Never say die

With a history of public blunders, can Advanced Cell Technology make embryonic stem-cell therapies a reality?

BY CORIE LOK

"Oh crap, this really puts us in the spotlight!" thought Robert Lanza when he first heard the news. Advanced Cell Technology (ACT), the biotechnology company in Marlborough, Massachusetts, of which Lanza is chief scientific officer, had for more than a year been operating in the shadow of Geron, a rival company in Menlo Park, California. Geron was bigger and better funded than ACT, and it was the first company to be approved by the US Food and Drug Administration (FDA) to test a therapy in humans based on embryonic stem (ES) cells. ACT was second. But in November, Geron announced that it was halting its trial to focus instead on cancer drugs. And with the announcement, Lanza says, he felt the weight of the ES-cell field fall on his shoulders.

Lanza and his company have had plenty of experience in the spotlight, but the attention has not always been flattering. Since the late 1990s, ACT has gained a reputation as a renegade company, accused of overhyping results to raise attention and money. Critics say that the company has damaged the field more than once with its high-profile, controversial announcements, such as one describing the company's attempts to clone a human embryo[1] in 2001. ACT's actions — and the

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Robert Lanza has been a public face for Advanced Cell Technology's many ups and downs.

highly politicized nature of stem-cell research — scared off investors, leaving the company teetering on the verge of bankruptcy for most of the past decade.

But the scrappy biotech refused to die, in part because of Lanza's doggedness. ACT is now performing early-phase clinical trials testing the safety of implanting retinal cells derived from human ES cells into the eye to treat certain types of blindness.

Lanza says that this time, he aims to do things right: direct good science focused on treating disease, publish in reputable journals with rigorous peer-review processes and work with high-quality collaborators and clinical centres for its trials. "We're a different company now," says Lanza.

Not everyone is convinced. Even if positive results emerge from these trials, ACT will still face major challenges in getting an ES-cell-based therapy approved for wider use. And some in the field are sceptical about ACT's reformation. "Can you really trust a company that has a spotty record?" says Arthur Caplan, a bioethicist at the University of Pennsylvania in Philadelphia.

It's not just Lanza who has a stake in the answer. With Geron out of the game, ACT's success or failure will be important for a field looking to prove itself worthy of further research funding. "If the trials are positive, that would fundamentally transform the debate," says Christopher Thomas Scott, director of the Program on Stem Cells and Society at Stanford University in California.

PROBLEM CHILD

ACT began in the mid-1990s as an animal-cloning outfit owned by Avian Farms, a Maine-based poultry genetics company. ACT quickly shifted focus when Michael West — who founded Geron — became its chief executive in 1998. Human ES cells had just been isolated for the first time, and researchers were excited about their potential use in regenerative medicine.

But many were concerned that patients' immune systems would reject cells derived from unrelated embryos. To solve this, West proposed 'therapeutic cloning' — taking the nucleus out of a patient's cell, transferring it into an egg cell to create a cloned embryo, then using that embryo to derive patient-matched stem-cell lines.

In 1999, using money he had made at Geron, West bought ACT. Lanza, a physician who had spent the past 20 years working in academic research and biotech on organ and cell transplantation, was one of West's first recruits. The team moved quickly to try to make therapeutic cloning a reality.

If the American public had not yet heard of human cloning or ACT by the fall of 2001, it could hardly have missed the hype that began on 25 November that year. West appeared on *Meet the Press*, a nationally televised US political talk show, to discuss a paper, published that day, in which ACT scientists described the first cloning of a human embryo. "We've taken the first halting steps toward what we think is going to be a new area of medicine," West said.

West appeared on several other news shows in the following days. CNN and *US News and World Report* heralded the work as a breakthrough, and West and his team hailed the "dawn of a new age in medicine" in a report for *Scientific American* (now owned by Nature Publishing Group).

In the paper[1], published in the now-defunct online journal *e-biomed*, West, Lanza and their colleagues showed that they could pull a nucleus from a human egg cell, replace it with a whole adult ovarian cell and generate an embryo that divided into six cells. It then stopped growing, far short of the 100-cell blastocyst stage from which stem cells can be derived.

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The work pressed a political hot button. That summer, President George W. Bush had approved federal funding for human ES-cell research, but only for a small number of cell lines that had already been created. He also voiced staunch opposition to human cloning of any kind, and a bill to ban it had been advancing through the US Congress, much to the chagrin of researchers who saw promise in therapeutic cloning.

ACT's announcement stoked fears that scientists were trying to clone humans for reproductive purposes — and conflated reproductive cloning and human-embryonic-stem-cell research in many people's minds. "It gave critics plenty of ammunition to insist that if stem-cell research was funded, human reproductive cloning would be funded too," says Caplan. "It had a huge deleterious impact for years."

