Keeping Up with the Cloneses

The ability to replicate living things holds huge benefits. Creating a crowd of mini-me's isn't one of them

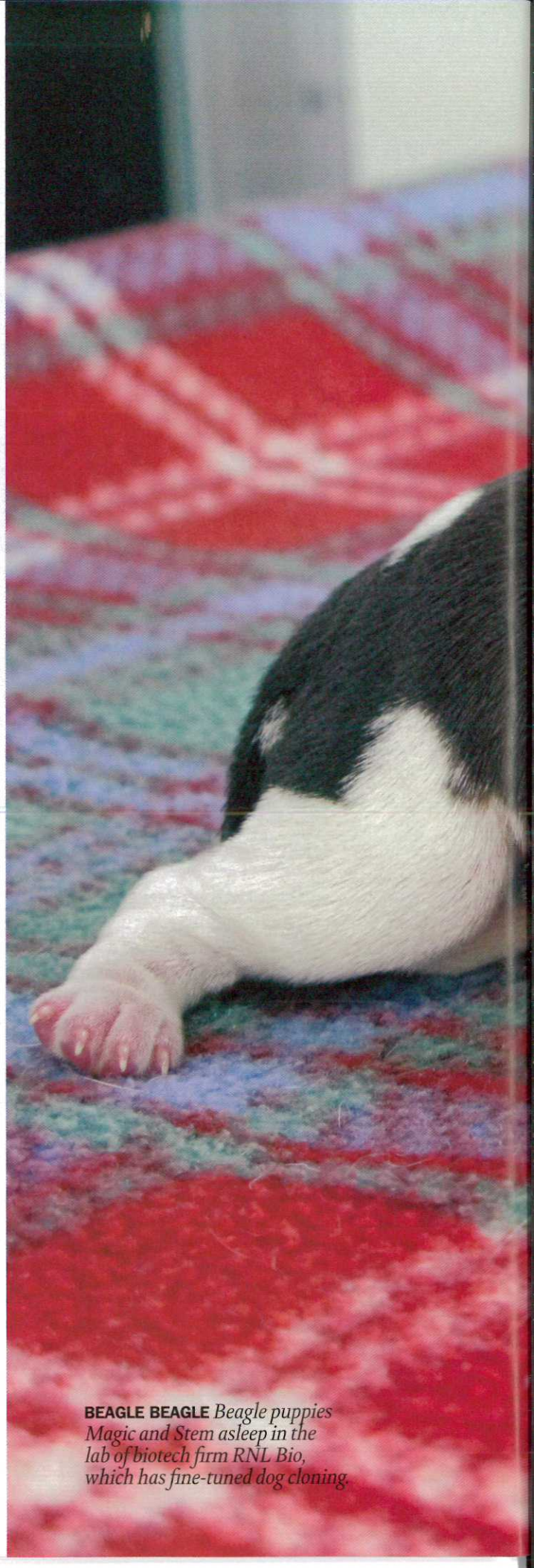
by

ALICE PARK

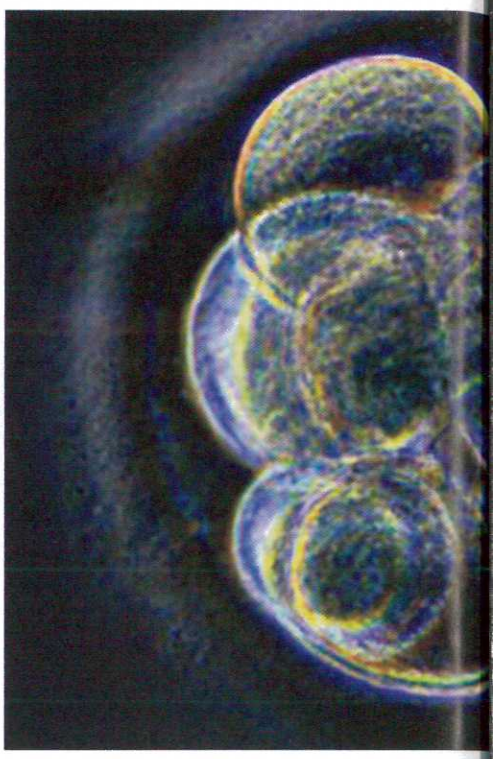
MICHAEL ZUK HAS HIGH HOPES FOR cloning; so high, in fact, that he spent $31,000 on what is purported to be a tooth of John Lennon's. It is his dream that the DNA contained within it will someday seed the re-creation of the legendary Beatle. Imagine.

