The Voice of the Donor for a Cure

Juvenile Diabetes Cure Alliance

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A Look at Commercial Practical Cure Prospects

Conclusions:

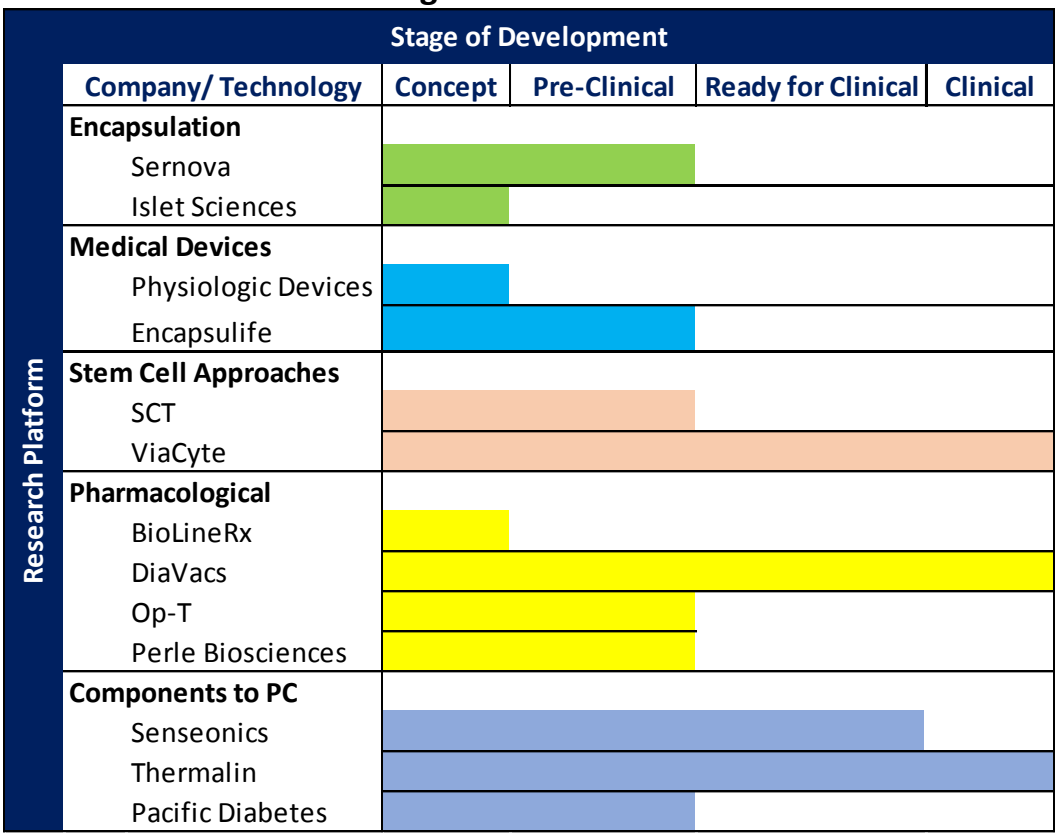
- This report will offer a representative look at *smaller commercial enterprises* pursuing pathways that may result in a Practical Cure.
- Commercial entities are uniquely positioned to make a Practical Cure commercially available by 2025 because they are motivated by *speed to market* and can tap capital markets to advance programs.
- We determined which commercial entities are advancing a potential Practical Cure with screening metrics that evaluate stage of development, funding, and technology.
- Overall, commercial Practical Cure efforts are still early in development. Most are in the initial stages, or, at the latest, in Phase I/II human trials. No company has advanced a true Practical Cure to the pivotal Phase III trials, which is the final stage before FDA approval.
- As always, we invite commentary from our readers and encourage commercial entities who are conducting Practical Cure research to contact us for screening and inclusion in future reports.

This report will profile 13 small to mid-size corporations—both public and private—that are conducting work that could directly or indirectly support a Practical Cure by 2025. Eleven companies are based in the U.S. while the other two are in Israel and Canada. We have organized detailed summaries on each company's research platform, and more critically, stage of development and speed to market. (See the Appendix on pages 4-7 for individual summaries.)

Commercial enterprises differ from the non-profits in their approach to Practical Cure research in terms of funding and motivation. Companies generally approach medical research with the sole goal of commercializing technology to make profits for their share-holders. Larger companies typically have sufficient capital, and have already picked their direction, which focuses more on treatment improvements and less on a Practical Cure. Commercial efforts that do focus on Practical Cure research are uniquely positioned to make a solution commercially available by 2025 because they are motivated by *speed to market*. As opposed to research initiatives funded by non-profit or academic institutions, commercial entities are less tied to annual grant cycles and are more readily able to tap capital to advance research programs.

