Juvenile Diabetes Research Foundation: Mission, Strategy, and Priorities

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JDRF MISSION AND OVERARCHING RESEARCH STRATEGY

Since its founding more than 40 years ago by parents of children affected by type 1 diabetes, the Juvenile Diabetes Research Foundation (JDRF) has been committed to finding a cure for all those individuals living with the disease (1). Today, JDRF acknowledges that this commitment will not likely be fulfilled in the near term. Although our ultimate goal—curing type 1 diabetes—remains unchanged, we are equally committed to better treating and preventing the disease. These goals aim to ensure that both children and adults living with type 1 diabetes remain healthy so that they can fully benefit from a cure when it becomes available. JDRF focuses on supporting the development and delivery of new therapies and devices that will ease the daily burden and challenges of managing type 1 diabetes and on the prevention of diabetes complications. Additionally, to protect future generations from developing type 1 diabetes, JDRF is supporting approaches to prevent the disease. Thus, JDRF is striving to cure, treat, and prevent type 1 diabetes.

To this end, JDRF-led research is addressing and will continue to address type 1 diabetes at every life stage. Our goals now encompass stopping or slowing the progression of type 1 diabetes in individuals who are newly diagnosed, reversing it in those who have lived with the disease for years, preventing the disease in people at risk today and in future generations, and improving type 1 diabetes treatment by providing better tools to achieve optimal glucose control for people at all stages of the disease.

The field of type 1 diabetes research has progressed impressively over the past 4 decades, in part because of JDRF funding. Although historically we have been identified as a funding organization focused exclusively on exploratory and basic research in academia, over the last 5 years our role has broadened significantly in scope. This expansion in our role is absolutely necessary to accelerate the advancement of transformative treatments and eventually of cure therapies for type 1 diabetes.

JDRF has evolved from being primarily a funding agency to a strategically focused, priority-driven international research organization that proactively partners with the academic community, biotechnology and pharmaceutical companies, disease organizations and foundations, government and regulatory agencies, healthcare payers, and, most importantly, individuals living with type 1 diabetes (Fig. 1) to leverage its resources and accelerate its mission. We have expanded our research funding base to include academic, foundation, and corporate partnerships that contribute meaningfully to what is becoming a robust research pipeline for type 1 diabetes therapeutics. Across this pipeline, JDRF funds research programs at all stages—from exploratory and discovery phases through to preclinical and clinical development. We have also aggressively increased our advocacy efforts to assist in defining regulatory pathways for devices and will be expanding our efforts to include drugs. JDRF is committed to leveraging and translating this knowledge base to discover, develop, and deliver drugs and devices that have clinical impact.

JDRF prioritizes its funding for type 1 diabetes research in four interrelated therapeutic areas: autoimmune therapies, β-cell therapies, prevention of complications, and glucose control. Each therapeutic area encompasses a diverse portfolio of research programs that span from exploratory to preclinical proof-of-principle and on to clinical proof-of-concept research. The organization's overarching strategy focuses on addressing critical gaps and challenges, catalyzing innovative and transformational research, advancing and translating research, creating collaborations, and accelerating time lines at all stages of research development. To facilitate downstream partnering and follow-on funding, JDRF increasingly supports product development by "de-risking" projects, thereby decreasing the barriers of entry for future funders. JDRF is uniquely positioned to accelerate and integrate the development of combination therapies that will be required to deliver clinically significant therapeutic and curative solutions to individuals with type 1 diabetes.

JDRF's experienced scientists identify new opportunities by continuously surveying the type 1 diabetes research landscape and sponsoring and attending workshops, conferences, and advisory panels, and meet frequently with companies to actively solicit promising research opportunities. Once identified as viable research targets, these opportunities undergo scientific peer-review and input on mission relevance by JDRF lay volunteers.

The role and responsibilities of JDRF extend to the translation of promising scientific discoveries into commercially viable therapies. Our success will be measured by the wide clinical availability of those new therapies and, ultimately, the delivery of a cure for and prevention of type 1 diabetes.

