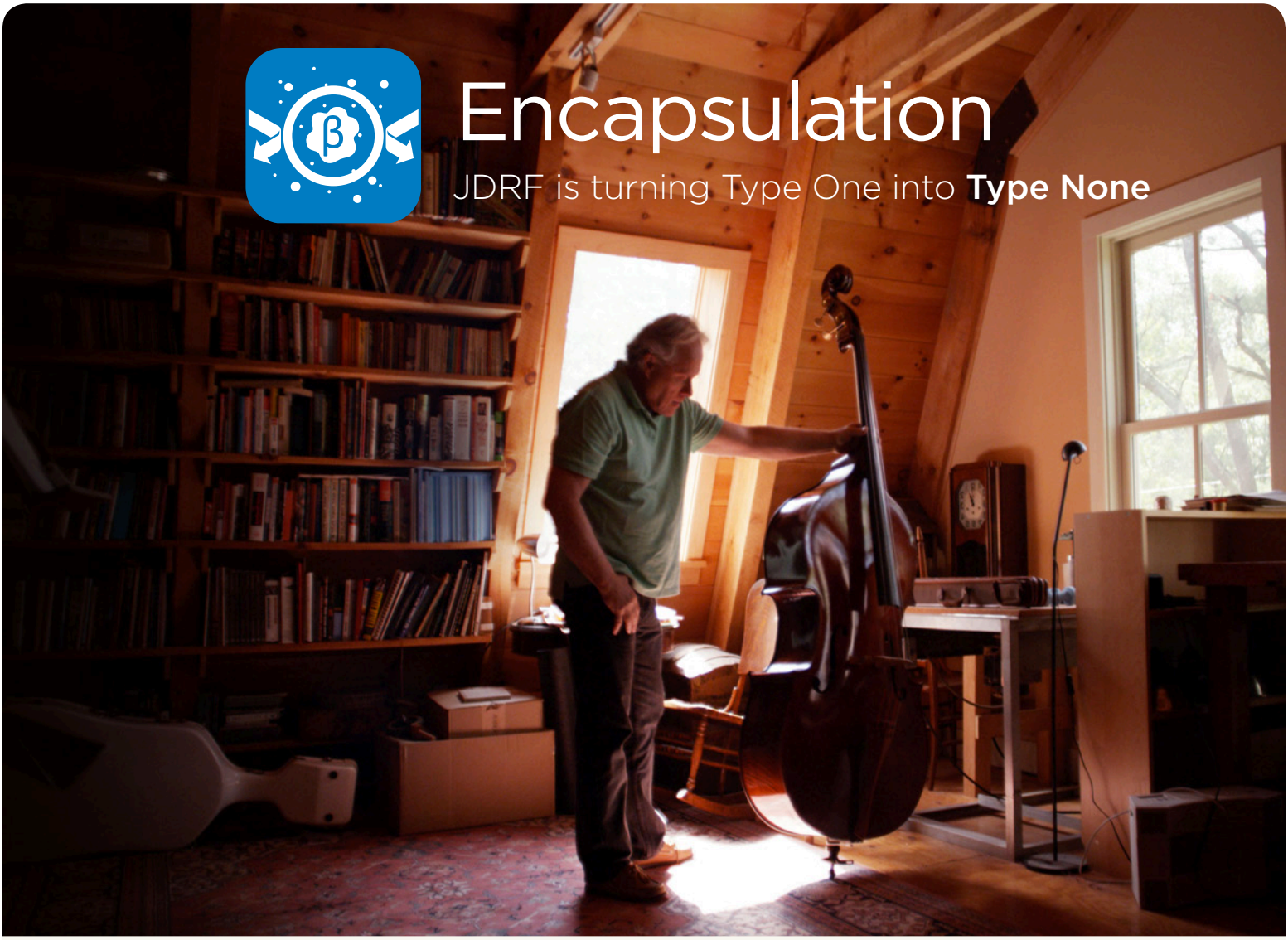


Encapsulation

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. This will take time. We know there will not likely be a single "eureka" moment that magically eradicates T1D. So meanwhile, through research and advocacy, we're driving the discovery, development, and delivery of therapies and technologies that will progressively reduce the day-to-day challenges of managing T1D, improve glucose control, and ensure that patients are as healthy as possible until we reach our ultimate goals of a cure and universal prevention of T1D.

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 on replacement of beta cells through encapsulation therapy. Beta cell encapsulation involves putting insulin producing beta cells in a protective barrier and implanting them beneath the skin. These encapsulated beta cells will sense a person's glucose levels and produce insulin as needed, while the barrier shields them from the body's autoimmune attack that initially triggered the onset of T1D.

