Robb Report

Health & Wellness

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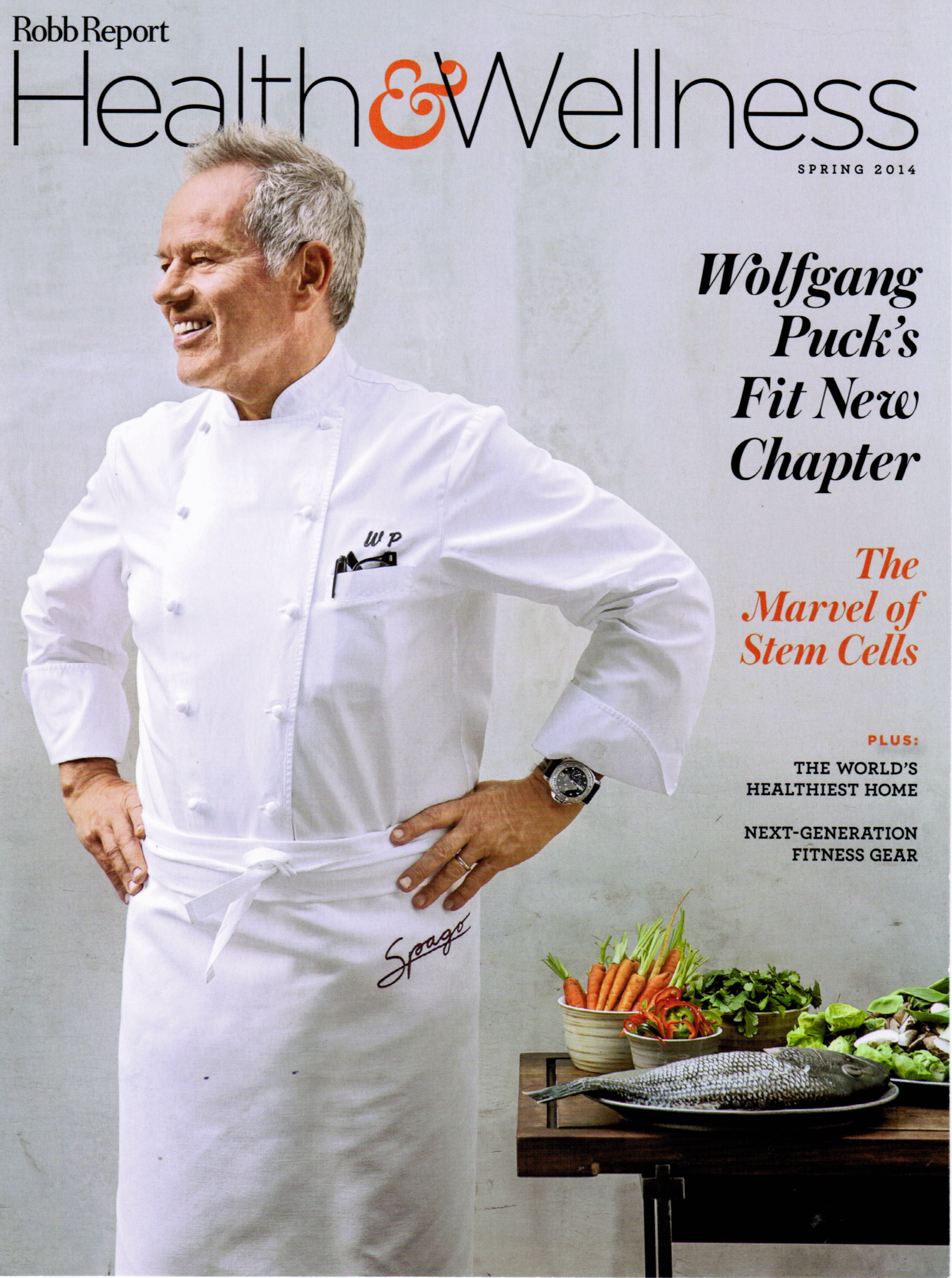

Wolfgang Puck's Fit New Chapter

The Marvel of Stem Cells

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By harnessing the power of regeneration residing in our own bodies, stem-cell therapies have transformed science fiction into reality. Already they have repaired damaged hearts, restored vision to clouded sight, and put the jump back in athletes' knees.

