



IMMUNE TOLERANCE NETWORK

PATIENT REFERRAL INFORMATION PACKAGE

MULTICENTER TRIAL OF THE EDMONTON PROTOCOL FOR ISLET TRANSPLANTATION

For residents of the United States only

Immune Tolerance Network
Suite 200
5743 South Drexel Ave
Chicago, IL
60637

www.immunetolerance.org



IMMUNE TOLERANCE NETWORK

BEFORE YOU APPLY – PLEASE READ

FOR THE MULTICENTER CLINICAL TRIAL OF THE EDMONTON PROTOCOL FOR ISLET TRANSPLANTATION

The Immune Tolerance Network (ITN) is currently accepting referrals for enrollment in a multicenter trial of the Edmonton Protocol for islet transplantation. The trial will take place at a number of clinical centers around the globe, beginning in September, 2000.

Enrollment in the trial is limited

Interested applicants should be advised that enrollment in the trial is very limited. Due to very high profile of this trial, we expect to receive many more applications from individuals meeting all the criteria than we have room for. As such, meeting all of the entry criteria listed will not guarantee that you will be selected for an islet transplant.

Risks involved in the Procedure

It is important to keep in mind that the Edmonton Protocol is an *experimental* treatment for diabetes. Although it appears to be very effective at reversing the need for insulin shots, the long term effectiveness and side effects of this procedure are not yet known.

Following islet transplantation, patients are required to take a group of medications known as immunosuppressants, drugs which prevent the body from reacting to the transplanted islets that have been introduced into the liver. These drugs must be taken each and every day following the transplant, while the islet cells continue to work. These experimental drugs are designed to decrease the activity of the immune system and therefore carry a number of potential risks, many of which are not yet well-defined. These risks could include and increased susceptibility to various infections and cancer. . Therefore, children (<18 years of age) cannot be considered for participation due to the potential risks of this procedure.

Objectives of the Trial

The ITN multicenter clinical trial of the Edmonton Protocol has been developed with several goals in mind. Our first objective is to verify that the procedures developed by the Edmonton team can be successfully repeated at other clinical centers. We will do this using slightly larger patient numbers than the initial research of the Edmonton group to try and further define how effective the technique truly is. In the long-term, the goal of the ITN is to replace the immunosuppressive therapies currently required following islet transplantation, with new treatment approaches designed to prevent the destruction of the transplanted islet cells while causing fewer side-effects and posing fewer risks.



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BACKGROUND ON ISLET TRANSPLANTATION

USING THE EDMONTON PROTOCOL

How are Islet Transplants Performed?

Pancreatic islets contain B-cells that produce the natural insulin that regulates how the body utilizes glucose (or sugar). In Type I (or "juvenile") diabetes, the immune system mistakenly attacks these cells leaving sufferers unable to produce necessary quantities of insulin. Islet transplantation offers the hope of restoring the body's normal insulin production levels by implanting functioning islet cells procured from cadaver donors.

In the procedure, the islets are separated from the surrounding tissue of the donor pancreas by a machine. Typically, islets are cultured before transplant, however, the Edmonton protocol uses freshly isolated islets. In addition, the Edmonton protocol uses the islets of two separate donors over two or more transplant procedures for each patient, in order to maximize the number of insulin-producing cells.

Once the islets have been isolated, the rest of the procedure can be done the same day, often as an out-patient surgery. Using X-rays as a guide, the islets are injected into the portal vein of the patient's liver. Once in the portal vein, normal blood flow carries the islets to the liver where they become lodged in capillaries. It is there that the islets may begin to produce insulin, just as they normally would in the pancreas – in essence, the liver now does the job the pancreas would normally do.

What happens after the transplant?

The environment in the liver for newly transplanted islet cells is very unfriendly. In type I diabetics, the "autoimmune" destruction that led to the initial development of diabetes continues its attack on the new cells. In addition, the body's natural defenses go on full alert, recognizing the transplanted islets as a foreign invader and launching a second "alloimmune" response. Because of this destructive environment, transplant recipients must currently take "immunosuppressive" drugs that prevent the destruction of the islets by the immune system. Patients generally stay on this therapy for the remainder of their lives.

