Islet Cell Resource Consortium
Administrative and Bioinformatics Coordinating Center

The ICR Newsletter

Volume 2, Issue 2, May 30, 2008

ABCC Sponsored Counting Workshop for Islet Researchers to be Held at the ADA Meeting in San Francisco Next Week

All are invited to attend one of two workshops to be held during the 68th Scientific Sessions of the American Diabetes Association in San Francisco. The interactive presentations and panel discussions will be held Saturday, June 7th from 6:30-8:00pm in the Pacific Room C of the SF Marriott at 55 Fourth St., San Francisco, CA 94103 and on Monday June 9th in the Nob Hill Room A&B at the Marriott. The workshop will focus on the needs of human islet recipients of the ICR distribution program and the transition from working with rodent islets to research with human islets. Not only will registrants receive an ICR Counting Manual that includes exercises with sized photos of human islets and the opportunity to have your counts compared to those of experts in the field, but the ABCC will present methods for mixing your preparations to insure a homogenous suspension of islets, techniques for sampling islet preparations, and tips on equipment that might make your counting simpler and more accurate. We will also supply you with an instructional CD that you can take back to your laboratory and use as a teaching tool for those technicians at your center that were not able to attend our seminar. Registration for the upcoming workshop can be made at http://icr.coh.org/workshops.asp. There is no fee for attending this teaching workshop but we do require registration prior to the event. We encourage all to participate!

Executive Highlights

The National Institutes of Health (NIH) supports multi-faceted fundamental research and clinical programs requiring human pancreatic β-cells. Access to this resource provides a cornerstone to understanding the pathogenesis of diabetes and the hopes for curative treatments including islet transplantation. Due to their respective functional disparities, it is also evident that human islet investigations cannot always be supplanted with islets obtained from murine models. Through NIH and the Juvenile Diabetes Research Foundation funding, the ICR's provide an invaluable service to the research community by producing and distributing high quality human islets in North America. The success of this program is witnessed by the enormous, yet bittersweet growth in both the number of investigators requesting human islets and the numbers of islets that have been distributed. We are gratified by the diverse and poignant research activities in human islet cell biology but are also concerned that available funds cannot fully sustain the growing programs. This concern will require the development and implementation of equitable policies in the near future assuring a continuum of these precious resources. We invite you to contribute your suggestions for how to best approach this dilemma as the policies rapidly evolve. Please direct all comments to Janice Sowinski in the ICR Coordinating Center (JSowinski@coh.org).

Mike Appel

Director, Islet Biology and Transplantation Research Program, NIH/NIDDK

The Critical Need for Human Islets for Diabetes Research

An Editorial by Dr. Andrew Stewart, Chairman of the ICR Human Islet Working Group

The Need and Impact of the Islet Cell Resource (ICR) Consortium as a Source of Human Islets for Research.

For the better part of the last century, including the last decade, most pancreatic beta cell research was performed in animals, such as mice, rats, hamsters, guinea pigs, dogs, pigs, and monkeys. While now manifestly inaccurate, it was until recently widely assumed that human islets and beta cells would perform precisely the same as their counterparts in lower species. The growing appreciation that this is not the case has helped to focus attention on the inescapable need to study human beta cells. Concurrently, the unique ability of the ICR to generate human islets for research has allowed many laboratories around the country to begin to study human beta cells, and this has contributed to the growing list, of ways in which human beta cells differ from their mouse and rat counterparts. This new standard, in turn, coupled with the growing awareness of the ICRC in the beta cell community, has drawn increasing numbers of what were formerly rodent beta cell researchers into the realm of human beta cell biology. Indeed, increasingly, observations in mouse and rat beta cells are being held to a new standard in beta cell grant and manuscript reviews: events observed in rodents need to be confirmed and shown to be relevant to human beta cells. In quantitative terms, the growth in human islet distribution and use for research by the ICR Consortium has grown immensely. For example, in 2004, there were 19 institutions that requested human islets for research from the ICR. By 2006, this number had grown to 75, and had further increased to 94 by the February 2008. Thus, between 2004 and 2008, there was an approximate 400% increase in the number of institutions requesting human islets for research. Importantly, within any single institution, the number of investigators using human islets has also grown. In 2004, there were 23 investigators requesting human islets for research from the ICR. By 2006, this number had grown to 109, and by February of 2008, 147 investigators were using ICR-derived human islets for research, an increase of 540%. Looked at in another way, the absolute number of human islets distributed for research in 2004 was 2.9 million. By 2006, this had increased to 18.1 million, and by February 2008 was on pace to reach 40 million human islets, an increase of some 1200%. *(Continued on page 5)*

