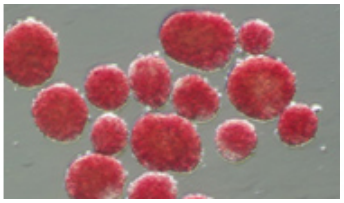
# Clinical Islet Transplantation Consortium


## WELCOME

The Clinical Islet Transplantation (CIT) Consortium is a network of clinical centers and a data coordinating center established in 2004 to conduct studies of islet transplantation in patients with type 1 diabetes.

Studies conducted by the CIT Consortium will focus on improving the safety and long-term success of methods for transplanting islets, the insulin-producing cells of the pancreas, in people whose own islets have been destroyed by the autoimmune process that characterizes type 1 diabetes.

The network includes the following centers:

University of Miami
Miami, Florida

University of Pennsylvania
Philadelphia, Pennsylvania

Baylor College of Medicine
Houston, Texas

Uppsala University
Uppsala, Sweden

University of Minnesota
Minneapolis, Minnesota

Emory University
Atlanta, Georgia

University of Alberta
Edmonton, Alberta, Canada

Karolinska University
Stockholm, Sweden

# Who is in the CIT Consortium?

The CIT Consortium was created by the National Institutes of Health (NIH). Two NIH Institutes — the National Institute of Diabetes & Digestive & Kidney Diseases (NIDDK) and the National Institute of Allergy and Infectious Diseases (NIAID) — sponsor the consortium.

The consortium consists of the following principal investigators and centers:

- **Dr. Bernhard Hering**
  University of Minnesota
  Minneapolis, Minnesota

  Dr. Hering is Professor of Surgery, the Eunice L. Dwan Diabetes Research Chair, and Director of Islet Transplantation and Scientific Director of the Diabetes Institute for Immunology and Transplantation at the University of Minnesota. He is a member of the Steering Committees of several NIH-sponsored research consortia, including the Clinical Islet Transplant Consortium, the Immune Tolerance Network, the Human Islet Cell Resource Program, the Nonhuman Primate Transplantation Tolerance Collaborative Study Group, and the Immunobiology of Xenotransplantation Cooperative Research Program. He is co-director of the Juvenile Diabetes Research Foundation (JDRF) Islet Transplant Center at the University of Minnesota/University of California San Francisco. Dr. Hering co-founded the International Islet Transplant Registry and is Medical Director of the NIH-sponsored Collaborative Islet Transplant Registry (CITR). He has served as President of the Cell Transplant Society and as Councilor of the International Pancreas and Islet Transplant Association, and is currently a member of the Council of the International Xenotransplant Association. He sits on the editorial boards of several professional journals and has authored over 200 articles and 25 book chapters on islet transplantation.

- **Dr. Olle Korsgren**
  Uppsala University
  Uppsala, Sweden

  Dr. Olle Korsgren started his medical studies at the University of Uppsala, Sweden. He then received a Research Trainee Award from the Swedish Medical Research Council. After completing his thesis in 1991, he received a 4-year Research Career Award from the Swedish Medical Research Council. He became a Specialist in Clinical Immunology and Senior staff member at the Department of Clinical Immunology, University Hospital, Uppsala in 2001, and received a 6-year Senior Research position from the Swedish Medical Research Council. In 2002 he was appointed Professor of Transplantation Immunology at Uppsala University. Since 2006 he holds the position as Professor of Cell Transplantation at the same University.

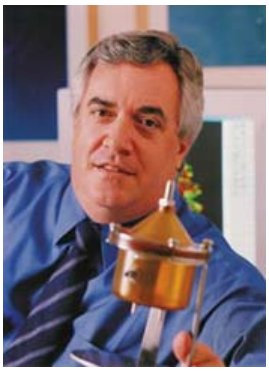
  Dr. Korsgren's research activity has been focused on making islet transplantation a possible treatment for patients with type I diabetes. This has led him into several different areas from the ontogeny of the fetal pancreas and the development of techniques to make human islet isolation possible to the immununological problems involved in islet allo- and xenotransplantation. He is the Principal Investigator of the Nordic Network for clinical islet transplantation.

  Dr. Korsgren has received several honors and awards, and he is frequently invited to give seminars and lectures at international meetings and workshops. He serves on the editorial boards of several scientific journals. Dr. Korsgren has authored more than 200 scientific publications. An inventor, he has been awarded five patents.

