HUMAN CLINICAL TRIALS IN XENOTRANSPLANTATION

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APPLICATION DATE: ONGOING

CHILDREN WITH DIABETES FOUNDATION
WWW.CWDFOUNDATION.ORG

LETTER OF INTENT RECEIPT DATE: ONGOING
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THIS RFA CONTAINS THE FOLLOWING INFORMATION

PURPOSE:

The purpose of this RFA is to solicit applications from institutions currently participating in human trials of xenotransplantation research or those who are developing xenotransplantation studies for the cure of Type 1 Diabetes (T1DM). We also encourage novel approaches from scientists who wish to contribute to the field, even if this is their current focus. The goals are to (1) achieve normal levels of glycemia in patients with T1DM; (2) develop effective strategies to improve xenograft survival; and (3) to achieve these goals without long-term immunosuppression. The goal of this RFA is to encourage safe, novel and effective strategies for broad application of safe and efficacious xenotransplantation in the clinics.

RESEARCH OBJECTIVES

Background

Human cadaveric islet cells are not a practical solution to our goal of finding a therapy for T1DM; this is due to lack of quality, need for immunosuppression, and a lack of supply. Xenotransplantation offers a solution to the severe shortage of islet cells to treat T1DM patients. Porcine sources of islet cells are of

interest due to the unlimited resource (reproductive capacity) as well as cell similarities to humans. However, xenotransplantation poses challenges, including the immune response of the recipient against the xenograft, the physiological limitations, and potential transmission of xenogeneic infectious agents, such as porcine endogenous retrovirus (PERV), from the graft to the recipient. The first and the most challenging hurdle to xenotransplantation has been rejection, caused by xenoreactive natural antibodies (XNA) which can destroy the xenograft within minutes to hours by the recipient's blood.

Animal genetic engineering has led to lines of genetically modified pigs with diminished potential for rejection. These pig lines include transgenic strains expressing various human complement regulatory proteins. Transgenic pigs expressing human complement regulatory proteins have been developed. These strategies may reduce the frequency of hyperacute rejection and prolong survival of some xenografts in porcine to nonhuman primate (NHP) transplantation models from a few hours to a few weeks. Although the gal epitope still contributes to delayed acute vascular rejection and has contributed in NHP models, the field has moved forward into human models. Therefore, this RFA is targeted towards a porcine/xeno to human model, as long as efficacy, safety and eventual affordability are demonstrated.

Physiological incompatibility is a challenge to successful xenotransplantation. Although porcine insulin has been used to effectively treat diabetic patients, porcine islets transplanted into heterotopic environments (i.e. liver in human and under the kidney capsule and muscle in some NHP studies) may not function in a physiologically compatible manner. Longevity, growth, and development issues should be addressed. Successful strategies to overcome rejection and prolong the survival of xenografts will allow opportunities to investigate novel therapeutic approaches.

The third major barrier to xenotransplantation is potential transmission of an infectious agent to the recipient and then more broadly to the general population. The animals used as the source of xenografts can be bred in specific pathogen-free conditions, vaccinated, caesarian derived, medicated, and routinely screened to eliminate most, if not all, known zoonotic agents. One known company, and perhaps more have overcome this hurdle due to unique sources. However, endogenous retroviruses, whose DNA is integrated into the donor genome, or new and yet unidentified infectious agents may not be removed by conventional means. Although the patients transplanted with porcine cells or tissues show no evidence of PERV infection thus far, the effects of long-term exposure to xenografts, especially in immunosuppressed recipients, are unknown. Investigators have made significant progress in assessing the risk of infection. Investigation and monitoring should be incorporated as part of any study in order to increase understanding of the risks.

Recent advances include current reports of human clinical trials, and with new and novel resources. The mechanisms of rejection and compatibility between xenografts and recipients will facilitate the development of strategies for clinical application.

Research Scope

We will support porcine to human models of xenotransplantation to address immunological and physiological issues critical to the engraftment, survival, and function of xenografts in patients with Type 1 Diabetes. The research focus may include: (1) proposals to enhance the survival and prevent rejection of the islets (i.e.: encapsulation) ; (2) development of effective strategies to prolong xenograft survival, including immune tolerance induction; and (3) characterization of the biology of the xenograft post-transplantation.

Research studies may enhance the future success of the therapy by including, but are not limited to the following:

o Mechanisms of rejection and tolerance.
o Characterization of the immune responses post-transplantation
o Evaluation of the immune responses from the same animal source but in different stages of development, e.g. neonatal vs. adult islets
o Preparing the host with immune tolerance induction and/or anti-inflammatory agents
o Reducing host toxicity in xenotransplantation models
o Delineation of the mechanisms of accommodation and/or tolerance induction
o Development of effective strategies, including encapsulation, to prolong xenograft survival and eliminate the use of immunosuppressive drugs

This RFA will not support animal models of xenotransplantation. Our foundation has already very successfully supported NHP models which have been extremely positive and have been positively recognized by the international community.

SUPPORT

All investigator-initiated applications and will be reviewed within three months of receipt of the application. Funding will be distributed after proof of institutional support and verification of DSMB approval. Applications that are not funded may be resubmitted.

FUNDS AVAILABLE

The Children With Diabetes Foundation intends to commit approximately $1M to fund 2 to 4 new grants in response to this RFA. An applicant may request a project period of up to 3 years. The research will vary, and the duration of each award will also vary. An annual review will be required to provide ongoing funds for subsequent years.

