and to give access, on reasonable grounds, to new therapeutic methods being tested. Healthcare conducted at the cutting edge of research can therefore find itself on the border between established healthcare and clinical research.

The concept of vital indication does not appear in the Swedish law books. According to the medical dictionary it means "the circumstance in which certain action must be taken to save a patient's life". What this normally means is a condition that can be fatal within a few hours, days or possibly a week or so. The term "compassionate use" appears in the EU's pharmaceutical regulation (Regulation (Ec) No 726/2004 of the European Parliament and of the Council) referring, for example, to the treatment of a disease that is seen as life-threatening and that does not respond satisfactorily to an approved drug.

Clinical research aims to increase medical knowledge for the benefit of groups of patients, while clinical innovation is usually used to help individuals.

Many seriously ill patients want access to new, unproven methods while also wanting to help improve medical knowledge of their condition and its treatment. Similarly, researchers and clinicians might want to help individual patients while involving them in a research project. The decisive factor is if it concerns the medical search for new knowledge, the development and scientific testing of new methods.

Many of the authors have maintained that the aim of the treatment was to save the patient's life and not to conduct a study on a seriously ill patient, and that the treatment should therefore not be regarded as research.

KI shares Dag Lundberg's conclusion that the treatment had a dual purpose: to save the patient and to generate new molecular biological and immunological knowledge.

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The ethical application that was later submitted included two patient cases, indicating a planned series of experiments and an intention to conduct research. The investigation found that according to an entry in the medical records on 18 November 2011, experimental treatment was begun after a care conference held on the same date and that the carers decided to treat the patient in the form of a study. The treatment involved instilling mononuclear cells from the patient's own blood intrathecally via a bronchoscope. There was no relevant animal data to refer to nor any result from similar studies on humans. The method was, in other words, completely unproven.

The treatment was carried out with repeated intrathecal instillations. A total of 23 bronchoscopies were performed over 14 days. Extensive tissue screening (biopsies and blood tests) using advanced analyses – a natural feature of research – was also done.

KI finds, contrary to what the Expert Panel says, that on the basis of these assertions the care given to the patient as of 18 November 2011 until the patient's death was of an explorative research character corresponding to preclinical research on a human being. This conclusion KI believes is substantiated further by the consent that was obtained from the patient's family to use the experimental treatment.

Scientific misconduct

Since there is no definition in Sweden of "oredlighet i forskning" (scientific misconduct), the case should be considered from the rules, scientific demands and generally accepted ethical norms that were in effect at the time of the research in question.

The research that commenced on 18 November 2011 lacked any biological hypothesis based on either *in vitro* or *in vivo* (animal) data. The notebook also lacks notes on any advance discussion of the risks and benefits of the treatment, the theory on which it was based, the results of preclinical or other studies demonstrating effect, and safety; nor of any discussion that followed from the deterioration of the patient's condition, in spite of which it was decided to continue the experimental treatment. This contravenes articles 14, 16, 17 and 21 of the 2013 Declaration of Helsinki (articles 31, 21, 18 and 12 of the 2008 version). There was also no approval in place from the Regional Ethical Review Board for the clinical treatment.

KI shares Dag Lundberg's conclusion that the treatment constitutes scientific misconduct.

The scientific paper was composed at a time where there was no suspicion of scientific misconduct. An ethical permit application for extended molecular biological and immunological analyses of biological material and publication was made on 19 December 2012. The ethical issue of gathering and publishing data from a deceased patient was examined by the Ethical Review Board and approved on 23 January 2013.

The paper mostly reports positive findings and to a much lesser extent the negative effects. However, this in itself does not qualify as scientific misconduct.

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The responsibilities of the corresponding author and co-authors

The "Vancouver Convention" states that the assessment of author responsibility must be based on the premise that all authors of a paper are expected to clear up any confusion or lack of clarity that appears after publication.

As regards assessing responsibility for the established scientific misconduct, it is KI's view that whoever puts his or her name to a scientific paper bears responsibility for it, with the corresponding author having a greater responsibility than the other co-authors.

Many of the authors assert that they did not take part in the clinical treatment of the patient and that their contribution to the article was solely analytical. Ana Teixeira and Björn Anderstam also state that they told Philipp Jungeluth that they did not consider their contribution to justify co-authorship status.

