

## From non-obese diabetic to Network for the Pancreatic Organ Donor with Diabetes: New heights in type 1 diabetes research

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### Abstract

Since the discovery of therapeutic insulin in 1922 and

the development of the non-obese diabetic spontaneous mouse model in 1980, the establishment of Network for Pancreatic Organ Donor with Diabetes (nPOD) in 2007 is arguably the most important milestone step in advancing type 1 diabetes (T1D) research. In this perspective, we briefly describe how nPOD is transforming T1D research *via* procuring and coordinating analysis of disease pathogenesis directly in human organs donated by deceased diabetic and control subjects. The successful precedent set up by nPOD is likely to spread far beyond the confines of research in T1D to revolutionize biomedical research of other disease using high quality procured human cells and tissues.

**Key words:** Type 1 diabetes; Network for the Pancreatic Organ Donor with Diabetes; Non-obese diabetic mouse; Transitional type 1 diabetes research

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**Core tip:** Type 1 diabetes (T1D) strikes early in life with monumental impact on life style and long term health of affected children. There is currently no cure for T1D or mechanisms to protect at risk individuals. A major obstacle is the difficulty in translating the interventions that succeeded in preventing or reversing the disease in the non-obese diabetic mouse model into human immunotherapies. Network for Pancreatic Organ Donor with Diabetes has been established in 2007 to study the disease directly in humans by procuring and offering well preserved tissues to investigators. These efforts, as indicated by published results, are paying off by providing critical new insights that are expected to facilitate development of efficacious immunotherapies.

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## MAIN TEXT

Type 1 diabetes (T1D) is a form of diabetes mellitus that results from the autoimmune destruction of the insulin-producing beta cells in the pancreas, manifested clinically as hyperglycemia. T1D accounts for 5% to 10% of diabetes cases in the world and about 80000 children develop the disease each year. During the last century, research of T1D passed through several critical milestones (Table 1). Prior to the discovery and use of insulin as a replacement therapy in 1922, T1D was invariably fatal<sup>[1,2]</sup>. Advances in insulin delivery and formulation are allowing many patients to live out their respective life expectancies. Nonetheless, insulin replacement is not a cure and it has to be taken daily. In addition, the dose needs to be adjusted frequently for successful management of blood glucose levels and their maintenance within an acceptable range. Achieving these goals is challenging and patients develop bouts of hypo- and hyper-glycemia as well as serious long term cardiovascular complications<sup>[3]</sup>. To alleviate these problems, there have been intensive and sustained efforts to develop a cure that protects high risk individuals and perhaps reverses hyperglycemia in new-onsets. For this purpose, scientists have been using small animals to understand disease pathogenesis better, which is critical for finding a cure. Indeed, the discovery of the pancreas as the sole source of insulin almost a century ago was based on the development of severe diabetes in depancreatized experimental animals<sup>[2]</sup>. In the 1980s, these efforts were seriously boosted by the development of the non-obese diabetic (NOD) mouse as a spontaneous model of the diseases<sup>[4]</sup>. Extensive studies of NOD mice over the years led to significant understanding of the disease pathogenesis and identification of large numbers of molecules and cell types that stood out as potential therapeutic targets<sup>[5]</sup>. Clinical relevance of the findings derived from NOD mice are substantiated by identification of their counterparts in humans. Strategies to block or reverse disease in NOD mice were mostly successful<sup>[6]</sup>, raising the hope of translating them into effective and safe immunotherapies. Results of clinical trials, however, were rather disappointing as they largely failed to achieve the expected efficacy to preserve C-peptide or protect high risk individuals, dashing hopes. There were several comprehensive reviews of the major trials and their outcomes including an excellent concise review by Atkinson *et al*<sup>[7]</sup>.

Assessment of the reasons behind the failure of the selected agents in the clinic is leading to more appreciation of biological differences between the highly heterogeneous human population and the NOD inbred mouse and to the role of the environment as barriers that challenge the assumption that “what works in NOD mice will work in humans”. Changes in environmental

factors (including viral infections, changes in diet) rather than changes in allele frequency, which would not occur so rapidly, are likely responsible for the rapid increase of the incidence of T1D in western countries. Together these factors pointed to the importance of studying the disease directly in humans. However, regular access to well characterized human organs has been very difficult and not available at central facilities. Consequently, most of the clinical research has been limited to the analysis of peripheral blood mononuclear cells. Facing the reality that most if not all of what worked in NOD mice failed in the clinic, a foresighted group of researchers conceived and implemented the idea of studying the disease directly in humans using donated organs. This led to the established of the Network for Pancreatic Organ Donors with Diabetes (nPOD). For complete information about nPOD, supporting agencies and how to get involve, please visit: <http://www.jdrfnpod.org/>. As indicated in their website, nPOD biobank receives organs from donors, worldwide, and distributes tissues and cells to nPOD researchers. These efforts are allowing scientific investigation of T1D directly in well-preserved high quality human tissues and organs by researchers with diverse scientific specialties and interests. The ultimate goal of this diverse group of research converges on studying and understanding different aspects of the disease and eventually developing therapeutic modalities to protect high risk individuals and perhaps reverse disease at onset. Fruitfulness of these efforts are indicated by a stream of new discoveries some of which confirmed similarities to what have been known in the NOD mouse, whereas others identified significant departures (for complete list of these publication, please visit nPOD website). Most of these notable differences, particularly in the pancreas and potential roles of viral infections in driving disease pathogenesis have been elegantly described in recent reviews by Pugliese *et al*<sup>[8]</sup> and Kaddis *et al*<sup>[9]</sup>.

## CONCLUSION

Access to donated human organs procured by nPOD is providing the opportunity to study the disease directly in humans. Studies of these organs is already leading to new critical insights that are expected to help better understanding of T1D and development of new modalities that can prevent T1D or preserve C-peptide in new-onset patients. However, NOD mouse still remain valid model for identification of new targets such as FasL<sup>[10]</sup> and for functional understanding of observations made in humans. Particularly useful will be development of robust humanized mice that can be reconstituted by lymphocytes isolated from different human organs, particularly the pancreas. In addition, new innovative studies are directed towards combining reconstitution of humanized mice with peripheral mononuclear cells (PMNCs) with transplanted organs. At least but not least, success of the nPOD model is likely to inspire establishment of similar networks to study various

**Table 1** Milestones in type 1 diabetes research

Use of depancreatized mice showed that T1D is due to the absence of internal pancreas secretion (1889)
Identification and synthesis of insulin for therapy (1922)
Development of spontaneous NOD mouse model (1980)
Establishment of nPOD to study disease using organs and tissues procured from patients, high risk individuals and non-diabetic controls (2007)

T1D: Type 1 diabetes; NOD: Non-obese diabetic; nPOD: Network for Pancreatic Organ Donors with Diabetes.

human diseases.

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