

Human islet distribution during COVID-19 pandemic: the impact on diabetes research

B. J. Olack¹, E. Linetsky², J. C. Niland¹

¹Department of Diabetes and Cancer Discovery Science, Integrated Islet Distribution Program, City of Hope, Duarte, CA, USA

²Department of Surgery, cGMP Cell Processing Facility, Diabetes Research Institute, University of Miami Miller School of Medicine, Miami, FL, USA

Corresponding Author: B. J. Olack; e-mail: bolack@coh.org

Keywords: Diabetes research, Human islet distribution.

THE SHUTDOWN

As 2020 began and there were mostly whispers of a new virus causing deaths in Asia, the Integrated Islet Distribution Program (IIDP, originally called the Islet Cell Resource) at City of Hope (COH) was beginning its 17th year of coordinating the distribution of isolated human islets to diabetes investigators intra- and internationally. The Program, funded through the National Institutes of Health (NIH) - and specifically for the past 12 years, the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) - had distributed >258.5 million Islet Equivalents (IEQ; a term for actual islets standardized to the mass of 150 μ m diameter islets)¹ to 384 research studies since 2004, with >9.8 million IEQs being shipped in 2019 alone². The number of active studies applying for human islets in March of 2020 had reached 150 and demand was being met by the IIDP Islet Isolation Centers (ICCs), with >2.3 million IEQs having been distributed in early 2020, averaging >1 million IEQ per month².

As the death rate from the virus rose exponentially across Asia, Europe, and the Middle East and both coasts of North America had increasing cases of patients testing positive for COVID-19 (caused by severe acute respiratory syndrome coronavirus 2: SARS-CoV-2), a pandemic was declared by the World Health Organization March 11th³. That same day, the IIDP halted islet distribution to all its approved investigators until more was known about the mechanisms of viral spread and guidelines for transplant organ donor testing could be established by the Centers for Disease Control and Prevention

(CDC), the American Society of Transplantation (AST), and the United Network for Organ Sharing (UNOS), to ensure the safety of our IIC staff and all recipient researchers.

Following the March 13th issuance of a national emergency declaration for the United States⁴ under both the Stafford Act⁵ and the National Emergencies Act⁶, many universities, research institutes, and hospitals closed their facilities to all but essential workers. These actions brought much of the medical research conducted in this country to a dramatic halt. This commentary describes how diabetes research using human pancreatic islets has been drastically altered over the past six months, due to COVID is based on the IIDP experience and on interviews conducted with IIC staff members and IIDP recipient investigators.

IMPACT ON THE IIDP

Although human islet distribution had to be suspended by the IIDP for 15 weeks, the program was not sitting idle. The IIDP's home institution, COH, closed down the campus to all non-essential workers. However, the majority of the IIDP staff already worked from their home offices and the rest adapted to these new requirements easily, as most of the IIDP work is done through telecommunication and online shared technology. All staff continued to work on database and website improvements while closely monitoring the establishment of new guidelines and testing recommendations by the transplantation authorities under CDC and Health and Human Services guidance. The IIDP website programmers readied the online islet isolation broadcast requirements to reflect these new regulations. In addition,



This work is licensed under a [Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International License](https://creativecommons.org/licenses/by-nc-sa/4.0/)

the IIDP worked closely with the IICs to coordinate the reopening of their individual facilities as controlled by their own institutions based on the viral spread in their specific communities and states. The IIDP also kept in constant communication with its NIDDK representatives regarding the progress of the NIH in its responding to COVID-19, and with IIDP investigators regarding their struggles to continue research at their individual institutions.

IMPACT ON THE IICs

While the IIDP islet distribution program closed for three months during the summer until regulations and donor testing could become clarified, the staff at the individual IICs staff were unable to continue the isolation of human islets from pancreata. Most centers were mandated to shelter in place or were furloughed as a result of financial burdens imposed on academic centers as a result of the COVID-19 pandemic, much like the experience of the business world.

Many academic research laboratories, including several IIDP IICs, are associated with university hospitals, and as such they were asked to relinquish all personal protection equipment (PPE) to support patient care staff during the early shortages of the pandemic, thereby leaving the IICs unable to perform islet isolations even after the IIDP gave the green light for the distribution program to reopen. Not surprisingly, three of the five isolation centers also reported a dramatic drop in eligible donor pancreata offered throughout the summer months of 2020.