KI believes that Paolo Macchiarelli, as corresponding author and initiator of the research study, bears most responsibility for the scientific misconduct established. He was the one with the primary scientific interest in the developments that preceded that paper and who had the opportunity to perform experiments of a preclinical nature on a human being. When he was invited to the ECMO clinic for consultation he made reference to his own unpublished study on rats, which although producing unclear results, gave the clinicians and the patient's family hope of a possible way forward for the patient.

First author Philipp Jungeluth also bears some responsibility for the scientific misconduct committed in having a crucial influence on the research conducted and on the paper's composition. The paper mentions that he and clinician Bernhard Holzgraefe made equal contributions to the paper. Clinician Håkan Kalzén was also involved in the care given to the patient and the research process upon which the paper was based. Through their involvement they have thus supported the careers' decision of 18 November 2011.

As regards the other clinicians and researchers who contributed to the paper, KI finds that they worked in disciplines that were remote from the treatment of the patient and that ethical approval had been obtained for the paper.

KI therefore finds that Paolo Macchiarelli, Philipp Jungeluth, Bernhard Holzgraefe and Håkan Kalzén are the ones to be held responsible for the scientific misconduct that preceded the published paper.

Sanctions and other consequences

Paolo Macchiarelli was dismissed by KI's staff disciplinary board in March 2016. Since Philipp Jungeluth, Bernhard Holzgraefe and Håkan Kalzén no longer work at KI no action in terms of labour law will be taken.

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The published paper "*Autologous peripheral blood mononuclear cells as treatment in refractory acute respiratory distress syndrome*" is based on data produced through scientific misconduct during the basic clinical research process. Even though the published paper as such obtained an ethical permit, the underlying research did not. The paper presents its data in an un-nuanced and overwhelmingly positive manner, which might still entail a risk that other patients will be subjected unnecessarily to similar treatment before adequate preclinical data is available to warrant human studies. The journal *Respiration* will therefore be urged to withdraw the article forthwith.

The decision on this matter has been taken by Vice-Chancellor Ole Petter Ottersen after presentation by legal counsel Helena Scarabin. Also participating in the final handling of the case was Professor Anders Ekblom and head of the Legal Office Helén Törnqvist.

Ole Petter Ottersen

Helena Scarabin

Response from Philipp Jungebluth

Dear Editor,

First of all, I would like to apologize for the trouble our manuscript caused you and your journal. Besides, I want to express my gratitude for the possibility to provide explanation for the ongoing unfortunate matter at the Karolinska Institutet (KI).

I certify that all published data are entirely correct and none of them constitute scientific misconduct. The presented case report (published as “Autologous Peripheral Blood Mononuclear Cells as Treatment in Refractory Acute Respiratory Distress Syndrome”) [1] provides clinical and associated postclinical data of a young patient treated in compassionate use at the Karolinska University Hospital in Stockholm (Sweden) in November 2011.

The following points were considered before the treatment was started and until the publication of the case report:

- 1 Kenneth Palmer, the former head of the extracorporeal membrane oxygenation (ECMO) center at the Karolinska University Hospital in 2011 contacted us regarding a young patient with a severe inhalation trauma. In a meeting at his unit he asked us whether there would be any treatment on an experimental level that might be helpful for the patient since all conventional therapeutic strategies did not show any beneficial effect.
- 2 We presented the experimental data that existed at that time (both our preliminary data but also data of other research and clinical groups) and the underlying hypothesis of using autologous progenitor cells and erythropoietin in order to reduce inflammation. Both agents (autologous cells and erythropoietin) are in daily clinical use around the world.
- 3 The decision to initiate and proceed with the compassionate treatment was then made by the former head of the ECMO center Kenneth Palmer.
- 4 The approval and informed consent to perform and initiate the treatment was obtained from the parents of the patient after they received a detailed explanation and elucidation regarding the experimental nature of the treatment including all potential risks.
- 5 The patient showed an immediate improvement to the treatment, and everyone at the ECMO unit was excited by this good response at that time (data included in the paper). Therefore, we decided to share and publish this unique clinical case.
- 6 We applied for the ethical approval to analyze the cells of the patient and for publication of the data. The ethic committee at KI in Stockholm approved our application.
- 7 During the submission process, Kenneth Palmer suddenly requested to be removed from the author list of the manuscript for an unknown reason (in light of the subsequent developments, his request seems odd).

