National Islet Cell Resource Center Consortium Annual Report 2008

Prepared by
Administrative and Bioinformatics Coordinating Center (ABCC)
of the National Islet Cell Resource Center Consortium
City of Hope National Medical Center
Duarte, CA

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To all interested members of the public, the diabetes research community, and members and staff of the National Islet Cell Resource Center Consortium (ICR):

The 3rd Annual Report of the National Islet Cell Resource Center (ICR) Consortium provides updated information on the activities that stem from ongoing activities of the Consortium. In addition it provides a detailed description and analysis of the steps in preparation, viability assessment, storage, and distribution of islets. It also includes interim reports on special Consortium projects to develop standard methods for the assay of islet cell production of insulin, establishing optimal shipping conditions, and developing a mutually validated method for assessment of islet viability. Although the data presented include current and past participants in the ICR Consortium, the current membership and geographic distribution is shown on page 11-12. The ICRs and the work described herein derive support from funds provided by the Juvenile Diabetes Research Foundation International (JDRFI) and a cooperative agreement with the National Institutes of Health through the National Center for Research Resources (NCRR) and the National Institute of Diabetes, Digestive and Kidney Diseases (NIDDK).

The 3rd Annual Report was assembled by the staff of the ABCC under the leadership of Barbara Olack and James Cravens. In addition, data sharing agreements with the United Network for Organ Sharing (UNOS) and the Collaborative Islet Transplant Registry (CITR) facilitated the compilation of this report.

The 3rd Annual Report highlights the use of human pancreatic islet cells in laboratory-based studies relevant to Type 1 and Type 2 diabetes mellitus. Relatively few of the islets have been used for clinical transplantation because relatively few were requested by transplantation teams for that purpose. In contrast, laboratory studies consumed about 90% of the islets produced with the result that there is a robust list of publications based on studies performed in whole or in part with ICR Consortium islets.

The diabetes research community owes a debt of gratitude to the ICR investigators who, with their laboratory teams, have provided more than 20 million islets per year to more than 150 laboratory investigators at little or no cost to the investigators. Beginning in 2009 a necessary rebudgeting required that, going forward, investigators were asked to provide funds to help cover the costly supplies, equipment, and human resources used in the preparation of human islets.

Of no less importance to the equitable supply of islets to investigators, the ABCC under the direction of Joyce Niland continues to provide a web-based, distribution system that assures an orderly supply of islets to investigators based on their needs, their position in the queue, and their readiness to receive them.

All of us continue hope that the research made possible through the availability of human cadaver pancreatic islet cells will provide new insights into islet physiology, genetics, and composition that will, in turn, bring us ever closer to the promise of a better life for people with Type 1 and Type 2 diabetes mellitus.

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Executive Summary

Current progress in islet cell biology, immunology, and transplantation research would not be possible without the significant contributions of the National Islet Cell Resource Center (ICR) Consortium.

Since its inception in July 2001, the ICR Consortium has maintained a threefold purpose: 1) to provide pancreatic islets of cGMP-quality to eligible investigators for use in FDA-approved, IRB-approved human clinical transplantation protocols for Type 1 diabetes mellitus (T1DM); 2) to optimize the harvest, purification, function, storage, and shipment of islets while developing tests that characterize the quality and predict the effectiveness of islets transplanted into human patients with T1DM; and since 2004, 3) to provide pancreatic islets for use in basic science research studies.

The ICR Consortium is funded by the National Center for Research Resources (NCRR), the National Institute of Diabetes, Digestive and Kidney Diseases (NIDDK), the Department of Health and Human Services, and the Juvenile Diabetes Research Foundation International (JDRFI).

Ten ICR Centers were funded during the initial five years of the program (2001-2006): Columbia University, Joslin Diabetes Center, Puget Sound Blood Center, Southern California Islet Resource Center, University of Colorado Health Science Center, University of Miami, University of Minnesota, University of Pennsylvania, University of Tennessee, and Washington University.

Currently, the ICR Centers are an interactive group of eight academic laboratories supported by the same funding mechanism through August 31, 2009: Southern California Islet Consortium, Chicago Consortium (University of Illinois, Chicago; Northwestern University), University of Alabama, University of Miami, University of Minnesota, University of Pennsylvania, and University of Wisconsin. The Administrative and Bioinformatics Coordinating Center (ABCC) of the ICR Consortium coordinates and collects data for the ICR and is located at the City of Hope National Medical Center in Duarte, CA.

The Executive Summary provides a broad overview of the 3rd Annual Report of the ICR Consortium. The main goals of this Annual Report are to highlight the accomplishments and successes of the ICR program, as well as to help define its path for the future.

Report data represent pancreatic islet isolation information collected from the 10 original ICRs, as well as the 8 current ICRs, and are presented both cumulatively, from July 1, 2001 to August 31, 2008, as well as annually for each program year ending on August 31st (i.e., 2008 annual data span the period from September 1, 2007 to August 31, 2008). This Report is a brief overview of the information gathered.

Synopsis of Combined Clinical and Basic Science Data from ICR 3rd Annual Report (July 2001 – August 2008)

METHODS FOR REPORT

The data in the 3rd Annual Report of the National Islet Cell Resource Center Consortium are presented in two parts. **All Exhibits represent cumulative data from 2001 to August 31, 2008 unless otherwise specified as both cumulative data and 2008. The designation "2008" represents the data from islet isolation records entered between September 1, 2007 and August 31, 2008, the latest grant funding period.**

Part I represents the comprehensive summary of all islet isolations collected through the Islet Cell Processing (ICP) database from the ten centers involved in the original ICR grant and the eight current centers, regardless of usage (clinical transplant, basic science research, or not used). By strictly keeping accurate records of the many steps necessary for successful islet isolation, the ICR Consortium hopes to identify critical factors consistent with successful islet isolation and subsequent transplantation. In order to organize the data entry, the ICP database has been divided into 11 sections, or data forms, that can be cross-referenced as needed to allow the evaluation of different aspects of the process. These sections are: General Information, Organ Recovery Information, Pancreas Characterization at ICR, Collagenase Information, Pancreas Distention Information, Digestion Information, Islet Characterization Post-Digestion, Purification Information, Islet Microbiology Results Information, Mouse Data Information, and Clinical Islet Transportation Information. Data from each of these sections are presented in Part I as separate Chapters.

Part II represents the summary data for islet isolations that were used for basic science studies.

PART I. COMPREHENSIVE DATABASE SUMMARY

GENERAL INFORMATION

Chapter 1 reports information pertaining to pancreas identification and subsequent distribution of the islet preparations. The mean number of pancreata processed per ICR center is 76.9 ± 57.7, with a range from 10 to 196.

In the past seven years of the ICR grant, approximately 299.8 million islet equivalents (IEQ) were isolated by the ICR centers, of which 65.1 million (21.7%) were isolated in 2008 alone. Of the total 1076 documented pancreata, 202 were used in clinical islet transplantation, and 809 were used for basic science studies. Sixty-five pancreata were not used, with the primary reasons (32.3%) being that consent for research was not obtained and that islet quantity or quality did not meet clinical criteria. In 2008, 11 pancreata were used in clinical transplantation, 212 were used for basic science research, and 15 could not be used. This represents a 366% increase in ICR funded clinically transplanted isolations over last year.

In general, islet preparations used for clinical transplantation tended to have higher islet equivalence than those used for basic science studies or were not used; however, aside from a few outlying data points, islets produced for basic science use were similar to clinically transplanted islets in terms of viability, purity, and potency, and this trend has been consistent throughout the duration of the ICR grant.

PANCREAS RECOVERY DATA

The second chapter documents data collected during the procurement of the pancreata and subsequent shipping of the organs to the ICR centers. No specific donor information is required to be entered into the database by the ICR centers due to an agreement between the ABCC and the United Network for Organ Sharing (UNOS), which allows the download of donor information from the UNOS database system. A comprehensive analysis of donor factor data will be included in the upcoming Clinical Islet Transplantation Registry (CITR) Report.

Of the 1076 total isolations performed during the seven years of the ICR grant, 762 (70.8%) pancreata were obtained through remote procurement teams, 308 (28.6%) were harvested locally, and the teams responsible for the recovery of the remaining 6 (0.6%) were not documented. In 2008, slightly fewer pancreata were procured remotely (157 of the total 238 isolations; 66.0%), whereas 80 (33.6%) were harvested locally. Cumulative data showed little statistical difference observed in the comparison of islet characteristics between remotely- and locally-obtained pancreata for isolation.

The mean time from cross-clamp to pancreas recovery for the harvested pancreata was 41.62 minutes. The mean duration of cold ischemia as defined by the ABCC as time between cross-clamp and start of dissection was approximately 8.4 hours (505.74 minutes), or 9.2 hours (551 minutes) by center-specific definitions. Ranges for all other processing times were likely large due to the inclusion of experimental isolations for which ICRs were testing the feasibility of long storage times in certain preservation solutions.

There were relatively small discrepancies between the documentation of pancreas quality by the Organ Procurement Organization (OPO) at the time of organ recovery and that of the ICR at time of processing: of the 672 pancreata that were documented as intact by the procurement team in the operating room, 21 (3.1%) were actually reported as not intact upon arrival at the ICR; however, 53

additional pancreata were documented as not intact upon receipt at the ICR that were not documented as damaged by the OPO. Thus, a total of 108 (10%) of the 1076 pancreata received by the ICR centers were reported as not intact. A disappointment in the past year was the decrease in documentation by the OPO of pancreas quality, from 20.2% pancreata not documented in 2007, to 37.8% not documented in 2008. This was increase in over 70% of non-documented cases by the OPO from last year's all time low of 20.2% non-documented.

The majority of pancreata both cumulatively and in 2008 were shipped using University of Wisconsin (UW) solution (59.9% and 61.3%, respectively). In 2008 the use of the oxygen-enriched two-layer method (TLM) decreased to 13.5% of the total preservation solutions used; however, in this past year increasing numbers of pancreata were shipped using histidine-tryptophan-ketoglutarate (HTK) solution (21.8%), a less expensive solution. There appear to be no statistical differences in islet characteristics based on the types of preservation solutions used.

PANCREAS CHARACTERIZATION AT ICR

The data in Chapter 3 review the quality of the pancreata upon arrival at the ICR centers. Documented details include: the amount of fat on and within the pancreatic tissue, whether the pancreas was received as an intact organ or if surgical damage had occurred, if the pancreas had any macroscopic damage such as hematoma, bruising, or extensive cauterization, and if the pancreas was edematous.

Pancreas surface fat is characterized at the ICRs as being "clean," "light," "moderate," "heavy," or was not documented. Fatty infiltration of the pancreata is characterized as "none," "patchy," "moderate," "heavy," or was not documented. The majority of pancreata over the seven years of the ICR grant were characterized as having either moderate (30.9%) or heavy (29.6%) surface fat, and little (21.2%) to no (20.3%) fatty infiltration. The ABCC has developed a Fat Index (as defined in the *Definition of Terms*) to relate both the fat infiltrate and surface fat in terms of islet isolation quality. In general, islets isolated from pancreata with more surface fat and more infiltrated fat yielded a slightly larger number of IE.

Of the 1076 pancreata reported to the ABCC, 195 (18.1%) had macroscopic damage, and 113 (10.5%) were reported as having edema. Overall, intact pancreata yielded slightly higher numbers of IE post purification, but there was no statistical difference in the rest of the islet quality parameters. The number of IE post purification could have been influenced by the amount of tissue isolated in some cases. The total IEQ count post purification tended to be higher with pancreata not damaged; however, the correlation was less apparent with respect to viability, purity, and potency.

Pancreatic edema could indicate trauma or poor donor management, and edematous organs are usually avoided by most ICR centers when possible. A slightly lower mean and median IEQ yield was observed in edematous pancreata isolated by the ICR consortium; however, little difference in viability or purity of islets was seen.

DIGESTION ENZYMES USED

Chapter 4 reviews the types of enzymes used during islet isolation. For the second year in a row, centers struggled to find workable enzymes that would yield the maximum quantity and quality of human islets that they had experienced prior to the bovine tissue contamination problems of 2006. Serva products were used most often in 2008 with their NB1 Premium Grade accounting for 48.7% of the isolations and their NB1 GMP Grade being used for 16.8% of the digestions. Sigma Type IV Collagenase also made resurgence this past year also being used in 16.8% of the isolations. Two

new products were introduced in 2008. Vitacyte perfected their enzyme blend and began marketing their CIzyme products and Roche introduced a new mammalian-free enzyme, 2000 MDFT. These new enzyme blends appear to be yielding an above average number of IEQs and AIs in comparison to past collagenase blends that were used in previous years.

The enzyme used in the isolation process is most commonly dissolved in a buffered salt solution for infusion into the pancreas and for the dissociation process. Hank's Buffered Salt Solution (HBSS) was the most common base solution used (60.7%), followed by Perfusion and Priming solutions (Mediatech, Inc.) that also have a base of HBSS (29.9% overall).

Sixteen different additives were used in addition to the enzyme in the dissociation solution. The most prevalent additive was a form of DNAse [either porcine or recombinant (Pulmozyme, Genentech)] used in 54.3% of the processed pancreata. In 36.1% of the isolations, additional calcium chloride was added to the enzyme solution.

PANCREAS DISTENTION DATA

Chapter 5 reflects data concerning the dissection or trimming of the pancreata and the subsequent distention of the organ using the selected enzymes. The amount of trimming that is necessary for efficient islet isolation is controversial. According to the data collected by the ICR, times for dissection range from no dissection to almost 3 hours, with a mean time of approximately 41.3 minutes and a median time of 40 minutes.

The average weight of the tissue used for human islet isolations post-trimming and pre-distention among the ICR centers was 101 grams, although several organs weighed up to 250 grams.

Pancreas ductal distention is reported to the ABCC by two methods: manual distension using a syringe, and automatic perfusion distention using electric pumps and varying speeds. Approximately two-thirds of the reported pancreata were distended using the automatic perfusion method, and one-third was distended manually. For the third year, manual distention shows an increase in the total number of IEQs in the post digestion counts over the perfusion method.

The ICR centers may also choose to divide the pancreas after distention into smaller pieces in order to increase enzyme activity and yield better digestion of the pancreatic tissue. With the revision of the database, the ABCC began collecting this information on isolations entered after May of 2006. Of the 429 documented cases for which the number of pieces was recorded, centers reported cutting the pancreas into a median of 10 pieces, with a range from 2 to 31. Of those reporting, only 247 isolations recorded the size of the pieces, with the majority being between 1 cm and 3 cm in length.

As can be expected, the numbers of IEQs and Actual Islets (AI) reported post digestion seem to correlate with the quality of the distention.

ORGAN DIGESTION DATA

Chapter 6 describes the methods of digestion, solutions used (other than the enzymes), and the completeness of the process for islet isolation. Overwhelmingly, the process used by the ICR centers was a variation of the Ricordi method.

Of the dilution solutions used in the digestion process, 86.3% of the reported digestions used Roswell Park Memorial Institute (RPMI) products as base solutions for dilution, which include

RPMI, Mediatech Dilution Solution, and Miami RPMI Formulation #2. Approximately 55% of the isolations have the base solution supplemented with human serum albumin (HSA) and 35.5% have added a form of DNAse (Pulmozyme) most commonly used to protect the islets from the enzymatic process after they were released.

The digestion time varied with the age of donor and size of the pancreas. The mean duration of enzymatic digestion reported to the ABCC was 19.0 ± 10.3 minutes, with a range from 3 to 97 minutes. The dilution phase averaged 37.9 ± 18.8 minutes, bringing the mean total digestion time to 57.3 ± 17.9 minutes, with a range from 15 to 160 minutes.

One measurement of a successful digestion is the amount of tissue remaining in the chamber at the end of the digestion process. The total weight of the remaining tissue averaged 25.8 grams. Of the remaining tissue, only 33.9% (10.8 grams) of it was documented by the ICR centers as pancreatic digestible tissue (tissue that could have held islets).

ISLET CHARACTERIZATION POST DIGESTION

Chapter 7 describes the information collected on the islet preparation post digestion but prior to purification. To gather this information, the ICR centers collect a calibrated sample of the post digestion slurry, stain the preparation with dithizone to identify the islet cells, and manually count the number of islets in the aliquot. This process is usually repeated by several technicians, and then counts are averaged in order to document a reliable number. A microscopic grid aids in the sizing of the stained islets. “Actual islets” (AI) are the number of islets counted, regardless of size. “Islet equivalents” (IE) represent a calculated figure based on the size of the islets times the number of islets. The comparison of these two factors gives the “islet index.” An islet index of 1 is considered an average preparation, with the average size of the islets in the preparation being 150µ.

Of the 845 isolations performed for which IEQ counts post digestion were recorded, the mean IEQ count post digestion was 394,153.9 ± 201,963.5. This large standard deviation implies a great deal of variation. Centers reported AI on approximately half of the isolations but of the information available, the isolations yielded a mean AI of 372,794.7 ± 204,533.8 with a calculated islet index of 1.1 ± 0.4. The average IE yield for the last seven years continues to drop most probably due to the Collagenase problems experienced in the past two years of data collection and the resulting increase in the proportion of basic science islet preparations in the database.

The reported mean packed cell volume of tissue after digestions is 41.7 ± 18.2 mL, with a median value of 40 mL. The mean percentage of trapped islets (islets that are still surrounded by the acinar tissue) was documented in 612 isolations and averaged 23.3%. Almost one-third of the reported isolations documented the percentage of positively-stained dithizone cells (mean of 2.8%).

There is some controversy on the importance of collecting any information on the characteristics of islets immediately following the digestion phase.

ISLET PURIFICATION DATA

Chapter 8 provides information on the methods, solutions, and details of how the purification processes of the islet isolations are executed. All isolations that were reported used density gradients on the COBE 2991 Cell Processor. As the number of COBE runs conducted per isolation was not recorded until May of 2006, therefore, approximately one third of the records (371

isolations) do not have this information documented; however, of the 657 isolations that do report the number of runs, more than half of the isolations required two COBE runs per preparation.

The majority (89.6%) of the runs were done as a continuous gradient, a technique where a device known as a gradient maker is utilized to allow a mixing of a heavy and a light density gradient to be mixed and pumped onto the COBE Processor in a continuous linear density from heavy to light. Islets have a lighter density than the contaminating acinar tissue; therefore, the purification is accomplished as the continual spinning of the COBE allows the islets to seek their matching density in the gradient.

Several types of density gradients were reported but over half of the purification runs were done using Bicoll (Biochrom AG, Berlin) density gradient (polysucrose 400 and amidotrizoic acid)**.** The use of Optiprep (Iodixanol based) has increased this past year in comparison to previous years (most probably due to its requirement to be used by CIT centers) and has now been used in 267 runs. Euroficoll (Eurocollins and Ficoll DL400) was used in 142 runs, and an additional 299 runs were conducted using other Ficoll-based solutions. Ficoll-based density gradients other than Bicoll and Euroficoll appear to yield the highest IEQ counts post purification by a small margin.

ISLET CHARACTERIZATION POST PURIFICATION

Chapter 9 reports the information that was collected on the details of the islet preparation post purification but prior to culture. A small aliquot is extracted from a well-mixed suspension of the islet preparation after purification steps have been performed and counted, usually by several technicians using a microscopic grid for sizing of the dithizone-stained islets. Results were then averaged in order to report a reliable number.

An average of 294,820.7± 169,488.0IEQ with ranges from 667 to 1,132,083 and AI average of 253,183.2±156,106.2 (2,500 to 1,022,000), respectively, were reported for islets isolated during the period from 2001 – August 31, 2008. The average islet index of 1.3 ± 0.6 shows that isolated islets were larger than 150µ in diameter on average. Measured packed cell volume post purification averaged 3.6 mL, an approximately 90% decrease from pre-purification statistics. Purity by dithizone staining was 70.9%, with a range from 12.8 to 100%. Islet viability was reported as 91.1% ± 8.7%.

Islet preparations that have a majority of small islets (average of <75µ in diameter) tend to have a lower viability, possibly due to damage from the isolation process. These documented particles may well be fractions of islets rather than small whole islets.

It should be noted that from 2001-2003, only pancreata used for clinical transplantation were required to be entered in the ICP database. Therefore, the overwhelming majority of pancreata reported in these years was clinically transplanted, and data obtained from this period could reflect a skewed average yield. A slight drop in average post purification IEQ per isolation was noted in the past two years, possibly from the problems experienced with collagenase enzymes.

ISLET CULTURE DATA

Chapter 10 gives information concerning the solutions, islet concentrations, vessels, times, and temperatures of islet culture conditions for both basic science research and clinical transplantation. Once islets are purified, they are often held in culture for some amount of time before further testing, and additional characteristics are documented. Approximately three/fourths of the isolations recorded in this Report were cultured for some amount of time. Fifteen hundred and fifty

five separate culture parameters are collected by the various ICR programs. Over 98% of all cultured islets were held in a base of Connaught's Medical Research Laboratories Media 1066 (CMRL 1066), either supplemented or not.

Different additives were frequently used to supplement the base media to encourage islet health while being held in culture. In particular, human serum albumin (HSA) was added to the majority of cultured islets either by the manufacturer (as in Mediatech Miami Medium #1A Culture Media and CMRL 1066, Supplemented) or by the ICR center, followed by Vitamin E, Insulin Transferrin Selenium (ITS), and Nicotinamide, a principal form of Vitamin B-complex. Sodium hydroxide or sodium bicarbonate was also often used as a buffer in the base media, and combinations of amino acids and vitamins supplemented many of the cultures. Ciprofloxacin was the dominant antimicrobial used in the cultures.

The average culture time reported was 86.7 ± 67 hours, with a range from 6 hours to almost 10.8 days. The ranges for all parameters indicated in this table were wide, possibly as the result of the differences in culture times. The post-culture actual islets averaged 216,055.1 ± 160,936.0, with a range from 2,500 to 1,960,000. The IE averaged 232,683.8 ± 161,240.6, ranging from 667 to 880,834 IEQs. The islet index of 1.2 has remained steady over the past few years with packed cell volume dropping to 2.2 mL from 2.4mL last year. Consequently, the post culture purity increased to 71.3 ± 14.7% (71.0 ± 15.1% in 2007) and the viability by staining rose to 90.1 ± 9.2% (88.3% ± 13.3% in 2007). The mean stimulation index was reported at 3.2, but results ranged from 0.1 to 27.1.

The majority of the isolations where both pre- and post-culture counts were reported had a decrease in the counts after culture; however, the data imply that culturing had less of an effect on the islet index recovery.

FINAL ISLET PREPARATION DATA

The data reported in Chapter 11 represents the entire islet preparation prior to transplantation or distribution for research. The majority of the preparations entered in this category were isolations that went on to clinical transplants. While these final data were less in number, outcomes in most cases appeared to be skewed by the clinical results.

From July 2001 through August 2008 the mean actual islet count was 285,828.7 ± 160,059.6, ranging from 10,486 to 887,400. In comparison, IEQs averaged 324,009.4 ± 180,150.2 and ranged from 4,003 to 884,700. The islet index remained relatively consistent at 1.2 ± 0.5, and packed cell volume averaged 2.7 mL ± 2.8 mL. The purity was reported as a mean of 68.8%, with a range from 10% to 100% and a median of 70%. Viability by inclusive and exclusive dye-staining was reported as 91.8% ± 7.1%, and potency by stimulation index averages 2.8 ± 2.8, ranging from 0.2 to 27.1.

Other parameters collected had significantly less documentation. There were only 35 reports of beta cell percentage (mean of 42.1%), 35 isolations with total beta cells (376.4 x 10^6), 70 documentations of insulin content (195.7 µU/IEQ), and 93 reports of DNA content at an average of 32.5 ng/IEQ.

MICROBIOLOGY OF ISLET PREPARATIONS

Sterile preparations are essential, for both the safety of patients receiving a clinical transplant, and for the basic science researchers that invest time and resources into experiments on the islet

preparations received through the ICR Consortium. Chapter 12 documents the results reported by all ICR centers concerning the testing of islet preparations at different stages of the process for microbial contamination, including gram stains, aerobic, anaerobic, fungal, and mycoplasma contamination from all reported isolations. The collection of data from specific times during the isolation process was added to the ICP database in May of 2006, thus resulting in the low numbers for Transport Fluid, Post Purification and Post Culture results. Contamination data has always been collected by the ABCC for the Final Preparation. Ninety-six contaminants were documented in the 317 Transport Fluid samples reported over the past seven years. Three samples were reported for Post Digestion with no contaminants found. Only one contaminant, a fungal growth, was reported among 187 Post Purification samples, showing that contamination from the original pancreas can be diluted out through the isolation process. One hundred and fifty-four Post Culture samples were taken and 1 aerobic positive culture was determined. Of the 660 Final Preparations that were analyzed, 18 positive contaminations (2.8%) were reported. Of these, 12 were aerobic cultures, 3 were anaerobic cultures, and 3 were fungal growths. Gram stain results would have been further identified in the specific testing, so those results were not included in these totals.

In some cases, the endotoxin results were reported to the ABCC as actual EU/ml, and in some they were reported as less than the sensitivity of the assay (<EU/ml). If the sample is from a preparation intended for clinical transplantation, the most informative data is reported as EU/kg of the body weight of the recipient. According to FDA regulations, EU cannot be higher than 5 EU/kg per injection. The mean EU/kg reported to the ABCC is 1.06 ± 1.5, with a range from 0.04 to 5.0.

MOUSE BIOASSAY OF ISOLATED ISLETS

The mouse bioassay is a well-accepted test for islet potency. Chapter 13 reports the statistics from the ICR centers' mouse transplantation experiments when used as a quality-control mechanism. Approximately one-quarter of the preparations used the mouse assay as a means for islet potency documentation.

The Non-Obese Diabetic / Severe Combined Immunodeficiency Disease (NOD/SCID) was the most frequently reported mouse strain used (42.6% of the time). The NOD/SCID mouse is characterized by a functional deficit in NK cells, absence of circulating complement, and defects in the differentiation and function of antigen-presenting cells as well as a lack of T and B cells, making them a strategic model for transplantation studies. The Athymic Nude mouse strain was used in 24.3% of the experiments. A growing number of centers are investigating the use of genetically altered knock-out (-/-) mice such as the B/6 or Balbc rag-/- and the naturally-occurring diabetic Akita mouse with or without rag-/-.

The most common transplant site was the kidney subcapsular space, although one center incorporated the use of Matrigel (a soluble basement membrane matrix which provides a physiological setting for islets) subcutaneously. The preferred test for judging outcome was permanent blood glucose under 200mg/dL (used in 77.4% of the transplants), followed by C-peptide greater than1ng/ml.

Because ICR centers used different numbers of mice for transplantation studies as well as different amounts of islets, the mean cure rate was 48.1% ± 44.5%, with ranges from 0 to 100%. This low percentage may be based on the practice of many centers to vary the dose of islets transplanted in order to establish the threshold of IEQ necessary for a cure (Data not collected).

PART II: BASIC SCIENCE ISLET DISTRIBUTION

This part of the Annual Report describes data pertaining to the islet isolations that were used for basic science research.

It is clear from the data that the ICR Consortium program has expanded since its inception. The number of IEQs distributed annually by the ICR Consortium has steadily grown since the first funding period, from 1.3 million IEQ in 2004 to 22.3 million IEQ in 2008.

Similarly, the number of approved institutions and research studies has steadily increased, from just 16 institutions and 19 studies in 2004, to 105 institutions and 156 studies in 2008. As many as 3.03 million IEQs were distributed in the month of January 2008 alone, compared to 1.02 million IEQ in the month of July 2008. The University of Pennsylvania was the most active ICR in terms of number of shipments (176) and recipients (66) in 2008.