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Islet Research History Lessons – Culturing for Transplant

Since Islets of Langerhans were first discovered as the source of insulin, researchers have had different reasons to develop culturing techniques that would allow them to work with the fragile cells *in vitro*. Those interested in transplantation as a possible treatment of diabetes, saw the opportunity of working with isolated islets as a source of tissue that could possibly be manipulated in culture prior to transplantation in order to reduce the immunogenicity of the tissue, something impossible to do with a whole pancreas. Techniques began in the late 70's to modulate the islets with different culture methods. Kevin Lafferty employed exposure of islet cultures to high oxygen levels in order to destroy the oxygen sensitive "passenger leukocytes" and reduce immunogenicity. Paul Lacy's group found that prolonged culture at low temperature (24°C) achieved similar results in rodent transplant studies. It was around this time in the 80's that the common islet media switched from Roswell Park Memorial Institute (RPMI) 1640 Medium, a formula designed for the culturing of lymphoid cells, to Connaught Medical Research Laboratories (CMRL) 1066, first designed as a serum-free media. Although the islets seemed to have little preference, the passenger leukocytes were not nearly as happy in the CMRL and the new "islet media" was born. Although many laboratories have added their magic supplements to the mixture over the years, CMRL 1066 is still the base media for islet culturing in clinical transplant laboratories.

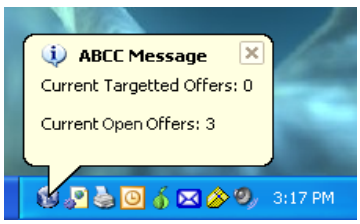
Role of the cAMP sensor Epac as a determinant of KATP channel ATP sensitivity in human pancreatic β-cells and rat INS-1 cells

Guoxin Kang, Colin A. Leech, Oleg G. Chepurny, William A. Coetzee and George G. Holz

J Physiol. 2008 Mar 1;586(5):1307-19

Protein kinase A (PKA)-independent actions of adenosine 3_,5_-cyclic monophosphate (cAMP) are mediated by Epac, a cAMP sensor expressed in pancreatic β-cells. Evidence that Epac might mediate the cAMP-dependent inhibition of β-cell ATP-sensitive K+ channels (KATP) was provided by one prior study of human β-cells and a rat insulin-secreting cell line (INS-1 cells) in which it was demonstrated that an Epac-selective cAMP analogue (ESCA) inhibited a sulphonylurea-sensitive K+ current measured under conditions of whole-cell recording. Using excised patches of plasma membrane derived from human β-cells and rat INS-1 cells, we now report that 2_-*O*-Me-cAMP, an ESCA that activates Epac but not PKA, sensitizes single KATP channels to the inhibitory effect of ATP, thereby reducing channel activity. In the presence of 2_-*O*-Me-cAMP (50 μM), the dose–response relationship describing ATP-dependent inhibition of KATP channel activity (*NP*o) is left-shifted such that the concentration of ATP producing 50% inhibition (IC50) is reduced from 22 μM to 1 μM for human β-cells, and from 14 μM to 4 μM for rat INS-1 cells. Conversely, when patches are exposed to a fixed concentration of ATP(10 μM), the administration of 2_-*O*-Me-cAMP inhibits channel activity in a dose-dependent and reversible manner (IC50 12 μM for both cell types). A cyclic nucleotide phosphodiesterase-resistant ESCA (Sp-8-pCPT-2_-*O*-Me-cAMPS) (*Continued on page 3*)

New Features from the ABCC



✸Islet Notification Service (INS) ✸ The ABCC officially launched the new INS on April 30th 2008. The service alerts islet researchers when they have been chosen through the Matching Algorithm Islet Distribution (MAID) system for the receipt of islets by an announcement of "You've got Islets!" on their computer screen. Currently the system only works for PC users but we hope that the Mac people will be able to see and hear this alert in the future.

MEET THE STAFF

ABCC Director

Dr. Joyce Niland

Director of the Administrative and Bioinformatics Coordinating Center (ABCC) for the ICR for the past 6 years is only one of many hats that Dr. Joyce Niland wears at the City of Hope National Medical Center (COH). She also serves as the Chair of Information Sciences at COH, encompassing the Departments of Biostatistics, Clinical Research Information Management, and Biomedical Informatics. Dr. Niland is a Full Professor in the Beckman Research Institute at COH, and adjunct Professor at the University of Southern California (USC) Keck School of Medicine. She is the Associate Director for Information Sciences for the COH Cancer Center, and holds the first Edward & Estelle Alexander Endowed Chair in Information Sciences.

