

# THE ENDLESS POSSIBILITIES OF BETA CELL REGENERATION

By Robert S. Dinsmoor

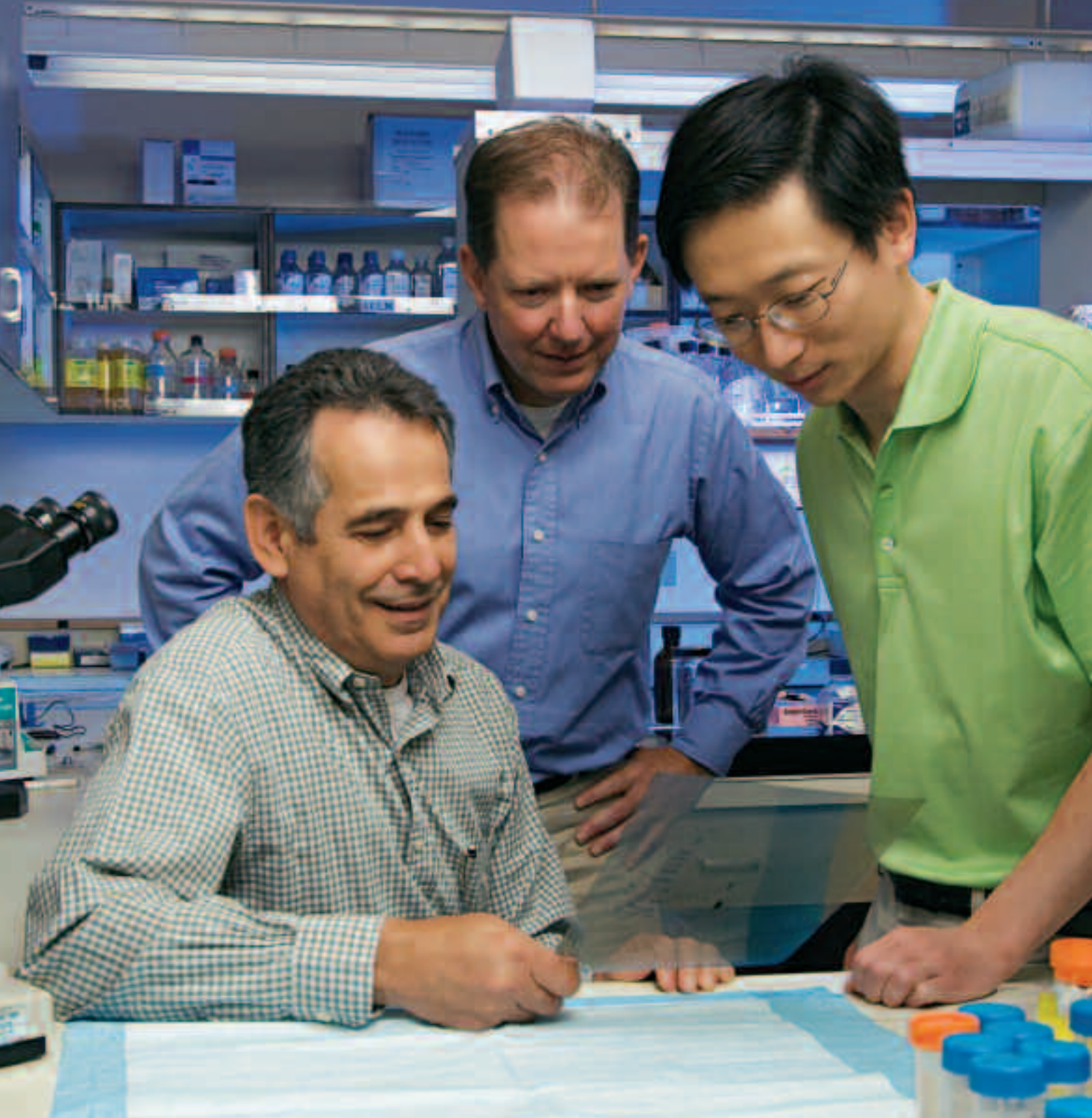
**Over the past two decades,** there has been growing evidence that the beta cells of the pancreas, which are destroyed in type 1 diabetes, may actually be able to regenerate under certain circumstances. Recognizing the potential of this phenomenon in delaying the onset of or curing type 1 diabetes, JDRF recently initiated a groundbreaking research collaboration in beta cell regeneration. If researchers can discover exactly how beta cells regenerate, they may be able to devise ways of regenerating beta cells in some stage of diabetes to delay its development or cure it. Harnessing the beta cells' ability to regenerate might also eventually be exploited to provide a virtually unlimited supply of insulin-producing cells to transplant into people with diabetes, or at least improve the yield of existing islet transplantation protocols.

