Immature and full of potential, stem cells haven’t yet differentiated into the specialized cells that form body parts, like the museum specimens (left) stacked in the Berlin lab of pathologist Rudolf Virchow. He pioneered the idea, in the 1800s, that disease begins at the cellular level.

The Power to Divide

stem cells could launch a new era of medicine, curing deadly diseases with custom-made tissues and organs. But science may take a backseat to politics in deciding if—and where—that hope will be realized.

By Rick Weiss | Photographs by Max Aguilera-Hellweg, M.D.
hoping for a cure

Eleven-year-old David Dalmat waits in a Paris hospital for a bone marrow transplant to treat his sickle-cell anemia. In use for decades, such transplants are an example of an "adult" stem cell therapy in which stem cells in donated bone marrow regenerate a patient's blood and immune system. To thwart his disease—and fend off the risk of rejection—David's own bone marrow has been wiped out by radiation and chemotherapy. Until it's regrown, he's a "boy in a bubble," isolated from a microbe-infested world.
IN THE BEGINNING, one cell becomes two, and two become four. Being fruitful, they multiply into a ball of many cells, a shimmering sphere of human potential. Scientists have long dreamed of plucking those naive cells from a young human embryo and coaxing them to perform, in sterile isolation, the everyday miracle they perform in wombs: transforming into all the 200 or so kinds of cells that constitute a human body. Liver cells. Brain cells. Skin, bone, and nerve.

The dream is to launch a medical revolution in which ailing organs and tissues might be repaired—not with crude mechanical devices like insulin pumps and titanium joints but with living, homegrown replacements. It would be the dawn of a new era of regenerative medicine, one of the holy grails of modern biology.

Revolutions, alas, are almost always messy. So when James Thomson, a soft-spoken scientist at the University of Wisconsin in Madison, reported in November 1998 that he had succeeded in removing cells from spare embryos at fertility clinics and establishing the world's first human embryonic stem cell line, he and other scientists got a lot more than they bargained for. It was the kind of discovery that under most circumstances would have blossomed into a major federal research enterprise. Instead the discovery was quickly engulfed in the turbulent waters of religion and politics. In church pews, congressional hearing rooms, and finally the Oval Office, people wanted to know: Where were
the needed embryos going to come from, and how many would have to be destroyed to treat the millions of patients who might be helped? Before long, countries around the world were embroiled in the debate.

Most alarmed have been people who see embryos as fully vested, vulnerable members of society, and who decry the harvesting of cells from embryos as akin to cannibalism. They warn of a brave new world of "embryo farms" and "cloning mills" for the cultivation of human spare parts. And they argue that scientists can achieve the same results using adult stem cells—immature cells found in bone marrow and other organs in adult human beings, as well as in umbilical cords normally discarded at birth.

Advocates counter that adult stem cells, useful as they may be for some diseases, have thus far proved incapable of producing the full range of cell types that embryonic stem cells can. They point out that fertility clinic freezers worldwide are bulging with thousands of unwanted embryos slated for disposal. Those embryos are each smaller than the period at the end of this sentence. They have no identifying features or hints of a nervous system. If parents agree to donate them, supporters say, it would be unethical not to do so in the quest to cure people of disease.

Few question the medical promise of embryonic stem cells. Consider the biggest United States killer of all: heart disease. Embryonic stem cells can be trained to grow into heart muscle cells that, even in a laboratory dish, clump together and pulse in spooky unison. And when those heart cells have been injected into mice and pigs with heart disease, they’ve filled in for injured or dead cells and sped recovery. Similar studies have suggested stem cells’ potential for conditions such as diabetes and spinal cord injury.

Critics point to worrisome animal research showing that embryonic stem cells sometimes grow into tumors or morph into unwanted kinds of tissues—possibly forming, for example, dangerous bits of bone in those hearts they are supposedly repairing. But supporters respond that such problems are rare and a lot has recently been learned about how to prevent them.

The arguments go back and forth, but policymakers and governments aren’t waiting for answers. Some countries, such as Germany, worried about a slippery slope toward unethical human experimentation, have already prohibited some types of stem cell research. Others, like the U.S., have imposed severe limits on government funding but have left the private sector to do what it wants. Still others, such as the U.K., China, Korea, and Singapore, have set out to become the epicenters of stem cell research, providing money as well as ethical oversight to encourage the field within carefully drawn bounds.

