Emerging Concepts and Success Stories in Type 1 Diabetes Research: A Road Map for a Bright Future

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Type 1 diabetes treatment stands at a crucial and exciting crossroad since the 2022 U.S. Food and Drug Administration approval of teplizumab to delay disease development. In this article, we discuss four major conceptual and practical issues that emerged as key to further advancement in type 1 diabetes research and therapies. First, collaborative networks leveraging the synergy between the type 1 diabetes research and care community members are key to fostering innovation, know-how, and translation into the clinical arena worldwide. Second, recent clinical trials in presymptomatic stage 2 and recent-onset stage 3 disease have shown the promise, and potential pitfalls, of using immunomodulatory and/or β-cell protective agents to achieve sustained remission or prevention. Third, the increasingly appreciated heterogeneity of clinical, immunological, and metabolic phenotypes and disease trajectories is of critical importance to advance the decision-making process for tailored type 1 diabetes care and therapy. Fourth, the clinical benefits of early diagnosis of β-cell autoimmunity warrant consideration of general population screening for islet autoantibodies, which requires further efforts to address the technical, organizational, and ethical challenges inherent to a sustainable program. Efforts are underway to integrate these four concepts into the future directions of type 1 diabetes research and therapy.

ARTICLE HIGHLIGHTS

- We discuss four key emphasis areas to pursue the ongoing acceleration of progress in type 1 diabetes research and care.
- Collaborations and communications should continue and expand between the research and care communities.
- Further clinical development of disease-modifying therapies is key.
- Identification of biomarkers of type 1 diabetes heterogeneity is needed for better disease stratification.
- Type 1 diabetes screening programs should be implemented in the general population.

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Nearly 50 years ago, emerging knowledge gains garnered from the fields of genetics, pathology, and immunology led to the notion that type 1 diabetes is an autoimmune disease (1–3). Over time, research efforts involving basic, translational, and clinical investigations have advanced our understanding of disease pathophysiology and improved methods to screen for preclinical stages of type 1 diabetes, guiding patient enrollment in clinical trials. Credit for these advances goes to countless academic investigators, consortia, funding agencies, industry partners, and lay individuals, as well as scientific societies such as the Immunology of Diabetes Society (IDS), which has provided an essential scientific forum, thus catalyzing scientific progress that has impacted clinical research in type 1 diabetes. Four concepts appear to be instrumental in empowerment in earlier success stories and form the basis of this article. First and foremost, we recognize the benefits of collaboration within the type 1 diabetes community. Second, translational efforts represent a major success story in the history of type 1 diabetes research, with a pipeline of agents that hold promise for disease prevention and/or preservation of β-cell function. Third, an emerging body of evidence suggests "heterogeneity" in the disease, although controversy remains on how to best define and address such heterogeneity. Fourth, it now appears to be time to consider and implement screening programs or at least "early detection programs" in the general population to deeply impact type 1 diabetes development. We believe these four concepts can continue to guide efforts to promote and accelerate future progress in the field.

THE BENEFITS OF COLLABORATION IN TYPE 1 DIABETES RESEARCH

It has been appreciated for decades that understanding the pathogenesis and natural history of type 1 diabetes and developing disease-modifying therapies (DMTs) require collaboration among community actors. With the shared ambition and willingness to improve care and therapeutic outcomes, effective teamwork nurtured by complementary expertise and know-how is critical to generating new knowledge and sustaining innovation.

Many funders, including Breakthrough T1D (formerly JDRF), The Leona M. and Harry B. Helmsley Charitable Trust (Helmsley), the National Institutes of Health (NIH), and the European Commission, have been instrumental in facilitating collaboration. Consortia have been established to develop tools and platforms for novel biomarker analyses, both for type 1 diabetes diagnosis and disease prediction (e.g., standardized assays for islet cell autoantibodies and T-cell workshops, promoted by the IDS) (4,5). Other efforts have sought to improve our understanding of the β-cell destructive process through studies of the human pancreas (e.g., the Network for Pancreatic Organ donors with Diabetes [nPOD] [www.npod.org] and Human Islet Research Network [HIRN] [www.hirnetwork.org]) and through natural history studies starting in early life (e.g., The Environmental Determinants of Diabetes in the Young [TEDDY] [https://teddy.epi.usf.edu] and Environmental Determinants of Islet Autoimmunity [ENDIA] [www.endia.org.au]). These collaborations have bridged several continents, with comprehensive contribution from researchers across different backgrounds.