JDRF'S TYPE 1 DIABETES STAGE–SPECIFIC RESEARCH STRATEGY AND PRIORITIES

JDRF is focused on type 1 diabetes stage–specific approaches for preventing, curing, and improving the treatment of type 1 diabetes (Fig. 2). For fiscal year 2012, JDRF's research priorities (Fig. 3) have been established and

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FIG. 1. JDRF partners across the type 1 diabetes (T1D) landscape to deliver on its strategy and mission.

announced in detail to the research community (www.jdrf.org/priorities).

At-risk and prediabetes stages. The rising incidence of type 1 diabetes (2–4) that is associated with an earlier age of onset (3,4) and higher incidence rates among the low-to-moderate human leukocyte antigen risk groups (5) have prompted JDRF to prioritize the prevention of childhood-onset type 1 diabetes using childhood population-based approaches. In addition, the organization is targeting the prevention of type 1 diabetes in relatives of individuals affected by the disease. Preventing type 1 diabetes before β-cell function decreases below critical levels may prove to be technically less challenging than curing established type 1 diabetes—an approach that will require restoring lost β-cell function and controlling β-cell–specific autoimmunity.

JDRF will be supporting research in both primary (i.e., pre–β-cell autoimmunity) and secondary (i.e., post–β-cell autoimmunity) prevention (www.jdrf.org/prevention) (Fig. 2). Primary prevention will likely prove to be more cost effective than secondary prevention and may prove to be the only viable approach for preventing type 1 diabetes within the first few years of life. However, primary prevention will also likely have a longer clinical development timeline because of the length and size of primary prevention trials compared with secondary prevention clinical trials (6). The primary prevention strategy of JDRF presumes an approach using universal infant-childhood immunization with three distinct vaccine targets: *1*) immunoregulation of β-cell antigen-specific immune responses, as detailed below; *2*) a viral etiology such as enterovirus; or *3*) microbiome-induced immunoregulation. Undoubtedly, type 1 diabetes preventive vaccines for universal administration in infancy and childhood will need to have proven safety and efficacy. It may be possible to accelerate their clinical development by initially conducting trials in genetically high-risk groups and by assessing the prevention of β-cell–specific autoimmunity (i.e., autoantibodies) as an interim clinical end point.

JDRF's secondary prevention strategy targets childhood-onset type 1 diabetes, as well as the disease in relatives of