## **WHAT IS BETA CELL REGENERATION?**

Scientists now understand, in broad strokes, how the pancreas develops from the embryo. The embryo has three layers of cells called the ectoderm, the endoderm, and the mesoderm. The ectoderm forms the skin and central nervous system. The mesoderm gives rise to the cells from which blood, bone, and muscle are formed. The endoderm forms the respiratory and digestive tracts, including a

primitive gut tube, which eventually forms the gastrointestinal tract. The gastrointestinal tract forms buds, which eventually take the form of the pancreas. From these pancreatic buds, small branches form that become the pancreatic ducts, which carry important digestive enzymes from the pancreas to the gastrointestinal tract. From cells that appear to proliferate within these ducts, clusters of cells known as the islets of Langerhans form. These islets are made up of four





L TO R: UC SAN DIEGO'S ALBERTO HAYEK, M.D., JDRF'S RICK JACK, PH.D., AND SCRIPPS RESEARCH INSTITUTE'S SHENG DING, PH.D.

different types of endocrine cells—alpha cells, beta cells, gamma cells, and delta cells—all of which secrete important hormones. It is the beta cells, which make and secrete insulin, that gradually are destroyed in the type 1 diabetes disease process, when the body launches a misguided immune attack on the islets.

It has been known for some time that mammals (including humans) eventually regenerate some types of cells to replace injured

cells. There is also growing evidence that humans and animals have some ability to regenerate beta cells. In pregnant or obese individuals, for example, the mass and number of beta cells expands considerably to meet the body's increased insulin requirements. Diabetes researchers are now trying to find out the exact mechanisms behind this regeneration so that they can stimulate the process to treat diabetes.



HARVARD'S DOUGLAS MELTON, PH.D.

Beta cell regeneration raises tantalizing possibilities for treatment of type 1 diabetes. People in the earliest stages of the disease could be treated to delay—or prevent—full-blown clinical diabetes.

years. However, there are not nearly enough donor pancreases available each year to provide islets to everyone who could benefit from an islet transplant. In many cases, it takes multiple donor organs to induce insulin independence in a single transplant recipient. Ideally, this problem could be solved by exploiting the principles of beta cell regeneration to grow large numbers of functional beta cells from donor organs in tissue culture

and then transplanting the expanded beta cells.

At the very least, researchers hope that beta cell regeneration could be used to enhance currently used islet transplantation protocols: “We hope to be able to replicate human islets to the point in which, at minimum, we could at least have the same degree of success as whole organ transplants,” says Alberto Hayek, M.D., professor of pediatrics at the University of California-San Diego and director of the Islet Research Laboratory at the Whittier Institute in La Jolla, California. “Right now, you need two or three pancreases to get enough islets to do one islet transplant. With whole pancreas transplantation, this ratio is one to one. So, if we can replicate cells in vitro and reverse the ratio, could we get enough cells out of one pancreas to transplant into three recipients? That would be a very big advance in the field of islet transplantation using today’s technology.”

No organization is more committed to exploring the possibilities of beta cell regeneration than JDRF. In March 2004, JDRF hosted a Beta Cell Regeneration Workshop in New York City. The purpose of the workshop was to cull the perspectives of 25 of the world’s leading scientists and to shift this line of research into high gear to achieve tangible results as quickly as possible. Out of this workshop grew the Regeneration of Beta Cell Function (RBCF)