The decision that has now been taken by the KI is purely politically motivated. The explanation for their decision is poor and the accusations they made are false and incorrect. KI handles similar cases obviously dissimilar and arbitrary. Other groups at KI (“In vivo Effects of Mesenchymal Stromal Cells in Two Patients with Severe Acute Respiratory Distress Syndrome” [2]) perform similar systemic cell-based treatments (partly without any scientific background), but our local application of autologous progenitor cells and erythropoietin comply with scientific misconduct.

The whole conflict at KI started when Dr. Grinnemo, a former cooperative partner and group leader at KI stole and misused data from our group in 2013. In the following, he was proven to be guilty of scientific misconduct for using our data without approv-

al by the KI Ethics Committee. He took revenge by accusing us of unethical scientific and clinical behavior.

Since then, various accusations have been made against our group, and clearly Karolinska Institutet applies different levels of justice in similar cases.

Everything around the treatment and the preparation of the manuscript was correctly done by us. We followed all existing guidelines at Karolinska Hospital and Institutet at that time, but suddenly after alleged accusations against us and a reevaluation of our work, the manuscript constitutes scientific misconduct.

Karolinska University Hospital and Institutet put a lot of pressure on various co-authors of the manuscript who are still working at KI in order to keep them silent and not to speak up. It is a scandal how they protect the University’s credibility regardless of the costs for individual scientists.

Whether one should have performed such an experimental treatment in a patient that did not respond to conventional treatment may be disputable and must be further discussed in order to move forward in science and medicine. The decision for the treatment in November 2011 was made by the responsible medical doctors of the department and based on the existing scientific knowledge at that time. I am still convinced by our therapeutic hypothesis and do not see any relevant risk for a patient by the local application of his own cells and erythropoietin.

No matter what one may think about the ethical aspect of such a treatment, there cannot be found any scientific misconduct in our publication and the respective data.

In summary,

- 1 The clinical team did all in their power to maximize the chance for this patient who was in a severe state and did not respond to conventional therapy.
- 2 After seeing the clinical improvement, the postclinical team tried to understand parts of the mode of action of the therapy to share it with the scientific community.

Dr. Philipp Jungebluth, February 28, 2018

Response from Paolo Macchiarini

Dear Editor,

Thank you very much for the opportunity to state my point of view regarding Karolinska Institutet’s (KI) request, after requesting opinion from the Swedish Central Ethical Review Board (CEPN) to retract the manuscript “Autologous Peripheral Blood Mononuclear Cells as Treatment in Refractory Acute Respiratory Distress Syndrome” published in *Respiration* [1].

I cannot agree more with the Editor’s and publishing house’s request (and wish) to provide a platform for discussions and a forum for a scientific debate. Furthermore, I agree that the background of the conflict between the two parties should be transparent to the readers and audience to enable them to form their own opinion.

Dr. Jungebluth wrote about the dynamics that led to KI’s investigation. I shall here start with a clarification of my, and my team’s, involvement with this case and my opinions thereon.

Initial Contact

I was asked for a clinical consultation because of my clinical expertise in patients with end-stage diseases and organ failure – I

was not employed by the Intensive Care Unit (ICU) but by the Ear, Nose and Throat (ENT) Department – and because of my background in translational medicine and stem cell therapy. The clinicians in charge of the case (e.g., the head of the extracorporeal membrane oxygenation (ECMO) department Dr. Kenneth Palmer) confirmed that they had done their very best and could not see any possible alternative standard treatment, leaving only the option of discontinuing the ECMO – the patient was already on venous-arterial ECMO and had been for several days, a therapeutically applicable recourse only in patients where all standard treatments fail. Not only was there no improvement, but also a worsening of his health status was documented, especially in both lungs (ischemic lungs and upper airway). I talked about our previous, unpublished clinical experience in Italy with the regeneration of the airway and the preclinical rat experience with intratracheal injection of mesenchymal stromal cells in a pulmonary hypertension model [3], and they were interested. The head of the ICU (Dr. Kenneth Palmer) asked me to present this technology and preliminary results, which I did, immediately, to the staff members of the ECMO unit. These were dedicated doctors, trying to find a way to save a dying patient's life.