Other collaborations are focusing on conducting clinical trials, key examples being the NIH-supported Immune Tolerance Network (ITN) (www.immunetolerance.org) and Type 1 Diabetes TrialNet (TrialNet) consortium (www.trialnet.org). TrialNet was launched in 2000, built on the earlier effort of the Diabetes Prevention Trial–Type 1 (DPT-1), a pioneering prevention study with investigation of the effects of prophylactic insulin therapy (both subcutaneous and oral) in arresting β-cell destruction (6,7). Since then, many trials have been conducted, supported by efficient infrastructure and organization. Clinical studies have been instrumental in developing DMTs, models for disease staging, and means to avoid diabetic ketoacidosis (DKA) at clinical onset through improved markers of disease risk/progression and a practical staging classification. TrialNet has been organized into geographical centers of reference, with training and community building through frequent meetings, and has brought several key concepts to the forefront, including the need for screening for early diagnosis of type 1 diabetes and introduction of DMTs at different stages of disease. These efforts are an example of collaborative progress in our field, contributing to the regulatory approval of teplizumab as the first DMT for type 1 diabetes.

In Europe, a slightly different model of collaboration has emerged for studies for investigation of disease mechanisms and therapeutic targeting, driven by incentive grants from the European Commission within the framework of the Innovative Medicines Initiative (IMI)/Innovative Health Initiative (IHI). These consortia include not only academic investigators but also industry partners, foundations (JDRF, Helmsley), and people living with type 1 diabetes. As such, the projects INNODIA and INNODIA HARVEST (www.innodia.eu) were created in 2015 and 2020, respectively, with a focus on the collection of bio-samples from people at different stages of type 1 diabetes, data integration, and development of master protocols for natural history studies and clinical trials, a first-in-class for type 1 diabetes (8). These master protocols were reviewed by the European Medicines Agency and formed the basis for four intervention studies in stage 3 type 1 diabetes in INNODIA/INNODIA HARVEST. The time points of assessment, the bio-samples collected, the tools and technologies used, and the end points are aligned and standardized across trials, thus allowing for improved data comparison. In 2022, a nonprofit organization, called INNODIA iVZW (www.innodia.org), was created to promote faster and more efficient execution of DMT trials at all stages of type 1 diabetes, through expansion of the clinical trial site network and provision of advice to potential trial sponsors on population and

biomarker selection, protocol design, and site selection. Recently, IHI has supported the launch of a new consortium called European action for the Diagnosis of Early Non-clinical Type diabetes For disease Interception (EDENT1FI) (www.edent1fi.eu) to implement general population islet autoantibody screening in Europe. This project focuses on how to organize screening for early detection of type 1 diabetes and appropriate follow-up monitoring, how to communicate regarding screening and implications of early diagnosis of type 1 diabetes, and how to integrate these screening and monitoring activities in the health care system of individual countries.

Meanwhile, clinical trials and screening networks are being formed in other parts of the world (e.g., Australian Tyre Industry Council [ATIC], www.atic.org.au; UK Type 1 Diabetes [UKT1D] Research Consortium, www.type1diabetesresearch.org.uk; CANScreenT1D; Qatar-based Type 1 Diabetes Islet Autoantibody Screening Initiative in the Middle East and North Africa [DIA-MENA]; China Alliance for Type 1 Diabetes [CAT1D]; and Diabetes Research India [DRI], www.diabetesresearchindia.org), opening opportunities for worldwide cooperation.

In summary, establishing a collaborative environment in the type 1 diabetes research field has played a key role in advancing our understanding of type 1 diabetes pathogenesis, biomarkers, therapeutics, and prevention. Open communication channels, an uncompromising emphasis on global collaboration, and a sense of urgency between the different networks worldwide should lead us closer to the ultimate goal of preventing and curing type 1 diabetes.

RECENT ADVANCES IN DMTS FOR TYPE 1 DIABETES

The path to improved type 1 diabetes treatment has progressed in part due to collective trial achievements (Table 1). Among these, drugs that target inflammation and cytokine signaling have emerged as a promising approach, with investigators in recent positive phase II studies in stage 3 disease testing antibodies against IL-21 in combination with liraglutide (9) or against TNF-α (10), or using subcutaneous ustekinumab to target IL-12 and IL-23 receptors (11).

