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Type 1 Diabetes TrialNet – An International Collaborative Clinical Trials Network

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Type 1 Diabetes TrialNet is an international consortium of clinical research centers aimed at the prevention or delay of type 1 diabetes (T1D). TrialNet researchers are working to achieve this goal through understanding of the natural history of the disease, identification of persons at risk, and clinical evaluation of exciting new therapies that balance potential risks and benefits.

TrialNet evolved from the Diabetes Prevention Trial-Type 1 (DPT-1), which was created in 1993 and conducted two simultaneous studies intended to prevent progression from autoimmunity to T1D: (1) evaluation of parenteral insulin in subjects with projected 5-year T1D risk of greater than 50%,¹ and (2) evaluation of oral insulin in subjects with projected 5-year T1D risk of 25–50%.² Although protective effects of injected insulin were not demonstrated in the parental DPT-1 study, the trial did demonstrate, in a very large cohort, that: (1) the diabetes risk of relatives of people with T1D could be accurately predicted based on genetic evaluation and tests of autoantibodies in blood, and (2) trials requiring massive screening efforts to identify eligible subjects and involving intensive treatment regimens could be efficiently accomplished.

The ability to predict risk accurately, the knowledge from earlier clinical studies that immunosuppression can alter the course of the disease (albeit with unacceptable toxicities),^{3–5} and the anticipation of a pipeline of potential therapies for study (based on clinical trials in other autoimmune disorders and demonstration of efficacy in animal models of T1D⁶), led to the recommendation for expansion of DPT-1 to a larger network to complete the oral insulin trial and “to participate in the design and execution of pilot and expanded studies of new agents to prevent or ameliorate type 1 diabetes, and in natural history and genetics studies in populations screened for or enrolled in these studies.”⁷

TrialNet consists of 16 cooperative agreements to: 14 parent Clinical Centers in North America, a Coordinating Center (CC) for assistance in study design, study monitoring, data processing, analyses, administrative operations, and a Chairman’s Office providing scientific and medical leadership, protocol/ consent/volunteer handbook development, and oversight of the receipt and review of proposals for future TrialNet studies. Five additional Clinical Centers in Europe and Australia receive infrastructure support from the Juvenile Diabetes Research Foundation (JDRF). In addition to the Clinical Centers, TrialNet also employs 15 “Major” Affiliates in North America, 155 regular Affiliate sites, and 100 Participating Physicians; all are supported by their regional Clinical Centers and screen T1D family members for autoimmunity and eligibility for TrialNet studies. The Network is supported by 20 central laboratories and support units.

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Goals

TrialNet seeks to prevent or delay the development of T1D in persons at risk. Testing new therapies, especially immunotherapies, in individuals (including children) who do not yet have clinical disease usually requires safety and efficacy information in individuals with overt diabetes. Thus, in addition to prevention trials, TrialNet tests interventions to decrease β -cell destruction and/or enhance β -cell survival in persons with T1D with residual β -cell function. Long-term studies have demonstrated that the longer individuals maintain β -cell function, as measured by stimulated C-peptide production, the better protected they are from serious complications;⁸⁻⁹ thus it is anticipated that intervention studies in this population will also provide clinical benefits to the participants. In addition, TrialNet evaluates methodologies that enhance the conduct of its clinical trials, which includes tests of outcome assessment methodology, the evaluation of surrogate markers, and mechanistic studies laying the foundation for future clinical trials.

With a T1D incidence of 15,000 persons per year in the United States,¹⁰ the pool of subjects eligible for new onset trials is relatively small, and is further limited by required age and enrollment within weeks after diagnosis. To date, less than one in ten families approached agree to participate largely due to the time demands and potential risks of these studies. This large multi-center network enables efficient recruitment for studies with sufficient power to evaluate the risks and benefits accrued. To accomplish TrialNet's primary objective of prevention, large numbers of relatives must be screened to identify those with moderate (~35% five year) risk of clinical disease. This network is able to screen up to 20,000 subjects per year through a Natural History Study (NHS) that provides the framework for identification, risk characterization and potential recruitment of subjects into trials, and also allows the collection of data and samples to elucidate the mechanisms leading to the development of T1D.