Zuk, a Canadian dentist, even has ideas about how he'd raise John 2.0—"as my son"—but he shouldn't get too far ahead of himself. There's still a long and winding road to his "son's" first open-mic night. Because although science has come close to figuring out how to clone humans, society isn't quite ready to find out what might happen if it does.

The desire to make mini-me's—actual, living, genetically faithful replicas—has long lurked around the edges of legitimate research. But Xeroxed life was the exclusive product of nature's whim (specifically, in those unpredictable moments when a single egg cleaves into identical beings) until the



BEAGLE BEAGLE *Beagle puppies Magic and Stem asleep in the lab of biotech firm RNL Bio, which has fine-tuned dog cloning.*

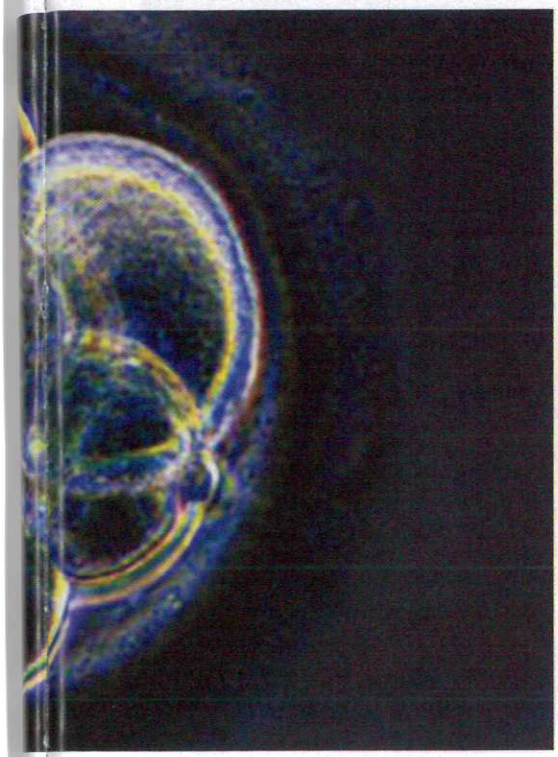


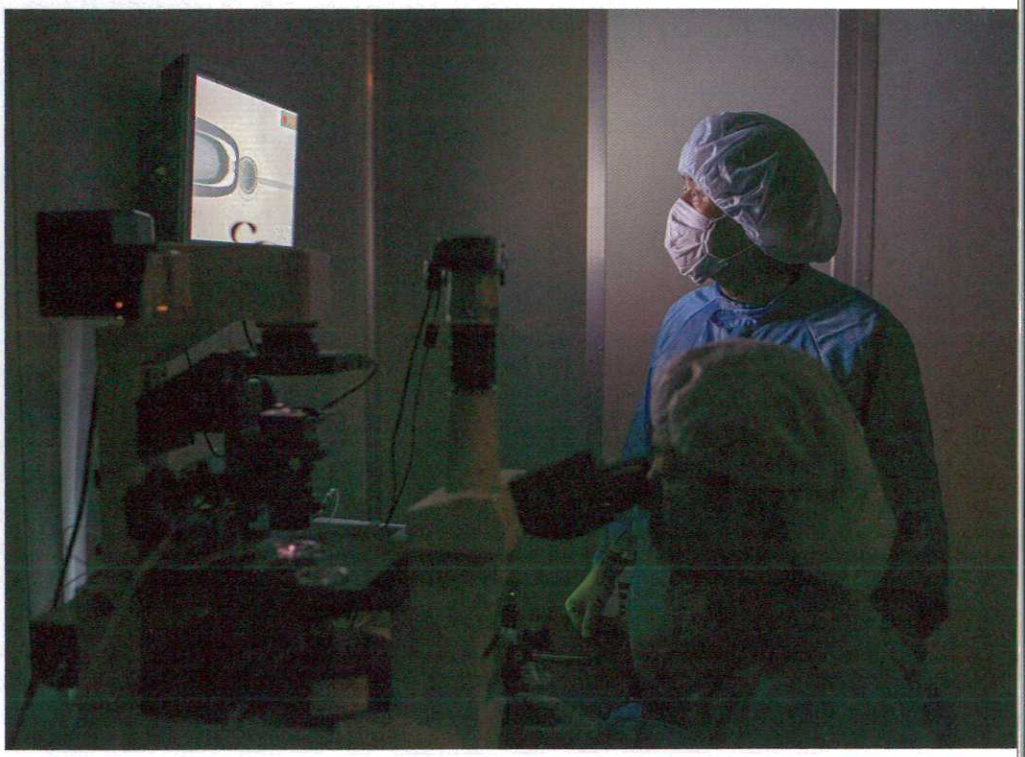
1950s, when scientists replicated that event in frogs. It took another 40 years or so before the first mammal, an organism much more complex than an amphibian, received the same treatment. Only in the past decade did scientists finally clone human cells, although they did not allow these cells to continue developing into anything more.

Actually, researchers don't even like to use the words "human" and "clone" in the same sentence, lest their intentions be misinterpreted. As far as science is concerned, the purpose of cloning isn't to forge reunions with the dearly departed or to help narcissists extend their footprints. Human cloning is focused on a single, decidedly less Frankensteinian outcome: the creation of stem cells, those crucial entities that in early development spur the growth of each of the hundreds of different kinds of human cells. Embryos of a sort are produced on the way to this stem-cell creation, and, yes, those embryos are technically donor clones, but there are no expectations for these "clones" beyond the purpose they have been grown to serve.

