JDRF Encapsulation Research Update

Stephen L. Newman, M.D.
Vice Chairman, JDRF Board of Directors
Global Leader in T1D Research

- Largest charitable funder of T1D research worldwide
- Represent the Patient: Volunteer board with personal connections to T1D
- Goal: progressively remove the impact of T1D from people’s lives until we achieve a world without T1D
- Greater than 20 MD/PhDs
- Manage $568M in active research projects worldwide (funded $106M in FY13)

Research Funding Breakdown

- $106 million
  - $24 million Artificial Pancreas
  - $15 million Encapsulation
  - $9 million Complications
  - $5 million Glucose Control (including Smart Insulin)
  - $9 million Prevention
  - $28 million Restoration
  - $16 million Biomarkers and Other Research Priorities*
JDRF Programs Target All T1D Stages

- Prevention
- Smart Insulin
- Artificial Pancreas
- Restoration
- Encapsulation
- Complications

Beta Cell Mass

At Risk
Pre-Diabetes
Recent Onset
Established Diabetes

Time

Diagnosis

Adapted from Eisenbarth
JDRF Encapsulation Research Program

Imagine a future without insulin injections

• Replacing a person’s lost beta cells
• Protecting implanted beta cells from the immune system attacks
• Restoring independence from insulin injections and pumps for extended periods of time
• Improving control and reducing burdens of T1D

Implantable, beta cell replacement therapies restoring insulin independence without the need for intensive immune suppression

FY14 Funding:
• 14% of JDRF Research Budget
• $13 Million
Pancreas and Islet Transplant Can “Cure” T1D

PRE HbA1c 8.9%

Y2 HbA1c 5.3%
Y3 HbA1c 5.3%
Y4 HbA1c 5.7%

Source: Ali Naji, UPenn, CIT trial subject005
What is Encapsulation?
Cells + Encapsulation Technology

Cell Source
- Stem cells
- Cell lines
- Xeno (pig islets)

Characteristics
- Replenishable
- Fully functional
- Purified
- Scalable

Enabling Technologies
- Encapsulation
Rationale for Encapsulation Research

- Long-term encapsulated islet function shown in multiple animal studies
- Macro-encapsulation affords retrievability
- Limited human trials so far showed good safety profiles
- Several first-generation designs in clinical testing now
- Several replenishable human cell sources are becoming available, making encapsulation the rate limiting step
ViaCyte’s Islet cells survive and make insulin
ViaCyte Launches Phase 1 Trial: First trial of human stem cell-derived islet source (islet precursor)

ViaCyte’s VC-01™ Investigational Stem Cell-Derived Islet Replacement Therapy Successfully Implanted into First Patient
SAN DIEGO, Oct. 29, 2014 /PRNewswire/

JDRF-Funded Islet Encapsulation Program Reaches Historic Milestone
– First Ever Person with Type 1 Diabetes Receives Experimental Encapsulated Human Stem Cell-Derived Beta Cell Replacement Therapy –
Living Cell Technologies – encapsulated pig islets

- High health status pigs
  - No xeno-relevant viruses, bacteria and parasites.
  - Herd now bred in documented bio-isolation.
  - Three year health records and regular monitoring.
- Alginate-based microcapsules
- JDRF sponsored part of New Zealand clinical trial, as approved by the NZ regulatory authority
Beta O2 - βAir device

- Pilot trial showed long-term cell function and survival; decrease in HbA1c
- Follow up trial with 8 patients
JDRF Encapsulation Consortium - Driving Innovation and Collaboration

- Acceleration of successful technologies
- Standardization and technology comparison
- Data, protocol, and reagent sharing
- Fostering next generation technologies
  - More novel biomaterials and macro-encapsulation designs
  - Optimize local immune modulation approaches
  - Mechanistic studies to understand critical parameters for durable islet function (e.g., fibrosis, oxygen, vascularization, etc.)
- Key industry players with commercial capabilities involved
JDRF TransCelerate: Accelerated Translational Research with CXCL12-Eluting Islet Microcapsules

January 12, 2015

Mark Poznansky, MD, PhD
Timothy Brauns, MBA
Vaccine and Immunotherapy Center
Massachusetts General Hospital
Multiple Actions of CXCL12 Supporting Islets

- Selective recruitment and retention of immunosuppressive regulatory T cells
- Differential chemorepulsion of effector and memory T cells
- Pro-angiogenesis – blood vessel growth to support islets
- Pro-islet survival
## TransCelerate Investigative Team

