Researchers have engineered novel devices to house and protect insulin-secreting beta cells inside the body, and they are combining that technology with human stem cell-derived or even animal-derived beta cells. Their aim is to construct what is essentially a bioartificial pancreas, supplied with readily available lab-grown cells and designed to restore normal, or near-normal, insulin production and glucose regulation to patients with type 1 diabetes. Two small companies operating in this space recently entered human clinical trials and several others are in the wings, as this challenging but potentially game-changing advance reaches a pivotal juncture.

While the diabetes community is focusing much of its current attention on the mechanical artificial pancreas arena, where researchers are working to integrate insulin pumps with continuous glucose sensors (see “Diabetes Devices: Engineering the Future,” The MedTech Strategist, October 29, 2014), other groups have been exploring another, related avenue – cell transplantation and encapsulation technologies for diabetes – and have recently reached some important milestones. They aim to construct what is often called a bioartificial pancreas, which would be a potentially game-changing advance for patients with type 1 diabetes (T1D). The hope is that these cell-based systems would enable patients to achieve normal or near-normal glucose regulation for an extended period of time without the need to manage multiple external devices.

This work is an offshoot of islet transplantation, in which pancreatic islet cells are harvested from deceased donors and injected into a T1D recipient via the portal vein in the liver, where they are able to survive and produce insulin. More than 1,000 patients worldwide have received donor islet transplants to date, according to Albert Hwa, PhD, director of Discovery Science at the Juvenile Diabetes Research Foundation (JDRF), and the technique has been enormously successful in restoring insulin independence to these patients. However, the extremely limited supply of healthy donor islets and the need for recipients to take lifelong immunosuppressive drug therapy to prevent immune system rejection of the donor cells makes this approach impractical for the vast majority of diabetes sufferers.
To overcome these limitations, researchers have been working to develop lab-grown cells and cell encapsulation technologies capable of providing an unlimited source of insulin-producing cells that can be implanted into the patient in a minimally invasive manner and protected from the host’s immune system so that immunosuppressive drugs are not needed. The goal is an ambitious one, as the normal human pancreas is a complicated structure, with several different types of cells involved in glucose regulation (see Figure 1).

Progress toward this goal has depended in large part on trial and error along the way, and the road has been long and the going slow. However, parallel achievements over the past several years in the fields of cell biology and device engineering are now bringing the dream of a bioartificial pancreas closer to clinical reality. New methods of growing and differentiating human (and animal) stem cells on a large scale, combined with advances in device-based cell macroencapsulation technologies, are enabling researchers to construct bioartificial pancreas systems that could be practical on a commercial scale. Three separate groups working in this area announced important milestones last month, including two companies that recently entered human clinical trials with novel, device-based cell transplantation systems.

Cell Therapy Reaches Pivotal Juncture

ViaCyte

One of those companies is San Diego, CA-based ViaCyte Inc., which has been working in this area for more than a decade. The company was founded in 1999 as Novocell and in 2004 merged with two other cell therapy companies – CyThera and Bresagen – retaining the Novocell name. The company was renamed ViaCyte in 2010.

From the beginning, Novocell was focused on cell replacement therapy for diabetes and initially attempted to deliver human islets in a microencapsulation format. That technology involves placing some type of immunoprotective coating directly onto a group of cells prior to transplantation to protect them from host rejection and eliminate the need for immunosuppressive drug therapy.

However, results of a limited clinical trial with that technology were not positive, according to Michael Scott, PhD, ViaCyte’s chief development officer and VP of the company’s device program, who spoke recently with The MedTech Strategist. As a result, the firm began to re-think its approach.

Following the merger with CyThera and Bresagen, the company shifted its focus to a renewable, large-scale cell technology treatment for T1D using cells derived from pluripotent stem cells. Over about a seven-year period, starting in 2004, a team of dedicated scientists, including about a dozen PhD biologists, worked on stem cell expansion, aggregation, and differentiation techniques that were scalable and able to produce large quantities of viable pancreatic progenitor cells. In the process, the firm amassed a considerable intellectual property base, Scott says.

As Scott explains, “The key elements are being able to expand the numbers of cells significantly – something like 1,000-fold in two weeks – to provide the raw material needed to be able to treat large numbers of patients;
developing the methodologies necessary to scale the differentiation processes; and having the specific manufacturing steps required to reproducibly turn pluripotent embryonic stem cells into differentiated pancreatic endoderm cells.”