Cloning—or, more precisely, somatic cell nuclear transfer (SCNT)—involves implanting DNA from the fully developed cell of an adult into an egg that has been emptied of its own genetic material. The resulting hybrid is then chemically and electrically fused and stimulated to divide, as if the egg had been fertilized by a sperm. After a few days, scientists extract the stem-cell layer that has grown in the developing "embryo" so it can be cultivated more efficiently as a continuous source of new cells of all types, cells that are genetically identical to, and thus unlikely to be rejected by, the original DNA donor. Stem cells, however they are derived, may prove to be a versatile life preserver, helping to treat everything from diabetes to Alzheimer's to heart disease. No wonder some experts prefer to call the process that spawns them therapeutic cloning.

Put aside the good it can do, though, and SCNT's history is a rocky one, both ethically and scientifically. From the moment a quiet British scientist successfully cloned the first mammal, in 1996, a significant section of the public has been wary. Congress promptly called the scientist and a host of other experts to testify about the ethical implications of turning the technique on humans. The idea of calling up, at will, copies of living or dead human beings—whether celebrities or lost loved ones—raises serious moral questions about the human condition that are nowhere close to





TWOS AND FAUXS *From left: space-cult leader Raël, a clone fabulist; a three-day-old cloned embryo in England; Hwang Woo-suk (standing) back at work a decade after faking clone research*

being resolved. It's why scientists working with SCNT have never allowed any of the "embryos" they create to develop past the stem-cell stage.

While human cloning is banned in the U.K., currently the U.S. has no laws against human cloning, but not for lack of trying: more than a few attempts to ban it have faltered in Congress. But if human cloning isn't forbidden, it is not exactly supported either. Federal research dollars can't be used to bankroll related studies, nor can federal funding be used to pay for SCNT stem-cell generation. Laws in the U.K. are harsher in this area as well, capping the existence of SCNT-created embryos at 14 days.

