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Stem Cell Research: The Quest Resumes

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Scientific inspiration can come from anywhere — a person, an event, even an experiment gone awry. But perhaps nothing can drive innovation more powerfully than the passion born of tragedy. Or, in Douglas Melton's case, near tragedy. The co-director of the Harvard Stem Cell Institute (HSCI) is one of the leading figures in the search for cures for presently incurable diseases, and his breakthrough work is challenging many long-held beliefs about the ways biology and human development work.

But it was a very personal experience that brought Melton to stem cells, one that 17 years later he still finds difficult to discuss. When his son Sam was 6 months old, he became ill with what his parents thought was a cold. He woke up with projectile vomiting and before long began taking short, shallow breaths. After several hours, he started to turn gray, and Melton and his wife Gail brought the baby to the emergency room. For the rest of that afternoon, doctors performed test after test, trying to figure out what was wrong. "It was a horrific day," says Melton.

It was not until that evening that a nurse thought to dip a testing strip into Sam's urine and they finally got a diagnosis. The boy's body was flooded with sugar; he had Type 1 diabetes. Then, as now, the disease had no cure, and patients like Sam need to perform for themselves the duties their pancreas cannot — keeping track of how much glucose they consume and relying on an insulin pump to break down the sugars when their levels climb too high. The diagnosis changed not only Sam's life but the lives of his parents and older sister Emma as well. Throughout Sam's childhood, Gail would wake every few hours during the night to check his blood sugar and feed him sugar if his concentration fell too low or give him insulin if it was too high. "I thought, This is no way to live," says Melton. "I decided I was not just going to sit around. I decided I was going to do something."

Trained as a molecular biologist in amphibian development, Melton began the work he pursues today: trying to find a way to make insulin-producing cells by using stem cells. "It was a

courageous thing to do because he was at the pinnacle of his career," says Gail. "He brought home textbooks on the pancreas to figure it all out." Nearly two decades later, Melton is convinced that stem cells will be a critical part of new therapies that will treat and maybe cure not only diabetes but also other diseases for which there are no answers today.

Melton's confidence is testament to the extraordinary advances in stem-cell science, some of which have brought the promise of breakthrough therapies for conditions like diabetes, Parkinson's and heart disease closer than ever before. The cells filling petri dishes in freezers and incubators in Melton's lab and others around the world are so vastly different — in provenance, programming and potential — from the stem cells of just two years ago that even the scientists leading this biological revolution marvel at the pace at which they are learning, and in some cases relearning, rules of development. Until recently, the field has revolved around either embryonic stem cells — a remarkably plastic class of cells extracted from an embryo that could turn into any of the body's 200 tissue types — or their more restricted adult cousins, cells taken from mature organs or skin that were limited to becoming only specific types of tissue. On Jan. 23, after nearly a decade of preparation, the Food and Drug Administration approved the first trial of an embryonic- stem-cell therapy for a handful of patients paralyzed by spinal-cord injuries.

But today the field encompasses far more than just embryonic and adult stem cells; it has expanded into the broader field of regenerative medicine, and Melton's lab at Harvard is at the vanguard, bringing the newest type of stem cells, which do not rely on embryos at all, closer to the clinic, where patients will actually benefit. Last summer, Melton stunned the scientific community with yet another twist, finding a way to generate new populations of cells by reprogramming one type of fully mature cell so it simply became another, bypassing stem cells altogether. "If I were in high school, I can't imagine anything more interesting than stem cells," says Melton. "This is so cool. It's so amazing that cells in the body have this potential that we can now unlock by asking question after question."

A Battle Joined

That hidden power in each of us did not become obvious until 1963, when Canadian researchers Ernest McCulloch and James Till first proved the existence of stem cells, in the blood. These cells possess the ability to divide and create progeny — some of which will eventually expire, others that are self-renewing. The pair irradiated mice, destroying their immune cells. They then injected versatile bone-marrow cells into the animals' spleens and were surprised to see a ball of

cells grow from each injection site. Each mass turned out to have emerged from a single stem cell, which in turn generated new blood cells.

That discovery led, 35 years later, to James Thomson's isolation of the first human embryonic stem cells, at the University of Wisconsin in 1998. And that milestone in turn inspired researchers to think about directing these cellular blank slates to eventually replace cells that had been damaged or were depleted by disease. The key lay in finding just the right recipe of growth factors and nutrients to induce a stem cell to become a heart cell, a neuron, an insulin-making cell or something else. It would take decades, the researchers all knew, but new therapies were sure to come.

Then, in 2001, everything changed. The use of discarded embryos made embryonic-stem-cell research deeply controversial in the U.S. Citing moral concerns, then President Bush restricted federal funding for the study of human embryonic stem cells. Under the new policy, U.S. government funds could be used only to study the dozens of embryonic cell lines already in existence — many of which proved not to be viable.

