JDRF REQUESTS APPLICATIONS FOR:
DEVELOPING AND TESTING NOVEL ENCAPSULATION TECHNOLOGIES

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, 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 posed by chronic systemic immunosuppression. Recent 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\(^1\)\(^2\)\(^3\)\(^4\)\(^5\). An ideal encapsulation system should maintain long-term islet mass 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 cadaveric human islets, however, remain variable, and the number of cadaveric pancreata cannot meet the demand of T1D patients. Porcine islets therefore represent a readily available, scalable and better quality-controlled cell source. At the same time, several commercial entities begin to position human embryonic stem cell (hESC) derived pancreatic progenitors as potential future cell sources while designing encapsulation systems. Retrievable macro-encapsulation designs have been recognized as a critical enabling technology that will facilitate pluriotent stem cell-derived products to enhance the safety profile.

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PARTICIPATION IN THE JDRF ENCAPSULATION CONSORTIUM

JDRF believes that a truly collaborative consortium approach is needed to foster technical advances, replication and standardization in this field. In 2013 JDRF established the JDRF Encapsulation Consortium (JEC). The purpose of the JEC is several fold. It aims to reduce experimental redundancy and to facilitate data and reagent sharing. In addition, the consortium should be able to support direct comparison of mature technologies at similar development stages. Ultimately, JEC is expected to behave as a continuous pipeline, producing more than one encapsulated beta cell product (e.g., porcine, human embryonic stem cell-derived progenitor, human embryonic stem cell-derived mature beta cell, human induced pluripotent stem cell (hiPSC)-derived, etc.) ready for clinical testing.

All funded principal investigators from this call for applications will be required to participate in 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, governed under a confidentiality and non-disclosure policy. Prior to awarding funds, PIs and subcontractors will be required to agree to JDRF’s Grant Policies and Procedures, including an Intellectual Property Policy and a Confidentiality Non-Disclosure policy. Continuation of funding will require active participation in the consortium and will be contingent upon results.

OBJECTIVES

JDRF is soliciting applications 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 or hiPSC-derived cell products a translatable technology applicable in the clinical setting.

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

- Development and testing of novel bioengineered materials or devices that can maintain encapsulated islet cell mass and function long-term in immune competent animal models without immunosuppression
- Retrievable macro-encapsulation device development and testing with human pluripotent/embryonic stem cell-derived beta cell products that have demonstrated functional competence
- Elucidation of mechanisms to maintain durable mass and function of encapsulated islet cells
- Modification of cells and/or associated materials to optimize local immune modulation for long-term beta cell/islet survival and function without systemic immune suppression.
- IND/IDE-enabling study of a defined encapsulation product design that will enable the submission of clinical investigation applications to regulatory authorities.
- Clinical investigation of encapsulation technologies supported by robust preclinical data.
- Confirmation of appropriate assays and animal models that can be predictive of an encapsulation system’s biocompatibility in human
- Rational design and testing of combinations of more than one encapsulation technology (e.g., combining a macro-encapsulation design with a novel biomaterial coating)
All proposals should clarify the long-term goal of the research and its clinical outlook – i.e., what will be the envisioned cell and encapsulation combination? Currently, cell products derived from porcine sources and human pluripotent stem cells are considered the most likely candidates to make clinical impact. The following preclinical testing paradigm is recommended for screening and testing novel encapsulation designs:

<table>
<thead>
<tr>
<th>Approaches intended for porcine cell source</th>
<th>Approaches intended for human cell source</th>
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<td>2. Demonstration of device+cell source long-term β cell function and xeno-geneic protection in vivo in</td>
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<td>1. Immunodeficient rodent hosts with intended porcine cell source</td>
<td>1. Immunodeficient rodent hosts with intended human cell source</td>
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<td>2. Xenogeneic immuno-protection in a rodent model with intended porcine cell source</td>
<td>2. Allogeneic immuno-protection in a rodent model with appropriate allogeneic rodent cell source</td>
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<td>3. Xenogeneic immuno-protection in a large animal model with intended porcine cell source</td>
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- **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-immune protective features

**ANNOUNCEMENT INTRODUCTION AND PUBLIC Q&A**
JDRF will hold an announcement introduction meeting via web and teleconference on May 15, 2014 at 11AM-12PM US Eastern time, to which all interested prospective applicants are invited. JDRF scientists will give an overview of the goals of this initiative, explain the application process and answer initial questions on applications. A brief tutorial on JDRF's new grant application portal (RMS360) will also be given. Please click here for the call information.

**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 for-profit entities as well as nonprofit organizations, public and private universities, colleges, hospitals, laboratories, units of state and local governments. There are no citizenship requirements.
LEVELS OF FUNDING AND GRANT MECHANISM
Each project may request up to total $350,000 USD per year (including 10% indirect costs), for up to three years. Applicants should discuss with JDRF Programmatic Contact (see below) when proposing large projects involving multiple components with higher budget figures, to determine the suitability of such a proposal.

Innovative pilot and feasibility studies without significant preliminary data may request up to total $150,000 USD per year for one year (including 10% indirect costs).

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.

TO APPLY:
Both academic and industry researchers are welcome to apply (please see the above eligibility criteria). The indirect costs cannot exceed 10% of the total direct costs. Applicants are strongly advised to consult with the JDRF Programmatic Contact by July 1, 2014 to discuss the responsiveness of their proposal to this program. Inquiries in this area should be referred to Albert Hwa, Ph.D., ahwa@jdrf.org, +1-212-479-7663.

KEY DATES
- Full applications should be submitted no later than August 1, 2014 at 5 p.m. EST via RMS360 (http://jdrf.smartsimple.us).

<table>
<thead>
<tr>
<th>Announcement Date</th>
<th>Announcement Introduction and Public Q&amp;A</th>
<th>Full Online Application Deadline</th>
<th>Funding Decision Notification</th>
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<tr>
<td>April 7, 2014</td>
<td>May 15, 2014</td>
<td>August 1, 2014</td>
<td>January 2015</td>
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PROGRAMMATIC CONTACT
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ADMINISTRATIVE CONTACT
Bridget Donnelly
Research Administrator
If you have any grant-specific questions as you work within RMS360, please contact the administrative contact listed above.

For any non grant-specific inquiries or issues, please contact SmartSimple Support Services via email support@smartsimple.com or phone (866) 239-0991. Support hours are Monday through Friday between 5:00am and 9:00pm US Eastern Standard Time.