INTEGRATED ISLET DISTRIBUTION PROGRAM

The Newsletter

A Quarterly Update of IIDP Activities of Interest

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Inside this Issue

IIDP Expands Investigators' Abilities to Generate Customized Reports with New Data Hub Portal

The IIDP database team has added enhanced capability for investigators to generate and view data reports for their islet shipments. Recently, the team developed two different report generation tools for our researchers to capture either United Network for Organ Sharing (UNOS) data for specific isolations from which they obtained islets (UNOS Data Download) or to produce an Islet Data Checklist that is now mandated by certain journals (*Diabetes and Diabetologia*). The IIDP is happy to announce that the expansion of these search options is now available to investigators within the new **Data Hub**. This interactive tool allows users to view and download a wide range of data elements. In addition to the previously released programmed reports, we now feature an easy-to-use Dynamic Dataset Filtering system where users can quickly choose data about their shipments by different categories. It also offers a Report Generator System that allows users to view and/or download reports in Excel or CSV format. Once an investigator sets specific filters and/or shipments which they are interested in for their experimental analysis, those parameters can be saved for future re-use or modified as needed as your database grows.

The link to the Data Hub is displayed at the top of each investigator's Dashboard, on the secure site launch page (Figure 1). Next, parameters can be set for batch type, center provider, and donor categories (Figure 2). After choosing the shipments of interest, investigators will have the opportunity to choose pre-programmed reports like the Checklist, or choose individual data points to customize a user-defined report.

The IIDP expects to provide additional pre-programmed reports in the future and welcomes any suggestions by our investigators for additional summaries. These new features are meant to assist IIDP researchers with data analyses, presentations, and publications. As always, your feedback and helpful input is always welcome.

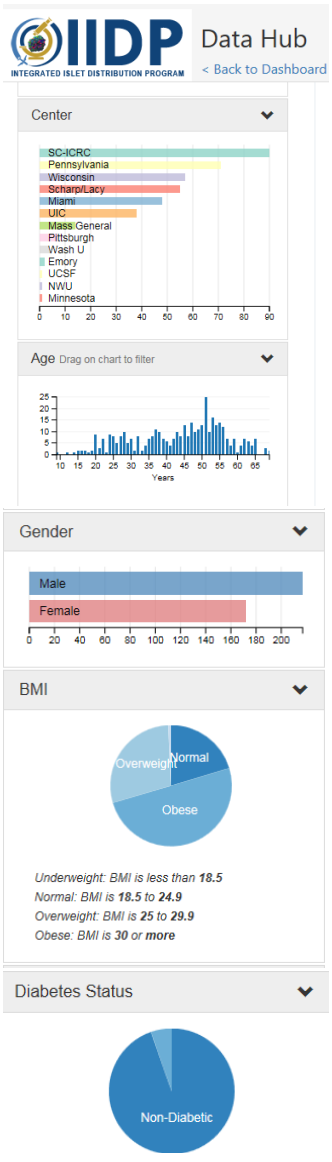

Figure 2. Examples of Filters that may be chosen.

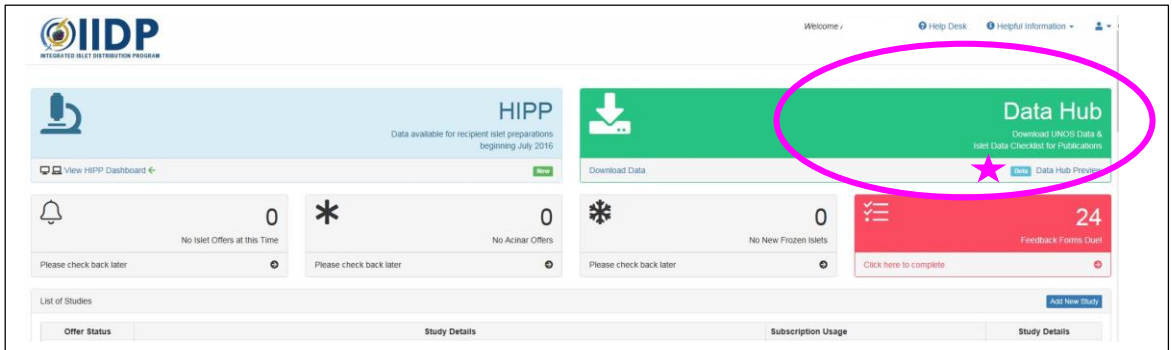

Figure 1. Click on the Data Hub Link ★ to enter the portal and set the parameters for your research.