An unanticipated problem that plagued all of our facilities was the drastic reduction of commercial airline flights⁷, the usual means of donor organ delivery from donor hospitals to the islet isolation centers. Many centers reverted to only accepting pancreata from local hospitals or those within reasonable driving distance, to stay within the maximum cold ischemia time, while avoiding last minute air flight cancellations and averting a waste of the precious resources that also resulted in financial losses for the IICs.

THE REOPENING PROCESS

By early June of 2020 duplicate negative testing results on all organ donors were mandated by AST and the documentation of these results were implemented through UNOS. With additional direction from the CDC and support from NIH, the IICs felt it again safe to accept available donor pancreata for isolation in order to offer human islets for re-

search studies. As facilities began to slowly open in mid-June, IIC staff revised their Standard Operating Procedures (SOPs) for human islet isolation as needed, to include donor acceptance criteria of proven COVID-19 negativity, social distancing and mask-wearing prior to and following sterile procedures and continued strict adherence to universal precautions. For most centers, there was the need to negotiate and comply with their individual institutions on the number of essential workers allowed into laboratory buildings, resulting in minimal crews necessary to complete an islet isolation.

As IICs gradually reported to the IIDP that they were ready to become active again, the IIDP had the complicated task of trying to balance the needs of those investigators who were allowed to return to their laboratories and were desperately seeking islets again, and the number of IICs required to supply those investigators with the needed tissue. As the number of investigators ready to receive islets was still limited (approximately one third of the number pre-COVID), the IIDP monitored the islet need in the research community in order to prevent islet waste and be able to provide financial compensation for the cost of an IIC's work. The IIDP encouraged all approved researchers to update their need and availability to accept islets for their research via the program's secure website on a weekly basis. The team worked closely with the IICs to report acceptance of a pancreas prior to the isolation and islet broadcasts so the other IICs could gauge the pending islet "market". In addition, the IIDP had to coordinate shipments of sample islets to the Human Islet Phenotyping Program (HIP), whose staff also was still limited in their access to laboratories at Vanderbilt. The IIDP website was updated daily to provide as much information to both the IICs and the researchers on the status of islet distributions and the demand for islets. The IIDP also encouraged the IICs to take advantage of the opportunity to flash freeze any islets that remained after the investigators' needs were met, to build a repository of endocrine tissue that could potentially be used for future studies or for DNA extraction for the new IIDP genotyping program.

IMPACT ON DIABETES RESEARCHERS

Just as the IICs and the IIDP encountered COVID-related setbacks, the researchers that depended on human islets for their studies were confronted with similar and, in many cases, worse effects from the

pandemic. Even after the more than three-month shutdown of the IIDP IICs, many researchers still were not ready to accept human islets from the program. Most had to negotiate with their home institutions for the return to their laboratories, including making changes to their workflow to maintain social distancing, through lab reconfigurations and split-shift staffing, and in some cases, furloughing or dismissing some of their technical staff.

Although the IIDP provides human islets to researchers for their experiments, many laboratories incorporate animal studies with their human islet studies. Institutional animal facilities were affected by the virus-initiated closedowns for the majority of IIDP researchers. Many investigators had ongoing experiments that were interrupted before reaching conclusion, adding significant monetary burden to an already financially strapped research environment. Research laboratories also reported similar obstacles to what IICs experienced, such as their hospitals commandeering PPE for patient care and the lack of available supplies due to national shortages.

Publications are critical for all researchers. Although the laboratory closings may have resulted in some additional time to write manuscripts on completed experiments, closures prevented many others from finishing their scientific work. Also, many investigators had manuscripts returned from journal reviewers requesting additional or revised data which they could not readily provide. Due to laboratory closedowns, the reduction in animal availability, the inability to begin culture experiments, and the lack of islet distributions, published works were delayed or even prevented.

IMPACT ON TRAINEES

During interviews with several IIDP principal investigators (PIs) and a NIDDK program scientist, major concerns were voiced not only for the health of their staff, but also the well-being and careers of their post-doctoral fellows, graduate students, and other trainees, in light of how the three month or more lab closures affected their experimental schedules. Some M.D./Ph.D. students were on a strict time course to finish their bench work before resuming their medical school training, and their timelines were drastically impacted by the shutdown. In addition, many universities have frozen their hiring of any new faculty⁸ placing many graduate students and post-doctoral fellows in limbo and possibly affecting their career opportunities for years to come⁹.

