The Voice of the Donor for a Cure

Juvenile Diabetes Cure Alliance

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Aaron Gorin

Director of Research Analysis

212.308.7433

apg@thejdca.org

Joshua Levy

JDCA Fellow

publicjoshualevy@gmail.com

An Overview of Type 1 Diabetes Cure Platforms

Conclusions:

- This report explains the basic biology of type 1 diabetes and various scientific approaches to curing the disease.
- The overview is intended as a primer for next week's "Human Clinical Trials Update," which monitors Practical Cure projects that are being tested in humans.
- JDCA Fellow Joshua Levy contributed to this report. He is a highly regarded type 1 blogger and parent who has been following type 1 diabetes cure research in pre-clinical and human clinical trials for the past ten years.

Introduction

In preparation for next month's update on the Practical Cure projects in human clinical trials, this report provides readers with background on the different approaches that scientists are taking in pursuit of a cure for type 1 diabetes.

We have identified five distinct pathways to curing type 1. JDCA fellow Joshua Levy shared his expertise in distinguishing each approach and the rationale behind it. A type 1 parent and blogger, Joshua has been extensively monitoring cure research in clinical and pre-clinical trials for the past decade.

Our current report begins by reviewing the biology of type 1 diabetes, particularly as it relates to the role of the immune system. We then explain how each of the five cure pathways engages with different biological aspects of the disease, and give a brief snapshot of research underway in each cure pathway. We will elaborate the research that has already made it to human clinical trials in our next report.

Background on the Immune System in Type 1 Diabetes

Since most methods of curing type 1 diabetes are based on understanding the immune system, here is some basic background on how the immune system works. The goal of a properly functioning immune system is to destroy foreign cells, but not hurt the body's own cells. Four kinds of immune cells are instrumental in this process:

1. Killer T-cells destroy foreign cells.
2. DC cells determine if a type of cell is foreign or not, and communicate this information to killer T-cells.
3. B-cells carry communication between T-cells and organize their attacks.
4. Regulatory T-cells destroy killer T-cells when they malfunction and attack the body's own cells.

There are many different types of each of the cells described above. The different types are usually named after proteins on their outside. These proteins are named CDx (where "x" is a number), and the most common as it relates to type 1 are CD20 (a B-cell), as well as CD4, CD3, and CD8 (all Killer-T cells). Cells of the immune system are not permanent; they die and are replaced all the time.

A person gets type 1 diabetes because their own immune system attacks and destroys the beta cells that make insulin in the pancreas. When the immune system is mistakenly destroying the body's own cells, it is called "the autoimmune attack."

Most researchers agree that stopping the autoimmune attack would cure newly diagnosed diabetics if they were treated before the majority of their beta cells had been destroyed. But there is no evidence that stopping the autoimmune attack alone would cure people with established type 1 diabetes, because their bodies have killed all or most of their beta cells.

Whether a potential cure would require a new source of insulin is a key distinction in how scientists envision a cure. Some researchers think an established type 1 diabetic would naturally and quickly regrow beta cells after the autoimmune attack was stopped. Other researchers believe that the regrowth process would take years or would never happen naturally. These researchers believe that a cure for established type 1 diabetics would require a second treatment to help the body regrow beta cells, or to implant new ones, or something similar. Of the pathways listed below, 1 and 5 belong to the former camp, while 2, 3, and 4 belong to the latter.

Pathway 1: Modifying the Immune System

The immune system has a complex process to determine if a cell type is dangerous or not. When this process fails, the immune system mistakenly attacks the body's own cells. Cure researchers are experimenting with three distinct ways to correct the immune system malfunction: 1) balancing the autoimmune attack, 2) blocking the autoimmune attack, and 3) training the immune system.

- **Balancing the immune system:** Type 1 diabetes can be seen as an imbalanced immune system that has become too aggressive, either because the body is making too many broken killer T-cells that are destroying the body's own beta cells, or because the body is making too few regulatory T-cells to keep the aggressive killer T-cells in line. Therefore boosting the regulatory side might put the immune system back into balance.

  Some researchers are trying to cure type 1 diabetes by helping the body make more regulatory T-cells. The regulatory cells which are being amplified are general purpose regulatory cells. That is a good place to start, but it would be even better if the researchers could multiply a regulatory cell that specifically targeted autoimmune cells (the "bad" cells that are attacking the wrong target). Unfortunately, the technology does not appear to be there yet, although many researchers are working on it.

- **Blocking the autoimmune attack:** A direct way to stop type 1 diabetes is to stop the autoimmune attack. Because the immune system is complex, there are potentially many different ways to stop it. In order to succeed, any treatment that blocks the autoimmune attack must be relatively specific: it must stop the body from attacking its own beta cells, but not the foreign invaders that should be destroyed.

  As mentioned above, any treatment that stopped the body's immune system from attacking the beta cells would be a "honeymoon cure," which means it would work for newly diagnosed diabetics. If the body naturally regrew beta cells, then stopping the autoimmune attack would also cure established type 1 diabetics. Or, if combined with a treatment that grew new beta cells, stopping the autoimmune attack would become a cure for established type 1 diabetics.

- **Training the immune system:** It may be possible to cure type 1 diabetes by training (or retraining) the immune system not to attack the body's own beta cells.

  In many ways this approach is similar to how allergies are treated. Allergies are also caused by the immune system attacking the wrong things, such as the food or pollen proteins it incorrectly identifies as harmful. Allergies have been successfully treated by giving the person very small amounts of the thing they are allergic to. Over a long time, the immune system learns to ignore that allergen.

  Some diabetes researchers are trying similar tactics. They give someone small amounts of the same substance the immune system is mistakenly attacking in the hopes that the immune system will be trained not to attack it any more. This technique is sometimes called "antigen cell retraining" or "antigen specific therapy."

