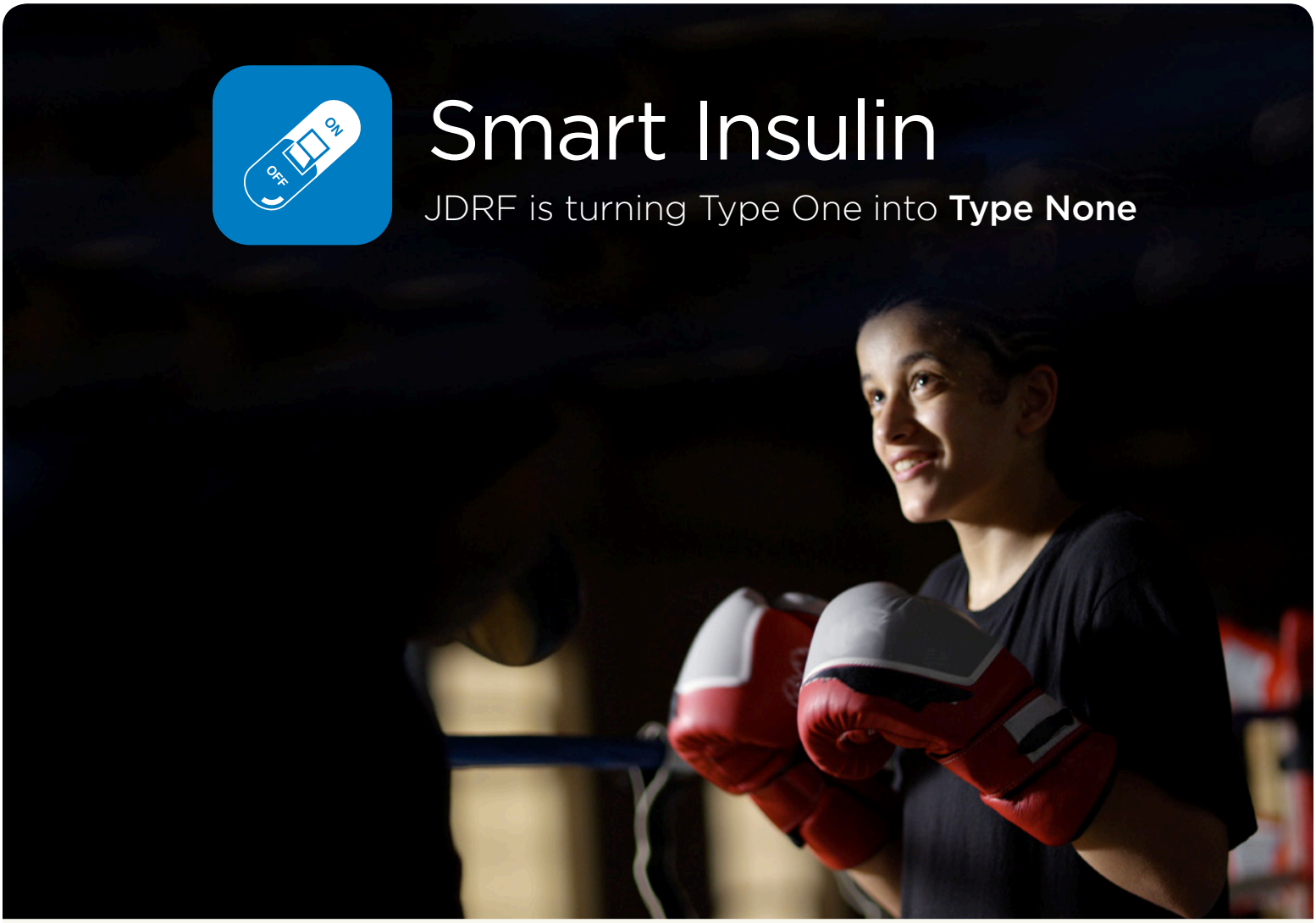

Smart Insulin

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.

This paper is on smart insulin, part of our strategy to pursue therapies that keep those with T1D as healthy as possible so they can take advantage of the biologic cure when it arrives. Smart Insulin will give someone with T1D confidence that they have enough insulin to cover their needs for the day, no matter what they eat, how hard they exercise or how stressed they are at work or school. In the process, it would dramatically reduce the burden of managing T1D by minimizing the need for human interventions such as frequently measuring blood glucose, calculating insulin doses, and administering insulin.

WHAT IT IS

Beta cells in a normal functioning human pancreas release insulin into the bloodstream in response to high glucose levels. Insulin helps ensure that blood glucose levels stay in a safe range, neither too high nor too low. But in T1D, beta cells are destroyed in an autoimmune attack and the body no longer produces sufficient insulin to regulate glucose levels.

Smart insulin is a drug designed to circulate in the body and turn on when its needed and off when its not. Smart insulin would ensure perfect glucose control throughout any given day. In essence, smart insulin is a glucose-responsive insulin, an insulin in a form that renders it essentially inert until it is needed. A person with T1D would take a shot, or a pill, of this insulin—enough to cover the needs of a day—and the bound insulin would circulate in the body until blood glucose levels start to rise. As glucose rises, the binding element of the insulin releases the insulin so it is free to do its job. As glucose levels return to normal, the release of insulin stops until it is needed again. In other words, smart insulin would automatically activate or deactivate in response to the glucose in the blood, thus giving tighter control essentially as if the beta cells were working normally.

