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CONSENT FORM

Anti-inflammatory therapy to improve outcomes in patients with chronic pancreatitis undergoing total pancreatectomy islet autotransplantation

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Invitation to Participate in Research

You are invited to participate in a research study evaluating the effect of treatment with one of two medications, called etanercept and alpha-1 antitrypsin, on the function of transplanted islets. Islets are clusters of insulin producing cells from the pancreas. You were selected as a possible participant in this study because you have chronic pancreatitis and are scheduled to have your pancreas removed and your islets transplanted into your liver. This procedure is called total pancreatectomy with islet autotransplantation (TPIAT).

Etanercept is FDA-approved for treatment of psoriasis and certain forms of arthritis. Alpha-1 antitrypsin is FDA- approved for patients with chronic lung disease due to alpha-1 antitrypsin deficiency. Use of both agents in islet autotransplantation is considered research. We ask that you read this form and ask any questions you may have before agreeing to be in the study.

This study is being conducted by the Departments of Pediatrics and Surgery. It is funded by the National Institutes of Health.

Study Purpose

The purpose of the study is to test whether either of two drugs can improve the number of islets that survive the transplant process. We know that when we place the islets into the vessels of the liver, this causes inflammation around the islets that can cause damage. As many as half of the islets may not survive the transplant process. There are studies in animals and in donor islet transplant recipients that suggest these two drugs can protect islets from this inflammation at the time of transplant. We hope to screen up to 60 participants, in order to get a total of 45, 15 in each arm.

The two drugs that we are testing are listed below. Participants are assigned at random to receive either **one** of the drugs, **or** no medication (control group).

1) **Etanercept** (brand name Enbrel ®): This drug blocks the action of a key part of the inflammation response called TNF alpha. This drug is marketed for arthritis and psoriasis and

has been used safely in patients who receive a donor islet transplant. Participants assigned to this drug receive 6 doses total—on the day of surgery, and at days 3, 7, 10, 14, and 21 after surgery.

2) **Alpha-1 antitrypsin** (brand name Aralast NP ®): This drug reduces inflammation, protects beta cells (the insulin producing cells of the islet), and improves islet graft survival in treated mice. This drug is marketed to replace the protein alpha-1 antitrypsin in adults who have deficiency. Participants assigned to this drug receive a total of 6 doses—the first 1 day before surgery, and then additional doses at day 3, 7, 14, 21, and 28 after surgery.

The primary goal of this study is to see if taking either drug during the period that the islets are settling into the liver (called engraftment) after islet autotransplant increases the number of islets that survive and function at 3 months post-transplant. We will also study if one drug works better than the other. Other goals of this study are to see if either of these medications results in better islet function, lower insulin needs, or more patients off insulin at 1 and 2 years after surgery, and whether these medications effect long-term insulin needs (at 3, 4, and 5 years after surgery).

Study Procedures
If you agree to participate in this study, we would ask you to do the following:

Screening
First, you will be asked to review and sign this consent form. If you agree to participate in the study, we will then draw **screening** blood labs and ask you additional questions about your health. This is done to make sure you are eligible to participate in the study. If we find that you are not eligible to participate in the study, then you will be withdrawn from the study and no further visits are needed. You will also have baseline testing performed to see how well your islets are working in your pancreas before we remove the pancreas and transplant the islets.

These tests are called “mixed meal tolerance test” and “glucose potentiated arginine-induced insulin secretion” and are described later in this consent form. If you are eligible to participate, you will be assigned to one of the three treatment arms and seen back for follow up, as described below.

Study drug assignment and treatment
If you qualify to continue in the study, you will be assigned to one of three treatment arms using a randomization schedule prepared by our statistician. You cannot choose to have one therapy or the other. The three study groups (or “study arms”) are:

1) **Etanercept:** If you are assigned to this group, you will receive etanercept 50 mg through an intravenous line on the morning of transplant, and then 25 mg subcutaneously (injected under the skin) at 3 days, 7 days, 10 days, 14 days, and 21 days after transplant. If you are in the hospital, we will administer these doses in the hospital. If you have been discharged, we will ask you to return to the research center for a 30 minute visit to receive the medication on those dates.
2) **Alpha-1 antitrypsin:** If you are assigned to this treatment group, you will receive an infusion of the medication by an intravenous line on the day before surgery, and then at 3, 7, 14, 21, and 28 days after surgery. This medicine is administered in the hospital or in the research center (depending on if you are inpatient or outpatient) and takes about 2 hours to infuse. You will need an IV catheter for the medication. If you do not already have a central line or IV, one will be placed at each visit that the medication is infused and then removed.
3) **Standard care:** You will receive usual care for your TPIAT, and the study investigators will follow you very closely for glucose control and insulin adjustments to increase the likelihood that your islets survive and function normally after transplant. You will need to return for the visits described below.