TrialNet's Top Five Accomplishments (2001–2007)

1. TrialNet has created a large and effective network to screen relatives of persons with T1D for risk, to conduct trials for prevention and for β -cell preservation, and to lay the foundation for future generations of trials. This infrastructure of staff, equipment, and resources serves not only TrialNet studies but also recruits for T1D trials led by the Immune Tolerance Network (ITN)¹¹ and for the T1D Genetics Consortium (T1DGC).¹² Within the TrialNet Steering Committee, there has been ever-increasing integration and collaboration among endocrinologists, immunologists, and clinical trialists which has been essential for the increasingly rapid review, development, and implementation of network trials. Protocol concepts are submitted from scientists throughout the world; some are network investigators and others have never previously been involved with TrialNet. The review process functions smoothly and efficiently, with simultaneous reviews of scientific merit, clinical feasibility, ethics, and safety, followed by overall review by a prioritization committee whose job it is to assess the current scientific landscape and then determine how proposed trials mesh with TrialNet's goals and opportunities. Protocols referred from these committees are voted on by the Steering Committee. By involving scientists from across the world, TrialNet has effected a change in the consensus opinion of the T1D community such that trials interdicting the disease process are now considered feasible and highly justified. The network makes it possible to do carefully targeted studies more quickly and efficiently. And, with testimony from TrialNet and others, the FDA has recognized that interventional trials are appropriate and has accepted the preservation of β -cell function (C-peptide) as a clinically relevant and satisfactory end point. Moreover, the TrialNet network provides a fertile environment for the training of young investigators – both clinicians involved in clinical trials and basic scientists studying the genetics and immunology of T1D. In addition to clinical trials,

TrialNet encourages investigators from both within and outside of the network to submit ancillary mechanistic studies that can be conducted with subjects enrolled in TrialNet studies and/or with the samples that were collected from those studies and subsequently archived in the NIDDK Repository.

2. TrialNet completed the DPT-1 Oral Insulin Trial.² Although the report indicated that oral insulin did not delay or prevent T1D in the entire enrolled group, based on post hoc analyses, a subgroup was identified in which oral insulin appeared to provide a projected 5-year delay in the development of T1D. TrialNet and an external advisory committee convened by NIH considered this exploratory evidence to provide a strong justification for the conduct of a trial to definitely determine whether oral insulin can delay T1D in a similar cohort. This led to designing an Oral Insulin Prevention Trial focusing on subjects with similar characteristics to the cohort that appeared to have benefit in the DPT-1 Trial. As in most prevention trials, the NHS, described earlier, provides a gateway for this trial, and has in fact supported recruitment of subjects well ahead of schedule. In addition, many analyses using the data resources and samples obtained during DPT-1 have been completed. To date, 22 papers have been published and 6 more submitted for publication. These papers present significant new findings on the genetic, metabolic, and immunologic aspects of the evolution of the T1D disease process.