In such varied political climates, scientists around the globe are racing to see which techniques will produce treatments soonest. Their approaches vary, but on one point, all seem to agree: How humanity handles its control over the mysteries of embryo development will say a lot about who we are and what we’re becoming.

FOR MORE THAN HALF of his seven years, Cedric Seldon has been fighting leukemia. Now having run out of options, he is about to become a biomedical pioneer—one of about 600 Americans last year to be treated with an umbilical cord blood transplant.

Cord blood transplants—considered an adult stem cell therapy because the cells come from infants, not embryos—have been performed since 1988. Like bone marrow, which doctors have been transplanting since 1968, cord blood is richly endowed with a kind of stem cell that gives rise to oxygen-carrying red blood cells, disease-fighting white blood cells, and other parts of the blood and immune systems. Unlike a simple blood transfusion, which provides a batch of cells destined to die in a few months, the stem cells found in bone marrow and cord blood can—if all goes well—burrow into a person’s bones, settle there for good, and generate fresh blood and immune cells for a lifetime.

Propped on a hospital bed at Duke University Medical Center, Cedric works his thumbs furiously against a pair of joysticks that control a careening vehicle in a Starsky and Hutch video game. “Hang on, Hutch!” older brother Daniel shouts from the bedside, as a nurse, ignoring the screeching tires and gunshots, sorts through a jumble of tubes and hangs a bag of cord blood cells from a chrome pole. Just an hour ago I watched those cells being thawed and spun in a centrifuge—awakening them for the first time since 2001, when they were extracted from the umbilical cord of a newborn and donated by her parents to a cell bank at Duke. The time has come for those cells to prove (Continued on page 15)
With more and more countries aggressively developing stem cell therapies, the United States is in real danger of being left behind.

**The stem cell race**

Although embryonic stem cell science got its start in the U.S., the rest of the world is fighting to take the lead. With one of the most research-friendly climates in Europe, the United Kingdom allows scientists to extract stem cells from embryos left over from in vitro fertilization as well as to clone embryos specifically for study. At the U.K. Stem Cell Bank—the first of its type in the world—vessels (left) for cold-stored cell lines are a repository for the future, says the bank's director Glyn Stacey. Researchers can deposit and withdraw both adult and embryonic stem cells.

"The idea is to apply the same rigorous standards to all cells," Stacey says. Scientists hope to create batches of stem cells as uniform as the drugs produced by pharmaceutical companies.

What some see as a shift of research overseas comes in the wake of ethical concerns that have led to U.S. funding restrictions. But many countries, such as Austria and Ireland, have also strongly opposed embryonic work. The loudest no vote comes from the Vatican, which has deemed embryonic research, like abortion, "a gravely immoral act." Not all Roman Catholics agree: Says Fiorenza DiFranco (above, at far left), whose grandson was baptized at St. Peter's Basilica, "If a therapy can help people, it's not the role of church or government to ban it."

Italian adult stem cell scientist Graziella Pellegrini harbors her own concerns but agrees the research must go on: "If we ban the work," she says, "we risk hypocrisy because we will all gain from what is learned by others." —Jennifer S. Holland
A five-day-old embryo is smaller than the period at the end of this sentence. It has no identifying features or hints of a nervous system.

Proponents of embryonic stem cell work present a different picture: Photographed inside the eye of a needle (right) by an electron microscope, a five-day-old embryo is the tiny package from which the controversial cells are usually plucked. Supporters point out that embryos slated for disposal by fertility clinics are a wasted resource, and that the stem cells themselves aren't equipped to develop into a baby if implanted in a uterus. Yet these unspecialized bits have the ability to become any human tissue—a potentially powerful tool for creating healthy tissues and organs to cure deadly diseases.

The public outcry over embryonic research has sent scientists scrambling to find less divisive stem cell sources. Adult stem cells may prove more abundant and malleable than previously thought, but researchers still advocate studying both types.

"It will be difficult to do an end run around the ethical quarrels," says bioethicist Tom Murray, president of the Hastings Center in New York. "We're now having to confront subtle distinctions about life's beginnings that have enormous scientific and religious implications." —J.S.H.
what are embryonic stem cells?

**two sources of embryos**

Most embryonic stem cells used for research are extracted from embryos created by in vitro fertilization. But scientists are working on getting cells from embryos produced by therapeutic cloning, in which the nucleus of, say, a skin cell is inserted into an egg whose nucleus has been removed. Either way, after five days scientists transfer the embryo's inner cell mass—with its coveted 40 or so stem cells—to a lab dish lined with feeder cells. As the cells proliferate they are re-plated onto fresh culture dishes. After many months, if the original stem cells have grown into millions of healthy cells without beginning to differentiate into specialized cells, they are referred to as an embryonic stem cell line—capable of reproducing ad infinitum.