The standard of care group is a very important part of this study because this is the only way we know if the medications work.

Study visits

While you are in the study, you will be asked to return to the University of Minnesota for short visits at 7, 14, 21, and 28 days after surgery to draw blood labs and review your medical history. If you are in the etanercept group and are discharged earlier than 10 days after surgery, you will also come for a visit on day 10 to receive your medication dose. For some of these study visits, you will still be in the hospital and we or your transplant doctor will do the visit in the hospital. You will also have blood drawn at various times over the first week post-transplant to measure levels of inflammation and islet loss. You will have safety labs performed, including following liver enzymes and blood counts.

You will then return for testing of the islets ("**metabolic testing**") at 3 months, 1 year, and 2 years after your TPIAT surgery.

After the 2 year follow up is done, we ask to talk to you by telephone once yearly at 3, 4, and 5 years after your surgery, and have your routine clinical labs done each year. You will not need any extra labs for the study, just the same ones that you will need for your clinical care. During the yearly telephone follow up, we would review your daily insulin use, blood sugars, and results from your clinical testing including hemoglobin A1c (average marker of blood sugar control) and glucose and C-peptide. This helps us keep track of how everyone in the study does long- term.

Metabolic testing at study visits. You will have the tests below done before surgery, at 3 months, 1 year, and 2 years after surgery. Because these are very specialized tests, they must be done at the University of Minnesota and could not be done in your home clinic:

DAY 1**:** Glucose potentiated arginine-induced insulin secretion (GPAIS): This test involves giving a single dose of intravenous glucose and measuring the insulin and C-peptide levels almost every minute for 10 minutes after this from an IV catheter. These levels are used to calculate how much insulin you cells have produced and stored; we call this part of the test "IVGTT" for IV glucose tolerance test. We will then infuse 20% dextrose to target a blood glucose of 230 mg/dL for about 45 minutes. A protein called arginine will be given through an IV catheter, and insulin and C-peptide levels will be measured for 10 minutes. Both the glucose and the arginine signal the islets to make insulin; this is called the maximally stimulated acute insulin response (or AIRmax). This test is the best technique we have to measure the number of islets engrafted. Two IV lines are needed for this test. If your blood sugar is above 120 mg/dL, we may give you some insulin to lower your blood sugar before starting the test, or ask you to reschedule the test.

DAY 2; Mixed meal tolerance test: You will drink a Boost beverage (like a meal supplement) and glucose, C-peptide, insulin levels, and glucagon and GLP-1 will be drawn before consuming the Boost beverage and at 30 minute intervals for 2 hours. If your blood sugar is above 180 mg/dL, we may give you some insulin to lower your blood sugar before starting the test. On this day, we will also have you wear a continuous glucose monitor, which is a little sensor that is placed under your skin (much like an insulin injection would be), that measures your blood sugar levels continuously for 3-4 days. You will mail this device back to the study coordinator 4 days later.

Some blood samples may be stored frozen, in a secure freezer, until they are run. Over the entire 2 years that you need to have labs done for the study, you will have no more than 45 tablespoons of blood drawn (660 mL) total. Most of the blood draws are done for the metabolic testing visits. At these visits for

metabolic testing, you will 8 tablespoons (about 128 mL) of blood drawn over 2 days. This is an amount the body can safely replace.

In between the study visits, we will ask you to record your blood sugars and insulin doses and send these numbers to us twice a month for the first three months and then at least once a month thereafter. The study physicians will use this information to help you adjust your insulin doses, in conjunction with your local endocrinologist.

Your routine post-operative care will not be affected by your participation in this study.

Discontinuation of Study Drug for Medical Reasons
If it becomes medically necessary for the Investigators to discontinue your study drug, you will still be considered a participant in the study and we will continue to follow your progress at the remaining study visits. This is important because there may be an effect of the drug, even if you receive only a partial course.

Blood and urine banking
If you are willing to be in additional research studies:

One fasting blood sample (3-5 mL, or one teaspoon of extra blood) and a urine sample will be taken as part of the study and may be used now or in the future for research purposes. These will be obtained at the same time as your other blood draws; you will not have to undergo any special procedures for this purpose. We may also save extra sample left from the mixed meal test, if sample remains after the glucose and C-peptide measures are done. (You would not have 'extra' blood drawn for that purpose.) These blood samples will be frozen and stored in a secure freezer, identified by a study code only. These specimens will not be used for genetic testing.

