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ESSAY

The deadly legacy of a stem cell charlatan

Paolo Macchiarini misled the world over his breakthroughs in regenerative medicine, but why did most of the institutions that supported him bear no responsibility for hosting a rogue stem cell surgeon? It's time for them to launch full and independent investigations, argue John Rasko and Carl Power

John E J Rasko, Carl Power

By 2008 it looked like a medical revolution was under way. Before us lay a new world, where any injured organ could be replaced with one custom-made in the laboratory. Leading us there was the charismatic Italian surgeon Paolo Macchiarini, who'd begun replacing damaged windpipes with tissue engineered ones. Each was made of a scaffold and seeded with the patients' own stem cells, which were meant to turn it into a living, functioning organ. The era of "regenerative medicine" was upon us.

But early 2016 woke us from this dream. Swedish television broadcast *Experimenten*, a blistering three part investigation into Macchiarini,[1] exposing him as a charlatan whose engineered windpipes did more harm than good, something he'd lied about for years. The scandal ruined his career and shook his Swedish employer, the Karolinska Institute, to its very foundations.[2] Home to the Nobel Prize in medicine, this illustrious university was dubbed by some as the "Chernobyl of ethics."

The Karolinska later found Macchiarini guilty of scientific misconduct and called for several of his articles to be retracted.[3] Many commentators expected that he would finish his career behind bars for the deaths of his three Karolinska patients, but that hasn't happened. After years of delay a Swedish court acquitted Macchiarini of five of the six charges against him, convicting him of harming just one person through negligence. The punishment? A suspended sentence of two years' probation. Macchiarini's lawyer was so pleased he dubbed it a "five-sixths victory." Not that the case is closed. Both sides have lodged appeals, prosecutors demanding jail time, Macchiarini full acquittal. The new trial is currently under way. Whatever the outcome, it won't save Macchiarini's scientific reputation. The Karolinska's verdict will stand.

Avoiding a scandal

With Macchiarini's career as a stem cell superstar ended, it's tempting to draw a line under the whole affair. But a big awkward question remains: why was the scandal mostly confined to Stockholm? After all, Macchiarini implanted laboratory built windpipes into only three people there; he apparently did the same to another 17 elsewhere, including hospitals in Spain, Italy, Russia, the UK, and the US.[4] Almost all these people are now dead and, so far as we know, none of the survivors got what they'd surely hoped for: a regenerated windpipe. Yet, to our knowledge, only the Karolinska has publicly admitted that, while there, Macchiarini engaged in scientific fraud and unethical human experimentation.

A hardened optimist might assume that Macchiarini committed his worst sins at the Karolinska. But that's not the picture *Experimenten* painted. It suggested that Macchiarini behaved much the same wherever he went. Were the Swedish reporters right about him at Karolinska but wrong about him elsewhere? Perhaps. But we think there is a more plausible explanation: the other institutions that hosted Macchiarini managed to keep a lid on his misconduct better than Karolinska did.

Like any big organisations, universities and hospitals are jealous of their reputations and, for that reason, prone to hide their dirty laundry. That's certainly what the Karolinska did. For years its vice chancellor, Anders Hamsten, tried his best to quash complaints raised by four of Macchiarini's own colleagues. He might have succeeded had they not told their story to the reporters behind *Experimenten* and had this exposé not sparked public outrage. It was the combined efforts of whistleblowers, journalists, and the public that compelled the Karolinska to come clean. Perhaps the scandal didn't spread beyond Stockholm because this combination of forces didn't occur elsewhere.

Outside Sweden, Macchiarini has faced criminal charges only in Italy. These arose from his time at Careggi University Hospital, Florence, 2010-12, but had nothing to do with the windpipe replacements he carried out there, all of which failed miserably. Instead Careggi accused him of administrative misbehaviour, including forgery and abuse of office. After nine years of court cases and appeals, Macchiarini was cleared of those charges.

Apart from the Karolinska, only University College London has shown much concern about Macchiarini's engineered airways. In 2017 it held a special inquiry into the matter that found that some mistakes had been made, but nothing major.[5] UCL couldn't have asked for a better outcome—especially as it put some distance between UCL's head of regenerative medicine, Martin Birchall, and his former collaborator Macchiarini.

Birchall and Macchiarini had shared the glory for creating the world's first tissue engineered airways. These were made of real windpipes, cut from cadavers and chemically stripped of all cells, leaving a scaffold

ready to be repopulated with the patient's own stem cells. After the pair parted company, in 2011, Birchall (mostly) stuck with this method, while Macchiarini developed an alternative: plastic scaffolds, made to order. With Macchiarini's downfall, his plastic airways lost all credibility. Doubt also spread to the cadaver derived windpipes, but their reputation was to some extent rescued by UCL's special inquiry, which found no fault with the work of Birchall and his team.