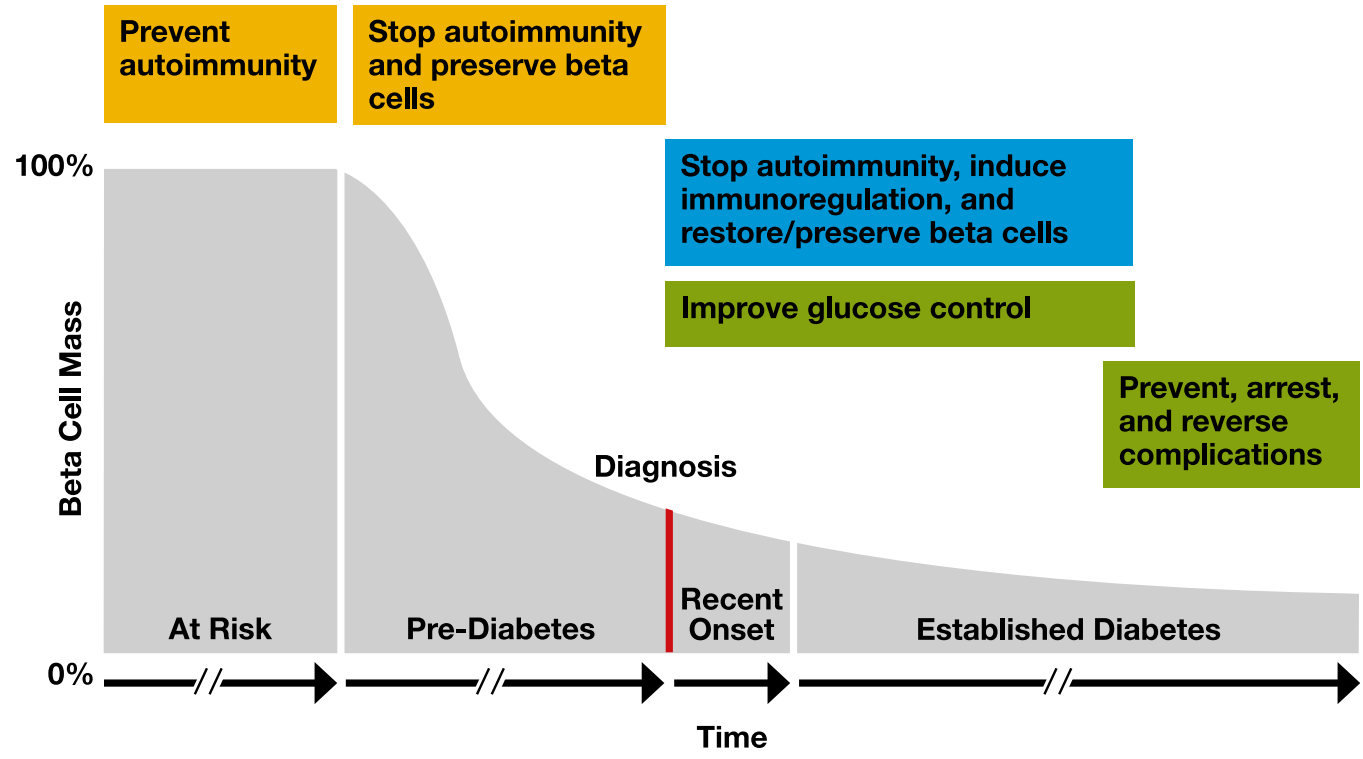

FIG. 2. JDRF's stage-specific therapeutic strategies to prevent, treat, and cure type 1 diabetes (adapted from ref. 7).

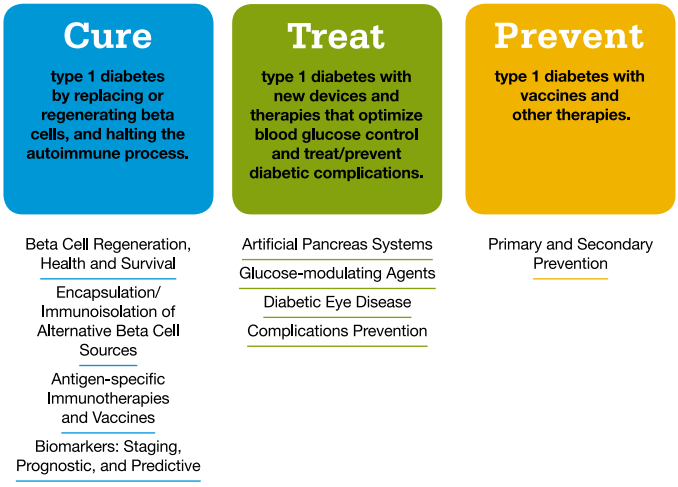

FIG. 3. JDRF's fiscal year 2012 research priorities to cure, better treat, and prevent type 1 diabetes.

individuals with type 1 diabetes. Considered collectively, JDRF is focused on the development of population-based, cost-effective methods to screen for β-cell–specific autoimmunity as well as methods to determine the precise stage of disease progression to allow for tailored, substage-specific interventions that prevent insulin dependence. Toward this end, JDRF will pursue combination preventive therapies that target *1*) islet inflammation; *2*) β-cell–specific autoimmunity; *3*) β-cell health, stress, and survival; *4*) dysglycemia; and/or *5*) insulin resistance. To accelerate this strategy, secondary prevention trials will be designed using reversal of dysglycemia or prevention of progression to the next substage of type 1 diabetes as interim clinical end points toward the ultimate end point of prevention of insulin dependence. JDRF is committed to increasing the identification of at-risk relatives of all ages of individuals with type 1 diabetes, which in turn will increase the number of potential subjects for clinical trials.

Recent-onset type 1 diabetes. In recent-onset type 1 diabetes, JDRF's long-term goal is to induce a durable, insulin-independent remission. Interim goals in the recent-onset setting are to support the development of therapies and devices that restore normal glucose metabolism, as well as to save or preserve residual β-cells, which are present but dysfunctional at the time of diagnosis. At this stage of disease, therapeutic interventions that preserve β-cells may have the potential to improve glucose control, decrease risk of short- and long-term diabetes complications, and improve opportunities for inducing sustainable insulin independence.