Scientists, meanwhile, dismissed the finding. The ACT team hadn't gained new insight into the human developmental process, says George Daley, a stem-cell researcher at Children's Hospital Boston in Massachusetts. "I was not in a position to defend the cloning that they were doing because it was ineffective in what they were trying to do," he says. "It was more for publicity than for science."

Jose Cibelli, who was first author on the paper and left ACT in 2002 for a faculty position at Michigan State University in East Lansing, says that in an ideal world he would have waited until the team could grow the embryos to the blastocyst stage before publishing the work. But he had heard rumours that other groups were pursuing the same goal, and he was worried about getting scooped. (A successful derivation of stem cells from a cloned human embryo was not reported until October 2011, and these stem cells had three sets of chromosomes rather than two[2].)

West says that he pushed ahead with publication in the interest of transparency. "It was our policy not to hide what we were doing and why," he says. "We wanted to be honest, accurate and open."

The announcement ended up hurting the company, however. ACT was trying to raise a needed round of venture-capital financing when the cloning news broke. The negative attention combined with the political uncertainty around stem-cell funding killed the deal, says Greg Bonfiglio, who was with Anthem Venture Partners of Santa Monica, California, at the time, and would have been the lead investor on that round.

SCRAPING BY

The disappearance of the venture funding sent ACT on a financial downward slide from which it would take nearly ten years to recover, says Bonfiglio, who has dealt with the company on several more occasions. Researchers at Geron, meanwhile, had successfully derived neurons from human embryonic stem cells[3] and were pursuing research that would eventually look to repair the damage caused by spinal-cord injuries, a possible use for embryonic stem cells that was much touted at the time. ACT was largely dismissed as a sideshow.

Lanza is now the longest-serving employee of the company. He says that a "tough childhood" in Stoughton, a town south of Boston, Massachusetts, helped him to develop a thick skin.

Unlike many Boston-area academics, Lanza has the 'R'-dropping accent of the region, most noticeable when he talks about one of his main preoccupations: Stargardt's disease. "Stahgahdt's" — as he says it — is one of the two types of degenerative blindness his company is targeting in its clinical trials. The other, the 'dry' form of age-related macular degeneration, is the most common cause of age-related blindness. Both diseases result from the death of retinal cells, a process that Lanza suspects can be slowed or even halted using stem-cell-derived replacements.

After the venture funding fell through, West sold ACT's animal-cloning division to generate revenue. By 2004, however, money had again started to run low. But Lanza and West had recently hired Irina Klimanskaya, who, as a researcher at Harvard University in Cambridge, Massachusetts, had helped to derive many of the institution's first human ES-cell lines and who had a knack for working with scant resources. At ACT, she began optimizing a protocol for transforming ES cells (derived from embryos donated through

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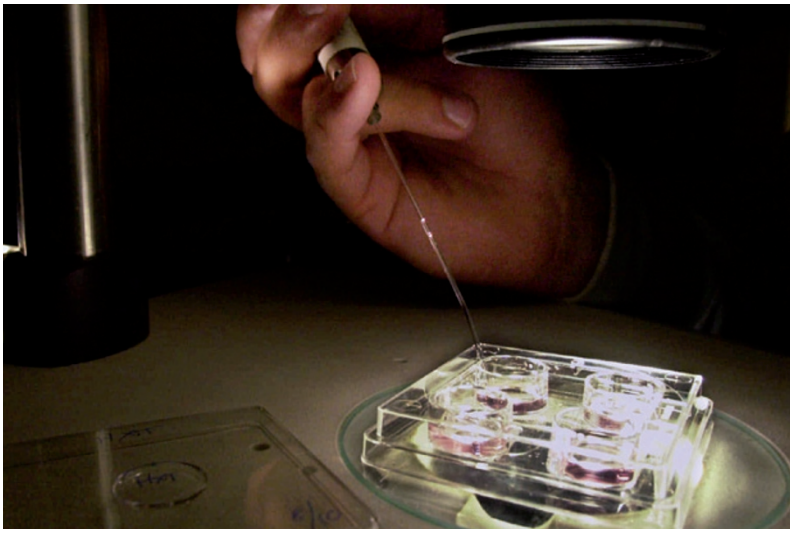
1998 ACT scientists and collaborators announce the successful generation of cloned transgenic cattle.



E. AMENDOLA/AP

2001 With a full media blitz, ACT publishes its efforts to clone a human embryo for the purpose of growing stem cells.

fertility clinics) into retinal pigmented epithelial (RPE) cells. These are lost in both Stargardt's and dry age-related macular degeneration[4].

Stopping vision loss didn't quite have the dramatic appeal of Geron's goal of reversing paralysis. But focusing on the eye may have been a wise decision, say experts.