But the inquiry lacked the investigative grunt needed to find much fault. Its own report hints at the problem: "The Inquiry team are not experts in airway transplantation." Apparently, they didn't need such expertise because they were "focused principally on the governance and regulatory approval of cases." A very narrow scope indeed, one bound to miss the bleeding heart of the matter. Surely the focus should have been on whether patients were properly cared for and their cases accurately reported.

Some of the issues and evidence that the special inquiry overlooked have come to light in the media under headlines such as "UK teen dies after stem cell windpipe transplant" and "'Cover-up' over UCL stem cell deaths."[6 7] These stories raised serious questions about the treatment of patients by UCL and its clinical partner, Great Ormond Street Hospital. For instance, was the windpipe replacement given to 15 year old Shauna Davison in 2012 really justified on compassionate grounds? Why wasn't she and her family told about the death of another UCL patient, Keziah Shorten, who'd received a similar transplant? Why was Shauna's new airway frozen and thawed before surgery, something bound to weaken it? And why wasn't a tubular stent used to ensure it stayed open?

Not only was Shauna's treatment questionable, her case was misreported in journal articles, grant applications, clinical trial approvals, patient information brochures, and other official documents. In some of these, her transplant was described as a "success," with her death attributed to "unknown" or "unrelated" causes. In fact, she died two weeks after the operation when her new airway collapsed.[8]

This is just a sample of what UCL's investigators didn't uncover. Who knows what they'd have found had they looked more closely.

Success stories?

Birchall and his UCL colleagues continue to believe in Macchiarini's early achievements. They insist that cadaver derived scaffolds seeded with stem cells really work. Occasionally. Enough to establish "proof of concept." But let's look at this proof.

In the scientific literature there remain only two big success stories: that of Claudia Castillo, the first person to receive a tissue engineered airway (Barcelona, 2008), and Ciaran Finn-Lynch, the first child to receive one (London, 2010). These were Macchiarini's first breakthroughs in regenerative medicine, both made in collaboration with Birchall, and both reported in the *Lancet*.[9 10] Macchiarini was the main author of the first, Birchall of the second.

According to these articles, Claudia and Ciaran were both doing well at the time of publication, their own stem cells busily turning their transplants into living, functioning airways. The truth, however, was rather different.

A couple of years before its special inquiry, UCL held an internal investigation into Ciaran's case, after an external complaint from one of Macchiarini's critics. The investigation found that Birchall's paper downplayed the importance of a stent used to keep the new airway open and overstated the contribution of stem cells to tissue regeneration. The investigators said that "none of the evidence presented by Professor Birchall . . . demonstrate[s] that the addition of stem cells . . . played any therapeutic role." In short, there was no proof of a breakthrough in regenerative medicine, a conclusion shared by others.[11] Although UCL found a "misleading element" in Birchall's paper, it put this down to error rather than deliberate fraud and decided to deal with it through "education and training." It was all done on the quiet. UCL didn't make its ruling public or ask the *Lancet* to correct the paper, much less retract it.

The misrepresentation of Claudia's transplant is even more egregious. Here is the key outcome of Macchiarini's 2008 *Lancet* paper: "The graft immediately provided the recipient with a functional airway, improved her quality of life, and had a normal appearance and mechanical properties at 4 months." However, the Hospital Clinic Barcelona has an entirely different story. In 2018, its medical director informed the *Lancet* that Claudia's new airway collapsed three weeks after her operation, needing a stent installed—the first of many—to keep it open. This was confirmed the following year by the hospital's head of thoracic surgery in a letter published by the *Lancet*.[12] The letter also revealed that Claudia struggled with her transplant for eight years. As it replaced only the left branch of her airway, she was able to survive its failure. It was finally removed in 2016 along with her left lung.

A stented windpipe cannot possibly look and act like a normal one, which means that the success that Macchiarini claimed in 2008 was bogus. All this is well known to the *Lancet* and the Hospital Clinic Barcelona, yet neither seems willing to draw the obvious conclusion: Macchiarini lied.

The *Lancet* has long resisted calls to retract Macchiarini's 2008 paper, arguing that the Hospital Clinic Barcelona was best placed to investigate misconduct.[13] It's true enough that if the hospital requested a retraction the *Lancet* would be likely to oblige, as it did when the Karolinska asked it to withdraw two other articles by Macchiarini. Such requests are hard to deny. (That said, for five years the journal *Respiration* refused to heed the Karolinska's recommendation that another Macchiarini paper be retracted. It only recently complied.[14])

Does this let the *Lancet* off the hook? Not according to the authors of an open letter published last year in *The BMJ*.[15] In their view the *Lancet*'s inaction shows that, like the hospital, it prefers to protect its reputation rather than denounce scientific fraud.

