Islet Cell Resource Consortium
Administrative and Bioinformatics Coordinating Center

The ICR Newsletter

Volume 3, Issue 1, February 28, 2009

RFP Issued by NIH Begins the Transition for Future Human Islet Distribution for Research

At the October 2008 Steering Committee meeting of the Islet Cell Resource (ICR) Consortium, the National Center for Research Resources confirmed that the ICR grant will end on July 31, 2009. Later that month, Dr. Dan Rosenblum, ICR Program Officer, informed investigators approved to receive islets through the ICR that the resource would terminate. He also informed them of the NIH plan to continue its support of a system for distributing high quality human islets to approved investigators for laboratory research. When support for the ICR Consortium ends on July 31, 2009, the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) will take the lead in the support of human cadaver pancreatic islet distribution. The NIDDK will provide additional information in a program announcement.

On December 29th, 2008, the NIH issued Request for Proposal (RFP) Number NIH-NIDDK-08-099-SB for an Islet Distribution Coordinating Center. The RFP clearly states that the NIDDK plans to contract with a coordination center to manage the distribution of human cadaver pancreatic islet cells. The contract will enable participants in the Clinical Islet Transplantation Consortium (CIT) who have isolated islet cells intended for but not suitable for clinical transplant to provide islets for laboratory investigation. The current members of the CIT Consortium are: University of Miami, University of Minnesota, University of Edmonton, University of Pennsylvania, Emory University, University of California at San Francisco, University of Illinois at Chicago, and Northwestern University. It is anticipated that about half of the islet cell isolations intended for transplant might not meet clinical standards and could be made available to laboratory investigators. In addition, the RFP mentions the possibility that the Coordinating Center might subcontract with one or more additional islet production facilities to supplement the CIT production of islet cells. The additional production centers could be selected jointly by the contractor, an External Evaluating Committee and the Project Officer.

Executive Highlights

On February 17th, 2009 President Barack Obama signed the American Recovery and Reinvestment Act into law of which $10.4 billion was made available to the National Institutes of Health (NIH) through September of 2010. According to a statement issued on February 20th by Raynard S. Kington, Acting Director of the NIH, the majority of the funds are appropriated for the support of scientific research priorities including $7.4 billion to be transferred to the Institutes, Centers, and Common Fund based on a percentage-based formula.

Many types of funding mechanisms will be supported, but, in general, NIH will focus scientific activities in several areas:

1) Recently peer reviewed highly meritorious R01 and similar mechanisms capable of making significant advances in two years. R01 are projects proposed directly from scientists across the country.

2) New R01 applications that have a reasonable expectation of making progress in two years. The adherence to this time frame is in direct response to the spirit of the law.

3) Accelerating the tempo of ongoing science through targeted supplements to current grants. (*For example, to competitively expand the scope of current research awards or supplement an existing award with additional support for infrastructure (e.g., equipment) that will be used in the two-year availability of these funds.)*

4) Supporting new types of activities that fit into the structure of the ARRA. (*For example, it will support a reasonable number of awards to jump start the new NIH Challenge Grant program. This program is designed to focus on health and science problems where progress can be expected in two years. The number of awards and amount of funds will be determined, based on the scientific merit and the quality of applications.)*

5) Additional funding mechanisms as appropriate.

According to Kington, "The impact of this stimulus to scientists cannot be overstated."

The full text of Kington's statement can be found at *http://www.aamc.org/advocacy/library/laborhhs/22009niharracall.pdf*

The Islet Distributing Coordinating Center contract will extend from August 1, 2009 through July 31, 2014. Applications for the contract were due February 11, 2009. The ABCC has submitted an application for this contract and sincerely hopes to be able to continue working with all ICR members and investigators into the distant future if successful for this contract bid.