Introduction

ICR Mission Statement

The Islet Cell Resource Centers (ICRs), funded by the National Center for Research Resources, the National Institute of Diabetes and Digestive and Kidney Diseases, components of the National Institutes of Health, Department of Health and Human Services, and the Juvenile Diabetes Research Foundation International comprise an interactive group of eight academic laboratories charged with three major goals: 1) to provide pancreatic islets of cGMP-quality to eligible investigators for use in FDA-approved, IRB-approved transplantation protocols; 2) to optimize the harvest, purification, function, storage, and shipment of islets while developing tests that characterize the quality and predict the effectiveness of islets transplanted into patients with diabetes mellitus; and 3) to provide pancreatic islets for basic science studies.

Islet Cell Processing Data System

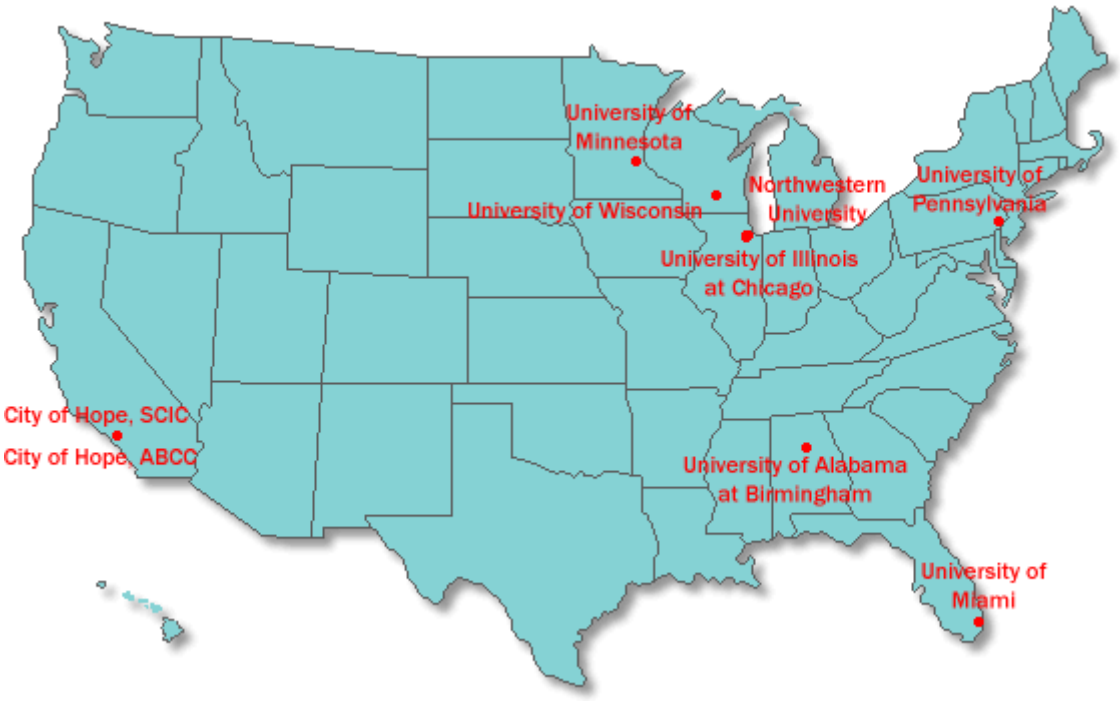
The Islet Cell Processing Data System (ICP) is a web-based data repository mandated by the ICR Consortium and designed by the Administrative and Bioinformatics Coordinating Center (ABCC) to house pertinent information collected by the ICR centers during islet processing. The database consists of 11 sections, each focusing on a specific phase of pancreas procurement, pancreas digestion, islet purification, islet culture, islet testing or islet transport prior to transplantation. The web-based data collection system became available to the original 10 ICR centers in late 2004, and data entry training occurred between December 2004 and January 2005. Ongoing support of data entry and quality-assurance monitoring has continued by the ABCC to assure that all entered information is accurate and verified.

Participating ICRs are required to enter all ICR-supported islet isolations for both clinical and basic research. ICR centers are encouraged to enter any islet isolations performed at their centers not funded through the ICR, whether research or clinical, and may use the statistical expertise provided by the ABCC and the data system to analyze their individual center's data.

In May 2006, a major revision of the ICP system was launched to capture more details of the isolation process. A second major revision was completed in November or 2008. The ABCC supplied training guides specifying the improvements to the database and conducted a teleconference training course with required participation by all ICR centers. The improved systems included the entry of specific details of the purification process,

information regarding the preparation transport for clinical transplants, unique details for individual culture situations and self-calculating storage and ischemia times.

The data outlined in this report are a collection of isolation information from the 10 original ICR centers, as well as the eight current centers, from pancreata isolated between 2001 and August 31st, 2008.



Current Contributing ICR Centers

Chicago Consortium: University of Illinois, Chicago & Northwestern University, Chicago, IL
Southern California Islet Consortium, Duarte, CA
University of Alabama – Birmingham, AL
University of Miami, Miami, FL
University of Minnesota, Minneapolis, MN
University of Pennsylvania, Philadelphia, PA
University of Wisconsin, Madison, WI

The ICP Sections

The islet isolation process is a comprehensive procedure that involves the participation and dedication of both health care workers and research scientists. It is essential that all participants in this procedure keep accurate records of the many steps necessary for successful islet isolation. It is the goal of the ICR Consortium to identify critical factors for successful islet isolation and subsequent transplantation by analyzing the collective information gathered from a large number of the major islet processing centers in North

America. Over 435 unique data points can be entered for each batch record, with a minimum of approximately 139 points of information required from each isolation. In order to organize the data entry, the ICP database has been divided into 12 sections, or data forms. These data forms, as well as the information they contain, can be cross-referenced, as needed, to allow evaluation of different aspects of the process. Following is a list of the data forms contained in the ICP and a short summary of their contents.

General Information:
This first data form requires the ICR to enter identification data for the pancreas and the in-house isolation number, as well as information about the outcome of the isolation. By categorizing the final result of the isolation process (Clinical Transplant, Basic Research, or Not Used), the ICP system manages the availability of the subsequent forms for data entry.

Organ Recovery Information:
The data required for this form should come directly from the sheets supplied with the pancreas by the Organ Procurement Organization (OPO) that direct the shipment of the organ to the ICR center for processing. It is essential that the OPO personnel record accurate times and information regarding the quality and handling of the procured pancreas prior to packaging and shipment.

Pancreas Characterization at ICR:
This section of the database insures that there are no discrepancies between the information gathered in the operating suite during procurement and visualization of the organ after arrival at the ICR center.

Collagenase Information:
This data form documents the information about the enzymes that are used for the digestion process, including concentrations, volumes, and the attributes of the base solutions.

Pancreas Distension Information:
This form examines the times and temperatures of both the dissection of the pancreatic tissue from the *en bloc* tissue that is sent to the processing centers, and the method of enzyme infusion of the organ. A supplemental screen allows detailed input of additional data if mechanical distension of the organ is performed. In addition, data are gathered on the manipulation of the pancreas prior to loading into the digestion chamber.

Digestion Information:
The first part of this section asks for many of the essential time points depicting the different phases in the digestion of the pancreatic tissue, as well as methods and temperatures used in the process. During the May 2006 revision, important questions evaluating the remaining chamber tissue were added to this section.

Islet Characterization Post Digestion:
This form records the evaluation of the preparation pre-purification. The information gathered at this point in the isolation process can give insight into the quality of the

pancreas itself prior to isolation as well as the attributes of the enzymes being used in the digestion process.

Purification Information:
This section is divided into four distinct data forms, each capturing a different phase in the isolation process after the digestion is completed. The first form titled, 'General Purification Data,' collects the basic information about the type of purification performed, the type of gradients used, and the amount of tissue used in each step. The next form, 'Purification/Rescue Run Data,' asks for specifics of each aliquot of tissue that was collected and analyzed. The third form, 'Culture Data,' references the culture procedures and the specific data collected on islets from each culture parameter. The second and third forms allow for multiple parameters performed on the purified tissue. The last form in this section is entitled 'Final Islet Preparation Data,' and pertains to the summary of any islet characteristics performed prior to shipping or transplant.

Islet Microbiology Results Information:
The purpose of this form is to gather the results of any contamination of the preparation prior to or during the processing. Samples from five different time points using six different microbiological assays can be entered into the database, with the opportunity to specify the identified contaminate where necessary.

Mouse Data Information:
This form allows the center to enter the general results of bioassays performed with the final islet preparation. Details for this form include: mouse species used, number of transplants performed, and determinants of a successful or failed experiment.

Clinical Islet Transportation Information:
The last section, added during the revision of the ICP system in May of 2006, is only available to the entry technician for pancreata used for clinical transplant as specified within the first form ('General Information')**.** If a clinical transplant is performed, this section captures the data from product release to patient infusion including time lapse, holding container(s), and transport media.

Methods for Report

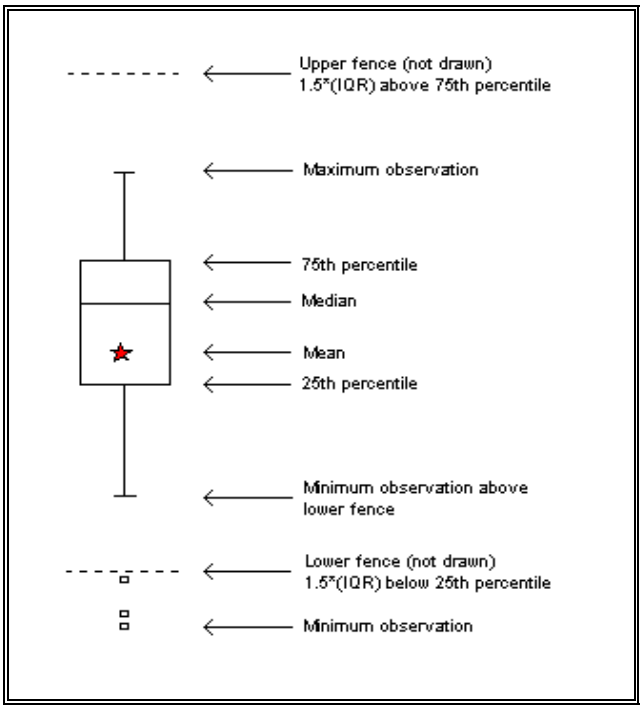
The ABCC adheres to strict quality control and assurance procedures in the collection of data for the Report. All data submitted to the ICP have been reviewed through several mechanisms. Prospective entry errors in the database are first distinguished through the ABCC-generated 'Inconsistencies Report,' which recognizes entered data that does not fit normal parameters or have timing issues. Each participating ICR is subject to an initiating visit with extensive database training, followed by an on-site annual review by the ABCC Quality Assurance personnel. The source documents for a percentage of the batch records from which the data have been taken and entered into the ICP system are reviewed against the entries in the ICP system. Monitoring reports, with suggestions for improvement, data discrepancies, and all action items are sent to the ABCC directors, the Information Standard Subcommittee (ISS), and the Steering Committee (SC) for review.

In addition, prior to freezing the records on December 29, 2007, additional outlying data queries were sent to the ICR centers. Through each quality-review process, the ICR centers are able to examine the discrepancies and confirm or correct accordingly.

Data in this report are presented in two parts. Part I is a comprehensive summary of all isolations collected through the ICP database from the 10 centers involved in the original ICR grant as well as the 8 current centers. Part II is a collection of the data from islet isolations that were used for basic science studies.

Data in this report are depicted as tables, boxplots, bar graphs, scatter plots, and/or pie charts for ease of interpretation and clarification. **All Exhibits represent cumulative data from 2001 to August 31, 2008 unless otherwise specified as both cumulative data and 2008 data. The designation "2008" represents the data from islet isolation records entered between September 1, 2007 and August 31, 2008, the latest grant funding period.**

Boxplots are used in the report to summarize numeric data. The 'star' (★) in the boxplot represents the statistical mean. The lower line of the box represents the 25th percentile, the upper line of the box represents the 75th percentile, and the line within the box represents the median (50th percentile). All values between the 25th and 75th percentiles comprise the middle 50th percentile or interquartile range (IQR). All values within 1.5*(IQR) above the 75th percentile or 1.5*(IQR) below the 25th percentile are indicated by the whisker. All values deviating from the interquartile range by more than 1.5*(IQR) are considered outliers and are indicated by individual squares.



Definition of Terms

AI: refers to Actual Islets or the yield of islets based on number. The sizes of the islets are not taken into account.

Body Mass Index (BMI): BMI is defined as the individual's body weight (in kilograms) divided by the square of their height (in meters). BMI was specified between 1830 and 1850 by the Belgian polymath, Adolphe Quetelet, during the course of developing "social physics."

Fat Index: An ABCC calculation combining the surface fat and fat infiltrate designated by the centers. A numeric value is assigned by adding the numeric values (0 through 3) representing surface fat and fat infiltrate to arrive at a value between 0 and 6:

0=None (No fat infiltration and clean surface fat)
1=Very Low
2=Low
3=Moderate
4=High
5=Very High
6=Heavy (heavy fat infiltration and heavy surface fat)

Histidine-Tryptophan-Ketogluterate (HTK): Originally created as a cardioplegic solution for open heart surgery, HTK solution is now also used as an organ preservation solution. Histidine provides a very potent buffering system, low potassium levels lower anaerobic glycosis and lactate acidosis potential, and the low sodium content contributes to the lowering of energy consumption. Tryptophan in the product protects against cellular edema by inhibiting amino acid transport, and mannitol acts as a free radical scavenger and protects against cellular edema.

IEQ**:** One Islet Equivalent equals one Actual Islet (AI) having a diameter of 150µm. The yield of pancreatic islets is calculated based upon islet number and size, and is expressed as islet equivalents.

Islet Index: The ratio of islet equivalents to actual islets (IEQ/AI=Islet Index). An Islet Index larger than 1 indicates that the average size of islets in a given preparation is larger than 150µm in diameter.

Islet Viability: For this report, islet viability is defined as the percentage of positive islets calculated after staining with an inclusion dye such as Acridine Orange, Fluorescein Diacetate, or Syto Green 13, and an exclusion dye such as Ethidium Bromide, Propidium Iodide, or Trypan Blue.

Perfluorodecalin (PFC*):* A fully-fluorinated, odorless, colorless, non-toxic perfluorocarbon-based liquid that has a very high capacity to store and release oxygen.

This substance comprises the bottom layer in the Two-Layer Method of pancreas preservation and storage.

***Pulmozyme* (*Alfa Dornase*):** Pulmozyme is the manmade form of a naturally-occurring substance called *DNAse* that is manufactured and sold by Genentech, Inc. as an inhalation therapy for Cystic Fibrosis.

Stimulation Index (SI): The ratio between the insulin output of isolated islets at high and low glucose stimulation.

Two-layer Method (TLM): A method of pancreas preservation developed by Kuroda *et al.* to reduce ischemic injury during preservation. Briefly, the gland is immersed in preservation solution and maintained at the interface between oxygenated perfluorocarbon and UW and transported to the cell processing laboratory within 24 hours.

University of Wisconsin Solution (UW): Developed by Belzer *et al.* at the University of Wisconsin in the late 1980s for preservation of the liver, kidney, and pancreas. It contains a number of components such as glutathione, adenosine, raffinose, hydroethyl starch, lactobionate and allopurinol. It has been a standard preservation solution in organ procurement since the early 1990s.

Part One: Comprehensive Database Summary

The data comprising Part I consist of information collected from 1076 human islet isolations between July 2001 and August 31st of 2008, the first seven years of funding for the ICR Consortium. All pancreata are included in Part I regardless of usage (clinical transplant, basic science research, or not used). All 10 participating ICRs from the first funding period (2001-2006), as well as the 8 current ICRs, contributed data to this summary.

Of the documented pancreata, 202 went on to clinical islet transplantation, and 809 were used for basic science studies. Sixty-five pancreata were deemed unacceptable for processing. 70.8% of the pancreata were obtained through a remote procurement team, showing the growing acceptance of islet transplantation as a viable therapy throughout the United States.

Approximately 299.8 million islet equivalents (IEQ) have been isolated by the ICR centers over the past seven years. More than 92.1 million have been clinically transplanted, and over 201.1 million have been utilized in basic science studies.

Chapter 1: General Information

This first chapter reports all of the information pertaining to pancreas identification and the subsequent distribution of the islet preparation.

Exhibit 1 shows that of the 551 pancreata intended for clinical use, 202 (36.7%) went forward to clinical islet transplantation, while 304 (55.1%) did not meet clinical criteria and were used for basic science studies. Only 45 pancreata (8.2%) intended for clinical use did not meet the standards set for either clinical or basic science studies. In addition, 525 pancreata were intended for basic science isolations, of which 505 were used for islet distribution and in-house research. Graphics show the large decrease in clinical transplantation in the past few years of collected data due to the Collagenase problems in 2006 through 2008.

Exhibit 2 lists the reasons given for non-use of pancreata. The most prevalent reason for the pancreata not being used is the absence of consent for research in the event that islet quantity or quality did not meet clinical criteria (32.3%).

Exhibit 3 shows the number of islets isolated by the ICR centers since 2001. Of the 299.8 million IEQ reported, 21.7% were isolated in the past year. The majority of islets isolated have been used for basic science research (67.1%), with 90.4% of the last year's islets distributed to approved investigators in laboratories around the country or used for in-house research projects by participants in the Islet Cell Consortium. Exhibits 4 and 5 illustrate the breakdown of pancreas use and islet yield by ICR center. The mean number of pancreata processed per ICR center was 76.9 ± 57.7, with a range from 10 to 196. The majority of pancreata processed by each center went to basic science studies. The mean number of IEQ per center is 21.4 million ± 16.0 million with a median of 16.8 million IEQ. It should be noted that six of the 14 ICR centers listed are no longer producing islets for the ICR Consortium since their funding ended in 2006.

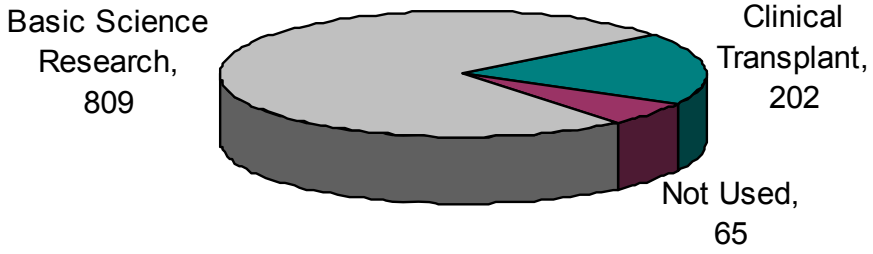
Exhibits 6-8 depict the isolations and subsequent data entry by year. Isolations occurring between July 2001 and August 2008 have been reported, but the ICP database was not available for data entry until January of 2005. The elapsed time between isolation and data entry has steadily improved over the last four years, and the majority of data is now entered within weeks of the isolation, a strategy encouraged by the ABCC and made simpler with the improved web-based distribution system.

Exhibits 9 and 10 show a logical trend that preparations progressing to clinical transplantation tend to have higher islet equivalence then those used for basic science studies or that go unused; however, aside from a few outlying data points, islets produced by the ICR which were used for basic science studies are similar to those used in clinical transplantation in viability and purity as shown in Exhibits 12-13. In addition, there seems to be little difference between the past year's results and the cumulative data over the past seven years with the exception of islet purity which has improved in 2008.

Exhibit 1
Intended and Actual Use of All Isolations Reported to ICR

	Actual Use			
	Clinical Transplant	Basic Science Research	Not Used	*Total Intended Uses*
Intended Use				
Clinical Transplant	202	304	45	*551*
Basic Science Research	0	505	20	*525*
Total Actual Uses	*202*	*809*	*65*	*1076*

Cumulative



2008 Only

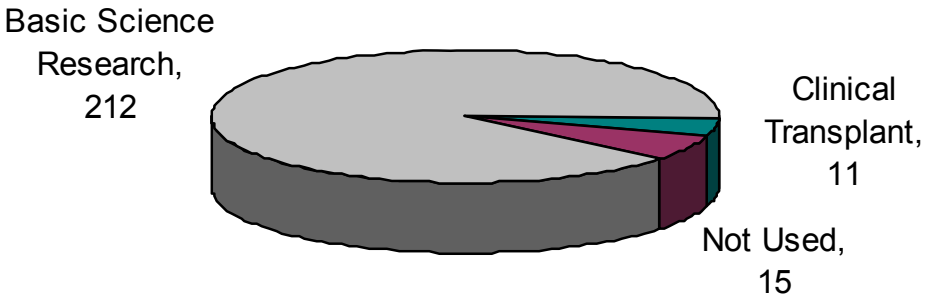


Exhibit 2
Reasons Isolations Were Not Used

Reason	N	%
QNS for TX; No Research Consent	21	32.3
Poor Organ Quality: Poor Purification	9	13.8
Poor Procurement	7	10.8
Poor Outcome: Insufficient Islet Number and Quality	6	9.2
Ischemia Time Longer than SOP Limit	4	6.2
Microbial Contaminated Organ / Preparation	4	6.2
Poor Organ Quality: Specifics Not Reported	4	6.2
Equipment Malfunction: Islets Lost / Damaged	3	4.6
Reason Not Documented	2	3.1
Significant Down Time	2	3.1
Poor Donor Management	1	1.5
Poor Donor Quality: Prolonged Hospitalization	1	1.5
Poor Organ Quality: Severe Edema	1	1.5
All Unused Isolations	*65*	*100.0*

Exhibit 3
Total Post Purification IEQs Isolated by Islet Use

Islet Use	IEQs Isolated 2001 - 2007	IEQs Isolated 2008	*IEQs Isolated Cumulative*
Basic Science Research	142,241,261	58,883,899	*201,125,160*
Clinical Transplant	86,685,304	5,440,542	*92,125,846*
Not Used	5,726,064	776,958	*6,503,022*
All Isolations	*234,652,629*	*65,101,399*	*299,754,028*

Exhibit 4
All Isolations and Islet Uses by Center

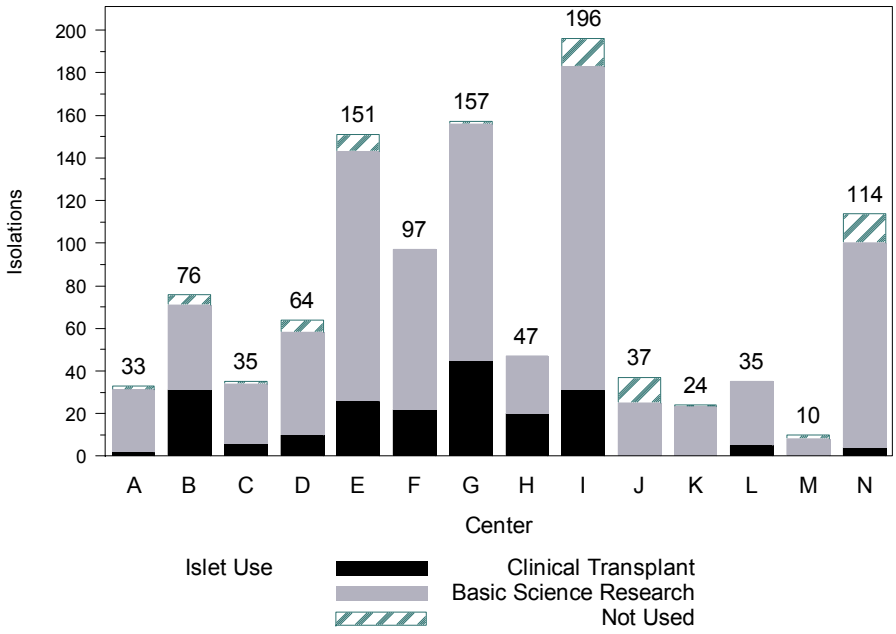


Exhibit 5
Total Post Purification IEQs Isolated by Center

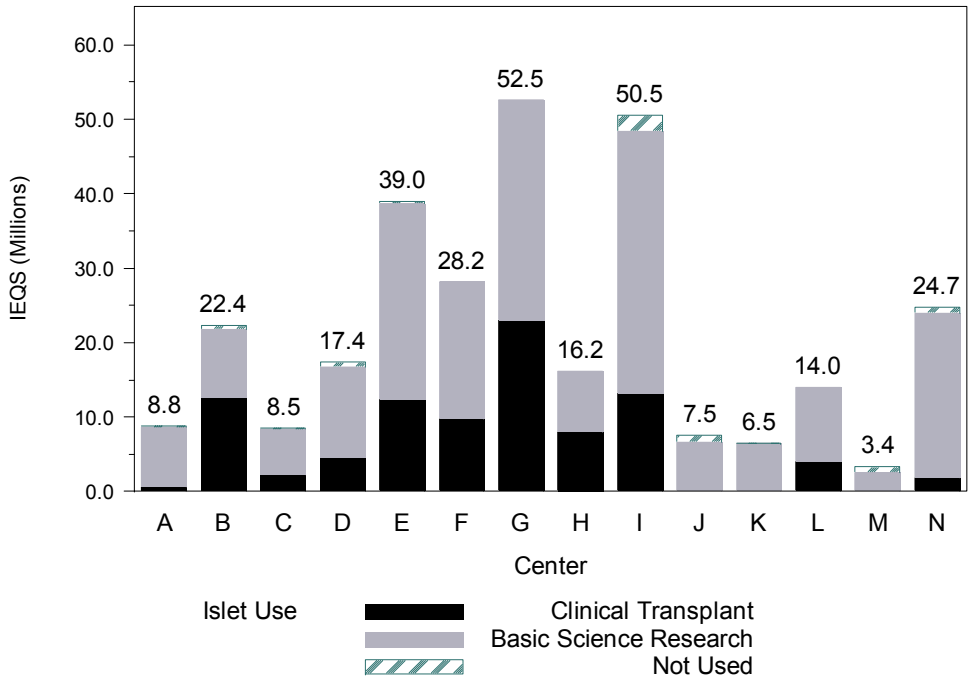
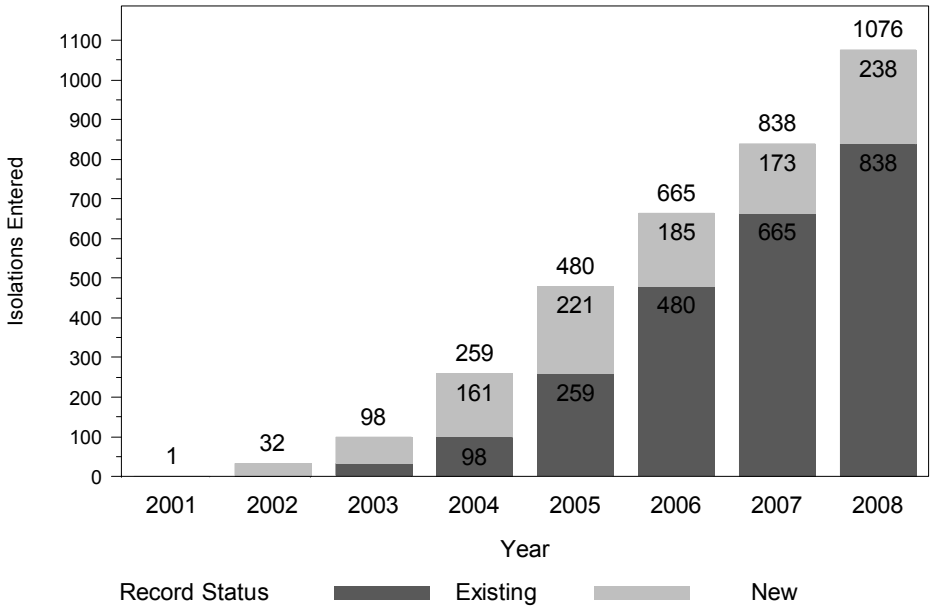
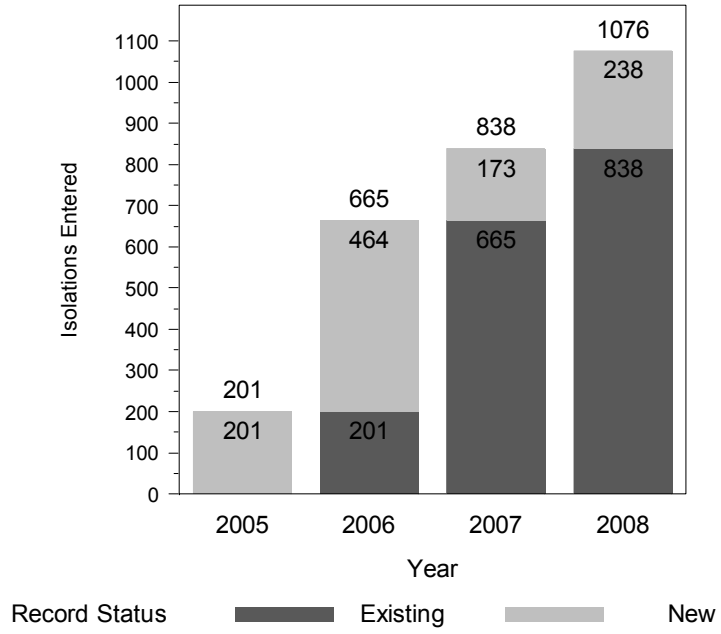


Exhibit 6
Total Isolations Reported to ABCC by Year of Pancreas Recovery



*Year defined as the 12 month period ending on August 31st of the year indicated.

