

Dear Professor Leong

We request that you retract two papers that were published in Biomaterials. They are:

1. Asnaghi MA, Jungebluth P, Raimondi MT, Dickinson SC, Rees LEN, Go T, Cogan TA, Dodson A, Parnigotto PP, Hollander AP, Birchall MA, Conconi T, Macchiarini P, Mantero S. A double-chamber rotating bioreactor for the development of tissue-engineered hollow organs: From concept to clinical trial. *Biomaterials* 2009;30(29):5260-9.
2. Curcio E, Macchiarini P, De Bartolo L (2010). Oxygen mass transfer in a human tissue-engineered trachea. *Biomaterials* 2010;31(19):5131-6.

We will start by explaining the concerns about the paper by Asnaghi and colleagues.

It reports a device that is described as a “bioreactor” for producing “tissue-engineered hollow organs”. It was used to produce a “tissue-engineered airway” that was transplanted into a patient with a stenosis of her left main bronchus, as described in the *Lancet*. (Macchiarini et al. 2008) The five year follow up of the patient was also reported in the *Lancet*. (Gonfiotti et al. 2014)

We are sure that you are aware that both those papers made false claims about the clinical outcome in that patient and, as a result, they have been retracted by the *Lancet*. (*Lancet* 2023a, *Lancet* 2023b) You may also be aware that for five years after the editor, Richard Horton, knew that the publication had been falsified the *Lancet* had refused to retract the papers. The *Lancet* was compelled to retract the papers after we obtained a ruling about falsification from the Swedish National Board for Assessing Research Misconduct. (Murray & Wilmshurst 2023)

You will also be aware that some of the same group of authors have had a number of other falsified publications retracted. It seems clear that after falsifying the data in the original 2008 *Lancet* paper, Macchiarini and some of his co-authors falsified further publications to support the original lies. The evidence shows that the *Biomaterials* paper by Asnaghi and colleagues is part of the same tissue of lies. By its publication the authors attempt to give undeserved scientific credence to the original false 2008 *Lancet* paper by suggesting that the authors had spent a long period in incremental scientific developments, including designing the “bioreactor”. In its turn, the *Biomaterials* paper derives credibility from the false claims of clinical efficacy.

As we explain below, the incremental scientific developments and the use of pseudoscientific processes and equipment were the modern equivalent of the theatrical deception of snake-oil salesmen. The airway implanted by Macchiarini in Barcelona was supposedly “tissue-engineered” using the “bioreactor” in the Bristol laboratory of Macchiarini’s co-principal investigator, Martin Birchall. The 2008 *Lancet* paper credits him as the person who “wrote the report” we now know is false. On various websites, Birchall claims that he led the team that performed this now discredited procedure. Subsequently Birchall moved to University College London where he led a team that performed further transplantations of “tissue-engineered” airways. In most of those cases they merely squirted so-called “stem cells” on decellularized airways immediately before surgery with no use of the so-called “bioreactor” to grow anything whatsoever. (Elliott et al 2012) So it is clear that Birchall realised that the “bioreactor” was no more than pseudoscientific hogwash.

Thirteen of the 14 authors of the paper by Asnaghi and colleagues were also authors of the falsified 2008 *Lancet* paper by Macchiarini et al - namely Asnaghi, Jungebluth, Dickinson, Rees, Go, Cogan,

Dodson, Parnigotto, Hollander, Birchall, Concorni, Macchiarini and Mantero. Several of these authors have been found guilty of research misconduct by official inquiries, such as by the Swedish National Board for Assessing Research Misconduct (Nämnden för prövning av oredlighet i forskning or Npof) and by the Karolinska Institute. Macchiarini has also received criminal convictions in Italy and Sweden.

The paper in Biomaterials by Asnaghi and colleagues repeats the false claims about the clinical outcome in the patient first reported in the Lancet in 2008. Many of the authors of the paper by Asnaghi and colleagues were aware that the claims were false because they were responsible for the original lies in the 2008 Lancet paper. Below we provide some examples of the false claims about clinical outcome in the paper by Asnaghi et al.