The clinicians talked first to the parents and then asked me to talk to them. I did, and because of the Swedish language, other members of the team translated whenever it was necessary. Since this was such a dramatic and difficult case, I happen to remember very well that I told the parents that I couldn't possibly know what the outcome would be and that the alternative – to continue the ECMO until the almost certain conclusion of the patient's death – had been explained before to them by the clinicians in charge. I explained about the risks of the procedure (intratracheal injection route, impossibility of taking bone marrow because the patient was fully heparinized, risks of airway bleeding, insufficient number of cells taken from the peripheral blood, etc.). I was given to understand also that extra care should be taken with the collection of data since the injuries were sustained whilst the patient was at work and therefore may be needed in subsequent legal action.

I had to leave the country after this initial consultation, but had no concerns about the subsequent care of the patient or collection of the clinical information – I was, indeed, kept updated via telephone and email exchanges.

Obviously I have no knowledge of what was written in the medical records in this case (and I was not asked, as is usually demanded in other countries, to write about my consultation in the medical records, but I speak and write no Swedish, so perhaps that was the reason; besides, I had no access permission to the medical records for patients in Sweden – this has been verified by an internal investigation and is publicly available upon request at the Karolinska University Hospital), but it cannot possibly be taken to mean that I, or my team, considered our suggestions for ways to save the life of this patient as part of an emergency consultation in any way “a study.” I shall discuss this in more detail later.

CEPN Critiques about Clinical Indications

One of the major critiques of the CEPN was that it was not evident that the patient's condition was of such an alarming nature that it acutely motivated compassionate treatment, or that there was a vital indication for treatment, and there was thus time to have informal contact with the regional ethical review board.

Evidently, a patient on ECMO is in a life-threatening condition, especially if ECMO does not yield the expected effects, and there are

very strict guidelines for its implementation (Extracorporeal Life Support guidelines). I was shocked to read that Prof. Lundberg (external expert of the CEPN) felt that he can take the view that “...it was not evident that the patient's condition was of such an alarming nature” having merely read the medical records, against worldwide accepted ECMO indications and the opinion of the patient's healthcare providers who were experienced and dedicated ECMO (and advanced ICU) specialists including the head of ECMO, and running one of the biggest and most experienced ECMO Units in Europe, who were alarmed enough to reach out for a consultation with someone from another department in an attempt to save the patient's life.

As for the need for contact with the regional ethical board, during the consultation with the clinicians on the 18th of November, I actually discussed this matter with the head of the ICU (Kenneth Palmer), in order to satisfy *myself* that local regulations were respected. He expressed that this was simply a healthcare decision in these circumstances, and he was also sure that the use of cell therapy in this context was within all guidelines. CEPN (Mr. Sviden and other authorities) confirmed that this was the correct mode of practice, when we checked before publication.

Innovation versus Healthcare

Secondary to the health of the patient, ALL “innovative” treatments should serve such a double purpose. In attempting to save a patient's life, we should always – as long as it is of no detriment to the patient, and consent is given – collect as much data as possible to inform future decisions. However, this does not conflict with the fact that this was an acute case in which every opinion was sought in order to attempt to save a patient's life, all conventional options having been tried.

The opinions that Prof. Lundberg expressed in his report about the presumed priorities of the teams involved in the care of this patient are totally disrespectful of the Hippocratic Oath. All doctors have, as their number one priority, their patient's health and wellbeing. I actually feel that the healthcare providers of this poor boy, who attempted every possible solution to this tragic acute injury, should be congratulated for their efforts. They were desperately searching for a possible last therapeutic resource knowing that the situation was catastrophic.

CEPN also stated that the laboratory part of the study cannot be considered separately as it is conditioned upon the completion of the innovative clinical treatment. I am still unsure what Prof. Lundberg means by “cannot be considered separately” – perhaps he means that any failings he perceives in the clinical work means that all authors, regardless of their role, are equally guilty with regard to those failings? If so, then clearly this is absurd. Ethical approvals for the later laboratory part of the study were obtained separately, as they require separate kinds of permissions (e.g., storage and analysis of blood samples). Many researchers needed to be involved in laboratory analysis who were not clinical, and would not have been in contact with the patient, and vice versa. Of course, therefore, there is separation between the roles and responsibilities of different authors, and different legal and ethical requirements for different aspects of what is covered by the manuscript.