Exhibit 7
Total Isolations Reported to ABCC by Year of Data Entry



*Year defined as the 12 month period ending on August 31st of the year indicated.

Exhibit 8
Time from Pancreas Recovery to ABCC Data Entry
by Year of Pancreas Recovery

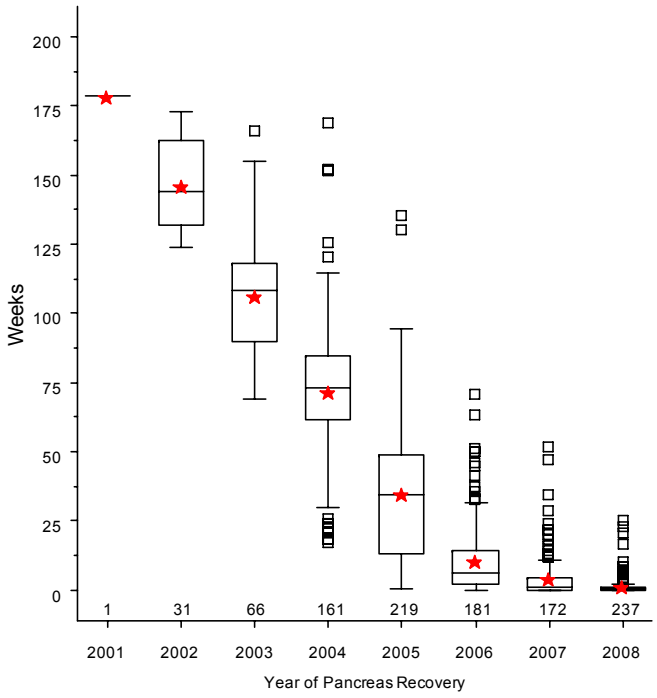


Exhibit 9
Post Purification IEQ Count by Islet Use

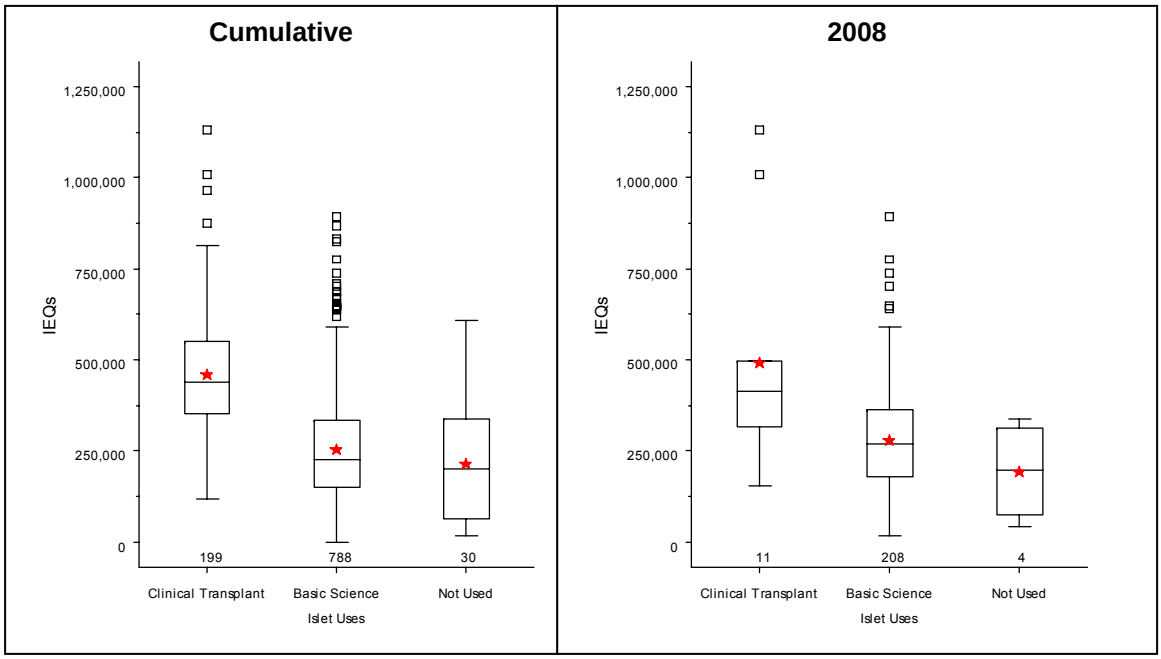


Exhibit 10
Post Purification Actual Islet Count by Islet Use

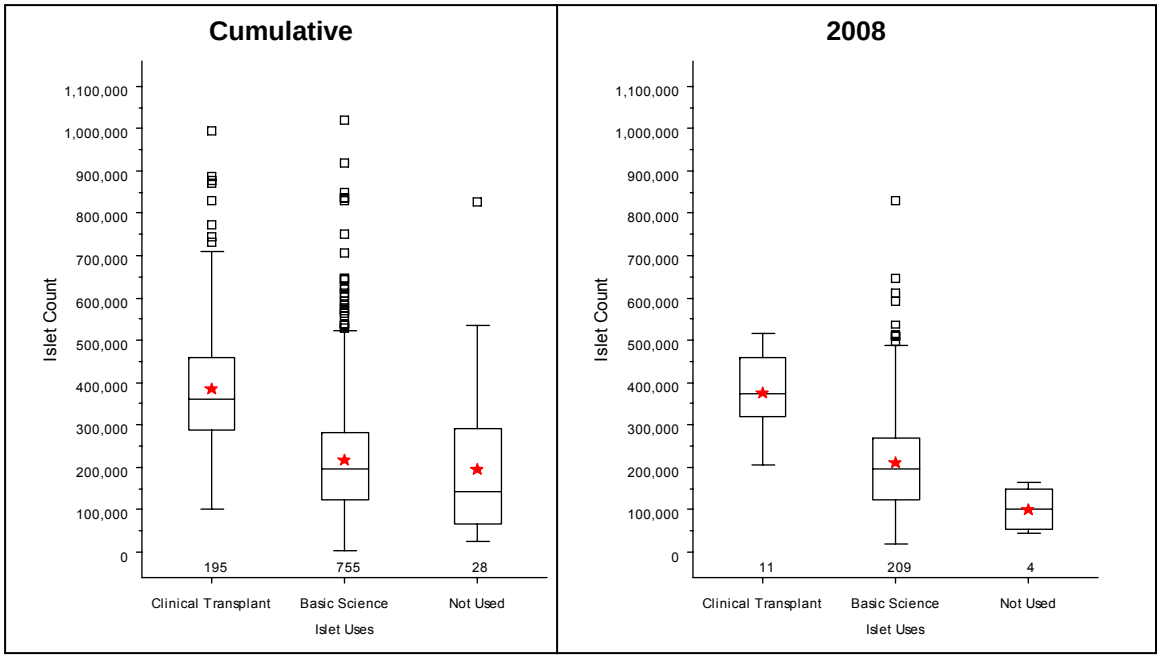


Exhibit 11
Post Purification Islet Index by Islet Use

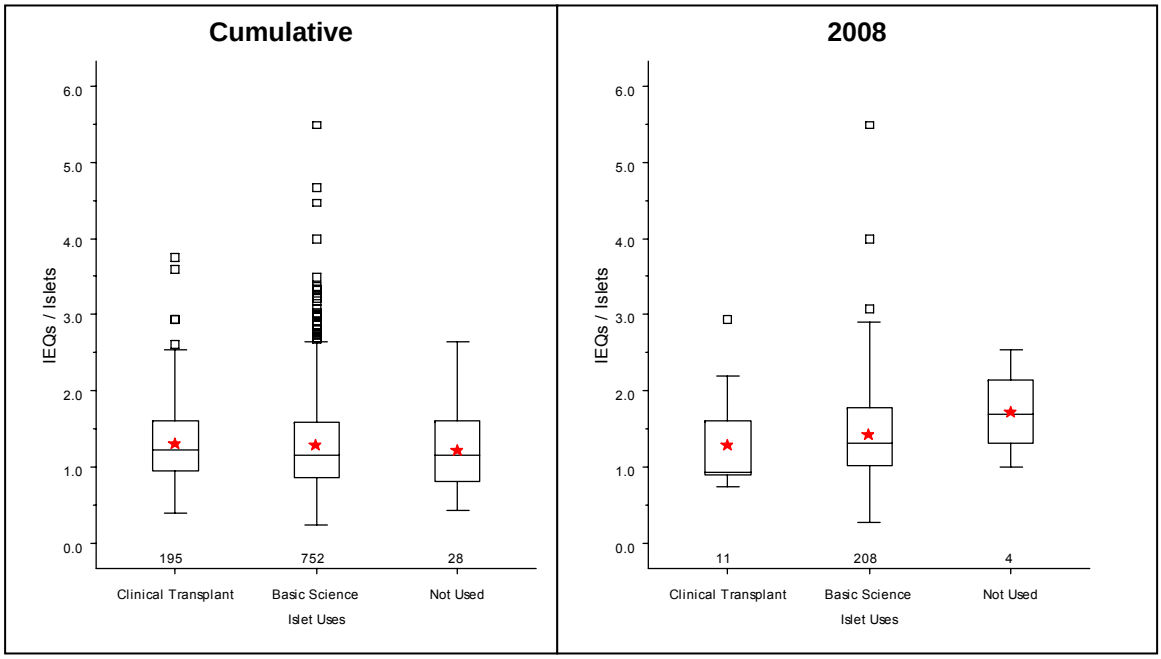


Exhibit 12
Post Purification Islet Viability by Islet Use

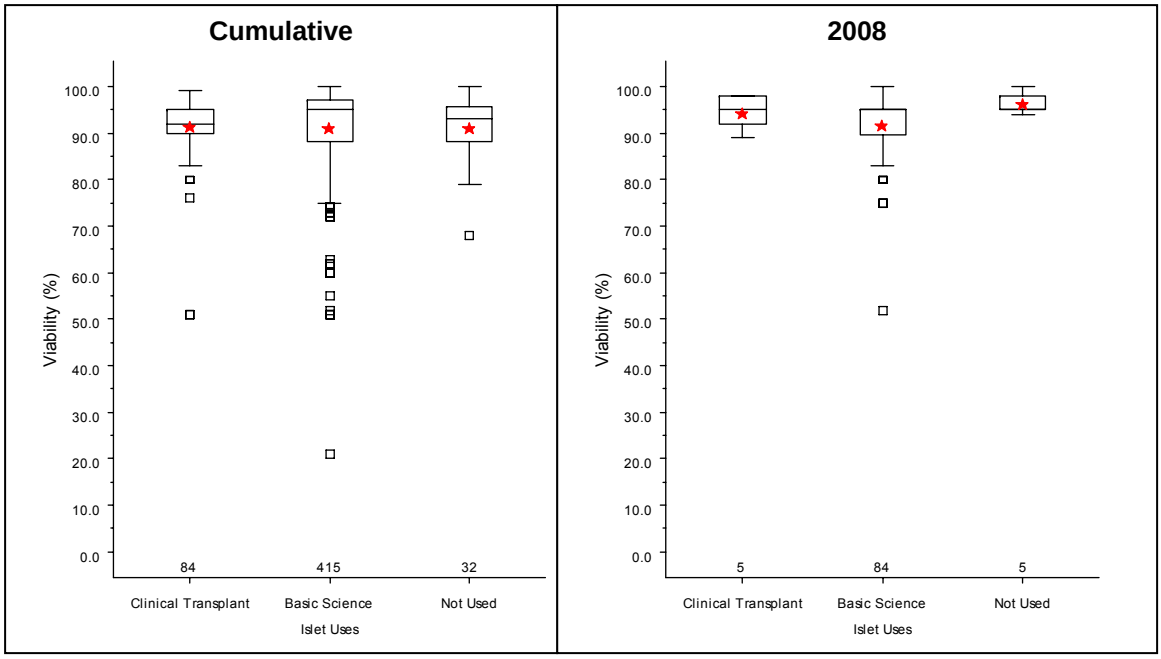
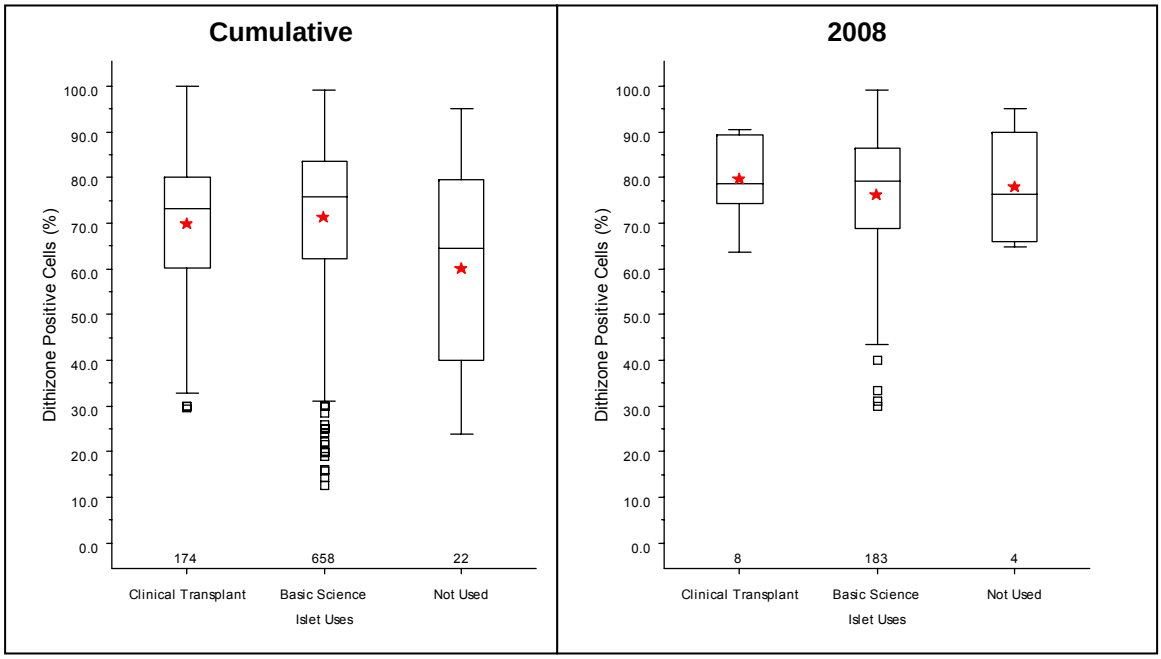


Exhibit 13
Post Purification Purity by Islet Use



Chapter 2: Organ Recovery Information

This second chapter documents the data collected during the procurement of the pancreata and the subsequent shipping to the ICR centers. No specific donor information is required to be entered by the ICR centers into the database because of an agreement between the ABCC and the United Network for Organ Sharing (UNOS) that allows the download of information from the UNOS database system. This information is then merged into the ICP database system.

More than one-quarter of the pancreata documented in the database are recovered for the ICR centers by their local procurement team, and the remaining organs are retrieved by an unrelated recovery team (Exhibit 14).

Exhibit 15 summarizes times and specific storage parameters of the pancreas from aortic cross-clamp to the beginning of isolation. The data show a mean duration of 41.6 minutes from cross-clamp to pancreas recovery. Ranges for all other times are large, possibly due to experimental isolations in which centers were testing the feasibility of beginning isolations after long storage times in certain preservation solutions. The median cold ischemia time is approximately 9.2 hours (551 minutes) as self-reported by center-specific definitions, and 8.4 hours (505.7 minutes) when calculated as the ABCC-adjusted cold ischemia time, defined as the time between cross-clamp and start of dissection.

Exhibit 16 shows that there is a relatively small discourse between the documentation of the pancreas quality by OPO at time of recovery and that of the ICR at time of processing. Of the 672 pancreata that were documented as intact by the procurement team in the operating room, 21 (3.1%) were actually reported as not intact upon arrival at the ICR; however, 53 additional pancreata were documented as not intact upon receipt at the ICR that were not documented as damaged by the OPO. A total of 108 of the 1076 (10%) pancreata received by the ICR centers were reported as not intact.

The majority of pancreata received by the ICR centers were shipped on University of Wisconsin (UW) solution (59.9%); however, a growing number were shipped from the operating room on HTK during the past year and less pancreata utilized the two-layer method.

Exhibits 18 through 22 provide a comparison of islet characteristics based on preservation solution used during shipment of the pancreas from the OPO to the ICR center. There appear to be no statistical differences among any of the solutions used.

Exhibits 23 through 27 show a variety of results post islet isolation comparing remote versus local procurement of pancreata. Statistical analysis shows very little difference in the overall quality of the isolated islets in the parameters compared between the two types of procurement teams.

Exhibit 14
Procurement Team

	2008		Cumulative	
	N	%	N	%
Procurement Team				
Remote	157	66.0	762	70.8
Local	80	33.6	308	28.6
Not Documented	1	0.4	6	0.6
All Isolations	*238*	*100.0*	*1076*	*100.0*

Exhibit 15
Organ Recovery Times

	N	Mean	SD	Min	25th %	Median	75th %	Max
Time from Cross Clamp to Pancreas Recovery (min)	708	41.62	21.86	5	27	38	51	187
Time in Shipping Preservation Solution (min)	729	422.33	254.04	25	257	370	545	2790
Time in ICR Preservation Solution (min)	143	213.87	260.24	9	40	72	282	1198
Total Pancreas Preservation Time (min)	739	447.41	277.44	25	267	385	567	2790
Self-Reported Duration of Cold Ischemia (min)	1048	551.00	277.71	53	369	496	692	2880
ICR-Adjusted Duration of Cold Ischemia (min)*	994	505.74	299.82	53	316	443	622	3377

*ICR-Adjusted Duration of Cold Ischemia is defined as the time between cross-clamp and the start of dissection. Self-Reported Duration of Cold Ischemia relies on center-specific definitions.

Exhibit 16
Pancreas Condition
Post Procurement versus Arrival at ICR

Cumulative

	Intact at ICR						*Total Pancreata Post Procurement*	
	Yes		No		Not Documented			
	N	%	N	%	N	%	*N*	*%*
Intact Post Procurement								
Yes	646	68.3	21	19.4	5	22.7	*672*	*62.5*
No	1	0.1	34	31.5	0	0.0	*35*	*3.3*
Not Documented	299	31.6	53	49.1	17	77.3	*369*	*34.3*
Total Pancreata at ICR	*946*	*100.0*	*108*	*100.0*	*22*	*100.0*	*1076*	*100.0*

2008

	Intact at ICR						*Total Pancreata Post Procurement*	
	Yes		No		Not Documented			
	N	%	N	%	N	%	*N*	*%*
Intact Post Procurement								
Yes	130	63.1	5	19.2	2	33.3	*137*	*57.6*
No	0	0.0	11	44.0	0	0.0	*11*	*4.6*
Not Documented	76	36.9	10	40.0	4	66.7	*90*	*37.8*
Total Pancreata at ICR	*206*	*100.0*	*26*	*100.0*	*6*	*100.0*	*238*	*100.0*

Exhibit 17
Summary of Preservation Solutions Reported to ABCC

		2008		Cumulative	
		N	%	N	%
During Shipping	**Upon Arrival at ICR**				
Saline	P Phase 2	0	-	1	0.1
HTK	Not Changed	36	15.1	94	8.7
	Eurocollins	0	-	1	0.1
	P Phase 2	15	6.3	26	2.4
	Other	1	0.4	3	0.3
Two-Layer	Not Changed	29	12.2	232	21.6
	Eurocollins	0	-	5	0.5
	P Phase 2	3	1.3	20	1.9
	UW	0	-	6	0.6
UW	Not Changed	137	57.6	572	53.2
	Eurocollins	0	-	1	0.1
	P Phase 2	7	2.9	14	1.3
	Two-Layer	0	-	53	4.9
	UW	1	0.4	3	0.3
	Other	1	0.4	1	0.1
Not Documented	Not Changed	6	2.5	26	2.4
	P Phase 2	1	0.4	13	1.2
	Two-Layer	0	-	1	0.1
	UW	1	0.4	2	0.2
	Other	0	-	1	0.1
	Not Documented	0	-	1	0.1
All Isolations		*238*	*100.0*	*1076*	*100.0*