### THE PROMISE OF REGENERATION

Beta cell regeneration raises tantalizing possibilities for the treatment of type 1 diabetes. It is known, for example, that the autoimmune destruction of beta cells is gradual and that many individuals with long-standing diabetes still have detectable levels of C-peptide, a by-product of insulin production in the pancreas. Further, it may be that the efficiency of the body’s natural regeneration of beta cells is marred by hyperglycemia (high blood sugar), which can damage newly regenerated beta cells, and by the autoimmune process that caused diabetes in the first place—and will likely attack newly regenerated beta cells as well. If researchers could intensify diabetes control, learn to turn off the autoimmune response, and give patients something that would stimulate beta cell growth, regeneration and restoration of functional beta cell mass might occur even in established diabetes. Alternatively, people in the very earliest stages of the disease could be treated to delay the onset of—or prevent—full-blown clinical diabetes.

Insights into the mechanisms behind beta cell regeneration could be a boon to islet transplantation. The success of the Edmonton Protocol has shown that islet transplantation can essentially restore insulin independence in individuals with type 1 diabetes for several

Program, in which JDRF is committing \$10 million over two years. The goal of this aggressive initiative is to develop novel ways to activate beta cell regeneration as an alternative to islet transplantation. In phase 1 of the program, researchers will try to increase functional beta cells in culture and in vivo in animal models. Phase 2 will explore methods to induce beta cell regeneration in individuals with type 1 diabetes.

JDRF has brought together an international team of 16 scientists from 13 universities and medical centers from five countries who will collaborate in a milestone-driven program, with monthly feedback to JDRF, in order to fast-track potential therapies. According to Rick Jack, Ph.D., a JDRF consultant who is overseeing the RBCF Program, JDRF will play a managerial role to accelerate this area of research, making sure researchers get the material, tools, and information they need to meet their research goals in a timely fashion. A major focus of the program will be to use a very powerful technology called high-throughput screening to assess tens of thousands of small-molecule compounds (which might be most suitable for patients to take orally) and determine whether any of them cause proliferation of beta cells.

“We’re also looking for ways to keep beta cells happy in culture,” says Dr. Jack. “Program scientists are studying extracellular matrices, complex biological molecules that make up the material in between cells. And there may in fact be specific extracellular matrix proteins that keep beta cells happy.”

A third area is finding biomarkers to show whether someone actually has increased numbers of beta cells. “That would not only make the research go faster, but somewhere down the line, it would be a very useful diagnostic tool for physicians working with patients with newly diagnosed diabetes,” says Dr. Jack.

## WHERE DO THE NEW CELLS COME FROM?

To make beta cell regeneration happen, researchers need to know the mechanisms behind it. Research in the 1980s, much of it by JDRF researchers, showed clearly that regeneration of the pancreas could be stimulated in experimental animal models by ligating the pancreatic duct or surgically removing portions of the pancreas. Yet, the source of these new beta cells, both in laboratory animals and in man, has been hotly debated.

On the one hand, some researchers believe it happens by a process called *neogenesis*: Some kind of stem cell or precursor cell in the pancreas or its ducts differentiates into a beta cell. (Stem cells are unique cells in the body that can readily divide and differentiate into other, more specialized cells, with some of the progeny remaining as stem cells to retain this capacity throughout the lifetime of the host.) On the other hand, some believe that beta cells beget beta cells, perhaps using an intervening transformation back to a more primitive cell.

Susan Bonner-Weir, Ph.D., and colleagues at Joslin Diabetes Center and Harvard Medical School in Boston have suggested that cells lining the pancreatic ducts could in fact give rise to insulin-secreting cells. In 2000, they reported in *Proceedings of the National Academy of Sciences* that when ductal cells isolated from adult

pancreatic tissue were cultured, they could be induced to differentiate into clusters containing both ductal and endocrine cells. These cells, when cultured, could produce insulin in response to exposure to glucose—just like bona fide beta cells.

More recently, two studies have suggested that there are multipotent precursor cells that could give rise to beta cells and other pancreatic cells. Raewyn Seaberg, Ph.D., and colleagues in the Department of Medical Genetics and Microbiology at the University of Toronto in Canada, reported on identifying pancreatic and ductal cells in mice that could differentiate into certain types of nerve cells as well as the alpha, beta, and delta cells of the pancreas. Further, the newly generated “beta-like” cells were able to release insulin in a glucose-dependent manner, just like normal beta cells. They reported their findings in the September 2004 issue of *Nature Biotechnology*. Meanwhile, Dr. Atsushi Suzuki of the Salk Institute for Biological Studies in La Jolla, California, along with colleagues in Japan, found similar multipotent progenitors in mice. They reported their findings in the August 2004 issue of the journal *Diabetes*.

