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Immune markers and tolerance in transplantation
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a) Statement of the health problem or issue

Although heart transplantation is now a life-saving treatment for patients with heart failure, there are complications that limit its long-term effectiveness. One of these complications is damage to the blood vessels in the transplanted heart, a process called cardiac allograft vasculopathy (CAV). This causes blood flow to the heart muscle to be blocked and the heart muscle dies. CAV is typically diagnosed by an angiogram. This is an invasive test that involves inserting a tube in the leg artery and moving the tube to the heart. Dye is then injected into the blood vessels of the transplanted heart. CAV is caused by damage from the immune system attacking the transplanted heart. This is because the immune system sees the transplanted heart as "foreign." CAV can occur even though heart transplant recipients are taking powerful medications to prevent rejection. In order to improve outcomes in transplantation, new ways to diagnose and treat CAV are needed.

b) Objective of your program

The objective of this project is to develop new ways to detect and treat CAV. Our first goal is to determine if a blood test can identify heart transplant recipients with CAV. This would be better than an angiogram because it is a non-invasive test. This test relies on detecting antibodies in the blood. We believe that certain antibodies appear when there is damage to the blood vessels. Our second goal is to find a new way to treat CAV. We believe that this can be done by promoting tolerance. This is a state where the immune system of the heart transplant recipient recognizes the heart as "self" and does not reject it. This would also allow heart transplant recipients to stop taking their anti-rejection medications, which have many side effects.

c) How will you undertake your work?

For our first goal of finding a new say to detect CAV, we have developed specialized "chips." We make these chips with a robot that spots different proteins onto the "chip." We add blood to the "chip" and can then measure antibodies binding to the "chips." We currently have blood samples from many heart transplant patients. Some of the patients have severe CAV and others do not. We are going to do a large study with all of these patient samples to see if there are antibodies that are present in the patients with CAV. We will also be able to compare antibody levels with the results from angiograms. For our second goal of developing a new way to treat CAV, we have developed a mouse heart transplant model. Over time, these mice develop blood vessel changes similar to CAV. We are testing if an innovative therapy called autologous hematopoietic stem cell transplantation (HSCT) can treat CAV. This will be done by first performing transplants in the mice and then treating them with HSCT.

d) What is unique/innovative about your program?

In this project, we are developing innovative ways to both detect and treat CAV in heart ransplantation. The best test for CAV that we are developing measures over 200 antibodies in the blood. This type of test is only done in a few specialized centers. We believe that increases in some of these antibodies will indicate that there is damage to the blood vessels of the transplanted heart. This test would be much better than an angiogram because it is not invasive and requires only a drop of blood. The method that we are investigating to treat CAV in mice is also innovative. The approach we are using to promote tolerance is called hematopoietic stem cell transplantion (HSCT). This is a therapy used in some autoimmune diseases. We are now testing if it can induce tolerance in heart transplantation. We are currently investing if HSCT can promote tolerance in liver transplant recipients in a clinical trial (ASCOTT). If this trial is a success, we will be able to offer this innovative therapy to heart transplant recipients.

e) How is the proposed research directly relevant to heart disease and/or stroke?

Heart transplantation is in many cases the only solution for patients with end-stage heart failure. Unfortunately, many heart transplant recipients develop CAV and serious problems related to the anti-rejection medications they must take. The research proposed here is directly relevant to heart disease because we are developing new ways to make heart transplantation a safer therapy. First, we are developing a blood test that can be used to detect CAV. This would allow for CAV to be diagnosed at earlier times and would not involve an angiogram. Second, we are developing new methods of promoting tolerance in heart transplantation. This could prevent CAV from getting worse and would also allow patients to stop taking anti-rejection medications. If the results of our studies prove successful, similar approaches be used in some patients with heart failure caused by autoimmune disease. This is a case where a patient's immune system attacks their own heart. This could lessen the need for heart transplantation in the first place.

f) What is the impact of the proposed research to heart disease and/or stroke (e.g. to the health and quality of life of people with these conditions)?

We often tell patients that heart transplantation is a treatment and not a cure for heart failure. This is because they will experience of a whole new set of problems after transplantation. If we can develop therapies to induce tolerance, heart transplantation would become a cure for heart failure. This would dramatically improve the lives of heart transplant recipients. First, survival after heart transplantation would be better because the problems like CAV would be eliminated. Second, patients would not have to take anti-rejection medications. This would allow patients to resume a "normal" lifestyle without living with the side-effects caused by the medications. They would no longer have to worry about infections causing serious problems because they would have a strong and working immune system to protect them. Patients would also no longer need to have as many doctor visits. And patients would not need heart biopsies that carry a small but real risk to the patient.