The Quiet Revolutionary

Dr. Ihor Lemischka takes a low-key approach to groundbreaking stem cell research.

By Philip Berroll

In 2007, Ihor Lemischka, Ph.D. was a professor of molecular biology at Princeton University, where he had worked for more than two decades. His research in stem cell biology and its possible medical uses had brought him international renown.

But he was not satisfied.

"Princeton has no medical institution," he explains. "And in stem cell research, you sort of hit a glass ceiling when you don't have access to a medical institution or school. I was mostly working with mouse cells, and I really wanted to get more involved in studying human stem cells and human diseases."

So when Dr. Lemischka was offered the directorship of Mount Sinai's Black Family Stem Cell Institute, he eagerly accepted – and now says, "My only regret is that I didn't do it sooner."
At Mount Sinai, Dr. Lemischka, who is also Professor of Gene and Cell Medicine at the Mount Sinai School of Medicine, is building what he calls "a world-class stem cell institute" where he is taking his research to the next level – to the threshold of a revolutionary breakthrough in the treatment of genetics-based disease.

Dr. Lemischka, a low-key personality who speaks in calm, measured tones, is careful to avoid hyperbole in discussing his work. But as he describes its potential – the hope that it could lead to a cure for such devastating conditions as diabetes and Parkinson's and Alzheimer's diseases – his enthusiasm comes through.

"I find it to be probably the most exciting time ever in my career right now," he says.

From a Few Cells, a World of Knowledge

Dr. Lemischka, who holds a B.A. from Johns Hopkins and a Ph.D. from M.I.T., is a specialist in induced pluripotent stem cell (iPSC) research, which uses stem cells taken from adult patients to study the causes of genetics-rooted disease.

The research technique, derived from what is known as the Yamanaka technology (named for Dr. Shinya Yamanaka of Kyoto University, who first developed it) begins with the removal of skin cells from adult patients. Then three or four genes are introduced into the cells. The genes' DNA "reprograms" the cells into pluripotence – meaning that they have the potential to turn into any of the 220 cell types in the human body. And because the iPS cells are genetically identical to those of the patient, they will contain the same genetic mutation that caused that person's particular disease.

The significance of this is profound. "We now have a way to develop tools that allow us to understand the ideology of complex, genetics-based diseases," says Dr. Lemischka, "and from there, to build a platform for better diagnostics for these diseases – and the discovery of drugs to treat them."

In addition, Dr. Lemischka foresees a day when iPSC technology could be used to create healthy cells that could then be transplanted into patients, replacing diseased tissue in organs such as the heart.

"If you were to derive, say, some transplantable cells from a patient's iPS cells and then try to put them back into the patient, because of the shared genetic identity there's no problem of immune system rejection," he observes. "For example, even if you were lucky enough as a researcher to get a biopsy sample of human heart tissue, you can't grow human cardiac cells; but with iPS cells, we can make as many cardiac muscle cells as we want."

An Early Breakthrough

Not long after arriving at Mount Sinai, Dr. Lemischka had his first opportunity to put his expertise to use.

Pediatric cardiologist Bruce Gelb, MD, the director of Mount Sinai's Child Health and Development Institute, and his research team had discovered the first gene ever associated with two common genetic diseases, Noonan and LEOPARD syndromes ("LEOPARD" is an acronym for the first letters of seven symptoms associated with the disease). But Dr. Gelb wanted to learn more about LEOPARD's deadliest symptom, hypertrophic cardiomyopathy (HCM) – a cardiac

condition in which heart cells become enlarged and the heart muscle thickens and grows too stiff to function properly.

So the two researchers joined forces. Using skin cell samples from two LEOPARD patients, they used the iPS protocols to produce a limitless supply of heart cells – exact copies of those in the patients. And they found that the copied cells were enlarged in the same manner as the originals. This was a major research achievement: through iPSC technology, Drs. Lemischka and Gelb had produced one of the world's first *in vitro* (often referred to as "disease in a dish") models of cardiovascular disease – an important advance in tackling one of the greatest challenges to global health.