3. TrialNet has developed four prevention studies, three of which are based on the population screened for risk in the NHS. These include: (1) the vanguard phase of the TrialNet Oral Insulin Prevention Trial (referred to above and currently enrolling slightly ahead of schedule) in subjects with normal glucose tolerance who have at least two autoantibodies, one of which must be anti-insulin, a group with 35% risk of T1D within 5 years; (2) a study to be initiated in mid-2008 evaluating GAD-alum vaccine in subjects with normal glucose tolerance and at least two autoantibodies, one of which must be anti-GAD and the other of which cannot be anti-insulin, a group with 25–50% risk of T1D within 5 years; and (3) a study of an anti-CD3 monoclonal antibody in subjects with two autoantibodies and dysglycemia (impaired glucose tolerance, impaired fasting glucose, or an OGTT-stimulated glucose value greater than 200 mg/dl at 30, 60, or 90 minutes). DPT-1 data demonstrated that this population has a 78% risk of developing T1D within 5 years. Of note, the GAD and anti-CD3 prevention studies could not be initiated until favorable safety and efficacy data were obtained on the use of these agents in new-onset T1D, including children. In addition to these three prevention studies, all of which recruit subjects from the NHS cohort, a fourth pilot prevention study has been implemented. This pilot study, called the Nutritional Intervention to Prevent (NIP) Autoimmunity in T1D, involves the supplementation of at-risk newborns (based on HLA haplotypes) with omega-3-fatty acid docosahexaenoic acid (DHA). This study recently completed recruitment and results, including DHA measurements in the treatment and control groups, will be available in early 2009 and will help guide the decision whether to proceed with development of a full-scale study.

4. TrialNet has approved eight studies in new-onset T1D spanning an array of mechanisms that have been proposed as potentially important in the onset and progression of T1D. Thus TrialNet has shown its value for rapid translation of basic science findings and cutting edge immunology into T1D clinical trials. These studies involve an array of mechanisms, including immunosuppressive agents (mycophenolate mofetil (MMF) and daclizumab), therapies directed at T-cells (anti-CD3 and thymoglobulin), therapies directed at B-cells (anti-CD20 rituximab), therapies directed at co-stimulation (CTLA-4-Ig abatacept), antigen-specific therapy (GAD-alum vaccine), and therapies aimed at improving β -cell function and/or mass (exenatide), and a study evaluating early aggressive meticulous glycemic control facilitated by use of a continuous glucose sensor augmented insulin pump. Two trials in new

onset T1D have completed enrollment. The first involves initial treatment with antiCD25 (daclizumab), and continuous treatment with mycophenolate mofetil [MMF]; this trial will reach primary outcome in January 2009. The second new onset trial involves a 4-week course of treatment with antiCD20 (rituximab); this trial will reach primary outcome in September 2008. Of note, the Rituximab Study completed enrollment in 14 months, and the time from concept proposal to completion of enrollment was less than 2 years. In February 2008, TrialNet launched its third new onset intervention study to evaluate the effect of CTLA-4 Ig (abatacept) co-stimulation blockade on autoimmunity. TrialNet anticipates launch of a fourth new onset trial testing antigen based therapy (GAD-alum) in May 2008. A fifth study evaluating early aggressive/meticulous glycemic control facilitated by use of a continuous glucose sensor-augmented insulin pump and including very young children, will begin in fall 2008. TrialNet centers also participate in ITN-led new-onset trials, including those testing anti-CD3 and thymoglobulin as well as a phase 1 study examining the combination of IL-2 and rapamycin. TrialNet has also approved development of the first combination trial of immunotherapy (antiCD3) and an agent which may improve β -cell survival (exenatide). In addition to these approved trials, TrialNet receives a continuous flow of new protocol proposals, attesting to the large pipeline of new ideas. For example, in a recent protocol review cycle, TrialNet reviewed proposals for trials involving autologous ex vivo engineered dendritic cells and a microsphere formulation vaccine for antigen-specific tolerance induction. Although approved trials span a variety of mechanisms, it should be noted that TrialNet has reviewed 24 protocols that have not been approved, attesting to the rigor of the review process as well as the desire to focus on trials with novel mechanisms that are deemed most likely to be safe and effective.