In the Abstract, Asnaghi et al. falsely state “one year post-operatively, graft and patient are healthy”. In reality, three weeks after the surgery, the graft collapsed and required stenting. (Castells 23 July 2018, Molins 2019, Schneider et al. 2022, Lancet 2023a) Lung function did not improve. Eventually after repeated stent implantation, the patient required a right pneumonectomy. (Molins 2019, Lancet 2023a) The early graft collapse and need for stenting was a major reason for retraction of the 2008 Lancet paper. (Lancet 2023a)

The Results section by Asnaghi et al. concludes with sub-section 3.6 “Graft outcomes”. The last two sentences of that sub-section also provides an entirely false description that suggests that the patient had a good clinical outcome.

In the Discussion section, Asnaghi et al. falsely claim “the graft is functioning well and there is no sign of rejection one year post-implantation”. The fact that the graft collapsed and required stenting within three weeks of implantation proves that it was not functioning well. Confirmation that that claim was false was a major reason from retraction of the 2008 Lancet paper. (Lancet 2023a)

In the Conclusion section, Asnaghi et al. wrote “Ultimate validation of the bioreactor’s effectiveness was provided by its central role in the first stem cell-derived, tissue-engineered organ, which continues to function well ten months post-implantation.” Again it is dishonest to claim that the graft was functioning well at that time. In fact, at no point did the graft function well.

Not all the false claims in the paper by Asnaghi et al. are related to clinical efficacy.

In the last sentence of the introduction, the authors state that there was a “step-wise work plan”, which included an “*in vivo* trial in an animal model” before “a first-time-in-man transplantation of the resultant recellularized construct”. In reality, the method of preparing the graft was cobbled together in weeks without a “step-wise work plan” and there were no appropriate *in vivo* tests in an animal model performed before the graft implantation in the patient described in the 2008 Lancet paper. The evidence for this comes from Professor Anthony Hollander, who is an author of both the 2008 Lancet paper and the paper by Asnaghi et al.

In relation to the speed of preparing the graft, Hollander wrote in an article for his university “I was having a pub lunch with my family when Martin [Birchall] rang me about this woman who needed a new windpipe. My first reaction was that it was crazy to think we could put together a plan to save her in just a few weeks. My second was that it was a chance to prove that what we had been saying

for so long was actually true – that you can use tissue engineering and adult stem cells to make a difference to patients’ lives.” (Bristol University, 1 April 2009)

In his chapter in the book “Contested Cells”, Hollander describes how in March 2008 Birchall asked him to help in preparation of the airway for transplantation into a patient in Barcelona who was “going to die”. (Hollander, 2010) In fact the patient who had the airway transplantation in June 2008 was not at risk of death, but Birchall’s false statement to Hollander echoes the false excuses given for breaching the Human Tissue (Quality and Safety for Human Application) Regulations 2007 when the airway was prepared for transplantation in Birchall’s laboratory in Bristol University. (Special Inquiry into Regenerative Medicine Research at UCL, 2017.) It should be a concern of Biomaterials that the authors did not reveal that they had broken the law in the UK in preparing the airway graft.

In the same book chapter, Hollander wrote that the trachea transplant had not been tested on animals prior to the operation in Barcelona. (Hollander, 2010) Hollander also wrote that the transplant should have been tested in an animal model before an airway was implanted in a patient, but that did not happen. He wrote the team did have some animal data (a bench test involving pig intestine) but what was done was significantly different from what was done to the patient in Barcelona who is described in the 2008 Lancet paper.

The breach of the Human Tissue (Quality and Safety for Human Application) Regulations 2007 when preparing the graft in Bristol University was not the only breach of regulations.

In the Methods section, sub-section 2.6 titled “Bioreactor cultivation of the trachea construct”, Asnaghi et al. wrote “Ethical permission was obtained from the Spanish Transplantation Authority and the Ethics Committee of the Hospital Clinic Barcelona”. In fact, the invasive procedures in Spain to harvest cells for the culture in Bristol occurred before ethics approvals were granted in Spain. Pieces of the patient’s nasal and bronchial epithelium that were to be used for “stem cell production” were received in Bristol University on 1 April 2008, which was before Barcelona Ethics Committee approval had been granted on 2 April 2008 and before the Catalan Transplant Organization (OCAT) authorized the procedure on 18 April 2008. (Castells, 4 May 2018. Bristol University FOI response 161007.)

The final paragraph of the Methods section of Asnaghi et al. describes imaging of the patient reported in the 2008 Lancet paper and the first sentence says “as previously reported” when referring to that now retracted Lancet publication. The use of a false and retracted paper as justification calls into question that entire paragraph in the paper by Asnaghi et al.