Exciting new findings have highlighted the potential for targeting type I interferons, which mediate their effects via downstream Janus kinase (JAK)1/2 and tyrosine protein kinase 2 (TYK2). Notably, JAK inhibitors affect the immune system but may also impact β-cell stress pathways, offering potential to interrupt the deleterious dialogue between these compartments. The Baricitinib in New-onset Type 1 Diabetes (BANDIT) study demonstrated sustained C-peptide preservation after 48 weeks of treatment with the oral JAK1/2 inhibitor baricitinib in stage 3 type 1 diabetes, without severe side effects (12), thus providing critical safety experience with this class in anticipation of testing in early-stage disease or in combination with other agents. A second new-onset trial testing the JAK inhibitors abrocitinib and ritlecitinib was recently initiated by TrialNet (clinical trial reg. no. NCT05743244, clinicaltrials.gov). Another agent recently purported to target β-cell oxidative stress is verapamil. Positive clinical trials showing efficacy of verapamil to preserve C-peptide in recent-onset stage 3 type 1 diabetes were reported (13,14) both in adult and pediatric patients, with potential synergistic effects on immune cells. Additionally, the Diabetes Virus Detection (DiViD) intervention study reported that treatment with pleconaril and ribavirin to target persistent enterovirus infection in the pancreas yielded higher 12-month stimulated C-peptide compared with placebo (15). These results are in line with a novel vaccination strategy against coxsackie B virus (16), the ultimate goal of which is primary prevention (17). Lastly, encouraging results were announced in patients with recent-onset stage 3 type 1 diabetes treated with a therapy combining teplizumab and *Lactococcus lactis* genetically modified to express human proinsulin and IL-10 (18).

Trials with mitigated/negative outcomes were also recently reported. The phase IIb Low-dose rhIL-2 in Patients With Recently-diagnosed Type 1 Diabetes (DIABIL-2) (clinical trial reg. no. NCT02411253, clinicaltrials.gov) testing low-dose IL-2 in newly diagnosed stage 3 type 1 diabetes failed to meet its primary efficacy end point, with similar C-peptide loss compared with placebo, though a small group of IL-2–treated responders had improved C-peptide over the 12-month follow-up (19). Evidence of partial C-peptide preservation in a subgroup of patients was also reported in another study with low-dose IL-2, the Interleukin-2 Therapy of Autoimmunity in Diabetes (ITAD) trial. The explanation for these suboptimal results may lie in the dose and/or frequency of IL-2 administration. On the other hand, low-dose IL-2 had excellent safety, remains the only available treatment promoting immune regulation via induction of regulatory T cells, and is conceptually different from more conventional therapies designed to suppress certain immune functions. Thus, low-dose IL-2 should continue to be explored. It may be highly beneficial in combination therapy, which has already begun in stage 3 type 1 diabetes (clinical trial reg. no. NCT05153070, clinicaltrials.gov), and in the prevention of type 1 diabetes, for which its safety profile and lack of antidrug antibody induction will be important. Also disappointingly, treatment of individuals with stage 1 disease with abatacept (CTLA4-Ig) did not show a statistically significant impact on progression to glucose intolerance (stage 2) compared with placebo (20). However, abatacept treatment increased C-peptide compared with placebo, suggesting that costimulation blockade could still yield benefits. TrialNet is currently testing abatacept in combination with the B lymphocyte–targeting agent rituximab in the recent-onset, stage 3 disease RELAY trial (NCT03929601). Of note, tight glycemic control in new onset patients using hybrid closed loop systems did not

Table 1—Highlighted published large positive randomized controlled efficacy trials with testing of DMTs in type 1 diabetes

	Intervention	Trial name and targeted population (age)	Outcome
Immune modulation	Teplizumab (anti-CD3 Ab)	TN-10 study: stage 2 disease (8–45 years)	Delay in time to T1D (24,25)
		Protégé study: new-onset T1D (8–35 years)	Negative primary outcome (1 year of insulin use and HbA_{1c}) (64), but 14-day full-dose regimen preserved 2-year C-peptide AUC (65)
		PROTECT: new-onset T1D (8–17 years)	Increased week-78 C-peptide vs. placebo (26)
	Low-dose ATG	New-onset T1D (12–45 years)	Higher 12-month C-peptide AUC vs. placebo (27)
	Golimumab (anti–TNF-α Ab)	T1GER: new-onset T1D (6–21 years)	Higher 52-week C-peptide AUC vs. placebo (10)
	Abatacept (CTLA4-Ig)	TN-18 study: stage 1 disease (6–45 years)	No significant difference in progression to glucose intolerance; increased 12-month C-peptide AUC vs. placebo (20)
		TN-09 study: new-onset T1D (6–45 years)	Higher 2-year C-peptide AUC vs. placebo (66)
	Alefacept (fusion protein binding CD2)	T1DAL: new-onset T1D (12–35 years)	No significant difference at 12-month primary end point but higher 24-month C-peptide area AUC vs. placebo (67,68)
	Rituximab (anti-CD20 Abs)	TN-05: new-onset T1D (8–40 years)	Higher 12-month C-peptide AUC vs. placebo (69)
β-Cell protection	Verapamil (calcium channel blocker)	New-onset T1D (18–44 years)	Higher 12-month C-peptide AUC vs. placebo (13)
		CLVer: new-onset T1D (7–17 years)	Preserved 52-week C-peptide AUC (14)
	Imatinib (tyrosine kinase inhibitor)	New-onset T1D (12–45 years)	Higher 12-month C-peptide AUC vs. placebo (70)
	Baricitinib (JAK1/2 inhibitor)	BANDIT: new-onset T1D (10–30 years)	Higher 12-month C-peptide AUC vs. placebo (12)
Combination	Anti–IL-21 and liraglutide (GLP-1 receptor agonist)	New-onset T1D (18–45 years)	Combination treatment, but not IL-21 alone, preserved 54-week C-peptide AUC vs. placebo (9)
Antiviral treatment	Pleconaril and ribavirin	DiViD intervention study: new-onset T1D (6–15 years)	Higher 12-month C-peptide AUC vs. placebo (15)