While extremely difficult for the burgeoning career of a young diabetes researcher requiring human islets, these travails also have affected many experienced investigators world-wide¹⁰.

IMPACT ON FUNDING

Another major concern facing many diabetes researchers is the reduction of funding due to the pandemic, especially from major philanthropic organizations such as JDRF, the American Diabetes Association, and the Helmsley Charitable Trust, to name a few. Although fundraising events have been held virtually since early spring of 2020, many grants funded through these charitable organizations have been forced to be postponed, reduced, and/or revoked due to the economic crisis caused by the pandemic, resulting in a 45% decline in donations¹¹. Interviewed PIs noted that these organizations often fund fellows and trainees with start-up grants, and several reported that these have become quite limited.

Since 2017 the IIDP has been the fortunate recipient of the Islet Award Initiative (IAI)¹² funding from JDRF, which allows approved applicants who are new to human islet research to receive up to 100,000 IEQs per approved applicant at no cost to the young investigator. While there will be no new infusion of funds into the IAI program at this time, JDRF has allowed a no cost extension to the IIDP for this important initiative, through the remainder of 2020 and into the Spring of 2021, at which time the IIDP hopes to resubmit for continued IAI funding.

DATA-DRIVEN RESEARCH OPPORTUNITIES

For the past few years the IIDP has focused on increasing investigator access to additional data related to donors and their isolated islets. This fairly new avenue to scientific data may present an ideal opportunity for the many researchers without full access to their laboratories and common university facilities¹³. In December of 2018, the IIDP provided its researchers with access to data from the IIDP HIPP, which has been providing post-shipment phenotyping on all IIDP shipments. Information including dynamic glucose stimulated insulin and glucagon release data from perfusion assay, hormone content, immunohistochemistry staining, purity assessment and viability evaluation is available on samples sent to HIPP from IIDP islet shipments since July of 2016. In October of 2019, the IIDP merged datasets for donor information from UNOS

and the IICs with pre-shipment and post-shipment islet quality data and developed an online tool to allow IIDP researchers to download all relevant information for specified islet shipments they received. The system allows researchers to set cohort parameters, filter particular data elements, and download files via the Report Generator to allow easy access to and analysis of background data for all their human islet experiments.

By the end of 2020, after proper vetting and NIH/IIDP approval of their research proposal, any researcher will be able to access data on all of the IIDP islet isolations, to conduct hypothesis-driven data mining and statistical analyses via the newly developed IIDP Research Data Repository tool. The IIDP's emphasis on data provisioning may be a glimmer of light for researchers quarantined in their home offices and unable to begin new, physical experiments in their limited laboratories.

RETURN TO PRODUCTION

The IIDP is gradually approaching pre-COVID distribution numbers. Four of the five IICs have been able to bring their staff back into their laboratories in limited numbers, accepting only those pancreata from cadaveric organ donors that have at least two negative SARS-CoV-2 test results for human islet isolation and subsequent distribution to diabetes researchers. In the past three months, IICs have offered human islets from 19 isolations and have distributed a total of 263 shipments, nearing pre-virus numbers of 21 isolations and 271 shipments from January to mid-March 2020. IEQ offers have increased from 812,500 to 1,567,310 IEQs per month, since reopening following the shutdown. However, IIDP numbers are still down - even in the most recent month of September 2020 at the time of this writing, IEQs offered represented 58% of pre-shutdown 2020 monthly average offerings. The number of islets being accepted overall by researchers has increased each month since mid-June (463,170 IEQs accepted) to over 1 million accepted mid-August through mid-September, equaling pre-shutdown distribution numbers.

CONCLUSIONS

Although it appears overall that the numbers for the IIDP distribution program are reaching some normalcy, at the time of this writing the pandemic does not have any clear evidence of disappearing soon in the United States, and most academic research

facilities are still limited in laboratory occupancy by their staff at any given time. COVID testing requirements continue to limit the number of viable pancreas donors. For those pancreata that do qualify, transportation from the Organ Procurement Organization or donor hospital to the IIC remains challenging with respect to the ongoing limitations of commercial airline flights. However, as the IIDP investigators and IICs' staff are all learning to cope with their restrictions and overcome new adversities brought on by the pandemic, with the ongoing support of the IIDP, the quest for a cure is stronger than ever and continues to drive the diabetes research community towards their goals.

