

The New York Times

He Promised to Restore Damaged Hearts. Harvard Says His Lab Fabricated Research.

By **Gina Kolata**

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For Dr. Piero Anversa, the fall from scientific grace has been long, and the landing hard.

Researchers worldwide once hailed his research as revolutionary, promising the seemingly impossible: a way to grow new heart cells to replace those lost in heart attacks and heart failure, leading killers in the United States.

But Harvard Medical School and Brigham and Women's Hospital in Boston, his former employers, this month accused Dr. Anversa and his laboratory of extensive scientific malpractice. More than 30 research studies produced over more than a decade contain falsified or fabricated data, officials concluded, and should be retracted. Last year the hospital paid a \$10 million settlement to the federal government after the Department of Justice alleged that Dr. Anversa and two members of his team were responsible for fraudulently obtaining research funding from the National Institutes of Health.

"The number of papers is extraordinary," said Dr. Jeffrey Flier, until 2016 the dean of Harvard Medical School. "I can't recall another case like this."

Dr. Anversa's story has laid bare some of the hazards of modern medical research: the temptation to embrace a promising new theory, the reluctance to heed contrary evidence and the institutional barriers to promptly stopping malfeasance. Even after three independent researchers were unable to reproduce his findings in 2004, Harvard hired him in 2007 and his lab continued to churn out studies upholding his theory.

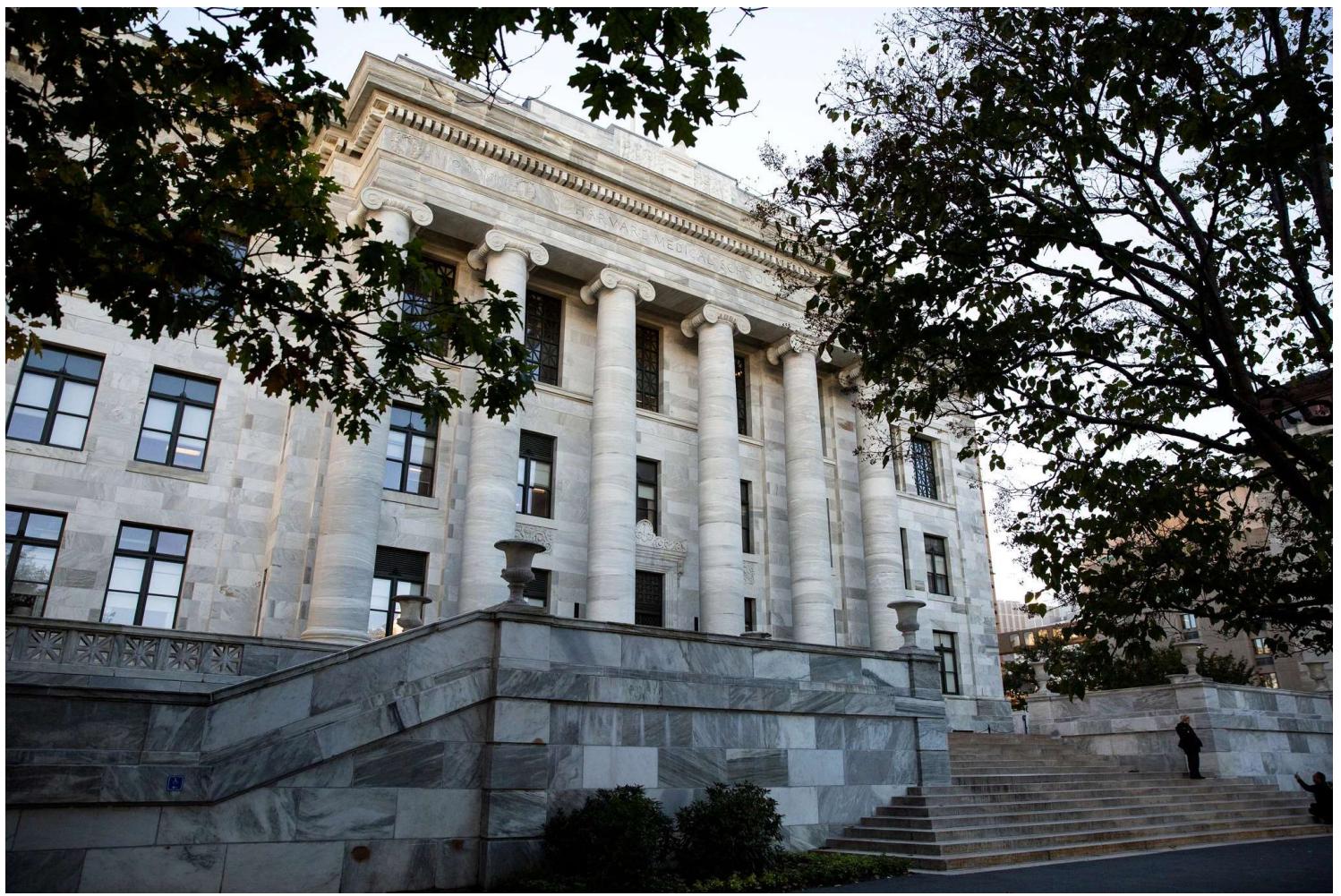
"Science at this level is like a battleship, and it's really hard to turn it around," said Dr. Jonathan Moreno, a professor of bioethics at the University of Pennsylvania. "People get emotionally invested, financially invested, professionally invested."

