Be unstoppable: An Update on Research Progress Q&A

CURES

Dr. Rakeman said that Teplizumab suppresses part of the immune system. Does it therefore increase the risk of any other disease or is it beta cell specific?

- Answer: Teplizumab targets a part of the immune system called the T cell, which we know to be involved in the pathogenesis of T1D. Because it is known to decrease the numbers of these cells in the blood, a common side effect of Teplizumab treatment is a transient condition called “lymphopenia.” Transient, or short-lived, lymphopenia is generally not concerning. Teplizumab treatment has also been associated with Epstein-Barr virus (EBV) reactivation in a limited number of people. This effect also was transient.

What are your thoughts on gene therapy to transform current cells into working beta cells?

- Answer: We know that if we turn on or turn off certain genes we can transform other cells in the body into insulin-producing beta “like” cells. However, we don’t yet have a way to safely restrict these gene therapy approaches to the pancreas. We will need to use targeted drug delivery technologies, like those being used in oncology right now, to restrict these gene therapy approaches to the pancreas. JDRF is building a program to develop targeted drug delivery systems to address this need.

What is the anticipated timeline for implementing universal screening for T1D autoantibodies? What is the plan to ensure screening is universal (e.g., federal legislation)?

- Answer: JDRF believes that screening all children for islet autoantibodies during well-child visits is feasible and should be implemented as part of public health policy. This will not only enable enrollment into prevention trials, but in the short term, aim to reduce hospitalization and life-threatening DKA incidents at onset of stage 3 T1D. JDRF has and continues to support early screening efforts through its funding of longitudinal studies such as Fr1da and ASK, which offer opportunities for children with no known risk for T1D to be screened for islet autoantibodies during wellness visits. Data from the TEDDY study, which also screened the general population for genetic risk, suggests that early detection can raise awareness and help prevent DKA. There are a number of activities that will impact the timeline towards adoption, including health economics research, psychosocial research, and interactions with government, payers, and health policy authorities to understand both the economic and individual benefits for screening and prevention of T1D in order to implement the appropriate policies toward prevention of T1D.
Many people with T1D have been waiting a long time for a cure and are therefore very skeptical that a cure will be found. We are learning of so many exciting advances but how close are we? How many more years before a cure is found?

• Answer: It is always difficult to put timelines on development of new drugs and therapeutics – especially when we are trying to do something that has never been done before, which is to cure a chronic disease. What we can say for certain is that we are closer than ever to cures for T1D. Clinical trials have shown us that we can slow down T1D – preserve beta cells and insulin production in people with T1D and delay diagnosis in people at high risk of T1D. Trials are ongoing to put beta cells back into people with T1D and showing early success. For the first time ever, we have evidence from clinical trials showing us that it is possible to slow down and potentially stop T1D in those at the earliest stages and reverse T1D in later stages. JDRF has the plan to translate these results into new drugs and therapies and make them available to people with T1D.

Is there application of the CRISPR gene editing tool in present or future T1D research?

• Answer: Absolutely, this is a high-priority research area for JDRF. CRISPR gene editing technologies are currently being used to enhance the function of transplanted beta/islet cell preparations and confer protection from immune rejection. While there is a lot of exciting progress in the gene editing approach, it is in early stages of development.

• Additionally, we have been funding research that uses CRISPR to help discover new pathways for beta cell survival and regeneration. This powerful tool can be used to systematically delete every gene in a beta (or alpha or other) cell and tell us which gene helps control these different aspects of islet biology.

• Right now we don’t yet have a way to safely deliver the CRISPR machinery into a person to induce proliferation or survival. Many companies are working on ways to use CRISPR technologies therapeutically, focusing on ways to restrict the CRISPR activities only to the cell of interest. This is an important step to mitigate any possible safety concerns that could be caused by deleting a gene in the entire body.

When we tell supporters the science in immunotherapies and beta cell therapies is at a unique point where science is moving fast, how can we set expectations around how many years until there are cures for T1D? 10 years? 20? Less? More?