About five years ago, the company also began developing a cell macroencapsulation technology – basically a device to house and protect the cells in the body. According to Scott, macroencapsulation approaches to cell transplantation therapy are more durable than microencapsulation approaches and they are typically retrievable from the body, whereas microencapsulated cells cannot be removed once they are implanted. Both of these attributes are key to the firm’s technology.

The company’s current cell encapsulation device, called Encaptra, is small – about 1-inch wide, 3-inches long, and less than a millimeter thick – and it is designed to be implanted subcutaneously in the lower back and/or flank (see Figure 2). The device incorporates a semipermeable membrane that separates the cells within from the host’s immune system. The membrane has pores that are sized to allow for free diffusion of glucose, oxygen, insulin, and other cell products into and out of the device, but the pores are small enough to prevent the migration of mammalian cells. This enables nutrients to enter and reach the cells and insulin to exit and reach the tissues, but host immune cells are unable to cross the membrane, thus the device blocks the cell-to-cell contact believed to be required for alloimmune destruction to occur.

Unlike some others working in this field, the company is implanting pancreatic progenitor cells, rather than mature, insulin-producing beta cells, a choice the firm made after careful consideration. According to Paul Laikind, PhD, ViaCyte’s president and CEO, “The reason we stop [the cell differentiation process] at the pancreatic progenitor cell stage is we believe it’s more effective to let the cells go through the final stages of differentiation in vivo.” And while Laikind applauds other recent milestones in this field involving more mature beta cells – including the work published last month by Harvard researcher Douglas Melton, PhD, who reported in the journal Cell that he had, for the first time, developed a method in the lab to take human stem cells and derive massive quantities of insulin-producing beta cells for potential use in transplantation therapy – Laikind points out several potential advantages to ViaCyte’s approach.

For one thing, when the cells are first implanted, he says, they must survive in a very hypoxic (low oxygen) environment until the encapsulation device becomes vascularized. “And mature beta cells are very metabolically active cells – they do not survive well in a hypoxic environment,” he explains. Second, the progenitor cells are believed to release angiogenic factors that help build up the vascular system in vivo. And third, as ViaCyte’s progenitor cells mature, they not only form beta cells, but also alpha, delta, and other cell types. “So we believe we’re making islet tissue, not just beta cells, and we think there’s an advantage to that,” says Laikind. “Ultimately, the intent behind this design is to deliver what we hope to be a bioartificial endocrine pancreas capable of producing essentially all of the endocrine hormones that the normal human pancreas is capable of delivering.”

ViaCyte is now putting its cell replacement therapy to the ultimate test: human clinical trials. The company reached an important and long-awaited milestone in October when it initiated an FDA IND-approved Phase I/II clinical study with its cell therapy system, which it calls VC-01, consisting of the firm’s proprietary human pancreatic progenitor cells encapsulated in the Encaptra device. The open-label, dose-escalating trial will evaluate VC-01 in up to 40 T1D patients with little or no insulin-producing beta cell function.

According to Scott, between two and six Encaptra devices will be implanted into each patient in this dose-ranging study, along with up to four of the firm’s smaller “mouse-sized” devices, each about the size of a thumbnail, which will be used as “sentinels” that can be explanted periodically during the trial to evaluate the viability and health of the cells. None of the patients will take immunosuppressant drugs.
Laikind points out that there are actually many locations on the body where the Encaptra device can be implanted. The VC-01 cells are designed to not only produce insulin, but other regulatory factors as well, including glucagon and somatostatin, he says, and thus they need to have a good blood supply. “But all they need is access to the systemic circulation, so they can go in many different locations.” As this is a dose-finding study, the company will be evaluating how many implants are needed to produce the best results.

The study will involve two patient cohorts -- an initial group of three to six patients, enrolled only at the Sanford Stem Cell Clinical Center at the University of California, San Diego (UCSD), followed by a second cohort of about 36 patients. Eventually, the firm expects to have about a half-dozen centers participating, with sites in the US and possibly Canada as well. “We expect this to move fairly quickly,” says Laikind. “We’ve had a tremendous outpouring of interest from the patient community in this approach, so I think enrollment will go quickly.”

The first patient in the study was implanted in late October at UCSD. The initial three patients in the trial will be enrolled on a sequential basis, he explains, to enable the company to ensure the therapy is safe and well tolerated before moving on to the next patient. Part of that evaluation will involve regular explantation of those sentinel devices, which Laikind says will be excised periodically during the trial to provide interim looks at how well the cells are holding up, differentiating, and how the vascularization process is progressing.