Immunosuppressive therapies used in islet transplantation have typically contained steroids. In the Edmonton protocol, immunosuppression is achieved using a combination of three drugs - *Sirolimus*, *tacrolimus* and *Zenapax* - none of which contain steroids. It is believed that the lack of steroids has contributed to the success of the Edmonton Protocol, because steroids themselves may be toxic to newly transplanted islets.

Is Islet Transplantation a Cure for Diabetes?

In principle, yes! The Edmonton protocol is a remarkable breakthrough and a sign that we can indeed conquer Type I diabetes. However, at present, the supply of cadaver pancreas would severely limit the number of patients who could receive transplants. As well, with any experimental technique, it is important that the effects of the treatment are fully known - immunosuppression is generally associated with a number of side effects, including increased risks of infection and even cancer. For islet transplantation to offer a true cure to diabetes, we must first:

- confirm the results obtained in the patients treated so far, in a larger patient population
- determine the long-term risks associated with immunosuppression
- investigate the biological reasons behind both the development of diabetes and the rejection or acceptance of transplanted islet cells
- develop new, more specific methods of inhibiting the auto and alloimmune reactions against transplanted islet cells.

The Immune Tolerance Network Trial and Beyond

The ITN will perform its multicenter trial of the Edmonton Protocol to meet all of these goals. This trial will serve as the gold standard method for islet transplantation and allow the ITN to concentrate its efforts on finding new, more specific alternatives to life-long immunosuppressive treatments.

Several new therapies currently being tested in laboratories around the world appear to be able to very specifically block harmful alloimmune and autoimmune responses, while leaving beneficial, disease-fighting immune responses intact. The ITN is committed to bringing these therapies into the clinic quickly and the ITN multicenter trial of the Edmonton Protocol is the first step in realizing our goals.



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COMPLETING YOUR APPLICATION

FOR THE MULTICENTER CLINICAL TRIAL OF THE EDMONTON PROTOCOL FOR ISLET TRANSPLANTATION

Please read all the documentation provided prior to filling out the forms.

Spend some time looking over the criteria for enrollment in the trial. After considering each point, if you still feel you may qualify or are unsure whether any of the criteria apply, you should make an appointment with your physician to further investigate if you are indeed a suitable candidate.

Prior to your appointment with your physician, you should complete and sign the “Islet Transplant Patient Information Form”. This will provide the ITN with some very basic information regarding your diabetes and overall health. You should also complete the letter that authorizes your physician to provide the ITN with additional medical information pertaining to your condition.

Discuss with your physician how each of the enrollment criteria applies to you. If, after reviewing all the criteria, your physician agrees that you are a suitable candidate, he/she should complete and sign the “Referral for Islet Transplant” form provided in this package. Your physician must mail this form together with the Patient Information Form you completed, to:

Patient Referrals

Immune Tolerance Network
Suite 200
5743 South Drexel Ave.
Chicago, IL
60637

Once received, the ITN will evaluate all the referrals received and identify a subset of individuals who appear to meet the basic criteria. These individuals will be asked to submit to a secondary evaluation consisting of a series of interviews and laboratory tests aimed at further assessing their suitability for the trial. The tests will take place at an ITN clinical center or a laboratory contracted by the ITN. Note that only those individuals passing to the secondary evaluation phase will be contacted by the ITN.

Note on Confidentiality: The information you provide to the ITN will be kept in the strictest of confidence and will be used only for the purpose of evaluating your suitability for involvement in the clinical trial. The information you provide will not be shared with other individuals or organizations under any circumstances, without your express written consent.