Ab, antibody; ATG, anti-thymocyte globulin; AUC, area under the curve; CLVer, Hybrid Closed Loop Therapy and Verapamil for Beta Cell Preservation in New Onset Type 1 Diabetes; GLP-1, glucagon-like peptide 1; T1D, type 1 diabetes; T1DAL, Inducing Remission in New-onset Type 1 Diabetes with Alefacept; T1GER, A Study of SIMPONI to Arrest β-Cell Loss in Type 1 Diabetes; TN, TrialNet.

lead to preservation of insulin secretion (21,22). Lastly, a prevention study with the aim of targeting innate immunity with hydroxychloroquine in individuals with stage 1 disease was halted due to a negative futility analysis for effects on progression to stage 2 (23).

What does the future hold for DMTs aimed at delaying and ultimately preventing disease? The FDA approval of teplizumab as the first DMT for delaying progression from stage 2 to stage 3 type 1 diabetes marks a turning point for the field and provides a reference against which next-generation agents can be evaluated (24,25). Moreover, Provention Bio's Type 1 Diabetes Trial Evaluating C-Peptide with Teplizumab (PROTECT) showed that teplizumab significantly preserved C-peptide in children with recent-onset disease (26), providing a basis to seek FDA approval also for stage 3 type 1 diabetes. Promising results with low-dose anti-thymocyte globulin in individuals with stage 3 disease (27) are being followed up by INNODIA in the Minimum effective low dose-Anti-human thymocyte globulin (MELD-ATG) trial (clinical trial reg. no. NCT04509791, clinicaltrials.gov) and with stage 2 disease by TrialNet (Screen TO Prevent Type 1 Diabetes [STOP T1D]; NCT04291703), potentially offering an "induction-like" treatment as an alternative to teplizumab. INNODIA also completed recruitment for a study to test a proinsulin peptide immunotherapy (NCT04524949). Lastly, further investigation is underway on benefits of drugs impacting dysfunctional β-cell responses. Indeed, INNODIA is verifying the efficacy of verapamil (Verapamil SR in Adults with Type 1 Diabetes [Ver-A-T1D]; NCT04545151), and investigators in the TArgeting Type 1 Diabetes Using POLyamines (TADPOL) trial are testing difluoromethylornithine, an inhibitor of the polyamine biosynthesis pathway, in recent-onset stage 3 type 1 diabetes (NCT05594563).