The study will follow patients for safety and tolerance as well as efficacy. The primary efficacy endpoint is a stimulated measurement of C-peptide, which is produced when insulin is made in beta cells, and thus is a marker for endogenous insulin production by the transplanted cells. In addition, the researchers will track patients’ exogenous insulin usage and their blood glucose readings. All of the patients will be injecting insulin, at least initially, and their insulin usage will be followed prior to implanting the device, to obtain a baseline measurement.

Based on what ViaCyte has observed in animal models, it will likely take two to three months before the implanted progenitor cells mature and reach their full insulin producing capacity. But what the company hopes to see is a reduction in the need for insulin injections as the trial progresses, Laikind explains. The researchers also will track hypoglycemia during the trial, and the firm hopes to document a reduction in hypoglycemic episodes as well.

Exactly how long the implanted cells will live and function is another question the company will be looking to answer. Since the device prevents circulating macrophages from entering and performing any cleanup, there may be an accumulation of exhausted material within the devices. “So we do think the cells will eventually die,” Laikind says. In animal studies, the cells remained viable for the life of the animal, which is up to one year post-implant in the animal models studied. “We don’t know how long that will be in humans,” he points out, “but we’re hoping it will be at least one year and possibly up to two or three years or even longer before we need to replace them.” When/if the system reaches commercial use, that replacement process would involve explanting the existing device(s) and reimplanting new ones, and the company expects both the initial implant procedure as well as any subsequent replacement procedures will be performed in an outpatient setting likely under local anesthesia.

ViaCyte plans to follow patients in the clinical study for two years before removing the device(s), and FDA has requested that follow-up continue for another three years following explantation to make sure there are no long-term ill effects from the therapy.

However, the six-month mark will be the first key data collection point. Six-month follow-up data will be compiled and analyzed and used to guide discussions with regulatory authorities regarding additional clinical trials of the therapy.

The company is already considering additional studies. Once sufficient safety data is collected from the first study, the firm has plans to initiate a study in hypoglycemic-unaware patients, which could start as early as the second half of 2015.

According to Laikind, hypoglycemic-unaware patients reportedly comprise some 25-30% of the T1D patient population. These patients have little or no warning signs when they experience hypoglycemia following insulin injection, and thus they are at increased risk for a severe hypogly-
The islets make up only 2% of the pancreas’ total 100-gram mass, but those two grams of cells consume 80% of the oxygen coming into the pancreas.

–Dan J. Gelvan

significant reduction in the need for exogenous insulin would be very beneficial. “Once we get some experience in that patient population,” he says, “we are considering applying for a breakthrough product designation from the agency [FDA] for that group, and that could lead to an accelerated development pathway.”

The company also believes this could eventually be a treatment option for certain patients with type 2 diabetes. But that would be a very different therapy, explains Laikind. “In the case of T1D, we see it as having the potential to provide a functional cure, essentially radically changing the way these patients manage the disease. In the case of type 2, however, it’s a very different disease.”

In type 2 patients, says Laikind, the beta cells can wear themselves out over time, eventually becoming dysfunctional in a way that’s very similar to type 1 disease. “So we believe [cell therapy] could be useful in those later-stage type 2 patients, but it’s more of an adjunctive therapy in that setting.” Still, it’s a huge patient population, he concedes, and a worthwhile pursuit. “Even the insulin-dependent portion of the type 2 diabetes population dwarfs the size of the market for type 1. So even as an adjunct in that area, it could be very important from a commercial aspect.”

It’s a bit too early to speculate about ViaCyte’s ultimate commercial success; however, the company is certainly one to watch in the months ahead. Along with the clinical trial results, it will be equally interesting to see how the company’s financial future plays out, especially given the long and difficult road the firm traveled to get where it is today.

The company garnered some early VC financing, completing a Series C round in 2007, and it initiated a follow-on C-1 round with insiders about a year ago (that round closed in August of this year, bringing in a total of $16.5 million). However, without the support of nonprofits like the JDRF and the California Institute for Regenerative Medicine (CIRM), both of which have contributed considerable funding to the effort, it is doubtful ViaCyte could have made it this far. (In September, CIRM awarded ViaCyte a $16.6 million Accelerated Development Pathway Grant to help the company with its clinical development program.)