New IIDP Features

The IIDP is dedicated to facilitating and supporting leading edge diabetes research which is reliant on human islets. Here are our latest updates:

New data search application for all IIDP information: *The IIDP has just released a new data search and download application for investigators to filter specific data from chosen isolations. (See Data Hub article on page 1 for more information.)*

Distribution of Non-Islet Pancreatic (Acinar) Tissue now with added trypsin Inhibitor: *To improve the quality of Non-islet Pancreatic Tissue (NIPT) the IIDP has been requested to add trypsin inhibitor to all tissues being distributed. This process began in mid-September, 2019. (See article to the right for additional details.)*

Change in Flash Frozen Islet aliquot size: *All frozen islet aliquots processed after September 1st, 2019 will be available at 1,000 IEQ/sample. (See article to the right)*

Bonus Islets increase from 5-10%, free of charge: *Beginning September 3rd, the IIDP was granted permission from NIH to increase the amount of bonus islets added to shipments when extras are available, from 5% to now 10%. The IIDP hopes that these additional islets will help to alleviate any discrepancies in post shipment islet numbers received by the investigators without any additional expense to the IIDP Isolation Centers.*

Islet Award Initiative (IAI): *The next application deadline is January 7th, 2020! Go to https://iidp.coh.org/ for more details. Please contact Janice Sowinski jsowinski@coh.org or Carol Swanson cswanson@coh.org for more information.*

Pancreas sections: *Julie Hom will now be the contact for IIDP Centers to send the fixed pancreas blocks from which the islets are isolated for sectioning and staining. Any investigators interested in obtaining sections, may contact Julie at jhom@coh.org .*

Follow IIDP on Social Media

*Visit our website at **https://iidp.coh.org***
*Follow us on Twitter: **@iidp_at_coh***
*Like us on Facebook: **@IntegratedIsletDistributionProgram***
*Contact us at **IIDP-email@coh.org** Call us at **626-536-5641***

Think Out of the Box! Can You Use Tissues Other than Fresh Islets for Portions of your Experiments?

Non-Islet Pancreatic Tissue (NIPT): In the May 2019 Newsletter, a new initiative was announced to IIDP investigators that would allow researchers to receive fresh and/or frozen NIPT, a byproduct of the process of pancreatic digestion for islet isolation. This new NIPT program was developed in response to requests from the diabetes research community. After four months of broadcasting to those investigators who expressed interest in NIPT, which is mostly acinar tissue, the acceptance of these broadcasts has been modest. In the last newsletter, Dr. Carmella Evans-Molina, IIDP co-PI, wrote an informational editorial on the exciting publications focusing on such interesting work as exocrine dysfunction as part of diabetes pathogenesis (PMID 26358584), the relationship of serum trypsinogen levels in persons with multiple autoantibodies and established type 1 diabetes compared to controls (PMID 28115475), and the utilization of acinar tissue for β cell replacement and differentiation strategies (PMID 25402613).

The IIDP is again publicizing this new opportunity to receive pancreatic tissue that could possibly be used for some of the experiments listed above, as well as being a tissue source for DNA isolation and other scientific testing at a much less expensive rate ($250/shipment) then fresh, purified human islets. In response to another suggestion from IIDP researchers, the IIDP is now investing in the addition of Trypsin Inhibitor from Glycine Max (soybean) in the NIPT holding and transport media to ensure quality tissue upon receipt. Sign up now! Don't delay for this great deal!

