JDRF Announces a Request for Applications for Innovative Research in Angiogenesis for Type 1 Diabetes and its Complications

JDRF will contribute up to $1 million to fund investigator initiated innovative grants or innovative partnership grant awards with a project period of 1 year.

Type 1 diabetes is an autoimmune disease characterized by destruction of insulin-producing beta cells in the pancreas that over time may ultimately result in pathogenic diabetic complications. The purpose of the initiative is to improve our understanding of the effects of type 1 diabetes on angiogenesis, in order to exploit its therapeutic potential for diabetic complications and pancreatic islet transplantation. This new initiative seeks to facilitate novel scientific discoveries and potentially translate findings in basic angiogenesis research to the clinical problems of:

- Excess blood vessel growth in proliferative diabetic retinopathy.
- Impaired vascular responses leading to inadequate blood vessel growth in diabetic vascular disease, diabetic neuropathy and diabetic wound healing.
- Improvement of the revascularization process in transplanted pancreatic islets to improve graft survival.

JDRF will support individual investigator initiated or multidisciplinary research to improve our understanding of the effects of Type 1 diabetes on accelerated mechanisms involved in the development of angiogenesis or the development of novel therapies for the treatment of pathogenic angiogenesis in Type 1 diabetes. 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 involve 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.

PURPOSE OF THIS RFA

The purpose of this RFA is to enhance understanding of the effects of Type 1 diabetes on the development of new blood vessels from preexisting vessels (angiogenesis), in order to open new therapeutic avenues to treat diabetic vasculopathies. This RFA seeks basic, pre-clinical or clinical studies on the mechanisms of abnormal angiogenesis seen in the complications of diabetes in wound healing, nephropathy, and neuropathy. For pancreatic islet transplantation, we aim to foster research on improving the revascularization process in the transplanted islets to improve graft survival.

RESEARCH OBJECTIVES

Background

The significant morbidity and mortality of Type 1 diabetes mellitus result predominantly from its complications, including blindness, renal failure, amputations, strokes and cardiac events. Hyperglycemia is the metabolic hallmark of diabetes and leads to widespread cellular damage. Endothelial cells, which poorly regulate intracellular glucose, may be particularly vulnerable to hyperglycemia. Under appropriate physiologic and pathophysiologic conditions, growth factors, such as vascular endothelial growth factor (VEGF) and fibroblast growth factor (FGF), are released to initiate angiogenesis. Studies suggest that the metabolic abnormalities of diabetes alter the angiogenic process. There are several mechanisms by which, angiogenesis may be vulnerable to the metabolic abnormalities of diabetes, although the extent and nature of this vulnerability is not well understood. Non-enzymatic glycation that leads to advanced glycation end-products in serum and tissues can inhibit extracellular matrix (ECM) degradation, leading to both a decrease in the release of angiogenic factors from the ECM and an expansion of ECM and

hypoxia-induced neovascularization. Hyperglycemia has also been associated with altered expression of growth factors (VEGF, FGF, angiogenin and 12-HETE) and ECM proteins.

Type 1 diabetes is also associated with a chronic inflammatory state that damages micro- and macrovessels, and may impede the growth of new vessels. The metabolic defects of diabetes are extensive, however clinical trial and epidemiologic data indicates that hyperglycemia is central to the pathogenesis of vascular complications of Type 1 diabetes. This may be advantageous for developing therapies as compared to other conditions such as cancer in which mutagenesis is an ongoing process that creates unique tumor phenotypes. Therefore, novel therapies to inhibit or stimulate angiogenesis that are being developed for other conditions may be highly efficacious for diabetic complications and will be considered in this RFA.

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 proangiogenic 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.

Diabetic Neuropathy

The effects of diabetes on angiogenesis in neural tissues other than the retina have not been well studied. 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. Hence, an important future area of inquiry will be to determine whether these diabetic complications are accompanied by angiogenesis, and whether (as in the retina) the newly formed vessels are abnormal.

Diabetic Wound Healing

Impaired wound healing is a common condition in diabetes associated with a delay in progression beyond the inflammatory and proliferative phases of normal wound healing. Animal models of diabetes show reduced angiogenesis in healing of skin incisions. In diabetic patients, the blood vessels at the wound edge are abnormal with cuffing of collagen and other proteins, the fibroblasts have decreased proliferative capacity and an abnormal morphology and the ECM shows prolonged presence of fibronectin. Topical treatment of wounds with single growth factors have shown only minimal efficacy. A better understanding of the abnormalities in angiogenesis in diabetic wounds could lead to new targets for intervention. For example, the circulating endothelial progenitor cells (EPC), which play a critical role in forming new vessels, are dysfunctional in diabetes. Discovery of the defects in these cells and the means to correct them could lead to autologous cell therapies for diabetic wounds. The accessibility of wounds also makes them a good model system for developing biomarkers and imaging tools for angiogenesis.

Diabetic Nephropathy

A role for excessive angiogenesis in the early phases of diabetic nephropathy has been suggested. Glomerular capillary surface increases early in diabetes, and studies in diabetic animals suggest that an anti-angiogenic peptide can inhibit the early lesions of diabetic nephropathy. Embryonic vasculopathy associated with maternal diabetes may be due to abnormal angiogenesis. The abundant expression of angiogenic factors in the placenta of non-diabetic women is altered in diabetic women and correlates with vascular malformations.

