JDRF Special Program Announcement: Regeneration of Beta Cell Function in Type 1 Diabetes Mellitus – An Interdisciplinary Team Approach

Purpose:

The goal of the Regeneration of Beta Cell Function (RBCF) special program is to discover and develop therapeutics for regeneration of human beta cells in type 1 diabetes. An integrated interdisciplinary team approach will focus on human beta cell regeneration both in vitro and in vivo in animal models.

Background:

A cure for type 1 diabetes will require either replacement or regeneration of functional, glucose-responsive islets with simultaneous prevention of their immune destruction. JDRF has an ongoing goal to improve islet transplantation by developing approaches to induce immune tolerance, replacing the need for chronic immunosuppression, and by addressing the limited source of transplantable islets. A potential alternative to islet transplantation is to activate the regeneration of endogenous or host beta cell function. Recent investigations suggest this is an attainable goal and compel JDRF to institute a pro-active, coordinated approach to accelerate the discovery, development, and delivery of beta cell regeneration therapeutics for type 1 diabetes. JDRF proposes to develop an integrated, fast-track, milestone-driven research program, with collaboration among scientists in the academic, industry, and government sectors.

With control of the autoimmune process in experimental models of type 1 diabetes, new islet cells are regenerated. Endogenous renewal capacity appears to be limited, however, and not robust enough to overcome damage from the multiple insults of autoimmunity, inflammation, and hyperglycemia. With obesity or pregnancy in animals as well as in humans, beta cell mass increases. The cell source and mechanisms of islet regeneration in experimental models of type 1 diabetes, obesity, and pregnancy are highly debated and may differ between animals and humans. It is also unclear whether there is ongoing regeneration in patients with type 1 diabetes or prediabetes. Recent investigations have suggested that even in patients with long-standing diabetes, some islet mass is preserved and pockets of islet regeneration occur in the pancreas. If low-level regeneration occurs in type 1 diabetes, then it may increase after successful islet transplantation with restoration of euglycemia and control of autoimmunity by islet-sparing immunosuppressive therapy.

Recent scientific advances suggest that now is an optimal time to mount a fast-track research program targeting beta cell regeneration. These advances include:

- Evidence of residual islet mass and functional reserves in diabetes
- Evidence of physiological responses of increased islet mass in obesity, pregnancy, and insulin resistance
- Evidence of regeneration in animal models of diabetes or pancreatic injury
- New understanding of regeneration, development and differentiation, cell cycle regulation, and genetic regulation

- Potential for new technologies to assess induction of regenerated beta cells
- Current practice of islet transplantation that may allow evaluation of autologous regeneration in the setting of euglycemia and control of autoimmunity

JDRF's vision for the Regeneration of Beta Cell Function program is to develop novel strategies that restore lasting, physiological glucose regulation in patients with established type 1 diabetes by activating functional beta cell regeneration in the absence of cell transplantation. JDRF proposes to develop a deliverable intervention or therapeutic that restores human beta cell function while simultaneously controlling the ongoing immune response to regenerated beta cells.

The RBCF Program will be an aggressive, milestone-driven program with a 24-month Phase I effort with the goal of demonstrating both a 100-fold increase of functional human beta cells in-vitro and a 10-fold increase of functional human beta cells in-vivo in animal models.

Based on the successful completion of Phase I, the subsequent Phase II program will establish methods to induce functional beta cell regeneration in humans with type 1 diabetes. The interim discoveries from this program will likely be applied to other relevant aspects of the JDRF portfolio, including: increasing the engraftment and viability of transplanted cadaver islets, expanding cadaver islets to allow transplantation of multiple patients with type 1 diabetes from a single donor organ, and enhancing the success of living donor islet transplantation.

Objectives and Scope:

The biological factors regulating beta cell regeneration (proliferation, neogenesis, etc) are complex and poorly understood. A successful strategy to identify potential therapeutics requires an interdisciplinary, integrated approach to beta cell regeneration.