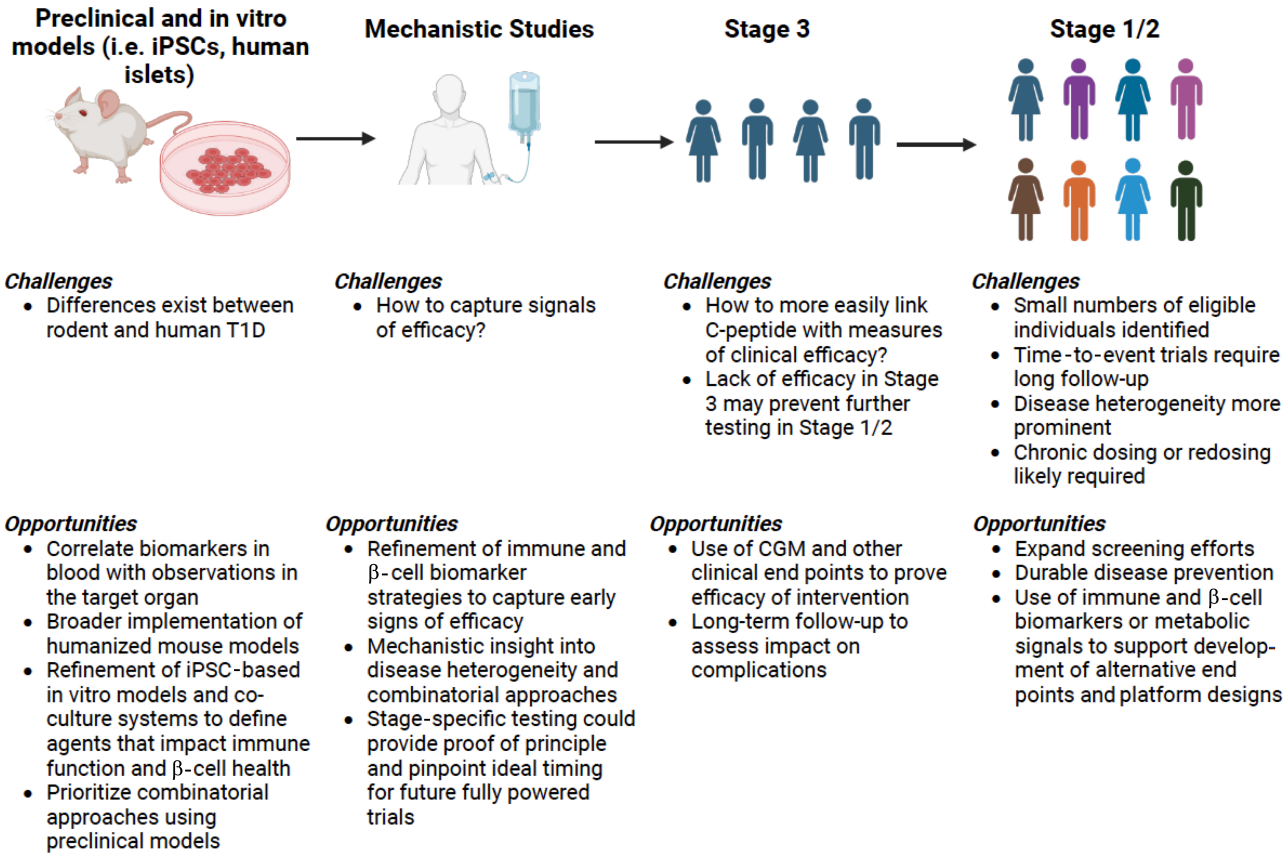

Figure 1—Opportunities and challenges in studying and optimizing disease modification in type 1 diabetes. Created with BioRender (biorender.com). CGM, continuous glucose monitoring; IPSCs, induced pluripotent stem cells; T1D, type 1 diabetes.

However, these new therapeutic options and our improved understanding of disease pathophysiology also pose new challenges (Fig. 1). The first is that a relatively small percentage of individuals are identified in the presymptomatic stages of disease, before they ultimately go on to develop clinical type 1 diabetes. Larger-scale screening is necessary to identify more individuals who stand to benefit from treatment and, practically, to test more interventions and regimens and to delay clinical progression. Because most individuals developing type 1 diabetes do not have a family history, this may require screening of the general population. (See General Population Screening.) In addition, improved patient stratification and early biomarkers of disease heterogeneity or therapeutic efficacy are needed for clinical trials to be performed more effectively and for regimens to be modulated according to projected outcomes. (See *Biomarkers of Type 1 Diabetes Heterogeneity for Patient Stratification*.)

Second, it is likely that combination therapies that target different arms of the autoimmune response will be required for more enduring impact. Also, treatments that include immunomodulatory and β-cell–protective agents hold promise, as it is increasingly appreciated that stressed or dying β-cells accelerate and amplify the autoimmune attack (28). These types of approaches could be assessed with adaptive (platform) trial designs with interim analyses and predefined decision criteria to rapidly test multiple combinations side by side (29).

Third, DMTs should also be considered in the context of other areas of therapeutic development in type 1 diabetes. For example, the advent of induced pluripotent stem cell–derived islets as a replacement therapy may increase β-cell mass, thus allowing DMTs to be more efficacious and widening the time frame for therapeutic intervention. Such therapeutic approaches will need to be integrated into the existing "diabetology toolkit," which also includes novel insulin delivery technologies.

BIOMARKERS OF TYPE 1 DIABETES HETEROGENEITY FOR PATIENT STRATIFICATION

Clinical success is tightly associated with improving stratification strategies to identify the right patients to treat at the right time with the right drug. Indeed, there is significant individual variability in disease progression, severity of symptoms, and clinical features at stage 3 onset, as well as in further C-peptide decline thereafter (30–31). Together with clinical and longitudinal follow-up data, we now can explore pathology and molecular findings in-depth and then examine these results in the context of variable disease phenotypic features. The recognition of this heterogeneity has led to the concept of disease endotypes (32). If

robustly defined, these endotypes could support more targeted therapeutic approaches and the implementation of personalized medicine (33,34).

