Persistence is the Twin Sister of Excellence
An Important Lesson for Attempts to Prevent and Reverse Type 1 Diabetes

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Perspective is the twin sister of excellence. One is a matter of quality; the other, a matter of time.

Marabel Morgan

Consider 2011 as the culminating year for the decade of clinical trials seeking to alter immune-mediated destruction of β-cells in type 1 diabetes. Emphasizing this past decade is not meant to diminish earlier studies (1), or the seminal trial in 1984 demonstrating the effects of cyclosporine on preservation of β-cell function (2); indeed it was the sobering results from the latter study (i.e., better insulin secretion but worsening renal function) that pushed the field to test new approaches aimed at achieving some sort of tolerance—i.e., a safe, short-term intervention that would enable a “reset” of the immune system away from self-destruction and provide long-term clinical benefits. To achieve such a goal would not be easy, but would require a remarkable degree of persistence.

To this end, in 2002 and 2005 reports from two trials using modified anti-CD3 antibodies hinted at the promise for such a new approach (3,4). Since then, early evidence has been reported that therapies of similar therapeutic purpose but targeting completely different mechanistic pathways (e.g., antigen based with GAD65-alum, anti-B lymphocyte) may have also beneficially altered the disease course after type 1 diabetes onset (5–8). But 2011 is a key year not only because results of a number of major clinical trials will be reported from nonprofit- or federally funded studies, but it represents the year that results will be disclosed from studies involving “big pharma,” often in association with biotech companies. And it is with this notion that we will build our case for the importance of these trial results for all those interested in type 1 diabetes.

Drug development requires collaboration between academia, regulatory authorities, and pharmaceutical companies. As recently highlighted by the new Center for Translational Medicine and Therapeutics at the National Institutes of Health (NIH) (9), putting these pieces together is the only way science will affect human health in a meaningful way. Unfortunately, until 2001 big pharma did not, to a meaningful degree, play in the space of altering immune destruction of β-cells. What brought them in?

One reason was the strategic planning, intensive negotiating, and persistent lobbying by the Juvenile Diabetes Research Foundation (JDRF), individual investigators (both inside and outside of academia), and NIH leadership. Another key was the acceptance by the Food and Drug Administration and European Regulatory authorities of C-peptide as an appropriate end point to regulatory approval. Third was the push from academic investigators acting collectively in networks, such as the NIH Immune Tolerance Network (ITN) and Diabetes TrialNet who, through collaboration, demonstrated the feasibility of performing large clinical trials with efficiency. Finally, the notion of “reformulating” drugs pharma designed for other disorders and seeing their potential application in settings of type 1 diabetes grew increasingly attractive.

Now that all the required players are at the table and we have the benefit of a decade of experience working together, it is sobering to ask whether such engagement will continue if results of the major clinical trials due to report in 2011 (Table 1) are negative. Scientifically, either negative or positive results help the field and stimulate new questions; but if negative results discourage big pharma, the field of type 1 diabetes will suffer a setback. There are also implications if the trial results are seen as positive. For example, a drug showing positive influences on the disease may sway interest away from other promising agents due to fears of competition for limited market space. From observing drug development in other autoimmune diseases, it is unlikely that any single study will be compelling enough from a risk/benefit perspective to fundamentally alter clinical care in an immediate fashion; yet there may be impacts on the design of future studies. Our advice, and hope, is that careful scrutiny of these trials together will allow investigators to tackle the complex clinical and regulatory issues surrounding identification of those individual therapies providing the most benefit and, subsequently, to identify how to combine approaches to maximal effect. Regardless of positive or negative outcomes, the need for the partnership between the aforementioned entities will remain.

This having been said, the implications of these trial results (Table 1) go far beyond the issue of whether pharma will continue to support this area. As of this writing, the United States Congress has agreed to funding for the Special Type 1 Diabetes appropriation, thus allowing for continuation of individually or network-funded clinical trials for at least a short season. In addition to learning from this critical decade of trials to plan new studies, we must plan for the future by training clinical investigators—and rewarding them with academic promotions and grants for...
collaborative efforts, including participation in clinical trials. Although this challenge is not unique to type 1 diabetes, the insufficient supply of diabetologists for both clinical care and research is of considerable concern. Yet, clinical trials do not happen without understanding of basic scientific concepts. We must reject the false dichotomy of basic or clinical research, supporting one at the exclusive expense of the other. Both are incredibly important and indeed, at the close of 2010, it is remarkable how many fundamental questions regarding type 1 diabetes remain: Is it a disease of flares and remissions? Do β-cells regularly regenerate? Why is there heterogeneity in clinical course? New tools, technology, and analytic approaches from talented individuals within and outside the diabetes research field should be developed and applied to human tissues including blood samples and cadaveric specimens. Clearly, improved biomarkers are also needed: those that track with disease, those that track with therapy, and those that track in response to therapy.

Finally, it is important to consider the impact these clinical trial results will have on patients and families living with type 1 diabetes. Like other diseases, only a very tiny fraction of individuals participate in clinical trials (10). If a series of negative results are reported during 2011, what will be the impact on their willingness to participate in new studies? If there are positive results, how will the research community collectively address the clinical importance of the reported outcomes? Individuals with diabetes and their families are already burdened with the emotional, physical, and financial costs of the disease; investigators must stay connected, must listen, and must solicit ideas from those directly dealing with diabetes.

Writing just before 1 January 2011, we plan to ring in this important year with hopeful anticipation of the results culminating from this past decade of clinical trials. Whatever the results, a key challenge is to remain persistent. We must continue to build on the infrastructure, the human capital, and the goodwill generated to date in order to see a means for the prevention and cure of this disease brought to fruition.

ACKNOWLEDGMENTS

Support for the studies that helped form these editorial opinions derived from the Juvenile Diabetes Research Foundation, NIH, the Benaroya Research Institute, the Brehm Coalition for Type 1 Diabetes Research, the American Diabetes Association, and the Jeffrey Keene Professorship.

M.A.A. is a member of the Scientific Advisory Board of Diamyd Medical AB, the manufacturer of Diamyd, and of the Scientific Advisory Board of Tolerx, the manufacturer of Otelixizumab. He is a member of the medical education–based Advisory Board for GlaxoSmithKline, which also has an interest in Otelixizumab. No other potential conflicts of interest relevant to this article were reported.

This editorial is dedicated to the late Mark Pescovitz (Indiana University), a champion for clinical trials in type 1 diabetes, including but not limited to those involving anti-CD20. He was a role model for persistence in guiding many of the ideas posed within this editorial, and his contributions to the research community will last for many, many years. Beyond this, the authors would like to thank their colleagues for years of wide-ranging, provocative, and thoughtful discussions regarding type 1 diabetes clinical research.

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**TABLE 1**

A sampling of large clinical trials seeking to reverse type 1 diabetes whose results are due for reporting in 2011

| Drug            | Compound       | Type of trial                      |
|-----------------|----------------|-----------------------------------|
| Abatacept       | CTLA4-Ig       | Phase II (NIH TrialNet)           |
| Diamyd          | GAD-alum       | Phase III (Diaprevent)            |
| DiaPep277       | HSP peptide    | Phase III                         |
| Prochymal       | Mesenchymal stem | Phase II                        |
| Teplizumab      | Anti-CD3       | Phase II/III (Protégé)            |
| Otelixizumab    | Anti-CD3       | Phase III (Defend-I)              |

Note: not every clinical trial for type 1 diabetes that is due to report study results was indicated for the sake of brevity or because of study size or lack of public information. HSP, heat shock protein.