



Restoration

JDRF is turning Type One into **Type None**



Type 1 diabetes (T1D) is an extraordinarily complex disease. Finding the cure—a short-term clinical intervention, with minimal side effects, after which all aspects of T1D are gone forever—requires restoring beta cell function to provide insulin and blocking or reversing the autoimmune

attack so the newly restored beta cell function is protected.

As the world's leading private funder of research to cure T1D, JDRF is pursuing multiple strategies to restore beta cell function and we are making significant progress on each. This paper focuses on the progress we are

making through research and advocacy to drive discovery, development, and delivery of therapies to restore beta cell function by expanding beta cell mass, extending the length of time the new beta cells live, and delaying their death.



WHAT IT IS

Beta cell restoration represents a full biological cure for people with established T1D. This drug or biologic based therapy would stimulate restoration of the body's own beta cells, and in so doing restore the body's capacity to regulate the release of life-sustaining insulin. In persons in the at-risk setting who are not yet fully insulin dependent, the program aims to introduce therapies to prevent the loss of beta cell function, or maintain it. In restoring functional beta cell health, our parallel goal is to ensure that such therapies can block or ameliorate the deadly autoimmune attack on beta cells. In short, blocking the autoimmune attack, in combination with beta cell restoration, offers the potential to achieve the elusive dream of finding a durable biological cure for T1D.

WHY IT MATTERS

The restoration of normal beta cell function would free those with T1D from the need for multiple daily insulin injections, carb counting, and blood glucose monitoring. But more than leaving the demands of managing T1D behind forever, it also would mean that the deadly complications associated with T1D will be prevented, leading to healthier and more fulfilling lives, and saving individuals, families, and public and private health insurers tens of

billions of dollars. We believe this is a future we can and will achieve.

JDRF'S IMPACT

In less than a decade of research, JDRF funding has led to extraordinarily rapid advances in the beta cell survival and restoration field. We have demonstrated in animals that it is possible to generate new beta cells and to transform non-beta cells into new beta cells; identified multiple ways to induce beta cell survival and restoration; started building a pipeline of beta cell survival and regenerating therapies; and identified indicators, known as biomarkers, of beta cell death.

BACKGROUND

Up until just a few years ago, the prevailing scientific thinking was that the cells in the body that store and release insulin (beta cells) were innocent bystanders and defenseless victims of the immune system's misguided assault on them.



But over the last decade much about what we thought we knew about the fate and role of beta

cells in T1D began to change with the emergence of the field of beta cell restoration. It is a field pioneered by JDRF and one that JDRF continues to lead and catalyze through its Beta Cell Survival and Restoration Program.

We've learned (in part due to JDRF funding) that beta cells not only continued to be present in the pancreas, but new ones were still being formed in some individuals who have had T1D for 50 years or more. JDRF also established that most pregnant women with T1D—similar to pregnant women without T1D—show some level of increased beta cell function in response to meeting the expanding insulin demands of pregnancy.

Recent JDRF-funded research has also established another under-appreciated fact about the role of beta cells in T1D. JDRF scientists have established that even before a diagnosis of T1D, beta cell function is compromised. Scientists now think that the beta cells may go into a stress mode prior to onset of diabetes and

may even be complicit in their own destruction. This finding suggests that there could be successful intervention strategies early on in the course of the disease to slow or stop beta cell death.

These and other exciting insights and findings in the beta cell field spurred us to develop a strategic and aggressive Beta Cell Survival and Restoration Program.



THE JDRF BETA CELL SURVIVAL AND RESTORATION PROGRAM

The JDRF Beta Cell Survival and Restoration Program is based on a simple principle: the body can heal itself. If someone cuts their knee, it bleeds, a scab forms, and the wound heals. We believe the body can heal T1D as well, though it will need a little help to do so. Our research is focused on expanding the number of beta cells (beta cell mass) present in someone with T1D so normal insulin production can

survive the immune attack. Even more exciting is research into possible therapies that go one step

In the process, they regress to a state of low insulin production. So we are exploring whether it is

We can make full restoration of normal beta cell function possible.

further and trigger the proliferation of these surviving beta cells. At the same time, these therapies, or others under study, may also trigger growth of new beta cells that, in conjunction with immune therapies,

possible to return these hiding beta cells to normal function.

Still another area of current research is to convert or reprogram other cells to behave like beta cells. This is a very promising area of inquiry. For example, the pancreas also includes islet alpha cells. Scientists know that alpha cells and beta cells are derived from the same embryonic lineage so JDRF is exploring how to coax alpha cells to become functional beta cells. If this can be successfully done it would create a new source of insulin-producing beta cells, thus expanding beta cell mass considerably.



resume, extending the life and/or improving the health of under-performing beta cells (beta cell function), and delaying or preventing beta cell death.

JDRF is looking at therapies that extend the life of beta cells that

could lead to full restoration of normal beta cell function.

Recent discoveries suggest that in the pre-diagnosis stages of T1D, beta cells recognize that they are under immune attack and they may go into hiding to protect themselves.

WHERE WE ARE TODAY

JDRF has already made impressive progress in understanding beta cell function in just a few years and we are zeroing in on a number of potential pathways to generate new beta cells at a level sufficient to restore normal insulin production.