WHAT IT IS

Beta cell encapsulation is a non-invasive procedure which involves putting insulin producing beta cells in a protective barrier and implanting them beneath the skin. These encapsulated beta cells will sense a person's glucose levels and produce insulin as needed, while the barrier shields them from the body's autoimmune attack that initially triggered the onset of T1D. Encapsulation keeps the newly implanted cells alive by hiding them from the immune system, providing a safe environment where they can function normally. The cells can constantly assess the amount of glucose in the blood and release exactly the correct amount of insulin. What's especially exciting about encapsulation therapy is that it overcomes one of the major obstacles that has slowed progress in the islet transplant field—the need for lifetime administration of powerful and toxic immunosuppressive drugs to prevent the immune system from destroying the newly introduced islets.

This therapy is not an abstract idea being nurtured in a lab. Indeed, in just a few short years, there have been a series of exciting advances in the encapsulation field, almost of all of them stemming directly from JDRF funding. Today, three companies, including two funded by JDRF, are conducting, or are moving towards human clinical trials of encapsulation therapies. And another non-profit research foundation funded in part by JDRF is moving ahead with yet a third encapsulation design and it too expects to launch human trials within 12-24 months.

WHY IT MATTERS

Beta cell encapsulation therapy has the potential to virtually eliminate the relentless daily management burden for those living with T1D. No need for multiple daily insulin injections or pump therapy, no more constant blood testing or wearing continuous glucose monitors, and no more carb counting. In short, people with T1D would be liberated to go about their daily lives for extended periods of time as if they didn't even have the disease at all. Technically, it isn't a cure; the immune system still wants to destroy beta cells—it just can't find the ones inside the device. For people with T1D who are on duty all day every day just to stay alive, it will sure feel like a cure.

> People with T1D would be liberated to go about their daily lives for extended periods of time, as if they didn't even have the disease at all.

JDRF'S IMPACT

JDRF has built the most advanced encapsulation research and development program in the world. We catalyzed a sleepy field just a few years ago and remain the acknowledged leader in the space. We have helped bring one product to early human testing with several others heading to human trials in the next year. We have invested in multiple approaches to encapsulation to avoid going all-in with one technology, a multiple shots-on-goal approach we believe increases the likelihood of success, and has the opportunity to impact second and third generation approaches. Finally, we have brought the world's leading scientists from multiple disciplines into a cooperative and focused consortium structured to resolve the critical remaining challenges we face, an initiative we know will accelerate the push to bring an encapsulation product to those with T1D.

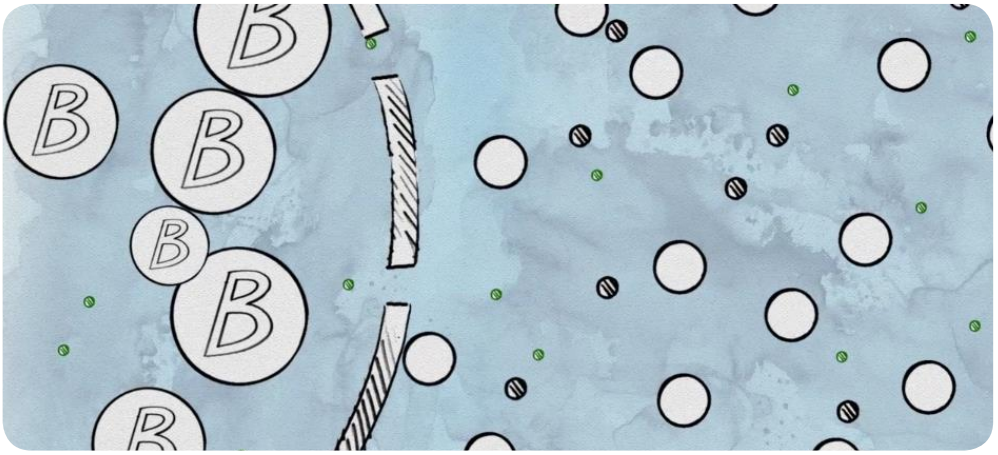
BACKGROUND

Beta cell encapsulation attracted considerable activity in the 1980s and 1990s. But faced with significant scientific obstacles, researchers gradually drifted away from the field. And so encapsulation research remained under-funded for the next 20 years.

But things began to change in 1999 when JDRF-funded researchers in Canada harvested islet cells from the pancreas of organ donors, transplanted them into T1D patients, and achieved insulin independence in many patients. However, islet transplants had two drawbacks: first, patients required massive amounts of toxic drugs to prevent the immune system from attacking the new

insulin cells (so-called immuno-suppressive drugs); and second, the available supply of islet cells for transplant procedures was sharply constrained making it impossible to perform the procedure on large numbers of T1D patients.

The Edmonton Protocol, as it became known, while not without issues, proved that cell replacement therapies could work. Meanwhile, significant advances in the biomaterials engineering and cell supply fields,[1] prompted JDRF to take another look at the feasibility of beta cell encapsulation, and in 2007 JDRF launched its Beta Cell Encapsulation Program.



THE JDRF BETA CELL ENCAPSULATION PROGRAM

The goal of the JDRF Beta Cell Encapsulation Program is to develop encapsulated beta cell products to safely provide normal glucose control to individuals living with T1D.