Then again, it wasn't always clear that cloning would be worthy of so much attention. In 2004 a South Korean group at Seoul National University claimed to have replicated human cells as a first step to generating stem cells. Within a year, the group reported accomplishing the feat using cells from patients with spinal cord injuries, opening up for the first time the possibility that stem cells could be harvested to replace damaged or malfunctioning ones to treat disease. As it turned out, the results were fake; the stem cells in question hadn't even been produced by SCNT. The fraud was a reminder of just how complicated manipulating DNA, especially human DNA, is. In fact, while dozens of species were and continue to be cloned by SCNT—mice, cats, dogs, even primates—human cells remained stubbornly resistant.

The history of cloning research has been rocky both ethically and scientifically.

Then, in 2013, Shoukhrat Mitalipov and his colleagues at Oregon Health & Science University

successfully accomplished just that. The process took only a few months, a surprisingly short period considering the significance of the accomplishment. The Oregon scientists cut the work time by modifying the procedure that had been effective before in sheep and other species and by applying what they had learned in previous experiments with monkey eggs.

In many ways, the proof was in the details. For starters, using eggs donated by healthy volunteers made a significant difference. Most previous cloning attempts had been made with discarded eggs from in vitro fertilization clinics; they were probably degraded or of otherwise lesser quality, which could have reduced their chances of surviving the DNA transfer process. From the monkey studies, the team also knew that introducing the donor DNA into the egg required a gentle touch and that infusing a bit of caffeine into the process could also help. (Other scientists had used caffeine to help reprogram donor DNA back to an embryonic state, before it became a mature cell and was still able to become any of the body's hundreds of different cell types, but it may also help stabilize the egg to accept donor genes.) Says Mitalipov, "Even though there wasn't anything people hadn't tried in other species or we hadn't tried with monkey cells, the right combination, timing and concentration made the difference."