Finally there are concerns about some of the images in the paper by Asnaghi et al., because they have been used elsewhere by some of the same authors with entirely different claims about their provenance.

As shown below in image concerns number 1, Figure 9, in Asnaghi et al. is reported to show “Histology of graft biopsies taken by bronchoscopy **two months after implantation** in a patient.” Panels A and B in figure 9 in Asnaghi et al, also appear as panels 2b and 2a respectively in figure 2 of another paper in Biomaterials by Curcio et al. In Curcio et al. the second sentence of the results section states “Tracheal biopsies **before implantation** shows epithelial cells on the endoluminal surface (Fig. 2a) and chondrocytes on the external surface of the graft (Fig. 2b).” (The legend to the

figures also states these images were from biopsies “**before implantation**”). Because at least one and possibly both of these papers in Biomaterials has false provenances for these images and because some of the authors of the papers have been found to have repeatedly falsified publications, we believe that the paper by Asnaghi et al. and the paper by Curcio et al. should be retracted. (In this paragraph, words in bold are our emphasis.)

Turning to the paper by Curcio et al., it also makes false claims about the clinical outcome in the patient reported in the now retracted 2008 Lancet paper by Macchiarini et al. The first sentence of the introduction repeats the false claims that the airway transplantation had been successful “thereby avoiding the need to remove her left lung and for immunosuppression, and allowing her to lead a near normal life”. She did not lead a normal life because she had no improvement in lung function and required repeated stent implantations before eventually she had a left pneumonectomy. (Molins, 2019)

To add to concerns above about the images in the paper by Asnaghi et al., during a presentation by Macchiarini in 2013, a slide shows the same image as in panel 9A of Asnaghi et al. but the legend says that the tissue was obtained “Pre-implant”, which contrasts with the statement in Asnaghi et al. See image concerns number 2 below. The presentation is available on youtube (<https://www.youtube.com/watch?v=GH3GLqCIVY4>) and the image can be seen 27 minutes 20 seconds into the recording.

As a result of the large numbers of concerns about falsification in the paper by Asnaghi et al. we request that you retract it. We also believe that the paper by Curcio et al. should be retracted.

Yours sincerely

Professor Patricia Murray

Dr Peter Wilmschurst

References (We will supply copies of references that you are unable to obtain.)

Asnaghi MA et al. A double-chamber rotating bioreactor for the development of tissue-engineered hollow organs: From concept to clinical trial. *Biomaterials* 2009;30(29):5260-9.

Bristol University (1 April 2009). “Claudia’s Story”. <https://www.bristol.ac.uk/news/2009/6190.html>

Bristol University Freedom of information response 161007 FOIA.

Castells (4 May 2018). Letter from Prof Antoni Castells, Medical Director of Hospital Clinic Barcelona to Prof Patricia Murray dated 4 May 2018.

Castells (23 July 2018). Email from Prof Antoni Castells, Medical Director of Hospital Clinic Barcelona to Prof Patricia Murray dated 23 July 2018.

Curcio E, Macchiarini P, De Bartolo L (2010). Oxygen mass transfer in a human tissue-engineered trachea. *Biomaterials* 2010;31(19):5131-6. doi.org/10.1016/j.biomaterials.2010.03.013.

Elliott MJ, et al (2012). Stem-cell-based, tissue engineered tracheal replacement in a child: a 2-year follow-up study. Lancet 2012;380(9846):994–1000. doi:10.1016/S0140-6736(12)60737-5. [https://www.thelancet.com/journals/lancet/article/PIIS0140-6736\(12\)60737-5/fulltext](https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(12)60737-5/fulltext)

Gonfiotti A, et al (2014). The first tissue-engineered airway transplantation: 5-year follow-up results. Lancet 2014;383:238-44. [https://www.thelancet.com/journals/lancet/article/PIIS0140-6736\(13\)62033-4/fulltext](https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(13)62033-4/fulltext)

Hollander A (2010). A Case Study of Experimental Stem Cell Therapy and the Risks of Over-Regulation. In: Contested Cells: Global Perspectives on the Stem Cell Debate. Ed: Capps BJ. 2010. <https://doi.org/10.1142/p661>

Lancet (2023a). Retraction: Clinical transplantation of a tissue-engineered airway. 2023;402:1510. [https://www.thelancet.com/journals/lancet/article/PIIS0140-6736\(23\)02341-3/fulltext](https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(23)02341-3/fulltext)

Lancet (2023b). Retraction: The first tissue-engineered airway transplantation: 5-year follow-up results. [https://www.thelancet.com/journals/lancet/article/PIIS0140-6736\(23\)02340-1/fulltext](https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(23)02340-1/fulltext)

Macchiarini P, et al (2008). Clinical transplantation of a tissue-engineered airway. Lancet 2008;372:2023-30. [https://www.thelancet.com/journals/lancet/article/PIIS0140-6736\(08\)61598-6/fulltext](https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(08)61598-6/fulltext)

Molins L (2019). Patient follow-up after tissue-engineered airway transplantation. Lancet 2019;393(10176):1099.