Exhibit 18
Post Purification IEQ Count by Preservation Solution

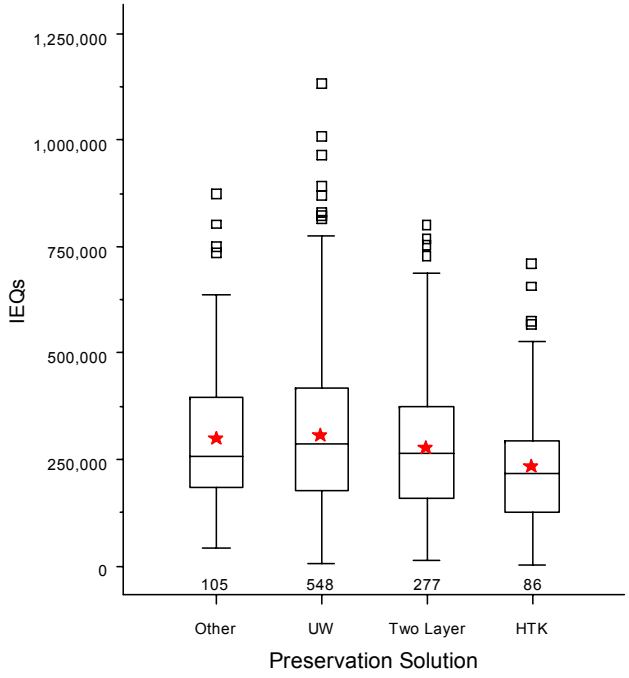


Exhibit 19
Post Purification Actual Islet Count by Preservation Solution

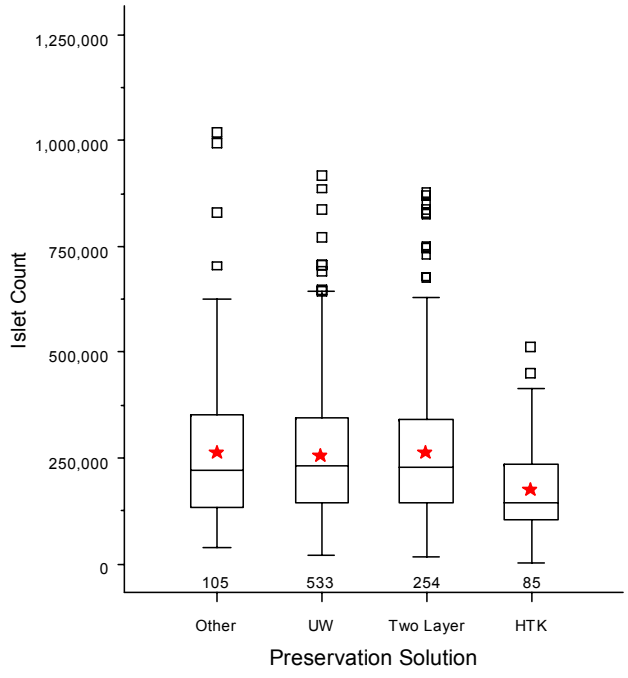


Exhibit 20
Post Purification Islet Index by Preservation Solution

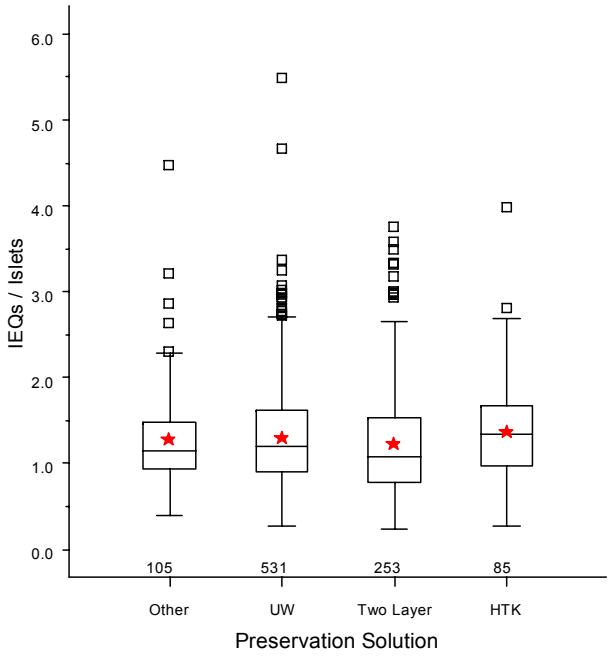


Exhibit 21
Post Purification Islet Viability by Preservation Solution

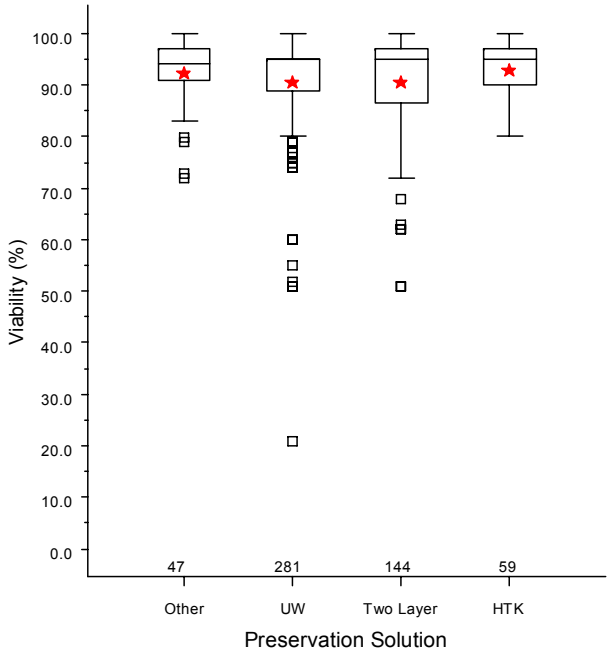


Exhibit 22
Post Purification Purity by Preservation Solution

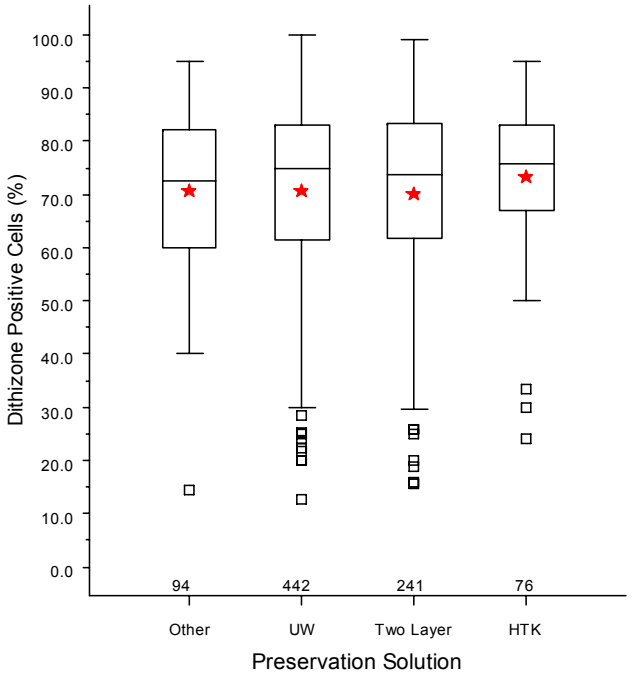


Exhibit 23
Post Purification IEQ Count by Procurement Team

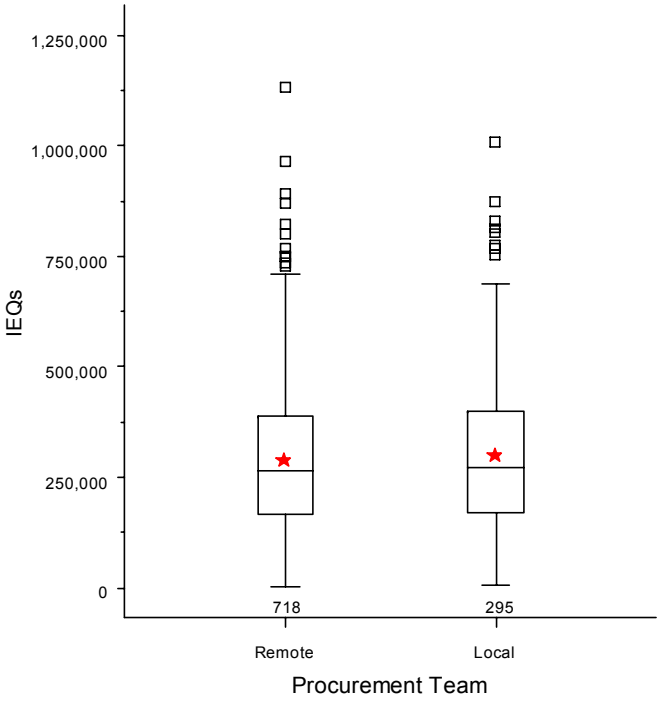


Exhibit 24
Post Purification Actual Islet Count by Procurement Team

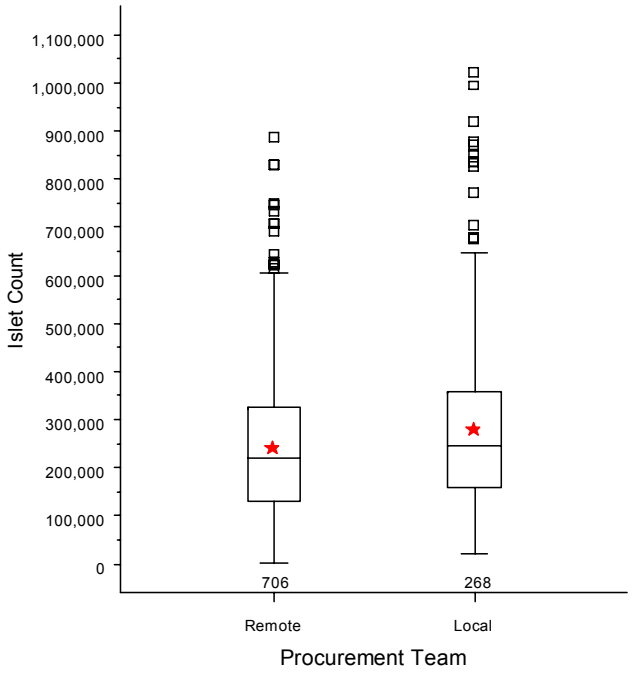


Exhibit 25
Post Purification Islet Index by Procurement Team

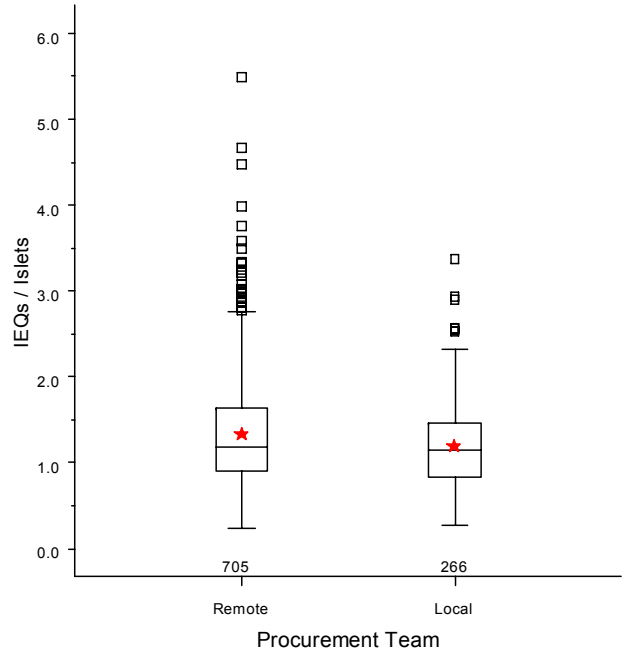


Exhibit 26
Post Purification Islet Viability by Procurement Team

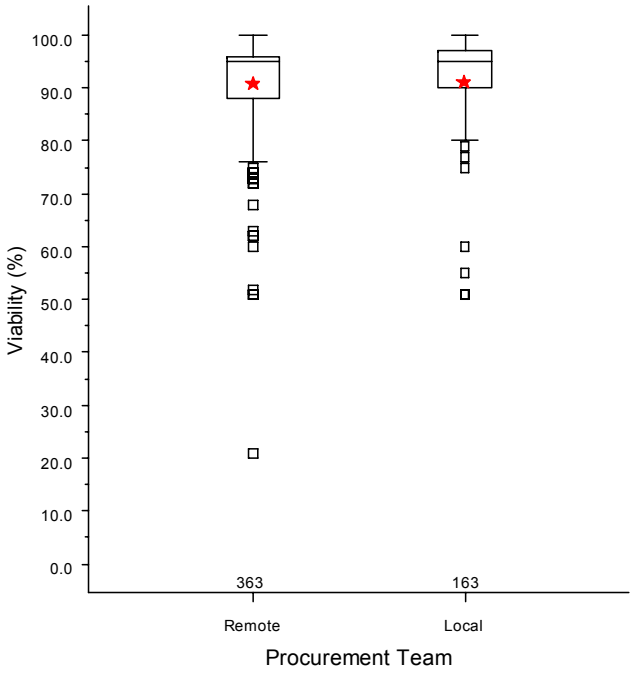
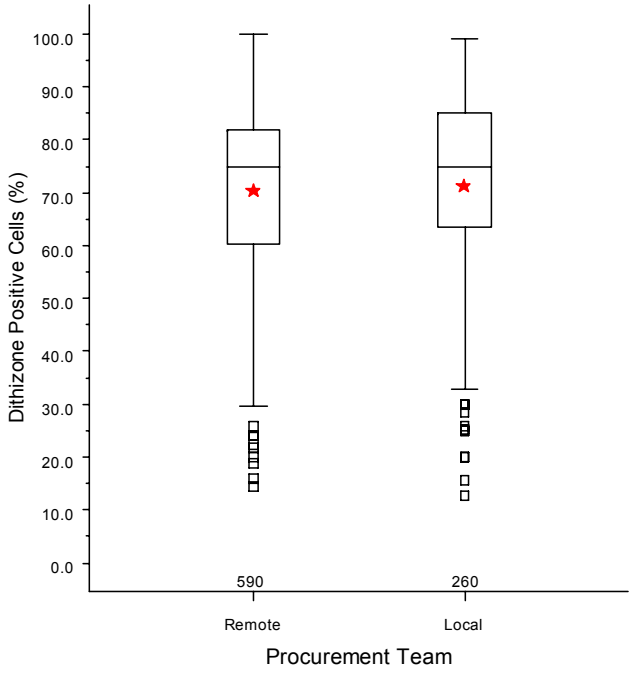


Exhibit 27
Post Purification Purity by Procurement Team



Chapter 3: Pancreas Characterization at ICR

The quality of the pancreata upon arrival at the ICR centers is the topic of chapter 3. Details that are documented include: the amount of fat on and within the pancreatic tissue, whether the pancreas was received as an intact organ or if surgical damage had occurred, if the pancreas had any macroscopic damage, such as hematoma, bruising, or extensive cauterization, and if the pancreas was edematous.

Exhibit 28 shows that 204 (19.0%) of the 1076 pancreata reported had light surface fat, 332 (30.9%) had moderate surface fat, while 318 (29.6%) had heavy surface fat. Exhibits 29 through 32 depict the various quality of islet isolation based on the fat content and/or fat infiltrate of the organ. For Exhibits 33 and 34, the ABCC has developed a Fat Index as defined in the *Definition of Terms* to combine both the fat infiltrate and surface fat as a measure of isolation quality. In general, islets isolated from pancreata with more surface fat and more infiltrated fat yielded a slightly larger number of IE.

Exhibit 36 summarizes the initial condition of the pancreas upon arrival at the ICR. 10% of pancreata reported to the ABCC reported were not intact, 18.1% had other macroscopic damage, and 10.5% were reported as having edema. Overall, intact pancreata yielded slightly higher numbers of IE post purification. The number of IE post purification could have been influenced by the amount of tissue isolated in some cases. Exhibits 40 through 42 depict the islet quality from pancreata with or without macroscopic damage. There were no statistical differences in any of the islet quality parameters measured based on macroscopic damage.

Pancreatic edema could indicate trauma or poor donor management, and these types of organs are usually avoided by most ICR centers when possible. Exhibit 43 shows a lower mean and median IEQ yield in edematous pancreata isolated by the ICR Consortium, although Exhibits 44 and 45 show little difference in viability and purity based on pancreata edema.

Exhibit 28
Pancreas Fat Content Assessed by Islet Laboratory

	N	%
Pancreas Surface Fat		
Clean	89	8.3
Light	204	19.0
Moderate	332	30.9
Heavy	318	29.6
Not Documented	133	12.4
Fat Infiltration		
None	218	20.3
Patchy	228	21.2
Moderate	219	20.4
Heavy	201	18.7
Not Documented	210	19.5
All Pancreata	*1076*	*100.0*

Exhibit 29
Post Purification IEQ Count by Pancreas Surface Fat

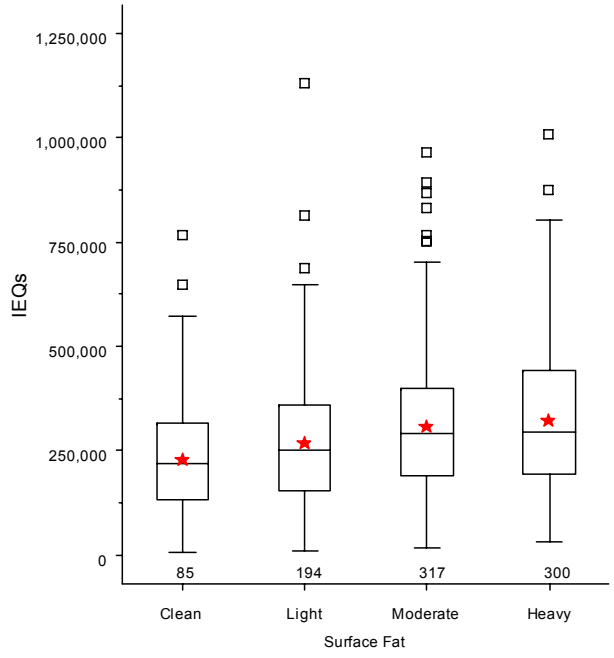


Exhibit 30
Post Purification Islet Index by Pancreas Surface Fat

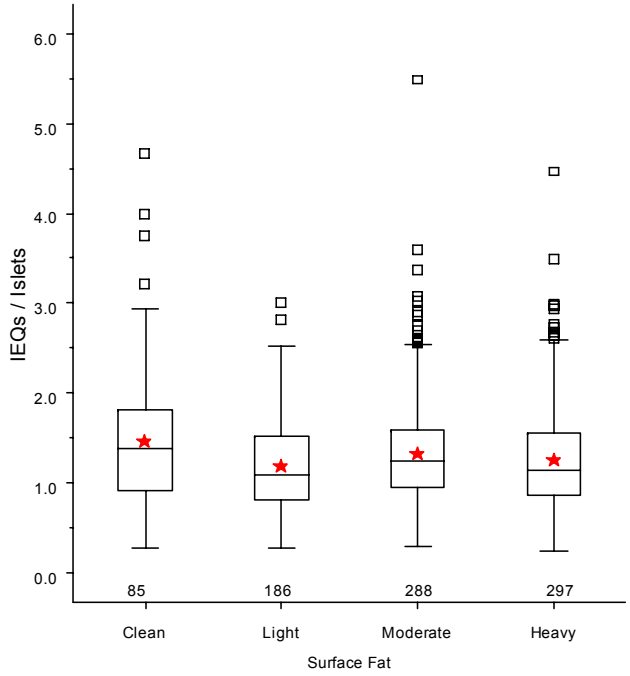


Exhibit 31
Post Purification IEQ Count by Pancreas Fat Infiltration

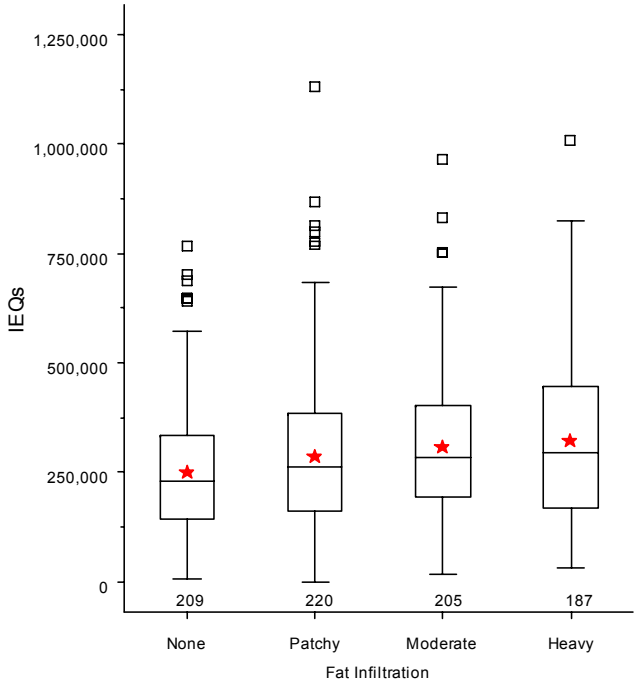


Exhibit 32
Post Purification Islet Index by Pancreas Fat Infiltration

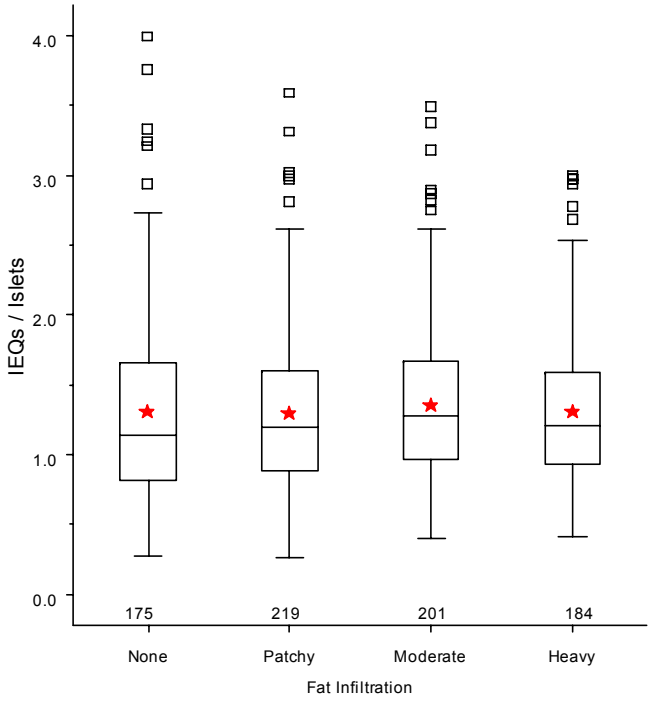


Exhibit 33
Post Purification IEQ Count by Fat Index

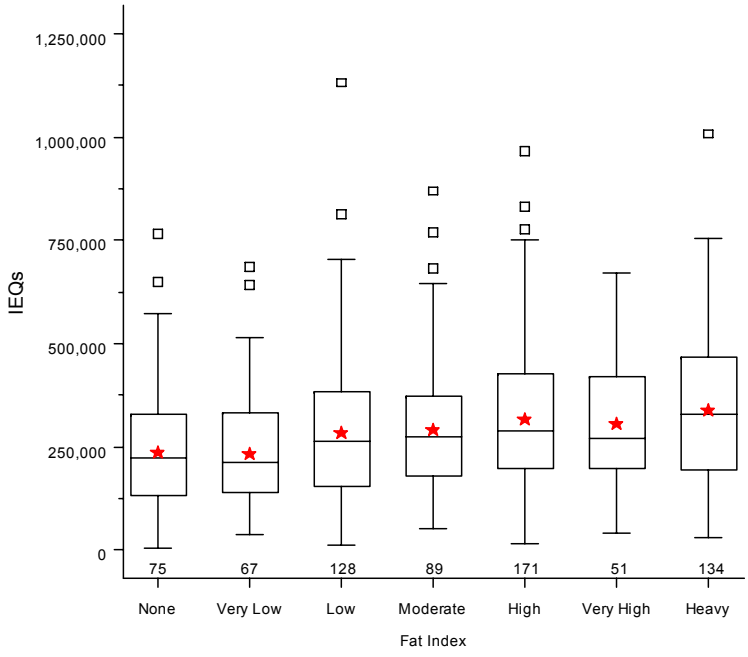


Exhibit 34
Post Purification Islet Index by Fat Index

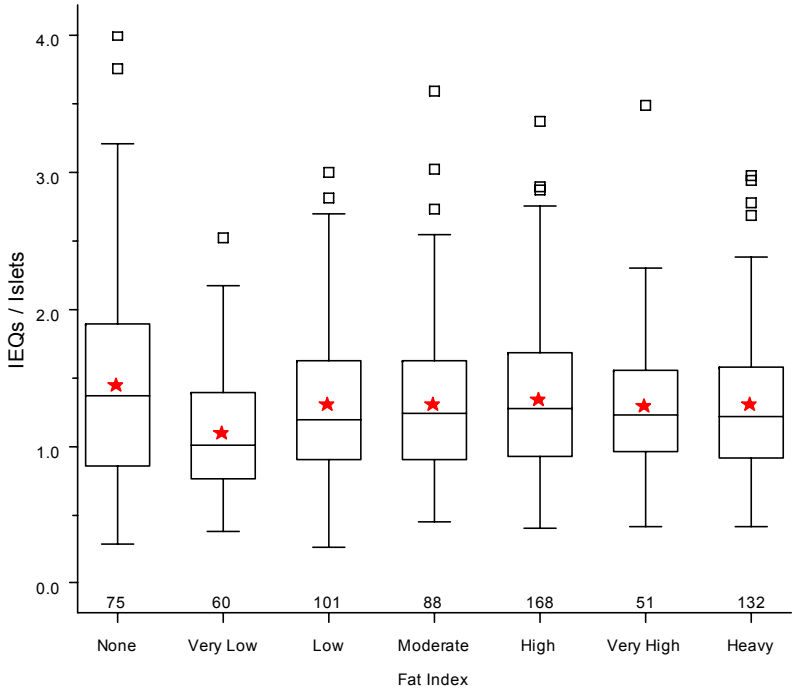


Exhibit 35
Comparison of Surface Fat and Fat Infiltration upon Arrival at ICR

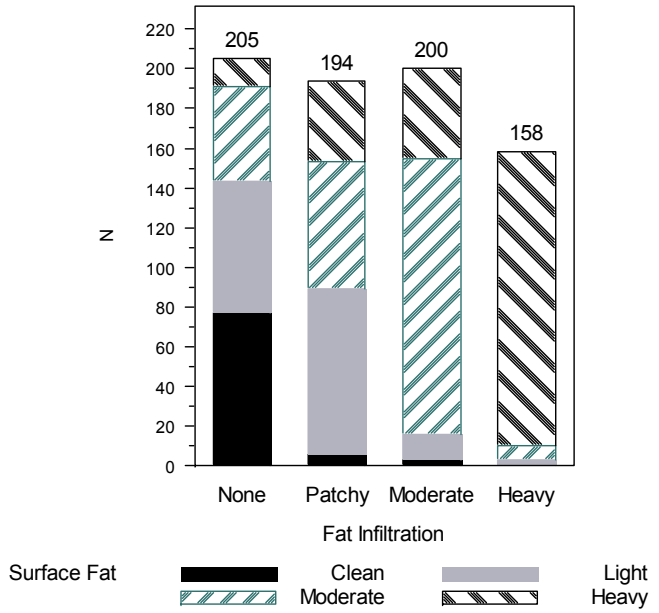


Exhibit 36
Pancreas Condition upon Arrival at Islet Laboratory

	N	%
Pancreas Intact		
Yes	946	87.9
No	108	10.0
Not Documented	22	2.0
Macroscopic Damage		
Yes	195	18.1
No	844	78.4
Not Documented	37	3.4
Edema		
Yes	113	10.5
No	879	81.7
Not Documented	84	7.8
All Pancreata	*1076*	*100.0*