By Erin O'Donnell
Illustrations by Brian Stauffer

The Spectacular Now

WHEN FRED LESIKAR ARRIVED at the hospital in October 2009 suffering sharp pain in his upper back, neck, and triceps, doctors found the 59-year-old retired small-business owner in the midst of a major heart attack, with an arterial blockage of more than 90 percent. His cardiologist inserted a stent and treated him with blood thinners. ¶ Recovering at home in Menifee, Calif., a few weeks later, Lesikar was watching the morning news when he heard about a clinical trial at Cedars-Sinai Medical Center in Los Angeles. Eduardo Marbán, MD, PhD, director of the Cedars-Sinai Heart Institute, was studying a therapy using a patient's own heart tissue to create stem cells capable of repairing the heart damage after a heart attack. Because Lesikar's cardiac function had been reduced by 30 percent, he was especially intrigued. "It was only 5:30 in the morning, but I immediately left a message at Cedars-Sinai," he recalls.

After extensive testing, Lesikar was randomly assigned to the experimental therapy. In a brief, minimally invasive procedure, a doctor snipped a peppercorn-sized chunk of cardiac tissue from his right ventricle. The sample was then taken to a laboratory, where scientists cultured and multiplied the cells in a process developed by Dr. Marbán. After about a month, the process yielded some 25 million heart cells, some of which literally beat in the dish. In a second brief procedure, doctors went back down the artery blocked during Lesikar's heart attack and infused the damaged area of the heart with the lab-grown cells.

Lesikar says he began to feel noticeably better within three months of the treatment. His heart's pumping ability improved over time to roughly the normal range, and the scarred area of his heart shrank by 40 percent as the "dead" cells were replaced with new, healthy ones. Dr. Marbán's study revealed that in addition to new heart tissue, patients also grew new blood vessels. "Along with the change in exercise and diet, I feel better than I did before the heart attack," Lesikar says.

The emergence of stem-cell therapies and regenerative medicine have yielded new possibilities in healthcare, with some therapies producing almost-miraculous results, particularly in the areas of heart and eye disease and orthopedic injury. Blood stem cells have been used successfully for decades to treat a variety of serious diseases, most commonly blood cancers. Studies such as Dr. Marbán's suggest that it is possible to intentionally regrow tissues, even those "that we have always been taught would never, ever regrow under any circumstances," Dr. Marbán says. If these results can be verified with further studies (and Dr. Marbán's company, Capricor Therapeutics Inc., is currently engaged in a Phase 2 clinical trial), this opens a world of scientific possibility. "We can look for ways to regrow all sorts of tissues that we have previously consigned to permanent injury. In the case of kidney disease, we might be able to do away with some instances of dialysis. We might make heart transplants obsolete," he says. "We might even, in the wildest fantasies, reverse memory loss in Alzheimer's. Who knows? If we can do this kind of thing in one tissue, why not in another?"

the science /

Reprogramming Cellular Potential

THE TERM "STEM CELL" REFERS TO SEVERAL TYPES OF CELLS THAT have the ability to divide and create identical copies of themselves and to develop into specialized tissues, such as skin, kidneys, or hair. The objective is to use them to treat various human diseases in which cells are damaged, dysfunctional, or diseased.

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One type, the human embryonic-derived stem cell, exists only in the earliest days of an embryo's development and can become any of the more than 200 different cell types in the human body. These cells are called *pluripotent cells,* because they can develop into so many various tissue types. Adult stem cells are undifferentiated cells found in people of all ages and in most of the body's tissues, including the heart, skin, and intestine. They multiply by cell division to replenish dying cells and repair damaged tissues, and they self-renew indefinitely. These stem cells are destined to become cells from their tissue of origin, but they can grow into a variety of cells related to that tissue. Adult stem cells found in bone marrow, for example, can become red or white blood cells or platelets. Both types of stem cells are already in clinical trials.

Even more progressive, researchers have discovered a new source of stem cells, *induced pluripotent stem (iPS) cells*. These begin as any type of mature body cell and are genetically reprogrammed in the lab to return to an embryo-like state. They are then coaxed to become any of the different cell types in the body. In 2012, Shinya Yamanaka, MD of Kyoto University in Japan, and Sir John Gurdon of the Gurdon Institute in Cambridge, England, won the Nobel Prize for discovering iPS cells. The FDA has not yet approved the use of iPS cells in humans, although iPS therapies are preparing to enter non-human clinical trials. Research published in the journal *Nature* in January revealed a surprising new way to create pluripotent stem cells: exposing mature cells to environmental stress rather than cancer-causing factors. Hoping to identify a safer approach to reverting the cells back into an early, undifferentiated state, scientists found that soaking mature cells from mice in a mild acid solution for 30 minutes changed them into stem cells. More research is needed to learn why this occurs and to see if these stem cells behave as other stem-cell types do.