Murray P, Wilmschurst P (2023). <https://drpeterwilmschurst.wordpress.com/2023/10/05/swedish-national-board-for-assessing-research-misconduct-confirms-that-research-which-the-lancet-refused-to-retract-is-fraudulent/>

Schneider L, Murray P, Lévy R, Wilmschurst P. Time to retract Lancet paper on tissue engineered trachea transplants. BMJ2022;376:o498. doi: 10.1136/bmj.o498

Special Inquiry into Regenerative Medicine Research at UCL (29 September 2017.)

Image concerns

1. Duplicated images described differently in Asnaghi et al and Curcio et al.

Fig, 9A, 9B from Asnaghi et al (Biomaterials 2009)

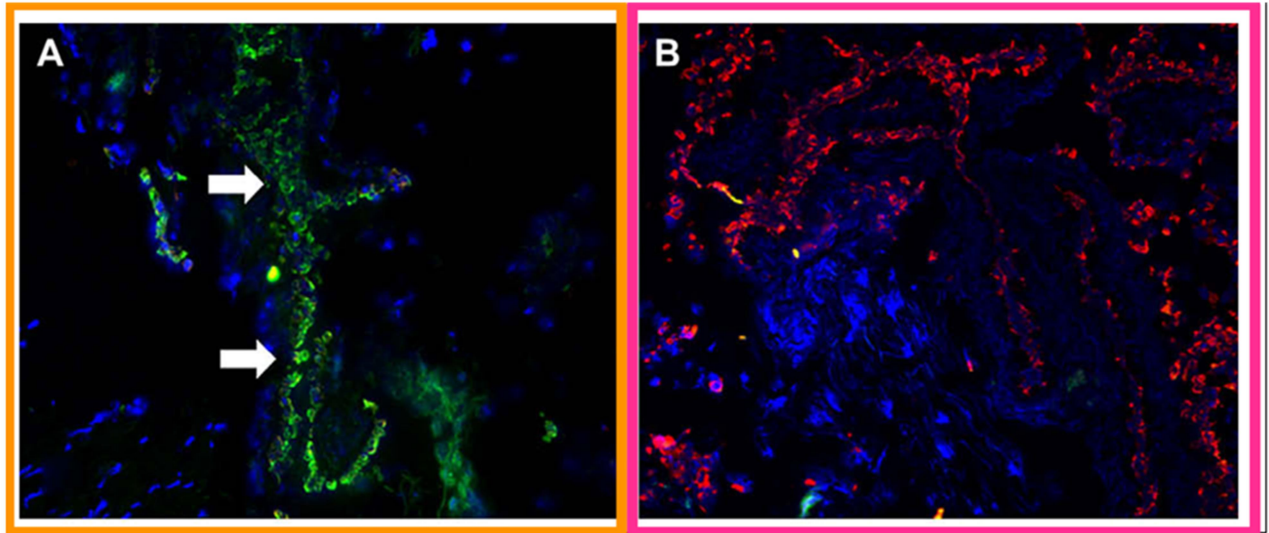
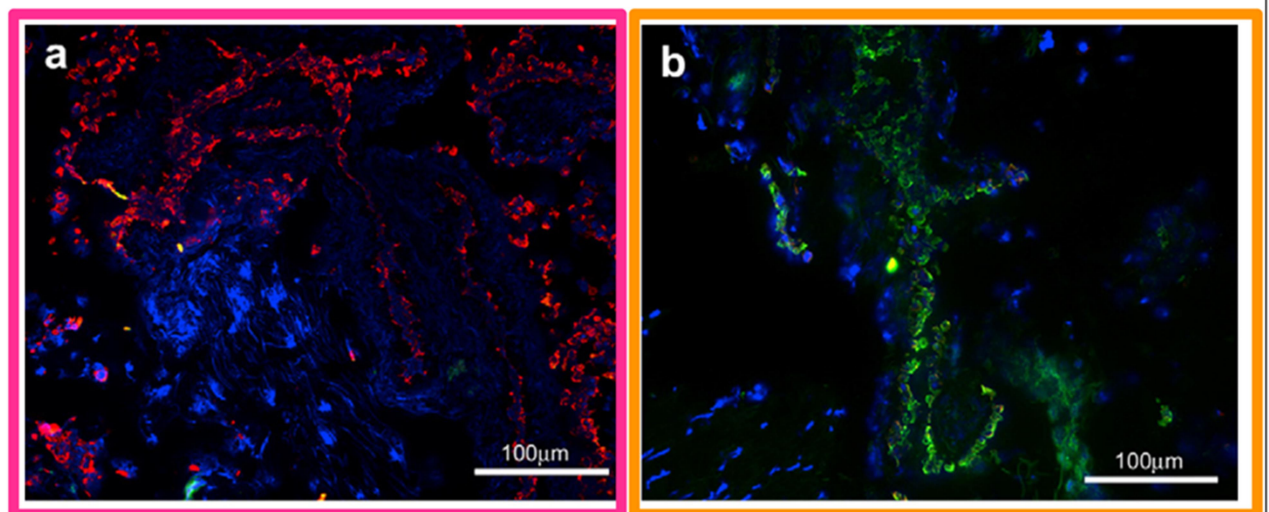