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CRITERIA FOR ENROLLMENT

FOR THE MULTICENTER CLINICAL TRIAL OF THE EDMONTON PROTOCOL FOR ISLET TRANSPLANTATION

IMPORTANT:

Only **Type I Diabetics between the ages of 18-65 ,diagnosed at least 5 years ago**, will be eligible for participation in the trial. In addition, you must have conscientiously adhered to dietary and lifestyle modifications and an optimal insulin regime, but despite your best efforts, **at least one of the following applies:**

- "brittle" diabetes (i.e. you practice tight control, are in good compliance with insulin schedule, and still experience rapid, out-of-proportion blood glucose changes)
- hypoglycemic unawareness - you do not adequately feel the onset of low blood sugar
- you have had a least 1 hypoglycemic reaction in the last 1.6 years that cannot be otherwise explained and required outside help
- you have progressive secondary complications (such as vision, kidney, nerve or vascular problems), despite an optimal insulin regime
- failure of intensive insulin management, as judged by an independent endocrinologist

You will be ineligible for participation if any of the following apply:

- you have severe cardiac disease (e.g recent heart attack, angio evidence of non-correctable CAD, evidence of ischemia on functional cardiac exam, etc.)
- active alcohol or substance abuse - includes cigarette smoking (must be abstinent for >6 months)
- major psychiatric illness (as assessed by psychological or psychiatric consultation).
- active infection, including hepatitis C, hepatitis B, HIV, or positive skin test for TB
- any history of malignancy, except squamous or basal skin cancer
- obesity (BMI > 28)
- untreated proliferative retinopathy.
- positive pregnancy test, intent for future pregnancy, or failure to follow effective contraceptive measures, or presently breast-feeding.
- previous transplant, or evidence of sensitization on PRA (>20%).
- insulin requirement >0.7 iU/kg/day.
- HbA1C > 12%.
- untreated hyperlipidemia.



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ISLET TRANSPLANT PATIENT INFORMATION FORM

This form must be completed and signed by the patient. After completing this form, take it to your physician and along with a copy of the release form, ask him/her to complete an Islet Transplant Referral Form. Your physician should submit this form and the referral form to the Immune Tolerance Network directly.

Personal Information (please print)			
Name (Last, First)		Sex: <input type="checkbox"/> Male <input type="checkbox"/> Female	Date of Birth (DD/MM/YY)
Street Address			
City	State/Prov	Zip/Postal Code	E-Mail Address
Home Telephone	Work Telephone		Fax Number
Health Care Provider		Policy ID Number	

Doctor's Name and Address (please print)	
Name	
Address, City, State/Prov	
Telephone	Fax Number

Clinical Center	
Select the clinical center closest to your place of residence:	<input type="checkbox"/> Miami, Florida <input type="checkbox"/> Minneapolis, Minnesota <input type="checkbox"/> Boston, Massachusetts <input type="checkbox"/> St. Louis, Missouri <input type="checkbox"/> Washington, D.C. <input type="checkbox"/> Seattle, Washington

Patient's Signature	
I, _____ certify that the information contained within this document is true, to the best of my ability.	
Signed: _____	Date: _____

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Glucose Levels and Insulin Doses

We require 7 blood sugar tests a day for two days in a row. Please indicate your levels in the following table. All post meal blood sugar levels should be measured 2 hours following meal.

Day 1 - Date: _____								
Time of Day	Breakfast	After Breakfast	Lunch	After Lunch	Supper	After Supper	Bed Time	3 a.m. (optional)
Glucose Level								
Insulin Dose and Type								

Day 2 - Date: _____								
Time of Day	Breakfast	After Breakfast	Lunch	After Lunch	Supper	After Supper	Bed Time	3 a.m. (optional)
Glucose Level								
Insulin Dose and Type								

Medications

In the table below, list any medications you are currently taking.

Name of Drug	Amount Taken	When is your medication taken

List known allergies to medications: _____

Significant Medical History

In the table below, list any significant illnesses or major surgeries you have had. Begin with the date of onset of your diabetes.

Major Illness or Surgery <i>(attach additional page, if necessary)</i>	Date (month/year)
Onset of Type I Diabetes	_____

Date: _____, 2000

Dear Doctor _____,

I, _____ give you permission to release any information related to me diabetes and overall health to the Immune Tolerance Network for evaluation of my suitability to be included as a participant in a clinical trial of the "Edmonton Protocol" for islet transplantation.

Thank you

Signature

Name (please print)

Date

[complete, sign and present this letter to your physician to authorize him/her to release your confidential information to the ITN.]