**turning cells into medicine**

Embryonic stem cells' ability to develop into any type of cell—called pluripotency—is both a benefit and a bane to scientists, who must keep harvested cells from maturing and then mold their identities to suit patients' needs.

"One of the greatest challenges in this work is to harness and direct cell differentiation," says Harvard cell biologist Douglas Melton. To tell one stem cell to form blood, another skin, and another liver tissue—what's nature's secret? Complex combinations of growth factors and chemical and genetic signals drive the process, which researchers are only beginning to pin down. Until they do, embryonic stem cell therapies won't make the leap from lab mice to humans.
what are adult stem cells?

where they've been found
- brain
- blood
- cornea
- retina
- heart
- fat
- skin
- dental pulp
- bone marrow
- blood vessels
- skeletal muscle
- intestines

a more grown-up cell

The adult body has a small number of stem cells in many tissues and organs—where they lie low until activated by illness or injury. Unlike embryonic stem cells, adult stem cells haven’t proved able to morph into every kind of cell and may be limited to becoming cell types within their tissue of origin. An adult stem cell in the brain, for example, can become a neuron or glial cell—but not a bone or liver cell.

Similarly stem cells from a newborn’s cord blood (considered adult cells because they aren’t from embryos) produce only blood cells. Recently, though, cord tissue has been found to contain mesenchymal cells capable of generating bone and cartilage.

In general, adult stem cells are scarcer in the body and harder to culture than embryonic cells, yet large numbers are needed for therapies.

hints of progress

So far only adult stem cells have been tested in humans, though research on both adult and embryonic cells progresses apace as scientists seek treatments for myriad diseases. “This is the century of cells,” says Harvard biologist Douglas Melton. Results are preliminary, but they hint at a transformation in medicine. Some disease updates:

heart disease

Adult bone marrow stem cells injected into heart arteries are believed to improve cardiac function in victims of heart attack or heart failure.

leukemia and other cancers

In various studies leukemia patients treated with stem cells from bone marrow and umbilical cord blood emerged free of disease; donor blood stem cells have also reduced non-Hodgkin’s lymphoma and pancreatic and ovarian cancer in some patients.

rheumatoid arthritis

Adult stem cells may be helpful in jump-starting repair of eroded cartilage. In human trials, joint pain lessened temporarily after donor stem cell therapy in some patients, and some then responded better to standard drug therapies.

parkinson’s disease

Since fetal tissue implants had mixed success in reducing neurological symptoms, some researchers say the best hope is that a patient’s own neural stem cells may eventually be coaxed to mature into the dopamine-producing cells needed to treat the disease.

type 1 diabetes

Basic research is focused on understanding how embryonic stem cells might be trained to become the type of pancreatic islet cells that secrete insulin. Recent developments using proteins to spur cell differentiation may speed progress.
Proponents say it’s immoral not to use leftover embryos to save lives, while opponents warn of a brave new world of “embryo farms.”

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donation decision

“If they had a heartbeat, that would make a big difference. But embryos are bunches of cells, and I couldn’t throw them down the sink when they could further science,” says Marie Dooley, far left, one of the small percentage of parents who, after undergoing in vitro fertilization (IVF), donated her excess embryos to stem cell research. Dooley conceived two of her three children through IVF before “helping to make history” with her donation to Harvard.

Nearly 400,000 IVF embryos are in storage in the U.S., but less than 3 percent have been donated for research. Almost as many are designated to be discarded each year. Only a fraction of those that do arrive in the labs are suitable for study. —J.S.H
(Continued from page 7)

For days Cedric has endured walloping doses of chemotherapy and radiation in a last-ditch effort to kill every cancer cell in his body. Such powerful therapy has the dangerous side-effect of destroying patients' blood-making stem cells, and so is never applied unless replacement stem cells are available. A search of every bone marrow bank in the country had found no match for Cedric's genetic profile, and it was beginning to look as if he'd run out of time. Then a computer search turned up the frozen cord blood cells at Duke—not a perfect match, but close enough to justify trying.