After doing her undergraduate training in Human Biology at Stanford University, Dr. Joyce Niland went on to receive her Doctoral degree in Biometry from USC. Collaborating in translational research for over 25 years, Dr. Niland is internationally recognized in the field of biomedical informatics. Since 1996 she has directed the Data Coordinating Center for the National Comprehensive Cancer Network outcomes research study, overseeing development of an Internet-based data system to measure the quality of care across our nation's cancer centers. Dr. Niland is PI for COH's participation in the NCI's caBIG™ initiative, to create shared software models and systems to speed cancer research.

Dr. Niland has published over 90 peer-reviewed papers in biomedical research, several book chapters, and a textbook in informatics tools for clinical trials. She has served as President of the Stanford Professional Women of Los Angeles, and the Southern California American Statistical Association. In recognition of her contributions to advancing biomedical research, Dr. Niland received the City of Hope Medical and Scientific Achievement award in 2004.

Joyce lives in Pasadena with her husband, Stan and their Labradoodle, Kendric. When not busy with her many professional responsibilities, Joyce most enjoys hanging out at the beach with her best buddies, Stan and Kendric, and globe-trotting for business and fun.

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FEATURED ICR:

UNIVERSITY OF ALABAMA - BIRMINGHAM

The University of Alabama – Birmingham is one of the four new kids on the block that became part of the ICR in the second round of funding in 2006. Dr. Juan Contreras is the Director of the ICR Islet Processing Facility and actively leads an experienced team of researchers. The cGMP isolation facility is part of the Southern Tissue Center, one of the first tissue processing centers in the country. The UAB ICR Center not only works with human islets but their research involves the isolation and transplantation of rodent, porcine, and primate islets as well. Taking advantage of the newly established UAB Comprehensive Diabetes Center, headed by Dr. John Corbett, the Contreras lab is expanding its research goals and forming new collaborations with other highly motivated investigators in the field. A very important part of the UAB program is their focus on autotransplantation of islets for those patients who require a pancreatectomy because of chronic or acute pancreatitis. The UAB Islet Isolation Facility has preformed 40 autotransplants in the last 2-3 years. Without this heroic treatment, these patients would suffer from very severe and debilitating diabetes. Another major interest of the UAB ICR is understanding and development of therapies to prevent deleterious effects of brain-death on islet biology and engraftment. The UAB ICR is a great asset to the ICR Consortium and their southern hospitality makes their contributions to the program that much more pleasant.

ICR Director: Juan L. Contreras; **Associate Director:** Devin E. Eckhoff
Islet Quality Control Manager: Cheryl Smyth **Peri-Clinical Laboratory Manager:** Stacie Bryant
Quality Assurance Manager : Henry Fisher **GMP Facility Manager:** Scott Hall
Islet Quality Control and Research: Hank Fortinberry
Islet Processing / Quality Control: Brett Yancey, Brandon Moore, Houghston Head, Kristie Reynolds, Hong Caihy

Research Paper

(*Continued from page 2*) also inhibits KATP channel activity, thereby demonstrating that the inhibitory actions of ESCAs reported here are unlikely to arise as a consequence of their hydrolysis to bioactive derivatives of adenosine. On the basis of such findings it is concluded that there exists in human β-cells and rat INS-1 cells a novel form of ion channel modulation in also inhibits KATP channel activity, thereby demonstrating that the inhibitory actions of ESCAs reported here are unlikely to arise as a consequence of their hydrolysis to bioactive derivatives of adenosine. On the basis of such findings it is concluded that there exists in human β-cells and rat INS-1 cells a novel form of ion channel modulation in which the ATP sensitivity of KATP channels is regulated by Epac.