Participation in this extra research is voluntary, and if you choose not to allow the extra research it will in no way affect your care as part of the study. These samples will be stored indefinitely, for research testing if new assays are developed in the future. At any time, you may contact the researchers to request that your samples be withdrawn from research use, and any identifiable samples still in their possession will be destroyed.

You will indicate whether you are willing to allow these extra samples by initialing one of the lines at the end of the form.

Risks of Study Participation
The study has the following risks. An IV line (tube into your vein) will be placed for the blood draws in the metabolic testing, or (in the alpha-1 antitrypsin group) for medication administration. This can be associated with bruising or soreness, or rarely infection. There is a risk of low blood sugar during either of the tests, which cause symptoms like shakiness, heart racing, or drowsiness. The arginine for GPAIS may give you the sensation of a metallic taste in their mouth that is very brief (last a few minutes). You will have an elevated blood sugar during the GPAIS, around 200 mg/dL. However, this is very brief—only 1 hour—and we do not do this until your islets are engrafted. Your islets will not be harmed by the study tests.

The Boost drink for the MMTT does contain milk and soy protein. Please let the investigators know right away if you have a milk protein or soy protein allergy. In this case, this test would either not be done, or if possible, a substitute 'meal' with a similar carbohydrate and protein content that is safe for you will be used. The Boost does not contain any lactose and it is also gluten-free, so it is safe to drink if you are

lactose intolerant or have celiac disease (a gluten sensitivity). Boost drink may cause nausea and discomfort.

If you are assigned to one of the medications, you may have adverse effects of the medication. Possible side effects are detailed in the table on the next page. Etanercept can increase your risk of infection. Your risk is limited because – unlike most patients treated with this medication— you are not on any other medications to suppress your immune system, and you will be receiving this drug only for a few weeks. The most common adverse event with etanercept is an injection site reaction. Alpha-1 antitrypsin is generally well tolerated, with most common side effect being a small, reversible elevation in liver enzyme levels, headaches, or muscle aches.

Table: Reported adverse events with either medication. Association with drug is not always known. Reported events are from either marketing studies (with comparison control group) or from post-marketing reports. Some patients on etanercept were also on other medications that could increase risks.

	Mild to moderate	Serious (all rare)
Alpha-1 antitrypsin (Aralast NP ®)	Elevated liver enzymes (ALT or AST, 11%) Headache (0.3- 7%) Musculoskeletal discomfort (0-7%) Sore Throat ("Pharyngitis") (1.6%) Cough (0.6%) Sleepiness (0.3%) Rash (1.5%) Itching ("Pruritus") (1%) Altered taste (1.5%) Decreased platelet count, a clotting factor (1.5%) Joint swelling (1.5%) Infusion reactions: fever, chills, chest pain, shortness of breath, dizziness, visual change (0.1%) Transient increase in white blood cell count	Serious allergic reaction (or "Anaphylaxis")
Etanercept (Enbrel ®)	Injection site reaction (37%) Mild infection (most often URI, 35%) Headache (17%) Runny nose ("Rhinitis") (12%) Sore Throat ("Pharyngitis") (9%) Cough (6%) New autoantibodies (3-15%) Present in <5%: GI upset or pain, rash, edema, sinusitis, and elevated liver enzymes Other (<1%): Low blood counts Skin cancer (non-melanoma) Rare infections including legionella, listeria, fungal pneumonia	Serious allergic reaction (or "Anaphylaxis") Serious infection, including blood infection ("Sepsis") Rare infection, including TB Neurologic condition called demyelinating disease Blood cancer or pre-malignancy

Pregnancy and Birth Control

The effects of these medications on an unborn child are unknown. Because of the unknown risk, a pregnancy test will be done to make sure women of childbearing potential are not pregnant before they can receive study medications and we recommend that women of childbearing potential use an effective form of birth control (oral contraceptives, Norplant, Depo-Provera or barrier devices) throughout the first 2 years of the study. If you stop using birth control during the study or an unexpected pregnancy occurs, you should inform the study investigators immediately.

Potential Benefits of Study Participation

If you are on one of the study drugs, and the drug is successful, you might be more likely to come off insulin or need only a low dose of insulin; however, we do not know that this will happen. You will be closely followed by a study endocrinologist to help you with adjustments to your insulin therapy during the study. Close blood glucose management helps increase the success of the islet transplant, regardless of what group you are assigned. You will be given your results from the study visits, and in this respect will have a little more information about the function of your islets. We hope that the information gathered as a part of this study will also help other patients with chronic pancreatitis who are having their pancreas removed and an islet transplant.