Dr. Anversa, 80, now lives in his son's elegant apartment on the Upper East Side. It has high ceilings, Oriental rugs and a marble fireplace, but little evidence of the life he once led at the forefront of science, save for a framed 2001 front page article in The New York Times about his work.

He is slightly stooped and walks gingerly — hip trouble, he said. The stress has made sleep difficult, but he adheres to a routine: in bed by 9 p.m., up before dawn. He spends most days writing grant proposals that he hopes to submit should he ever land another job.

He insists that he did nothing wrong, that his stunning results are real, and that he was betrayed by a rogue colleague who altered data in paper after paper. On a recent afternoon, he sat on the sofa, pecking on his laptop with two fingers, calling up emails from people who had supported him.

"I am an 80-year-old man who has worked all his life in an attempt to have an impact on heart failure," Dr. Anversa said, his voice rising. "Now I am isolated."



Harvard's investigation of Dr. Anversa's laboratory took five years to complete and ended with the university saying 31 papers it produced should be retracted. Kayana Szymczak for The New York Times

His is a particularly acrid cautionary tale of scientific hubris.

"It's kind of been the longest-running version of 'Mean Girls,'" said Dr. Richard T. Lee, a professor of stem cell and regenerative biology at Harvard. "Except most of the characters were adult men."

"It was like he grew the heart back"

At a meeting of the American Heart Association in 2000, Dr. Anversa, then a professor at New York Medical College in Valhalla, strode to the podium and delivered a dramatic announcement: In mice, bone marrow contained stem cells that could be used to regenerate heart muscle.

He was suggesting that a basic tenet of cardiology — that the human heart cannot be regenerated — was wrong. If he was correct, he had discovered hope for millions of heart patients.

The presentation was replete with colorful slides of small and underdeveloped cells — new heart muscle cells maturing, he said.

“It was like he grew the heart back,” recalled Dr. Charles Murry, director of the Institute for Stem Cell and Regenerative Medicine at the University of Washington in Seattle.

The hypothesis, widely held at the time, was that the body had stem cells — immature primitive cells — that in the right environment could turn into any other cells in the body. Put a stem cell into the liver, scientists hoped, and it would turn into a liver cell. Put a stem cell into the heart, Dr. Anversa said, and it really could turn into a heart cell. He and his colleagues published the research in 2001 in *Nature*.

“Unsurprisingly, companies started popping up and taking bone marrow cells and injecting them into peoples’ hearts,” Dr. Murry said. “The thing goes viral worldwide. It was freaking unbelievable.”

Dr. Anversa’s group later reported something even more astounding. Bone marrow was known to have stem cells that can grow into blood cells. But no one ever thought the heart had stem cells. Yet he reported that it did and that those heart stem cells can be removed, grown in petri dishes, and injected back into the heart to regenerate the muscle after a heart attack.

The virtuoso defense

From the very beginning, there were scientists who doubted Dr. Anversa’s claims. He had not been the first to wonder if stem cells from bone marrow could be transformed into heart cells. Dr. Murry and Loren Field, a professor of medicine at Indiana University School of Medicine, had tried the experiment in the late 1990s. They saw no new heart cells and moved on, never publishing those data.

They sat together in the audience when Dr. Anversa presented his findings in 2000. Dr. Murry turned to Dr. Field and asked, “How the hell did we miss this?” They returned to their labs to redo the experiment. But again, they could not make the process yield

new heart cells.