Gordon Weir, M.D., head of the section of islet transplantation and cell biology at Harvard Medical School in Boston says there has been a lot of circumstantial evidence that beta cells come from ductal cells, at least in humans. “When you study human pancreases in postmortem examinations, you find islets that are next to ducts that look like they’re ballooning out from the ducts. It’s guilt by association, but it suggests that neogenesis may be relatively more important in humans than it is in mice,” he reflects.

On the other hand, the notion that beta cells may replicate by self-duplication also has strong support. In the May 2004 issue of *Nature*, Douglas Melton, Ph.D., and colleagues at Harvard University reported on using a technique called genetic lineage tracing to try to determine the origins of new beta cells that formed after pancreatectomy (pancreas removal) in mice. “The purpose of that experiment was to determine the source of new beta cells in the adult animal. The question was whether new beta cells were derived from a stem cell or a progenitor, and the answer is no,” Dr. Melton says. “Namely, the new beta cells in the adult animal come from old beta cells. That is to say, pre-existing beta cells replicate to make new beta cells, and there was absolutely no evidence for beta cells coming from a stem cell in the adult mouse.”

Dr. Melton’s laboratory is now focusing on the mechanisms behind beta cell replication. “Do all beta cells replicate? At what rate do they replicate? How might we stimulate the replication? I think those are all subjects worthy of our attention,” he says. “We want to mark islets genetically so we can accurately quantitate their rate of replication. How often do they divide? Does the neighbor do the division? That sort of thing. Once we know that, we want to look for factors that are responsible for stimulating that division. This would mean using robotic screening to look for chemicals that can stimulate beta cell replication.”

## ONE POTENTIAL MECHANISM

One potential mechanism for beta cell regeneration called epithelial-to-mesenchymal transition (EMT), which also shows features of



L TO R: HARVARD MEDICAL SCHOOL'S GORDON WEIR, M.D., AND JOEL HABENER, M.D.

beta cell replication, was first proposed in the September 2004 issue of the *Journal of Clinical Investigation*. According to the lead author of the study, Rohit Kulkarni, M.D., Ph.D., an investigator at Joslin Diabetes Center and assistant professor of medicine at Harvard Medical School, EMT has traditionally been studied in the contexts of embryonic development and the growth of cancer cells, but never before in the context of beta cell regeneration.

In a study supported by JDRF, Dr. Kulkarni and colleagues at Joslin, as well as Ulupi Jhala, Ph.D., at the Whittier Institute in La Jolla, California, studied compensatory beta cell regeneration in two different genetically engineered mouse models of insulin resistance, called IRS/IRS-1 and LIRKO. They found that the regeneration occurred through a process suggestive of EMT, in which cells take

on a more primitive form in order to replicate before differentiating into beta cells.

Yet, did EMT involve replication of existing beta cells or neogenesis? “While our studies certainly support the concept of replication, we have not observed evidence linking neogenesis with EMT,” says Dr. Kulkarni. “However, we like to think that perhaps there is a precursor cell within the islet itself—a beta cell stem cell, if you like—which is different from a ductal cell.”

Dr. Kulkarni says his next focus is on exactly how EMT operates. “We’re taking islets from these mice that show EMT, analyzing the genes they express and the protein complexes they form, and comparing them side by side with control islets where EMT is not operative. We hope to identify novel protein complexes which are

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occurring during the EMT process, which will allow us to focus on the critical signaling pathways underlying the process” he explains.

“The second approach has been to use rodent models to study two proteins, called E-cadherin and beta-catenin, which we think are critical to the EMT process. We’re creating mouse models which specifically lack these proteins or are deficient in them, and then seeing whether we still get this proliferation response. And that will tell us whether these proteins really are critical,” he says.