5. TrialNet conducts methodological and mechanistic studies to improve the conduct of future trials and to improve understanding of the T1D disease process and how it is impacted by interventions. Two of these have been completed: (1) a comparison of the Mixed Meal Tolerance Test (MMTT) and Glucagon Stimulation Test (GST) for assessment of C-peptide showing the MMTT test to be superior, thereby resolving a long-standing controversy, and (2) the first of a series of studies evaluating and validating various T cell assays. The latter involved the evaluation of blinded samples from the same subjects by four T cell laboratories in North America (ELISpot, immunoblot, T cell proliferation, and tetramer) and a parallel test of the ELISpot assay in the UK. Samples were drawn on two occasions to compare reproducibility, sensitivity, and specificity. It is well understood that biomarkers for T1D disease progression are essential for the monitoring of therapeutic interventions and as surrogates for T1D prevention and/or reversal. The first step towards this goal is the development and rigorous evaluation of assays that are reproducible enough to be used longitudinally in treated individuals. This study represents the first blinded evaluation of T cell assay reproducibility in a large multi-center network with ongoing external quality control of all assays, an essential component for multi-center clinical trials. TrialNet will continue to use this process to assess new biomarkers of T1D progression.

In addition to these methodologic/mechanistic studies, each TrialNet protocol incorporates specific mechanistic assays germane to that specific study. In addition, samples are collected and stored for future access by investigators from within or outside of TrialNet who submit proposals for their use. Samples collected include DNA, RNA, serum, and peripheral blood mononuclear cells (PBMCs).

Finally, viral studies have been conducted in immunomodulatory intervention studies examining both serology and viral load, particularly for EBV. This represents the first time that viral studies have been conducted in T1D in a systematic way, and observations from these studies are essential for the monitoring of interventions.

Program Management

TrialNet is led by an Executive Committee consisting of study leadership from the Chairman's Office, the Coordinating Center, NIDDK, and NIAID. This committee provides ongoing (weekly) oversight, discusses issues related to Trial conduct, and coordinates various Study Group activities. The TrialNet Steering Committee, comprised of the principal investigator and a co-investigator from each clinical center, principal investigator from the Coordinating Center and each major laboratory, and representatives from NIDDK, NIAID, NICHD, and JDRF, meets 2–3 times yearly to evaluate proposed and ongoing protocols and to reach consensus for TrialNet activities.

A Data and Safety Monitoring Board (DSMB) (appointed by NIDDK, NIAID, and NICHD) reviews all diabetes protocols and informed consent materials from TrialNet, the Immune Tolerance Network (ITN) and the Autoimmunity Centers of Excellence (ACE). The DSMB monitors protocol progress and reviews all safety issues. It meets at least 4 times per year; twice in-person and twice by teleconference.

A TrialNet External Advisory Committee (EAC), appointed by NIDDK, NIAID, and NICHD, provides expert advice and external review of overall TrialNet activities.

TrialNet's intensive, streamlined protocol review process involves 5 separate committees: (1) Scientific Review Committee (with veto power), (2) Clinical Feasibility Committee, (3) Infectious Disease Safety Review Committee, (4) Ethics Committee, and (5) Intervention Strategies and Prioritization Committee (which meets last and considers reports of the other 4 committees). Several of these committees include outside experts. Protocols may be advanced from these committees for approval by the Steering Committee. Once a protocol is approved, associated mechanistic studies are developed by a Mechanistic Studies Committee. Following Steering Committee approval, the NIH seeks guidance from its external advisors (the DSMB and/or the EAC) to decide whether to move forward with protocol implementation.

Multiple subcommittees within TrialNet meet regularly by teleconference and at Steering Committee meetings to address relevant issues.

TrialNet Interactions With the Scientific Community

TrialNet is a major partner and leader in interactions with other networks and groups.

Conduct of Studies

The development of research concepts is an integral part of TrialNet. Interested researchers submit proposals regularly to TrialNet for T1D clinical trials. Protocol Development Guidelines are available on the TrialNet public web site (<http://www.diabetestrialnet.org>) and opportunities are regularly promoted at relevant scientific meetings.

TrialNet welcomes the submission of Ancillary Studies and Sub-Studies to be conducted either prospectively as an adjunct to ongoing protocols, or through access to collected samples and data. The ancillary study policy and application form are available on the TrialNet public web site.