• Answer: Overall, science in beta cell therapies is moving fast due to several recent developments: better understanding of how to build bioengineered tissues, significant progress in generating a reliable beta/islet cell source that can be manufactured and scaled-up for clinical use, and the development/testing of alternative strategies to protect transplanted cells from immune rejection. While we would like to see many more clinical trials in this area, research needs to be done to test the safety and efficacy of these therapeutic approaches.

Can you please speak to the increased incidence of T1D diagnosis?

• Answer: Rates of incidence of T1D are rising around the world. T1D is a complex interaction between genetics and the environment and the recent upticks suggest a greater contribution of environmental
factors. Studies like TEDDY, DIPP, and others are studying the natural history of T1D from early childhood to understand what factors impact the development of T1D.

**With the reduction in funding for TrialNet, how can/should we continue to get testing for our high-risk family members? We had been doing TrialNet, but recently were told my kids aren’t eligible anymore...**

- **Answer:** TrialNet no longer offers routine annual rescreening to children who initially screen negative for autoantibodies. Additionally, TrialNet has increased the age of entry into the Pathway to Prevention study from 1 year to 2.5 years old, as children must be at least 3 years to enroll in a prevention trial. Individuals should discuss alternate options for measuring autoantibodies with their physicians.

**Please describe briefly our work in microbiome research.**

- **Answer:** Our work in the microbiome space has progressed tremendously over the past several years. In fact, recent evidence has demonstrated that changes in several features of the intestinal microbiome are linked with the onset of T1D. Building on these findings we are now poised to take the next step and investigate the role, function and therapeutic potential of these features.

**IMPROVING LIVES**

**Can you elaborate on the statement that insulins targeted to the liver are “where they should go?”**

- **Answer:** In a non-diabetic individual with a normal, healthy pancreas, insulin is secreted from the pancreas and its first stop is the liver, where the insulin causes the liver to store glucose for later use. After stopping at the liver, insulin is then distributed systemically to the peripheral tissues (such as muscle and adipose) to enable circulating glucose in the blood to enter the cells where it can be metabolized for energy. Conversely, the currently standard of insulin therapy in T1D is to deliver insulin into the periphery (usually via subcutaneous injection/infusion) – thus resulting in a non-physiologic distribution of insulin in the body.

**What’s the latest update on smart insulin and are human trials starting soon?**

- **Answer:** The first clinical trial on a smart insulin (AKA glucose responsive insulin, or GRI) was performed by Merck and published in 2019; although the drug demonstrated a glucose-responsive effect, its effects were inferior to what was seen in animals and it is not being advanced further. The GRI projects supported by JDRF are currently in animal testing or early discovery, and we are optimistic that some will be in clinical trials within five years, though drug development is highly unpredictable. GRIs are also being pursued by big pharma, with Lilly and Novo both having made high profile GRI acquisitions (Glycostasis and Ziylo, respectively) in recent years.
Is JDRF evaluating and/or supporting any research into salivary glucose detection or non-invasive glucose detection?

- Answer: We are always interested in novel ways to detect glucose in T1D – ways that have the potential to be more accurate and/or less invasive than current systems. While we are not currently pursuing salivary detection (due to accuracy concerns), we remain interested in other approaches such as those that use pain-free microneedles.

Are our efforts in glucose control also addressing insulin resistance, especially in adults diagnosed with T1D for many years?

- Answer: We have a deep appreciation for how different T1D can be from patient to patient and from day to day. Part of our efforts to understand this “heterogeneity” more thoroughly indeed include investigations into insulin resistance, which is increasingly understood to be an important unmet clinical need for T1D, and we have active grants in this area.

How can people get involved in the psychological research that is being discussed?

- Answer: The Novel Interventions in Children’s Healthcare (NICH) study is being conducted by a team of investigators at Oregon Health & Science University (OHSU). The four sites in the study are: OHSU, Stanford/UCSF, Los Angeles Children’s and Kansas City Mercy. Please refer to https://www.ohsu.edu/doernbecher/novel-interventions-childrens-healthcare-nich to learn more about the project and how to get involved.

CENTERS OF EXCELLENCE

Where can we learn more about our Centers of Excellence?

