Research Focus
Profile: Type 1 Diabetes TrialNet

Jay Skyler will turn 70 years old on his next birthday, but he expects that in his lifetime "we'll get to the point where type 1 diabetes is obliterated".

Skyler, deputy director for clinical research and academic programmes at the University of Miami’s Diabetes Research Institute, FL, USA, should know. Before stepping down last summer, he was the founding chairman of Type 1 Diabetes TrialNet, an international consortium of scientists exploring ways to prevent, delay, or reverse the progression of the disease by studying its natural history, identifying high-risk individuals, and testing new therapies.

TrialNet was established in 2002 in response to the US Surgeon General’s report Healthy People 2000, which identified diabetes as one of the top public health issues in the USA. Congress created the Diabetes Research Working Group to develop a plan for diabetes research, which included clinical trials to prevent type 1 diabetes. "I don’t think there can be cure without prevention", Skyler says. "Those things go in parallel."

Thanks to increased funding from the US National Institutes of Health and the JDRF (formerly the Juvenile Diabetes Research Foundation), TrialNet has expanded in recent years to 19 clinical centres in North America and six international centres. Additionally, there are more than 200 affiliated sites in North America, the UK, Australia, New Zealand, Sweden, Italy, Germany, and Finland.

Around 29 million Americans have diabetes, but only about 5% of them have type 1, an autoimmune disease in which the immune system mistakenly destroys the insulin-producing β cells of the pancreas. "The prevention trials that are going on now couldn't possibly be done without a consortium", says Kevan Herold, principal investigator (PI) for TrialNet at Yale University, New Haven, CT, USA. "You can’t just do that as a single PI."

Because type 1 diabetes is relatively rare, "it takes more infrastructure to be able to recruit people for our trials", says Judith Fradkin, director of the Division of Diabetes, Endocrinology, and Metabolic Diseases at the National Institute of Diabetes and Digestive and Kidney Diseases, one of TrialNet’s funders. "Studying people who don’t yet have clinical disease absolutely requires this type of infrastructure."

TrialNet’s precursor, the Diabetes Prevention Trial of Type 1 (DPT1), screened more than 100,000 non-diabetic relatives of patients with type 1 diabetes for the presence of islet cell antibodies to enrol a total of 711 in two randomised trials of low-dose insulin, says Skyler, DPT1 chairman. DPT1 consisted of ten clinical centres in the USA and Canada, each of which had a network of affiliates. "We actually designed the original DPT1 trial by really looking carefully at the Pediatric Oncology Group, which the National Cancer Institute had started", Skyler says. "Because we were dealing with kids too, we thought that was a good model to look at."

In DPT1, relatives were studied because their risk of developing type 1 diabetes is 10-20 times higher than that of the general population. Those found to have antibodies after screening went on to have genetic, immunological, and metabolic testing to quantify their risk of developing type 1 diabetes in the next 5 years. The high-risk relatives were randomised to daily injected insulin or a control group that was closely observed. Intermediate-risk relatives were randomised to oral insulin or a placebo. The low-dose insulin was not found to delay or prevent type 1 diabetes in people with a high risk of developing the disease within the next 5 years. However, the research showed that it was possible to identify people at high risk of developing type 1 diabetes over the next 5 years and enrol them in a large, multicentre, randomised controlled trial.

TrialNet deserves credit for bringing more attention to type 1 diabetes and the notion of preventing it, says Richard Insel, a member of the organisation’s executive committee. "TrialNet, as well as the precursor to TrialNet, has provided an understanding of the natural history of type 1 diabetes”, he says.

TrialNet, and DPT1 before it, has needed to screen tens of thousands of relatives because only about 5% have islet cell antibodies, Insel says, adding that most people with type 1 diabetes do not have a relative with the disease.

Prevention studies could be smaller and shorter if scientists had a marker for β-cell destruction instead of having to wait years to see if trial participants develop diabetes, Fradkin says. "We would like a more precise measure of the progression", she says. Researchers cannot rely on participants’ blood glucose levels because “your glucose doesn’t really become abnormal until you’ve lost most of your β cells”, Fradkin says.

So far, several interventions have slowed the loss of β-cell function in at-risk or newly diagnosed individuals but have not yet reversed it. In virtually every case, the effect has been only transient, Skyler says. But, Fradkin notes, “Even if you just delayed the onset of type 1 diabetes 2 or 3 years, that’s another 2 or 3 years of care-free childhood.”

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