"Ready?" the nurse asks. Mom and dad, who have spent hours in prayer, nod yes, and a line of crimson wends its way down the tube, bringing the first of about 600 million cells into the boy's body. The video game's sound effects seem to fade behind a muffling curtain of suspense. Although Cedric's balloon-laden room is buoyant with optimism, success is far from certain.

"Grow, cells, grow," Cedric's dad whispers.

His mom's eyes are misty. I ask what she sees when she looks at the cells trickling into her son.

"Life," she says. "It's his rebirth."

IT WILL BE A MONTH before tests reveal whether Cedric's new cells have taken root, but in a way he's lucky. All he needs is a new blood supply and immune system, which are relatively easy to re-create. Countless other patients are desperate to regenerate more than that. Diabetics need new insulin-producing cells. Heart attack victims could benefit from new cardiac cells. Paraplegics might even walk again if the nerves in their spinal cords could regrow.

In a brightly lit laboratory halfway across the country from Cedric's hospital room, three teams of scientists at the University of Wisconsin in Madison are learning how to grow the embryonic stem cells that might make such cures possible. Unlike adult stem cells, which appear to have limited repertoires, embryonic stem cells are pluripotent—they can become virtually every kind of human cell. The cells being nurtured here are direct descendants of the ones James Thomson isolated seven years ago.

For years Thomson and his colleagues have been expanding some of those original stem cells into what are called stem cell lines—colonies of millions of pluripotent cells that keep proliferating without differentiating into specific cell types. The scientists have repeatedly moved each cell's offspring to less crowded laboratory dishes, allowing them to divide again and again. And while they worked, the nation struggled to get a handle on the morality of what they were doing.

It took almost two years for President Bill Clinton's administration to devise ethics guidelines and a system for funding the new field. George W. Bush's ascension prevented that plan from going into effect, and all eyes turned to the conservative Texan to see what he would do. On August 9, 2001, Bush announced that federal funds could be used to study embryonic stem cells. But to prevent taxpayers from becoming complicit in the destruction of human embryos, that money could be used only to study the stem cell lines already in the works as of that date—a number that, for practical reasons, has resulted in about two dozen usable lines. Those wishing to work with any of the more than a hundred stem cell lines created after that date can do so only with private funding.

Every month scientists from around the world arrive in Madison to take a three-day course in how to grow those approved cells. To watch what they must go through to keep the cells happy is to appreciate why many feel hobbled by the Bush doctrine. For one thing—and for reasons not fully understood—the surest way to keep these cells alive is to place them on a layer of other cells taken from mouse embryos, a time-consuming requirement. Hunched over lab benches, deftly handling forceps and pipettes with blue latex gloves, each scientist in Madison spends the better half of a day dissecting a pregnant mouse, removing its uterus, and prying loose a string of embryos that look like little red peas in a pod. They then wash them, mash them, tease apart their cells, and get them growing in lab dishes. The result is a hormone-rich carpet of mouse cells upon which a few human embryonic stem cells are finally placed. There they live like pampered pashas.

If their scientist-servants don't feed them fresh liquid nutrients at least once a day, the cells die of starvation. If each colony is not split in half each week, it dies from overcrowding. And if a new layer of mouse cells is not prepared and provided every two weeks, the stem cells grow into weird and useless masses that finally die.
By contrast, scientists working with private money have been developing embryonic stem cell lines that are harder, less demanding, and not dependent on mouse cells. Bypassing the use of mouse cells is not only easier, but it also eliminates the risk that therapeutic stem cells might carry rodent viruses, thereby potentially speeding their approval for testing in humans.

Here in the Madison lab, scientists grumble about how fragile the precious colonies are. “They’re hard to get to know,” concedes Leann Crandall, one of the course’s instructors and a co-author of the 85-page manual on their care and feeding. “But once you get to know them, you love them. You can’t help it. They’re so great. I see so many good things coming from them.”

A FEW AMERICAN scientists are finding it is easier to indulge their enthusiasm for stem cells overseas. Scores of new embryonic stem cell lines have now been created outside the U.S., and many countries are aggressively seeking to spur the development of therapies using these cells, raising a delicate question: Can the nation in which embryonic stem cells were discovered maintain its initial research lead?

“I know a lot of people back in the U.S. who would like to move into embryonic stem cell work but who won’t because of the political uncertainties,” says Stephen Minger, director of the Stem Cell Biology Laboratory at King’s College in London, speaking to me in his cramped and cluttered office. “I think the United States is in real danger of being left behind.”