ACKNOWLEDGEMENTS:

The authors would like to thank the Islet Isolation Center Directors and staff, especially the following for their input towards this article: Brian Haight, Peter Chlebeck, Dr. Chengyang Liu, and Leonard Medrano. Gratitude as well is given to the IIDP principal investigators who provided their views regarding the pandemic effect on their research, especially through the in-depth interviews provided by Drs. Debbie Thurmond, Bridget Wagner, and Carmella Evans-Molina. The authors also appreciate the assistance of James Cravens, Janice Sowinski, and Andrea Lynch in editing the manuscript.

FUNDING:

BJO and JCN are supported by the NIDDK-funded Integrated Islet Distribution Program (IIDP) (RRID: SCR_014387) at City of Hope, NIH Grant #2UC4DK098085. EL is funded by the Diabetes Research Institute Foundation (DRIF).

ORCID:

Barbara J. Olack: 0000-0001-6645-8215
Elina Linetsky: 0000-0002-7664-7578
Joyce C. Niland: 0000-0002-3001-517X

CONFLICT OF INTEREST:

The authors have no conflicts of interest to disclose.

REFERENCES

1. Ricordi C, Gray DW, Hering BJ, Kaufman DB, Warnock GL, Kneteman NM, Lake SP, London NJ, Soggi C, Alejandro R, Zeng Y, Scharp DW, Viviani G, Falqui L, Tzakis A, Bretzel R, Federlin K, Pozza G., James RFL, Rajotte R, Di Carlo V, Morris PJ, Sutherland DER, Starzl TF, Mintz DH, Lacy PE. Islet isolation assessment in man and large animals. *Acta Diabetol Lat* 1990; 27: 185-195.
2. Integrated Islet Distribution Program. Program Statistics. 2020. Available at: <https://iidp.coh.org/Overview/Program-Statistics>. (Accessed Sept 18, 2020).

3. Ghebreyesus TA. WHO Director-General's opening remarks at the media briefing on COVID-19. March 11, 2020. Available at: <https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020>. (Accessed Sept 24, 2020).
4. Trump D. Proclamation on Declaring a National Emergency Concerning the Novel Coronavirus Disease (COVID-19) Outbreak. Available at: <https://www.whitehouse.gov/presidential-actions/proclamation-declaring-national-emergency-concerning-novel-coronavirus-disease-covid-19-outbreak/>. (Accessed Sept 24, 2020).
5. United States 100th Congress. Public Law 100-707 Nov. 23, 1988 [H.R. 2707] (Stafford Disaster Relief and Emergency Assistance Act)1988. Available at: <https://www.hsdl.org/?view&did=806354>. (Accessed Sept 24, 2020).
6. United States 94th Congress. Public Law 94-412 Sept. 14, 1976 [H.R.3884] (National Emergencies Act)1976. Available at: <https://www.congress.gov/bill/94th-congress/house-bill/3884>. (Accessed Sept 24, 2020).
7. Freedman MJ, Alcantara C, Ulmanu M. How coronavirus grounded the airline industry. April 1, 2020. Available at: <https://www.washingtonpost.com/graphics/2020/business/coronavirus-airline-industry-collapse/>. (Accessed Sept 24, 2020).
8. Myers KR, Tham WY, Yin Y, Cohodes N, Thursby JG, Thursby MC, Schiffer P, Walsh JT, Lakhani KR, Wang D. Unequal effects of the COVID-19 pandemic on scientists. *Nat Hum Behav* 2020; 4: 880-883.
9. Woolston C. Pandemic darkens postdocs' work and career hopes. *Nature* 2020; 585: 309-312.
10. Korbel JO, Stegle O. Effects of the COVID-19 pandemic on life scientists. *Genome Biol* 2020; 21: 113.
11. McCarthy M. Saving diabetes research from the COVID-19 crush. 2020. Available at: <https://www.healthline.com/diabetesmine/diabetes-research-pandemic-crush>. (Accessed Sept 18, 2020).
12. Integrated Islet Distribution Program. Islet Award Initiative. 2020. Available at: <https://iidp.coh.org/Investigators/Islet-Award-Initiative>. (Accessed Sept 24, 2020).
13. Forrester N. How the coronavirus pandemic is changing virtual science communication. *Nature Career Q&A* 2020; 10.1038/d41586-020-02075-0.