Too Many Co-Authors

Prof. Lundberg stated that “As many as 26 career researchers have put their names to the case study involved, which would indicate that they considered the co-authorship as a potential merit and that they, at the time, considered the study as research.”

Later analysis of the samples (it was late because we had to have all the legal requirements and permissions in place, and it took some time – understandably – to contact the parents to ensure their informed consent, outside of the traumatic circumstances of the acute healthcare emergency) does not imply that the initial impetus for the procedure was anything other than an attempt to save a patient's life, if this is what is meant by this point. In fact, applying such logic to any postevent analysis quickly shows how absurd such reasoning would be (does carrying out an autopsy imply that the pathologist considered the *death* part of a “study”? No, it means that he or she was trying to learn from an event).

In fact, the merits of the report were appreciated by the reviewers of the manuscript, who recognize the need for such data and such experimental attempts to save the lives of patients with this devastating condition.

Scientific Misconduct

Prof. Lundberg then states, “I find that the following indicates that such misconduct has taken place. The responsible researchers have, presumably due to gross negligence:

- 1 Failed to document a risk/benefit analysis and the associated ethical considerations prior to making the decision to start the innovative treatment.”

I cannot comment on what was, or was not, documented after the consultation on 28th November, although given the condition of the patient and the fact that the clinicians stated that all conventional treatments had failed, the potential benefits would have outweighed the risks to such an extent that it may not have seemed necessary to document them.

This appears to be a criticism of the healthcare records held at Karolinska University Hospital, and not of the manuscript or its authors (the “responsible researchers” as Prof. Lundberg phrases it). I do not, however, agree with such criticism. I here attach my email correspondence with the authorial team, requesting documentation of the ethical approvals that were sought at each stage of both the treatment and the research. You will see in this email and its attachments (the ethical approval from CEPN, the biobanking permissions) that each of these was addressed satisfactorily. CEPN, as has been mentioned before, confirmed that in this case ethical permission was NOT required for the treatment, but only for publication (which was subsequently sought and granted). The correct permissions were also held for all other parts of the process (see above).

- 2 “Failed to contact the regional ethical review board, despite reasonably having time for an informal consultation.”

It is Prof. Lundberg's own retrospective assessment that there was time (and need) for such a consultation, against the decision of the head of ECMO and the clinical staff in charge of the case at the time, as I have already pointed out. As also already stated above, contact retrospectively with CEPN confirms that in this case, consultation/approval with the regional ethical review board was not necessary.

- 3 “Used a severely ill patient, without ethical approval, as a means to carry out advanced preclinical research.”

This is an extremely serious accusation, made without any justification. To allege that any medical professional would “use” a patient is beyond comprehension. This statement is defamatory in the extreme.

- 4 “Carried out the innovative treatment, despite its insubstantial theoretical foundation and insufficient knowledge from ade-

quate animal testing. Extrapolated a hypothesis in several steps regarding a potentially beneficial anti-inflammatory effect from the treatment with no scientific evidence. It was thus assumed that mononuclear cells from the blood have the same effect as stem cells from bone marrow and that local intratracheal installation is equivalent to intravenous administration.”

As Prof. Lundberg himself accepts, there is evidence that stem cells from bone marrow have an anti-inflammatory effect, but the patient's condition precluded a bone marrow aspiration. Attempting to use mononuclear cells from his blood was the only (see above explanation) option that we could give. Given his life support system, as Prof. Lundberg also acknowledges, intravenous use brought considerable risks, and, for example, our previous pre-clinical and experimental experience in Italy and Spain of intratracheal use gave us the hypothesis that this would be a safer alternative with a chance of efficacy. Indeed, the manuscript itself demonstrates that the hypothesis has some support and an anti-inflammatory therapeutic effect was reported – as is well acknowledged by the expert reviewers.

- 5 “Failed in the article to account for parallel conventional clinical treatment and discuss the possibility that such treatment could provide an explanation for the temporary improvement in the patient's status.”

Had any peer reviewer requested any further details about the patient's treatment then we would happily have supplied them, and should the journal wish, we could add such information. I cannot see how this can be listed as grounds for “scientific misconduct.”

- 6 “Considering the minor evidentiary value of the unverified study, strongly exaggerated the significance of the achieved results, which could evidently mislead a less critical reader.”

