Request for Applications for Targeting Vasculature in Type 1 Diabetes

Type 1 diabetes is an autoimmune disease characterized by the destruction of insulin-producing beta cells in the pancreas that affects islet biology and over time may result in pathogenic diabetic complications. The purpose of the initiative is to assess the feasibility of exploiting differences found in the vasculature of the islets or tissues affected by diabetic complications to allow targeting of therapeutic agents or of molecules to improve diagnosis, prevention and treatment of type 1 diabetes.

JDRF will support investigator-initiated or multidisciplinary research. Applications may be submitted by non-profit and for-profit institutions, both public and private, from both domestic and overseas institutions. In addition, JDRF recognizes that support of research in this area may require innovative and novel public-private partnerships. Investigators may submit more than one application as part of different collaborative groups, however there should be no scientific or budgetary overlap.

JDRF will commit up to $1 Million to fund innovative grant awards of up to $110,000 total costs with a project period of up to 1 year.

PURPOSE OF THIS RFA

The purpose of this RFA is to develop and/or test novel approaches to targeting specific vascular beds, in order to open new therapeutic avenues for type 1 diabetes or develop new tissue-specific imaging techniques. This RFA invites proposals for basic or pre-clinical studies on vascular targeting of islets or tissues affected by complications of type 1 diabetes including diabetic retinopathy, neuropathy and nephropathy. The RFA seeks to capitalize upon recent developments in cancer and vascular biology by the application of novel approaches to tissue-specific molecule delivery to the area of type 1 diabetes. Researchers from diverse areas in vascular research are encouraged to submit applications to this request.

RESEARCH OBJECTIVES

Background

The significant morbidity and mortality of Type 1 diabetes mellitus result predominantly from its complications, including hypoglycemia, blindness, renal failure, amputations, strokes and cardiac events. Hyperglycemia, hyperlipidemia and insulin deficiency are metabolic hallmarks of diabetes and lead to widespread cellular damage. Endothelial cells, which poorly regulate intracellular glucose, may be particularly vulnerable to these insults. In addition, abnormal angiogenesis can occur in islets and is a feature of several diabetic complications.

The vascular beds of individual tissues are known to differ in structure and metabolic function, as well as in the expression of tissue-specific adhesion molecules. This heterogeneity of the microvasculature in different normal tissues, following pathological insult including diabetes, and at different stages of angiogenesis has been well documented by multiple methods including in vivo phage display. Molecules known to be specific to a particular tissue can be thought of as vascular ‘zip codes’. Ligand-directed profiling can select functional compounds from combinatorial libraries based on the expression of these cell surface molecules, which in turn could be exploited as drug targets in diabetes.

Recent research, particularly in the field of cancer biology, highlights the potential of vascular bed targeting as a method for specific modes of delivery for existing drugs. Modes of delivery known to be safe in one disease may be adapted to others. Vascular zip code molecules have previously been shown to be useful guidance elements in therapeutic targeting, for example in targeting anti-cancer agents to experimental tumors. Targeted delivery vehicles can provide a circulating reservoir of drug, lower the effective dose of a drug and reduce the exposure of healthy tissue to the drug. Novel therapies that are being developed for other conditions may be highly efficacious for diabetic complications and will be considered in this RFA. In addition, the development of vascular-specific molecular targeting approaches may suggest novel tissue-specific imaging methods. These methods might enable better understanding of disease pathogenesis, allow imaging of islets and better diagnosis of diabetic complications. Alterations of vasculature in response to prolonged hyperglycemia may provide specific ligands for vascular targeting in type 1 diabetes.

Diabetic Retinopathy

Anti-angiogenic approaches are currently in development for diabetic retinopathy. Abnormal angiogenesis in diabetes is most clinically apparent in proliferative diabetic retinopathy. The neovascularization is preceded by the selective destruction of pericytes, capillary failure and hypoxia that leads to the release of pro-angiogenic substances. The resulting vessels have increased permeability and are prone to rupture. Macular edema is another form of retinopathy in which increased permeability of blood vessels leads to deposition of extracellular protein. Therefore, the goal of effective therapy for diabetic retinopathy is not only to decrease the excess vessel growth, but also to restore normal vessel permeability and blood flow to the retina. Changes in gene expression, including expression of cell surface receptors have been documented in microvessels in diabetic retinopathy. These proteins may represent possible targets for directing therapeutics to diseased tissue.

Diabetic Neuropathy

The effects of diabetes on microvasculature in neural tissues other than the retina are not well described. It is known that angiogenic remodeling occurs in the central nervous system in response to stimuli such as exercise or traumatic and ischemic injury. It is also known that diabetes has deleterious effects on the peripheral and central vasculature, as well as on neurons themselves. For example, there is increased risk of stroke and other types of cerebrovascular accidents in diabetes. Structural and functional changes observed in the microvasculature in diabetic neuropathy may be involved in the resulting nerve damage. Therapeutic intervention may therefore be directed to the abnormal vasculature as well as the nerve.