WHY IT MATTERS

Blood sugar control is the most challenging and trickiest aspect of managing T1D. If a person administers too much or too little insulin, blood sugars could come crashing down or soaring up, leading to severe side effects, including unconsciousness and even death. Today's synthetic insulins, administered through pumps or injections, are imperfect regulators of blood glucose levels. Smart insulin would be transformative. It would prevent high and low blood sugar surges, significantly decrease the need to regularly test blood glucose levels and reduce the chances of short and long-term complications of T1D. Whether it comes in a pill or an injection, just one dose of smart insulin will give someone with T1D confidence that they have enough insulin to cover their needs for the day, no matter what they eat, how hard they exercise or how stressed they are at work or school. In the process, it would dramatically reduce the burden of managing T1D by minimizing the need for human interventions (such as frequently measuring blood glucose, calculating insulin doses, and administering insulin). Ultimately, smart insulin could even make devices like the artificial pancreas obsolete.

JDRF'S IMPACT

JDRF's search for innovative therapies for T1D led it to catalyze funding for early stage research on smart insulin. As a direct result of the work funded by the National Institutes of Health (NIH) and JDRF, the pharmaceutical firm Merck is now providing significant private sector resources to the smart insulin field, as described below. At the same time, JDRF is reaching out to a wider universe of scientists across multiple disciplines to attract innovative ideas that we hope will lead to key breakthroughs accelerating research on smart insulin.

BACKGROUND

Early in this century, a chemical engineer named Todd Zion was experimenting with chemically modifying insulin so it would automatically react to changing blood glucose levels as part of his work on his doctoral thesis at the Massachusetts Institute of Technology. Zion formed a company called Smart Cells, Inc. to pursue the concept but funding was a challenge as is often the case for biotechnology start-ups with unproven ideas.

How JDRF helped this promising idea move forward is an example of the many ways JDRF leadership can make a difference. Thanks to advocacy in Congress by JDRF for the $150 million a year Special Diabetes Program, the NIH was able to provide Zion with several grants, starting in 2004, which enabled him to develop his idea further.

In 2008, JDRF stepped in under its Industry Discovery and Development Partnership Program to support discovery and assessment of the safety and efficacy of smart insulin drug candidates in animal models of T1D. The IDDP program was specifically created to provide early stage funding to companies developing drugs, treatments, and technologies to address T1D. Such funding is typically extremely difficult to raise given the enormous risks associated with early drug development work and the high rate of failure.

Throughout this time, JDRF put its credibility as the world's largest T1D research organization behind Smart Cells, highlighting its promise as a potential breakthrough therapy to scientific, government, and business leaders. Just 2 years after JDRF's IDDP investment, the pharmaceutical giant Merck & Co. acquired Smart Cells for up to $500 million based on achievement of milestones, thus bringing its drug development expertise and substantial financial capacities to the smart insulin field. The acquisition validated

JDRF has been a leader in advancing the smart insulin field.

JDRF's strategy of utilizing its funding and influence to de-risking promising T1D research and accelerate its progress through the research and development pipeline to people with T1D.

THE JDRF SMART INSULIN PROGRAM

Smart insulin is a tremendously exciting idea but is still at a very early stage of development. JDRF is not satisfied with having only one possible product under active development—as mentioned, failure rates for new drug development are high.
There is no known precedent of any drug for any disease designed to work automatically in response to a signal like rising blood glucose. Bringing smart insulin from its current state to patients will require conquering a series of biologic and chemical challenges. JDRF concluded that it would be valuable to attract additional innovative thinkers both within the and beyond the diabetes field to present ideas toward solving the complex issues associated with smart insulin. To that end, JDRF announced a "Glucose Responsive Insulin (GRI) Grand Challenge Prize" in September 2011.

WHERE WE ARE TODAY

The GRI Challenge Prize is a creative means to stimulate the development of novel ideas from a diverse array of disciplines including nanotechnology, formulation science, pharmacology, endocrinology, and chemical engineering, in order to advance development of smart insulin. The first phase of the GRI Challenge, called the Ideation Phase, sought submissions from anyone with an idea that offers potential solutions to the following issues:

- How to deliver appropriate amounts of insulin in response to glucose levels to maintain effective control;
- How to prevent overdosing of insulin, which causes the most serious short-term adverse effects in people with T1D.

JDRF received a total of 63 full applications in response to the challenge, each of which went thorough internal and external reviews. From this group, three were selected to receive the SI Ideation Prize, including one individual scientist and two teams of scientists. The three winning projects are now being further developed.

NEXT STEPS

Phase 2 of the GRI Challenge will be the discovery phase building on the winning ideas in Phase 1. This phase will provide experimental design and validation of potential smart insulin drugs, culminating in pre-clinical proof of principal studies in animal models. The final phase of the challenge will take the most promising drugs to human clinical trials.

SUMMARY

Over the last decade, JDRF has been a leader in advancing the smart insulin field. It was our early support of Todd Zion's Smart Cells, Inc. at the company's riskiest stage that sustained the idea and validated the initial concept. And by de-risking the discovery research and proving that smart insulin is a potential T1D therapy, Merck has made a financial commitment to take the concept further along the development pipeline. Beyond its support of Smart Cells, JDRF has continued to provide leadership, most recently through the GRI Grand Challenge Prize which has drawn an exciting group of scientists to the field. But we still have a great deal to learn to determine if smart insulin will work. JDRF estimates that it will take at least $25 million over the next 5 years alone to expand our knowledge of the therapy and its potential. 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 smart insulin therapy.

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