“I can’t emphasize enough how critically important the [nonprofit investment] was,” says Laikind. “This company is VC-backed, but it’s been around a long time.” He notes that before the recent follow-on round, there was a drought of about six or seven years since the firm’s last venture financing. “You can imagine a company trying to aggressively move this technology forward that hadn’t funded in six to seven years. What filled that gap was JDRF and CIRM. They were critically important, and continue to be critically important to the success of this program.”

Now, as the company moves forward into clinical trials, it is also attracting more interest from corporate investors. In August, ViaCyte announced an agreement with Janssen Research & Development LLC (part of Johnson & Johnson) that provides Janssen with a “future right to evaluate a transaction related to VC-01.” As part of the deal, ViaCyte received $20 million from Janssen and Johnson & Johnson Development Corp., a longstanding investor in the company. The $20 million payment included a rights fee and a note convertible into equity at a later date.

Beta-O2 Technologies

Another company working in this area is Beta-O2 Technologies Ltd. Founded in 2004 and based in Israel, Beta-O2 recently initiated a pilot clinical trial in Sweden with its Bair Bio-Artificial Pancreas, another device-based cell therapy system for T1D. However, unlike ViaCyte, Beta-O2 is focused solely on developing the optimal device for cell encapsulation and does not intend to produce its own cell line. Instead, the company is seeking to partner with others on the cells. Dan J. Gelvan, PhD, chairman of the board at Beta-O2, who spoke recently with The MedTech Strategist, says the company’s device creates an optimal microenvironment suitable for a variety of cell types, including, potentially, pig xenograft cells.
The βair Bio-Artificial Pancreas is unique in that it allows the patient to periodically infuse oxygen into the device to ensure that the high density of cells within receive enough oxygen to keep them healthy and functioning for a long period of time. According to Gelvan, the company’s work is an engineering solution aimed at solving two huge obstacles: how to house enough cells in a small device to produce an effective dose of insulin, and how to make sure that dense mass of cells receives enough oxygen to survive and function well.

Company researchers learned early on, Gelvan says, that cell therapy solutions would need to deliver a large number of cells – about 400,000 islet cells per patient – in order for patients to be independent of insulin injections, and those cells would have to be packed into a fairly small device to be easily implantable in patients. So the challenge was to engineer a device that could address those needs and keep the cells healthy.

The islets make up only 2% of the pancreas’ total 100-gram mass, explains Gelvan, but those two grams of cells consume 80% of the oxygen coming into the pancreas. Thus, getting enough oxygen to the cells became a central goal of the company’s project. The entire process was very typical of how Israeli medtech companies work, he points out. “They start with the problem and then they engineer the solution.”

Beta-O2’s solution is a circular macroencapsulation device that is a bit smaller than an ice hockey puck (about 68 mm in diameter and 18-mm wide). Inside the device are three chambers: a middle chamber reserved for oxygen storage and delivery, and two chambers on either side that hold the cells. The device is implanted subcutaneously with two injection ports placed just under the skin that are connected to the middle chamber (see Figure 3). The ports enable patients to infuse oxygen into the device, something that must be done every 24 hours to keep the cells healthy, using an external “smart” injector system that automates and verifies the process.

The cell chambers contain two types of alginate polymer scaffolds: one made of high guluronic acid alginate for islet immobilization, and one consisting of high mannuronic acid (HM) alginate impregnated in a Teflon membrane to protect the cells from the host’s immune system. According to the company, impregnating the Teflon membranes with HM alginate makes them impermeable to cells and host immune system particles, while allowing free passage of glucose and insulin.

The firm’s current device can hold up to 200,000 islet cells, Gelvan says, so two would be needed to deliver the total required 400,000 cells. However, the pilot clinical work the company is doing in Sweden utilizes islet cells from deceased donors, and rarely do such harvested islets yield that large a quantity of viable cells, he explains. As a result, the first patient enrolled, who was implanted last month at Uppsala University Hospital, received only one device containing about 170,000 cells. The company plans to slowly enroll the remaining seven patients in this study over the course of the next year, following the patients carefully for insulin use, C-peptide levels, and the incidence of both hyper- and hypoglycemia.

As this is a safety trial, all patients, per-protocol, will be explanted after six months. And provided the six-month outcomes show the device is safe (which the company expects to be the case, given its extensive preclinical work), the next step would be to submit for approval to conduct a larger European Phase II/III trial in support of CE marking for the device. That study is expected to enroll 50 patients and follow them for 12 months, says Gelvan. Although the company is first seeking approval for the device in Europe, it hopes to eventually bring it to the US market as well.