Exhibit 37
Post Purification IEQ Count by Intact Pancreas

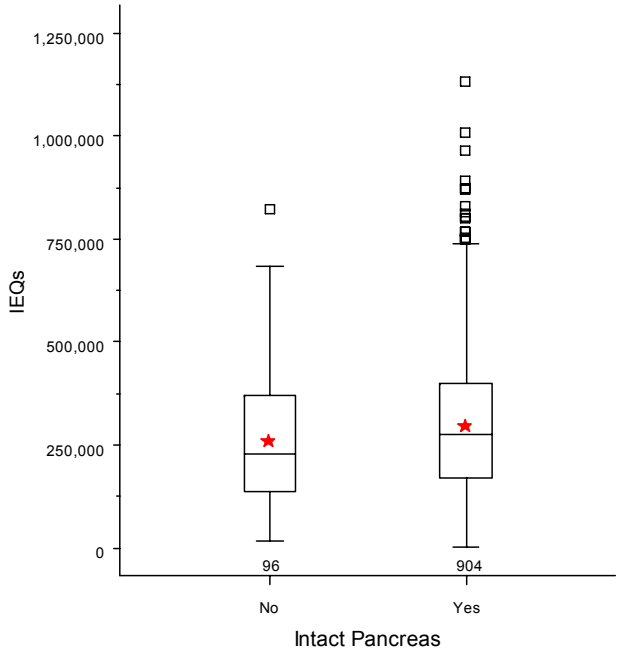


Exhibit 38
Post Purification Islet Viability by Intact Pancreas

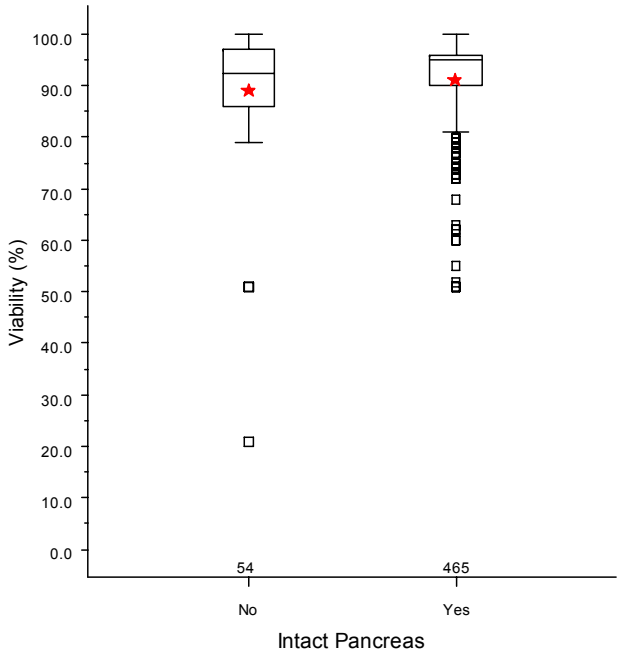


Exhibit 39
Post Purification Purity by Intact Pancreas

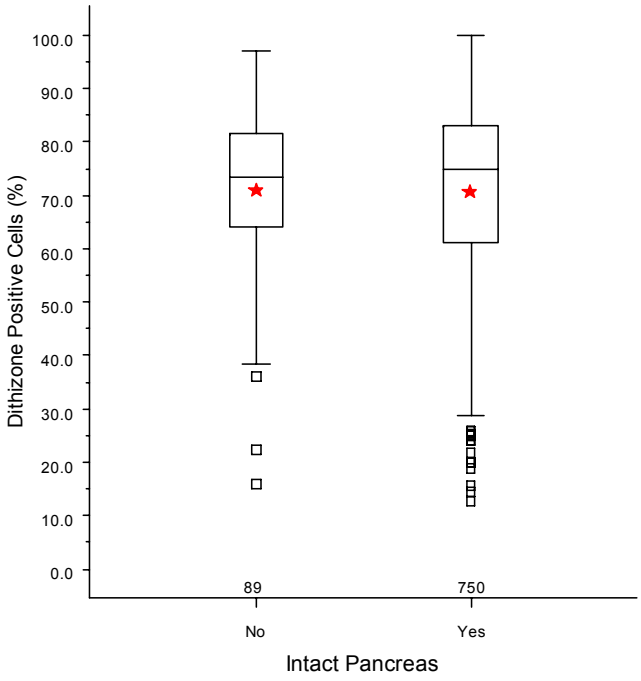


Exhibit 40
Post Purification IEQ Count by Pancreas Macroscopic Damage

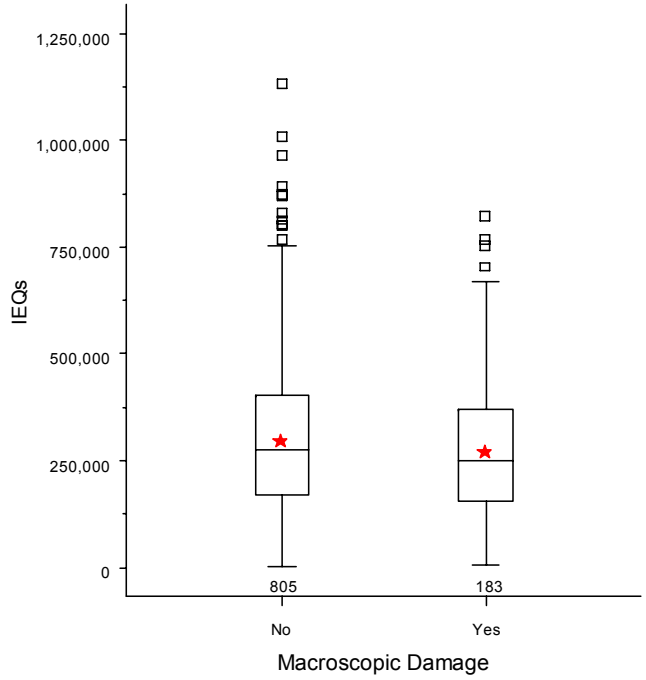


Exhibit 41
Post Purification Islet Viability by Pancreas Macroscopic Damage

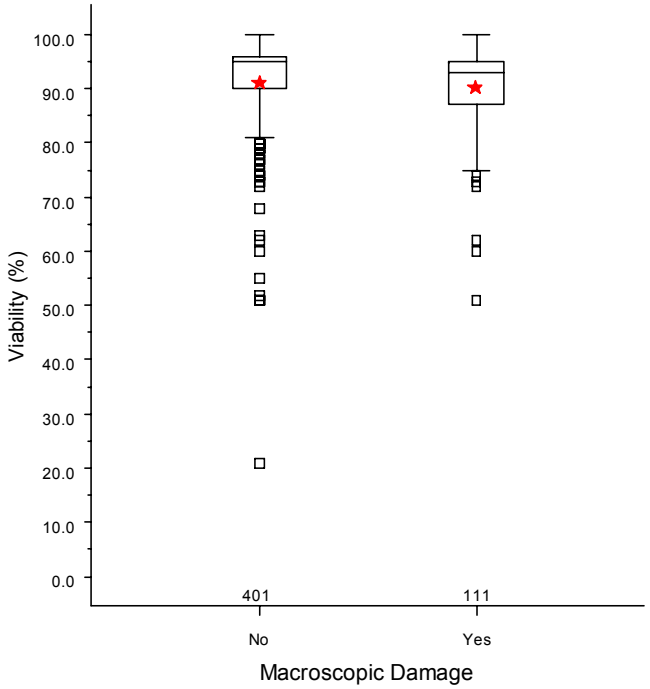


Exhibit 42
Post Purification Purity by Pancreas Macroscopic Damage

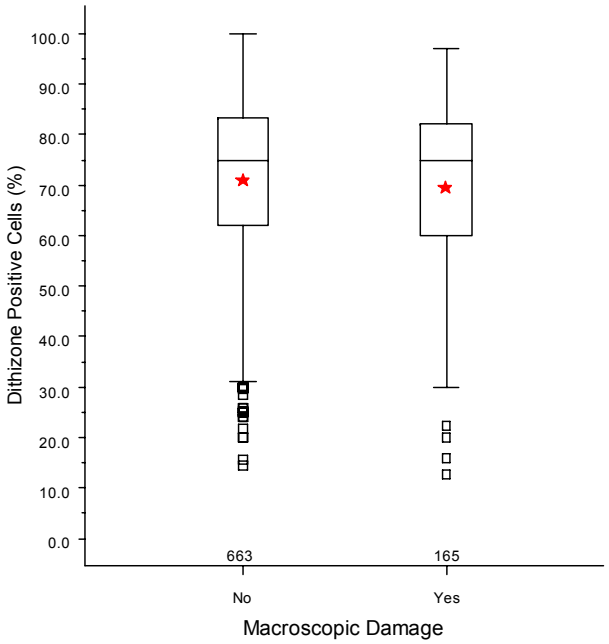


Exhibit 43
Post Purification IEQ Count by Pancreas Edema

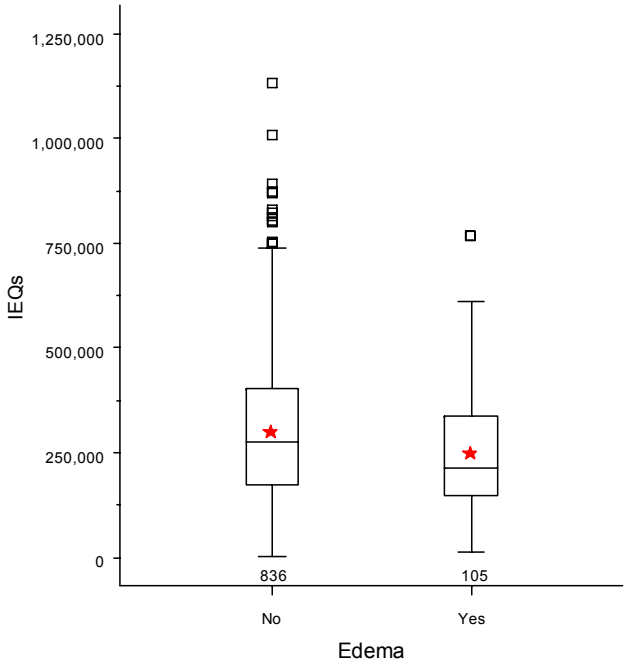


Exhibit 44
Post Purification Islet Viability by Pancreas Edema

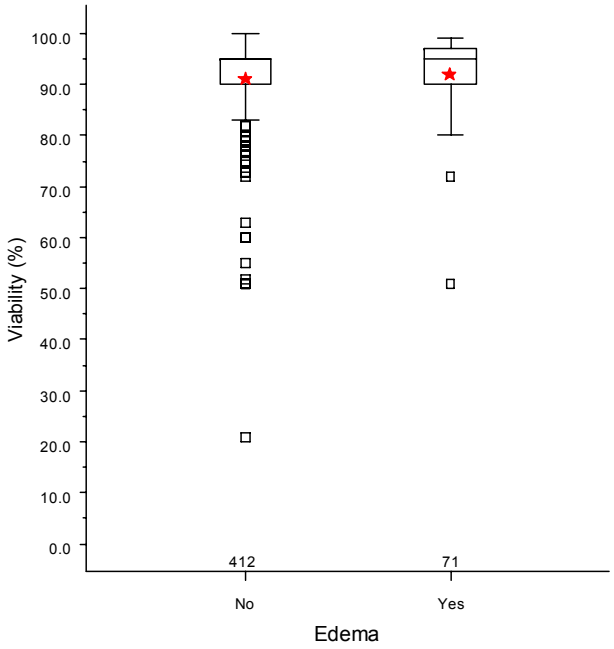
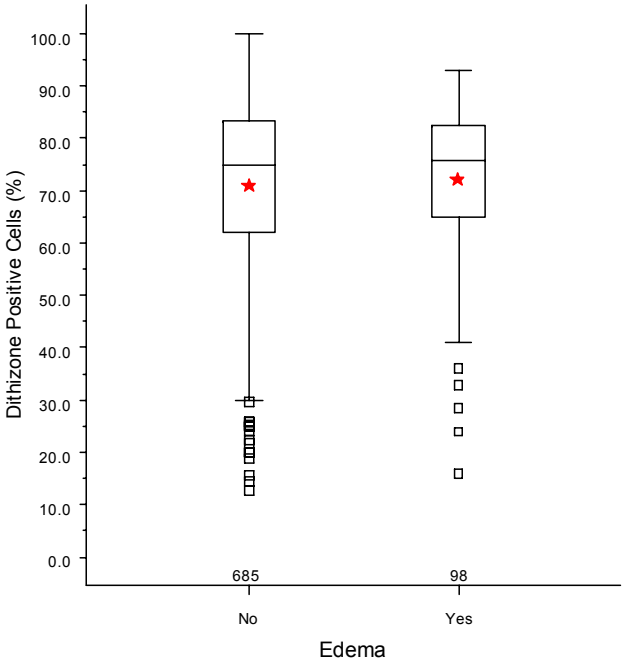


Exhibit 45
Post Purification Purity by Pancreas Edema



Chapter 4: Collagenase Information

For the second year in a row, centers struggled to find workable enzymes that would yield the maximum quantity and quality of human islets that they had experienced prior to the bovine tissue contamination problems of 2006. Serva products were used most often in 2008 with their NB1 Premium Grade accounting for 48.7% of the isolations and their NB1 GMP Grade being used for 16.8% of the digestions. Sigma Type IV Collagenase also made resurgence this past year also being used in 16.8% of the isolations. Two new products were introduced in 2008. Vitacyte perfected their enzyme blend and began marketing their CIzyme products and Roche introduced a new mammalian-free enzyme, 2000 MDFT.

The enzyme used in the isolation process is most commonly dissolved in a buffered salt solution for infusion into the pancreas and for the dissociation process. Hank's Buffered Salt Solution (HBSS) was the most common base solution used (60.7%). In addition, Perfusion and Priming solutions (Mediatech Inc) products that have a base of HBSS were used in 29.9% of the pancreata reported by the ICRs.

Sixteen different additives were used in addition to the enzyme in the dissociation solution. The most prevalent additive was a form of DNAse (either porcine or recombinant (Pulmozyme, Genentech). DNAse was used in 54.3% of the processed pancreata. In 35.1% of the isolations, additional calcium chloride was added to the enzyme solution.

Exhibits 49-52 illustrate the influence of the type of collagenase used on the quantity and quality of isolated islets. In the Cumulative Exhibits, the "other"category represents the following enzyme types: CIzyme C1:C2 (7 records), Collagenase P (5 records), and collagenase types reported as "Other" (55 records). In the 2008 Exhibits, "other" category represents: Liberase HI (2 records) and collagenase types reported as "Other" (64 records).

Exhibit 46
Collagenase Summary

		2008		Cumulative	
		N	%	N	%
Collagenase Manufacturer	**Collagenase Type**				
Serva	NB1 Premium Grade	116	48.7	162	15.1
	NB1 GMP Grade	40	16.8	67	6.2
	Crude	0	-	16	1.5
Sigma	Collagenase Type IV	40	16.8	54	5.0
Roche	Liberase Blendzyme	0	-	19	1.8
	Liberase HI	2	0.8	613	57.0
	Collagenase P	1	0.4	5	0.5
	Custom Blend	0	-	87	8.1
	Collagenase 2000 MFT	16	6.7	16	1.5
	Other Combinations	0	-	3	0.3
Vitacyte	CIzyme Collagenase HA (CIzyme C1:C2)	19	8.0	19	1.8
No Collagenase Used	Pancreata Not Used	0	-	1	0.1
All Isolations		*238*	*100.0*	*1076*	*100.0*

Exhibit 47
Summary of Collagenase Base Media

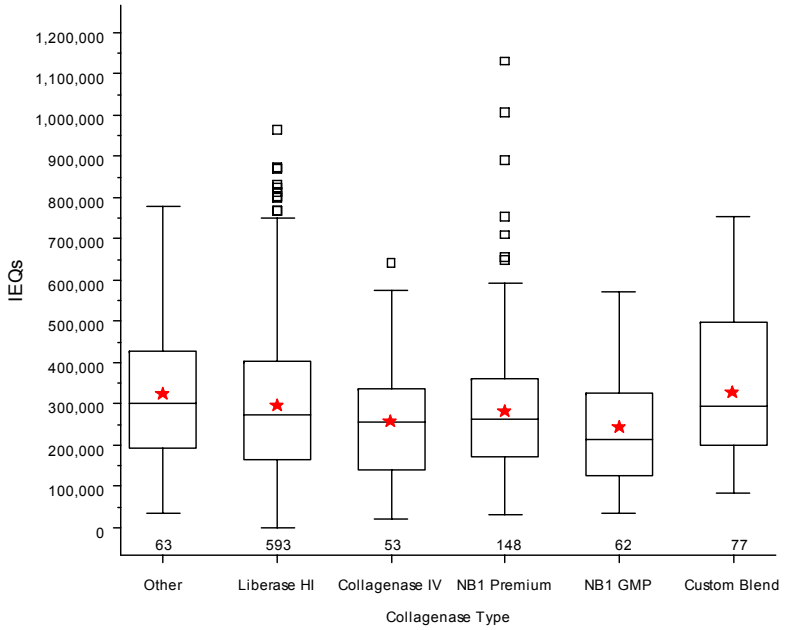
	N	%
Collagenase Base Medium		
Mediatech Perfusion Solution	245	22.8
Hanks Balanced Salt Solution (HBSS)	653	60.7
H/P Phase 1	73	6.8
Mediatech Priming Solution	76	7.1
Phosphate Buffered Saline (PBS)	3	0.3
Other	14	1.3
Not Documented	12	1.1
All Isolations	*1076*	*100.0*

Exhibit 48
Summary of Collagenase Additives

	N	%
Collagenase Additive		
Bovine Serum Albumin (BSA)	1	0.1
Calcium Chloride (CaCl)	388	36.1
Ciprofloxacin	20	18.6
D-Mannitol	3	0.3
DNAse (Pulmozyme)	584	54.3
EGCG	1	0.1
Ethylene Diamine Tetraacetic Acid (EDTA)	1	0.1
HEPES	339	31.5
Heparin	138	12.8
L-glutamine	83	7.7
Pefabloc	103	9.6
Polyheme	2	0.2
Sodium Hydroxide (NaOH)	160	14.9
Tagatose	1	0.1
Trasylol	11	10.2
n-Acetyl-Cysteine (NAC)	1	0.1
All Additives	1836	100.0

Exhibit 49
Post Purification IEQ Count by Collagenase Type

Cumulative



2008

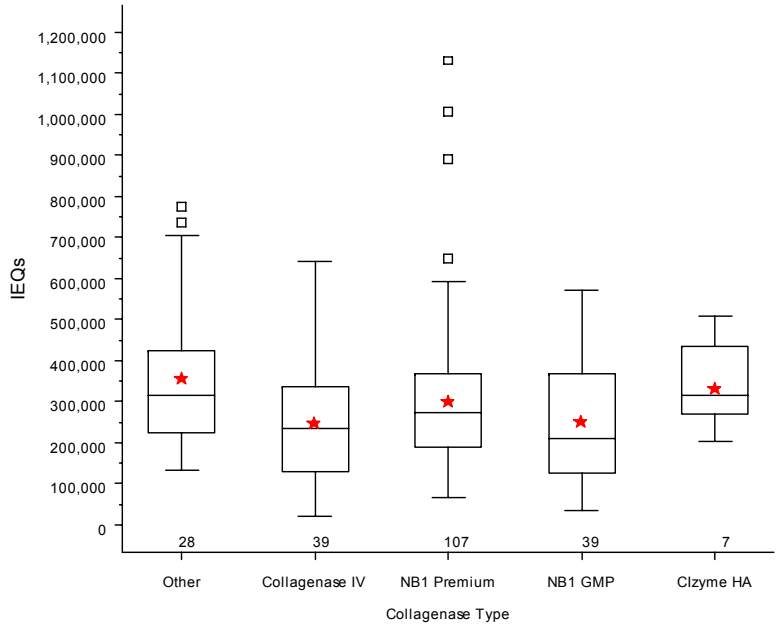
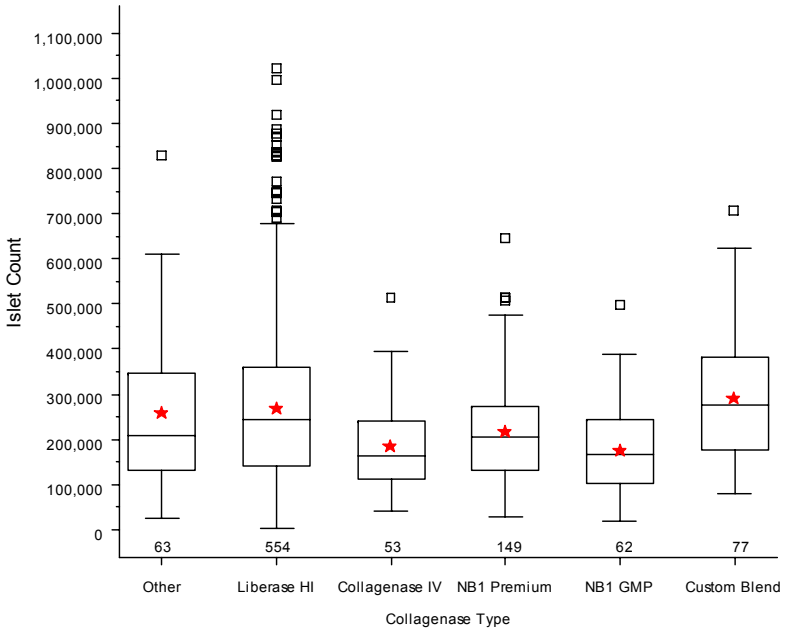


Exhibit 50
Post Purification Actual Islet Count by Collagenase Type

Cumulative



2008

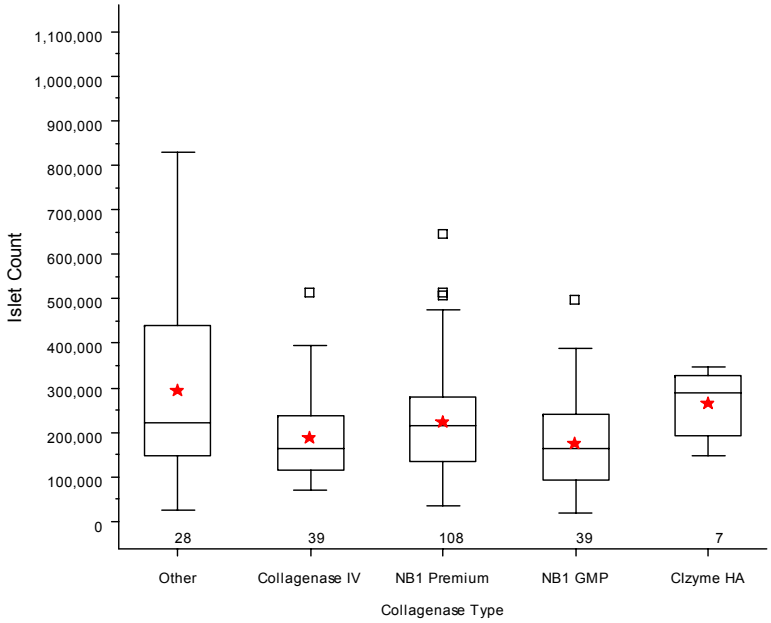
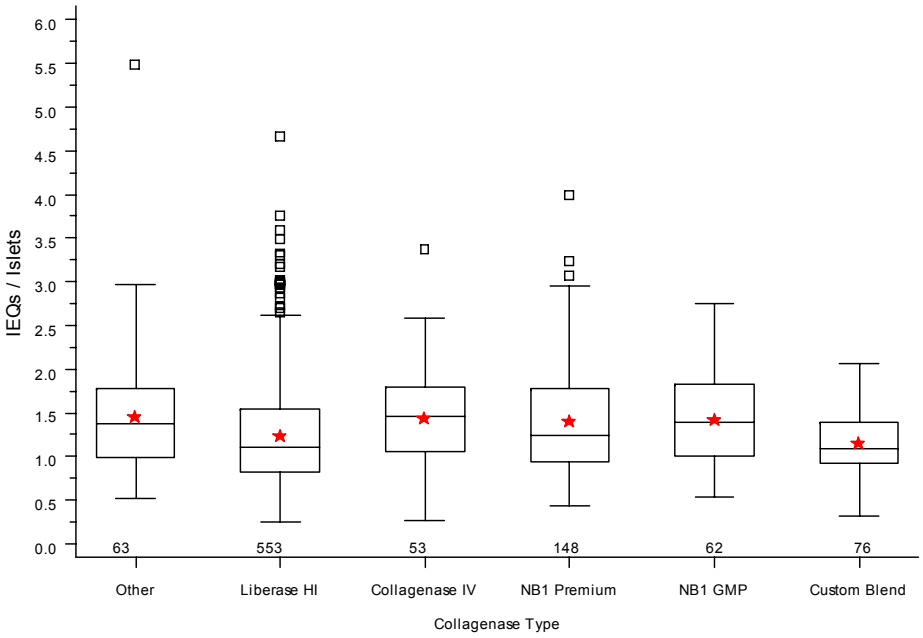


Exhibit 51
Post Purification Islet Index by Collagenase Type

Cumulative



2008

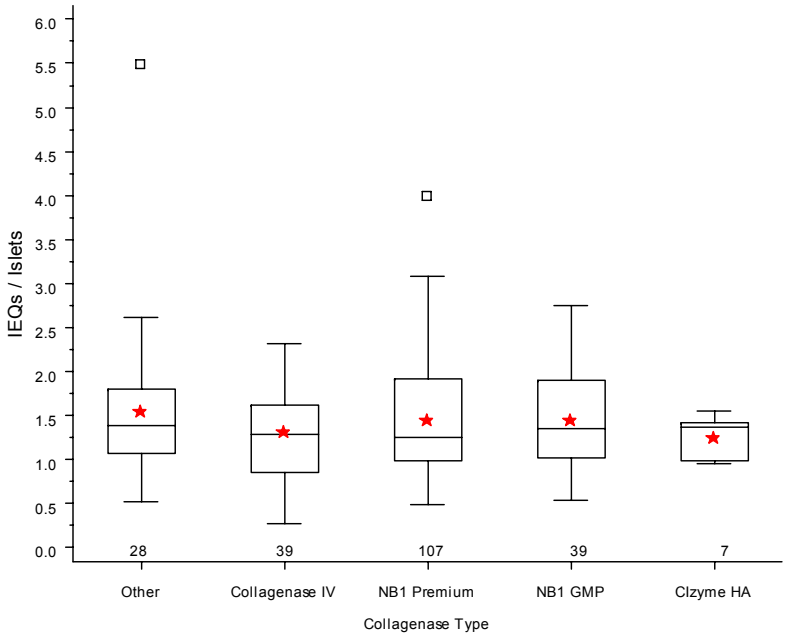
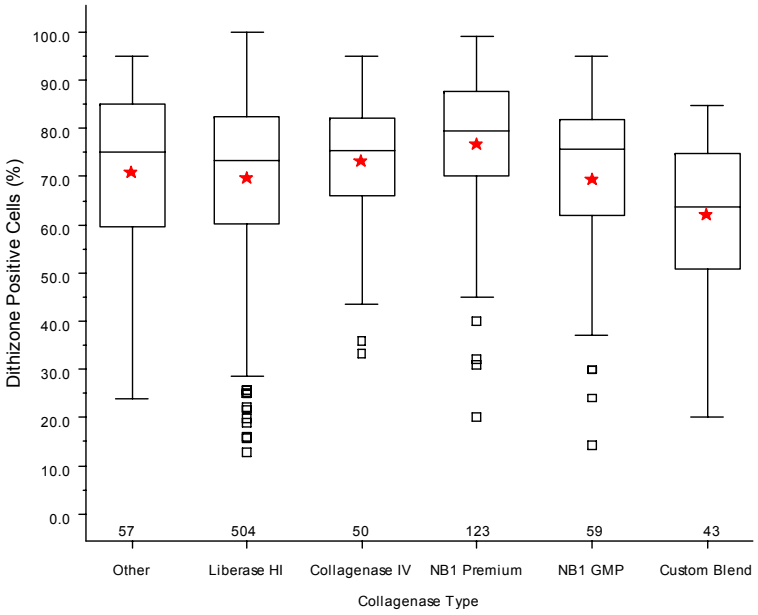
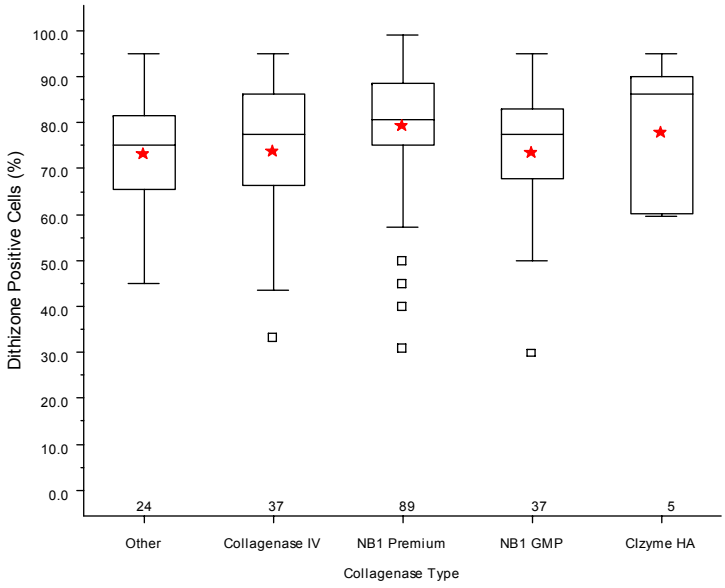


Exhibit 52
Post Purification Purity by Collagenase Type

Cumulative



2008



Chapter 5: Pancreas Distention Information

This set of exhibits reflects the data collected concerning the dissection or trimming of the pancreata and the subsequent distention of the organ using the selected enzymes. The amount of trimming that is necessary for efficient islet isolation is controversial. According to the data collected by the ICR, times for dissection range from no dissection to almost three hours (Exhibit 53), with a mean time of approximately 41.3 minutes and a median time of 40 minutes.

Exhibit 54 tabulates the weights of reported pancreata post trimming and pre-distention. The common weight of the tissue used for human islet isolations among the ICR centers was approximately 100 grams by both mean and median, although several organs weighed up to a quarter of a kilogram.

Pancreas ductal distention is reported to the ABCC by two methods: manual distention using a syringe, and automatic perfusion distention using electric pumps and varying speeds. Exhibit 55 shows that approximately two-thirds of the reported pancreata were distended using the automatic perfusion method, while one-third were manually distended. A breakdown of parameters measured during the perfusion method is detailed in Exhibit 56, showing average temperatures of 10.5 and 10.6° C, mean pressures of 130.5 and 130.9 mmHg, and flow rates of 59.2 and 62.6 mL/min for body and tail and pancreatic head, respectively.

In many procedures, the centers chose to divide the pancreas after distention into smaller pieces with the hope of increasing the enzyme activity and yielding a better digestion of the pancreatic tissue. With the revision of the database, the ABCC began collecting this information on the isolations entered after May of 2006. The data shown in Exhibits 57-59 depict the details of the division of the pancreas from a limited number of isolations performed after the database revision date. Of the 429 documented cases for which the number of pieces was recorded, centers reported cutting the pancreas into a median of 10 pieces, with a range from 2 to 31 (Exhibit 58). Of those reporting, only 247 isolations recorded the size of the pieces (Exhibit 59), with the majority being between 1 cm and 3 cm in length.

Exhibits 61-63 depict the influence of the type of distention on the quality of the digestion. For the third year in a row, manual distention seems to show an increase in the total number of IEQs in the post digestion counts over the automatic perfusion method. (Exhibit 61)

Exhibits 64-66 compare the quality of the islets with the quality of the distension. As one might expect, the numbers of IEQs and AI reported post digestion seem to correlate with the quality of the distention.