Phase I research programs may need to address the following or other relevant topics:

- Mechanisms of beta cell regeneration and kinetics of beta cell turnover
- Potential for beta cell regeneration in established type 1 diabetes and in the setting of islet transplantation with restoration of euglycemia and islet-sparing immunosuppression
- Mechanisms of increased beta cell mass in physiologic conditions such as obesity and pregnancy
- Factors that stimulate:
    - Beta cell proliferation and functional differentiation
    - Beta cell neogenesis from precursors
    - De-differentiation of beta cells
    - Prevention of apoptosis of beta cells
    - Transdifferentiation of non-beta cells to beta cells
- Role of non-beta cells and factors in beta cell regeneration including:
    - Other components of islets and the pancreas, including other islet cells, extracellular matrix, and the beta cell milieu
    - Non-islet cells (e.g. inflammatory cells, bone marrow precursors, duct cells, etc)
- Specific technical challenges:
    - Developing high-throughput, functional screens for compounds that induce human beta cell proliferation, differentiation, or neogenesis
    - Lineage tracing to analyze the basis of human beta cell neogenesis

Mechanisms of Support and Letter of Intent

JDRF will fund contracts to develop an integrated, multi-disciplinary RBCF Program with a well-defined program, specific goals and objectives, and project milestones. Members of interdisciplinary scientific teams will be required to work collaboratively to focus on achieving the Phase I objectives and milestones. Participating investigators of each research team will be expected to meet by videoconference or teleconference on a monthly basis with JDRF and other team members. In addition, written monthly reports and quarterly detailed progress reports will be required from each principal investigator. Quarterly funding is contingent upon progress towards accomplishing milestones.

JDRF requests Letters of Intent (LOI) that describe a 24-month Phase I effort focused on achieving the Phase I goals described above. Proposals are encouraged from interdisciplinary scientific teams of investigators based at different institutions (academic and/or industry) that address the goals and technical challenges described above and integrate the research into a single proposal. In the absence of an integrated team, a single laboratory may submit a proposal addressing one or more of those challenges provided they are willing to be integrated into a team assembled by JDRF. All applications, from teams and individuals, will be integrated into a team science program. Proposals using human islets or beta cells are strongly encouraged. New investigators from fields of research outside of diabetes are encouraged to participate.

The LOI should be organized as follows (10-page limit, excluding scientific and lay abstracts, biosketches, and abstracts of other funding):

1) Scientific and lay abstracts.
2) The project goal. State the Program goals and objective or challenge to be addressed in the proposal.
3) The approach. Define the research plan, including: the research challenges and how they will be addressed; unique or revolutionary aspects of the approach; and plans to demonstrate the success of the research effort within the 24-month period of funding. LOIs must describe specific, interim quantitative milestone(s) that will be achieved to make progress toward the ultimate 24-month goal of the RBCF program.
4) The budget. Provide a cost estimate and justification for resources required annually.
5) The management plan.
    a. Team applications: Provide a brief description of the research and technical expertise of the principal investigator and key team members, along with a management plan describing how different disciplines represented on the team will be integrated.
    b. Individual investigator applications: State willingness to be part of a larger team and work collaboratively on the ultimate goal of regeneration of beta cell function in type 1 diabetes. What unique skills or intellectual expertise do you bring to a team?
6) Title, award amount, duration, and abstract of current other funding.
7) Biosketches of key members of the team.

Funds Available

JDRF will commit up to $5M/yr for each of 2 yrs for the RBCF program. Budget requests from teams and individual investigators should be based on work scope and project timelines.

Receipt and Review Schedule

JDRF plans to release this special program with two receipt deadlines, June and December 2004. The schedule for June 2004 is below:

June 1, 2004	Letter-of-Intent (LOI) is required, due June 1
June 15, 2004	LOI decision
August 1, 2004	Applications due
September 2004	Review of applications
October 2004	Team assembly and negotiations
November 2004	Anticipated contract start date

Where to Submit LOIs

If you intend to submit an LOI, you should contact one of the JDRF program staff for further details:

Richard Insel, M.D., rinsel@jdrf.org; telephone 212-479-7604;
Brian Flanagan, Ph.D., blfanagan@jdrf.org; telephone 212-479-7549; or
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