Dr. Jhala, on the other hand, is using a more molecular approach toward this problem. According to Dr. Jhala, identifying the master regulators of EMT within beta cells would help chart a molecular roadmap and identify critical mechanisms for initiating and executing the beta cell replication program.

Other research groups have now published on EMT as well. A study reported in the December 2004 issue of *Science* showed that EMT could be induced in human islets “in the test tube.” Marvin C. Gershengorn, M.D., and colleagues at the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), a component of the National Institutes of Health (NIH) in Bethesda, Maryland, studied adult human islets donated postmortem. They removed islet cells from cadaver pancreases and exposed the cells to a medium containing fetal bovine serum, which induced them to undergo EMT.

## “REAL” BETA CELLS

**PART OF JDRF’S ROLE** in the field of beta cell regeneration may someday be to make sure regenerated beta cells meet specific standards. “When you regenerate beta cells, important questions arise,” says Christopher Rhodes, Ph.D., associate scientific director of the Pacific Northwest Research Institute in Seattle. “After a bout of regeneration, it’s important to be able to stop that regeneration, so you don’t have too much of a good thing. Too many beta cells can increase the incidence of hypoglycemia. And the other concern is that, after several bouts of beta cell division and replication, does it still function like a beta cell at the end of the day? You need a cell that is only secreting insulin at the right moments in time. A normal beta cell does not usually secrete insulin when you haven’t eaten. It only secretes insulin when your blood sugar

goes up. If you have a cell that is making and secreting insulin in an uncontrolled manner—just pushing it out, then again you risk hypoglycemia, which can be very, very dangerous.”

Dr. Rhodes, who will begin chairing JDRF’s Medical and Scientific Review Committee on July 1, feels that JDRF could play an important role here. He will be developing a laboratory program to study the function of beta cells that have been regenerated through different approaches to determine whether the newly formed beta cells are sensing their environment and manufacturing and secreting insulin just like bona fide beta cells. “We would like to test those beta cells as a service to other researchers, but we also envisage this as a means of testing human islets prior to transplantation to make sure they’re functioning well,” he says.

The new cells, which they dubbed human-islet-derived precursor cells (or hIPCs), were able to reproduce readily, doubling in number every 60 hours; however, they lost their capacity to secrete insulin. The researchers then exposed some of the hIPCs to a culture medium that did not contain the fetal bovine serum, which caused them to spontaneously develop into islet-like clusters and to begin producing insulin at very low levels.

“Our study shows that we can obtain from human cadaveric islets a cell population that can do two important things we need them to do,” explains Dr. Gershengorn, who is director of the division of intramural research at NIDDK. “We proliferate them in culture and then, when they have been expanded manifold, we can induce them to differentiate back into the hormone-expressing cells of the islets.”

According to Dr. Gershengorn, they were able to exploit key differences between epithelial and mesenchymal cells in inducing beta cell regeneration. “The mesenchymal cells have two very important characteristics. One, they know how to migrate, or move around, especially to form aggregates. Two, they know how to proliferate, and we must take advantage of both of these to form islets. These cells proliferate as a monolayer of cells adherent to the tissue culture surface. When we induce them to begin to differentiate, they migrate together to form cell clusters. These clusters, which allow cell-to-cell interaction, allow for the induction of the epithelial program. In other words, they begin expressing a new set of genetic markers that allow them to differentiate and to interact with each other. Over time, once they have started to achieve this epithelial phenotype, they start to express endocrine genes as well—the genes we find in an adult islet. They begin making insulin, glucagon, and somatostatin. They also make important proteins, expressed in the mature islet, that allow for glucose-stimulated insulin secretion,” he explains.

The regenerated islet clusters did not secrete that much insulin—only about  $\frac{1}{5,000}$  as much insulin as is produced by healthy islets—when studied over several weeks. Yet, Dr. Gershengorn notes that insulin secretion increased over time. He and colleagues plan to study these cells in animal models over a longer period of time to see whether insulin secretion increases. They are also working to define culture environments that optimize growth, proliferation, and differentiation—without the use of fetal bovine serum. “People often refer to serum as a ‘black box,’” he says. “There are a lot of things in it that are obviously good, but we don’t know what they are. So, we want to wind up with a chemically defined medium in which we can both proliferate the cells and then optimally differentiate them.”