The ICR Newsletter

Investigator Research Paper

Survey of the Human Pancreatic Beta Cell G1/S Proteome Reveals a Potential Therapeutic Role for Cdk-6 and Cyclin D1 in Enhancing Human Beta Cell Replication and Function in Vivo. Fiaschi-Taesch N, Bigatel TA, Sicari B, Takane KK, Salim F, Velazquez-Garcia S, Harb G, Selk K, Cozar-Castellano I, Stewart AF. **Diabetes: 2009 Jan 9**

Objectives: To comprehensively inventory the proteins that control the G1/S cell cycle checkpoint in the human islet, and compare them to those in the murine islet. To determine if these might therapeutically enhance human beta cell replication. To determine if human beta cell replication can be demonstrated in an in vivo model. To enhance human beta cell function in vivo. Research Design and Methods: 34 G1/S regulatory proteins were examined in human islets. Effects of adenoviruses expressing cdk-6, cdk-4 and cyclin D(1) on proliferation in human beta cells was studied both in vitro and in an in vivo model. Results: Multiple differences between murine and human islets occur, most strikingly the presence of cdk-6 in human beta cells vs. its low abundance in the murine islet. Cdk-6 and cyclin D(1) in vitro led to marked activation of retinoblastoma protein phosphorylation and cell cycle progression, with no induction of cell death. Human islets transduced with cdk-6 and cyclin D(1) were transplanted into diabetic NOD-SCID mice and markedly outperformed native human islets in vivo, (*continued on page 3)*

New Features from the ABCC

✸Islet Study Collaborations✸The ABCC now has the ability to link together different studies that have an agreed upon collaboration so that each participant in the collaboration will get islets from the same preparation (See full article "ABCC Allocation System Can Now Allow Collaborative Studies to Obtain the Same Islet Preparations" on page 5 of this Newsletter issue.)

✸Easier Identification of Islet Shipment Confirmations✸ Through our web-based Helpdesk, we learned from a PI that better identification of islet shipments that were confirmed or denied was needed by our users. The ABCC now identifies by UNOS number and ICR Center name the islets shipments that are being confirmed or denied. This may be helpful in the event that multiple shipment alerts arrive on the same day.

✸Drop-down Updates✸The ABCC has added new drop-downs for some of the commonly used additives and enzyme units to make data entry easier. *Remember to use the Helpdesk Icon to alert us to any problems.*

✸Flash Frozen Islets✸ Watch for the new option to distribute and receive flash frozen, non-viable islets from preparations that are not placed through our regular distribution method. ICR centers will soon have the option to list aliquots of 10,000 IEQs in an inventory list and interested users may request shipment of the stored preparations. *More info to be provided by email in the coming weeks!*

MEET THE STAFF

Dajun Qian
Senior Statistician

Dr. Dajun Qian is an Assistant Research Scientist at the City of Hope National Medical Center. He received his undergraduate and graduate degrees in Applied Mathematics and Statistics from Fudan University in China, and his doctoral degree in Biostatistics from the University of Southern California. His research involves the development and evaluation of statistical methods for genomic data analysis in areas of haplotype reconstruction, detection of copy number variation, and association testing of complex human traits. He has co-authored over 30 and first-authored 5 peer-reviewed papers in statistical genetics and biomedical research. Dajun has been a senior statistician for the Administrative and Bioinformatics Coordinating Center (ABCC) for the National Islet Cell Resource Consortium (ICR) since 2002. He reviews study design and analysis plan in a range of protocols for hypothesis-driven, post-hoc exploratory and genomic data studies. He developed the multi-objective optimization algorithm for the ICR web-based islet allocation system which is used by the ABCC for the fair distribution of human islets for research. Dajun moved to California over 15 years ago and now lives in Rancho Cucamonga with his wife. He enjoys family, sports and traveling, and plays soccer on Sundays.

The ICR Newsletter

FEATURED ICR:

UNIVERSITY OF MINNESOTA

The ICR center at the University of Minnesota (UM) formally part of the Diabetes Institute for Immunology and Transplantation is now part of the newly named Schulze Diabetes Institute after a generous gift for future diabetes research from the Schulze Family Foundation. UM-ICR, under the leadership of Dr. Bernhard Hering, has been part of the ICR consortium since 2001 and has been a leader in human islet and pancreas transplantation since the early 1970's under the guidance of Dr. David Sutherland. The UM transplant program has notable achievements in the advancement of innovative tolerance protocols as well as the largest list of successful auto-islet transplants in the world. Dr. Hering and his team are also at the forefront of xenotransplantation as a therapy for diabetes and have developed a large research program with porcine islets as a possible source for transplant. The UM ICR has been instrumental in working with the consortium in developing the standardized shipping protocol and under the leadership of Drs Papas and Hering has developed prominent expertise in islet viability assays, specializing in the oxygen consumption rate (OCR) as a tool for measuring potency, and has used the validated potency assay based on OCR to evaluate and implement improvements in pancreas preservation, islet isolation, and islet culture protocols.