A major area of current focus in the beta cell program is to take existing drugs—approved for use for other conditions—and explore whether these drugs,



alone or in combination with others, may have a positive impact on either reducing beta cell stress and/or inducing more beta cell survival. We're also funding pioneering research to create new

people with type 2 diabetes, the current human trial sponsored by JDRF is examining whether the drug may have anti-inflammatory effects on beta cells, thereby helping the body to maintain

in an ongoing clinical trial;

- Two more clinical trials testing whether existing drugs play a role in beta cell health, survival, and restoration are planned once they receive regulatory approval;
- JDRF provided critical early funding to establish that a particular protein in the body (DG770) showed promise in triggering beta cell proliferation as well as the formation of new beta cells. This research attracted major pharmaceutical companies and AstraZeneca is now actively involved in advancing this forward. It represents one example of how JDRF's approach to research is accelerating products through the pipeline to the patient. Without JDRF's early discovery research, it is highly unlikely that the massive resources of large biotech and pharmaceutical firms would have been drawn to this area. In fact, if this compound were

JDRF is looking at drugs to improve beta cell health and survival.

compounds and identify other molecules that might have a positive effect on beta cell health and restoration. Consider:

- In Zürich, Switzerland, JDRF-funded researchers are working with a drug called Gevokizumab, which is made by biotech company XOMA. The drug has been approved by the FDA for use in blood vessel and eye inflammation conditions. Based on evidence that the drug has improved glucose control in
- Sitagliptin (Januvia®), which is used by people with T2D and lansoprazole (Prevacid®), an over-the-counter drug used to control acid reflux, have been shown in studies of diabetic mice to promote beta cell survival and beta cell restoration. JDRF is helping to support a clinical study with Sanford Health to explore whether these two existing drugs have the same effects on humans



brought to market, JDRF would receive royalties in consideration of its catalyzing role in advancing the product to patients.

- The Genomics Institute of the Novartis Research Foundation, in collaboration with JDRF, has

government. To that end, JDRF has spearheaded partnerships with major pharmaceutical companies, biotechnology companies, universities, and research institutes to advance the field. Moreover, devising effective therapies without a way to bring

academic institutions, and Joslin Diabetes Center and the Broad Institute in the non-profit area. As part of this effort, JDRF has urged Congress to continue funding for the Special Diabetes Program, which funds many leading academic centers through its Beta Cell Biology Consortium.

NEXT STEPS

Our short and mid-term focus is on establishing proof in human clinical studies that one or more of the repurposed drug candidates will indeed enhance beta cell survival in humans and that it can be safely tolerated by patients (proof of concept). Another key area is identifying biomarkers, or indicators of disease progress and progression, that will facilitate early detection of subtle changes in beta cell health and function so we gain greater insight into beta cell stress and dysfunction.

Any effort to restore beta cells must also involve parallel efforts to tame the autoimmune attack. If beta cell restoration efforts are to succeed, they must be combined with effective immune therapies that allow the new and/or healthy beta cells to thrive and function normally, and JDRF has an aggressive immunotherapy research program as well. A high priority of immunotherapy research is developing therapies that promote tolerance to the beta cell autoantigens that trigger the attack on beta cells. Some of



been screening thousands of compounds to identify ones that may preserve beta cells and induce new beta cell restoration. Several have shown promise in animal models and isolated human islets/beta cells. The goal is to have several advanced late stage clinical candidates for development.

PARTNERSHIPS

JDRF recognized early on that progress in the beta cell restoration area would benefit from collaboration among academic investigators, industry, and

them to market is hardly helpful to the T1D community. The cost of conducting human clinical trials is staggering. By engaging industry partners at key stages of the research pipeline JDRF has added huge resources to the field that will ensure that clinical trials to prove that a therapy is safe and effective can be conducted when promising therapies emerge. Our list of partners in the beta cell restoration and survival field ranges from GNF, Lilly, Pfizer, Johnson & Johnson, and Sanofi in the pharmaceutical arena, to XOMA, Biogen, and Develogen in the biotechnology field, to worldwide



JDRF's work in the prevention field, particularly our exploration into developing an antigen-specific T1D vaccine, may also be applicable in the restoration field.

JDRF is seeking to accomplish something never before done in biomedical research: reverse an autoimmune attack and restore the body to normal function. Understandably, this will raise many questions among regulators in the U.S. and around the world who will need to be convinced that a given therapy is safe and effective for patients. In addition, public and private health insurers

will need to understand the therapy and provide adequate coverage so it is affordable and available to all those with T1D. These will not be easy hurdles to overcome, but JDRF is already working to keep key parties up to speed on the current science so the regulatory light can turn to green quickly when we are ready to move forward.

SUMMARY

JDRF's work on beta cell restoration, and its work on blocking the autoimmune attack,

has made it a pioneer in the field. Clinical trials are already underway in key areas of the program. But we've set an ambitious goal to accomplish what no one has ever done: reverse an autoimmune disease. JDRF estimates that an additional \$150 million will be required over the next 5 years to realize our dream. We need your help, and the help of many others, to make it happen. Please donate as much as you can to bring us closer to the day when a biologic cure for T1D is available to all.

Support our efforts to make restoration a success—
and together, we will turn Type One into **typenone**