
JDRF REQUESTS EXPRESSIONS OF INTEREST FOR:

THE FORMATION OF A COLLABORATIVE CONSORTIUM TO ADDRESS ENCAPSULATION FOR BETA CELL REPLACEMENT

BACKGROUND & PURPOSE

One of JDRF's therapeutic goals is to restore beta cell function in type 1 diabetes (T1D) by replacement/transplantation of beta cells/islets. Pancreatic islet transplantation has been efficacious in selected patients in improving metabolic control and quality of life, and in preventing severe hypoglycemia in patients with medically unstable T1D. Despite improvements in cadaveric pancreas procurement, islet isolation, and islet purification, major scientific and technical challenges remain that must be addressed before beta cell replacement will be widely incorporated into the clinical management of established T1D; examples include serious side effects from chronic immunosuppression, islet sensitivity to certain immunosuppressants, the insufficient human islet supply from cadaveric pancreata, incomplete development status of islets from a pluripotent cell source, and the desire for an alternative transplantation site. JDRF's role is to enable the scientific community to address these challenges with the ultimate goal of developing safe and effective transplantation approaches available to large numbers of individuals with T1D.

Encapsulation, which is defined as bioengineered barriers/devices surrounding transplanted cells that can provide a degree of protection from the immune system, presents a unique approach to overcome the limitation to wider adoption of cell replacement for T1D posed by chronic immunosuppression. Recent meeting reports on encapsulated porcine and human islets transplanted into non-human primates or patients continue to indicate that encapsulation may be a promising approach to provide long-term islet protection from the immune system. An ideal encapsulation system should support long-term islet survival and function, permitting physiological insulin secretion for glucose regulation, while preventing the host immune system from destroying the foreign donor tissue. Currently there are only two readily available beta cell sources – human and porcine islets. The yield and quality of human islets, however, remain variable, and the number of cadaveric pancreata is unlikely to meet the demand of T1D patients. Porcine islets therefore represent a scalable and better quality-controlled cell source. Thus, as a first goal, this call for Expressions of Interest (EOIs) welcomes proposals to develop and test novel encapsulation technologies with a short-term goal of allowing immunosuppression-free human islet function and a long-term goal of overcoming the pig-to-human xenogeneic barrier.

On the other hand, as new beta cell sources are being developed with pluripotent stem cell sources, a macro-encapsulation device may be a solution to mitigate teratoma concerns and to afford retrievability in circumstances where the graft should be removed from the patient. As several commercial entities begin to position human embryonic stem cell (hESC) derived pancreatic progenitors as potential cellular therapeutics for T1D, macro-encapsulation has been recognized as a critical enabling technology that will facilitate these products to become broadly applicable to many patients. Thus, the second goal of this call for EOIs is to engage the broader scientific community to collaborate with researchers and companies that can produce transplantable pancreatic progenitors and to develop and test suitable macro-encapsulation devices with features of immune-protection and

retrievability. Ultimately, the funded projects should help produce devices that will be combined with these progenitor cell products as clinically applicable therapeutics worthy of commercial development.

Participation in the JDRF Encapsulation Consortium

It is thought that a truly collaborative consortium approach is needed to foster replication and standardization in this field. This call for EOIs is meant to support multiple projects all working towards the goal of successful encapsulation technologies that will enable long-term function of human/porcine islets or hESC-derived pancreatic progenitors implanted into a non-immunosuppressed host. Each EOI can have its own specific research questions and focus. However, all funded principal investigators will be required to participate in annual in-person consortium meetings as well as regular teleconferences for scientific and administrative updates. It is expected that investigators will share unpublished data and reagents within the consortium, under a confidentiality agreement. All PIs and subcontractors will be required to agree to JDRF's Grant Policies and Procedures, including an Intellectual Property Policy and a Data Sharing and Confidentiality Agreement, before funds will be awarded. Continuation of funding will require active participation in the consortium and will be contingent upon results. After the consortium is established for one year, additional funding for cross-team research projects and pilot & feasibility studies will be made available on a competitive basis to facilitate independent replication of promising results and protocol standardization. An independent scientific advisory committee will be convened to evaluate and advise on the individual projects and the consortium as a whole.

OBJECTIVES

JDRF is soliciting EOIs to encourage collaborations among bioengineers, chemists, immunologists, transplant researchers, and pancreatic beta cell biologists to incorporate engineering concepts and designs into current efforts toward improving islet encapsulation as a key component of cell replacement therapy for T1D. Ultimately, the funded projects should have established milestones and make progress toward making encapsulated human islets/porcine islets/hESC-derived pancreatic progenitors a translatable technology applicable in the clinical setting.

To achieve this, JDRF is soliciting EOIs for proposals addressing aspects of the following (not intended to be exclusive or all-encompassing):

For technologies intended for encapsulating human or porcine islets

- Development and testing of novel bioengineered materials or devices that support encapsulated islet function in vivo in immunocompetent animal models with little or no immunosuppression
 - Demonstration of immune protection must be included as a major milestone within the grant period (i.e., simply focusing on technology development without key proof-of-concept experiments is not acceptable)
- In vivo mechanistic studies in transplant models that will define the failure mechanisms of encapsulated islets using existing and prior encapsulation designs
 - Studies should aim to discern effects and causal relationships of beta cell exhaustion/stress, mechanism of rejection by innate immunity, innate, allo-, xeno-, and/or auto-immunity, hypoxia, and other defined pathways that will inform on next-generation designs

For technologies intended for encapsulating hESC-derived pancreatic progenitors

- Proposals involving the use of hESC-derived pancreatic progenitors must address immune-protection, cell maturation and functional assessment, device retrievability, and teratoma risks. The devices must be tailored for potential commercially viable cell product(s). Applications should describe how the proposed device can be scaled and manufactured for ultimate patient delivery.
 - The EOI and the application must demonstrate the cell source provider's ability to produce pancreatic progenitors from hESC with yields and consistency capable of satisfying the demand of the encapsulation project. The cell source provider must have already demonstrated the pancreatic progenitors can consistently mature into diabetes-correcting, functioning grafts in immunodeficient animals.

