Prevention

OVERALL VISION AND LONG-TERM OBJECTIVES

The JDRF Prevention Program aims to prevent or delay Stage 3 type 1 diabetes (T1D) through the development of vaccines and therapeutics. As an intermediate goal, JDRF aims to prevent the presentation of diabetic ketoacidosis (DKA) at the initiation of Stage 3 T1D.

To achieve these goals, JDRF is pursuing:

- Microbiome, viral and antigen-specific based approaches to prevention
- Mechanistic trials to alter disease course in the early stages of T1D
- Biomarker strategies to refine risk and rate of progression
- Approaches to screening and monitoring to reduce DKA at the initiation of Stage 3 T1D

OVERVIEW

Several developments have increased the importance of prevention of T1D. First, the incidence and prevalence of childhood onset T1D have been increasing over the last several decades in multiple countries with approximately a 2–4% annual increase in incidence, with penetration to low-moderate human leukocyte antigen (HLA) risk groups, suggesting a lowered threshold for its development. In the United States, the SEARCH study has shown a 2.7% increase in annual incidence from 2002 to 2009. In some countries, the disease is also occurring at a much earlier age, with a markedly increased age-incidence in the 1–5 year age range. Designing clinical trials to prevent T1D requires both insights into the natural history of the disease and the ability to detect an at-risk target population for trials.

In 2015, recognizing that T1D starts with an asymptomatic phase, JDRF, along with key academic partners, funding organizations and patient and professional organizations, defined stages of T1D that are now recognized:

- Stage 1: Multiple (two or more) islet autoantibody-positive/normoglycemic
- Stage 2: Multiple islet autoantibody-positive/dysglycemic (glucose intolerance)
- Stage 3: Clinically defined T1D

Both primary prevention of T1D (prevention of Stage 1 or 2) and secondary prevention (prevention of Stage 3) are priorities for JDRF.

PRIMARY PREVENTION

For primary prevention of T1D, JDRF will support testing of three different preventive therapeutic approaches:

1. T1D enteroviral vaccines, including epidemiologic data demonstrating that a limited number of enteroviral serotypes are associated with beta cell autoantibody seroconversion as well as
interrogating the mechanisms associated with enteroviral infection suggest a pathway for beta cell destruction.

2. Vaccines or therapeutic approaches that confer robust immunoregulation early in life based on principles of intestinal microbiota-induced healthy immunoregulation. This approach is based on the hypothesis that the increasing incidence of T1D is arising from altered development or maintenance of healthy microbiota-induced immunoregulation due to changes in the environment.

3. Tolerogenic beta cell autoantigen vaccines that induce durable beta cell-specific immunoregulation/immune tolerance. This area is covered under JDRF’s Immunotherapies program.

Diabetes preventive vaccines and/or therapies will carefully need to weigh risks and benefits and, ideally, not require companion diagnostics for their application.

At this time, JDRF will not pursue alternative primary prevention approaches including nutritional/vitamin-based approaches (e.g., introduction of solid food in the first year of life, breast milk vs. cow’s milk proteins, supplementation of vitamin D or polyunsaturated fatty acids, etc.), although results from ongoing natural history clinical trials of at-risk subjects (The Environmental Determinants of Diabetes in the Young (TEDDY) and other studies) could alter JDRF’s future strategy.

**Gaps and Challenges**

Current important gaps and challenges of primary prevention that JDRF will address include:

1. Lack of cost-effective at-risk screening to increase the pool of subjects for clinical trials and support Stage 1 and 2 therapeutic development.

2. Lack of biomarkers that detect risk prior to the development of Stage 1.

3. Lack of refined, validated biomarkers to improve disease stages and progression for designing clinical trials and for serving ultimately as surrogates of efficacy of prevention approaches.

4. Incomplete understanding of human T1D heterogeneity and pathogenesis.

5. Limited epidemiologic studies of enterovirus association with T1D.

6. Incomplete understanding of the basis of healthy microbiota-induced immunoregulation and the specific defects in predisposing to T1D in order to develop scientifically rationally defined sustainable preventive approaches.

7. Lack of approaches to induce immune tolerance robustly and safely in humans.

**SECONDARY PREVENTION**

Secondary prevention can be considered early treatment of T1D. In addition to providing a means to prevent or delay progression to Stage 3, these strategies may also inform specific primary prevention approaches. The strategy for secondary prevention of T1D is to:

1. Assess and screen for risk of developing T1D, with an intermediate goal of preventing DKA in this population.

2. Precisely predict the rate of progression.
3. Intervene with T1D stage- or pathway-specific therapies to halt progression and prevent Stage 3.