Recently the *Lancet* made a minimal concession to its critics by publishing "expressions of concern" for Macchiarini's 2008 paper, along with its five year follow-up.[16] Indeed, this was so minimal that the reasons for concern aren't even mentioned, leaving readers to puzzle it out for themselves.

Deadly legacy

Millions of research dollars have been spent trying to build on Macchiarini's bogus breakthroughs. Millions more might be spent if the scientific record is not set straight. The Macchiarini scandal forced Birchall and his colleagues to abandon three clinical trials, two in the UK (together worth almost £5m) and one Europe-wide (worth €6.8m). But some of Birchall's associates have new plans and new funding to pursue their work on tissue engineered airways.

More important than wasted money is wasted life. The "success" of Claudia's and Ciaran's transplants justified giving other patients the same procedure, leading to the deaths of several, such as Shauna Davison and Keziah Shorten.[8] Left unchallenged, Macchiarini's legacy remains a deadly one.

We've all heard of dodgy clinics offering unproved stem cell therapies to desperately ill people who are unable to wait for mainstream medicine to provide a cure. Macchiarini's case suggests that some of the world's best hospitals and research institutes have done something similar.

We've named just a few of the institutions where Macchiarini performed his windpipe replacements. There's every reason to think that, like the Karolinska, they each betrayed the trust of their patients along with that of the general public. To regain that trust they should undertake a full and independent investigation of Macchiarini and his associates. As the Karolinska was forced to do years ago.

Right of reply: responses received by *The BMJ*

The BMJ offered institutions and individuals named in this Essay the chance to respond to the allegations made against them. The edited and shortened responses are given below. The full, unedited responses are available as a PDF in Related Content.

Martin Birchall

University College London responded on Birchall's behalf: "As part of our research misconduct process, two UCL screening panels (2015, 2018)) carefully considered the allegations against Professor Martin Birchall. Both screening panels, on the basis of evidence provided, concluded that there was a lack of intent to mislead by Professor Birchall."

Anders Hamsten

Declined to comment.

Careggi University Hospital (Florence) press office

"Macchiarini left Careggi University Hospital (CUH) in 2012 following accusations of advising some patients to undergo private surgery, which is illegal for doctors in the Italian national health service; he was subsequently acquitted in 2021. At CUH PM [Paolo Macchiarini] performed five compassionate use trachea transplantations on highly complex patients, obtaining ethics committee approval and informed consent from each patient. The responsible governmental authority (National Transplant Centre) also approved these procedures.

"These surgeries were locally and nationally approved as compassionate treatment and took place before the research protocol was approved in October 2011.

"Since PM's termination, CUH has fully cooperated with other institutional bodies to provide all the requested information regarding clinical and legal matters."

Hospital Clinic Barcelona

Antoni Castells and Laureano Molins responded: "It is unfair to state that our hospital avoided denouncing PM's paper to protect our reputation.

"Since 2018 we have been collaborating with all authorities, committees, and scientific bodies regarding the *Lancet* 2008 article and PM's research activities in Barcelona. Furthermore, in 2019 Dr Molins reported the patient's long term follow-up, demonstrating that tissue engineered airway transplantation was unsuccessful. These facts confirm that our hospital has always acted properly, transparently, and without hiding any data.

"Our hospital appointed an ad hoc internal commission in 2016 to review PM's research activities in Barcelona. Additional clinical data to those previously reported by PM were included in Dr Molins's letter. Although we informed the *Lancet* editor that it was necessary to place a stent because of graft collapse three weeks after transplantation, it is important to point out that this information arose from colleagues who worked with PM in 2008, but unfortunately we have not been able to find such procedure documented in the patient's medical record. In fact, as it was communicated to the Swedish National Board for the Assessment of Research Misconduct, a bronchoscopy indeed demonstrated stenosis of the left bronchus three weeks after transplantation, but the first documented stent was the one placed in the transplanted bronchus in October 2008 (four months after transplantation)."

Great Ormond Street Hospital (GOSH) press office

"A special inquiry in 2017 found no concerns about GOSH or its staff and described our processes to consider compassionate or exceptional use of treatments as robust. The inquiry also considered that the Clinical Ethics Service 24 (CES) team based at GOSH was a highly professional and well structured team with clear lines of reporting and standards for operating.