In an effort to preserve residual β-cell function at this stage, JDRF is pursuing therapeutic approaches that target: a) islet inflammation (e.g., anti-inflammatories, inhibitors to cytokines/chemokines mediating β-cell loss); b) β-cell-specific autoimmunity (e.g., immunomodulators, β-cell antigen immunoregulatory therapeutics and vaccines); c) β-cell survival (i.e., agents to reduce pathologic β-cell stress and maintain β-cell health or agents blocking β-cell death); and/or d) glucose intolerance (i.e., routine insulin delivery and insulin delivered by closed loop technologies for consistent and tight regulation of glucose control). These therapies will likely prove most effective when used in combination because β-cell dysfunction in the recent-onset type 1 diabetes setting is considered to result from a contribution of inflammation, autoimmunity, β-cell stress, and insulin resistance (7–10).

To accelerate this strategy, JDRF has prioritized the development of staging, prognostic, and predictive biomarkers, all for the purpose of aiding in the design of clinical trials and assessing trial outcomes. Novel biomarkers or imaging approaches are required to detect islet inflammation, β-cell stress, functional β-cell number and total mass, and β-cell autoimmunity and immunoregulation. The generation of durable insulin independence will likely require both induction of long-term β-cell-specific immunoregulation combined with expansion of residual functional β-cell mass with β-cell regenerative approaches, as described below.

Established type 1 diabetes

Glucose control. Although significant progress has been made in our understanding of type 1 diabetes, the development and delivery of a widely applicable cure with an acceptable safety profile for established disease is not near term. In the interim, it is critical not only to enhance the quality of life for people living with type 1 diabetes by improving diabetes management and by supporting research and development for devices and drugs that optimize glucose control but also to prevent or slow the progression of diabetes complications. There remains a significant opportunity to improve glycemic control in people with type 1 diabetes as evidenced by the fact that less than 50% of individuals with type 1 diabetes are achieving target HbA_{1c} levels, individuals with target HbA_{1c} levels still spend significant portions of the day with hypo- and hyperglycemia, and that hypoglycemia remains a significant daily barrier to achieving lower levels of HbA_{1c} (11–13). Thus, JDRF has prioritized the development of closed-loop systems for automated insulin delivery, which will be developed in a step-wise manner until fully automated, implantable, multihormonal, closed-loop systems for full metabolic control are realized (14). In the near term, systems that automate insulin reduction or cessation could significantly reduce hypoglycemia exposure. It will be critical to develop systems with insulin dosing that provide increased stringency of glucose control. JDRF has prioritized these research areas and has created the JDRF Artificial Pancreas Project (APP), a consortium of leading clinical researchers, mathematicians, and engineers who are partnering with industry and testing new algorithms and clinical approaches to accelerate the development of closed-loop technologies (15).

In parallel, faster-acting insulin, improved insulin delivery, and other glucose-modulating therapies that decrease insulin requirements or the risk of hypoglycemia are being supported by JDRF. The nonphysiological delivery of insulin (subcutaneous vs. portal) provides a significant challenge to closed-loop control. Improved insulin kinetics will allow for improved device systems with less risk for both hyper- and hypoglycemia. In addition, other hormones such as glucagon and amylin are either dysregulated or absent in type 1 diabetes. JDRF is confident that restoring more physiological regulation of these hormones could improve glucose regulation. One novel and potentially transformative approach that JDRF is prioritizing is glucose-responsive insulin —an insulin that is released in real-time in the body based on glucose levels to maintain euglycemia. JDRF has recently announced a Glucose-Responsive Insulin Grand Challenge Prize to catalyze activity and identify novel approaches for this area of research (https://www.innocentive.com/help-jdrf-combat-diabetes).

Complications. In addition to improving glucose control, JDRF is focused on developing approaches to prevent, delay onset of, or arrest diabetes complications. Although improved glucose control should lead to a significantly

decreased risk of complications, the rates of complications today remain high, and the development of complications remains an ever-present fear for individuals with type 1 diabetes. To address the need for large and long complication clinical trials to evaluate effects on diabetes complications, JDRF is supporting the development of prognostic and predictive biomarkers of complications risk, staging, progression, and responses to therapies. In the short term, improved screening technologies and diagnostics as well as improved patient access to diabetic care management and reimbursement for therapies are required for earlier diagnosis of complications (e.g., diabetic eye disease) and are being supported through research funding and advocacy efforts. The long-term JDRF complication strategy is to identify and validate novel targets and pathways for drug discovery and development of prognostic biomarkers based on characterizing the genetics and epigenetics of individuals with established type 1 diabetes who have remained completely free of diabetes complications in spite of poor glucose control (16).