- **Dr. Ali Naji**
  University of Pennsylvania
  Philadelphia, Pennsylvania

Dr. Ali Naji is the J. William White Professor of Surgery, director of the JDRF-Penn Islet Transplantation Program, and associate director of the Institute for Diabetes, Obesity and Metabolism at the University of Pennsylvania School of Medicine. Dr. Naji completed his clinical residency and fellowship training in general, vascular and transplantation surgery at the Hospital of the University of Pennsylvania in Philadelphia. Dr. Naji has served on several NIH study sections including Surgery/Anesthesia/Trauma, Immunological Sciences and Transplantation/Tolerance/Tumor Immunology. He is an associate editor for the journals Transplantation, Diabetes and Transplantation Immunology. His basic research efforts have focused on the immunobiology of transplantation and immune pathogenesis of autoimmune diabetes. Specifically his investigations were the first to demonstrate the critical role of recurrent anti-beta cell autoimmunity as a basis for the failure of islet transplantation for treatment of Type 1 diabetes mellitus (T1D). Most recently, his group's efforts have focused on the role of B lymphocytes in the pathogenesis of T1D and organ transplant rejection demonstrating the requisite role of B lymphocytes as antigen presenting cells in the pathogenesis of islet inflammation and immunologic rejection. Translation of his basic research in islet transplantation studies have demonstrated the efficacy of B lymphocyte targeting for the induction of islet allograft tolerance in diabetic non-human primates. Dr. Naji and his group plan to determine the clinical efficacy of B lymphocyte directed immunotherapy as part of the cooperative NIH sponsored islet transplantation consortium.

- **Dr. Camillo Ricordi**
  University of Miami
  Miami, Florida



Dr. Ricordi spent four years (1989-1993) as Director of Cellular Transplantation at the University of Pittsburgh Transplantation Institute. Since 1993, he has been at the University of Miami, where he holds the Stacy Joy Goodman Chair. He serves as Professor of Surgery, Medicine, Biomedical Engineering, Pathology, Microbiology and Immunology. Dr. Ricordi is also Chief of the Division of Cellular Transplantation, Department of Surgery, and Scientific Director and Chief Academic Officer of the Diabetes Research Institute. Dr. Ricordi was president of the Cell Transplant Society (1992-94), co-founder of the National Diabetes Research Coalition (Chairman 1997) and president of the International Association for Pancreas and Islet Transplantation (1999-2001; IPITA). Currently a member of the council of the International Transplantation Society, he also served on the council of the American Society of Transplant Surgeons (2000-2002). Dr. Ricordi is also serving on the NIH/NCRR Islet Cell Resources (ICRs) Executive Committee, as Chairperson of the Clinical Islet Transplant Consortium (NIDDK-NIAID), on the NIH-NIDDK Strategic Planning Committee, and on the NIH Expert Panel on Transplantation Research. Dr. Ricordi is also known for inventing the machine (pictured) that made it possible to isolate large numbers of islet cells from the human pancreas. He performed the first series of clinical islet transplants that reversed diabetes after implantation of donor purified islets into the liver of recipients with diabetes.

- **Dr. James Shapiro**
  University of Alberta
  Edmonton, Alberta, Canada

Born in Leeds, England, Dr James Shapiro obtained his Medical Degree at the University of Newcastle-upon-Tyne and trained in Surgery at the University of Bristol. In 1993, He came to the University of Alberta in Canada to train in liver transplantation and hepatobiliary surgery, continuing research studies in experimental islet transplantation begun as a medical student. He earned a Ph.D. studying new drug combinations for possible testing in islet transplantation. He then further trained in liver surgery in Vancouver, in living donor liver transplant surgery in Japan, and in whole pancreas transplant surgery at the University of Maryland. In 1998, he returned to the University of Alberta as a multi-organ transplant surgeon.

Dr. Shapiro was asked to lead the Clinical Islet Transplant Program team in Edmonton; Together with Drs. Lakey, Ryan, Rajotte, Kneteman and Korbutt, he developed and tested a new protocol that used a steroid-free anti-rejection regimen coupled with sufficient numbers of transplanted islets. This research has since become known as the "Edmonton Protocol." In 1999, Dr. Shapiro initiated the pancreas transplant program at the University of Alberta, and in the same year performed the first emergency living-related donor liver transplant in Canada.