Public attitudes about stem cells for therapeutic use appear to be shifting. In the late 1990s, some groups expressed concern about the use of embryonic stem cells—taken from unused embryos donated by parents after they underwent in vitro fertilization—based on ethical, moral, or religious views. But that debate has largely subsided, researchers say, in part due to new technologies, including iPS cells. "The ability to reprogram cells to give us pluripotent cells from sources other than embryos has relieved the cloud of ethical concern that many people had, and that's a net positive," says David Scadden, MD, director of the Massachusetts General Hospital Center for Regenerative Medicine and co-director of the Harvard Stem Cell Institute.

Public support for stem-cell research has also grown with the hope that these therapies might someday treat or even cure devastating diseases, such as amyotrophic lateral sclerosis (ALS, or Lou Gehrig's disease). "If you actually talk to people who have a relative or friend with a life-threatening or serious disease, they are very willing to accept stem-cell therapies if they are done in an ethically appropriate way," explains Ellen Feigal, MD, senior vice president for research and development at the California Institute for Regenerative Medicine (CIRM). This agency was founded in 2004 after California voters approved Proposition 71, an initiative that devoted $3 billion over 10 years to stem-cell research. CIRM is currently the largest source of stem cell research funding in the world.

the hope /

Seeing Promise

DR. FEIGAL SAYS ONE OF CIRM'S GOALS IS TO HELP the most promising projects—those that are not only safe but also likely to improve many lives and have measurable outcomes—to move as quickly as possible through the regulatory process. Within the next decade, she expects several therapies to gain US Food and Drug Administration (FDA) approval, including those to treat macular degeneration.

A leading cause of vision loss in Americans ages 60 and older, age-related macular degeneration provides an ideal situation to learn about applying stem cell therapies, says Steven Schwartz, MD, of the Jules Stein Eye Institute at UCLA. "The eye is a perfect target for a number of reasons: You may not need a lot of therapeutic cells; you can detect the cells with both diagnostic imaging and clinical examination; and after they are transplanted, you can measure their function" with non-invasive diagnostic studies, Dr. Schwartz explains. Patients who receive the treatment may not need a cocktail of immunosuppressant drugs, because parts of the eyes are "immunoprivileged," meaning they typically mount less of an immune response compared to other organs.

Dr. Schwartz is currently leading two Phase 1 clinical trials, testing the safety of stem-cell therapy in patients with age-related macular degeneration and Startgardt macular dystrophy, a form of macular degeneration found in younger people. He and his colleagues use embryonic stem cells (which they chose, in part, because they are scalable and the science is much further along) to make retinal pigment epithelial cells, which they place beneath the retina. Early results are positive: The first patients seem to have experienced no safety problems, such as abnormal cell growth, and they say they are seeing more clearly. "Vision is very hard to measure and quantify in patients who are nearly blind and legally blind to begin with," Dr. Schwartz says. Sometimes seeing just a few letters on an eye chart is a major improvement. "In this early uncontrolled study, we have had some patients who seem to be seeing much better and others in whom we cannot tell if the improvement is real or a placebo effect," Dr. Schwartz says. "I cannot quantify that right now, except to say that, if the results hold up, they will be pretty hopeful."

Diabetes is another area where stem cell therapies could produce tremendous benefit. CIRM is working with ViaCyte Inc., a company in San Diego, Calif., on a human embryonic stem cell-derived therapy enclosed in a device about the size of a credit card. The device would be implanted under the skin and release what are known as progenitor cells that produce insulin in response to blood-glucose levels. "It will react in real time and produce just the right amount of insulin," Dr. Feigal says. She expects the device to enter clinical trials later this year.

One of the only stem-cell therapies currently in wide use, bone marrow transplants have been conducted for more than three

/ futures

Trials & Tabulations

FOR INVESTMENT OPPORTUNITIES with Capricor Therapeutics Inc., visit *capricor.com*. For investment opportunities with ViaCyte, visit *viacyte.com* or contact Paul Laikind, PhD, president and chief executive officer, at plaikind@viacyte.com. Dr. Ellen Feigal at the California Institute for Regenerative Medicine (CIRM) can also help with information for investing in regenerative medicine technology as well as philanthropic and investment opportunities across CIRM's portfolio. efeigal@cirm.ca.gov

For a list of stem cell clinical trials that are currently recruiting patients, visit the US National Institutes of Health website, *clinicaltrials.gov*.

decades, most often in patients with blood cancers such as leukemia. To receive a bone marrow transplant, patients usually need a sibling with a perfect genetic match, but only 25 to 30 percent of people have such a match, says Robert Brodsky, MD, director of the Division of Hematology at the Johns Hopkins University School of Medicine. He and his colleagues have developed a way to perform bone-marrow transplants with "half-match" relatives, such as a parent, a child, and some of their siblings and half-siblings, who share only half of the patient's genetic material. "That really expands the donor pool," Dr. Brodsky explains. "Nearly everyone has a match now."