Funding for Diabetes Research at Risk: Please Help!

by: Debbie Campbell, National Manager, Government Relations for the JDRF

The Special Statutory Funding Program for Type 1 Diabetes Research (Special Diabetes Program) was enacted by Congress just over 10 years ago. It currently, provides $150 million in annual funding for type 1 research administered through NIH. The Program is set to expire on September 30, 2009 if Congress doesn't act now to reauthorize this extremely productive research funding effort. The Program has funded clinical trials to demonstrate the benefits of human islet transplantation and established the use of human islet preparations for treatment of individuals with severe complications of diabetes. It has funded studies including the examination of the potential benefits of islet transplantation following kidney transplantation, standardization of islet preparations, and the definition of less toxic approaches to immunosuppression. Please send a letter to Congress and ask them to reauthorize the Special Diabetes Program this year for $200 million a year in a multi-year effort by clicking on this website: https://secure2.convio.net/adap/site/Advocacy?cmd=display&page=UserAction&id=1282

Happy Birthday to the ICR Islet Allocation System!

As most of you can remember, the ICR Islet Allocation System was launched in late February of 2007 and the first islet offer broadcast went out on March 7, 2007. Since its inception, the need for human islets for basic science research has increased substantially, and the ICR Islet Allocation System has risen to the challenge. Here's a look back on the development of basic science islet distribution over the past year.

	March 2007	March 2008
Active Protocols	44	84
Active ICR Centers	5	8
Islet Offers per Month	5	14
IEQs Shipped per Month	437,800	1,723,800
Shipments per Month	17	64

System Improvements since March 2007

- Implementation of Open Offers (elimination of first come, first served Mass Offers)
- Change from 120-minute to 30-minute Open Offer time trigger (i.e. more IEQs distributed via targeted offers vs. open offers)
- Addition of culture duration preference
- Enforcement of approved protocol limits
- FedEx package tracking
- Electronic User Feedback Form
- Eligibility based on user compliance
- Islet Notification Service (INS) widget
- Center-specific variances and holds

Between 3/7/07 and 5/20/08, a total of 25,522,790 IEQs were distributed via 1,034 shipments through the ICR Islet Allocation System. Overall, 96 ICR-approved protocols from 61 institutions have received islets through the Allocation System. The overwhelming majority of feedback in regards to the Allocation System has been positive from both the ICR centers and the investigators receiving islets. The ABCC is grateful for all feedback, and many of the most beneficial system improvements have been developed in response to user feedback. Please continue to send your comments to James Cravens (jcravens@coh.org).

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Coming Events:

American Transplant Congress 2008
http://www.atcmeeting.org/2008/ May 31st –June 4th, Toronto, Ont. Canada *Look for the ABCC/ICR booth!*

68th Scientific Sessions of the American Diabetes Association
http://professional.diabetes.org/Congress_Display.aspx?TYP=9&CID=58000 June 6th-10th, San Francisco, CA
ABCC/ICR will have a booth here as well!

ICR Sponsored Counting Workshop for Islet Researchers *At the ADA*
Registration at: http://icr.coh.org/workshops.asp
June 7th and 9th, SF Marriott, San Francisco, CA

ICR Steering Committee Meeting
October 2nd, 2008, Hyatt Regency, Newport Beach, CA

ICR Consortium 4th Annual Islet Workshop
Registration at: http://icr.coh.org/workshops.asp
October 3rd, Hyatt Regency, Newport Beach, CA

ICR Consortium Statistics

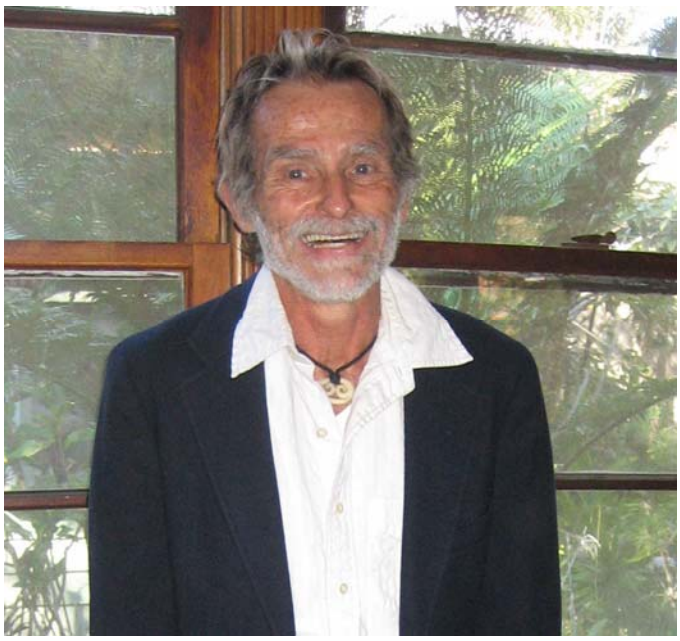
Isolations Reported in the ABCC Database				
To Date	Total	Clinical	Research	Not Used*
2008	111	3	98	10
Cumulative	1046	209	772	65