TrialNet provides access to a robust clinical trial network for other NIH supported consortia, for outside investigators as well as for public and private companies for which T1D might not provide a sufficient market to justify an industry sponsored trial. TrialNet actively solicits proposals from all interested parties. Thus, TrialNet makes its network available to the general scientific community and to industry, facilitating the translation of new ideas and

therapies to clinical trials and mechanistic studies by providing access to exemplary studies performed by highly qualified scientists. This is consistent with the NIH Road Map. Moreover, the rapid review process and subsequent dialogue allow efficient testing of new ideas and therapies. The TrialNet network optimally utilizes resources, both financial and human, that would not otherwise be available to the community and funding groups because of the low incidence of T1D and the large effort required to screen at-risk relatives.

Participation in the NIDDK Repository

Data and samples from DPT-1 are made available to researchers through the NIDDK Repository (<http://www.niddkrepository.org>). DPT-1 data, DNA samples, including whole genome amplified (WGA) samples, and residual serum samples from OGTT tests from enrolled subjects have been deposited in the NIDDK Repository. Proposals for access to data and samples are accepted at any time, and non-renewable samples are subject to stringent review for scientific merit.

TrialNet NHS samples are being stored at the NIDDK Repository. For example, NHS has samples from over 250 subjects with 5-year T1D risk greater than 50% and from 144 individuals who developed diabetes while being followed in the NHS.

Any investigator can propose an Ancillary Study or a Sub-Study to be conducted either prospectively or using stored samples. Proposals are reviewed by TrialNet's Ancillary Studies committee, which considers scientific merit, feasibility, and ability of the proposed study to integrate with TrialNet's operation without interfering with study goals. The Ancillary Study Committee has received 18 study proposals and 5 have been approved to date.

Collaboration with Other Consortia and Agencies

Immune Tolerance Network (ITN).¹¹ TrialNet collaborates with the ITN (<http://www.immunetolerance.org/>) to facilitate implementation of clinical trials designed by ITN. More than 90% of ITN T1D study subjects have been recruited and followed at TrialNet sites. Conversely, the ITN assists TrialNet with sample collection, RNA purification, PBMC isolation, sample tracking, storage, and analysis of mechanistic samples. A coordinating committee facilitates the TrialNet-ITN interactions and a common DSMB is used for T1D studies. Representatives from the ITN serve as full members of the TrialNet Mechanistic Study Committee.

Type 1 Diabetes Genetics Consortium (T1DGC).¹² TrialNet collects samples for the T1DGC (<http://www.T1Dgc.org>), an international effort to identify genes that determine T1D risk. TrialNet investigators supplied T1DGC with 74.8% (1024 of 1369 families) of the affected sibpair or trio families collected in North America. Data and cell line samples are available to researchers world-wide.

Juvenile Diabetes Research Foundation (JDRF). TrialNet works closely with JDRF (<http://www.jdrf.org>). JDRF provides infrastructure support for TrialNet international sites, votes on the TrialNet Steering Committee, and participates on several other TrialNet committees. JDRF actively promotes participation in TrialNet studies to member families and the community.

Autoantibody Standardization. TrialNet has been an active participant in a NIDDK-led program to standardize and harmonize autoantibody measurements in all NIDDK-sponsored research networks, as well as the CDC-led DASP (diabetes autoantibody standardization program) (<http://www.cdc.gov/diabetes/projects/ndl.htm>).

Clinical Islet Transplant Consortium (CITC). TrialNet communicates regularly with the CITC (<http://www.citisletstudy.org>) on clinical and mechanistic issues. TrialNet has provided the CITC with materials to enable performance of standardized clinical evaluations on subjects receiving a potentially neurotoxic agent and has shared information concerning mechanistic collections and assays.