This broader pool of donors creates options for patients with sickle-cell anemia, a disease in which the body produces misshapen red blood cells, causing excruciating pain. The disease can be treated with bone-marrow transplants, but eligible full-match donors are rare. So Dr. Brodsky and his collaborators developed a protocol to transplant bone marrow from half-match donors in sickle-cell patients. In successful cases, the defective stem cells that produced the sickle-shaped red blood cells are replaced with healthy stem cells, and patients are completely cured.

Results of a preliminary clinical trial showed that among 17 sickle-cell patients, 11 transplants were successful, prompting the Clinical Research Forum to name this one of the Top 10 Clinical Research Achievements of 2012. Dr. Brodsky suspects that a similar treatment could help people with autoimmune diseases by "rebooting" their immune systems, and he is poised to launch a clinical trial that will treat patients with lupus.

While some researchers and clinical trial patients hunger for swift results, still more dream of future developments that sound like science fiction: cures for ALS and a host of rare and devastating childhood diseases; treatments to grow motor neurons in patients with spinal cord injuries; and therapies to stimulate the growth of insulin-producing Beta islet cells in diabetic patients.

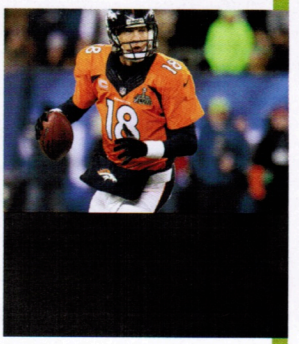
Clinical trials are essential to determining whether these treatments will help and are safe. Many of the most promising therapies are only in a Phase 1 or Phase 2 clinical trial and still face many hurdles before FDA approval. However, research is moving forward, says Dr. Scadden. "But, of course, the pace is incredibly slow for people suffering, which is frustrating for those of us wanting to make a difference for those patients. Only through the ongoing commitment of talented young scientists and, frankly, the continued investment on the part of our nation will we be able to get there."

In the meantime, Dr. Feigal of CIRM encourages interested parties to volunteer for clinical trials. "Participate in the clinical trials so that we can get the answers sooner," she says. Stem-cell therapies are also a growth area for investment, with pharmaceutical companies just starting to fund research on the use of stem-cell therapies. "Sustainable sources of funding are going to be important to make sure this technology continues to advance and thrive," Dr. Feigal says. "Opportunities to help the enterprise abound." ✦

KEVIN C. COX/GETTY IMAGES

Joint Effort

STEM-CELL TREATMENT HAS BECOME increasingly popular for elite athletes—including Denver Broncos quarterback Peyton Manning, who underwent the procedure in Europe in 2011—seeking to heal orthopedic trauma and degeneration. Orthopedic spine surgeon Kenneth Pettine, MD, co-founder of the Orthopedic Stem Cell Institute, The Spine Institute, and Rocky Mountain Associates in Orthopedics in Johnstown, Colorado, has successfully treated patients with a range of orthopedic problems, including back and neck injuries and arthritis, using bone marrow concentrate (BMC). This fluid is composed of the patient's own mesenchymal stem cells (which can become cartilage cells, bone cells, or fibroblasts), as well as red and white blood cells and other bone-marrow components. For this procedure, the patient is mildly sedated while the doctor draws bone marrow from the patient's hip. The marrow is then spun in a centrifuge and injected into the area of injury.



Denver Broncos quarterback Peyton Manning underwent a stem-cell treatment in 2011.

Dr. Pettine believes BMC provides relief from injuries because it has anti-inflammatory properties; it stimulates blood vessel development, increasing blood flow to an injured area; and the stem cells help replace damaged tissues with new, healthy cells. Dr. Pettine himself recently underwent BMC treatment for arthritis in his ankles and a knee. After a month, he says that his knee, which he had considered replacing, is now 50 percent better. But he acknowledges what he calls "legitimate criticism that [BMC therapies] have not been subjected to a prospective randomized study," and that most clinics are not collecting follow-up data on these procedures. At the Spine Institute, he and his staff are tracking outcomes of 400 patients.

He predicts that these therapies will reshape the practice of orthopedic medicine: There may come a day when he will no longer perform 10 surgeries a week. Patients in his clinic pay $5,000 to $7,000 out of pocket for BMC treatment, but that is a fraction of the $50,000 to $75,000 charge to insurance when Dr. Pettine operates on a patient's back. "In three to five years, insurance companies are not going to authorize most spine surgeries, or hip or knee replacements, until patients fail this therapy," he says.