As seen in the diagram below, the thirteen companies we profiled can be grouped into four Practical Cure approaches (encapsula-tion, artificial pancreas, stem cell therapy, and pharmacology), plus one "other" category for supporting therapies that are not a standalone Practical Cure. These groups track the segments we laid out in our previous reports.

Commercial Entities' Progress toward a Potential Practical Cure



One key takeaway is that for the most part, many of the companies are still in the developmental stage, meaning that animal testing has been completed, but the products are not yet ready for human trials. Currently only two of the standalone Practical Cure companies, ViaCyte and Diavacs, are at the point of starting human clinical trials. (Last year we profiled Viacyte as one of six Practical Cure projects in human clinical trials. We will be adding Diavacs to the list for our upcoming report on Practical Cure re-search in human clinical trials.)

Practical Cure Screening Test

To determine which entities have the most attributes of a Practical Cure effort, we screened according to three metrics:

1. **Progress through clinical trials:** As shown in the diagram below, enrollment in human trials is the first clinical phase on the long road to FDA approval and ultimately commercialization. Human trials generally take 5-12 years from Phase I to FDA approval, thus, any product that cannot start dosing in humans by 2019 is unlikely to qualify as a Practical Cure. Generally speaking, it takes a few years from pre-clinical results to human trials, so we view the most likely Practical Cure companies as those *which* ***have already started or already completed preliminary animal testing***. Technologies which have not yet performed animal trials are unlikely to move quickly enough to launch products by 2025.

2. **Financial backing:** We also believe that having adequate funding and/or a track record of funding support is a useful metric to understand the company's ability to execute its strategic plan and move quickly through trials.

3. **Entirety of a Cure:** Most importantly, we assess whether, if successful, the company's product would constitute a true "Practical Cure," or if it would only be an incremental benefit, and/or is only intended for certain populations (i.e. pre-diagnosed, newly diagnosed/honeymooners) and not for all people with established type 1.

The chart below represent screening results from best to worst positioning according to **green**, **yellow**, and **red** respectively, with **grey** as unknown.

Practical Cure Screening Results

	Encapsulation		Artificial Pancreas		Stem Cell		Pharmacological				Components		
	Sernova	Islet Sci	Phys Dev	Encapsulife	SCT	ViaCyte	BiolineRx	DiaVacs	Op-T	Perle	Senseonics	Thermalin	Pac Diab
CLINICAL DEVELOPMENT													
What is the stage of development of your technology?													
What is the earliest you can dose in humans?													
When could you be on the market? in what geographies?													
FUNDING													
What is your current funding- how much cash in the bank?													
How much more capital is needed to get to human trials?													
TECHNOLOGY													
What is the technology involved?													
Who is product intended for (pre-dx, honeymoon, mature t1s)?													
What will the problem treat? (complications vs. eradication)?													
What clinical benefit will the technology accomplish?													
What is the anticipated side effect profile?													
What is the anticipated burden of maintenance for the product?													

As the chart shows, some progress has been made within each research platform, but the next stage of evolution towards a Practical Cure remains to be seen. The next two years should yield key data to validate the platforms and companies, and we will provide updates as new information becomes available. As always, **we seek input from the community to broaden the list and bring potential Practical Cure work to our attention.**

A forthcoming report on Practical Cure projects in human clinical trials will further review progress by Viacyte and Diavacs. A separate report later in the year will focus on potential Practical Cure efforts by larger companies.

APPENDIX

Encapsulation

Sernova

Type: Public, Canada-based company

Technology: Focused on regenerative medicine through a Cell Pouch, an implantable medical device for therapeutic cells. Its first product intends to use proprietary "Sertolin" technology to provide immune protection for islet cells in the Cell Pouch with the goals of reducing exogenous insulin and improving glucose control. The implantation procedure, as currently conceived, would involve co-transplantation of immune-regulatory cells in a site outside the liver.

Development Progress: At the Islet Transplantation Association World Congress in 2013, Dr. Shapiro (U of Alberta) presented successful safety data in two patients. The company has now begun enrolling for its Phase I/II study to evaluate safety and efficacy of the Cell Pouch for therapeutic islet transplantation. The study will enroll 20 patients with unstable type 1 diabetes and will follow the standard Edmonton Protocol of immunosuppressants. Results will incorporate three-years of follow up.

Islet Sciences

Type: Public, North-Carolina based company

Technology: Product portfolio includes products for type 1 diabetes detection, immunotherapy, and islet encapsulation and transplantation. The treatment involves an injection of islet cells protected from the immune system by a novel encapsulation process. Encapsulation technology would surround islet cells with Islet Sciences' highly purified alginate which should reduce chances of inflammation. Islet cells are harvested in vast quantities from pathogen-free pigs (xenotransplantation).