Minger could be right. He is one of at least two high-profile stem cell scientists to move from the U.S. to England in the past few years, something less than a brain drain but a signal, perhaps, of bubbling discontent.

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Adult stem cells from Arno Christoleit’s own hip helped repair his ailing heart. In a German study Christoleit and other heart attack patients had cells from their bone marrow injected into their coronary arteries. “Cardiac function increased significantly,” says Helmut Draxler of the Medical University of Hannover. Whether the cells actually convert to cardiac cells isn’t clear, but their presence seems to power the repair.

The research climate is good here, says Minger. In 2003 his team became the first in the U.K. to grow colonies of human embryonic stem cells, and his nine-person staff is poised to nearly double. He’s developing new growth culture systems that won’t rely on potentially infectious mouse cells. He’s also figuring out how to make stem cells morph into cardiac, neural, pancreatic, and retinal cells and preparing to test those cells in animals. And in stark contrast to how things are done in the U.S., Minger says, he’s doing all this with government support—and oversight.

The Human Fertilisation and Embryology Authority (HFEA), the government agency that has long overseen U.K. fertility clinics, is now also regulating the country’s embryonic stem cell research. In closed-door meetings a committee of 18 people appointed by the National Health Service considers all requests to conduct research using embryos. The committee includes scientists, ethicists, lawyers, and clergy, but the majority are lay people representing the public.

To an American accustomed to high security and protesters at venues dealing regularly with embryo research, the most striking thing about the HFEA’s headquarters in downtown London is its ordinariness. The office, a standard-issue warren of cubicles and metal filing cabinets, is on the second floor of a building that also houses the agency that deals with bankruptcy. I ask Ross Thacker, a research officer at the authority, whether the HFEA is regularly in need of yellow police tape to keep protesters at bay.

“Now that you mention it,” he says, “there was a placard holder outside this morning…”

Aha!

“…but he was protesting something about the insolvency office.”

Thacker politely refrains from criticizing U.S. policy on embryo research, but he clearly takes pride in the orderliness of the British system. The committee has approved about a dozen requests to create stem cell lines in the past 18 months, increasing the number of projects to 35. Most were relatively routine—until a strongly-willed fertility doctor named Alison Murdoch decided to ask for permission to do something nobody had done before: create cloned human embryos as sources of stem cells.

As controversial as embryonic stem cell research can be, cloning embryos to produce those stem cells is even... (Continued on page 22)
Many suspect that new kinds of adult stem cells may be found that are as versatile as those found in embryos.

Like the body mending a scraped knee, a hefty dose of stem cells enables the eye to grow fresh, healthy tissue. Such tissue engineering is an improvement over corneal grafts from cadavers, which carry a risk of rejection.

To understand the precise mechanisms driving successful eye repairs, Michael Young and Henry Klassen of the Schepens Eye Research Institute at Harvard have enlisted the help of some unusual pigs. By introducing a fluorescent gene from a jellyfish, Randall Prather at the University of Missouri created pigs that glow green—providing the eye researchers with the perfect cellular marker. When Young and his co-workers implant retinal cells from the fluorescent animals into normal-colored pigs with retinal injury, they can track the green cells and monitor their actions.

"What they do is find the retinal injury and repair it," Young says. "It seems the damage instructs the cells, tells them what to do."

The technique is extremely delicate, requiring keyhole surgery through the back of the eye. But in controlled studies the treatment has given some animals a new view of the world.

—J.S.H.
Under the right conditions, the cells can grow into blobs of heart muscle that beat in spooky unison in laboratory dishes.

recipe for reconstruction

It's a long strange trip to get stem cell research from freezer to fruition. One goal for Anthony Atala at Wake Forest University's Institute for Regenerative Medicine is to engineer human organs, which he likens to baking a cake. For a homegrown bladder (right), take a thumbnail-size biopsy of the patient's own organ, harvest and nurture its cells, then slather the slurry onto a collagen scaffold and watch it grow. The scaffold beneath eventually disintegrates.

Perfecting replacement organs is a tall order, though, and so far none are up to snuff for transplant. The body can absorb only a small amount of tissue without blood vessels—about the size of a pencil eraser, says Atala. Another problem: Sometimes an adult's diseased organ can't provide sufficient or healthy enough cells to seed such a surrogate.

Embryonic stem cells are one possible alternative, kept on ice in Atala's lab (left) with vials of other research ingredients—including serum laced with growth factors designed to spur the cells to become specific tissue types.