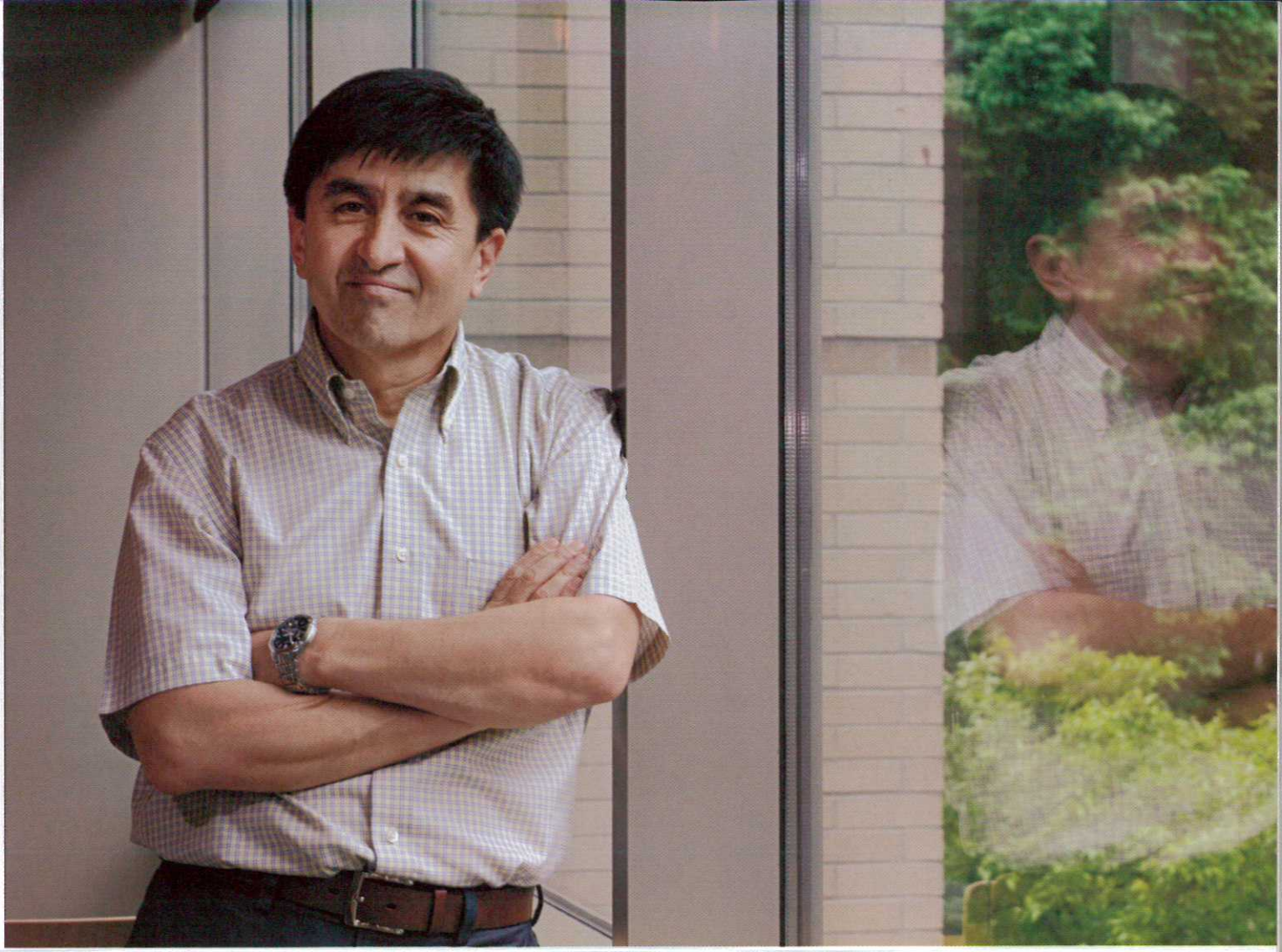
The tweaked technique has been moderately efficient, with eight eggs generating four embryonic-stem-cell lines. Mitalipov, though, anticipates being able to produce one line per egg soon. "We knew the history of failure, that several legitimate labs had tried but couldn't make it work," he says. "I thought we'd need 500 to 1,000 eggs and several years to optimize the process. But in the first experiment we got a blastocyst [a five- to seven-day-old embryo], and within a couple of months we had an embryonic-stem-cell line. We couldn't believe it."

The strong start, though, was in the end only a first step. Mitalipov used fetal cells, which almost assuredly means they are easier to reprogram, being so close to their embryonic origin. Whether an adult cell, which has lost that early ability to grow into any of the body's cells, could undergo the same transformation remained an open question. A year later, an international group of scientists answered it. In 2014 Robert Lanza of Advanced Cell Technology in Massachusetts and others used SCNT to clone two cells, one from a 35-year-old man, the other from a 75-year-old man. This time, though, the researchers let some of the introduced DNA sit for two hours in the egg before chemically and electrically activating it, 90 minutes longer than Mitalipov had. The extra time, they theorized, would allow the genetic material to better acclimate to its new environment and to interact with the egg's development factors. The team used 77 eggs from four donors, activating 38 after 30 minutes, the rest after 120. None of the first group continued to develop, but two in the second group did. "There is a massive molecular change occurring. You are taking a fully differentiated cell, and you need to have the egg do its magic," explains Lanza. "You need to extend the reprogramming time before you can force the cell to divide."