Flash Frozen Islets: The IIDP has been supplying flash frozen islets to investigators since 2010, but for years the aliquots available were frozen at 10,000 IEQ per sample, a number requested by investigators mainly for protein extraction or RNA isolation studies. At that time, assays were not as efficient as current methods and required numbers of this denomination. In 2015, centers were asked to reduce the aliquot numbers to 5,000 IEQ per tube, which lowered the cost of each aliquot by half. As of September 1st, 2019, IIDP Centers will now be freezing islets that have not been distributed through broadcasts in aliquots of 1,000 IEQ per sample, and no more than 10 samples per isolation. This change should increase the variety of islets frozen and also in the newer isolations, significantly decrease the cost for this valuable tissue. For those researchers who are interested in comparing specific factors from multiple islet isolations and performing these assays at the same time, frozen islet aliquots may be the perfect solution! The IIDP's priority is the distribution of live, human islets for experiments, but the alternative of flash frozen islets may be an optimal solution for many.

FEATURED IIDP ISLET ISOLATION CENTER:

UNIVERSITY OF PENNSYLVANIA

The Islet Isolation Team at the University of Pennsylvania has been part of the islet distribution program at City of Hope since its inception in 2002. Ali Naji, M.D., PH.D., the J. William White Professor of Surgical Research, Associate Director, Institute for Diabetes, Obesity, and Metabolism, University of Pennsylvania School of Medicine, and recipient of the Thomas E. Starzl Prize in Surgery and Immunology in April of 2018 for his years as an organ transplant surgeon, has led the islet laboratory for over 40 years. In addition to providing islets to the IIDP, the team at U Penn also continues to run an active islet transplant program, and Dr. Naji is the Principal Investigator of the Human Pancreas Analysis Program (HPAP), a consortium which brings together investigators with expertise in pancreas procurement and islet isolation, immunology, genomics, epigenomics and islet bioenergetics to study cells and tissues relevant to beta cell loss of type 1 diabetes mellitus. A new focus of the U Penn Islet Lab is the isolation and distribution of islets from pediatric and adolescent donors, something that has not been offered previously by the IIDP. U Penn has been a pioneer in young islet donor isolations, a process that is difficult to master and normally yields islets that are mostly imbedded in acinar tissue. Dr. Naji hopes that this scarce resource will be beneficial to investigators accepting IIDP islets and will provide novel results to those in the field of diabetes research.

Thank You for Your 14 Years of Service to the IIDP
Martha Antler

Martha Antler has been a familiar name and face in the IIDP organization even before the distribution of human islets began at City of Hope. She has been the contact for all IIDP and IAI applicants, the recipient of all histology samples sent from each pancreas isolated by the IIDP Centers, and the point person to make sure those samples are prepared for histological sectioning and posting on our website. Martha has scheduled a multitude of meetings, conference calls, and Exchange Sessions over the years and has often been the face that investigators and Center staff see at the IIDP Booths at national meetings and symposiums. She contributed many other important administrative responsibilities for the islet program.

As of the end of August, "M", as she was known to many of us, ended her career with the IIDP and the City of Hope. We all wish her success, happiness, and fun in her future endeavors and thank her for her dedication to the field of diabetes research and her very special interest in finding the cure.

Love you M!

The IIDP Team

U Penn Islet Isolation Team: *(left)* **Ali Naji, MD, PhD** – PI and Transplant Surgeon. *(right)* **Xi Zuo, MD** - Islet Isolation / Function Assays / Islet Shipment; **Yanijing Li** - Islet Isolation / Functional Assays / Islet Shipment; **Chengyang Liu, MD –** Lab Director; **Zaw Min, MD –** Inventory Manager / Islet Isolation / Islet Shipment; **Wei Wang, MD** - Islet Isolation / Histology Specialist.

Featured Investigator Research Publication

Utilizing Human Islets Provided through the IIDP

Differential expression and release of exosomal miRNAs by human islets under inflammatory and hypoxic stress.

Saravanan PB, Vasu S, Yoshimatsu G, Darden CM, Wang X, Gu J, Lawrence MC, Naziruddin B

Diabetologia. 2019 Oct;62(10):1901-1914. doi: 10.1007/s00125-019-4950-x. Epub 2019 Aug 1.

Abstract:

AIMS/HYPOTHESIS:

Pancreatic islets produce non-coding microRNAs (miRNAs) that regulate islet cell function and survival. Our earlier investigations revealed that human islets undergo significant damage due to various types of stresses following transplantation and release miRNAs. Here, we sought to identify and validate exosomal miRNAs (exo-miRNAs) produced by human islets under conditions of cellular stress, preceding loss of cell function and death. We also aimed to identify islet stress signalling pathways targeted by exo-miRNAs to elucidate potential regulatory roles in islet cell stress.

