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Summary of the Keystone Islet Workshop (April 2014): The Increasing Demand for Human Islet Availability in Diabetes Research

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Serving as a "call to action," the Keystone Symposia on Molecular and Cellular Biology: Emerging Concepts and Targets in Islet Biology (Keystone Islet Workshop) held in April 2014 provided a much-needed forum on islet biology and the increasing pressure of the supply and demand relationship of human islets for research. The result of the workshop was a white paper that has been shared with the leadership of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), JDRF, and the American Diabetes Association (available from http://www.joslin.org/news/White-Paper-on-Human-Islet-Availability-for-Diabetes-Research.html). A brief summary is provided here.

STATEMENT OF THE PROBLEM

Pressure for research on the "pipeline" of human islets has become increasingly acute for several reasons.

- First, there is widespread acceptance that, while broadly similar, important functional and morphological differences occur between rodent and human islet cells; thus, there is an urgent need to directly address applicability of rodent findings to the pathophysiology of all types of diabetes (1–3). Because of these important differences, the National Institutes of Health (NIH)/NIDDK and JDRF have urged researchers to use human islets in their diabetes research, as illustrated by the recent requests for applications (RFAs) from the NIDDK for the Human Islet Research Network (HIRN) initiative (4–9) and recent JDRF RFAs (10,11).
- Second, there has been an explosion in investigator requests for human islets for research, either to confirm previously published findings in rodent islets or to generate new data.
- Third, scientific grant review committees and scientific journals have set the bar higher by demanding data on human islets in grant applications and peer-reviewed manuscripts.

While the need is urgent, obtaining human islets for research from living or cadaveric donors is difficult. This challenge contrasts with other diabetes-relevant tissues (e.g., adipose, skeletal muscle, and even liver) that are more easily obtained by percutaneous biopsy. There are also inadequate numbers of pancreas donors. The Integrated Islet Distribution Program (IIDP) has been a tremendous boon for the diabetes research community with their organized and concerted approach to obtaining and distributing high-quality cadaveric human islet tissues to researchers (12). As human islets do not grow continuously in culture and have a shelf life of 7–10 days and islets from a given cadaver donor must be shared among many investigators, the actual number of available islets in real time is limited. In practical terms, these factors translate to teams of investigators obtaining human islets once or twice per month, using them actively for a week, and then having to wait for the next shipment. These issues are reflected in the increasing number of new IIDP investigators requesting human islets (increase from 35 in 2010 to 104 in 2014) and the average wait time to obtain human islets of at least 2 weeks. Thus with a more plentiful islet supply, human β-cell research could move twice as fast as it currently does. Also of note, up to 80%

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of investigators are requesting additional islets from patients with type 1 or type 2 diabetes.

POTENTIAL SOLUTIONS TO HUMAN ISLET AVAILABILITY FOR RESEARCH

While the need for more islets and the problem of poor availability are now well recognized by researchers (13) and the NIH, the scientific community as a whole is challenged with crafting a solution. The Keystone Islet Workshop allowed for frank discussions and yielded multiple suggestions for potential solutions.

Double the Availability of Human Islets

The "doubling" concept is based on the notion that, on average, human islet investigators have access to human islets half as often as needed and that the "price" for doubling the numbers of human islets distributed by IIDP (estimated at ~$2 million) was minor relative to the overall NIDDK budget. Additional funding sources were a major topic.

Options discussed included:

- Increasing financial support for existing centers (given the static number of IIDP islet isolation centers), thus allowing them to increase their efforts (rather than open new centers);
- Providing IIDP with a long-term human islet commitment analogous to the NIH-funded Mouse Metabolic Phenotyping Centers;
- Having JDRF and the industry provide financial support for the IIDP, given that stakeholders share a common goal of islet cell regeneration to enable better therapeutics; and
- Adapting either the JDRF-sponsored Network for Pancreatic Organ Donors with Diabetes (nPOD) program and/or the IIDP to include islet distribution for type 2 diabetes islets (a similar JDRF program already exists in Europe).

There was concern that with the upcoming end of the NIDDK-sponsored Clinical Islet Transplantation (CIT) program human islet availability may actually decline. Further, pancreata are not harvested from many cadaver donors of other organs; thus, these organs that could be used for research are lost. Greater involvement of organ procurement organizations (OPOs) along the lines that nPOD has followed may expand the supply of human pancreata. This would require IIDP and/or JDRF/nPOD to educate OPO personnel and involve organ transplant surgeons in pancreas harvesting.

Encourage Novel Approaches to Using, Obtaining, and Conserving Human Islet Cells

Developing human islet supply-demand RFAs from NIH and JDRF might encourage novel approaches to using, obtaining, and conserving human islet cells.

For example, the RFA might challenge investigators to *1*) develop miniaturized assays using human islets so that each assay would require fewer islets or *2*) devise better standardization methods to rapidly and accurately define viability and functional quality of donor islets with the potential to reduce the number of required replicates in human islet experiments. Such tests, performed by the IIDP, would allow for uniform/standardized testing results available to all recipients of a given islet batch. This is especially critical when isolating islets from patients with type 1 or type 2 diabetes to reassure investigators that the donor islets are of good quality. In addition, collection and distribution of critical donor characteristics would allow investigators to more appropriately interpret the data generated in their experiments.

Most islet biology investigators support the notion that increased human islet availability is critical to accelerating human diabetes research and patient care. We encourage NIH/NIDDK, JDRF, and pharma and biotech industries to partner and support greater long-term access to human islets for research toward the ultimate goals of better prevention or reversal of, as well as a cure for, diabetes.

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