ELIGIBLE INSTITUTIONS

The applicant may submit (an) application(s) if the institution has any of the following characteristics:

o For-profit or non-profit organizations
o Public or private institutions, such as universities, colleges, hospitals, and laboratories
o Foreign institutions are eligible to apply, but they are encouraged to include collaborators or subcontracts within the U.S.

INDIVIDUALS ELIGIBLE TO BECOME PRINCIPAL INVESTIGATORS

Individuals with the skills, knowledge, and resources necessary to carry out the proposed research are invited to apply. An updated CV should be included with the Letter of Intent. A letter of support from the hosting institution is also requested. All letters of support are encouraged, from peers, patients and institutions.

SPECIAL REQUIREMENTS

The Children With Diabetes Foundation is a 501(3) organization which utilizes only unpaid volunteers, and as such, we do not allow for institutional overhead to be paid. A letter from the institution shall be required, prior to distribution of funds, verifying that 100% of all requests will fund the trial.

1. Description of Research Projects

Applications must include the research plan(s) and project goal(s) to be completed during the award period. The language should be written so that a "lay" reviewer will find it to be clear and achievable. The applicant must clearly state interim objectives to be achieved during the project, identify critical decision points that could require a revision, and provide a timeline. The application must demonstrate the scientific and technical expertise required to design, conduct, and be successful.

2. Collaboration

The Children With Diabetes Foundation welcomes and encourages cooperation with the NIH, JDRF, ADA and other non-profit organizations. Letters of support and cooperation will enhance the application and the ultimate success of our mutual goal!

In the event that additional funds for collaborative opportunities, pilot projects, or establishment of resources (e.g. porcine islet isolation core) are requested, our committee will provide consideration.

3. Oversight
The Children With Diabetes Foundation will meet annually to review the progress reports of awardees. Continued funding will be contingent upon progress.

4. Intellectual Property Rights

Institutions and investigators are expected to share information developed under this funding agreement. Applicants are expected to submit for publication the results of their studies, whether positive or negative, to peer-reviewed journals.

TERMS AND CONDITIONS

1. Rights and Responsibilities

The Principal Investigator(s) will: determine and coordinate the project; set goals; implement guidelines; and, attend meetings, if requested.

2. CWDF Responsibilities

During performance of the award, the CWDF officers, will remain accessible and will work collaboratively to achieve our mutual goal, a cure for patients with T1DM.

3. Collaborative Responsibilities

The CWD Officers, in coordination with other funding organizations, will schedule the meetings and actively participate in developing the meeting agendas.

The CWDF officers will prepare an annual report containing the following: progress of ongoing and newly-initiated projects; manuscripts published, in press, and in preparation; presentations at meetings.

The CWDF officers will:

o Provide feedback;
o Establish protocols for the review of new projects, if additional funds are available;
o Advise on emerging needs, and impediments;
o Encourage publication of results

WHERE TO SEND INQUIRIES

We encourage inquiries concerning this RFA and welcome the opportunity to answer questions from potential applicants. Inquiries may be sent to: info@CWDFOUNDATION.org

LETTER OF INTENT

Prospective applicants are asked to submit a letter of intent that includes the following information:

o Title of proposed research
o Name, address, email, and phone number of the Principal Investigator
o Names of other key personnel
o Participating institutions (including alliances with other non-profits)

SUBMITTING AN APPLICATION

We are interested in your success, past and future. You may use a JDRF or NIH form to create your proposal. We care about content and learning about you and your project. We are interested in learning about you, your project, your passion and your past successes. The CWDF believes that the best indicator for future success is a proven track record of past success. Please describe.
Please send your proposal via email to:
info@cwdfoundation.org

Don't print out extra copies; do not mail us information. We want you to focus on a cure – not paperwork! We forward to our review board (our officers and directors) electronically.

REVIEW PROCESS

Applications will be evaluated for merit by a review group convened, by the CWDF. Applications will:

o Undergo a selection process for applications deemed to have merit, based upon our definition of a cure:

Eventually, the ultimate outcome must be:

1) Efficacious

2) Safe
3) Affordable

REVIEW CRITERIA

The goals of CWDF supported research are to cure T1DM. We believe this is through prevention for the next generation (WE ARE WORKING ON THAT TOO!) and a cure for those currently suffering. We believe that encapsulated porcine islet cell research is currently a lead prospect towards achieving the goal of restoring euglycemia to those diagnosed with T1DM. If the human trials are successful, the disease may not be "cured", but it would be controlled, providing enhanced health and restoration of normal blood sugars, thus eliminating complications associated with hypo and hyperglycemia.

SIGNIFICANCE: Human Clinical Trials have already been started. How is this proposal going to add to that work?

APPROACH: Please describe the framework, design, and methods, including potential problem areas.

INNOVATION: Describe the novel concepts, approaches and/or methods.

INVESTIGATOR: Describe the training and experience that makes the team capable to carry out this work.

ENVIRONMENT: Describe the facilities and the scientific environment in which the work will be done that will contribute to the probability of success. Describe unique features of the environment and provide evidence of institutional support.

ADDITIONAL REVIEW CRITERIA:
SHARING RESEARCH DATA:
Applicants are expected to include a data sharing plan.

BUDGET:
The proposed budget and the requested period of support in relation to the proposed research will be determined by the nature of the clinical trial.

AWARD CRITERIA
Award criteria that will be used to make award decisions include:

o Scientific merit of the proposed project
o Availability of funds

Joint Ventures:
The CWDF welcomes collaboration with other non-profit and governmental agencies. We strongly encourage and will participate actively in any efforts to move forward towards our mutual goal, a cure for T1DM.