Alternatives to Study Participation

You can choose to not participate in this study. This study does not affect your eligibility for pancreatectomy and islet autotransplant. You will receive the same care from your transplant surgeon regardless of whether you choose to participate.

Study Costs/Compensation

The study medications will be provided by the study. The laboratory studies that are done as part of this protocol will be paid for by the study. However, if you have additional labs (outside of the study protocol) done for routine clinical follow up as part of your study visit, these non- research labs will be billed to your insurance as per standard of care.

If you need to travel back for visits (are not from the Minneapolis-St Paul metro area), we will reimburse travel expenses up to $750 for your 2-day follow up study visit at 3 months, 1 year, and 2 years. This may include your costs for your flight or your gas/mileage depending on if you drive or fly, taxi / parking, and two nights hotel, as well as a daily meal stipend. We will also cover up to 2 nights at a hotel to a maximum of $250 when you are here before surgery, as you may need to arrive a couple days early for study screening.

You will also receive a stipend to recognize your time and efforts in participating in this study. This is given to everyone, regardless of need to travel. You will receive $100 for completing each of the 2 days of testing ($50/day) at at the 3 month, 1 year, and 2 year visits, to compensate you for your time.

All total, the maximum reimbursement you can receive for travel + stipend for the entire study is $2,800 dollars [$2,500 in travel expenses reimbursed + $300 stipend].

Payment you receive as compensation for participation in research [excluding coverage of travel costs for research visits] is considered taxable income. If you are participating in multiple studies, you may receive additional payment for research. If payment to an individual equals or exceeds $600 in any one calendar year, the University of Minnesota is required to report this information to the Internal Revenue Service (IRS). Research payments to study participants that equal or

exceed $600 during any calendar year will result in a FORM 1099 (Miscellaneous Income) being issued to you and a copy sent to the IRS."

Research Related Injury

In the event that this research activity results in an injury, treatment will be available, including first aid, emergency treatment and follow-up care as needed. Care for such injuries will be billed in the ordinary manner to you or your insurance company. If you think that you have suffered a research related injury, let the study physicians know right away.

Confidentiality

The records of this study will be kept private. The study investigators and study staff will have access to your data. In any publications or presentations, we will not include any information that will make it possible to identify you as a subject. Your record for the study may, however, be reviewed by clinical monitors, the Food and Drug Administration (FDA), and by departments at the University with appropriate regulatory oversight. A copy of this signed informed consent document along with a statement that you are participating in a study will be entered into your medical record. Lab results that affect your clinical care—hemoglobin A1c levels and mixed meal tolerance test results—will be posted to your electronic medical record. Labs that are performed for research purposes will not be included in the medical record and will remain confidential unless you request this information be shared with other doctors caring for you. To these extents, confidentiality is not absolute.

Protected Health Information (PHI)

Your PHI created or received for the purposes of this study is protected under the federal regulation known as HIPAA. Refer to the attached HIPAA authorization for details concerning the use of this information.

Voluntary Nature of the Study

Participation in this study is voluntary. Your decision whether or not to participate in this study will not affect your current or future relations with the University of Minnesota Medical Center, Fairview. If you decide to participate, you are free to withdraw at any time without affecting those relationships.

Contacts and Questions

The primary investigator conducting this study is Dr. Melena Bellin. You may ask any questions you have now, or if you have questions later, **you are encouraged to** contact the P.I.at 612-625-4686.

To share feedback privately about your research experience, including any concerns about the study, call the Research Participants Advocate Line: 612-625-1650 (Toll Free: 1-888-224-8636)

or go to z.umn.edu/participants .

Certificate of Confidentiality

To help protect your privacy, the National Institutes of Health has granted a Certificate of Confidentiality. The researchers can use this Certificate legally to refuse to disclose information that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings, for example, if there is a court subpoena. The researchers will use the Certificate to resist any demands for information that would identify you, except as explained below.

The Certificate does not prevent a researcher from reporting information learned in research when required by other state or federal laws, such as mandatory reports to local health authorities for abuse or neglect of children/vulnerable adults, or information to the Food and Drug Administration (FDA) when required in an FDA audit. However, the Certificate limits the researcher from disclosing such information in follow up civil, criminal, legislative or administrative legal proceedings if the information was created or compiled for purposes of the research.