Collaboration with Industry

Most TrialNet clinical trials involve one or more proprietary compounds and thus are conducted with joint sponsorship of the corporate entities that control the rights to these compounds. Joint sponsorship is negotiated with each corporation in the form of a Clinical Trial Agreement (CTA) or a Cooperative Research and Development Agreement (CRADA) between the sponsor and NIDDK. NIDDK currently has CTAs with Roche (MMF/DZB Study), Genentech (Rituximab Study), Eli Lilly (Oral Insulin Study), Mead-Johnson (NIP Study), Martek (NIP Study), Bristol-Myers Squibb (CTLA-4 Ig Study), and Diamyd (GAD-alum Vaccine Studies), and is negotiating with MacroGenics (Anti-CD3 Prevention Study) and Medtronic Diabetes (Metabolic Control Study).

Other Benefits from TrialNet Studies

Characterization of risk:benefit of therapies to alter autoimmunity. While TrialNet enrolls only subjects prior to diagnosis or with residual β -cell function, the cure of individuals with longstanding disease through islet transplant or regeneration will require control of autoimmunity regardless of the source of new insulin-secreting cells. Thus, TrialNet studies will inform cell replacement efforts by evaluation of therapies to halt immune mediated beta cell destruction.

Characterization of risk:benefit of tolerogenic strategies in children. Information regarding the impact of TrialNet therapies on the pediatric population will be applicable to clinical investigations in other autoimmune diseases that predominantly affect adults.

Problems Encountered

At its inception, TrialNet investigators faced many challenges including the following questions, among many. Is T1D sufficiently like other autoimmune diseases (such as rheumatoid arthritis) to justify the testing of effective treatments in those diseases in the T1D model? What contributes to the heterogeneity within T1D risk categories and clinical course? What is the role of insulin resistance in the progression of T1D? Can the disease course or its response to treatment be tracked over time through measures of T cell activity or other biomarkers? How can we learn about underlying mechanisms of disease and/or treatment? What is an acceptable risk profile for therapies being used in children? How can we answer questions about efficacy while minimizing exposure? What degree of scientific certainty and clinical data is needed to select a therapy for a clinical trial? What is the most efficient and robust design for a T1D clinical trial? What measures should be used as clinical trial outcomes? How can the network best protect human subjects? These types of questions were debated at Steering Committee meetings, and still are considered in selection of studies.

Other issues included

1. Rebuilding the network: The DPT-1 study group developed a robust network of academic and community practices to facilitate enrollment of its two trials which was nearly complete at TrialNet's inception. Expansion of the mission, a change of coordinating center, and increasing demands on physicians in practice (academic and private center) limited the time and staff available to participate in research. Further, it took some time for TrialNet to

review and select the next trials for development, which led to delays in initiating sites for trial implementation and screening. Moreover, the 14 TrialNet North American Clinical Centers, though widely dispersed, left some major geographic areas (e.g. Washington/Baltimore, Chicago) without TrialNet representation. To fill the gaps, a solicitation for major affiliate sites was eventually issued and 15 major affiliates were awarded infrastructure funding to participate in multiple TrialNet studies. These sites have doubled the capacity of the network to recruit, treat and follow subjects in TrialNet studies.

Shortly after TrialNet began, it was recognized that the international community had much to contribute to the network both intellectually and logistically. With the agreement of the NIDDK, the JDRF solicited applications for international clinical centers to join TrialNet. Four European sites and one Australian site were selected, and all are fully represented on the Steering Committee. These sites have contributed to the screening of subjects for the NHS, enrollment of subjects into the new onset intervention studies and into the Oral Insulin Prevention Study, and in mechanistic studies.

2. Protocol development: Initially, TrialNet relied solely on the research community to bring new study proposals to the network. Eventually the Prioritization Committee was established to prioritize incoming applications and to evaluate emerging therapies and to proactively pursue promising therapies for study.

The initial protocol review process relied heavily on primary review at the level of the Steering Committee. After a few years, the protocol submission and review process was modified to facilitate thorough and rapid review and prioritization of protocols (described above) before coming to the Steering Committee for formal consideration.