IEQs Reported in the ABCC Database				
To Date	Total	Clinical	Research	Not Used*
2008	15,802,628	152,787	14,505,575	1,144,266
Cumulative	270,785,598	91,898,715	171,572,158	7,314,725

Cumulative data reported from 12/1/2004 to 5/20/08

** Not Used-Poor quality pancreata and/or islets; or no permission for research*

ICR Basic Science Distribution Program Activity (2/1/2004 to 5/20/2008)			
To Date	# Approved Protocols	#Shipments	#IEQs Distributed
2008	13	416	9,963,900
Cumulative	153	2332	65,015,139



City of Hope Islet Transplant Patient

Jerry Alley

"I have a future and I now look forward to Life!"

These are the jubilant words of islet transplant recipient Jerry Alley. Diabetes struck Jerry during his college years but he was determined to live an active and productive life. Spending much of his time in Hawaii, Jerry moved back to California to be closer to family and friends and to seek better care for his diabetes.

"After 41 years of being insulin dependent, and with over 300 hypoglycemic reactions with seizures, I'm still alive and now insulin free! Despite checking my blood sugars 15 to 17 times in a 24 hour period, I would still be prone to hypoglycemic comas. I received my first islet cell infusion on January 8th of 2008 and after a second infusion on February 28th I am reaction free! I can't believe my blood sugars are in range, thanks to the wonderful doctors and staff at City of Hope in Duarte, California. At age 60 the best is yet to come. All my family, friends and I can say is, "Thank You."

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Critical Need Editorial *(Continued from page 1)*

Still another quantitative index of quality and quantity of human islet research supported by the ICR is provided by the extensive and growing list of high quality publications that have resulted from ICR-derived human pancreatic islets which to date, include articlesin such high impact journals as *The Proceedings of the National Academy of Sciences, Nature Medicine, CELL, CELL Metabolism, The Journal of the American Medical Association (JAMA), Diabetes, the Journal of Biological Chemistry, the American Journal of Transplantation, The Journal of Clinical Endocrinology and Metabolism, Diabetologia,* and others. With this track record, there can be no question that the research being performed with ICR islets is copious, and of the very highest quality and clinical and scientific impact.

The ICR Consortium Human Islet Availability Conundrum

With this growth in need, visibility, priority and relevance come increased costs of pancreas acquisition, islet isolation, quality control, personnel, distribution and reporting. The current production and use of islets exceeds the ability of the ICRC to meet what is a clear-cut and important demand. This now puts the ICRC in a position of needing to make difficult choices at the very time that human beta cell research is taking center stage in diabetes research. Which promising projects need to be terminated? Which investigators and/or institutions should be discontinued? Should certain labs and investigators abandon human islet research? Should key projects be allowed to continue, but at a slower pace, so that the fewer islets can be shared with greater numbers of investigators? Are there alternate sources of human islets outside the ICRC? Should the ICRC allow the US beta cell scientific effort in this area to default to other countries with more readily available human islets? Should individual investigators with shrinking NIH, ADA and JDRF research budgets be forced to purchase human islets from ICRC? If so, what pricing and priority structure would allow fair distribution of human islets, but not discourage researchers from extending mouse studies to human islets? These are critical questions facing the ICRC as it tries to accommodate the veritable explosion of human islet demand.

The previous editorial is an excerpt from the upcoming ICR Annual Report.

The First Annual Upper Midwest Islet Club Conference Held at Vanderbilt University

The unique meeting of the UMIC was held April 30th to May 2nd and featured presentations from young investigators, post doctoral and graduate students from throughout the Midwest whose research is focused on islet physiology, development and pathology. The organizers of this conference, all of whom are long-time ICR islet users, wanted to provide a forum for young diabetes researchers to gather, interact, and present the studies of which they are currently working. The "Lacy Medal Lecture" in honor of Dr. Paul E. Lacy of Washington University in St. Louis was given this year by Dr. Donald Steiner of the University of Chicago. Six of the presentations given at the conference thanked the ICR for providing human islets for their work. The ABCC staged a booth at the meeting and assisted the researchers with answers to questions about the availability of human islets for their future studies.

Pictures courtesy of Duff Green of the Vanderbilt Diabetes Center