The Minnesota group has shipped over 7.8 million islets to ICR investigators for research studies and has transplanted 29 diabetic patients with islet allografts since becoming an ICR center. The UM human islet transplant program is known for its high success rate after single-donor islet transplantation and its favorable long-term insulin-independent islet allograft survival rates.

ICR Director: Bernhard Hering **ICR Co-Director:** Klearchos Papas **Islet Core Director:** Balamurugan Appakalai **Islet Core Associate Director:** Tom Gilmore **Islet Laboratory Supervisor:** Josh Wilheim **Islet Core Research Fellow:** Gopalakrishnan Loganathan **Islet Quality Control/Assurance Manager:** Kate Mueller **Research & Development:** Stathis Avgoustiniatos **Executive Office & Admin Specialist:** Denice Dudero **Nurse Coordinator:** Janet Bricher **Site Coordinator:** Sandra C. White

Investigator Research Paper

Continued from page 2) maintaining glucose control for the entire six weeks of study. Conclusions: The human G1/S proteome is described for the first time. Human islets are unlike their rodent counterparts in that they contain easily measurable cdk-6. Cdk-6 overexpression, alone or in combination with cyclin D(1) strikingly stimulates human beta cell replication, both in vitro as well as in vivo, without inducing cell death or loss of function. Using this model, human beta cell replication can be induced and studied in vivo.

This section of the Newsletter will feature an abstract from a peer-reviewed paper reporting scientific studies conducted using islets received through the ICR Human Islet Distribution system. To alert us to a recently published paper that fits this profile, please contact us at abcc@coh.org.

2009 Rachmiel Levine Diabetes Symposium

March 18-21, 2009

***Disney's Grand California Hotel*® and Spa, Anaheim, CA**

Discounted registration fees if you are an ICR Scientist!

Please direct questions to the Program Coordinator, at (800) 679-4673 or levinesymposium@coh.org.

Full Program Online at www.levinesymposium.com

The ICR Newsletter

Coming Events:

9th Annual Rachmiel Levine Diabetes Symposium
http://www.sciencering.com/forums/viewtopic.php?t=298
March 18th-21st, 2009, Disney's Grand Californian Hotel and Spa - Anaheim, CA

American Transplant Congress
http://www.atcmeeting.org/
May 30th - June 3rd, 2009, Boston, MA

American Diabetes Association 69th Scientific Sessions
http://professional.diabetes.org/Congress_Display.aspx?TYP=9&SID=128&CID=57909
June 5th-9th, Morial Convention Center - New Orleans, LA

Endocrine Society Annual Meeting
June 5th-9th, Washington, DC

ICR Consortium Statistics

Isolations Reported in the ABCC Database				
To Date	Total	Clinical	Research	Not Used*
2009	42	5	35	2
Cumulative**	1197	210	918	69

IEQs Reported in the ABCC Database				
To Date	Total	Clinical	Research	Not Used*
2009	1,568,054	0***	1,135,254	432,800
Cumulative**	320,304,914	93,331,210	220,037,882	6,935,822

ICR Basic Science Distribution Program Activity			
To Date	# Approved Protocols	#Shipments	#IEQs Distributed
2009	3	143	3,931,592
Cumulative**	176	2953	82,616,277

**Not Used-Poor quality pancreata and/or islets; or no permission for research*
***Cumulative data reported from 12/1/2004 to 2/25/2009*
****The 5 clinical isolations entered in 2009 are currently missing post purification IEQ counts*

ICR Need for Subscription Fees

By Janice Sowinski

In 2008, the NIH, the ICR Steering Committee, and the ICR ABCC evaluated the supply versus demand issues associated with the distribution of human islets through the ICR centers, and cost reimbursement to the ICR islet isolation centers. It was estimated that around 23 million islets would be distributed by these centers in 2008 while the request for islets was calculated at 58 million, more than twice the available supply. A modest cost sharing program for accessing human islets was put in place in January 2009, in order to supplement the reimbursement of the islet isolation centers for the cost of isolating high quality human islets and to assure that islets are distributed to dedicated projects.