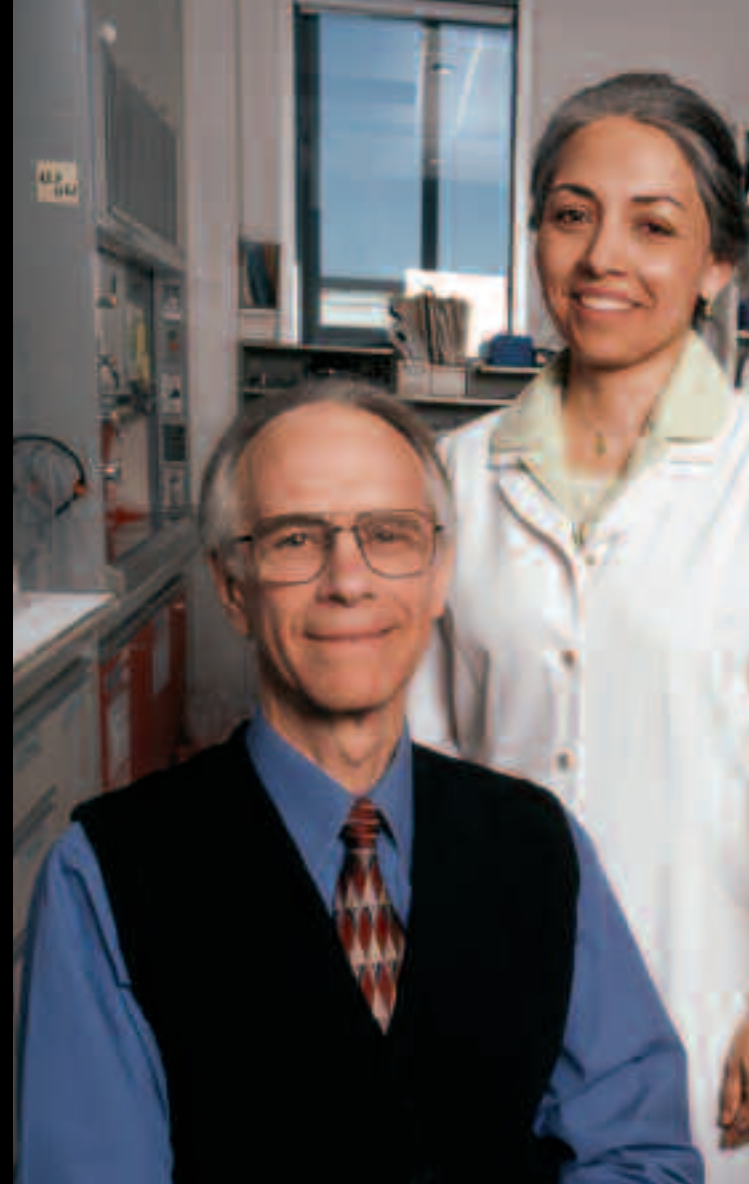
**“This potential therapy has moved rapidly into human clinical trials.”**

### AGENTS THAT STIMULATE BETA CELL REGENERATION

Naturally, researchers are eager to identify and study substances that can be used to stimulate beta cell regeneration. One key player is a growth factor called glucagon-like peptide-1 (GLP-1). “GLP-1 is made in the intestine and is released in response to meals,” explains Joel Habener, M.D., professor of medicine at Harvard Medical School and chief of the Laboratory of Molecular Endocrinology at Massachusetts General Hospital in Boston. “The first biologic action of GLP-1 we were interested in was that its action on beta cells is glucose dependent, so that when blood glucose levels fall below normal levels, its action—stimulating the secretion of insulin—clearly goes away.”

They soon discovered other potentially beneficial effects in diabetes: It delayed gastric emptying, which blunted hyperglycemia after meals. It curbed appetite. Though the concept was controversial at first, they found that it caused beta cell growth. Most recently, they discovered that it could inhibit apoptosis, or programmed cell death, in beta cells. “So, it has a number of wonderful effects in diabetes,” says Dr. Habener.