Prof. Lundberg may believe the wording of the manuscript is inappropriate, but the reviewers of it were of a different opinion, and appreciated what we were attempting to do for this patient, and our reporting of it in order to pass knowledge on to the scientific community. It is not uncommon for peers to differ in their opinions on published manuscripts, but I would dispute his single opinion of “strong exaggeration,” and place it against those of the expert peer reviewers. There was no misrepresentation of the facts of the case, nor, I believe, were our conclusions misguided.

- 7 “Neglected the established ethical publication practice by including 26 authors: an unreasonable number, considering the contributions of the individual researchers and the insubstantial scientific value of the publication.”

This is the beauty of the multidisciplinary effort to save patients (clinically) and provide international scientific collaboration (some co-authors are outside Sweden because they did specific evaluations requiring expertise and equipment not available in Sweden). It has been always my philosophy that all members that have contributed to a work should be acknowledged, and there is nothing “unethical” about that. The detail of the contribution of each author could be listed should this be deemed necessary. In my personal opinion, it is far more unethical to exclude involved researchers from the author list, in order to increase your own presumed contribution.

- 9 “Denied all ethical responsibility in their statements, relaying the blame by systematically and categorically referring to other clinically active colleagues. This does not strengthen their case.”

As I have already stated, perhaps Prof. Lundberg was not aware of the responsibilities and situation in this case. I hope that my explanation above clarifies it.

Questions about the clinical record-keeping or the clinical decision-making in this case must be answered by those responsible for those records or decisions. As I say, I do not believe that any wrong decisions were made by those responsible (as confirmed by CEPN when checked), so there is no “blame” to be “relayed.” However, since I did not make those decisions, nor see (let alone write) the medical records, I simply cannot answer detailed questions about them – as stated in the previous response.

As I have also said, I believe that the clinical team in this case deserves congratulations (and gratitude) for their attempt to beat the odds for this patient. Such denigrating criticism of people who attempt to save the lives of dying patients does nothing to serve the needs of patients. If this had been your son, what would you have liked the team to do? And, after they had attempted their very best, how would you like them to be treated by the establishment and their peers?

I also feel that I have to comment on Prof. Lundberg’s statement that: “A wave of somewhat unbridled enthusiasm for stem cell treatments, including the type that was so forcefully promoted by Prof. Macchiarini, washed over all the units of Karolinska University Hospital at the time of the study. The fact that Prof. Macchiarini at the time had the express support of the KI management obviously reinforced his local authority. It would only be human in that situation if clinically active researchers were to find it difficult to keep a level head and decline an offer to collaborate with him.”

Prof. Lundberg states that he retired in 2006 and hence has no experience of the “somewhat unbridled enthusiasm” he claims was “washing over all the units” of the Hospital in 2011. Clearly, he has been exposed to too many colorfully worded media reports about my work and my apparently irresistible and malign influence. Nevertheless, Prof. Lundberg unconsciously ignores the fact that KI had already by that time an excellent, long-lasting and well-published history of clinical stem cell application and research (e.g., Prof. Katarina Le Blanc, Prof. Outi Hovatta, etc.).

The truth in this case is that a patient was dying, and his doctors were keen to try anything to save his life. I suggested an experimental option, and everyone, including the patient’s family, were aware what the chances of success were. CEPN themselves retrospectively confirmed that these decisions, taken with the patient’s best interests at heart, did not require any ethical consultation or approval before initiation of the attempt. It was good practice to collect all the data possible in this case, and all ethical permissions were granted for the collection, storage, analysis, and publication of these data.

Prof. Lundberg and KI may criticize the wording of the manuscript, but there are no grounds for accusations of scientific misconduct. Indeed, I believe the clinical team deserves praise and thanks for their efforts to save a patient’s life, and I believe the laboratory researchers did good, careful analyses in order to try to learn from this case and pass the knowledge gained to others who may find themselves with a similar case to deal with.

I shall end by remembering KI vision (<https://ki.se/en/about/startpage>), which all our efforts were made to confirm: “Our vision is to make a significant contribution to the improvement of human health; our mission is to conduct research and education and to interact with the community.” It is totally in line with the spirit and content of the present manuscript!