Development Progress: Currently in animal testing for lead product, Islet Sciences-P, a vialed suspension of microencapsulated porcine cells for injection into the abdominal cavity. Following animal testing, the company intends to pilot human clinical studies employing Islet Sciences' encapsulation technology in patients with end stage renal disease who have received transplanted kidneys.

Medical Device

Physiologic Devices

Type: Private, California-based company (spun out of the Alfred Mann Foundation)

Technology: Developing a fully implanted, closed loop artificial pancreas incorporating insulin delivery. The device is small enough for pediatric use and would control glucose levels automatically. The device may be paired with a fast-acting insulin and rapid sensor readings to anticipate and prevent hypoglycemia day and night.

Development Progress: The program is currently conducting a feasibility study in diabetic mice. Completion is expected in 2014. Following this, researchers intend to launch the first phase of human study in a commercial product incorporating a glucose sensor and a new insulin pump in 2015.

Encapsulife

Type: Private, Tennessee-based company

Technology: Developing a bio-artificial pancreas. The device will contains tens of thousands of living pancreas islets harvested from pigs or live human donors. These cells would be encased in a polymer capsule, fashioned into a pancake-like patch the size of a half-dollar coin, and implanted under the skin. The device is intended to protect the islets from the autoimmune system, and to stimulate the islets to produce insulin and secrete them like a working pancreas.

Development Progress: In 2007, the company presented data in which 9 dogs were successfully treated for seven months. More recently, type 1 was reversed without immunosuppressants in small monkeys. The company is currently set to launch preparations for Phase I human trials.

Stem Cell Approaches

Viacyte

Type: Private, California-based company

Technology: Regenerative medicine focused on the goal of technology as a "replacement endocrine pancreas." Relative to type 1 diabetes, Viacyte's lead compound (its VC-01 combination product) intends to integrate PEC-01 cells (a proprietary pancreatic cell derived through differentiation of human embryonic stem cell line) and its Encaptra drug delivery system (a proprietary immune-protecting and retrievable encapsulation device). The product would be implanted under the patient's skin and then the cells would theoretically produce mature pancreatic cells that would synthesize and secrete insulin and other compounds, thus regulating blood glucose.

Development Progress: Viacyte has a Pre-clinical results in mice that were treated for up to a year, showing sufficient blood glucose control while on the product. The company has received significant funding from the JDRF, venture capital funds, and the state of California. Viacyte is currently planning to initiate the Phase I trial in the first half of 2014.

SymbioCellTech (SCT)

Type: Private, Utah-based company

Technology: Focused explicitly on creating a "Practical Cure" for type 1 via a single injection into the abdomen (peritoneal cavity). The injection would contain a fused cell comprised of a mesenchymal stem cell (MSC) and a Beta Cell. The theory is that the MSC would act as a 'cloaking device' to keep the immune system from recognizing the beta cells, so the fused cell would produce insulin and be protected against the auto-immune attack. SCT plans to grow these B-MSCs in mass quantities in their lab. After injection, the B-MSCs would deliver insulin directly to the liver.

Development Progress: Animal data in STZ Diabetic rats as well as STZ-Diabetic mice has shown potential. The company is currently preparing to dose in dogs and then humans. The company is pursuing a veterinary as well as a human approach to market. For humans, the company is targeting its pre-IND meeting with the FDA by year end 2014. If successful, it would start dosing in mid-2016 with the goal of completing human clinical trials by the end of 2019 and being on the market in 2020. The company has raised $2.5 million to date. It currently requires $6 million to prepare for human trials, and estimates that its human program would require $14 million through product launch.

Pharmacologic Approaches

BioLineRx

Type: Public, Israel-based company

Technology: Announced on January 8 it intends to develop and commercialize a monoclonal antibody called BL-9020 for the treatment of type 1. BioLineRx will be doing the pre-clinical and clinical development of the compound that targets the Natural Killer receptor NKP-46, which has been linked to type 1 diabetes. Specifically, as part of the autoimmune attack, the NKP-46 receptor recognizes pancreatic beta cells, leading to their destruction. Inhibition of Natural Killer cells that are targeted on the pancreas is a potentially novel mechanism which could modify the course of type 1 cure research.

Development Progress: The drug is designed to prevent destruction of beta cells. Data in pre-clinical mouse models suggest the compound is effective in the honeymoon period and can preserve surviving cells.

