Type 1 Diabetes & Glucose-Responsive Insulin: 
Background information

This document provides high-level information about type 1 diabetes, insulin and glucose-responsive insulin. Additional information can be obtained by clicking on the reference links provided on the Challenge Landing Page.

What is diabetes? What is type 1 diabetes?

Diabetes is a metabolic disease characterized by the body’s inability to control its blood glucose levels. This can arise from an insufficient production and/or action of a hormone called insulin which breaks down glucose. Diabetes is one of the major causes of morbidity and mortality in the world, irrespective of age, gender, race, or locale. It poses an enormous socio-economic burden and significantly erodes the quality of life of people and families affected by the disease.

Normal fasting blood glucose levels range between 70 mg/dl and 100 mg/dl (mg/dl means milligrams of glucose in 100 milliliters of blood) or between 4 mM and 6 mM. A blood glucose level below 70 mg/dl indicates what people refer to as “hypoglycemia” (low blood sugar). A blood glucose level above 200 mg/dl indicates "hyperglycemia" (high blood sugar). Fasting blood glucose higher than 100 mg/dl indicates pre-diabetes or outright diabetes. Two to three hours after eating, glucose levels should be less than 140mg/dl, and if they are over 200 mg/dl, you are diagnosed with diabetes.

One specific form of diabetes is called type 1 diabetes, formerly known as insulin-dependent diabetes mellitus (IDDM) or juvenile diabetes. Type 1 diabetes is an autoimmune disease in which the insulin-producing cells in the pancreas are destroyed. As a result, people with type 1 diabetes are completely dependent on external sources of insulin throughout their lifetime. Although type 1 diabetes may strike at any age, onset most often occurs during childhood, adolescence, or young adulthood.

To survive, people with type 1 diabetes must measure their blood glucose levels and administer insulin in response to those glucose levels, multiple times every day for the rest of their lives. Regardless of how diligently glucose levels are monitored and even in the most compliant of patients, dangerous lows and highs of glucose levels can
occur; and a substantial portion of any given day is spent in such dangerous blood glucose zones. These dangerous glucose levels are the primary cause of diabetic complications. Hypoglycemia is a challenge to achieving tight glucose control, and very low blood sugar can result in cognitive impairment, unconsciousness, seizures, and even death. At the other end of the spectrum, hyperglycemia also leads to devastating complications, including kidney failure, blindness, nerve damage, amputation, heart attack, stroke, and pregnancy related complications. Maintaining blood glucose levels within a normal range is a challenge for people with type 1 diabetes, and avoiding the onset of complications is never guaranteed. In so many ways, type 1 diabetes is a tremendous burden for people with the disease and their families.
How does the body normally produce insulin?

Physiologically, insulin is produced by special cells in the pancreas called beta cells, to control glucose levels in the blood, as shown in the figure below:

1. High levels of glucose (yellow dots) are detected in the blood and a message is sent to the pancreas
2. In response, the beta cells of the pancreas release insulin to the liver
3. The insulin has an effect on a number of other cells, including but not limited to, muscle cells, red blood cells and fat cells
4. In response to insulin, these cells absorb glucose out of the blood, almost like a sponge, causing the levels of glucose in the blood to go down, back to the normal range as depicted by the reduced number of glucose (yellow dots) in the final image below
What are the issues with today’s insulin treatments?

Since the discovery of insulin in 1922 – a lifeline for people with type 1 diabetes – research advances over time have helped to improve insulin, the delivery of insulin, and the management of blood glucose levels. The advent of faster-acting insulins, and devices such as syringes, insulin pumps, and blood glucose meters have helped significantly improve diabetes management. However, even with diligent monitoring and progress in the development of advanced insulin drugs, type 1 diabetes (and insulin-dependent type 2 diabetes) is far from being conquered or easily controlled due to the suboptimal way insulin is currently administered to patients with the disease. Thus, current methods of diabetes management are cumbersome and benefits of treatments remain sub-optimal:

*Cumbersome disease management:* People with type 1 diabetes must manually measure levels of glucose in their blood by either using the traditional method of pricking one’s finger, or by using a continuous glucose monitor (CGM), a device that senses glucose levels via a needle inserted under the skin. Then, based on these measurements, they must adjust glucose levels by taking multiple injections of insulin daily or by continually infusing insulin with a pump via needles placed under the skin. In addition, multiple other factors beyond insulin affect glucose values, making control hard in people living a normal life outside a controlled hospital setting. This requires diligence and a tremendous amount of manual effort by the user.