"The eye is an ideal place to begin this type of experimental work," says Michael Young, an ophthalmology researcher at the Schepens Eye Research Institute in Boston. Surgeons already have protocols for injecting cells directly into the eye, and they can measure changes in the retina just by peering into it. The eye is relatively sealed off from the immune system compared with other parts of the body, which may reduce the risk of cell rejection.

Moreover, transplanted RPEs do not need to form synapses, or connections, with neurons, unlike other retinal cell types. "If cell-based therapy in the eye is going work, it's got to work with the RPEs," says Thomas Reh, a neurobiologist at the University of Washington in Seattle.

By 2004, Lanza and his team were ready to start testing the RPE cells in animals — but they were paralysed by a lack of money. The cells sat in a freezer for almost a year. Meanwhile, the company's phone service was turned off, purchases of basic lab supplies grew harder to justify and the skeleton crew of remaining scientists wondered week to week whether they would get paid.

Some left, but Klimanskaya opted to stay on. "I believe in the company, in the cells, in the technology and in my own skills," she says. "Why should I quit?"

Out of desperation, West agreed at the end of 2004 to take the company public to gain access to a new source of funding. But the legal, accounting and marketing costs of going public through an initial public offering (IPO) were far beyond the company's reach. Instead, in early 2005, ACT merged with Two Moons Kachinas, an obscure, Utah-based outfit that sold Native American dolls. Two Moons was essentially a 'shell' company, allowing ACT to take it over and become a publicly traded firm. This 'reverse merger' was much cheaper than an IPO, but the US$8 million it raised had more strings attached.

As part of the deal, investors required the company to name a new chief executive. "The issue with ACT at that time was never about the quality of the science team," says Bonfiglio, who led the deal. "The business skills were not resident on that team." The new chief executive, William Caldwell, had more than 30 years of experience in banking, transportation and telecommunications, but none in biotech.

OUT OF THE ASHES

With the infusion of cash, ACT went on a hiring spree. West, who became the company's president and chief scientific officer, moved to California and recruited several researchers in hope of starting a lab that could tap into funding from the San Francisco-based California Institute for Regenerative Medicine (CIRM), a $3-billion, state-backed fund for stem-cell research.

Meanwhile, Lanza built up his team in Massachusetts and forged ahead with the RPE transplantation studies in rats. In 2006, positive results began to materialize[5] and ACT opened its new headquarters, a 1,400-square-metre research facility in Alameda, California, which included a lab capable of growing cells according to the strict standards required for human trials.

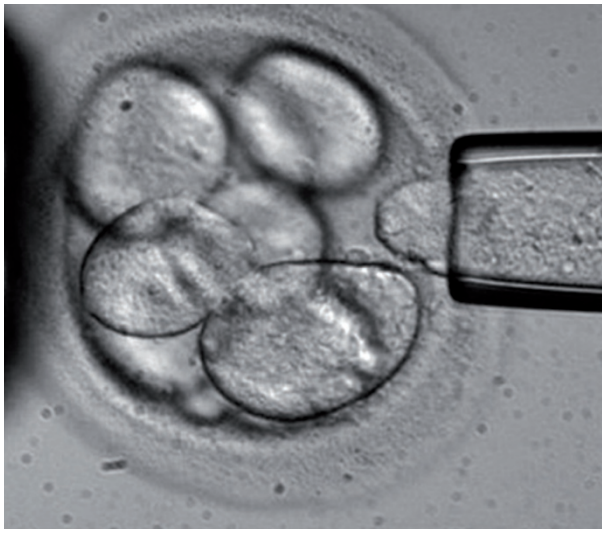
Just as optimism was running high, the company made another very public stumble. In August 2006, Lanza and his co-authors published a paper[6] in *Nature* showing that a single cell could be plucked from an 8–10-cell human embryo and grown into stem cells. Lanza wanted to show that it was possible to derive stem cells without destroying the embryo, to sidestep ethical concerns.

In fact, the embryos were destroyed in the experiments, but that had not been made clear in the original version of the paper, the press releases about it or in some of Lanza's press interviews. *Nature* issued two clarifications after its original press release, but many news organizations had already reported that the embryos were unharmed. When the truth became clear, critics pounced.

Opponents of ES-cell research saw the debacle as an attempt to mislead the public, and scientists criticized the method as impractical and still ethically problematic. Biopsying embryos puts them at risk, says Daley, so some will be lost.

Lanza says that the *Nature* paper was only meant to be a proof of principle and that the company soon perfected the technique so that embryos survived. But the episode reinforced perceptions that the company hyped its results, this time to boost its stock value. If that was the intent, the effect was short-lived. The increase in share price on the day of the announcement — from $0.42 to $1.83 — would be reversed in the weeks and months that followed.