The decision sent some leading scientists abroad, to Britain, Singapore and China, where the governments were more receptive to their work. Others who stayed behind but lacked private funding shifted their attention from embryos to the less versatile adult stem cells. Federally backed scientists, like Melton, who continued embryonic work were forced to adopt a byzantine system of labeling and cataloging their cell cultures and equipment so that government money was not used to grow forbidden cells — and government microscopes were not even used to look at them.

Those days may soon be over. Barack Obama campaigned on a promise to lift the research ban and support "responsible oversight" of the stem-cell field. For scientists, that means "we can stop the silliness," says Melton.

As welcome as that change will be, it may be less urgent now — owing primarily to the work of scientists like Melton. While embryonic stem cells remain the gold standard for any treatments that find their way into the clinic, newer techniques using the next-generation stem cells may soon surpass the older ones.

The Fighter

In looks and demeanor, Melton is the quintessential professor, soft-spoken and thoughtful, someone who appears more mentor than maverick. Born and raised on the South Side of

Chicago, he developed an early fascination with animal development; that curiosity led to a bachelor's degree in biology at the University of Illinois in 1975, then a second undergraduate degree, in the history and philosophy of science, at Cambridge University on a Marshall Scholarship. Melton remained there for his Ph.D. work, studying under Sir John Gurdon — the first to clone a frog. At Harvard, Melton teaches a frequently oversubscribed undergraduate course on science and ethics, in which he uses his keen sense of logic to provoke. When the class discussed the morality of embryonic-stem-cell research, Melton invited Richard Doerflinger of the U.S. Conference of Catholic Bishops to present arguments against the field. Melton asked Doerflinger if he considered a day-old embryo and a 6-year-old to be moral equivalents; when Doerflinger responded yes, Melton countered by asking why society accepts the freezing of embryos but not the freezing of 6-year-olds.

Clearly, Melton does not shrink from a fight. As Washington's squeeze on stem-cell research tightened in the early part of this decade, he decided to take action, providing life support for what remained of the U.S. stem-cell community. Not convinced that an entire field could make much progress relying on a few dozen cell lines of questionable quality, in 2004 he used funds HSCI receives from the Juvenile Diabetes Research Foundation and the Howard Hughes Medical Institute, as well as from Harvard alumni, and developed a more streamlined method for generating stem-cell lines from embryos. He created more than 70 new ones and has since distributed 3,000 copies to scientists around the country for free.

"Doug drew a line in the sand," says Alan Trounson, president of the California Institute of Regenerative Medicine, the organization charged with dispensing state money for embryonic-stem-cell research. "He turned the tables on an Administration that was incredibly negative toward stem cells and showed [it] we are not going to tolerate being put out of this field by ideological views that we don't think are correct." Melton's motivation was, again, both professional and intensely personal. Two months after Bush announced his ban, Melton's daughter Emma, then 14, also received a diagnosis of Type 1 diabetes.

In part owing to the restrictive U.S. policy, the momentum in stem-cell research seemed to shift overseas. In 2004, South Korean researcher Hwang Woo Suk announced that he had generated the first human embryonic stem cells from healthy people — and in the following year, from afflicted patients themselves — using an abbreviated cloning method. The latter feat would mean that cardiac patients could essentially donate themselves a healthy new heart without fear of rejection.

The news was huge — but it was also a lie. In 2006, Hwang admitted he had falsified his results. (Melton's colleague at HSCI, Kevin Eggan, finally created embryonic stem cells from patients in 2008.) Although Hwang became a pariah, he had the right idea. Melton and others had been trying to do just what the Korean scientist claimed to have done — grow a new population of a patient's own cells. The key to the process is a supply of fresh, good-quality human eggs, which incubate skin cells taken from a patient. Building up such a stockpile, however, proved practically impossible. The egg-extraction process is invasive and carries certain risks; after the state of Massachusetts prevented donors from being compensated for their eggs, out of fear the women would feel coerced, HSCI ended up with only one volunteer out of more than two years of recruiting.

Melton faced mounting political pressure too. In 2004, voters in California approved a measure providing \$3 billion in state funding to embryonic-stem-cell research. That threatened to draw scientists in the stem-cell community west, and Melton took pains to foster a "band of brothers" mentality. "I tried to create a cocoon here," he says, "and tell people that your job is to focus on the science. Don't worry what the politicians say." By then, Melton's team was one of only a handful in the country working on embryonic stem cells and was making headway in teasing apart the myriad critical steps needed to guide these impressionable cells into becoming insulin-generating cells. Both as a scientist and as a father, Melton remained convinced that the federal restrictions simply could not survive. He continued to insist that "the science is so significant that it will change the policy."