Restoring β-cell function. A biological cure for type 1 diabetes requires not only restoring β-cell function by either endogenous regeneration or exogenous replacement of islets or β-cells, but also preventing their immune destruction. JDRF is pursuing both approaches, each of which has distinct advantages and challenges. Regeneration approaches could be potentially applied to individuals across the various stages of type 1 diabetes, whereas islet replacement is likely more restricted to people with established type 1 diabetes. Replacement also has the commercial challenges of cell-based therapies. Both replacement and regeneration approaches require the discovery and development of novel therapies, which would be accelerated with the development of predictive and prognostic biomarkers, including biomarkers of β-cell function, mass, stress, and destruction as well as autoimmunity.

Cadaveric pancreas or islet transplantation has demonstrated proof-of-concept for durable reversal of hypoglycemia unawareness, reversal and/or stabilization of other diabetes complications, and for some, induction of long-term insulin independence (17). However, because of the limited source of cadaver pancreata and the requirement for general immunosuppression to prevent graft rejection, current transplantation approaches are restricted in their application. To address this challenge, JDRF is funding opportunities to support alternative islet transplantation sources, such as porcine islets and human islet surrogates derived from human embryonic stem cell–generated pancreatic endoderm progenitors. To thwart autoimmune or allo/xenoimmune (i.e., foreign graft rejection) destruction of these cell sources and to allow for their potential retrievability because of the risk of tumor formation from residual stem cells or immature cells in stem cell–derived cell sources, transplants involving either of these cell types will likely need to be encapsulated. This could involve either micro- and/or macroencapsulation designs. Encapsulation of islets remains a recognized challenge, and JDRF will be supporting an islet encapsulation consortium to proactively address this challenge.

Therapeutics to regenerate endogenous β-cell mass will need to be safe, and one approach to enhance chances for safety is to exploit pathways used for β-cell expansion in the settings of growth, pregnancy, obesity, or insulin resistance or after β-cell injury or loss. Therefore, JDRF is supporting insights into these mechanisms and is specifically focused on regenerative therapeutics targeting *1*) β-cell proliferation; *2*) neogenesis from β-cell precursors; or *3*) reprogramming or *trans*-differentiation of non–β-cells to glucose-responsive, insulin-secreting cells. Novel agents that promote β-cell survival are required to both preserve residual β-cells and help maintain viability of newly regenerated or replaced β-cells and are being developed.

Regenerated β-cells in the setting of type 1 diabetes are likely to remain susceptible to autoimmune attack, especially if the new β-cells are experiencing β-cell stress. To prevent their autoimmune destruction, β-cell–specific immune tolerance should ideally be induced prior to the administration of β-cell regenerative therapies. A challenge to inducing β-cell–specific immunoregulation or tolerance in established type 1 diabetes is the presence of β-cell–specific immune memory cells, which appear to persist even decades after diagnosis of type 1 diabetes (18). Antigen-specific tolerogenic therapies and vaccines have been prioritized by JDRF to specifically address this residual population of immune memory cells and to induce sustainable β-cell–specific immunoregulation (19–21). β-Cell antigen-specific immunotherapies and vaccines will have application not only in established type 1 diabetes but also in the at-risk and recent onset type 1 diabetes stages. Importantly, it is thought that such interventions will prove safer than global immunomodulatory approaches. Additional immunotherapies or immunomodulatory agents will need to be applied or developed to address any autoimmune attack on regenerated β-cells that proved resistant to initial β-cell–specific immunomodulation.

In the immediate period after β-cell replacement or regeneration, β-cells may be even more susceptible to cell death as the result of glucose variability. During this critical period, the use of closed-loop artificial pancreas systems that enable consistent, well-controlled glucose regulation to bridge the period until full restoration of full β-cell function occurs may prove essential for increasing the chances of success of β-cell replacement or regeneration therapies.