These effects are of great interest to pharmaceutical companies. Amylin Pharmaceuticals, of San Diego, in collaboration with Eli Lilly and Company of Indianapolis, Indiana, is developing and testing a long-acting analog of GLP-1 called exenatide (brand name Byetta) in patients with type 1 and type 2 diabetes. In fact, Byetta received marketing approval from the U.S. Food and Drug Administration in April 2005 as an adjunctive treatment for type 2 diabetes that is not already adequately controlled by a combination of metformin and a sulfonylurea drug. Novo-Nordisk A/S has developed another long-acting GLP-1 analog called liraglutide, which is currently being tested in type 2 patients. In fact, five other companies now have GLP-1 analogs under development.



L TO R: ALEX RABINOVITCH, M.D., WILMA L. SUAREZ-PINZON, M.SC.,

NIDDK is sponsoring a clinical trial to study the effects of exenatide in patients who have had type 1 diabetes for at least five years but whose pancreases still make some insulin. The trial is designed to determine whether exenatide can improve the pancreas’s ability to make insulin and help control blood glucose. Because there is concern that the drug could activate the autoimmune process that causes diabetes, it will be tried with and without adjunctive immunosuppression.

“We’re very interested in GLP-1 from the standpoint of islet transplantation,” says Dr. Weir.

Harvard’s Dr. Habener agrees that growth factors such as GLP-1 have potential in islet transplantation. “When we put islets into the liver of patients with type 1 diabetes, they’re suddenly without a blood supply. They’re in a foreign environment. They’re getting bombarded by glucose from the portal vein. They’re getting immunosuppression, which is bad for beta cells. It’s a miracle that some of them survive.”

Dr. Habener and his colleagues Enrico Cagliero, M.D., at Massachusetts General Hospital, Dr. Weir at Joslin Diabetes Center, and Dariush Elahi, Ph.D. at the University of Massachusetts in Worcester,



JONATHAN R.T. LAKEY, PH.D., AT THE UNIVERSITY OF ALBERTA

are about to embark on a clinical trial of giving GLP-1 or a GLP-1 analog to islet transplant patients at the time of transplantation and continuously for eight weeks thereafter. “We hope to cut down on the stress-induced death of beta cells that occurs when they’re transplanted,” says Dr. Weir. “We might get some division of beta cells in the liver or we might get precursor cells to make new beta cells. We might stimulate something going on in the pancreas. We would all love to see something like that.”

Camillo Ricordi, M.D., and colleagues at the Diabetes Research Institute in Miami, Florida, will also study exenatide in islet transplantation as part of the NIH’s clinical islet transplantation consortium. In their clinical trial, exenatide will be given to patients who have already undergone islet transplantation, but who still require some injected insulin, to see whether exenatide can restore insulin independence.

The Massachusetts researchers are planning a similar trial and hoping that the work can be carried out as part of a larger consortium. “I hope that GLP-1 studies could be done collectively among several centers so as to increase the power and certainty of the results,” says Dr. Habener.

Other growth factors look equally promising. In the late 1980s, Stephen J. Brand, M.D., then an associate professor in the Gastrointestinal Unit at Massachusetts General Hospital and Harvard Medical School, received a JDRF research grant to study the possible role of a growth factor called gastrin in the development of the pancreas. Gastrin, a hormone that is released when food enters the stomach, stimulates acid secretion to promote digestion of the newly arrived food. Dr. Brand knew that gastrin is also briefly expressed in the developing pancreas at around the time that the pancreatic islets are forming. He hypothesized that gastrin might play an important role in islet neogenesis and might be used to make beta cells regenerate. Further, he noted that patients with a rare gastric ulcer disease called Zollinger-Ellison syndrome have very high levels of gastrin in their bloodstream for long periods of time—with apparently no ill effects. “That gave me complete confidence that gastrin at any dose is safe,” he recalls.

To study the therapeutic potential of gastrin, Dr. Brand first worked with mice that were genetically manipulated to express large amounts of gastrin to see whether they developed increased beta cell mass. To his very great disappointment, they didn’t. He then hypothesized that it might take two signals—or two growth factors—working in tandem to actually trigger beta cell regeneration. In 1993, Dr. Brand, along with two other JDRF-funded researchers (Dr. Bonner-Weir and Timothy Wang, M.D.) and five colleagues, published a study in the *Journal of Clinical Investigation* using mice that were genetically manipulated to overexpress not only gastrin but also another growth factor called transforming growth factor-alpha (or TGF-alpha). “These mice, in which we had TGF-alpha and gastrin together, indeed had increased islet mass. And that showed that we needed both signals,” Dr. Brand recalls.