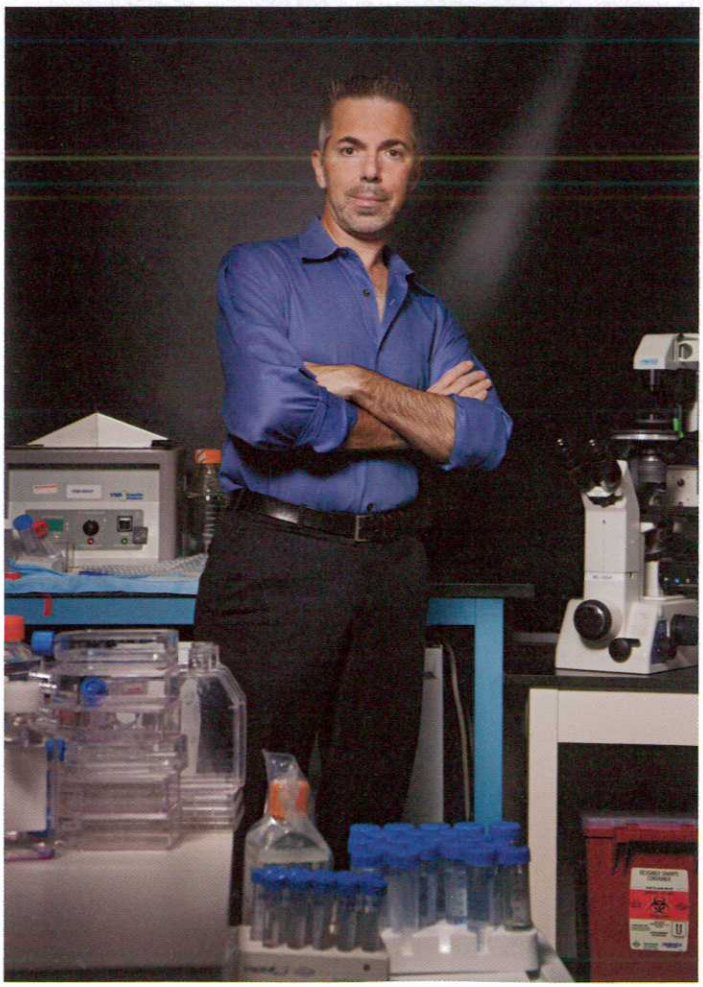
A 5% efficiency rate may not seem impressive, but, Lanza says, it's not so bad when you consider that the stem cells appear to have had their genetic history completely erased, returned to that blank slate before committing to—and when they still could be—any cell type. "This procedure works well," he says, "and works with adult cells."

The payoff of human cloning may be a source of therapeutic replacement cells.

Ultimately, Lanza says, these adult cells may be another source of replacement cells for those in need of them—for the dead motor neurons of Parkinson's patients, for example, or the inefficient insulin-making cells of people with diabetes. To date, there is only one such trial approved by the Food and Drug Administration that is ongoing: it uses retinal cells made from stem cells extracted from excess IVF embryos. Those cells, made by Lanza's Advanced Cell Technology, have offered some benefit to patients with macular degeneration, a condition that causes progressive blindness.



MONKEY DONE
Shoukhrat Mitalipov of Oregon Health & Science University successfully cloned rhesus monkeys, such as Chrysta.



BANKING ON BENEFITS
Advanced Cell Technology has cloned cells from adult men ages 35 and 75; bottom: chief scientific officer Robert Lanza

Cells made from SCNT, though, could provide another choice for patients who might need it: the opportunity to grow their own cells and tissues. "It's good to know we have something in our back pocket. It's good knowing we have another way to help patients should we need it," he says.

Such legitimate efforts to distinguish stem-cell-based SCNT from human cloning, however, haven't stopped less-legitimate groups from making their own claims. Clonaid—a company affiliated with the Raëlian sect, which believes that life on Earth was created by extraterrestrial beings—claims to have created the first human clone, Eve, in 2002. But as the director admits on its website, "Clonaid prides itself on never releasing the identity of the numerous individuals who have been cloned." In other words, feel free to be skeptical.

There will always be those who envision a world of mini-me's and extra John Lennons. But in the real world, researchers will continue to debate ethicists about the merits of SCNT and about the best ways to ensure that its lifesaving potential doesn't become a victim of worst-case fears. "They've become kind of cursed cells," says Mitalipov. And that's a shame, because as the centerpiece of a new era in medicine, they could certainly be a blessing. Even if they can't help get the Beatles back together again.