Fig. 9. Histology of graft biopsies taken by bronchoscopy two months after implantation in a patient.

Fig, 2A, 2B from Curcio et al (Biomaterials 2010)



and post (4 days) implant are shown in Fig. 2. Tracheal biopsy before implantation shows epithelial cells on the endoluminal surface (Fig. 2a) and chondrocytes on the external surface of the graft (Fig. 2b). Four days after implantation, all stem-cell-derived

2. Duplicated images described differently in Asnaghi et al and a Macchiarini presentation

Macchiarini presentation from 2013 (27min and 20 sec)



Fig. 9A, 9B from Asnaghi et al (Biomaterials 2009)

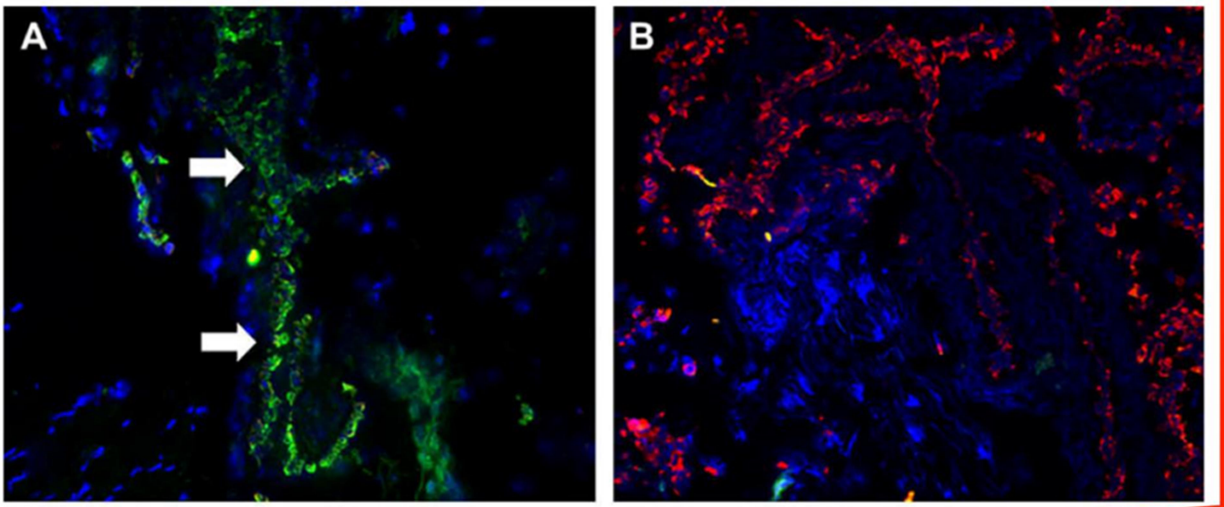


Fig. 9. Histology of graft biopsies taken by bronchoscopy **two months after implantation** in a patient. Superficial section (A)