And, last but not least, the different *modus vivendi* of KI and Hospital is worth a few lines. The decision from KI regarding this particular *Respiration* manuscript work is a clear demonstration on how individuals are treated differently. A similar case (KI referenced 2-2336 and 2-2259, these are public documents) which was reported to KI in 2015 was not properly investigated and KI decided that there was no misconduct. The authors of that study state to have performed “first-in-man” study using a specific population of mesenchymal stem cells for the treatment of ARDS. Before the treatment they had neither performed any animal studies nor applied for ethical permission for this treatment.

Most likely, the following paragraph from the KI’s recent decision against our work applies to these researchers as well: “The patient record also lacks notes on any advance discussion of the risks and benefits of the treatment, the theory on which it was based, the results of preclinical or other studies demonstrating effect, and safety.”

However, it appears as if KI in that case did not care to investigate the patient charts. Why the discrepancy in case handling – maybe simply because I am now *persona non grata* and the official (and foreigner) scapegoat of KI’s oceanic deficiencies and autoestimation? Of note, I acknowledged receipt of the CEPN verdict submitted about this paper – two and a half weeks after KI made a press release about the receipt of these questions and claimed that they were alleging “research misconduct.” KI appears therefore to have abandoned any attempts at compliance with the internationally accepted requirement for any accusations of misconduct to be investigated in a confidential manner, to ensure fairness to all parties.

Prof. Paolo Macchiarini, March 8, 2018

Response from Bernhard Holzgrefe

Dear Editor,

I am grateful for the opportunity to explain my point of view regarding the article “Autologous Peripheral Blood Mononuclear Cells as Treatment in Refractory Acute Respiratory Distress Syndrome,” which was published in *Respiration* [1]. The paper is a case report describing an experimental treatment with endotracheal applied autologous peripheral blood-derived mononuclear cells (PBMCs) in a patient suffering from severe acute respiratory distress syndrome treated with invasive mechanical ventilation (IMV) and venoarterial extracorporeal membrane oxygenation (va ECMO). IMV and ECMO were initiated because of a burn-induced airway damage caused by inhalation of hydrated lime. The patient was initially on venovenous ECMO (vv ECMO), but the circuit had to be changed to va ECMO because of hypoxia-induced circulatory failure. The patient was treated at the ECMO center of the Karolinska University Hospital, Stockholm, Sweden.

In the same year, another paper was published by researchers from Karolinska Institutet (KI) about 2 patient cases treated with systemically administered mesenchymal stromal cells during vv ECMO [2].

As one of the co-authors I have been accused of scientific misconduct in 2016 when it was suggested that the treatment was initiated as a research study without approval of the local ethical committee. An investigation was launched by the KI. The KI requested a statement of the expert group on misconduct in research at the

Central Ethical Review Board of Sweden (Centrala etikprövningsnämnden – CEPN), which appointed a special advisor in this matter. The advisor judged that, based on his analysis, the responsible researchers are guilty of misconduct in research. However the CEPN “considered that it is not possible to establish that the measures have been implemented within the framework of research.” “The deficiencies, which the advisor highlighted, have occurred within the care of the patient” and “that these essentially lie within the framework of healthcare and not research” [4]. In contrast to the expert group statement, the KI decided in January 2018 that 4 authors were responsible for scientific misconduct [5]. KI’s decision was in my opinion mainly supported by the fact that there was no approval from the local ethical committee for the treatment with PBMCs (Method section 1).

At the time of treatment (2011), I was employed as a consultant/attending physician at the ECMO department of the Karolinska University Hospital, and I had started my doctoral (PhD) studies at the KI in May 2011. My role during the treatment was that of a medical doctor (and not as a researcher) who was part of a

team treating this patient. After the patient had died, it was decided to write a case report, and I applied for ethical approval, biobanking, and a patient data registry for writing this case report. We also received written informed consent from the next of kin for this. Here, I had the role of a researcher and all necessary approvals were obtained as stated by the CEPN [4].

It has never been my intention to perform a clinical experimental study in a severely sick patient without ethical approval, which I have been accused for. I was working as a physician in the ECMO unit and delivered medical care to the patients, which in this particular case included the PBMC treatment. Furthermore, I was not authorized to take a final decision to start the PBMC treatment.

Bernhard Holzgraefe, April 4, 2018

Disclaimer

The statements, opinions, and data contained in this Editor’s Note are solely those of the individual authors and contributors.

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