To improve efficiency in protocol development, a Protocol Development Team, consisting of staff from the Chairman's Office, Coordinating Center, and NIDDK, was convened to lead the development all protocols, coordinating activities of the individual committees that oversee each protocol. A common template is used and IRB and regulatory issues are considered early in the process (e.g. explicitly citing the federal code that qualifies these studies for children) to expedite protocol development. This group prepares and standardizes responses to IRB and GCRC questions posed to TrialNet investigators and posts them on a web site to provide accurate responses to these questions in a timely manner.

3. Increased regulatory requirements for the conduct of clinical trials. TrialNet's need to include multiple academic centers as well as community based practices in the network as well as TrialNet's inclusion of children without clinical disease has substantially increased scrutiny and regulatory requirements. Further, the decision to include international sites in the network has significantly increased TrialNet's regulatory burden because of increasingly stringent individual country requirements and European Union regulations, including issues with customs and investigational drug import, liability insurance, and reporting. The recent changes in the European Union regulations regarding the conduct of clinical trials abroad has posed numerous regulatory and logistical challenges to the full incorporation of the international sites into TrialNet studies. With the assistance of regulatory experts (CROs) those challenges are being met and the international sites will soon be participating fully in the recruitment, treatment, and follow-up of all TrialNet prevention studies.

4. Developing consensus. The TrialNet Steering Committee consists of adult and pediatric diabetes clinical trialists as well as basic/translational immunologists. While this composition imparts tremendous strength and depth to the group, it took some time to develop systems and review processes that would facilitate a reasonable balance between scientific rationale and safety/ feasibility issues during the selection of therapies to be studied by the network. In addition, robust discussions about clinical trial design had to be

carefully balanced with the desire for consistency between trials whenever possible while addressing issues unique to a particular therapy. Finally, there were, and continue to be, serious and thoughtful discussions about the relative risks and benefits of therapy. This has slowly evolved into a culture in which TrialNet clinicians are becoming increasingly comfortable with immunotherapy while the basic scientists develop an increasing understanding of the inherent limitations of clinical trials. While robust debate continues, there is a level of respect and trust that promises continued success. Thus, TrialNet has developed into an example of how to do translational/clinical research as it is envisioned by the NIH Road Map (<http://nihroadmap.nih.gov>). Further, TrialNet consensus has carried over into the diabetes community at-large, where there is increasing willingness of families and individuals with diabetes to participate in these studies. Data from the first round of TrialNet new-onset studies will soon be ready for analysis which will inform and facilitate the development of new studies.

5. Working with corporate entities. In recent years, new information has been generated about novel therapies for other autoimmune diseases. However, many companies have been reluctant to use their new therapies in TrialNet studies, because (1) T1D is not as common as other autoimmune diseases (smaller market), and (2) TrialNet studies include children, causing some companies to hold back. Thus, until a therapy has FDA approval for another indication, there is little willingness to test that drug in T1D. Further, the TrialNet Steering Committee has repeatedly discussed the importance of combination therapies. Although this makes scientific sense, it increases a company's risks for unexpected side effects and/or possible unfavorable comparisons to a competitor. TrialNet has actively addressed many of these issues. For example, in order to encourage companies to enter the T1D market, TrialNet investigators and their colleagues compiled relevant data to convince the FDA to allow C-peptide preservation as a clinical outcome in trials for individuals with new-onset T1D. This coordinated effort resulted in the inclusion of this principle in the recently issued FDA Draft Guidelines for Diabetes Therapies (<http://www.fda.gov/cder/guidance/7630dft.pdf>), a significant accomplishment. Further, TrialNet is cooperatively developing protocols with considerable flexibility in intellectual property and related issues. Finally, TrialNet continues to be in close contact with industry and actively solicits their participation in network studies.