Dr. Shapiro is Principal Investigator of the international multi-center trial of islet transplantation testing the Edmonton Protocol at 9 international sites, sponsored by the Immune Tolerance Network. He is also Principal Investigator and Director of the Juvenile Diabetes Research Foundation (JDRF) Clinical Center for Islet Transplantation created in 2001 at the University of Alberta. In 2002, Dr. Shapiro was awarded the Canadian Institutes of Health Research/Wyeth Clinical Research Chair in Transplantation at the University of Alberta.

In 2005,Dr. Shapiro received a Meritorious Service Medal from the Governor General of Canada for his work towards the development of a new treatment for Diabetes. He was also named one of the "Physicians of the Century", by the College of Physicians and Surgeons of Alberta and the Alberta Medical Association. In 2006, he was named one of Nature Biotechnology's most remarkable and influential personalities from the past 10 years, in Biopharmaceuticals.

Dr. Shapiro maintains an active immunology/transplant research laboratory focused on aspects of tolerance induction relating to islet transplantation with emphasis on costimulatory blockade and chimerism, with translational potential to clinical islet recipients. In early 2004, Dr. Shapiro was awarded an Alberta Heritage Foundation for Medical Research Scholarship to support his on-going tolerance research.

The Clinical Trials Statistical & Data Management Center's (CTSDMC) purpose is to coordinate the statistical and data management functions for the CIT Consortium. The center is a unit within the Department of Biostatistics in the College of Public Health at the University of Iowa. The project director for CTSDMC studies is:

- **Dr. William Clarke**
  University of Iowa
  Iowa City, Iowa

Dr. Clarke is Professor of Biostatistics at The University of Iowa. He has a B.S in Mathematics from the University of Oregon and M.S. and Ph.D. degrees in Statistics from the University of Iowa. He is the Director of the Clinical Trials Statistical and Data Management Center in the Department of Biostatistics, which supports the development and conduct of multicenter clinical trials. Since its inception in 1989, the center has supported multicenter clinical trials in neurology, anesthesia, nephrology, and diabetes. He serves as Director of the Data Coordinating Center for the Clinical Islet Transplantation Consortium.

# What is diabetes?

Diabetes is a serious disease, which, if not controlled, can be life threatening. It is often associated with long-term complications that can affect every system and part of the body. Diabetes can contribute to eye disorders and blindness, heart disease, stroke, kidney failure, amputation, and nerve damage. It can affect pregnancy and cause birth defects, as well.

The most common form of diabetes is type 2 diabetes, which is a result of insulin resistance (a condition in which the body fails to properly use insulin), combined with relative insulin deficiency. Most Americans who are diagnosed with diabetes have type 2 diabetes.

CITC is focused on research in the area of type 1 diabetes.

## Type 1 Diabetes

Type 1 diabetes results from the body's failure to produce insulin, the hormone that "unlocks" the cells of the body, allowing glucose to enter and fuel them.

It is an autoimmune disease in which the body views the beta cells (insulin producing cells found in the islets of the pancreas) as a foreign substance, so the patient's immune system attacks the islets and kills them.

It is estimated that 5-10% of Americans who are diagnosed with diabetes have type 1 diabetes. Most people with type 1 diabetes do not have a family history of the disease. We do not know how to prevent the onset of type 1 diabetes.

## Common Treatments for Type 1 Diabetes

### Intensive Insulin Therapy

There are many different insulins for many different situations and lifestyles, and there are more than 20 types of insulin sold in the United States. These insulins differ in how they are made, how they work in the body, and price. A molecule that is identical to human insulin can be manufactured. In addition, insulin can be obtained from pigs, as people will respond to pig insulin. Future availability of animal insulin is uncertain.

Insulin may be taken by means of a shot (often several times a day), or infused through catheter (a small needle) attached to an insulin pump. Recently an inhalable insulin has been approved by the FDA.

It is important for anyone with diabetes to be careful about the type, timing and amount of food they eat. People with diabetes also need to monitor their bloodsugars carefully through frequent finger prick glucose testing. A person with diabetes may experience long term complications if tight blood sugar control is not maintained; likewise, control that is too tight may result in severe hypoglycemic (low blood sugar) reactions.