Diabetic Nephropathy

A role for excessive angiogenesis and mesangial matrix expansion in the early phases of diabetic nephropathy has been suggested. Glomerular capillary surface area increases early in diabetes, and studies in diabetic animals suggest that a treatment with anti-angiogenic peptide can inhibit the early lesions of diabetic nephropathy. Unique molecular signatures which differentiate kidney from other types of microvasculature could enable targeted therapeutics for diabetic nephropathy

Pancreatic Islet Transplantation and Imaging

The islet endothelium is highly fenestrated to facilitate trans-endothelial movement of secreted hormones, has a unique expression of surface markers, and produces a number of vasoactive substances and growth factors. These characteristics may be advantageous in the specific targeting of islet endothelium to treat early phase T1D or in the context of imaging or revascularization for islet transplantation. In early phases of T1D, an increased expression of surface leucocyte-homing receptors on the islet endothelial cells enables immune cells to enter the endocrine tissue and cause beta-cell destruction. Following islet transplantation, clinical outcome is determined by the number of islets that engraft and the efficiency of engraftment. Targeting the islet endothelium would be helpful to image the presence of endgrafted islets or produce localized angiogenic signals to encourage development of a functional capillary system in the transplanted islets.

Research Topics

The objective of this RFA is to stimulate innovative research on novel approaches for vascular targeting in order to target therapies or develop imaging tools to improve the diagnosis and treatment of type 1 diabetes.

Research proposals must focus on vascular targeting, be directly relevant to the pancreatic islet endothelium or microvascular complications of type 1 diabetes and can use tissue culture methods and/or animal models. Both basic and pre-clinical studies will be considered. Applications can propose independent studies, however collaborations between researchers with experience in diabetes complications research and another discipline such as cancer drug delivery, vascular biology or synthetic chemistry are strongly encouraged. Researchers should be successful independent investigators with a track record of successful research accomplishments.

Examples of topics for investigation under this RFA include, but are not limited to:

- Development and testing of compounds successfully targeting micro- and macrovasculature relevant to type 1 diabetes
- Encapsulation and targeting (macro to nano scale) of one or multiple therapeutic compounds to islets or tissues relevant to diabetic microvascular complications
- Adaptation of targeting approaches successful in another field, for example existing nanoparticles used in cancer biology, to diabetic microvascular complications or islets
- Targeting approaches that use a fluorescent dye or other marker to evaluate drug delivery
- Targeting of anti-angiogenesis therapeutics to neovascularized tissue in diabetic retinopathy
- New approaches to targeted imaging of islets or specific tissues relevant to diabetic complications
- Targeted gene delivery to islets or tissues relevant to diabetic complications, such as kidney, nerve or eye

Award Information

Mechanism(s) of Support

JDRF will provide individual investigator driven innovative grants of up to $110,000 total costs for one year.

- The JDRF innovative grant mechanism is intended to fund researchers with promising new approaches with potential high impact that may not be supported by extensive preliminary data. Funding will be provided for a period of one year to develop preliminary data and/or to test the feasibility of an innovative idea.

Please see JDRF's detailed application guidelines for submission guidelines.

Review Criteria

The applications will be strictly evaluated on whether the research applies to type 1 diabetes, even if the proposed research could also apply to type 2 diabetes.

Review and Selection Process

Applications that are complete and responsive to the RFA will be evaluated for scientific and technical merit by an appropriate peer review group convened by JDRF in accordance with JDRF review criteria.

Inquiries

We encourage your inquiries concerning this novel funding opportunity and welcome the opportunity to answer questions from potential applicants. Inquiries may fall into three areas: scientific/research, peer review, and financial or grants management issues.

JDRF is committed to the publication and dissemination of all information and materials developed using JDRF resources.

Inquiries about applications in the area of complications should be referred to Helen Nickerson, Ph.D. (hnickerson@jdrf.org; telephone 212 479 7522) or in the area of islet biology and transplantation to Adrianne Wong (awong@jdrf.org; telephone 212 479 7642). Administrative enquiries should be directed to Calissia Alvarez (calvarez@jdrf.org; telephone 212 479 7668)

Application

To facilitate the recruitment of an appropriate peer review group, JDRF requests an intent to submit. Please email Helen Nickerson (hnickerson@jdrf.org) with brief details of your proposed studies by February 23rd 2007.

To access the application form and for details on electronic submission, please consult the proposalCENTRAL website: https://v2.ramscompany.com/ and. Applicants must use proposalCENTRAL™ to apply for this mechanism. proposalCENTRAL™ is JDRF's web-based grant management service provider.

Both current and new Users of this system can register and apply using the following URL: https://v2.ramscompany.com/Login.asp. Click here: Information for Applicants for specific guidelines and tips when applying on proposalCENTRAL™. You can download specific instructions and guidelines for this mechanism within the application on proposalCENTRAL™.

All applications must be completed using the required templates provided on the proposalCENTRAL™ Website; click on the link marked: Vascular Targeting Initiative.

Dates for Applications

Application Availability: December 15th, 2006

Intent to submit: February 23rd 2007

Date Online Application deadline: March 12th, 2007

Response to applicants: July 2007

Earliest Funding start date: September 1, 2007