Pancreatic Islet Transplantation

The success of the “Edmonton Protocol” has generated considerable enthusiasm that the scientific and technical challenges facing pancreatic islet transplantation, an emerging experimental treatment for type 1 diabetes, can be overcome. Despite recent advances in islet transplantation major obstacles and gaps in our scientific knowledge need to be overcome for enhancing its broader implementation. Such challenges include: (1) reducing the islet mass required for successful transplantation so that the number of patients that can receive this treatment is increased, (2) developing approaches to prevent islet cell death and apoptosis immediately after transplantation into the liver, (3) developing strategies to enhance islet cell survival as recent results with human islet transplantation indicates that the number of patients exhibiting long-term insulin independence declines with time, consistent with a progressive decline in islet mass over time. Thus, a major obstacle to improved islet survival is the delay in the revascularization of islets after transplantation.

Research Topics

The objective of this RFA is to stimulate research on the abnormal angiogenesis seen with Type 1 diabetes and the mechanisms that lead to these abnormalities in order to develop therapies, biomarkers and imaging tools to improve the diagnosis and treatment of diabetic complications.
Remarkable progress has been made towards the understanding of normal and pathologic angiogenesis and in particular for diabetes, the abnormalities in angiogenesis in diabetic retinopathy. The goal of this RFA is in part to extend studies of angiogenesis beyond diabetic retinopathy to other complications of diabetes, including peripheral, coronary and cerebral arterial disease, neuropathy, wound healing, nephropathy and embryopathy. Where defects in angiogenesis are well documented, research in common underlying mechanisms of abnormal angiogenesis would be appropriate for this RFA.

Pancreatic islet transplantation is an emerging experimental treatment for type 1 diabetes, but major obstacles and gaps in our scientific knowledge preclude islet transplantation from being widely adapted. One of the critical factors required for the success of this approach is the revascularization of transplanted islets. Islet isolation severs vascular connections, and islet grafts must re-establish vascular connection (revascularization) through: (1) re-connecting intra-islet endothelial cells (ECs) with host vasculature, (2) recruiting host endothelial cells and vessels, and (3) recruiting endothelial progenitors (EPCs) to differentiate de novo and incorporate into newly formed vasculature in islet graft. However, our knowledge about how islet grafts are revascularized and the molecular factors that regulate the revascularization process is incomplete.

Research proposals must focus on BOTH Type 1 diabetes and angiogenesis and can use tissue culture methods, and animal models. Basic, pre-clinical and clinical studies will be considered. Research on the effects of diabetes on specific components of vessels (e.g. endothelial cells, pericytes, ECM) would be a strength especially where linked to a functional assessment of angiogenesis. Applications proposing research on the impact of diabetes on existing blood vessels will not be considered as part of this RFA.

Applications can propose collaborative research partnerships between researchers with experience in diabetes and angiogenesis. Each research partner should be a successful independent investigator with a track record of successful research accomplishments.

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

- The impact of the chronic inflammatory state produced by hyperglycemia and diabetes on angiogenesis.
- The abnormalities in pericytes produced by diabetes that leads to vascular instability during angiogenesis.
- The changes associated with diabetes in endothelial progenitor cells that alter their targeting to specific tissues and formation of new blood vessels.
- The effects of diabetes on reducing the quality of newly formed blood vessels, especially changes in permeability.
- Studies to determine how normal neuroglial-retinal interactions with vascular cells are perturbed by diabetes.
- Characterization of accelerated angiogenesis in the pathophysiology of diabetic nephropathy including any changes that occur between early and late stage disease.
- The effects of diabetes on angiogenesis in the central and peripheral nervous systems, including possible effects on the capacity to mount normal angiogenic responses to stimuli such as exercise and tissue injury.
- Mechanistic studies to better understand the failure of administration of a single angiogenic growth factor to significantly improve arterial disease or wound healing.
- Identification of molecular factors that regulate the revascularization process post transplantation.
- Studies on developmentally regulated signals that stimulate vascular growth and maturation and how these are impaired by diabetes.
- Mechanistic studies to better understand how islet grafts are revascularized.
- Development of approaches, both in vitro and in vivo, to improve the efficacy of islet revascularization.

Award Information

Mechanism(s) of Support

JDRF will provide innovative grant support of up to $110,000 total costs *OR* up to $220,000 total costs for innovative partnership grants 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.

- In a partnership innovative grant award, each of the research partners will serve as a co-principal investigator within a collaborative project. The level of effort proposed by the collaborating independent investigators should be appropriate for the scope of the project.

Please see JDRF's detailed guidelines for the submission of Innovative Grants applications.

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.

This program encourages collaboration. Each collaborator must submit a separate proposal. Each proposal will be evaluated independently for funding. Partnership grant applications will NOT be reviewed individually, but as components of a single research project, and, as such, the individual applications within a collaborative project will receive the same reviewers' comments within the individual summary statements.

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.

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 this area should be referred to Antony Horton Ph.D. ahorton@jdrf.org; tel 212-479-7662) or Aaron Kowalski Ph.D. akowlalski@jdrf.org; tel: 212-479-7-512) for all inquiries related to angiogenesis and complications, for inquiries related to islet cell revascularization, please contact Brian Flanagan, Ph.D. (bflanagan@jdrf.org; tel 212-479-7549).

NOTE: All applications must be submitted electronically. For details on electronic submission Please consult the proposalCENTRAL website: https://v2.ramscompany.com/ and click on the link marked: Innovative Research in Angiogenesis Initiative.

Receipt Dates for Applications

Deadline for Application: March 31st 2005 **Funding to commence:** June 2005 (or subsequent months).