Unable to raise enough money from conventional sources, Caldwell turned to last-resort financing. ACT borrowed cash from investors and then repaid them in shares on a monthly basis, using the lowest share price of the previous month. As that price dropped, ACT had to issue more and more shares, forcing the price down even further. Caldwell completed several rounds of this 'death-spiral financing' between 2005 and 2010 to keep Lanza's RPE research going, and the company sank further into debt.



ADVANCED CELL TECHNOLOGY/AP

2006 ACT scientists demonstrate a possible way to derive stem cells from embryos without destroying them.

R. HUTCHINSON/UCLA

2011 ACT begins a clinical trial testing surgical implantation of retinal cells derived from embryonic stem cells as a treatment for blindness.

By 2007, West says, he was not getting along with Caldwell and left ACT to head another company to develop products for ES-cell research. In 2008, ACT closed its Alameda facility — the CIRM funding never materialized — but Caldwell stayed in Los Angeles. By the time the markets crashed later that year, ACT's stock price had dwindled to pennies. Caldwell lost all of his executives, and the entire RPE development team left.

Still, Lanza was convinced that RPE therapy held the key to the company's survival. He was, moreover, impressed with Caldwell's dedication to the project. "He got all excited [about the science], and that was important," Lanza says. "He was really my partner." The two worked tirelessly throughout 2009 to rebuild the company. Caldwell eked out funding so that Lanza and his team could do the studies needed for FDA approval of the clinical trials. "We knew we had one chance," says Lanza.

In November 2010, when a fax arrived saying that the trial had been approved, a cheer went through the office. "We came out of the ashes," says Lanza. "It was a long time coming."

There was little time for celebration, however. The team still needed approval from the clinical centres conducting the trials before they could start treating patients.

Lanza usually began each morning by answering a slew of e-mails from Caldwell, who often worked later hours in Los Angeles. So he was concerned when, on the morning of 14 December, his inbox was empty. The call came later that afternoon from Caldwell's wife. The man who had kept ACT afloat for the past six years had died unexpectedly, aged 63. Describing the loss now, Lanza becomes quite emotional and almost can't continue. "It was like I lost a father," he says.

The company faced yet another bleak period. But Gary Rabin, an investment banker who had been on ACT's board since 2007, stepped in as interim leader. Within two weeks, he had secured $25 million in financing from two firms that Caldwell had been courting. Rabin, who is now ACT's chairman and chief executive, says that the funding is enough to pay for the company's two ongoing trials and should last through 2012.

THE CHALLENGES AHEAD

Now, the company's future hinges on the outcome of the trials. Final results won't be out until 2013, and they will show mainly whether the cell transplants are safe. The patients enrolled in the trial are in the late stages of vision loss, so the chances of dramatic improvement are remote, experts say.

Still, Rabin and Lanza are optimistic. If the treatment is safe and even moderately effective, they say they would consider partnering with a pharmaceutical company to help take the programme forward — although they are still working out their plan. Scott, with Stanford's Program on Stem Cells and Society, says that positive results could fire up patient advocacy groups, which can be powerful in building support. And a good outcome could encourage investment in other stem-cell therapy companies, says Bonfiglio, who is now managing partner at Proteus Venture Partners in Palo Alto, California.

But even if the trial results are positive, ACT will face enormous challenges in commercializing the technology. The company will have to show the FDA that its RPE cells can slow vision loss in bigger and more expensive clinical trials.

And even if the treatment works, storing and distributing the cells, which often have short shelf-lives, is expensive and logistically difficult, says Chris Mason, head of the Stem Cell and Regenerative Medicine Bioprocess Group at University College London.

These challenges were thrown into stark relief when Geron halted its stem-cell trial in November, having decided that the hurdles to commercializing the therapy were too great. Now, it is up to ACT to face them. "The departure of Geron from the field will ultimately place a greater burden on ACT in terms of educating the FDA and establishing standards for safety and efficacy," Bonfiglio says.

ACT is not entirely alone: other stem-cell-based therapies are moving towards the clinic. For example, a consortium of research groups called the London Project to Cure Blindness aims to test RPE transplants from embryonic stem cells in patients with macular degeneration this year. A group in Japan hopes to test a similar approach in humans using stem cells from reprogrammed adult cells within the next three years.

Still, some who have tracked ACT's trajectory say that the company might have what it takes to succeed. "What has kept ACT going is persistence, tenacity and vision," says Ronald Green, ACT's long-time ethics adviser and a professor of religion and ethics at Dartmouth College in Hanover, New Hampshire.

Lanza says that at times he considered giving up and working on something less controversial. "If I wasn't a stubborn Italian," he says, "I would have thrown up my hands at least 25 times." ■

Corie Lok *is* Nature*'s Research Highlights Editor.*

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