As noted above, embedded in JDRF's stage-specific strategy is the discovery and validation of prognostic and predictive biomarkers for more precise staging of risk and progression, as well as for surrogate end points of efficacy of therapeutic interventions, which will accelerate therapeutic development and clinical evaluation. The success of JDRF's research strategy also requires an enhanced understanding of the pathogenesis and heterogeneity of human type 1 diabetes at all stages. To this end, JDRF initiated and fostered the development of an innovative, internationally based effort that is designed to collect pancreata and related tissues (e.g., spleens, lymph nodes, cells of the immune system) from people across all stages of type 1 diabetes. This program, known as the Network for Pancreatic Organ Donors with Diabetes, collects tissues from organ donors who meet specific criteria and then distributes the tissues to investigators seeking to address questions surrounding the etiology, pathogenesis, and heterogeneity of type 1 diabetes (www.jdrfnpod.org).

JDRF'S PARTNERS

JDRF recognizes that effective development and delivery of new therapies and devices to prevent, treat, or cure type 1 diabetes will not occur in a timely manner without fully leveraging its resources with partners (Fig. 1).

Academia. JDRF has historically focused its research funding in the academic sector with several different grant mechanisms, as described (www.jdrf.org/grants). In fiscal year 2011, JDRF funded $116 million of research, representing

459 grants (261 new grants and 198 prior committed grants) in 18 countries (Fig. 4). It is important to note that JDRF continues to strongly support research in academia, with more than 85% of its current funding committed to academic-based research. Funding decisions are based on the most promising and innovative research proposals that fall within the research priorities discussed above, with preferential consideration given to research that aims to identify and validate new targets and pathways as well as prognostic and predictive biomarkers, investigations that improve the understanding of the pathogenesis and heterogeneity of human type 1 diabetes, and proof-of-concept, mechanistic-based clinical trials. Indeed, JDRF remains committed to assist academic investigators translate their research, in order to ensure that promising ideas advance from the bench to the clinic.

Industry. To more effectively translate academic research and to accelerate the clinical development of potential type 1 diabetes drugs and devices, JDRF has recently developed multiple product discovery and development partnerships with biotechnology and pharmaceutical companies (www.jdrf.org/partnerships). Addressing gaps and critical acceleration points in the type 1 diabetes research pipeline, these partnerships target potentially innovative therapies at early stages of development that would not have been initiated or advanced in a timely manner without JDRF financial or strategic involvement. Since 2005, JDRF has supported 41 product-focused projects with 33 companies, representing a commitment of $75 million research funding, which was slightly less than 10% of JDRF's total research commitments during this time period.

With these partnerships, JDRF hopes to advance products to a new value inflection point capable of attracting follow-on funding for further clinical development. In fact, subsequent to JDRF's initial funding commitment, eight of JDRF's industry product-focused partnerships secured follow-on funding from larger pharmaceutical companies either in the form of a licensing transaction or company acquisition. Over the last 5 years, these product-focused partnerships have spurred other companies to take interest in the type 1 diabetes research and development area, resulting in an overall increase in investment by multinational companies in diabetes products and devices. Although JDRF has committed only a small part of its overall research funding to this type of partnership (less than 10% in fiscal year 2011), industry partnerships are a critical aspect of JDRF's funding strategy since they aim to accelerate the translation of potential therapeutic opportunities for people with type 1 diabetes. It should be noted that these industry partnerships are structured as milestone-based contracts, include a modest and capped royalty-based return to JDRF to support other research, and incorporate diligence obligations.

JDRF also partners with companies to cosponsor academia-based discovery research for the purpose of identifying and validating new targets and pathways. To help accelerate clinical development opportunities, JDRF also participates in nonfinancial collaboration agreements with the diabetes industry to address biomarker development, clinical trial design, disease-specific staging and patient stratification, and regulatory approval and reimbursement, as detailed below.