DiaVacs

Type: Private, Pennsylvania-based company

Technology: Focused on inducing immune tolerance in children who have auto-immune diseases. The company is seeking to reprogram dendritic cells (immune cells that activate immune response) to induce tolerance. The company has perfected the immunology and technology to take a patient's own dendritic cells from their blood, modify the cells, and vaccinate the patient. These modified cells are injected under the skin, where they are absorbed, trafficked to the pancreatic lymph nodes, and thereby induce tolerance. This therapy has been shown to be safe and effective in animal models of type 1, and was also safe when given to type 1 diabetics who have had the disease for 5 years or longer.

Development Progress: Researchers have shown initial results that allow for immune tolerance induction in 'honeymoon' stage mouse models. The company's Phase I trial showed the treatment to be safe in 10 patients with a beta cell mass of 0. 4 of the 10 patients saw a reproduction of c-peptide (an indicator of the body's insulin production), indicating potential for immune tolerance even in longstanding type 1 patients. Currently, the company is preparing for its Phase II trial, and is targeting 80 patients in two tranches. First, 10 patients will be dosed this year, and the company intends to present 6 months of outcome data in January of 2015. If the first 10 patients' data is safe, then the company will raise money to proceed with the last 70 patients.

Op-T, Inc.

Type: Private, Colorado-based company

Technology: Focused on detection and control of T-cells that contribute to the onset of type 1. They would theoretically bring back normal immune function through a therapeutic peptide that restores levels of a type of T-cells, called Th40. In testing, Th40 cells drastically increased in both humans and NOD mouse model of type 1 diabetes.

Development Progress: On the therapeutic side, the peptide has been tested in 400 NOD mice (focusing on early onset/honeymoon), who showed improved islet function and demonstrated that immune cells are not diminished by treatment. The company is preparing to conduct its Phase I study within the next 12-18 months. If the study is successful, Op-T currently targets licensing and/or partnering with Pharma who will complete the approval process and establish distribution.

Perle Biosciences

Type: Private, Maryland-based company

Technology: Focused on combining regeneration with immune suppression. The technology is based on the identification of a specific human regulatory gene (REG) which can potentially transform human pancreatic ductal tissue into new beta cells under certain conditions.

Development Progress: The first two human trials (called "Insulin Independence Trial") would use Cyclosporine & Lansoprazole (i.e. a common OTC medicine plus an immune system suppressant). Trials are currently recruiting and enrolling 120 subjects in 2 groups of 60 people for 2 years. The first group will be newly diagnosed type 1 diabetics, while the second group will be long-standing type 1 diabetics.

Potential *Components* of Practical Cure

Senseonics

Type: Private, Maryland-based company

Technology: Developing an implantable continuous glucose monitoring system that is designed to enable accurate, safe, and long term continuous glucose measurement by integrating 3 components: a smart sensor, a smart transmitter, and an app on a smartphone. Relative to current technology (e.g. Abbott Navigator, DexCom G4), Senseonics believes that it has several advantages: better sensor durability (180 days), higher accuracy, no oxygen/electrochemical interference, a more patient-friendly interface (wireless communication & passive telemetry), and less frequent calibration. Potential component of a Practical Cure as part of an Artificial Pancreas.

Development Progress: To date, the company has conducted several pilot clinical trials with durations from 30 days to 6 months in the U.S. and internationally. It intends to enroll for its pivotal trial in the U.S. in 2014, which will test 75 patients over 6 months, with data read out by year-end 2014. They will simultaneously go for approval in Europe. If trials proceed, the launch would come in the EU in 2015 with U.S. commercialization in 2016.

Pacific Diabetes Technologies

Type: Private, Oregon-based company

Technology: Developing an "intelligent infusion set" which intends to combine glucose sensing and insulin delivery in a single consumable, potentially reducing pain, infection risk, and cost. The infusion set would be comprised of a full component suite: needle, sensor, housing, infusion line, electronic module, and monitoring software. Potential component of a Practical Cure when used alongside an Artificial Pancreas.

Development Progress: PDT intends to start its animal studies in Q2/2014, and start human trials with its commercial sensor module and insert in Q1/15. If the trial goes well, PDT would conduct EU trials in Q3/15 and file for approval/launch in the EU in Q1/16 and in the US in Q1/17.

Thermalin

Type: Private, Massachusetts-based company

Technology: Developing multiple technologies to include ultra-rapid-on/ultra-rapid-off formulations of new insulin analogues, infusion set technologies which further accelerate insulin absorption, insulin formulations which extend the life of an infusion set to a week or more, and ultra-concentrated/ultra-stable insulin designed for the next generation of implantable insulin pumps. The platform technology is principally based around developing new insulin analogues which have shorter signaling and/or are so stable they can be stored inside a body for many months.

Development Progress: Its first product, an ultra-concentrated rapid-acting insulin designed to enable miniaturized patch pumps, will enter human clinical studies in the first half of 2015.

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Sources:

1. Public company presentations from each company
2. Discussions with senior management from each company