METHODS:

Human islets were subjected to proinflammatory cytokine and hypoxic cell stress and miRNA from exosomes was isolated for RNA sequencing and analysis. Stress-induced exo-miRNAs were evaluated for kinetics of expression and release by intact islets for up to 48 h exposure to cytokines and hypoxia. A subset of stress-induced exo-miRNAs were assessed for recovery and detection as biomarkers of islet cell stress in a diabetic nude mouse xenotransplant model and in patients undergoing total pancreatectomy with islet auto-transplantation (TPIAT). Genes and signalling pathways targeted by stress-induced exo-miRNAs were identified by Kyoto Encyclopedia of Genes and Genomes (KEGG) analysis and direct interactions of miRNAs with downstream signalling targets were validated in human islet cells using the miRNA Tests for Read Analysis and Prediction (MirTrap) system.

RESULTS:

Global exo-miRNA sequencing revealed that 879 miRNA species were released from human islets and 190 islet exo-miRNAs were differentially expressed in response to proinflammatory cytokines, hypoxia or both. Release of exo-miRNAs hsa-miR-29b-3p and hsa-miR-216a-5p was detected within 6 h of exposure to cytokines and hypoxia. The remaining subset of stress-induced exo-miRNAs, including hsa-miR-148a-3p and islet cell damage marker hsa-miR-375, showed delayed release at 24-48 h, correlating with apoptosis and cell death. Stress and damage exo-miRNAs were significantly elevated in the circulation in human-to-mouse xenotransplant models and in human transplant recipients. Elevated blood exo-miRNAs negatively correlated with post-transplant islet function based on comparisons of stress and damage exo-miRNA indices *(continued)*

Program Statistics

2019	Cumulative
# Subscribers*	
156	380
# Shipments*	
950	13,426
# IEQs Distributed*	
8.3 Million	257.1 Million
# Publications**	
35	702

***Since 2004** ****Since 2002**

with Secretory Unit of Islet Transplant Objects (SUITO) indices. KEGG analysis and further validation of exo-miRNA targets by MirTrap analysis revealed significant enrichment of islet mRNAs involved in phosphoinositide 3-kinase/Akt and mitogen-activated protein kinase signalling pathways.

CONCLUSIONS/INTERPRETATION:

The study identifies exo-miRNAs differentially expressed and released by islets in response to damage and stress. These exo-miRNAs could serve as potential biomarkers for assessing islet damage and predicting outcomes in islet transplantation. Notably, exo-miRNAs 29b-3p and 216a-5p could be detected in islets prior to damage-released miRNAs and indicators of cellular apoptosis and death. Thus, these stress-induced exo-miRNAs may have potential diagnostic value for detecting early islet stress prior to progressive loss of islet cell mass and function. Further investigations are warranted to investigate the utility of these exo-miRNAs as early indicators of islet cell stress during prediabetic conditions. (*Click here for the full paper.)*

Congratulations Carmella!

The IIDP would like to recognize the newest achievement by Co-Principal Investigator, Carmella Evans-Molina, M.D., Ph. D. as director of the Center for Diabetes and Metabolic Diseases at Indiana University School of Medicine. She succeeds IIDP investigator, Dr. Raghu Mirmira, M.D., Ph. D., who was the director for the past 5 years. For more info on Dr. Evans-Molina please see the original article at:

https://medicine.iu.edu/news/2019/10/evans-molina-named-director-of-diabetes-research-center/

IIDP Publication Reminders:

1. Please remember to submit all publications generated from IIDP islets, to *Carol Swanson* at *cswanson@coh.org* for cataloging on our website.
2. The following acknowledgement should be documented in all publications where IIDP human Islets were used:
   Human pancreatic islets were provided by the NIDDK-funded Integrated Islet Distribution Program (IIDP) at City of Hope, NIH Grant # 2UC4DK098085.
3. **RRID** is an asset to your current and future experiments; be sure to include in all publications!
4. For a **complete list** of publications that utilized human islets provided through the IIDP, go to https://iidp.coh.org/Publications.