Embryonic cells' splendid ability to metamorphose into various cell types is also their limitation: Not surprisingly, bladders infused with bone from stem cells gone awry aren't clinically useful, says Jason Hipp, one of some 60 institute researchers working on how to keep the cells from going haywire.

Meanwhile, Atala and his team are already sculpting tissues and whole organs—from blood vessels to livers—for future clinical trials. "The goal," he says, "is to make as many as we can, eventually replacing diseased parts with functioning ones." —J.S.H.
(Continued from page 17) thornier. Much of the world became familiar with cloning in 1997, when scientists announced they’d cloned a sheep named Dolly. The process involves creating an animal not from egg and sperm but by placing the nucleus of a cell inside an egg that’s had its nucleus removed. It’s since been used to replicate mice, rabbits, cats, and cattle, among others.

As in many other countries and a few U.S. states, it’s illegal in the U.K. to create cloned human babies (called reproductive cloning), because of concerns that clones may be biologically abnormal and because of ethical issues argued, by watching how the disease damage nerve and muscle cells grown from those stem cells, and then testing various drugs on them. It’s the kind of experiment that could never be done in a person with the disease.

The HFEA deliberated for five months before giving Murdoch permission to make human embryo clones in her lab at the Centre for Life in Newcastle, a sprawling neo-illuminated complex of buildings that strikes a decidedly modern note in the aging industrial hub. But there was a catch: It takes an egg to make a clone. And under the terms of HFEA approval, Murdoch was not allowed to use only those eggs being disposed of by the center’s fertility clinic after they failed to fertilize when mixed with sperm.

It’s not a perfect arrangement, Murdoch says. After all, eggs that have failed to fertilize are almost by definition of poor quality. “They’re not brilliant,” she says of the eggs. “But the U.K. has decided at the moment that these are the most ethical sort to use. So that’s really all we can work with.” As of April the group hadn’t managed to clone any embryos, despite numerous attempts.

No such obstacle faced Woo-Suk Hwang and his colleagues at Seoul National University in February 2004 when they became the world’s first to clone human embryos and extract stem cells from them. The South Korean government allows research on human embryos made from healthy eggs—in this case, donated by 16 women who took egg-ripening hormones.

Cloning is an arduous process that requires great patience and almost always ends in failure as cells burst, tear, or suffer damage to their DNA, but the Koreans are expert cloners, their skills sharpened in the country’s state-funded
livestock-cloning enterprise. In Hwang’s lab alone, technicians produce more than 700 cloned pig or cattle embryos every day, seven days a week, in a quest to produce livestock with precise genetic traits. “There is no holiday in our lab,” Hwang told me with a smile.

But there is something else that gives Koreans an edge over other would-be cloners, Hwang says. “As you know, Asian countries use chopsticks, but only the Koreans use steel chopsticks,” he explains. “The steel ones are the most difficult to use. Very slippery.” I look at him, trying to tell if he’s kidding. A lifetime of using steel chopsticks makes Koreans better at manipulating tiny eggs? “This is not simply a joke,” he says.

Time will tell whether such skill will be enough to keep Korea in the lead as other countries turn to cloning as a source of stem cells. The competition will be tough. China has pioneered a potentially groundbreaking technique that produces cloned human embryos by mixing human skin cells with the eggs of rabbits, which are more easily obtained than human eggs. A few privately funded researchers in the U.S. are also pursuing therapeutic cloning.

**YET THE BIGGEST COMPETITION** in the international race to develop stem cell therapies may ultimately come from one of the smallest of countries—a tiny nation committed to becoming a stem cell superpower. To find that place, one need only track the migration patterns of top scientists who’ve been wooed there from the U.S., Australia, even the U.K. Where they’ve been landing, it turns out, is Singapore.

Amid the scores of small, botanically rich but barely inhabited islands in the South China Sea, Singapore stands out like a post-modern mirage. The towering laboratory buildings of its Biopolis were created in 2001 to jump-start Singapore’s biotechnology industry. Like a scene from a science fiction story, it features futuristic glass-and-metal buildings with names like Matrix, Proteos, and Chromos, connected by skywalks that facilitate exchanges among researchers.

Academic grants, corporate development money, laws that ban reproductive cloning but allow therapeutic cloning, and a science-savvy workforce are among the lures attracting stem cell researchers and entrepreneurs. Even Alan Colman—the renowned cloning expert who was part of the team that created Dolly, the cloned sheep—has taken leave of his home in the U.K. and become the chief executive of ES Cell International, one of a handful of major stem cell research companies blossoming in Singapore’s fertile environs.