Over the years, these factors continued to show promise, although eventually TGF-alpha was replaced with a structurally similar growth factor called epidermal growth factor (EGF). According to Dr. Brand, subsequent unpublished studies in rats showed that a 10-day course of gastrin/EGF resulted in beta cell regeneration and improved glucose tolerance for up to four months. In 1999, Dr. Brand patented the rights to the gastrin/EGF combination and, in 2000, started a small biotech firm in Woburn, Massachusetts, called Waratah Pharmaceuticals Corporation to develop islet neogenesis therapy (I.N.T.), using EGF and gastrin. (Born in Australia, Dr. Brand named the company after a brilliant red flower that is a symbol of renewal and rebirth in Aboriginal mythology.) In 2002, Waratah merged with a biotech firm in Toronto, Canada, called Transition Therapeutics, Inc.

This potential therapy has moved rapidly into human clinical trials. On February 26, 2004, Transition Therapeutics announced that it had finished an extended phase 1 clinical trial of therapy with I.N.T. in people with type 1 diabetes. The trial, designed to test the safety of the therapy, showed no serious or unexpected side effects. In August 2004, Transition Therapeutics exclusively licensed the treatment technology to pharmaceutical giant Novo Nordisk. On January 25, Transition Therapeutics announced that it had received clearance from the U.S. Food and Drug



STEPHEN BRAND, M.D.

Administration to test the therapy in patients with type 2 diabetes in the United States.

In a project funded jointly by JDRF, Waratah Pharmaceuticals, and Transition Therapeutics and reported in the March 2005 issue of the *Journal of Clinical Endocrinology and Metabolism*, Dr. Brand, Wilma Suarez-Pinzon, MSc., Jonathan R.T. Lakey, Ph.D., and Alex Rabinovitch, M.D., of the University of Alberta in Edmonton, Alberta,

Canada, studied the effects of EGF plus gastrin in human islets in the laboratory. The researchers cultured human islets for four weeks in medium containing neither agent, gastrin or EGF alone, or a combination of EGF and gastrin. The islets were then cultured for another four weeks in control medium. “At the end of the second month, there were three times as many insulin-producing beta cells as we started with,” Dr. Rabinovitch reports.

Next, they implanted human islets into NOD-SCID mice—nonobese diabetic mice with a deficient immune system—so as to sidestep the problems of transplant rejection and autoimmunity. Then, they injected some of the mice with the EGF-gastrin combination. “In the mice treated with EGF-gastrin, we saw about a threefold increase in insulin content and beta cell numbers,” says Dr. Rabinovitch. “Most important, when we injected glucose into the mice, there was a brisk secretion of insulin from the human islet grafts, so the beta cells were functional.”

They have also been studying various combinations of GLP-1 analogues, EGF, and gastrin in NOD mice. “What we’re finding is that some of these combinations can reduce hyperglycemia in already diabetic NOD mice,” Dr. Rabinovitch says.

## THE LIST GOES ON...

The list of potential therapeutic agents continues to grow, and here JDRF is playing a crucial role. Dr. Hayek has identified another key player in beta cell regeneration called hepatocyte growth factor (HGF). HGF has long been thought to play a role in regulating beta cell function and proliferation. In a recent JDRF-funded study, Dr. Hayek and colleagues were able to get beta cells to proliferate in a three-dimensional fibrin gel using treatment with HGF.

Now, as part of JDRF’s RBCF program, Dr. Hayek is collaborating with Sheng Ding, Ph.D., at the Scripps Research Institute in La Jolla, California, to screen a huge library of clinical compounds to determine whether any of them have the same effects as HGF, using a state-of-the-art screening technology called high-throughput screening. “With this truly state-of-the-art technology, thousands of compounds can be screened in relatively small amounts of time—which, in the past, would have taken a year,” says Dr. Hayek.