Beta-O2 is currently in discussions with several potential cell partners, and Gelvan says it has already “been courted by various groups that have stem cells.” Although the company is intrigued by the stem cell opportunity, the firm’s primary focus remains on the device itself. “Our strategy is to continue to provide the best microenvironment [for the cells],” he explains. “We are excited about
the opportunity to put stem cells into our device because we think we have as much to offer to cells derived from a stem cell population as to a donated cell.”

Even if cell therapy technology provides only two years of freedom from insulin injections before the cell encapsulation devices need to be replaced, that would be very appealing.

And the firm believes its system has the potential to keep cells alive for a long period of time. The company previously performed a single first-in-human implant in Germany and followed that patient for 10 months before the device was explanted. In that case, the cells were still fully functional and fully glucose responsive after the 10-month time period.

Moreover, clinical experience with islet transplantation (using immunosuppressive drug therapy) supports the notion that islet cell transplants can survive in the body for extended periods. In some cases, Gelvan says, people have had functioning islets for up to nine or 10 years following transplantation. “So that might be an indicator of how long these other cells will last,” he says. “I wouldn’t say it’s a definitive indicator – and we have not done long-term studies with our system – but it’s certainly something we’re looking at.”

Beta-O2 has raised around $22 million in funding since its inception, including some VC money (investors include SCP Vitalife Partners, Aurum Ventures, Pitango Venture Capital, and Saints); and, like ViaCyte, Beta-O2 has benefited greatly from nonprofit funding over the years. Funding from organizations like JDRF (which recently awarded the company a grant to help fund its pilot study in Sweden) and various Government of Israel offices has been essential to the company’s success, Gelvan says, not only from a financial perspective, but also in terms of validation and support. “This has been very important and it remains important,” he stresses. “We thrive out of it; this is our ecosystem as a start-up and we really need this.”

Huge Potential Implications

There are several other commercial entities working in the diabetes cell therapy arena, along with a long list of academic researchers. Other companies active in this space include Islet Sheet Medical Company LLC, based in California, which is encapsulating cells into alginate sheets (the company is supported by the Hanuman Medical Foundation in San Francisco); and Living Cell Technologies Ltd. (LCT), based in New Zealand, which is working with microencapsulated pig cells (from specially bred “clean” pigs) for several clinical applications. LCT holds a 50% interest in New Zealand-based Diatranz Otsuka Ltd. (a joint venture between
LCT and Otsuka Pharmaceutical Factory), which is developing DIABECELL, an encapsulated pig islet therapy for T1D. In addition, there are a few big corporate entities that have performed research in this area, including Novo Nordisk A/S, which is working on stem cell-derived beta cell transplantation in collaboration with researchers from the University of California, Irvine; and Johnson & Johnson, which has conducted some research as part of its Betalogics internal venture, now part of J&J’s Janssen Research & Development LLC group, which recently invested in ViaCyte.

Exactly which (if any) cell therapy technology, or combination thereof, will prove both effective and safe remains to be determined. However, if this approach eventually proves successful in pivotal clinical trials, the implications for the future management of T1D would be huge. Although the T1D segment makes up only 5-10% of the total diabetes population, these are patients that wrestle with serious quality of life issues (including potentially serious complications such as hypoglycemia) on a daily basis, and their younger ranks are robust adopters of new technology solutions (see Figure 4.)

As JDRF’s VP, Artificial Pancreas, Aaron J. Kowalski, PhD (who himself has type 1 diabetes) points out, even if cell therapy technology provides only two years of freedom from insulin injections before the cell encapsulation devices need to be replaced, that would be very appealing. “The goal is to try to dramatically improve diabetes care and management. So if [cell therapy] can normalize blood sugar levels for some prolonged period of time, that’s really what we’re looking for.”

Kowalski says JDRF is excited about the progress the field has made recently, particularly ViaCyte’s move into human clinical trials. “When you look at the history of encapsulating islets and trying to restore normal blood sugar levels with foreign cells, this is probably the biggest advance so far. We’re not to the goal line yet, but [this milestone] is the culmination of many, many years of work.” He also notes that JDRF continues to support multiple lines of research in this arena – including not only ViaCyte and Beta-O2, but Dr. Melton at Harvard and others as well – in order to have “multiple shots on goal.” In fact, the organization has made the area a top priority, he says, and has formed a large “encapsulation consortium” comprised of academic researchers as well as a handful of corporate entities. “We’re big believers in competition drives innovation,” notes Kowalski. “Having companies competing against each other seems to make things happen faster and better.”