- Answer: JDRF recently launched two Centers of Excellence, one in Northern California at UCSF and Stanford University and one at the University of Michigan. Both Centers build on considerable expertise and research infrastructure at the host universities and will give the investigators the resources and freedom to pursue collaborative and potentially transformative research projects that could not be supported under traditional funding mechanisms – bringing us closer to cures and better treatments for T1D. Please refer to https://www.jdrf.org/blog/2019/09/04/jdrf-launches-first-center-excellence-aiming-accelerate-type-1-diabetes-research for the announcement of the Northern California Center, and look for additional information and communications from JDRF about our Centers of Excellence in the coming months.

ADVOCACY / ACCESS

What are the chances the SGLT inhibitors can be approved in USA?

- Answer: Two SGLT inhibitors are currently under review at FDA and we understand the companies are actively working with the Agency to address outstanding questions about the risks and benefits of
these drugs. While we cannot comment on the chances of success, we are confident the companies and FDA will thoroughly explore the evidence to find a path forward. JDRF continues to fund research to support the further development of adjunct therapies, including SGLT inhibitors, that will be able to address some of the unmet needs with T1D management today.

Knowing that bringing drugs to market is a long process, it’s so exciting to hear of the progress we are making. Can you help us understand this process of getting these treatments into the hands of patients?

- Answer: Drug development is a lengthy process! There are also several variations of how it is done, but in short, once a drug is discovered in the laboratory, a company has to first demonstrate in the lab and in animals the basic safety of the drug. Then, the company conducts a series of studies in humans, called clinical studies, usually in three phases, to first establish basic safety in people and the correct dosage and then to test whether the drug has the desired effect. After this research, the company submits all of the data and evidence as well as information on their manufacturing process and facility to FDA who reviews all of this to determine if it demonstrates that the drug is safe and effective for its intended use. Once a drug is FDA approved, the company works with public and private insurers to ensure that people will have access to the drug through their insurance benefit.

Can JDRF consider getting involved on the Advocacy side as it relates to access to more affordable life insurance policies for those with T1D and a documented history of good control and limited/no hospitalization/side effects of T1D?

- Answer: JDRF has historically focused its advocacy on areas related to curing T1D and improving the lives of those with T1D through research and access to research advances. While life insurance policies are very important and certainly impact the T1D population, we have not had the opportunity to work on these issues in the past. It is helpful to know there is an interest from the community and we will be mindful of this if opportunities arise in the future.

What happens if SDP is not renewed?

- Answer: Since its inception in 1997 (officially signed into law in 1998), the Special Diabetes Program (SDP) has been reauthorized 10 times. From a policy standpoint the program has never been in a better place. Earlier in 2019 JDRF circulated a letter of support for the SDP in both the House and the Senate. In the House 85% of Members signed the letter, and in the Senate 69% of Members signed. Any recent delays in reauthorizing the program have not been related to the underlying policy. But, with that said, hypothetically if the program were to not be reauthorized, it would create a funding gap that JDRF would not be able to make up.

We have a state senator who wants to create state legislation about affordable insulin. How do we best get guidance from the JDRF national office?

- Answer: This is something that strategically JDRF has spent a lot of time thinking about. We’ve decided that in the interest of donor dollars, we can make the most impact by focusing on Federal issues. Advocating at the state level is very different than advocating at the Federal level. Every state has a different definition of lobbying, and different “thresholds.” This would require us in most states to
register and have a presence, both of which would be resource- and time-intensive. Given these factors, we’ve made the (difficult) decision to focus our donor dollars where they can make the most impact.

LOOKING FORWARD / OTHER

Can there be a video training for employees who are not as familiar with T1D? We all “know” what the disease is but do we know what a CGM/pump is really doing? Or how to help someone who is having a low? Or how to administer glucagon?

- Answer: The Mission team is working on a technology guide and possibly video. Please stay tuned for further information.

Some current corporate foundations are changing their focus to access to healthcare – especially the underserved communities. How are we measuring these results? Will we have any funding opportunities for mid-level donors regarding this focus?

- Answer: We are focused on doing the greatest good in the shortest time for all people with T1D, certainly included the underserved communities. In that vein, we are committed to ensuring access, affordability, and adoption of therapies for better outcomes by people with T1D and healthcare providers. We are therefore open to – and seeking – support from all-level donors to achieve our Mission.