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<th>Organization</th>
<th>Leader</th>
<th>Role</th>
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<tr>
<td>Massachusetts General Hospital/ Vaccine and Immunotherapy Center (Boston, MA)</td>
<td>Mark Poznansky, Director, Vaccine and Immunotherapy Center (VIC)</td>
<td>Project management</td>
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<tr>
<td></td>
<td>Timothy Brauns, Assoc. Director, VIC</td>
<td>Islet microencapsulation</td>
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<td>CXCL12 characterization</td>
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<td>Jim Markmann, Chief, Div. of Transplantation Surgery</td>
<td>Primate islet isolation</td>
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<td>Auto/allograft NHP studies</td>
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<td>Initial xeno NHP studies</td>
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<td>University of Minnesota (Minneapolis, MN)</td>
<td>Bernhard Hering, Director, Schulze Diabetes Institute</td>
<td>Adult porcine islet isolation and characterization</td>
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<td>University of Arizona (Tucson, AZ)</td>
<td>Klearchos Papas, Scientific Director, Institute for Cellular Transplantation</td>
<td>Primate and porcine islet viability studies</td>
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<td>University of California, Irvine (Irvine, CA)</td>
<td>Jonathon Lakey, Director of Research, Faculty of Medicine</td>
<td>Alginate characterization</td>
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<td>Elliot Botvinick, Associate Professor, Biomedicalal Engineering</td>
<td>Microcapsule characterization</td>
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<tr>
<td>University of Groningen (Groningen, NLD)</td>
<td>Paul de Vos, Associate professor, Chair Immunoendocrinology and Transplantation Biology</td>
<td>Alginate immunogenicity characterization</td>
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<tr>
<td>University of Minnesota Preclinical Research Center (St. Paul, MN)</td>
<td>Melanie Graham, Director, UM PRC</td>
<td>Follow on xeno NHP studies</td>
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Project will be Overseen by Two Committees

- **Operational Team (meets fortnightly)**
  - Mark Poznansky, (MGH—Chair)
  - Timothy Brauns, (MGH – Project Manager)
  - Melanie Graham, (U Minnesota PRC)
  - Bernhard Hering, (U Minnesota Schulze Diabetes Center)
  - James Markmann, (MGH)
  - Klearchbos Papas, (U Arizona)

- **Steering Committee (meets quarterly)**
  - All members of operational team above
  - Albert Hwa, (JDRF)
  - David Scharp, (Prodolabs)
  - David Sachs, (MGH)
  - Cenk Sumen, (Progenitor Cell Therapeutics)
Teaming Diagram for CEXM Production, Characterization and Testing

- **Massachusetts General Hospital**
  - CXCL12 characterization
  - Islet microencapsulation
  - Islet viability and function in primates
  - Islet efficacy in primates

- **University of Minnesota**
  - Islet harvest & Isolation
  - Recombinant CXCL12 (Peprotech)

- **University of Arizona**
  - Islet viability
  - Microencapsulated islet viability

- **University of Groningen**
  - Alginate immunogenicity analysis
  - Ultrapurified alginate (NovaMatrix)

- **University of California Irvine**
  - Alginate physiological assessment
  - Microcapsule pre-implant physiological assessment
  - Microcapsule post-implant physiological assessment

- **University of Minnesota (Preclinical Research Center)**
  - Islet efficacy in primates

**Key**
- Product supply/mfg
- Product characterization
- Primate studies
Novel Biomaterials (Langer at MIT)

MIT: Dan Anderson, Robert Langer

Joslin: Gordon Weir

Univ. of Mass.: Dale Greiner, David Harlan
Novel macro-encapsulation membranes

Titania nanotubular membranes

Silicon nanochannels

Alumina nanoporous capsules

Dr. Tejal A. Desai UCSF
Biohybrid device for proper islet function

Modulating the Local Environment

- Encapsulation
- Vascular Infiltration
- Co-delivery of “helper” cells
- Bioactive Surfaces
- Localized Drug Delivery
- Mechanical Protection
- In situ oxygen generation

Multi-functional Platform

Dr. Camillo Ricordi, University of Miami.
Significant Encapsulation Research Progress

- Multiple programs moved in the clinical phase
- Multiple sources of cells identified
- Multiple device types in development
- Multiple research teams testing possible new options in animal models