To understand encapsulation therapy it's useful to imagine a deep-sea diver in a shark cage. The diver can conduct experiments, take photos, and carry out other tasks from inside the cage while being safely protected from sharks. The encapsulation therapy would work much the same way. However, in this case the "cage" would surround the beta cells so they are protected from the immune system attack, yet the "cage" is porous enough to allow the cells to survive, detect glucose levels, and release insulin.

Since launching our program, JDRF has prioritized several areas of research required to accelerate delivery of encapsulation therapy to patients. These include continuing research into ways to create a replenishable, scalable supply of beta cells (so that millions of T1D patients could have the therapy once it is proven safe and effective), identifying the optimal material to use for the permeable barrier that will protect the beta cells (so the autoimmune attack is rebuffed), and testing different device designs (so we can identify which one works best from a performance and safety standpoint). JDRF has also begun to engage the U.S. Food and Drug Administration on this cutting edge field to lay the groundwork for regulatory review of these novel products.

JDRF understands that successful T1D therapies require cooperation and collaboration amongst researchers around the world. This is especially true in the case of encapsulation because it crosses so many different disciplines. So, early in 2013, JDRF formed the JDRF Encapsulation Consortium. The consortium, similar to what JDRF organized to move artificial pancreas systems to market, is already fostering collaborations among bioengineers, chemists, immunologists, transplant researchers, and pancreatic beta cell biologists to incorporate engineering concepts and designs into current efforts toward improving islet cell encapsulation, and it will play a central role in bringing this therapy to patients as soon as possible.

WHERE WE ARE TODAY

Over the last 5 years alone, JDRF has provided substantial funding for scientific research in encapsulation and xenotrans-plantation (transplanting insulin-

[1]JDRF was a leader in the effort to advance the stem cell research field. We funded early science in the field and led advocacy efforts to eliminate restrictions on stem cell research. The ongoing research in beta cell encapsulation is one of the very first real-world applications of this science to humans.

producing islet cells from one species, e.g., pigs, to another, e.g., humans). Today, JDRF is working with two biotechnology firms, as well as another leading T1D research foundation, to move encapsulation to the human clinical trial phase. Specifically:

> JDRF has made exciting progress in the encapsulation field.

- JDRF is partnering with ViaCyte, a California biotechnology company, to support the development of a first-of-its-kind beta cell encapsulation therapy for T1D.[2] ViaCyte's approach converts stem cells into immature pancreatic endocrine cells that are then placed into a macro-encapsulation device where they develop into fully functioning islets producing various hormones like a normal pancreas would, including insulin and glucagon. Testing in diabetic mice has confirmed that the ViaCyte device maintained blood sugars at normal levels. ViaCyte has announced it intends to test the device in human clinical trials in 2014.
- JDRF has also supported a project conducted by Living Cell Technologies, a New Zealand company, involving the encapsulation of pig-derived islets for implantation into humans. Pig islets are very similar to human islets and these pigs are specially bred solely for human transplant purposes to remain disease free. In this project, the pig islets will be encapsulated in an alginate-based material derived from seaweed that is known to be compatible for use in humans. LCT has already conducted small human trials with this product in several countries around the world. The results of the studies are still being compiled but preliminary results show the product has had a positive effect on reducing dangerous low blood sugar (hypoglycemia) events. More results are expected soon.
- JDRF is co-funding another promising encapsulation strategy being carried out by a team of investigators at the Diabetes Research Institute at the University of Miami. They are trying to create an encapsulation device that can provide the optimal environment for islets to survive and function for a long time. DRI hopes to take the first part of this device to human clinical trials in 2014.

[2]Significant additional funds for the initiative come from the California Institute for Regenerative Medicine, created by a California state initiative adopted by voters and strongly supported by JDRF.

NEXT STEPS

JDRF, in cooperation with the consortium, is currently working intensively to identify novel biomaterials to encapsulate and protect beta cells during transplantation. One project, which is also partially funded by the Leona M. and Harry B. Helmsley Charitable Trust (HCT), is headed by Dr. Robert S. Langer, an internationally renowned researcher at the Massachusetts Institute of Technology's Center for Cancer Research.[3] We're excited about the early results that have raised hopes that we are on the threshold of creating new biomaterials to act as protective, semi-permeable shields that would allow beta cells to sense glucose and produce insulin, but be protected from immune destruction.

We're also evaluating the relative strengths of various types of designs to house the implanted islets. We're trying to determine which ones will work best, the strengths and weaknesses of various designs, and other key questions. Other priority areas of research today are identifying the most effective ways to modulate the immune system at the implant site and determining optimal transplant sites.

SUMMARY

Over the last few years, JDRF has been a leader in pushing the beta cell encapsulation field forward. We have made enormous, exciting, and tangible progress. But much work remains. JDRF estimates that an additional $60 million will be required over the next 5 years to bring this therapy to people with T1D. We need your help, and the help of many others, to make it happen. Please donate as much as you can to accelerate progress on beta cell encapsulation.

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

[3]Dr. Langer recently received the National Medal of Technology and Innovation, the highest honor bestowed by the U.S. Government upon scientists, engineers, and inventors.