Exhibit 53
Duration of Dissection

	N	Mean	SD	Min	25th %	Median	75th %	Max
Duration of Dissection (mins)	1018	41.3	23.5	0.0	24.0	40.0	57.0	179.0

Exhibit 54
Pre-Distention Pancreas Weight

	N	Mean	SD	Min	25th %	Median	75th %	Max
Pre-Distention Pancreas Weight (g)	1061	101.0	32.2	0.0	80.0	96.3	118.5	250.0

Exhibit 55
Types of Distention by Pancreas Piece

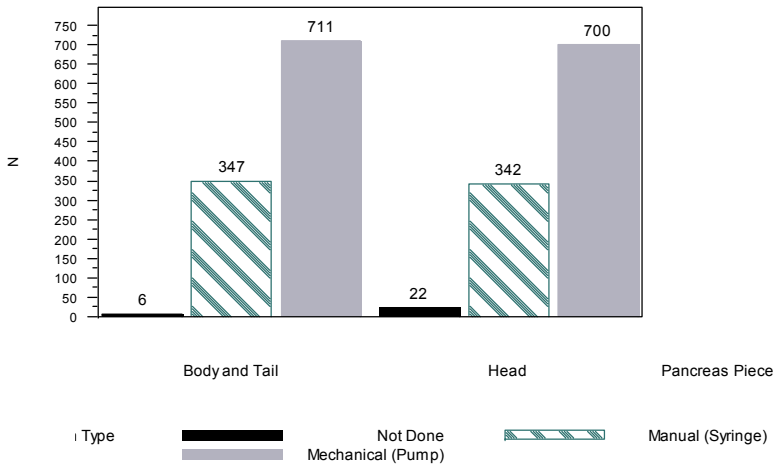


Exhibit 56
Summary of Perfusion Information

		Number of Perfusions	Mean	SD	Min	25th %	Median	75th %	Max
Perfusion Temperature (C)									
	Body and Tail:	2607	10.5	5.0	0.0	7.3	10.0	12.7	38.0
	Head:	2439	10.6	5.2	0.0	7.3	10.0	12.7	41.0
Perfusion Pressure (mmHg)									
	Body and Tail:	3604	130.5	52.8	1.0	80.0	140.0	180.0	300.0
	Head:	3471	130.9	53.6	1.0	80.0	140.0	180.0	300.0
Perfusion Flow Rate (mL/min)									
	Body and Tail:	1078	59.2	41.4	0.0	30.0	50.0	79.0	360.0
	Head:	1060	62.6	48.7	0.0	30.0	50.0	80.0	389.0

Exhibit 57
Frequency of Cut Pancreata Prior to Digestion

	N	%
Pancreas Cut		
Yes	599	55.7
No	15	1.4
Not Documented	462	42.9
All Pancreata	*1076*	*100.0*

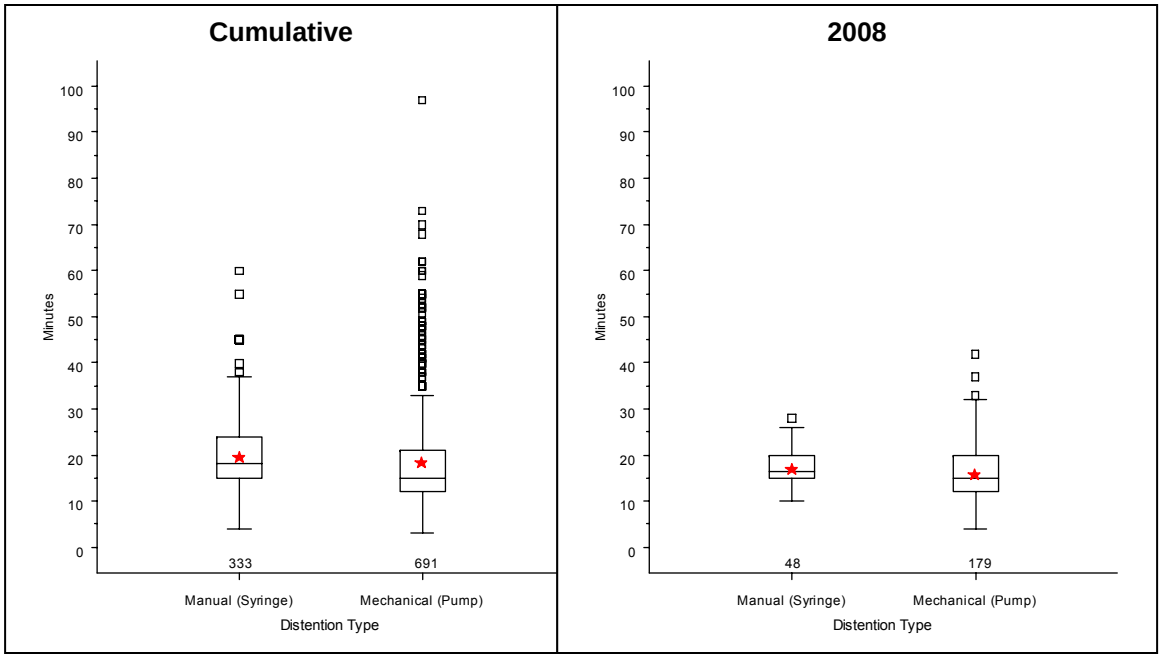
Exhibit 58
Number of Pancreata Pieces Prior to Digestion

	Number of Pancreata	Mean	SD	Min	25th %	Median	75th %	Max
Number of Pieces	429	10.3	3.4	2	9	10	12	31

Exhibit 59
Average Length of Pancreata Pieces Prior to Digestion

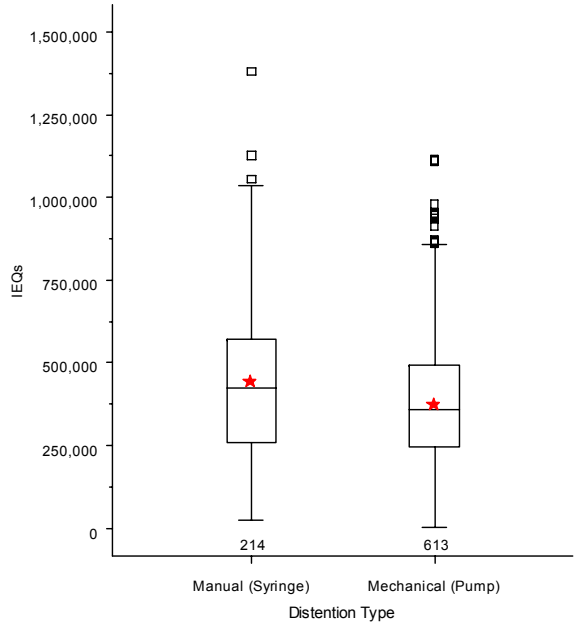
	N	%
Length of Pancreata Pieces		
1 - 3 cm	167	27.9
3 - 6 cm	78	13.0
>12 cm	2	0.3
Unknown	352	58.8
All Cut Pancreata	*599*	*100.0*

Exhibit 60
Duration of Digestion by Distention Type



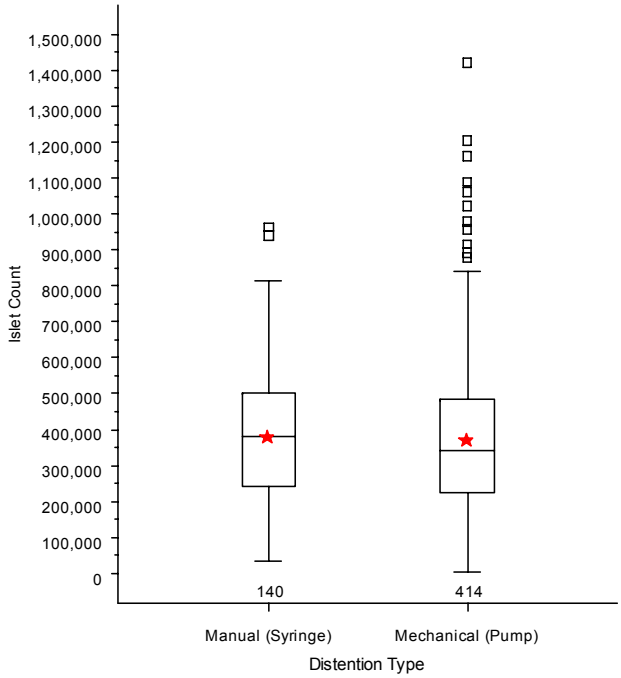
*only displays records with same distention type used for both Body & Tail and Head

Exhibit 61
Post Digestion IEQ Count by Distention Type



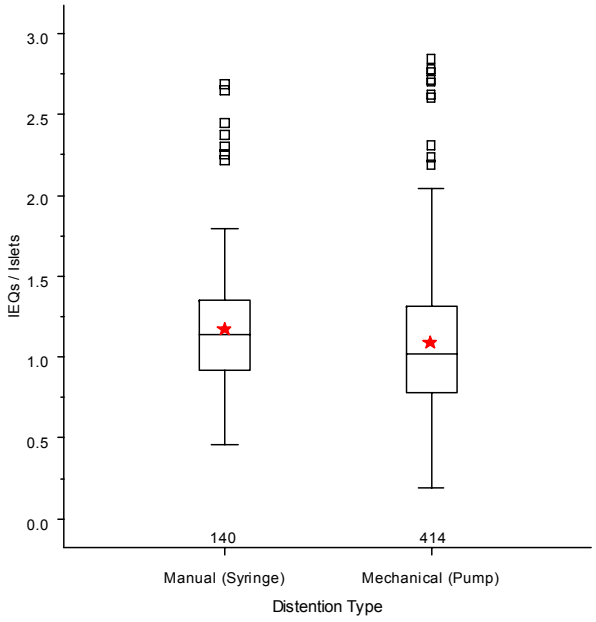
*only displays records with same distention type used for both Body & Tail and Head

Exhibit 62
Post Digestion Actual Islet Count by Distention Type



*only displays records with same distention type used for both Body & Tail and Head

Exhibit 63
Post Digestion Islet Index by Distention Type



*One record indicating manual distention and Islet Index=10.5 was omitted for display purposes.

*only displays records with same distention type used for both Body & Tail and Head

Exhibit 64
Post Digestion IEQ Count by Distention Quality

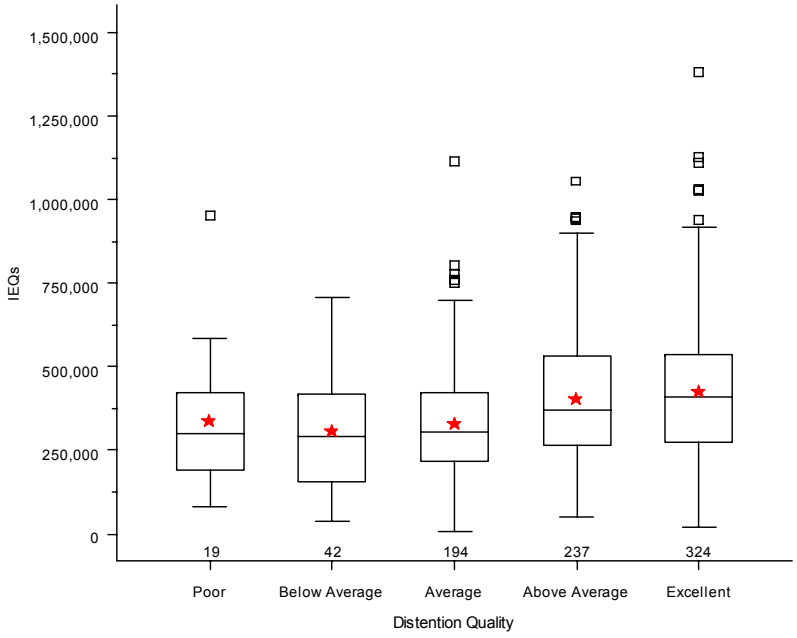


Exhibit 65
Post Digestion Actual Islet Count by Distention Quality

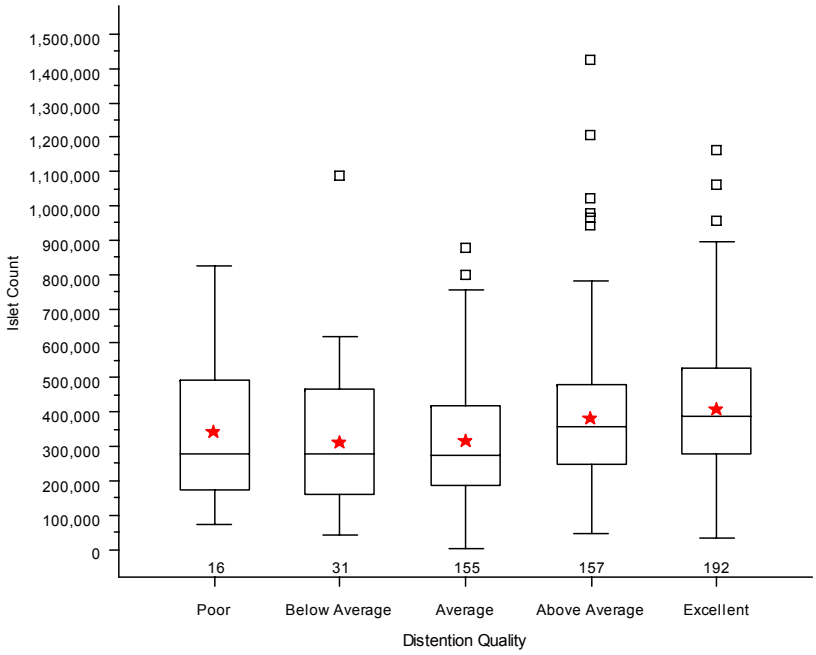
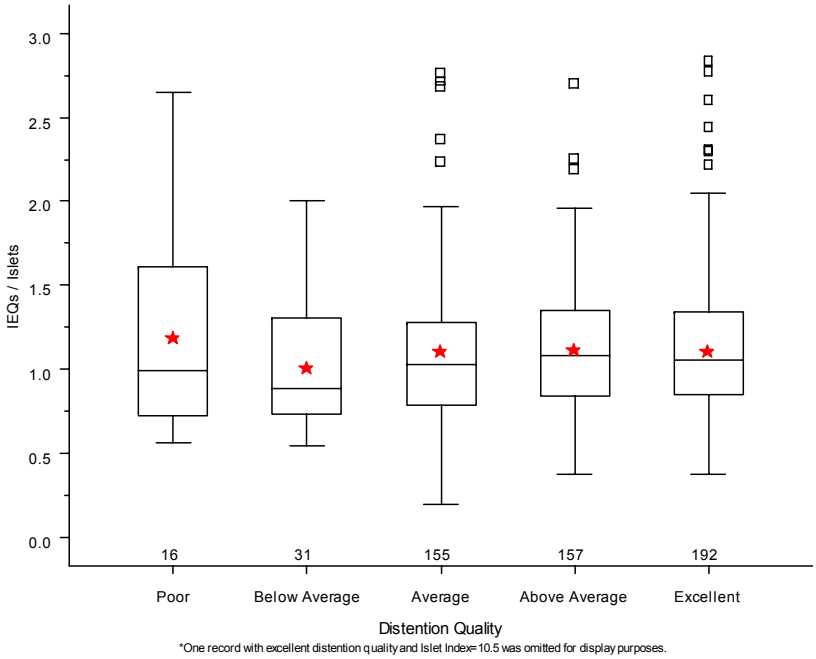


Exhibit 66
Post Digestion Islet Index by Distention Quality



*One record with excellent distention quality and Islet Index=10.5 was omitted for display purposes.

Chapter 6: Digestion Information

Chapter 6 describes the methods of digestion, the solutions used in addition to the enzymes, and the completeness of the process for islet isolation. Exhibit 67 shows that the overwhelming process used by the ICR centers is a variation of the Ricordi method. This popular method involves a two-piece chamber separated by a screen. The pancreas and enzymes are placed in the bottom portion of the chamber with stainless steel or titanium marbles, and the entire apparatus is shaken to allow both chemical and mechanical breakdown of the pancreas. Tubing to and from the chamber permits additional temperature controlled solutions to be pumped through the system allowing the free islets to be collected for purification.

Exhibit 68 lists the variety of dilution solutions used in the digestion process. 86.3% of the reported digestions used the Roswell Park Memorial Institute (RPMI) as base solution for dilution. This includes RPMI, Mediatech Dilution Solution, and Miami RPMI Formulation #2. 85.4% of the isolations supplemented the base solution. Exhibit 69 shows the assortment of additives used to enhance or buffer the digestion process. More than half of the digestions reported adding human serum albumin (HSA) to the dilution solution and more than one-third used a form of DNAse to protect the islets from the enzymatic process after they were released.

The digestion time varies with the age and size of the pancreas. Exhibit 70 shows that the mean duration of enzymatic digestion reported to the ABCC was 19.0 ± 10.3 minutes, with a range from 3 to 97 minutes. The dilution phase averaged 37.9 ± 18.8 minutes, making the mean total digestion time 57.3 ± 17.9 minutes, ranging from 15 to 160 minutes.

The first sign of a successful digestion is measured by the amount of tissue remaining in the chamber at the end of the digestion process. Exhibit 70 shows that the total weight of the remaining tissue averaged 25.8 grams. Of the remaining tissue, only 33.9% (10.8 grams) of it was documented by the centers as pancreatic digestible tissue (tissue that could have held islets).

Exhibit 67
Summary of Digestion Methods

	N	%
Digestion Method		
Ricordi	224	20.8
Modified Ricordi	832	77.3
Two-Step	4	0.4
Other	1	0.1
Not Done	1	0.1
Isolation Not Used	14	1.3
All Isolations	*1076*	*100.0*

Exhibit 68
Summary of Dilution Solutions Used

	N	%
Dilution Solution		
Connaught Medical Research Laboratories (CMRL)	3	0.3
Hanks Balanced Salt Solution (HBSS)	100	9.3
Rosewell Park Memorial Institute (RPMI)	607	56.4
Minimal Essential Media	1	0.1
Media 199 (M199)	18	1.7
Mediatech Dilution Solution	182	16.9
Miami RPMI Formulation #2 (RPMI #2)	140	13.0
Other	12	1.1
Not Documented	13	1.2
Additives Used		
Yes	919	85.4
No	143	13.3
Not Documented	14	1.3
All Isolations	*1076*	*100.0*

Exhibit 69
Dilution Additives Used

	N	%
Dilution Additive		
AB Serum	2	0.2
Aprotinin (Trasylol)	5	0.5
Bovine Serum Albumin (BSA)	33	3.1
Ciprofloxacin	58	5.4
DNAse (Pulmozyme)	382	35.5
Dulbecco's Phosphate-Buffered Saline (DPBS)	58	5.4
Fetal Bovine Serum (FBS)	7	0.7
Gentamycin	1	0.1
Glutithione	1	0.1
HEPES	171	15.9
Heparin	56	5.2
Horse Serum	14	1.3
Human Serum Albumin (HSA)	592	55.0
Insulin	22	2.0
Nicotinamide (Niacinamide)	173	16.1
Pefabloc	3	0.3
Penicillin/Streptomycin	21	2.0
SOD	4	0.4
Sodium Hydroxide (NaOH)	151	14.0
Trolox/Vitamin E	286	26.6
n-Acetyl-Cysteine (NAC)	1	0.1
All Dilution Additives	*2041*	-

Exhibit 70
Duration of Digestion and Composition of Remaining Pancreatic Tissue

	N	Mean	SD	Min	25th %	Median	75th %	Max
Duration of Enzymatic Digestion (mins)	1050	19.0	10.3	3.0	13.0	17.0	22.0	97.0
Duration of Dilution Phase (mins)	809	37.9	18.8	0.0	26.0	35.0	46.0	120.0
Total Digestion Time (mins)	809	57.3	17.9	15.0	45.0	55.0	65.0	160.0
Pre-Distention Weight (g)	1061	101.0	32.2	0.0	80.0	96.3	118.5	250.0
Weight of Tissue Remaining (g)	677	25.8	17.9	0.0	12.8	22.0	32.8	100.0
Digestible Pancreatic Tissue (%)	361	33.9	24.4	0.0	10.0	30.0	50.0	90.0
Weight of Digestible Tissue Remaining (g)	360	10.8	12.8	0.0	2.3	6.4	14.2	79.2

Chapter 7: Islet Characterization Post Digestion

This Chapter describes the information collected post digestion on the islet preparation prior to purification. To gather this information, the ICR centers take a calibrated sample of the post digestion slurry, stain the preparation with dithizone to identify the islet cells, and manually count the number of islets in the aliquot. This process is usually repeated by several technicians and then counts are averaged in order to document a reliable number. A microscopic grid aids in the sizing of the stained islets. Actual islets are the number of islets counted regardless of size. Islet equivalents are a calculated number based on the size of the islets times the number of islets. The comparison of these two factors gives the islet index. An islet index of 1 is considered an average preparation (the average size of the islets in the preparation is 150μ).

Exhibit 71 reports that ICR centers only collected post digestion IEQ counts in 845 of the 1076 isolations performed during this Report's time period. The mean IEQ count post digestion was 394,153.9 ± 201,963.5, but this large standard deviation implies a great deal of variation. Less centers record the number of actual islets counted, but of the information collected, the isolations yielded a mean of 372,794.7 ± 204,533.8 with a calculated islet index of 1.1 ± 0.4. The average IE yield for the last seven years dropped 6.6% from the first five-year total, most probably again due to the Collagenase problems of the last few years of data collection.

The reported mean packed cell volume of tissue after digestions is 41.7 ± 18.2 mL, with a median value of 40 mL. More than half of the isolations documented the percentage of trapped islets (islets that are still surrounded by the acinar tissue) with a mean of 23.7%. Almost a third of the reported isolations documented the percentage of positively stained dithizone cells (mean of 2.8%).

Of the centers that reported performing viability stains on the post digestion preparation, the average viability was 82.3% ± 14.3%. The viability is evaluated by the use of both inclusion and exclusion dyes.

There remains a controversy on the importance of taking any information on the characteristics of islets post digestion. Exhibits 72A and B show the breakdown by center of which isolations have documented pre-purification information on the isolated islets. Overall, 78.5% of the isolations have Post Digestion IEQ numbers reported.

Exhibit 71
Post Digestion Statistics

	N	Mean	SD	Min	25th %	Median	75th %	Max
Total Actual Islet Count	564	372,794.7	204,533.8	3,867	227,250	345,500	485,000	1,424,136
Total IEQs	845	394,153.9	201,963.5	5,000	248,815	373,583	513,033	1,381,125
Islet Index	564	1.1	0.4	0.2	0.8	1.1	1.3	3.1
Total Packed Cell Volume (mL)	866	41.7	18.2	2.1	30.0	40.0	50.0	115.0
Percent Trapped Islets (%)	612	23.7	23.3	0.0	5.0	20.0	30.0	98.0
Insulin Content (µU/IEQ)	26	59.7	69.3	0.4	5.0	28.5	114.9	220.5
DNA Content (ng/IEQ)	27	251.7	164.9	5.1	132.0	268.1	352.0	578.1
Dithizone Positive Cells (%)	340	2.8	3.5	1.0	2.0	2.0	3.0	50.0
Islet Viability (%)	36	82.3	14.3	29.0	75.0	85.0	93.5	100.0

Exhibit 72A
Post Digestion Count Frequency by Center

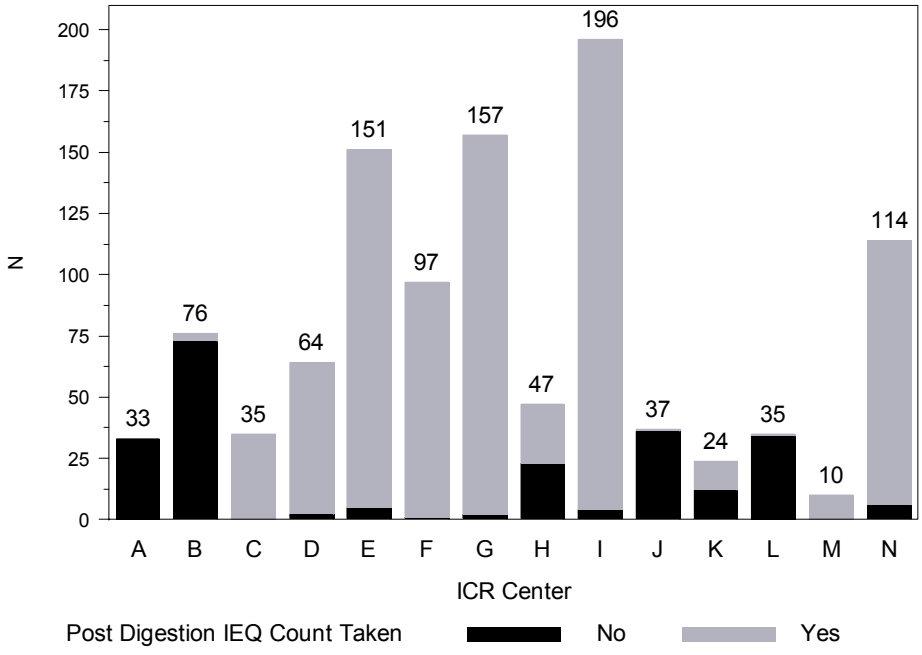


Exhibit 72B

	Post Digestion IEQ Count Taken			
	No		Yes	
	N	%	N	%
ICR Center				
A	33	100.0	0	0.0
B	73	96.1	3	3.9
C	0	0.0	35	100.0
D	2	3.1	62	96.9
E	5	3.3	146	96.7
F	1	1.0	96	99.0
G	2	1.3	155	98.7
H	23	48.9	24	51.1
I	4	2.0	192	98.0
J	36	97.3	1	2.7
K	12	50.0	12	50.0
L	34	97.1	1	2.9
M	0	0.0	10	100.0
N	6	5.3	108	94.7
All ICR Centers	*231*	*21.5*	*845*	*78.5*

Chapter 8: Purification Information

Chapter 8 provides information on the methods, solutions, and details of how the purification processes of the islet isolations are executed. All isolations that were reported used density gradients on the COBE 2991 Cell Processor. The 42 isolations in Exhibit 73 that were reported as “Not Done” and/or “Not Documented” were stopped prior to purification. The number of COBE runs conducted per isolation is a question that was added to the database in May of 2006. Therefore, approximately one third of the records (371 isolations) do not have this information documented; however, of the 657 isolations that did report the number of runs, more than half of these isolations required two COBE runs per preparation (Exhibit 74).

Exhibit 75 gives a summary of the COBE runs reported by the ICR centers. 89.6% of the runs were done as a continuous gradient, a technique where a device known as a gradient maker is utilized to allow a mixing of a heavy and a light density gradient to be mixed and pumped onto the COBE Processor in a continuous linear density from heavy to light. The purification is accomplished when the continual spinning of the COBE allows the islets to seek their matching density in the gradient. Islets have a lighter density than the contaminating acinar tissue.

Several types of density gradients were reported but over half of the purification runs were done using Bicoll (Biochrom AG, Berlin) density gradient (polysucrose 400 and amidotrizoic acid)**.** Optiprep (Iodixanol based) use increased to 267 runs this year, Euroficoll (Eurocollins and Ficoll DL400) was used in over 100 runs and an additional 299 runs were conducted using other Ficoll based solutions.

The information reported in Exhibit 76 was also added during the May 2006 revision. Of the 1236 COBE runs listed, a mean of 22.4 mL of packed cells was documented as loaded per COBE run.

Exhibit 77 shows the correlation between the specific gradient used and the IEQ post purification. Ficoll based density gradients other than Bicoll and Euroficoll appear to yield the highest IEQ counts post purification by a small margin.