Populations that can be targeted for secondary prevention include (1) relatives of individuals with T1D, who have a 15-fold increased risk of T1D; (2) infants and children who have been screened at birth for high risk genetic markers, such as HLA genes; and (3) individuals in the general population who have been screened for autoantibodies. The presence or development of beta cell-specific autoantibodies in both these populations is currently used to screen for high risk. Because the majority (>85%) of individuals diagnosed with T1D do not have a family history of T1D, cost-effective, rational screening approaches need to be developed to target the wider childhood population. This type of universal childhood population-based screening for beta cell-specific autoantibodies represents an alternative approach for identifying at-risk subjects.

Secondary prevention interventions to robustly arrest disease progression and prevent Stage 3 T1D may require combining therapies that target multiple pathways such as beta cell-specific autoimmunity, inflammation, beta cell survival and/or metabolic regulation. Smaller and shorter proof-of-concept prevention clinical trials will be prioritized because they can catalyze the field and help garner industry commitment to prevention of T1D.

Gaps and Challenges
Current gaps and challenges for JDRF’s secondary prevention strategy that JDRF will address, with some overlap with primary prevention, include:

1. Lack of tailored, safe, stage- or pathway-specific interventions.
2. Limited number of subjects willing to participate in prevention trials.
3. Lack of cost-effective at-risk screening to increase the pool of subjects for natural history and intervention clinical trials.
4. Lack of refined, validated biomarkers of improve disease stages and progression for conducting clinical trials and serving ultimately as surrogates of efficacy of disease prevention.
5. Incomplete understanding of human T1D heterogeneity and pathogenesis and limited understanding of how timing of intervention influences response to therapy.
6. Lack of appreciation by individuals and families as well as regulatory agencies of the inevitable progression to Stage 3 T1D from early stages of the disease and of the potential benefit/risk of interventions to arrest progression.

JDRF will adopt a comprehensive approach to prevention. The current extensive infrastructure (TrialNet, TEDDY, DIPP, Fr1da, ENDIA, ASK, etc.) will need to be leveraged, including the ongoing risk screening, natural history studies and prevention clinical trials, and biobanks. In light of JDRF’s public health approach to prevention, it will be critical that the SEARCH program that monitors T1D incidence and prevalence in children in the United States is maintained to follow trends.

In adopting a comprehensive prevention strategy, JDRF will need to increase awareness by families with individuals with T1D, the general population, health care providers, regulatory agencies, and payors of the opportunities of risk detection, including prevention of DKA, the continuum of disease progression.
and inevitability of Stage 3 from earlier disease stages, opportunities to participate in natural history and intervention prevention trials, and the benefit/risk of preventive interventions as they develop. A business model that models economics of prevention will need to be developed.

**SHORT-TERM OBJECTIVES AND PRIORITIES**

1. Supporting general population screening programs, which include monitoring disease progression, based on detection of islet autoantibodies in children at well-child visits, which has the potential in the short-term to decrease hospitalization and life-threatening DKA at onset of Stage 3. This will require a concerted effort among funders, academia, industry, regulatory authorities, payers, government bodies, health care providers, and the T1D community.

2. Supporting the development of improved assays to enable T1D risk detection in the general population or increased capability to screen in enriched populations (HLA at-risk, relatives) to facilitate recruitment for clinical research focused on identifying environmental triggers and natural history of T1D, along with interventions to prevent T1D.

3. Conducting prevention clinical trials to preserve beta cell function and delay onset of Stage 3 T1D, including proof-of-concept clinical trials with existing and novel therapies and with combination therapies that target different aspects of beta cell dysfunction and loss.

4. Identifying and validating biomarkers that:
   a. Stage T1D in the at-risk setting
   b. Predict risk/rate of progression
   c. Serve as surrogates of efficacy of preventive interventions.

5. Supporting early stage development of an enteroviral vaccine for primary prevention and refining the approach with additional epidemiologic and mechanistic data.

6. Investigating the complex interactions between the intestinal microbiota and several interacting systems in the body (immune, intestinal integrity and function, metabolism, beta cell function, etc.) with a goal to develop scientifically rational approaches to prevent or delay all stages of T1D.

7. Changing the perception of benefit/risk of interventions in the at-risk setting based on the concept that Stage 3 T1D will invariably occur over time once Stage 1 is fully established.

8. Supporting the qualification of islet autoantibodies by regulatory authorities (i.e., FDA and EMA) to facilitate their ease of use in clinical studies by researchers and industry.