"We are committed to openness and transparency at GOSH and have published the results of Shauna's treatment."[17]

University College London press office

"UCL and its staff have been open and transparent. In 2016 UCL commissioned an independent special inquiry[5] which carried out a thorough investigation of the involvement of UCL and its personnel in regenerative medicine research but with particular focus on the field of tracheal and large airway tissue engineering.

"The purpose was to explore the governance framework and authorisation of programmes particularly in relation to the manufacture of medical devices (including cellularised cadaveric grafts) in respect of the UCL airway transplantation programme. Issues that related to clinical care and compassionate use are matters for NHS trusts, along with the General Medical Council and other regulatory bodies, and were beyond the scope of the inquiry. Despite this, we communicated with NHS partners and recommended they check and review their compassionate use procedures.

"The inquiry made a series of recommendations, and UCL has acted on all of them.

"UCL takes the integrity of its research very seriously, and we are always seeking to improve our processes and raise our standards. Any research undertaken at UCL is required to conform to the highest legal, ethical, and regulatory standards, and we will not hesitate to take the necessary action, if and when this falls short."

Karolinska Institute press office

"KI has not conducted investigations regarding the operations performed by PM. The operations were performed in PM's role as a physician employed by Karolinska University Hospital."

"KI has conducted investigations regarding PM's research, as a researcher employed by KI, reported in scientific papers after the operations. KI found PM responsible for scientific misconduct in the published papers."

Lancet Group

A press officer said: "The *Lancet* journals take issues relating to scientific misconduct extremely seriously and follow best practice guidelines set by the Committee on Publication Ethics (COPE). In accordance with best practice, authors' institutions are best placed to lead independent investigations into scientific misconduct, and during the course of this complex case the *Lancet* has referred all allegations it has received to the authors' respective institutions, including the Hospital Clinic Barcelona and UCL. The outcomes of the independent investigations we have received to date have not concluded that a retraction of the 2008 paper is warranted. We continue to monitor this case closely.

"In 2019 the *Lancet* published a follow-up report[12] of the patient whose procedure was outlined in the 2008 paper, as well as a correction to the original paper.[18] In February 2023, following advice from COPE, the *Lancet* published an Expression of Concern on both the original paper and the follow-up report."[16 19]

Paolo Macchiarini

The BMJ tried to—but ultimately could not—obtain current contact information for PM.

Biographies

John Rasko is a clinical haematologist, pathologist, and scientist whose research focuses on gene and stem cell therapy and molecular biology. He heads the Department of Cell and Molecular Therapies at Royal Prince Alfred Hospital, Sydney, and the Centenary Institute's gene and stem cell therapy programme and is a professor of medicine at the University of Sydney. Carl Power is a freelance writer and editorial research officer at the Centenary Institute. Together they write about the history of medicine. A fuller account of the Macchiarini scandal can be found in their book *Flesh Made New: The Unnatural History and Broken Promise of Stem Cells* (https://www.harpercollins.com.au/9780733340147/flesh-made-new).

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Competing interests: We have read and understood BMJ's policies on declaration of interests and declare: John E J Rasko is an employee of Sydney Local Health District at Royal Prince Alfred Hospital as senior staff specialist in the capacity of head of Department of Cell and Molecular Therapies. He is seconded as a programme head at the Centenary Institute (honorary). He is responsible for undertaking investigator initiated and pharma sponsored clinical trials of immunotherapies, cellular therapies, and gene therapies. He does voluntary service for the Australian Cancer Research Scientific Advisory Board (not for profit); the board of directors/advisory committee for Cure the Future Foundation (not for profit); Medical Scientific Advisory Board, Rare Voices Australia (not for profit); New Directions in Leukaemia Research Board of Directors (not for profit); and the data safety monitoring committee for investigator initiated aplastic anaemia trial (DIAAMOND Ava). Paid committees: Human Research Ethics Committee, Genea; chair, Gene Technology Technical Advisory Committee, Office of the Gene Technology Regulator, Australian Government. He holds shares in Rarecyte, Woke Pharmaceutical, and is co-founder of AAVec Bio, improving human gene therapies. Supply of material (MTA) or consultancy or honoraria with Rarecyte, Gilead, Roche, Novartis, Bluebird Bio, SPARK therapeutics, Cynata, and Pfizer. Fellowships and research or education grants include NHMRC, NSWCC, CINSW, Therapeutic Innovation Australia, and philanthropic foundations. Planned roles in next 12 months: non-executive director, Woke Pharmaceuticals (non-listed company); non-executive director, Kennerton Capital (non-listed company).

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