“You don’t have to fly from New York to San Diego to see what’s going on in other labs,” says Robert Klupacs, the firm’s previous CEO. “You just walk across the street. Because Singapore is small, things can happen quickly. And you don’t have to go to Congress at every turn.”

The company’s team of 36, with 15 nationalities represented, has taken advantage of that milieu. It already owns six stem cell lines made from conventional, noncloned embryos that are approved for U.S. federal funding. Now it is perfecting methods of turning those cells into the kind of pancreatic islet cells that diabetics need, as well as into heart muscle cells that could help heart attack patients. The company is developing new, mouse-free culture systems and sterile production facilities to satisfy regulators such as the...
Recipients of stem cell transplants are the world's first generation of regenerated people, a seamless blend of old and new.

Mending the mind

"After two strokes and brain damage, I considered calling [assisted-suicide advocate] Dr. Kevorkian," says recovering lupus patient Katherine Hammons (comforting a fellow patient, right). Instead she entered an ongoing study in which oncologist Ann Traynor, now at the University of Massachusetts, treats lupus patients with stem cells from their own bone marrow. Six years after therapy, Hammons's progress has exceeded expectations: Even damage previously thought permanent is healing. "I'm reborn," Hammons says. "I've crossed Kevorkian off my list."

More recently Traynor treated Margaret Laperle (wired for an electroencephalogram, right) who is just beginning to recover from the lupus-related psychosis that stalled her own medical career. "It shows that even people with tremendous disability can regain function," says Traynor, who reports that 75 percent of her study patients remain in remission two to eight years after treatment.

Meanwhile scientists at Stem-Cells, Inc. in Palo Alto are using mice (left) to test the limits of human brain cells— with mind-boggling results. When neuronal stem cells from a human fetus were transplanted into a mouse brain, they didn't just survive; they started working right alongside the mouse's own neurons.

"These cells might not only repair local lesions, but also offer protection from progressive neurodegenerative diseases," says company co-founder Irving Weissman. The results inch scientists closer to treating Parkinson's, brain-damaging genetic disorders, and perhaps spinal cord injuries, he says. —J.S.H.

24 NATIONAL GEOGRAPHIC • JULY 2005
U.S. Food and Drug Administration. It hopes to begin clinical tests in humans by 2007.

Despite its research-friendly ethos—and its emphasis on entrepreneurial aspects of stem cell science—Singapore doesn’t want to be known as the world’s “Wild West” of stem cell research. A panel of scientific and humanitarian representatives spent two years devising ethical guidelines, stresses Hwai-Loong Kong, executive director of Singapore’s Biomedical Research Council. Even the public was invited to participate, Kong says—an unusual degree of democratic input for the authoritarian island nation.

The country’s policies represent a “judicious balance,” he says, that has earned widespread public support.

Widespread, perhaps, but not universal. After my conversation with Kong, a government official offered me a ride to my next destination. As we approached her parked car, she saw the surprise on my face as I read the bumper sticker on her left rear window: “Embryos—Let Them Live. You Were Once an Embryo Too!”

“I guess this is not completely settled,” I said. “No,” she replied, choosing not to elaborate.

**THAT BUMPER STICKER** made me feel strangely at home. I am an American, after all. And no country has struggled more with the moral implications of embryonic stem cell research than the U.S., with its high church attendance rates and pockets of skepticism for many things scientific. That struggle promises to grow in the months and years ahead. Many in Congress want to ban the cloning of human embryos, even in those states where it is currently legal and being pursued with private funding. Some states have already passed legislation banning various kinds of embryo research. And federally backed scientists are sure to become increasingly frustrated as the handful of cell colonies they’re allowed to work with becomes an ever smaller fraction of what’s available.

Yet one thing I’ve noticed while talking to stem cell experts around the world: Whenever I ask who is the best in the field, the answers are inevitably weighted with the names of Americans. The work of U.S. researchers still fills the pages of the best scientific journals. And while federal policy continues to frustrate them, they are finding some support. Following the lead of California, which has committed 300 million dollars a year for embryonic stem cell research for the next decade, several states are pushing initiatives to fund research, bypassing the federal restrictions in hopes of generating well-paying jobs to boost their economies. Moves like those prompt some observers to predict that when all is said and done, it will be an American team that wins the race to create the first FDA-approved embryonic stem cell therapy.