Exhibit 73
Summary of Purification Types

	N	%
Purification Types		
Density Gradient	1034	96.1
Not Done	22	2.0
Not Documented	20	1.9
COBE Used		
Yes	1028	95.5
No	7	0.7
Not Documented	41	3.8
All Isolations	*1076*	*100.0*

Exhibit 74
Number of Documented COBE Runs per Pancreas

	N	%
Number of COBE Runs		
1	214	20.8
2	341	33.2
3	74	7.2
4	22	2.1
5	6	0.6
Not Documented	371	36.1
All Isolations Using COBE	*1028*	*100.0*

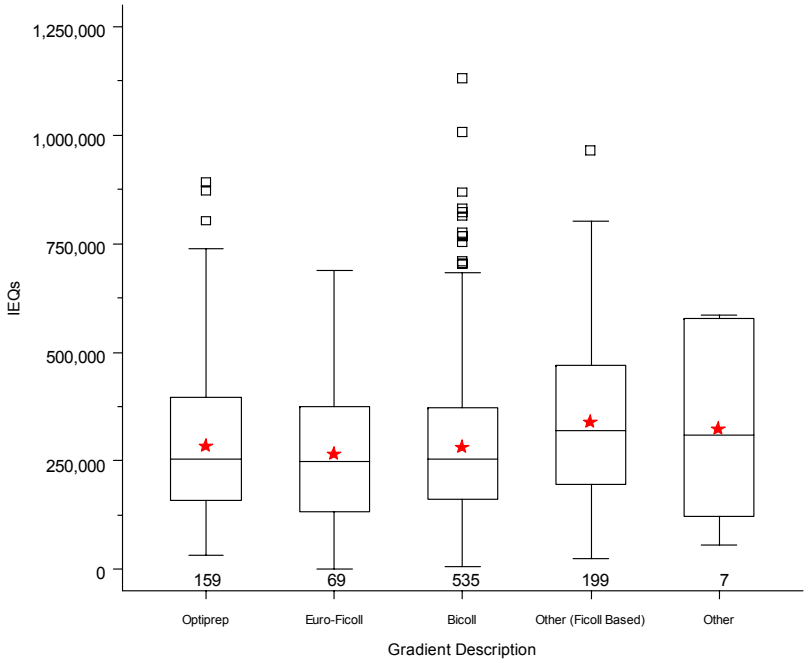
Exhibit 75
Summary of All COBE Runs

	N	%
Gradient Type		
Continuous	1439	89.6
Discontinuous	166	10.3
Missing	1	0.1
Gradient Description		
Bicoll	880	54.8
Euro-Ficoll	142	8.8
Optiprep	267	16.6
Other (Ficoll Based)	299	18.6
Other	17	1.1
Not Documented	1	0.1
All COBE Runs	*1606*	*100.0*

Exhibit 76
Packed Cell Volume (mL) per COBE Run

	N	Mean	SD	Min	25th %	Median	75th %	Max
Packed Cell Volume per COBE Run (mL)	1236	22.4	8.2	0.3	18.0	20.0	25.0	90.0

Exhibit 77
Post Purification IEQs by Gradient Description



Chapter 9: Islet Characterization Post Purification

This chapter reports the information that is collected on the details of the islet preparation post purification but prior to culture. This information is collected in a similar fashion as the samples described in Chapter 7: Post Digestion Islet Characterization. A small aliquot is extracted from a well mixed suspension of the islet preparation after purification steps have been performed and counted, usually by several technicians using a microscopic grid for sizing of the dithizone-stained islets. Results are then averaged in order to report a reliable number.

Exhibit 78 gives a comprehensive look at the characteristics of the purified islets yielded by the ICR centers for this Report. An average of 294,820.7± 169,488.0IEQ compares to 253,183.2± 156,106.2actual islets with ranges from 667 to 1,132,083 and 2,500 to 1,022,000, respectfully. The average islet index of 1.3 ± 0.6 shows that the preparations reporting these statistics are larger than 150μ in diameter by the counting grids. Measured packed cell volume post purification averages 3.6 mL, an approximately 91% decrease in volume from pre-purification statistics. Purity by dithizone staining is 70.9% with a range from 12.8 to 100%. Islet viability was reported as 91.1% ± 8.7%.

The rest of the statistics given in Exhibit 78 were reported on a much smaller scale reflecting many centers' practice of not routinely collecting information on the number of beta cells, insulin content, DNA content, and percentage of beta cells, especially at this point in the process.

Exhibit 79 depicts the correlation between islet index and islet viability. This graph implies that islet preparations that have a majority of small islets (average of <75μ in diameter) tend to have a lower viability, possibly due to damage from the isolation process. These documented particles may well be fractions of islets rather than small whole islets.

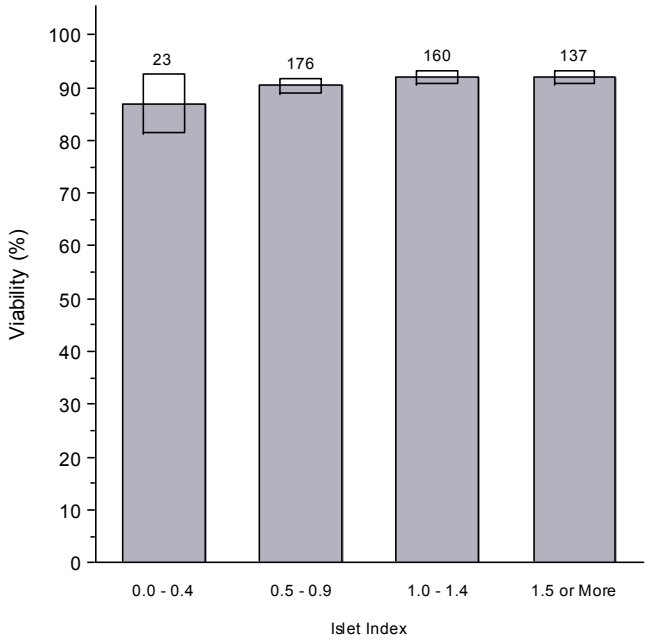
Exhibit 80 displays the post purification IEQ per ICR center. All centers' median isolation numbers are between 200,000 and 400,000.

Exhibit 81 describes the IEQ post purification by year of pancreas recovery. It should be noted that in the years 2001 – 2003, only pancreata used for clinical transplantation were required to be entered in the ICP database. Therefore, the overwhelming majority of pancreata reported in these years was clinically transplanted and could reflect a skewed average yield. In addition, after a slight drop of average post purification IEQ per isolation noted in 2007, possibly due to the collagenase crisis, the average has risen this past year.

Exhibit 78
Post Purification Statistics

	N	Mean	SD	Min	25th %	Median	75th %	Max
Total Actual Islet Count	978	253,183.2	156,106.2	2,500	136,429	222,500	331,250	1,022,000
Total IEQs	1018	294,820.7	169,488.0	667	166,984	268,855	394,837	1,132,083
Islet Index	976	1.3	0.6	0.2	0.9	1.2	1.6	5.5
Total Packed Cell Volume (mL)	890	3.6	4.4	0.1	1.3	2.3	4.0	41.9
Total Beta Cells (10^6)	29	399.9	206.0	36.0	281.0	383.0	510.0	947.0
Insulin Content (µU/IEQ)	76	248.4	179.1	3.3	120.2	202.5	311.0	747.0
DNA Content (ng/IEQ)	74	26.0	39.6	0.4	10.7	16.0	27.0	282.0
Dithizone Positive Cells (%)	854	70.9	16.6	12.8	61.8	74.8	82.9	100.0
Percent Beta Cells (%)	17	41.9	20.7	18.0	31.0	35.0	47.0	90.0
Islet Viability (%)	531	91.1	8.7	21.0	89.0	95.0	96.0	100.0

Exhibit 79
Viability by Islet Index
Categorical Assessment with Error Bars



Error Bar Confidence Limits = 95%

Exhibit 80
Post Purification IEQs by Center

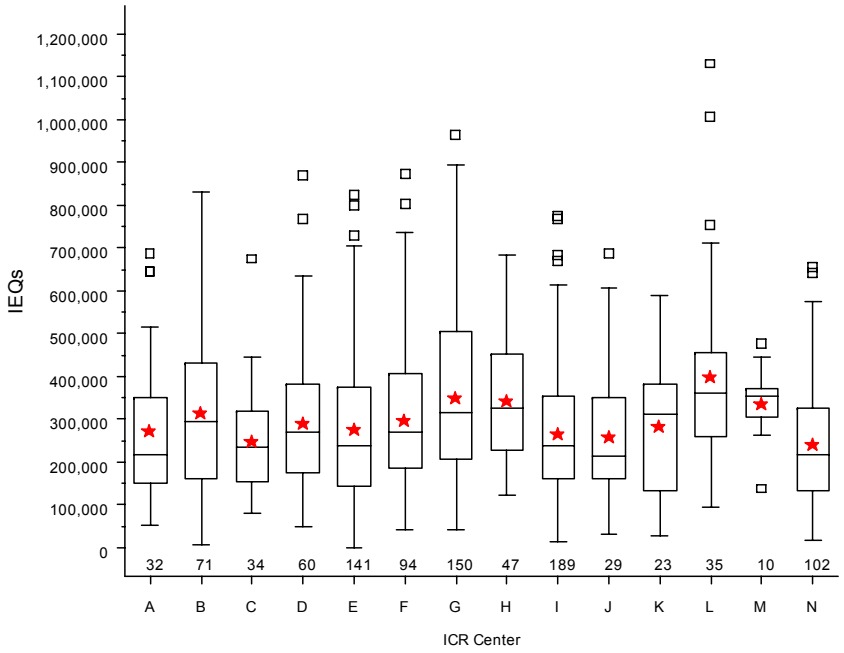
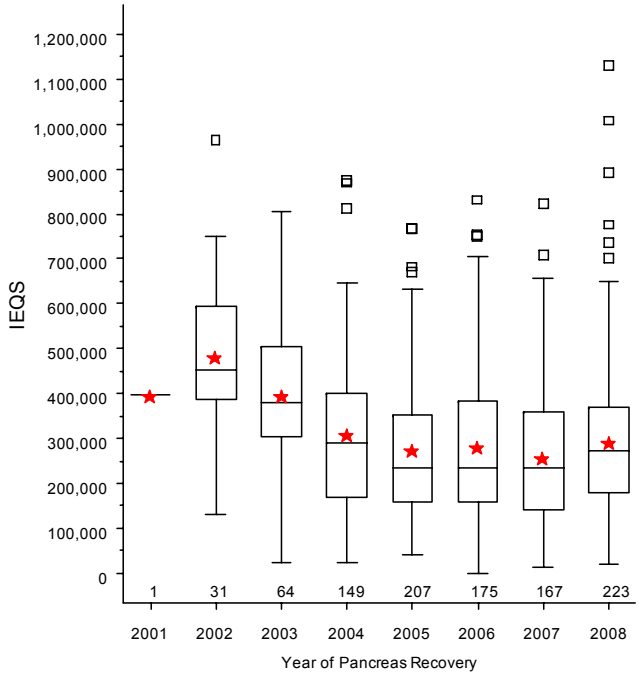


Exhibit 81
Post Purification IEQs by Year of Pancreas Recovery



Chapter 10: Culture Information

This chapter gives information concerning the solutions, islet concentrations, vessels, times, and temperatures of islet culture conditions for both basic science research and clinical transplantation. Once islets are purified, they are often held for some amount of time before further testing and additional characteristics are documented. Exhibit 85 shows that approximately three-fourths of the isolations recorded in this Report were placed on culture for some amount of time. Fifteen hundred and fifty-five separate culture parameters are depicted. Almost 99% of all cultured islets were held in a base of Connaught's Medical Research Laboratories Media 1066 (CMRL 1066), either supplemented or not (Exhibit 83).

Exhibit 84 lists 30 different additives that are used to supplement the base media to encourage islet health while being held in culture. Human serum albumin (HSA) was added to a majority of the cultured islets followed by Vitamin E and Nicotinamide, a principal form of Vitamin B-complex. Sodium hydroxide or sodium bicarbonate was often used as a buffer in the base media and combinations of amino acids and vitamins supplement many of the cultures. Ciprofloxacin was the dominant antimicrobial used in the cultures.

Exhibit 85 reflects the outcomes documented post culture. Some culture periods lasted hours, while some lasted days. The average culture time reported was 86.7 hours, with a range from 6 hours to almost 10.8 days. The ranges for all parameters indicated in this table are wide, possibly a result of the differences in culture times. The actual islet average was 216,055.1 ± 160,936.0, with a range from 2,500 to 1,960,000. The islet equivalent average was 232,683.8± 161,240.6, ranging from 667 to 880,834 IEQ. The islet index had a slight drop to 1.2 from post purification (1.3) through culture, with packed cell volume dropping to 2.2 mL. Consequently, the post culture purity increased to 71.3% ± 14.7% and the viability by staining remained relatively high at 90.1% ± 9.2%. The mean stimulation index was reported at 3.2 but results ranged from 0.1 to 27.1.

Exhibits 87 and 88 show that the majority of the isolations where both pre and post culture counts are reported had a decrease in the counts after culture; however, Exhibit 89 shows that culturing had less of an affect on the islet index recovery.

Exhibit 82
Culture Summary

	N	%
Culture Performed		
Yes	815	75.7
No	261	24.3
All Isolations	*1076*	*100.0*

Exhibit 83
Culture Media Summary

	N	%
Base Medium		
Rosewell Park Memorial Institute (RPMI) 1640	10	0.6
Mediatech Miami Medium #1A Culture Media	285	18.3
Mediatech CMRL 1066, Supplemented	319	20.5
Media 199 (M199)	1	0.1
Conaught Medical Research Laboratories (CMRL 1066)	934	60.1
Other	6	0.4
All Cultures Reported	*1555*	*100.0*

Exhibit 84
Culture Additives Summary

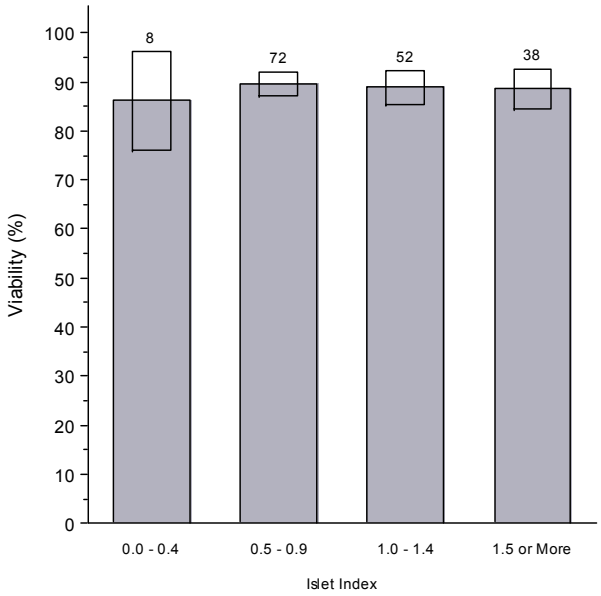
	N	%
Culture Additive		
3-isobutyl-1-methylxantine (IBMX)	1	0.1
AB SERUM	13	0.8
Antibiotic Antimycotic Solution	26	1.7
Aprotinin (Trasylol)	1	0.1
Bovine Serum Albumin (BSA)	37	2.4
Ciprofloxacin	328	21.1
D-glucose	4	0.3
DNAse (Pulmozyme)	2	0.1
Dulbecco's Phosphate-Buffered Saline (DPBS)	52	3.3
Fetal Bovine Serum (FBS)	33	2.1
Fungizone	1	0.1
Gentamycin	3	0.2
Glutathione	99	6.4
HEPES	238	15.3
Heparin	203	13.1
Human Serum Albumin (HSA)	609	39.2
Insulin Transferrin Selenium (ITS)	283	18.2
Insulin-Like Growth Factor-1 (IGF-1)	58	3.7
L-glutamine	232	14.9
Linoleic Acid	166	10.7
Nicotinamide (Niacinamide)	283	18.2
Non essential amino acid	5	0.3
Pefabloc	8	0.5
Penicillin/Streptomycin	72	4.6
Pyruvate	169	10.9
Sodium Bicarbonate (NaHCO3)	161	10.4
Sodium Hydroxide (NaOH)	233	15.0
Trolox/Vitamin E	300	19.3

	N	%
Zinc Sulfate (ZnSO4)	174	11.2
n-Acetyl-Cysteine (NAC)	4	0.3
All Additives	3798	100.0

Exhibit 85
Outcome Measures Post Culture

	N	Mean	SD	Min	25th %	Median	75th %	Max
Total Culture Time (hrs)	63	86.7	67.0	6.0	24.0	72.0	135.0	260.0
Total Actual Islet Count	452	216,055.1	160,936.0	2,500	111,250	184,000	294,317	1,960,000
Total IEQs	473	232,683.8	161,240.6	667	114,659	196,000	318,283	880,834
Islet Index	449	1.2	0.6	0.2	0.8	1.0	1.4	3.5
Total Packed Cell Volume (mL)	302	2.2	1.7	0.2	1.0	1.7	3.0	11.7
Percent Trapped Islets (%)	274	14.3	21.1	0.0	0.3	5.0	20.0	100.0
Total Beta Cells (10^6)	9	288.1	173.3	60.0	153.0	304.0	328.0	643.0
Insulin Content (µU/IEQ)	47	222.6	235.4	0.1	72.0	135.0	252.0	1,000.0
DNA Content (ng/IEQ)	76	13.9	32.5	0.1	5.0	7.3	14.0	282.0
Stimulation Index	495	3.2	2.8	0.1	1.6	2.6	3.6	27.1
Dithizone Positive Cells (%)	375	71.3	14.7	5.0	60.0	73.1	81.7	99.0
Islet Viability (%)	488	90.1	9.2	26.0	87.0	93.0	96.0	100.0

Exhibit 86
Viability by Islet Index
Categorical Assessment with Error Bars



Error Bar Confidence Limits = 95%

Exhibit 87
Change in IEQ Count
Post Purification to Post Culture

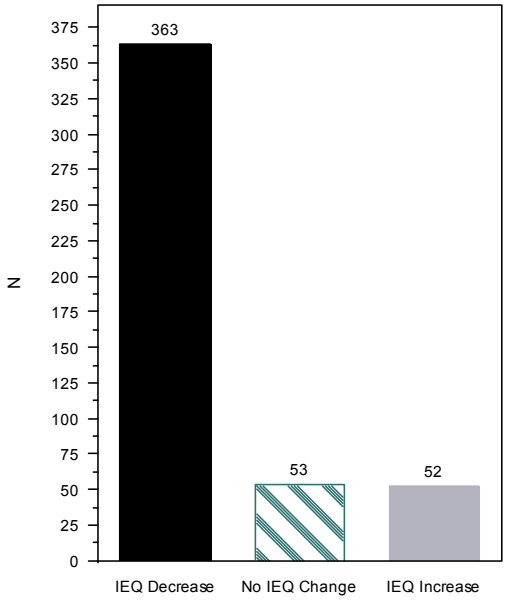


Exhibit 88
Change in Actual Islet Count
Post Purification to Post Culture

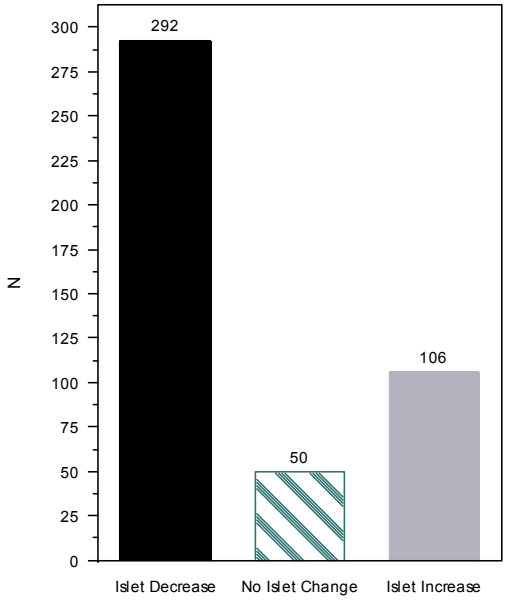
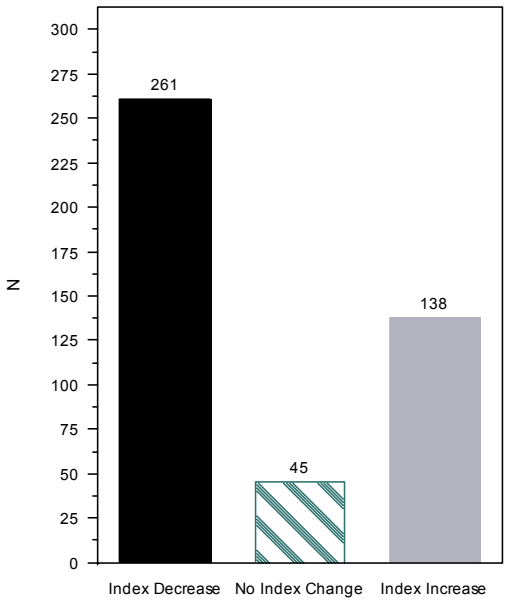


Exhibit 89
Change in Islet Index
Post Purification to Post Culture



Chapter 11: Final Islet Preparation Information

This chapter depicts information that represents the entire islet preparation prior to transplantation or distribution for research. In some cases, where the information is a duplicate of prior data already collected in the post-purification or post culture documents, the ICR centers are not required to re-enter the information as a final summary. However, if information is collected from several purification runs or several culture batches, these Exhibits allow for a final summary of the preparation. In addition, the majority of the preparations entered in this category are of isolations that went on to clinical transplants. These final data are less in number, yet outcomes in most cases appear to be skewed by the clinical results.

Exhibit 90 reflects the data submitted on the characteristics of the final preparation of isolated islets from 2001 through August 2008. The actual islet count had a mean of 285,828.7± 160,059.6, ranging from 10,486 to 887,400. In comparison, IEQs averaged 324,009.4 ± 180,150.2 and ranged from 4,003 to 884,700. The islet index remained relatively consistent at 1.2 ± 0.5 and packed cell volume averages 2.7 mL ± 2.8 mL. The purity was reported as a mean of 68.8% with a range from 10% to 100%, and a median of 70%. Viability by inclusive and exclusive dye-staining was reported as 91.8% ± 7.1% and potency by stimulation index averages 2.8 ± 2.8, ranging from 0.2 to 27.1.

Other parameters collected had significantly less documentation. There were only 35 reports of beta cell percentage (mean of 42.1%), 35 isolations with total beta cells (376.4 x 10^6), 70 documentations of insulin content (195.7 µU/IEQ), and 93 reports of DNA content at an average of 32.5 ng/IEQ.

Exhibit 91 and 92 depict the progression of reported IEQs and AIs, respectively, through the preparation process. The unusual rise of the final prep totals may have been influenced once again by the majority of clinical transplant preparations reported in this category. Islet index remained constant through the progression (Exhibit 93). Exhibit 94 once again showed a slight drop in viability in islets that have an index of less than 0.5, or 75µ in diameter.

Exhibit 90
Final Islet Preparation Statistics

	N	Mean	SD	Min	25th %	Median	75th %	Max
Total Actual Islet Count	265	285,828.7	160,059.6	10,486	178,000	267,500	388,875	887,400
Total IEQs	325	324,009.4	180,150.2	4,003	190,723	316,350	422,200	884,700
Islet Index	263	1.2	0.5	0.3	0.8	1.1	1.5	3.2
Total Packed Cell Volume (mL)	248	2.7	2.8	0.1	1.2	2.2	3.5	29.0
Percent Trapped Islets (%)	153	15.5	21.0	0.0	0.0	9.0	20.0	90.0
Total Beta Cells (10^6)	35	376.4	192.4	60.0	239.0	383.0	505.0	915.0
Insulin Content (µU/IEQ)	70	195.7	216.2	1.1	23.2	166.9	268.0	1,000.0
DNA Content (ng/IEQ)	93	32.5	82.6	0.0	10.5	17.0	26.9	750.0
Stimulation Index	215	2.8	2.8	0.2	1.3	2.1	3.4	27.1
Dithizone Positive Cells (%)	308	68.8	18.8	10.0	57.0	70.0	85.0	100.0
Percent Beta Cells (%)	35	42.1	20.2	18.0	27.0	33.0	56.0	90.0
Islet Viability (%)	302	91.8	7.1	56.0	90.0	94.5	96.0	100.0

Exhibit 91
Comparison of IEQ Counts

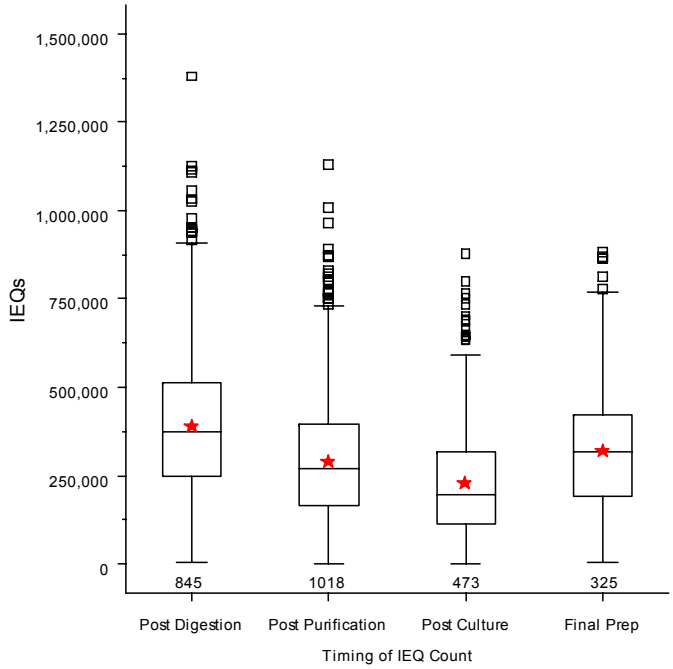


Exhibit 92
Comparison of Actual Islet Counts

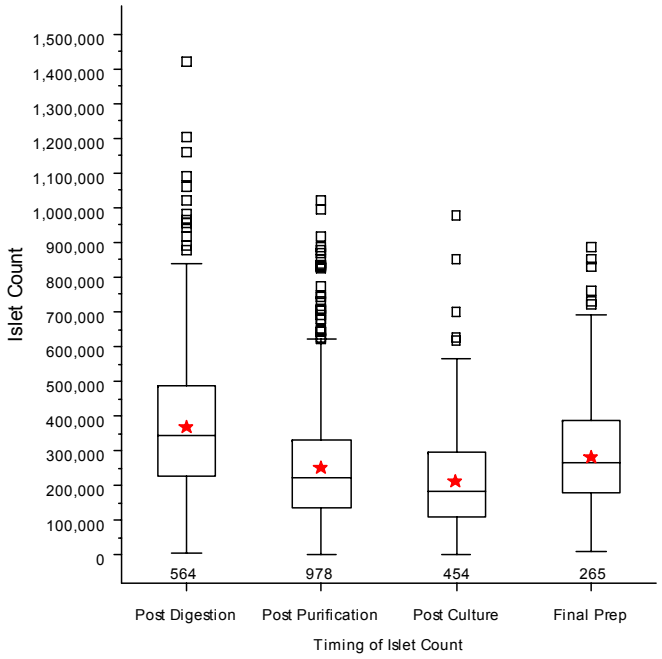


Exhibit 93
Comparison of Islet Index

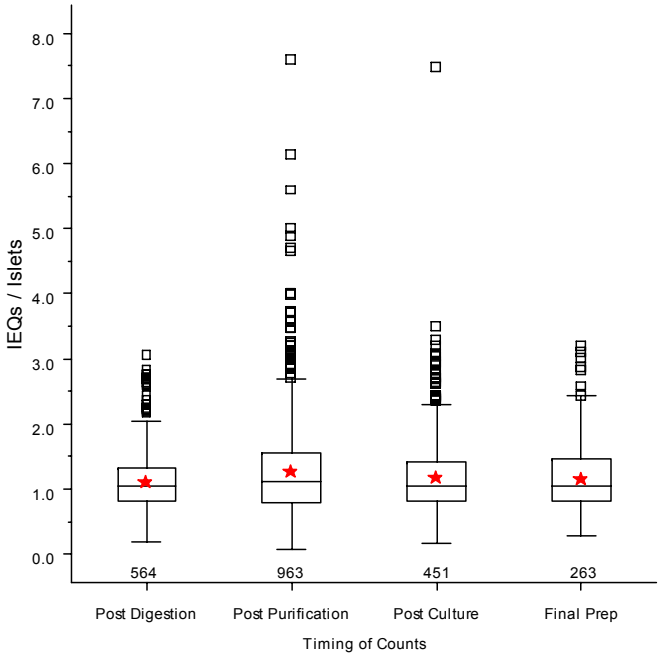
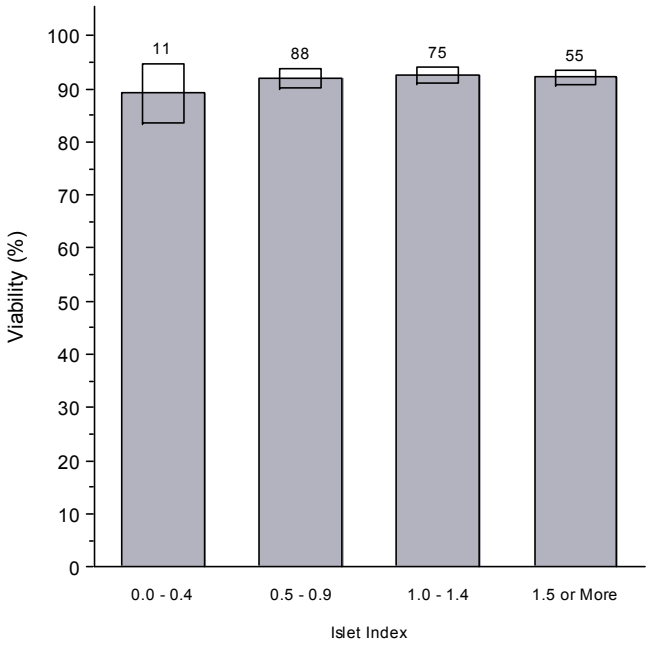


Exhibit 94
Viability by Islet Index
Categorical Assessment with Error Bars



Error Bar Confidence Limits = 95%

Chapter 12: Microbiology

Sterile preparations are essential for both the safety of patients receiving a clinical transplant and for the basic science researchers that invest time and resources into experiments on the islet preparations received through the ICR Consortium. This chapter documents the results reported by all ICR centers concerning the testing of the preparation at different stages of the process for microbial contamination.