In the study of human pancreas pathology in type 1 diabetes investigators have identified heterogeneity in the degree of insulitis, cellular composition of islet infiltrates, extent of β-cell destruction, islet cell HLA class I hyperexpression, and the processing/localization of proinsulin (32,35,36). While such differences may to some extent represent different stages during disease progression, the association with age at onset supports the concept of two essential endotypes segregated into children and young adults. Type 1 diabetes endotype 1 (T1DE1) is characterized by a younger age at diagnosis (<7 years), more severe insulitis, higher prevalence of $CD20^+$ B lymphocytes in the islet infiltrates, fewer residual β-cells, and proinsulin accumulation in surviving β-cells (37), the last of which may represent the pancreatic pathology correlate of the increased blood proinsulin–to–C-peptide ratio observed during clinical progression (38). A second endotype, type 1 diabetes endotype 2 (T1DE2), has been described in patients who developed diabetes at an older age (≥13 years) and is characterized by mild insulitis, a paucity of $CD20^+$ B lymphocytes, and a greater proportion of remaining β-cells.

The heterogeneity of type 1 diabetes extends beyond pancreas pathology to the targeted autoantigens (39), as well as other genetic factors that influence the diversity of the immune response and its severity/aggressiveness. Thus, not all patients respond to all or the same autoantigens, and the timing of the individual responses may vary. For example, autoantibody responses to insulin are typically associated with the presence of HLA-DRB1*04:01/DQA1*03:01/DQB1*03:02 haplotypes, while responses to the GAD antigen are associated with HLA-DRB1*03:01/DQB1*02:01 haplotypes. In the context of antigen-based interventions, the recognition of this diversity is of obvious importance in selection of patients who are more likely to respond. Studies of both living patients and organ donors with type 1 diabetes support the concept that the presence of *TCF7L2* polymorphisms linked to type 2 diabetes is associated with a less pronounced autoimmune phenotype and less severe β-cell destruction, suggesting that β-cell alterations may play a relatively dominant pathogenic role in these patients, which holds therapeutic implications (40). While the role of islet autoimmunity remains central in the disease, it has become increasingly evident that β-cell dysfunction is also a critical component (41). As noted, the pancreas of children with recent-onset type 1 diabetes exhibits greater β-cell loss compared with that of teenagers and adult patients with stage 3 disease, in whom an estimated 40%–60% of residual islets stain positive for insulin (42). The functional assessment of insulin secretion in living patients supports these pathology findings; at clinical diagnosis, insulin secretion is more severely impaired in younger age-groups (30,43), who also have a more rapid decline before and after clinical onset. Longitudinal studies with evaluation of insulin secretion pre- and postdiagnosis revealed that impairment becomes more pronounced during the 6-month intervals that precede and follow disease onset (44). Immune and proteomic signatures also appear within the year before diagnosis (45), suggesting changes that are reflective of the pancreas-immune cross talk.

The degree of β-cell heterogeneity is also increasingly appreciated, as it may impact secretory function, senescence, and susceptibility/resistance to autoimmunity. Data supporting this hypothesis include the description of $CD63^{hi}$ β-cells possessing enhanced glucose-stimulated insulin secretion (46) and the recognition of β-cell subsets with leader ("hub/pacemaker") functions over "follower" β-cells (47). It is possible that different subsets may be preferentially targeted by autoimmunity and/or stress, and their loss may drive dysfunction in the remaining β-cells. On the other hand, some β-cells may be targeted in autoimmunity because they have senescent phenotypes (48), or, conversely, others may resist autoimmunity, for example by upregulating PD-L1 (49). Strategies to address β-cell functional subsets in disease progression will be helpful in further advancement of type 1 diabetes therapies.

Overall, the appreciation of type 1 diabetes heterogeneity, whether observed in the context of pancreas pathology, failed immune tolerance, or clinical features, is of critical importance and may advance the development of improved therapies. In fact, disease heterogeneity is reflected by heterogeneity in the response to treatment, which may be overcome through identification of which patients may respond to which treatment(s) based on immune and β-cell set points. To this end, major advances could be achieved through use of simultaneous functional analysis and assessment of pancreas pathology, now partially possible with the use of pancreatic slices from organ donors (50). However, we are still lacking in vivo imaging techniques that could reveal ongoing disease and measure β-cell mass in living subjects, and pancreas biopsy remains impractical due to surgical risks.