Tom Okarma certainly believes so, and he intends to be that winner. Okarma is president of Geron, the company in Menlo Park, California, that has been at the center of the embryonic

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**better than bone marrow**

His sister Eusnel’s umbilical cord blood saved Neel Padonou from the ravages of sickle-cell anemia. More easily tolerated and less risky for both donor and recipient than bone marrow, cord blood is one in a growing line of so-called adult stem cell therapies now in clinical use. But embryonic stem cells may not be far behind: Researchers hope to test them in humans for the first time as early as next year.
stem cell revolution from the beginning. Geron financed James Thomson’s discovery of the cells in Wisconsin and has since developed more than a dozen new colonies. It holds key patents on stem cell processes and products. And now it’s laying the groundwork for what the company hopes will be the first controlled clinical trials of treatments derived from embryonic stem cells. Moreover, while others look to stem cells from cloned embryos or newer colonies that haven’t come into contact with mouse cells, Okarma is looking no further than the very first colonies of human embryonic stem cells ever grown: the ones Thomson nurtured back in 1998. That may seem surprising, he acknowledges, but after all these years, he knows those cells inside out.

“We’ve shown they’re free of human, pig, cow, and mouse viruses, so they’re qualified for use in humans,” Okarma says at the company’s headquarters. Most important, Geron has perfected a system for growing uniform batches of daughter cells from a master batch that resides, like a precious gem, in a locked freezer. The ability to produce a consistent product, batch after batch, just as drug companies do with their pills is what the FDA wants—and it will be the key to success in the emerging marketplace of stem cell therapies, Okarma says. “Why do you think San Francisco sourdough bread is so successful?” he asks. “They’ve got a reliable sourdough culture, and they stick with it.”

Geron scientists can now make eight different cell types from their embryonic lines, Okarma says, including nerve cells, heart cells, pancreatic islet cells, liver cells, and the kind of brain cells that are lost in Parkinson’s disease. But what Geron wants most at this point is to develop a treatment for spinal cord injuries.

Okarma clicks on a laptop and shows me a movie of white rats in a cage. “Pay attention to the tail and the two hind legs,” he says. Two months before, the rats were subjected to spinal cord procedures that left their rear legs unable to support their weight and their tails dragging along the floor. “That’s a permanent injury,” he says. He flips to a different movie: white rats again, also two months after injury. But these rats received injections of a specialized nervous system cell grown from human embryonic stem cells. They have only the slightest shuffle in their gait. They hold their tails high. One even stands upright on its rear legs for a few moments.

“It’s not perfect,” Okarma says. “It’s not like we’ve made a brand new spinal cord.” But tests show the nerves are regrowing, he says. He hopes to get FDA permission to start testing the cells in people with spinal cord injuries in 2006.

Those experiments will surely be followed by many others around the world, as teams in China, the U.K., Singapore, and other nations gain greater control over the remarkable energy of stem cells. With any luck the political and ethical issues may even settle down. Many suspect that with a little more looking, new kinds of stem cells may be found in adults that are as versatile as those in embryos.

At least two candidates have already emerged. Catherine Verfaillie, a blood disease specialist at the University of Minnesota, has discovered a strange new kind of bone marrow cell that seems able to do many, and perhaps even all, the same things human embryonic stem cells can do. Researchers at Tufts University announced in February that they had found similar cells. While some scientists have expressed doubts that either kind of cell will prove as useful as embryonic ones, the discoveries have given birth to new hopes that scientists may yet find the perfect adult stem cell hiding in plain sight.

Maybe Cedric Seldon himself will discover them. The stem cells he got in his cord blood transplant did the trick, it turns out. They took root in his marrow faster than in anyone his doctors have seen. “Everyone’s saying, ‘Oh my God, you’re doing so well,’” his mother says.

That makes Cedric part of the world’s first generation of regenerated people, a seamless blend of old and new—and, oddly enough, of male and female. His stem cells, remember, came from a girl, and they’ve been diligently churning out blood cells with two X chromosomes ever since. It’s a detail that will not affect his sexual development, which is under the control of his hormones, not his blood. But it’s a quirk that could save him, his mother jokes, if he ever commits a crime and leaves a bit of blood behind. The DNA results would be unambiguous, she notes correctly. “They’ll be looking for a girl.”}

STEM CELL DIVIDE Where do you stand on the future of stem cell research? Join our discussion, view additional images by photographer Max Aguilar-Hellweg, and find useful links to more information at nationalgeographic.com/magazine/0507.