For core facilities

- Analysis and transplant core service laboratories where independent testing of promising encapsulation technologies can be conducted. JDRF support for core facilities will be on a contractual basis where the payments will be tied directly to the funded activities.
 - Correlation of biocompatibility between in vitro screening tests, small and large animal models, and ultimately human subjects
 - Validation in large animal models the encapsulated islet/beta cell long-term function under commonly accepted immune challenge pairings (e.g., pig to non-human primate xenogeneic immunity)
 - These core laboratories must be open to collaboration with all members of the consortium
 - EOIs for analysis and transplant core service laboratories must propose a scientific research plan in addition to simply describing the capabilities of the laboratory
- ❖ Any novel material or device should address potential clinical utility, such as safety and manufacturing issues
- ❖ Proposals using novel biomaterials for the purpose of encapsulating islets must indicate significant advance of the new materials/technology over reported encapsulation results to date
- ❖ Simplistic "show-and-tell" experiments are discouraged. Step-wise investigation of why and how the technology may or may not support long-term islet function should be carefully considered.

This RFA is **not** intended to support:

- Encapsulation technologies that solely focus on imaging, addition of accessory cells (e.g., mesenchymal stem cells, sertoli cells, etc.), or other non-immunoprotective features

ELIGIBILITY

Applicants must hold an M.D., D.M.D., D.V.M., Ph.D., or equivalent academic degree and a faculty position or equivalent at a college, university, medical school, or comparable institution.

Applications may be submitted by domestic or foreign, public or private, non-profit or for-profit organizations. There are no citizenship requirements.

LEVELS OF FUNDING AND GRANT MECHANISM

Each project may request up to total \$350,000 USD per year, for up to three years. Applicants must discuss with JDRF Program Scientist when proposing multi-investigator projects with higher budget figures, to determine the feasibility of such a project.

Innovative pilot and feasibility studies without significant preliminary data may request up to total \$150,000 USD per year for one year.

Indirect costs may not exceed 10% of the direct costs.

Under the terms of the final grant award, written quarterly reports (~2-3 pages) will be required from the funded investigator as a basis for continued support.

In the full application, applicants must provide:

- Projected timelines on a quarterly basis for each specific aim
- Projected deliverables for each year

These will be reviewed and may be modified as work progresses during the course of the research program in discussion with the JDRF Program Scientist. Quarterly payments are released when quarterly milestones are met.

EXPRESSIONS OF INTEREST

EOIs should adhere to instructions printed in the template, which may be accessed on proposalCENTRAL. It should include, where applicable, the following information:

- Name, title, institution, and contact information of principal investigator, co-investigator and / or key collaborator
- Designation of team members with necessary bioengineering/material science/stem cell biology/beta cell biology/immunology/transplant expertise
- Name and participation level of any subcontractors
- Brief details of approach proposed, including rationale and references to published or preliminary data (preliminary data need not be presented in detail) (3 page limit)
- Short and long-term development goals set forth as milestones, as well deliverables
- Biosketch for each PI and co-PI
- Total estimated budget and project duration (up to 3 years)

EOIs will be selected based on scientific merit and programmatic priorities. After review by the JDRF Scientific team, selected EOIs will be invited for full application submission. EOIs are accepted on a rolling basis up until the deadline (March 26, 2012). EOI submission prior to the deadline is highly recommended to give JDRF opportunity to give feedback and time for EOI revision.

An approved EOI is required prior for submission of a full proposal. Please see below for complete instructions.

DEADLINES

- **RFA Release Date:**Friday, November 18, 2011
- **Expression of Interest Deadline:**Monday, March 26, 2012
- **Application Deadline:**.....Monday, June 18, 2012
- **Response to Applicants:**October 2012
- **Earliest Anticipated Start Date:**.....November 2012

INSTRUCTIONS

Applicants must register as an applicant and submit both their EOI and application using the templates available at JDRF's on-line application system [proposalCENTRAL](https://proposalcentral.altum.com/) (<https://proposalcentral.altum.com/>). The completed templates are to be submitted via the on-line application system.

Both academic and industry applicants are welcome. However, the indirect costs must not exceed 10% of the total direct costs. Applicants are strongly advised to consult with JDRF Program Scientist by February 1, 2012 to discuss the responsiveness of their proposal to this program. Enquiries in this area should be referred to Albert Hwa, Ph.D., ahwa@jdrf.org, +1-212-479-7663.

CONTACTS

PROGRAMMATIC

Albert J. Hwa, Ph.D.
Senior Program Scientist, Beta Cell Replacement
Juvenile Diabetes Research Foundation
26 Broadway, 14th Floor
New York, NY 10004
☎ 212-479-7663
💻 ahwa@jdrf.org

ADMINISTRATIVE

Bridget Donnelly
Grants Coordinator
☎ 212-479-7614
💻 Bdonnelly@jdrf.org

PROPOSAL CENTRAL

💻 <https://proposalcentral.altum.com/Login.asp>

💻 pcsupport@altum.com

☎ (301)-916-4557 ext. 227, or toll free in the US, (800)-875-2562 ext. 227

Assistance can be obtained Monday through Friday between 8:30am and 5pm U.S. Eastern Time