Dr. Anversa with Jan Kajstura, the balding man in the back, Dr. Annarosa Leri, fourth from right, and others at New York Medical College in Valhalla, N.Y., in 2001. Susan B. Markisz

Their paper was published in the journal *Nature* in 2004, along with another study by Irving Weissman, director of the Institute for Stem Cell Biology and Regenerative Medicine at Stanford University. He, too, failed to replicate Dr. Anversa's results. That same year, Dr. Bernd Fleischmann, a professor of physiology at the University of Bonn, reported in *Nature Medicine* that he had been unable to replicate Dr. Anversa's results. The Times covered the questioning of Dr. Anversa's findings in a 2005 article, "Tracking the Uncertain Science of Growing Heart Cells."

Other labs reported seeing a few heart cells generated, but nothing close to what Dr. Anversa reported.

"Those incremental results kept hope alive," Dr. Field said.

At one scientific meeting, Dr. Murry said he questioned Dr. Anversa's findings. On a screen, he put up a slide of heart cells from his lab and, next to it, a slide of heart cells from Dr. Anversa's laboratory. Then he put up a photoshopped image of his lab's cells.

They looked just like the image of the cells from Dr. Anversa's lab.

In the question-and-answer period, Dr. Anversa's colleague and collaborator, Dr. Bernardo Nadal-Ginard, took the microphone to offer a withering riposte to Dr. Murry

"I love Plácido Domingo," Dr. Nadal-Ginard recalled saying. "I wish I could sing like Plácido Domingo. I try and try to sing like Plácido Domingo, and I fail."

"You," he told Dr. Murry, "are not Plácido Domingo."

It became known as the virtuoso defense.

Harvard investigates

As Dr. Anversa's fame grew, along with grants, he earned perhaps the greatest of scientific plaudits in 2007: a professorship at Harvard Medical School and a position at its teaching hospital, Brigham and Women's, as director of its Center for Regenerative Medicine.

Officials at the hospital and university declined to discuss his hiring. In a statement, the hospital said: "Breakthrough science can often initially be perceived as controversial. Controversy regarding one's research findings is not enough to rule out an otherwise qualified individual."

In 2012 a new controversy emerged.

A key member of Dr. Anversa's team, Dr. Jan Kajstura, was the first author on a paper in Circulation that seemed to offer final proof that the heart could regenerate. He worked with a scientist at Lawrence Livermore National Laboratory, Bruce Buchholz, who measured carbon isotope levels in 36 hearts from people ranging in age from 2 to 78. Because of nuclear testing done in the 1950s, older people were exposed to more radioactive isotopes than younger people.

If the body cannot produce new heart cells, the amounts of radioactive carbon should have been higher in the heart cells of older people. But in that paper, Dr. Kajstura and his colleagues reported, older hearts did not have more radioactive carbon. Heart cells are constantly being replaced, they concluded.

When Dr. Buchholz read the paper, he was stunned. He had provided data on radioactivity levels to Dr. Kajstura, but the data published in the study had been altered to make the old hearts look the same as the young ones. Dr. Buchholz said in an interview that science depends on trust among collaborators, that he had implicitly trusted Dr. Anversa's group with his data. Now that trust was broken.



A banner from the University of Miami Hospital advertising the use of stem cells to regenerate hearts.
Dr. Nanette Bishopric

"I learned an unpleasant lesson," he said.

He called Dr. Anversa and demanded that the paper be retracted. If data had been changed, Dr. Anversa recalled telling him, it had not been with his knowledge. "I said, 'Bruce, you are saying Jan is a fraud,'" Dr. Anversa said in an interview.

Dr. Anversa said he confronted Dr. Kajstura, who did the analysis again. Dr. Anversa said he was reassured by the revised work and believed that the findings in the paper were still correct. But the hospital retracted the paper in 2014.

Dr. Kajstura did not respond to repeated messages left for him over the past week at his wife's office and with his daughter and his daughter-in-law. He did not seem to be home in Rochester, N.Y., last week, and a note was left there requesting an interview.

Even before the paper was officially retracted, Dr. Anversa's and Dr. Kajstura's careers began unraveling. On Jan. 10, 2013, investigators at Harvard Medical School and Brigham and Women's Hospital raided Dr. Anversa's laboratory, Dr. Anversa said, seizing computers and scientific notes. He hired a team of lawyers.