GENERAL POPULATION SCREENING

Prospective studies have shown the value of islet autoantibody testing in identifying people with stage 1/2 presymptomatic type 1 diabetes who will develop stage 3 disease (51,52). There is international consensus that the presence of two or more autoantibodies directed against different islet autoantigens represents an early presymptomatic stage of the disease. Screening for islet autoantibodies in combination with education and monitoring can prevent DKA at clinical onset and is a prerequisite for treating stage 1/2 patients with DMTs. For diagnosis of early-stage type 1 diabetes in children and adolescents from the general population, appropriate structures for screening and care of islet autoantibody–positive individuals need to be established in national health care systems.

Feasibility

Regarding the logistics and practical implementation of islet autoantibody screening in the general population, already existing and country-specific public health care structures should be used. Examples from Germany (Fr1da study) (53), Colorado (Autoimmunity Screening for Kids [ASK] study) (54), and other regions show that successful screening can be achieved. Indeed, the Fr1da study has demonstrated a highly effective screening strategy; primary care professionals (pediatricians) across the region screened >200,000 children aged 2–10 years for islet autoantibodies, diagnosed 0.3% of them with early-stage type 1 diabetes, and referred these affected children to local expert centers for education, disease staging, and monitoring (53,55,56). Lessons learned from these studies include the following: *1*) screening can be performed with capillary blood and integrated into regular pediatric care, *2*) islet autoantibodies are sensitive and specific when validated and confirmed in a central laboratory, and *3*) screening should be linked to regional clinical diabetes centers that metabolically stage, educate, counsel, and monitor individuals diagnosed with early-stage type 1 diabetes. As part of the EDENT1FI project, work is underway to implement islet autoantibody screening in the general population in several European countries over the next few years.

A specific and sensitive islet autoantibody screening strategy must incorporate several key aspects: *1*) screening for three or four major types of islet autoantibodies, i.e., autoantibodies against insulin (IAA), GAD (GADA), insulinoma-associated antigen-2 (IA-2A), and/or zinc transporter 8 (ZnT8A); *2*) use of two different detection methods for the initial screening test and the subsequent confirmatory test; and *3*) testing of two blood samples taken at different time points (53,57). This procedure enables a reliable diagnosis of the early stages of type 1 diabetes. Importantly, only persistently confirmed positivity for multiple islet autoantibodies should be communicated to the affected families as definitive.

Screening twice, at the ages of 2 and 6 years, leads to a sensitivity of >80% (58). The specificity/positive predictive value of this screening strategy is nearly 100%; i.e., almost all children who test positive for multiple islet autoantibodies will develop clinical type 1 diabetes within 20 years, 79% by the age of 15 years and 75% within 10 years (57). Reversion from testing positive for multiple autoantibodies to testing negative for autoantibodies is very rare and did not appear to be associated with a risk reduction for type 1 diabetes (59). Since teplizumab therapy is approved in the U.S. for children aged ≥8 years, screening should be performed at least once until the age of 17 years. Appearance of multiple autoantibodies after the age of 17 years is rare, so individuals who screen negative after that age should not be retested.

It is essential that qualified training and monitoring programs are in place for people positive for islet autoantibodies, especially for children and their families. Any person diagnosed with early-stage type 1 diabetes must be offered some form of follow-up for detection of progression to clinical disease and start insulin in time to prevent DKA (55,60). If possible, monitoring should always take place at a local diabetes center.

Autoantibody Assay Requirements

For the initial screening, multiplex assays that enable the detection of different types of islet autoantibodies (e.g., GADA, IA-2A, ZnT8A, IAA) in one test run should be preferred for reduction of costs. Currently, bridging ELISA, electrochemiluminescence, Antibody Detection by Agglutination PCR (ADAP), and luciferase immunoprecipitation system methods are used (61–63). The requirements for these screening tests are high sensitivity and specificity for the detection of type 1 diabetes–associated autoantibody signals, as well as high accuracy, reliability, and reproducibility of the test results. All laboratories involved in screening must participate in regular proficiency testing, such as the workshops organized by the IDS Islet Autoantibody Standardization Program (IASP) (4). Finally, population-level screening tests also need to be affordable. Availability of accurate point-of-care tests for the initial screening could help to improve logistics, reduce costs, and speed up diagnosis. The confirmatory tests should preferably have a test format different from that of the screening test to avoid false-positive results and should allow the detection of individual islet autoantibody types with high specificity. Standardization of these assays must be further advanced through harmonizing protocols and antigen constructs used for the same testing formats, and using common standard samples and calibrators for the calculation of common units for all test formats. The latter would be an important step forward for the comparability of quantitative test results and the establishment of common thresholds. Appropriate monoclonal antibodies could serve as a stable source for such calibrators.