And then, astonishingly, it did. In June 2006 a modest researcher from Japan made a startling announcement at the International Society for Stem Cell Research conference in Toronto. Shinya Yamanaka quietly described a study in which he took skin cells from a mouse and stirred them in with varying genetic cocktails made from a recipe list of 30 genes known to be important in development. When he hit on the right four genes and inserted them into the cells aboard retroviruses, he wiped the cells clean, reprogramming them and returning them to an embryo-like state without ever creating the embryo. Four genes, he told his audience, was all it took to undo a lifetime's worth of delicate genetic tapestry. No need for eggs, no need for embryos. Could it be that easy? Were the debate and controversy over embryonic stem cells now rendered moot? "It was unquestionably unexpected," says Melton of the breakthrough.

A year later, Yamanaka followed up his work by reporting success with the same four factors in turning back the clock on human skin cells. At about the same time, in Wisconsin, Thomson achieved the same feat using a different cocktail of genes. With those studies, what became

known as induced pluripotent stem cells (iPS cells) were suddenly a reality. Never mind the frustratingly fickle process needed to create embryonic stem cells; this was something any molecular-biology graduate student could do. "We figured somebody would have success with reprogramming. We just thought that somebody would come along a generation from now," says Dr. David Scadden, Melton's co-director at HSCI. "Yamanaka threw a grenade at all of that, and now all of the doors are open."

Beyond Stem Cells

Melton, for one, isn't wasting any time before running through those doors. The iPS technology is the ultimate manufacturing process for cells; it is now possible for researchers to churn out unlimited quantities of a patient's stem cells, which can then be turned into any of the cells that the body might need to repair or replace.

Before that can happen, however, Melton wants to learn more about how diseases develop. And iPS cells make that possible too. For the very first time, he can watch Type 1 diabetes unfold in a petri dish as a patient's cells develop from their embryonic state into mature pancreatic cells. The same will be true for other diseases as well. "There is a good reason we don't have treatments for diseases like Parkinson's," says Melton. "That's because the only way science can study them is to wait until a patient appears in the office with symptoms. The cause could be long gone by then, and you're just seeing the end stages." No longer. Now the major steps in the disease process will be exposed, with each one a potential target for new drugs to treat what goes wrong. "This is a sea change in our thinking about developmental biology," says Dr. Arnold Kriegstein, director of the Institute for Regeneration Medicine at the University of California, San Francisco. "I consider it a real transformative moment in medicine."

The true power of reprogramming, however, does not stop with the stem cell. This summer, Melton flirted with the rules of biology once again when he generated another batch of history-making cells, switching one type of adult pancreatic cell, which does not produce insulin, to a type that does — without using stem cells at all. Why, he thought, do we need to erase a mature cell's entire genetic memory? If it's possible to reprogram cells back to the embryo, wouldn't it be more efficient in some cases to go back only part of the way and simply give them an extreme makeover? Using mouse cells, Melton did just that, creating the insulin-producing pancreatic cells known as islets. "The idea now is that you can view all cells, not just stem cells, as a potential therapeutic opportunity," says Scadden. "Every cell can be your source."

Realizing that potential — and with it, the prospect of successful treatments for conditions like Parkinson's or diabetes — may still be a few years away. Even iPS cells have yet to prove that they are a safe and suitable substitute for the diseased cells they might eventually replace in a patient. Ensuring their safety would require doing away with dangerous genes that can also cause cancer, as well as the retroviral carriers that Yamanaka originally used. Melton's team has already replaced two of the genes with chemicals, and he anticipates that the remaining ones will be swapped out in a few years. There are also hints that the iPS cells' short-circuited development makes them different in some ways from their embryonic counterparts. In mice, embryonic stem cells can generate a new mouse clone; iPS cells from the animals have so far stopped short of the same feat, aborting in midgestation, suggesting that some development cues may be missing. "It certainly makes me cautious," says Eggen.

Even if iPS cells do not prove as stable and as versatile as embryonic stem cells when they're transplanted into patients, they remain a powerful research tool. And if nothing else, they will have opened our eyes to the remarkable plasticity of biology and made possible new ways of thinking about repairing and replacing damaged tissues so we may consider not only treating but also curing disease. "It's a wonderful time," says Scadden. "Keep your seat belt on, because this ride is going to be wild."

For patients like Sam and Emma Melton, that ride carries with it the possibility of being free of the insulin pumps and injections they endure to keep their blood sugar under control. "I definitely think about how my life would be different if there is a cure," says Sam. His father is keenly aware that the ability of stem cells and reprogramming science to provide that cure is far from guaranteed. But his initial confidence in the power of the technology hasn't waned. "Everything we learned about stem cells tells us this was a really powerful approach," he says. "It would be a great shame if we let it wither and just go away." Melton, for one, is determined not to let that happen.