In October 2008 NIH issued a notice to all ICR investigators that a subscription fee process would be implemented for users to access human islets. The fee schedule reflects the number of islets needed for a six month period, and the announcement provided lead time necessary to secure the subscription fee funding. Although NIH requested payment of the fee by December 31, 2008 if investigators wished to continue to receive islets for 2009, a grace period was issued through January 31, 2009 to ensure that all users had ample time to pay the semi-annual subscription fee. Since NIH and JDRF funding only partially reimburses the ICR centers for providing these islets, proceeds from the subscription fee will be used to augment the reimbursement of islet isolation centers.

As of January 31, 2009, among 115 active approved studies, 57 investigators (approximately 50%) have paid the subscription fee. Part of the delay for the remaining investigators is due to the need to identify supply funds that can be used to pay for these biomaterials. The ABCC is anticipating payment from at least an additional 12% of islet users in the very near future.

The ICR Newsletter

ABCC Allocation System Can Now Allow Collaborative Studies to Obtain the Same Islet Preparations

By James Cravens

In our ongoing efforts to meet the needs of our system's users, the ABCC has upgraded the Islet Allocation System to accommodate collaborations among individual studies (investigators). When two or more ICR-approved studies utilize this option, the Allocation System will treat the members of a collaborative group as "linked", and all studies within the group will receive islet offers from the same isolations. This allows the collaborators to compare their results based on a common batch of islets or work together towards a single result using the same islets.

Although the system will make offers to all members of the group simultaneously, each study will still have the freedom to accept or reject offers individually. This allows each study to maintain its own shipment history and customized requests for islet quantity.

Before setting up a collaboration with other ICR-approved investigators, each member study must be aware of the inherent limitations of linking your study to one or more other studies. Although each study is able to request an islet quantity based exclusively on the needs of that particular study, other islet parameters will need to be synchronized among all member studies of the collaborative group. Specifically, purity, viability, shipment frequency, islet type, and center preference criteria will need to be synchronized among all studies in the collaboration. Also, if one study is ineligible or on hold, the entire group will be ineligible for islet offers as well. Therefore, there will be added pressure to complete User Feedback forms and return the shipping materials in a timely manner.

If you have questions about this new option for collaborative groups or are interested in setting up a collaboration with other ICR-approved studies, contact James Cravens at jcravens@coh.org.

Karla Edge, Miami Islet Transplant Recipient, Is Grateful for Her New Life

Dear Researchers,

My name is Karla Edge and I became a type I diabetic when I was 6 years old. I quickly became a very brittle diabetic and became unaware of hypoglycemic reactions by the age of 25. I was able to have two miracle children but when I became pregnant with our first daughter, my diabetes became even more brittle. My diabetes became so devastating that I could no longer drive a car. I had to retire from work and could not be alone because my family feared the next reaction might be the last.

One day my sister informed me that the Diabetes Research Institute (DRI) in Miami was doing islet transplants for people with severe diabetes symptoms. I downloaded and sent in an application for the study.

Dr. Rudolfo Alejandro contacted me within a month and said that he felt I would be a good candidate. I did all the pretesting and met with both Dr. David Baidal and Dr. Tatiana Froud from the DRI.

I was put on the waiting list and received that wonderful call from Dr. Baidal in less than two weeks after my listing. He said they had some more testing to do but felt like they had found a match for me. While I was on the phone with Dr. Baidal I was checking my blood sugar; it was 35 mg/dl. The next morning my husband, Mike and I were on our way to Miami to receive my transplant. On September 19, 2005 Dr. Froud injected the islets and they seemed to start working immediately! Within two weeks time I was totally off insulin with only one donor's islets.

My quality of life after the transplant has improved so much. I didn't realize I could ever feel so good. My family and I never have to worry about my uncontrolled blood sugars. Every time I check my blood glucose, it is perfect! My husband used to be worried all the time about my blood sugar going too low. But now he can have a good night's sleep.

I would like to thank Drs. Alejandro, Froud, Baidal and my ARNP Andrea Curry for the excellent care they continue to give me, and the opportunity for me to have a more blessed life for myself and my family.

Karla