Summary

Type 1 Diabetes TrialNet is an NIH-sponsored international clinical trials network aimed at the prevention or delay of type 1 diabetes. The fundamental goal of TrialNet is to interdict the type 1 diabetes disease process by immune modulation and/or enhancement of β -cell proliferation and regeneration. To achieve this goal, TrialNet researchers are working to better understand the natural history of the disease, to identify persons at risk, and to clinically evaluate novel therapies that balance potential risks and benefits. The particular focus is on prevention studies. However, in addition, TrialNet evaluates therapies in individuals with newly diagnosed type 1 diabetes with preserved β -cell function to help determine the risk/benefit profile and gain an initial assessment of potential efficacy in preservation of β -cell function, so that promising agents can be studied in prevention trials.

References

1. Diabetes Prevention Trial – Type 1 Study Group. Effects of Insulin in Relatives of Patients with Type 1 Diabetes Mellitus. *New England Journal of Medicine*. 2002; 346:1685–1691. [PubMed: 12037147]
2. Diabetes Prevention Trial - Type 1 Diabetes Study Group. Effects of Oral Insulin in Relatives of Patients with Type 1 Diabetes Mellitus. *Diabetes Care*. 2005; 28:1068–1076. [PubMed: 15855569]

3. Feutren G, Papoz L, Assan R, Vialettes B, Karsenty G, Vexiau P, DuRostu H, Rodier M, Sirmai J, Lallemand A, Bach JF. for the Cyclosporin/Diabetes French Study Group. Cyclosporin Increases the Rate and Length of Remissions in Insulin Dependent Diabetes of Recent Onset: Results of A Multicentre Double-Blind Trial. *Lancet*. 1986; ii:119–124. [PubMed: 2873396]
4. The Canadian-European Randomized Control Trial Group. Cyclosporin-Induced Remission of IDDM After Early Intervention: Association of 1 Year of Cyclosporin Treatment with Enhanced Insulin Secretion. *Diabetes*. 1988; 37:1574–1582. [PubMed: 2903105]
5. Skyler JS, Rabinovitch A. Miami Cyclosporine Diabetes Study Group. Cyclosporine in Recent Onset Type 1 Diabetes Mellitus: Effects on Islet Beta Cell Function. *Journal of Diabetes and Its Complications*. 1992; 6:77–88. [PubMed: 1611143]
6. Shoda LK, Young DL, Ramanujan S, Whiting CC, Atkinson MA, Bluestone JA, Eisenbarth GS, Mathis D, Rossini AA, Campbell SE, Kahn R, Kreuwel HT. A comprehensive review of interventions in the NOD mouse and implications for translation. *Immunity*. 2005; 23:115–126. [PubMed: 16111631]
7. Request for Applications – Type 1 Diabetes TrialNet.
<http://grants.nih.gov/grants/guide/rfa-files/RFA-DK-01-003.html> and
<http://grants.nih.gov/grants/guide/rfa-files/RFA-DK-01-004.html>
8. Diabetes Control and Complications Trial Research Group. Effect of intensive therapy on residual beta-cell function in patients with type 1 diabetes in the diabetes control and complications trial. A randomized, controlled trial. *Annals of Internal Medicine*. 1998; 128:517–523. [PubMed: 9518395]
9. Steffes MW, Sibley S, Jackson M, Thomas W. Beta-cell function and the development of diabetes-related complications in the diabetes control and complications trial. *Diabetes Care*. 2003; 26:832–836. [PubMed: 12610045]
10. Incidence of Diabetes in the United States. <http://www.cdc.gov/diabetes/projects/cda2.htm>
11. Bluestone JA, Matthews JB. The immune tolerance network--an NIH/JDF-supported initiative to bring tolerance research into the clinic: a major new resource for clinical immunologists. *Clinical Immunology*. 2000; 96:171–173. [PubMed: 10964534]
12. Rich SS, Concannon P, Erlich H, Julier C, Morahan G, Nerup J, Pociot F, Todd JA. The Type 1 Diabetes Genetics Consortium. *Annals New York Academy of Science*. 2006; 1079:1–8.