"By getting a defective heart cell in a dish that recapitulates to a large extent – or even identically – a disease such as HCM," Dr. Lemischka explains, "you can track the development of these heart cells and ask, 'Where do you see the first example of something going amiss?' Having pinpointed that, you can say, 'Okay, let's see if we can find small molecules that delay, or reverse, or block this first thing that's gone wrong.' And it's not possible to do this in any other way."

The work of Drs. Lemischka and Gelb was widely praised after they published their findings as the cover story in the June 10, 2010 issue of *Nature*, the world's preeminent scientific journal. Since that time, Dr. Lemischka and his staff at the Black Family Stem Cell Institute – which includes his wife, Dr. Kateri Moore, who came with him from Princeton – have moved ahead with research involving a wide range of afflictions, including cancer, diabetes, liver disease and spinal cord injury, in collaboration with specialists in other disciplines at Mount Sinai.

"It's very exciting to work clinicians and translational researchers using human iPSC," he says. "Bringing together different groups with different sets of complementary expertise makes for a synergistic effort that is much greater than the sum of excellent parts."

Dr. Lemischka believes that even diseases affecting the brain are within the realm of possibility.

"I could imagine developing ways of treating Parkinson's disease," he says, "because we know quite a lot about it – we know which neurons are missing or damaged and we could make those

neurons in a dish filled with stem cells. And with Alzheimer's, to be able to study how the neurons might degenerate – in vitro, in a dish – allows you again to develop platforms for drug discoveries."

"Education is the Key"

Still, Dr. Lemischka makes it clear that iPSC research is not yet "as far advanced" as embryonic stem cell studies, which remains the most fully developed form of stem cell research. "We know that in many ways, iPS cells closely resemble embryonic stem cells," he notes, "but we don't know how exact that similarity is. Before we can say, 'These cells can replace embryonic stem cells,' we'll need to do in-depth comparative studies for quite a long time. We're all very excited about iPS cells, but to jump to the conclusion and say they're the same, and can already replace embryonic stem cell research, is way premature."

And because of the continued value of embryonic research, Dr. Lemischka does not shy away from addressing its main point of controversy: the extraction of cells from frozen embryos which are destroyed in the process.

"I do not object to somebody's personal moral, ethical or theological beliefs, such as the belief that a fertilized egg, an embryo, is the same as a human being – I'm respectful of that," he says. "But when a minority of people influences the government to dictate policy for the whole country, I feel that borders on a violation of church-state separation – which is one of the things this country was founded on."

Ultimately, says Dr. Lemischka, "education is the key" to changing minds. "I've seen it work," he adds. "I've had experiences where I would give a half-hour talk to a group of non-scientists – a retirement community, for example – and people have come up to me afterwards and said, 'I came here very anti-embryonic stem cell research, and now I have a different opinion. You've changed my mind.'"

And he is certain that concrete results will also help influence public opinion: "Once there's some cure – let's say, a child with diabetes is cured by stem cell transplants – it then becomes a

very different ballgame, because then the outcry from the public of 'How can you possibly deny my child this?' would become huge."

The Next Leap Forward

For all his enthusiasm, Dr. Lemischka cautions against predicting quick benefits from any form of stem cell research.

"We all believe that there will be stem cell-related cures," he says, "but we can't with any certainty say how soon. So it's important – and again, this is where education comes in – to create a realistic set of milestones which you can take the time to explain to the public. You don't say something like 'next year, we're going to be able to cure your father's Parkinson's.' Because then, inevitably, there's a public backlash – and it's the public that largely pays the bills, since we run in large part on federal or state money."

However, Dr. Lemischka acknowledges "that we see amazing advances happening every day. Keep in mind that there are *already* stem cell cures, such as cord blood transplantation" – a stem cell therapy widely used for leukemia, sickle-cell anemia and other diseases – "where you transplant a blood-forming stem cell from a donor to a recipient.

"It's one of the best things about being in this area, the fact that you don't know what's next. It's incremental, by and large – 99.9 percent of it. But every once in a while, you get something that moves the whole field forward with a leap. You can't anticipate these things, but you have to be open to them."

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