### Pancreas Transplant

The first pancreas transplant was performed in 1966. Long-term success has steadily improved and the risks have decreased. Whole organ pancreas transplant is a major operation and can be associated with complications, such as bleeding, infection, inflammation of the pancreas and clots in the blood vessels around the pancreas. It is most often performed when a patient also needs a kidney transplant. The success rate (long-term insulin independence) with pancreas transplantation was initially low, but increased dramatically in the 1980s. After one year about 85% of pancreas transplant recipients are insulin independent. By the 1990s, more than 1000 pancreas transplants a year were being done worldwide, the majority in the U.S.

## Islet Transplantation and Other Experimental Treatment Options

Islet transplantation is still in the experimental stages. The advantages over pancreas transplantation are that it does not require a major operation and the procedure has a small complication rate. Nevertheless, islet transplantation can be associated with bleeding, clotting of blood vessels in the liver, or damage to the gall bladder. At this time, the results are not as good as pancreas transplantation.

Lastly, it is important to note that individuals that receive a pancreas or islet transplant must take immunosuppressive medications as long as the pancreas or islets are functioning.

The risks and benefits of either procedure are complex and are not limited to the issues discussed in this brief summary.

# What is islet transplantation?

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The islets of the pancreas produce insulin. In type 1 diabetes, the insulin-producing cells in the islets have been destroyed.

In islet transplantation, islets from a deceased donor are infused (dripped) into a vein in the liver. (See Procedure.) If the transplant is successful, the islets lodge in the liver and start to produce insulin.

While islet transplantation has generated considerable interest, it's still considered an experimental procedure and is not an approved treatment.

## Rationale for Islet Transplantation

Insulin therapy, given by injection or insulin pump, is life-saving. However, it's not perfect. Most people with type 1 diabetes still have blood glucose levels that are above normal. This puts them at risk for the long-term complications of diabetes.

Those who are able to keep their blood glucose levels near normal often have trouble with low blood glucose (hypoglycemia). And after many years, some people lose the early symptoms that warn them that their blood glucose level is dropping. This is called hypoglycemia unawareness and raises the risk of severe hypoglycemia.

Some people have what doctors call labile, or brittle, diabetes. Blood glucose levels swing from high to low despite the best insulin plans.

The potential advantage of islet transplantation over administration of insulin by injection is that the transplanted islets would maintain normal blood sugar under all conditions, and would not produce excess insulin resulting in hypoglycemia.

In practice, there are problems to overcome in islet transplantation before it can be considered a standard therapy for people with type I diabetes.

- As with any organ transplant, the recipient of an islet transplant must take drugs every day to keep the body from rejecting the islets. These drugs put the person at risk for infections and certain cancers. They can also cause side effects that range from mild to severe. Some people who received an islet transplant have had to stop taking these medications, because of side effects and then their new islets stopped working.
- Sometimes, the islets don't "take." The new islets never produce insulin.

- Most people need two infusions at different times to get enough islets that are working, and some need three. So, even if islet transplantation is found to be effective, currently, there are not enough donor pancreases available to treat everyone with type 1 diabetes.
- In the majority of people who receive an islet transplant, the function of the islets deteriorates over time, and they must go back to taking some insulin. Since the number of people who have had successful islet transplants is small, and those have happened within the past 7 years, we do not know how long the islets will keep working.

The CIT Consortium is conducting studies to find methods that have higher success rates and fewer risks.

## History of Islet Transplantation

The concept of islet transplantation is not new. English surgeon Charles Pybus (1882-1975) tried to graft pancreatic tissue to cure diabetes. Most credit the recent era of islet transplantation research to Paul Lacy's studies dating back more than 3 decades.

The first human trials were done in the mid-1980s. By the late 1990s, methods had gotten better. But still, only 8 percent of recipients were free of the need for insulin therapy 1 year later.

In 2000, Dr. James Shapiro and his colleagues at the University of Alberta, in Edmonton, Canada, published a report describing seven consecutive participants who didn't need insulin injections for at least 4 months following one, two, or three islet transplantations. The transplants were done with a new protocol, using steroid-free immunosuppression and large numbers of donor islets.

This Edmonton protocol has been adapted by islet transplant centers around the world and has greatly increased islet transplant success.

## The Present

The goal of islet transplantation is to maintain normal blood sugar levels without the need risks of hypoglycemia.

Short-term findings from various islet transplant programs across North America have shown that:

- 63% of participants who got one islet transplant were still off insulin 6 months later.
- 75% of participants who got two islet transplants were still insulin-free 6 months after their second infusion.
- 54% of participants with three islet transplants were still off insulin 6 months after their third infusion.