Exhibit 95 documents the results of testing for gram stains, aerobic, anaerobic, fungal, and mycoplasma contamination from all reported isolations. The collection of data from specific times during the isolation process was added to the ICP database in May of 2006, thus resulting in the lower numbers for Transport Fluid, Post Purification and Post Culture results. Contamination data has always been collected by the ABCC for the Final Preparation. Ninety-six contaminants were documented in the 317 Transport Fluid samples reported. Three samples were reported for Post Digestion with no contaminants found. Only one contaminant, a fungal growth, also seen with the gram stain, was reported for the 187 Post Purification samples, showing that contamination from the original pancreas can be diluted out through the isolation process. Of the 660 Final Preparations that were analyzed, 18 positive contaminations (2.7%) were reported. Of these, 12 were aerobic cultures, 3 were anaerobic cultures, and 3 were fungal growths. Gram stain results would have been further identified in the specific testing so the results are not included in these totals.

Exhibit 96 indicates the endotoxin results recorded in the database. In some cases, the endotoxin results were reported to the ABCC as EU/ml, and in some they were reported as <EU/ml. The discrepancy in the units is based on the results of the endotoxin assay. If the amount of actual endotoxin in a sample is below a certain threshold detectable by the instrumentation, results are reported as below that threshold and are then multiplied by a dilution factor to give the final result. If the results are above the threshold, an actual number of EU/ml can be reported. If the sample is from a preparation going to clinical transplantation, the most informative data is reported as EU/kg of the body weight of the recipient. According to FDA regulations, EU can not be higher than 5 EU/kg per injection. The mean EU/kg reported to the ABCC is 1.06 ± 1.5 with a range from 0.04 to 5.00.

Exhibit 95
Microbiology Results at Various Time Points

	Time Point									
	Transportation Fluid		Post Digestion		Post Purification		Post Culture		Final Preparation	
	N	%	N	%	N	%	N	%	N	%
	317	-	3	-	187	-	154	-	660	
Gram Stain										
Positive	12	4.1	0	0.0	2	1.1	0	0.0	7	1.1
No Organism Seen	270	85.2	2	66.7	179	95.7	148	96.1	478	72.4
Not Done	29	9.1	1	33.3	4	2.1	5	3.2	166	25.2
Not Documented	5	1.5	0	0.0	2	1.0	1	0.6	9	1.4
Aerobic Culture										
Positive	71	22.4	0	0.0	0	0.0	1	0.6	12	1.8
No Growth	221	69.7	2	66.7	180	96.3	146	94.8	453	68.6
Not Done	18	5.7	1	33.3	4	2.1	6	3.9	152	23.0
Not Documented	7	2.2	0	0.0	3	1.6	1	0.6	43	6.5
Anaerobic Culture										
Positive	18	5.7	0	0.0	0	0.0	0	0.0	3	0.5
No Growth	290	91.5	2	66.7	181	96.8	151	98.1	487	73.8
Not Done	4	1.3	1	33.3	3	1.6	2	1.3	143	21.7
Not Documented	5	1.5	0	0.0	3	1.6	1	0.6	27	4.1
Fungal Culture										
Positive	6	1.9	0	0.0	1	0.5	0	0.0	3	0.5
No Growth	271	85.5	2	66.7	177	94.7	145	94.2	463	70.2
Not Done	36	11.4	1	33.3	5	2.7	6	3.9	168	25.5
Not Documented	4	1.3	0	0.0	4	2.1	3	1.9	26	3.9
Mycoplasma										
Positive	1	0.3	0	0.0	0	0.0	0	0.0	0	0.0
No Growth	17	5.4	0	0.0	18	9.6	36	23.4	239	36.2
Not Done	295	93.1	3	100.0	167	89.6	117	76.0	403	61.1
Not Documented	4	1.3	0	0.0	2	1.0	1	0.6	18	2.7

Exhibit 96
Total Endotoxin Units

	N	Mean	SD	Min	25th %	Median	75th %	Max
Total Endotoxin Units (EU/mL)	292	0.28	1.1	0.00	0.05	0.13	0.30	17.70
Total Endotoxin Units (<EU/mL)	324	0.37	0.4	0.00	0.10	0.40	0.40	2.74
Total Endotoxin Units (EU/kg Recipient)	21	1.06	1.5	0.04	0.19	0.46	1.29	5.00

*NOTE: Rows are mutually exclusive

Chapter 13: Mouse Bioassay

The mouse bioassay is a well respected test for islet potency. In this chapter, the statistics from the ICR centers' mouse transplantation experiments were reported when used as a quality control mechanism. Exhibit 97 shows that over one quarter of the preparations used the mouse assay as a means for islet potency documentation.

Exhibit 98 shows the breakdown of the types of mouse models used. The Non-Obese Diabetic / Severe Combined Immunodeficiency Disease (NOD/SCID) was the most frequently reported mouse strain used (42.6% of the time). The NOD/SCID mouse is characterized by a functional deficit in NK cells, absence of circulating complement and defects in the differentiation and function of antigen presenting cells (from the NOD) as well as a lack of T and B cells (from the SCID) making them a strategic model for transplantation studies. The Athymic Nude mouse strain was used in 24.3% of the experiments. A growing number of centers are investigating the use of genetically altered knock-out (-/-) mice such as the B/6 or Balbc rag-/- and the naturally occurring diabetic Akita mouse with or without rag-/-.

The most common transplant site was the kidney subcapsular space, although one center incorporated the use of Matrigel (a soluble basement membrane matrix which provides a physiological setting for islets) subcutaneously. The preferred test for judging outcome was permanent blood glucose under 200mg/dL (used in 77.4% of the transplants) followed by C-peptide greater than 1 ng/ml.

Because ICR centers use different numbers of mice for transplantation studies as well as different amounts of islets, Exhibit 99 depicts the percentage of mice cured for each islet isolation reported. The mean cure rate was 48.1% ± 44.5% with ranges from 0 to 100%. This low percentage may have been based on the practice of many centers to vary the dose of islets transplanted to establish the threshold of IEQ necessary for a cure (Data not collected).

Exhibit 97
Mouse Bioassay Summary

	N	%
Mouse Bioassay Conducted		
Yes	296	27.5
No	757	70.4
Not Documented	23	2.1
All Isolations	*1076*	*100.0*

Exhibit 98
Mouse Bioassay Description

	N	%
Mouse Model		
Nude/Athymic	72	24.3
SCID	17	5.7
NOD/SCID	126	42.6
Diabetic Nude	34	11.5
CD4 Knockout	3	1.0
Rag Knockout	9	3.0
Akita Rag Knockout	11	3.7
Other	21	7.1
Not Documented	3	1.0
Organ (Route of Transplantation)		
Kidney (Subcapsular)	283	95.6
Other (Matrigel: Subcutaneous)	10	3.4
Not Documented	3	1.0

	N	%
Outcome Used to Judge Cure		
Blood Glucose Permanently < 200 mg/dL	229	77.4
Insulin Permanently > 5 µU/L	2	0.7
C-Peptide Permanently > 1 ng/mL	26	8.8
Blood Glucose < 200 mg/dL and C-Peptide > 1 ng/mL	4	1.4
Insulin > 5 µU/L and C-Peptide > 1 ng/mL	4	1.4
Blood Glucose < 200 mg/dL, Insulin > 5 µU/L, and C-Peptide > 1 ng/mL	19	6.4
Insulin > 5 µU/L and Other	1	0.3
C-Peptide > 1 ng/mL and Other	1	0.3
Other	7	2.4
Not Documented	3	1.0
All Mouse Bioassays	*296*	*100.0*

Exhibit 99
Mouse Bioassay Success Rate

	N	Mean	SD	Min	25th %	Median	75th %	Max
Percentage of Mice Cured	293	48.1	44.5	0.0	0.0	50.0	100	100

Part Two: Basic Science Islet Distribution

Chapter 1: Basic Science Islet Distribution

The Islet Cell Resource Consortium began distributing islets for both clinical transplantation and basic research in 2004. The total islet cell distributions in 2004 totaled 1.3 million. By 2008, total distributions increased to 22.3 million. The anticipated demand in 2009 based on researcher applications exceeds 50 million islets.

The number of approved studies has similarly increased from 2004 when 19 investigators at 16 institutions received islets through the ICR. As of August 2008, 156 investigators at 105 institutions used ICR islets. The ICR receives researcher applications and requests for extension or increase of islet cell distributions on a weekly basis, thereby continually increasing the user pool and the demand for islets.

Review of the islet distribution data for the program year September 2007-August 2008 indicates that islet distribution varies significantly by month. During this period, islet distribution ranged from a low of just over 1 million IEQs in July 2008 to a high of over 3 million IEQs in January 2008.

The ICR tabulated the number of islet shipments and recipients for each Islet Center (n=8) from September 2007 to August 2008. Center G has been a Consortium member since 2004. It had the highest number of islet recipients (66) and the greatest number of shipments (176). Center M, only operational as a Consortium member since 2007, had the fewest number of shipments (70) but not the fewest number of recipients (44). A pie chart of the distributions made per center is presented in Exhibit 104, which also outlines the islet equivalents (IEQs) distributed by each center from September 2007 to August 2008.

For all graphs in this section, each year is defined as the 12 month period ending on August 31st of the year indicated.

Exhibit 100
IEQs Distributed for Basic Science Research by the ICR per Year

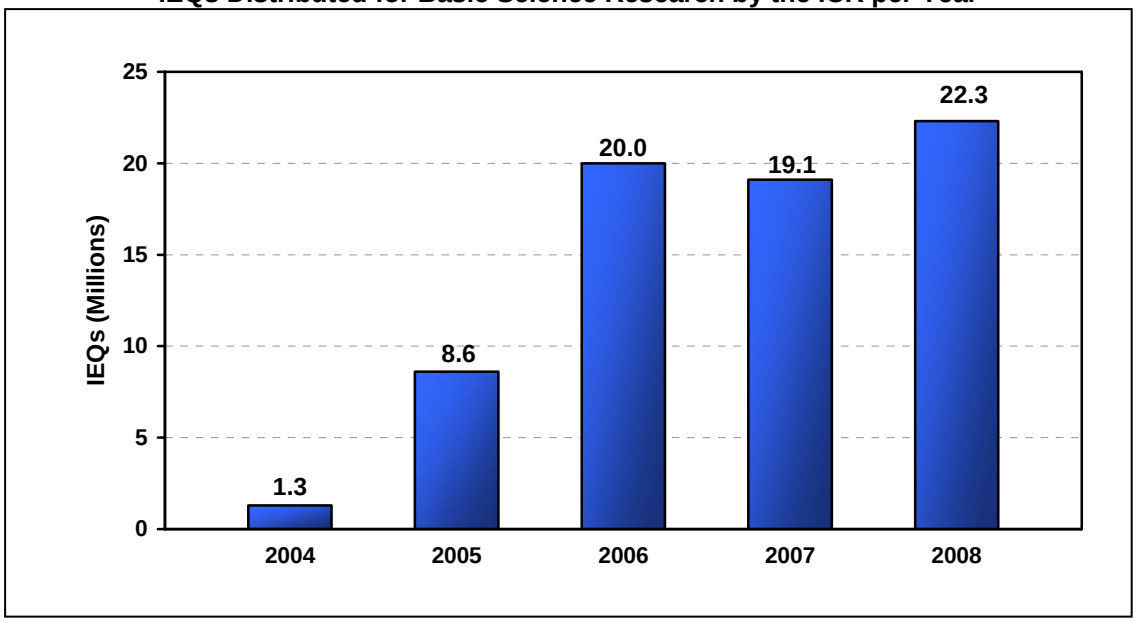


Exhibit 101
Total Number of ICR-Approved Studies and Institutions by Year

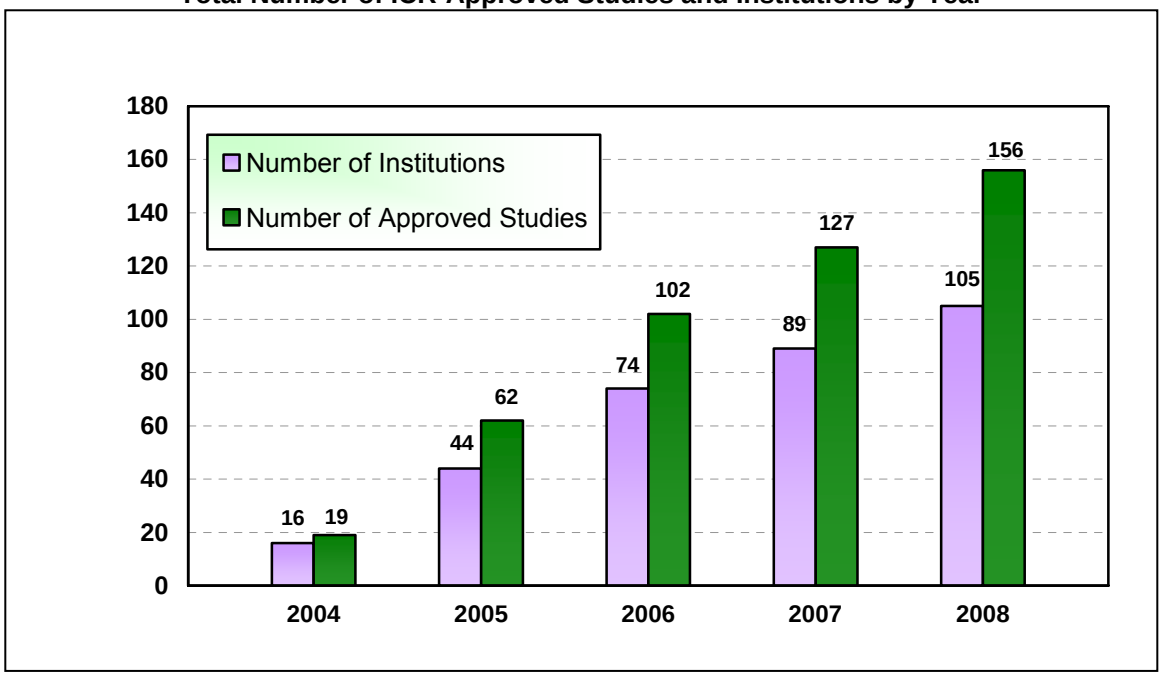


Exhibit 102
IEQs Distributed for Basic Science Research per Month in 2008
By Distribution Method

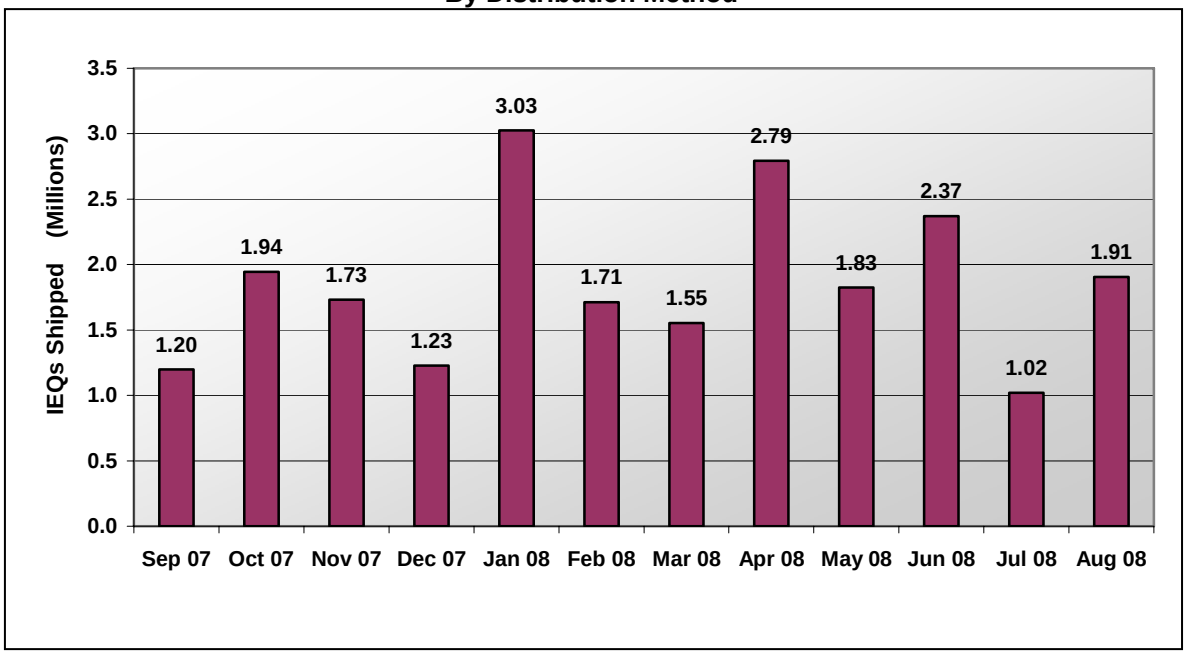


Exhibit 103
Number of Shipments and Recipients per ICR Center in 2008

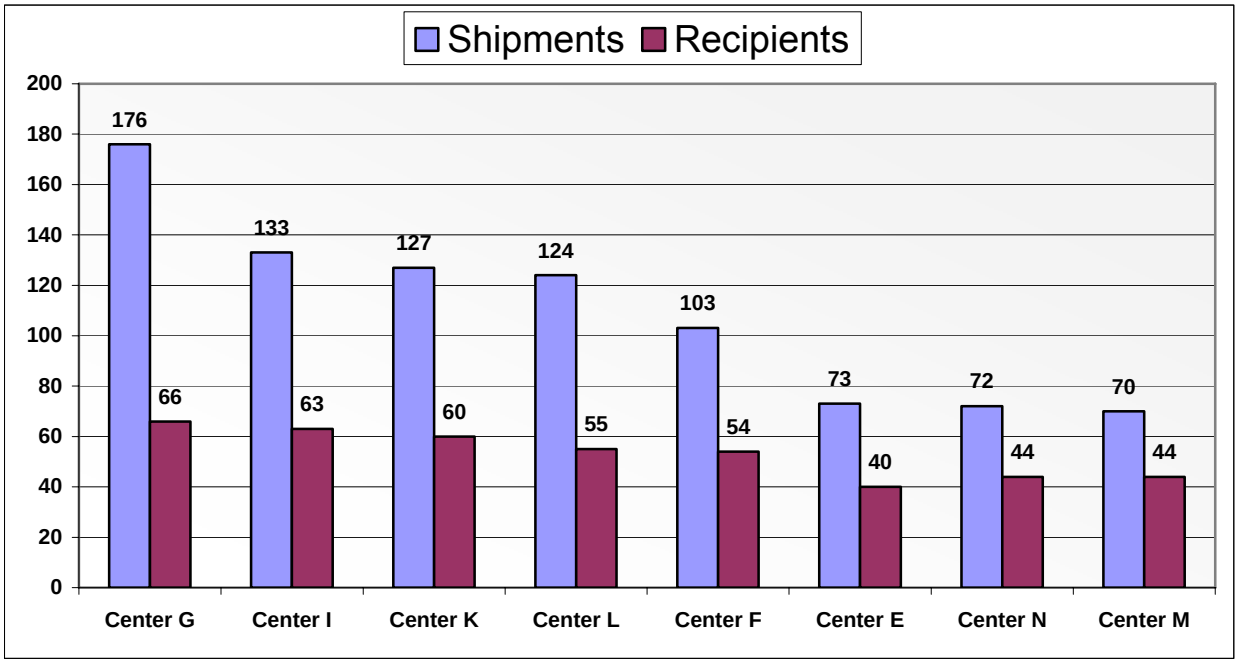
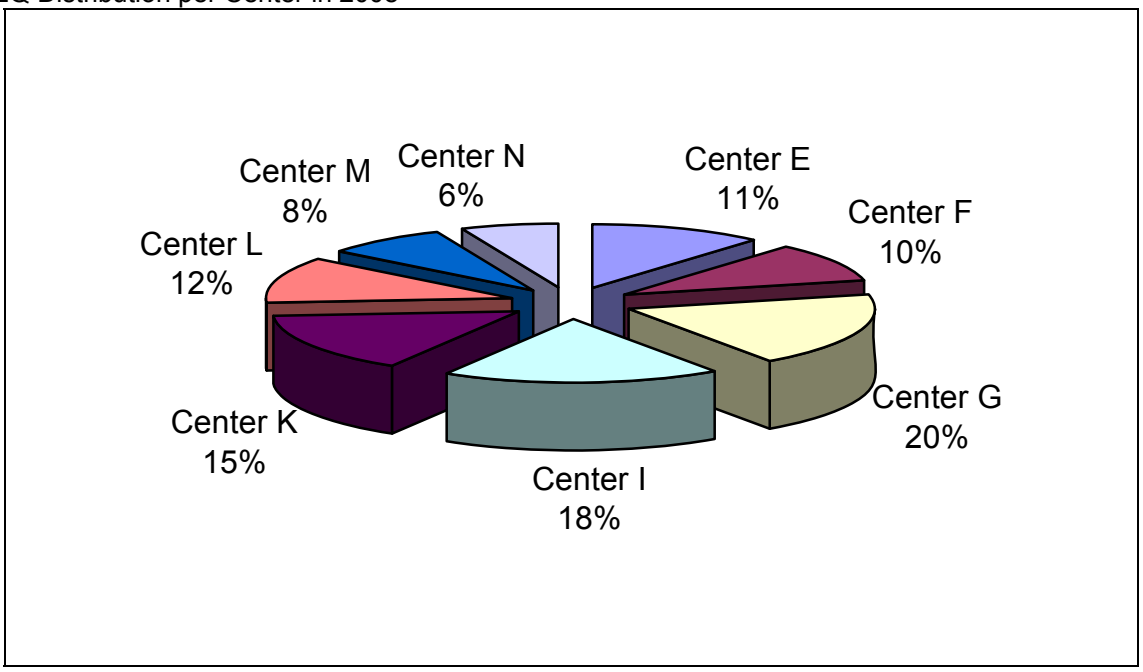


Exhibit 104
IEQ Distribution per Center in 2008



ICR Sponsored Publications

2009

1. Balamurugan AN, Akhov L, Selvaraj G, Pugazhenthi S: Induction of antioxidant enzymes by curcumin and its analogues in human islets: Implications in transplantation. Pancreas Vol 00, (00) Published Ahead of Print, 2 Feb 2009 [PubMed Abstract]

2. Chen H, Gu X, Su IH, Bottino R, Contreras JL, Tarakhovsky A, Kim SK: Polycomb protein Ezh2 regulates pancreatic beta-cell Ink4a/Arf expression and regeneration in diabetes mellitus. Genes & Dev. 2009 Apr 15; 23(8):975-85 [PubMed Abstract]

3. Correa-Medina M, Bravo-Egana V, Rosero S, Ricordi C, Edlund H, Diez J, and Pastori RL: MicroRNA miR-7 is preferentially expressed in endocrine cells of the developing and adult human pancreas. Gene Expr Patterns. 2009 Apr;9 (4):193-9. Epub 2008 Dec 24. [PubMed Abstract]

4. Fiaschi-Taesch N, Bigatel TA, Sicari B, Takane KK, Salim F, Velazquez-Garcia S, Harb G, Selk K, Cozar-Castellano I, Stewart AF: 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. Diabetes, 2009 Apr;58(4):882-93. Epub 2009 Jan 9. [PubMed Abstract]

5. Glas R, Sauter NS, Schulthess FT, Shu L, Oberholzer J, Maedler K: Purinergic $P2X_7$ receptors regulate secretion of interleukin-1 receptor antagonist and beta cell function and survival. Diabetologia 2009 Apr 25. [Epub ahead of print] [PubMed Abstract]

6. Huang J, Levitsky LL, Rhoads DB: Novel P2 Promoter-Derived HNF4α Isoforms with Different N-Terminus Generated by Alternate Exon Insertion. Exp Cell Res. 2009 Apr 15;315(7):1200-11 [PubMed Abstract]

7. Kaddis JS, Olack BJ, Sowinski J, Cravens J, Contreras JL, Niland JC: Human Pancreatic Islets and Diabetes Research. JAMA April 15, 2009 –Vol 301, No. 15 1580-87. [PubMed Abstract]

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11. Panakanti R, Mahato RI: Bipartite adenoviral vector encoding hHGF and hIL-1Ra for improved human islet transplantation. Pharm Res. 2009 Mar;26(3):587-96. Epub 2008 Nov 12. [PubMed Abstract]

12. Panakanti R, Mahato RI: Bipartite Vector Encoding hVEGF and hIL-1Ra for Ex Vivo Transduction into Human Islets. Mol Pharm. 2009 Jan-Feb; 6(1): 274-84. [PubMed Abstract]

13. Sarkar SA, Kutlu B, Velmurugan K, Kizaka-Kondoh S, Lee CE, Wong R, Valentine A, Davidson HW, Hutton JC, Pugazhenthi S: Cytokine-mediated induction of anti-apoptotic genes that are linked to nuclear factor kappa-B (NF-κB) signaling in human islets and in a mouse beta cell line. Diabetologia. 2009 Jun;52(6):1092-101. Epub 2009 Apr 3. [PubMed Abstract]

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16. Zhang S, Carper MJ, Lei X, Cade WT, Yarasheski KE, Ramanadham S: Protease inhibitors used in the treatmentof HIV induce β-cell apoptosis via the mitochondrial pathway and compromise insulin secretion. Am J Physiol Endocrinol Metab. 2009 Apr;296(4):E925-35. Epub 2009 Feb 10 [PubMed Abstract]

2008

17. Al-Abdullah IH, Bentsi-Barnes K, Valiente L, et al: Testing Combinations of Protease Inhibitor and Preservation Solution to Improve Islet Quality and Yield. Transplantation Proceedings 2008. 40(2): 390–392.[PubMed Abstract]

18. Avgoustiniatos ES, Hering BJ, Rozak PR, Wilson JR, Tempelman LA, Balamurugan AN, Welch DP, Weegman BP, Suszynski TM and Papas KK: Commercially available gas-permeable cell culture bags may not prevent anoxia in cultured or shipped islets. Transplant Proc. 2008 Mar;40(2):395-400. [PubMed Abstract]

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