Practical Cure Outlook: Potentially Practical Cure; the drug BCG and the drug combination Sitagliptin/Lansoprazole are being tested in humans as a way to block the autoimmune attack; Diavacs and the Stem Cell Educator are in human trials as a way to train the immune system.

Pathway 2: Self-Dosing Insulin

The idea here is simple: create a chemical that holds insulin and only releases that insulin when the sugar level in the surrounding region is high. You would not have to measure blood sugar levels or match insulin to food. Instead you would just take this "self-dosing" insulin compound and it would release insulin as needed based on what you ate or did not eat.

Practical Cure Outlook: Potentially Practical Cure, depending on the method and frequency of administration. Smart Insulin (in the US) and SIA-II (in India) are examples of self-dosing insulins. Neither has started human trials yet.

Pathway 3: Device to Replicate the Pancreas

This cure approach envisions a device designed to release synthetic insulin in response to the body's changing needs much as a properly functioning pancreas would. Below we detail three versions of this approach.

- **Chemical barrier artificial pancreas:** An idea similar to self-dosing insulin would be containing a supply of insulin in a chemical barrier which changed based on how much sugar was in the surrounding tissue. Some researchers are working on a chemical that insulin could only permeate when there is a lot of sugar in the nearby cells. This same chemical would hold in the insulin when the surrounding sugar level is low. You can think of this as a sort of chemical valve which is controlled by sugar levels.

  If perfected, such a chemical valve could be used to create an artificial pancreas device that would be easy to implant, would have no moving parts, and would not be electrically powered. You would give the device an injection of insulin to refill its supply. From a chemistry point of view, this might be easier to develop than self-dosing insulin, because the "valve" chemical would be totally different from the insulin and each could do its job separately. For self-dosing insulin, these two chemicals would need to be combined and work together.

- **Electro-mechanical (or computerized) artificial pancreas:** This is a device made by combining an insulin pump, a continuous glucose monitor, and a computer controller. If all of these devices are worn (as they are now), then most people would not consider that a cure for type 1 diabetes. However, if these devices could be combined into one implanted device, then it starts to look much more like a Practical Cure.

- **Bi-hormonal artificial pancreas:** Similar to the electro-mechanical artificial pancreas, this device has two separate pumps, one for insulin and the other for glucagon. This means the computer can lower blood glucose numbers by giving insulin, or raise them by giving glucagon. Such a device is likely to have much better control than a standard electro-mechanical artificial pancreas. It is also likely to trigger the same arguments about whether it is really a cure or just better treatment.

Practical Cure Outlook:

Potentially Practical Cure in the case of a chemical barrier artificial pancreas, which would be implanted in the body like an artificial organ. The chemical barrier artificial pancreas is still in early stage research. Electro-mechanical and bi-hormonal models are in human testing. It is debatable whether these machines fit a Practical Cure model, but future iterations may. Dr. Ed Damiano at Boston University is a leader in bi-hormonal artificial pancreas research, and we will continue to monitor his work.

Pathway 4: Encapsulated Islet Cell Transplantation

This potential cure is a cluster of beta cells, surrounded by a high-tech chemical coating, implanted in the diabetic person's body. The encapsulation acts as a physical barrier against the autoimmune attack, so the patient does not need to take any immune-suppressing drugs that would be required for normal beta cell transplantation.

The encapsulated beta cells could naturally grow and react to the body's sugar by generating insulin because the coating around the cells would allow blood sugar in and insulin out. The coating would also allow nutrients in and waste products out to maintain the health of the encapsulated cells. Sugar, insulin, nutrients, and waste products are all relatively small chemicals, while immune system cells are much larger. It should therefore be possible to create a chemical wrapper with holes large enough for the small chemicals to pass through, but too small for the larger immune system cells to get through.

There are several variations in encapsulation technology. First is the question of what sort of beta cells are put in the device. Companies have used pig cells, human cells from people who have died, live donor human cells, and cells

grown from different kinds of stem cells. Second is the encapsulation technology itself. Third is the size and shape of the device, and fourth is any extra treatment to help the device work even better.

Practical Cure Outlook: Potentially Practical Cure; over the last 20 years several different researchers have attempted to create an implanted encapsulated islet cell device to cure type 1 diabetes. Viacyte, Diabecell/LCT and Monolayer Cellular Device are leaders in the area.

Pathway 5: Pharmacological Approaches to Inflammation

Type 1 diabetics have notable pancreatic inflammation, especially around their beta cells. Most researchers believe that inflammation is a result of the body's immune attack. That is, the underlying autoimmune attack causes both inflammation and beta cell death.

However, some researchers believe that the underlying immune problem causes inflammation, and that this inflammation kills the beta cells. The key difference is that, in the second model, if you stop the inflammation you can stop the symptoms of type 1 diabetes. This second model is still a minority opinion.

Many drugs, such as Aspirin and Tylenol, have anti-inflammatory properties. Yet none have been found to impact type 1 diabetes, and people who take them do not seem to have a lowered risk for type 1 diabetes. Several researchers are testing anti-inflammatory drugs to see if they can stop type 1 diabetes from fully developing in newly diagnosed type 1 diabetics.

It is not clear how this approach could be applied to established type 1 diabetics, even if it works for newly diagnosed diabetics. More than other approaches described here, this one is very time dependent.

Practical Cure Outlook: Unlikely to be Practical Cure; Alpha-1 Antitrypsin (AAT), Atorvastatin (Lipitor), Canakinumab and Gleevec are leading candidates in this area. These drugs are already marketed for other indications but may be re-examined for usage in type 1.

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14 East 60th St, Suite 208
New York, NY, 10022

Phone: 212-308-7433

Email: info@thejdca.org

Website: thejdca.org

Sources:

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