Rates of insulin independence for all three groups were lower at one year, but for those who received one and two infusions, rates were above 50%.

One review showed that of 37 participants at three centers, 28 (76%) were still off insulin at 1 year. A study published in 2004 reported that of 11 islet recipients, 56% were still insulin-free at 1 year.

Recently, the results of a follow-up study of 65 participants receiving islet transplantation in Edmonton, Canada, were published.

- Out of the 65 participants, 47 had transplants that "took"; that is, they produced some insulin.
- Five subjects became insulin independent after one transplant.
- 52 participants had two transplants. Eleven had three transplants.
- 44 of 47 participants (94%) were insulin independent for at least 1 month.
- In 5 year follow-up, more than 80% had evidence of continued islet function. However fewer than 10% remained insulin independent .

Although these results offer promise, they reaffirm the need for more research.

## The Edmonton Protocol

Before the Edmonton protocol was developed, researchers used steroid-based immunosuppressant regimens. Many of these drugs damaged the insulin-producing cells or made recipients insulin resistant, which made more work for the new islets.

In the late 1990s, Dr. James Shapiro and colleagues at the University of Alberta, in Edmonton, Canada, introduced the following changes:

- They shortened the time between harvesting the pancreas from a donor and the transplant procedure.
- They infused many more islets than had been typically used in the past.
- They used an immunosuppressive protocol that included sirolimus, low-dose tacrolimus, and daclizumab. No glucocorticoids were given.

The Edmonton protocol has been adapted by islet transplant centers worldwide. Over **500** islet transplant procedures have been done with some variant of this protocol.

# The CITC Studies

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The CITC studies will focus on improving the safety and long-term success of transplanting islets (the insulin-producing cells of the pancreas) in people whose own islets have been destroyed by the autoimmune process that characterizes type 1 diabetes. Some studies will focus on improving combined islet and kidney transplants in patients with type 1 diabetes and kidney failure, a common complication of diabetes.

CITC studies will focus on:

- improving the isolation and viability of islets
- reducing complications of the islet transplant procedure (e.g., bleeding and clotting in the blood vessels of the liver)
- reducing the side effects of immunosuppression
- achieving good blood sugar control without hypoglycemia
- following the fate of islets after transplantation and determining why donor islets sometimes fail
- evaluating new ways to safely prevent immune rejection of donor tissues

# Links

## Participating Study Centers

Baylor College of Medicine - http://www.debakeydepartmentofsurgery.org/home/content.cfm?content_id=274&clinic_pk=11

Clinical Islet Transplant Program in Edmonton - http://www.med.ualberta.ca/islet/

Emory University - http://www.transplant.emory.edu

Karolinska Universit and Uppsala University - www.nordicislets.org

University of Miami - http://www.diabetesresearch.org/AbouttheDRI/AboutMain.htm

University of Minnesota, DIIT - Diabetes Institute for Immunology and Transplantation - http://www.diabetesinstitute.org/diabinst/home.html

## General Online Resources

ADA - American Diabetes Association - http://www.diabetes.org/about-diabetes.jsp

BCBC - Beta Cell Biology Consortium - http://www.betacell.org/

CDA - Canadian Diabetes Association - http://www.diabetes.ca/

Children with Diabetes - http://www.childrenwithdiabetes.com/index_cwd.htm

CITR - Collaborative Islet Transplant Registry - https://web.emmes.com/study/isl/index.html

Diabetes Action Research and Education Foundation - http://www.diabetesaction.org/site/PageServer?pagename=index

dLife - http://www.dlife.com/dLife/do/ShowContent

EASD - European Association for the Study of Diabetes - http://www.easd.org/#welcome.html

IDF - International Diabetes Federation - http://www.idf.org/home/

ITR - International Islet Transplant Registry - http://www.med.uni-giessen.de/itr/

ICR - Islet Cell Resource Centers - http://www.ncrr.nih.gov/clinical/cr_icr.asp

JDRF - Juvenile Diabetes Research Foundation - http://www.jdrf.org/

NIDDK - National Institute of Diabetes and Digestive and Kidney Diseases - http://diabetes.niddk.nih.gov/

NIAID - National Institute of Allergy and Infectious Diseases - http://www.niaid.nih.gov/publications/autoimmune.htm

UNOS - United Network for Organ Sharing - http://www.unos.org/