"These sudden visits with sequestration of computers and notebooks happened repeatedly over the years, making the working environment impossible," he wrote in an email.

Dr. Kajstura left the laboratory in 2013, Dr. Anversa said. In a statement, lawyers for Dr. Anversa and his colleague, Dr. Annarosa Leri, blamed Dr. Kajstura for digitally manipulating images published in scientific journals.

"Neither Dr. Anversa nor Dr. Leri ever altered or changed images or data at any time," the statement said. The researchers "stand by the scientific findings in their papers, including the existence and potential therapeutic benefits of cardiac stem cells."

A \$10 million settlement

Even as Harvard's investigation continued, many researchers clung to the cardiac stem cell hypothesis.

"This was a perfect storm of ego, wishful thinking and lack of accountability," said Dr. Jill C. Tardiff, a professor of medicine at the University of Arizona, and a heart-muscle cell researcher.

In 2014, yet another researcher, Jeffery D. Molkentin, a professor at the Cincinnati Children's Hospital Medical Center Heart Institute, tried to replicate Dr. Anversa's findings. Dr. Molkentin had spent years finding a way to trace the fate of what Dr. Anversa called cardiac stem cells when they were injected into the heart. Did they become heart cells?



Brigham and Women's Hospital and Partners Healthcare agreed to pay the federal government \$10 million in 2017 to settle allegations that Dr. Anversa and two of his colleagues fraudulently obtained research funding from the National Institutes of Health. Kayana Szymczak for The New York Times

"The answer was no," Dr. Molkentin said in an interview. He published his results in *Nature*. Two independent labs confirmed them.

In 2015, Dr. Anversa was forced out at Harvard. He moved to research posts in Switzerland and Italy, but was fired from both, he said, as the controversy followed him overseas.

Last year, the Department of Justice announced that Brigham and Women's Hospital and Partners Healthcare, a health care system founded by the Brigham and another Harvard-affiliated hospital, would pay \$10 million to settle allegations that Dr. Anversa, Dr. Leri and Dr. Kajstura knew, or should have known, that their work included "improper protocols, invalid and inaccurately characterized cardiac stem cells, reckless or deliberately misleading record-keeping, and discrepancies and/or fabrications of data and images."

Despite the setbacks, the National Heart, Lung and Blood Institute, part of the National Institutes of Health, has been conducting a \$7.9 million clinical trial of cardiac stem cells that began in 2015. Denis Buxton, associate director of the division of cardiovascular sciences at the institute, said Dr. Anversa's work was a "catalyst" for the study, although the institute does not believe that heart stem cells can turn into heart muscle. Still, some research indicates that heart stem cells and certain bone marrow cells may help form new blood vessels and heart cells, Dr. Buxton said.

But the institute announced on Monday that it is pausing the trial to review its "scientific foundations."

A final verdict

This month, Dr. Anversa got Harvard's conclusive findings on his life's work. In an Oct. 3 letter that Dr. Anversa provided to The Times, officials at Harvard and its teaching hospital told him that he had "committed research misconduct" in eight papers, some published and others submitted for publication, as well as in a grant application. Although he was the lead author on many of the other papers that Harvard said must be retracted, the university said the evidence did not support his being responsible for the malfeasance in those cases. Harvard did not name the culprit or culprits in its letter to Dr. Anversa.

But the university said 31 scientific papers produced by Dr. Anversa's laboratories, going back to 2001, should be retracted. University and hospital officials notified each journal of their conclusions as well as the Office of Research Integrity at the Department of Health and Human Services, which can recommend that the federal government ban researchers from receiving federal funds. Anyone associated with Harvard or the hospital who gives Dr. Anversa a reference must also describe his misconduct.

Dr. Anversa insists that he is being unfairly punished for what he says were Dr. Kajstura's deceptions. "How could I be so stupid as not to realize that he was cheating?" Dr. Anversa said.

But other scientists say that as the head of the lab and a principal author on many papers, he must accept responsibility for the work even if he did not commit the fraud.

It did not surprise some in academia that the bold promises of the research persisted despite the contested evidence.

“There was an argument in the philosophy of science about whether there is such a thing as a ‘crucial experiment,’” said Dr. Moreno, the ethics professor, referring to a study that answers a question once and for all.

“It turns out there isn’t. People can see what they want to see.”

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