*Sub-optimal benefits:* Regardless of the above advances, there is no insulin drug or insulin delivery technology available to people with type 1 diabetes today that possesses the biological profile necessary for maintaining physiological blood glucose control. Restoring non-diabetes-like glucose control without user intervention is a recognized need and requires better technologies. Whereas insulin in people without diabetes goes right to the tissues and cells that need it the most, insulin treatments for people with diabetes today deliver insulin under the skin at similar rates to all organs of the body, thus failing to restore the disrupted/missing balance in type 1 diabetes. Such erratic delivery of insulin and the inherent properties of today’s drugs are believed to be the primary causes of extremes of blood glucose levels, and hence of long-term diabetes-related complications.
**What is “glucose-responsive insulin”?**

Currently, all insulin treatments for people with diabetes release the same amount of insulin at fixed times throughout the entire body. However, in people without diabetes, the body secretes insulin in proportion to local blood glucose levels, delivering it to the body’s tissues and organs at the appropriate times and according to their specific needs. This helps the person without diabetes maintain a target blood glucose level throughout the day, and to eventually avoid diabetes-related complications.

Thus, the importance of finding novel mechanisms to deliver drugs in response to local glucose levels, similar to the function of a healthy pancreas, is critical. Glucose-responsive insulin is a drug that would deliver insulin proportional to local glucose levels throughout the day, closely mimicking physiologic insulin secretion. This would achieve many things. It would help individuals with insulin-dependent diabetes achieve tight glucose control, reduce the burden of frequent glucose measurements, and provide a relatively device-free diabetes management system, reducing the need for multiple devices in order to control blood sugar levels. The systems are anticipated to vastly improve the quality of life of people living with this disease.

Early research today shows promise that it may be possible to package insulin in safe and efficacious glucose responsive complexes. This area of research has perhaps the most promise in offering tight glucose control, relief from complications and substantial improvement in quality of life. It also has the potential to minimize manual intervention and error by avoiding frequent glucose measurements (via finger sticks or CGMs) and providing once daily or even less frequent dosing, further adding to the benefits. In its truest form, a glucose-responsive insulin can “replace” all existing insulin-based treatments - both drugs and devices – and can benefit all diabetes patients dependent on insulin treatment.

Glucose-responsive insulin could therefore be a transformative solution, vastly improving the quality of life of people with insulin-dependent diabetes.
Who is JDRF?

JDRF is the worldwide leader for research to cure, better treat and prevent type 1 diabetes. It contributes to the global agenda for diabetes research, and is the largest charitable funder and advocate of type 1 diabetes worldwide.

The mission of JDRF is to find a cure for diabetes and its complications through the support of research. Type 1 diabetes is an autoimmune disease that strikes children and adults suddenly, and can be fatal. Until a cure is found, people with type 1 diabetes have to test their blood sugar and give themselves insulin injections multiple times or use a pump - each day, every day of their lives. And even with that intensive care, insulin is not a cure for diabetes, nor does it prevent its potential complications, which may include kidney failure, blindness, heart disease, stroke, and amputation. JDRF estimates that there are up to three million people in the United States who have type 1 diabetes.

Since its founding in 1970 by parents of children with type 1 diabetes, JDRF has awarded more than $1.5 billion to diabetes research, including $107 million last year. More than 80 percent of JDRF's expenditures directly support research and research-related education. For more information, please visit www.JDRF.org.
Where else can I find more information about diabetes, insulin and glucose-responsive insulin?

Below is a brief list of references which may provide more details to build on the general information provided above (also available at the Challenge Landing Page):

Advantages and disadvantages of current insulin drugs:

Insulin analogs vs. physiological insulin secretion:

Clinical use of current insulin analogs

Challenges in managing T1D (background of diabetes in general)

Review of stimuli-responsive polymers in drug discovery, development and delivery (overview of what GRI is)

Specific examples of GRIs (review of what GRI is) -

Cost-benefit analysis of insulin analogs