Regulatory Issues

Screening in the context of public health care must be carried out in accordance with country-specific regulations and health care policies. Adequate information about the screening and voluntary participation must always be guaranteed. Participants must be informed about both the benefits and the potential disadvantages of early detection of presymptomatic type 1 diabetes. Published guidelines are becoming available for health care professionals on how to screen for early-stage type 1 diabetes, how to monitor and treat diagnosed individuals, and how to ensure timely insulin treatment to prevent DKA (60).

CONCLUSION

Gaining a comprehensive understanding of type 1 diabetes clinical, immunological, and metabolic features reflecting intrinsic disease heterogeneity and aggressiveness is a

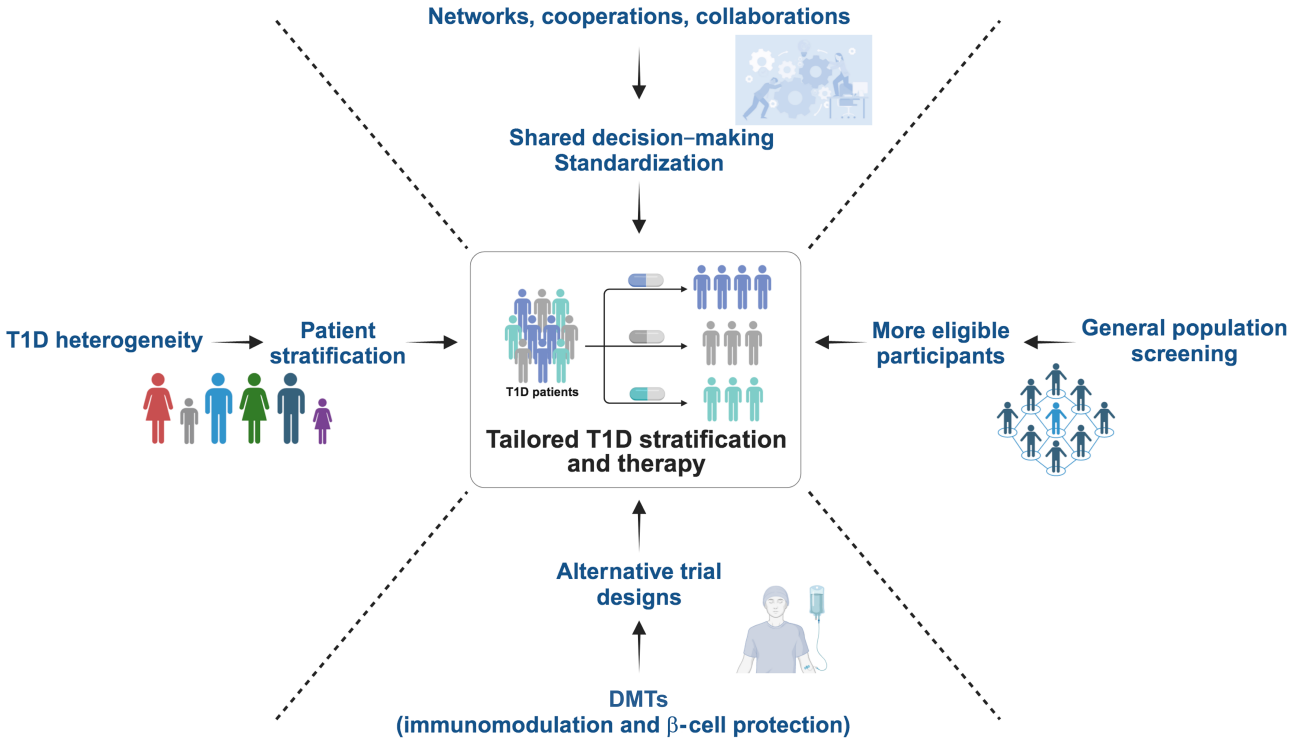

Figure 2—Road map for acceleration of type 1 diabetes research and therapy. Created with BioRender (biorender.com). T1D, type 1 diabetes.

prerequisite trajectory for successful treatment. As we look toward the future of care for type 1 diabetes, it is key to implement stratification strategies and develop approaches for precision medicine to optimize preclinical diagnosis, prognostic stratification, treatment options, and responses to therapies (Fig. 2). Building on the cohesive work and cooperation of researchers, clinicians, industry partners, funding agencies, health care professionals, and families, the initiatives launched worldwide will address those needs and allow for opportunities to reach sustained remission or prevention of type 1 diabetes.

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