Government research funders and nonprofit foundations. Through its volunteer and staff advocacy efforts, JDRF has historically partnered with foundations and government funding agencies to better integrate and coordinate type 1 diabetes research funding. Since 1997, JDRF helped secure $1.89 billion of type 1 diabetes research funding through the Special Statutory Funding Program for type 1 diabetes Research (SDP), a special appropriation that has created multiple research programs, research consortia, and clinical trials networks focused on preventing, treating, and curing type 1 diabetes, as described (http://www2.niddk.nih.gov/AboutNIDDK/ReportsAndStrategicPlanning/T1DStatutoryFundingProgress2010.htm). To enhance success of the SDP-funded type 1 diabetes programs, JDRF partners with National Institute of Diabetes and Digestive and Kidney Diseases. In addition, JDRF has partnered with multiple other institutes at National Institutes of Health (the National Institute of Allergy and Infectious Diseases [NIAID], the Eunice Kennedy Shriver National Institute of Child Health and Human Development [NICHD], the National Eye Institute [NEI], and the National Institute of Biomedical Imaging and Bioengineering [NIBIB]) and multiple internationally based agencies to leverage its resources and support global type 1 diabetes scientific investigation. JDRF has also partnered with several biomedical research foundations, including the Wellcome Trust and the Helmsley Charitable Trust. JDRF and the Helmsley Charitable Trust announced in November 2011 a formal collaboration committed to accelerating the delivery of clinically significant treatments for type 1 diabetes.

Regulatory agencies. In the past few years, JDRF has increasingly worked with regulatory agencies to ensure that new therapeutic interventions receive regulatory approval in an efficient timeframe. Efforts have focused on achieving greater clarity, transparency, and consistency in the regulatory pathway for diabetes-specific devices as well as the acceptance of biomarkers in the approval process. In the device area, JDRF successfully championed the designation of the artificial pancreas as a U.S. Food and Drug Administration Critical Path Initiative and is currently championing proposed guidance on a regulatory approval pathway for open- and closed-loop systems. JDRF recently completed a type 1 diabetes regulatory strategy assessment and will be expanding our regulatory advocacy efforts to include type 1 diabetes-specific drugs. JDRF has also held workshops with the Food and Drug Administration focused on β-cell replacement.

Healthcare payers. JDRF is committed to ensuring that new therapies and devices are affordable and available to

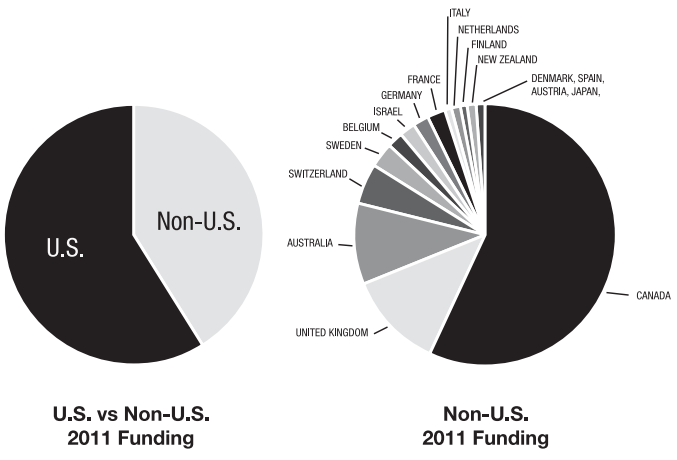

FIG. 4. JDRF, an international research organization, funded research in 18 countries in fiscal year 2011, with greater than 40% of JDRF research funding outside the U.S.

people living with type 1 diabetes regardless of socioeconomic status. With input directly from health insurance companies, JDRF funded an independent, 450-subject, 10-site clinical trial to demonstrate that the use of continuous glucose monitors (CGMs) improved glycemic control (13). This study helped catalyze healthcare payment for CGMs and created momentum in the device industry for improved CGMs and development of closed-loop systems.

SUMMARY

JDRF is an international organization whose goal is to cure and prevent type 1 diabetes, and until a cure is found, it will also fund innovative and potentially transformative research to decrease the burden of the disease and prevent diabetes complications. Its research strategy is based on filling critical gaps, catalyzing transformative approaches, and accelerating timelines and the translation of diabetes research. JDRF is implementing this strategy in a proactive, results-oriented manner and is pursuing it in close partnership with the academic community, biotechnology and pharmaceutical companies, the federal government, other disease organizations and foundations, regulatory agencies, and healthcare payers. Short-term success will be realized when new drugs and devices are available to and impact the lives of individuals with type 1 diabetes and final success will be achieved when the disease is cured and prevented.

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